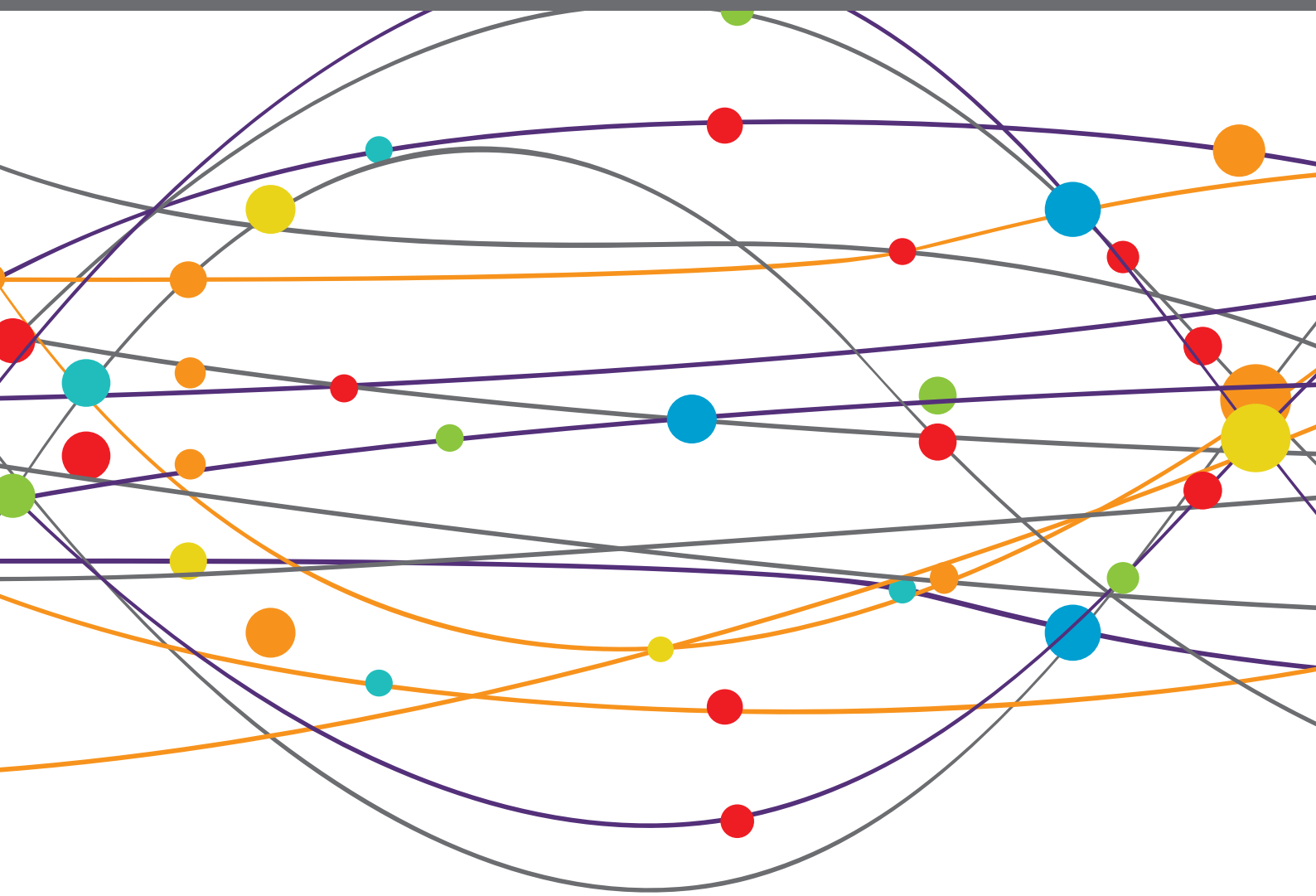
DEMENTIA IN LOW AND MIDDLE INCOME COUNTRIES

EDITED BY: Christopher Butler, Agustin Ibanez, Mario Alfredo Parra, Huali Wang, Kit Yee Chan, Rufus Olusola Akinyemi, Tala Al-Rousan, Suvarna Alladi, Kirsten Bobrow, Stefania Ilinca, Elissaios Karageorgiou, Ophir Keret, Maira Okada de Oliveira and Geeske Peeters

PUBLISHED IN: Frontiers in Neurology and Frontiers in Public Health



frontiers Research Topics

frontiers

ISSN 1664-8714
ISBN 978-2-88976-426-6
DOI 10.3389/978-2-88976-426-6

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: frontiersin.org/about/contact

DEMENTIA IN LOW AND MIDDLE INCOME COUNTRIES

Topic Editors:
Christopher Butler, Imperial College London, United Kingdom
Agustin Ibanez, Latin American Brain Health Institute (BrainLat), Chile
Mario Alfredo Parra, University of Strathclyde, United Kingdom
Huali Wang, Peking University Sixth Hospital, China
Kit Yee Chan, University of Edinburgh, United Kingdom
Rufus Olusola Akinyemi, University of Ibadan, Nigeria
Tala Al-Rousan, University of California, San Diego, United States
Suvarna Alladi, National Institute of Mental Health and Neurosciences (NIMHANS), India
Kirsten Bobrow, University of California, San Francisco, United States
Stefania Ilinca, Trinity College Dublin, Ireland
Elissaios Karageorgiou, Independent researcher, Greece
Ophir Keret, Rabin Medical Center, Israel
Maira Okada de Oliveira, University of São Paulo, Brazil
Geeske Peeters, Radboud University Nijmegen Medical Centre, Netherlands

Citation: Butler, C., Ibanez, A., Parra, M. A., Wang, H., Chan, K. Y., Akinyemi, R. O., Al-Rousan, T., Alladi, S., Bobrow, K., Ilinca, S., Karageorgiou, E., Keret, O., de Oliveira, M. O., Peeters, G., eds. (2022). Dementia in Low and Middle Income Countries. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88976-426-6

Table of Contents

frontiers in Public Health

ORIGINAL RESEARCH
published: 31 July 2020
doi: 10.3389/fpubh.2020.00342

A New Approach for Developing "Implementation Plans" for Cognitive Stimulation Therapy (CST) in Low and Middle-Income Countries: Results From the CST-International Study

Charlotte R. Stoner[1], Mina Chandra[2], Elodie Bertrand[3], Bharath DU[4], Helen Durgante[5], Joanna Klaptocz[6], Murali Krishna[4], Monisha Lakshminarayanan[7], Sarah Mkenda[8], Daniel C. Mograbi[3,9], Martin Orrell[10], Stella-Maria Paddick[11], Sridhar Vaitheswaran[7] and Aimee Spector[12]*

[1] Centre for Chronic Illness and Ageing, Centre for Mental Health, Institute for Lifecourse Development, School of Human Sciences, University of Greenwich, London, United Kingdom, [2] Atal Bihari Vajpayee Institute of Medical Sciences and Dr. Ram Manohar Lohia Hospital, Bangabandhu Sheikh Mujeeb Marg, New Delhi, India, [3] Department of Psychology, Pontifical Catholic University of Rio de Janeiro, Rio de Janeiro, Brazil, [4] Viveka Hospital, Mysore, India, [5] Department of Psychology, Federal University of Rio Grande do Sul (UFRGS), Rio Grande do Sul, Brazil, [6] Newcastle University Hospitals NHS Foundation Trust, Royal Vic Infirmary, Newcastle upon Tyne, United Kingdom, [7] Dementia Care in Schizophrenia Research Foundation (DEMCARES in SCARF), Chennai, India, [8] Occupational Therapy Department, Kilimanjaro Christian Medical University College, Moshi, Tanzania, [9] Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom, [10] Institute of Mental Health, University of Nottingham, Nottingham, United Kingdom, [11] Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, United Kingdom, [12] Research Department of Clinical, Educational and Health Psychology, University College London (UCL), London, United Kingdom

OPEN ACCESS

Edited by:
Stefania Ilinca, Trinity College Dublin, Ireland

Reviewed by:
Geeske Peeters, Radboud University Nijmegen Medical Centre, Netherlands
Debra Kellstedt, University of Nebraska Medical Center, United States
Ponnusamy Subramaniam, Universiti Kebangsaan Malaysia, Malaysia

***Correspondence:**
Charlotte R. Stoner
c.r.stoner@gre.ac.uk

Specialty section:
This article was submitted to Aging and Public Health, a section of the journal Frontiers in Public Health

Received: *24 March 2020*
Accepted: *18 June 2020*
Published: *31 July 2020*

Citation:
Stoner CR, Chandra M, Bertrand E, DU B, Durgante H, Klaptocz J, Krishna M, Lakshminarayanan M, Mkenda S, Mograbi DC, Orrell M, Paddick S-M, Vaitheswaran S and Spector A (2020) A New Approach for Developing "Implementation Plans" for Cognitive Stimulation Therapy (CST) in Low and Middle-Income Countries: Results From the CST-International Study. Front. Public Health 8:342. doi: 10.3389/fpubh.2020.00342

Background: Even with a strong evidence base, many healthcare interventions fail to be translated to clinical practice due to the absence of robust implementation strategies. For disorders such as Alzheimer's disease and other dementias, access to evidence-based interventions beyond research settings is of great importance. Cognitive Stimulation Therapy (CST) is a brief, group-based intervention, with consistent evidence of effectiveness.

Methods: An implementation focused, three-phase methodology was developed using extensive stakeholder engagement. The methods resulted in a standardized Implementation Plan for the successful translation of CST from research to practice. The methodology was developed using the Consolidated Framework for Implementation Research (CFIR) and refined in three countries that vary in levels of economic development and healthcare systems (Brazil, India and Tanzania).

Results: Five Implemention Plans for CST were produced. Each plan contained implementation strategies and action plans devised in conjunction with policy professionals, healthcare professionals, people with dementia and family carers, and an international team of researchers and clinicians.

Conclusion: This novel methodology can act as a template for implementation studies in diverse healthcare systems across the world. It is an effective means of devising socio-culturally informed Implementation Plans that account for economic realities, health equity and healthcare access.

Keywords: translational research, implementation, cognition, developing countries, methodology, psychosocial, dementia

INTRODUCTION

Cognitive Stimulation Therapy (CST) is a brief, group-based, psychosocial intervention for people living with mild to moderate dementia (1). Manualised CST consists of 14 sessions of 45-min duration each, occurring twice a week for 7 weeks. Each session follows a theme (e.g., current affairs, word games, faces) and is designed to stimulate a range of cognitive abilities, whilst providing an optimal learning environment, and the social benefits of a group (2). The original CST programme referenced here was developed in the United Kingdom (UK), due to the limited efficacy of medication prescribed for dementia (3). It has a consistent evidence base for improving cognition and quality of life for people with dementia (4, 5). In particular, memory, comprehension of syntax and orientation appear to be most impact by CST, whilst impact on executive function, attention, and praxis has not been documented (6). CST has also been widely implemented in UK National Health Service (NHS) Memory Clinics (7) and is consistently recommended for people with dementia in the UK (8, 9). Whilst many programmes similar to CST have since been developed, the original UK version remains the most consistently evidenced (10–12).

As manualised CST was developed in the UK, some activities such as the use of a group song to open and close sessions, and reminiscence about childhood may be less appropriate in other contexts and cultures. To ensure that CST remains cross-culturally valid, a standardized methodology involving three distinct stages was developed, where adaptations are generated and reviewed in collaboration with stakeholders. Where this methodology has been adhered to, consistent evidence for the effectiveness of CST has emerged across countries (10). However, after adaptation, implementation is needed to maximize global uptake of evidence-based interventions.

Barriers to implementing evidence based interventions can occur at multiple levels of a health system including the patient level, provider or group level, organizational level and policy level (13) and there is a growing recognition of the importance of implementation research including evaluating what works, where and why across multiple contexts. The Consolidated Framework for Implementation Research (CFIR) (14) is a meta-theoretical amalgamation of 19 previous implementation models that can inform this process. It incorporates theories of innovation, organizational change, knowledge translation, uptake and dissemination and is designed to offer an overarching typology for constructs associated with implementation science, where constructs and domains can be used to guide and evaluate the implementation process. The CFIR has been used widely and can underpin diverse programmes, from weight management initiatives (15) to pharmacological interventions in addiction services (16).

There is no existing methodological framework for implementing healthcare interventions that also accounts for differing economic development of countries, healthcare systems, and complex implementation issues such as those contained within the CFIR. Thus, the aim of this paper is to present a newly developed, three-stage, implementation methodology that facilitates the successful implementation of evidence-based interventions like CST in diverse settings. Whilst evidenced for CST, the methodology can be generalized to other programmes and interventions across diverse contexts, thereby facilitating the translation of interventions from research to practice globally.

MATERIALS AND METHODS

Implementation Plans were developed separately for three countries (Brazil, India, and Tanzania) using the CFIR. The CFIR is a taxonomy of factors intrinsic to the implementation or "scaling up" of interventions from research to practice and has been used successfully in a number of interventions (15, 17). Consisting of five domains (intervention characteristics, outer setting, inner setting, characteristics of individuals and process) and 39 constructs, the CFIR can be used to guide and evaluate the implementation process across multiple and diverse healthcare systems. In particular, the continual engagement of stakeholders is advocated to explore the barriers to and facilitators of implementation and inform the implementation process at a provider, service user and organizational or political level (**Table 1**).

For the current project, the CFIR was used to develop a three-stage, mixed methodology employing both stakeholder engagement and the development of a quantitative scoring system. In summary, the methods consisted of: [1] exploration of barriers to and facilitators of CST implementation, [2] development of implementation activities to overcome each barrier or support each facilitator, and [3] development and monitoring of formal Implementation Plans. To demonstrate cross cultural validity, this methodology was used in three diverse countries with differing levels of economic development and differing healthcare systems: Brazil, India, and Tanzania. Brazil is an upper-middle income country, with both a public [Sistema Único de Saúde (SUS)] and private healthcare system (18). India is a lower-middle income country, with a public government healthcare system covering primary, secondary,

TABLE 1 | Consolidated framework for implementation research (CFIR) domains and constructs.

CFIR domain	Construct
Intervention Characteristics	• Intervention source • Evidence strength and quality • Relative advantage • Adaptability • Trialability • Complexity • Design quality and packaging • Cost
Outer Setting	• Patient needs and resources • Cosmopolitanism • Peer pressure • External policies and incentives
Inner setting	• Structural characteristics • Networks and communications • Culture • Implementation climate
Characteristics of individuals	• Knowledge and beliefs about the intervention • Self-efficacy • Individual stage of change • Individual identification with organization • Other personal attributes
Process	• Planning • Engaging • Executing • Reflecting and evaluation

and tertiary care. However, bottlenecks in accessing these services can occur, leading people to seek private care (19). Tanzania is a low-income country, where the health system is descentralised and is pyramidal in structure. Dispensaries serve local communities, followed by health centers, hospitals and larger referral hospitals (20).

The three countries chosen for this work were part of the CST-International research programme (21) and teams in each country had previously completed the formal adaptation of CST (22–24) using the established methodology (25). As this was a stakeholder project and not a formal research study, no identifying information was collected from stakeholders beyond their job title and no formal analysis was conducted.

Phase 1: Exploration of the Barriers to and Facilitators of CST Implementation

Identifying Stakeholders

The Formative Method for Adapting Psychotherapy (FMAP) has previously been used to identify relevant stakeholders when adapting CST for different countries (25). This, combined with implementation theory, resulted in the identification of three groups of stakeholders from both public and private healthcare systems: Group [1] Decision makers or policy professionals who may commission or authorize the use of CST in services, group [2] healthcare professionals who may be expected to deliver CST as part of their regular duties, and group [3] those who may expect to receive CST and their supportive others.

Implementation Questions

All 39 constructs contained within the CFIR were examined and transformed into a series of questions addressing each of the five domains of implementation (see **Supplementary Material**). The questions were developed iteratively with researchers and clinicians from the UK, Brazil, India and Tanzania providing feedback and suggesting additional questions. Questions were designed to be all encompassing and cross-culturally valid. They could refer to differing awareness of dementia, healthcare systems and services including long-term care, private facilities and non-governmental organizations (NGOs). Further, questions were targeted according to stakeholder group and accounted for job role and responsibility, experience and expertise. A total of 39 questions were developed and a distinction was made between those considered essential to inform the implementation process and those deemed as supplementary. Thus, 15 questions (5 per group) were considered essential, with researchers in Brazil, India, and Tanzania required to ask them and 24 were classed as supplementary that could be asked if time allowed.

Stakeholder Meetings

Flexibility was needed when organizing stakeholder meetings and the format was amended to suit individual settings. However, all stakeholder meetings were required to be prefaced by introductory talks on both dementia and CST, ensuring equivalency of baseline knowledge. Further, all talks were tailored to ensure that the information presented was appropriate for the country or setting and the stakeholder group presented to. Following the talks, stakeholders were split into small groups, with one or two facilitators present. Facilitators asked each of the essential questions to the group, ensuring that all stakeholders were given an opportunity to express views. If there was time following thorough discussions of the essential questions, supplementary questions were put to stakeholders. Sessions were audio-recorded if attendees gave permission for this but as, this was not a formal research study, no formal qualitative analysis was undertaken.

Phase 2: Development of Implementation Activities

Compilation of Barriers and Facilitators

Every barrier and facilitator identified across stakeholder meetings were synthesized into tables specific to each country. Each barrier or facilitator was then grouped according to the CFIR construct they referred to and were also grouped according to a more generic research theme. These tables were discussed by the primary team in each country and by the wider international team, who proposed implementation activities designed to overcome barriers or reinforce facilitators identified. Researchers were asked to focus on tangible and realistic activities that could be achieved as part of the CST-International research programme (2018–2021). Activities proposed by the primary team in each country were subsequently discussed and agreed upon in teleconferences with the UK based team. All agreed upon activities were added to the table, next to the corresponding barrier or facilitator.

Reaching Consensus on Implementation Activities Proposed

As numerous barriers and facilitators were identified, the corresponding number of implementation activities was also high. Recognizing that it might not be feasible to use all activities proposed, a system was devised to ensure that activities considered essential to the successful implementation of CST were prioritized. Further, the team recognized that implementation activities were of ranging difficulty practically. As such, a secondary rating system was added to ensure that activities that were of relative ease were also prioritized. This resulted in a two-by-three matrix system (26), where both the perceived importance and ease of use for each implementation activity proposed could be captured. It was also important to ensure that stakeholders were re-engaged with to determine the importance and difficulty of each proposed activity. Thus, the completed table with barriers, facilitators and proposed activities were circulated firstly to each research team and then to all other stakeholders for feedback. Both the research team and stakeholders were asked to provide two ratings for each activity according to the two-by-three matrix (**Figure 1**).

It was stipulated that all stakeholders should be invited to provide ratings, in order to maximize the response rate. To analyse responses, a scoring system was used for the matrix where scores ranged from one (activity was both advisory and difficult) to 9 (activity was both essential and easy). The mode(s) for each activity was then calculated and results discussed during a consensus meeting in each country. Consensus was reached when members of the primary team in each site formally agreed upon which activities would be undertaken, prioritizing those with the highest modes judged most feasible. The teams did this by further splitting activities into those that were "essential" for successful implementation and those that the team would "further consider" if time and resources allowed.

Phase 3: Writing and Monitoring the Implementation Plan

The agreed upon implementation activities were formalized in a research document called an "Implementation Plan." Whilst plans could be written in the format or style most suited to each context, it was stipulated that all teams were required to continue using the CFIR and that each Implementation Plan should include:

1) A written summary of the barriers and facilitator tables, detailing which implementation activities were to be undertaken and the CFIR construct they referred to.
2) Justification for the number of activities that the team agreed to undertake, with reference to available time and resources.
3) Justification for decisions not to undertake an activity that had a high mode (8 = essential and intermediate or 9 = essential and easy), where applicable.
4) "Action plans" for the site where each activity to be undertaken was assigned to a member of staff and given a due date for when the action should be completed by.
5) A local barrier and facilitator checklist to be used by newly trained facilitators before commencing a CST group addressing logistical issues commonly faced when beginning CST.

After the Implementation Plan had been written and agreed upon by the local and international teams, it was routinely monitored by staff to ensure that actions were undertaken. Staff were encouraged to keep a record of completed actions and a research diary detailing which activities were successful and which were less so.

An overview of the methodology and process, with example results can be found in **Table 2**. More detail on results from each phase can be found in subsequent sections.

RESULTS

Phase 1: Exploration of the Barriers to and Facilitators of CST Implementation

Brazil

Four meetings took place between November 2018 and January 2020 in Rio de Janeiro and São Paulo involving 50 stakeholders (Group 1 = 15, Group 2 = 20, and Group 3 = 15). In Rio de Janeiro all three groups attended one session where they listened to introductory talks to dementia and CST by the research team before dividing into smaller groups, according to their designation (Group 1, 2, or 3) for the discussion. In São Paulo, three meetings where facilitated by the research team, with each stakeholder group attending introductory talks and taking part in small group discussions. Group 1 stakeholders included administrative directors of public health services and NGOs, primary care coordinators, private clinic administrators and private clinic administrators. Group 2 stakeholders included psychologists, nurses, speech therapists, social workers and occupational therapists. Group 3 consisted of people with dementia, their family members or supportive others and other members of the general public with experience of or an interest in dementia. In both locations, common barriers identified by Group 1 included a lack of awareness regarding treatment policies or guidelines for dementia or how policies were applied practically in the varied healthcare services. Group 2 stakeholders noted there could be high staff burden, with healthcare professionals lacking capacity to deliver what was perceived as an extra service alongside their usual duties. Group 3 stakeholders discussed a lack of support from the public sector and high levels of stigma.

India

Across three sites (Mysore, Chennai and New Delhi) a total of 77 stakeholders took part in discussions (Group 1 = 22, Group 2 = 31, and Group 3 = 24). Group 1 stakeholders included Government officers in charge of Ministry of Health programmes, representatives from the Alzheimer's and Related Disorders Society of India (ARDSI) and decision makers NGOs. Group 2 representatives included psychiatric nurses, research assistants, consultant psychiatrists, neurologists, geriatricians, neurology, and psychiatry residents and psychologists. For Group 3, people with dementia, family caregivers and community leaders responded. In all sites, Group

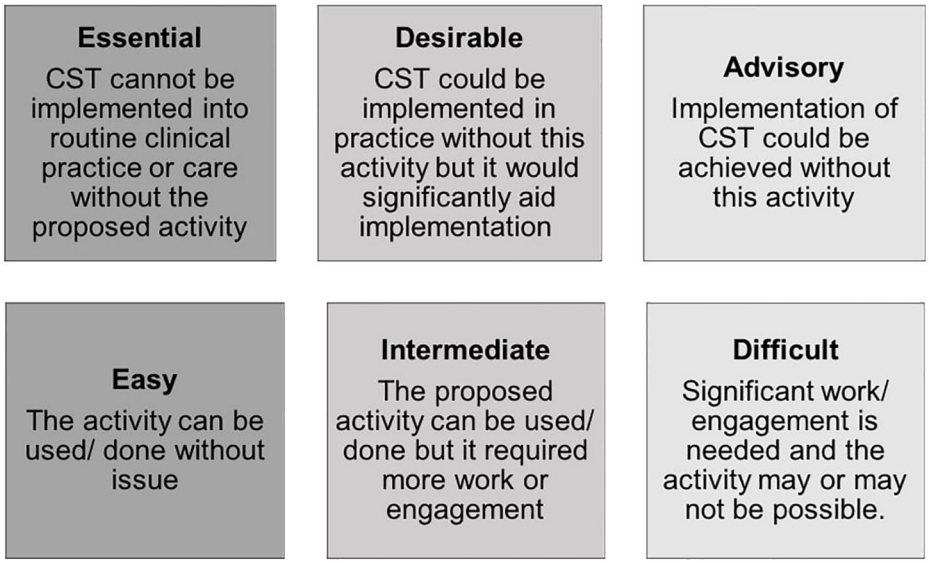


FIGURE 1 | Rating matrix for implementation activities.

1 stakeholders were interviewed individually, due to their limited availability. In Chennai, the decision was made to speak to nurses and nursing assistants separately from medical doctors to ensure that nurses were comfortable giving a view. Group 1 responders across sites noted that there was often a lack of national funding available for research and services for people with dementia and there was often a lack of communication between key policy professionals and professionals. Group 2 noted that stigma and the cost of services could impact attendance for dementia services and that psychosocial interventions were perceived as less valuable than medical interventions. Caregivers in Group 3, who had taken part in previous psychosocial interventions in Chennai, suggested that they viewed these interventions as beneficial, improving communication for the person with dementia. They also noted some logistical barriers including transportation difficulties and scheduling conflicts as caregivers had to take time off from employment to accompany persons with dementia to attend sessions.

Tanzania

Two meetings took place in Arusha and Moshi in October 2018 involving 49 stakeholders (Group 1 = 5, Group 2 = 33, and Group 3 = 11). Group 1 stakeholders included directors of services at local hospitals, regional mental health coordinators and heads of departments in a local hospital. Group 2 were mostly nurses, medical doctors, counselors and psychologists. Group 3 consisted of five people with dementia and six carers or supportive others. The people with dementia had previously participated in a pilot study of CST. Barriers identified in Tanzania included a lack of awareness of dementia as a disease, under-developed transport networks limiting the degree to which people with dementia could travel to a group and, similar to Brazil, high staff burden. However, carers and people with dementia in Group 3 described the benefits of meeting with their peers and the sharing of news across villages and towns. There were also more practical barriers identified in Tanzania associated with running CST groups. First, some sessions required the use of electronic equipment and electricity could not always be relied upon in more rural areas. Second, a small but significant proportion of older adults spoke only Chaga languages, thus creating a language barrier with some of their fellow attendees and Swahili speaking healthcare professionals. Third, meeting spaces could be difficult to source, with previous groups taking place in churches or school. Both were described as problematic with the former potentially leading to exclusion and the latter to embarrassment.

Phase 2: Development of Implementation Activities

Compilation of Barriers and Facilitators

Brazil

A total of 58 barriers and facilitators were identified across both sites within CFIR categories of: inner setting (implementation readiness, networks and communications, structural characteristics), outer setting (patient needs/resources, external policies, and incentives), intervention characteristics (cost, relative advantage, evidence strength and quality) and characteristics of individuals (knowledge and beliefs about the intervention). To overcome each barrier or support each facilitator, 41 implementation activities were proposed, with a minimum of one activity proposed for each area of the CFIR but activities proposed could address multiple barriers or facilitators.

India

As the India sites were diverse, research teams in each site wrote and compiled their own barrier and facilitator documents. In Chennai, a total of 133 barriers and facilitators were identified, and 49 implementation activities proposed. In Mysore, 26

TABLE 2 | Methodology overview and example results.

	Phase 1		Phase 2		Phase 3
Country	**Question asked *(CFIR construct)***	**Barrier/Facilitator identified**	**Implementation activity developed**	**Rating of activity by stakeholders**	**Refinement and inclusion in Implementation Plan**
Brazil	What training/support will staff need to implement CST e.g., time off regular duties/travel for training? *(implementation climate)*	Healthcare professionals, who might be expected to run CST work long hours, with competing demands. This means they may not have time to facilitate CST groups.	Venues offering CST groups will be required to guarantee staff are granted protected time for running groups and attending training	Essential and of Intermediate difficulty	Essential: CST facilitators will need protected time allocated for CST (training and running sessions). The research team should inform site management that protected time for staff is a requirement of the project when approaching/recruiting sites and ensure that site managers agree to this.
India	What organizations/charities/ government bodies are available to you to help support implementation? *(cosmopolitanism)*	There is a lack of awareness of CST as a treatment option. Networking with other organizations may improve awareness.	Research team to advertise CST through media and form a network of organizations that are interested in including CST in their service	Essential and of Intermediate difficulty	Essential: Researchers to advertise CST and create a network of organizations that show interest in CST who are regularly updated with local resources and use of the intervention
Tanzania	What are the known barriers people encounter when accessing services? *(patient needs and resources)*	Some older adults have visual impairments but no access to eye care. Visual impairments that cannot be compensated for will limit engagement with CST.	Screening for CST suitability should include a brief eye test	Desirable and of Intermediate difficulty	Further Consider: As part of screening procedures, participants can be referred to an ophthalmologist to address any visual impairments prior to commencing CST.

barriers and facilitators were identified, and e 62 identified activities to support implementation were proposed. Finally, in New Delhi, a total of 25 barriers and facilitators were identified, and 62 activities proposed (country total: 184 barriers/facilitators and 173 activities proposed). Activities fell under the CFIR domains of inner setting (structural characteristics, implementation climate, networks, and communications), outer setting (peer pressure, patient needs/resources, external policies and incentives, cosmopolitanism), intervention characteristics (complexity, cost, adaptability, design quality and packaging, evidence strength and quality, relative advantage) and characteristics of individuals (knowledge/beliefs about the intervention, motivation, values, self-efficacy).

Tanzania

A total of 55 barriers and facilitators were documented in Arusha and Moshi, within the CFIR categories of: inner setting (networks and communications, structural characteristics, culture), outer setting (patient needs/resources), intervention characteristics (cost, relative advantage, design quality, and packaging), and characteristics of individuals (knowledge/beliefs about the intervention). A total of 41 implementation activities were proposed to overcome all barriers and support all facilitators. For Tanzania, the research team discussed whether it was more feasible for CST facilitators to transport people with dementia who lived in very rural setting or whether it was feasible for people with dementia and carers to arrange their own transport. Ultimately a decision could not be made and so both activities were proposed, with the decision postponed until stakeholders could express a preference.

Reaching Consensus on Implementation Activities Proposed

Brazil

Thirty-three stakeholders from Phase 1 rated the 41 implementation activities according to their perception of how essential each activity was for successful implementation and how easy each were to do. Responders consisted of five members of the CST-International research team (two psychologists, one psychiatrist, one PhD candidate, and one research assistant) and 16 potential CST facilitators (Group 2), for whom professions included psychologists, nurses, physicians, gerontologists, speech therapists, recreation workers, and social workers. Six decision makers from the private and public sectors responded on behalf of Group 1 (local policy or decision makers). For Group 3 (people with dementia, caregivers and other interested parties), six caregivers responded.

The most common individual rating for activities was 8 (Essential and Intermediate), however, there was a large amount of variance in responses. For example, the implementation activity "CST training should be delivered where CST sessions are going to be offered" was rated as advisory and intermediate

(2) by two responders and essential and easy (11) by two responders. All activities were discussed at a local team meeting, with reference to how many could be implemented and the prioritization of those activities that were rated as both essential for implementation and easy to use. It was decided that activities rated as essential and easy/intermediate to use would always be categorized as "essential" and activities with lower modes would be categorized as "further consider." A total of 22 activities were considered essential for implementation success and nine were designated as further consider if time and resources allowed.

India

In Chennai, 12 stakeholders rated how essential and easy the identified activities to support implementation were. Responders consisted of four members of the CST-International research team (three consultant psychiatrists and one psychologist). Two decision makers from an NGO responded on behalf of Group 1. For Group 2, two potential CST facilitators (psychologists) and two psychiatrists responded. For Group 3, two caregivers responded.

The most common individual ratings for activities were 9 (Essential and Easy) and 8 (Essential and Intermediate). All activities were discussed at a local research team meeting, where it was decided activities rated as essential and easy/intermediate to implement would always be categorized as "essential" (40 activities). Some activities rated six (Desirable and Intermediate) or below were deemed too resource intensive. For example, under "Inner Setting" a mechanism that required "researchers to identify homes willing to deliver CST and pitch CST to them" was considered too resource intensive, involving creating an exhaustive list of care homes in Chennai. Six activities were further considered by the team.

In Mysore, 13 stakeholders rated the implementation activities. Responders consisted of four members of the CST-International research team (three psychiatrists and one speech pathologist) and three potential CST facilitators (Group 2) that included two psychologists and one psychiatric social worker. Three stakeholders responded on behalf of Group 1 and included a head of Department in Psychiatry in a State-run Medical College, a District Mental Health Officer and a District Psychiatrist. For Group 3, two caregivers and one person with dementia responded. All activities were discussed at a local team meeting, where it was decided that activities rated as essential and easy/intermediate (9/8) to implement would always be categorized as "essential" and activities with lower modes would be categorized as "further consider". This resulted in 16 "essential" activities and eight "further consider" activities.

For New Delhi, all identified stakeholders from Phase 1 rated the implementation activities (Group 1 = 10, Group 2 = 10, Group 3 = 8). All domain areas considered essential were shortlisted as mandatory for CST implementation (45 "essential" activities) while the consensus view was that domain areas considered advisory and desirable should be left to the discretion of the team depending on available resources and logistics. These nine activities were designated as "further consider."

Tanzania

16 stakeholders rated implementation activities for Arusha and Moshi. These consisted of four members of the CST-International team (two geriatricians, one registrar, and one senior research associate) and eight potential CST facilitators (Group 2), for whom professions included psychologists, medical officers and occupational therapists. A decision maker at a large university hospital responded on behalf of Group 1 (local policy or decision makers). For Group 3 (people with dementia, caregivers and other interested parties), two caregivers and one person with dementia responded.

The most common individual rating for activities was 6 (Desirable and Intermediate), however, there was a large amount of variance in responses. For example, the activity "psychoeducation should include information on the underlying pathology of neurodegenerative diseases" was rated as advisory and difficult (1) by two responders and essential and easy (11) by two responders. All activities were discussed at a local team meeting, with reference to how many could be implemented and the prioritization of those activities that were rated as both essential for implementation and easy to use. It was decided that activities rated as essential and easy/intermediate to implement would always be categorized as "essential" (15 activities) and activities with lower modes would be categorized as "further consider" (seven activities).

Phase 3: Writing and Monitoring the Implementation Plan

Brazil

The São Paulo and Rio de Janeiro sites were considered similar enough to allow for one Brazil Implementation Plan, with specific actions attributed to sites where appropriate. A draft implementation plan was circulated, and CST-Investigators were invited to comment and refine the plan. The fifth and final iteration of this plan was reviewed and approved by all members of the team. The 22 essential activities recorded in the Brazil Implementation Plan fell under CFIR domains of: knowledge/beliefs about the intervention, relative advantage, costs (direct and indirect), networks and communications, external policy and incentives and structural characteristics. The nine further consider activities fell under the CFIR categories of: patient needs and resources, adaptability, structural characteristics and individual stage of change. Ten members of the research across sites were assigned action plans consisting of their essential and further consider actions. An example of a Rio de Janeiro based researcher's action plan is given in **Table 3**. The Brazil local barriers and facilitators checklist contained four subsections: participants, facilities, travel and timing and materials. Example items included "Is group to be held in a neutral setting (e.g., it is not in a church)?," "can the building be reached by public transport?," and "have you got all the electronic devices needed for sessions (e.g., mobile phone with songs preloaded)?

India

The India sites were considered too diverse for one Implementation Plan and, therefore, three local level plans

TABLE 3 | Example action plan for Rio de Janeiro based researcher.

CFIR construct	Action point	Due by	Completed on
ESSENTIAL			
Patient needs and resources	CST-Investigators should approach leaders in community settings as possible sites offering CST	31.07.2020	
Patient needs and resources	CST-Investigators should approach managers of hospital outpatient clinics as possible sites offering CST	31.07.2020	
Relative advantage	CST-Investigators will explain the evidence-based benefits and the cost-effectiveness analysis indicating CST is a cheaper alternative to sites managers when approaching/recruiting sites	31.07.2020	
External policy and incentives	Contact with government stakeholders to discuss the possibility of implement CST at a policy level	31.08.2021	
FURTHER CONSIDER			
Adaptability	Adapt CST material for illiterate people, people with disabilities and people with severe dementia	31.08.2021	

were first developed. Each plan was developed iteratively with feedback from other Indian sites and from the international team. In Chennai, the 39 essential activities fell under CFIR constructs of: structural characteristics, implementation climate, external policies and incentives, patient needs and resources, cosmopolitanism, knowledge/beliefs about the intervention, other attributes, costs (direct and indirect), relative advantage, complexity, and evidence strength. The six further consider activities fell under: structural characteristics, external policies and incentives, patient needs and resources, costs (direct and indirect), and complexity.

In Mysore, the 16 essential activities fell under the CFIR constructs of: patient needs and resources, knowledge/beliefs about the intervention, costs (direct and indirect), design quality and packaging, network and communications, structural characteristics, adaptability, complexity, and implementation climate. Further consider activities (10) fell under: patient needs and resources, knowledge/beliefs about the intervention, costs (direct and indirect), structural characteristics, adaptability, complexity, and implementation climate.

In New Delhi, 55 activities were considered essential and seven were further considered. Essential activities fell under the CFIR domains of interventions characteristics, inner setting and outer setting. Examples specific essential activities under the domain of intervention characteristics included highlighting the advantages of group therapy during educational initiatives for carers and the use of culturally heterogeneous CST groups for participants.

Across all plans, seven researchers were assigned action plans and an example of a Mysore based researcher action plan is given in **Table 4**. Local barriers and facilitator checklists were largely similar across sites and all contained the same subsections as the Brazil checklist (participants, facilities, travel and timing and materials). Example items from the Mysore checklist included, "Are there enough chairs?," and "Have you agreed which times and dates CST sessions will be with carers?"

Tanzania

As in Brazil, it was decided that the Moshi and Arusha areas were similar enough to necessitate the use of one Implementation Plan. The plan was finalized over three iterations and the 15 essential actions fell under the CFIR categories of: patient needs and resources, knowledge/beliefs about the intervention, costs (direct/indirect), design quality and packaging, network and communications, structural characteristics, and culture. The seven further consider activities fell under the CFIR constructs of patient needs and resources, knowledge/beliefs about the intervention, costs (direct and indirect) and structural characteristics. Ten members of the team were assigned action plans, an example of which is given in **Table 5**. The local barriers and facilitators checklist contained items such as "Will there be access to drinking water?," "Have you checked when the local market day is?" and "Is there a contingency plan for sessions where you will need electricity?"

DISCUSSION

Using an innovative methodology developed using the CFIR and extensive stakeholder engagement, five Implemention Plans for CST were produced for three countries. The systematic development of methods in implementation research in LMICs has previously been suggested as an important means of facilitating cross-culturally valid research in this setting (27). The methods described here represent a first step in achieving this goal.

Each plan contained implementation strategies devised in conjunction with policy professionals, healthcare professionals, people with dementia and family carers, and an international team of researchers and clinicians. The use of this methodology resulted in unique plans suitable for diverse contexts including NGOs, public health services and private clinics in countries with varying levels of economic development or infrastructure. For example, the Brazil Implementation Plan contained strategies to implement CST in both private clinics and in the public system. In India, creating networks and collaborations between both NGOs and government healthcare facilities to facilitate information sharing was prioritized. In Tanzania, increasing awareness of dementia and treatment options amongst all stakeholders was a necessary step for successful implementation. The individualistic nature of the developed plans illustrates the flexibility of this methodology when applied to diverse contexts.

Barriers and facilitators documented here were consistent with those previously identified. A shortage of qualified

TABLE 4 | Example action plan for Mysore based researcher.

CFIR construct	Action point	Due by	Completed on
ESSENTIAL			
Knowledge/beliefs about intervention	Local advertising about CST in collaboration with NGOs and local media. Contact details should be provided if people want to get more information	1/6/2020	
Knowledge/beliefs about intervention	Adding information about global effects of CST, advantages of group therapy to the Dementia Awareness Course (DAC) delivered to carers	Completed	
Design quality and packaging	All CST facilitators should be given a local checklist and asked to complete this checklist prior to running their first CST group	Completed	
Network and communication	Supervision of CST Facilitators and online mentoring	1/6/2020 On-going	
Complexity	Include information about delayed results/prolonged duration of CST (7 weeks, 14 days) in Dementia Awareness Course (DAC) and advantages of group therapy, respite for caregivers, global effects of CST.	Completed	
FURTHER CONSIDER			
Structural characteristics	Deliver CST facilitator training course to potential paramedical staff and hiring these personnel exclusively for CST delivery	1/6/2021	

TABLE 5 | Example action plan for Tanzania researcher.

CFIR Construct	Action Point	Due by	Completed on
ESSENTIAL			
Knowledge/beliefs about intervention	Oversee the contacting of higher education institutes (focusing on nursing, occupational therapy, psychology) to discuss including CST in taught programmes, with reference to resources needed by institute.	30.08.2020	

professionals was identified here as a barrier to delivering CST and this shortage across services has also been suggested as negatively impacting on how a service user evaluates the quality of a healthcare service (28). In Brazil, it has been suggested that CST could be viewed as additional work for both caregivers and healthcare professionals (24). This is consistent with the barrier of healthcare professionals having competing demands on their time documented here. In India, the role of NGOs was identified here as an important facilitator for CST, creating networks across other NGOs and to government healthcare facilities. NGOs such as the 10/66 Research Group, have been identified as playing an important role in the facilitation of knowledge sharing both within India and internationally (29).

Whilst there is consistent evidence for the effectiveness of CST, less is known about its implementation to routine clinical care. To our knowledge, this is the first paper that provides a practical, evidence-based methodology for planning the systematic implementation of CST for people with dementia in diverse contexts. The resulting "Implementation Plans" developed as a result of using this methodology can be used to determine how best to implement CST. This moves the body of research concerning CST forward, from successful adaptation of the CST manual to effective implementation in varying countries and healthcare systems.

The CFIR provides a pragmatic structure for identifying, organizing and exploring constructs associated with implementation for healthcare interventions. In contrast to other studies where individual domains have been selected (30), all domains of the CFIR were examined and included in the current methods. This enabled an in-depth and holisitic exploration of the barriers to and facilitators of implementation in three diverse countries. Whilst these methods specifically address implementation issues for CST in different contexts, the methodology used can be generalized to other interventions in diverse countries.

Methodological Problems and Limitations

The methodology here was developed drawing on implementation science. However, as it was novel, there were some difficulties observed during its use as part of the CST-International trial. Examples of methodological problems presented here can act as further guidance or considerations for future use of the methodology. During Stage 1 in the Rio de Janeiro site, it was noted that during a small stakeholder discussion group of potential CST facilitators, the group was being led by a member of staff who was the hierarchical superior of the stakeholders. This may have influenced the answers given, however, no other groups were led by managers, limiting the effect of this.

During Phase 2, a large amount of variance was sometimes observed for activities in Tanzania, with the implementation activity "dementia awareness course for family carers should contain information on stigma associated with dementia" rated as essential/easy and advisory/difficult. It was not clear why there was a large variance and formal qualitative interviews alongside may have helped.

Future Research

Whilst not included here, a further Implementation Plan for Trissur using the same methodology is in development.

Once this plan is completed site leads will hold a consensus meeting to synthesize the local plans and create one National Implementation Plan for India. This plan will include information that is deemed relevant across sites and will ensure that the activities proposed target the full range of institutions involved with dementia care or treatment such as NGOs, government hospitals and charities.

This methodology is proposed as a "gold standard" for the implementation of CST and further evidence will be evaluated in future work planned in China. It should also be tested in more diverse settings to ensure the methodology can be used effectively in both LMICs and high-income countries (HICs). The methodology will also be disseminated via the International CST Centre, hosted by University College London (UCL) to ensure implementation of CST follows best practice for both the adaptation, and the implementation stage. The effectiveness of the strategies in Brazil, India and Tanzania will be evaluated as part of the CST-International body of work (21).

CONCLUSION

A practical, evidence-based methodology for the successful implementation of CST in diverse countries and healthcare systems was developed using implementation science frameworks. The methodology has been successfully used to create "Implementation Plans" for CST in Brazil, India, and Tanzania with further work in other countries planned. This methodology is the first of its kind and could be used as a template for the implementation of other non-pharmacological interventions for people with dementia, particularly in LMICs.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

The methodology described here was developed primarily by CS and AS, with support from all other co-authors. The manuscript was written by CS, with authors MC, BD, MK, ML, and SV contributing to information from India. EB, HD, and DM contributing to Brazil information and JK, SM, and S-MP contributing to Tanzania information. MO provided methodological advice and commented on drafts of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the following Global Alliance for Chronic Diseases (GACD) funding agencies: The United Kingdom Medical Research Council (MRC: MR/S004009/1) and the Indian Council of Medical Research (ICMR: Indo-foreign/67/M/2018-NCD-I). No funding bodies were involved in the design, collection, analysis, interpretation or writing of the research or manuscript. The views expressed are those of the authors and not necessarily those of GACD, the MRC or ICMR. DM acknowledges funding from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ).

ACKNOWLEDGMENTS

We would like to thank all CST-International investigators including Dr. S. P. Goswami, Dr. K. S. Shaji, Prof. Cleusa Ferri, Prof. Richard Walker, Dr. Catherine Dotchin, and Dr. W. Keith Gray. We would also like to thank all those who acted as stakeholders in Brazil, India, and Tanzania. Our thanks to Mr. Ssenku Safic, Dr. Marcella Yoseph, Mr. Aloyce Kisoli, Dr. Andrea Damas, and Dr. Jane Rogathi for their assistance with organizing stakeholder groups in Tanzania. We are grateful to Dr. Renata Naylor, Dr. Maria Aparecida Guimarães, Dr. Valeska Marinho, and Prof. Jerson Laks for assistance with organizing stakeholder meetings in Brazil. Finally, we would like to thank Dr. Arvind Kumar, Dr. Charan Singh, Dr. G. S. Grewal, and Captain K. L. Dagar for their assistance with organizing stakeholder meetings in the New Delhi site (India).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2020.00342/full#supplementary-material

REFERENCES

1. Spector A, Thorgrimsen L, Woods B, Royan L, Davies S, Butterworth M, et al. Efficacy of an evidence-based cognitive stimulation therapy programme for people with dementia: randomised controlled trial. *Br J Psychiatry.* (2003) 183:248–54. doi: 10.1192/bjp.183.3.248
2. Spector A, Orrell M, Davies S, Woods B. Can reality orientation be rehabilitated? Development and piloting of an evidence-based programme of cognition-based therapies for people with dementia. *Neuropsychol Rehab.* (2001) 11:377–97. doi: 10.1080/09602010143000068
3. Orrell M, Woods B. Editorial Comment. Tacrine and psychological therapies in dementia — no contest? *Int J Geriatr Psych.* (1996) 11:189–92. doi: 10.1002/(SICI)1099-1166(199603)11:3<189::AID-GPS312>3.0.CO;2-K
4. Woods B, Aguirre E, Spector AE, Orrell M. Cognitive stimulation to improve cognitive functioning in people with dementia. *Cochr Database Syst Rev.* (2012) CD005562. doi: 10.1002/14651858.CD005562.pub2
5. Aguirre E, Hoare Z, Streater A, Spector A, Woods B, Hoe J, et al. Cognitive stimulation therapy (CST) for people with dementia—who benefits most? *Geriat Psych.* (2013) 28:284–90. doi: 10.1002/gps.3823
6. Hall L, Orrell M, Stott J, Spector A. Cognitive stimulation therapy (CST): neuropsychological mechanisms of change. *Int Psych.* (2013) 25:479–89. doi: 10.1017/S1041610212001822
7. Royal College of Psychiatrists. *Memory Services National Accreditation Programme Fourth National Report: 2015–2016.* London: Royal College of Psychiatrists' Centre for Quality Improvement (2016).

8. National Institute for Health and Care Excellence (NICE). *Dementia: Supporting People With Dementia and Their Careers in Health and Social Care*. London: NICE (2006).
9. National Institute for Health and Care Excellence (NICE). *Dementia: Assessment, Management and Support for People Living With Dementia and Their Carers*. London, NICE (2018).
10. Lobbia A, Carbone E, Faggian S, Gardini S, Piras F, Spector A, et al. The efficacy of cognitive stimulation therapy (CST) for people with mild-to-moderate dementia: a review. *Europ Psychol.* (2018) 11:434–41. doi: 10.1590/1980-57642016dn11-040014
11. Gibbor L, Yates L, Volkmer A, Spector A. Cognitive stimulation therapy (CST) for dementia: a systematic review of qualitative research. *Aging Mental Health.* (2020) 1–11. doi: 10.1080/13607863.2020.1746741. [Epub ahead of print].
12. International Cognitive Stimulation Therapy (CST) Centre. *Cognitive Stimulation Therapy (CST) By Country*. Available online at: from ucl.ac.uk/international-cognitive-stimulation-therapy (2020).
13. Ferlie EB, Shortell SM. Improving the quality of health care in the United Kingdom and the United States: a framework for change. *Milbank Q.* (2001) 79:281–315. doi: 10.1111/1468-0009.00206
14. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. *BMC Implem Sci.* (2009) 4:50. doi: 10.1186/1748-5908-4-50
15. Damschroder LJ, Goodrich DE, Robinson CH, Fletcher CE, Lowery JC. A systematic exploration of differences in contextual factors related to implementing the MOVE! weight management program in VA: A mixed methods study. *BMC Health Serv Res.* (2011) 11:248. doi: 10.1186/1472-6963-11-248
16. Green CA, McCarty D, Mertens J, Lynch F, L., Hilde A, et al. (2014). A qualitative study of the adoption of buprenorphine for opioid addiction treatment. *J Subst Abuse Treat.* (2014) 46:390–401. doi: 10.1016/j.jsat.2013.09.002
17. (2009) 4. Keith RE, Crosson JC, O'Malley AS, Cromp D, Taylor EF. Using the Consolidated Framework for Implementation Research (CFIR) to produce actionable findings: a rapid-cycle evaluation approach to improving implementation. *Implem Sci.* (2017) 12:15. doi: 10.1186/s13012-017-0550-7
18. Massuda A, Hone T, Leles FAG, de Castro MC, Atun R. The Brazilian health system at crossroads: progress, crisis and resilience. *BMJ Global Health.* (2018) 3:e000829. doi: 10.1136/bmjgh-2018-000829
19. Prinja S, Aggarwal AK, Kumar R, Kanavos P. User charges in health care: evidence of effect on service utilization & equity from north India. *Indian J Med Res.* (2012) 136:868—76.
20. Manzi F, Schellenberg JA, Hutton G, Wyss K, Mbuya C, Shirima K, et al. Human resources for health care delivery in Tanzania: a multifaceted problem. *BMC Hum Resour Health.* (2012) 10:3–3. doi: 10.1186/1478-4491-10-3
21. Spector A, Stoner CR, Chandra M, Vaitheswaran S, Du B, Comas-Herrera A, et al. Mixed methods implementation research of cognitive stimulation therapy (CST) for dementia in low and middle-income countries: study protocol for Brazil, India and Tanzania (CST-International). *BMJ Open.* (2019) 9:e030933. doi: 10.1136/bmjopen-2019-030933
22. Mkenda S, Olakehinde O, Mbowe G, Siwoku A, Kisoli A, Paddick S, et al. Cognitive stimulation therapy as a low-resource intervention for dementia in sub-Saharan Africa (CST-SSA): adaptation for rural Tanzania and Nigeria. *Dementia.* (2016) 17:515–30. doi: 10.1177/1471301216649272
23. Raghuraman S, Lakshminarayanan M, Vaitheswaran S, Rangaswamy T. Cognitive stimulation therapy for dementia: pilot studies of acceptability and feasibility of cultural adaptation for India. *Am J Geriatr Psych.* (2017) 25:1029–32. doi: 10.1016/j.jagp.2017.04.014
24. Bertrand E, Naylor R, Laks J, Marinho V, Spector A, Mograbi DC. Cognitive stimulation therapy for brazilian people with dementia: examination of implementation' issues and cultural adaptation. *Aging Mental Health.* (2018) 23:1–5. doi: 10.1080/13607863.2018.1488944
25. Aguirre E, Spector A, Orrell M. Guidelines for adapting cognitive stimulation therapy to other cultures. *Clin Interv Aging.* (2014) 9:1003–7. doi: 10.2147/CIA.S61849
26. Paroutis S, Heracleous L, Angwin D. *Practicing Strategy: Text and Cases.* London, Sage (2016).
27. Stoner CR, Lakshminarayanan M, Durgante H, Spector A. Psychosocial interventions for dementia in low- and middle-income countries (LMICs): a systematic review of effectiveness and implementation readiness. *Aging & Mental Health*. (2019) 1–12. doi: 10.1080/13607863.2019.1695742. [Epub ahead of print].
28. Shayo EH, Senkoro KP, Momburi R, Olsen ØE, Byskov J, Makundi EA, et al. Access and utilisation of healthcare services in rural Tanzania: a comparison of public and non-public facilities using quality, equity, and trust dimensions. *Global Public Health.* (2016) 11:407–22. doi: 10.1080/17441692.2015.1132750
29. Prince MJ. The 10/66 dementia research group - 10 years on. *Ind J Psych.* (2009) 51:S8–S15.
30. Kirk MA, Kelley C, Yankey N, Birken SA, Abadie B, Damschroder L. A systematic review of the use of the Consolidated Framework for Implementation Research. *Implem Sci.* (2016) 11:72. doi: 10.1186/s13012-016-0437-z

Conflict of Interest: AS offers Cognitive Stimulation Therapy (CST) training courses on a consultancy basis. AS, MO, and CS are co-authors of the CST manuals. Royalties for these manuals are received by University College London.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Public Health

ORIGINAL RESEARCH
published: 10 September 2020
doi: 10.3389/fpubh.2020.00481

Risk Factors for Incident Dementia Among Older Cubans

Geeske Peeters[1,2*], *Arianna Almirall Sanchez*[1,2], *Jorge Llibre Guerra*[1,2,3], *Brian Lawlor*[1,2,4], *Rose Anne Kenny*[1,2,5,6], *Kristine Yaffe*[1,2,7] *and Juan Llibre Rodriguez*[8]

[1] *Global Brain Health Institute, Trinity College Dublin, Dublin, Ireland,* [2] *Global Brain Health Institute, University of California San Francisco, San Francisco, CA, United States,* [3] *Department of Neurology, Washington University School of Medicine, St. Louis, MO, United States,* [4] *Department of Psychiatry, Mercer's Institute for Successful Ageing, St. James's Hospital, Dublin, Ireland,* [5] *The Irish Longitudinal Study on Ageing, Trinity College Dublin, Dublin, Ireland,* [6] *The Irish Longitudinal Study on Ageing, Trinity College Dublin, Dublin, Ireland,* [7] *Department of Psychiatry, Neurology and Epidemiology, University of California, San Francisco, San Francisco, CA, United States,* [8] *Facultad de Medicina Finley–Albarrán, Universidad de Ciencias Médicas de la Habana, Havana, Cuba*

Introduction: Little is known about risk factors of dementia in Latin American countries. We aimed to identify socio–demographic, health and lifestyle risk factors of incident dementia in Cuban older adults.

Methods: Data were from 1,846 participants in the Cuban cohort of the 10/66 Dementia Research Group. Participants completed questionnaires, health examinations, and cognitive tests at baseline (2003–2006) and 4.5 years later (2007–2010). Associations between risk factors (baseline) and incident dementia (follow-up) were examined using logistic regression.

Results: Just over 9% of participants developed dementia. Overall, older age and low physical activity were associated with incident dementia. In those 65–74 years of age, depression, stroke and low physical activity were associated with incident dementia. In those ≥75 years of age, low physical activity, never eating fish, and smoking were associated with incident dementia.

Conclusions: Modifiable lifestyle factors play an important role in developing dementia in Cuban older adults. This knowledge opens up opportunities for preventive strategies.

Keywords: dementia, risk profile, lifestyle, older adults, epidemiology

OPEN ACCESS

Edited by:
Katherine Henrietta Leith, University of South Carolina, United States

Reviewed by:
Dorothy Farrar Edwards, University of Wisconsin, United States
Larry Kenith Olsen, Logan University, United States

***Correspondence:**
Geeske Peeters
geeske.peeters@gbhi.org

Specialty section:
This article was submitted to Aging and Public Health, a section of the journal Frontiers in Public Health

Received: *05 May 2020*
Accepted: *28 July 2020*
Published: *10 September 2020*

Citation:
Peeters G, Almirall Sanchez A, Llibre Guerra J, Lawlor B, Kenny RA, Yaffe K and Llibre Rodriguez J (2020) Risk Factors for Incident Dementia Among Older Cubans. Front. Public Health 8:481. doi: 10.3389/fpubh.2020.00481

INTRODUCTION

Two-thirds of the people living with dementia live in low- and middle-income countries (LMIC) (1). Due to population aging and changing lifestyles, the prevalence of dementia risk factors such as midlife hypertension and diabetes is rapidly increasing in these countries (2, 3). Over the coming decades, the largest increase in dementia prevalence will be in LMIC (1, 4). In 2015, 27.3 million people lived with dementia in LMIC. This number is projected to increase to 89.3 million in 2050 (1). Until there is a cure, implementation of evidence-based preventive strategies is crucial to reduce the impact of dementia on the society and the economy. There is strong evidence that the dementia risk in populations can be lowered by reducing the prevalence of risk factors (5, 6).

While many researchers have examined risk factors of dementia in high income countries (HIC), little is known about risk factors for dementia in LMIC. Findings from HIC cannot necessarily be extrapolated to LMIC as the prevalence of dementia and established risk factors differ between

LMIC and HIC (7, 8). A study in which population attributable fractions (PAF) were estimated for nine health and lifestyle factors, showed that for seven of the nine risk factors the PAF was much higher in Latin America than worldwide (6, 9). Moreover, the overall PAF was much higher in Latin America [55.8%, confidence interval [CI]: 54.9–56.7] than worldwide (35%, CI: 34.1–35.9), suggesting that health and lifestyle factors may contribute more to the dementia risk in Latin American countries than in other countries (9). Previous Latin American studies have shown associations between individual risk factors, such as tobacco use and APOE genotype, and dementia (10, 11). In two studies in Mexico (12) and Argentina (13) risk profiles of cognitive impairment were examined, but a comprehensive analysis of factors associated with increased dementia risk is lacking.

Given the absence of a cure and limited resources for healthcare in Cuba, the policy focus is on prevention. To guide preventive strategies, it is pivotal that we know which risk factors are most important for focused health promotion programs in Cuba. The aim of the present study was to identify risk factors for incident dementia in Cuban older adults. The focus was on socio-demographic, health and lifestyle factors, with a particular interest to identify potentially modifiable factors.

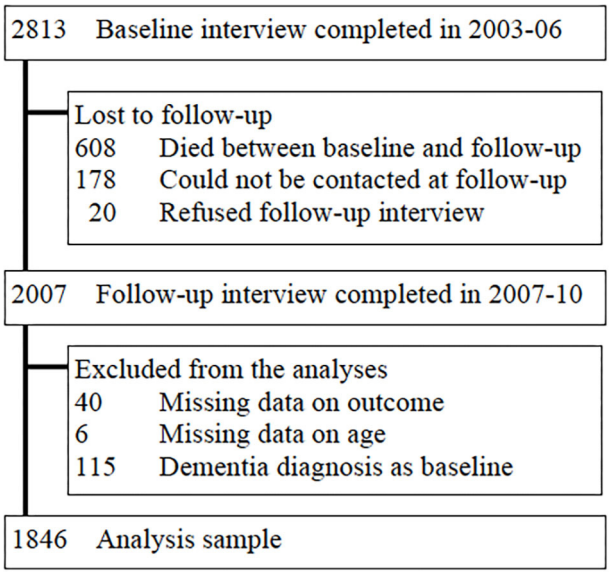


FIGURE 1 | Flow chart. Describing the flow of participants in the study, attrition, and selection of participants in the analyses sample.

METHODS

Setting and Study Design

The data used in this study were from the Cuban cohort of the 10/66 Dementia Research Group, a population-based cohort study designed to examine the prevalence and determinants of stroke, dementia and mortality in LMIC (14, 15). For the current analyses, data were used from the first (2003–2005) and second (2007–2010) data collection waves, that involved clinical and informant interviews, physical examination, and blood draws collected by trained interviewers (15). The variables were measured using the same methods across the data collection waves. Where available, translated, culturally adapted and validated instruments were used (see §2.3 for details per variable).

Written informed consent was obtained from all participants. The design of the 10/66 study and protocols for data collection were described in detail elsewhere (14) and were approved by the Medical Ethics committee of the University of Havana and the King's College London research Ethics Committee. Additional ethics approval for the current study was obtained from the Medical Ethics committee of the University of Havana and the Trinity College Dublin Faculty of Health Sciences Ethics Committee.

Participants

All residents aged 65 years and over in geographically defined catchment areas (urban and rural sites in Cuba) were invited to participate through door knocking (94% response rate) (14). Baseline surveys were completed by 2,813 participants in 2003–2005. Of these, 806 participants were lost to follow up (see **Figure 1** for further details) and 2007 participants completed the follow-up interview in 2007–2010 (average follow-up of 4.5 years, range 2–7) Participants with a dementia diagnosis at baseline ($n = 115$) or missing data on dementia diagnosis ($n = 40$) or age ($n = 6$) were excluded from the analyses. Therefore, data from 1,846 participants were included in the current analyses.

Measures

Incident Dementia

Incident dementia was operationalized using two methods previously developed and validated by the 10/66 Dementia Research Group (16, 17). The first method is a regression algorithm based upon: (a) a structured Geriatric Mental State interview (18), (b) cognitive tests including the Community Screening Instrument for Dementia (CSI-D) (19), verbal fluency task, object recognition and modified CERAD 10 word list learning task with delayed recall (20) and; (c) an informant interview (CSI-D) (19) for evidence of cognitive and functional decline. Participants scoring above a prediction probability cutpoint are defined as having dementia. The second method is based on operational definitions of the DSM IV criteria (21). Although the DSM-IV does not specify a criterion for the diagnosis of dementia, this could be inferred from the common elements of the DSM-IV criteria for each of the dementia sub-type diagnoses (21). The criteria for DMS-IV diagnosis were: impairment in memory and at least one other domain of cognitive function; impairment in social or occupational functioning, and representing a decrease from a previous level of functioning; not occurring exclusively during delirium; and not better accounted for by another mental disorder. Validation of the two definitions of dementia in the 10/66 cohort, demonstrated that the DSM-IV criterion was specific but insensitive to mild to moderate dementia (16). The 10/66 dementia algorithm corresponded better to clinician diagnosis

and was more sensitive to milder cases (16). To capture the maximum number of cases with dementia, all participants who met the criteria for at least one of the two definitions were classified as having dementia. Participants with dementia at baseline were excluded from the analyses. Participants with new onset dementia at follow-up were classified as having incident dementia.

Sociodemographic Factors

The socio-demographic variables were based on self- or informant-report and included: age ($\leq$75 years and >75 years), sex, level of education [completed primary or less, secondary, or tertiary education [i.e., college/university]], marital status (response options collapsed as married/cohabiting; widowed/divorced/separated; never married) and occupational class (professional trade; skilled laborer; laborer).

Health Factors

Hypertension was measured and dichotomized using the ISH criterion of $\geq$140 mmHg for systolic and $\geq$90 mmHg for diastolic bloodpressure. Waist circumference was measured using standard procedures and obesity was defined as a waist circumference of >102 cm. Total and LDL cholesterol were derived from blood samples and high levels were defined as levels exceeding the 75th percentile in the distribution (total: $\geq$6 mmol/L, LDL: $\geq$4.3 mmol/L). Presence of doctor diagnosed diabetes, stroke, head trauma (i.e., head injury with loss of conscious) and ischemic heart problems (i.e., myocardial infarction and/or angina) were based on self-report. Depression was measured using the Geriatric Mental State Examination, and its computerized algorithm AGECAT, which provided International Classification of Disease 10 (ICD10) depressive episode diagnoses (15). Hearing and eye problems were based on self-report and were considered present if these caused at least some difficulty in daily life. The presence of sleep complaints was based on the question "Have you had trouble sleeping recently?" Family history of dementia were based on self-report. Cognitive function was based on a sum score of the cognitive test battery.

Lifestyle Factors

Lifestyle factors were based on self-report or informant report if severely demented. Participants were asked to report the maximum usual consumptions by type of drink per week before and after the age of 65 years. Hazardous drinking was defined as 14 units/week for women and 21 units/week for men (with one unit being defined as a small glass of beer, a single measure of spirits [32 units per bottle], or one glass of wine or sherry). Smoking status was defined as never or ex-smoker vs. current smoker. Physical activity was assessed with the question: "Taking into account both work and leisure, would you say that you are: very, fairly, not very, or not at all physically active?" Participants were asked to report the frequency of fish and meat consumption (response options were: every day, some days, most days, or never) and the number of fruit and vegetable servings in the past 3 days (categorized as $\leq$3, 4–8, and $\geq$9).

Statistical Analysis

Descriptive statistics were used to describe and compare baseline characteristics of participants (i) with and without incident dementia, and (ii) whose data were included in the analyses with those who were lost to follow-up. While 40.8% of the sample had missing data on at least one risk factor, only two variables had more than 10% missing data. Multiple imputation by chained equations was used to impute missing values and 20 datasets were created (22). Pooled results are presented for the main analyses. Logistic regression was used to examine associations between potential risk factors and incident dementia. Univariable models were run for each potential risk factor separately, with adjustment for sex and education. The multivariable models included age, sex, education and all risk factors with odds ratios (OR) of $\leq$0.75 or $\geq$1.4 in the univariable models. These cut-points were based on effect size rather than *p*-values or confidence intervals (CI), as we wanted to prioritize clinical relevance over statistical significance. As previous studies have shown that the strength of associations between risk factors and dementia varies with age (23), the findings are presented for the total sample and separately for the age-groups 65–74 and $\geq$75 years.

RESULTS

Data from 1,846 participants without dementia at baseline were used for the current analyses (**Figure 1**). Participants whose data were included were younger, healthier and had better lifestyles than participants who were lost to follow-up (**Figure 1**, **Appendix Table A**). Of the included participants, 169 (9.2%) developed dementia between baseline and follow-up. Participants who developed dementia were older ($p < 0.001$), less likely to have completed tertiary education ($p = 0.002$), and more likely to be widowed, divorced, or separated ($p < 0.001$) at baseline than those who did not develop dementia. Moreover, they had poorer cognition, less healthy lifestyles and more health problems (**Table 1**). Among the 1,132 participants who were 65–74 years old at baseline, 61 (5.4%) had incident dementia. Among the 714 participants who were $\geq$75 years old at baseline, 108 (15.1%) had incident dementia.

In the total sample, statistically significant univariable associations with incident dementia were found for the risk factors age, education, marital status, obesity, stroke, depression, physical activity, fish consumption, fruit and vegetable consumption and family history (**Table 2**). In the multivariable model, these associations remained statistically significant for the risk factors age ($\geq$75 years vs. 65–74 years: OR = 2.70, 95% CI = 1.90–3.84), marital status (widowed/divorced/separated vs. married/cohabiting: OR = 1.63, 95% CI = 1.10–2.41), physical activity (somewhat active vs. highly active: OR = 1.81, 95% CI = 1.13–2.90; not (very) active vs. highly active: OR = 2.29, 95% CI = 1.49–4.16), fish consumption (regular vs. rarely: OR = 1.77, 95% CI = 1.06–2.95) and fruit and vegetable consumption ($\leq$3 vs. $\geq$9 servings: OR = 1.96, 95%CI = 1.15–3.35) (**Table 3**).

TABLE 1 | Baseline characteristics of participants with and without incident dementia in the Cuban cohort of the 10/66 study (n = 1,846).

	n	No Dementia (n = 1,677)	Incident dementia (n = 169)	*p-value*
Age (M ± SD)	1,846	73.1 ± 5.9	77.8 ± 6.5	< 0.001
Sex (*n*, %)	1,846			0.17
Female		1,103 (65.8)	120 (71.0)	
Male		576 (34.2)	49 (29.0)	
Education (*n*, % level completed)	1,843			0.002
Tertiary/college		310 (18.5)	15 (8.9)	
Secondary		473 (28.3)	43 (25.4)	
None/primary		891 (53.2)	111 (65.7)	
Marital status (n, %)	1,843			< 0.001
Married/cohabiting		787 (47.0)	54 (32.0)	
Widowed/divorced/separated		738 (44.1)	102 (60.4)	
Never married		149 (8.9)	13 (7.7)	
Occupational class (*n*, %)	1,753			0.02
Professional (1–3)		675 (42.3)	48 (30.8)	
Trade (4,5)		206 (12.9)	28 (18.0)	
Skilled laborer (6,7)		452 (28.3)	55 (35.3)	
Laborer (8,9)		264 (16.5)	25 (16.0)	
Hypertension (*n*, %)	1,842	960 (57.4)	109 (64.5)	0.07
Obesity (*n*, %)	1,838	694 (41.6)	53 (31.6)	0.01
High total cholesterol (*n*, %)	1,482	374 (28.0)	40 (27.0)	0.80
High LDL cholesterol (*n*, %)	1,126	239 (23.6)	33 (28.7)	0.23
Diabetes (*n*, %)	1,840	299 (17.9)	28 (16.6)	0.67
Depression (*n*, %)	1,827	458 (27.6)	61 (36.8)	0.01
Stroke (*n*, %)	1,842	80 (4.8)	17 (10.1)	0.003
Ischemic heart problem (*n*, %)	1,844	225 (13.4)	18 (10.7)	0.31
Head Trauma (*n*, %)	1,839	91 (5.4)	8 (4.8)	0.72
Hearing problem (*n*, %)	1,843	132 (7.9)	22 (13.0)	0.02
Eye problem (*n*, %)	1,840	436 (26.1)	62 (36.7)	0.003
Current high-risk alcohol use (*n*, %)	1,822	48 (2.9)	7 (4.1)	0.37
Past high-risk alcohol use (*n*, %)	1,824	107 (6.5)	13 (7.7)	0.54
Smoking (*n,* % current smoker)	1,842	313 (18.7)	30 (17.8)	0.76
Physical activity (*n*, %)	1,840			< 0.001
Highly active		515 (30.8)	27 (16.1)	
Somewhat active		777 (46.5)	81 (48.2)	
Not (very) active		380 (22.7)	60 (35.7)	
Fish consumption (*n*, % never)	1,842	129 (7.7)	23 (13.6)	0.008
Meat consumption (*n*, % never/some days)	1,842	1,077 (64.4)	112 (66.3)	0.62
Fruit & vegetable servings	1,843			0.001
9 or more in last 3 days		322 (19.2)	19 (11.2)	
4–8 in last 3 days		683 (40.8)	58 (34.3)	
3 or fewer in last 3 days		669 (40.0)	92 (54.4)	
Sleep complaints (n, %)	1,842	567 (33.9)	50 (29.6)	0.26
Family history (*n*, %)	1,842	291 (17.4)	38 (22.5)	0.10
Cognitive function (Md [IQR])	1,846	31.2 [30.0–32.1]	29.8 [27.7–31.2]	< 0.001

IQR, interquartile range; M, mean; Md, median; n, numer of participants with available data; SD, standard deviation.
Normally distributed continuous variables were described as means and standard deviation and groups were compared using the t-test. Not-normally distributed continuous variables were described as median and interquartile range and groups were compared using the Wilcoxon singed rank test. Categorical variables were described as numbers and percentages, and groups were compared using the Chi-squared test.

TABLE 2 | Univariable associations between potential risk factors and incident dementia in the total sample (n = 1,846), and stratified by age.

	Total sample		65–74 years		≥75 years	
	OR	**95% CI***	**OR**	**95% CI***	**OR**	**95% CI***
Age						
65–74 years	1					
≥75 years	2.87	2.05–4.02				
Sex						
Women	1		1		1	
Men	0.85	0.59–1.21	0.88	0.50–1.54	0.83	0.53–1.32
Education						
Tertiary	1		1		1	
Secondary	1.62	0.88–2.99	2.10	0.87–5.07	1.18	0.50–2.78
None/primary	1.85	1.05–3.27	2.57	1.12–5.88	1.30	0.59–2.83
Marital status						
Married/cohabiting	1		1		1	
Widowed/divorced/separated	1.70	1.16–2.48	1.79	1.00–3.19	1.63	0.99–2.69
Never married	1.13	0.60–2.15	1.62	0.64–4.10	0.84	0.35–2.03
Occupational class						
Professional (1–3)	1		1		1	
Trade (4,5)	1.48	0.88–2.50	1.43	0.63–3.23	1.55	0.77–3.11
Skilled laborer (6,7)	1.26	0.79–2.00	1.41	0.69–2.88	1.19	0.65–2.18
Laborer (8,9)	0.98	0.56–1.69	0.85	0.34–2.15	1.06	0.53–2.12
Hypertension	1.25	0.89–1.74	1.30	0.77–2.22	1.21	0.79–1.86
Obesity	0.62	0.44–0.89	0.56	0.32–0.99	0.67	0.42–1.05
Total cholesterol	0.98	0.67–1.43	1.23	0.69–2.18	0.83	0.50–1.37
LDL cholesterol	1.31	0.86–1.97	1.64	0.91–2.95	1.09	0.62–1.92
Diabetes	0.91	0.59–1.40	1.24	0.67–2.32	0.71	0.38–1.29
Head Trauma	0.96	0.45–2.04	0.87	0.26–2.86	1.03	0.39–2.74
Stroke	2.16	1.23–3.79	3.38	1.51–7.61	1.55	0.72–3.35
Ischemic heart problems	0.70	0.42–1.17	0.22	0.05–0.90	1.00	0.56–1.79
Depression	1.49	1.06–2.09	1.90	1.11–3.27	1.27	0.81–1.98
Hearing problem	1.32	0.80–2.16	0.98	0.30–3.26	1.41	0.81–2.44
Eye problem	1.39	0.99–1.95	1.02	0.56–1.86	1.64	1.08–2.50
Current high–risk alcohol use	2.24	0.96–5.26	2.53	0.91–7.00	1.71	0.34–8.54
Past high–risk alcohol use	1.60	0.83–3.07	2.17	0.92–5.10	1.11	0.40–3.07
Smoking status	1.29	0.83–2.01	0.77	0.40–1.50	2.17	1.19–3.96
Physical activity						
Highly active	1		1			1
Somewhat active	1.76	1.11–2.77	2.80	1.33–5.92	1.26	0.70–2.26
Not (very) active	2.47	1.52–4.01	2.77	1.20–6.42	2.17	1.19–3.95
Never eating fish	1.77	1.09–2.87	1.01	0.39–2.59	2.30	1.27–4.15
Never/some days eating meat	0.94	0.67–1.32	0.84	0.48–1.46	1.01	0.66–1.56
Fruit & vegetable servings						
9 or more in last 3 days	1		1		1	
4–8 in last 3 days	1.34	0.78–2.30	1.80	0.72–4.54	1.10	0.56–2.17
3 or fewer in last 3 days	2.16	1.28–3.62	2.88	1.19–7.00	1.77	0.92–3.39
Sleep complaints	0.74	0.52–1.05	0.70	0.39–1.26	0.75	0.48–1.18
Family history	1.53	1.03–2.26	1.67	0.92–3.03	1.41	0.83–2.37

OR odd ratio; 95%CI 95% confidence interval.
**Associations were adjusted for sex and education.*

In the younger age-group (65–74 years), statistically significant univariable associations with incident dementia were found for the risk factors education, marital status, obesity, stroke, ischemic heart problems, depression, physical activity, and fruit and vegetable consumption (**Table 2**). In the multivariable model, these associations remained statistically

TABLE 3 | Multivariable models for the total sample (n = 1,846), and stratified by age.

	Total sample		65–74 years		≥75 years	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Age						
65–74 years	1					
≥75 years	2.70	1.90–3.84				
Sex						
Women	1		1		1	
Men	0.84	0.54–1.29	0.78	0.39–1.56	0.88	0.50–1.56
Education						
Tertiary	1		1		1	
Secondary	1.72	0.90–3.31	2.29	0.89–5.87	1.16	0.45–2.99
None/primary	1.74	0.90–3.38	2.44	0.91–6.55	1.15	0.45–2.93
Marital status						
Married/cohabiting	1		1		1	
Widowed/divorced/separated	1.63	1.10–2.41	1.81	0.98–3.35	1.56	0.92–2.65
Never married	0.87	0.45–1.70	1.51	0.56–4.05	0.61	0.24–1.54
Occupational class						
Professional (1–3)	1		1		1	
Trade (4,5)	1.47	0.86–2.53	1.33	0.56–3.13	1.59	0.76–3.30
Skilled laborer (6,7)	1.14	0.70–1.85	1.15	0.53–2.48	1.11	0.58–2.11
Laborer (8,9)	0.77	0.43–1.40	0.67	0.25–1.79	0.82	0.38–1.75
Hypertension						
Obesity	0.63	0.43–0.91	0.58	0.32–1.05	0.64	0.39–1.03
Total cholesterol						
LDL cholesterol			1.66	0.89–3.08		
Diabetes						
Head trauma						
Stroke	1.81	1.00–3.28	3.08	1.25–7.58	1.41	0.62–3.22
Ischemic heart problems	0.71	0.42–1.21	0.23	0.05–0.99		
Depression	1.39	0.96–2.00	1.80	1.02–3.19		
Hearing problem					1.04	0.56–1.91
Eye problem					1.48	0.94–2.32
Current high–risk alcohol use	2.10	0.68–6.49	1.52	0.34–6.67	1.44	0.26–7.84
Past high–risk alcohol use	1.27	0.54–2.99	1.86	0.56–6.17		
Smoking status					2.21	1.17–4.16
Physical activity						
Highly active	1		1		1	
Somewhat active	1.81	1.13–2.90	2.74	1.27–4.36	1.24	0.67–2.28
Not (very) active	2.29	1.49–4.16	2.67	1.08–6.59	2.05	1.06–3.94
Never eating fish	1.77	1.06–2.95			2.44	1.28–4.66
Fruit & vegetable servings						
9 or more in last 3 days	1		1		1	
4–8 in last 3 days	1.26	0.72–2.21	1.68	0.65–4.36	1.07	0.53–2.16
3 or fewer in last 3 days	1.96	1.15–3.35	2.22	0.88–5.59	1.81	0.92–3.57
Sleep complaints	0.62	0.42–0.90	0.57	0.30–1.06		
Family history	1.47	0.98–2.22	1.70	0.91–3.19	1.42	0.82–2.48

OR Odds ratio, CI 95% confidence interval.
*Multivariable models include age, sex, education, plus all risk factors with ORs<0.75 or >1.40 in the univariable models (**Table 2**).*

significant for the risk factors stroke (yes vs. no: OR = 3.08, 95% CI = 1.25–7.58), ischemic heart problems (yes vs. no: OR = 0.23, 95% CI = 0.05–0.99), depression (yes vs. no: OR = 1.80, 95% CI = 1.02–3.19) and physical activity (somewhat active vs. highly active: OR = 2.74, 95% CI = 1.27–4.36; not (very) active vs. highly active: OR = 2.67, 95% CI = 1.08–6.59) (**Table 3**).

In the older age-group (≥75 years), statistically significant univariable associations with incident dementia were found for the risk factors eye problems, smoking status, physical activity and fish consumption (**Table 2**). In the multivariable model, these associations remained statistically significant for the risk factors smoking status (current vs. never/ex-smoker: OR = 2.21, 95% CI = 1.17–4.16), physical activity (not (very) active vs. highly active: OR = 2.05, 95% CI = 1.06–3.94) and fish consumption (regular vs. rarely: OR = 2.44, 95% CI = 1.28–4.66) (**Table 3**).

DISCUSSION

This study is the first to present a comprehensive identification of factors associated with incident dementia in Cuban older adults. The results show that the risk profiles are different for adults aged 65–74 years and those aged ≥75 years. The risk factors for which statistically significant associations were found with incident dementia, were predominantly health factors in the younger age group (i.e., stroke, ischemic heart problems, depression) and lifestyle factors in the older age group (i.e., smoking, physical activity, and fish consumption).

Changes in Risk Profiles With Age

The difference in risk profiles between the younger and the older age groups is in line with previous studies in which changes were found in associations between risk factors and dementia with age. For some risk factors, associations seem to become stronger with age (e.g., smoking) (24), whereas for other risk factors associations seem to weaken with age (e.g., APOεE4, blood pressure) (25–28). Several explanations may be possible. First, lifestyle has a delayed, long term effect on health in general and brain health in particular. Accumulation of lifestyle across the lifespan, particularly during midlife, may be more important than the lifestyle at a given point in time. Second, at older ages, the higher prevalence of other chronic conditions may weaken associations between risk factors and dementia (23), particularly for risk factors that are common across chronic conditions, such as lifestyle factors. Third, mixed patterns of dementia-pathology are more common at older ages (29). Different risk factors may be relevant for different dementia-pathologies and more difficult to identify in mixed pathologies. This may also explain why fewer risk factors were found in the older age group than in the younger age group.

Lifestyle Factors

In line with previous studies that attributed a large part of the dementia risk to lifestyle factors (9), lifestyle factors, particularly physical activity, dominate the risk profiles in this cohort of Cuban older adults. Previous studies using data from the wider Latin American 10/66 cohort including data from Dominican Republic, Mexico, Peru, Puerto Rico, Venezuela and Cuba (11), have demonstrated that better scores on a cardiovascular health index (based on physical activity, smoking, alcohol, hypertension, obesity, cholesterol, glucose, and intake of meat, fish, fruits and vegetables) was associated with lower risk of dementia (30). The current study adds that, when each factor is viewed independently, some but not all of these factors are associated with dementia and the associations differ for the younger and older age groups. These collective findings suggest that either the association of the cardiovascular health index with dementia risk is driven by individual factors rather than the overall cardiovascular burden, or that some individual factors are important only in combination with other factors.

The finding that never eating fish increases the risk of dementia in the older age group is consistent with findings from previous cross-sectional studies in Latin America (31) and other LMIC (32). The beneficial effects of fish consumption are attributed to the salutary effects of long-chain omega-3 polyunsaturated fatty acids on neurone membranes, vascular anti-inflammatory properties and neuroplasticity (33).

Health Factors

Stronger associations with dementia were found with stroke and depression in the younger age group, and with eye problems in the older age group. As explained above, the attenuation of the associations between chronic conditions and dementia with age may be explained by the higher prevalence of chronic conditions at older ages (23) and therefore reduced contrast between groups with and without dementia. Also, chronic conditions acquired at younger ages may reflect longer exposure to common underlying risk factors.

The association between depression and incident dementia has been previously demonstrated in the wider Latin American 10/66 cohort (34). That study identified substantial variation between the countries in strength of associations, with the strongest associations found in Cuba (Hazard Ratio [HR]: 2.48, CI: 1.52–4.06) and Venezuela (HR: 2.12, CI: 1.16–3.87) and no associations found in the Dominican Republic (HR: 1.01, CI: 0.62–1.62) and Puerto Rico (HR: 0.81, CI: 0.19–3.48). The researchers cited differences in prevalence of depression as the main explanation for these variations (34). It may be interesting to explore if these variations between countries remain after stratification by age group.

Consistent with other studies, both in LMIC (35) and HIC (36), stroke was a strong predictor of dementia, particularly in the younger age group. Similar to previous Latin American studies, diabetes was not associated with dementia (37). Contrary to our expectations, ischemic heart disease was associated with a reduced risk of dementia in the younger age group. This likely results from survival bias as participants with ischemic heart disease have higher mortality rates than participants without ischemic heart disease and the risk of dementia increases with age.

Hearing loss and vision loss have been associated with dementia in HIC (38–42), but evidence for these associations in Latin America or other LMIC is lacking. The current results suggest that eye problems, but not hearing problems, are associated with an increased risk of dementia in Cuban older adults, but only in the older age group. Two theories that may explain the associations between hearing and vision problems and dementia are the causal pathway and the shared etiological pathway (39). Panza et al. state there is currently no epidemiological evidence to support a causal pathway between hearing loss and dementia, but argue that more research is needed to test these theories (39). Some evidence for a shared etiological pathway between eye problems and dementia

comes from a review in which the researchers described the common underlying cardiovascular risk factors for cataract and dementia (43).

In a recent systematic review, the researchers found that insomnia was associated with a higher risk of Alzheimer's disease (three studies, pooled OR = 1.51, CI = 1.06–2.41) (44), but not with all-cause dementia (12 studies, pooled OR = 1.17, CI = 0.95–1.43) or vascular dementia (four studies, pooled OR = 1.13, IC = 0.94–1.35). In contrast, we found that sleep complaints were associated with a lower risk of dementia in the total sample (OR = 0.63, CI = 0.43–0.92). It may be that the question we used was insufficiently sensitive to pick up sleep disturbances. Also, participants who were already experiencing some cognitive decline at baseline (but did not yet meet criteria for dementia) may have been less likely to report sleeping complaints than participants with good cognitive function, resulting in reporting bias. The findings may also partly be explained by residual confounding.

Comparison With Risk Profiles in Other Latin American Countries

Few researchers to date have examined risk factors for dementia or cognitive impairment in Latin American countries. In a prospective study among 3002 Mexican older adults (aged 60+), risk factors were identified for severe cognitive impairment (defined as low score on the Cross-Cultural Cognitive Examination and difficulties with daily activities) (12). A cross-sectional study among 1453 Argentinean older adults (aged 60+) examined correlations between risk factors and cognitive impairment (defined as MMSE $\leq$ 22) (13). Comparison of the risk profiles identified in these two studies and the current study reveals some overlap but also some differences. In all three cohorts, higher age and low education were associated with dementia or cognitive impairment. Inactivity was associated with dementia or cognitive impairment in the Argentinean and Cuban cohorts, but not in the Mexican cohort. Stroke was associated with dementia or cognitive impairment in the Mexican and Cuban cohorts, but not in the Argentinean cohort. Diabetes was associated with cognitive impairment in the Mexican cohort only. Head trauma was associated with cognitive impairment only in the Argentinean cohort. Depression was associated with dementia only in the Cuban cohort. In the current study, we additionally identified not eating fish, fruit and vegetables as a risk factor for dementia. Differences in study design, sample characteristics and definition of the outcome likely explain variations in the findings across the three cohorts. The differences in risk profiles also suggest that intervention strategies require tailoring to the characteristics of the country.

Implications for Health Promotion

The current findings confirm that lifestyle and health factors are important contributors to the risk of dementia in Cuban older adults. The finding that lifestyle factors are important at older ages highlight that lifestyle interventions should not only focus on midlife, but should be continued in older ages. In the younger age group, depression and stroke were important risk factors for dementia. Given the large overlap in risk factors for stroke and dementia, health promotion programs targeting stroke will also help delay the onset of dementia and vice versa. Whether depression causes dementia, is a consequence of dementia or the two conditions are simply coinciding, is still up for debate (45, 46). We recommend that future studies evaluating depression treatment should include cognitive outcomes to examine whether adequate treatment of depression can lower dementia risk.

Strengths and Limitations

While the 10/66 cohort offers the best available data on incident dementia and its risk factors in Cuba, the study was relatively underpowered. Interpretation of the findings should take into account the relatively small sample and number of participants with incident dementia during the 4.5 years follow-up, resulting in wide confidence intervals. To maintain the maximum amount of available information and representativeness of the sample, we imputed missing values. Most missing values were due to blood samples being taken only in a subsample. About a third of participants (n = 806) were lost to follow-up; the main reason being death (n = 608). Participants whose data were included in the analyses were younger, healthier, and had better lifestyles. Hence the current results are representative for a somewhat more vital community-dwelling older population. While this study benefited from the comprehensive assessment of potential risk factors in this cohort, we may have missed factors that were not measured, for example, cognitive stimulation, social activity, other dietary components, exposure to air pollution and traumatic life events (47–49).

CONCLUSION

In conclusion, risk profiles for incident dementia differ for 65–74 year old adults and $\geq$75 year old adults in Cuba. In the younger age group, education, depression, stroke, and physical activity were associated with a higher dementia risk. In the older age group, smoking, physical activity, and not eating fish were associated with a higher dementia risk. Thus, modifiable lifestyle factors play an important role in developing dementia in Cuban older adults, even at higher ages. This knowledge opens up opportunities for development and implementation of preventive strategies. Preventive strategies may require tailoring to age groups.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. A request for access to the 10/66 Dementia Research Group data can be submitted to dementiaresearchgroup1066@kcl.ac.uk.

AUTHOR CONTRIBUTIONS

GP, JLG, KY, and JLR were responsible for the study design. GP and AA were responsible for the data analyses. GP was responsible for drafting the manuscript. All authors contributed to interpretation of the findings, provided critical feedback on drafts of the manuscript, and approved the final manuscript.

FUNDING

This work was supported by the Alzheimer's Association and Alzheimer's Society (GBHI ALZ UK-19-588148). GP, JLG, and AA are Atlantic Fellows for Equity in Brain Health and received fellowships from the Global Brain Health Institute. The Cuban Aging and Alzheimer's study is part of the 10/66 Dementia Research Group population-based research program in Cuba funded by the Wellcome Trust Health Consequences of Population Change Programme (GR066133—Prevalence phase and GR08002—Incidence phase).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2020.00481/full#supplementary-material

REFERENCES

1. Alzheimer's Disease International. *World Alzheimer's Report: The Global Impact of Dementia, an Analysis of Prevalence, Incidence, Cost and Trends*. London: Alzheimer's Disease International (ADI), (2015).
2. Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, et al. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. *Circulation.* (2016) 134:441–50. doi: 10.1161/CIRCULATIONAHA.115.018912
3. World Health Organization. *Global Report on Diabetes*. Geneva: WHO, (2016).
4. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimer's Dem.* (2013) 9:63–75.e2. doi: 10.1016/j.jalz.2012.11.007
5. Alzheimer's Disease International. *World Alzheimer Report 2014: Dementia and Risk Reduction*. London (2014).
6. Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol.* (2011) 10:819–28. doi: 10.1016/S1474-4422(11)70072-2
7. Llibre Rodriguez JJ, Ferri CP, Acosta D, Guerra M, Huang Y, Jacob KS, et al. Prevalence of dementia in Latin America, India, and China: a population-based cross-sectional survey. *Lancet.* (2008) 372:464–74. doi: 10.1016/S0140-6736(08)61002-8
8. Kalaria RN, Maestre GE, Arizaga R, Friedland RP, Galasko D, Hall K, et al. Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. *Lancet Neurol.* (2008) 7:812–26. doi: 10.1016/S1474-4422(08)70169-8
9. Mukadam N, Sommerlad A, Huntley J, Livingston G. Population attributable fractions for risk factors for dementia in low-income and middle-income countries: an analysis using cross-sectional survey data. *Lancet Global Health.* (2019) 7:e596–e603. doi: 10.1016/S2214-109X(19)30074-9
10. Rodriguez JJL, Cepero AV, Gil IYS, Medina AML, Llibre-Guerra JC, Llibre-Guerra JJ, et al. Incidence of dementia and association with APOE genotype in older Cubans. *Dement Neuropsychol.* (2014) 8:356–63. doi: 10.1590/S1980-57642014DN84000009
11. Otuyama LJ, Oliveira D, Locatelli D, Machado DA, Noto AR, Galduroz JCF, et al. Tobacco smoking and risk for dementia: evidence from the 10/66 population-based longitudinal study. *Aging Mental Health.* (2019). doi: 10.1080/13607863.2019.1647140. [Epub ahead of print].
12. Downer B, Veeranki SP, Wong R. A late life risk index for severe cognitive impairment in Mexico. *JAD.* (2016) 52:191–203. doi: 10.3233/JAD-150702
13. Arizaga RL, Gogorza RE, Allegri RF, Baumann PD, Morales MC, Harris P, et al. Cognitive impairment and risk factor prevalence in a population over 60 in Argentina. *Deme Neuropsychol.* (2014) 8:364–70. doi: 10.1590/S1980-57642014DN84000010
14. Prince M, Ferri CP, Acosta D, Albanese E, Arizaga R, Dewey M, et al. The protocols for the 10/66 dementia research group population-based research programme. *BMC Public Health.* (2007) 7:165. doi: 10.1186/1471-2458-7-165
15. Prina AM, Acosta D, Acosta I, Guerra M, Huang Y, Jotheeswaran AT, et al. Cohort Profile: The 10/66 study. *Int J Epidemiol.* (2017) 46:406–i. doi: 10.1093/ije/dyw056
16. Prince MJ, de Rodriguez JL, Noriega L, Lopez A, Acosta D, Albanese E, et al. The 10/66 Dementia Research Group's fully operationalised DSM-IV dementia computerized diagnostic algorithm, compared with the 10/66 dementia algorithm and a clinician diagnosis: a population validation study. *BMC Public Health.* (2008) 8:219. doi: 10.1186/1471-2458-8-219
17. Prince M, Acosta D, Chiu H, Scazufca M, Varghese M, Dementia Research G. Dementia diagnosis in developing countries: a cross-cultural validation study. *Lancet (London, England).* (2003) 361:909–17. doi: 10.1016/S0140-6736(03)12772-9
18. Copeland JR, Dewey ME, Griffiths-Jones HM. A computerized psychiatric diagnostic system and case nomenclature for elderly subjects: GMS and AGECAT. *Psychol Med.* (1986) 16:89–99. doi: 10.1017/S0033291700057779
19. Hall KS, Hendrie HC, Rodgers DD, Prince CS, Pillay N, Blue AW, et al. The development of a dementia screening interview in two distinct languages. *Int J Meth Psychiat Res.* (1993) 3:1–14.
20. Sosa AL, Albanese E, Prince M, Acosta D, Ferri CP, Guerra M, et al. Population normative data for the 10/66 Dementia Research Group cognitive test battery from Latin America, India and China: a cross-sectional survey. *BMC Neurol.* (2009) 9:48.doi: 10.1186/1471-2377-9-48
21. American Psychiatric Association. *Diagnostic and Statistical manual of Mental Disorders*. 3rd ed. Washington, DC: AMA (1987).
22. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med.* (2011) 30:377–99. doi: 10.1002/sim.4067
23. Bullain SS, Corrada MM. Dementia in the oldest old. *Continuum (Minneap Minn).* (2013) 19:457–69. doi: 10.1212/01.CON.0000429172.27815.3f
24. Zhong G, Wang Y, Zhang Y, Guo JJ, Zhao Y. Smoking is associated with an increased risk of dementia: a meta-analysis of prospective cohort studies with investigation of potential effect modifiers. *PLoS ONE.* (2015) 10:e0118333. doi: 10.1371/journal.pone.0118333
25. Corrada MM, Paganini-Hill A, Berlau DJ, Kawas CH. Apolipoprotein E genotype, dementia, and mortality in the oldest old: the 90+ Study. *Alzheimer's Dem.* (2013) 9:12–8. doi: 10.1016/j.jalz.2011.12.004
26. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta-Analysis Consortium. *JAMA.* (1997) 278:1349–56. doi: 10.1001/jama.278.16.1349
27. Li G, Rhew IC, Shofer JB, Kukull WA, Breitner JCS, Peskind E, et al. Age-varying association between blood pressure and risk of dementia in those aged 65 and older: a community-based prospective cohort study. *J Am Geriatr Soc.* (2007) 55:1161–7. doi: 10.1111/j.1532-5415.2007.01233.x
28. Ruitenberg A, Skoog I, Ott A, Aevarsson O, Witteman JC, Lernfelt B, et al. Blood pressure and risk of dementia: results from the Rotterdam study and the Gothenburg H-70 Study. *Dement Geriatr Cogn Disord.* (2001) 12:33–9. doi: 10.1159/000051233
29. Nelson PT, Head E, Schmitt FA, Davis PR, Neltner JH, Jicha GA, et al. Alzheimer's disease is not "brain aging": neuropathological, genetic, and epidemiological human studies. *Acta Neuropathol.* (2011) 121:571–87. doi: 10.1007/s00401-011-0826-y
30. Perales-Puchalt J, Vidoni ML, Llibre Rodríguez J, Vidoni ED, Billinger S, Burns J, et al. Cardiovascular health and dementia incidence among older adults in

Latin America: results from the 10/66 study. *Int J Geriatr Psychiatry.* (2019) 34:1041–9. doi: 10.1002/gps.5107
31. Albanese E, Dangour AD, Uauy R, Acosta D, Guerra M, Guerra SSG, et al. Dietary fish and meat intake and dementia in Latin America, China, and India: a 10/66 Dementia Research Group population-based study. *Am J Clin Nutr.* (2009) 90:392–400. doi: 10.3945/ajcn.2009.27580
32. Bakre AT, Chen R, Khutan R, Wei L, Smith T, Qin G, et al. Association between fish consumption and risk of dementia: a new study from China and a systematic literature review and meta-analysis. *Public Health Nutr.* (2018) 21:1921–32. doi: 10.1017/S136898001800037X
33. Cunnane SC, Plourde M, Pifferi F, Bégin M, Féart C, Barberger-Gateau P. Fish, docosahexaenoic acid and Alzheimer's disease. *Prog Lipid Res.* (2009) 48:239–56. doi: 10.1016/j.plipres.2009.04.001
34. Johansson L, Guerra M, Prince M, Hörder H, Falk H, Stubbs B, et al. Associations between depression, depressive symptoms, and incidence of dementia in latin america: a 10/66 dementia research group study. *J Alzheimer's Dis.* (2019) 69:433–41. doi: 10.3233/JAD-190148
35. Ojagbemi A, Owolabi M, Bello T, Baiyewu O. Stroke severity predicts poststroke delirium and its association with dementia: longitudinal observation from a low income setting. *J Neurol Sci.* (2017) 375:376–81. doi: 10.1016/j.jns.2017.02.039
36. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. *Lancet Neurol.* (2009) 8:1006–18. doi: 10.1016/S1474-4422(09)70236-4
37. Dos Santos Matioli MNP, Suemoto CK, Rodriguez RD, Farias DS, da Silva MM, Leite REP, et al. Diabetes is not associated with alzheimer's disease neuropathology. *J Alzheimer's Dis.* (2017) 60:1035–43. doi: 10.3233/JAD-170179
38. Loughrey DG, Kelly ME, Kelley GA, Brennan S, Lawlor BA. Association of age-related hearing loss with cognitive function, cognitive impairment, and dementia: a systematic review and meta-analysis. *JAMA Otolaryngol.* (2018) 144:115–26. doi: 10.1001/jamaoto.2017.2513
39. Panza F, Lozupone M, Sardone R, Battista P, Piccininni M, Dibello V, et al. Sensorial frailty: age-related hearing loss and the risk of cognitive impairment and dementia in later life. *Ther Adv Chronic Dis.* (2018) 10:2040622318811000. doi: 10.1177/2040622318811000
40. Brenowitz WD, Kaup AR, Lin FR, Yaffe K. Multiple sensory impairment is associated with increased risk of dementia among black and white older adults. *J Gerontol Series A Biol Sci Med Sci.* (2019) 74:890–6. doi: 10.1093/gerona/gly264
41. Naël V, Pérès K, Dartigues J-F, Letenneur L, Amieva H, Arleo A, et al. Vision loss and 12-year risk of dementia in older adults: the 3C cohort study. *Eur J Epidemiol.* (2019) 34:141–52. doi: 10.1007/s10654-018-00478-y
42. Rogers MAM, Langa KM. Untreated poor vision: a contributing factor to late-life dementia. *Am J Epidemiol.* (2010) 171:728–35. doi: 10.1093/aje/kwp453
43. Jefferis JM, Mosimann UP, Clarke MP. Cataract and cognitive impairment: a review of the literature. *Br J Ophthalmol.* (2011) 95:17–23. doi: 10.1136/bjo.2009.165902
44. Shi L, Chen S-J, Ma M-Y, Bao Y-P, Han Y, Wang Y-M, et al. Sleep disturbances increase the risk of dementia: a systematic review and meta-analysis. *Sleep Med Rev.* (2018) 40:4–16. doi: 10.1016/j.smrv.2017.06.010
45. Bennett S, Thomas AJ. Depression and dementia: cause, consequence or coincidence? *Maturitas.* (2014) 79:184–90. doi: 10.1016/j.maturitas.2014.05.009
46. Halahakoon DC, Lewis G, Roiser JP. Cognitive impairment and depression-cause, consequence, or coincidence? *JAMA Psychiatry.* (2019) 76:239–40. doi: 10.1001/jamapsychiatry.2018.3631
47. Peeters G, Kenny RA, Lawlor B. Late life education and cognitive function in older adults. *Int J Geriatr Psychiatry.* (2020) 35:633–9. doi: 10.1002/gps.5281
48. Litwin H, Schwartz E, Damri N. Cognitively stimulating leisure activity and subsequent cognitive function: a share-based analysis. *Gerontologist.* (2017) 57:940–8. doi: 10.1093/geront/gnw084
49. Guerchet M, Mouanga AM, M'Belesso P, Tabo A, Bandzouzi B, Paraïso MN, et al. Factors associated with dementia among elderly people living in two cities in Central Africa: the EDAC multicenter study. *JAD.* (2012) 29:15–24. doi: 10.3233/JAD-2011-111364

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 13 January 2021
doi: 10.3389/fneur.2020.578068

Ethnic Differences in Attending a Tertiary Dementia Clinic in Israel

Polina Specktor[1], Rachel Ben Hayun[1], Natalia Yarovinsky[1], Tali Fisher[1] and Judith Aharon Peretz[1,2]*

[1] Cognitive Neurology Institute, Rambam Health Care Campus, Haifa, Israel, [2] Technion – Israel Institute of Technology, Haifa, Israel

Introduction: Variations in lifestyle, socioeconomic status and general health likely account for differences in dementia disparities across racial groups. Our aim was to evaluate the characteristics of Arab (AS) and Jewish (JS) subjects attending a tertiary dementia clinic in Israel.

Methods: Retrospective data regarding subjects attending the Cognitive Neurology Institute at Rambam Health Care Campus between April 1, 2010, and April 31, 2016, for complaints of cognitive decline were collected from the institutional registry. AS and consecutive JS, aged ≥50 years without a previous history of structural brain disease, were included.

Results: The records of 6,175 visits were found; 3,246 subjects were ≥50 years at the initial visit. One hundred and ninety-nine AS and consecutive JS cases were reviewed. Mean age at first visit was 68.4 ± 8.8 for AS and 74.3 for JS ($p < 0.0001$). Mean education was 7.7 ± 4.8 years for AS and 11.3 years for JS ($p < 0.0001$). Mean duration of cognitive complaints prior to first visit did not differ between the groups. Initial complaints of both ethnicities were failing memory (97%) and behavioral changes (59%). Functional impairment was reported by 59% of AS and 45% of JS ($p = 0.005$). MMSE on first evaluation was 19.2 ± 7 for AS and 23.1 ± 5.9 for JS; $p = 0.001$. Alzheimer's disease was diagnosed in 32% AS and 23% JS, mild cognitive impairment in 12% AS and 21% JS. Normal cognition was diagnosed in 2% AS and 9% JS; $p = 0.0001$.

Conclusions: Compared to JS, AS attend a tertiary clinic when their cognitive impairment already affects their functional abilities providing a comprehensive benchmark for social health care interventions to reduce disparities.

Keywords: dementia, cognitive, ethnicity, disparities, cohort, epidemiology, Arab, Jew

OPEN ACCESS

Edited by:
Suvarna Alladi, Nizam's Institute of Medical Sciences, India

Reviewed by:
Elisa De Paula Franca Resende, Federal University of Minas Gerais, Brazil
Jennifer A. Deal, Johns Hopkins University, United States

****Correspondence:***
Polina Specktor
poly_specktor@yahoo.com

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: *30 June 2020*
Accepted: *10 December 2020*
Published: *13 January 2021*

Citation:
Specktor P, Ben Hayun R, Yarovinsky N, Fisher T and Aharon Peretz J (2021) Ethnic Differences in Attending a Tertiary Dementia Clinic in Israel. Front. Neurol. 11:578068. doi: 10.3389/fneur.2020.578068

INTRODUCTION

The estimated number of people living with dementia worldwide currently is approaching 50 million. This number is estimated to triple by 2050, as a result of anticipated increase in middle and lower income countries due to aging of their populations (1). Ethnicity is one of the factors influencing dementia prevalence as it impacts health seeking behavior, stigma and perceived futility of the diagnosis (2). Various countries have reported dementia incidence and prevalence to be higher in ethnic minorities (3); alas, they use fewer medical services (4).

Few studies have evaluated the prevalence of dementia in the different ethnic groups in Israel. The largest ethnic groups in Israel are Israeli Jews followed by Israeli Arabs, further divided into Muslims, Christians and Druze, with a smaller number of other ethnicities. The prevalence of Alzheimer's disease (AD) in the 60 years and older Arab population in Israel is estimated as 10–20.5% (5, 6); this is four times higher than the estimated prevalence in the Jewish population (7, 8). Factors, such as high consanguinity rates and genetic pre-disposition (9, 10), high illiteracy rates (5) and lower socioeconomic status (11), have been considered to contribute to this disparity.

The present study sought to determine the usage of tertiary dementia clinic services in Israel among Arab (AS) and Jewish (JS) subjects, explore their characteristics and investigate their diagnosis and compliance with treatment. Exploring the reasons for the differences between these ethnic groups may help to direct service planning, health education and development of interventions.

MATERIALS AND METHODS

This is a retrospective study regarding subjects attending the Cognitive Neurology Institute at Rambam Health Care Campus (CNIR). It was reviewed and approved by the Institutional Review Boards of Rambam Health Care Campus (# 0680-19-RMB). Written informed consent from the participants was not required to participate in this study in accordance with national legislation and institutional requirements because the study involved medical record review with no subject contact.

The CNIR is a tertiary referral center for diagnosis and treatment of cognitive impairment and dementia, located in Haifa, north Israel. We collected retrospective data on subjects attending the CNIR for complaints regarding acquired cognitive decline between April 2010 and April 2016 from the computerized institutional registry. Ethnicity was determined according to subject's name, records of the ministry of internal affairs, self-report. Inclusion criteria were first clinic visit of subjects 50 years and older with complaints regarding acquired cognitive decline.

Following screening of the CNIR registry, AS meeting inclusion and exclusion criteria were included in the study. First consecutive JS, attending the clinic at nearest date on the calendar, and meeting inclusion/exclusion criteria were added to the study.

Exclusion criteria included history of traumatic brain injury (TBI) or neurosurgery 1 year preceding the emergence of cognitive deterioration, evaluation for ADHD (attention deficit and hyperactivity disorder), evaluation for insurance purposes and cognitive screening prior to neurosurgical procedures. Patient characteristics, medical background, current diagnoses and follow-up visits were recorded.

Ethnicity was retrieved from the demographical data documentation. When unavailable, patient ethnicity was defined by name. Several studies across the world have examined the issue of ethnicity definition by subject's name. A meta-analysis performed by Pablo Mateos of several studies addressing the issue found a sensitivity of 0.67–0.95 and a specificity of 0.8–1 of such reports (12). As we defined only two broad ethnicities, Arab and Jew, and did not subdivide them according to religion or subethnicity, the specificity and sensitivity are probably much higher.

Ethnic demographic data involving northern Israel residents was extracted from the Central Bureau of Statistics registry.

Cognitive complaints were defined as complaints regarding memory, language, orientation, attention or cognitive slowing. Behavioral complaints were defined when significant changes in comportment and behavior, such as aggression, psychosis, disinhibition, apathy and mood disturbances, were reported. Functional impairment was defined as self-report of any difficulties performing ADL (activities of daily living) or IADL (instrumental ADL).

Dementia, AD and mild cognitive impairment (MCI) were diagnosed according to recommendations from the National Institute on Aging-Alzheimer's Association workgroup (NINCDS-ADRDA criteria) (13, 14). VD (vascular dementia) was diagnosed according to AHA/ASA recommendations (15). Subjects who met both criteria for primary degenerative dementia of the Alzheimer type and neuroimaging features of VD were diagnosed as mixed dementia (MD) (16).

A frontotemporal dementia (FTD) diagnosis was based on clinical presentation combined with ancillary tests (17, 18). Dementia associated with extrapyramidal disease (Lewy body dementia and dementia in Parkinson disease) was diagnosed in patients with prominent extrapyramidal manifestations and a corresponding cognitive profile (19, 20).

Pseudo-dementia was diagnosed in subjects who presented with complaints regarding cognitive deterioration that were clinically judged to be secondary to depression but not to a neurodegenerative condition (21).

Comparison of education, MMSE and duration of symptoms between the two ethnic groups was performed by Mann-Whitney non-parametric test. Patients' age, gender, marital status, medical background, diagnosis in the first and the last follow up, as well as number of follow-ups were compared by Chi square test.

Adjustment of MMSE for age and education years (adjusted MMSE: aMMSE) was based on the MMSE norms recommended by MMSE handbook published by Folstein (22).

P-value below 0.005 was considered as statistically significant. Data analysis was performed by SPSS Statistics 25 software.

RESULTS

A total of 6,175 visit records of 4,229 subjects attending the CNIR between April 1, 2010, and April 31, 2016, were reviewed; 3,246 subjects were $\geq$50 years at the initial visit. Two hundred and fifty-two (7.8%) AS $\geq$50 years were identified. Fifty-three AS were not included for further analysis due to meeting exclusion criteria or missing data. One hundred and ninety-nine AS were included; in 145 subjects, Arab ethnicity was documented in patients' files, ethnicity of the rest was defined by name. AS were coupled with consecutive JS who met inclusion and exclusion criteria (**Figure 1**).

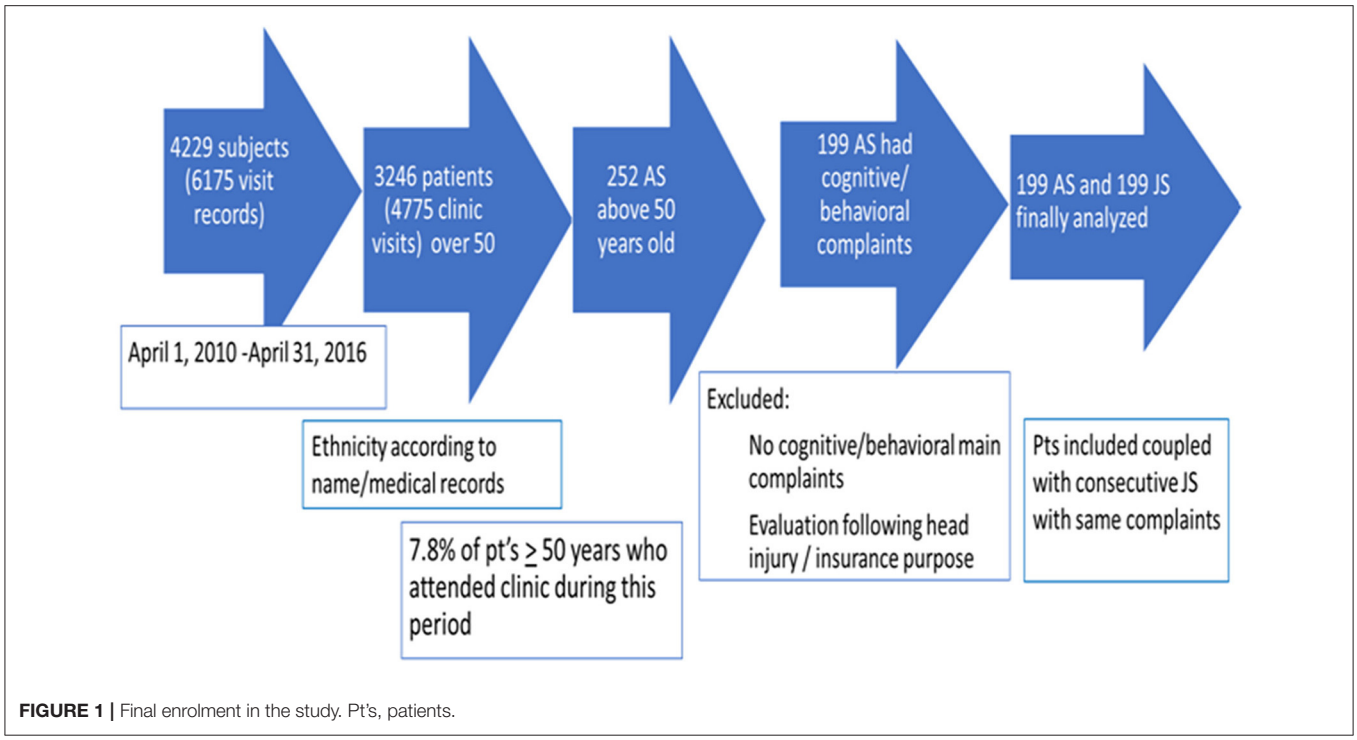


FIGURE 1 | Final enrolment in the study. Pt's, patients.

Mean age at first visit was 68.4 ± 8.8 for AS and 74.3 ± 9.3 years for JS ($p < 0.0001$). Mean education was 7.7 ± 4.8 years for AS and 11.3 ± 4.8 years for JS ($p < 0.0001$). Seventy-five percent AS and 58% JS were married; 1% AS and 1.5% JS were referred from nursing homes.

Mean duration of cognitive complaints prior to the first visit did not differ between the groups (AS 2.5 ± 3 years, JS 2.4 ± 2.7 years). Initial complaints of both ethnicities included failing memory (97%) and behavioral changes (59%). Functional impairment was reported by 59% of AS and 45% of JS ($p = 0.005$).

MMSE on first evaluation was 19.2 ± 6.9 for AS and 23.1 ± 5.9 for JS; $p = 0.001$ (**Table 1**). MMSE differences remained significant after correction for age and education years (25.4 ± 22.5 AS, 34.5 ± 22.7 JS, $p < 0.0001$) (22) (adjusted MMSE: aMMSE).

A low aMMSE (<15) was more prevalent in AS (41.2% AS, 25.8% JS, $p = 0.002$), female gender (41.5% female, 25.8% male, $p = 0.002$) and patients with behavioral and functional complaints (43% behavioral, 46% functional complaints; 20% and 19% without behavioral and functional complaints, respectively; $p < 0.0001$). The presence of cognitive complaints was not associated with lower scores on the aMMSE (33% with cognitive complaints, 22% without this complaint had aMMSE below 15, $p = 0.477$).

Past medical diagnoses and prescribed medications as written in the referral are described in **Table 2**. Vascular risk factors, family history of dementia, history of previous head injury and a background extrapyramidal disease did not differ between the groups. Hypertension diagnosis was more prevalent in JS (58% AS, 69% JS; $p = 0.017$). Background depression (based on medical records) was more prevalent in JS, although not significantly (25% AS, 33% JS; $p = 0.096$). History of malignancy was more prevalent in the Jewish population (11% AS, 23% JS; $p = 0.002$). JS used more antidepressants (24% AS, 34% JS; $p = 0.026$) and thyroid (6% AS, 13% JS; $p = 0.026$) medications.

TABLE 1 | Demographic data.

Parameter	AS	JS	*P*
	***N* = 199**	***N* = 199**	
Age at first visit (years ± mean)	68.4 ± 8.8	74.3 ± 9.3	<0.0001
Gender: Female, *N* (%)	95 (48)	100 (50)	0.689
Marital status: Married, *N* (%)	150 (75)	116 (58)	<0.0001
Nursing home care, *N* (%)	2 (1)	3 (1.5)	1
Education (years ± mean)	7.7 ± 4.8	11.3 ± 4.8	<0.0001
Family history of memory disorders, *N* (%)	56 (28)	40 (20)	0.391
Duration of symptoms prior to 1st visit (years ± mean)	2.5 ± 3	2.4 ± 2.7	0.618
Complaints on initial presentation			
Cognitive, *N* (%)	196 (98)	190 (95)	0.062
Behavioral, *N* (%)	125 (63)	109 (55)	0.103
Functional, *N* (%)	118 (59)	90 (45)	0.005
MMSE (1st visit)	19.2 ± 6.9	23.1 ± 5.9	<0.0001
Compliance			
Repeated visits: more than one, *N* (%)	90 (45)	96 (48)	0.9
Adherence to prescribed treatment (%)	95	94	1

AS, Arab subjects; JS, Jew subjects.

TABLE 2 | Background diagnoses.

Parameter	Total		JS		AS		Chi-square
	N	%	*N*	%	*N*	%	
Diabetes Mellitus	135	34.0	65	32.7	70	35.2	0.597
Hyperlipidemia	261	65.6	134	67.3	127	63.8	0.527
Hypertension	252	63	138	69	114	58	0.017
Vascular disease*	105	26.4	52	26.1	53	26.6	1.000
s/p stroke**	100	25.1	54	27.1	46	23.1	0.419
Other intracranial disease***	30	7.5	16	8.0	14	7.0	0.85
History of head trauma	39	9.8	23	11.6	16	8.0	0.312
Family history of dementia	96	24.1	40	20.1	56	28.1	0.391
History of malignancy	66	16.6	45	22.6	21	10.6	0.002
Extrapyramidal disease/ Essential tremor	52	13.1	29	14.6	23	11.6	0.457
Recurrent falls	27	6.8	18	9.0	9	4.5	0.109
Vision problems	101	25.4	58	29.1	43	21.6	0.107
Hearing problems	99	24.9	55	27.6	44	22.1	0.246
Sleep apnea	17	4.3	11	5.5	6	3.0	0.322
Depression	114	28.6	65	32.7	49	24.6	0.096
Medication list							
Dementia medication	54	13.6	21	10.5	33	16.6	0.081
Cardiovascular medication	331	83.2	171	85.9	160	80.4	0.169
Diabetes	118	29.6	52	26.1	66	33.2	0.124
Antidepressants	115	28.9	68	34.2	47	23.6	0.026
Anticonvulsants including Benzodiazepines	20	5	10	5	10	5	1
Opiates	4	1.0	2	1.0	2	1.0	1
Steroids	5	1.3	3	1.5	2	1.0	1
Antipsychotic	21	5.3	9	4.6	12	6.1	0.511
B12 treatment	65	16.5	28	14.2	37	18.9	0.224
Thyroid medication	38	9.6	26	13.1	12	6.1	0.026

AS, Arab subjects; JS, Jew subjects.
**Heart disease/peripheral vascular disease.*
***TIA, hemorrhagic and ischemic stroke.*
****Benign brain tumor, s/p brain hemorrhage, normal pressure hydrocephalus, white matter disease, s/p encephalitis or meningitis, brain aneurism and AVM.*

TABLE 3 | Diagnosis in the first/last visit.

		Total		JS		AS		*p*-value
		N	%	*N*	%	*N*	%	
First visit	All patients	398		199		199		0.000
	Normal cognition	21	5%	18	9%	3	2%	
	MCI	64	16%	41	21%	23	12%	
	Alzheimer dementia	109	27%	46	23%	63	32%	
	Vascular dementia	44	11%	15	8%	29	15%	
	Mixed dementia	77	19%	40	20%	37	19%	
	Frontotemporal dementia	7	2%	6	3%	1	0.5%	
	Extrapyramidal disease	9	2%	4	2%	5	2.5%	
	Pseudo-dementia	14	3.5%	1	0.5%	13	6.5%	
	Other	10	2.5%	5	2.5%	5	2.5%	
	UNKNOWN	43	11%	23	12%	20	10%	
Last visit	All patients	186		96		90		0.000
	Normal cognition	4	2%	4	4%	0	0%	
	MCI	18	10%	15	16%	3	3%	
	Alzheimer dementia	92	50%	39	41%	53	59%	
	Vascular dementia	6	3%	3	3%	3	3%	
	Mixed dementia	39	21%	22	23%	17	19%	
	Frontotemporal dementia	5	3%	5	5%	0	0%	
	Extrapyramidal disease	6	3%	4	4%	2	2%	
	Pseudo-dementia	5	3%	0	0%	5	6%	
	Other	4	2%	2	2%	2	2%	
	UNKNOWN	5	3%	1	1%	4	4%	

AS, Arab subjects; JS, Jew subjects.

Sixty-three AS (32%) and 46 JS (23%) were diagnosed with AD, 29 AS (15%) and 15 JS (8%) were diagnosed with VD. Twenty-three AS (12%) and 41 JS (21%) were diagnosed with MCI. Thirty-seven (19%) AS and 40 (20%) JS were diagnosed with MD. Normal cognition was diagnosed in three AS (2%) and 18 JS (9%). Frontotemporal dementia (FTD) was diagnosed in 0.5% AS and 3% JS. Pseudo-dementia was more prevalent in AS (6.5% AS; 0.5% JS). Dementia associated with extrapyramidal disease was diagnosed in 5 AS and 4 JS. The diagnosis could not be established at the initial visit in 11%. These subjects were referred for further evaluations.

Following initial recommendations, 90 (45%) AS and 96 (48%) JS returned to at least one follow-up visit; 25% AS and 25% JS returned to recurrent ($\geq$2) follow-up visits; mean number of follow up visits was 1.15 $\pm$ 1.8 for AS and 1.2 $\pm$ 2 for JS, p = 0.9. Two months to 10 years elapsed between the first to last visit; mean follow up was 2.58 $\pm$ 1.7 years for AS and 2.88 $\pm$ 2.38 years for JS; $p = 1$. Ninety-five percent of subjects followed the prescribed treatment.

During the last follow-up visit, normal cognition was recorded in four (4%) JS and no AS. Fifty-three AS (59%) and 39 JS (41%) were diagnosed with AD, three AS (3%) and 15 (16%) JS were diagnosed with MCI, 3% AS and 3% JS were found to have VD. Similar rates of MD were found in both groups; 19% AS and 23% JS (**Table 3**). Diagnosis was still deferred in 3% of subjects. Compared to the first visit, patients had similar rates of MD and two times higher rates of AD in both ethnicities. Normal cognition, MCI and VD were less prevalent on the last visits.

DISCUSSION

Despite the fact that the Arab population constitutes 37% of northern Israel residents 55 years and older and 17% of the Haifa district residents (23), AS constituted only 7.8% of the subjects that were evaluated in the CNIR.

In Israel, evaluations for cognitive deterioration within tertiary dementia clinics are only partially reimbursed by the national health care providers. According to the Israeli bureau of statistics, Arab salaried employees earn about 65% less than their Jewish counterparts (11). Accordingly, Arab households spend 42% less money on supplementary healthcare insurance than do Jewish ones (24). Indeed, prior studies support a correlation

between lower income and self-reported health in the Israeli Arab population (25). Therefore, the poorer financial status of AS may partially account for their underrepresentation in the clinic.

An additional cause for the under-representation of AS may be ethnicity dependent beliefs regarding dementia. AD may be associated with futility and stigma regarding "mental diseases and dementia" which may impede help seeking (26). Previous research exploring stigma among caregivers of persons with AD in Israel report pronounced stigma in Arab compared to Jewish population and suggest that a lower level of education may account for this difference (27). Also, prior works suggest that ethnic minorities often perceive cognitive decline as part of normal aging, delaying seeking medical help (28).

A low referral rate of ethnic minorities to cognitive clinics was shown in previous works (29); this may be another reason for AS underrepresentation and stand as an important intervention point.

To adjust for the imbalance in the number of subjects attending our clinic, we evaluated AS and immediately consecutive JS dyads, as stated. AS differed significantly from JS with regard to demographic and clinical characteristics.

AS were younger at their first visit compared to JS (68.4 ± 8.8 vs. 74.3 ± 9.3; $p < 0.0001$), nevertheless, they were referred for evaluation when they already reported functionally impairment and had a lower MMSE (**Table 1**). Similar findings were reported in Asian and black minorities residing in London, UK (30) and in the Latino minority in Philadelphia (31).

AS had a higher rate of AD (32 vs. 23% in JS) and of VaD (15 vs. 8% in JS). JS were more frequently diagnosed with normal cognition (2% in AS; 9% in JS) and with MCI (12% in AS; 21% in JS). This data correlates with previous studies that show higher rates of AD and VaD in the Arab population aged $\geq$60 (5, 6, 32).

A systematic review and meta- analysis found that, worldwide, people from minority ethnic groups with dementia access healthcare services in later stages of their illness (33). Our study supports this finding. Although our study did not show any differences in the duration of the reported symptoms between the onset of cognitive complaints and the first CNIR visit (2.5 ± 3 in AS, 2.4 ± 2.7 in JS), this value may be under-reported. This is supported by low rates of MCI, lower MMSE and higher rates of functional impairment documented on the first visit in AS in our study.

Other reasons for similar duration of symptoms despite poorer cognitive performance may be lower basic MMSE and a higher pace of cognitive decline in AS populations.

Higher AD prevalence and younger age at presentation of AS may have several reasons.

Alzheimer's disease is frequently heritable (34) and high rates of consanguineous marriages are reported between Israel Arabs (9, 35).

Compared to JS, AS had fewer schooling years (**Table 1**). Lower formal education in the Arab population in Israel was reported previously and is thought to reflect socio-demographic and ethno-religious elements (11, 36). Lower mean years of formal education tend to characterize members of minority groups compared to the majority group and were associated with AD in previous studies (37) and may partially explain higher AD rates in Arab population (8).

Vascular risk factors, such as diabetes and hypertension, are commonly associated with an increased risk for AD and dementia (38, 39). In the present study, the prevalence of diabetes was similar between AS and JS (**Table 2**), but, according to previous work, diabetes prevalence is higher in the Arab population (40). Similarly, hypertension was less prevalent in AS (**Table 2**), although poor blood pressure control was previously reported in the Arab population in Israel (41).

Depression is also regarded as a risk factor for AD (42, 43). Kaplan et al. (44) found depression rates 2.5 times higher in the Arab population compared to the Jewish population in Israel. In the present study, clinical, co-morbid diagnosis of depression was similar in both populations, while antidepressant use was higher in JS. As we collected community diagnoses, a possible reason for the discrepancy between our data and previous data is under-diagnosis and/or under-treatment of depression in ethnic minorities (45–47).

Interestingly, pseudo-dementia was diagnosed far more commonly in AS (13 vs. 1). Eleven of those AS patients had a previous depression diagnosis and nine were treated medically for depression. Somatization disorders in general are more frequently found in the Arab society (48, 49) and due to cultural and religious elements depression particularly tends to present with somatic complaints in Arab society (50, 51).

The prevalence of dementia in our study was similar to prior works. First visit diagnosis was AD in 27% of subjects, VaD in 11% and MD in 19%. Previous pathological and clinical studies in elderly onset dementia report AD in 20–40% of patients (52–54), VaD in 7.5–24% (53, 54), and MD in 13–40% (16, 54). During follow-up visits AD diagnosis was more frequent than in the first visit (50%), probably as MCI patients converted to AD and patients with deferred diagnosis were diagnosed with AD.

Our study showed a higher rate of past malignancy diagnosis in JS (21 AS, 45 JS). A higher rate of malignancy in the Jewish compared to the Arab population is consistent with the Israel cancer register (55) and may be due to differences in diet, genetic factors, the lower mean age of the Arab population and the more prevalent urban way of life of the Jewish population (56).

A low aMMSE (<15) was more prevalent in patients with behavioral and functional complaints. The presence of cognitive complaints was not associated with lower scores on the aMMSE. Prior studies did not show any difference in the number of cognitive complaints between MCI and dementia patients (57). Memory complaints were more common in mild-moderate dementia than in severe dementia (58). The presence of cognitive complaints usually does not correlate with dementia severity as those complaints usually evolve in the early stages of MCI and dementia and are the basic criteria for MCI and dementia diagnosis. As dementia progresses it usually affects more behavioral aspects (59) and functional abilities, correlating in our study with low aMMSE.

Although Arab patients are underrepresented in our study and may arrive at the tertiary clinic with more advanced disease, they have the same rate of compliance with treatment and continue follow up as the Jewish population. This good compliance with treatment and follow-up may reinforce the importance of creating public policies to bring Arab patients to the clinics earlier.

To the best of our knowledge, our study is the first that directly compares prevalence and characteristics of dementia in the two main ethnic groups in Israel (8). Its limitation is that it is retrospective and descriptive in nature, raising the need for future prospective comparative research.

In summary, our study reveals that AS arrive for evaluation younger but already report functional impairment and have lower MMSE, suggesting that AS under-representation in the clinic most probably reflects lower usage of this medical service. Reasons can be poorer awareness of dementia and lower referral rate, lower socioeconomic status and educational level and poorer control of risk factors in this population.

The importance of this study is in planning preventive measures and future interventions in order to reduce the disparity between ethnicities. Proactive educational interventions in the Arab community along with raising awareness about the importance of memory clinics among family physicians, district neurologists and the population itself, should be considered.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the data has been sufficiently de-identified and is available upon request. Requests to access the datasets should be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Boards of Rambam Health Care Campus (# 0680-19-RMB). Written informed consent from the participants was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

PS and JA conceived the research idea. PS, RB, NY, and JA performed evaluations of the subjects in the Rambam cognitive clinic. PS collected retrospect information about the clinic visits, prior diagnosis, treatment and follow ups and wrote the manuscript in consultation with JA and TF. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Prince M, Wimo A, Guerchet M, Ali G-C, Wu Y-T, Prina M. *World Alzheimer's report 2015: the global impact of dementia*. Alzheimer's Disease International (2015).
2. Phillipson L, Magee C, Jones S, Reis S, Skladzien E. Dementia attitudes and help-seeking intentions: an investigation of responses to two scenarios of an experience of the early signs of dementia. *Aging Ment Heal*. (2015) 19:968–77. doi: 10.1080/13607863.2014.995588
3. Smith K, Flicker L, Lautenschlager N, Almeida OP, Atkinson D, Dwyer A. High prevalence of dementia and cognitive impairment in Indigenous Australians. *Neurology*. (2008) 71:1470–3. doi: 10.1212/01.wnl.0000320508.11013.4f
4. Bowes A, Wilkinson H. "We didn't know it would get that bad": South Asian experiences of dementia and the service response. *Health Soc. Care Commun*. (2003) 11:387–97. doi: 10.1046/j.1365-2524.2003.00440.x
5. Bowirrat A, Friedland RP, Farrer L, Baldwin C, Korczyn A. Genetic and environmental risk factors for alzheimer's disease in israeli arabs. *J Mol Neurosci*. (2002) 19:239–45. doi: 10.1007/s12031-002-0040-4
6. Afgin AE, Massarwa M, Schechtman E, Israeli-Korn SD, Strugatsky R, Abuful A, et al. High prevalence of mild cognitive impairment and alzheimer's disease in arabic villages in Northern Israel: impact of gender and education. *J Alzheimers Dis*. (2012) 29:431–9. doi: 10.3233/JAD-2011-111667
7. Korczyn, AD, Kahana, E, Galper Y. Epidemiology of dementia in Ashkelon, Israel. *Neuroepidemiology*. (1991) 10:424–8.
8. Werner P, Friedland RP, Inzelberg R. Alzheimer's disease and the elderly in Israel: are we paying enough attention to the topic in the arab population? *Am J Alzheimers Dis Other Demen*. (2015) 30:448–53. doi: 10.1177/1533317515577130
9. Vardi-Saliternik R, Friedlander Y, Cohen T. Consaguinity in a population sample of Israel Muslim Arabs, Christian Arabs and Druze. *Ann Hum Biol*. (2002) 29:422–31. doi: 10.1080/03014460110100928
10. Farrer LA, Bowirrat A, Friedland RP, Waraska K, Korczyn AD BC. Identification of multiple loci for Alzheimer's disease in a consanguineous Israeli-Arab community. *Hum Mol Genet*. (2003) 12:415–22. doi: 10.1093/hmg/ddg037
11. Gharrah Ramsees. *Arab Society in Israel (7) Population, Society, Economy*. Jerusalem: Van Leer Institute Press (2015).
12. Mateos P. A review of name-based ethnicity classification methods and their potential in population studies. *Popul Space Place*. (2007) 13:243–63. doi: 10.1002/psp.457
13. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. (2011) 7:270–9. doi: 10.1016/j.jalz.2011.03.008
14. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. (2011) 7:263–9. doi: 10.1016/j.jalz.2011.03.005
15. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. (2011) 42:2672–713. doi: 10.1161/STR.0b013e3182299496
16. Zekry D, Hauw JJ, Gold G. Mixed dementia: epidemiology, diagnosis, and treatment. *Prog Geriatr*. (2002) 50:1431–8. doi: 10.1046/j.1532-5415.2002.50367.x
17. Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, et al. Classification of primary progressive aphasia and its variants. *Neurology*. (2011) 76:1006–14. doi: 10.1212/WNL.0b013e31821103e6
18. Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. (2011) 134:2456–77. doi: 10.1093/brain/awr179

19. Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord*. (2007) 22:1689–707. doi: 10.1002/mds.21507
20. McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor JP, Weintraub D, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB consortium. *Neurology*. (2017) 89:88–100. doi: 10.1212/WNL.0000000000004058
21. Kang H, Zhao F, You L, Giorgetta C, D V, Sarkhel S, et al. Pseudo-dementia: a neuropsychological review. *Ann Indian Acad Neurol*. (2014) 17:147–54. doi: 10.4103/0972-2327.132613
22. Folstein MF, Folstein SE, Fanjiang G. *Mini Mental State Examination*. Florida (2002).
23. CBC, Central Bureau of Statistics. *Population, by Population Group, Religion, Age and Sex, District and Sub-district*. Jerusalem (2017) 2.19.
24. Hayan I, Kornilenko I, Hertel D, Georgi M, Rotem N. Religion and Self-Definition of Level of Religiosity. In: *Society in Israel*. 10th ed. *Central Bureau of Statistics (Israel)*. (2016). p. 228–79.
25. Baron-Epel O, Weinstein R, Haviv-Mesika A, Garty-Sandalon N, Green MS. Individual-level analysis of social capital and health: a comparison of Arab and Jewish Israelis. *Soc Sci Med*. (2008) 66:900–10. doi: 10.1016/j.socscimed.2007.10.025
26. Xiao LD, Habel L, De Bellis A. Perceived challenges in dementia care by Vietnamese family caregivers and care workers in South Australia. *J Cross Cult Gerontol*. (2015) 30:333–52. doi: 10.1007/s10823-015-9264-y
27. Werner P, AboJabel H. Who internalizes courtesy stigma and how? A study among Israeli Arab family caregivers of persons with dementia. *Aging Ment Heal*. (2019) 0:1–8. doi: 10.1080/13607863.2019.1584790
28. Gray HL, Jimenez DE, Cucciare MA, Tong HQ, Gallagher-Thompson D. Ethnic differences in beliefs regarding alzheimer disease among dementia family caregivers. *Am J Geriatr Psychiatry*. (2009) 17:925–33. doi: 10.1097/JGP.0b013e3181ad4f3c
29. Subramaniam H, Mukaetova-Ladinska EB, Wilson A, Bankart J. Representation of Black, Asian and minority ethnic patients in secondary care mental health services: analysis of 7-year access to memory services in Leicester and Leicestershire. *BJPsych Bull*. (2020) 44:145–152. doi: 10.1192/bjb.2020.3
30. Mukadam N, Lewis G, Mueller C, Werbeloff N, Stewart R, Livingston G. Ethnic differences in cognition and age in people diagnosed with dementia: a study of electronic health records in two large mental healthcare providers. *Int J Geriatr Psychiatry*. (2019) 34:504–10. doi: 10.1002/gps.5046
31. Livney MG, Clark CM, Karlawish JH, Cartmell S, Negrón M, Nuñez J. Ethnoracial Differences in the Clinical Characteristics of Alzheimer Disease at Initial Presentation at an Urban Alzheimer's Disease Center. *Am J Geriatr Psychiatry*. (2011) 19:430–9. doi: 10.1097/JGP.0b013e3181f7d881
32. Bowirrat A, Treves TA, Friedland RP, Korczyn AD. Prevalence of Alzheimer's type dementia in an elderly Arab population. *Eur J Neurol*. (2001) 8:119–23. doi: 10.1046/j.1468-1331.2001.00183.x
33. Cooper C, Tandy A, Balamurali T, Livingston G. A systematic review and meta-analysis of ethnic differences in use of dementia treatment, care, and research. *Am J Geriatr Psychiatry*. (2010) 18:193–203. doi: 10.1097/JGP.0b013e3181bf9caf
34. Gatz M, Reynolds CA, Fratiglioni L, Johansson B, Mortimer JA, Berg S, et al. Role of genes and environments for explaining Alzheimer disease. *Arch Gen Psychiatry*. (2006) 63:168–74. doi: 10.1001/archpsyc.63.2.168
35. Sherva R, Baldwin C, Inzelberg R, Vardarajan B, Cupples LA, Lunetta K, et al. Identification of novel candidate genes for Alzheimer's disease by autosygocity mapping using genome wide SNP data from an Israeli-Arab community. *J Alzheimers Dis*. (2011) 23:349–59. doi: 10.3233/JAD-2010-100714
36. Okun BS, Friedlander D. Educational stratification among Arabs and Jews in Israel: historical disadvantage, discrimination, and opportunity. *Popul Stud*. (2005) 59:163–80. doi: 10.1080/00324720500099405
37. Chin A, Negash S, Hamilton R. Diversity and disparity in dementia: the impact of ethnoracial differences in Alzheimer's. *Alzheimers Dis Assoc Disord*. (2011) 25:187–95. doi: 10.1097/WAD.0b013e318211c6c9
38. Carnevale D, Perrotta M, Lembo G, Trimarco B. Pathophysiological links among hypertension and Alzheimer's disease. *High Blood Press Cardiovasc Prev*. (2016) 23:3–7. doi: 10.1007/s40292-015-0108-1
39. Shinohara M, Sato N. Bidirectional interactions between diabetes and Alzheimer's disease. *Neurochem Int*. (2017) 108:296–302. doi: 10.1016/j.neuint.2017.04.020
40. Jaffe A, Giveon S, Wulffhart L, Oberman B, Baidousi M, Ziv A, et al. Adult Arabs have higher risk for diabetes mellitus than Jews in Israel. *PLoS ONE*. (2017) 12:e0176661. doi: 10.1371/journal.pone.0176661
41. Abu-Saad K, Chetrit A, Eilat-Adar S, Alpert G, Atamna A, Gillon-Keren M, et al. Blood pressure level and hypertension awareness and control differ by marital status, sex, and ethnicity: a population-based study. *Am J Hypertens*. (2014) 27:1511–20. doi: 10.1093/ajh/hpu081
42. Wiels W, Baeken C, Engelborghs S. Depressive symptoms in the elderly-an early symptom of dementia? A systematic review. *Front Pharmacol*. (2020) 11:34. doi: 10.3389/fphar.2020.00034
43. Xia M, Yang L, Sun G, Qi S, Li B. Mechanism of depression as a risk factor in the development of Alzheimer's disease: the function of AQP4 and the glymphatic system. *Psychopharmacol*. (2017) 234:365–79. doi: 10.1007/s00213-016-4473-9
44. Kaplan G, Glasser S, Murad H, Atamna A, Alpert G, Goldbourt U, et al. Depression among Arabs and Jews in Israel: a population-based study. *Soc Psychiatry Psychiatr Epidemiol*. (2010) 45:931–9. doi: 10.1007/s00127-009-0142-1
45. Shao Z, Richie W, Bailey R. Racial and ethnic disparity in major depressive disorder. *J Racial Ethn Heal Disparities*. (2016) 3:692–705. doi: 10.1007/s40615-015-0188-6
46. Pickett Y, Weissman J, Bruce M. Racial differences in antidepressant use among older home health care patients. *Psychiatr Serv*. (2012) 63:827–9. doi: 10.1176/appi.ps.201100233
47. Bailey R, Mokonogho J, Kumar A. Racial and ethnic differences in depression: current perspectives. *Neuropsychiatr Dis Treat*. (2019) 15:603–9. doi: 10.2147/NDT.S128584
48. El-Rufaie OE, Al-Sabosy MM, Bener A, Abuzeid MS. Somatized mental disorder among primary care arab patients. *J Psychosom Res*. (1999) 46:549–55. doi: 10.1016/S0022-3999(98)00101-9
49. Abu-Kaf S, Shahar G. Depression and somatic symptoms among two ethnic groups in Israel: testing three theoretical models. *Isr J Psychiatry*. (2017) 54:32–40.
50. Deisenhammer E, Coban-Başaran M, Mantar A, et al. Ethnic and migrational impact on the clinical manifestation of depression. *Soc Psychiatry Psychiatr Epidemiol*. (2012) 47:1121–9. doi: 10.1007/s00127-011-0417-1
51. Hamdi E, Amin Y, Abou-Saleh MT. Problems in validating endogenous depression in the Arab culture by contemporary diagnostic criteria. *J Affect Disord*. (1997) 44:131–43. doi: 10.1016/S0165-0327(97)00037-2
52. Rajan KB, Weuve J, Barnes LL, Wilson RS, Evans DA. Prevalence and incidence of clinically diagnosed Alzheimer's disease dementia from 1994 to 2012 in a population study. *Alzheimers Dement*. (2018) 15:1–7. doi: 10.1016/j.jalz.2018.07.216
53. Stevens T, Livingston G, Kitchen G, Manela M, Walker Z, Katona C. Islington study of dementia subtypes in the community. *Br J Psychiatry*. (2002) 180:270–6. doi: 10.1192/bjp.180.3.270
54. Jellinger KA. Clinicopathological analysis of dementia disorders in the elderly–An update. *J Alzheimers Dis*. (2006) 9:61–70. doi: 10.3233/JAD-2006-9S308
55. Israel National Cancer Registry. *Ministry of Health Israel* (2013).
56. Miha B. Tendency in incidence of malignant diseases in Israel. *Review*. (2002) 6. Available online at: https://www.tnuva.co.il/Child_Nutrition/%D7%9E%D7%9B%D7%95%D7%9F-%D7%AA%D7%A0%D7%95%D7%91%D7%94-%D7%9C%D7%9E%D7%97%D7%A7%D7%A8/review/%D7%92%D7%99%D7%9C%D7%99%D7%95%D7%9F-6-%D7%AA%D7%96%D7%95%D7%A0%D7%94-%D7%95%D7%A1%D7%A8%D7%98%D7%9F

57. Salem LC, Vogel A, Ebstrup J, Linneberg A, Waldemar G. Subjective cognitive complaints included in diagnostic evaluation of dementia helps accurate diagnosis in a mixed memory clinic cohort. *Int J Geriatric Psychiatry*. (2015) 30:1177–85. doi: 10.1002/gps.4272
58. Grut M, Jorm AF, Fratiglioni L, Forsell Y, Viitanen M, Winblad B. Memory complaints of elderly people in a population survey: variation according to dementia stage and depression. *J Am Geriatr Soc*. (1993) 41:1295–300. doi: 10.1111/j.1532-5415.1993.tb06478.x
59. Zhao Q, Tan L, Wang HF, Jiang T, Tan MS, Tan L, et al. The prevalence of neuropsychiatric symptoms in Alzheimer's disease: systematic review and meta-analysis. *J Affect Disord*. (2016) 190:264–71. doi: 10.1016/j.jad.2016.04.054

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Public Health

PERSPECTIVE
published: 18 January 2021
doi: 10.3389/fpubh.2020.611998

Dementia Research in the Caribbean Hispanic Islands: Present Findings and Future Trends

Daisy Acosta[1†], *Jorge J. Llibre-Guerra*[2,3*†], *Ivonne Z. Jiménez-Velázquez*[4] *and Juan J. Llibre-Rodríguez*[1,5]

[1] Department of Internal Medicine, Universidad Nacional Pedro Henriquez Urena, Santo Domingo, Dominican Republic, [2] Department of Neurology, Washington University School of Medicine in St. Louis, St. Louis, MO, United States, [3] National Institute of Neurology and Neurosurgery, Habana, Cuba, [4] Department of Internal Medicine, Medical Sciences Campus, University of Puerto Rico, San Juan, Puerto Rico, [5] Finlay-Albarrán Medicine Faculty, Universidad de Ciencias Medicas, Habana, Cuba

During the last decade, the Caribbean Hispanic islands experienced accelerated demographic aging, representing the fastest aging region within Latin America. Age-related non-communicable diseases, including dementia, are now reported at high prevalence. The Caribbean islands share similar genetic ancestry, culture, migration patterns, and risk profiles, providing a unique setting to understand dementia in the Caribbean-Hispanics. This perspective article aimed to describe the impact of dementia in the Caribbean, at a local and regional level and reflect on research strategies to address dementia. We report on 10/66 project findings, described research projects and regional plans for the region. According to our results, the prevalence of dementia in the Caribbean is the highest in Latin America, with 11.7% in Dominican Republic, 11.6% in Puerto Rico, and 10.8% in Cuba. Preliminary data from new waves of the 10/66 study shows increasing numbers of dementia cases. Furthermore, dementia is expected to be one of the most serious medical and social issues confronted by Caribbean health systems. However, there is a scarcity of knowledge, awareness, and health services to deal with this public health crisis. In light of the new evidence, local and regional strategies are underway to better understand dementia trends for the region and develop policies aimed to decrease the impact of dementia. Implementation of our national plans is critical to deal with an aging population with high dementia rates. Current recommendations include emphasizing public health prevention campaigns to address modifiable risk factors and expand support to caregiver and family interventions.

Keywords: dementia, prevalence, incidence, Caribbean hispanics, regional policies

OPEN ACCESS

Edited by:
Maira Okada de Oliveira, University of São Paulo, Brazil

Reviewed by:
Hongdao Meng, University of South Florida, United States
Patricia M. Alt, Towson University, United States

***Correspondence:**
Jorge J. Llibre-Guerra
jorge.llibre@gbhi.org

†These authors have contributed equally to this work

Specialty section:
This article was submitted to Aging and Public Health, a section of the journal Frontiers in Public Health

Received: *30 September 2020*
Accepted: *18 December 2020*
Published: *18 January 2021*

Citation:
Acosta D, Llibre-Guerra JJ, Jiménez-Velázquez IZ and Llibre-Rodríguez JJ (2021) Dementia Research in the Caribbean Hispanic Islands: Present Findings and Future Trends. Front. Public Health 8:611998. doi: 10.3389/fpubh.2020.611998

INTRODUCTION

Epidemiological studies show a rapid increase in dementia in Hispanic populations (1, 2). Approximately twelve percent of older adults in the Latino population are diagnosed with Alzheimer's Dementia (AD), representing the highest growing proportion of AD cases in any ethnic group (3, 4). However, there is little to no understanding of disease onset, progression, and biomarker trajectories in Latino populations (5). Furthermore, most of the AD studies tend to include Latinos as a unique group, failing to sufficiently account for the real richness of linguistic, ethnic, ancestry, cultural, and socioeconomic diversity represented across Latino communities.

In relation to other Latino populations, Caribbean-Hispanics have several differences in customs, traditions, nutritional patterns, risk behaviors, and genetic admixtures, which may differentially impact the prevalence of dementia and expression of its symptoms. Furthermore, during the last decade, the Hispanic Caribbean islands (Cuba, Dominican Republic, and Puerto Rico) experienced accelerated demographic aging, representing the fastest aging region within Latin America, which posed a unique challenge for aging and dementia (6, 7). The Caribbean Hispanics represent 57.6% of the Caribbean population (Cuba = 11,326,616, Dominican Republic = 10,847,910, Puerto Rico = 3,193,694) region (6).

This perspective article aimed to examine the associations of genetics and socioeconomic determinants with dementia and describe the impact of dementia in the Hispanic Caribbean islands at a local and regional level. In addition, we present current research and describe future projects in the region. Finally, we share current dementia strategies aimed to address this epidemic within the Caribbean area.

AGING AND DEMENTIA IN THE CARIBBEAN HISPANIC

The Caribbean is undergoing increasingly rapid population aging with the proportion of older persons (60 and over) increasing from 10% in 2000 to 14% in 2015, and projected to reach 25% by 2050 (6). The rate of demographic aging is substantially faster than occurred in western industrialized societies in the past (8, 9). Consequently, compared to High-Income Countries, the Caribbean region must adapt more quickly to aging populations, posing a challenge to more fragile economies and less prepared health care systems. Low fertility rates, a decrease in birth rate, and increased life expectancy due to medical advancements are the main factors related to the Caribbean's aging phenomenon (7). In addition, migration has played a unique role in the aging process within the Caribbean Hispanic region; the three islands have experienced extensive diasporas in the last century, with these large migrations—primarily to the United States (US)—establishing such well-known communities as Little Havana in Miami, Hispanic Harlem, and Washington Heights, in New York (10, 11). Recently, migration from PR to US increased after Hurricanes Irma and Maria (Sept 2017). Migrants are often young, and their departure has re-shape the population structure, as a result the age structure of the population have change significantly in the Caribbean islands.

As number and proportion of older persons increase, a central question to the Caribbean region is whether the aging of this population will be accompanied by sustained or improved health, better quality of life, and sufficient social and economic resources. To date, the increase in life expectancy has not been coupled with improvements in lifestyle; risk behaviors such as consuming high fat and carbohydrate diets, smoking, and sedentarism are becoming more common. Likewise, population aging has been associated with a sustained increase in non-communicable diseases, including neurodegenerative disorders, like dementia (2, 12). Dementia has become one of the most serious medical and social issues confronted by Caribbean health systems, with a markedly elevated prevalence and incidence compared to other Latin American countries in general (2).

Since 2003, the three islands in a coordinated effort led a major epidemiological study (**Figure 1**) to determine dementia prevalence, incidence, and impact across Caribbean countries using a validated and standard methodology (13). The studies were done under the umbrella of the 10/66 protocols (13), a multinational research initiative aimed to provide a detailed evidence to inform the development and implementation of policies for improving the health and social welfare of older people in low and middle income countries (14). The 10/66 studies encompass new methods to dementia research in Low and Middle Income countries (LMIC) by developing a novel approach to diagnosing dementia (the 10/66 Dementia Diagnosis) and addressing difficulties in making diagnoses among older people with little or no education and the use of standardized protocols across all sites (13, 15). Although, the 10/66 study included several Latin America countries, India, and China, in this perspective article we focus on the Hispanic Caribbean studies. Further details of the 10/66 studies have been described elsewhere (4, 16).

In the Caribbean region, the 10/66 project surveyed 6833 residents, aged 65 and over, in Cuba (n = 2813) and the Dominican Republic (n = 2011) from 2003 to 2007, and in Puerto Rico (n = 2009) from 2006 to 2008. The interviews were done in a single phase, and the methodology allowed for the diagnosis of dementia and its subtypes, as well as other mental disorders. Data obtained included sociodemographic characteristics, physical health, anthropometric measures; information about risk factors, disability, frailty, utilization of health services, income, lifestyle (including nutrition and exercise), care characteristics, caregiver burden, and genetic risk markers (including ApoE-4); implemented together with a physical and neurological examination. An interview with a reliable informant was required. An incidence phase (second wave) was conducted 3 to 4 years after cohort enrollment, 2007 to 2011. A third wave of the 10/66 protocol is currently underway (details of this new wave are provided below).

The 10/66 studies in the Caribbean (**Figure 1**) have led to several publications on the prevalence and incidence of dementia and other chronic diseases (hypertension, stroke, anemia, diabetes), the impact of dementia in terms of disability, dependency, economic cost, care arrangements, and access to services (17–20). We have focused our attention on determinants of longitudinal outcomes, specifically incident dementia, mortality, dependence, risk factors, and course of dementia/ and Mild Cognitive Impairment. According to our epidemiological studies, using the same methodology in all three countries, the prevalence of dementia in individuals 65 years old and over is ∼11.7% in DR, 11.6% in the PR, and 10.8% in Cuba (**Table 1**). Preliminary data from a third wave of the 10/66 study suggest and in dementia prevalence relative to previous waves, probably related to a higher frequency of vascular risk factors and poor control of non-communicable diseases, including hypertension, diabetes, etc. With this continuing trend,

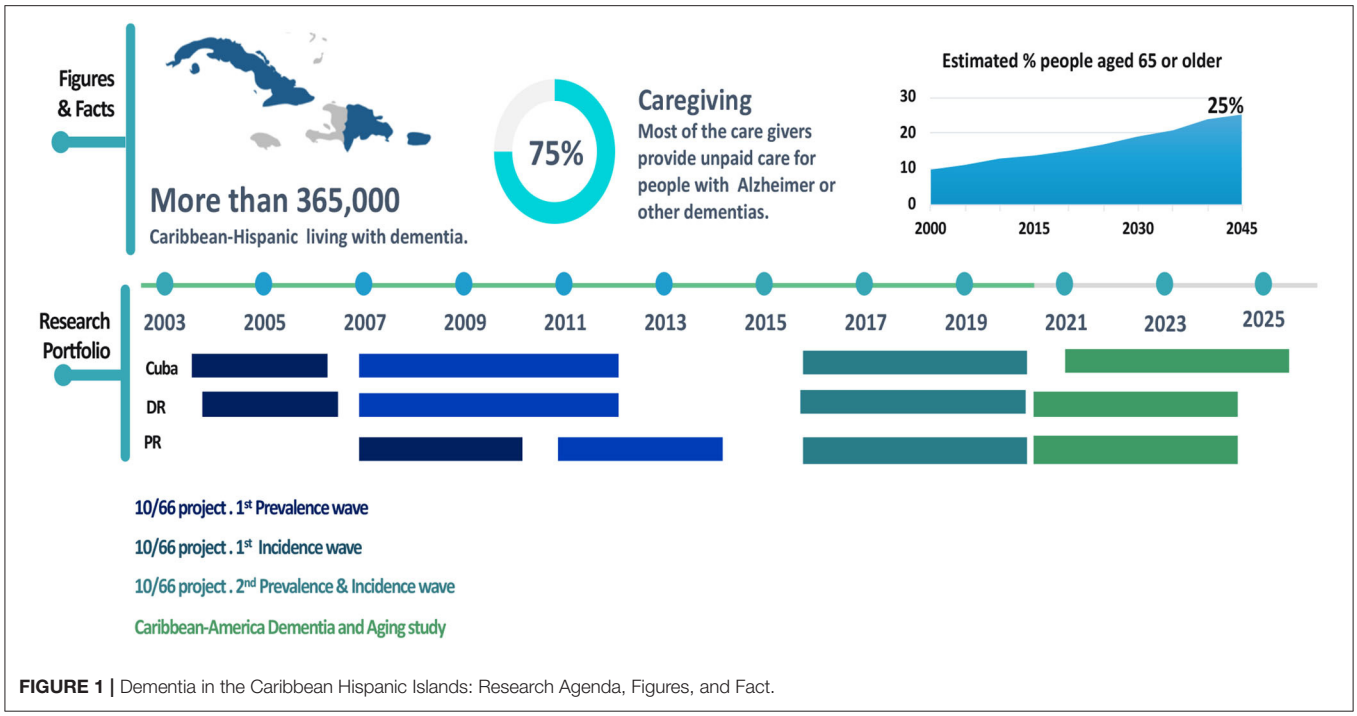


FIGURE 1 | Dementia in the Caribbean Hispanic Islands: Research Agenda, Figures, and Fact.

TABLE 1 | Caribbean Hispanics Islands population characteristics and 10/66 cohort profile.

	Cuba	Dominican Republic	Puerto Rico
Population Size, (No) millions	11.1	10.6	3.2
Over age 65, (%)	15	7	15
Life expectancy at birth (years)	80	74	80
Fertility rate (birth per woman)	1.7	2.4	1.1
10/66 baseline characteristics			
Participants, No	2813	2011	2009
Response Rate (%)	94	95	93
Age (years), No (%)			
65-69	715 (25.5)	533 (26.5)	414 (20.6)
70-74	747(26.6)	520 (25.9)	456 (22.7)
75-79	618 (22.0)	396 (19.7)	483 (24.0)
>79	726 (25.9)	561 (27.9)	656 (12.0)
Gender (F), No (%)	1836 (65.3)	1325 (66)	1347 (67.3)
Dementia, No (%)	292 (10.4)	235 (11.7)	233 (11.6)
Mild Cognitive Impairment, No (%)	42 (1.5)	26 (1.3)	68 (3.4)
Stroke, No (%)	216 (7.7)	175 (8.7)	168 (8.4)
Hypertension, No (%)	1624 (57.9)	968 (48.6)	518 (32.1)

by 2050, dementia in our countries may have one of the world's highest prevalence (with an estimated increase of 215%) (21, 22).

In the region, the main risk factors for dementia included: older age, family history of dementia, and lower levels of education. Poor cardiovascular health was associated with a higher incidence rate (23). Dementia is also among the top ten causes of death (4th-Puerto Rico, 6th-Cuba, 8th-Dominican Republic) (23, 24). However, due to the relative lack of early diagnosis and under registry on death certificates, current reports are likely to be under estimated.

Finally, the total direct and indirect costs of dementia was estimated to be 3.5 billion dollars, which is expected to double in 20 years (22).

As mentioned earlier, a third wave of assessments using an abbreviated form of the primary 10/66 survey is currently underway, ∼10 years after the original baseline surveys (2016–2020). For the new survey (third wave, $n = 6000$), we are revisiting the original catchment areas to generate a revised representative estimate of the prevalence of dementia for the residents who are 65 years old or older; the updated sample includes those individuals who, since the first wave of the survey have been incorporated into the age group of interest, either from having aged into it or from having moved into the areas. The new, third-wave prevalence survey includes a comprehensive assessment of health status, which will consist of spirometry, body mass index, visual acuity, grip strength, and tests to determine the presence of hearing impairment (16). The new wave aim to determine the changes in prevalence and incidence of dementia in the region and its associated risk factors—emphasizing cardiovascular issues—and to evaluate probable associations with APOE gene, markers of inflamation and immunusenescence. Moreover, a nested cohort of 300 individuals was randomly selected (150 with a high risk of incident dependence and 150 without) aimed to explore markers of frailty, including extensive laboratory testing of frailty biomarkers. This sub-group will be followed 18 months later to re-assess vital status, needs for care, disability,

cognitive function, and significant health-related life events in the intervening period.

POPULATION ADMIXTURE, GENETICS, AND CARIBBEAN HISPANICS

The Caribbean Hispanic population is highly multiethnic, reflecting its complex colonial origins. Intermarriage between diverse groups is widespread, and estimates of the percentage of African descent people vary enormously, ranging from 34 to 62% (population genetic admixture includes mainly European and African ancestry, with little contribution of Indigenous ancestry) (25, 26). This genetic ancestry pattern is different from the one described in South America, which includes predominantly European and Indigenous populations (27). The differences in genetics between the Caribbean-Hispanic and non-Caribbean Hispanics may yield relevant information regarding the influence of admixture background on dementia risk. For example, the risk of AD associated with the *APOE-ε4* allele has been found to vary according with African ancestry proportions (28, 29).

According to our studies, the association between dementia and *APOE-ϵ4* is weaker in Caribbean Hispanics compared to Caucasian populations. In the three Caribbean islands being an *APOE-ϵ4* carrier increases the risk to develop dementia by two folds (SHR 2.03 [1.32-3.11]); in Caucasian populations the risk among *APOE-ϵ4* carriers is 10 to 15 times higher than in non *APOE-ϵ4* carriers (28, 30, 31). To date only 3% of genetics studies in AD have been done in Hispanics population; (32, 33) like *APOE-ϵ4*, other genetic variants previously described in Caucasians (e.g., *TREM2, SORL1, ABCA7*) may have a differential risk among the Hispanic population; therefore the influences of genetic risk factors in Caribbean Hispanics should be explored in future studies.

The frequency of Dominantly Inherited Alzheimer disease (DIAD) is relatively high in the Caribbean countries compare to Europe and US; (33, 34) which can be attributable to common ancestors causing a founder effect during early colonization periods (35, 36). It is very likely that the establishment of new colonies in the Caribbean islands combined with a high degree of inbreeding among Caribbean populations (37) created a reduced amount of genetic variation within the new population settlements, influencing the spread of these mutations across the islands. In Cuba, Bertoli et al. (38) described a novel Presenilin 1 (PSEN1) pathogenic variant (*PSEN1_L174M*) affecting several families (280 family members) in the Cuban western provinces. Furthermore, two decades ago, a family study was developed in New York that included multiplex relatives affected with AD in Dominican Republic and Puerto Rico, leading to the discovery of novel *PSEN1* pathogenic variant *(PSEN1_G206A)* (36). Since 2008, a new Early Onset AD study has been conducted in Puerto Rico, leading to the discovery of 91 unrelated families featuring this pathogenic variant. A total of 682 family members have been evaluated and followed in one of the world's biggest cohorts of early-onset families (37, 39). Several studies, observational and clinical trials with novel medications are ongoing in Puerto Rico for family members of the PSEN1 families, as well as for sporadic AD cases.

REGIONAL AND LOCAL POLICIES IN THE CARIBBEAN

Education and Training in Dementia

As mentioned early, the prevalence of dementia is high among use Caribbean-Hispanics, yet knowledge, health services, and awareness of the disease are scarce (40). Awareness and early diagnosis are crucial elements to reduce dementia's impact, benefit patients and caregivers, and reduce treatment costs (41). Early detection can prompt evaluation for reversible causes, improve the care of comorbid illnesses, guide the selection of appropriate symptomatic therapies, and identify the needs for social support (41–43).

Unfortunately, cognitive impairment and dementia diagnosis depend mostly on clinical suspicion, and ∼50% of dementia cases are missed in primary care, delaying detection until later in the disease course. Furthermore, awareness about dementia diagnosis and care is not only relevant for health care professionals, but also for the general population, especially among those caring for someone with dementia; and these are unmet needs in LMIC (44, 45). Consequently, there is a current need to increase healthcare providers and caregivers' training options.

Several local and regional strategies have been implemented to address these issues. The Alzheimer's Research Center in Cuba has developed a multidisciplinary Master's degree program to improve early diagnosis, treatment, and support of people living with dementia (46). Through this program, trainees will gain the necessary knowledge to advance research on the dementia field and provide better care to dementia patients and their families. Similar strategies are underway in the Dominican Republic and Puerto Rico. For example, the Department of mental health of the Ministry of health in the Dominican Republic for the last 4 years has been training the primary care workforce in the mhGAP intervention guide (47) with the aim that by 2025, at least 50% of the estimated number of people with dementia will receive an accurate diagnosis.

Another need is to expand the training of caregivers. The regional Alzheimer Associations have led a caregiver awareness program to improve caretaking abilities and expand caregivers' support. A full training video-series featuring relevant topics regarding caretaking in dementia and advice from health care professionals are available to view and share free of charge. "Conversando con Los Cuidadores"—new series in Spanish-includes eight videos focusing on critical issues related to the work and role of those who provide care for relatives with dementia. Training of caregivers will enhance their management ability and enables them to handle disruptive situations. The Dominican Alzheimer's Association has been developing online and on-site training sessions to support and decrease the burden associated with caretaking. The 10/66 "Helping Caregivers to Care, train-the-trainer" intervention was tested in a randomized control trial in the DR, providing evidence on the relevance of

caregiver training to decrease the burden associated with care. This intervention continues to be widely used by the Dominican Alzheimer's Association to train caregivers (alz.co.uk/helping-carers-to-care). The University of Puerto Rico, Geriatric's Education Center, offers specialized courses to train caregivers in different sites, including a special arrangement with the Dominican Republic Embassy in PR, to train Dominican caregivers working in Puerto Rico. Likewise, there are multiple caregiver training programs in private universities on the island.

LOCAL AND REGIONAL PLANS TO ADDRESS DEMENTIA

In 2015, Cuba and the Alzheimer's Research Center announced the National plan for dementia, and it was adopted as a National dementia strategy by the Cuban Ministry of health in 2016 (23). The main goals of the Cuban national strategy included: 1—Increase awareness, information, education, and support for families; 2—Risk reduction (e.g., better control of cardiovascular risk factors, reduce physical inactivity, promote healthy diets among others); 3—Timely diagnosis and access to treatment; 4—Improve care for dementia patients and their families; 5—Reduce stigma around dementia; 6—Increase professional development and train families for patient care; 7—Promote basic, clinical and epidemiological research on dementia; 8—Familiarize health teams with laws protecting the rights of older adults and people with cognitive impairment; 9—Assess and improve the quality of health care, social care, and long-term care support and services. Furthermore, Cuba has taken the first steps in implementing the Global action plan on the public health response to dementia 2017–2025.

Similar to Cuba, in 2015, Puerto Rico launched the *Alzheimer's disease Action Plan* in response to the World Health Organization's (WHO) call to action, by rating AD and other dementias as a public health priority. The focal areas of the PLAN were divided into seven pillars: (1) Public Policy (2) Public Health Efforts and Epidemiologic Surveillance (3) Home and Community Caregiving Services (4) Education and Training (5) Diagnosis and Treatment, (6) Long Term Care Services, and (7) Long-Term Care Financing. Each area includes specifics goals to be accomplished by 2025.

Finally, in July 2020, the Dominican Republic's Ministry of Public Health, in close partnership with Asociación Dominicana de Alzheimer, announced a national strategy for dementia with similar action points as Cuba and Puerto Rico. Future efforts in the region are needed to achieve a coordinated response and plan to address the rising number of dementia cases.

UPCOMING RESEARCH EFFORTS

The Caribbean American Dementia and Aging Study (CADAS) is new research study funded through the National Institute of Health (R01AG064778) aimed to support regional research efforts to expand the previous waves of 10/66 studies to rural populations and facilitate a nationwide dementia estimate (**Figure 1**). Results from this project will be further compared with databases of Hispanic data collected in mainland USA, including the Health and Retirement Study (HRS) and Harmonized Cognitive Assessment Protocol (HCAP). In addition, in collaboration with the Alzheimer's Association, several countries in the region will launch the LatAm FINGERS, a multi-domain lifestyle intervention (diet and exercise), aimed to improve cognitive function (48). This study will be conducted from 2020 to 2022 and will recruit 1,300 participants from 13 countries in Latin America, including Argentina, Brazil, Bolivia, Chile, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, Mexico, Paraguay, Peru, Puerto Rico, and Uruguay; details of LatAm FINGERS has been described elsewhere (48). Both CADAS and LatAm fingers projects show the relevance of international collaboration to push regional and locals research agendas.

To better understand disease pathology and AD progression in Caribbean-Hispanics, a new Brain Bank is already in place in DR, another one is being organized in PR. Our final goal is to develop a Hispanic Caribbean Coordinating Center for neuropathology sample collection and storage. To maintain a coordinated research program, Caribbean researchers are meeting several times per year, promoting the work's continuity and keeping the international collaborations. More recently, the Ministry of Higher Education Science and Technology of the Dominican Republic awarded the Brain Bank research funding to expand research on AD pathology, with a special focus in Tau patho-physiology. This project is a joint consortium with a local university, "Pontificia Universidad Catolica Madre y Maestra" and Universidad Autonoma de Mexico (UNAM).

CONCLUSION

Dementia represents a challenge for public health in developing countries with rapid demographic transitions, such as those occurring in the Caribbean. We propose expanding our research efforts to rural areas and explore gene by environment interactions on dementia risk. Emphasis on genetic family studies and admixture and new clinical trials with Hispanic representation, should continue. The development of brain banks and the implementation of biomarker studies are current research priorities. Implementation of our national plans is critical to deal with an aging population with high dementia rates, ideally a true public health-focused approach should aim at social change and emphasize on public-health prevention campaigns directed to addressing modifiable risk factors and developing caregiver and family interventions.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://1066.alz.co.uk/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Universidad Nacional Pedro Henriquez Ureña,

Universidad de Ciencias Médicas de la Habana, University of Puerto Rico. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. JL-R, JL-G, IJ-V, and DA: study concept and design. JL-R, IJ-V, and DA: acquisition, analysis, or interpretation of data. JL-G and DA: drafting of the manuscript. All authors critical revision of the manuscript for important intellectual content. JL-G: project administration. JL-R: study supervision.

FUNDING

This review was supported by grants from the National Institute on Aging of the National Institutes of Health under Award Number R01AG064778, the Alzheimer's Association (SG-20-690363), Ministry of Higher Education Science and Technology (2018-2019-2A3-208) and the World Federation of Neurology (Grants-Aid program). The 10/66 Dementia Research Group's research has been funded by the Welcome Trust Health Consequences of Population Change program (GR066133 – Prevalence phase in Cuba and Brazil; GR080002 – Incidence phase in Peru, Mexico, Argentina, Cuba, Dominican Republic, Venezuela, and China). The content is solely the responsibility of the authors and does not represent the official views of the NIA, AA, MESCYT, WFN or WT.

ACKNOWLEDGMENTS

We acknowledge the participants' altruism and their families and to the 10/66 research group for their contributions to this study.

REFERENCES

1. Nitrini R, Bottino CMC, Albala C, Custodio Capuñay NS, Ketzoian C, Llibre Rodriguez JJ, et al. Prevalence of dementia in Latin America: a collaborative study of population-based cohorts. *Int Psychogeriatrics.* (2009) 21:622–30. doi: 10.1017/S1041610209009430
2. Rodriguez JJL, Ferri CP, Acosta D, Guerra M, Huang Y, Jacob KS, et al. Prevalence of dementia in Latin America, India, and China: a population-based cross-sectional survey. *Lancet.* (2008) 372:464–74. doi: 10.1016/S0140-6736(08)61002-8
3. Rocca WA, Petersen RC, Knopman DS, Hebert LE, Evans DA, Hall KS, et al. Trends in the incidence and prevalence of Alzheimer's disease, dementia, and cognitive impairment in the United States. *Alzheimers Dement.* (2011) 7:80–93. doi: 10.1016/j.jalz.2010.11.002
4. Prina AM, Mayston R, Wu Y-T, Prince M. A review of the 10/66 dementia research group. *Soc Psychiatry Psychiatr Epidemiol.* (2018) 2018:1-10. doi: 10.1007/s00127-018-1626-7
5. González HM, Tarraf W, Schneiderman N, Fornage M, Vásquez PM, Zeng D, et al. Prevalence and correlates of mild cognitive impairment among diverse hispanics/Latinos: study of latinos-Investigation of neurocognitive aging results. *Alzheimer's Dement.* (2019) 15:1507–15. doi: 10.1016/j.jalz.2019.08.202
6. Quashie NT, Jones F, Gény LR, Abdulkadri A. Population ageing and sustainable development in the Caribbean: where are we 15 years post MIPAA. *Int J Ageing Dev Countries.* (2018) 2:128–48.
7. Caribbean SC for the W on S the SF for P to M the C of A in LA the, Population C on, Education D of B SS and, The National Academies of Sciences E M. *Aging in Latin America and the Caribbean in Global Perspective.* (2015).
8. United Nations, Department of Economic and Social Affairs, Population Division. *World Population Ageing 2019: Highlights (ST/ESA/SER.A/430).* (2019).
9. Kinsella K. *Strengthening the Scientific Foundation for Policymaking to Meet the Challenges of Aging in Latin America and the Caribbean: Summary of a Workshop*. Washington, DC: The National Academies Press (2015).
10. Moya JC. A continent of immigrants: postcolonial shifts in the Western Hemisphere. *Hisp Am Hist Rev.* (2006) 86:1–28. doi: 10.1215/00182168-86-1-1
11. Rumbaut RG. The making of a people. In: M. Tienda, F. Mitchell, editors. *Hispanics and the Future of America.* National Academies Press (2006). p. 16–65. Available online at: https://ssrn.com/abstract=1877405.
12. Molero AE, Pino-Ramírez G, Maestre GE. High prevalence of dementia in a caribbean population. *Neuroepidemiology.* (2007) 29:107–12. doi: 10.1159/000109824
13. Prince MJ, De Rodriguez JL, Noriega L, Lopez A, Acosta D, Albanese E, et al. The 10/66 dementia research group's fully operationalised DSMIV dementia computerized diagnostic algorithm, compared with the 10/66 dementia algorithm and a clinician diagnosis: a population validation study. *BMC Public Health.* (2008) 8:219. doi: 10.1186/1471-2458-8-219
14. Prince MJ. The 10/66 dementia research group - 10 years on. *Indian J Psychiatry.* (2009) 51(Suppl 1):S8–S15.
15. Prince M, Ferri CP, Acosta D, Albanese E, Arizaga R, Dewey M, et al. The protocols for the 10/66 dementia research group population-based research programme. *BMC Public Health.* (2007) 7:165. doi: 10.1186/1471-2458-7-165
16. Prina AM, Acosta D, Acostas I, Guerra M, Huang Y, Jotheeswaran AT, et al. Cohort profile: the 10/66 study. *Int J Epidemiol.* (2016) 46:dyw056. doi: 10.1093/ije/dyw056
17. Sousa RM, Ferri CP, Acosta D, Guerra M, Huang Y, Jacob K, et al. The contribution of chronic diseases to the prevalence of dependence among older people in latin america, china and india: a 10/66 dementia research group population-based survey. *BMC Geriatr.* (2010) 10:53. doi: 10.1186/1471-2318-10-53
18. Llibre JDJ, López AM, Valhuerdi A, Guerra M, Llibre-Guerra JJ, Sánchez YY, et al. Frailty, dependency and mortality predictors in a cohort of Cuban older adults, 2003-2011. *MEDICC Rev.* (2014) 16:24–30. doi: 10.37757/MR2014.V16.N1.6
19. Prince M, Acosta D, Ferri CP, Guerra M, Huang Y, Rodriguez JJL, et al. Dementia incidence and mortality in middle-income countries, and associations with indicators of cognitive reserve: a 10/66 dementia research group population-based cohort study. *Lancet.* (2012) 380:50–8. doi: 10.1016/S0140-6736(12)60399-7
20. Pasquini L, Llibre Guerra J, Prince M, Chua K-C, Prina AM. Neurological signs as early determinants of dementia and predictors of mortality among older adults in Latin America: a 10/66 study using the NEUROEX assessment. *BMC Neurol.* (2018) 18:163. doi: 10.1186/s12883-018-1167-4
21. Coste EL, Prevalencia LA, Alzheimer D, Demencia DE. Informe ADI/Bupa. *La Demencia en América: el Coste y la Prevalencia del Alzheimer y Otros Tipos de Demencia.* (2013).
22. Prince M, Wimo A, Guerchet M, Gemma-Claire A, Wu Y-T, et al. *World Alzheimer Report 2015: The Global Impact of Dementia - An Analysis of Prevalence, Incidence, Cost and Trends*. London: Alzheimer's Disease International (2015). p. 84. Available online at: http://www.worldalzreport2015.org/
23. Llibre-Rodríguez, J. de J., Valhuerdi-Cepero A, López-Medina AM, Noriega-Fernández L, Porto-Álvarez R, Guerra-HernóndezMA, et al. Cuba's

aging and Alzheimer longitudinal study. *MEDICC Rev.* (2017) 19:31–5. doi: 10.37757/MR2017.V19.N1.6
24. Figueroa R, Steenland K, MacNeil JR, Levey AI, Vega IE. Geographical differences in the occurrence of Alzheimer's disease mortality: United States versus puerto rico. *Am J Alzheimers Dis Other Demen.* (2008) 23:462–9. doi: 10.1177/1533317508321909
25. Moreno-Estrada A, Gravel S, Zakharia F, McCauley JL, Byrnes JK, Gignoux CR, et al. Reconstructing the population genetic history of the caribbean. *PLoS Genet.* (2013) 9:e1003925. doi: 10.1371/journal.pgen.1003925
26. Homburger JR, Moreno-Estrada A, Gignoux CR, Nelson D, Sanchez E, Ortiz-Tello P, et al. Genomic insights into the ancestry and demographic history of South America. *PLoS Genet.* (2015) 11:e1005602. doi: 10.1371/journal.pgen.1005602
27. Mao X, Bigham AW, Mei R, Gutierrez G, Weiss KM, Brutsaert TD, et al. A genomewide admixture mapping panel for hispanic/Latino populations. *Am J Hum Genet.* (2007) 80:1171–8. doi: 10.1086/518564
28. Teruel BM, Rodríguez JJL, McKeigue P, Mesa T TC, Fuentes E, Cepero A AV, et al. Interactions between genetic admixture, ethnic identity, APOE genotype and dementia prevalence in an admixed cuban sample; a cross-sectional population survey and nested case-control study. *BMC Med Genet.* (2011) 12:43. doi: 10.1186/1471-2350-12-43
29. Rajabli F, Feliciano BE, Celis K, Hamilton-Nelson KL, Whitehead PL, Adams LD, et al. Ancestral origin of apoE ε4 Alzheimer disease risk in puerto rican and african american populations. *PLoS Genet.* (2018) 14:e1007791. doi: 10.1371/journal.pgen.1007791
30. Blue EE, Horimoto ARVR, Mukherjee S, Wijsman EM, Thornton TA. Local ancestry at aPOE modifies alzheimer's disease risk in Caribbean hispanics. *Alzheimers Dement.* (2019) 15:1524–32. doi: 10.1016/j.jalz.2019.07.016
31. Cruchaga C, Del-Aguila JL, Saef B, Black K, Fernandez MV, Budde J, et al. Polygenic risk score of sporadic late-onset Alzheimer's disease reveals a shared architecture with the familial and early-onset forms. *Alzheimer's Dement.* (2018) 14:205–14. doi: 10.1016/j.jalz.2017.08.013
32. Kunkle BW, Grenier-Boley B, Sims R, Bis JC, Damotte V, Naj AC, et al. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates a, tau, immunity and lipid processing. *Nat Genet.* (2019) 51:414–30. doi: 10.1038/s41588-019-0358-2
33. Llibre-Guerra JJ, Li Y, Allegri RF, Mendez PC, Surace EI, Llibre-Rodriguez JJ, et al. Dominantly inherited Alzheimer's disease in Latin America: genetic heterogeneity and clinical phenotypes. *Alzheimer's Dement.* (2020) 2020:alz.12227. doi: 10.1002/alz.044794
34. Cruts M, Van Duijn CM, Backhovens H, Van Den Broeck M, Wehnert A, Serneels S, et al. Estimation of the genetic contribution of presenilin-1 and−2 mutations in a population-based study of presenile alzheimer disease. *Hum Mol Genet.* (1998) 7:43–51. doi: 10.1093/hmg/7.1.43
35. DeGiorgio M, Jakobsson M, Rosenberg NA. Explaining worldwide patterns of human genetic variation using a coalescent-based serial founder model of migration outward from Africa. *Proc Natl Acad Sci USA.* (2009) 106:16057–62. doi: 10.1073/pnas.0903341106
36. Athan ES, Williamson J, Ciappa A, Santana V, Romas SN, Lee JH, et al. A founder mutation in presenilin 1 causing early-onset Alzheimer disease in unrelated Caribbean hispanic families. *J Am Med Assoc.* (2001) 286:2257–63. doi: 10.1001/jama.286.18.2257
37. Vardarajan BN, Schaid DJ, Reitz C, Lantigua R, Medrano M, Jiménez-Velázquez IZ, et al. Inbreeding among Caribbean hispanics from the dominican republic and its effects on risk of Alzheimer disease. *Genet Med.* (2015) 17:639–43. doi: 10.1038/gim.2014.161
38. Bertoli Avella AM, Marcheco Teruel B, Llibre Rodriguez JJ, Gomez Viera N, Borrajero Martinez I, Severijnen EA, et al. A novel presenilin 1 mutation (L174 m) in a large cuban family with early onset Alzheimer disease. *Neurogenetics.* (2002) 4:97–104. doi: 10.1007/s10048-002-0136-6
39. Lee JH, Cheng R, Vardarajan B, Lantigua R, Reyes-Dumeyer D, Ortmann W, et al. Genetic modifiers of age at onset in carriers of the g206A mutation in pSEN1 with familial Alzheimer disease among Caribbean hispanics. *JAMA Neurol.* (2015) 72:1043–51. doi: 10.1001/jamaneurol.2015.1424
40. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement.* (2013) 9:63–75.e2. doi: 10.1016/j.jalz.2012.11.007
41. Langa KM, Levine DA. The diagnosis and management of mild cognitive impairment: a clinical review. *JAMA.* (2014) 312:2551–61. doi: 10.1001/jama.2014.13806
42. Robinson L, Tang E, Taylor JP. Dementia: timely diagnosis and early intervention. *BMJ.* (2015) 350:3029. doi: 10.1136/bmj.h3029
43. Ashford JW, Borson S, O'Hara R, Dash P, Frank L, Robert P, et al. Should older adults be screened for dementia? It is important to screen for evidence of dementia! *Alzheimer's Dement.* (2007) 3:75–80. doi: 10.1016/j.jalz.2007.03.005
44. Parra MA, Baez S, Allegri R, Nitrini R, Lopera F, Slachevsky A, et al. Dementia in Latin America assessing the present and envisioning the future. *Neurology.* (2018) 90:222–31. doi: 10.1212/WNL.0000000000004897
45. Gonzalez FJ, Gaona C, Quintero M, Chavez CA, Selga J, Maestre GE. Building capacity for dementia care in Latin America and the Caribbean. *Dement Neuropsychol.* (2014) 8:310–6. doi: 10.1590/S1980-57642014DN84000002
46. Ms RIB, Drsc JJLMPH, Ms AF. Cuba ' s strategy for Alzheimer disease and dementia syndromes. *MEDICC Rev.* (2016) 2016:9-13. doi: 10.37757/MR2016.V18.N4.2
47. Keynejad RC, Dua T, Barbui C, Thornicroft G. WHO mental health gap action programme (mhGAP) intervention guide: a systematic review of evidence from low and middleincome countries. *Evid Based Ment Health.* (2018) 21:29–33. doi: 10.1136/eb-2017-102750
48. Kivipelto M, Mangialasche F, Snyder HM, Allegri R, Andrieu S, Arai H, et al. World-wide FINGERS network: a global approach to risk reduction and prevention of dementia. *Alzheimer's Dement.* (2020) 16:1078–94. doi: 10.1002/alz.12123

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

BRIEF RESEARCH REPORT
published: 01 March 2021
doi: 10.3389/fneur.2021.629251

Association of Leisure Activities With Cognitive Impairment and Dementia in Older Adults in Colombia: A SABE-Based Study

Alejandra Guerrero Barragán[1,2,3,4]*, *Diego Lucumí*[3] and *Brian Lawlor*[1,2,5]

[1] Global Brain Health Institute, Trinity College Dublin, Dublin, Ireland, [2] Global Brain Health Institute, University of California, San Francisco, San Francisco, CA, United States, [3] Escuela de Gobierno, Universidad de los Andes, Bogotá, Colombia, [4] Unidad de Servicios de Salud Occidente de Kennedy, Servicio de Neurología, Bogotá, Colombia, [5] Department of Psychiatry, Mercer's Institute for Successful Ageing, St. James's Hospital, Dublin, Ireland

Observational and interventional studies suggest that participation in leisure activities may help protect against cognitive decline in older people. This study aimed to examine the association between participation in leisure activities and cognitive impairment in older adults in Colombia. Data for this study were derived from the Colombian National Survey of Aging (SABE 2015), a cross-sectional survey with a sample size of 23,694 older adults representing the total population (mean age, 70.8 years; 57.3% females). Cognitive impairment was classified as cognitive impairment without dementia (CIWD) and dementia, according to the revised version of the Folstein Mini-Mental State Examination and the Lawton and Brody functional scale. Leisure activities were evaluated using six items of a questionnaire. Sex-stratified multinomial regression models were used to analyze the association of leisure activities with CIWD and dementia after adjusting for educational attainment, literacy, and other potential confounders. In adjusted models for men, leisure activities in later life were associated with a decreased risk of CIWD (odds ratio [OR], 0.73; 95% confidence interval [CI], 0.68–0.78) and dementia (OR, 0,52; 95% CI, 0.48–0.58). For women, leisure activities in later life were associated with a decreased risk of CIWD (OR, 0.72; 95% CI, 0.66–0.78) and dementia (OR, 0.48; 95% CI, 0.43–0.53). The findings suggest that greater participation in leisure activities in later life may act as a protective factor against CIWD and dementia among older adults in Colombia, independent of educational attainment and literacy.

Keywords: prevention, cognitive reserve, leisure activities, dementia, cognitive impairment

OPEN ACCESS

Edited by:
Huali Wang,
Peking University Sixth Hospital, China

Reviewed by:
Andreas Ihle,
Université de Genève, Switzerland
Robinson Ramírez-Vélez,
Public University of Navarre, Spain

***Correspondence:**
Alejandra Guerrero Barragán
alejandra.guerrero@gbhi.org

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: *24 November 2020*
Accepted: *26 January 2021*
Published: *01 March 2021*

Citation:
Guerrero Barragán A, Lucumí D and Lawlor B (2021) Association of Leisure Activities With Cognitive Impairment and Dementia in Older Adults in Colombia: A SABE-Based Study. Front. Neurol. 12:629251. doi: 10.3389/fneur.2021.629251

INTRODUCTION

With a rise in global life expectancy, the prevalence of dementia is rising. A new diagnosis of dementia is reported every 3 s. Currently, the disease affects more than 50 million people globally (1), 50% of those living in middle- and low-income countries. It is expected that this number will rise to 63% in 2030 and 68% in 2050 (2), with the Americas being one of the most affected regions with increasing prevalence and incidence rates of dementia (3).

Several protective factors for dementia have been described in the literature (4). Leisure activities, a term that refers to a range of tasks and activities outside work-related activities is

a promising factor for dementia prevention (5). Leisure activities can have a multidimensional profile, manifesting mental, social, and physical involvement (6). These activities are attractive, pleasant, and motivating to the individual and are more likely to be sustained over time (7, 8). Leisure activities usually constitute a relatively large part of daily life post-retirement and may provide mental stimulation, social engagement, and physical activity (6). Systematic reviews have found evidence suggesting that participation in leisure activities might significantly contribute to the prevention of later-life cognitive decline as a risk-preventing factor (5, 9). The most common categories associated with the preventive effect of leisure activities are cognitive, physical, and social activities (5, 10–12). Despite these benefits, there is a lack of standard definitions, measures, and methods for studying the role of leisure activities and their protective effects.

The most common explanatory mechanism for the preventive effect of leisure activities is that of the cognitive reserve theory (5, 13). The cognitive reserve theory suggests that innate intelligence or life experiences such as educational or occupational attainments may supply a reserve in the form of skill sets or repertoires that empower the brain to tolerate atrophies and insults and, as a result, allow some people to cope with progressing dementia better than others and delay symptom onset (14, 15). The cognitive reserve cannot be observed or directly measured, and proxy measures such as education, premorbid intelligence (IQ), linguistic ability, and occupational complexity are often used (14). Several studies have proposed that engagement in leisure activities may result in more functionally efficient or resilient cognitive networks or in recruiting alternate networks, providing a cognitive reserve that prevents or delays the onset of dementia (16–18). In this regard, it is unclear whether a high cognitive reserve delays symptoms onset, but any noticeable delay, for example, 1 or 2 years, would translate into tremendous public health benefits by reducing the prevalence of dementia in the population (14). While characteristics such as education and intelligence are relatively stable from young adulthood, there is increasing interest in the role of leisure activities in building up a cognitive reserve (14).

Although maintaining or building a cognitive reserve is a possible mechanism for dementia prevention (5, 9, 14), culture, poverty, and inequality are key obstacles to, and drivers of, the need for changes concerning the cognitive reserve. Sections of the society that are most deprived of basic needs, like low and middle income countries (LMIC), require these changes and will greatly benefit from them (4). It has been suggested that a low socioeconomic status (SES) is associated with less access to physical (19) and cognitive stimulating activities (20). In Latin America, low levels of education, high rates of brain injury, poor diet, a sedentary lifestyle, and a high risk of cardiovascular diseases are among the main risk factors behind the rapid growth in the number of people with dementia (21); however, there is a high potential for dementia prevention in the region (4, 22). Thus, there is an urgent need for dementia prevention policies in Latin America to reduce the burden and economic costs of dementia in the region (23–25).

In this study, we detail the association between participation in leisure activities and the risk of developing cognitive impairment without dementia (CIWD), or dementia, using the data from the Colombian National Survey of Aging (SABE 2015) (26). There are few papers focusing on cognitive outcomes from Colombian SABE, the effect of education in early life and the probability of cognitive impairment in later life in Colombia has been recently published (27) as well as the role of gait speed in dementia (28) and the mediating effect of physical fitness on cognitive functioning (29). To the best of our knowledge, this is the first study to analyze this topic in Colombia using this dataset.

MATERIALS AND METHODS

We conducted a secondary data analysis of a cross-sectional study using data from SABE Colombia 2015. SABE Colombia 2015 is the first study in Colombia representative of the national population of those aged at least 60 years. Individuals for SABE Colombia were selected following a multistage area probability sample design with a total sample size of 23,694 participants from 244 municipalities (urban and rural). Data collection took place between April and September 2015 (26). This study was approved by the Institutional Review Board of Universidad de los Andes, code ID 1114/2019.

The dependent variable was cognitive impairment, as measured in SABE 2015. This survey used the revised version of the Folstein Mini-Mental State Examination (MMSE), a validated international scale translated to Spanish (30). A cut-off point of 12 or less indicated cognitive impairment, while a score of 13 or above was normal (26). For dementia, functional impairment was evaluated using four items of the Lawton and Brody functional scale (31): phone use, transport use, handling medicines, and management of money. The lack of functionality for doing at least two of the four activities was defined as dependence and indication of dementia (32). If functional impairment was not detected, participants were classified as CIWD.

Independent variables were educational attainment, literacy (reading and writing), and participation in leisure activities. Educational attainment was established based on the 11 categories reported by SABE 2015. We classified participants into three groups in accordance with their educational qualifications: those who had an educational qualification lower than completion of primary school, those who had completed primary school, and those who had sought further qualifications after completion of high school. Literacy was reported using a yes/no question. Using an 18-item questionnaire reported by SABE 2015, we constructed a 6-item continuous variable for participation in leisure activities, among which five items were considered cognitively challenging (reading, solving math problems, solving puzzles, tabletop games, attending classes or courses) and one item that included physical activity.

Confounding variables included were age in years, area of residence (urban, rural), marital status (married/with a partner, separated/widower, single), living alone (yes/no), health insurance (subsidized, contribute, no affiliation), antecedent of forced displacement during life (yes/no), country region (residence in one of the six geographic areas of Colombia: Atlantic, Oriental, Orinoquia and Amazonia, Bogotá, Central,

TABLE 1 | Descriptive analyses.

Variable	*n*	%
Cognition		
Normal	19.004	80.2
Cognitive Impairment Without Dementia (CIWD)	2.109	8.9
Dementia	2.581	10.8
Residence Area		
Urban	17.189	72.5
Rural	6.505	27.4
Country Region		
Atlantic	6.202	26.1
Oriental	3.583	15.1
Orinoquia and Amazonia	1.394	5.8
Bogotá	2.003	8.45
Central	6.351	26.8
Pacific	4.161	17.5
Sex		
Men	10.112	42.6
Women	13.582	57.3
Marriage Status		
Married/With a Partner	12.557	53
Separated/Widower	8.456	35.7
Single	2.671	11.2
Living Alone		
Yes	2.201	9.2
No	21.493	90.7
Health Affiliation		
Subsidized	14.160	59.82
Contribute	8.998	38.01
No affiliation	512	2.16
Skin Color		
Light	11.465	48.3
Medium	8.706	36.7
Dark	3.523	14.8
Pension		
Yes	1.589	6.7
No	21.97	93.2
Lifetime Occupation		
Manual or dependent worker	15.061	64.89
Boss or independent worker	5.131	22.11
None	3.018	13
Income		
<1 minimum wage	13.468	68.7
Between 1 and 2 minimum wage	5074	25.8
More than 2 minimum wage	1.061	5.4
Physical Capital Tercile		
1	10.062	42.5
2	7.482	31.6
3	6.15	25.9
Educational Attainment		
Less than primary school	14.778	62.6
Completed primary school	6.325	26.8
More than high school	2.498	10.5
Literacy (Writing)		
No	18.523	78.2
Yes	5.149	21.7
Literacy (Reading)		
No	18.264	77.1
Yes	5.407	22.8

Pacific), skin color (light, medium, dark), pension (yes/no), lifetime occupation (manual or dependent worker, boss or independent worker, none), salary (<1 minimum wage, between 1 and 2 minimum wages, more than 2 minimum wages), and physical capital tercile (1–3).

Inclusion and Exclusion Criteria

The present study included the total SABE survey sample: participants aged 60 years and above, non-institutionalized, capable of communicating with the research team and able to provide written informed consent. If the MMSE was below 13 a proxy interview was developed (26).

Participants with missing data for leisure activities participation were excluded from this study.

Statistical Analyses

Descriptive analyses of data were conducted using frequencies and percentages for qualitative variables and means and standard deviations for quantitative variables. Unadjusted odds ratio (OR) was calculated using multinomial regression logistic analyses for dependent and independent variables. Multicollinearity was test using variance inflation factor (VIF). Finally, sex-stratified multinomial regression models were used to examine the association of leisure activities with CI and dementia after adjusting for educational attainment, literacy, and other potential confounders. Results are presented as OR with 95% confidence intervals. All analyses were performed using STATA release 16® (StataCorp LP, College Station, USA).

RESULTS

The sample size of the survey was 23,694 participants, 31 participants with missing data for leisure activities were excluded from this study, the final sample size was 23.663 with a mean age of 70.82 years (standard deviation [SD] 8.20); 57.3% were women. Most participants had an educational qualification lower than completion of primary school (62.6%), followed by those who had completed primary school (26.8%) and sought further qualifications after completion of high school (10.5%). Literacy was reported as 78.2 and 77.1% for reading and writing, respectively. The prevalence of CIWD was 8.9 and 10.8% for dementia (**Table 1**). The mean number of leisure activities participated in was 2.02 (SD 1.59) by those with normal

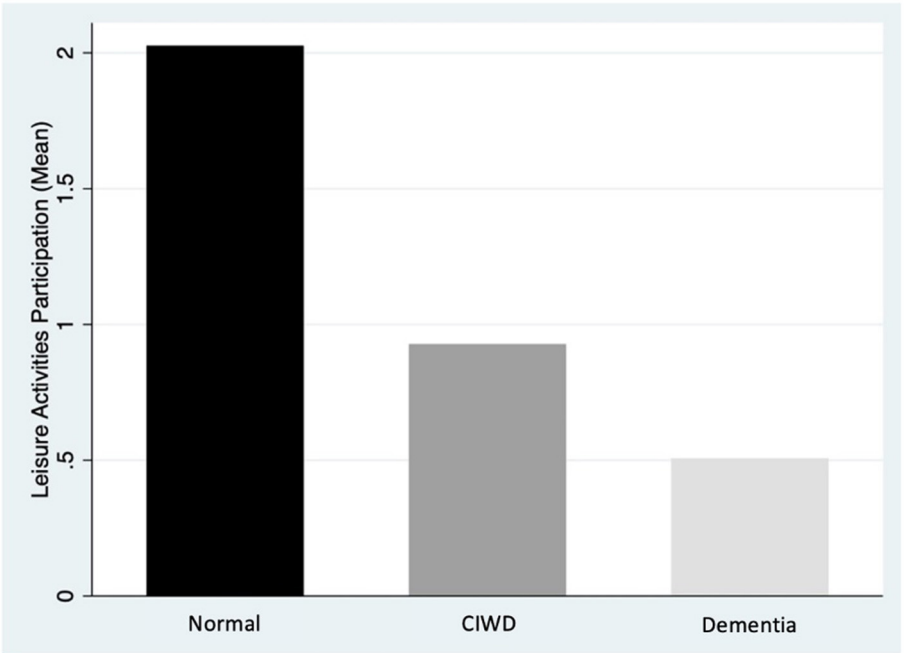


FIGURE 1 | Mean leisure activities participation. CIWD, Cognitive impairment without dementia.

TABLE 2 | Non-adjusted odds ratio for independent variables.

Variable	Cognitive Impairment OR (Confidence Interval)	Dementia OR (Confidence Interval)
Educational Attainment		
Less than primary school	10.18 (7.33–14.15)***	8.54 (6.52–11.17)***
Completed primary school	3.95 (2.80–5.56)***	2.42 (1.81–3.22)***
More than high school	REF	REF
Literacy (Writing)	4.57 (4.16–5.02)***	6.48 (5.95–7.07)***
Literacy (Reading)	4.70 (4.28–5.17)***	6.43 (5.90–7.02)***
Leisure Activities	0.56 (0.54–0.59)***	0.36 (0.34–0.38)***

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Statistical Significance.

cognition, 0.93 (SD 1.17) by those with CIWD, and 0.51 (SD 0.86) by those with dementia (**Figure 1**).

Unadjusted OR estimation showed that people who had an educational qualification lower than the completion of primary school were more likely to develop CIWD (OR 10.18; CI 7.33–14.15) and dementia (OR 8.54; CI 6.52–11.17) than those who had sought further educational qualifications after high school. Reading and writing illiteracy were associated with a higher likelihood of having either CIWD (OR 4.70, CI 4.28–5.17; OR 4.57, CI 4.16–5.02, respectively), or dementia (OR 6.43, CI 5.90–7.02; OR 6.48, CI 5.95–7.07, respectively). Participation in leisure activities was a protective factor against CIWD and dementia (OR 0.56, CI 0.54–0.59; OR 0.36, CI 0.34–0.38, respectively) (**Table 2**).

Analysis of multicollinearity showed high correlation between reading and writing literacy, the former was removed from the multinomial regression models. **Table 3** shows the results for sex-stratified multinomial regression models adjusted for potential confounders. In model 1, those who had an educational qualification lower than the completion of primary school (OR 7.27, CI 4.19–12.61) as well as those who had completed primary school (OR 3.02, CI 1.73–5.30) were significantly more likely to have CIWD than their counterparts with higher educational qualifications. Similar results were found for the association between those who had an educational qualification lower than the completion of primary school (OR 3.30, CI 2.06–5.28) and dementia in comparison with those who had the highest level of education. Model 2 for CIWD persisted with the association for those who had an educational qualification lower than the completion of primary school (OR 3.70, CI 2.12–6.47) and those who had completed primary school (OR 2.65, CI 1.51–4.64). Leisure activities were associated with a decreased risk of CIWD (OR 0.73, CI 0.68–0.78). For dementia, in model 2, the effect of educational attainment disappeared, and inability to read was significantly associated with greater risk (OR 2.77, CI 2.29–3.34). Participation in leisure activities decreased the risk of dementia (OR 0.52, CI 0.48–0.58).

In adjusted models for men, model 1 for CIWD showed significant results for those who had an educational qualification lower than the completion of primary school (OR 4.57, CI 2.71–7.70) and those who had completed primary school (OR 2.47, CI 1.45–4.21). For dementia, results were significant for those who had an educational qualification lower than the completion

TABLE 3 | Multinomial sex-stratified regression models.

Variable	Women				Men			
	Cognitive impairment without dementia		Dementia		Cognitive impairment without dementia		Dementia	
	Model 1[#] OR CI 95%	Model 2[#] OR CI 95%	Model 1[#] OR CI 95%	Model 2[#] OR CI 95%	Model 1[#] OR CI 95%	Model 2[#] OR CI 95%	Model 1[#] OR CI 95%	Model 2[#] OR CI 95%
Educational Attainment								
Less than primary school	7.27*** (4.19–12.61)	3.70*** (2.12–6.47)	3.30*** (2.06–5.28)	1.23 (0.74–2.03)	4.57*** (2.71–7.70)	2.42** (1.41–4.14)	3.46*** (1.97–6.07)	1.53 (0.83–2.83)
Completed primary school	3.02*** (1.73–5.30)	2.65** (1.51–4.64)	1.15 (0.71–1.87)	0.98 (0.59–1.64)	2.47** (1.45–4.21)	2.20** (1.28–3.77)	1.52 (0.84–2.73)	1.31 (0.70–2.45)
More than high school	REF	REF	REF	REF	REF	REF	REF	REF
Literacy (Reading)								
No		2.28*** (1.90–2.73)		2.77** (2.29 –3.34)		1.94*** (1.57–2.41)		1.68*** (1.34–2.11)
Yes		REF		REF		REF		REF
Leisure Activities		0.73*** (0.68–0.78)		0.52*** (0.48–0.58)		0.72*** (0.66–0.78)		0.48*** (0.43–0.53)

[#]*Adjusted for age, area, marital status, living partners, health affiliation, displacement, country region, race, occupation, salary, and physical assets.*
[*]$p < 0.05$, [**]$p < 0.01$, [***]$p < 0.001$.
CI, Confidence Interval.

of primary school (OR 3.46, CI 1.97–6.07). Model 2 for CIWD persisted with the association for those who had an educational qualification lower than the completion of primary school (OR 2.42, CI 1.41–4.14) and those who had completed primary school (OR 2.20, CI 1.28–3.77) and was significant for the inability to read (OR 1.94, CI 1.57–2.41). Leisure activities were associated with a decreased risk of CIWD (OR 0.72, CI 0.66–0.78). For dementia, in model 2, the effect of educational attainment disappeared; results for reading literacy were significant (OR 1.68, CI 1.34–2.11). Leisure activities decreased the risk of dementia (OR 0.48, CI 0.43–0.53).

DISCUSSION

This study's main objective was to investigate the effect of participation in leisure activities on reducing the risk of developing CIWD or dementia in Colombian older adults. We found that for CIWD, participation in leisure activities is linked with educational attainment as well as the ability to read. For dementia, participation in leisure activities in later life might impart a protective effect independent of educational attainment for men and women.

In this sample, more than two-thirds of the participants had low educational attainment. Low educational attainment has been associated with a higher risk of dementia and CIWD (33, 34). Our results suggest that when adjusted for leisure activities, the effect of education is significant for CIWD but not for dementia. Education attainment is an essential factor for cognitive reserve building (35); nonetheless, cognitive reserve is not only determined by education but also by other lifestyle factors in which leisure activities are included (4, 36). In individuals with CIWD, educational attainment has been shown to affect intellectual development during the entire adult life span. However, it was not associated with the cognitive decline rate, in contrast with mid/late-life cognitive activities, which was beneficial and delayed the onset of dementia (37). Previous studies had shown the protective effect of cognitive reserve factors such as education and literacy in LMIC (38). Our study contributes with evidence from this region on the potential role of leisure activities on cognitive reserve building, but further research is needed to clarify this association.

Illiteracy was associated as an independent risk factor in non-adjusted analysis for both CIWD and dementia in previous findings (39). Our study included illiteracy while evaluating writing and reading abilities separately; even though the effect of this difference is not known, it is presumed that acquiring one aspect of literacy over the other could lead to differential dementia risks (39). The ability to read provides the means to acquire and structure new knowledge for language skills and reinforces working memory, visual memory, visuospatial processing, and visuomotor skills (40–42). Our results indicate that an inability to read was associated with a higher risk of dementia independent of educational attainment for women; contradictory results have been found in the literature (39, 43).

The study findings suggest that greater participation in leisure activities in later life may be a protective factor against CIWD and dementia among older adults in Colombia after adjusting for education attainment, illiteracy, and other socioeconomic factors covariates. Previous studies have shown the protective effect of participation in leisure activities with a reduced risk of CIWD and dementia (9) and that the relationship between leisure activities and cognition is not driven by educational attainment (44) or SES (45). In contrast to these findings, a recent study based on longitudinal follow-up failed to support that leisure activity participation can lower the risk of dementia but instead suggested that

reduction in activity participation indicates possible prodromal dementia (46).

This study has several limitations. First, the study was based on a yes/no self-report questionnaire and frequency, intensity, or quality of the activities was measured. Thus, it is not possible to elucidate the underlying mechanisms for the protective effect described here (12). A study found that participation in several activities with varying cognitive complexity levels was a better predictor of cognitive impairment than increased activity frequency (47). We need to know the amount and frequency that generates a protective effect to be able to design a suitable intervention. Second, although gender, demographic, and SES covariates were adjusted, other known risk factors for dementia such as hypertension, diabetes, stroke, and depression were not included (48). In a cohort of Swedish older adults, moderate to high engagement levels in mental, social, and physical leisure activities were associated with a dramatically decreased risk of dementia in people with diabetes (49). Third, education was measured by years of school completed, and there was no measure of the quality of education. Higher literacy may be a more sensitive marker of cognitive reserve than higher education (50); thus we cannot rule out the possibility that leisure activities' protective effect is dependent on education. Further research is needed to clarify the association between education, leisure activities, and cognitive impairment. Furthermore, data from this study comes from a cross-sectional survey; long term, population-based or representative cohort studies are needed to estimate with more precision the role of lifestyle choices like leisure activities might play in reducing dementia risk (51).

Despite these limitations, this is the first study that demonstrates the protective effect of leisure activities using a survey representative of the Colombian population to the best of our knowledge. The public health implications from this finding are related to the importance of increasing late-life participation in leisure activities, their potential role in late-life cognition, and its benefits in people with and without cognitive impairment (52). Nevertheless, further research is needed to determine the amount of exposure, intervention period, and frequency for designing an effective intervention (53). The available research evidence suggests that it is not too late to increase physical and cognitive activity in old age (14) and policymaking for dementia primary prevention needs evidence for non-pharmacological interventions aiming to increase cognitive reserve (54). More research is required to stablish more reliable conclusions for dementia preventive factors and potential interventions.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the user agreement does not permit sharing the data directly. Requests to access the datasets should be directed to the Colombian Ministry of Health (repositorio@minsalud.gov.co).

ETHICS STATEMENT

This study was a secondary data analysis approved by the Institutional Review Board of Universidad de los Andes, code ID 1114/2019. And it was consider an investigation without risk according to Colombian Ministry of Health laws.

AUTHOR CONTRIBUTIONS

AG and DL were responsible for the study design and data analyses. AG was responsible for drafting the manuscript and interpretation of the findings. DL and BL provided critical feedback on drafts, and approved the final manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the Alzheimer's Association and Alzheimer's Society (GBHI ALZ UK-20-640663). AG is an Atlantic Fellow for Equity in Brain Health and received fellowships from the Global Brain Health Institute.

REFERENCES

1. Alzheimer's Disease International. *From Plan to Impact: Progress Towards Targets of the Global Action Plan on Dementia*. London: Alzheimer's Disease International (2018).
2. Alzheimer's Disease International. *World Alzheimer Report 2015- The Global Impact of Dementia: An Analysis of Prevalence, Incidence, Cost and Trends*. London: Alzheimer's Disease International (2015).
3. Organizacion Panamericana de la Salud ADI. *Demencia: Una Prioridad de Salud Publica*. Washington: Organizacion Panamericana de la Salud (2013).
4. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. (2020) 396:413–46. doi: 10.1016/S0140-6736(20)30367-6
5. Fallahpour M, Borell L, Luborsky M, Nygård L. Leisure-activity participation to prevent later-life cognitive decline: a systematic review. *Scand J Occup Ther*. (2015) 23:162–97. doi: 10.3109/11038128.2015.1102320
6. Karp A, Paillard-Borg S, Wang HX, Silverstein M, Winblad B, Fratiglioni L. Mental, physical and social components in leisure activities equally contribute to decrease dementia risk. *Dement Geriatr Cogn Disord*. (2006) 21:65–73. doi: 10.1159/000089919
7. Wa Lam LC, Cheng ST. Maintaining long-term adherence to lifestyle interventions for cognitive health in late life. *Int Psychogeriatr*. (2013) 25:171–3. doi: 10.1017/S1041610212001603
8. Cheng ST, Chow PK, Yu ECS, Chan ACM. Leisure activities alleviate depressive symptoms in nursing home residents with very mild or mild dementia. *Am J Geriatr Psychiatry*. (2012) 20:904–8. doi: 10.1097/JGP.0b013e3182423988
9. Yates LA, Ziser S, Spector A, Orrell M. Cognitive leisure activities and future risk of cognitive impairment and dementia: systematic review and meta-analysis. *Int Psychogeriatr*. (2016) 28:1791–806. doi: 10.1017/S1041610216001137
10. Tolppanen AM, Solomon A, Kulmala J, Kåreholt I, Ngandu T, Rusanen M, et al. Leisure-time physical activity from mid- to late life, body mass index, and risk of dementia. *Alzheimers Dement*. (2015) 11:434–43.e6. doi: 10.1016/j.jalz.2014.01.008

11. Akbaraly TN, Portet F, Fustinoni S, Dartigues JF, Artero S, Rouaud O, et al. Leisure activities and the risk of dementia in the elderly: results from the three-city study. *Neurology*. (2009) 73:854–61. doi: 10.1212/WNL.0b013e3181b7849b
12. Sajeev G, Weuve J, Jackson JW, Vanderweele TJ, Bennett DA, Grodstein F, et al. Late-life cognitive activity and dementia. *Epidemiology*. (2016) 27:732–42. doi: 10.1097/EDE.0000000000000513
13. Scarmeas N, Stern Y. Cognitive reserve and lifestyle. *J Clin Exp Neuropsychol*. (2003) 25:625–33. doi: 10.1076/jcen.25.5.625.14576
14. Cheng ST. Cognitive reserve and the prevention of dementia: the role of physical and cognitive activities. *Curr Psychiatry Rep*. (2016) 18:85. doi: 10.1007/s11920-016-0721-2
15. Stern Y. Cognitive reserve and Alzheimer disease. *Alzheimer Dis Assoc Disord*. (2006) 20:112–7. doi: 10.1097/01.wad.0000213815.20177.19
16. Scarmeas N, Levy G, Tang M-X, Manly J, Stern Y. Influence of leisure activity on the incidence of Alzheimer's Disease. *Neurology*. (2001) 57:2236–42. doi: 10.1212/WNL.57.12.2236
17. Crowe M, Andel R, Pedersen NL, Johansson B, Gatz M. Does participation in leisure activities lead to reduced risk of Alzheimer's disease? A prospective study of Swedish twins. *J Gerontol Ser B Psychol Sci Soc Sci*. (2003) 58:249–55. doi: 10.1093/geronb/58.5.P249
18. Richards M, Hardy R, Wadsworth MEJ. Does active leisure protect cognition? Evidence from a national birth cohort. *Soc Sci Med*. (2003) 56:785–92. doi: 10.1016/S0277-9536(02)00075-8
19. Cerin E, Leslie E. How socio-economic status contributes to participation in leisure-time physical activity. *Soc Sci Med*. (2008) 66:2596–609. doi: 10.1016/j.socscimed.2008.02.012
20. Cassarino M, Setti A. Environment as 'Brain Training': a review of geographical and physical environmental influences on cognitive ageing. *Ageing Res Rev*. (2015) 23:167–82. doi: 10.1016/j.arr.2015.06.003
21. Gonzalez FJ, Gaona C, Quintero M, Chavez CA, Selga J, Maestre GE. Building capacity for dementia care in Latin America and the Caribbean Francisco. *Dement e Neuropsychol*. (2014) 8:310–6. doi: 10.1590/S1980-57642014DN84000002
22. Mukadam N, Sommerlad A, Huntley J, Livingston G. Population attributable fractions for risk factors for dementia in low-income and middle-income countries: an analysis using cross-sectional survey data. *Lancet Glob Heal*. (2019) 7:e596–603. doi: 10.1016/S2214-109X(19)30074-9
23. Custodio N, Wheelock A, Thumala D, Slachevsky A. Dementia in Latin America: epidemiological evidence and implications for public policy. *Front Aging Neurosci*. (2017) 9:221. doi: 10.3389/fnagi.2017.00221
24. Baez S, Ibáñez A. Dementia in Latin America: an emergent silent tsunami. *Front Aging Neurosci*. (2016) 8:253. doi: 10.3389/fnagi.2016.00253
25. Parra MA, Baez S, Allegri R, Nitrini R, Lopera F, Slachevsky A, et al. Dementia in Latin America Assessing the present and envisioning the future. *Neurology*. (2018) 90:222–31. doi: 10.1212/WNL.0000000000004897
26. Gomez F, Corchuelo J, Curcio CL, Calzada MT, Mendez F. SABE Colombia: survey on health, well-being, and aging in Colombia - study design and protocol. *Curr Gerontol Geriatr Res*. (2016) 2016:7910205. doi: 10.1155/2016/7910205
27. Donovan GO, Hamer M, Sarmiento OL, Hessel P. Education in early life markedly reduces the probability of cognitive impairment in later life in Colombia. *Sci Rep*. (2020) 10:17685. doi: 10.1038/s41598-020-74822-2
28. Garcia-Cifuentes E, Márquez I, Vasquez D, Aguillon D, Borda MG, Lopera F, et al. The role of gait speed in dementia: a secondary analysis from the SABE Colombia study. *Dement Geriatr Cogn Disord*. (2020) 1–8. doi: 10.1159/000510494
29. Pérez-Sousa MÁ, del Pozo-Cruz J, Olivares PR, Cano-Gutiérrez CA, Izquierdo M, Ramírez-Vélez R. Role for physical fitness in the association between age and cognitive function in older adults: a mediation analysis of the SABE Colombia study. *Int J Environ Res Public Health*. (2021) 18:751. doi: 10.3390/ijerph18020751
30. Icaza MG, Albala C. *Minimental State Examinations (MMSE) del Estudio de Demencia en Chile: Analisis Estadistico*. Washington, DC: OPS Investig en Salud Pública Doc Técnicos. (1999) p. 7.
31. Luck T, Luppa M, Wiese B, Maier W, Den Bussche H Van, Eisele M, et al. Prediction of incident dementia: Impact of impairment in instrumental activities of daily living and mild cognitive impairment-results from the german study on ageing, cognition, and dementia in primary care patients. *Am J Geriatr Psychiatry*. (2012) 20:943–54. doi: 10.1097/JGP.0b013e31825c09bc
32. Ministerio de Salud y Protección Social. Oficina de Protección Social-MINSALUD, Departamento Administrativo de ciencia tecnología e innovación-C-. *SABE Colombia 2015: Estudio Nacional de Salud, Bienestar y Envejecimiento*. Bogotá: Minsalud. (2015).
33. Caamaño-Isorna F, Corral M, Montes-Martínez A, Takkouche B. Education and dementia: a meta-analytic study. *Neuroepidemiology*. (2006) 26:226–32. doi: 10.1159/000093378
34. Sharp ES, Gatz M. Relationship between education and dementia an updated systematic review. *Alzheimer Dis Assoc Disord*. (2011) 25:289–304. doi: 10.1097/WAD.0b013e318211c83c
35. Whalley LJ, Deary IJ, Appleton CL, Starr JM. Cognitive reserve and the neurobiology of cognitive aging. *Ageing Res Rev*. (2004) 3:369–82. doi: 10.1016/j.arr.2004.05.001
36. Polidori MC, Nelles G, Pientka L. Prevention of dementia: focus on lifestyle. *Int J Alzheimers Dis*. (2010) 2010:393579. doi: 10.4061/2010/393579
37. Vemuri P, Lesnick TG, Przybelski SA, Machulda M, Knopman DS, Mielke MM, et al. Association of lifetime intellectual enrichment with cognitive decline in the older population. *JAMA Neurol*. (2014) 71:1017–24. doi: 10.1001/jamaneurol.2014.963
38. Prince M, Acosta D, Ferri CP, Guerra M, Huang Y, Rodriguez JJL, et al. Dementia incidence and mortality in middle-income countries, and associations with indicators of cognitive reserve: a 10/66 Dementia Research Group population-based cohort study. *Lancet*. (2012) 380:50–8. doi: 10.1016/S0140-6736(12)60399-7
39. Arce Rentería M, Vonk JMJ, Felix G, Avila JF, Zahodne LB, Dalchand E, et al. Illiteracy, dementia risk, and cognitive trajectories among older adults with low education. *Neurology*. (2019) 93:E2247–56. doi: 10.1212/WNL.0000000000008587
40. Bramão I, Mendonça A, Faísca L, Ingvar M, Peterson KM, Reis A. The impact of reading and writing skills on a visuo-motor integration task: a comparison between illiterate and literate subjects. *J Int Neuropsychol Soc*. (2007) 13:359–64. doi: 10.1017/S1355617707070440
41. Petersson KM, Reis A, Ingvar M. Cognitive processing in literate and illiterate subjects: a review of some recent behavioral and functional neuroimaging data. *Scand J Psychol*. (2001) 42:251–67. doi: 10.1111/1467-9450.00235
42. Kosmidis MH, Zafiri M, Politimou N. Literacy versus formal schooling: influence. *Arch Clin Neuropsychol*. (2011) 26:575–82. doi: 10.1093/arclin/acr063
43. Zhang M, Katzman R, Salmon D, Jin H, Cai G, Wang Z, et al. The prevalence of dementia and Alzheimer's disease in Shanghai, China: impact of age, gender, and education. *Ann Neurol*. (1990) 27:428–37. doi: 10.1002/ana.410270412
44. Peterson RL, Gilsanz P, George KM, Ackley S, Glymour MM, Mungas DM, et al. Differences in association of leisure time activities and cognition in a racially/ethnically diverse cohort of older adults: findings from the KHANDLE study. *Alzheimers Dement Transl Res Clin Interv*. (2020) 6:1–9. doi: 10.1002/trc2.12047
45. Singh-Manoux A, Richards M, Marmot M. Leisure activities and cognitive function in middle age: Evidence from the Whitehall II study. *J Epidemiol Community Health*. (2003) 57:907–13. doi: 10.1136/jech.57.11.907
46. Sommerlad A, Sabia S, Livingston G, Kivimäki M, Lewis G, Singh-Manoux A. Leisure activity participation and risk of dementia: 18 year follow-up of the Whitehall II Study. *Neurology*. (2020) 95:e2803–15. doi: 10.1212/WNL.0000000000010966
47. Carlson MC, Parisi JM, Xia J, Xue QL, Rebok GW, Bandeen-Roche K, et al. Lifestyle activities and memory: variety may be the spice of life the women's health and aging study II. *J Int Neuropsychol Soc*. (2012) 18:286–94. doi: 10.1017/S135561771100169X
48. Frankish H, Horton R. Prevention and management of dementia: a priority for public health. *Lancet*. (2017) 390:2614–5. doi: 10.1016/S0140-6736(17)31756-7
49. Marseglia A, Wang HX, Rizzuto D, Fratiglioni L, Xu W. Participating in mental, social, and physical leisure activities and having a rich social network reduce the incidence of diabetes-related dementia in a cohort

of Swedish older adults. *Diabetes Care*. (2019) 42:232–9. doi: 10.2337/dc18-1428
50. Kaup AR, Simonsick EM, Harris TB, Satterfield S, Metti AL, Ayonayon HN, et al. Older adults with limited literacy are at increased risk for likely dementia. *J Gerontol Ser A Biol Sci Med Sci*. (2014) 69:900–6. doi: 10.1093/gerona/glt176
51. Henderson VW, Elias MF. Leisure activity for dementia prevention: more work to be done. *Neurology*. (2020) 95:895–6. doi: 10.1212/WNL.0000000000010962
52. Wells RE, Kerr C, Dossett ML, Danhauer SC, Sohl SJ, Sachs BC, et al. Can adults with mild cognitive impairment build cognitive reserve and learn mindfulness meditation? Qualitative theme analyses from a small pilot study. *J Alzheimers Dis*. (2019) 70:825–42. doi: 10.3233/JAD-190191
53. Iizuka A, Suzuki H, Ogawa S, Kobayashi-Cuya KE, Kobayashi M, Takebayashi T, et al. Can cognitive leisure activity prevent cognitive decline in older adults? A systematic review of intervention studies. *Geriatr Gerontol Int*. (2019) 19:469–82. doi: 10.1111/ggi.13671
54. Wu YT, Fratiglioni L, Matthews FE, Lobo A, Breteler MMB, Skoog I, et al. Dementia in western Europe: epidemiological evidence and implications for policy making. *Lancet Neurol*. (2016) 15:116–24. doi: 10.1016/S1474-4422(15)00092-7

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

REVIEW
published: 15 March 2021
doi: 10.3389/fneur.2021.640525

Neuroimaging Research on Dementia in Brazil in the Last Decade: Scientometric Analysis, Challenges, and Peculiarities

Liara Rizzi†, *Ítalo Karmann Aventurato*† *and Marcio L. F. Balthazar**

Department of Neurology, University of Campinas (UNICAMP), Campinas, Brazil

OPEN ACCESS

Edited by:
Agustin Ibanez, Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina

Reviewed by:
Sonia Maria Dozzi Brucki, University of São Paulo, Brazil
Jiu Chen, Nanjing Medical University, China

***Correspondence:**
Marcio L. F. Balthazar
mbalth@unicamp.br

†*These authors have contributed equally to this work and share first authorship*

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: *11 December 2020*
Accepted: *18 February 2021*
Published: *15 March 2021*

Citation:
Rizzi L, Aventurato ÍK and Balthazar MLF (2021) Neuroimaging Research on Dementia in Brazil in the Last Decade: Scientometric Analysis, Challenges, and Peculiarities. Front. Neurol. 12:640525. doi: 10.3389/fneur.2021.640525

The last years have evinced a remarkable growth in neuroimaging studies around the world. All these studies have contributed to a better understanding of the cerebral outcomes of dementia, even in the earliest phases. In low- and middle-income countries, studies involving structural and functional neuroimaging are challenging due to low investments and heterogeneous populations. Outstanding the importance of diagnosing mild cognitive impairment and dementia, the purpose of this paper is to offer an overview of neuroimaging dementia research in Brazil. The review includes a brief scientometric analysis of quantitative information about the development of this field over the past 10 years. Besides, discusses some peculiarities and challenges that have limited neuroimaging dementia research in this big and heterogeneous country of Latin America. We systematically reviewed existing neuroimaging literature with Brazilian authors that presented outcomes related to a dementia syndrome, published from 2010 to 2020. Briefly, the main neuroimaging methods used were morphometrics, followed by fMRI, and DTI. The major diseases analyzed were Alzheimer's disease, mild cognitive impairment, and vascular dementia, respectively. Moreover, research activity in Brazil has been restricted almost entirely to a few centers in the Southeast region, and funding could be the main driver for publications. There was relative stability concerning the number of publications per year, the citation impact has historically been below the world average, and the author's gender inequalities are not relevant in this specific field. Neuroimaging research in Brazil is far from being developed and widespread across the country. Fortunately, increasingly collaborations with foreign partnerships contribute to the impact of Brazil's domestic research. Although the challenges, neuroimaging researches performed in the native population regarding regional peculiarities and adversities are of pivotal importance.

Keywords: Alzheimer's disease, Brazil, dementia, mild cognitive impaiment, MRI, neuroimaging, scientometric analysis

INTRODUCTION

The majority of people with dementia live in low- and middle-income nations, as is the case of Brazil, the largest and the most populated country in Latin America (LA). LA is experiencing an unprecedented and fast demographic change in the last decades, with the increasing aging of the population (1). As well, Brazil has experienced significant changes in the population age pyramid. Nowadays, the country counts more than 30 million people over 60 years old (14% of the population), and by 2060 this number is projected to increase to 73 million (2). Such a consequence is the increase in the prevalence of dementia cases. In LA is expected a four-fold rise in subjects with dementia by 2050 (3). In Brazil, a recent meta-analysis, which included seven Brazilian studies, found a pooled dementia prevalence of 14.3% (6.8–23.9), but with substantial heterogeneity (4).

Neuroimaging research can provide useful diagnostic images and experimental outcomes that report and support evidence-based clinical practice (5). Moreover, is an essential part of dementia workup to exclude non-neurodegenerative causes of cognitive impairment, as well as to evaluate possible patterns of brain atrophy and cerebrovascular disease (6). Since the creation of the multicentric study Alzheimer's disease Neuroimaging Initiative (ADNI) in the United States in 2004, there was a significant increase both in the number of studies and Magnetic Resonance Imaging (MRI) techniques that have contributed to better understand the cerebral repercussions of the disease, even in the earliest phases (7). After then, different techniques have been improved, like brain volumetry (automated, manual, semi-automated), voxel-based morphometry (VBM), cortical thickness analyses, diffusion tensor imaging (DTI), and functional MRI (fMRI), especially functional connectivity, among others (8).

Outstanding the importance of neuroimaging examinations in dementia, especially in Alzheimer's disease (AD) and mild cognitive impairment (MCI), we aimed to evaluate the scientometric characteristics of Brazilian research in this field in the native population. We analyzed studies published on structural and functional neuroimaging in the last decade in a manner to assess the Brazilian scientific production in this relevant area, especially regarding original research papers. Questions addressed in this review included: journals nationalities and their impact factors, if international coauthorships, authors' gender, location of the neuroimaging research centers in Brazil, the main research funding agencies, number of publications per year, number of total citations for each paper, pathologies studied, and neuroimaging techniques utilized. Moreover, we discussed the peculiarities and challenges that this kind of research could found in a miscegenated population and a resource-limited country.

METHODS

PubMed (https://pubmed.ncbi.nlm.nih.gov/) was queried using the search strategy described in **Supplementary Material 1**. The results were inspected by IKA to select relevant matches. In brief, research papers were selected if they: (a) had a Brazilian author; (b) presented some kind of neuroimaging result, either quantitative or qualitative; (c) either concerned a primary or secondary neurological disease presenting with a dementia syndrome or represented cognitive aspects of the aging process; and (d) were published during or after the year of 2010 until to the date of access in the year of 2020.

Papers were classified according to their nature and design (e.g., review, longitudinal design, controlled trial), international participation in authorship, and journal nationality (Brazilian or international), first author gender, and the number of male and female authors. Web of Science (webofknowledge.com) was consulted for the number of citations received by each paper and the journal's impact factor (Journal Citation Reports™-JCR). Original research papers were further inspected and tabulated as to their MRI and other imaging methods (e.g.,18-FDG-PET), number of participants in each group (e.g., AD, MCI, controls), AD biomarker reporting, the Brazilian state where the study was performed, and funding agencies (the latter two were only accessed if the study concerned Brazilian participants).

Statistical analyses were performed using SciPy 1.5.3 (9), pandas 1.1.4 (10), and statsmodels 0.12.1 (11).

RESULTS

Article Selection

Figure 1 shows schematically the article selection process. The PubMed search resulted in 300 matches from which 135 met the aforementioned criteria. Thirty-two reviews or perspective articles were selected for a separate analysis. From the remaining 103 original research papers, 74 studied Brazilian subjects, among them: 9 case reports, 55 transversal studies, 8 longitudinal studies, and 2 controlled trials. Case reports were excluded from the main analyses. Selected articles are listed in **Table 1** with the main findings, and in **Supplementary Material 2** with all findings.

Reviews

Review papers found covered a wide range of topics. Nineteen out of 32 papers were published in non-Brazilian journals and 16/32 were coauthored by non-Brazilians. Concerning gender, males were the first authors in 20/32 papers, the median number of male and female authors were 5 and 2, respectively. Publication in international journals was correlated with international coauthorship ($\chi 2 = 4.66$, $p = 0.031$) and marginally correlated with a female first author ($\chi 2 = 3.12$, $p = 0.077$). The number of publications per year is presented in **Figure 2**. Time was not associated with an increasing number of publications during these years (Spearman $\rho = 0.42$, $p = 0.19$).

The median number of citations per article was 7 (IQR 2.75–23.75). A multivariate linear model showed a negative correlation of citation number with the Publication Year ($p = 0.045$). International Coauthorship, Journal Nationality, and First Author Gender showed no correlation. Due to the latency expected for an article to be cited, we repeated this analysis with papers published up to 2015, resulting in a median of 7 (IQR 6–33) citations. Regression results were non-significant. The journal's impact factor (JIF) was available for 21/32 papers, with

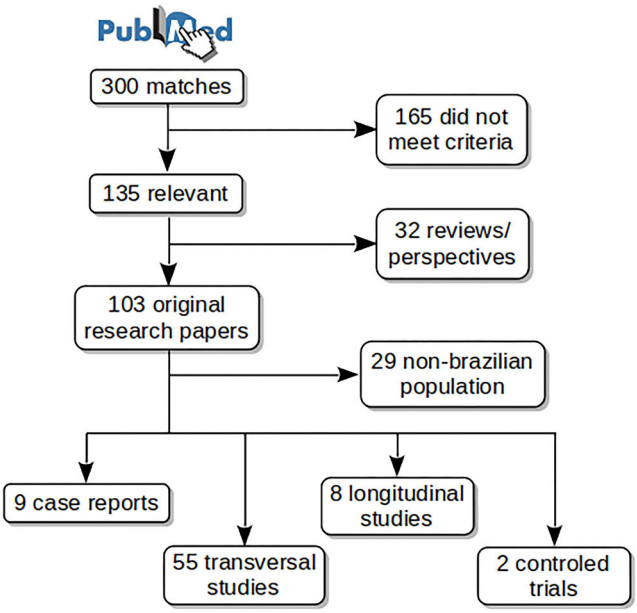


FIGURE 1 | PubMed search results and article selection.

a median of 4.35 (IQR 3.093–8.329). The multivariate regression showed no correlation with other variables.

Original Research

Figure 3 shows the characteristics of the selected papers. Concerning the number of publications per year, there was no trend toward increasing or decreasing the number of publications (Spearman $\rho = 0.13$, $p = 0.70$) (**Figure 3A**). The most studied pathologies were AD (54%, $n = 35$) and MCI (48%, $n = 31$), followed by vascular dementia (4.6%, $n = 3$) (**Figure 3B**). Most studies used morphometric methods (58%, $n = 38$) followed by fMRI (23%, $n = 15$) and closely by DTI (18%, $n = 12$) (**Figure 3C**). Some methods addressed by only a single study nonetheless worth mentioning included spectroscopy (40), texture analysis (21), magnetization transfer ratio, and relaxometry (39).

Regarding gender analyses of original research papers, we found that females are more frequently first-authors (60%). 26/65 of the first authors are male, with a significant time effect for female authorship (Wilcoxon rank-sum test, $p = 0.022$). However, when considering all co-authors, males are more frequent (5/4 ratio). The median number of male and female authors was 5 and 4, respectively, with significantly more male authors per paper (Wilcoxon sign-rank test, $p = 0.001$). These findings might indicate that gender inequalities are less relevant in this specific field. Nineteen-out-of-sixty-five articles were co-authored by non-Brazilians. The most common nationalities among those were North-Americans ($n = 14$), British ($n = 3$), German ($n = 2$), Chilean ($n = 2$) and Swiss ($n = 2$).

There is great heterogeneity in the distribution of the research centers in the country. Research activity in Brazil has been restricted almost entirely to a few centers in the Southeast of Brazil. The vast majority of studies were set in the state of São Paulo (65%, $n = 43$), with studies also from Rio de Janeiro (20%, $n = 13$), Minas Gerais (7.6%, $n = 5$), Rio Grande do Sul (4.5%, $n = 3$), Pernambuco and Goiás (each with 1.5%, $n = 1$) (**Figure 3D**). Funding could be the main driver for publications. The São Paulo Research Foundation (FAPESP) was the most common funding agency, supporting 33 studies, followed by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), responsible for the funding of 28 studies, and Coordenação de Aperfeiçoamento de Pessoal do Ensino Superior (CAPES), with 14 studies being supported. Other agencies worth mentioning include Fundação de Apoio a Pesquisa do Estado do Rio de Janeiro (FAPERJ, 3 studies), Fundação de Apoio a Pesquisa do Estado de Minas Gerais (FAPEMIG, 4 studies), and the Welcome Thrust (3 studies). Seventeen studies did not report the source of resources.

The median number of citations received by original research papers was 5 (IQR 2–18). Considering only articles published up to 2015, the median was 17 (IQR 5–28). We produced three multivariate linear models to better understand what drives citation: (a) a regression for author and journal variables; (b) a regression for imaging technique; and (c) a model for the disease studied. All models were repeated restricting the sample to papers published up to 2015. The first model included Publication Year, International Coauthorship, First Author Gender, and Journal Nationality, showing a significant effect for publication in an international journal ($p = 0.001$) and the publication year ($p < 0.001$). Repeating the analysis with the papers up to 2015, only the effect of publication in an international journal remained significant ($p = 0.037$). None of the imaging techniques were associated with citation numbers either with the full or restricted sample (all *p*s non-significant). AD studies were associated with a higher number of citations ($p = 0.003$) and MCI studies showed a correlation with fewer citations ($p = 0.04$). In the restricted sample, only AD studies remained significant ($p = 0.017$).

JIF was available for 55/65 papers, with a median of 2.94 (IQR 1.90–4.35). The same models described for citations were used to predict JIF. In the first model, omitting Journal Nationality as a regressor, International Coauthorship was marginally associated with a higher JIF ($p = 0.055$). For imaging technique, Amyloid PET ($p = 0.077$) and fMRI ($p = 0.061$) showed a marginal positive correlation with JIF. None of the specific pathologies were associated with JIF.

PECULIARITIES AND CHALLENGES THAT HINDER NEUROIMAGING DEMENTIA RESEARCH IN BRAZIL

Dementia research in low- and middle-income regions is challenging. Like other countries in LA, due to different historical processes that have occurred since the end of the fifteenth century, Brazil has its own social, cultural, racial, and regional peculiarities (147). The heterogeneity makes the diagnosis of dementia and mild cognitive

TABLE 1 | Main findings of articles included in the present review.

Author	Journal	Year	Type	Methods	Pathology	Reference
Balthazar et al.	J Int Neuropsych Soc	2010	T	Morph	AD, MCI	(12)
Balthazar et al.	J Int Neuropsych Soc	2010	T	Morph	AD, MCI	(13)
Porto et al.	Dement Neuropsychol	2010	CR	Quali	PCA	(14)
Chaves et al.	J Neuroinflamm	2010	T	Morph	AD	(15)
Oliveira et al.	J Alzheimers Dis	2010	T	Morph	AD	(16)
de Toledo Ferraz Alves et al.	Curr Opin Psychiatr	2010	R			(17)
Baldaçara et al.	Rev Bras Psiquiatr	2011	L	Morph	AD, MCI	(18)
Caramelli et al.	Dement Neuropsychol	2011	P			(19)
Avila et al.	Neurobiol Aging	2011	T	Morph	Depressed Eld.	(20)
de Oliveira et al.	Am J Neuroradiol	2011	T	Morph, Other	AD, MCI	(21)
Balthazar et al.	Dement Neuropsychol	2011	T	Morph	AD, MCI	(22)
Ferreira et al.	Clinics	2011	R			(23)
Ferreira et al.	Neurobiol Aging	2011	R			(24)
de Souza et al.	Lancet	2011	CR	Quali	HAND	(25)
Caixeta et al.	Clinics	2011	CR	Quali, SPECT	PPA	(26)
Oliveira et al.	Arq Neuro-Psiquiat	2011	T	Morph, DTI	PPA	(27)
de Toledo Ferraz Alves et al.	J Alzheimers Dis	2011	T	Morph	HE	(28)
Vasconcelos et al.	Clinics	2011	T	Morph	AD	(29)
Tiel et al.	Dement Neuropsychol	2012	T	Quali	Vasc	(30)
Lanna et al.	J Neurol Sci	2012	T	Quali, SPECT	Vasc	(31)
Simon et al.	Neurosci Biobehav R	2012	R			(32)
Alves et al.	PLoS ONE	2012	T	Morph, DTI	AD, MCI	(33)
Alves et al.	Dement Neuropsychol	2012	R			(34)
Sudo et al.	Dement Neuropsychol	2012	R			(35)
Borgio et al.	Arq Neuro-Psiquiat	2012	L	Morph	MCI	(36)
Squarzoni et al.	J Alzheimers Dis	2012	T	Morph	HE	(37)
Pedro et al.	Dement Geriatr Cogn	2012	T	Morph	AD, MCI	(38)
Foss et al.	Clinics	2013	T	Morph, Other	HE	(39)
Menezes et al.	Arq Neuro-Psiquiat	2013	T	Morph, Other	AD, MCI	(40)
Radanovic et al.	Expert Rev Neurother	2013	R			(41)
Sudo et al.	Arq Neuro-Psiquiat	2013	T	Quali	MCI	(42)
Dubois et al.	Lancet Neurol	2014	P			(43)
Lee et al.	Brain	2014	T	fMRI, Morph	FTD	(44)
Teipel et al.	Psychiat Res Neuroim	2014	T	Morph	PPA	(45)
Weiler et al.	Curr Alzheimer Res	2014	T	fMRI	AD	(46)
Andrade de Oliveira et al.	J Alzheimers Dis	2014	T	Morph	AD, MCI	(47)
Weiler et al.	Brain Connectivity	2014	T	fMRI	AD, MCI	(48)
Rondina et al.	Front Aging Neurosci	2014	T	Morph	HE	(49)
Balthazar et al.	Hum Brain Mapp	2014	T	fMRI	AD	(50)
Prezzi et al.	Arq Neuro-Psiquiat	2014	CR	Quali	D-EPS	(51)
Weiler et al.	Psychiat Res Neuroim	2014	T	DTI	AD, MCI	(52)
Kilimann et al.	J Alzheimers Dis	2014	L	Morph	AD, MCI	(53)
Ferreira et al.	Rev Bras Psiquiatr	2014	R			(54)
Vasconcelos et al.	Clinics	2014	T	Morph	AD	(55)
Tovar-Moll et al.	PLoS ONE	2014	T	DTI	D-EPS, FDT	(56)
Balthazar et al.	Psychiat Res Neuroim	2014	T	fMRI	AD	(57)
de Oliveira et al.	Acta Neurol Belg	2015	CR	Quali, SPECT	FTD	(58)
Yokoyama et al.	PLOS ONE	2015	T	Morph	HE	(59)
Prado et al.	Dement Neuropsychol	2015	R			(60)
Caixeta et al.	CP & EMH	2015	T	Morph	D-EPS, FTD	(61)

(Continued)

TABLE 1 | Continued

Author	Journal	Year	Type	Methods	Pathology	Reference
Forner et al.	Neurology	2015	T	Quali	CJD	(62)
Hayata et al.	Arq Neuro-Psiquiat	2015	T	Morph	AD	(63)
da Rocha et al.	Dement Neuropsychol	2015	R			(64)
Balardin et al.	Front Aging Neurosci	2015	T	fMRI	MCI	(65)
Weiler et al.	J Alzheimers Dis	2015	L	Morph, DTI	AD	(66)
Coutinho et al.	Int Psychogeriatr	2015	T	Quali	AD, MCI	(67)
Alves et al.	BioMed Res Int	2015	R			(68)
Promteangtrong et al.	Dement Neuropsychol	2015	R			(69)
Promteangtrong et al.	Dement Neuropsychol	2015	R			(70)
Haziot et al.	Dement Neuropsychol	2015	R			(71)
Boots et al.	Arch Clin Neuropsych	2015	T	Morph	HE	(72)
Diniz et al.	Mol Psychiatr	2015	T	Morph, Ami	MCI	(73)
Agosta et al.	CNS Neurosci Ther	2015	R			(74)
Hamelin et al.	Neurob]	2015	T	Morph, Ami	AD	(75)
Grothe et al.	Cereb Cortex	2016	T	Morph, FDG	MCI	(76)
Leuzy et al.	Brain Struct Funct	2016	T	Morph, FDG, Other	FTD	(77)
Resende et al.	eNeurologicalSci	2016	T	Quali	AD, MCI	(78)
Corrêa et al.	J Mag Reson Im	2016	L	Morph, DTI	HAND	(79)
McAleese et al.	BMC Med	2016	R			(80)
Corrêa et al.	J Neuroimaging	2016	T	Morph	HAND	(81)
Teixeira et al.	AGE	2016	T	Morph, DTI	MCI	(82)
Weiler et al.	Neurosci Biobehav R	2016	R			(83)
Wang et al.	P Natl Acad Sci	2016	T	Morph	AD	(84)
Ribeiro et al.	Dement Neuropsychol	2016	R			(85)
Alves et al.	Dement Neuropsychol	2017	R			(86)
Pascoal et al.	Mol Psychiatr	2017	T	Morph, FDG, Ami	HE	(87)
Lajoie et al.	NeuroImage Clin	2017	T	fMRI, Morph	AD	(88)
Vasconcellos et al.	Parkinson's Disease	2017	T	Quali	PD	(89)
Tascone et al.	PLOS ONE	2017	T	Morph	AD	(90)
Ebadi et al.	Front Neurosci	2017	T	DTI	AD, MCI	(91)
De Souza et al.	Prion	2017	CR	Quali	CJD	(92)
Shigaeff et al.	Arch Gerontol Geriat	2017	L	fMRI	EMS	(93)
Squarzoni et al.	Clinics	2017	L	Quali	HE	(94)
Fragoso et al.	RadioGraphics	2017	R			(95)
Radanovic et al.	Dement Neuropsychol	2017	T	Quali	AD, MCI	(96)
Resende et al.	Arq Neuro-Psiquiat	2017	T	DTI	MCI	(97)
Weiler et al.	J Psychiatr Neurosci	2017	T	fMRI	AD, MCI	(98)
Rabelo et al.	Neuroradiol J	2017	T	Quali	AD, MCI	(99)
Corrêa et al.	Neuroradiol J	2017	L	fMRI, Morph, DTI	HAND	(100)
Ramos Bernardes da Silva Filho et al.	NeuroImage Clin	2017	T	Morph	AD	(101)
Swardfager et al.	Alzheimers Dement	2017	T	DTI	AD	(102)
Swardfager et al.	Neurobiol Aging	2017	T	Morph	AD	(103)
Ferreira et al.	Rev Bras Psiquiatr	2017	T	Morph, FDG, SPECT	AD	(104)
Maia da Silva et al.	Front Neurol	2017	R			(105)
Smagula et al.	Am J Geriatr Psychiat	2018	T	fMRI, Morph	HE	(106)
Branco et al.	Psychiat Res Neuroim	2018	T	Morph, DTI	MND	(107)
Simon et al.	Front Aging Neurosci	2018	CT	fMRI, Morph	MCI	(108)
Teixeira et al.	Alzheimers Dement	2018	CT	Morph	MCI	(109)
Weiler et al.	Front Aging Neurosci	2018	T	fMRI	AD, MCI	(110)

(Continued)

TABLE 1 | Continued

Author	Journal	Year	Type	Methods	Pathology	Reference
Bertrand et al.	Neuropsychology	2018	T	Morph	AD	(111)
Ventura et al.	Neuroradiol J	2018	T	fMRI	HAND	(112)
Neale et al.	NeuroImage Clin	2018	R			(113)
Miotto et al.	Neural Plast	2018	R			(114)
Axelrud et al.	Am J Psychiat	2018	T	Morph	Infants	(115)
Resende et al.	Front Aging Neurosci	2018	T	Morph	AD, MCI	(116)
Martins et al.	Dement Neuropsychol	2018	CR	Quali, SPECT	FTD	(117)
Jaswal et al.	Neurobiol Aging	2018	T	Morph	AD	(118)
Rondina et al.	NeuroImage Clin	2018	T	Morph, FDG, SPECT	AD	(119)
Magalhães et al.	Mol Neurobiol	2018	T	fMRI, Morph	AD, MCI	(120)
Swardfager et al.	Neurology	2018	T	Morph	AD, Vasc	(121)
Resende et al.	Cogn Behav Neurol	2018	T	DTI	MCI	(122)
Foss et al.	Dement Neuropsychol	2019	T	Morph	HE	(123)
Axelrud et al.	Neurobiol Aging	2019	T	fMRI	AD Relatives	(124)
Wang et al.	Commun Biol	2019	T	Morph	AD	(125)
Betts et al.	Brain	2019	R			(126)
Staffaroni et al.	Brain	2019	T	fMRI, Morph	FTD	(127)
Drummond et al.	Aging	2019	T	DTI	AD, MCI	(128)
Oliveira et al.	Dement Neuropsychol	2019	R			(129)
Schilling et al.	Mol Psychiatr	2019	T	DTI, FDG, Ami	AD, MCI	(130)
Batista et al.	Cortex	2019	T	fMRI	Vasc	(131)
Therriault et al.	Mol Neurobiol	2019	T	fMRI, Morph, Ami	AD, MCI	(132)
Ferrari et al.	Medicine	2019	L	Morph, FDG	AD	(133)
Yamashita et al.	Neuroinformatics	2019	L	Morph, FDG	AD	(134)
De Carvalho Neto et al.	Prion	2019	CR	Quali	CJD	(135)
Gonçalves et al.	Brain Res	2020	T	Morph	FTD	(136)
Martins-Filho et al.	Dement Geriatr Cogn	2020	R			(137)
Blevins et al.	Acta Neuropathol	2020	R			(138)
Rossini et al.	Clin Neurophysiol	2020	R			(139)
Dalboni da Rocha et al.	Sci Rep	2020	T	DTI	AD, MCI	(140)
Busatto Filho et al.	J Neurosci Res	2020	T	Morph, FDG, Ami	AD, MCI	(141)
Dalboni da Rocha et al.	Brain Imaging Behav	2020	T	DTI	AD, MCI	(142)
Freitas et al.	Arq Neuro-Psiquiat	2020	CR	Quali	CJD	(143)
Ducharme et al.	Brain	2020	R			(144)
Ehrenberg et al.	Alzheimers Res Ther	2020	R			(145)
Simon et al.	Int J Psychophysiol	2020	L	fMRI	MCI	(146)

R, Review; CR, Case Report; P, Perspective; T, Transversal; L, Longitudinal; CT, Clinical Trial; AD, Alzheimer's Disease; FTD, Frontotemporal Dementia; HE, Healthy Elders; Vasc, Vascular Cognitive Impairment; MCI, Mild Cognitive Impairment; D-EPS, Dementia with extrapyramidal symptoms; CJD, Creutzfeld-Jacob Disease; EMS, Elders with metabolic syndrome; HAND, HIV Associated Neurocognitive Disorder; PPA, Primary Progressive Aphasia; PCA, Posterior Cortical Atrophy; Quali, Qualitative MRI evaluation/scales; Morph, Morphometric methods; DTI, Diffusion Tensor Imaging; fMRI, Functional MRI; FDG, [18-F]DG PET Scan; Ami, Amiloid PET Scan.

impairment particularly challenging in comparison with developed countries (148). Regarding specific biological characteristics, for example, we far from understand the particularities of Brazilians miscegenated population. The regional genomic distribution of Brazilians is linked with the different colonization history of each region. Genetic admixture has been influenced by the colonization process, resulting in Brazil becoming a genetically trihybrid population (genomic inheritance of European, African, and Amerindian groups have been traced) (147). Previous epidemiological studies have highlighted that overall dementia prevalence can vary substantially across different ethnic groups and geographical regions (149). These differences in dementia prevalence rates have been attributed to different susceptibility to pathological brain changes in each ethnicity (150). In this sense, neuroimaging research in Brazil should consider these aspects. Neuroimaging studies are required to better characterize how subclinical brain changes might differ among ethnicities, and whether such differences may help explain differences in cognitive performance.

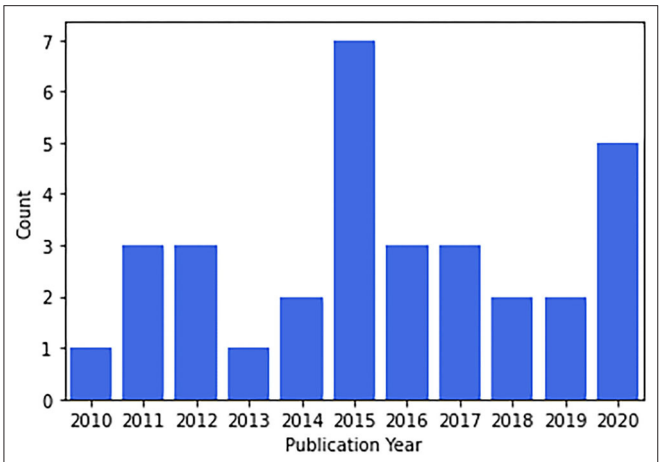


FIGURE 2 | Reviews published by year.

Neuroimaging research has provided evidence that previous or current adversities, such as low socioeconomic status or low levels of educational attainment, may reflect on interindividual variations in brain imaging measurements. Analysis from elderly individuals, recruited in an economically underprivileged area of São Paulo, showed reductions in both regional brain volumes and glucose metabolism in subjects with disadvantageous socioeconomic backgrounds (151, 152). Furthermore, education has a great impact on cognitive performance in older adults (153). A population census found that in 2018 nearly 52.6% of Brazilians over 25 years old did not have finished elementary school, and around 7.2% were unable to read or write (2). Variations in regional brain volumes were verified depending on the level of previous educational attainment (154). In this sense, ecological cognitive tests adapted to Brazilian characteristics (ex: including a wide range of schooling levels, illiterates, and stratified into groups of age and education) are important to be applied to more sophisticated methods, like body fluid biomarkers and neuroimaging.

Among chronic non-communicable diseases, those of the circulatory system are also the main cause of mortality worldwide, including Brazil, which has one of the highest rates in LA (155). Cerebrovascular damage, produced by midlife hypertension, diabetes, dyslipidemia, among other factors, may contribute to the onset and progression of cognitive dysfunction and dementia (156). Besides, Brazilians may have more cerebrovascular damage than other populations, as shown by Grinberg et al. (157) in a clinicopathological study with 1,291 individuals. In Brazil, cerebrovascular damage is one of the most neglected diseases, due to poor control of cardiovascular factors, especially hypertension, the main risk factor (155). In this context, it is surprising that only 4.6% of Brazilian original neuroimaging research was focused on vascular cognitive impairment. Dementia neuroimaging research in Brazil is highly focused on AD. Although AD is the most prevalent form of dementia, our results showed a disproportionate predominance to dementia epidemiology (158). The widespread interest in new drugs for AD may partially explain this finding (159). However, our study also showed that research involving AD was more likely to be cited, potentially feeding a vicious cycle. The underrepresentation of vascular dementia is particularly worrisome, as vascular risk factors and vascular pathology–either exclusive or mixed–are highly prevalent in Brazil. Once improvements in neuroimaging techniques allow detailed and sophisticated evaluation of many manifestations of cerebrovascular diseases, this topic must be considered a priority among Brazilian researchers.

The need for studies with the Brazilian population in this research field is an urgent matter. Scientific research, in general, is far from being fully developed and widespread across the country. Nowadays, even though Brazil is the 13th largest producer of research publications globally, its citation impact has historically been below the world average (160). The present work highlights some of the virtues and faults of the dementia neuroimaging research scenario in Brazil. Most of our findings are consistent with the Brazilian general scientific research background: a significant growth during the first decade of the twenty first century followed by relative stability. Furthermore, the trend toward a highly concentrated scientific production in the Southeast region along with average-to-low research impact also reflects the national tendency (160). Finally, health research is particularly affected by spatial restriction in the national territory, as the cultural, ethnic, and socioeconomic diversity is not captured by the published depictions of our reality.

Brazil has limited wherewithals, sequential financial crises, bad investment of financial resources, and a lack of priority in investing in science in the different governments. All these factors limit the quality of scientific research performed in Brazil and delay the incorporation of novelties to generate original scientific data of global relevance. One of the consequences of these facts was the failure to implement Brazilian ADNI. Lack of fundings, heterogeneity of resources, and lack of specialized centers across the different regions of the country have hampered the implementation of a large national multicenter study. Besides, only recently Brazilian researchers have started studying molecular neuroimaging, with only five amyloid PET studies, and no Tau PET studies in the last decade. Despite these difficulties, Brazilians are studying and refining new neuroimaging methods, such as functional and structural connectivity, DTI, and surface-based morphometry. Two Brazilian centers in São Paulo and Rio Grande do Sul are studying amyloid PET, and collaborative studies are taking place. Comparisons of Brazilian neuroimaging studies with other countries of Latin America are difficult, due to the lack of relevant studies in this research area as they share the same problems found in Brazil. However, our neighbor Argentina is moving forward in the field, with the establishment of the first ADNI of Latin America (161). This program currently accounts for approximately sixty participants that are evaluated by structural MRI analysis, and metabolic and amyloid PET scan (FDG and PiB). This kind of multicentric program notably will assist the development of neuroimaging studies in low- and middle-income nations in the future.

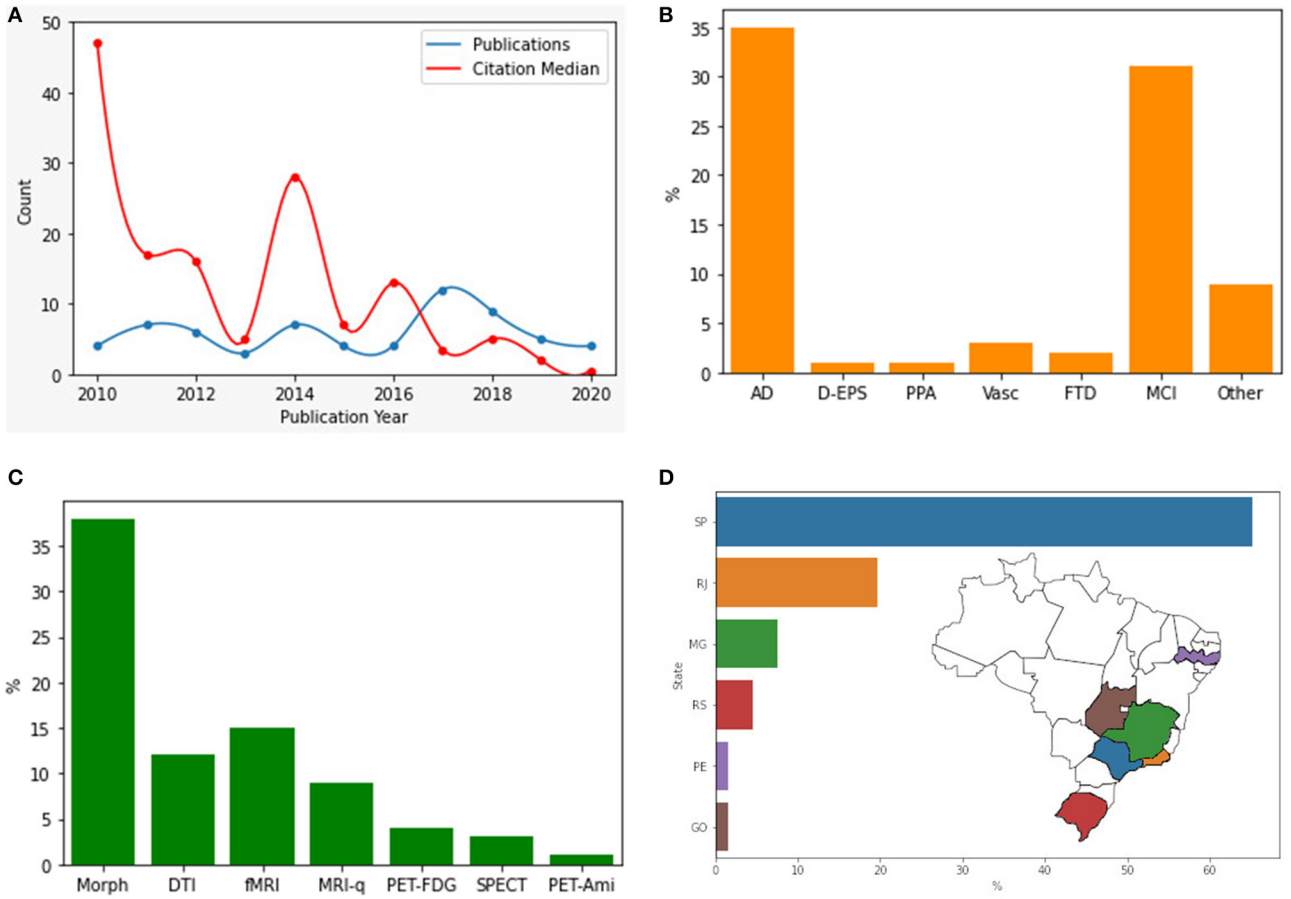


FIGURE 3 | Research articles in different categories. **(A)** Original research articles published by year and citations median. **(B)** Pathology addressed by the article. **(C)** Methodology used. **(D)** Location of main neuroimaging research centers in Brazil. AD, Alzheimer's Disease; D-EPS, Dementia with extrapyramidal symptoms; PPA, Primary Progressive Aphasia; Vasc, Vascular Dementia; FTD, Frontotemporal Dementia; MCI, Mild Cognitive Impairment; Morph, Morphometric; DTI, Diffusion Tensor Imaging; fMRI, functional MRI; MRI-q, MRI qualitative analysis; PET-FDG, 18-Fluorodeoxyglucose positron emission tomography; PET-Ami: amyloid marker positron emission tomography.

Fortunately, increasingly Brazilian researchers are working across country borders, within foreign partnerships, and the resulting papers contribute to the impact of Brazil's domestic research. Although the majority of foreign partnerships analyzed in this review were derived from North America and Europe, there are efforts to develop collaborations with our neighbors of LA. One promising group is the Latin America and Caribbean Consortium on Dementia (LAC-CD), which is a regional organization that oversees and promotes clinical and research activities on dementia. Collaborations like this certainly can set new networks to support research and increase the supply of regional and international grant proposals (162). Taken together, suggests that knowledge and technological exchange can drive the Brazilian research scenario toward a richer production. All the above-mentioned challenges require efforts toward solutions involving clinicians, researchers, and policymakers, to better understand and investigate the dementia context in a continental country such as Brazil.

CONCLUDING REMARKS

As illustrated along with this manuscript, neuroimaging research carried out in low- and middle-income countries, such as Brazil, are challenging. Nonetheless, they are extremely important to increase the global knowledge about brain impacts derived from the inherent characteristics of the population, and their relationship with the development of dementia. Neuroimaging researches performed in the native population regarding regional peculiarities and adversities are of pivotal importance, especially in a resource-limited country facing economic and political adversities. In this sense, neuroimaging studies should address dementia not merely from a clinical perspective, but also in a societal context, considering individuals' environment and peculiarities. Despite the aforementioned limitations, Brazilian researchers in dementia should be encouraged to deepen neuroimaging studies in Alzheimer's spectrum and other prevalent conditions, such as vascular dementia.

Because our focus was neurodegenerative diseases that primarily affect cognition, we did not evaluate normal aging or other conditions that may secondarily lead to dementia, such as Parkinson's disease, Motor Neuron diseases, Epilepsy, or infectious/parasitic diseases common in Brazil. Further studies might consider the whole spectrum of dementias.

AUTHOR CONTRIBUTIONS

All authors contributed to the preparation and writing manuscript and approved the submitted version.

FUNDING

This work was supported by grants from the São Paulo Research Foundation (FAPESP) (grants numbers: 18/15571-7 and 2019/23028-4).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.640525/full#supplementary-material

REFERENCES

1. Custodio N, Wheelock A, Thumala D, Slachevsky A. Dementia in Latin America: epidemiological evidence and implications for public policy. *Front Aging Neurosci*. (2017) 9:221. doi: 10.3389/fnagi.2017.00221
2. IBGE. *Instituto Brasileiro de Geografia e Estatística*. (2020) Available online at: https://www.ibge.gov.br/ (accessed November 10, 2020).
3. Parra MA, Baez S, Allegri R, Nitrini R, Lopera F, Slachevsky A, et al. Dementia in Latin America: assessing the present and envisioning the future. *Neurology*. (2018) 90:222–31. doi: 10.1212/WNL.0000000000004897
4. Farina N, Ibnidris A, Alladi S, Comas-Herrera A, Albanese E, Docrat S, et al. A systematic review and meta-analysis of dementia prevalence in seven developing countries: a STRiDE project. *Glob Public Health*. (2020) 15:1878–93. doi: 10.1080/17441692.2020.1792527
5. Márquez F, Yassa MA. Neuroimaging biomarkers for Alzheimer's d ase. *Mol Neurodegener*. (2019) 14:21. doi: 10.1186/s13024-019-0325-5
6. Arvanitakis Z, Shah RC, Bennett DA. Diagnosis and management of dementia: review. *JAMA*. (2019) 322:1589–99. doi: 10.1001/jama.2019.4782
7. Jack CR, Bernstein MA, Fox NC, Thompson P, Alexander G, Harvey D, et al. The Alzheimer's disease neuroimaging initiative (ADNI): MRI methods. *J Magn Reson Imaging*. (2008) 27:685–91. doi: 10.1002/jmri.21049
8. Weiner MW, Veitch DP, Aisen PS, Beckett LA, Cairns NJ, Cedarbaum J, et al. Impact of the Alzheimer's disease neuroimaging initiative, 2004 to 2014. *Alzheimer's Dement*. (2015) 11:865–84. doi: 10.1016/j.jalz.2015.04.005
9. Virtanen P, Gommers R, Oliphant TE, Haberland M, Reddy T, Cournapeau D, et al. SciPy 1.0: fundamental algorithms for scientific computing in Python. *Nat Methods*. (2020) 17:261–72. doi: 10.1038/s41592-019-0686-2
10. McKinney W, et al. Data structures for statistical computing in python. *Proc Python Sci Conf*. (2010) 445:51–6. doi: 10.25080/Majora-92bf1922-00a
11. Seabold S, Perktold K. Statsmodels J. Econometric and statistical modeling with python. *Proc Python Sci Conf*. (2010) 445:92–6. doi: 10.25080/Majora-92bf1922-011
12. Balthazar ML, Yasuda CL, Pereira FR, Bergo FP, Cendes F, Damasceno BP. Coordinated and circumlocutory semantic naming errors are related to anterolateral temporal lobes in mild AD, amnestic mild cognitive impairment, and normal aging. *J Int Neuropsychol Soc*. (2010) 16:1099–107. doi: 10.1017/S1355617710000998
13. Balthazar ML, Yasuda CL, Cendes F, Damasceno BP. Learning, retrieval, and recognition are compromised in aMCI and mild AD: are distinct episodic memory processes mediated by the same anatomical structures? *J Int Neuropsychol Soc*. (2010) 16:205–9. doi: 10.1017/S1355617709990956
14. Porto FHG, Machado GCL, Morillo LS, Brucki SMD. Progressive posterior cortical dysfunction. *Dement Neuropsychol*. (2010) 4:75–8. doi: 10.1590/S1980-57642010DN40100013
15. Chaves ML, Camozzato AL, Ferreira ED, Piazenski I, Kochhann R, Dall'Igna O, et al. Serum levels of S100B and NSE proteins in Alzheimer's disease patients. *J Neuroinflammation*. (2010) 7:6. doi: 10.1186/1742-2094-7-6
16. Oliveira PP, Nitrini R, Busatto G, Buchpiguel C, Sato JR, Amaro E. Use of SVM methods with surface-based cortical and volumetric subcortical measurements to detect Alzheimer's disease. *J Alzheimers Dis*. (2010) 19:1263–72. doi: 10.3233/JAD-2010-1322
17. de Toledo Ferraz Alves TC, Ferreira LK, Busatto GF. Vascular diseases and old age mental disorders: an update of neuroimaging findings. *Curr Opin Psychiatry*. (2010) 23:491–7. doi: 10.1097/YCO.0b013e32833e339c
18. Baldaçara L, Borgio JG, Moraes WA, Lacerda AL, Montaño MB, Tufik S, et al. Cerebellar volume in patients with dementia. *Braz J Psychiatry*. (2011) 33:122–9. doi: 10.1590/S1516-44462011000200006
19. Caramelli P, Teixeira AL, Buchpiguel CA, Lee HW, Livramento JA, Fernandez LL, et al. Diagnosis of Alzheimer's disease in Brazil: supplementary exams. *Dement Neuropsychol*. (2011) 5:167–77. doi: 10.1590/S1980-57642011DN05030004
20. Avila R, Ribeiz S, Duran FL, Arrais JP, Moscoso MA, Bezerra DM, et al. Effect of temporal lobe structure volume on memory in elderly depressed patients. *Neurobiol Aging*. (2011) 32:1857–67. doi: 10.1016/j.neurobiolaging.2009.11.004
21. de Oliveira MS, Balthazar ML, D'Abreu A, Yasuda CL, Damasceno BP, Cendes F, et al. MR imaging texture analysis of the corpus callosum and thalamus in amnestic mild cognitive impairment and mild Alzheimer disease. *AJNR Am J Neuroradiol*. (2011) 32:60–6. doi: 10.3174/ajnr.A2232
22. Balthazar MLF, Yasuda CL, Lopes TM, Pereira FRS, Damasceno BP, Cendes F. Neural correlates of lexical-semantic memory: a voxel-based morphometry study in mild AD, aMCI and normal aging. *Dement Neuropsychol*. (2011) 5:69–77. doi: 10.1590/S1980-57642011DN05020003
23. Ferreira LK, Busatto GF. Neuroimaging in Alzheimer's disease: current role in clinical practice and potential future applications. *Clinics (São Paulo)*. (2011) 66(Suppl .1):19–24. doi: 10.1590/S1807-59322011001300003
24. Ferreira LK, Diniz BS, Forlenza OV, Busatto GF, Zanetti MV. Neurostructural predictors of Alzheimer's disease: a meta-analysis of VBM studies. *Neurobiol Aging*. (2011) 32:1733–41. doi: 10.1016/j.neurobiolaging.2009.11.008
25. de Souza RK, Martins RT, da Rocha SF, Sato HK, Kowacs PA. Never too old. *Lancet*. (2011) 378:1676. doi: 10.1016/S0140-6736(11)61225-7
26. Caixeta L, Caixeta M. Primary progressive aphasia beginning with a psychiatric disorder. *Clinics (São Paulo)*. (2011) 66:1505–8. doi: 10.1590/S1807-59322011000800035
27. Oliveira FP, Costa JC, Marroni SP, Silva AM, Barreiro SH, Maeda FK, et al. Primary progressive aphasia patients evaluated using diffusion tensor imaging and voxel based volumetry-preliminary results. *Arq Neuropsiquiatr*. (2011) 69:446–51. doi: 10.1590/S0004-282X2011000400007
28. de Toledo Ferraz Alves TC, Scazufca M, Squarzoni P, de Souza Duran FL, Tamashiro-Duran JH, Vallada HP, et al. Subtle gray matter changes in temporo-parietal cortex associated with cardiovascular risk factors. *J Alzheimers Dis*. (2011) 27:575–89. doi: 10.3233/JAD-2011-110827
29. Vasconcelos LeG, Jackowski AP, Oliveira MO, Flor YM, Bueno OF, Brucki SM. Voxel-based morphometry findings in Alzheimer's disease: neuropsychiatric symptoms and disability correlations - preliminary results. *Clinics (São Paulo)*. (2011) 66:1045–50. doi: 10.1590/S1807-59322011000600021
30. Tiel C, Sudo FK, Alves CEO, Alves GS, Ericeira-Valente L, Moreira DM, et al. Behavioral and psychological symptoms and hippocampal atrophy in subcortical ischaemic vascular disease. *Dement Neuropsychol*. (2012) 6:175–9. doi: 10.1590/S1980-57642012DN06030011

31. Lanna ME, Alves CE, Sudo FK, Alves G, Valente L, Moreira DM, et al. Cognitive disconnective syndrome by single strategic strokes in vascular dementia. *J Neurol Sci*. (2012) 322:176–83. doi: 10.1016/j.jns.2012.08.004
32. Simon SS, Yokomizo JE, Bottino CM. Cognitive intervention in amnestic Mild Cognitive Impairment: a systematic review. *Neurosci Biobehav Rev*. (2012) 36:1163–78. doi: 10.1016/j.neubiorev.2012.01.007
33. Alves GS, O'Dwyer L, Jurcoane A, Oertel-Knöchel V, Knöchel C, Prvulovic D, et al. Different patterns of white matter degeneration using multiple diffusion indices and volumetric data in mild cognitive impairment and Alzheimer patients. *PLoS ONE*. (2012) 7:e52859. doi: 10.1371/journal.pone.0052859
34. Alves GS, Sudo FK, Alves CEO, Ericeira-Valente L, Moreira DM, Engelhardt E, et al. Diffusion tensor imaging studies in vascular disease: a review of the literature. *Dement Neuropsychol*. (2012) 6:158–63. doi: 10.1590/S1980-57642012DN06030008
35. Sudo FK, Alves CEO, Alves GS, Ericeira-Valente L, Tiel C, Moreira DM, et al. Dysexecutive syndrome and cerebrovascular disease in non-amnestic mild cognitive impairment: a systematic review of the literature. *Dement Neuropsychol*. (2012) 6:145–51. doi: 10.1590/S1980-57642012DN06030006
36. Borgio JG, Baldaçara L, Moraes WoS, Lacerda AL, Montaño MB, Jackowski AP, et al. Hippocampal volume and CDR-SB can predict conversion to dementia in MCI patients. *Arq Neuropsiquiatr*. (2012) 70:839–42. doi: 10.1590/S0004-282X2012001100003
37. Squarzoni P, Tamashiro-Duran J, Souza Duran FL, Santos LC, Vallada HP, Menezes PR, et al. Relationship between regional brain volumes and cognitive performance in the healthy aging: an MRI study using voxel-based morphometry. *J Alzheimers Dis*. (2012) 31:45–58. doi: 10.3233/JAD-2012-111124
38. Pedro T, Weiler M, Yasuda CL, D'Abreu A, Damasceno BP, Cendes F, et al. Volumetric brain changes in thalamus, corpus callosum and medial temporal structures: mild Alzheimer's disease compared with amnestic mild cognitive impairment. *Dement Geriatr Cogn Disord*. (2012) 34:149–55. doi: 10.1159/000342118
39. Foss MP, Diniz PR, Formigheri P, Salmon CE, Speciali JG, Santos AC. Magnetic resonance imaging and neuropsychological testing in the spectrum of normal aging. *Clinics (São Paulo)*. (2013) 68:1197–205. doi: 10.6061/clinics/2013(09)04
40. Menezes TL, Andrade-Valença LP, Valença MM. Magnetic resonance imaging study cannot individually distinguish individuals with mild cognitive impairment, mild Alzheimer's disease, and normal aging. *Arq Neuropsiquiatr*. (2013) 71:207–12. doi: 10.1590/0004-282X20130003
41. Radanovic M, Pereira FR, Stella F, Aprahamian I, Ferreira LK, Forlenza OV, et al. White matter abnormalities associated with Alzheimer's disease and mild cognitive impairment: a critical review of MRI studies. *Expert Rev Neurother*. (2013) 13:483–93. doi: 10.1586/ern.13.45
42. Sudo FK, Alves CE, Alves GS, Ericeira-Valente L, Tiel C, Moreira DM, et al. White matter hyperintensities, executive function and global cognitive performance in vascular mild cognitive impairment. *Arq Neuropsiquiatr*. (2013) 71:431–6. doi: 10.1590/0004-282X20130057
43. Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL, Blennow K, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol*. (2014) 13:614–29. doi: 10.1016/S1474-4422(14)70090-0
44. Lee SE, Khazenzon AM, Trujillo AJ, Guo CC, Yokoyama JS, Sha SJ, et al. Altered network connectivity in frontotemporal dementia with C9orf72 hexanucleotide repeat expansion. *Brain*. (2014) 137(Pt 11):3047–60. doi: 10.1093/brain/awu248
45. Teipel SJ, Flatz W, Ackl N, Grothe M, Kilimann I, Bokde AL, et al. Brain atrophy in primary progressive aphasia involves the cholinergic basal forebrain and Ayala's nucleus. *Psychiatry Res*. (2014) 221:187–94. doi: 10.1016/j.pscychresns.2013.10.003
46. Weiler M, Fukuda A, Massabki LH, Lopes TM, Franco AR, Damasceno BP, et al. Default mode, executive function, and language functional connectivity networks are compromised in mild Alzheimer's disease. *Curr Alzheimer Res*. (2014) 11:274–82. doi: 10.2174/1567205011666140131114716
47. Andrade de Oliveira A, Carthery-Goulart MT, Oliveira Júnior PP, Carrettiero DC, Sato JR. Defining multivariate normative rules for healthy aging using neuroimaging and machine learning: an application to Alzheimer's disease. *J Alzheimers Dis*. (2015) 43:201–12. doi: 10.3233/JAD-140189
48. Weiler M, Teixeira CV, Nogueira MH, de Campos BM, Damasceno BP, Cendes F, et al. Differences and the relationship in default mode network intrinsic activity and functional connectivity in mild Alzheimer's disease and amnestic mild cognitive impairment. *Brain Connect*. (2014) 4:567–74. doi: 10.1089/brain.2014.0234
49. Rondina JM, Squarzoni P, Souza-Duran FL, Tamashiro-Duran JH, Scazufca M, Menezes PR, et al. Framingham coronary heart disease risk score can be predicted from structural brain images in elderly subjects. *Front Aging Neurosci*. (2014) 6:300. doi: 10.3389/fnagi.2014.00300
50. Balthazar ML, Pereira FR, Lopes TM, da Silva EL, Coan AC, Campos BM, et al. Neuropsychiatric symptoms in Alzheimer's disease are related to functional connectivity alterations in the salience network. *Hum Brain Mapp*. (2014) 35:1237–46. doi: 10.1002/hbm.22248
51. Prezzi ED, Vasconcellos LF, Marussi VH. Overlapping MRI findings in progressive supranuclear palsy - corticobasal syndrome. *Arq Neuropsiquiatr*. (2014) 72:569–70. doi: 10.1590/0004-282X20140065
52. Weiler M, de Campos BM, Nogueira MH, Pereira Damasceno B, Cendes F, Balthazar ML. Structural connectivity of the default mode network and cognition in Alzheimer?s disease. *Psychiatry Res*. (2014) 223:15–22. doi: 10.1016/j.pscychresns.2014.04.008
53. Kilimann I, Grothe M, Heinsen H, Alho EJ, Grinberg L, Amaro E, et al. Subregional basal forebrain atrophy in Alzheimer's disease: a multicenter study. *J Alzheimers Dis*. (2014) 40:687–700. doi: 10.3233/JAD-132345
54. Ferreira LK, Tamashiro-Duran JH, Squarzoni P, Duran FL, Alves TC, Buchpiguel CA, et al. The link between cardiovascular risk, Alzheimer's disease, and mild cognitive impairment: support from recent functional neuroimaging studies. *Braz J Psychiatry*. (2014) 36:344–57. doi: 10.1590/1516-4446-2013-1275
55. Vasconcelos LeG, Jackowski AP, Oliveira MO, Flor YM, Souza AA, Bueno OF, et al. The thickness of posterior cortical areas is related to executive dysfunction in Alzheimer's disease. *Clinics (São Paulo)*. (2014) 69:28–37. doi: 10.6061/clinics/2014(01)05
56. Tovar-Moll F, de Oliveira-Souza R, Bramati IE, Zahn R, Cavanagh A, Tierney M, et al. White matter tract damage in the behavioral variant of frontotemporal and corticobasal dementia syndromes. *PLoS ONE*. (2014) 9:e102656. doi: 10.1371/journal.pone.0102656
57. Balthazar ML, de Campos BM, Franco AR, Damasceno BP, Cendes F. Whole cortical and default mode network mean functional connectivity as potential biomarkers for mild Alzheimer's disease. *Psychiatry Res*. (2014) 221:37–42. doi: 10.1016/j.pscychresns.2013.10.010
58. de Oliveira FF, de Barros LA, Bertolucci PH. A patient with agrammatic primary progressive aphasia developing frontotemporal dementia. *Acta Neurol Belg*. (2015) 115:763–6. doi: 10.1007/s13760-015-0446-8
59. Yokoyama JS, Lee AK, Takada LT, Busovaca E, Bonham LW, Chao SZ, et al. Apolipoprotein ε4 is associated with lower brain volume in cognitively normal Chinese but not white older adults. *PLoS ONE*. (2015) 10:e0118338. doi: 10.1371/journal.pone.0118338
60. Prado LGR, Bicalho ICS, Magalhães D, Caramelli P, Teixeira AL, de Souza LC. C9ORF72 and the FTD-ALS spectrum: a systematic review of neuroimaging studies. *Dement Neuropsychol*. (2015) 9:413–21. doi: 10.1590/1980-57642015DN94000413
61. Caixeta L, Vieira RT, Paes F, Carta MG, Nardi AE, Arias-Carrión O, et al. Comparative study of subcortical atrophy in patients with frontotemporal dementia and dementia with extrapyramidal signs. *Clin Pract Epidemiol Ment Health*. (2015) 11:125–9. doi: 10.2174/1745017901511010125
62. Forner SA, Takada LT, Bettcher BM, Lobach IV, Tartaglia MC, Torres-Chae C, et al. Comparing CSF biomarkers and brain MRI in the diagnosis of sporadic Creutzfeldt-Jakob disease. *Neurol Clin Pract*. (2015) 5:116–25. doi: 10.1212/CPJ.0000000000000111
63. Hayata TT, Bergo FP, Rezende TJ, Damasceno A, Damasceno BP, Cendes F, et al. Cortical correlates of affective syndrome in dementia due to Alzheimer's disease. *Arq Neuropsiquiatr*. (2015) 73:553–60. doi: 10.1590/0004-282X20150068
64. da Rocha AJ, Nunes RH, Maia ACM. Dementia in motor neuron disease: reviewing the role of MRI in diagnosis. *Dement Neuropsychol*. (2015) 9:369–79. doi: 10.1590/1980-57642015DN94000369

65. Balardin JB, Batistuzzo MC, Martin MaG, Sato JR, Smid J, Porto C, et al. Differences in prefrontal cortex activation and deactivation during strategic episodic verbal memory encoding in mild cognitive impairment. *Front Aging Neurosci*. (2015) 7:147. doi: 10.3389/fnagi.2015.00147
66. Weiler M, Agosta F, Canu E, Copetti M, Magnani G, Marcone A, et al. Following the spreading of brain structural changes in Alzheimer's disease: a longitudinal, multimodal MRI study. *J Alzheimers Dis*. (2015) 47:995–1007. doi: 10.3233/JAD-150196
67. Coutinho G, Drummond C, de Oliveira-Souza R, Moll J, Tovar-Moll F, Mattos P. Immediate story recall in elderly individuals with memory complaints: how much does it contribute to memory assessment? *Int Psychogeriatr*. (2015) 27:1679–86. doi: 10.1017/S1041610215000307
68. Alves GS, Oertel Knöchel V, Knöchel C, Carvalho AF, Pantel J, Engelhardt E, et al. Integrating retrogenesis theory to Alzheimer's disease pathology: insight from DTI-TBSS investigation of the white matter microstructural integrity. *Biomed Res Int*. (2015) 2015:291658. doi: 10.1155/2015/291658
69. Promteangtrong C, Kolber M, Ramchandra P, Moghbel M, Houshmand S, Schöll M, et al. Multimodality imaging approach in Alzheimer disease. Part I: structural MRI, functional MRI, diffusion tensor imaging and magnetization transfer imaging. *Dement Neuropsychol*. (2015) 9:318–29. doi: 10.1590/1980-57642015DN94000318
70. Promteangtrong C, Kolber M, Ramchandra P, Moghbel M, Houshmand S, Schöll M, et al. Multimodality imaging approaches in Alzheimer's disease. Part II: 1H MR spectroscopy, FDG PET and Amyloid PET. *Dement Neuropsychol*. (2015) 9:330–42. doi: 10.1590/1980-57642015DN94000330
71. Haziot MEJ, Barbosa Junior SP, Vidal JE, de Oliveira FTM, de Oliveira ACP. Neuroimaging of HIV-associated neurocognitive disorders. *Dement Neuropsychol*. (2015) 9:380–4. doi: 10.1590/1980-57642015DN94000380
72. Boots EA, Schultz SA, Almeida RP, Oh JM, Koscik RL, Dowling MN, et al. Occupational complexity and cognitive reserve in a middle-aged Cohort at risk for Alzheimer's disease. *Arch Clin Neuropsychol*. (2015) 30:634–42. doi: 10.1093/arclin/acv041
73. Diniz BS, Sibille E, Ding Y, Tseng G, Aizenstein HJ, Lotrich F, et al. Plasma biosignature and brain pathology related to persistent cognitive impairment in late-life depression. *Mol Psychiatry*. (2015) 20:594–601. doi: 10.1038/mp.2014.76
74. Agosta F, Weiler M, Filippi M. Propagation of pathology through brain networks in neurodegenerative diseases: from molecules to clinical phenotypes. *CNS Neurosci Ther*. (2015) 21:754–67. doi: 10.1111/cns.12410
75. Hamelin L, Bertoux M, Bottlaender M, Corne H, Lagarde J, Hahn V, et al. Sulcal morphology as a new imaging marker for the diagnosis of early onset Alzheimer's disease. *Neurobiol Aging*. (2015) 36:2932–9. doi: 10.1016/j.neurobiolaging.2015.04.019
76. Grothe MJ, Heinsen H, Amaro E, Grinberg LT, Teipel SJ. Cognitive correlates of basal forebrain atrophy and associated cortical hypometabolism in mild cognitive impairment. *Cereb Cortex*. (2016) 26:2411–26. doi: 10.1093/cercor/bhv062
77. Leuzy A, Zimmer ER, Dubois J, Pruessner J, Cooperman C, Soucy JP, et al. In vivo characterization of metabotropic glutamate receptor type 5 abnormalities in behavioral variant FTD. *Brain Struct Funct*. (2016) 221:1387–402. doi: 10.1007/s00429-014-0978-3
78. Resende EPF, Costa-Silva L, Carmona KC, Machado TH, Machado JCB, Guimarães HC, et al. Ischemic cerebrovascular burden evaluated by magnetic resonance imaging in an elderly Brazilian community: the Pietà study. *eNeurologicalSci*. (2016) 5:30–4. doi: 10.1016/j.ensci.2016.11.011
79. Corrêa DG, Zimmermann N, Tukamoto G, Doring T, Ventura N, Leite SC, et al. Longitudinal assessment of subcortical gray matter volume, cortical thickness, and white matter integrity in HIV-positive patients. *J Magn Reson Imaging*. (2016) 44:1262–9. doi: 10.1002/jmri.25263
80. McAleese KE, Alafuzoff I, Charidimou A, De Reuck J, Grinberg LT, Hainsworth AH, et al. Post-mortem assessment in vascular dementia: advances and aspirations. *BMC Med*. (2016) 14:129. doi: 10.1186/s12916-016-0676-5
81. Corrêa DG, Zimmermann N, Netto TM, Tukamoto G, Ventura N, de Castro Bellini Leite S, et al. Regional cerebral gray matter volume in HIV-positive patients with executive function deficits. *J Neuroimaging*. (2016) 26:450–7. doi: 10.1111/jon.12327
82. Teixeira CV, Rezende TJ, Weiler M, Nogueira MH, Campos BM, Pegoraro LF, et al. Relation between aerobic fitness and brain structures in amnestic mild cognitive impairment elderly. *Age (Dordr)*. (2016) 38:51. doi: 10.1007/s11357-016-9912-3
83. Weiler M, Northoff G, Damasceno BP, Balthazar MLF. Self, cortical midline structures and the resting state: implications for Alzheimer's disease. *Neurosci Biobehav Rev*. (2016) 68:245–55. doi: 10.1016/j.neubiorev.2016.05.028
84. Wang Y, Necus J, Kaiser M, Mota B. Universality in human cortical folding in health and disease. *Proc Natl Acad Sci U S A*. (2016) 113:12820–5. doi: 10.1073/pnas.1610175113
85. Ribeiro LG, Busatto G. Voxel-based morphometry in Alzheimers disease and mild cognitive impairment: systematic review of studies addressing the frontal lobe. *Dement Neuropsychol*. (2016) 10:104–12. doi: 10.1590/S1980-5764-2016DN1002006
86. Alves GS, de Carvalho LA, Sudo FK, Briand L, Laks J, Engelhardt E. A panel of clinical and neuropathological features of cerebrovascular disease through the novel neuroimaging methods. *Dement Neuropsychol*. (2017) 11:343–55. doi: 10.1590/1980-57642016dn11-040003
87. Pascoal TA, Mathotaarachchi S, Mohades S, Benedet AL, Chung CO, Shin M, et al. Amyloid-β and hyperphosphorylated tau synergy drives metabolic decline in preclinical Alzheimer's disease. *Mol Psychiatry*. (2017) 22:306–11. doi: 10.1038/mp.2016.37
88. Lajoie I, Nugent S, Debacker C, Dyson K, Tancredi FB, Badhwar A, et al. Application of calibrated fMRI in Alzheimer's disease. *Neuroimage Clin*. (2017) 15:348–58. doi: 10.1016/j.nicl.2017.05.009
89. Vasconcellos LF, Pereira JS, Adachi M, Greca D, Cruz M, Malak AL, et al. Correlation of MRI visual scales with neuropsychological profile in mild cognitive impairment of Parkinson's disease. *Parkinsons Dis*. (2017) 2017:7380102. doi: 10.1155/2017/7380102
90. Tascone LDS, Payne ME, MacFall J, Azevedo D, de Castro CC, Steffens DC, et al. Cortical brain volume abnormalities associated with few or multiple neuropsychiatric symptoms in Alzheimer's disease. *PLoS ONE*. (2017) 12:e0177169. doi: 10.1371/journal.pone.0177169
91. Ebadi A, Dalboni da Rocha JL, Nagaraju DB, Tovar-Moll F, Bramati I, Coutinho G, et al. Ensemble classification of Alzheimer's disease and mild cognitive impairment based on complex graph measures from diffusion tensor images. *Front Neurosci*. (2017) 11:56. doi: 10.3389/fnins.2017.00056
92. De Souza RKM, Josviak ND, Batistela MS, Santos PSF, Landemberger MC, Ramina R. First case of V180I rare mutation in a Brazilian patient with Creutzfeldt-Jakob disease. *Prion*. (2017) 11:465–8. doi: 10.1080/19336896.2017.1397869
93. Shigaeff N, Amaro E, Franco FGM, Jacinto AF, Chiochetta G, Cendoroglo MS, et al. Functional magnetic resonance imaging response as an early biomarker of cognitive decline in elderly patients with metabolic syndrome. *Arch Gerontol Geriatr*. (2017) 73:1–7. doi: 10.1016/j.archger.2017.07.002
94. Squarzoni P, Tamashiro-Duran JH, Duran FLS, Leite CC, Wajngarten M, Scazufca M, et al. High frequency of silent brain infarcts associated with cognitive deficits in an economically disadvantaged population. *Clinics (São Paulo)*. (2017) 72:474–80. doi: 10.6061/clinics/2017(08)04
95. Fragoso DC, Gonçalves Filho AL, Pacheco FT, Barros BR, Aguiar Littig I, Nunes RH, et al. Imaging of Creutzfeldt-Jakob disease: imaging patterns and their differential diagnosis. *Radiographics*. (2017) 37:234–57. doi: 10.1148/rg.2017160075
96. Radanovic M, Stella F, Silva LG, Talib LL, Forlenza OV. Increased CSF levels of total Tau in patients with subcortical cerebrovascular pathology and cognitive impairment. *Dement Neuropsychol*. (2017) 11:419–25. doi: 10.1590/1980-57642016dn11-040012
97. Resende EPF, Tovar-Moll FF, Ferreira FM, Bramati I, de Souza LC, Carmona KC, et al. Integrity of white matter structure is related to episodic memory performance in the low-educated elderly. *Arq Neuropsiquiatr*. (2017) 75:778–84. doi: 10.1590/0004-282x20170158
98. Weiler M, de Campos BM, Teixeira CVL, Casseb RF, Carletti-Cassani AFMK, Vicentini JE, et al. Intranetwork and internetwork connectivity in patients with Alzheimer disease and the association with cerebrospinal fluid biomarker levels. *J Psychiatry Neurosci*. (2017) 42:366–77. doi: 10.1503/jpn.160190

99. Rabelo AG, Teixeira CV, Magalhães TN, Carletti-Cassani AFM, Amato Filho AC, Joaquim HP, et al. Is cerebral microbleed prevalence relevant as a biomarker in amnestic mild cognitive impairment and mild Alzheimer's disease? *Neuroradiol J*. (2017) 30:477–85. doi: 10.1177/1971400917720465
100. Corrêa DG, Zimmermann N, Ventura N, Tukamoto G, Doring T, Leite SC, et al. Longitudinal evaluation of resting-state connectivity, white matter integrity and cortical thickness in stable HIV infection: preliminary results. *Neuroradiol J*. (2017) 30:535–45. doi: 10.1177/1971400917739273
101. Ramos Bernardes da Silva Filho S, Oliveira Barbosa JH, Rondinoni C, Dos Santos AC, Garrido Salmon CE, da Costa Lima NK, et al. Neuro-degeneration profile of Alzheimer's patients: a brain morphometry study. *Neuroimage Clin*. (2017) 15:15–24. doi: 10.1016/j.nicl.2017.04.001
102. Swardfager W, Yu D, Ramirez J, Cogo-Moreira H, Szilagyi G, Holmes MF, et al. Peripheral inflammatory markers indicate microstructural damage within periventricular white matter hyperintensities in Alzheimer's disease: a preliminary report. *Alzheimers Dement (Amst)*. (2017) 7:56–60. doi: 10.1016/j.dadm.2016.12.011
103. Swardfager W, Yu D, Scola G, Cogo-Moreira H, Chan P, Zou Y, et al. Peripheral lipid oxidative stress markers are related to vascular risk factors and subcortical small vessel disease. *Neurobiol Aging*. (2017) 59:91–7. doi: 10.1016/j.neurobiolaging.2017.06.029
104. Ferreira LK, Rondina JM, Kubo R, Ono CR, Leite CC, Smid J, et al. Support vector machine-based classification of neuroimages in Alzheimer's disease: direct comparison of FDG-PET, rCBF-SPECT and MRI data acquired from the same individuals. *Braz J Psychiatry*. (2018) 40:181–91. doi: 10.1590/1516-4446-2016-2083
105. Maia da Silva MN, Millington RS, Bridge H, James-Galton M, Plant GT. Visual dysfunction in posterior cortical atrophy. *Front Neurol*. (2017) 8:389. doi: 10.3389/fneur.2017.00389
106. Smagula SF, Karim HT, Rangarajan A, Santos FP, Wood SC, Santini T, et al. Association of hippocampal substructure resting-state functional connectivity with memory performance in older adults. *Am J Geriatr Psychiatry*. (2018) 26:690–9. doi: 10.1016/j.jagp.2018.03.003
107. Branco LMT, de Rezende TJR, Roversi CO, Zanao T, Casseb RF, de Campos BM, et al. Brain signature of mild stages of cognitive and behavioral impairment in amyotrophic lateral sclerosis. *Psychiatry Res Neuroimaging*. (2018) 272:58–64. doi: 10.1016/j.pscychresns.2017.11.010
108. Simon SS, Hampstead BM, Nucci MP, Duran FLS, Fonseca LM, Martin MDGM, et al. Cognitive and brain activity changes after mnemonic strategy training in amnestic mild cognitive impairment: evidence from a randomized controlled trial. *Front Aging Neurosci*. (2018) 10:342. doi: 10.3389/fnagi.2018.00342
109. Teixeira CVL, Ribeiro de Rezende TJ, Weiler M, Magalhães TNC, Carletti-Cassani AFMK, Silva TQAC, et al. Cognitive and structural cerebral changes in amnestic mild cognitive impairment due to Alzheimer's disease after multicomponent training. *Alzheimers Dement (N Y)*. (2018) 4:473–80. doi: 10.1016/j.trci.2018.02.003
110. Weiler M, Casseb RF, de Campos BM, de Ligo Teixeira CV, Carletti-Cassani AFMK, Vicentini JE, et al. Cognitive reserve relates to functional network efficiency in Alzheimer's disease. *Front Aging Neurosci*. (2018) 10:255. doi: 10.3389/fnagi.2018.00255
111. Bertrand E, Azar M, Rizvi B, Brickman AM, Huey ED, Habeck C, et al. Cortical thickness and metacognition in cognitively diverse older adults. *Neuropsychology*. (2018) 32:700–10. doi: 10.1037/neu0000458
112. Ventura N, Douw L, Correa DG, Netto TM, Cabral RF, Lopes FCR, et al. Increased posterior cingulate cortex efficiency may predict cognitive impairment in asymptomatic HIV patients. *Neuroradiol J*. (2018) 31:372–8. doi: 10.1177/1971400918782327
113. Neale N, Padilla C, Fonseca LM, Holland T, Zaman S. Neuroimaging and other modalities to assess Alzheimer's disease in Down syndrome. *Neuroimage Clin*. (2018) 17:263–71. doi: 10.1016/j.nicl.2017.10.022
114. Miotto EC, Batista AX, Simon SS, Hampstead BM. Neurophysiologic and cognitive changes arising from cognitive training interventions in persons with mild cognitive impairment: a systematic review. *Neural Plast*. (2018) 2018:7301530. doi: 10.1155/2018/7301530
115. Axelrud LK, Santoro ML, Pine DS, Talarico F, Gadelha A, Manfro GG, et al. Polygenic risk score for Alzheimer's disease: implications for memory performance and hippocampal volumes in early life. *Am J Psychiatry*. (2018) 175:555–63. doi: 10.1176/appi.ajp.2017.17050529
116. Resende EPF, Rosen HJ, Chiang K, Staffaroni AM, Allen I, Grinberg LT, et al. Primary school education may be sufficient to moderate a memory-hippocampal relationship. *Front Aging Neurosci*. (2018) 10:381. doi: 10.3389/fnagi.2018.00381
117. Martins LT, Teixeira IA, Laks J, Marinho V. Recognizing late onset frontotemporal dementia with the DAPHNE scale: a case report. *Dement Neuropsychol*. (2018) 12:75–9. doi: 10.1590/1980-57642018dn12-010011
118. Jaswal G, Swardfager W, Gao FQ, Nestor SM, Ganda A, Cogo-Moreira H, et al. Reduced substantia innominata volume mediates contributions of microvascular and macrovascular disease to cognitive deficits in Alzheimer's disease. *Neurobiol Aging*. (2018) 66:23–31. doi: 10.1016/j.neurobiolaging.2018.01.025
119. Rondina JM, Ferreira LK, de Souza Duran FL, Kubo R, Ono CR, Leite CC, et al. Selecting the most relevant brain regions to discriminate Alzheimer's disease patients from healthy controls using multiple kernel learning: a comparison across functional and structural imaging modalities and atlases. *Neuroimage Clin*. (2018) 17:628–41. doi: 10.1016/j.nicl.2017.10.026
120. Magalhães TNC, Weiler M, Teixeira CVL, Hayata T, Moraes AS, Boldrini VO, et al. Systemic inflammation and multimodal biomarkers in amnestic mild cognitive impairment and Alzheimer's disease. *Mol Neurobiol*. (2018) 55:5689–97. doi: 10.1007/s12035-017-0795-9
121. Swardfager W, Cogo-Moreira H, Masellis M, Ramirez J, Herrmann N, Edwards JD, et al. The effect of white matter hyperintensities on verbal memory: mediation by temporal lobe atrophy. *Neurology*. (2018) 90:e673–e82. doi: 10.1212/WNL.0000000000004983
122. Resende EPF, Tovar-Moll FF, Ferreira FM, Bramati I, de Souza LC, Carmona KC, et al. White matter microstructure in illiterate and low-literate elderly Brazilians: preliminary findings. *Cogn Behav Neurol*. (2018) 31:193–200. doi: 10.1097/WNN.0000000000000173
123. Foss MP, Diniz PRB, da Roza DL, Gefen T, Maher AC, Formigheri P, et al. Anatomic and neuropsychological findings in low-educated cognitively intact elderly from a Brazilian cohort. *Dement Neuropsychol*. (2019) 13:378–85. doi: 10.1590/1980-57642018dn13-040003
124. Axelrud LK, Sato JR, Santoro ML, Talarico F, Pine DS, Rohde LA, et al. Genetic risk for Alzheimer's disease and functional brain connectivity in children and adolescents. *Neurobiol Aging*. (2019) 82:10–7. doi: 10.1016/j.neurobiolaging.2019.06.011
125. Wang Y, Necus J, Rodriguez LP, Taylor PN, Mota B. Human cortical folding across regions within individual brains follows universal scaling law. *Commun Biol*. (2019) 2:191. doi: 10.1038/s42003-019-0421-7
126. Betts MJ, Kirilina E, Otaduy MCG, Ivanov D, Acosta-Cabronero J, Callaghan MF, et al. Locus coeruleus imaging as a biomarker for noradrenergic dysfunction in neurodegenerative diseases. *Brain*. (2019) 142:2558–71. doi: 10.1093/brain/awz193
127. Staffaroni AM, Ljubenkov PA, Kornak J, Cobigo Y, Datta S, Marx G, et al. Longitudinal multimodal imaging and clinical endpoints for frontotemporal dementia clinical trials. *Brain*. (2019) 142:443–59. doi: 10.1093/brain/awy319
128. Drummond C, Coutinho G, Monteiro MC, Assuncao N, Teldeschi A, de Souza AS, et al. Narrative impairment, white matter damage and CSF biomarkers in the Alzheimer's disease spectrum. *Aging (Albany NY)*. (2019) 11:9188–208. doi: 10.18632/aging.102391
129. Oliveira LM, Nitrini R, Román GC. Normal-pressure hydrocephalus: a critical review. *Dement Neuropsychol*. (2019) 13:133–43. doi: 10.1590/1980-57642018dn13-020001
130. Schilling LP, Pascoal TA, Zimmer ER, Mathotaarachchi S, Shin M, de Mello Rieder CR, et al. Regional Amyloid-β load and white matter abnormalities contribute to hypometabolism in Alzheimer's dementia. *Mol Neurobiol*. (2019) 56:4916–24. doi: 10.1007/s12035-018-1405-1
131. Batista AX, Bazán PR, Conforto AB, Martins MDGM, Hoshino M, Simon SS, et al. Resting state functional connectivity and neural correlates of face-name encoding in patients with ischemic vascular lesions with and without the involvement of the left inferior frontal gyrus. *Cortex*. (2019) 113:15–28. doi: 10.1016/j.cortex.2018.11.016
132. Therriault J, Wang S, Mathotaarachchi S, Pascoal TA, Parent M, Beaudry T, et al. Rostral-caudal hippocampal functional convergence is reduced

across the Alzheimer's disease spectrum. *Mol Neurobiol*. (2019) 56:8336–44. doi: 10.1007/s12035-019-01671-0
133. Ferrari BL, Neto GCC, Nucci MP, Mamani JB, Lacerda SS, Felício AC, et al. The accuracy of hippocampal volumetry and glucose metabolism for the diagnosis of patients with suspected Alzheimer's disease, using automatic quantitative clinical tools. *Medicine (Baltimore)*. (2019) 98:e17824. doi: 10.1097/MD.0000000000017824
134. Yamashita AY, Falcão AX, Leite NJ, Initiative AsDN. The residual center of mass: an image descriptor for the diagnosis of Alzheimer disease. *Neuroinformatics*. (2019) 17:307–21. doi: 10.1007/s12021-018-9390-0
135. De Carvalho Neto EG, Gomes MF, De Oliveira M, Guete MIN, Santos IP, Monteiro MD, et al. The worst is yet to come: probable sporadic Creutzfeldt-Jakob disease in a well-controlled HIV patient. *Prion*. (2019) 13:156–9. doi: 10.1080/19336896.2019.1648985
136. Gonçalves SAB, Caramelli P, Mariano LI, Guimarães HC, Gambogi LB, Resende EPF, et al. Apathy in frontotemporal dementia is related to medial prefrontal atrophy and is independent of executive dysfunction. *Brain Res*. (2020) 1737:146799. doi: 10.1016/j.brainres.2020.146799
137. Martins-Filho RK, Zotin MC, Rodrigues G, Pontes-Neto O. Biomarkers related to endothelial dysfunction and vascular cognitive impairment: a systematic review. *Dement Geriatr Cogn Disord*. (2020) 49:365–74. doi: 10.1159/000510053
138. Blevins BL, Vinters HV, Love S, Wilcock DM, Grinberg LT, Schneider JA, et al. Brain arteriolosclerosis. *Acta Neuropathol*. (2021) 141:1–−24. doi: 10.1007/s00401-020-02235-6
139. Rossini PM, Di Iorio R, Vecchio F, Anfossi M, Babiloni C, Bozzali M, et al. Early diagnosis of Alzheimer's disease: the role of biomarkers including advanced EEG signal analysis. Report from the IFCN-sponsored panel of experts. *Clin Neurophysiol*. (2020) 131:1287–310. doi: 10.1016/j.clinph.2020.03.003
140. Dalboni da Rocha JL, Bramati I, Coutinho G, Tovar Moll F, Sitaram R. Fractional anisotropy changes in parahippocampal cingulum due to Alzheimer's disease. *Sci Rep*. (2020) 10:2660. doi: 10.1038/s41598-020-59327-2
141. Busatto Filho G, Duran FLS, Squarzoni P, Coutinho AMN, Rosa PGP, Torralbo L, et al. Hippocampal subregional volume changes in elders classified using positron emission tomography-based Alzheimer's biomarkers of β-amyloid deposition and neurodegeneration. *J Neurosci Res*. (2021) 99:481–501. doi: 10.1002/jnr.24739
142. Dalboni da Rocha JL, Coutinho G, Bramati I, Moll FT, Sitaram R. Multilevel diffusion tensor imaging classification technique for characterizing neurobehavioral disorders. *Brain Imaging Behav*. (2020) 14:641–52. doi: 10.1007/s11682-018-0002-2
143. Freitas CS, Pinheiro MGM, Fonte EJD, Hazin AN, Smid J, Barbosa BJAP. Posterior cortical ribboning in the Heidenhain variant of Creutzfeldt-Jakob disease. *Arq Neuropsiquiatr*. (2020) 78:241. doi: 10.1590/0004-282x20190176
144. Ducharme S, Dols A, Laforce R, Devenney E, Kumfor F, van den Stock J, et al. Recommendations to distinguish behavioural variant frontotemporal dementia from psychiatric disorders. *Brain*. (2020) 143:1632–50. doi: 10.1093/brain/awaa018
145. Ehrenberg AJ, Khatun A, Coomans E, Betts MJ, Capraro F, Thijssen EH, et al. Relevance of biomarkers across different neurodegenerative diseases. *Alzheimers Res Ther*. (2020) 12:56. doi: 10.1186/s13195-020-00601-w
146. Simon SS, Hampstead BM, Nucci MP, Duran FLS, Fonseca LM, Martin MDGM, et al. Training gains and transfer effects after mnemonic strategy training in mild cognitive impairment: a fMRI study. *Int J Psychophysiol*. (2020) 154:15–26. doi: 10.1016/j.ijpsycho.2019.03.014
147. Moura RR, Coelho AV, Balbino VeQ, Crovella S, Brandão LA. Meta-analysis of Brazilian genetic admixture and comparison with other Latin America countries. *Am J Hum Biol*. (2015) 27:674–80. doi: 10.1002/ajhb.22714
148. Fam J, Mahendran R, Kua EH. Dementia care in low and middle-income countries. *Curr Opin Psychiatry*. (2019) 32:461–4. doi: 10.1097/YCO.0000000000000523
149. Morris JC, Schindler SE, McCue LM, Moulder KL, Benzinger TLS, Cruchaga C, et al. Assessment of racial disparities in biomarkers for Alzheimer disease. *JAMA Neurol*. (2019) 76:264–73. doi: 10.1001/jamaneurol.2018.4249
150. Wong LCK, Wong MYZ, Tan CS, Vrooman H, Venketasubramanian N, Cheng CY, et al. Interethnic differences in neuroimaging markers and cognition in Asians, a population-based study. *Sci Rep*. (2020) 10:2655. doi: 10.1038/s41598-020-59618-8
151. Tamashiro-Duran JH, Squarzoni P, de Souza Duran FL, Curiati PK, Vallada HP, Buchpiguel CA, et al. Cardiovascular risk in cognitively preserved elderlies is associated with glucose hypometabolism in the posterior cingulate cortex and precuneus regardless of brain atrophy and apolipoprotein gene variations. *Age (Dordr)*. (2013) 35:777–92. doi: 10.1007/s11357-012-9413-y
152. Scazufca M, Menezes PR, Vallada HP, Crepaldi AL, Pastor-Valero M, Coutinho LM, et al. High prevalence of dementia among older adults from poor socioeconomic backgrounds in São Paulo, Brazil. *Int Psychogeriatr*. (2008) 20:394–405. doi: 10.1017/S1041610207005625
153. Ortega LFV, Aprahamian I, Borges MK, Cação JC, Yassuda MS. Screening for Alzheimer's disease in low-educated or illiterate older adults in Brazil: a systematic review. *Arq Neuropsiquiatr*. (2019) 77:279–88. doi: 10.1590/0004-282x20190024
154. Rzezak P, Squarzoni P, Duran FL, de Toledo Ferraz Alves T, Tamashiro-Duran J, Bottino CM, et al. Relationship between brain age-related reduction in gray matter and educational attainment. *PLoS ONE*. (2015) 10:e0140945. doi: 10.1371/journal.pone.0140945
155. Lotufo PA, Goulart AC, Passos VMA, Satake FM, Souza MFM, França EB, et al. Cerebrovascular disease in Brazil from 1990 to 2015: global burden of disease 2015. *Rev Bras Epidemiol*. (2017) 20(Suppl.01):129–41. doi: 10.1590/1980-5497201700050011
156. Cortes-Canteli M, Iadecola C. Alzheimer's disease and vascular aging: JACC focus seminar. *J Am Coll Cardiol*. (2020) 75:942–51. doi: 10.1016/j.jacc.2019.10.062
157. Grinberg LT, Nitrini R, Suemoto CK, Lucena Ferretti-Rebustini RE, Leite RE, Farfel JM, et al. Prevalence of dementia subtypes in a developing country: a clinicopathological study. *Clinics (São Paulo)*. (2013) 68:1140–5. doi: 10.6061/clinics/2013(08)13
158. Daroff RB, Jankovic J, Mazziotta JC, Pomeroy SL, Bradley WG. *Bradley's Neurology in Clinical Practice*. 7th ed. London, NY: Elsevier (2016). 2 volumes.
159. Huang LK, Chao SP, Hu CJ. Clinical trials of new drugs for Alzheimer disease. *J Biomed Sci*. (2020) 27:18. doi: 10.1186/s12929-019-0609-7
160. Cross D, Thomson S, Sinclair A. *Research in Brazil: A Report for CAPES by Clarivate Analytics*. Clarivate Analytics (2018).
161. Russo MJ, Gustafson D, Vázquez S, Surace E, Guinjoan S, Allegri RF, et al. Creation of the Argentina-Alzheimer's disease neuroimaging initiative. *Alzheimers Dement*. (2014) 10(Suppl.1):S84–7. doi: 10.1016/j.jalz.2013.09.015
162. Ibanez A, Parra MA, Butlerfor C. The Latin America and the caribbean consortium on dementia (LAC-CD): from networking to research to implementation science. *J Alzheimer's Dis*. (2021):1–16. doi: 10.3233/JAD-201384

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

PERSPECTIVE
published: 15 March 2021
doi: 10.3389/fneur.2021.633777

Expanding Representation of Low and Middle Income Countries in Global Dementia Research: Commentary From the Alzheimer's Association

Claire Sexton[1], *Heather M. Snyder*[1]*, *Lakshmi Chandrasekaran*[1], *Susan Worley*[2] *and Maria C. Carrillo*[1]

[1] Alzheimer's Association, Chicago, IL, United States, [2] Independent Science Writer, Bryn Mawr, PA, United States

Alzheimer's disease (AD) and all other dementia represent a global challenge, with an estimated 50 million individuals in the world living with dementia today. In low and middle income countries (LMICs), the burden of disease often is greater, and some of these countries are projected to have some of the largest increases in dementia prevalence during the next few decades. As the world's largest voluntary health organization dedicated to AD and all other dementia, the Alzheimer's Association is committed to its vision of a world without dementia and recognizes the needs, challenges, and opportunities for dementia research in all parts of the world, and especially in LMICs. Currently, the Association is devoting more than $215 million in funding to nearly 600 best-of-field projects in 31 countries, including a significant number of projects that advance and support LMIC-specific research. The innovative work in LMICs is focused on addressing unmet needs or challenges associated with the many unique cultural, demographic, and economic characteristics of these countries. The Association also is expanding leading global forums such as the Alzheimer's Association International Conference (AAIC). In an effort to create new learning and participation opportunities, the Association also has been partnering with other international organizations and collaborating with local leadership to provide AAIC Satellite Symposia (AAIC SS) in LMIC regions around the world. In 2021 and beyond, the Association is committed to continuing these LMIC-focused initiatives, identifying gaps in LMIC research and resources, and enhancing collaboration and communication among researchers in these regions.

Keywords: Alzheimer's, dementia, convening, funding, collaboration, public health

OPEN ACCESS

Edited by:
Huali Wang,
Peking University Sixth Hospital, China

Reviewed by:
Nicolas Farina,
Brighton and Sussex Medical School, United Kingdom
Yuan-Pang Wang,
University of São Paulo, Brazil

***Correspondence:**
Heather M. Snyder
hsnyder@alz.org

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: *26 November 2020*
Accepted: *09 February 2021*
Published: *15 March 2021*

Citation:
Sexton C, Snyder HM, Chandrasekaran L, Worley S and Carrillo MC (2021) Expanding Representation of Low and Middle Income Countries in Global Dementia Research: Commentary From the Alzheimer's Association. Front. Neurol. 12:633777. doi: 10.3389/fneur.2021.633777

INTRODUCTION

The need for global coordinated research that will reach and benefit all communities around the world has perhaps never been greater. For several decades, in response to the global challenge of dementia, the Alzheimer's Association has recognized that all countries are critical and integral components of international research efforts in the global mission to eradicate dementia.

Accordingly, the Association is dedicated to ensuring complete representation of those countries with a World Bank designation of middle or lower middle income (1), many of which have a projected prevalence of dementia that is much higher than the anticipated prevalence in higher income countries (2, 3).

Since its founding in 1980, the Alzheimer's Association has had an increasingly global focus. This focus has included a growing awareness of the needs of low-income and middle-income countries (LMICs), as well as the importance of their inclusion in the global research enterprise—an awareness initially informed in large part by the work of the 10/66 Dementia Research Group (DRG). This research group, established in 1998 as a part of Alzheimer's Disease International (ADI), brought together researchers with a special focus on LMICs and succeeded in challenging the belief, prevalent in the 1990s, that dementia was relatively rare in these countries (4, 5). The name of the research group reflected an imbalance at that time such that ∼66% of all people with dementia lived in LMICs, yet only about 10% of population-based research was being conducted in these regions (4). Due largely to the efforts of the 10/66 DRG, ADI noted that within a decade this disparity had lessened, so that by 2009 ∼39% of dementia prevalence studies were conducted in LMICs, including 18 studies in Latin America and the Caribbean (6).

In subsequent years, the Alzheimer's Association has supported and joined in efforts by other international organizations, including ADI and the World Health Organization, to significantly advance our understanding of and approach to LMICs and to help inform strategies for addressing dementia by countries around the world (7–9). By 2013, a steadily growing awareness of the need for full global cooperation in the effort to combat dementia led to a gathering of the G8 countries in London, where leaders developed a multinational response to the crisis (10). During the same period, the Alzheimer's Association and other leading global organizations began to strongly encourage the development of national or country-wide plans for addressing dementia (7, 8). By 2015, the WHO published an international "Call for Action" recommending that all countries develop national public health strategies aimed at reducing the impact of dementia (11), and in 2017 developed specific guidelines for approaching dementia intended for healthcare providers, governments, policy-makers, and other stakeholders, including those in LMICs (12).

In the absence of effective treatments for dementia, a guiding principle for all of these efforts has been to accelerate research with the aim of stopping or slowing symptomatic illness for as long as possible, while providing high-quality dementia care and supporting the well-being of individuals with symptoms and/or their carers. Efforts to prevent or post-pone dementia are likely to have the greatest benefit in low-income and middle-income countries, where most dementia occurs, and where individuals are most likely to encounter poverty, inequality, and limited access to health care (3). Yet the prevalence of AD and other dementia continues to increase at a rapid pace in many LMICs (2, 3). In response, the Alzheimer's Association, in collaboration with a wide range of international organizations, is redoubling its efforts to advance research around the globe. In a collaboration between the Alzheimer's Association and the National Institute on Aging (NIA), for example, the International Alzheimer's and Related Dementias Research Portfolio (IADRP) was established to both collate and categorize the dementia research portfolios of major funding organizations but also is focused on gaining a comprehensive assessment of the current landscape of AD research in all parts of the world (https://iadrp.nia.nih.gov/) (13). Through such partnerships, the Association aims to facilitate the global conversation about all aspects of dementia and ensure LMICs are well-represented in that conversation, with the goal of eventually reducing future prevalence of dementia, and in turn reducing its socioeconomic consequences.

This article contains a summary of existing Alzheimer's Association initiatives that support research in LMICs, spanning funding and partnering on research studies, as well as convening researchers both globally and regionally. While it is important to note that LMICs are not homogenous, and that funding and convening activities are unique in each country, we also provide examples in each section for illustrative purposes.

FUNDING CRITICAL RESEARCH/PILOT STUDIES

Since 1982, the Alzheimer's Association has supported a wide range of projects involving basic science, social and behavioral research and clinical research through numerous investigator-initiated peer-reviewed grant programs. These programs became international in 2000, at that time reaching researchers in more than 50 countries through their applications, awarded funding and review process (13). Today the Association has nearly 600 best-of-field projects, more than $215 M projects in 31 countries, including many dedicated to research in LMICs—with the examples that follow in this section all part of the Alzheimer's Association's portfolio of funded research studies.

A significant number of these projects, some of which are funded in partnership with the Global Brain Health Institute (GBHI) and Alzheimer's Society (UK), are conducted in LMICs by researchers who reside in these regions (14). Though these projects have a vast range in terms of scope and subject, they generally have the common goal of addressing challenges in these countries and regions of the world. Findings from these studies often are used to inform local and national health care policies. These projects—which have ranged from tailoring mental ability tests in the Democratic Republic of the Congo, to evaluating brain health among Syrian refugees after forced migration, to using digital media and film arts to augment dementia care and improve outcomes in India—emphasize the importance of re-evaluating assumptions derived from research conducted primarily in high-income countries (HICs), to develop diagnostic tests and other tools or resources that are free of cultural, socioeconomic, educational, and other biases (14).

Despite the current shift toward biological definitions of AD and other dementia (15), for example, instruments currently available in LMICs continue to rely heavily on psychometric evaluations and clinical interviews. Because many of the cognitive and functional assessment tools used in these regions

were originally developed and validated in HICs (5), one goal is to adapt these tools so that they can be used more effectively in LMICs. In one current project, involving a collaboration between the University of Botswana and the University of California, San Francisco (UCSF), Dr. Lingani Mbakile-Mahlanza, D.Psyc, and her team are examining whether currently available computerized and paper-based tests used to diagnose dementia can be culturally adapted and validated to improve the diagnosis of individuals in Botswana. This study also is examining whether some risk factors for dementia, often identified in HICs, are relevant in sub-Saharan Africa (14). Another funded study, taking place in Egypt under the leadership of Dr. Rufus Akinyemi, PhD, MSc, MWACP, FMC, aims to determine whether universal social network platforms, such as Facebook, may be used to develop unbiased tools for identifying individuals at risk for developing dementia and developing pathways to early intervention (14). In Belo Horizonte, Brazil, Dr. Elisa de Paula França Resende, MD, of Universidade Federal de Minas Gerais—Faculdade de Medicina, and her team are exploring the effects of basic literacy acquired late in life on potential improvements in brain connectivity and memory, a subject that has been understudied among elderly populations with low educational attainment in low-income countries (14). And in Turkey, Dr. Derya Durusu Emek Savas and their team are exploring unique cognitive training strategies that may help to improve cognition in individuals with mild cognitive impairment (MCI), and potentially delay progression from MCI to AD (14).

In the absence of curative interventions for dementia, caregiving and the well-being of caregivers is another important focus of dementia-related care and research supported by these investigator-initiated grants. In Guadalajara, Mexico, for example, Dr. Brenda Perez Cerpa, MD, is funding the evaluation of a decision aid for families of individuals with advanced dementia (14). The aim of the project is to determine how this tool might improve the quality of connections between families and healthcare providers, and in turn improve end-of-life care.

LARGER COLLABORATIVE STUDIES

The Alzheimer's Association is devoted not only to developing but also to expanding multinational studies and projects—from international clinical trials to prevention, biomarker validation, and health care utilization studies—to ensure that they include genetically, ethnically, and culturally diverse populations. For some well-established studies already underway, the Association is committed to providing additional funding to ensure greater inclusion of LMICs. One such multinational study is the Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU), based at Washington University School of Medicine in St. Louis (16). The DIAN-TU is the world's first prevention trial platform for at-risk families with dominantly inherited Alzheimer's disease (DIAD). This series of interventional therapeutic trials is evaluating the safety, tolerability, and effectiveness of drugs that have the potential to prevent, delay, or possibly reverse changes in the brain associated with dementia. DIAN-TU is led by director and principal investigator Randall J. Bateman, MD, the recipient of an Alzheimer's Association research grant for this project. Recently the Alzheimer's Association contributed funding to permit the inclusion of new sites throughout Central and South America, including in Argentina, Brazil, Colombia and Mexico. This expansion will be used to establish a multicenter registry of pre-symptomatic and symptomatic individuals in Latin America (both gene carriers and non-carriers), and will enable comparison of clinical, psychometric, neuroimaging and biomarker data from Latin American DIAD families with corresponding data from non-Latin American DIAD families (16).

A similarly large collaboration aimed at preventing dementia is the World Wide FINGERS network (17, 18), which was launched in 2017 and has brought together more than 30 participating countries in a global network of multimodal lifestyle intervention trials aimed at dementia risk reduction and prevention. These trials are modeled after the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial, the first randomized controlled trial (RCT) to show that it is possible to prevent cognitive decline among older at-risk individuals using a multidomain lifestyle intervention (19). With support from the Alzheimer's Association, a Latin American first-of-its-kind study, LatAm-FINGERS, is in the final planning stages and will involve 1,300 subjects from Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Dominican Republic, Ecuador, Mexico, Paraguay, Peru, Puerto Rico, and Uruguay (17, 18). The study participants, individuals who are thought to be at a higher risk of cognitive decline due to a range of factors such as sedentary lifestyle, poor diet, and/or a suboptimal metabolic-cardiovascular profile, will be randomly assigned to one of two interventions. The study, which begins recruiting subjects in second quarter of 2021, will aim to evaluate both the feasibility and efficacy of a FINGER multi-domain lifestyle intervention across Latin America.

In January 2020, the Alzheimer's Association also joined leaders in dementia research from Latin America, the GBHI, the Tau Consortium, and the National Institutes of Health (NIH) in forming a new multinational consortium that likewise aims to expand dementia research in Latin America. Research Dementia, Latin America, or ReDLat, is designed to identify unique genetic, social, and economic determinants of health that contribute to the development of AD and other dementia in Latin America. By collecting and analyzing neuroimaging, genetic, and behavioral data from more than 4,000 individuals in Argentina, Brazil, Chile, Colombia, Mexico, Peru, and the US, ReDLat investigators expect to broaden our understanding of the genetic and environmental determinants of dementia, particularly in diverse and underserved populations in Latin America. This large-scale 5-year project is bringing together experts in the fields of neurology, neuropsychology, geriatrics, psychiatry, neuroscience, and genetics from across Latin America.

In July 2020, the Alzheimer's Association highlighted its work with researchers from all around the world, and led by the team at University of Texas, San Antonio, to support and advance critical research in response to the current pandemic crisis, with a special focus on research examining the neurological sequelae of SARS-CoV-2 following acute infection. Although much remains

to be known about the long-term consequences of SARS-CoV-2 infection, several research studies suggest that COVID-19 is associated with neurological complications (20). Thus, there is an urgent need to investigate the downstream impact of COVID-19 on the brain, and address unanswered questions regarding the effects of SARS-CoV-2 on the cerebrovascular system. In this network, the Alzheimer's Association joins representatives from more than 30 countries, with technical guidance from the WHO, as a member of an international, multidisciplinary consortium dedicated to collecting and evaluating data on the short- and long-term consequences of the viral infection on the central nervous system (CNS), as well as examining differences across countries (21).

INTERNATIONAL MEETING FORUMS AND ORGANIZATIONS

The Alzheimer's Association has long been dedicated to fostering international collaboration among dementia researchers in all countries, in part by providing a range of inspiring forums and professional opportunities. The Alzheimer's Association International Conference (AAIC) is the world's largest gathering of researchers from around the world whose work is focused on AD and other dementia (22). As a part of the Alzheimer's Association's research program, AAIC serves as a catalyst for generating new findings about dementia and nurturing a vital, collegial research community. In July 2019, AAIC drew ∼6,000 leading experts from 56 countries, including over 400 attendees from 23 LMICs, to Los Angeles to share leading basic science and clinical research discoveries, including new directions for the diagnosis, prevention, and treatment of dementia. In order to defray costs associated with AAIC registration, housing and travel expenses, 119 travel fellowships were awarded to researchers based in LMICs. These awards are competitive and based on financial need, with priority given to applicants who are scientists, early career investigators, post-doctoral fellows, or students based in LMICs.

In July 2020, in response to the global pandemic, AAIC was held virtually for the first time. This free, on-line conference attracted the meeting's largest audience to date, with more than 33,000 registered attendees and featuring more than 3,000 scientific presentations. The online accessibility of the AAIC experience further enabled dementia scientists from every corner of the world to share and discuss the latest research findings, and network to build new international collaborations, with over 7,000 registered attendees from 93 LMICs. A growing focus on LMICs was also evident in the many presentations that examined or highlighted issues faced by regions comprising these countries, including a plenary session led by Dr. Vijayalakshmi Ravindranath, a scientific leader from the Indian Institute of Science in Bengaluru, India. Such presentations included a systematic review of culturally tailored dementia interventions for minority ethnic groups in low- and middle-income countries, a description of a cognitive assessment test adapted and validated for use by older adults in a Brazilian indigenous community, an examination of multi-morbidity as a correlate of dementia among older people in Central Africa, an overview of socioeconomic determinants of dementia among Caribbean Hispanics, and an examination of cognitive dysfunction among middle-aged adults with type 2 diabetes in South Africa.

SATELLITE SYMPOSIA

In December 2015, AAIC launched a series of satellite symposia to extend the reach of AAIC across the globe and provide more learning and participation opportunities to people from all countries, including LMICs. When the first satellite research symposium was held in Mexico City, the prevalence of dementia in Mexico, Brazil, the Andean Area, and Central America was expected to increase by more than 400% between 2010 and 2050 (6). Moreover, the Pan American Health Organization warned that problems associated with this increase would likely be compounded by a fragile health care infrastructure and lack of access to health services and sanitation in these regions. Yet the meeting convened at an auspicious time and on an optimistic note, as the first national dementia plan in a Spanish-speaking country had just been established in Mexico the previous year (6).

This first AAIC satellite symposium (AAIC SS) underscored the value of ensuring the incorporation of previously neglected LMIC cohorts in international studies, in part by highlighting unique characteristics of studies across Latin American populations, including those assessing prevalence and incidence of both risk factors and dementia (23). The results of epidemiologic studies and national surveys presented at the meeting (e.g., SABE) revealed unique challenges facing older Mexicans and other Latinos with dementia, such as low literacy and inadequate health care resources, and also pointed to potential solutions to these problems, such as the use of videos in public places to increase awareness of cognitive impairment among the elderly. Subsequent symposia in Brazil and Argentina provided forums for a deeper examination of these issues, as well the communication of new directions in public policy in these countries.

During the development of all AAIC SS, one aim has been to select locations that permit greater involvement of regions comprising LMICs. The second AAIC SS meeting, for example, which took place in Bulgaria, in collaboration with researchers at the University of Varna and the University of Pittsburgh, brought this conversation closer to Eastern Europe, provided a forum for showcasing dementia research in neighboring countries, and engaged the expertise of leading researchers in that region of the world. In 2018, an AAIC SS meeting held in Bengaluru, India provided a forum for exploring emerging dementia research in South Asia and similarly engaged leading dementia researchers throughout that region, including in LMICs.

All meetings sponsored by the Alzheimer's Association, including AAIC and all satellite symposia, aim to encourage collaboration among professionals from all countries, including LMICs. In 2008, the Alzheimer's Association established a new means to support the dementia research community by creating the International Society to Advance Alzheimer's Research and Treatment (ISTAART) (24). This esteemed professional society

for scientists, physicians, and other professionals interested in dementia science is the first international collegial organization to support and encourage the interests of all areas of AD and dementia investigation. In April 2019, ISTAART launched a new tiered dues structure for individuals from low, lower-middle and upper-middle economies (based on the World Bank's annual classification system). Since April 2019, ISTAART membership from low to upper middle income countries has nearly doubled, expanding access to ISTAART benefits spanning the Alzheimer's and Dementia journal family, Alzheimer's Association meetings, and Professional Interest Areas (PIAs) (24).

FUTURE DIRECTIONS

In line with the UN's Sustainable Development Goal number three to ensure healthy lives and promote well-being for all at all ages, the global dementia research enterprise continues to strive for effective prevention and treatment throughout the world. A critical goal will be to sustain recent efforts to ensure inclusion of LMICs—where two-thirds of people with dementia reside—in large-scale, multinational research studies. Another important goal will be to identify modifiable risk factors in LMICs and determine practical, cost-effective ways of addressing them (3). Opportunities to seek funding and convene the dementia research community, with an emphasis on these areas, will continue to serve as a priority for the Association. Toward these ends, the Alzheimer's Association is committed to continuing its core mission of fostering and expanding partnerships, ensuring the continuation of LMIC-focused projects, identifying gaps in LMIC research and resources, and enhancing collaboration and communication among all researchers in LMIC regions. Such strategies are not independent, and it will be the sum of these approaches that will ultimately impact upon this goal.

DATA AVAILABILITY STATEMENT

The original contributions generated in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

HS, LC, and CS provided outline and specific details for sections of the manuscript. SW supported initial draft. MC oversight of the full manuscript and strategy development. All authors contributed to the article and approved the submitted version.

FUNDING

The Alzheimer's Association provided full funding for the preparation of this manuscript.

REFERENCES

1. *World Bank Country Report on LMIC*. Available online at: https://data.worldbank.org/country/XO (accessed November 25, 2020).
2. Patterson C. *World Alzheimer Report 2018*. London: Alzheimer's Disease International (2020).
3. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. (2020) 396:413–46. doi: 10.1016/S0140-6736(20)30367-6
4. Prince M, Acosta D, Chiu H, Scazufca M, Varghese M. Dementia diagnosis in developing countries: a cross-cultural validation study. *Lancet*. (2003) 361:909–17. doi: 10.1016/S0140-6736(03)12772-9
5. Prina AM, Mayston R, Wu YT, Prince M. A review of the 10/66 dementia research group. *Soc Psychiatry Psychiatr Epidemiol*. (2019) 54:1–10. doi: 10.1007/s00127-018-1626-7
6. *ADI 2015 World Annual Report: The Global Impact of Dementia: An Analysis of Prevalence, Incidence, Cost and Trends*. (2015). Available online at: https://www.alzint.org/resource/world-alzheimer-report-2015/ (accessed November 25, 2020).
7. Rosow K, Holzapfel A, Karlawish JH, Baumgart M, Bain LJ, Khachaturian AS. Countrywide strategic plans on Alzheimer's disease: developing the framework for the international battle against Alzheimer's disease. *Alzheimers Dement*. (2011) 7:615–21. doi: 10.1016/j.jalz.2011.09.226
8. Wortmann M. Importance of national plans for Alzheimer's disease and dementia. *Alzheimers Res Ther*. (2013) 5:40. doi: 10.1186/alzrt205
9. World Health Organization. Call for action by the participants in the first WHO ministerial conference on global action against dementia. Geneva (2015).
10. G8 Health Ministers. G8 Dementia Summit Declaration. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/265869/2901668_G8_DementiaSummitDeclaration_acc.pdf. (Last accessed September 9, 2020).
11. Orrell M, Brayne C; INTERDEM (early detection and timely INTERvention in DEMentia); Alzheimer Europe; Alzheimer's Disease International; European Association of Geriatric Psychiatry. Dementia prevention: call to action. Lancet. 2015 Oct 24;386(10004):1625. doi: 10.1016/S0140-6736(15)00528-0
12. World Health Organization. *Global Action Plan on the Public Health Response to Dementia 2017-2025*. Geneva: World Health Organization (2017).
13. *International Alzheimer's and Related Dementias Research Portfolio (IADRP)*. Available online at: https://iadrp.nia.nih.gov/about. (accessed September 25, 2020).
14. *Alzheimer's Association International Research Grant Program*. Available online at: https://www.alz.org/research/for_researchers/grants/types-of-grants (accessed September 25, 2020).
15. Jack CR, Jr., Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. (2018) 14:535–62. doi: 10.1016/j.jalz.2018.02.018
16. *The Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU)*. Available online at: https://dian.wustl.edu/our-research/our-collaborators/ (accessed September 25, 2020).
17. *World Wide Fingers*. Available online at: https://alz.org/wwfingers/overview.asp (accessed September 25, 2020).
18. Kivipelto M, Mangialasche F, Snyder HM, Allegri R, Andrieu S, Arai H, et al. World-wide FINGERS network: a global approach to risk reduction and prevention of dementia. *Alzheimers Dement*. (2020) 16:1078–94. doi: 10.1002/alz.12123
19. Ngandu T, Lehtisalo J, Solomon A, Levälahti E, Ahtiluoto S, Antikainen R, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet*. (2015) 385:2255–63. doi: 10.1016/S0140-6736(15)60461-5
20. Pryce-Roberts A, Talaei M, Robertson NP. Neurological complications of COVID-19: a preliminary review. *J Neurol*. (2020) 267:1870–3. doi: 10.1007/s00415-020-09941-x

21. *Alzheimer's Association International Cohort Study of Chronic Neurological Sequelae of SARS-CoV-2*. Available online at: https://www.alz.org/research/for_researchers/partnerships/sars-cov2-global-brain-study (accessed November 25, 2020).
22. *Alzheimer's Association International Conference*. Available online at: alz.org/aaic (accessed November 25, 2020).
23. Snyder H, Cardenas-Aguayo, Alonso A, Bain L, Iqbal K, Carrillo M. Alzheimer's disease research in Ibero America. *Alzheimer Dement*. (2016) 12:749–54. doi: 10.1016/j.jalz.2016.04.007
24. *ISTAART, International Society to Advance Alzheimer's Research & Treatment*. Available online at: alz.org/ISTAART (accessed November 25, 2020).

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 23 March 2021
doi: 10.3389/fneur.2021.637000

Patient and Public Involvement for Dementia Research in Low- and Middle-Income Countries: Developing Capacity and Capability in South Asia

Jahanara Miah[1], Saima Sheikh[1], Rachel C. Francis[2], Gayathri Nagarajan[3], Sojan Antony[4], Maryam Tahir[5], Rabia Sattar[5], Anum Naz[5], Sehrish Tofique[5], Mostazir Billah[6], Sajib Saha[6] and Iracema Leroi[7] on behalf of the SENSE-Cog Asia Working Group and the SENSE-Cog Asia Research Advisory Team*

[1] Division of Neuroscience and Experimental Psychology, University of Manchester, Manchester, United Kingdom, [2] Department of Speech Language Pathology, All India Institute of Speech & Hearing, Mysuru, India, [3] Dementia Care in SCARF – DEMCARES, Chennai, India, [4] Department of Psychiatric Social Work, National Institute of Mental Health and Neurosciences, Bengluru, India, [5] Division for Neurocognitive Disorder, Pakistan Institute of Living & Learning, Karachi, Pakistan, [6] Hearing Care Center Ltd., Renaissance Hospital & Research Institute, Dhaka, Bangladesh, [7] School of Medicine, Global Brain Health Institute, Trinity College, Dublin, Ireland

OPEN ACCESS

Edited by:
Elissaios Karageorgiou, Independent Researcher, Athens, Greece

Reviewed by:
Hany Ibrahim, Ain Shams University, Egypt
Judith Aharon Peretz, Rambam Health Care Campus, Israel

***Correspondence:**
Iracema Leroi
iracema.leroi@tcd.ie
orcid.org/0000-0003-1822-3643

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: 02 December 2020
Accepted: 22 February 2021
Published: 23 March 2021

Citation:
Miah J, Sheikh S, Francis RC, Nagarajan G, Antony S, Tahir M, Sattar R, Naz A, Tofique S, Billah M, Saha S and Leroi I (2021) Patient and Public Involvement for Dementia Research in Low- and Middle-Income Countries: Developing Capacity and Capability in South Asia. Front. Neurol. 12:637000. doi: 10.3389/fneur.2021.637000

Background: Patient and public involvement (PPI) is an active partnership between the public and researchers in the research process. In dementia research, PPI ensures that the perspectives of the person with "lived experience" of dementia are considered. To date, in many lower- and middle-income countries (LMIC), where dementia research is still developing, PPI is not well-known nor regularly undertaken. Thus, here, we describe PPI activities undertaken in seven research sites across South Asia as exemplars of introducing PPI into dementia research for the first time.

Objective: Through a range of PPI exemplar activities, our objectives were to: (1) inform the feasibility of a dementia-related study; and (2) develop capacity and capability for PPI for dementia research in South Asia.

Methods: Our approach had two parts. Part 1 involved co-developing new PPI groups at seven clinical research sites in India, Pakistan and Bangladesh to undertake different PPI activities. Mapping onto different "rings" of the Wellcome Trust's "Public Engagement Onion" model. The PPI activities included planning for public engagement events, consultation on the study protocol and conduct, the adaptation of a study screening checklist, development and delivery of dementia training for professionals, and a dementia training programme for public contributors. Part 2 involved an online survey with local researchers to gain insight on their experience of applying PPI in dementia research.

Results: Overall, capacity and capability to include PPI in dementia research was significantly enhanced across the sites. Researchers reported that engaging in PPI activities had enhanced their understanding of dementia research and increased the meaningfulness of the work. Moreover, each site reported their own PPI activity-related outcomes, including: (1) changes in attitudes and behavior to dementia and research

involvement; (2) best methods to inform participants about the dementia study; (3) increased opportunities to share knowledge and study outcomes; and (4) adaptations to the study protocol through co-production.

Conclusions: Introducing PPI for dementia research in LMIC settings, using a range of activity types is important for meaningful and impactful dementia research. To our knowledge, this is the first example of PPI for dementia research in South Asia.

Keywords: patient and public involvement, dementia research, co-production, co-creation, low- and middle-income countries, capacity and capability, public engagement onion model

INTRODUCTION

Associated with population aging, dementia is emerging as an increasingly prevalent condition, particularly in low- and middle-income countries (LMIC) where about two-thirds of the world's population with dementia reside (1). In South Asia alone, the proportion of people living with dementia is estimated as 5.1 million (2). Health and social care services for this population, or for older people in general, is limited (3) or, in many areas, non-existent. Thus, developing such services, guided by locally obtained evidence, is a priority; however, in many LMICs, research capability for non-communicable diseases (NCD) in general is still developing (4), and for dementia research, this situation is magnified. Thus, building capacity and capability to conduct dementia research is essential (5), and is aligned with the priorities outlined in the 2019 position statement, "*Roadmap for Dementia Research in Pakistan"* developed by an international group of expert stakeholders interested in dementia research in South Asia (6).

The involvement of people with the lived experience of a health condition, and their families, "Patient and Public Involvement" (PPI) is a cornerstone of any applied research, particularly involving international collaborations where cultural adaptation of interventions and methods to local contexts is required. PPI is well-established in several high-income countries, particularly the United Kingdom, Australia, and Canada (7–9) and is viewed as an active involvement characterized in the form of consultation, collaboration or user control (10, 11). However, in many LMICs, the concept and practice of PPI for both research and service development is not well-known (12, 13), and is potentially challenging due to the established patient-professional hierarchical structures prevalent in many LMIC health systems.

The common ethos of PPI is defined as "research being carried out 'with' or 'by' patients and public members rather than 'to', 'about' or 'for' them" (10, 14). It recognizes the centrality of the patient and public's viewpoints and concerns, and the acknowledgment that their perspective may differ from those of researchers (15–17). In under-resourced LMIC settings, the theoretical underpinnings of PPI (18–21) take on greater significance including, the following, as conceptualized by Greenhalgh et al. (22): (1) the "*emancipatory imperative*", which suggests that involving people in research addresses power imbalances between participants, who may be vulnerable populations, and researchers, and encompasses the social justice principle of "inclusion"; (2) the "*efficiency imperative*", which addresses the need to reduce "research waste" (23, 24) by addressing critical research questions pertinent to the population in question, and the need to accelerate the research trajectory from "proof-of-principle" to implementation (16, 17, 21, 25); and (3) the "*political imperative*" which holds that knowledge should be co-created by researchers and lay stakeholders (26–29). In addition, if the research involves international partners, particularly those from HIC, all three imperatives are important, particularly to safeguard against the risk of "research imperialism" (30).

An additional and important driver to undertake PPI is the need to provide a platform for people with dementia (PwD) and their care partners to communicate their experiences and to have an influence on research (8, 11, 23, 26, 28, 31–37). Recently, increased accessibility through technology is providing greater opportunities for people with dementia to be empowered and to have their voices "heard"; however, in many LMIC settings access to such technology may still be limited, particularly for older people such as those living with dementia and their care partners.

There is, therefore, a need to strengthen the capacity of PPI in LMIC, particularly for newly emerging areas of research and practice, such as dementia care (6). Furthermore, PPI in LMIC settings plays a pivotal role in cultural adaptation of interventions where the language, cultural practices, context and health literacy may be limited (38). Here, we have synthesized our learning and reflection on PPI capacity building in LMIC (22), developed in the context of a dementia-related feasibility study in seven sites across three South Asian countries: Bangladesh, Pakistan, and India (representing the three most populous countries of the eight countries making up South Asia). The research was a pilot study to ascertain local feasibility and acceptability of a non-pharmacological intervention focussed on hearing rehabilitation in PwD [the SENSE-Cog intervention (39, 40)], adapted for the South Asian context. We report: (i) how the local research teams co-developed PPI activities with PPI stakeholders in each site; (ii) the nature of each site's PPI activities; and (iii) the impact of the work through the reported experiences of the researchers and the PPI stakeholders. The operational framework for our approach was based on the Wellcome Trust's "Public Engagement Onion" model (41) (**Figure 1**). We used GRIPP2 (42) (Guidance for Reporting Involvement of Patients and the Public) checklist to report our PPI activity (**Supplementary File 1**).

Abbreviations: PPI, Patient and public Involvement; PwD, Person with Dementia; LMIC, Low- and middle-income countries; KAP, Knowledge, Attitude, Practice.

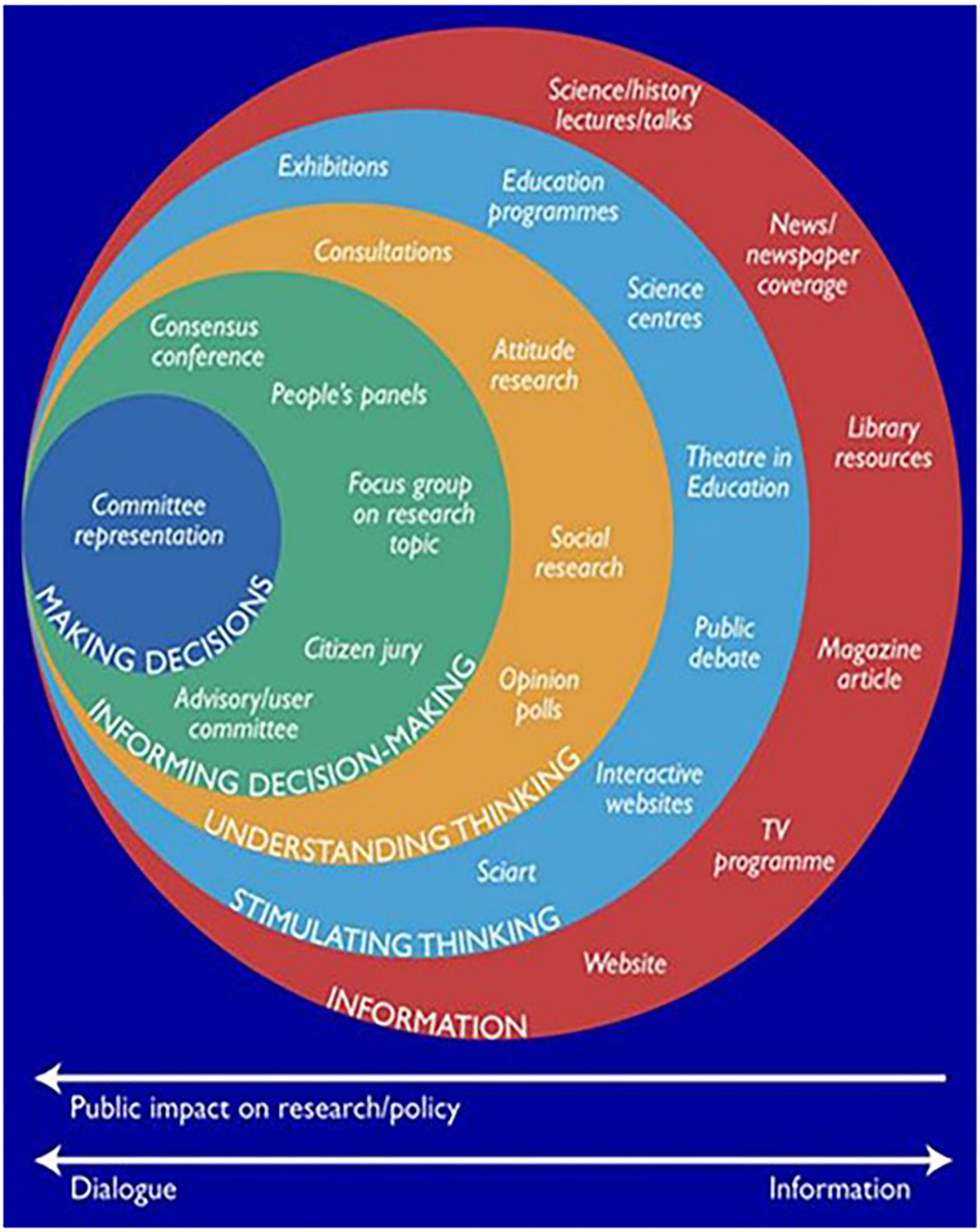


FIGURE 1 | The "Public Engagement Onion" model (41) (Image courtesy of the Wellcome Trust).

BACKGROUND TO THE FEASIBILITY STUDY SENSE-COG ASIA

SENSE-Cog Asia is an ongoing feasibility study of a psychosocial intervention to improve quality of life in PwD through enhancing hearing function, culturally adapted for South Asian settings. Based on the European SENSE-Cog trial (40, 43) (www.sense-cog.eu), this single arm, open-label, study has four phases: (1) cultural adaptation of intervention; (2) feasibility and acceptability evaluation; (3) capacity and capability building for dementia research; and (4) PPI. Participant dyads (PwD and their care partners) are being recruited across the study

sites. Each dyad receives the adapted SENSE-Cog intervention, over an 8-week period, delivered by a trained "Hearing Support Practitioner". The intervention comprises the following components: clinical assessment and provision of hearing devices by an audiologist for the PwD; adherence support with hearing aids (or other hearing devices) for the PwD and their care partner; and knowledge, awareness and communication skills' training on sensory-cognitive impairment (including dementia education) for care partners. The main outcomes are feasibility and acceptability of the intervention. Exploratory outcomes are quality of life and other dementia-related outcomes. Below, we elaborate on Phase 4 of the project, the PPI activity.

METHODS

Phase 4 Process: Patient and Public Involvement

Project Team

The PPI project team comprised two researchers (JM and SS) based in Manchester (UK) and seven researchers based in each of the South Asian settings with backgrounds in medicine, social work, occupational therapy, health sciences, speech therapy, audiology, psychology, physical therapy, and nursing. The seven researchers were identified from each clinical site and took on the role of local PPI coordinator. Site principal investigators were also involved, to oversee support for PPI coordinators in embedding PPI within the local research sites.

Setting

The research sites were in Pakistan (Lahore, Karachi and Rawalpindi); India (Mysuru, Chennai and Bengaluru); and Bangladesh (Dhaka). This work took place from March 2019 to March 2020.

Training and Support

PPI was a new concept for the designated researchers, thus, to equip them for their new role as local PPI coordinators, the UK-based researchers delivered two half-day PPI training sessions *via* video conference. We adapted the training from a previous PPI training we used in Europe (15). The training covered the principles of PPI, as well as operational aspects regarding how PPI coordinators could recruit and establish a PPI group and implement PPI activities. Site principal investigators also attended the training. The PPI training information was translated into local languages, case studies used for training were set in the local settings with South Asian names, and images used reflected the local diversity. Although we provided the basic training on the principles of PPI to raise awareness and embed the PPI concept in their work programmes, more importantly, we were guided by the local PPI coordinators who led the initiatives on addressing the cultural diversity represented within each study site.

After the PPI coordinator training, our initial plan was to have regular team meetings with the PPI coordinators *via* video conference to create a sense of doing the work together. However, local challenges due to technology provision in some sites precluded this. Instead, we conducted one-to-one meetings with PPI coordinators to support them in preparing and planning for their PPI groups and activities. One-to-one meetings included discussions about whom to involve as PPI contributors, what resources were needed to support the PPI contributors, and how the PPI coordinators role differed from that of their usual role as researchers. Local PPI coordinators were also supported in developing their knowledge, values, and attitude regarding PPI in research. Thus, the approach was to facilitate the local PPI coordinators to implement PPI practice as well as to learn simultaneously through its application in the research project.

Implementation Process of PPI

We use the term "public contributor" to refer to the patient and public members involved in the PPI activities in this project. Each local PPI coordinator recruited and set up their PPI group differently across sites, depending on the local context and in addressing local social and cultural issues. PPI groups were set up in each clinical site and consisted of between 2 and 4 public contributors. The numbers of PPI contributors recruited were kept to a minimum, to allow the PPI coordinators to effectively implement the learning from the training into practice and also manage and support a PPI group who were not familiar with the PPI concept. PPI contributors were recruited using flyers (**Supplementary File 2**) disseminated through local medical charities and patient representative organizations. In addition, PPI coordinators and representatives from local medical charities and patient representative organizations also communicated verbally about the PPI opportunities with existing patients and carer groups and other social networks to ensure the inclusion of people with illiteracy issues. Protocols to manage transport and reimbursement for PPI contributors were developed locally. Public contributors included people with dementia or memory problems, care partners, or community members with an interest in contributing to research. There were no set inclusion or exclusion criteria for recruiting PPI contributors, unlike a strict research study, the requirements were quite loose as PPI work attempts to get the widest, most inclusive and representative viewpoints and perspectives to inform the research work. Individuals required no specific skills to join the PPI groups, but needed to have lived or caring experience of dementia or a special interest in dementia.

The PPI coordinators worked with their PPI group to familiarize them to the dementia research project (5) and to acquaint group members of their role within the project. PPI contributors role was to provide advice on the running of the dementia research project (5) and/or work with the research teams to plan, make decisions and develop dissemination activities. PPI groups were provided with clear questions to aid the researchers to gain meaningful input. Meetings took place monthly or as required by each site. We used monitoring forms (**Supplementary File 3**) to capture the feedback from the PPI activities to demonstrate the impact of PPI (**Table 1**). On-going one-to-one support for PPI coordinators was provided by the

TABLE 1 | Dementia-related PPI activities and impact across the seven sites based on the "Public Engagement Onion" model.

Public engagement onion spectrum	Activity type	PPI activities	Impact
Collaborating	Making decisions	PPI groups set-up	• Endorsed research relevance. • Validated intervention. • Contributed to intervention development. • Identified awareness and education needs on the research topic.
Consulting	Informing decision-making	Recruitment material and flyers, information documents for dementia research	• Documents reworded and inappropriate English words were translated.
		Combined a public engagement and awareness-raising event with a survey of professional stakeholders	• Ascertained knowledge, awareness and practice on the research topic. • Survey data guided study design and recruitment.
		Dementia care skills event for professionals	• Planned event and identified key topics. • Inter-professional collaboration and dialogues engaged professionals normally not involved in decision-making.
		Assessment of hearing screening for older adults	• Questions re-phrased to make it relevant culturally.
	Understanding thinking	Discussion group panel with professionals	• Reviewed and suggested amendments to topic guides. • Developed questions for discussion.
Informing	Stimulating thinking	Dementia awareness role-play in residential care homes	• Planned role-play and highlighted issues on carer burden issues and tell-tale signs of dementia.
		Dementia awareness event for public	• Contributed toward reducing stigma in the community.
	Information	Dementia awareness radio programme	• Reviewed topics for the radio programme. • Invited to plan for future dementia awareness sessions.
		Dementia information sheets	• Reviewed ease of understanding, readability, alternative wording and images.
		Dementia awareness community walk	• Contributed to raising of awareness.
		World Alzheimer's day poster competition	• Contribute toward reducing stigma in the community.
		Dementia newsletter	• Reviewed wording and topics relevant to public members.

UK-based PPI team (JM and SS), *via* telephone, emails, and skype meetings.

We encouraged the PPI coordinators to adopt the "Public Engagement Onion" model (41) (**Figure 1**), to help them decide with their PPI groups on the PPI activity to be undertaken. Different sites chose different layers representing one or two of the "rings" in the "Public Engagement Onion" model (31). The "Public Engagement Onion" (41) offers a range of approaches in different forms, as there is no one optimal involvement approach (9, 15, 44, 45). The rings consist of basic engagement activities with larger audiences to more intense activities with small groups and having a greater impact.

Research Teams' Experiences of PPI

We conducted a short survey using self-completed questionnaires to understand the entire research teams' (n = 18, across all sites) experiences of applying PPI in dementia research and to add depth to the reported learning. We included researchers, research assistants, and principal investigators who were involved in supporting the PPI coordinators in implementing, supporting, and conducting PPI group meetings. The questionnaires included items relating to any previous PPI involvement experience, their view on the importance of PPI and how PPI influenced them or their work. Items included a free text box to allow the respondent to explain their answer or give further insights. The survey questionnaire is provided in **Supplementary File 4**. The surveys were completed anonymously. We analyzed the responses quantitatively supported by qualitative thematic analysis of open text responses.

Ethics Statement

We did not require ethical approval for the involvement of patients or public, as they are not acting in the same way as research participants (46) and no data were collected directly from PPI contributors. We included safeguarding aspects in the PPI coordinators training modules to ensure the protection of PPI contributors, including maintaining confidentiality, distress protocols, and correct training of coordinators. For the researcher survey, responses from the research team were collected anonymously with informed consent.

RESULTS

Implementation of PPI

A key challenge for PPI coordinators was explaining the concept of PPI, which was new to potential PPI contributors. Due to the lack of awareness of the PPI concept and doubts regarding the benefits of PPI in general, some individuals were reluctant to be involved and had to be encouraged. The main concern raised was that working on an equal footing with health professionals in an advisory capacity was new territory for them, and they were uncertain about what was expected of them. They expressed doubt about whether their involvement could be beneficial or valued.

PPI coordinators were concerned about finding "suitable people" and recognized the need to approach potential individuals directly to explain the role and the concept of PPI. They spent a substantial amount of time explaining about PPI at different community centers, with community groups and at public meetings, at care homes and outpatient clinics. Other challenges reported included low general and health literacy levels, travel time, and the financial cost to attend the meetings, particularly for those traveling from rural areas. These issues were addressed by assuring individuals with low literacy that PPI coordinators would verbalize all the information using local dialects and collate the feedback by taking notes. Inclusion of less educated participants, or those from rural areas, was considered important for inclusion. For those traveling from rural areas, the PPI meetings were arranged around hospital appointments to save travel time and avoid additional costs. In addition, reimbursement for the travel cost and time were provided, however some sites decided to only cover the travel expenses. PPI coordinators reported that it was unusual to pay public members expenses and reimbursements for meetings. This added another layer of complexity for most sites as there were some infrastructure challenges identified by PPI coordinators. There was an absence of a policy or guidance for remunerating public contributors in research projects and a lack of guidance on what was reasonable compensation. Therefore, the team developed expense sheets for the project and agreed on local rates for reimbursement that were realistic but still guided by Public Involvement Standards guidance (47), which were established in the UK for UK-based PPI. Researchers questioned whether this aspect of the guidance was contextually appropriate.

A total of 27 people were recruited for the PPI activities across the seven sites, consisting of 8 PwD, 14 carers and 5 members of the public. The PPI groups in each site decided on the preferred meeting times and settings. The first meetings with the PPI groups were mainly focussed on equipping them to acknowledge that their knowledge and expertise of the lived experiences were as important as clinicians and researchers, although it was different.

Impact of PPI on the Research Project

The impact of PPI on a given research project can be characterized by changes to the research, as well as researchers and PPI contributors and the wider community (48). **Tables 1**, **2** illustrates the demonstrable impact of the different PPI activities on different aspects of the research project.

Range of PPI Activities

As shown in **Table 1**, each site chose a different type of PPI activity within the "Public Engagement Onion" model, ranging in level and magnitude of involvement through to engagement. For example, the Bengaluru site undertook PPI-led modification of the study participant information documents, including patient information sheets, for use in all sites. Groups in Lahore, Karachi and Rawalpindi undertook various public engagement events, ranging from dementia awareness role-play in residential care homes, discussion groups, radio program and developed dementia awareness newsletter (**Supplementary File 5**). The group in Mysuru consulted on the study protocol and conduct, providing insight into local adaptation and co-developed dementia training for professionals and dementia awareness-raising training for public members. Chennai's group developed dementia information sheets for use in the intervention trial, after ethical approval. In Dhaka, the group supported audiologists in adapting a hearing screening checklist for older adults, which were needed for the study protocol. Finally, in Dhaka, the group chose to conduct a large-scale public engagement event to raise awareness of sensory-cognitive health, attended by 100 participants. The event provided a platform for key stakeholders (public, doctors, medical students, occupational therapists, social workers, and physiotherapists) to have a dialogue about dementia and hearing impairment that had not previously been discussed in such settings. Key discussions were focussed on strengthening the legal laws on the Mental Health Act in relation to people with dementia and lacking the capacity to consent and focus on strengthening a workforce to address dementia care through capacity building. During the event, 56 participants filled out a Knowledge, Attitude, Practice [KAP (49)] survey regarding sensory-cognitive health (the results of the Dhaka PPI engagement event survey are reported below). KAP is used to gather data on what is known, assumed and practiced in relation to a specific topic (49).

Each site in this study is a case study in their own right. However, we have chosen to use two case studies in this paper to reflect the most interesting in terms of the approach used and the PPI tasks undertaken by two PPI groups in India. We illustrate in **Table 2** how PPI was implemented and the impact of their activities.

Research Teams' Awareness of PPI Survey Results

Ten researchers took part in the survey. Of these, five were PPI coordinators (researcher background), one researcher, two research assistants, and two principal investigators. Most researcher respondents (80%) reported that they had no previous experience of PPI work; 10% was unsure and 10% reported having some experience of PPI, mainly with professional stakeholders. All participants viewed PPI as an important factor in dementia research. Most of the participants said they are "very likely" (70%) or "likely" (20%) to apply PPI principles to other projects or as part of their work in their department, whereas, 10% were neutral on this subject. The positive responses in

TABLE 2 | Case studies of two PPI groups and the impact of their PPI activities.

Case Study 1: Mysuru, India site

The Mysuru PPI advisory group advised on the development of a dementia awareness-training event for members of the public during Alzheimer's Awareness month in September 2019.

The Mysuru PPI advisory group attended a series of 2-hour meetings. The group consisted of carers and volunteers. The meeting was held on days agreed amongst the group that would be the most convenient.

The aim of the meeting was to gather views on dementia awareness training at a very early stage of the planning. Three contributors participated in the meeting to help develop the dementia awareness training and one member provided input remotely *via* telephone. Face to face, group meetings enabled the PPI contributors to discuss their views and providing the opportunity to all the contributors to put forward their ideas. The PPI group provided feedback about each of the three components:

- Where and how the training should be advertised.
- The key topics to be covered by the training.
- The agenda

The research team and the PPI coordinator worked with the PPI group to develop plans for awareness training. They focused on whether the language used to introduce the subject of dementia in the training was appropriate. There was agreement that the word "dementia" raises concerns. So the suggestion was that the word "memory loss" should be used and as more sympathetically worded, and embraced varying features of the condition. The group also highlighted the need for more information about local support available to persons with dementia, and the need for awareness materials to be provided in Kannada (local language). The feedback from the PPI contributors resulted in the following changes:

- The training focussed on preventative measures and signposting resources for care partners.
- Training included activities to keep the person with dementia busy and engaged.
- The training included lists of do's and don'ts for care partners.
- Training included prompts for care partners to discuss that "it is Ok to have a nurse to help" and issues on stigma on receiving care from nurses, to overcome high levels of stigma and discrimination in the community.
- Training content used layman's terms as suggested by PPI contributors e.g., to use the terms "memory loss" instead of dementia.

Case Study 2: Bengaluru, India site

The Bengaluru site consisted of a "virtual PPI advisory group" with eight public contributors. PPI activities were organized *via* a virtual discussion group. To ensure equality of involvement, those who could not attend the virtual sessions or did not have services to participate, PPI coordinators arranged a consultation with them using telephone or face-to-face meeting dependent on the PPI contributor's preference. The approach taken by the Bengaluru PPI coordinator was firstly to set up a series of discussion topics for the groups to discuss issues and challenges faced by PwD and care partners, to set the context. Thereafter, discussions led to the introduction of the dementia study and the relevance of PPI input. Consecutive discussions consisted of items about the study intervention design, Hearing Support Practitioner's communications manual and patient information sheet to receiving feedback that could help the research team improve its documentation for the trial.

- Feedback highlighted that care partners, due to various reasons, sometimes limit the participation of the PwD but the Hearing Support Practitioner's should ensure that the PwD is encouraged to talk during sessions.
- Suggestion for re-wording recommended for the participant information sheet and informed consent sheet, emphasizing that both the PwD and care partners are warned about what the research study entails, and commitments involved.
- The relevance of the intervention was recognized and approved by the group.

The group recommended the benefits of wearing the hearing aid and how it could reduce the burden on care partners to be shared with everyone, and not just as part of the research activity. The issues relating to equality between researchers and study participants highlighted as important factors by ensuring accessibility for all, and not the selected few.

The feedback from the PPI advisory groups resulted in the following changes:

- Hearing Support Practitioner's communications manual reworded and notes included to ensure that the participation of the PwD is encouraged during the intervention, which could be limited sometimes by care partners.
- Patient information sheet and consent forms reworded using the simple local language.
- Researchers assured through PPI advisory groups validation that PwD and care partners would benefit from the intervention.
- Researcher's notes as part of the intervention delivery emphasized the need to explain to the care partners and patients about their role in dementia research, to ensure equality by promoting the study widely to provide the opportunity for all to participate in the research study.
- Bengaluru research site promoted volunteers led outreach activities for promoting the rights and dignity of people living with dementia and promoting the benefits of using a hearing aid for PwD.

Other issues identified by the group highlighted:

- The need for general awareness and education about the research topic.
- Researchers to explore options of providing virtual session as part of the intervention.

The research team addressed the transport-related issues for PPI advisory group members by the use of smartphones in urban and suburban settings with a view to enabling many care partners to participate with the online group without affecting the caregiving responsibilities and increasing digital literacy.

applying PPI in their work were supported by comments outlined in **Table 3**.

As shown in **Figure 2**, 90% of the researcher respondents reported that they had improved their understanding of PPI and that PPI had increased the meaningfulness and relevance of their work. Sixty percent said that PPI enabled knowledge sharing and 40% felt that PPI informed the study and led to joint working on the research project.

Finally, 90% of respondents reported that PPI changed their attitudes and behavior, including a broadening of their perspectives about the challenges faced by patient and care partners, and understanding the types of challenges that might be

TABLE 3 | Exemplar quotes illustrating the impact of the PPI activities on researchers.

Theme	*Quotes*
Unique experience of illness and insights into the needs and priorities of a PwD and care partners	*"Involvement in this project help me to interact more with the patients this was the experience in understanding the family better" (ID9)* *"Working with the public contributors made it a different experience, it gave us insights into what are the real challenges for people like the cost of traveling into the hospitals, particularly from the villages, it's far and for some it means having to arrange overnight accommodation, which is additional cost for them. So it's useful to get that insight." (ID8)* *"PPI is very helpful to getting understand your targeted population and their problems when you involve them in group discussions." (ID4)* *"Throughout the Sense Cog Asia project I have learned a lot. It was one of the best opportunity to learn purely about the challenges of patients and their care partners. Involvement of public in this project was quite challenging task. True representation and involvement of public in project is only can achieved if they are given opportunity to give us their valuable opinion about project design and implementation." (ID1)* *"Gives insight into people's lives and how they are dealing with the conditions, it helps us as researchers to understand some of the changes they would face in relation to dementia research and what the intervention means to them" (ID7)*
Improved understanding of PPI	*"Co-creation helps us to understand ground reality. It also helps to frame need based research problems." (ID5)* *"You get to now (sic) how you can you improve research design and strategies." (ID4)* *"Yes. PPI learn me research differently." (ID9)* *"Because it improves the relevance of the study and more practical goals or research questions can be taken up" (ID3)* *"Yes, definitely I will do that because this is the best way to evaluate your project connection with your participants moreover it helps in any trial to investigate the progress of your project outcome." (ID1)*
Challenges of PPI	*"Time consuming. Conflict of opinion and level of interest of public makes it difficult to achieve the outcome of this project" (ID1)* *"It's new idea. I need to give more time in research project" (ID2)* *"Patients getting more involved and trying to rule over the researcher. Coordinating timing for meeting" (ID3)* *"Most of the carers are daughters-in-law and I think they are hindered from talking openly about certain things because if they were to do it, it is seen as disrespecting the elder member. May be we need to think about it for the intervention too; that might be an issue" (ID8)* *"It's time consuming, I think because it's new thing for us, it has taken us longer to understand it fully and also to adapt to a new way of working" (ID7)*

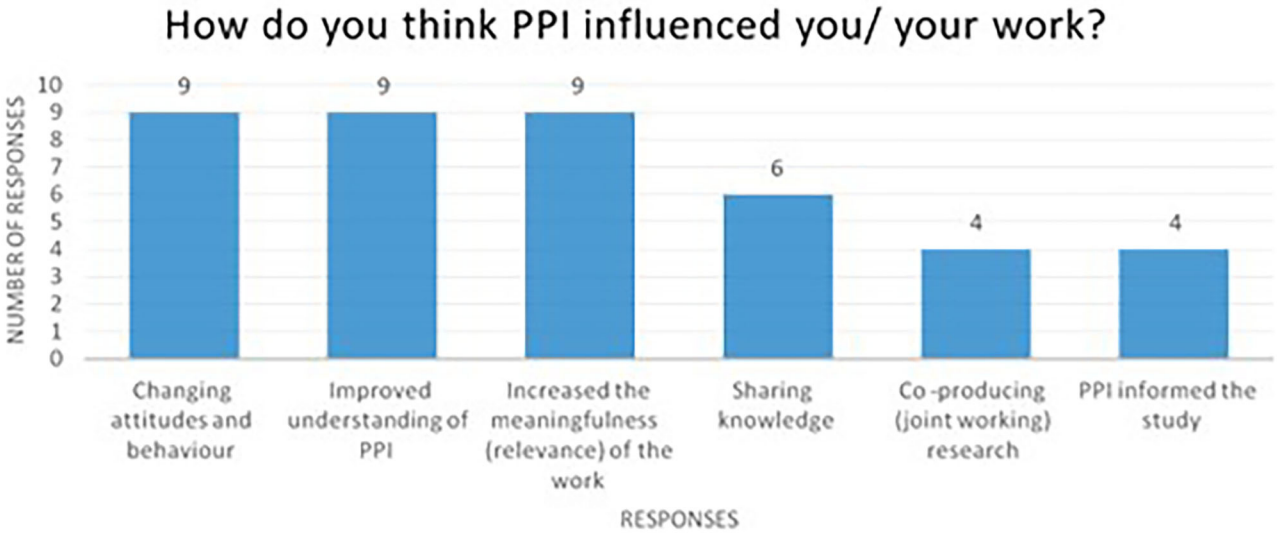


FIGURE 2 | Survey results showing how PPI influenced the researchers and/or their work.

faced by PwD and care partners in taking part in the intervention. It also provided an opportunity for researchers to interact with PwD and their care partners outside of the research study. Some researchers reported how the PPI activities had helped them to understand what needs to be done from an organizations perspective in helping to raise awareness about dementia for the public. Exemplar quotes illustrating the impact of the PPI activities on researchers are shown in **Table 3**.

The disadvantages of PPI were also reported by respondents. These included the view that PPI was time-consuming and was an added burden to the already busy role of a researcher. They viewed PPI as a new way of working, which took time to fully understand and adapt to. A few respondents commented how PPI presented conflicts of interest from public contributors and made it difficult to achieve the outcome of the study, particularly as it challenged the authority of the researcher. For example, one

TABLE 4 | Dhaka KAP survey demographics.

	Number	Percentage
Gender (*N* = 55)		
Female	21	38.2%
male	34	61.8%
Years in profession (*N* = 55)		
<2	5	9.1%
2–5	11	20.0%
5–10	18	32.7%
>10	21	38.2%
Highest qualification (*N* = 55)		
Postgrad	19	34.5%
Degree or equivalent	22	40.0%
Dip or equivalent	10	18.2%
A level or equivalent	2	3.6%
GCSE or equivalent	1	1.8%
Other qualifications	1	1.8%
Job title (*N* = 55)		
Service manager	10	18.2%
Registered nurse etc.,	1	1.8%
Care worker	6	10.9%
Allied health	34	61.8%
Other	6	7.3%
Received training in dementia (*N* = 56)		
No	51	91.1%
Yes	5	8.9%

participant commented *"Patients getting more involved and trying to rule over the researcher"* (ID3). Another researcher highlighted a cultural challenge for PPI contributors as family care partners, particularly for daughters-in-law. The researcher felt that in-group settings, particularly in settings where women are not often asked for their opinions, the adult children, or daughters-in-law were hindered from talking openly about issues relating to care partner burden, as it was viewed as *"disrespecting" (ID8)* the older adult they are caring for. Another point highlighted by a researcher was the difficulty of persuading those with "*cognitive deficiency" (ID10)* to attend the meetings and the challenges arising from involving them in the meetings.

Dhaka PPI Engagement Event Survey

Fifty-six participants completed the KAP surveys in Dhaka and were included in the analysis. Findings are outlined in **Tables 4**, **5**.

Demographics

Respondents were generally male (61.8%) and equally, a majority (61.8%) of respondents were allied health professional workers. Respondents were relatively experienced (32.7% of respondents having worked 5–10 years and 38.2% with over 10 years' experience) and moderately highly qualified. However, only 8.9% reported having received training in dementia awareness.

Knowledge: Over 50% of respondents reported being aware of brief hearing screening tests, but don't have the training and expertise to administer and interpret the results and 50% reported being aware of referral pathways. Although, 40% of respondents reported being confident in helping PwD with use of assistive hearing, other respondents reporting neutral and lower, cited the main reason given for not being confident was lack of training (**Supplementary File 6**).

Attitudes: Most respondents (69.1%) agreed that hearing screening would be acceptable to PwD and 72.7% agreed they would find clinical guidelines for assessment and management of hearing useful. Additionally, respondents (41%) reported that most residents who needed to use a hearing aid did not use them effectively. The most reported reasons for ineffective use were aids not effective, not being tolerated, aids hard to use or not fitting correctly.

Practice: Most respondents (65.5%) reported they did not carry our testing or checking of hearing aids. Only 17.0% of respondents reported that there were specially designated staff responsible for hearing care in their facility. Most respondents (92.6%) reported they did have any training and support to use sensory support equipment.

DISCUSSION

Through this project, we established a community of researchers and public contributors undertaking PPI practice by encouraging researchers to consider and explore PPI methods, develop a positive attitude toward PPI, and implement PPI. The purpose of capacity building was to facilitate a bottom-up approach, consistent with the ethos of PPI, of gaining self-confidence, and learning about PPI in research. To our knowledge, this is the first PPI for research involving PwD, persons with memory problems, care partners, and community members in LMICs.

We purposely used a multifaceted framework of implementation and evaluation, based on the "Public Engagement Onion" (41). A bespoke approach, involving different underlying theoretical approaches, is appropriate, considering the diverse nature of the different study sites, which differed by country, language, research experience and dementia awareness and expertise, and the novelty of the concept for both researchers and public contributors. Avoidance of "off-the-shelf" approaches has been supported by some PPI authors [i.e., Greenhalgh et al. (22)] and this ensured that the PPI stakeholders at each site could select the approach most suited to them, aligned with a plurality of theoretical frameworks, and recognizing the importance of context, making it relevant to the people "on the ground." Introducing an innovation model such as PPI does not necessarily transform to uptake in all settings, as consideration needs to be given to the local socio-cultural and health system contexts when implementing PPI. It should involve working and engaging with local communities, stakeholders and community leadership networks, and viewed as a continuous learning process.

Our work included a focus on (1) study feasibility and preparation; (2) partnership building for dementia research capacity and capability building; (3) education and awareness-raising; and (4) ensuring power balance and equity in researcher-participant relationships. Regarding the latter, as dementia

TABLE 5 | Dhaka KAP survey responses.

Knowledge items

Questions	Strongly disagree		Disagree		Neutral		Agree		Strongly agree		Total
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*
I am aware of brief hearing tests that could be used with PwD	13	23.2%	5	8.9%	7	12.5%	26	46.4%	5	8.9%	56
I have the training and expertise to administer and interpret the results of a brief hearing test	16	29.1%	13	23.6%	8	14.5%	15	27.3%	3	5.5%	55
I am aware of, and would be able to use, appropriate referral pathways for PwD who failed a brief hearing screen	12	21.4%	7	12.5%	9	16.1%	22	39.3%	6	10.7%	56
I am confident in helping PwD with use of assistive hearing devices	11	20.0%	3	5.5%	19	34.5%	17	30.9%	5	9.1%	55

Attitude toward hearing support for PwD

Questions	Strongly disagree		Disagree		Neutral		Agree		Strongly agree		Total
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*
A brief hearing screen would be acceptable to PwD	1	1.8%	10	18.2%	6	10.9%	23	41.8%	15	27.3%	55
I would find clinical guidelines for assessing and managing hearing impairment in PwD care useful	4	7.3%	5	9.1%	6	10.9%	23	41.8%	17	30.9%	55
Most PwD who need a hearing aid (or other assistive hearing device) use one effectively	11	19.6%	12	21.4%	9	16.1%	17	30.4%	7	12.5%	56

Practice related to hearing support for PwD

Questions	No		Yes		Total (*N*)
	N	%	*N*	%	
Do you carry out testing or checking of hearing aids?	36	65.5%	19	34.5%	55
Does your facility have specifically designated staff that are responsible for the care of hearing impairments (e.g., putting a hearing aid in, changing batteries)?	44	83.0%	9	17.0%	53
I have training and support to use hearing aids, amplifiers etc.,	50	92.6%	4	7.4%	54

research develops in LMICs, particularly in collaboration with international partners, it is critical, at the outset, to address issues of equity and inclusion (50) and it is important to assume and be vigilant for the risk of research imperialism for any international collaboration, and PPI may have an important role in addressing this. PPI can support this by placing the voices of PwD, persons with memory problems, care partners, and community members (28, 51) at the center of the research, thus de-centralizing the researcher, who is often a medical professional representing a power imbalance (52) with PwD and their care partners (53–56). Illustrating this emancipatory aspect of PPI, our researcher survey highlighted the challenges of public contributors "taking control" or being treated as equals in the partnership. This represents "uncharted waters" for many medical professions in LMIC settings like South Asia (57, 58), where the relationship between medical professionals and patients is more vertical compared to many HICs (59), and communication is determined by accepted social differences (52, 60). However, it is worth noting that hierarchical dynamics are still common in some cultural contexts, holding an authoritative hierarchical position within their communities, and power imbalances naturally emerge between researchers and subjects, and not necessarily due to research imperialism and colonialism, but due to local sociocultural practices. In this context, PPI has the potential

to foster equity by disrupting traditional boundaries of social structure, which is central to a partnership approach.

Many PwD in LMICs fall into the "triple jeopardy" of being older, female, and from the poorest communities. This can be conceptualized through the lens of intersectionality (50, 61), where several socially determined risk factors coalesce to predispose and precipitate the emergence of dementia and perpetuate poor outcomes (62). Thus, when embarking on research with this vulnerable population, the needs and perspectives of the PwD and their family must be prioritized. A robust PPI approach will support this and address the social justice principle of "inclusion."

The political imperative, which holds that knowledge should be co-created by researchers and lay stakeholders, was demonstrated in several of our PPI activities, although it emerged as a challenge not endorsed as an outcome by some researchers in the survey. For the researchers who reported that the PPI work *had* helped them focus their research on the needs of the public contributors, this represented a significant paradigm shift away from paternalism toward partnership.

A significant practical barrier during PPI implementation work was the recognition of how payment to PPI contributors, an important element of INVOLVE guidance (63), might not be appropriate nor is practiced in most LMIC settings. This compounds issues of exclusion, in that those who get involved are those who can afford the time and money to do so. The Bengaluru case study illustrates how the use of virtual groups can enhance PPI access for a particular group; however, this approach also has its limitations by excluding those without access to technology. Therefore, during PPI implementation, researchers should consider how to reach beyond clinical and hospital settings and "go to the people."

Since a focus in underserved areas is often on the most impactful research in the shortest timespan to address areas of greatest need, studies of interventions with an existing evidence-base are often undertaken. An example of this is the global adaptation and implementation trial of Cognitive Stimulation Therapy for dementia (38, 64). Adopting an intervention developed elsewhere into a context with a markedly different language, socioeconomic and cultural context requires adaptation prior to evaluation to enhance the appropriateness, uptake and chance for subsequent "scale-up" of the intervention (6, 46, 65–67).

Although PPI in dementia research has progressed substantially, evidence supporting the impact of PPI is still developing and descriptions of impact are sparse and frequently lack consistency due to inadequate conceptualization, and inconsistent reporting (16, 44, 68–72), thus rendering the evaluation of impact difficult. Nonetheless, it is critical to develop a strong evidence base for PPI by demonstrating impact (17, 73), as we have illustrated here (**Tables 1**, **2**, researcher survey, monitoring forms), and thus moving the PPI agenda forward in a significant and applicable way (17, 22, 73, 74).

Limitations

We recognize that the PPI concept and the approach we introduced into SENSE-Cog Asia study could be viewed as Eurocentric and to a certain extent as a form of colonialism by some researchers in LMIC. However, the core of our work on PPI is about the democratization of health and health knowledge, which in many LMIC (and HIC, particularly non-English HIC) settings is challenging as structures remain moderately vertical and patriarchal. The model of "doctor knows best" is still very prevalent. Thus, PPI could have a "disruptive" role in breaking those traditional boundaries in LMIC settings, which may be positive.

Principles of PPI training and support include (17, 47, 73) training public contributors regarding the basics of research. Although we explained the PPI contributor's role in providing input to support research, we provided only basic research training to PPI contributors due to limited resources and time constraints. Much of our time was spent on introducing the concept of PPI. Moreover, PPI coordinators were identified locally within the research team, which may have contributed to power imbalance (75), whereas independent PPI coordinators may have been more appropriate.

In addition, due to limited resources, we did not include the perspectives of PPI contributors to capture their view on how they embraced the PPI concept, their experience and its impact, which is a vital perspective to capture when implementing new concepts. These data would have been valuable by enabling us to explore alignment between the perceived experiences of PPI coordinators and contributors. The absence of these data may make the "Implementation of PPI" section in the results section appear somewhat subjective. However, this subjective aspect is also important, as it represents as proof of concept to establish feasibility and acceptability of our approach, which was the main aim. Future work in this area can apply more rigor to the methodology and training and increase the rollout to support other studies and ensure the sustainability of the PPI groups.

Despite our efforts to be inclusive, PPI contributors recruited in this study were to a certain extent biased toward a particular demographic of educated, literature and largely middle-class people. For future research studies in newly developing research centers, such as those sites with whom we worked with need to be mindful in addressing the issues of inclusion in PPI recruitment, by increasing the reach to rural areas, poor and vulnerable, and digitally disadvantaged communities.

CONCLUSION

We have synthesized our learning and reflection on PPI capacity building in LMICs in some South Asian contexts and emphasized the need to strengthen PPI practice in LMICs, particularly for newly emerging areas of research and practice, such as dementia care. PPI must be recognized as an integral part of applied research in LMIC countries, but requires sufficient investment in time, resources, and commitment to ensure PPI is effectively led and research outcomes are relevant to the intended beneficiaries. "Learning by doing" (45, 74, 76) will be necessary to make more explicit the various factors that support and inhibit PPI processes and tailor different types of involvement practice (22) to change the research landscape globally.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JM, SSh, and IL conceptualized and led the project. JM and IL led the manuscript preparation. All authors participated in refining and implementing the work and contributed to the critical review and final version of the manuscript.

FUNDING

Funding for SENSE-Cog Asia feasibility study was secured from the University of Manchester Research Partner Development/Pump-Priming Grant under Global Clinical Research Fund GCRF (P122809).

ACKNOWLEDGMENTS

M. M. Hafiz, Rabeya Ferdous, Md. Ripon, Sajib Saha, M. Muinul Hafiz, M. Biswash, M. Sakel, Sir William Beveridge Foundation, Bangladesh; M. Krishna, India; Ms. Rakhshata, Chaithra K. C., M. Sandeep, S. P. Goswami, All India Institute of Speech and Hearing, Mysuru, India; Abirami Marimuthu, Vaishnavi Ramanujam, V. Sumanthi, Sridhar Vaitheswaran, Schizophrenia Research Foundation (SCARF), Chennai, India; Mathew Varghese, P. T. Sivakumar, (NIMHANS) Banglore India Anum Naz, Rabia Amjad, Maham Rasheed, Amna Noureen, Marvi S. Channah, Maira Usman, Shanker Lal, Sehrish Toufique, Nasim Chaudhry, Nusrat Husain, Pakistan Institute of Living and Learning, Pakistan. The authors would like to acknowledge the older adults, care partners and public members as part of the PPI Advisory Groups in Bangladesh, Pakistan, and India.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.637000/full#supplementary-material

REFERENCES

1. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimer's Dement.* (2013) 9:63–75. doi: 10.1016/j.jalz.2012.11.007
2. Alzheimer's Research UK. *Dementia Statistics Hub*. Available online at: https://www.dementiastatistics.org/statistics/global-prevalence/ (accessed September 25, 2020).
3. Sabzwari SR, Azhar G. Ageing in Pakistan-a new challenge. *Ageing Int.* (2011) 36:423–7. doi: 10.1007/s12126-010-9082-z
4. Huffman MD, Labarthe DR, Yusuf S. Global cardiovascular research training for implementation science, health systems research, and health policy research. *J Am Coll Cardiol.* (2015) 65:1371–2. doi: 10.1016/j.jacc.2015.02.023
5. Leroi I, Vaitheswaran S, Sheikh S, Miah J, Chaudhry N, Husain N, et al. Capacity and capability building for applied dementia research in low- and middle-income countries: two exemplars from South Asia. *Indian J of Med Res.* (2021) (in press).
6. Leroi I, Chaudhry N, Daniel A, Dunne R, Eman S, Farina N, et al. A roadmap to develop dementia research capacity and capability in Pakistan: a model for low- and middle-income countries. *Alzheimer's Dement.* (2019) 5:939–52. doi: 10.1016/j.trci.2019.11.005
7. Department of Health. *The Local Government and Public Involvement in Health Act.* London: Department of Health (2007). Available online at: https://www.legislation.gov.uk/ukpga/2007/28/content (accessed September 25, 2020).
8. CIHR. *Guidelines for Health Research Involving Aboriginal People.* Ottawa: Canadian Institutes of Health Research (2007). Available online at: https://cihr-irsc.gc.ca/e/29134.html (accessed August 25, 2020).
9. Brett J, Staniszewska S, Mockford C, Herron-Marx S, Hughes J, Tysall C, et al. Mapping the impact of patient and public involvement on health and social care research: a systematic review. *Health Expect.* (2014) 17:637–50. doi: 10.1111/j.1369-7625.2012.00795.x
10. INVOLVE. *Briefing Notes for Researchers.* (2012). Available online at: . (accessed August 25, 2020).
11. NIHR. *Standards Development Partnership*. National Standards for Public Involvement. Available online at: (accessed September 15, 2020).
12. Cook N, Siddiqi N, Twiddy M, Kenyon R. Patient and public involvement in health research in low and middle-income countries: a systematic review. *BMJ Open.* (2019) 9:e026514. doi: 10.1136/bmjopen-2018-026514
13. Luck A. *International Public Engagement.* (2016). Available online at: https://wellcome.org/sites/default/files/international-public-engagement-wellcome-sep16.pdf (accessed September 29, 2020).
14. INVOLVE. *National Institute for Health Research (NIHR)-Wide Learning and Development for Public Involvement: Working Group Report and Recommendations.* (2015). Available online at: https://www.invo.org.uk/wp-content/uploads/2016/03/FINAL-NIHR-LD-report-July-2015.pdf (accessed September 20, 2020).
15. Miah J, Dawes P, Leroi I, Parsons S, Starling B. A protocol to evaluate the impact of involvement of older people with dementia and age-related hearing and/or vision impairment in a multi-site European research study. *Res Involv Engagem.* (2018) 4:44. doi: 10.1186/s40900-018-0128-9
16. Miah J, Dawes P, Leroi I, Starling B, Edwards S, Parsons S. Patient and public involvement in dementia research in the European Union: a scoping review. *BMC Geriatr.* (2019) 19:220. doi: 10.1186/s12877-019-1217-9
17. Miah J, Parsons S, Lovell K, Starling B, Leroi I, Dawes P. The impact of involving people with dementia and their care partners in research: a qualitative study. *BMJ Open.* (2020) 10:e039321. doi: 10.1136/bmjopen-2020-039321
18. Wicks P, Richards T, Denegri S, Godlee F. Patients' roles and rights in research. *BMJ.* (2018) 362:k3193. doi: 10.1136/bmj.k3193
19. Ward PR, Thompson J, Barber R, Armitage CJ, Boote JD, Cooper CL, et al. Critical perspectives on "consumer involvement" in health research: epistemological dissonance and the know-do gap. *J Sociol.* (2010) 46:63–82. doi: 10.1177/1440783309351771
20. Madden M, Speed ES. Beware zombies and unicorns: towards critical patient and public involvement in health research in a

neoliberal context. *Front Sociol.* (2017) 2:1–6. doi: 10.3389/fsoc.2017.00007
21. Oliver S, Liabo K, Stewart R, Rees R. Public involvement in research: making sense of the diversity. *J Health Serv Res Policy.* (2015) 20:45–51. doi: 10.1177/1355819614551848
22. Greenhalgh T, Hinton L, Finlay T, Macfarlane A, Fahy N, Clyde B, et al. Frameworks for supporting patient and public involvement in research: Systematic review and co-design pilot. *Health Expectations.* (2019) 22:785–801. doi: 10.1111/hex.12888
23. Paul Glasziou, Chalmers. I. Research waste is still a scandal—an essay. *BMJ.* (2018) 363:k4645. doi: 10.1136/bmj.k4645
24. Minogue V, Cooke M, Donskoy AL, Vicary P, Wells B. Patient and public involvement in reducing health and care research waste. *Res Involv Engagem.* (2018) 4:5. doi: 10.1186/s40900-018-0087-1
25. Venuta R, Graham ID. Involving citizens and patients in health research. *J Ambul Care Manag.* (2010) 33:215–22. doi: 10.1097/JAC.0b013e3181e62bd7
26. Bartlett R. Scanning the conceptual horizons of citizenship. *Dementia.* (2016) 15:453–61. doi: 10.1177/1471301216644114
27. Beresford P. From "other" to involved: user involvement in research: an emerging paradigm. *Nordic Soc Work Res.* (2013) 3:139–48. doi: 10.1080/2156857X.2013.835138
28. Gove D, Diaz-Ponce A, Georges J, Moniz-Cook E, Mountain G, et al. European working group of people with dementia. Alzheimer Europe's position on involving people with dementia in research through PPI (patient and public involvement). *Aging Mental Health.* (2018) 22:723–9. doi: 10.1080/13607863.2017.1317334
29. Alzheimer Europe. *The Ethics of Dementia Research.* (2011). Available online at: https://www.alzheimer-europe.org/Ethics/Ethical-issues-in-practice/2011-Ethics-of-dementia-research (accessed September 26, 2020).
30. Bradley M. *North-South Research Partnerships: Challenges, Responses and Trends—A Literature Review and Annotated Bibliography. Working Paper 1, IDRC Canadian Partnerships Working Paper*. Available online at: https://idl-bnc-idrc.dspacedirect.org/handle/10625/36539 (accessed September 26, 2020).
31. Blackburn S, McLachlan S, Jowett S, Kinghorn P, Paramjit G, Higginbottom A, et al. The extent, quality and impact of patient and public involvement in primary care research: a mixed methods study. *Res Involv Engagem.* (2018) 4:16.doi: 10.1186/s40900-018-0100-8
32. World Health Organization. *Ninth Futures Forum on health systems governance and public participation.* (2006). Available online at: https://www.euro.who.int/en/publications/abstracts/ninth-futures-forum-on-health-systems-governance-and-public-participation-2006 (accessed March 28, 2020).
33. World Health Organization. *People-Centred and Integrated Health Services: An Overview of the Evidence. Interim Report.* (2015). Available online at: (accessed March 28, 2020).
34. World Health Organisation. *Process of Translation and Adaptation of Instruments.* (2018). Available online at: (accessed February 10, 2019).
35. Group SDW. *Core Principles for People with Dementia in Research*. Available online at: http://www.dementiavoices.org.uk/wp-content/uploads/2014/06/Involving-people-with-dementia-in-research1.pdf (accessed July 28, 2020).
36. Dementia. *EWgopw*. Available online at: https://www.alzheimer-europe.org/Alzheimer-Europe/Who-we-are/European-Working-Group-of-People-with-Dementia (accessed March 28, 2020).
37. NIfH Research. *NIHR annual report 2015/16.* National Institute for Health Research (2016). Available online at: https://www.nihr.ac.uk/about-us/documents/NIHR-Annual-Report-2015-16.pdf (accessed September 12, 2020).
38. Chaudhry N, Tofique S, Husain N, Couture D, Glasgow P, Husain M, et al. Montessori intervention for individuals with dementia: feasibility study of a culturally adapted psychosocial intervention in Pakistan (MIRACLE). *BJPsych Open.* (2020) 6:e69.doi: 10.1192/bjo.2020.49
39. Hooper E, Simkin Z, Abrams H, Camacho E, Charalambous AP, Collin F, et al. Feasibility of an intervention to support hearing and vision in Dementia: the SENSE-Cog field trial. *J Am Geriatr Soc.* (2019) 67:1472–7. doi: 10.1111/jgs.15936
40. Leroi I, Simkin Z, Hooper E, Wolski L, Abrams H, Armitage CJ, et al. Impact of an intervention to support hearing and vision in dementia: The SENSE-Cog field trial. *Int J Geriatr Psychiatry.* (2020) 35:348–57. doi: 10.1002/gps.5231
41. Wellcome Trust. *Community Engagement – Under the Microscope.* (2011). Available online at: https://wellcome.ac.uk/sites/default/files/wtvm054326_0.pdf (accessed September 12, 2020).
42. Staniszewska S, Brett J, Simera I, Seers K, Mockford C, Goodlad S, et al. GRIPP2 reporting checklists: tools to improve reporting of patient and public involvement in research. *BMJ.* (2017) 358:j3453. doi: 10.1136/bmj.j3453
43. Regan J, Frison E, Collin F, Dawes P, Hann M, Himmelsbach I, et al. Individualised sensory intervention to improve quality of life in people with dementia and their companions (SENSE-Cog trial): study protocol for a randomised controlled trial. *Trials.* (2019) 20:80.doi: 10.1186/s13063-018-2973-0
44. Staley K. "Is it worth doing?" measuring the impact of patient and public involvement in research. *Res Involv Engagem.* (2015) 1:6.doi: 10.1186/s40900-015-0008-5
45. Staley K, Cockcroft E, Shelly A, Liabo K. "What can I do that will most help researchers?" A different approach to training the public at the start of their involvement in research. *Res Involv Engagem.* (2019) 5:10. doi: 10.1186/s40900-019-0144-4
46. Amadea Turk, Anne-Marie Boylan, Louise Locock. *A Researcher's Guide to Patient and Public Involvement*. Available online at: https://oxfordbrc.nihr.ac.uk/wp-content/uploads/2017/03/A-Researchers-Guide-to-PPI.pdf (accessed September 11, 2019).
47. INVOLVE. *Developing Training and Support for Public Involvement in Research*. Eastleigh (2012). Available online at: https://www.invo.org.uk/wp-content/uploads/2012/11/INVOLVETrainingSupport2012.pdf (accessed September 11, 2019).
48. Staniszewska S, Denegri S, Matthews R, Minogue V. Reviewing progress in public involvement in NIHR research: developing and implementing a new vision for the future. *BMJ Open.* (2018) 8:e017124. doi: 10.1136/bmjopen-2017-017124
49. Data collection. *Quantitative methods. The KAP survey model (Knowledge, Attitude & Practices)*. Available online at: file://nask.man.ac.uk/home\protect\T1\textdollar/Downloads/KAP%20(1).pdf (accessed August 21, 2020).
50. Shimmin C, Wittmeier KDM, Lavoie JG, Wicklund ED, Sibley KM. Moving towards a more inclusive patient and public involvement in health research paradigm: the incorporation of a trauma-informed intersectional analysis. *BMC Health Serv Res.* (2017) 17:539. doi: 10.1186/s12913-017-2463-1
51. Di Lorito C, Birt L, Poland F, Csipke E, Gove D, Diaz-Ponce A, et al. A synthesis of the evidence on peer research with potentially vulnerable adults: how this relates to dementia. *Int J Geriatr Psychiatry.* (2016) 32:58–67. doi: 10.1002/gps.4577
52. Zeichner CI. *Modern and Traditional Health Care in Developing Societies: CONFLICT and Cooperation.* Lanham. MD: University Press of America (1988).
53. O'Shea A, Boaz AL, Chambers M. A hierarchy of power: the place of patient and public involvement in healthcare service development. *Front Sociol.* (2019) 4:1–12. doi: 10.3389/fsoc.2019.00038
54. Nordling L. Research: Africa's fight for equality. *Nature.* (2015) 521:24–5. doi: 10.1038/521024a
55. Powell MP, Young AJ, Kim H. A journey in capacity building: revisiting the mullins framework for meaningfully engaging patients in patient centered outcomes research. *Front Public Health.* (2018) 6:343. doi: 10.3389/fpubh.2018.00343
56. Ceasar J, Peters-Lawrence MH, Mitchell V, Powell-Wiley TM. The Communication, Awareness, Relationships and Empowerment (C.A.R.E.) Model: an effective tool for engaging Urban Communities in Community-Based Participatory Research. *Int J Environ Res Public Health.* (2017) 14:1422. doi: 10.3390/ijerph14111422
57. Hofstede G. *Culture's Consequences, Comparing Values, Behaviors, Institutions, and Organizations Across Nations.* Newbury Park, CA: Sage (2003).
58. Claramita M, Utarini A, Soebono H, Van Dalen J, Van der Vleuten C. Doctor–patient communication in a Southeast Asian setting: the conflict

between ideal and reality. *Adv Health Sci Educ Theory Pract.* (2011) 16:69–80. doi: 10.1007/s10459-010-9242-7
59. Maguire P, Piceathly C. Key communication skills and how to acquire them. *BMJ.* (2002) 325:697–700. doi: 10.1136/bmj.325.7366.697
60. Helman C. *Culture, Health and Illness.* Oxford: Butterworth-Heinemann (1994).
61. Wilson Y, White A, Jefferson A, Danis M. Intersectionality in clinical medicine: the need for a conceptual framework. *Am J Bioeth.* (2019) 19:8–19. doi: 10.1080/15265161.2018.1557275
62. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet.* (2020) 396:413–46. doi: 10.1016/S0140-6736(20)30367-6
63. INVOLVE. *Briefing Notes for Researchers: Involving the Public in NHS, Public Health and Social Care Research.* (2012). Available online at: https://www.invo.org.uk/wp-content/uploads/2012/04/INVOLVEBriefingNotesApr2012.pdf (accessed September 11, 2019).
64. Spector A, Stoner CR, Chandra M, Vaitheswaran S, Du B, Comas-Herrera A, et al. Mixed methods implementation research of cognitive stimulation therapy (CST) for dementia in low and middle-income countries: study protocol for Brazil, India and Tanzania (CST-International). *BMJ.* Open. (2019) 9:e030933. doi: 10.1136/bmjopen-2019-030933
65. Bernal G, Jiménez-Chafey MI, Domenech Rodríguez MM. Cultural adaptation of treatments: a resource for considering culture in evidence-based practice. *Prof Psychol Res Pract.* (2009) 40:361–8. doi: 10.1037/a0016401
66. Stoner CR, Lakshminarayanan M, Durgante H, Spector AJA. Psychosocial interventions for dementia in low-and middle-income countries (LMICs): a systematic review of effectiveness and implementation readiness. *Aging Mental Health.* (2019):1–12. doi: 10.1080/13607863.2019.1695742
67. Barrera M Jr, Castro FG. A heuristic framework for the cultural adaptation of interventions. *Clin Psychol Sci Pract.* (2006) 13:311–6. doi: 10.1111/j.1468-2850.2006.00043.x
68. Bethell J, Commisso E, Rostad HM, Puts M, Babineau J, Grinbergs-Saull A, et al. Patient engagement in research related to dementia: a scoping review. *Dementia.* (2018) 17:944–75. doi: 10.1177/1471301218789292
69. Gamble C, Dudley L, Allam A, Bell P, Goodare H, Hanley B, et al. Patient and public involvement in the early stages of clinical trial development: a systematic cohort investigation. *BMJ Open.* (2014) 4:e005234.doi: 10.1136/bmjopen-2014-005234
70. Dudley L, Gamble C, Preston J, Buck D, EPIC Patient Advisory Group, Hanley B, et al. What difference does patient and public involvement make and what are its pathways to impact? Qualitative study of patients and researchers from a cohort of randomised clinical trials. *PLoS ONE.* (2015) 10:e0128817. doi: 10.1371/journal.pone.0128817
71. Dudley L, Gamble C, Allam A, Bell P, Buck D, Goodare H, et al. A little more conversation please? Qualitative study of researchers' and patients' interview accounts of training for patient and public involvement in clinical trials. *Trials.* (2015) 16:190. doi: 10.1186/s13063-015-0667-4
72. Staniszewska S, Brett J, Mockford C, Barber R. The GRIPP checklist: strengthening the quality and transparency of reporting for patient and public involvement in research. *Int J Technol Assess Health Care.* (2011) 27:391–9. doi: 10.1017/S0266462311000481
73. Miah J, Dawes P, Leroi I, Starling B, Lovell K, Price O, et al. Evaluation of a research awareness training programme to support research involvement of older people with dementia and their care partners. *Health Expect.* (2020) 23:1177–90. doi: 10.1111/hex.13096
74. Edelman N, Barron D. Evaluation of public involvement in research: time for a major re-think? *J Health Serv Res Policy.* (2016) 21:209–11. doi: 10.1177/1355819615612510
75. Ocloo JE, Fulop NJ. Developing a "critica" approach to patient and public involvement in patient safety in the NHS: learning lessons from other parts of the public sector? *Health Expect.* (2012) 15:424–32. doi: 10.1111/j.1369-7625.2011.00695.x
76. Boyd EM, Fales AW. Reflective learning: the key to learning from experience. *J Humanist Psychol.* (1983) 23:99–117. doi: 10.1177/0022167883232011

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

SYSTEMATIC REVIEW
published: 25 March 2021
doi: 10.3389/fneur.2021.627761

Dominant and Modifiable Risk Factors for Dementia in Sub-Saharan Africa: A Systematic Review and Meta-Analysis

Akin Ojagbemi[1]*, *Akinkunmi Paul Okekunle*[2,3] and *Opeyemi Babatunde*[4]

[1] Department of Psychiatry, College of Medicine, University of Ibadan, Ibadan, Nigeria, [2] Department of Epidemiology and Medical Statistics, College of Medicine, University of Ibadan, Ibadan, Nigeria, [3] Department of Food and Nutrition, College of Human Ecology, Seoul National University, Seoul, South Korea, [4] School of Medicine Primary Care Center Versus Arthritis Keele University, Staffordshire, United Kingdom

OPEN ACCESS

Edited by:
Agustin Ibanez, Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina

Reviewed by:
Serhiy Dekhtyar, Karolinska Institutet (KI), Sweden
Arun Bokde, Trinity College Dublin, Ireland

***Correspondence:**
Akin Ojagbemi
drakinjagbemi@yahoo.com; aa.ojagbemi@ui.edu.ng

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: *10 November 2020*
Accepted: *25 February 2021*
Published: *25 March 2021*

Citation:
Ojagbemi A, Okekunle AP and Babatunde O (2021) Dominant and Modifiable Risk Factors for Dementia in Sub-Saharan Africa: A Systematic Review and Meta-Analysis. Front. Neurol. 12:627761. doi: 10.3389/fneur.2021.627761

Background: Sub-Saharan Africa (SSA) is projected to have a rapid increase in the number of people living with dementia by 2050. Yet, there is currently no robust evidence on the risk factors for dementia in the sub-region that could inform context specific interventions.

Methods: We conducted a systematic review and meta-analysis of observational studies to determine the dominant and modifiable risk factors for dementia in SSA. We searched MEDLINE, EMBASE, PsychINFO, and African Journals Online using keywords for dementia and Alzheimer's disease as well as the.mp operator for all 47 SSA countries or regions. We included peer-reviewed original studies with epidemiological designs, conducted random effect meta-analysis and determined the dominant and modifiable risk factors for dementia using the inverse of variance method.

Results: A total of 44 studies out of 2,848 met criteria for syntheses. The pooled annual incidence of dementia from 5,200 cohort risk years was 2.0% [(95% Confidence Interval (CI) = 1.0–4.0%)]. The pooled prevalence was 5.0% (95% CI = 2.0–7.0%). Older age was the dominant risk factor for both prevalent [(Standard error (S.E = 0.3, weight = 25.2%)] and incident dementia (S.E = 0.02, weight = 95.8%), while low educational attainment (S.E = 0.19, weight = 32.6%) and poor predementia cognitive functioning at baseline (S.E = 0.2, weight = 20.5%) were the best ranked modifiable risk factor for incident dementia.

Conclusion: Low formal educational attainment which, in SSA, may represent a stable index of low socioeconomic position and health disadvantage over the life course, was the most prominent modifiable risk factor for incident dementia. Findings have implications for deliberate policies targeted at access to education across the life course as a primary prevention strategy against dementia in SSA.

Keywords: low-and middle-income countries, Sub-Saharan Africa, dementia prevalence, dementia incidence, risk factors

INTRODUCTION

Sub-Saharan Africa (SSA) is set to have one of the largest increases in the population of older people worldwide (1), and by 2050, approximately 161 million persons who are 60 years or older will be residents of the sub-region (2). The prevalence and incidence of dementia increases with age (2, 3). Yet, there is currently no robust evidence on the risk factors for dementia in SSA that could inform context specific interventions.

In our previous study (3), we found a 4% pooled prevalence of clinically diagnosed dementia from an overall sample 6964 community-dwellers who were 60 years or older. The previous review (3), and others conducted by Alzheimer's Disease International (2, 4), had searched databases until May 2016, and as there were few published information on incidence of dementia at the time, the evidence was limited to cross-sectional prevalence of dementia in SSA.

In the succeeding four and half years, the literature on the epidemiology of dementia in SSA has been boosted by the publication of new data which have provided valuable additional information. In particular, longitudinal follow-up data (5–9) may serve to build on evidence provided by cross-sectional surveys of dementia in SSA. Such data should allow for an investigation of the links between cross-sectionally identified risk predictors (3) and subsequent onset of dementia. Longitudinal studies may also provide evidence for the relative importance of each modifiable risk factor for incident dementia, information required for the prioritization of primary prevention targets within limited resource contexts of SSA.

The aim of the present study was to conduct a systematic review and meta-analyses of epidemiological studies on dementia in SSA. Specifically, in addition to new information on the annual incidence of dementia in SSA, we aimed to identify key modifiable risk factors for onset of dementia among elders in SSA communities. Estimates of general hospital frequency, community prevalence, as well as their correlates was also profiled.

METHODS

This review followed conventional recommendations for the methodology and reporting of systematic reviews as described in the guidelines of the National Institute of health and Care Excellence (NICE) and Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) (10, 11). We registered our study protocol in the International prospective register of systematic reviews (#CRD42021214843).

Search Strategy

An initial search of the African Journals Online (AJOL) database was conducted on 15th September 2020. This was followed by a search of the MEDLINE, PsychINFO, and Embase databases. For these searches, a facet analyses was constructed using appropriate modifications of the PICO framework (10). The following keywords identified according to facets in the modified PICO were searched with the "explode" operator to retrieve other similar terms: dementia or "Alzheimer's disease", AND epidemiology OR frequency OR prevalence OR incidence OR factors OR "risk factors" OR "associated factors" (**Box 1**). We next combined a search of each of the 47 SSA countries or regions by name using the.mp. operator. A second stage consisting of hand searching of the reference list of relevant articles retrieved from the databases was also implemented. Limits on language and publication dates were not imposed in conducting the searches.

BOX 1 | MEDLINE search terms using the Pubmed interphase.

[(dementia OR "Alzheimer's disease") AND (epidemiology OR frequency OR prevalence OR incidence OR factors OR "risk factors" OR "associated factors' OR outcome OR mortality)] AND (Angola OR Benin OR Botswana OR "Burkina Faso" OR Burundi OR Cameroun OR "Central African Republic" OR Chad OR Congo OR "Cote d'Ivoire" OR Eritrea OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR Guinea-Bissau OR Kenya OR Lesotho OR Liberia OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mozambique OR Namibia OR Niger OR Nigeria OR Rwanda OR Senegal OR "Sierra Leone" OR Somalia OR "South Africa" OR "United Republic of Tanzania" OR Togo OR Uganda OR Zaire OR Zambia OR Zimbabwe OR "Sub Saharan Africa" OR sub-Saharan Africa) AND ((y_5[Filter]) AND (humans[Filter])).

Inclusion Criteria

Studies were included if; (1) they investigated epidemiological phenomena such as frequencies, prevalence, incidence, risk or associated factors, (2) they included participants with any type of dementia regardless of setting, method of ascertainment or diagnosis, (3) descriptive and analytical cross-sectional studies, prospective and retrospective cohort studies, case control studies, randomized controlled trials, non-randomized controlled trials, as well as quasi-experimental studies.

Exclusion Criteria

We excluded the following types of studies, (1) review papers, case series, individual case reports, expert opinions, discussion papers, and position papers; and (2) studies focusing solely on qualitative data.

Study Assessments and Data Extraction

Study assessment for inclusion and exclusion criteria as well as subsequent data extraction was conducted by two independent assessors (AO and APO) based on the descriptions in the original article. The following information were extracted from each included study: first author name, publication year, diagnostic criteria, sample size, average age at baseline, the proportion of females, hospital frequency, community prevalence, average follow-up time, cohort risk years, annual incidence, adjusted relative risks/hazard ratios/odds ratios (RRs/HRs/ORs) with their 95% confidence intervals (Cis), the number of participants and cases for each exposure level and the main covariates of Alzheimer's disease or dementia. Only studies with usable data and appropriate analytical techniques were combined in meta-analyses.

Statistical Methods

Meta-analysis was conducted using estimates reported in the original articles. The 95% C.I of each estimate was used to generate standard errors (S.E) using methodologies developed by the Cochrane collaboration (12). The summary estimates together with their S.E are presented.

As heterogeneity was expected due to differences in the type of dementia assessments (clinical diagnostic criteria or rating scales) as well as setting of studies, a random effect meta-analysis model was chosen. To reduce the extent of methodological heterogeneity, we combined studies with similar diagnostic procedures in the same subgroup meta-analysis. To determine the extent of statistical heterogeneity, we estimated the percentage of total variation in estimates reported across studies that is due to heterogeneity, rather than chance. This was computed using the I^2 test. In the present study, values of $I^2 > 50\%$ were chosen as evidence of statistical heterogeneity (13). Publication bias was assessed with the aid of a funnel plot.

For the objective of investigating the most important factors associated with dementia by rank, we used the log of effect ratios and the corresponding S.E of the associations. The inverse of variance method was used for weighting. All analyses were conducted using the Cochrane review manager (Revman) version 5.3 software (14).

RESULTS

The combined database and hand searches identified a total of 3127 records. After removing duplicates in the databases ($N = 1{,}648$ articles), 1,479 titles and abstracts were screened. From these, 51 articles with information relevant to the review were retrieved and their full text evaluated. After reading through the texts, 7 articles were further excluded because they examined broadly defined cognitive impairment and did not provide information about participants with dementia (**Figure 1**). Of the Seven excluded articles, one each was from Senegal (15), Cameroun (16), South Africa (17), Tanzania (18), and Rwanda (19), while the remaining two were from Nigeria (20, 21).

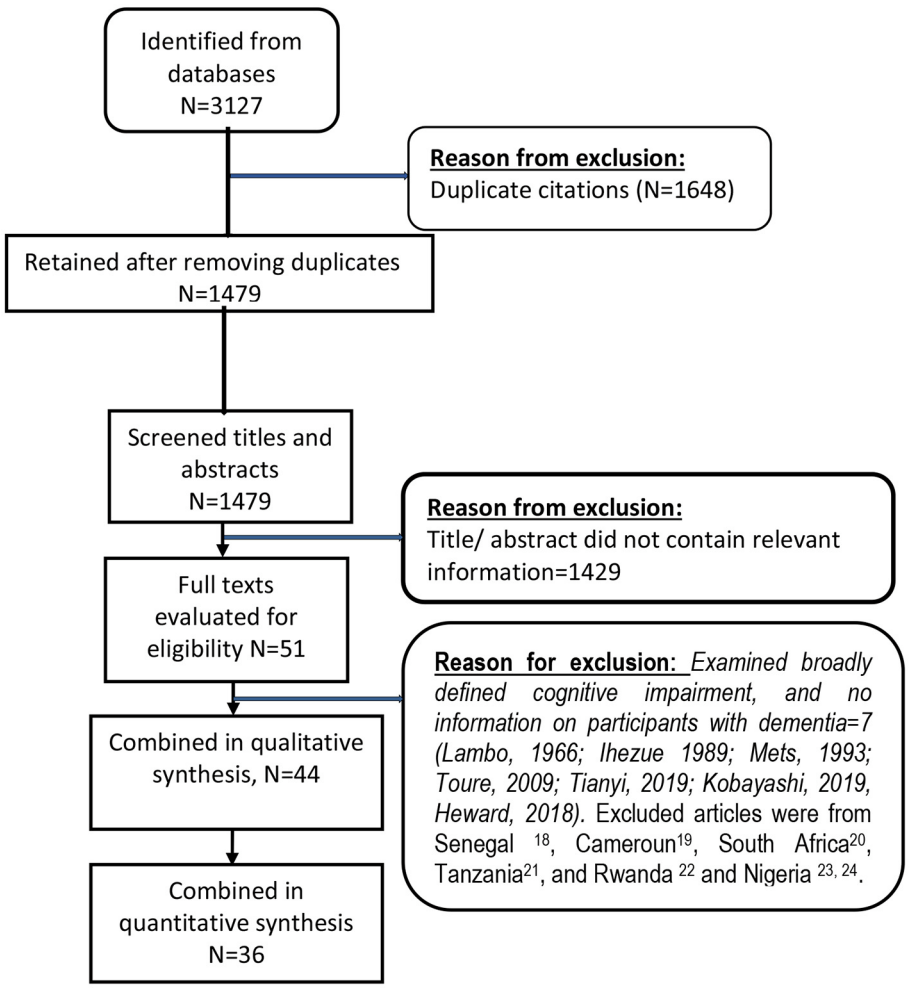


FIGURE 1 | Flow chart showing details of included and excluded studies.

TABLE 1 | Characteristics of studies of prevalence and incidence of dementia in sub-Saharan Africa.

References	Country	Setting	Definition of dementia	Sample size	Female%	Age, mean (SD)	Frequency (%)
Hospital or nursing home studies							
Ogunniyi et al. (22)	Nigeria	General hospital medical In-patients	ICD 9 criteria	37	24.3	67 (9.0)	0.6
Osuntokun et al. (23)	Nigeria	Autopsy	Histological hallmarks	198	46.0	40-85	0
Baiyewu et al. (30)	Nigeria	Nursing homes	DSM III-R criteria	23	47.8	78.7 (8.6)	48
Napon et al. (27)	Burkina Faso	General hospital In- and outpatient	DSM IV	15,817	33.3	62.2[f]	0.5
Siddiqi et al. (25)	Zambia	General hospital Out/Inpatient	Clinician best judgment	811	52.2	39[f] (15–80)[g]	2.9/4.0 Out/Inpatient
Toure et al. (31)	Senegal	Primary care center for the elderly	Clinician best judgment	507	<50	72.4 (5.25)	8.87
Amoo et al. (29)	Nigeria	Neuropsychiatric hospital In- and out-patient	ICD 10 criteria	240,294	52.8	70.1 (9.8)	0.05
Ramlall et al. (32)	South Africa	Residential homes for the elderly	DSM IV-TR	140	69.3	75.2 (8.9)	7.9
Ouango et al. (24)	Burkina Faso	General hospital In- and outpatients	Clinician best judgment	7,974	40.2	49–90[g]	1.9
Callixte et al. (26)	Cameroun	Neurology Outpatient	ICD 10 criteria	912	50.8	68.8 (7.2)	12.4
Paddick et al. (28)	Tanzania	General hospital medical In-patients	DSM IV	507	44.4	75[a] (67–81)[g]	18.7

References	Country/Location	Definition of dementia	Sample size	Female (%)	Age, mean (SD)	Prevalence (%)
Community based cross-sectional surveys						
Clinically diagnosed dementia						
Osuntokun et al. (33)	Nigeria (Idikan)	DSM III-R	930	61.2	40–85	0
Hendrie et al. (6)[a]	Nigeria (Idikan)	ICD 10/DSM III-R	2,494	71.4	81.0 (9.9)	2.29
Guerchet et al. (34)	Benin (Djidja)	DSM-IV	502	57.0	76.1 (9.4)	2.6
Yusuf et al. (35)	Nigeria (Zaria)	ICD 10/DSM IV	322	60.2	75.5 (9.4)	2.8
Guerchet et al. (36)[b]	CAR (Bangui)	DSM IV/Alzheimer's Association	496	55.6	77.4 (7.3)	8.1
Guerchet et al. (36)[b]	Congo (Brazzaville)	DSM IV/Alzheimer's Association	520	40.9	74.7 (6.7)	6.7
Paddick et al. (37)[c]	Tanzania (Hai)	DSM IV	1,198	56.2	≥70[e]	6.4
Ogunniyi et al. (38)	Nigeria (Lalupon)	DSM IV/Alzheimer's Association	613	69.7	72.9 (8.9)	2.9
Guerchet et al. (4)[d]	CAR (Nola)	DSM IV	475	N/A	N/A	8.4
Guerchet et al. (4)[d]	Congo (Gamboma)	DSM IV	529	N/A	N/A	5.7
		Rating scales defined dementia				
Ochayi et al. (39)	Nigeria (Jos)	CSID	280	89.0	77.2 (9.7)	6.4
Gureje et al. (40)	Nigeria (West/Central regions)	10 Words list learning/Delayed recall test	2,152	53.8	74.5 (8.4)	10.1
Paraiso et al. (41)	Benin	CSID/Five word test	1,139	54.1	73.4 (7.2)	3.7
Van der Poel and Heyns (42)	South Africa (Muangang)	CSID, Geriatric mental state, 10 words list	200	N/A	N/A	6
de Jager et al. (43)	South Africa (Eastern Cape)	CSID	1,382	68.6	71.3 (8.3)	11

References	Country/location	Definition of dementia	Years of observation (Cohort risk)	Female %	Age, mean (SD)	Annual Incidence (%)
Community-based longitudinal observation for incident dementia						
Hendrie et al. (6)	Nigeria (Idikan)	CERAD Neuropsychological battery/ICD 10 and DSM III-R criteria	5 (2459)	58.9	77.9 (8.0)	1.4

(Continued)

TABLE 1 | Continued

References	Country/location	Definition of dementia	Years of observation (Cohort risk)	Female %	Age, mean (SD)	Annual Incidence (%)
Gureje et al. (7)	Nigeria (West and North-central regions)	10-word listing, delayed recall tests and CHIF	3 (1225)	40.4	74.5 (8.4)	2.2
Samba et al. (8)	Rural and Urban Congo	DSM IV	2 (847)	≈59.7	73.0 (6.6)	2.38
Ojagbemi et al. (5)	West and North-central Nigeria	10-word listing, Delayed recall tests and CHIF	5 (1894)	40.2	74.4 (8.8)	2.1
Gao et al. (9)	Western Nigeria	CERAD Neuropsychological battery/ICD 10 and DSM III-R criteria	N/A (1895)	67	75.7 (5.4)	1.4

Not included in the table are thirteen duplicate publications from six major research programs (Indianapolis Ibadan Dementia Project, Epidemiology of Dementia in Central Africa-EDAC-, Epidemiology of Dementia in Central Africa-EPIDEMCA-, EPIDEMCA Follow-up, Ibadan Study of Aging, Kilinmajaro cohort from the Hai District of rural Tanzania); SD, Standard deviation; DSM, Diagnostic and Statistical Manual of Mental disorders; III-R, Text revision of 3rd edition; IV, 4th Edition; IIDP, Indianapolis Ibadan Dementia Project; ICD 10, 10th Revision of the International Classification of Diseases; EDAC, Epidemiology of Dementia in Central Africa; CAR, Central African Republic; EPIDEMCA, Epidemiology of Dementia in Central Africa; CSID, Community Screening Instrument for Dementia.

[a] *Reported in four studies with 21.6% also meeting 10/66 dementia research group criteria.*

[b] *Reported in five studies.*

[c] *Reported in three studies.*

[d] *Reported in four studies.*

[e] *All participants were 70 years or older.*

[f] *Median.*

[g] *Range.*

Studies included were published between February 1992 and December 2019. Over 60% of identified studies were publications of data from 6 major research programs (Indianapolis Ibadan Dementia Project, Epidemiology of Dementia in Central Africa-EDAC-, Epidemiology of Dementia in Central Africa-EPIDEMCA-, EPIDEMCA Follow-up, Ibadan Study of Aging, Kilinmajaro cohort from the Hai District of rural Tanzania). Studies represented all regions in SSA: West, East, Central, and Southern Africa. However, about 45.2% of identified studies were from one country, Nigeria.

Types of Study Settings and Designs

Eight studies (22–29) relied on hospital records (**Table 1**). Also included in **Table 1** are two report of cognitive examination conducted on older people living in residential or nursing homes in Nigeria (30) and South Africa (32), respectively. One study was conducted in a Senegalese primary health center (PHC) (31) (**Table 1**). The majority (64.5%) of identified studies were community based, including reports of eight prospective longitudinal observations of between 2- and 10-years duration (5–9, 44–46).

Ascertainment of Dementia

The majority of included studies used a two staged procedure and made formal clinical diagnoses of dementia according to codified criteria (47, 48). However, two hospital based (24, 25) and one PHC study (31) relied on clinicians' best judgement of dementia. Also, seven community based cross-sectional surveys (5, 7, 39–41, 43, 49) used rating scales, including the community screening instrument for dementia, ten words list and delayed recall test, five words test and geriatric mental state examination.

Meta-Analysis

A total of 36 studies provided usable data for quantitative syntheses (**Figure 1**).

Prevalence and Incidence of Dementia

Figure 2 presents a forest plot showing the prevalence and incidence of dementia in SSA. Pooled data from seven studies including 266, 352 patients generated a frequency of 3.0% (95% C.I = 1.0–5.0%) for dementia in hospital settings. There was an indication of statistical heterogeneity in this estimate ($I^2 = 85\%$, $p < 0.001$). Heterogeneity was investigated and found to be due to rate outliers of 12.4% (26) and 18.7% (28) reported in two studies. A community prevalence of 9.0% (95% C.I = 6.0–11.0%) was estimated from five studies including 5,153 persons who underwent rating scales assessments for dementia. The pooled community prevalence of clinically diagnosed dementia from ten studies including 8,069 participants was 5.0% (95% C.I = 2.0–7.0%). The pooled annual incidence of dementia from five studies with a total of 5,200 cohort risk years was 2.0% (1.0–4.0%).

Risk Factors for Dementia

Older age was the most cited and independent factor associated with prevalent dementia (31, 34, 35, 39–41, 50–53) in SSA (**Figure 3**). Older age was also the dominant risk factor for incident dementia in the sub-region (**Table 2**). **Figure 4** contains the pooled modifiable risk factors for incident dementia in SSA ranked according to estimates of S.Es of their independent association with incident dementia. The strongest evidence on modifiable risk factors is the association of low educational attainment and poor pre-dementia cognitive functioning (cognitive reserve) with incident dementia. The association of vascular and other social risk factors was less precise by demonstrating large S.Es (**Figure 4**).

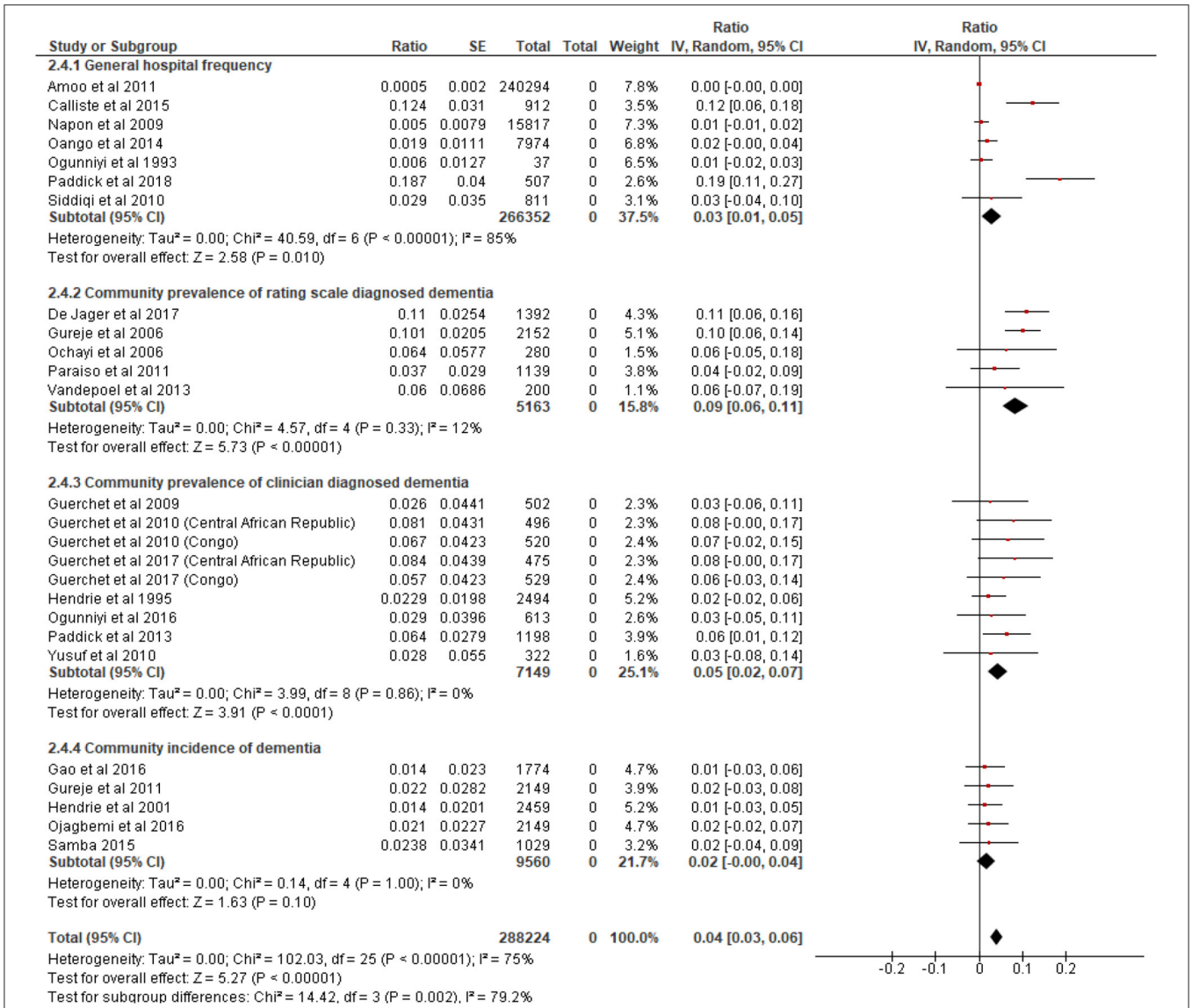


FIGURE 2 | Forest plot showing hospital frequency, community prevalence and incidence of dementia in sub-Saharan Africa. We centered the display of the estimates on the point of zero for better illustration.

Publication Bias and Sensitivity Analysis

The funnel plot in **Supplementary Figure 1** showed no clear evidence of publication bias. Sensitivity analyses conducted according to geographical location of studies suggest that studies from Nigeria reported distinctly low rates of dementia compared with studies conducted in other parts of SSA (**Supplementary Figure 2**).

DISCUSSION

The pooled annual incidence of dementia in SSA is ≈2%, while the pooled prevalence is ≈5 and 9%, respectively, when diagnosed using clinical assessment criteria and rating scales. Age was the dominant risk factor for both prevalent and incident dementia, while low educational attainment and poor pre-dementia cognitive functioning were the prominent modifiable risk factors for incident dementia in SSA.

Our findings overlap with pooled global estimates (54) of dementia prevalence, incidence and dominant risk factors as well as estimates derived from other low- or middle-income countries (LMICs) (54, 55). Notably, there is still a significant gap in the literature on the pooled incidence of dementia from across LMICs to which our findings could be compared (54). Our current estimate of 5% prevalence of dementia is higher than our previous rate of 4% (3) because of the inclusion of data from six additional studies: two from South Africa and one each from Congo, Central African Republic, Tanzania, and Nigeria. The

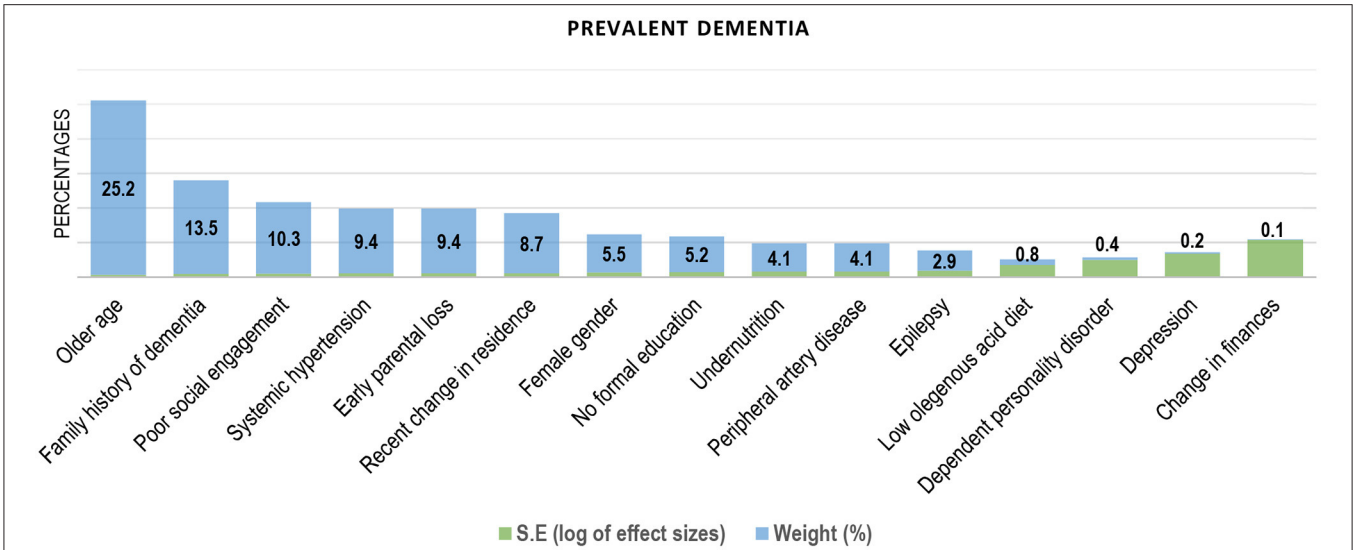


FIGURE 3 | Factors associated with prevalent dementia in Sub-Saharan Africa (ranked by the inverse of variance method).

TABLE 2 | Independent risk factors for incident dementia in Sub-Saharan Africa (ranked by the inverse of variance method).

Independently associated factors	Standard errors	Weight %
Age	0.02	95.8
Low formal education	0.19	1.1
Poor predementia cognitive functioning	0.24	0.7
Apolipoprotein E4 homozygosity	0.29	0.5
Rural place of residence	0.35	0.3
Female gender	0.37	0.3
Systemic hypertension	0.38	0.3
Cholesterol	0.38	0.3
Poor social engagement	0.42	0.2
Low density lipoprotein	0.45	0.2
History of smoking	0.45	0.2
Low occupational attainment	0.46	0.2
Low economic status	0.67	0.1

estimated 2% annual incidence of dementia in the present study is also higher than the 1.3% estimated previously (2, 4). These increases in rates may suggest greater awareness of dementia in the sub-region since 2016 or, otherwise, more people may now be living with dementia in SSA compared to when pooled estimates of dementia incidence and prevalence were last conducted. An increase in rates of dementia over time could be expected as it is in keeping with the phenomenon of global population aging and the projected increase in the number of older people living with dementia in SSA and other LMIC contexts (1).

The inclusion of six additional studies estimating prevalence of dementia in five SSA countries thus meant that our pooled estimate of prevalence is likely more reflective of the occurrence of dementia in the sub-region. However, some of the risk factors identified from cross-sectional studies may be prone to the effect of reverse causality. This effect may have resulted in larger sizes of association between dementia and, for example, poor social engagement or recent change in residence (as would be expected for placement in long term institutional care). Conversely, the impact of factors such as depression, undernutrition and changes in finances, which may be increasingly associated with dementia overtime may be under-estimated in cross-sectional investigations. This is because cross-sectional analyses are inadequate in providing robust evidence for the direction of association between relevant health conditions overtime.

Our meta-analysis of modifiable risk factors for incident dementia included five studies. Previous systematic reviews of incidence of dementia in SSA have relied on two (2) or four studies (4). We were able to identify one additional study estimating the incidence of dementia in rural and urban Congo after a follow-up period of 2 years. Unlike our estimate of prevalence, the annual incidence of dementia reported in the present study is unlikely to be generalizable to all SSA regions. This is partly because 45.2% of the evidence is from one country, Nigeria. A sensitivity analyses conducted by geographical location of identified studies showed that studies from Nigeria reported distinctly low rates of dementia relative to studies conducted in other parts of SSA. This would suggest that the relatively large numbers of studies from Nigeria could have led to an underestimation, rather than overestimation, of the true rates of dementia in SSA. Even though our funnel plot showed no clear evidence of publication bias, the observation that many African studies are published in less visible or less accessible media could also have affected our pooled estimates. We note that our search strategy included the African journals online database. However, our failure to incorporate gray literature in our searches would mean that a few studies may have been missed, and their results not included in our meta-analyses.

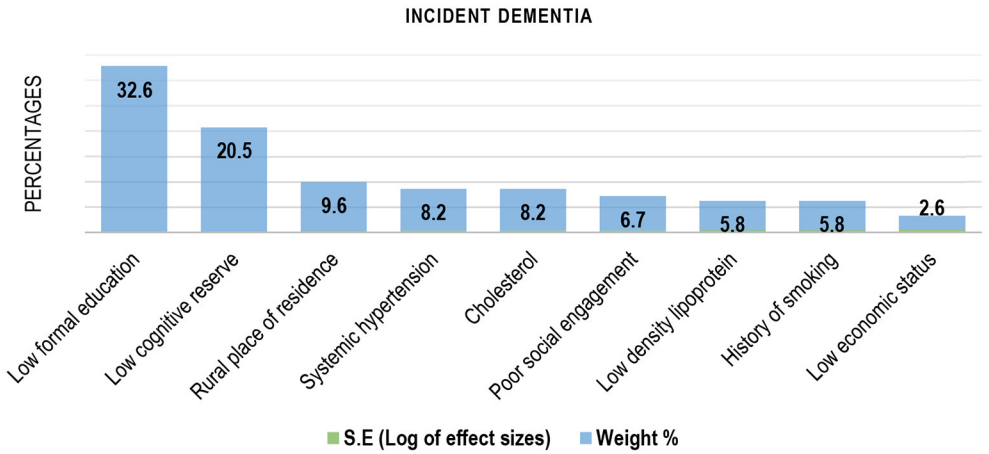


FIGURE 4 | Modifiable risk factors for Incident dementia in Sub-Saharan Africa (ranked by the inverse of variance method).

Most of the primary citations identified for the present systematic review did not report rates of dementia according to relevant age groups and sex. As such, our reported estimates are not age or gender standardized. This methodological limitation could, in part, have accounted for the differences in rates reported in the present study and those reporting age and gender standardized rates (2). Variations in pooled rates of dementia have also been previously reported to reflect the use of different dementia-ascertainment procedures (56). In the present systematic review, we have combined data comprising similar diagnostic procedures in the same meta-analysis model. Whereas, previous estimates had been based on data pooled from studies regardless of dementia ascertainment procedures.

Our findings in relations to risk factors for dementia in the present study were not surprising. Life course higher educational attainment and pre-dementia cognitive functioning have been demonstrated as indices of biological (57) and socio-economic (58) protection against the neuro-degenerative changes that may result in dementia in older people. This phenomenon is often viewed as being indicative of cognitive reserve (59). Similar to reports from higher income countries (56–58), these proxy indicators of cognitive reserve also appear to have important association with incident dementia in SSA.

In SSA, low formal educational attainment in particular may be considered as a stable index of low economic status over the life course (60). In most of SSA were there is a steady socio-economic differential in health across the lifespan (60), the disadvantage of belonging in a low economic status may accumulate over the life-course (61). This accumulation may, in turn, translate to significant risks to health, including the possibility of dementia by the age of 65 years (62). We note that educational attainment was assessed in the reviewed studies as either the number of years of formal education completed or whether participants attended primary, secondary or higher education. On the other hand, pre-dementia cognitive functioning was defined by the performance of participants on the learning phase of the 10-word listing test (10-WDRT). Scores on this test were dichotomised as "poor," for dementia free participants who scored <1 standard deviation (SD) below the mean score for 3 administrations of the 10-WDRT, and good for the other dementia free respondents (63).

Research and Clinical Implications

In line with the phenomenon of socio-economic differential in health, individuals surviving to old age in most of SSA, where life expectancy at birth is relatively low (64), may include a comparatively healthier section of the population. This group may also have a lower latent risk of dementia while those with higher cumulative morbidity may be more likely to die at a younger ages (60). In a country like Nigeria, as an example, it is projected that despite an average life expectancy at birth of about 52 years (65), the population surviving to the age of 65 years may have the prospect of an additional 15 years of life (66, 67). It is important to note that Nigeria also provided about 50% of the studies included in the present review.

Despite biases related sample size which was partly due to several studies reporting from the same cohort, our meta-analysis makes several additions to the literature on the epidemiology of dementia in SSA. First, the addition of six new studies published in the last 4 years and a half resulted in some increase in sample size, as well as the possibility of greater precision and generalization of our findings to most of SSA. Second, we were able to conduct sub-group analyses demonstrating that pooled rates of dementia are higher when combining studies using rating scales ascertainment. Whereas, hospital-based studies as well as those using clinical diagnostic criteria report lower rates. The low frequency of dementia found in hospital-based studies included in the present systematic review may reflect a possible low healthcare utilization which may also result from prevailing sociocultural practices and pathways to care (68).

Conclusion

The estimated pooled annual incidence of clinically diagnosed dementia in SSA is ≈2%, and the prevalence is ≈5%. Estimated rates vary according to dementia assessment procedures and types of study populations. As reported globally, older age was

the dominant risk factor for dementia in the present study, while low educational attainment was the most prominent modifiable factor. The present study adds to the literature on the epidemiology of dementia in SSA by generating potentially more precise and generalizable estimates due to larger sample size. The findings have implications for deliberate policies targeted at access to education across the life course as a primary prevention strategy against dementia in SSA.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

AO conceived and designed the study. Material preparation, data collection and analysis were performed by AO and APO. The first draft of the manuscript was written by AO and OB. All authors read and approved the final draft.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.627761/full#supplementary-material

REFERENCES

1. United Nations. *World Population Ageing 2019*. New York, NY: United Nations, Department of Economic and Social Affairs PD (2020).
2. Alzheimer's Disease International. *World Alzheimer Report 2015. The Global Impact of Dementia an Analysis of Prevalence, Incidence, Cost & Trends*. London: Alzheimer's Disease International (2015).
3. Ojagbemi A, Bello T. The low prevalence of dementia in Sub-Saharan Africa- a systematic review and meta-analysis of geographical variations and associations. *Afr J Med Med Sci.* (2020) 49:9–21.
4. Guerchet M, Mayston R, Prince M, Aboderin I, Akinyemi R, Paddick SM, et al. *Dementia in SubSaharan Africa, Challenges and Opportunities*. London: Alzheimer's Disease International. (2017). p. 16–34.
5. Ojagbemi A, Bello T, Gureje O. Cognitive reserve, incident dementia, and associated mortality in the ibadan study of ageing. *J Am Geriatr Soc.* (2016) 64:590–5. doi: 10.1111/jgs.14015
6. Hendrie HC, Ogunniyi A, Hall KS, Baiyewu O, Unverzagt FW, Gureje O, et al. Incidence of dementia and Alzheimer disease in 2 communities: Yoruba residing in Ibadan, Nigeria, and African Americans residing in Indianapolis, Indiana. *JAMA*. (2001) 285:739–47. doi: 10.1001/jama.285.6.739
7. Gureje O, Ogunniyi A, Kola L, Abiona T. Incidence of and risk factors for dementia in the Ibadan study of aging. *J Am Geriatr Soc.* (2011) 59:869–74. doi: 10.1111/j.1532-5415.2011.03374.x
8. Samba H, Guerchet M, Bandzouzi BN, Kehoua GTC, Mbelesso P, Lacroix P, et al. Incidence of dementia among older adults in central Africa: first results from the republic of Congo in the EPIDEMCA-FU study. *Alzheimers Dement.* (2015) 11:P221–P2. doi: 10.1016/j.jalz.2015.07.247
9. Gao S, Ogunniyi A, Hall KS, Baiyewu O, Unverzagt FW, Lane KA, et al. Dementia incidence declined in African-Americans but not in Yoruba. *Alzheimers Dement.* (2016) 12:244–51. doi: 10.1016/j.jalz.2015.06.1894
10. National Institute for Health and Care Excellence. *The Guidelines Manual: Process and Method Guide*. London: National Institute for health and Care Excellence (2012).
11. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Open Med.* (2009) 3:e123–30. doi: 10.1371/journal.pmed.1000097
12. Cochrane Collaboration. *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester: John Wiley (2011).
13. Habib AG, Yakasai AM, Owolabi LF, Ibrahim A, Habib ZG, Gudaji M, et al. Neurocognitive impairment in HIV-1-infected adults in Sub-Saharan Africa: a systematic review and meta-analysis. *Int J Infect Dis.* (2013) 17:e820–31. doi: 10.1016/j.ijid.2013.06.011
14. *The Cochrane Collaboration. Review Manager (RevMan) [Computer program]. Version 5.3. ed*. The Nordic Cochrane Centre, Copenhagen: The Cochrane Collaboration (2014).
15. Toure K, Coumé M, Ndiaye Ndongo ND, Thiam MH, Zunzunegui MV, Bacher Y, et al. Risk factors for dementia in a senegalese elderly population. *Afr J Neurol Sci.* (2009) 28:1–15. doi: 10.4314/ajns.v28i1.55126
16. Tianyi FL, Agbor VN, Njamnshi AK, Atashili J. Factors associated with the prevalence of cognitive impairment in a rural elderly cameroonian population: a community-based study in Sub-Saharan Africa. *Dement Geriatr Cogn Disord.* (2019) 47:104–13. doi: 10.1159/000496825
17. Kobayashi LC, Mateen FJ, Montana L, Wagner RG, Kahn K, Tollman SM, et al. Cognitive function and impairment in older, rural South African adults: evidence from "health and aging in africa: a longitudinal study of an INDEPTH community in rural South Africa". *Neuroepidemiology.* (2019) 52:32–40. doi: 10.1159/000493483
18. Heward J, Stone L, Paddick SM, Mkenda S, Gray WK, Dotchin CL, et al. A longitudinal study of cognitive decline in rural Tanzania: rates and potentially modifiable risk factors. *Int Psychogeriatr.* (2018) 30:1333–43. doi: 10.1017/S1041610217002861
19. Mets TF. The disease pattern of elderly medical patients in Rwanda, central Africa. *J Trop Med Hyg.* (1993) 96:291–300.
20. Lambo TA. Psychiatric disorders in the aged: epidemiology and preventive measures. *West Afr Med J.* (1966) 15:121–4.
21. Ihezue UH, Okpara E. Psychiatric disorders of old age in Enugu, Nigeria. Sociodemographic and clinical characteristics. *Acta psychiatrica Scandinavica.* (1989) 79:332–7. doi: 10.1111/j.1600-0447.1989.tb10267.x
22. Ogunniyi A, Lekwauwa UG, Falope ZF, Osuntokun BO. Clinically-diagnosed dementing illnesses in Ibadan: features, types and associated conditions. *Afr J Med Med Sci.* (1993) 22:61–4.
23. Osuntokun BO, Ogunniyi A, Junaid TA, Lekwauwa UG. Autopsy survey for Alzheimer's disease in Nigerian Africans: a preliminary report. *Afr J Med Med Sci.* (1995) 24:75–9.
24. Ouango JG, Goumbri P, Karfo K, Nana B, Ouédraogo A. Socio-demographic, clinical and therapeutic characteristics of dementia in Burkina Faso. *Neurol Psychiatr Geriatr.* (2014) 14:163–8. doi: 10.1016/j.npg.2013.11.003
25. Siddiqi OK, Atadzhanov M, Birbeck GL, Koralnik IJ. The spectrum of neurological disorders in a Zambian tertiary care hospital. *J Neurol Sci.* (2010) 290:1–5. doi: 10.1016/j.jns.2009.12.022
26. Callixte KT, Clet TB, Jacques D, Faustin Y, Francois DJ, Maturin TT. The pattern of neurological diseases in elderly people in outpatient consultations in Sub-Saharan Africa. *BMC Res Notes.* (2015) 8:159. doi: 10.1186/s13104-015-1116-x
27. Napon C, Traore S, Idris S, Niakara A, Ouango GJ, Kabré A, et al. Dementias in sub-Saharan Africa: clinical and etiological aspects in hospital environment in ouagadougou (Burkina Faso). *Afr J Neurol Sci.* (2009) 28:unpaginated. doi: 10.4314/ajns.v28i1.55132
28. Paddick SM, Lewis EG, Duinmaijer A, Banks J, Urasa S, Tucker L, et al. Identification of delirium and dementia in older medical inpatients in Tanzania: a comparison of screening and diagnostic methods. *J Neurol Sci.* (2018) 385:156–63. doi: 10.1016/j.jns.2017.12.006

29. Amoo G, Akinyemi RO, Onofa LU, Akinyemi JO, Baiyewu O, Ogunlesi AO, et al. Profile of clinically-diagnosed dementias in a neuropsychiatric practice in Abeokuta, south-western Nigeria. *Afr J Psychiatry.* (2011) 14:377–82. doi: 10.4314/ajpsy.v14i5.5
30. Baiyewu O, Adeyemi JD, Ogunniyi A. Psychiatric disorders in Nigerian nursing home residents. *Int J Geriatr Psychiatry.* (1997) 12:1146–50. doi: 10.1002/(SICI)1099-1166(199712)12:12<1146::AID-GPS679>3.0.CO;2-X
31. Toure K, Coume M, Ndiaye M, Zunzunegui MV, Bacher Y, Diop AG, et al. Risk factors for dementia in a senegalese elderly population aged 65 years and over. *Dement Geriatr Cogn Disord Extra.* (2012) 2012:160–8. doi: 10.1159/000332022
32. Ramlall S, Chipps J, Pillay BJ, Bhigjee AL. Mild cognitive impairment and dementia in a heterogeneous elderly population: prevalence and risk profile. *Afr J Psychiatry.* (2013) 16:1–10. doi: 10.4314/ajpsy.v16i6.58
33. Osuntokun BO, Ogunniyi AO, Lekwauwa UG. Alzheimer's disease in Nigeria. *Afr J Med Medical Sci.* (1992) 21:71–7.
34. Guerchet M, Houinato D, Paraiso MN, von Ahsen N, Nubukpo P, Otto M, et al. Cognitive impairment and dementia in elderly people living in rural Benin, west Africa. *Dement Geriatr Cogn Disord.* (2009) 27:34–41. doi: 10.1159/000188661
35. Yusuf AJ, Baiyewu O, Sheikh TL, Shehu AU. Prevalence of dementia and dementia subtypes among community-dwelling elderly people in northern Nigeria. *Int Psychogeriatr IPA.* (2011) 23:379–86. doi: 10.1017/S1041610210001158
36. Guerchet M, M'Belesso P, Mouanga AM, Bandzouzi B, Tabo A, Houinato DS, et al. Prevalence of dementia in elderly living in two cities of Central Africa: the EDAC survey. *Dement Geriatr Cog Disord.* (2010) 30:261–8. doi: 10.1159/000320247
37. Paddick SM, Longdon AR, Kisoli A, Dotchin C, Gray WK, Dewhurst F, et al. Dementia prevalence estimates in sub-Saharan Africa: comparison of two diagnostic criteria. *Glob Health Action.* (2013) 6:19646. doi: 10.3402/gha.v6i0.19646
38. Ogunniyi A, Adebiyi AO, Adediran AB, Olakehinde OO, Siwoku AA. Prevalence estimates of major neurocognitive disorders in a rural Nigerian community. *Brain Behav.* (2016) 6:e00481. doi: 10.1002/brb3.481
39. Ochayi B, Thacher TD. Risk factors for dementia in central Nigeria. *Aging Ment Health.* (2006) 10:616–20. doi: 10.1080/13607860600736182
40. Gureje O, Ogunniyi A, Kola L. The profile and impact of probable dementia in a sub-Saharan African community: results from the Ibadan study of aging. *J Psychosom Res.* (2006) 61:327–33. doi: 10.1016/j.jpsychores.2006.07.016
41. Paraiso MN, Guerchet M, Saizonou J, Cowppli-Bony P, Mouanga AM, Nubukpo P, et al. Prevalence of dementia among elderly people living in Cotonou, an urban area of Benin (West Africa). *Neuroepidemiology.* (2011) 36:245–51. doi: 10.1159/000328255
42. Van der Poel R, Heyns P. Algorithmic case prediction inrelation to local clinician diagnosis in an indigenous SouthAfrican population. In: *27th International Conference of Alzheimer's Disease International (ADI)*. London (2012).
43. de Jager CA, Msemburi W, Pepper K, Combrinck MI. Dementia prevalence in a rural region of South Africa: a cross-sectional community study. *J Alzheimers Dis.* (2017) 60:1087–96. doi: 10.3233/JAD-170325
44. Hall K, Gureje O, Gao S, Ogunniyi A, Hui SL, Baiyewu O, et al. Risk factors and Alzheimer's disease: a comparative study of two communities. *Aust N Z J Psychiatry.* (1998) 32:698–706. doi: 10.3109/00048679809113126
45. Ogunniyi A, Lane KA, Baiyewu O, Gao S, Gureje O, Unverzagt FW, et al. Hypertension and incident dementia in community-dwelling elderly Yoruba Nigerians. *Acta Neurol Scand.* (2011) 124:396–402. doi: 10.1111/j.1600-0404.2011.01491.x
46. Ogunniyi A, Gao S, Unverzagt FW, Baiyewu O, Gureje O, Nguyen JT, et al. Weight loss and incident dementia in elderly Yoruba Nigerians: a 10-year follow-up study. *Int Psychogeriatr IPA.* (2011) 23:387–94. doi: 10.1017/S1041610210001390
47. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental disorders: 4th edition (DSM IV) text revision (ed).* 4th ed. Text revision ed. Washington DC: American Psychiatric Association (1994).
48. World Health Organisation. *International Classification of Diseases: 10th revision (ICD 10).* 10th Revision ed. Geneva: World Health Organisation (1992).
49. Vanderpoel R, Heyns M, Dementia at, Group. R. Algorithmic case prediction of dementia in relation to local clinicain diagnosis in an indegenous South Africa population. In: *27th International Conference of Alzheimer's Disease International London* (2012).
50. Ogunniyi A, Gureje O, Baiyewu O, Unverzagt F, Hall KS, Oluwole S, et al. Profile of dementia in a Nigerian community–types, pattern of impairment, and severity rating. *J Natl Med Assoc.* (1997) 89:392–6.
51. Guerchet M, Mouanga AM, M'Belesso P, Tabo A, Bandzouzi B, Paraiso MN, et al. Factors associated with dementia among elderly people living in two cities in Central Africa: the EDAC multicenter study. *J Alzheimers Dis.* (2012) 29:15–24. doi: 10.3233/JAD-2011-111364
52. Mbelesso P, Tabo A, Guerchet M, Mouanga AM, Bandzouzi B, Houinato D, et al. [Epidemiology of dementia in elderly living in the 3rd borough of Bangui (Central African Republic)]. *Bull Soc Pathol Exot.* (2012) 105:388–95. doi: 10.1007/s13149-012-0247-8
53. Longdon AR, Paddick SM, Kisoli A, Dotchin C, Gray WK, Dewhurst F, et al. The prevalence of dementia in rural Tanzania: a cross-sectional community-based study. *Int J Geriatr Psychiatry.* (2013) 28:728–37. doi: 10.1002/gps.3880
54. Fiest KM, Jette N, Roberts JI, Maxwell CJ, Smith EE, Black SE, et al. The prevalence and incidence of dementia: a systematic review and meta-analysis. *Can J Neurol Sci.* (2016) 43 (Suppl. 1):S3–50. doi: 10.1017/cjn.2016.18
55. Poon AN, Xiang Y, Zavalishina Y, Ayanian S, Aitken CF, Procter AC, et al. Systematic review estimating the burden of dementia in the WHO Southeast Asia Region using Bayesian and frequentist approaches. *J Glob Health.* (2020) 10:020701. doi: 10.7189/jogh.10.020701
56. Prince M, Acosta D, Ferri CP, Guerra M, Huang Y, Llibre Rodriguez JJ, et al. Dementia incidence and mortality in middle-income countries, and associations with indicators of cognitive reserve: a 10/66 Dementia Research Group population-based cohort study. *Lancet.* (2012) 380:50–8. doi: 10.1016/S0140-6736(12)60399-7
57. Jones RN, Manly J, Glymour MM, Rentz DM, Jefferson AL, Stern Y. Conceptual and measurement challenges in research on cognitive reserve. *J Int Neuropsychol Soc.* (2011) 17:593–601. doi: 10.1017/S1355617710001748
58. Scazufca M, Almeida OP, Menezes PR. The role of literacy, occupation and income in dementia prevention: the São Paulo ageing & health study (SPAH). *Int Psychogeriatr IPA.* (2010) 22:1209–15. doi: 10.1017/S1041610210001213
59. Fratiglioni L, Wang HX. Brain reserve hypothesis in dementia. *J Alzheimers Dis.* (2007) 12:11–22. doi: 10.3233/JAD-2007-12103
60. Ojagbemi A, Bello T, Luo Z, Gureje O. Living conditions, low socioeconomic position, and mortality in the Ibadan study of aging. *J Gerontol B Psychol Sci Soc Sci.* (2017) 72:646–55. doi: 10.1093/geronb/gbv093
61. Mensah FK, Hobcraft J. Childhood deprivation, health and development: associations with adult health in the 1958 and 1970 British prospective birth cohort studies. *J Epidemiol Community Health.* (2008) 62:599–606. doi: 10.1136/jech.2007.065706
62. Chandola T, Ferrie J, Sacker A, Marmot M. Social inequalities in self reported health in early old age: follow-up of prospective cohort study. *BMJ.* (2007) 334:990. doi: 10.1136/bmj.39167.439792.55
63. Levy R. Aging-associated cognitive decline. Working Party of the International Psychogeriatric Association in collaboration with the World Health Organization. *Int Psychogeriatr IPA.* (1994) 6:63–8. doi: 10.1017/S1041610294001626
64. Wang H, Dwyer-Lindgren L, Lofgren KT, Rajaratnam JK, Marcus JR, Levin-Rector A, et al. Age-specific and sex-specific mortality in 187 countries, 1970-2010: a systematic analysis for the global burden of disease study 2010. *Lancet.* (2012) 380:2071–94. doi: 10.1016/S0140-6736(12)61719-X
65. *Country Statistics.* (2008). Available online at: www.unicef.org/infobycountry/niger_statistics (accessed December 15, 2014).
66. Gureje O, Ogunniyi A, Kola L, Afolabi E. Functional disability in elderly Nigerians: Results from the Ibadan Study of Aging. *J Am Geriatr Soc.* (2006) 54:1784–9. doi: 10.1111/j.1532-5415.2006.00944.x
67. World Health Organisation. *The World Health Report 2008: Primary Health Care- Now or Never*. Geneva: World Health Organisation (2008).
68. Gureje O, Nortje G, Makanjuola V, Oladeji BD, Seedat S, Jenkins R. The role of global traditional and complementary

systems of medicine in the treatment of mental health disorders. *Lancet Psychiatry*. (2015) 2:168–77. doi: 10.1016/S2215-0366(15)00013-9

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

PERSPECTIVE
published: 15 April 2021
doi: 10.3389/fneur.2021.628368

Bilingualism: A Global Public Health Strategy for Healthy Cognitive Aging

Sahan Benedict Mendis[1]*, *Vanessa Raymont*[2] *and Naji Tabet*[3]

[1] South London and Maudsley NHS Foundation Trust, London, United Kingdom, [2] Oxford Brain Health Clinical Trials Unit, Oxford, United Kingdom, [3] Center for Dementia Studies, Brighton and Sussex Medical School, Brighton, United Kingdom

Dementia is a global public health priority which cost global societies $818 billion in 2015 and is disproportionately impacting low and middle-income countries (LMICs). With limited availability of disease modifying drugs to treat Alzheimer's disease (AD), researchers have increasingly focused on preventative strategies which may promote healthy cognitive aging and mitigate the risk of cognitive impairment in aging. Lifelong bilingualism has been presented as both a highly debated and promising cognitive reserve factor which has been associated with better cognitive outcomes in aging. A recent metanalysis has suggested that bilingual individuals present on average 4.05 years later with the clinical features of AD than monolinguals. Bilinguals are also diagnosed with AD ∼2.0 years later than monolingual counterparts. In this perspective piece we critically evaluate the findings of this metanalysis and consider the specific implications of these findings to LMICs. Furthermore, we appraise the major epidemiological studies conducted globally on bilingualism and the onset of dementia. We consider how both impactful and robust studies of bilingualism and cognition in older age may be conducted in LMICs. Given the limited expenditure and resources available in LMICs and minimal successes of clinical trials of disease modifying drugs we propose that bilingualism should be positioned as an important and specific public health strategy for maintaining healthy cognitive aging in LMICs. Finally, we reflect upon the scope of implementing bilingualism within the education systems of LMICs and the promotion of bilingualism as a healthy cognitive aging initiative within government policy.

Keywords: bilingualism, cognitive reserve, dementia, healthy cognitive aging, global public health, low and middle income countries, contextual challenges

OPEN ACCESS

Edited by:
Maira Okada de Oliveira, University of São Paulo, Brazil

Reviewed by:
John A. E. Anderson, Center for Addiction and Mental Health (CAMH), Canada
Anthoula Charalampos Tsolaki, Aristotle University of Thessaloniki, Greece

***Correspondence:**
Sahan Benedict Mendis
sahan.mendis@nhs.net

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: *11 November 2020*
Accepted: *16 March 2021*
Published: *15 April 2021*

Citation:
Mendis SB, Raymont V and Tabet N (2021) Bilingualism: A Global Public Health Strategy for Healthy Cognitive Aging. Front. Neurol. 12:628368. doi: 10.3389/fneur.2021.628368

INTRODUCTION

Twenty first century societies are rapidly transitioning to aging populations which are often characterized by a burden of age related conditions such as dementia (1). There are about 50 million individuals living with dementia (2); a figure that is forecasted to increase to 115 million by the year 2050 (3). The global economic cost of dementia was measured at US $818 billion in 2015 (4). The burden of dementia significantly impacts low and middle countries (LMICs)[1] and by 2050 we anticipate that 71% of all people living with dementia will reside in LMICs (1).

[1] A low and middle country has a GNI less than $12536 (5).

Whilst there have been limited successes of clinical trials and disease modifying drugs (6), researchers have focused on developing public health strategies that may promote healthy aging and support the delay of onset of dementia (7). This approach may be germane to LMICs where minimal resources and unstable health systems may make running of clinical trials more challenging and logistically difficult. In these settings, dementia may be viewed as part of a normal aging process and a highly stigmatized condition and associated with limited provision of care for individuals with dementia. These additional factors may complicate how dementia prevention is addressed in non-communicable disease (NCD) policies in LMIC settings (8). There are potential promising economic benefits of delaying the onset of dementia. A recent study has demonstrated that a 1 year delay of onset of dementia reduces formal costs in 2030 by $70 billion and informal costs by $43 billion compared to no delay on dementia onset (9).

Cognitive reserve is a hypothetical construct which posits that enriching lifetime experiences and activities support the brain in mitigating the impact of pathological damage over time (10–15). This may enable individuals to cope better with brain damage and sustain greater degrees of brain damage before demonstrating functional deficits (10). Cognitive reserve factors have been associated with the delay of onset of dementia and better cognitive outcomes in aging (16). These factors include educational attainment (17), the cohesion of social networks (18), occupational complexity (19), enhanced physical activity, and cognitively stimulating activities (20). Bilingualism has been positioned as a powerful cognitive reserve factor (21) which may be associated with the delay in onset of dementia. Encouragingly cognitive reserve may be malleable even in older age which may provide significant opportunities for interventional studies of cognition in later life (22).

A recent metanalysis by Paulavicius et al. (23) revealed that studies that explored the relationship between bilingualism and age of onset of dementia revealed an average of 4.5 years in the delay of presentation of dementia amongst bilinguals. In this perspective piece, we critically review bilingualism as a cognitive reserve factor and examine the key studies of bilingualism explored in both high income countries (HICs) and LMICs. We discuss the implications of these findings to a global health context. We commentate on the key study findings of the above metanalysis. We address some of methodological limitations of the current evidence and suggest ways in which these can be overcome.

We propose that incorporating bilingualism into dementia public health policy to delay the onset of dementia is an important and specific strategy in maintaining healthy cognitive aging in LMICs. We reflect how bilingualism can be incorporated into governmental and educational policy and overall health strategy in LMICs settings and the challenges associated with this.

WHAT IS BILINGUALISM?

Bilingualism can be classified as individuals' ability to communicate using two languages either actively using speech or listening, or passively using writing, reading, or listening. The bilingual experience is a dynamic process and proficiency may differ according to the level of exposure to other users of each language and level of opportunity to use each language (24). Bilinguals can be described as either simultaneous; where an individual is exposed to both languages to a significant degree from birth, or alternatively sequential, where meaningful exposure to the second language is developed after the age of three (24). Bilingualism does not require any special education or intellectual ability. It is a common phenomenon, and ∼50 % of the global population are proposed to have some bilingual or plurilingualism proficiency (25). Bilingual children and adults may experience difficulties with "lexical access" and reduced verbal fluency and this may lead to "tip of the tongue" experiences (26). Bilingual proficiency can be observed in different social and cultural contexts. Daily contact with two languages is observed globally in diverse settings, such as Europe (Switzerland, Belgium, and Luxemburg), Asia (India, Philippines), Africa (Senegal, South Africa), and North America (Canada).

THE CASE FOR BILINGUALISM AS A COGNITIVE RESERVE FACTOR

Lifelong bilingualism has been positioned as a cognitive reserve factor (21) and promoting buffering against age related cognitive decline. There are two distinct models of cognitive reserve; brain reserve and neuronal compensation (10, 27). The brain reserve model asserts that existing brain networks are more resilient toward deregulation because of heightened efficiency. This may be mediated through enhanced "brain hardware" (10), which may be practically achieved through increased dendritic volume, brain synapses or overall brain volume (10). These networks may facilitate brain activity when performing more complex tasks and may enable the brain to cope more effectively with degeneration. In neuronal compensation, the brain recruits additional areas that are not normally used to perform the skills that have been lost in the degenerated brain (10). Other models of cognitive reserve include a life course perspective (14), scaffolding theory (28), or the concept of brain maintenance (15).

NEUROIMAGING

Bilinguals simultaneously attend to two competing languages for selection which may induce neuroplasticity (29) and lead to remodeling of brain architecture and function (30). Schweizer and colleagues (21) who analyzed linear CT brain looking at brain atrophy, discerned that greater amounts of neuropathology are needed before the clinical symptoms of AD become apparent in bilinguals. Similarly, another study using PET demonstrated that bilinguals had greater regional glucose uptake than monolinguals (31). Bilingual brains have been shown to have specific activity in the frontotemporal and subcortical networks which are involved in interference inhibition, and may facilitate language switching (32). This was not demonstrated in monolinguals. Bilinguals may have increased capacity for conflict resolution through augmentation of anterior cingulate cortex activity (33).

The bilingual experience may promote more widely distributed neural activity (30), recruitment of overlapping neural regions which are not usually found in monolinguals (34)

or enhancing neural activity in regions involved in executive function (30). Bilingual adults may display greater gray matter volume particular in the anterior cingulate cortex (35) parietal lobes (36), corpus callosum (37) the basal ganglia (30, 38) and the frontoparietal network (FPN) (30). Bilinguals show greater white matter integrity and gray matter functional connectivity compared to monolinguals (30). Functional MRI studies reveal that although bilinguals have equal performance in non-verbal executive tasks there is less frontal activation than monolinguals (30). This suggests that bilinguals do not rely on "top down" mechanisms in cognitive functions (30). Overall, researchers suggest that the shift from anterior to posterior brain activation amongst bilinguals "anterior-to-posterior and subcortical shift" /BAPSS (30) may provide some evidence why bilingualism is associated with improved cognitive performance in older age and delayed onset of dementia.

NEUROPSYCHOLOGY, EPIDEMIOLOGY, AND LAB STUDIES

The positive findings which are reflected in the neuroimaging studies of bilinguals are also depicted in multiple neuropsychological and epidemiological studies of bilingual adults. Bilinguals have been shown to outperform monolinguals in tests of executive function, such as cognitive control (39), working memory (40), inhibition (41), and attention (42). However, other researchers may refute findings linking bilingualism and improved executive function because many studies may be limited by small sample sizes (43), socioeconomic factors (44), education, and geographical location (45). These factors are known to have significant impact on performance of executive function (46). By contrast, Nichols et al. (47) compared the performance 11,041 (5,994 monolinguals and 5,047 bilinguals) participants on a battery of 12 executive tasks and found there was no significant difference between the two groups on executive function. These findings were independent of case mix factors (47). However, it is important to note that this study only included 744 people in the matched bilingual and monolingual sample and defined bilingualism based on a single question "How many languages do you speak (47)?" This simplistic and imprecise approach to measuring bilingual proficiency may misrepresent the nuanced complexities of bilingual proficiency and we suggest the findings of this study should be interpreted with some caution. The overall findings suggest that bilingualism and executive function research should be conducted in diverse sociocultural milieus to ascertain whether the bilingual advantage applies in different contexts.

A 12 year longitudinal Israel based study of 814 elderly Jewish people revealed trilinguals performed better on cognitive tasks than monolinguals and bilinguals (48). These findings were independent of educational achievement, occupation, age, place of birth, and immigration (48). A study explored 853 participants who were recruited into the Lothian cohort 1936 study (49). This followed adults whose age 11 IQ was measured as part of the Scottish Mental Survey 1947 (49). Repeated cognitive testing between 2008 and 2010 revealed that bilingual participants performed better than monolinguals in both reading and executive function tests, as well as in tests of intelligence (49). Another study observed that bilinguals with amnesic-type mild cognitive impairment had a reduced rate of conversion to AD compared to monolingual counterparts (50). This delay was not demonstrated in mild cognitive impairment participants with multiple domain deficits (50). Bilinguals are twice more likely to recover cognitively from stroke than monolinguals (51). Bilingualism has been associated with better ratio of CSF AD biomarkers (52).

DOES BILINGUALISM DELAY THE ONSET OF DEMENTIA? KEY FINDINGS FROM A SYSTEMATIC REVIEW

Having explored the contextual evidence supporting bilingualism as a cognitive reserve factor, we now evaluate the systematic review from Paulavicius et al. (23) exploring bilingualism and age of onset of dementia and the specific epidemiological studies exploring this relationship.

This systematic review reported findings from eight studies which examined the relationship between bilingualism and the age of onset of dementia. Metanalysis from these studies determined that bilinguals (53) with AD presented with delayed clinical features (694 individuals; mean difference MD 4.05 years; 95% CI:1.87–6.22) and are diagnosed (1,012 participants: MD 2.0 years; 95% CI 0.08–3.92) (23). This study incorporated studies which were cross sectional, cohort, case control or retrospective in design. Six of the selected studies consisted of only AD patients and four of the studies had a mixture of immigrant and non-immigrant populations. The study pooled data from four studies that had investigated the age of onset of AD symptoms (23). Secondly, five studies which determined the age of AD diagnosis were pooled. All the selected studies were retrospective in design (23). Another systematic review which examined the impact of bilingualism on the risk of cognitive decline found that bilingualism was not associated with a reduced incidence of dementia (54). This study only included prospective studies and studies of different types of dementia (54). Overall, studies suggest that bilingualism is associated with a delayed onset of clinical presentation of dementia but not reduced risk of developing dementia or reduced incidence of dementia (54–56).

STUDIES OF BILINGUALISM IN HICS

Tables 1, **2**, respectively outlines the key studies of bilingualism conducted in HICs and LMICs. Twelve key studies of bilingualism were conducted in HICs (53, 57–59, 61, 63–66, 72, 73) and all investigated spoken bilingualism. Of the 12 studies, six studies were conducted in USA (58, 61–64, 67), four studies in Canada (53, 57, 59, 65), one study in Belgium (60) and one study in Wales (66). Nine studies involved a retrospective analysis of bilinguals vs. monolinguals. Eight studies revealed a delay of onset of dementia in bilinguals whilst four studies did not find a difference between monolinguals and bilinguals (63–66). Three studies were prospective and had a cohort or cross-sectional

design (63–65) and did not find a delay of onset of dementia associated with bilingualism. All but one Canadian study revealed a positive relationship between bilingualism and delayed onset of dementia (53, 57, 59). Similar findings were found in the Belgium study (60). The sample size for these studies ranged from 86 to 1,616 subjects. Gollan et al. (58) explored bilingual objectively measures of linguistic proficiency using the Boston Naming Task. Zahodne et al. (63) also used an objective measure of English reading level. All studies used different operational definitions of bilingualism and different linguistic profiles and varying pairs of languages.

STUDIES OF BILINGUALISM AND AGE OF ONSET OF DEMENTIA IN LMICs

Alladi and colleagues (68) evaluated hospital records of 648 patients of which 391 were bilinguals diagnosed with dementia in specialist clinics in Hyderabad, India and retrospectively evaluated age of diagnosis. This study examined patients with a variety of dementia diagnosis' including vascular dementia, Alzheimer's Disease (AD) and frontotemporal dementia (FTD) (68). This study identified that the bilinguals' mean age of dementia onset was 4.5 years later than monolinguals (68). Bilingualism was significantly associated with the delay of age of onset of dementia, with generalized linear modeling analysis revealing a significant level [$F_{(1,458)} = 4.89$, $p = 0.027$] after adjustment for immigration, socioeconomic status, illiteracy, education, and residence in rural and urban areas, number of languages spoken and occupational status (68). The study participants were from an autochthonous population where both the monolingual and bilingual participants were born and raised in India (68). This study evaluated important covariates as described above and determined that the findings were independent of these factors (68). In illiterate bilinguals the delay of onset of dementia was 6 years compared to monolingual counterparts (68).

A further Hyderabad based study explored the case records of 193 patients diagnosed with FTD of which 121 were bilingual (69). In this study the age of diagnosis was measured between bilinguals and monolinguals and determined that amongst bilinguals with behavioral variant FTD the age of onset of dementia was 5.7 years later in bilinguals 62.6 vs. 56.5 $p = 0.006$ in monolinguals (69). This finding was independent of the similar case mix factors as observed in the 2007 Hyderabad study (69). Ellajosyula et al. (70) investigated a retrospective South Indian sample of individuals diagnosed with either AD or FTD in a memory clinic. There were 183 patients with dementia where 55 were monolinguals and 129 were bilinguals or multilinguals (70). The study did not find a significant difference in the age of onset of dementia between the two groups (70).

A study explored the relationship between Mandarin and Cantonese bilingualism and age of onset of dementia in 129 patients diagnosed with probable AD, including 48 Cantonese monolinguals, 20 Mandarin monolinguals, and 61 Cantonese/Mandarin bilinguals (71). The study determined that bilingualism was independently associated with delay of onset of dementia [$P = 5.497$, $p = 0.017$ (71)].This study utilized the Bilingual Aphasia Test (BAT) (74) to obtain a detailed language history. All the key studies examined spoken bilingualism only.

BILINGUALISM AND COGNITIVE RESERVE RESEARCH: THE GLOBAL CONTEXT

Our review of key studies investigating bilingualism and the age of the onset of dementia reveal a dearth of studies conducted in LMICs. It may be particularly challenging to directly extrapolate the findings from studies conducted in HICs to LMIC settings (75). Immigration and the potential healthy migrant effect may confound the findings of some studies conducted in HICs. In studies conducted in LMICs bilinguals observed may be from autochthonous populations and in populations where there is a lot of language switching (68). Many contextual challenges including the high prevalence of illiteracy and HIV, unemployment and key differences in employment in both rural and urban settings exist (75). Examples include the unskilled, illiterate craft maker, or illiterate factory worker. The differing ethnic and genetic profiles, such as ApoE may interact or modify the benefits of bilingualism on individuals (75). Other important issues include the high prevalence of head injuries and vascular risk factors and poorly resourced health systems may further complicate assessment and interpretation of research findings (75).

We determine that interactive factors, such as ethnicity, poverty, epigenetics, polluted environments, social deprivation, differing cultures, economics, and politics may have a significant impact in how bilingualism and cognitive reserve research is conducted and interpreted (75). A detailed list of potential interactive factors is outlined in **Figure 1**. We suggest that tools which formally assess bilingual fluency, such as a culturally amended Boston naming task or BAT, should accompany self-reported fluency of language use. We recommend strict and standardized study definitions of bilingualism should be employed in studies.

Specific challenges may arise when utilizing neuropsychological tests in many LMIC settings for bilingualism and dementia research. Traditionally these tests have been derived for educated and English-speaking western populations and may have limited applicability to other cultures (76, 77). Although, Alladi and colleagues (68) successfully used culturally and linguistically amended versions of the Addenbrookes Cognitive Examination and Dementia Rating Scale there are other specific challenges to consider. High rates of illiteracy in LMIC settings may further complicate the adaptation of these tests (77). There have been attempts to derive culturally unbiased and educationally fair testing (77). Researchers assert that focusing on cognitive tools that emphasizes visual skills, such as the Oxford Cognitive Screen (OCS-Plus) (78) may help to overcome this difficulty. The OCS-Plus is a visual orientated cognitive tool which assesses nine domains of cognition (78). A validation study of the OCS-Plus in a South African study sample in which 45% of the sample did not have any formal education revealed that the OCS-Plus had excellent construct and external

TABLE 1 | Studies of bilingualism and age of onset of dementia in HICS.

Name, country of study participants and year	Description of study design	Key study findings	Methodological limitations	Conclusions	Additional commentary covariables
Bialystok et al. (53) Canada	This study examined whether bilingualism was associated with delay of onset of dementia. Retrospective analysis of 184 patients attending Baycrest in Toronto memory clinic 93 were bilinguals and 91 were monolinguals with dementia. Onset of cognitive impairment reports, and age of diagnosis of cognitive symptoms noted. Bilinguals defined as those who spent the majority of their lives, at least from early adulthood, regularly using at least two languages.	The difference between monolinguals and bilinguals of 4.1 years in age of onset of symptoms $f_{(1,178)} = 9.16$, $p < 0.003$, with no difference between men and women, $F < 1$. The power of this effect with $\alpha = 0.05$ is 0.87 Bilinguals were 3.2 years older than monolinguals at the time of the initial clinic appointment, a difference that was also significant, $F_{(1,180)} = 5.93$, $p < 0.02$	Subject to recall bias. 38 patients unaccounted. Bilingual participants were mainly francophone and immigrants 81/93.	Bilingualism may delay the age of onset of clinical features of dementia.	Immigration may propagate healthy worker effect in the bilingual population. Retrospective sample Relatively small bilingual population. Study controlled for gender, occupation and level of education. The bilinguals included speakers of 25 different languages
Craik et al. (57) Canada	211 consecutive patients attending clinic in Toronto with AD. 102 bilinguals and 109 monolinguals were selected. Age of onset of cognitive impairment and demographic information, such as factors including occupation, education, and linguistic history taken out of 102 bilingual participants and 109 monolingual participants tested. Bilinguals defined as individuals having spent the majority of life, at least from early adulthood, regularly using at least two languages	Bilinguals were diagnosed 4.1 years later than monolinguals $F_{1,\ 207} = 12.02$, $p < 0.0006$, and the report of onset of symptoms was 5.3 years later than monolinguals. $F_{1,\ 205} = 16.25$, $p < 0.0001$	Majority of bilingual participants were immigrants. 21 different first languages were spoken amongst b Yiddish ($n = 24$), Polish ($n = 12$), Italian ($n = 11$), Hungarian ($n = 9$), and French ($n = 7$). Questionnaires about fluency of languages given to participants but was not formally assessed.	Bilingualism delays the onset cognitive symptoms.	No effect from immigration, and monolinguals achieved more formal education. Groups were very similar on occupational and cognitive attainment. Immigration status was analyzed as an independent factor.
Gollan et al. (58) USA	This study examined the impact of increasing bilingual proficiency in Spanish speaking AD bilingual patients in terms of age of onset of diagnosis. Bilingualism proficiency and age of diagnosis of Alzheimer's disease and age of diagnosis assessed in 44 participants. Spanish and English-speaking bilinguals. Degree of bilingualism was measured using the Boston naming test, and bilingual index. These were participants attending the UCSD Alzheimer's research Center.	Later age of diagnosis on more bilingually proficient participants. Greatest difference found in those with low levels of education and those with Spanish dominant linguistic proficiency Being more bilingually proficient may delay the onset of cognitive symptoms of dementia.	Only bilinguals studied in this project. Retrospective analysis	There may be an upper limit to the level of protection conveyed by bilinguals, as greatest delay in cognitive symptoms observed was most pronounced in the least educated participants.	Objective measures of bilingual proficiency using Boston naming test.

(Continued)

TABLE 1 | Continued

Name, country of study participants and year	Description of study design	Key study findings	Methodological limitations	Conclusions	Additional commentary covariables
Bialystok et al. (59) Canada	Study investigating the relationship between bilingualism and age of onset of cognitive symptoms of dementia and rate of deterioration of cognitive symptoms in monolinguals and bilinguals with dementia. Participants were selected from the Sam and Ida Ross Memory Clinic at Baycrest, Toronto, Canada. 74 patients with MCI and 75 patients with AD (35 monolinguals) and (40 bilingual) and participants were followed up over a year. All patients were interviewed to obtain details of their language use, onset of their condition, and lifestyle habits. Bilinguals were defined as those who had spent most of their lives beginning at least in early adulthood, speaking two or more languages fluently on a daily or at least weekly basis.	Significant delay in the onset of cognitive symptoms in patients with MCI and AD (3.2 and 7.2 years, respectively). Mean age of onset of dementia monolinguals was 70.9 vs. 78.2 in bilinguals. The rate of executive function decline was approximately the same in both bilinguals and monolinguals with Alzheimer's disease. Bilinguals were older than monolinguals for both onset of symptoms [$F_{(1,145)} = 10.75$, $p = .001$] and age of first clinic visit [$F_{(1,146)} = 9.35$, $p = .003$].	Prospective assessment of the rate of decline of symptoms in bilingual and monolingual groups. Retrospective analysis of the date of diagnosis of dementia. All subjects were proficient in English, but bilinguals additionally spoke other languages such as Farsi, French, Italian, Russian, and Yiddish.	Bilingualism delays the age of onset of AD	47% of the patients from the Craik et al. (57) study was also used in this study. The delayed onset of cognitive symptoms in the bilingual group were independent of lifestyle factors. Language and Social Background Questionnaire (LSBQ) assessed immigration history, education, and language use. Onset of symptoms interview explored when next of kin noticed the symptoms of dementia.
Woumans et al. (60) Belgium	The study aim was to evaluate the age of onset of dementia in monolinguals or bilinguals in a sample in Belgium. 69 monolinguals with AD and 65 bilinguals with AD were identified from 2 university hospitals in Ghent and Brussels. Non-immigrant sample of bilingual participants were recruited. Participants were considered bilingual if they rated themselves as "good" or higher for all four L2 skills and spoke this L2 at least weekly before and now were obtained from patient and caregiver interviews. Multiple linear regression performed.	A delay of 4.6 years in clinical manifestation and 4.8 years in diagnosis of dementia in bilinguals compared to monolinguals. Group [$F_{(1,109)} = 6.18$, $p = .014$, Beta = 4.64 years], Average age of manifestation of dementia in monolinguals was 71.5 and bilinguals was 76.1	Retrospective study	Bilingualism delays the clinical manifestation of dementia.	Age of language 2 acquisition did not affect the findings. Bilinguals consisted of a combination of French and Dutch. Linguistic history and social background information Proficiency measured by Likert scale and frequency of use of language assessed. No objective measurement of bilingual proficiency.
Mendez et al. (61) USA	The study aim was to evaluate the effects of bilingualism on the age of diagnosis of dementia. In clinics in California USA with a large immigration population 253 patients with probable early onset AD identified and investigated for demographic variables, native language nature of presentation, ages of onset and presentation. Mini-Mental State Examination, digital	74 bilinguals (29%) and 179 monolinguals were recruited in the study. There was a variety of L1s Bilinguals had significant delays in age of onset of dementia ($p = 0003$) and age of presentation ($t = -3.03$; df 251, $p = 0.003$) Bilinguals had worse MMSE scores on presentation.	Retrospective study design Logistic regression performed for bilingual and monolingual groups.	Bilingualism delays the onset of dementia	Most of the bilinguals were from immigrant population who spoke a variety of L1s (Farsi, Spanish, Chinese, Tagalog, Arabic etc) Majority of bilinguals regressed back to their native L1. Amongst bilinguals language use in the first years of life, the later acquisition of English, immigrant status, the proficiency in using both

(Continued)

TABLE 1 | Continued

Name, country of study participants and year	Description of study design	Key study findings	Methodological limitations	Conclusions	Additional commentary covariables
	spans, word fluencies, naming, and memory were measured.				languages on a daily basis, and change in language used.
de Leon et al. (62) USA	This retrospective study explored the difference in age of onset of dementia in bilinguals and monolinguals in 287 well-characterized participants with either amnestic Alzheimer's dementia or logopenic variant primary progressive aphasia (lvPPA) Individuals were selected from those seen at the University of California, San Francisco Memory and Aging Center (MAC)	Of the 287 participants, 247 were monolinguals and 40 participants were monolingual. Of the 246 monolinguals 179 had amnesic AD and 63 monolinguals had lvPPA. Amongst the bilinguals 28 had Amnesic AD and 16 had lvPPA. Participants who spoke two or more languages were classed as bilinguals. If charts did not state information regarding exposure to or experience with a second language, they are monolingual. lvPPA cohort, bilingual speakers were significantly older than monolinguals at the time of diagnosis Bilinguals(M = 68.2) Monolingual(M = 62.8) for the monolingual This finding was not found in Amnesic AD	Retrospective design No objective rating of bilingual proficiency. Bilinguals were more likely to be immigrants to USA.	Bilingualism was associated with a significant delay in onset of dementia in lvPPA patients. This difference was not observed in Amnesic AD.	Study excluded participants who enrolled in second language classes for only a few years without ongoing experience. Study excluded individuals that had immigrated to a country which have a majority different primary language but it was not evident whether they were in formal school or employed in their adopted country or participants expressed minimal proficiency in a second language. Two raters independently determined monolingual or bilingual status for each patient. Analyses of covariance (ANCOVAs) were used to assess the effects of bilingualism and clinical diagnosis on age at symptom onset.
Zahodne et al. (63) USA	Large prospective USA study investigating the Spanish speaking community of initially non-demented individuals living in Manhattan. 1,067 participants from the Washington/Hamilton Heights Inwood Columbia Aging Project (WHICAP) who were tested in Spanish and followed at 18–24 month intervals for up to 23 years.	282 of the participants converted to dementia. Bilingualism was not associated with a reduced conversion or reduced rates of cognitive decline. Bilingualism was associated with better performance in memory tasks and executive function.	No objective measure of Spanish proficiency taken.	Bilingualism may not be associated with delayed impairment of cognitive function.	Bilingualism was tested by self-rating and objective test in reading ability in English was conducted.
Lawton et al. 2014 (64) USA	Secondary analysis of 81 (55 Alzheimer's Disease 26 Vascular Dementia) participants who developed dementia. Study sample taken from the Sacramento Area Latino Study on Aging cohort study. 1,789 Hispanic Americans were enrolled for this study and the participants were self-identified Hispanics and none of the participants had dementia at the start of the study. These 81 community dwelling participants performed cognitive tests, and the age of diagnosis were determined.	Mean age of diagnosis was 81.1 in monolingual group and 79.9 in bilingual group. ANOVA revealed that the mean age of dementia diagnosis of the bilingual participants (79.31 years) was not significantly different from that of the monolingual participants (81.10), $F_{(1,77)} = 1.27$, $p = 0.26$, $\eta 2p = 0.02$.	Bilingualism not associated with delay of onset of dementia.	Over 50% of the population were immigrants to USA. 57% of the bilingual group were multilingual and were not analyzed separately to bilingual group. Small study sample. Language proficiency in each language not objectively measured. Small study sample	Large study sample taken Hispanic bilinguals only targeted. Bilinguals were significantly better educated than monolinguals with dementia. No significant difference in education levels in US born bilinguals or monolinguals. Likert scales used to identify frequency of language use.

(Continued)

TABLE 1 | Continued

Name, country of study participants and year	Description of study design	Key study findings	Methodological limitations	Conclusions	Additional commentary covariables
	Cognitive tests performed included the MMSE English Neuropsychological Assessment Scale.				
Yeung et al. (65) Canada	Study explored whether bilingualism is associated with dementia in cross sectional or prospective analyses of older adults. 1,616 community living older adults were assessed and followed 5 years later. Measures included subjective memory loss, modified MMSE Dementia defined as cut off on modified MMSE. Language status defined as first language English, bilingual English, English as second language.	No association between speaking more than one language and dementia. English as a second language participants had poorer education, and more likely to be diagnosed with dementia compared to those speaking English as a first language.	Bilingualism is not associated with a delayed onset of dementia.	Original sample had 2,890. Over 1,200 participants lost to follow up, 443 refused, 131 participants had missing data, Self-reported measurement of education and multilingualism were documented. No independent measure of bilingualism. 9.6% cognitive impairment in English as second language group. Differences in participant numbers between English as first language and English as second language group. Modified MMSE poor indicator of cognitive dysfunction No neuroimaging information provided. 3MS- is highly English specific and therefore ESL group may find it difficult to perform.	Overall poorly designed study and big losses to follow up Self-reporting of language proficiency leading to bias. Large losses to follow up. Different sample sizes in different groups. Community based study. Large disparity in the levels of education between the groups which may have resulted in bias. Genetic factors not measured. Measures of cognitive ability were poor. Study did not have specific age of onset of dementia information.
Clare et al. (66) Wales	Welsh cross sectional cohort study compared the time of diagnosis of Alzheimer's disease in 49 monolingual English speakers and bilingual 37 and English and Welsh speakers. These participants were then requested to perform executive function and neuropsychological testing.	Bilinguals did not show significant advantages in executive function compared to monolinguals, but there was some increased ability in inhibition and conflict resolution in bilinguals.	A non-significant delay in cognitive impairment diagnosed in bilinguals with dementia compared to monolinguals.	Only 24 of 37 bilingual Welsh and English participants were selected for performing executive function cognitive tasks.	Bilinguals came in touch of medical care later than monolinguals with dementia. Bilinguals shared a common societal and cultural milieu. Bilinguals were found to be significantly less educated, and more likely to be on cholinesterase inhibitors.

(Continued)

TABLE 1 | Continued

Name, country of study participants and year	Description of study design	Key study findings	Methodological limitations	Conclusions	Additional commentary covariables
	Language questionnaire was created to explore the level of language proficiency. Cognitive reserve info ascertained by lifetime of experience of questionnaire. Variety of executive function tests given to participants. All participants had a screening MMSE score of 18/30. Participants selected from the neurodem research register. Power calculations revealed that there needed to be 42 participants in both groups in order to show a significant statistical different in the age of the onset of dementia. Structured interview was given in the language of choice.	Bilinguals were diagnosed not significantly 3 years later than monolinguals, but were also more significantly cognitively impaired than monolinguals.		Underpowered study particularly with small bilingual population may have contributed toward the inconclusive results.	Participants were assessed 1.5–2 years post-diagnosis. Higher dropout rate in bilinguals with Alzheimer's compared to monolinguals. Difficult to recruit bilinguals to the study.
Akhlaghipour et al. (67) USA	This retrospective study examined the relationship between speaking more than one language and the age of onset of the clinical symptoms of Alzheimer's disease, and (2.) to investigate if there is asymmetrical language impairment with reversion to L1(dominant language) once there is clinical dementia. This identified 74 bilingual and 179 monolingual patients. Dependent variables were age of onset and presentation.	Bilingualism was associated with statistically significant delay in ages of onset and presentation of clinical dementia ($p = 0.003$). MMSE score was significantly lower in monolingual compared to bilinguals ($p = 0.004$). Improved scores in F word fluency, category fluency, and delayed verbal recall among bilinguals compared to monolingual patients.	Bilingualism is associated with delayed onset of dementia	Only supplementary information provided No information provided on the proficiency of languages or assessment of proficiency of languages.	No documented measurement of the average number of years of delay of onset of dementia in bilinguals compared to monolinguals.

TABLE 2 | Studies of Bilingualism and age of onset of dementia in LMICs.

Name, country of study participants and year	Description of study design	Key study findings	Methodological limitations	Conclusions	Additional commentary covariables
Alladi et al. (68) India	Case records of 648 patients with dementia (391 bilingual) diagnosed at a specialized memory clinic in Hyderabad India were appraised. The subjects had AD, $n = 240$FTD, $n = 116$ vascular dementia $N = 189$ Lewy Body Dementia $n = 55$ Mixed dementia $N = 48$	Univariate GLM analysis showed that bilingualism was significantly associated with delay of dementia [$F_{(1,458)} = 4.89$, $p = 0.027$) This finding was independent of casemix factors Bilinguals with dementia presented on average 4.5 years later than the monolinguals. 3.2 year delay in bilinguals with AD 3.7 year delay in bilinguals with Vascular dementia 6 year delay in bilinguals with Frontotemporal dementia. Amongst illiterate bilinguals delay of onset of dementia was 6 years (65.0 vs. 59.0 years, $p = 0.03$) These findings were independent of confounding variables No additional benefit in speaking more than two languages	Retrospective analysis of case records Spoken fluency in languages not formally assessed	Bilingualism may delay the onset of cognitive symptoms associated with dementia independent of other risk factors. Protection was also found in illiterate bilinguals; therefore, results may be independent of the level of educational attainment.	Diverse linguistic groups in study sample including speakers of Telugu-, Dakkhini-, and the Hindi Case mix factors measured literacy, years of education, sex, dementia subtype, vascular risk factors, stroke, occupational status, rural/urban dwelling, family history of dementia, and dementia severity
Alladi et al. (69) India	This study examines whether bilingualism delays the age of onset of frontotemporal dementia FTD. Dementia patients were split into aphasic and behavioral groups. Case recordings of 193 patients presenting with FTD of which 121 were bilingual and age of onset of first symptoms were compared between bilinguals and monolinguals. Participants were selected from those attending dementia clinics in Hyderabad	The age of dementia in bilingual behavioral FTD (62.6) was over 6 years delayed than monolinguals (56.6, $p = 0.006$). No difference was found in aphasic groups. This delay was independent of rural/urban dwelling, literacy, and education, gender and family history of dementia.	Retrospective design Monolingual and bilinguals were compared using independent samples *t*-tests. One-way test of variance.	Bilingualism delays the onset of dementia in only behavioral variants and not aphasic groups.	A variety of different dementias including behavioral variant of FTD, semantic dementia, corticobasal dementia, progressive supranuclear palsy, and FTD-motor neuron disease. The languages combinations included Telugu and Hindi, Telegu, English and Hindi and Telugu and Dakkani. Spoken fluency was not formally assessed.
Ellajosyula et al. (70) India	Case records of patients diagnosed with dementia in a South Indian clinic were selected. There were 183 patients diagnosed with dementia 109 AD and 74 FTD. 55 30.1% were monolinguals and 128 69.9 % bilinguals or multilinguals. Age of onset of dementia ascertained.	No significant difference between bilinguals/multilinguals and the age of onset of dementia.	Bilingualism may not delay the onset of cognitive symptoms of dementia	Relatively small monolingual population. Retrospective analysis	Bilinguals and multilinguals were analyzed together. Case records were analyzed

(Continued)

TABLE 2 | Continued

Name, country of study participants and year	Description of study design	Key study findings	Methodological limitations	Conclusions	Additional commentary covariables
Zheng Y et al. (71) China	Retrospective study exploring whether Cantonese /Mandarin bilingualism is associated with a delayed onset of dementia. 29 patients diagnosed with probable AD, including 48 Cantonese monolinguals, 20 Mandarin monolinguals, and 61 Cantonese/Mandarin bilinguals were analyzed.	Cantonese/Mandarin bilinguals were found to be an older age at AD onset, and were 5.5 years older at the first clinic visit than Mandarin monolinguals and Cantonese monolinguals Multiple linear regression analysis performed on study participants which revealed that bilingualism was statistically significantly associated with dementia delay. ($P = 5.497$, $p = 0.017$)	Bilingualism associated with delayed onset of dementia	Small study sample Retrospective analysis	

validity in detecting cognitive impairment (79). Perhaps we should employ tools, such as OCS Plus in measuring cognition in certain LMICs where low education or literacy levels prevail.

Although the limited neuroimaging resources particularly in rural areas make it challenging to research bilingualism and cognitive reserve, there are examples of big, funded neuroimaging studies conducted in LMICs such as the Health and Aging in Africa: A Longitudinal Study of an INDEPTH Community in South Africa(HAALSI) (79) and the Bangladesh Early Adversity Neuroimaging study (BEAN) (80).We advocate that major global stakeholding funders encourage applicants to present novel approaches, such as researching cognitive reserve in the bilingual brain within LMIC settings. We recommend that both prospective and retrospective studies to be conducted in diverse linguistic and cultural milieu such as South Africa, parts of Latin America and central Asia. Reproducibility of findings in different settings are imperative to understanding how bilingualism and cognitive reserve research is operationalized in a variety of environs.

FUTURE RESEARCH DIRECTIONS

Finally, we address how future studies of bilingualism and cognitive reserve could be conducted to help us understand the potential benefits of bilingualism in a globalized context. We propose that studies of bilingualism could be performed in high risk and vulnerable populations, such as individuals with mild cognitive impairment (MCI), those with a strong family history of cognitive impairment or genetically susceptible populations. Furthermore, we suggest that prospective studies could be explored in bilingual and monolingual cohorts with a strong vascular history (75), culturally diverse illiterate populations (75), those with limited educational attainment (75), and in specific cultural groups (81). This may help to determine if and how bilingualism may moderate or delay the clinical presentation of cognitive impairment in those with pre-existing risk factors. There may be scope to conduct large longitudinal studies of bilingualism and cognitive aging in densely populated communities in Latin America (82) and mainland China (83) where a range of diverse risk factors are frequently present. Novel and region specific strategies which include the Latin American and Caribbean Consortium on Dementia (LAC-CD1) (84), an approach funded by the Alzheimer's Association and the Global Brain Health Institute may promote the practical implementation of these approaches.

With the advent of neuroimaging modalities and possible increased availability of investigations in LMICs it may be possible to examine how bilingualism may be linked with specific structural neuroimaging findings such as volumetric temporal lobe changes. More relevant information may also be gained from functional magnetic resonance imaging and diffusion tensor imaging. The use of specific neuroimaging techniques, such as fluorodeoxyglucose positron emission tomography (FDG-PET) may be helpful (85), as is the visualization of early amyloid and tau aggregates also assessed through PET. We suggest that studies can also explore the relationship between bilingual proficiency in

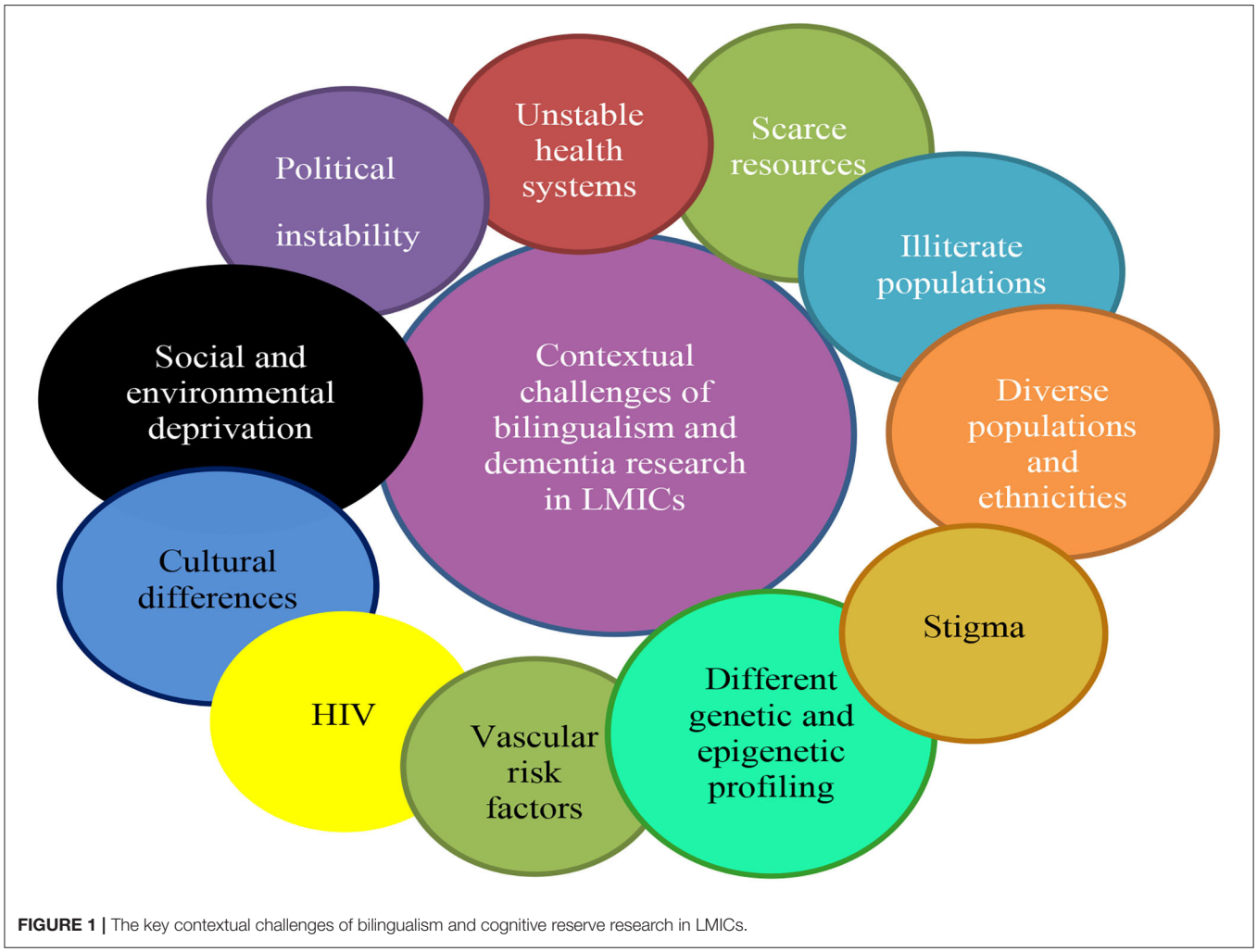


FIGURE 1 | The key contextual challenges of bilingualism and cognitive reserve research in LMICs.

older adults with the presence of CSF or plasma biomarkers for AD in addition to APOE status.

We emphasize that taking a detailed linguistic history is particularly salient in establishing bilingual proficiency in studies of bilingualism and cognitive reserve. Practical considerations include structured documentation of the level of frequency of language use, subjective linguistic competency, age of acquisition of languages, context of use, formal competency assessment of verbal fluency of languages, formal qualifications in each language and degree of language switching. These factors could be compiled in a structured linguistic competency questionnaire. We assert that by employing a more global and structured approach to linguistic competency we may be able to devise a rating scale which may provide an objective measure of linguistic proficiency.

DISCUSSION

Bilingualism: A Global Public Health Strategy for Healthy Cognitive Aging

We now propose bilingualism as a significant public health initiative for healthy cognitive aging in LMICs and consider how this could be incorporated into policy. The G8 and WHO have highlighted that upscaling public health indicatives should be a focus on dementia management in LMICs (86). We encourage that adopting bilingualism into dementia policy in LMICs could be formalized through organizations such the Alzheimer's Disease International (87) and STRiDE: Strengthening responses to dementia in developing countries which advocate the public health approach (88).

There is an intrinsic value of delaying the onset of dementia (9). A delay of AD onset of 5 years may represent a 41% lower prevalence of lower cost of AD in 2050 (9). In HICs this delay may also equate to 2.7 additional life years and lower informal costs (9). We highlight that delaying the onset of dementia may be even more significant in LMICs where treatments are not freely available, and nursing and care needs are frequently placed on the children of those diagnosed with dementia. This may lead to significant losses of occupational and economic productivity amongst individuals of working age.

We discuss how bilingualism-based measures could be practically adopted within public health strategies in LMICs. One approach would be to promote bilingualism from childhood. Benson explored how bilingual language

programs can be incorporated into school curriculum in LMICs using examples from Guinea-Bissau, Niger, Mozambique, and Bolivia (89). Benson suggests that bilingual teaching programs which are decentralized, linked to local culture and proficiency in mother tongue and include specialist language teachers may be more likely to be successful and welcomed by parents (89). Successful programs include the Nigerian six-year Yoruba medium project (90) and Guinea-Bissau bilingual project which integrated subject matter into themes, such as preventive health and improved gardening methods (91).

Whilst we have demonstrated the contribution of bilingualism toward cognitive reserve, we consider whether language learning in older age could be a feasible public health strategy to delay the onset of dementia in LMICs. Prior research has suggested that brain training may foster positive brain changes in healthy adults (92) and older people (93). This may indicate that mental stimulation may promote neuroplasticity even in the older adult. Learning a second language may cultivate healthy brain aging through engagement of additional brain networks (94).

A study which examined the benefits of one week of intensive Scottish Gaelic language training in older monolinguals revealed that these participants had improved in task switching cognitive tests (95). Improved cognitive performance was maintained at 9 months follow up in individuals who practiced Gaelic for at least 5 hours a week following the end of training (95). However, these findings were not replicated in a study of Spanish monolinguals who learnt Basque (96). Differences in the study design may have impacted the overall study findings. We suggest that future studies employ wide ranging and different bilingual linguistic profiles and are conducted in varied cultural and economic settings may help to discern more robust evidence in favor of bilingualism. Computer based approaches in language lessons has been explored (97), but we suggest less resource intense methods might be appropriate in LMICs.

Bak and colleagues (95) suggest that weekly 5 hours of minimum language training may be required to produce the cognitive benefits of bilingualism (95). In many LMICs where multiple languages are spoken, the principle language taught in schools may not necessarily be the mother tongue (89). Given this, we suggest that a personalized teaching program which incorporates local cultural practices and proficiency of inborne languages might be more beneficial in these settings. Conversely, in older populations where the proficiency may lie in the mother tongue, formal learning of a secondary language may be more advantageous in promoting healthy cognitive aging.

CONCLUSION

This perspective has examined the role of bilingualism as a cognitive reserve factor from a wide range of evidential sources. We have explored studies of bilingualism conducted in both HICs and LMICs and reflected upon an important metanalysis that demonstrated that bilingualism is associated with a significant delay of onset of dementia. We determine that many key studies of bilingualism are limited by inconsistent working definitions of bilingualism and few have utilized objective measures of bilingual fluency. Furthermore, while several retrospective bilingualism studies have identified a significant delay in dementia onset this finding has not been replicated in prospective studies. We suggest that future research should explore the reasoning behind this discrepancy. Contextual challenges in LMICs including the high prevalence of illiteracy, HIV, socio-cultural and environmental disparities, and differing risk factors may complicate the overall picture.

Whilst finding a definitive treatment is the gold standard in dementia research, we suggest that public health measures that may promote the delay of clinical features of dementia, such as language lessons for the elderly or augmenting pre-existing bilingual proficiency in older age is important. This may be particularly salient in LMICs where cheap, pragmatic, and easily accessible approaches are warranted. If we are to harness the key benefits that bilingualism may provide, we encourage major stakeholders including governmental and health system providers to develop social programs and interventions to support the preservation of a second language.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

SM was the principle author for this paper and derived the key topics for discussion in this paper. NT and VR provided general feedback and editorial comments. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

This paper was completed as part as an NIHR academic clinical fellowship in Old Age Psychiatry based at Brighton and Sussex Medical School.

REFERENCES

1. United Nations. *Division World Population Aging*. Department of Economic and Social Affairs Population (2015)
2. World Health Organization. *Risk Reduction of Cognitive Decline and Dementia: WHO Guidelines*. World H, Organization (2019).
3. Prince MJ, Prina M, Guerchet M. *World Alzheimer report 2013: Journey of caring: an analysis of long-term care for dementia*. Alzheimer's Disease International (2013).
4. Wimo A, Guerchet M, Ali G-C, Wu Y-T, Prina AM, Winblad B, et al. The worldwide costs of dementia 2015 and comparisons with 2010. *Alzheimers Dement*. (2017) 13:1–7. doi: 10.1016/j.jalz.2016.07.150

5. *World Bank Country and Lending Groups (Country Classification)*. World B, Group (2020).
6. Huang L-K, Chao S-P, Hu C-J. Clinical trials of new drugs for Alzheimer disease. *J Biomed Sci*. (2020) 27:18. doi: 10.1186/s12929-019-0609-7
7. Cahill S. *WHO's Global Action Plan on the Public Health Response to Dementia: Some Challenges and Opportunities*. Taylor & Francis (2020).
8. Ferri CP, Jacob K. Dementia in low-income and middle-income countries: different realities mandate tailored solutions. *PLoS Med*. (2017) 14:e1002271. doi: 10.1371/journal.pmed.1002271
9. Zissimopoulos J, Crimmins E, St Clair P. The value of delaying alzheimer's disease onset. *Forum Health Econ Policy*. (2014) 18:25–39. doi: 10.1515/fhep-2014-0013
10. Stern Y. Cognitive reserve. *Neuropsychologia*. (2009) 47:2015–28. doi: 10.1016/j.neuropsychologia.2009.03.004
11. Stern Y. Cognitive reserve and Alzheimer disease. *Alzheimer Dis Asso Disord*. (2006) 20:S69–74. doi: 10.1097/00002093-200607001-00010
12. Stern Y, Arenaza-Urquijo EM, Bartrés-Faz D, Belleville S, Cantilon M, Chetelat G, et al. Whitepaper: defining and investigating cognitive reserve, brain reserve, and brain maintenance. *Alzheimers Dement*. (2020) 16:1305–11. doi: 10.1016/j.jalz.2018.07.219
13. Satz P, Cole MA, Hardy DJ, Rassovsky Y. Brain and cognitive reserve: mediator (s) and construct validity, a critique. *J Clin Exp Neuropsychol*. 2011;33(1):121–30. doi: 10.1080/13803395.2010.493151
14. Richards M, Deary IJ. A life course approach to cognitive reserve: a model for cognitive aging and development? *Ann Neurol*. (2005) 58:617–22. doi: 10.1002/ana.20637
15. Nyberg L, Lövdén M, Riklund K, Lindenberger U, Bäckman L. Memory aging and brain maintenance. *Trends Cogn Sci*. (2012) 16:292–305. doi: 10.1016/j.tics.2012.04.005
16. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol*. (2012) 11:1006–12. doi: 10.1016/S1474-4422(12)70191-6
17. Roe CM, Xiong C, Miller JP, Morris JC. Education and Alzheimer disease without dementia. Support for the cognitive reserve hypothesis. *Neurology*. (2007) 68:223–8. doi: 10.1212/01.wnl.0000251303.50459.8a
18. Bennett DA, Schneider JA, Tang Y, Arnold SE, Wilson RS. The effect of social networks on the relation between Alzheimer's disease pathology and level of cognitive function in old people: a longitudinal cohort study. *Lancet Neurol*. (2006) 5:406–12. doi: 10.1016/S1474-4422(06)70417-3
19. Boots EA, Schultz SA, Almeida RP, Oh JM, Koscik RL, Dowling MN, et al. Occupational complexity and cognitive reserve in a middle-aged cohort at risk for Alzheimer's disease. *Arch Clin Neuropsychol*. (2015) 30:634–42. doi: 10.1093/arclin/acv041
20. Cheng S-T. Cognitive reserve and the prevention of dementia: the role of physical and cognitive activities. *Curr Psychiatry Rep*. (2016) 18:85. doi: 10.1007/s11920-016-0721-2
21. Schweizer TA, Ware J, Fischer CE, Craik FIM, Bialystok E. Bilingualism as a contributor to cognitive reserve: evidence from brain atrophy in Alzheimer's disease. *Cortex*. (2012) 48:991–6. doi: 10.1016/j.cortex.2011.04.009
22. Lenehan ME, Summers MJ, Saunders NL, Summers JJ, Ward DD, Ritchie K, et al. Sending your grandparents to university increases cognitive reserve: the Tasmanian healthy brain project. *Neuropsychology*. (2016) 30:525. doi: 10.1037/neu0000249
23. Paulavicius AM, Mizzaci CC, Tavares DRB, Rocha AP, Civile VT, Schultz RR, et al. Bilingualism for delaying the onset of Alzheimer's disease: a systematic review and meta-analysis. *Eur Geriatr Med*. (2020) 11:651–8. doi: 10.1007/s41999-020-00326-x
24. American Speech Language Hearing Association. *Knowledge and Skills Needed by Speech-Language Pathologists and Audiologists to Provide Culturally and Linguistically Appropriate Services*. Association AS-L-H (2004).
25. Hammer K. Bilingual: life and reality, by François Grosjean, Cambridge, Massachusetts, and London, England, Harvard University Press, 2010, 276 pp., $26.95,£ 19.95 (hardcover), ISBN 978-0-674-04887-4. *Sociolinguistic Studies*. (2013) 6:595–602. doi: 10.1558/sols.v6i3.595
26. Pyers JE, Gollan TH, Emmorey K. Bimodal bilinguals reveal the source of tip-of-the-tongue states. *Cognition*. (2009) 11:323–9. doi: 10.1016/j.cognition.2009.04.007
27. Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. *J Int Neuropsychol Soc*. (2002) 8:448–60. doi: 10.1017/S1355617702813248
28. Goh JO, Park DC. Neuroplasticity and cognitive aging: the scaffolding theory of aging and cognition. *Restor Neurol Neurosci*. (2009) 27:391–403. doi: 10.3233/RNN-2009-0493
29. Bialystok E, Craik FI, Luk G. Bilingualism: consequences for mind and brain. *Trends Cogn Sci*. (2012) 16:240–50. doi: 10.1016/j.tics.2012.03.001
30. Grundy JG, Anderson JAE, Bialystok E. Neural correlates of cognitive processing in monolinguals and bilinguals. *Ann N Y Acad Sci*. (2017) 1396:183–201. doi: 10.1111/nyas.13333
31. Kowoll ME, Degen C, Gorenc L, Küntzelmann A, Fellhauer I, Giesel F, et al. Bilingualism as a contributor to cognitive reserve? evidence from cerebral glucose metabolism in mild cognitive impairment and Alzheimer's disease. *Front Psychiatry*. (2016) 7:62. doi: 10.3389/fpsyt.2016.00062
32. Hervais-Adelman AG, Moser-Mercer B, Golestani N. Executive control of language in the bilingual brain: integrating the evidence from neuroimaging to neuropsychology. *Front Psychol*. (2011) 2:234. doi: 10.3389/fpsyg.2011.00234
33. Price CJ, Green DW, Von Studnitz R. A functional imaging study of translation and language switching. *Brain*. (1999) 122:2221–35. doi: 10.1093/brain/122.12.2221
34. Abutalebi J, Green DW. Neuroimaging of language control in bilinguals: neural adaptation and reserve. *Bilingualism Lang Cogn*. (2016) 19:689–98. doi: 10.1017/S1366728916000225
35. Abutalebi J, Guidi L, Borsa V, Canini M, Della Rosa PA, Parris BA, et al. Bilingualism provides a neural reserve for aging populations. *Neuropsychologia*. (2015) 69:201–10. doi: 10.1016/j.neuropsychologia.2015.01.040
36. Wei M, Joshi AA, Zhang M, Mei L, Manis FR, He Q, et al. How age of acquisition influences brain architecture in bilinguals. *J Neurolinguistics*. (2015) 36:35–55. doi: 10.1016/j.jneuroling.2015.05.001
37. Coggins Iii PE, Kennedy TJ, Armstrong TA. Bilingual corpus callosum variability. *Brain Lang*. (2004) 89:69–75. doi: 10.1016/S0093-934X(03)00299-2
38. Alexander GE, Crutcher MD. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends Neurosc*. (1990) 13:266–71. doi: 10.1016/0166-2236(90)90107-L
39. Bialystok E, Craik F, Luk G. Cognitive control and lexical access in younger and older bilinguals. *J Exp Psychol Learn Mem Cogn*. (2008) 34:859. doi: 10.1037/0278-7393.34.4.859
40. Grundy JG, Timmer K. Bilingualism and working memory capacity: a comprehensive meta-analysis. Second *Lang Res*. (2016) 33:325–40. doi: 10.1177/0267658316678286
41. Hernández M, Costa A, Fuentes LJ, Vivas AB, Sebastián-Gallés N. The impact of bilingualism on the executive control and orienting networks of attention. *Bilingualism Lang Cogn*. (2010) 13:315–25. doi: 10.1017/S1366728909990010
42. Brito NH, Murphy ER, Vaidya C, Barr R. Do bilingual advantages in attentional control influence memory encoding during a divided attention task? *Bilingualism Lang Cogn*. (2016) 19:621–9. doi: 10.1017/S1366728915000851
43. Paap KR, Johnson HA, Sawi O. Should the search for bilingual advantages in executive functioning continue? *Cortex*. (2016) 74:305–14. doi: 10.1016/j.cortex.2015.09.010
44. Morton JB, Harper SN. What did Simon say? Revisiting the bilingual advantage. *Dev Sci*. (2007) 10:719–26. doi: 10.1111/j.1467-7687.2007.00623.x
45. Blumenfeld HK, Marian V. Cognitive control in bilinguals: advantages in Stimulus–Stimulus inhibition. *Bilingualism (Cambridge, England)*. (2014) 17:610. doi: 10.1017/S1366728913000564
46. Noble KG, Norman MF, Farah MJ. Neurocognitive correlates of socioeconomic status in kindergarten children. *Dev Sci*. (2005) 8:74–87. doi: 10.1111/j.1467-7687.2005.00394.x
47. Nichols ES, Wild CJ, Stojanoski B, Battista ME, Owen AM. Bilingualism affords no general cognitive advantages: a population study of executive function in 11,000 People. *Psychol Sci*. (2020) 31:548–67. doi: 10.1177/0956797620903113
48. Kavé G, Eyal N, Shorek A, Cohen-Mansfield J. Multilingualism and cognitive state in the oldest old. *Psychol Aging*. (2008) 23:70. doi: 10.1037/0882-7974.23.1.70

49. Bak TH, Nissan JJ, Allerhand MM, Deary IJ. Does bilingualism influence cognitive aging? *Ann neurol*. (2014) 75:959–63. doi: 10.1002/ana.24158
50. Ossher L, Bialystok E, Craik FI, Murphy KJ, Troyer AK. The effect of bilingualism on amnestic mild cognitive impairment. *J Gerontol B Psychol Sci Soc Sci*. (2013) 68:8–12. doi: 10.1093/geronb/gbs038
51. Alladi S, Bak TH, Mekala S, Rajan A, Chaudhuri JR, Mioshi E, et al. Impact of bilingualism on cognitive outcome after stroke. *Stroke*. (2016) 47:258–61. doi: 10.1161/STROKEAHA.115.010418
52. Estanga A, Ecay-Torres M, Ibañez A, Izagirre A, Villanua J, Garcia-Sebastian M, et al. Beneficial effect of bilingualism on Alzheimer's disease CSF biomarkers and cognition. *Neurobiol Aging*. (2017) 50:144–51. doi: 10.1016/j.neurobiolaging.2016.10.013
53. Bialystok E, Craik FI, Freedman M. Bilingualism as a protection against the onset of symptoms of dementia. *Neuropsychologia*. (2007) 45:459–64. doi: 10.1016/j.neuropsychologia.2006.10.009
54. Mukadam N, Sommerlad A, Livingston G. The relationship of bilingualism compared to monolingualism to the risk of cognitive decline or dementia: a systematic review and meta-analysis. *J Alzheimers Dis*. (2017) 58:45–54. doi: 10.3233/JAD-170131
55. Anderson JA, Hawrylewicz K, Grundy JG. Does bilingualism protect against dementia? A meta-analysis. *Psychon Bull Rev*. (2020) 27:952–65. doi: 10.3758/s13423-020-01736-5
56. Brini S, Sohrabi HR, Hebert JJ, Forrest MR, Laine M, Hämäläinen H, et al. Bilingualism is associated with a delayed onset of dementia but not with a lower risk of developing it: a Systematic review with Meta-Analyses. *Neuropsychol Rev*. (2020) 30:1–24. doi: 10.1007/s11065-020-09426-8
57. Craik FI, Bialystok E, Freedman M. Delaying the onset of Alzheimer disease: bilingualism as a form of cognitive reserve. *Neurology*. (2010) 75:1726–9. doi: 10.1212/WNL.0b013e3181fc2a1c
58. Gollan TH, Salmon DP, Montoya RI, Galasko DR. Degree of bilingualism predicts age of diagnosis of Alzheimer's disease in low-education but not in highly educated Hispanics. *Neuropsychologia*. (2011) 49:3826–30. doi: 10.1016/j.neuropsychologia.2011.09.041
59. Bialystok E, Craik FI, Binns MA, Ossher L, Freedman M. Effects of bilingualism on the age of onset and progression of MCI and AD: evidence from executive function tests. *Neuropsychology*. (2014) 28:290. doi: 10.1037/neu0000023
60. Woumans E, Santens P, Sieben A, Versijpt J, Stevens M, Duyck W. Bilingualism delays clinical manifestation of Alzheimer's disease. *Bilingualism Lang Cogn*. (2015) 18:568–74. doi: 10.1017/S136672891400087X
61. Mendez MF, Chavez D, Akhlaghipour G. Bilingualism delays expression of Alzheimer's clinical syndrome. *Dementia and Geriatric Cognitive Disorders*. (2019) 48:281–9. doi: 10.1159/000505872
62. de Leon J, Grasso SM, Welch A, Miller Z, Shwe W, Rabinovici GD, et al. Effects of bilingualism on age at onset in two clinical Alzheimer's disease variants. *Alzheimers Dement*. (2020) 16:1704–13. doi: 10.1002/alz.12170
63. Zahodne LB, Schofield PW, Farrell MT, Stern Y, Manly JJ. Bilingualism does not alter cognitive decline or dementia risk among Spanish-speaking immigrants. *Neuropsychology*. (2014) 28:238. doi: 10.1037/neu0000014
64. Lawton DM, Gasquoine PG, Weimer AA. Age of dementia diagnosis in community dwelling bilingual and monolingual Hispanic Americans. *Cortex*. (2014) 66:141–5. doi: 10.1016/j.cortex.2014.11.017
65. Yeung CM, John PDS, Menec V, Tyas SL. Is bilingualism associated with a lower risk of dementia in community-living older adults? Cross-sectional and prospective analyses. *Alzheimer Dis Assoc Disord*. (2014) 28:326–32. doi: 10.1097/WAD.0000000000000019
66. Clare L, Whitaker CJ, Craik FI, Bialystok E, Martyr A, Martin-Forbes PA, et al. Bilingualism, executive control, and age at diagnosis among people with early-stage Alzheimer's disease in Wales. *J Neuropsychol*. (2016) 10:163–85. doi: 10.1111/jnp.12061
67. Akhlaghipour G, Chavez D, Mendez M. Bilingualism associated with delay in dementia onset and loss of the second language (5259). *Neurology*. (2020) 94:5259.
68. Alladi S, Bak TH, Duggirala V, Surampudi B, Shailaja M, Shukla AK, et al. Bilingualism delays age at onset of dementia, independent of education and immigration status. *Neurology*. (2013) 81:1938–44. doi: 10.1212/01.wnl.0000436620.33155.a4
69. Alladi S, Bak TH, Shailaja M, Gollahalli D, Rajan A, Surampudi B, et al. Bilingualism delays the onset of behavioral but not aphasic forms of frontotemporal dementia. *Neuropsychologia*. (2017) 99:207–12. doi: 10.1016/j.neuropsychologia.2017.03.021
70. Ellajosyula R, Narayanan J, Ramanan S, Chandrashekar S, Sabnis P. *Bilingualism Does Not Delay the Age at Onset of Dementia-A Study From Memory Clinic in South India (P6. 206)*. AAN Enterprises (2015).
71. Zheng Y, Wu Q, Su F, Fang Y, Zeng J, Pei Z. The protective effect of cantonese/mandarin bilingualism on the onset of Alzheimer disease. *Dement Geriatr Cogn Disord*. (2018) 45:210–9. doi: 10.1159/000488485
72. Bialystok E, Poarch G, Luo L, Craik FIM. Effects of bilingualism and aging on executive function and working memory. *Psychol Aging*. (2014) 29:696–705. doi: 10.1037/a0037254
73. Akhlaghipour G, Chavez D, Mendez M. *Bilingualism Associated With Delay in Dementia Onset and Loss of the Second Language (5259)*. AAN Enterprises (2020).
74. Paradis M. Principles underlying the Bilingual Aphasia Test (BAT) and its uses. *Clin Linguist Phon*. (2011) 25:427–43. doi: 10.3109/02699206.2011.560326
75. Alladi S, Hachinski V. World dementia: one approach does not fit all. *Neurology*. (2018) 91:264–70. doi: 10.1212/WNL.0000000000005941
76. Waheed W, Mirza N, Waheed MW, Malik A, Panagioti M. Developing and implementing guidelines on culturally adapting the Addenbrooke's cognitive examination version III (ACE-III): a qualitative illustration. *BMC Psychiatry*. (2020) 20:492. doi: 10.1186/s12888-020-02893-6
77. Watermeyer T, Calia C. Neuropsychological assessment in preclinical and prodromal Alzheimer disease: a global perspective. *J Glob Health*. (2019) 9:010317. doi: 10.7189/jogh.09.010317
78. Demeyere N, Haupt M, Webb S, Strobel L, Milosevich E, Moore M, et al. The Oxford Cognitive Screen – Plus (OCS-Plus): a tablet based short cognitive screening tool for milder cognitive impairment. *PsyArXiv*. (2020). doi: 10.31234/osf.io/b2vgc
79. Humphreys GW, Duta MD, Montana L, Demeyere N, McCrory C, Rohr J, et al. Cognitive function in low-income and low-literacy settings: validation of the tablet-based Oxford cognitive screen in the health and aging in Africa: a longitudinal study of an INDEPTH Community in South Africa (HAALSI). *J Gerontol B Psychol Sci Soc Sci*. (2017) 72:38–50. doi: 10.1093/geronb/gbw139
80. Perdue KL, Jensen SK, Kumar S, Richards JE, Kakon SH, Haque R, et al. Using functional near-infrared spectroscopy to assess social information processing in poor urban Bangladeshi infants and toddlers. *Dev Sci*. (2019) 22:e12839. doi: 10.1111/desc.12839
81. Calia C, Johnson H, Cristea M. Cross-cultural representations of dementia: an exploratory study. *J Glob Health*. (2019) 9:011001. doi: 10.7189/jogh.09.011001
82. Parra MA, Baez S, Sedeño L, Gonzalez Campo C, Santamaría-García H, Aprahamian I, et al. Dementia in Latin America: paving the way toward a regional action plan. *Alzheimers Dement*. (2021) 17:295–313. doi: 10.1002/alz.12202
83. Jia L, Quan M, Fu Y, Zhao T, Li Y, Wei C, et al. Dementia in China: epidemiology, clinical management, and research advances. *Lancet Neurol*. (2020) 19:81–92. doi: 10.1016/S1474-4422(19)30290-X
84. *(LAC-CD) LAaCCoD*. Available online at: http://lac-cd.org/home/ (accessed March 10, 2021).
85. Ou Y-N, Xu W, Li J-Q, Guo Y, Cui M, Chen K-L, et al. FDG-PET as an independent biomarker for Alzheimer's biological diagnosis: a longitudinal study. *Alzheimers Res Ther*. (2019) 11:57. doi: 10.1186/s13195-019-0512-1
86. Reich MR, Takemi K. G8 and strengthening of health systems: follow-up to the Toyako summit. *Lancet*. (2009) 373:508–15. doi: 10.1016/S0140-6736(08)61899-1
87. Wortmann M. Dementia: a global health priority - highlights from an ADI and World Health Organization report. *Alzheimers Res Ther*. (2012) 4:40. doi: 10.1186/alzrt143
88. Farina N, Ibnidris A, Alladi S, Comas-Herrera A, Albanese E, Docrat S, et al. A systematic review and meta-analysis of dementia prevalence in seven developing countries: a STRiDE project. *Glo Public Health*. (2020) 15:1–16. doi: 10.1080/17441692.2020.1792527

89. Benson C. Real and Potential Benefits of Bilingual Programmes in Developing Countries. *Int J Bilingual Educ Bilingualism*. (2002) 5:303–17. doi: 10.1080/13670050208667764
90. Fafunwa AB. Education in the mother-tongue: a nigerian experiment–the six-year (yoruba medium) primary education project at the University of Ife, Nigeria. *West Afr J Educ*. (1975) 19:213–27.
91. Benson CJ. *Teaching Beginning Literacy in the "mother Tongue": A Study of the Experimental Crioulo/Portuguese Primary Project in Guinea-Bissau*. Los Angeles, CA: University of California, (1994).
92. Lampit A, Hallock H, Valenzuela M. Computerized cognitive training in cognitively healthy older adults: a systematic review and meta-analysis of effect modifiers. *PLoS Med*. (2014) 11:e1001756. doi: 10.1371/journal.pmed.1001756
93. Valenzuela MJ, Jones M, Caroline Rae WW, Graham S, Shnier R, Sachdev P. Memory training alters hippocampal neurochemistry in healthy elderly. *NeuroReport*. (2003) 14:1333–7. doi: 10.1097/01.wnr.0000077548.91466.05
94. Rodríguez-Fornells A, Cunillera T, Mestres-Missé A, de Diego-Balaguer R. Neurophysiological mechanisms involved in language learning in adults. *Philos Trans R Soc B Biol Sci*. (2009) 364:3711–35. doi: 10.1098/rstb.2009.0130
95. Bak TH, Long MR, Vega-Mendoza M, Sorace A. Novelty, challenge, and practice: The impact of intensive language learning on attentional functions. *PloS ONE*. (2016) 11:e0153485. doi: 10.1371/journal.pone.0153485
96. Ramos S, Fernández García Y, Antón E, Casaponsa A, Duñabeitia JA. Does learning a language in the elderly enhance switching ability? *J Neurolinguistics*. (2017) 43:39–48. doi: 10.1016/j.jneuroling.2016.09.001
97. Ware C, Damnee S, Djabelkhir L, Cristancho V, Wu Y-H, Benovici J, et al. Maintaining cognitive functioning in healthy seniors with a technology-based foreign language program: a pilot feasibility study. *Frontiers Aging Neurosci*. (2017) 9:42. doi: 10.3389/fnagi.2017.00042

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 29 April 2021
doi: 10.3389/fneur.2021.629507

Sleep Timing and Risk of Dementia Among the Chinese Elderly in an Urban Community: The Shanghai Aging Study

Xiantao Li[1], Ding Ding[2], Qianhua Zhao[2], Wanqing Wu[2], Zhenxu Xiao[2], Jianfeng Luo[3], Kristine Yaffe[4,5,6] and Yue Leng[5,6]**

[1] Department of Critical Care Medicine, Huashan Hospital, Fudan University, Shanghai, China, [2] Institute of Neurology, Huashan Hospital, Fudan University, Shanghai, China, [3] Department of Biostatistics, School of Public Health, Fudan University, Shanghai, China, [4] Departments of Psychiatry and Behavioral Sciences, Neurology, and Epidemiology, University of California, San Francisco, San Francisco, CA, United States, [5] Department of Neurology, Memory and Aging Center, Global Brain Health Institute, University of California, San Francisco, San Francisco, CA, United States, [6] Department of Psychiatry and Behavioral Sciences, University of California, San Francisco, San Francisco, CA, United States

OPEN ACCESS

Edited by:
Christopher Butler,
University of Oxford, United Kingdom

Reviewed by:
Magda Tsolaki,
Aristotle University of Thessaloniki, Greece
Antonio Giuliano Zippo,
National Research Council (CNR), Italy

***Correspondence:**
Ding Ding
dingding@huashan.org.cn
Yue Leng
yue.leng@ucsf.edu

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: 15 November 2020
Accepted: 31 March 2021
Published: 29 April 2021

Citation:
Li X, Ding D, Zhao Q, Wu W, Xiao Z, Luo J, Yaffe K and Leng Y (2021) Sleep Timing and Risk of Dementia Among the Chinese Elderly in an Urban Community: The Shanghai Aging Study. Front. Neurol. 12:629507. doi: 10.3389/fneur.2021.629507

Background: Growing evidence has suggested a link between poor sleep quality and increased risk of dementia. However, little is known about the association between sleep timing, an important behavior marker of circadian rhythms, and dementia risk in older adults, and whether this is independent of sleep duration or quality.

Methods: We included data from 1,051 community-dwelling older men and women (aged≥ 60y) without dementia from the Shanghai Aging Study. At baseline, participants reported sleep timing, duration, and quality using the Chinese version of the Pittsburgh Sleep Quality Index (CPSQI). Dementia diagnosis over the following 7.3 years was determined by neurologists using DSM-IV criteria. We used Cox proportional hazards models to examine the association between bedtime (before 9 p.m., after 11 p.m. vs. 9–11 p.m.), rise time (before 6 a.m., after 8 a.m. vs. 6–8 a.m.), and risk of dementia.

Results: A total of 238 (22.8%), 675 (64.5%), and 133 (12.7%) participants reported going to bed before 9 p.m., between 9 and 11 p.m., and after 11 p.m., respectively, while 272 (26%), 626 (59.9%), and 148 (14.2%) reported getting up before 6 a.m., between 6 and 8 a.m., and after 8 a.m., respectively. Participants who reported going to bed earlier had a lower education level, were less likely to be smokers, more likely to have hypertension or diabetes, and had longer sleep duration but poorer sleep quality compared to those who reported a later bedtime. We found 47 incidents of dementia among 584 participants followed up over an average of 7.3 years. After adjustment for demographics, education, income, body mass index, depressive symptoms, smoking, alcohol use, physical activity, comorbidities, APOE4 genotype, and baseline MMSE, those with a bedtime of before 9 p.m. were two times more likely to develop dementia [hazard ratio (HR)=2.16 (95%CI: 1.06–4.40)], compared to those going to bed between 9 and 11 p.m. Later bedtime (i.e., after 11 p.m.) showed the opposite but had a non-significant association with dementia risk (HR=0.15, 95%CI: 0.02–1.29). We did not find an association for rise time and risk of dementia.

Conclusion: Earlier sleep timing in older adults without dementia was associated with an increased risk of dementia. Future studies should examine the underlying mechanisms of this association and explore the usefulness of sleep timing as a preclinical marker for dementia.

Keywords: sleep, dementia, epidemiological analysis, longitudinal, low- and lower-middle-income countries

INTRODUCTION

Sleep patterns change markedly with age, including altered sleep timing and duration, poor sleep quality, and increased sleep disturbances (1). These sleep changes are often more severe among those with neurodegenerative diseases including severe cognitive impairment, and have also been associated with increased risk of developing dementia. Growing evidence suggests a relationship between circadian rhythm disruption and risk of neurodegenerative diseases (2). Prospective studies reported a 1.5-2 fold increase in dementia risk associated with lower sleep efficiency, longer sleep latency, sleep-disordered breathing, or long daytime napping (3–5). However, the association between sleep timing, an important behavior marker of circadian rhythms, and risk of dementia is poorly understood. On the other hand, the impact of sleep duration or quality on such an association also needs careful consideration.

Compared to western populations, the Chinese elderly are much more likely to sleep and rise earlier, and take a nap in the afternoon. Factors owing to the genetics, culture, environment, or lifestyle of the Chinese population are also different from the western population. Through the prospective phase of the Shanghai Aging Study, the current study aimed to determine the longitudinal association between reported sleep timing and risk of dementia among older Chinese adults, and to study whether this association is independent of sleep duration or quality.

METHODS

Study Design and Participants

During 2010–2011, community residents aged 60 years or older were consecutively enrolled based on a government-maintained residents list of the Jingansi community in central Shanghai. Participants were excluded if they: (1) had severe mental delay or schizophrenia; (2) had difficulties of vision, hearing, or speaking, and (3) were not capable of accomplishing a neuropsychological evaluation. A detailed description of the design and procedure of the Shanghai Aging Study has been published elsewhere (6).

This study was approved by the Medical Ethics Committee of Huashan Hospital, Fudan University, Shanghai, China. A written informed consent was obtained from all of the participants and/or their legal guardian.

Participant Characteristics

Study participants underwent a clinical interview either at Huashan Hospital or at their homes. At baseline, demographic characteristics were collected via an interviewer-administered questionnaire including age, sex, education, income, cigarette smoking, alcohol consumption, and physical activity. Cigarette smoking was defined as a person who had smoked daily within the past month. Alcohol consumption was defined as a person who had had at least one episode of alcohol drinking weekly during the past year. Medical histories such as hypertension, diabetes, and heart diseases were self-reported and further confirmed from medical records. Body mass index (BMI) was calculated as weight in kilograms (kg) divided by height in meters (m) squared. High depressive symptoms were determined to be present if the Center for Epidemiologic Studies Depression Scale (CESD) score was $\geq$16 (7).

DNA was extracted from blood or saliva samples from each participant to conduct Apolipoprotein E (APOE) genotyping by the Taqman SNP method (8). Presence of at least one ε4 allele was classified as APOE ε4 positive.

Measurement of Sleep Quality

At baseline, participants reported sleep quality over a one-month time interval through the Chinese version of the Pittsburgh Sleep Quality Index (CPSQI), which contains seven "component" scores: sleep quality, latency, duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction (9, 10). A global score of subjective sleep quality (range 0–21) was then determined by the sum of the seven component scores with the higher scores representing poorer subjective sleep quality (10). Participants were asked their bedtime, time of falling asleep, rise time, and sleep duration. Bedtime was categorized to "before 9 p.m., after 11 p.m., and 9–11 p.m."; and rise time was categorized to "before 6 a.m., after 8 a.m., and 6–8 a.m."

Neurological, Neuropsychological Assessments, and Diagnosis

At baseline, neurologists examined each participant for their motor responses and reflexes. Each participant was administered a battery of neuropsychological tests for global cognition, executive function, spatial construction function, memory, language, and attention. The battery contained (1) the Mini-Mental State Examination; (2) Conflicting Instructions Task (Go/No Go Task); (3) Stick Test; (4) Modified Common Objects Sorting Test; (5) Auditory Verbal Learning Test; (6) Modified Fuld Object Memory Evaluation; (7) Trail-making tests A and B; and (8) RMB (Chinese currency) test. Participants with $\geq$6 years of education were given tests 1 to 5, and 7; and all others were given tests 1 to 4, 6, and 8. Normative data and more details of these tests were reported elsewhere (11). All tests were conducted in Chinese by study psychometrists. Neurologists also administered the Clinical Dementia Rating (CDR) (12) and the

TABLE 1 | Baseline characteristics of the 584 participants by bedtime.

	At or before 9 p.m.	9–11 p.m.	After 11 p.m.	*P*-value
N (%)	238 (22.8%)	675 (64.5%)	133 (12.7%)	
Age	75.6 (SD 8.0)	70.7 (SD 7.9)	68.8 (SD 7.5)	0.71
Female	139 (58.7%)	392 (58.3)	64 (48.1%)	0.08
Income≥1200RMB/month	231 (97.0%)	663 (98.2%)	128 (96.1%)	0.380
College education or more	32 (13.5%)	234 (34.8%)	53 (39.9%)	**<0.001**
BMI	25.5 (SD 3.8)	24.9 (SD 3.3)	24.7 (3.6)	0.186
Current smoking	14 (5.9%)	54 (8.1%)	26 (19.6%)	**<0.001**
Alcohol drinking	23 (9.8%)	44 (6.6%)	16 (12.0%)	**0.05**
Physical activity	83 (35.6%)	202 (30.4%)	54 (40.9%)	**0.04**
Depression symptoms	31 (12.9%)	84 (12.4%)	17 (12.6%)	0.990
Hypertension	161 (67.9%)	368 (54.7%)	68 (51.1%)	**0.001**
Heart disease	44 (18.6%)	97 (14.5%)	17 (12.9%)	0.23
Diabetes	49 (20.7%)	113 (16.8%)	12 (9.0%)	**0.02**
APOE e4	45 (21.6%)	89 (14.4%)	19 (14.6%)	**0.04**
Sleep duration	6.9 (SD 1.3)	6.9 (SD 1.2)	6.7 (SD 1.1)	0.245
Sleep efficiency	85.0 (SD 13.6)	83.1 (SD 14.4)	85.7 (SD 12.6)	0.171
PSQI score	4.48 (SD 3.07)	4.87 (SD 3.45)	4.91 (SD 3.14)	0.538
MMSE	27.6 (SD 2.9)	28.1 (SD 2.2)	28.6 (SD 2.0)	**0.01**
MMSE at follow-up*	23.8 (SD 7.1)	27.3 (SD 2.9)	27.4 (SD 3.8)	**<0.001**
Incident of dementia*	26 (24.5%)	20 (5.0%)	1 (1.2%)	**<0.001**

**Among the 584 participants who completed the follow-up interview. Bold values indicate statistically significant.*

Lawton and Brody scale of Activity of Daily Living (ADL) (13) to elicit memory complaints and functional abilities.

A panel of neurologists, neuropsychologists, and research coordinators reviewed all the examinations for each participant at baseline and reached a consensus diagnosis for dementia using DSM-IV criteria (14). Detailed diagnostic procedures have been reported elsewhere (6).

Follow-Up Procedure

From April 1, 2014 to December 31, 2016, dementia-free participants with complete sleep quality data at baseline were evaluated at follow-up. Cognitive function was evaluated using the same neuropsychological battery at baseline. Consensus diagnosis of incident dementia was conducted by the same panel of experts using the same diagnostic criteria as at baseline.

Statistical Analysis

Mean with standard deviation (SD), or median (Q1, Q3), and number with frequency (%) were used to describe continuous and categorical variables, respectively. Student's *t*-test was used to analyze the differences for continuous variables, while Pearson's chi-squared test was used to analyze the differences for categorical variables. The incidence of dementia was calculated as the number of new-onset dementia cases divided by the cumulative person-years of follow-up period. Cumulative incidence of dementia were estimated with the Kaplan-Meier product-limit method and compared by the log-rank test. Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for the association between bedtime (before 9 p.m., after 11 p.m. vs. 9–11 p.m.), rise time (before 6 a.m., after 8 a.m. vs. 6–8 a.m.), and risk of dementia. Model 1 adjusted for age, sex, education. Model 2 further adjusted for cigarette smoking, alcohol consumption, hypertension, diabetes, heart disease, stroke, APOE ε4, BMI, and MMSE. In further sensitivity analysis, we additionally adjusted sleep duration and quality as covariables. Model 3 additionally adjusted for covariables including sleep duration and efficiency.

All the *p*-values and 95% CIs were estimated in a two-tailed manner. Differences were statistically significant at $p < 0.05$. Data were analyzed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

We evaluated 1,051 community-dwelling older men and women without dementia. As shown in **Table 1**, 238 (22.8%), 675 (64.5%), and 133 (12.7%) participants reported going to bed before 9 p.m., between 9 and 11 p.m., and after 11 p.m., respectively. A total of 272 (26%), 626 (59.9%), and 148 (14.2%) participants reported getting up before 6 a.m., between 6 and 8 a.m., and after 8 a.m., respectively. The "early birds" (who reported going to bed earlier) had a lower education level, were less likely to be smokers and drinkers, less likely to do physical activity, more likely to have hypertension or diabetes, more likely to be an APOE e4 carrier, and had lower MMSE scores at baseline and follow-up compared to the "night owls" (who reported going to bed later). Over an average of 7.3 years of follow-up, we found 47 (8.0%) incident dementia cases among 584 study

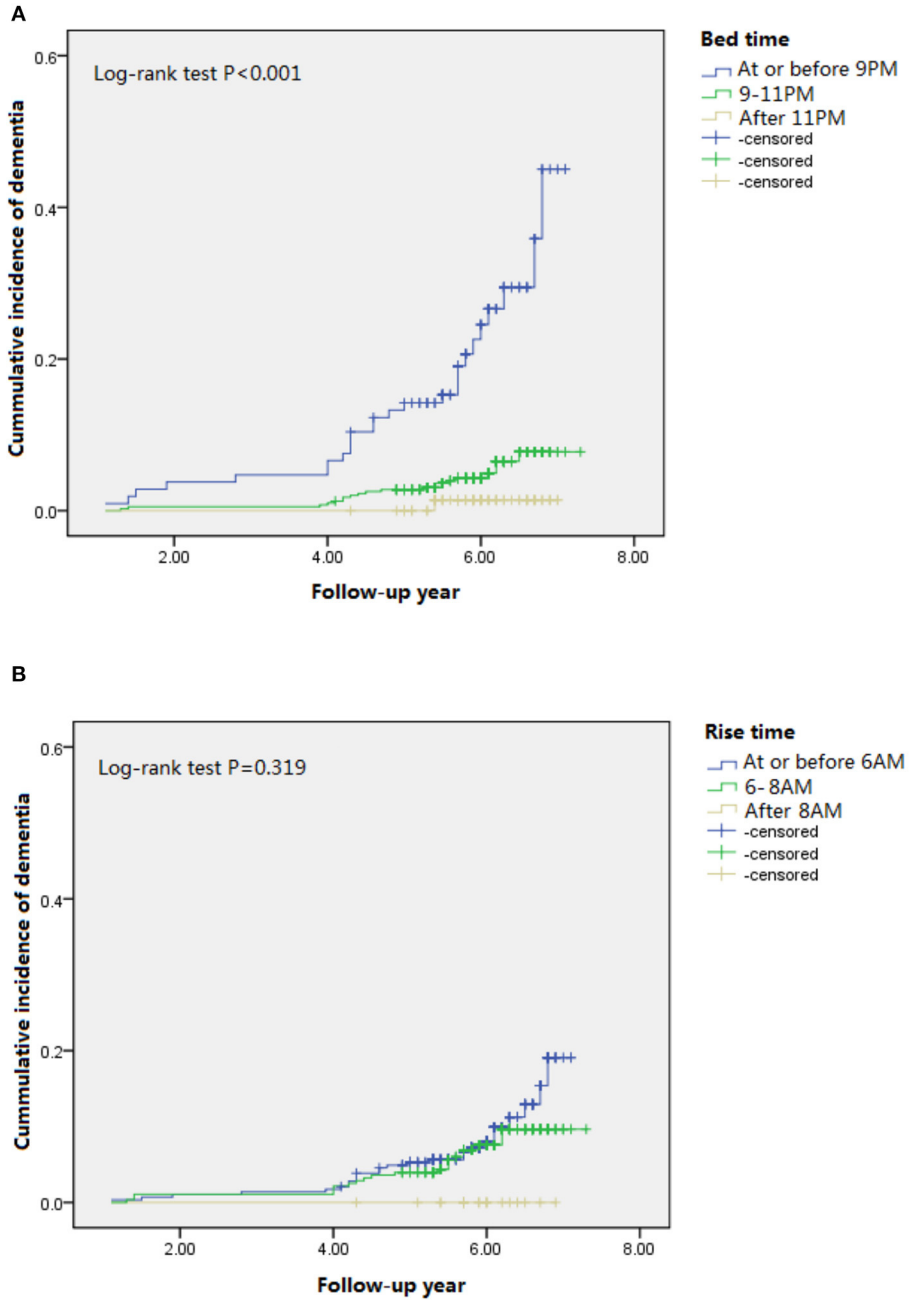


FIGURE 1 | Cumulative incident plots of dementia in participants with different bedtime **(A)** and rise time **(B)** during the follow-up.

participants who completed the follow-up interview. The highest dementia incidence was found in participants who reported going to bed before 9 p.m., and the lowest dementia incidence was found in those who reported going to bed after 11 p.m. ($p < 0.001$). Significant difference of the cumulative incidence of dementia was found among three groups when reporting bedtime (**Figure 1A**), but not among those three groups when reporting rise time (**Figure 1B**).

Table 2 indicates the HR of incident dementia by bedtime and rise time reporting from the participants. Unadjusted HRs and **those from** model 1 were 5.31 (95%CI 2.96–9.51) and 2.72 (95% CI 1.50–4.96). After adjustment for demographics, education, income, BMI, depressive symptoms, smoking, alcohol use, physical activity, comorbidities, APOE4 genotype, and baseline MMSE, those with a bedtime of before 9 p.m. were almost three times more likely to develop dementia

TABLE 2 | Hazard ratio (95%CI) of dementia by bedtime and rise time.

Bedtime	At or before 9 p.m.	9–11 p.m.	After 11 p.m.
Incident of dementia, *N* (%)	26 (24.5%)	20 (5.0%)	1 (1.2%)
Unadjusted HR	5.31 (2.96–9.51)	1	0.24 (0.03–1.80)
HR adjusted in model 1	2.72 (1.50–4.96)	1	0.24 (0.03–1.81)
HR adjusted in model 2	2.16 (1.06–4.40)	1	0.15 (0.02–1.29)
HR adjusted in model 3	2.00 (0.94–4.29)	1	0.12 (0.01–1.05)
Rise time	**At or before 6 a.m.**	**6–8 a.m.**	**After 8 a.m.**
Incident of dementia, *N* (%)	26 (9.1%)	21 (7.6%)	0
Unadjusted HR	1.25 (0.71–2.22)	1	-
HR adjusted in model 1	1.17 (0.65–2.09)	1	-
HR adjusted in model 2	1.49 (0.72–3.10)	1	-
HR adjusted in model 3	2.10 (0.93-4.74)	1	-

Model 1: adjusted for age, sex, education.
Model 2: adjusted for age, sex, education, income, body mass index (BMI), depressive symptoms, smoking, alcohol use, physical activity, comorbidities, APOE4 genotype, and baseline MMSE.
Model 3: adjusted for age, sex, education, income, body mass index (BMI), depressive symptoms, smoking, alcohol use, physical activity, comorbidities, APOE4 genotype, baseline MMSE, sleep duration, and efficiency.

[HR=2.16 (95%CI: 1.06–4.40)], compared to those going to bed between 9 and 11 p.m. Later bedtime (i.e., after 11 p.m.) showed the opposite but had a non-significant association with dementia risk (unadjusted HR = 0.24, 95%CI 0.03–1.80; adjusted HR in model 1=0.24, 95% CI 0.03–1.81; adjusted HR in model 2 = 0.15, 95%CI: 0.02–1.29). The association slightly attenuated (adjusted HRs in model 3 were 2.00 (95%CI: 0.94–4.29) for earlier bedtime and 0.12 (95%CI: 0.01–1.05) for later bedtime) after further adjustment for sleep duration and efficiency. We did not find an association for rise time and risk of dementia.

DISCUSSION

We found that earlier bedtime, not rise time, was associated with an increased risk of dementia in older Chinese adults without dementia and this was independent of demographics, life style, comorbidities, and APOE genotype.

Our results suggest that earlier bedtime may be an early marker of AD through the prospective study design. This speculation is supported by a recent Mendelian randomization (MR) analysis from the largest genome-wide association studies of the UK Biobank (N = 446,118), the Psychiatric Genomics Consortium (N = 18,759), and the International Genomics of Alzheimer's Project (N = 63,926). This MR analysis found that higher risk of AD, based on genetic risk score, was significantly associated with being a "morning person," who prefers going to bed and waking earlier and is less active in the first half of the night (15). Other studies have reported the association between sleep timing and risk of cognitive impairment. An Italian study of 48 patients with AD and age-matched non-dementia controls showed an advanced bedtime in AD patients, especially for moderate to severe cases (16). Another study compared melatonin levels and sleep onset in 30 older patients with mild cognitive impairment (MCI) with 28 healthy controls, and found that MCI patients had early melatonin secretion onset, but the melatonin levels did not differ between groups. Additionally, patients with MCI had greater wake after sleep onset and increased rapid eye movement sleep latency (17). An analysis with 11,247 older individuals from the Swedish Twin Registry raised evidence that delayed rising time predicted dementia incidence after the 17-year-follow up (18). Different with this study, we did not find an association of rising time with dementia onset risk. It might be induced by the limited sample size with the relatively shorter follow-up time.

The exact mechanism which can explain the association of sleep timing with dementia risk is still under investigation. The circadian clock regulates the timing of sleep. Circadian rhythms are generated in specific brain structures to control a complex network of coupled self-sustained clocks in the brain and in the peripheral organs (2). Mutations in the core circadian clock genes in mice and humans manifest as abnormal sleep patterns, including short sleep time, early or late sleep phase, or unstable and fragmented sleep-wake rhythms (19, 20). Age-related changes in sleep-wake cycles may cause circadian dysfunction and result in earlier bedtimes and waking times, increased sleep fragmentation, and increased daytime sleepiness, which might be early indicators of declining health in late life (21, 22). Notably, the association between sleep timing and risk of dementia was slightly attenuated after adjustment for sleep duration and efficiency. The association between circadian rhythms and dementia could be explained by other potential mechanisms, such as protein aggregation from the brain, inflammation, synaptic homoeostasis, and oxidative stress, which are key pathogenic processes in the development of neurodegenerative diseases (2).

Strengths of the current study include a well-representative community-dwelling sample of the Chinese elderly, prospective follow-up for a relatively long period of time, detailed examination of cognitive function, and adjudicated diagnosis of dementia by experts. Our study cannot avoid the following limitations. First, sleep timing and quality were collected by the self-reported PSQI questionnaire, which could include recall bias. Second, even though we followed the participants for an of average 5 years, it may not be long enough to distinguish risk of dementia vs. an early marker of dementia. A longer follow-up can provide a solution for such reverse causality. Third, the relatively high lost-to-follow up rate with fewer incident dementia cases does not allow us to analyze the association with dementia subtypes. Fourth, there are still some potential confounding factors which could not be collected, but may impact the sleep-dementia association, although we tried to adjust covariables as much as possible in our multivariable statistical models.

CONCLUSION

Our findings demonstrate that earlier sleep timing in older adults without dementia was associated with an increased risk of dementia. Future studies should examine the underlying mechanisms of this association and explore the usefulness of sleep timing as a preclinical marker for dementia.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethics Committee of Huashan Hospital, Fudan University, Shanghai, China. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XL, DD, and YL contributed to the design of the study, data analysis and interpretation, and drafting of the manuscript. All authors contributed to critical revision of the manuscript for important intellectual content.

FUNDING

DD was supported by grants from the Shanghai Municipal Science and Technology Major Project (No. 2018SHZDZX01) and ZJ LAB, National Natural Science Foundation of China (81773513), Scientific Research Plan Project of Shanghai Science and Technology Committee (17411950701 and 17411950106), and the State Key Laboratory of Neurobiology and Frontiers Center for Brain Science of Ministry of Education, Fudan University. YL was supported by the National Institute on Aging (NIA) (R00AG056598), and received funding from GBHI, Alzheimer's Association, and Alzheimer's Society (GBHI ALZ UK-19-591141). Support was provided by NIA grant K24AG031155, awarded to KY.

REFERENCES

1. Leng Y, Wainwright NW, Cappuccio FP, Surtees PG, Luben R, Wareham R, et al. Self-reported sleep patterns in a British population cohort. *Sleep Med.* (2014) 15:295–302. doi: 10.1016/j.sleep.2013.10.015
2. Leng Y, Musiek ES, Hu K, Cappuccio FP, Yaffe K. Association between circadian rhythms and neurodegenerative diseases. *Lancet Neurol.* (2019) 18:307–18. doi: 10.1016/S1474-4422(18)30461-7
3. Blackwell T, Yaffe K, Ancoli-Israel S, Schneider JL, Cauley JA, Hillier TA, et al. Study of Osteoporotic Fractures Group. Poor sleep is associated with impaired cognitive function in older women: the study of osteoporotic fractures. *J Gerontol A Biol Sci Med Sci.* (2016) 61:405–10. doi: 10.1093/gerona/61.4.405
4. Yaffe K, Laffan AM, Harrison SL, Redline S, Spira AP, Ensrud KE, et al. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. *JAMA.* (2011) 10:306:613–9. doi: 10.1001/jama.2011.1115
5. Leng Y, Redline S, Stone KL, Ancoli-Israel S, Yaffe K. Objective napping, cognitive decline, and risk of cognitive impairment in older men. *Alzheimers Dement.* (2019) 15:1039–47. doi: 10.1016/j.jalz.2019.04.009
6. Ding D, Zhao Q, Guo Q, Meng H, Wang B, Yu P, et al. The Shanghai Aging Study: study design, baseline characteristics, and prevalence of dementia. *Neuroepidemiology*. (2014) 43:114–22. doi: 10.1159/000366163
7. Beekman AT, Deeg DJ, Van Limbeek J, Braam AW, De Vries MZ, et al. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subject in the Netherlands. *Psychol Med.* (1997) 27:231–5. doi: 10.1017/S0033291796003510
8. Smirnov DA, Morley M, Shin E, Spielman RS, Cheung VG. Genetic analysis of radiation-induced changes in human gene expression. *Nature*. (2009) 459:587–91. doi: 10.1038/nature07940
9. Luo J, Zhu G, Zhao Q, Guo Q, Meng H, Hong Z, et al. Prevalence and risk factors of poor sleep quality among Chinese elderly in an urban community: results from the Shanghai aging study. *PLoS ONE.* (2013) 25:8:e81261. doi: 10.1371/journal.pone.0081261
10. Tsai PS, Wang SY, Wang MY, Su CT, Yang TT, et al. Psychometric evaluation of the Chinese version of the Pittsburgh Sleep Quality Index (CPSQI) in primary insomnia and control subjects. *Qual Life Res.* (2005) 14:1943–52. doi: 10.1007/s11136-005-4346-x
11. Ding D, Zhao Q, Guo Q, Meng H, Wang B, Luo J, et al. Prevalence of mild cognitive impairment in an urban community in China: a cross-sectional analysis of the shanghai aging study. *Alzheimers Dementia*. (2015) 11:300–9.e2. doi: 10.1016/j.jalz.2013.11.002
12. Lim WS, Chong MS, Sahadevan S. Utility of the clinical dementia rating in Asian populations. *Clin Med Res*. (2007) 5:61–70. doi: 10.3121/cmr.2007.693
13. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist*. (1969) 9:179–86. doi: 10.1093/geront/9.3_Part_1.179
14. Samuel G. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association (1994).
15. Huang J, Zuber V, Matthews PM, Elliott P, Tzoulaki J, Dehghan A. Sleep, major depressive disorder, and Alzheimer disease: a Mendelian randomization study. *Neurology.* (2020) 6:95:e1963–70. doi: 10.1212/WNL.0000000000010463
16. Liguori C, Romigi A, Nuccetelli M, Zannino S, Sancesario G, Martorana A, et al. Orexinergic system dysregulation, sleep impairment, and cognitive decline in Alzheimer disease. *JAMA Neurol.* (2014) 71:1498–505. doi: 10.1001/jamaneurol.2014.2510
17. Naismith SL, Hickie IB, Terpening Z, Rajaratnam SM, Hodges JR, Bolitho S, et al. Circadian misalignment and sleep disruption in mild cognitive impairment. *J Alzheimers Dis.* (2014) 38:857–66. doi: 10.3233/JAD-131217
18. Bokenberger K, Strom P, Dahl Aslan AK, Johansson AL, Gatz M, Pedersen NL, et al. Association between sleep characteristics and incident dementia accounting for baseline cognitive status: a Prospective Population-Based Study. *J Gerontol A Biol Sci Med Sci.* (2017) 72:134–9. doi: 10.1093/gerona/glw127
19. Toh KL, Jones CR, He Y, Eide EJ, Hinz WA, Virshup DM, et al. An hPer2 phosphorylation site mutationin familial advanced sleep phase syndrome. *Science.* (2001) 291:1040–43. doi: 10.1126/science.1057499
20. Laposky A, Easton A, Dugovic C, Walisser J, Bradfield C, Turek F. Deletion of the mammalian circadian clock gene BMAL1/Mop3alters baseline sleep architecture and the response to sleepdeprivation. *Sleep.* (2005) 28:395–409. doi: 10.1093/sleep/28.4.395
21. Mander BA, Winer JR, Walker MP. Sleep and human aging. *Neuron.* (2017) 94:19–36. doi: 10.1016/j.neuron.2017.02.004

22. Leng Y, Stone K, Ancoli-Israel S, Covinsky K, Yaffe K. Who take naps? Self-reported and objectively measured napping in very old women. *J Gerontol A Biol Sci Med Sci.* (2018) 73:374–9. doi: 10.1093/gerona/glx014

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

BRIEF RESEARCH REPORT
published: 04 May 2021
doi: 10.3389/fneur.2021.630958

Clinical Impact of PET With ^{18}F-FDG and ^{11}C-PIB in Patients With Dementia in a Developing Country

Andres Damian[1,2*], *Fabiola Portugal*[2], *Nicolas Niell*[1,2], *Adriana Quagliata*[1], *Karina Bayardo*[2], *Omar Alonso*[1,2] *and Rodolfo Ferrando*[1,2]

[1] Centro Uruguayo de Imagenología Molecular (CUDIM), Montevideo, Uruguay, [2] Centro de Medicina Nuclear e Imagenología Molecular, Hospital de Clínicas, Universidad de la República (UdelaR), Montevideo, Uruguay

Introduction: The objective of this study was to evaluate the clinical impact PET with ^{18}F-FDG and ^{11}C-PIB in patients with dementia in a developing country.

Methodology: Retrospective study of the patients referred for the evaluation of dementia to the only PET center in Uruguay. A total of 248 patients were identified, from which 70 patients were included based on the availability of medical history and clinical follow-up. Main outcomes included change in diagnosis, diagnostic dilemma and AD treatment. We evaluated the association of clinical outcomes with PET concordance with baseline diagnosis, diagnostic dilemma, level of education, AD pathology/Non-AD pathology (AD/Non-AD), baseline diagnosis and ^{11}C-PIB PET result.

Results: Baseline clinical diagnosis was concordant with ^{18}F-FDG and ^{11}C-PIB PET results in 64.7 and 77.1% of the patients, respectively. Change in diagnosis after PET was identified in 30.0% of the patients and was associated with discordant ^{18}F-FDG ($p = 0.002$) and ^{11}C-PIB ($p < 0.001$) PET results, previous diagnostic dilemma ($p = 0.005$), low education ($p = 0.027$), Non-AD baseline diagnosis ($p = 0.027$), and negative ^{11}C-PIB PET result ($p < 0.001$). Only the last variable remained significant in the multivariate analysis (adjusted $p = 0.038$). Diagnostic dilemma decreased after PET from 15.7 to 7.1% ($p = 0.11$) and was associated with Non-AD diagnosis ($p = 0.002$) and negative ^{11}C-PIB PET result ($p = 0.003$). Change in AD treatment after PET occurred in 45.7% of the patients.

Conclusion: ^{18}F-FDG and ^{11}C-PIB PET had a significant clinical impact in terms of change in diagnosis and treatment in patients with dementia in a developing country, similar to that reported in high-income countries.

Keywords: PET, Alzheimer's, amyloid, dementia, neuroimaging, biomarkers, clinical diagnosis, impact

OPEN ACCESS

Edited by:
Maira Okada de Oliveira, University of São Paulo, Brazil

Reviewed by:
Arun Bokde, Trinity College Dublin, Ireland
Nilton Custodio, Peruvian Institute of Neurosciences (IPN), Peru

***Correspondence:**
Andres Damian
andres.damian@cudim.org

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: *18 November 2020*
Accepted: *06 April 2021*
Published: *04 May 2021*

Citation:
Damian A, Portugal F, Niell N, Quagliata A, Bayardo K, Alonso O and Ferrando R (2021) Clinical Impact of PET With ^{18}F-FDG and ^{11}C-PIB in Patients With Dementia in a Developing Country. Front. Neurol. 12:630958. doi: 10.3389/fneur.2021.630958

INTRODUCTION

The expected increase in the prevalence of neurodegenerative diseases in the coming years will particularly affect low- and middle-income countries (1). In this context, it is imperative to evaluate the clinical impact of dementia biomarkers to gather relevant information for the construction of rational diagnostic algorithms.

There is a considerable amount of evidence supporting the clinical use of ^{18}F-FDG PET in the evaluation of patients with cognitive impairment (2, 3). This information has led to the incorporation of ^{18}F-FDG into clinical and research guidelines in dementia (4, 5). In the last 15 years, PET with amyloid tracers has also gained ground in the field, becoming one of the leading amyloid biomarkers (5, 6).

Access to high-cost diagnostic biomarkers, such as PET studies, shows significant global heterogeneity, with clear inequities between high- and low- and middle-income countries. PET cameras per million inhabitants can vary from 0.007 to 3.2 between low- and middle- and high-income countries, respectively (7). In this context, the Latin America and Caribbean region (LAC) averages 0.47 PET cameras/million inhabitants, a number clearly below the recommended 2–2.5 (7, 8). The low accessibility to high-cost biomarkers is generally accentuated in populations of public health systems and outside of large cities, which has determined their low representation in the scientific literature (9, 10).

Recently, important clinical studies are been carried out to stablish the clinical impact of amyloid and ^{18}F-FDG PET in the clinical practice (11–15). Although there is now significant evidence about the clinical impact of incorporating these tools in the assessment of patients with cognitive impairment, most of the literature comes from high-income countries. There is little evidence on the clinical impact of these tools in less developed health systems and populations that are usually underrepresented in the clinical literature in the field of dementia.

The objective of the present work is to study the clinical impact of PET with ^{18}F-FDG and ^{11}C-PIB in patients with cognitive impairment referred for clinical evaluation in a developing country.

METHODOLOGY

Study Population

We retrospectively reviewed the Uruguayan Center of Molecular Imaging (CUDIM) database, identifying patients who had undergone both ^{18}F-FDG and ^{11}C-PIB PET/CT between April 2011 and May 2020. All patients had been referred for evaluation of cognitive impairment from different public and private specialized medical centers because of an uncertain diagnosis despite a complete clinical evaluation by a neurologist, neuropsychological assessment and structural imaging. Of the 248 available patients, we had access to the medical history and clinical follow-up (mean follow-up 4.5 years, range 0.5–8 years) in 70 cases, which were finally included in the analysis. All 70 patients were evaluated with ^{11}C-PIB PET/CT and 51 of them also underwent ^{18}F-FDG PET/CT. A summary of patient characteristics is presented in **Table 1**.

TABLE 1 | Population characteristics.

All patients (n = 248)			
Age (mean ± SD; range)	70.2	±9.62	50–87
Gender (% female)	142	57.3%	
Patients with follow-up (n = 70)			
Age (mean ± SD; range)	67.29	±10.22	48–86
Gender (% female)	42	60%	
Formal education (mean ± SD; range)	11.69	±5.5	0–23
MMSE (mean ± SD; range)	23.84	5.66	5–30
Disease duration in years (mean ± SD; range)	3.04	3.10	0.5–20
Baseline diagnosis (n, %)			
AD	61	87.1%	
Non-AD	9	12.8%	

AD, Alzheimer's Disease; MMSE, Mini-Mental State Examination; SD, Standard Deviation.

Clinical Evaluation

A complete medical history from the patient and a close informant as well as a detailed general and neurological physical examination was performed by a dementia specialist in all patients. Laboratory tests included complete blood cell count, calcium, glucose, renal and liver function, vitamin B12, folate, thyroid stimulating hormone and serological tests for syphilis and HIV. The global cognitive function was assessed with the Mini-Mental State Examination (MMSE) and the Addenbrooke's Cognitive Examination (ACE). The neuropsychological evaluation consisted of tests evaluating memory, language, praxis, visual-spatial abilities, attention and executive function. Test performed in all centers included the Rey Auditory Verbal Learning test, category fluency test, Boston Naming test, Rey-Osterrieth Complex Figure test, clock drawing test, forward and backward digit span tests, Trail Making tests A and B, Stroop Color Test, Symbol Digit Modalities test and the Neuropsychiatric Inventory scale. Dementia severity was assessed with the Clinical Dementia Rating scale (CDR). All patients underwent structural magnetic resonance imaging (MRI) of the brain.

Image Acquisition and Interpretation

PET/CT imaging was performed within 1 month from referral. Both ^{18}F-FDG and ^{11}C-PIB images were obtained on a GE Discovery 690 or a GE Discovery STE PET/CT scanner on separate days within a 2-month period. For ^{18}F-FDG PET, patients fasted for 6 h and abstained from tea, coffee, alcohol and nicotine. Images were performed if blood glucose levels were below 150 mg/dl. Patients received an intravenous injection of 3.0 MBq/kg of ^{18}F-FDG in a dimmed quiet room with no external stimuli. Forty minutes later, 3D PET/CT images were acquired. For ^{11}C-PIB PET/CT, the patient was positioned in the scanner, a low dose CT was acquired for attenuation correction and anatomical correlation, and a full dynamic 3D PET/CT acquisition was performed after the intravenous administration of 4.0 MBq/kg of the radiotracer.

Images were analyzed and interpreted by at least two experienced nuclear medicine physicians independently and the discrepancies were solved by consensus. ^{18}F-FDG PET results were reported following previously described criteria (2). Briefly, an Alzheimer's disease (AD) pattern was reported when hypometabolism in parietotemporal cortex and posterior cingulate gyrus was detected and metabolism was preserved in occipital and sensory-motor cortex, basal ganglia and

cerebellum. Other characteristic patterns of neurodegenerative dementia were also considered, including frontal and temporal hypometabolism in frontotemporal dementia (FTD) and posterior parietal and occipital hypometabolism in Lewy body dementia (LBD) (2). If no such pattern was present on ^{18}F-FDG PET images, the study was reported as a non-degenerative disease. Quantification through Z-score maps was available for interpretation of all ^{18}F-FDG PET images (CortexID, GE Heathcare, UK). ^{11}C-PIB PET was reported as positive or negative considering the presence or absence of significant cortical uptake, as described elsewhere (6, 16).

Study Approval and Patient Consent

Written informed consent was obtained from all patients or caregivers. The study was approved by the ethics committee of the Uruguayan Center of Molecular Imaging.

Data Analysis

Based on the methodology of previous reports with similar approaches (17, 18), baseline clinical diagnosis before PET was classified as associated with Alzheimer's disease pathology (AD) when the patient had a diagnosis of possible or probable AD based on the NIA-AA criteria ($n = 38$), amnestic mild cognitive impairment (MCI, $n = 22$) or LBD ($n = 1$). Non-AD baseline diagnosis was considered when the patient had a previous diagnosis of FTD ($n = 5$), semantic dementia ($n = 1$) or non-fluent primary progressive aphasia ($n = 3$). Baseline diagnosis on referral was based on previous clinical, neuropsychological and structural imaging information. The patients that have been referred with more than one clinical diagnosis were classified as diagnostic dilemmas and the first diagnosis listed was considered for AD/Non-AD classification. Concordance between PET and baseline diagnosis was established considering ^{18}F-FDG and ^{11}C-PIB patterns described above. LBD was considered within the AD category because of the high prevalence of amyloid deposits in the disease. After PET/CT imaging, the reports were disclosed to the referring physician and incorporated in the regular diagnostic work-up of the patients. Changes in diagnosis (whether or not the diagnosis change after disclosure of PET result), pharmacological AD treatment (addition or suspension of AD related treatment including donepezil, memantine, galantamine, or rivastigmine) and diagnostic dilemma (whether or not the patient had more than one clinical diagnosis) were evaluated by three experienced physicians and considered as the outcomes for the study. The definite diagnosis was the main diagnosis defined by the neurologist after the disclosure of PET results, considering clinical follow-up and all neuropsychological, laboratory and imaging information. For the statistical analysis, the association of the outcomes with the following variables was assessed individually using Fisher's exact test: PET concordance with baseline diagnosis, formal education ($\leq$ 9 years or $>$ 9 years), AD/Non-AD baseline diagnosis, baseline diagnostic dilemma and ^{11}C-PIB PET result. Additionally, logistic regression analysis was performed exploring the following predictors of the outcomes: baseline AD/Non-AD diagnosis, baseline diagnostic dilemma, discordance of ^{11}C-PIB PET with baseline diagnosis, discordance of ^{18}F-FDG PET with baseline diagnosis and ^{11}C-PIB PET result. A p value lower than 0.05 was considered significant.

RESULTS

Concordance Between PET Studies and Baseline Diagnosis

The concordance between PET results and previous clinical diagnosis was 77.1% for ^{11}C-PIB PET and 64.7% for ^{18}F-FDG PET. No significant differences were found between ^{18}F-FDG and ^{11}C-PIB PET ($p = 0.23$). Considering only the MCI subgroup, we found a 77.3 and 70.5% concordance with previous diagnosis for ^{11}C-PIB and ^{18}F-FDG, respectively, with no significant differences in comparison with the rest of the patients ($p = 0.98$ for ^{11}C-PIB and $p = 0.77$ for ^{18}F-FDG). ^{11}C-PIB and ^{18}F-FDG PET agreed in the classification of 90.2% of the patients.

Change in Diagnosis After PET

Overall change in diagnosis after PET was observed in 30.0% of the patients. When compared separately, a significant association was found between the discordance of PET with baseline diagnosis and the change in diagnosis after PET ($p < 0.001$ for ^{11}C-PIB and $p = 0.002$ for ^{18}F-FDG PET). In addition, the change in diagnosis after PET was associated with lower educational level ($p = 0.027$), Non-AD baseline classification ($p = 0.027$), the presence of a diagnostic dilemma prior to PET (p 0.005) and a negative ^{11}C-PIB PET result (p <0.001). The MCI subgroup showed a 18.2% in change in diagnosis, with no significant differences in comparison with the rest of the patients ($p = 0.17$). In the multiple logistic regression model, only the negative result of the ^{11}C-PIB PET study remained statistically significant (β-coefficient = −2.43, Standard Error = 1.09, $p = 0.038$) **Figure 1**. Change in diagnosis was observed in overall in 21 patients, 14 with baseline AD classification (9 with AD, 4 with amnestic MCI and 1 with LBD) and 7 with baseline non-AD classification (5 with FTD, 1 with SD and 1 with non-fluent APP). The patients in which a change in diagnosis after PET was observed had a disease duration of 3.5 ± 2.6 years. No diagnostic changes were found in patients with both ^{18}F-FDG and ^{11}C-PIB PET results concordant with baseline diagnosis. **Figure 2** shows two examples of patients in which PET results determined a change in diagnosis.

Diagnostic Dilemma

The diagnostic dilemma decreased from 15.7 to 7.1% after PET, even though the decrease was not statistically significant ($p = 0.11$). Nevertheless, the change in dilemma was associated with baseline Non-AD classification ($p = 0.002$), and negative ^{11}C-PIB PET result ($p = 0.03$). In the logistic regression analysis, no significant results were obtained for this outcome.

Change in Treatment

A change in pharmacological treatment related to AD after PET was observed in 45.7% of the patients, either including or retiring AD related pharmaceuticals. There was no significant association between treatment change and ^{18}F-FDG or ^{11}C-PIB PET discordance, baseline AD/Non-AD-diagnosis, baseline diagnostic dilemma or ^{11}C-PIB PET result.

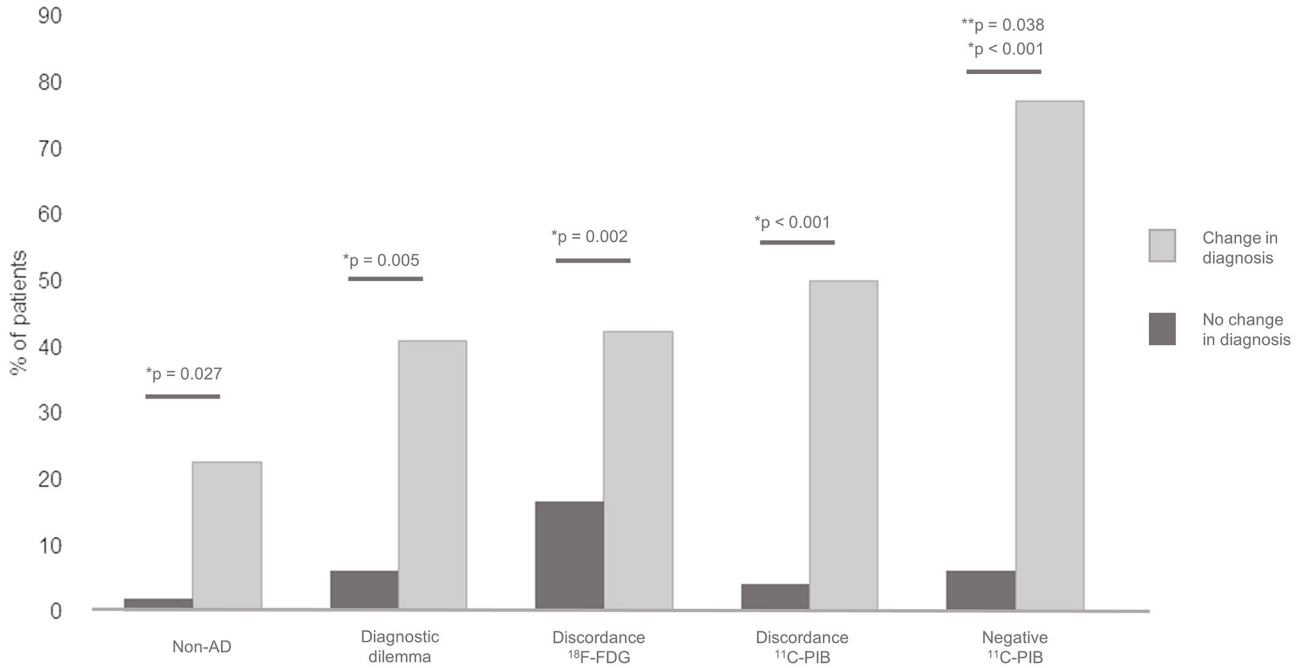


FIGURE 1 | Association between diagnostic change and baseline Non-AD diagnosis, previous diagnostic dilemma, ^{18}F-FDG PET discordance with baseline diagnosis, ^{11}C-PIB PET discordance with baseline diagnosis and negative ^{11}C-PIB PET result. *Individual comparison significance. **Mutivariate logistic regression significance.

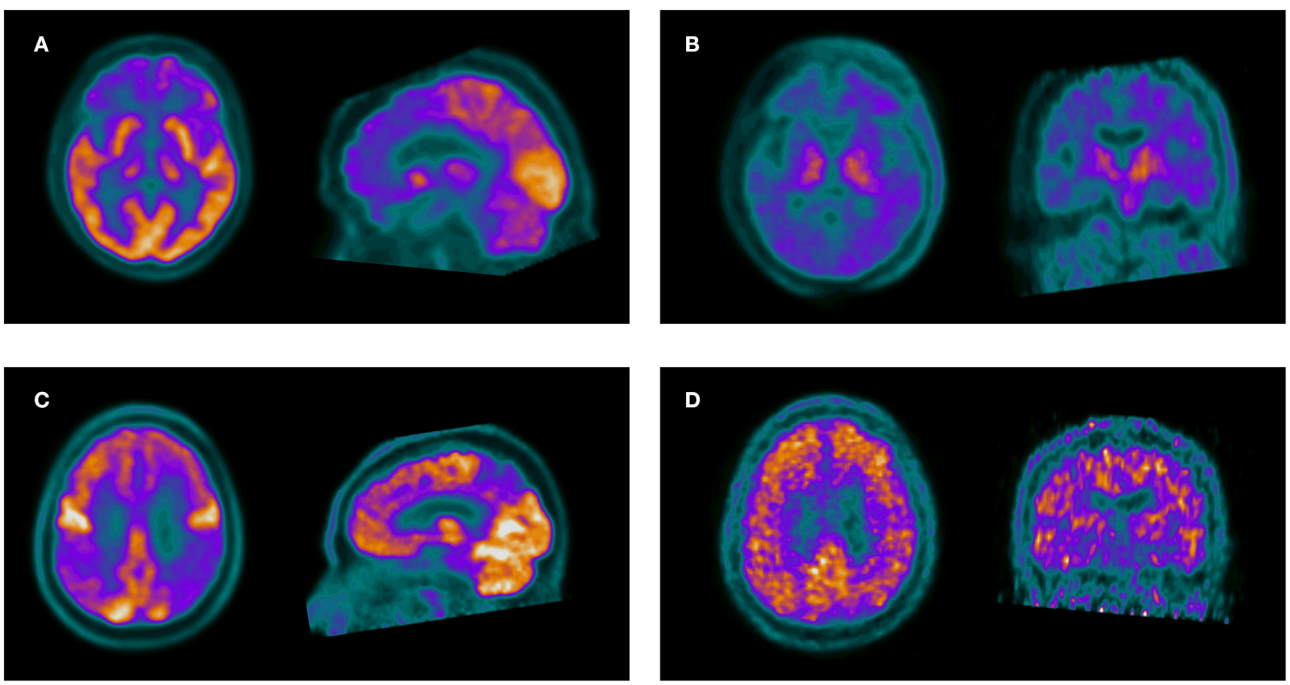


FIGURE 2 | The upper row shows a 56-year-old woman with memory complaints and change in behavior, referred with overlapping symptoms of AD, FTD and a baseline diagnosis of AD. Axial and sagittal slices of 18F-FDG PET **(A)** show frontal hypometabolism suggestive of FTD. Axial and coronal ^{11}C-PIB PET slices **(B)** are negative for amyloid deposition, confirming FTD. The lower row shows a 68-year-old male with symptoms of a non-fluent progressive aphasia. ^{18}F-FDG PET **(C)** shows posterior parietal and precuneus hypometabolism suggestive of AD. ^{11}C-PIB PET **(D)** confirms AD pathology.

DISCUSSION

In the present study, the clinical impact of ^{18}F-FDG and ^{11}C-PIB PET/CT was assessed in patients with cognitive impairment, exploring the change in diagnosis, specific AD treatment and diagnostic dilemma after PET. The study aimed to provide evidence about the usefulness of these techniques focusing on a particular cohort of patients referred from public and private institutions in a developing country like Uruguay. This constitutes the main strength of the study, given that populations from less developed health systems tend to be underrepresented in clinical studies with high-cost techniques. It is worth to notice that the study involved patients from both the public and private systems and represents the nationwide experience, since the institution where the study was carried out is the only PET center in Uruguay, providing assistance to the whole population.

Firstly, we observed a high overall agreement between PET results and baseline clinical diagnosis (70% of the patients). Although this phenomenon may vary depending on the characteristics of the population studied and the previous clinical and neuropsychological characterization, a high concordance has been reported, associated with a confirmatory role of PET studies in a significant proportion of the patients (17, 18).

The agreement was higher in the MCI subgroup, with 77.3 and 70.7% concordance for ^{11}C-PIB and ^{18}F-FDG, respectively. The percentage of concordance previously reported for MCI patients has been variable. Lage et al. showed a concordance of 57 and 20% for ^{11}C-PIB and ^{18}F-FDG (17), while Sánchez-Juan et al. described a concordance of 80% for both radiotracers (18). In our region, Chrem Mendez et al. described a concordance of 68.8% for ^{11}C-PIB (19) and Coutinho et al. showed 37% positive ^{11}C-PIB results in amnestic MCI patients (20).

Regarding the clinical contribution of PET studies, we observed a change in diagnosis in 30% of the patients. Previous studies have shown variable results. In a recent systematic review by Fantoni et al. (13) amyloid PET resulted in a revised diagnosis in 31% of the cases. Other studies that incorporate both ^{18}F-FDG and ^{11}C-PIB PET reported changes of 9% (18) and 17% (17). These differences may vary depending on the methodological design and the clinical setting in which the study is performed, with reported values that can reach up to 79% (21–31). In the MCI subgroup we found a change in diagnosis in 18.2% of the patients, less than in the complete group but not statistically different. Nevertheless, it should be considered that all these patients had amnestic MCI and the impact of PET in terms of change in diagnosis may be higher in non-amnestic MCI patients. In concordance with previous results from other groups, the change in diagnosis after PET in our series was associated with the presence of a previous diagnostic dilemma, which highlights the importance of PET imaging in patients with a challenging diagnosis.

Both ^{11}C-PIB and ^{18}F-FDG PET discordance with baseline diagnosis were associated with a diagnostic change, with ^{11}C-PIB PET discrepancy as the most significant variable of the two. Similar results have been reported by Sánchez-Juan et al. (18) and Lage et al. (17) showing that amyloid PET discordance was the factor that most influenced the change in diagnosis. Moreover, ^{11}C-PIB PET result was the only variable that remained significant in the multivariate analysis. These results remark the importance of the evaluation of amyloid deposits in the brain for the referring physician. Several studies have demonstrated the high negative predictive value of amyloid PET, with reported values of up to 100% (32, 33). Thus, a negative result practically rules out AD, providing critical information for the physician to change the diagnosis.

It should be noted that although our study was carried out in a different population than most of the previous reports, the results were similar anyway, highlighting the importance of amyloid imaging as a determining factor for clinical decisions. A particularly interesting finding was the association between a low level of formal education and the change in diagnosis after PET imaging. Previous studies have described that dementia diagnosis may be challenging in individuals with low literacy. Low education can affect the formal testing of cognitive performance and motor skills (34–36). It is therefore likely that these patients might benefit more from the inclusion of biomarkers in their diagnostic workup, because of difficulties that may arise in clinical and neuropsychological assessment due to the low education level (37, 38). Change in diagnosis was also associated with baseline non-AD classification, but this result should be taken carefully since the vast majority of our patients had a previous AD diagnosis. When evaluating the change in diagnostic dilemma after PET, an association with Non-AD diagnosis was also found.

We observed a 45.7% change in AD treatment after PET. Other authors have reported similar values, with associations with PIB discordance that were not significant in our analysis (17, 18). Recently, Rabinovici et al. reported results of the multicenter IDEAS study that included 13.444 patients evaluated with amyloid PET in the USA. They described a change in patient management in 60.2% of the patients with MCI and 63.5% of the patients with AD, mostly related with specific drug treatment, which changed in 43.6% of patients with MCI and 44.9% of patients with dementia (11).

Even though only nine countries in the LAC region have cyclotrons for the production of radiotracers, the access to PET in the region has improved in the last few years, with an annual growth of ∼21% (7, 8). Access to amyloid tracers has also improved and the proposed A-T-N criteria are increasingly being applied to classify the patients in research studies (19, 20, 39–44). Regarding the clinical utility of amyloid PET, Chrem Mendez et al. described 76.2% concordance of ^{11}C-PIB PET with baseline diagnosis in patients with AD, and a range of concordance of 54.5–100% in other forms of cognitive impairment (19). It is important to emphasize on the complementary role of ^{18}F-FDG and ^{11}C-PIB in the diagnosis of patients with dementia, since the patterns of hypometabolism on the ^{18}F-FDG scan can help to distinguish between different clinical entities in amyloid negative patients. This issue has been recently addressed in our region by Coutinho et al. (20) and Parmera et al. (44). A single ^{18}F-FDG PET scan can be enough to provide an accurate diagnosis when a disease-specific hypometabolic pattern is identified, avoiding the need for more expensive techniques like amyloid PET.

The main limitation of our study is the sample size, mostly affecting the subgroup of Non-AD patients. Also, our sample did not include patients with other forms of cognitive impairment at baseline diagnosis, like non-amnestic MCI, vascular dementia, atypical parkinsonism or Parkinson's dementia, in which ^{18}F-FDG or amyloid PET have proved useful for clinical characterization (45, 46). Another limitation is the lack of availability of tau biomarkers that are currently under development in our center. Nevertheless, several publications from other authors included similar sample sizes and the literature from developing countries is still very limited. Racial/ethnic disparities can influence dementia risk and care. The inclusion of underrepresented populations in dementia science represents an urgent need for diverse perspectives to protect public health (47). This constitutes the main strength of our work.

The results presented provide important information about the clinical impact of PET studies in developing countries. New prospective studies including larger populations are needed to evaluate the efficacy of these techniques in this setting. Comparison with other biomarkers and cost-effectiveness analysis will be needed for the inclusion of these tools in the diagnostic algorithms of patients with dementia taking into account the optimization of available resources.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comité de Ética del Centro Uruguayo de Imagenología Molecular. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AD and RF conception and design of the research. AD, FP, AQ, KB, and NN data collection. AD, RF, and FP statistical analysis, creation of the tables, figures, and writing of the manuscript. AD, FP, AQ, NN, KB, OA, and RF reviewed the manuscript and approved the final version. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Custodio N, Wheelock A, Thumala D, Slachevsky A. Dementia in Latin America: epidemiological evidence and implications for public policy. *Front Aging Neurosci.* (2017) 9:221. doi: 10.3389/fnagi.2017.00221
2. Schöll M, Damián A, Engler H. Fluorodeoxyglucose PET in neurology and psychiatry. *PET Clin.* (2014) 9:371–90. doi: 10.1016/j.cpet.2014.07.005
3. Engler H, Damian A, Bentancourt C. PET and the multitracer concept in the study of neurodegenerative diseases. *Dement Neuropsychol.* (2015) 9:343–9. doi: 10.1590/1980-57642015DN94000343
4. Jack CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimer's Dementia.* (2018) 14:535–62. doi: 10.1016/j.jalz.2018.02.018
5. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the national institute on aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's Dementia.* (2011) 7:263–9. doi: 10.1016/j.jalz.2011.03.005
6. Johnson KA, Minoshima S, Bohnen NI, Donohoe KJ, Foster NL, Herscovitch P, et al. Appropriate use criteria for amyloid PET: a report of the amyloid imaging task force, the society of nuclear medicine and molecular imaging, and the Alzheimer's association. *Alzheimer's Dementia.* (2013) 9:e-1-16. doi: 10.1016/j.jalz.2013.01.002
7. Paez D, Giammarile F, Orellana P. Nuclear medicine: a global perspective. *Clin Trans Imaging.* (2020) 8:51–3. doi: 10.1007/s40336-020-00359-z
8. Páez D, Orellana P, Gutiérrez C, Ramirez R, Mut F, Torres L. Current status of nuclear medicine practice in Latin America and the Caribbean. *J Nucl Med.* (2015) 56:1629–34. doi: 10.2967/jnumed.114.148932
9. Parra MA, Baez S, Sedeño L, Gonzalez Campo C, Santamaría-García H, Aprahamian I, et al. Dementia in Latin America: paving the way toward a regional action plan. *Alzheimer's Dement.* (2020) 17:295–313. doi: 10.1002/alz.12202
10. Parra MA, Baez S, Allegri R, Nitrini R, Lopera F, Slachevsky A, et al. Dementia in Latin America assessing the present and envisioning the future. *Neurology.* (2018) 90:222–31. doi: 10.1212/WNL.0000000000004897
11. Rabinovici GD, Gatsonis C, Apgar C, Chaudhary K, Gareen I, Hanna L, et al. Association of amyloid positron emission tomography with subsequent change in clinical management among medicare beneficiaries with mild cognitive impairment or dementia. *JAMA - J Am Med Assoc.* (2019) 321:1286–94. doi: 10.1001/jama.2019.2000
12. Brendel M, Schnabel J, Schönecker S, Wagner L, Brendel E, Meyer-Wilmes J, et al. Additive value of amyloid-PET in routine cases of clinical dementia work-up after FDG-PET. *Eur J Nucl Med Mol Imaging.* (2017) 44:2239–48. doi: 10.1007/s00259-017-3832-z
13. Fantoni ER, Chalkidou A, O'Brien JT, Farrar G, Hammers A. A systematic review and aggregated analysis on the impact of amyloid PET Brain imaging on the diagnosis, diagnostic confidence, and management of patients being evaluated for Alzheimer's disease. *J Alzheimer's Dis.* (2018) 63:783–96. doi: 10.3233/JAD-171093
14. Leuzy A, Savitcheva I, Chiotis K, Lilja J, Andersen P, Bogdanovic N, et al. Clinical impact of [18 F]flutemetamol PET among memory clinic patients with an unclear diagnosis. *Eur J Nucl Med Mol Imaging.* (2019) 46:1276–86. doi: 10.1007/s00259-019-04297-5
15. Perini G, Rodriguez-Vieitez E, Kadir A, Sala A, Savitcheva I, Nordberg A. Clinical impact of 18F-FDG-PET among memory clinic patients with uncertain diagnosis. *Eur J Nucl Med Mol Imaging.* (2020) 48:612–22. doi: 10.1007/s00259-020-04969-7
16. Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh compound-B. *Ann Neurol.* (2004) 55:306–19. doi: 10.1002/ana.20009
17. Lage C, Suarez AG, Pozueta A, Riancho J, Kazimierczak M, Bravo M, et al. Utility of amyloid and FDG-PET in clinical practice: differences between secondary and tertiary care memory units. *J Alzheimer's Dis.* (2018) 63:1025–33. doi: 10.3233/JAD-170985
18. Sánchez-Juan P, Ghosh PM, Hagen J, Gesierich B, Henry M, Grinberg LT, et al. Practical utility of amyloid and FDG-PET in an academic dementia center. *Neurology.* (2014) 82:230–8. doi: 10.1212/WNL.0000000000000032
19. Patricio CM, Gabriela C, Julieta RM, Marcos FS, Federico N, Griselda R, et al. Concordance between 11C-PIB-PET and clinical diagnosis in a memory clinic. *Am J Alzheimers Dis Other Demen.* (2015) 30:599–606. doi: 10.1177/1533317515576387

20. Coutinho AM, Busatto GF, de Gobbi Porto FH, de Paula Faria D, Ono CR, Garcez AT, et al. Brain PET amyloid and neurodegeneration biomarkers in the context of the 2018. NIA-AA research framework: an individual approach exploring clinical-biomarker mismatches and sociodemographic parameters. *Eur J Nucl Med Mol Imaging.* (2020) 47:2666–80. doi: 10.1007/s00259-020-04714-0
21. Apostolova LG, Haider JM, Goukasian N, Rabinovici GD, Chételat G, Ringman JM, et al. Critical review of the appropriate use criteria for amyloid imaging: effect on diagnosis and patient care. *Alzheimer's Dement Diagn Assess Dis Monit.* (2016) 5:15–22. doi: 10.1016/j.dadm.2016.12.001
22. Bensaïdane MR, Beauregard JM, Poulin S, Buteau FA, Guimond J, Bergeron D, et al. Clinical utility of amyloid PET imaging in the differential diagnosis of atypical dementias and its impact on caregivers. *J Alzheimer's Dis.* (2016) 52:1251–62. doi: 10.3233/JAD-151180
23. Frederiksen KS, Hasselbalch SG, Hejl A-M, Law I, Højgaard L, Waldemar G. Added diagnostic value of 11C-PiB-PET in memory clinic patients with uncertain diagnosis. *Dement Geriatr Cogn Dis Extra.* (2012) 2:610–21. doi: 10.1159/000345783
24. Grundman M, Pontecorvo MJ, Salloway SP, Doraiswamy PM, Fleisher AS, Sadowsky CH, et al. Potential impact of amyloid imaging on diagnosis and intended management in patients with progressive cognitive decline. *Alzheimer Dis Assoc Disord.* (2013) 27:4–15. doi: 10.1097/WAD.0b013e318279d02a
25. Grundman M, Johnson KA, Lu M, Siderowf A, Dellagnello G, Arora AK, et al. Effect of amyloid imaging on the diagnosis and management of patients with cognitive decline: impact of appropriate use criteria. *Dement Geriatr Cogn Disord.* (2016) 41:80–92. doi: 10.1159/000441139
26. Ossenkoppele R, Prins ND, Pijnenburg YAL, Lemstra AW, Van Der Flier WM, Adriaanse SF, et al. Impact of molecular imaging on the diagnostic process in a memory clinic. *Alzheimer's Dement.* (2013) 9:414–21. doi: 10.1016/j.jalz.2012.07.003
27. Schipke CG, Peters O, Heuser I, Grimmer T, Sabbagh MN, Sabri O, et al. Impact of beta-amyloid-specific florbetaben pet imaging on confidence in early diagnosis of Alzheimer's disease. *Dement Geriatr Cogn Disord.* (2012) 33:416–22. doi: 10.1159/000339367
28. Zannas AS, Doraiswamy PM, Shpanskaya KS, Murphy KR, Petrella JR, Burke JR, et al. Impact of 18F-florbetapir PET imaging of β-amyloid neuritic plaque density on clinical decision-making. *Neurocase.* (2014) 20:466–73. doi: 10.1080/13554794.2013.791867
29. Zwan MD, Bouwman FH, Konijnenberg E, Van Der Flier WM, Lammertsma AA, Verhey FRJ, et al. Diagnostic impact of [18F]flutemetamol PET in early-onset dementia. *Alzheimer's Res Ther.* (2017) 9:2. doi: 10.1186/s13195-016-0228-4
30. Boccardi M, Altomare D, Ferrari C, Festari C, Guerra UP, Paghera B, et al. Assessment of the incremental diagnostic value of florbetapir F 18 imaging in patients with cognitive impairment: the incremental diagnostic value of amyloid PET with [18F]-florbetapir (INDIA-FBP) study. *JAMA Neurol.* (2016) 73:1417–24. doi: 10.1001/jamaneurol.2016.3751
31. Pontecorvo MJ, Siderowf A, Dubois B, Doraiswamy PM, Frisoni GB, Grundman M, et al. Effectiveness of florbetapir PET imaging in changing patient management. *Dement Geriatr Cogn Disord.* (2017) 44:129–43. doi: 10.1159/000478007
32. Nordberg A, Carter SF, Rinne J, Drzezga A, Brooks DJ, Vandenberghe R, et al. A European multicentre PET study of fibrillar amyloid in Alzheimer's disease. *Eur J Nucl Med Mol Imaging.* (2013) 40:104–14. doi: 10.1007/s00259-012-2237-2
33. Mallik A, Drzezga A, Minoshima S. Clinical amyloid imaging. *Semin Nuclear Med.* (2017) 47:31–43. doi: 10.1053/j.semnuclmed.2016.09.005
34. Youn JH, Siksou M, Mackin RS, Choi JS, Chey J, Lee JY. Differentiating illiteracy from Alzheimer's disease by using neuropsychological assessments. *Int Psychogeriatr.* (2011) 23:1560–8. doi: 10.1017/S1041610211001347
35. Caramelli P, Poissant A, Gauthier S, Bellavance A, Gauvreau D, Lecours AR, et al. Educational level and neuropsychological heterogeneity in dementia of the Alzheimer type. *Alzheimer Dis Assoc Disord.* (1997) 11:9–15. doi: 10.1097/00002093-199703000-00003
36. Kim H, Chey J. Effects of education, literacy, and dementia on the clock drawing test performance. *J Int Neuropsychol Soc.* (2010) 16:1138–46. doi: 10.1017/S1355617710000731
37. Fichman HC, Fernandes CS, Nitrini R, Lourenço RA, Paradela EM de P, Carthery-Goulart MT, et al. Age and educational level effects on the performance of normal elderly on category verbal fluency tasks. *Dement Neuropsychol.* (2009) 3:49–54. doi: 10.1590/S1980-57642009DN30100010
38. Kosmidis MH. Challenges in the neuropsychological assessment of illiterate older adults. *Language Cogn Neurosci.* (2018) 33:373–86. doi: 10.1080/23273798.2017.1379605
39. Méndez PC, Calandri I, Nahas F, Russo MJ, Demey I, Martín ME, et al. Argentina-Alzheimer's disease neuroimaging initiative (Arg-ADNI): neuropsychological evolution profile after one-year follow up. *Arq Neuropsiquiatr.* (2018) 76:231–40. doi: 10.1590/0004-282x20180025
40. Allegri RF, Chrem Méndez P, Calandri I, Cohen G, Martín ME, Russo MJ, et al. Prognostic value of ATN Alzheimer biomarkers: 60-month follow-up results from the argentine Alzheimer's disease neuroimaging initiative. *Alzheimer's Dement Diagn Assess Dis Monit.* (2020) 12:e12026. doi: 10.1002/dad2.12026
41. Russo MJ, Cohen G, Mendez PC, Campos J, Nahas FE, Surace EI, et al. Predicting episodic memory performance using different biomarkers: Results from Argentina-Alzheimer's disease neuroimaging initiative. *Neuropsychiatr Dis Treat.* (2016) 12:2199–206. doi: 10.2147/NDT.S107051
42. Sanchez JS, Hanseeuw BJ, Lopera F, Sperling RA, Baena A, Bocanegra Y, et al. Longitudinal amyloid and tau accumulation in autosomal dominant Alzheimer's disease: findings from the Colombia-Boston (COLBOS) biomarker study. *Alzheimer's Res Ther.* (2021) 13:27. doi: 10.1186/s13195-020-00765-5
43. Busatto GF, de Gobbi Porto FH, Faria D de P, Squarzoni P, Coutinho AM, Garcez AT, et al. *In vivo* imaging evidence of poor cognitive resilience to Alzheimer's disease pathology in subjects with very low cognitive reserve from a low-middle income environment. *Alzheimer's Dement Diagn Assess Dis Monit.* (2020) 12:e12122. doi: 10.1002/dad2.12122
44. Parmera JB, Coutinho AM, Aranha MR, Studart-Neto A, de Godoi Carneiro C, de Almeida IJ, et al. FDG-PET patterns predict amyloid deposition and clinical profile in corticobasal syndrome. *Mov Disord.* (2020) 36:651–61. doi: 10.1002/mds.28373
45. Arbizu J, Luquin MR, Abella J, de la Fuente-Fernández R, Fernandez-Torrón R, García-Solís D, et al. Neuroimagen funcional en el diagnóstico de pacientes con síndrome parkinsoniano: actualización y recomendaciones para el uso clínico. *Rev Esp Med Nucl Imagen Mol.* (2015) 34:215–26. doi: 10.1016/j.remn.2014.02.001
46. Arbizu J, García-Ribas G, Carrió I, Garrastachu P, Martínez-Lage P, Molinuevo JL. Recomendaciones para la utilización de biomarcadores de imagen PET en el proceso diagnóstico de las enfermedades neurodegenerativas que cursan con demencia: documento de consenso SEMNIM y SEN. *Rev Esp Med Nucl Imagen Mol.* (2015) 34:303–13. doi: 10.1016/j.remn.2015.03.002
47. Hill CV. Sankofa-highlighting legacy in the pursuit of equity for dementia science. *JAMA Neurol.* (2020) 78:271–27. doi: 10.1001/jamaneurol.2020.4481

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

REVIEW
published: 10 May 2021
doi: 10.3389/fneur.2021.629442

Brain SPECT as a Biomarker of Neurodegeneration in Dementia in the Era of Molecular Imaging: Still a Valid Option?

Rodolfo Ferrando [1,2]* *and Andres Damian* [1,2]

[1] *Centro de Medicina Nuclear e Imagenología Molecular, Hospital de Clínicas, Universidad de la República (UdelaR), Montevideo, Uruguay,* [2] *Centro Uruguayo de Imagenología Molecular (CUDIM), Montevideo, Uruguay*

Biomarkers are playing a progressively leading role in both clinical practice and scientific research in dementia. Although amyloid and tau biomarkers have gained ground in the clinical community in recent years, neurodegeneration biomarkers continue to play a key role due to their ability to identify different patterns of brain involvement that sign the transition between asymptomatic and symptomatic stages of the disease with high sensitivity and specificity. Both ^{18}F-FDG positron emission tomography (PET) and perfusion single photon emission computed tomography (SPECT) have proved useful to reveal the functional alterations underlying various neurodegenerative diseases. Although the focus of nuclear neuroimaging has shifted to PET, the lower cost and wider availability of SPECT make it a still valid alternative for the study of patients with dementia. This review discusses the principles of both techniques, compares their diagnostic performance for the diagnosis of neurodegenerative diseases and highlights the role of SPECT to characterize patients from low- and middle-income countries, where special care of additional costs is particularly needed to meet the new recommendations for the diagnosis and characterization of patients with dementia.

Keywords: SPECT, PET, biomarkers, Alzheimer's disease, dementia, neurodegeneration, low- and middle-income countries

OPEN ACCESS

Edited by:
Christopher Butler, University of Oxford, United Kingdom

Reviewed by:
Elena Rodriguez-Vieitez, Karolinska Institutet (KI), Sweden
John Dimitrios Papatriantafyllou, Third Age Day-Care Center IASIS, Greece

***Correspondence:**
Rodolfo Ferrando
rodolfo.n.ferrando@gmail.com

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: *14 November 2020*
Accepted: *06 April 2021*
Published: *10 May 2021*

Citation:
Ferrando R and Damian A (2021) Brain SPECT as a Biomarker of Neurodegeneration in Dementia in the Era of Molecular Imaging: Still a Valid Option? Front. Neurol. 12:629442. doi: 10.3389/fneur.2021.629442

INTRODUCTION

Functional brain imaging includes a set of techniques that reveal biochemical, physiological, or electrical properties of the central nervous system. The most developed of these techniques are single photon emission tomography (SPECT), positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Of them, the first two are the most widely used and validated techniques in clinical practice, while the third is still limited to scientific research in dementia, and is the most appropriate modality for brain activation or connectivity studies. Magnetic resonance spectroscopy (MRS) is another functional technique that has clinical utility mostly in the evaluation of brain tumors, although it does not have yet defined clinical applications in dementia. SPECT and PET are nuclear medicine techniques that use radiopharmaceuticals for the evaluation of different functional phenomena (classically brain perfusion for SPECT or metabolism for PET), although today there is a plethora of tracers that allow the study of many molecular events in the brain.

SPECT is currently one of the most widely available imaging techniques for the study of brain function. It has been used successfully for the diagnosis of dementias since the 1980's, while PET made its way to the clinic in the following decade. Most recently, the evolution of nuclear techniques toward molecular imaging has allowed the *in vivo* detection of characteristic phenomena of neurodegenerative diseases such as disorders of dopaminergic function, beta-amyloid deposits or tau protein aggregates using specific tracers. Imaging of dopamine receptors, particularly dopamine transporter SPECT, already has consensual clinical applications in the study of encephalopathies associated with parkinsonism.

TECHNICAL CONSIDERATIONS

Brain SPECT

SPECT is a nuclear medicine imaging modality in which a gamma-emitter radiotracer is injected into the patient and tomographic images of its distribution are then obtained. The uptake of the radiotracer depends on the biochemical behavior of the tracer in the body (1).

The development of brain perfusion radiotracers consolidated the use of brain SPECT in the 1990's. The first radiotracers used were diffusible molecules (e.g., ^{133}Xe), whose uptake depend on the arrival to the brain through the arterial system (cerebral perfusion) and on the concentration gradient between arterial blood and brain tissue. Through the application of kinetic analysis models, it was possible to obtain an absolut measure of the regional cerebral blood flow (rCBF) with ^{133}Xe. Nevertheless, the low energy gamma rays emitted by ^{133}Xe and its fast clearance from the brain determined a low spatial resolution. Few years later static tracers were developed (IMP, HIPDM, HMPAO, and ECD). These radiotracers are extracted by the brain on the initial arterial pass after peripheral i.v. administration and retained in proportion to the rCBF distribution. They are rather stable *in vivo* for at least 1 h, allowing images to be obtained for several minutes after injection. The most extensively used static radiotracers are ^{99m}Tc-ECD (ethylcysteinate-dimer) and ^{99m}Tc-HMPAO (hexamethyl propylene amine oxime) (2), with considerable technical, economic and logistical advantages (3). Their main characteristic is lipophilicity, which allows free diffusion through the blood-brain barrier with high extraction in the first pass through the cerebral circulation after the intravenous injection. This property determines an uptake that is proportional to the cerebral blood flow, maintaining a strong linear relationship at least up to 80 ml/min/100 g. After cellular uptake, these compounds are retained at the intracellular level for a long time (6 h for ECD and 4 h for the stabilized HMPAO kit) due to their transformation into hydrophilic compounds, with a fixed regional distribution that represents the functional state of the brain at the time of injection (2).

The close relationship between perfusion and neuronal metabolism is well-documented both in physiological conditions and in the vast majority of pathological processes, allowing the identification of hypometabolic regions through the corresponding decrease in perfusion using blood flow tracers (the same concept applies to fMRI). Tomographic images are acquired 45–60 min after injection for ECD and 60–90 min for HMPAO. Usually with a two-detector gamma camera a total acquisition time of 30 min is sufficient to achieve optimal image quality with a radiopharmaceutical dose of 925 MBq (25 mCi). The contrast of the images is usually higher with ECD than with HMPAO, and the dosimetry is slightly more favorable for ECD. The small differences in the normal brain distribution of both tracers are not considered relevant when interpreting clinical studies (2).

In addition to brain perfusion tracers, significant advances have been observed in recent years in the use of dopamine transporter (DAT) radiotracers. One of the most widely used DAT SPECT radiotracers is the tropane analog ^{123}I-FP-CIT, which is used to demonstrate the presynaptic dopaminergic depletion in degenerative parkinsonisms. It has shown a good correlation with the severity and duration of Parkinson's disease, as well as clinical utility in the differential diagnosis between different forms of dementia. Given the low availability and high cost of ^{123}I in low- and middle-income countries, many centers have opted for ^{99m}Tc-labeled DAT radiotracers such as 99mTc-TRODAT, which has proven to perform well for the characterization of degenerative parkinsonisms (4–6). Typically, studies with ^{99m}Tc-TRODAT require the administration of a dose of 925 MBq (25 mCi) and a delayed acquisition of 30 min at 3–4 h after injection to obtain images of adequate quality.

Brain PET

PET is a nuclear imaging modality that allows obtaining tomographic images of the regional distribution in the brain of radiopharmaceuticals labeled with positron-emitting isotopes. The emitted positrons have a small trajectory in the body (usually a few millimeters) before each positron reacts with an electron of the subject in a process called annihilation, that results in the emission of two photons in opposite directions. PET scanners have rings of multiple detectors located around the patient that detect the coincidence of this pair of photons. By this process it is possible to infer the place where the positron was emitted and reconstruct tomographic images (7–9).

Positron-emitting radionuclides are produced in particle accelerators called cyclotrons and their half-life ranges from <2 to 110 min, which is acceptable for emission imaging. In the case of radiotracers labeled with ^{18}F, which has a half-life of 110 min, the tracer can be produced and transported for injection and acquisition to distant centers. With ^{11}C or ^{15}O labeled radiotracers (20 min and 2 min half-life, respectively) the production and the study should be performed in the same center. The physical characteristics of this radioactive emission and its detection process provide PET with greater sensitivity and spatial resolution compared to SPECT. Nevertheless, it is worth to notice that this complex process and sophisticated equipment made the cost of PET several times higher than SPECT (1).

The most widely used radiopharmaceutical in clinical practice is the glucose analog ^{18}F-fluorodeoxyglucose (^{18}F-FDG). Brain metabolism depends particularly on glucose as the main energy substrate (10). This determines a high normal FDG uptake in the brain with high quality images, allowing a direct measurement of regional brain glucose metabolism. If dynamic image acquisition

is performed, it is possible to quantify glucose consumption in absolute values using kinetic models. This technique is not used in clinical practice due to its complexity and the need for simultaneous arterial blood sampling. The typical acquisition starts 30–60 min after the injection of the tracer. The patient must remain in psychophysical rest for at least 30 min after the injection of the radiopharmaceutical due to the prolonged period of cerebral glucose uptake. The usual dose is 370 MBq (10 mCi) of ^{18}F-FDG and image acquisition takes about 20 min (7).

It is also possible to measure absolute rCBF with different PET radiotracers, among which ^{15}O-H_2O stands out as the gold standard for non-invasive absolute quantification (11). The minimum requirement for this procedure is the acquisition of dynamic studies for their analysis using kinetic models. Since ^{15}O has a 2-min half-life, it is possible to make several acquisitions on the same day. Typically, the dose to be administered is 300–500 MBq and the acquisition of each study does not take more than 10 min.

Since the early 2000's, amyloid imaging with PET started to gain ground as a new biomarker in patients with AD. The first radiotracer developed was the thioflavin T analog ^{11}C-PIB (12) and later fluorinated analogs were incorporated (^{18}F-florbetaben, ^{18}F-florbetapir, and ^{18}F-flutemetamol) extending the use of this modality in many countries. The imaging protocol and the quantification of the amyloid burden in the brain may vary depending on the radiotracer, but there are usually well-stablished criteria to determine if a patient has significative amyloid depositions. More recently, Tau tracers have been developed and included in the framework for research in AD (13).

CLINICAL UTILITY OF SPECT AND PET IN ALZHEIMER'S DISEASE

Diagnosis of Alzheimer's Dementia

Although many patients with Alzheimer's disease (AD) have a characteristic clinical presentation, some forms of the disease may present with atypical symptoms. Diagnostic difficulties may rise in early disease stages, in atypical presentations or in clinical scenarios in which the differential diagnosis with other forms of dementia is challenging (14, 15). Murray et al. published a series of 889 cases of AD with histopathological confirmation, describing three well-defined subtypes with different clinical characteristics, of which the hippocampal-sparing subtype (11% of cases) was associated with atypical clinical presentation and previous diagnostic errors with higher frequency in comparison with the typical and predominantly limbic subtypes (16). Up to 25% of AD cases may show an atypical clinical presentation, supporting the use of functional neuroimaging biomarkers in diagnosis. Moreover, the hippocampal-sparing subtype represents a challenge for structural MRI, which usually relies on the identification of hippocampal atrophy as a hallmark for the diagnosis of AD (16).

SPECT and PET are the functional imaging modalities that have the most robust scientific support for their clinical application in dementias, and have been used successfully for several decades. The typical pattern of AD on SPECT or PET images is characterized by the presence of bilateral hypoperfusion or hypometabolism in the posterior parietal, temporal, and posterior cingulate cortex with preservation of the primary visual and sensorimotor cortex, basal ganglia, thalamus, brainstem and cerebellum. Generally, there is a lower degree of frontal involvement, which increases with the progression of the disease, usually sparing the motor cortex. The presence of this pattern has a high diagnostic accuracy, although other patterns with marked asymmetry, even unilateral, or with marked frontal involvement can be seen (2, 8, 17).

Usually there is a good correlation between SPECT/PET findings and symptom severity, although on certain clinical situations (including early-onset AD or in subjects with high intellectual level) this relationship may be more limited, with alterations that tend to be more severe in earlier clinical stages of the disease. This phenomenon is probably related to the concept of cognitive reserve. Those individuals with higher reserve are able to develop alternative strategies to compensate for the loss of functions related to the progress of the pathological process, thus delaying the onset of symptoms (18).

Studies on the diagnostic performance of SPECT in dementias showed variable results. The use of different radiopharmaceuticals, equipment, inclusion criteria and confirmation methods largely explain the variability of the findings. A systematic review by Dougall et al. evaluated the diagnostic accuracy of 45 studies performed with HMPAO in comparison with clinical diagnosis (DSM-III-R and NINCDS-ARDRA criteria) between the years 1988 and 2002 (19). The authors described a sensitivity of 77% and specificity of 89% for the diagnosis of AD compared to normal controls, 71 and 76% compared to vascular dementia, and 72 and 78% compared to frontotemporal dementia, using cross-sectional clinical diagnosis as the gold standard.

Regarding ^{18}F-FDG PET, the meta-analysis of Patwardhan et al. included 15 articles published between 1989 and 2003, 10 of which included comparison with normal controls, showing sensitivity and specificity of 86% for the latter case (20). The final reference was clinical diagnosis in nine of the studies and histopathological confirmation in one. Five studies compared AD with other forms of dementia, showing similar sensitivity and significantly lower specificity (18–86%). Recently, Nestor et al. reviewed the evidence on the clinical use of ^{18}F-FDG PET in diverse clinical scenarios, recommending the use of ^{18}F-FDG for the differential diagnosis of other forms of dementia (21).

Of particular interest are the studies that evaluated the diagnostic accuracy of SPECT or PET using histopathological confirmation as a reference, since the assessment of the pathological hallmarks of AD is considered the most appropriate gold standard for research. Read et al. reported a sensitivity of 93% for SPECT compared with 73% for clinical diagnosis in a series of 27 patients that underwent autopsy (22). Bonte et al. published a series of articles using SPECT, in which the population studied progressively increased from 1993 and onwards. The final report of this series in 2011 included 73 patients and showed a sensitivity of 94%, specificity of 85%, positive predictive value of 92%, negative predictive value of

88%, and accuracy of 90% (23). Jobst et al. included 104 patients with dementia (80 of them with AD) and reported a sensitivity, specificity, and accuracy of 89, 80, and 83%, respectively (24).

It is important to notice that some of these studies were published more than 20 years ago and used the equipment available at that time, with a performance likely below the current standards in the field. Since then, many technical advances have been incorporated into clinical routine, including iterative reconstruction methods (OSEM), scatter correction, attenuation correction using CT maps in hybrid equipment and resolution recovery. All of them have contributed to improving the quality of the images with a probable positive impact on the diagnostic performance of SPECT. El Fakhri et al. demonstrated the advantages of several of these improvements in patients with mild cognitive impairment (MCI) (25).

Regarding PET, Silverman et al. published results of a multicenter study that included 138 patients (97 patients with AD, 23 with non-AD neurodegeneration and 18 with no neurodegenerative dementia), one of the largest series existing to date, and reported values of 94% sensitivity, 73% specificity, and 88% accuracy (26). Previously, Hoffman et al. published an institutional series of 22 patients with AD and other dementias in which they described a sensitivity of 88% and a specificity of 67% (27). Jagust et al. in a series of 44 patients (including 20 patients with AD, 9 normal controls, and patients with mixed dementia and LBD among others) reported values of 84 and 74%, respectively (28).

Additional Value of SPECT and PET in the Clinical Context

Most of the studies previously mentioned included SPECT or PET interpretation blinded to clinical information, which does not represent the usual situation in practice, in which clinical information is used to support image interpretation, improving the diagnostic performance. The data might therefore be interpreted as a conservative estimate of the usefulness of these modalities as an isolated diagnostic tool, and probably do not reflect their true impact as complementary tools to clinical evaluation. The importance of a diagnostic test often lies in the additional information that provides over the already available clinical data. Thus, even assuming that the diagnostic performance of SPECT/PET in AD could be similar to neuropsychological tests, the combination of both can increase the diagnostic accuracy. In this regard, Jagust et al. (29) analyzed data from the aforementioned work by Jobst et al. (24) evaluating the additional impact of SPECT on clinical diagnosis and reported that a positive SPECT increased the probability of AD in histopathology from 84 to 92% for the diagnosis of probable AD and from 67 to 84% for the diagnosis of possible AD. A clinical diagnosis of possible AD with a positive SPECT was associated with the same probability of AD as the clinical diagnosis of probable AD, whereas a diagnosis of probable AD with positive SPECT implies a very high probability of AD on neuropathology. Claus et al. in a study carried out in a community population found that when the previous probability of AD was 50%, the additional information provided by SPECT increased the diagnostic certainty by 34% (30). Silverman et al. in a retrospective analysis of 167 patients studied with FDG PET with an average clinical follow-up of 3 years reported that when the initial clinical evaluation predicted progressive deterioration (based on suspected neurodegenerative disease), 94% of the patients with a positive PET finally deteriorated while the percentage dropped to 25% when PET was negative (31). According to Jagust et al., the clinical diagnosis was associated with a 70% probability of AD in histopathology, while this value increased to 84% with a positive PET and decreased to 31% with a negative PET. A clinical diagnosis not compatible with AD was associated with pathology of AD in 35% of the patients, which increased to 70% with a positive PET (28).

The Value of Quantification

Many studies have evaluated the impact of semi-quantitative methods on the diagnostic performance of SPECT in dementia, demonstrating an increase in accuracy with respect to visual interpretation and a decrease in interobserver variability. Voxel-based analysis transforms the images of each subject to a common stereotaxic space and then applies statistical tests to identify groups of voxels that differ between groups of patients or between patients and normal controls. This analysis can be applied similarly to SPECT and PET images. Originally developed for the use in research studies, it has gained acceptance in clinical practice to determine the statistical deviation of images of an individual subject from a database of normal controls. The two most widely used tools are Statistical Parametric Mapping (SPM) and Tridimensional Stereotactic Surface Projections (3D-SSP), both of which are freely accessible. It has been shown that with the use of these tools the sensitivity and specificity of SPECT can be increased to above 90 and 85%, respectively for the diagnosis of AD, even in early stages (32, 33). Alternatively, a region of interest (ROI) approach can be used to compare the uptake in predefined regions of the brain with normal controls. The defined ROIs should include the brain areas most frequently involved in the different types of dementia (such as posterior parietal cortex, precuneus and posterior cingulate in AD, the dorsolateral, medial and ventral frontal cortex and anterior cingulate in frontotemporal dementia, or the posterior parietal and occipital cortex in Lewy body disease) Different reference regions can be used for intensity normalization when applying a semi-quantitative approach. Usually, a region not affected in the disease and with low variability between patients and controls is chosen (for instance the pons, cerebellum or the whole brain for AD).

The semi-quantitative approach is widely available and usually easy to implement, even in centers from low- and middle-income countries. In contrast, the full quantitative approach requires the acquisition of dynamic studies, the implementation of kinetic analysis, a specific training of the staff and, in some cases, arterial blood sampling. All these issues have led to a more widespread use of the semi-quantitative approach in clinical practice, while full quantification is usually reserved for research purposes.

Prognostic Value for Conversion From Mild Cognitive Impairment to Alzheimer's Dementia

Of particular importance is the potential of functional imaging techniques for the diagnosis of AD in the early disease stages, such as MCI. The identification of subjects at high risk of evolution to AD at the MCI stage can allow the intervention in the initial clinical phase of the disease with the aim of delaying the evolution of symptoms and the appearance of dementia. The presence of hypoperfusion in SPECT or hypometabolism in PET in the posterior parietal cortex, precuneus, and posterior cingulate in patients with MCI has been consistently associated with an increased risk of progression to AD (34–36). In particular, posterior cingulate has been identified as a region that provides high discriminative power. SPECT reports showed an accuracy of ∼75–80% when using image quantification techniques (37–39). Nobili et al. described a sensitivity of 81% and specificity of 86% for hippocampal hypoperfusion as a predictive marker of conversion to AD. Silverman et al. reported maintained sensitivity and specificity (95 and 71%, respectively) for PET in the subgroup of patients with mild AD in their retrospective multicenter study of patients evaluated for dementia with histopathological confirmation (26). A meta-analysis by Yuan et al., which included 24 studies with a total of 1,112 patients, found sensitivity and specificity values of 89 and 85%, respectively for PET, 84 and 70% for SPECT, and 73 and 81% for MRI, for prediction of conversion from MCI to AD (40). A review by Frisoni et al. reported pooled sensitivity and specificity for conversion of MCI to AD of 76 and 74%, respectively for PET and 78 and 64%, respectively for SPECT (41).

CLINICAL USE OF SPECT AND PET IN THE DIFFERENTIAL DIAGNOSIS OF DEMENTIA

Frontotemporal Dementia

The presence of anterior temporal and frontal hypoperfusion or hypometabolism typically identifies patients with frontotemporal dementia (FTD), as opposed to the posterior temporoparietal pattern characteristic of AD. Using this criterion, a systematic review by Yeo et al., which included 10 studies that used SPECT, reported sensitivity and specificity of 80% using clinical follow-up as a reference (42). Even though there may be varying degrees of posterior cortical involvement in FTD, as well as atypical AD presentations with marked frontal involvement, in general, the balance between the severity of the anterior and posterior cortical involvement provides good results to discriminate both clinical entities. Sjögren et al. reported a sensitivity of 88% and a specificity of 79% for HMPAO SPECT using an anterior-to-posterior ratio quantification strategy to differentiate FTD from other forms of dementia. Specificity increased to 96% compared to early-onset AD (43). The relative preservation of the posterior cingulate cortex in FTD and the indemnity of the primary sensorimotor cortex and subcortical gray structures in AD, have been described as other useful findings. Méndez et al. retrospectively evaluated 134 patients referred for clinical suspicion of FTD and reported sensitivity and specificity of 37 and 100% for clinical follow-up at 2 years, 64 and 70% for MRI and 91 and 75% for SPECT/PET (44). Read et al. studied 27 patients with dementia (including eight patients with FTD and 11 with possible or probable AD) and neuropathological confirmation and found that SPECT was able to correctly classify 93% of the cases, while clinical evaluation was successful in classifying the patients in 74% of the cases (22).

SPECT and PET can identify dysfunctional patterns that contribute not only to the differential diagnosis between AD and FTD, but also to the diagnosis of the different FTD variants. The behavioral variant of FTD presents with a predominant medial prefrontal, anterior cingulate, middle and inferior frontal gyri and superior temporal hypometabolism (45). The semantic variant of primary progressive aphasia presents with anterior temporal hypoperfusion or hypometabolism with a clear left predominance, while the non-fluent variant shows involvement of the left frontal operculum. The logopenic variant is characterized by defects of the left posterior temporoparietal cortex and the underlying pathology is more likely AD.

Lewy Body Dementia

Lewy body dementia (LBD) shows a pattern of hypoperfusion or hypometabolism that usually involves the posterior parietotemporal cortex (similar to AD) but sparing the posterior cingulate and usually with extension to the occipital cortex. Occipital involvement, particularly of the primary visual cortex, has been identified as the most valuable sign for differentiating LBD from AD. Lobotesis et al. reported sensitivity of 65% and specificity of 87% for the differential diagnosis between LBD and AD by SPECT using this criterion (46). Shimizu et al. reported a sensitivity and specificity of 85% using voxel-based analysis (47). PET studies showed similar, and in some cases superior, diagnostic performance. Minoshima et al. reported a sensitivity of 90% and specificity of 80% for hypometabolism of the occipital cortex in the differential diagnosis with AD (48). Based on the involvement of the occipital cortex and the relative preservation of the posterior cingulate (posterior cingulate island sign), the diagnostic criteria of McKieth et al. (49, 50) recognize the role of SPECT/PET as a supportive marker for the diagnosis of LBD. It has to be considered that occipital involvement may be present in other pathologies such as Parkinson's dementia and may be absent in a non-negligible percentage of patients with LBD who show a perfusion or metabolic pattern very similar to AD. LBD is characterized by striatal dopaminergic deficiency that is related to parkinsonism, one of the core symptoms of the disease. The decrease in DAT density at the presynaptic dopaminergic terminal is a consequence of the degeneration of nigrostriatal neurons, a phenomenon that can be measured through specific SPECT tracers. The most widely used of them is ^{123}I-FP-CIT (ioflupane). This image modality allows the differential diagnosis with AD with high performance. The reduction in striatal uptake of ^{123}I-FP-CIT was able to distinguish LBD and AD with a sensitivity of 88% and specificity of 100% in a series of 20 patients with histopathological confirmation, while the initial clinical diagnosis showed a sensitivity of 77% and specificity of 42% (51). In a multicenter study that included 326 patients using clinical diagnosis as a reference, McKieth

et al. reported sensitivity of 78% and specificity of 90% (52). The 2017 consensus criteria for LBD consider reduced striatal uptake in DAT SPECT/PET as an indicative biomarker of the disease (50). DAT SPECT has not shown the same utility for the differential diagnosis between LBD and FTD, since in the latter the presence of extrapyramidal signs is not uncommon. In this regard, perfusion SPECT has much greater utility. Although ^{123}I-FP-CIT may not be available in many low- and middle-income countries due to its high cost and the low availability of ^{123}I, other alternatives like ^{99m}Tc-TRODAT-1 have shown excellent correlation with ^{123}I-FP-CIT in various diseases associated with parkinsonism. Although DAT imaging has demonstrated greater accuracy than perfusion/metabolic imaging in the differential diagnosis between LBD and AD, this particular scenario is not always present in clinical practice. The differential diagnosis may often present with different types of dementia like FTD, parkinsonism-related dementias, vascular dementia, and others, and DAT imaging is less likely to solve the problem than perfusion/metabolic imaging in these cases. Moreover, it is not clear if the impact of DAT imaging in LBD is the same when clear features of parkinsonism are present or not. It seems reasonable to hypothesize that reduced uptake of a DAT tracer in the context of parkinsonian signs is less likely to provide relevant additional information, and perfusion/metabolic imaging can make a more considerable difference. Taking these considerations into account, it may be reasonable to start with perfusion/metabolic imaging in many cases, and reserve DAT imaging for a second stage when necessary, enabling significant savings due to the higher cost of the latter. This is exemplified in **Figures 1A,B**.

Parkinsonism-Related Dementias

At a certain point of the disease, up to 30–40% of patients with Parkinson's disease (PD) may have dementia symptoms and up to 75–80% of patients with PD may develop dementia during a 10 year period (15, 53, 54). The cognitive impairment that usually presents in PD is typically of the frontal-subcortical type and do not reach the MCI stage, while those cases that progress to dementia are characterized by predominant posterior cortical symptoms (15). This phenomenon can be identified by SPECT or PET by the presence of a dysfunctional pattern similar to that of AD. Although more frequent extension to the occipital cortex and greater preservation of the medial temporal structures have been described in PD dementia in comparison with AD, the findings in both diseases may be indistinguishable (55). The pattern of PD dementia can be even more difficult to distinguish from AD than the one of LBD. However, these diseases are usually differentiated by the temporal course of the appearance of dementia symptoms and extrapyramidal signs (50). Although the vast majority of parkinsonisms are PD, the so-called atypical parkinsonisms can represent up to 15% of the cases and their clinical diagnosis can be particularly complex. Among them are multisystemic atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) (55, 56). These diseases are associated with a higher prevalence of dementia and are characterized by a frequent compromise of the post-synaptic dopaminergic system, unlike PD. Post-synaptic D2 receptor SPECT may be useful for the differential diagnosis between PD and atypical parkinsonism, although some reports indicate that its diagnostic accuracy would be suboptimal (57, 58). Furthermore, its high cost, low availability and its inability to differentiate between different forms of atypical parkinsonism considerably limit its use in clinical practice. Various publications have shown that perfusion SPECT or FDG PET (associated with DAT imaging) have a higher performance for the differential diagnosis between these diseases (57, 59). Atypical parkinsonisms are characterized by the presence of striatal hypoperfusion or hypometabolism, unlike PD. On the other hand, cerebellar involvement orients to MSA, while a frankly asymmetric cortical-subcortical pattern is characteristic of CBD (**Figures 1C,D**), and PSP shows alterations in the superior and medial frontal cortex, thalamus and pons (55, 60). Thus, perfusion/metabolic imaging can not only confirm the diagnosis of atypical parkinsonism revealing striatal involvement but also contribute to the differential diagnosis of the specific disease.

Vascular Dementia

In the diagnosis of vascular dementia (VD), structural images (especially MRI) play a leading role (15, 61). SPECT and PET have traditionally been reserved for equivocal cases. However, 15–20% of patients with VD have mixed dementia, more frequently VD and AD. In these cases, functional images are useful to confirm or rule out the presence of associated AD. Multi-infarct dementia is characterized by multiple asymmetric focal defects with well-defined borders scattered in the cerebral cortex, frequently in borderline territories of the cerebral arteries, which can be associated with subcortical and cerebellar defects. Dementia due to strategic infarct shows a well-defined extensive defect in a specific vascular territory. The presence of crossed cerebellar diaschisis is frequent in both cases and is considered an element of diagnostic value. When the strategic infarct is located in subcortical structures such as the internal capsule or the thalamus, cortical hypoperfusion is usually associated due to disruption of the thalamocortical projections (diaschisis). Subcortical vascular dementia is characterized by hypoperfusion of subcortical gray structures associated with diffuse moderate cortical involvement that mostly affect the frontal cortex, as a result of diaschisis phenomena associated with white matter abnormalities. The presence of bilateral posterior temporoparietal perfusion defects, characteristic of AD, differs from the typical patterns of VD, allowing the differential diagnosis between both diseases as well as the diagnosis of association between both. Some authors like Nagata et al. state that the information provided by SPECT/PET is useful in the differential diagnosis between VD, AD and mixed dementia and should be taken into account in the diagnostic guidelines (61). SPECT with vasodilator stimulation with acetazolamide has shown to be capable of providing additional information in the differential diagnosis of VD with AD, increasing the performance of images at rest (62).

Finally, SPECT and PET also have diagnostic utility in other less frequent dementias, including traumatic brain injury, AIDS dementia, autoimmune or paraneoplastic encephalitis, neurolupus, Behcet's disease, exposure to neurotoxins,

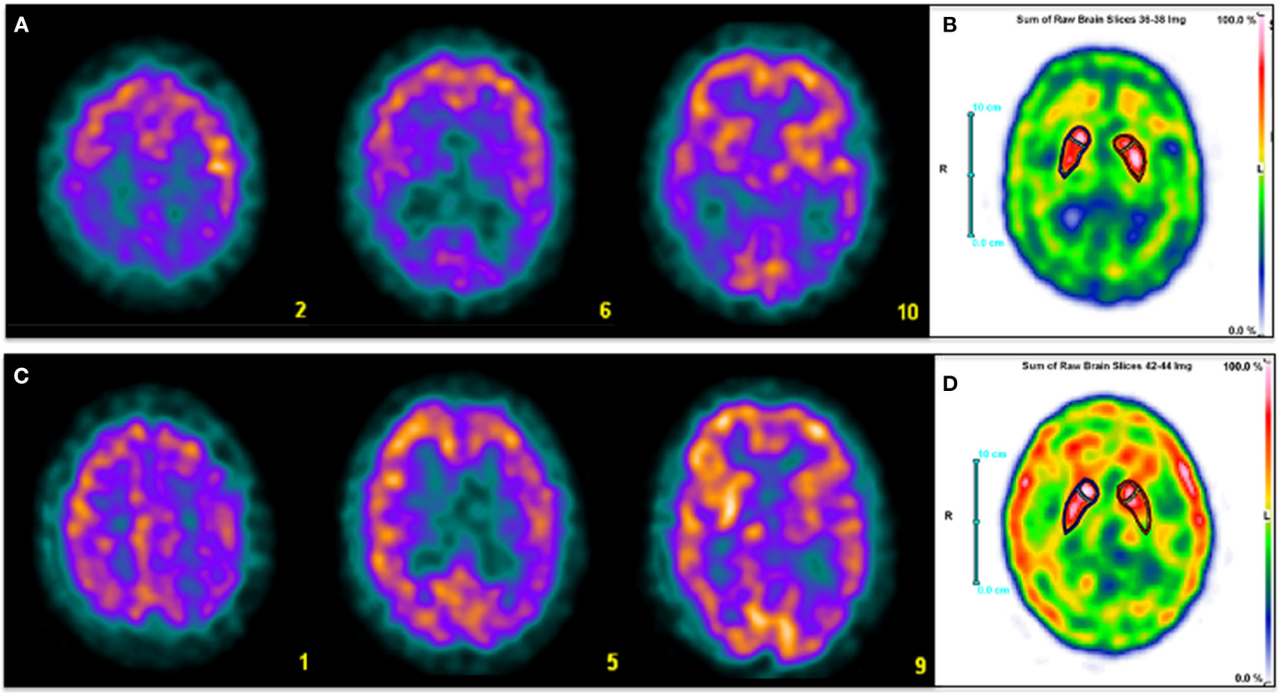


FIGURE 1 | Three selected transaxial slices of the perfusion SPECT **(A,C)** and a sum of three consecutive axial slices at the level of basal ganglia of DAT SPECT **(C,D)** of two patients referred for clinical evaluation of cognitive impairment. Superior row corresponds to a 59-year-old man with fluctuating cognitive impairment with frontal-subcortical profile in the neuropsychological examination. A typical pattern of LBD is depicted, with severe bilateral posterior parietotemporal and occipital hypoperfusion **(A)**. DAT imaging shows mildly reduced presynaptic dopamine transmission in right putamen and left caudate nucleus **(B)**. Inferior row shows a 63 year-old man with amnestic cognitive impairment and right extra-pyramidal signs. Diffuse hypoperfusion involving left parietal, frontal and temporal cortex, ipsilateral basal ganglia and thalamus **(C)** is associated with reduced left striatal dopamine transmission with posterior putamen predominance **(D)**. Findings are consistent with CBD. Clinical diagnosis was made based on perfusion SPECT in both patients. DAT SPECT images were performed later for academic purposes.

psychiatric diseases, Creutzfeld-Jacob disease, Huntington's disease and other low incidence degenerative encephalopathies (2, 8, 11, 63).

A separate chapter deserves late-life depression (which occurs frequently with a predominance of cognitive symptoms), in which the identification of involvement of the posterior temporoparietal cortex indicates a high probability of underlying AD.

COMPARISON OF SPECT AND PET WITH OTHER BIOMARKERS OF NEURODEGENERATION

Structural imaging is routinely used in the evaluation of patients with dementia. CT or MRI have been proven to change clinical diagnosis in 19% of patients and clinical management in 15% of them, even with conservative use, usually by detecting stroke, tumors or other diseases not suspected as the cause of symptoms (64). However, visual interpretation of structural imaging does not reliably detect neurodegenerative processes in early stages (65). Hippocampal volume measure is one of the best-established markers for AD. Pucci et al. reported 79% sensitivity and 69% specificity in distinguishing AD patients from normal controls, although the mean MMSE score was 15 in this population (66). Jack et al. found sensitivity of 82% and specificity of 80%, with similar values in a subset of milder patients (67).

The studies comparing the performance of different biomarkers are more limited. In a meta-analysis by Yuan et al., FDG PET performed slightly better than SPECT and MRI in the prediction of conversion from MCI to AD, with similar results for SPECT and MRI (40). Frisoni et al. found lower sensitivity and specificity for MRI compared to PET and SPECT (41). These results are probably related to the low specificity of medial temporal atrophy, which occurs in a proportion of cognitively healthy older people, as well as other pathological conditions (68). The authors also found that diagnostic accuracy of imaging biomarkers is highly dependent on how the biomarker is measured, and they identified four different metrics for medial temporal lobe atrophy on MRI. Standard operating procedures are needed to obtain reliable results in clinical practice and are not always available, particularly in developing countries (69). It should be noted that the accuracy of hippocampal measure is dependent upon, and influenced by, the dementia state and disease severity of patients studied. A mildly affected brain would be much more difficult to diagnose than a severely demented one. Moreover, quantification of hippocampal volumes is time-consuming and requires considerable neuroanatomic expertise

or specific software. Only a few MRI centers in our country perform this procedure.

The analysis of CSF for increased concentrations of tau proteins is another recognized biomarker for AD. Markers of tau accumulation include increased total tau or phosphorylated-tau (p-tau) and are clearly associated with AD pathology. While changes in tau can also reflect general damage to neurons and synapses, p-tau occurs solely in AD and is therefore a more specific biomarker. Together with low CSF Ab42, elevated CSF tau provides a high likelihood of progression to AD in patients with MCI. A large meta-analysis by Mitchell that included 19 studies with a total of 2.300 AD patients and normal controls reported sensitivity of 78%, specificity of 88%, positive predictive value of 93% and negative predictive value of 73% (70). The same meta-analysis also included 18 studies with AD and non-AD dementia patients and found values of 72, 78, 86, and 58%, respectively for distinguishing both groups.

It is important to emphasize that standardization of CSF biomarkers is still limited and results often vary between different laboratories (71). Each laboratory must define its own normal limits and, ultimately, it will be necessary to define well-established normative values, which is still in process (72). The need to perform a lumbar puncture, a procedure that is regarded as complicated, time-consuming and invasive for many clinicians, is another well-recognized limitation of these biomarkers. Recent developments enabled the measurement of AD biomarkers in blood samples. Plasma p-tau has shown analytical validity and first evidence of clinical validity. While the results are very promising, sufficient data about the effect of covariates on the biomarker measurement, assay comparison and cut-off criteria are still lacking (73).

Regarding comparison with other biomarkers, a review and meta-analysis by Bloudek et al., finally including 119 studies, found that FDG PET was most accurate than SPECT and p-tau in discriminating AD from normal controls with sensitivity of 90% and specificity of 89%. Compared to demented controls (including MCI), PET sensitivity was maintained at 92% and specificity decreased to 78%. For discrimination of AD from non-AD dementias (excluding MCI), p-tau and SPECT had nearly identical performance with sensitivity of 79% and specificities of 80 and 81%, respectively (74).

A recent systematic review by Fink et al. found that individual CSF biomarkers and biomarker ratios had moderate sensitivity (62–83%) and specificity (53–69%) for distinguishing neuropathologically defined AD from non-AD pathology, while β-amyloid 42 (Aβ42)/p-tau ratio, total tau (t-tau)/Aβ42 ratio, and p-tau appeared more accurate than Ab42 and t-tau alone. Median sensitivity and specificity for amyloid PET were 91 and 92%, respectively, 89 and 74% for FDG PET, 64 and 83% for SPECT, and 91 and 89% for medial temporal lobe atrophy on MRI. Sensitivity and specificity of MRI was considerably lower for distinguishing AD from other specific types of dementia like LBD or FTD (75).

In one of the few studies that compared multiple biomarkers in the same group of patients, Morinaga et al. included 207 patients with probable AD from a single memory clinic. AD findings were observed in 77.4% of all AD patients with MRI, 81.6% with SPECT, 93.1% with FDG PET and 94.0% with CSF biomarkers. At the stage of Clinical Dementia Rating (CDR) 0.5, sensitivity was 90.0% for CSF, 80.8% for SPECT, 71.4 for FDG PET and 65.5% for MRI. At the stage of CDR 1, FDG PET (96.7%) and CSF biomarkers (95.5%) were the most sensitive. At CDR 2, all biomarkers showed high sensitivity (76).

Although MRI and CSF biomarkers have shown similar performance to SPECT and FDG-PET in distinguishing AD from non-AD patients, they cannnot reliably differentiate between different types of non-AD dementia, reducing their applicability in clinical practice with respect to functional imaging techniques. The availability of these biomarkers in developing countries is limited for several reasons already mentioned. While PET suffers from similar limitations because of its high cost, brain SPECT is available in all nuclear medicine facilities at a much lower cost.

DIRECT COMPARISON BETWEEN SPECT AND PET IN ALZHEIMER'S DISEASE

The technical characteristics of PET determines an overall higher performance over SPECT, in particular its greater sensitivity (referred to the detection efficiency of the radioactive emission) and spatial resolution. Even though significant, the differences in spatial resolution between both modalities are not of great magnitude, with values of 3–4 mm for PET and 5–8 mm for SPECT. The spatial resolution of PET is limited to 1–2 mm due to the positron emission range, while SPECT has no theoretical limitations in this regard, which has led to sub-millimeter resolutions in small animal equipment, exceeding the spatial resolution of their PET analogs. Dedicated brain SPECT cameras have the same spatial resolution as PET, although their availability is very limited and there has been no significant expansion of its use in clinical practice.

A critical question is to what extent the technical differences between both modalities influence the clinical diagnosis of neurodegenerative diseases, that is, whether or not they translate into considerable differences in diagnostic performance. The answer requires a critical review of the available literature. Considering systematic reviews or meta-analyses of the diagnostic value of both techniques in AD, Dougall et al. reported a sensitivity of 77% and specificity of 89% for SPECT (19) while Patwardhan et al. including studies from the same time period reported a 86% sensitivity and specificity for PET (20). These results indicate a higher sensitivity and slightly lower specificity for PET.

Frisoni et al. reviewed the diagnostic and prognostic accuracy of different AD imaging biomarkers (amyloid PET, FDG PET, perfusion SPECT and MRI) and their operating procedures or metrics (visual analysis and different quantitative and semiquantitive approaches) (41). Interestingly, they found that different metrics can account for equal or more variation in the accuracy than the types of markers used. Pooled sensitivity and specificity for AD diagnosis for all metrics were 86 and 84%, respectively for PET and 76 and 84%, respectively for SPECT. Quantification increased SPECT sensitivity more than 10% to

the same range as PET while it had very little effect on PET sensitivity (41).

Clinical diagnosis was used as a reference in most of the publications included in review studies. Very few studies included neuropathological confirmation as a reference, considered the most appropriate gold standard. The studies by Jobst et al. (24) and Bonte et al. (23) show pooled sensitivity, specificity, and accuracy of 91, 81, and 85% for SPECT. According to the studies of Silverman et al. (26, 77) and Hoffman et al. (27), pooled values of 92, 70, and 85% (sensitivity, specificity, and accuracy, respectively) are obtained for PET (the study by Jagust et al. which reported lower values for PET in 2007 is not included). According to these data, compared to neuropathological confirmation, the accuracy is similar for both techniques.

There are also few studies that have directly compared SPECT and PET in the same sample of patients. Kuwabara et al. studied nine patients with AD with different nuclear imaging modalities including ^{123}I-IMP and HMPAO SPECT, and ^{15}O-H_2O and ^{18}F-FDG PET. They described that even though there was a slightly lower performance of SPECT for the detection of areas with mild hypoperfusion, both SPECT and PET were able to detect parietal abnormalities in all AD patients (78). Messa et al. studied 21 patients with probable AD by both techniques and found bilateral posterior temporoparietal involvement in 90% of cases with SPECT and 100% with PET (79). Mielke et al. in the same year, on a similar sample of patients, reported that PET discriminated AD patients from normal controls only marginally better than SPECT (80). Herholz et al. studied 26 patients with mild to moderate AD and six normal controls with SPECT and PET and analyzed the results using voxel-based analysis (SPM), demonstrating a correlation coefficient of 0.90 for posterior temporoparietal cortex and posterior cingulate defects in both studies (81). The defects were more pronounced on PET images, but both techniques were able to adequately separate all patients from normal controls. Scatter correction was not used for SPECT studies at that time, and it is known that this procedure, widely available today, allows to considerably increase the contrast of the images. Döbert et al. studied 24 patients with clinical suspicion of dementia onset (12 of them with MCI) using clinical follow-up as a reference and found greater sensitivity for PET without differences in specificity, although the sensitivity values were low for both techniques (82). Nihashi et al. found no significant differences between FDG PET and IMP SPECT in 14 patients with moderate probable AD relative to normal controls using statistical analysis with 3D-SSP (83). More recently, Ito et al. published a comparative series using FDG PET and ^{99m}Tc-ECD SPECT in 55 patients with cognitive impairment classified as probable AD ($n = 28$), MCI due to AD ($n = 12$) or no AD ($n = 15$) according to the NIA-AA criteria recommended for research studies, including MRI and ^{11}C-PIB amyloid imaging (84). The results were interpreted by three independent observers with variable experience. The image acquisition and processing techniques used reflect the state of the art of SPECT and PET today. The diagnostic accuracy was in the range of 60–70% for both techniques and was practically identical, with no significant differences between them. The low performance demonstrated by both techniques in this study with respect to previous reports may be related to the fact that all the patients had cognitive impairment, and normal controls were not included in the analysis. In the same year, O'Brien et al. compared 38 patients with AD, 30 with LBD and 30 normal controls (85). Specificity for dementia/no-dementia was 85 and 90%, respectively for PET and 71 and 70%, respectively for SPECT. The patients in this study were not clinically referred, limiting the applicability of the results, and the authors relied on clinical diagnosis of probable AD or LBD without follow-up. Moreover, the inclusion of patients with LBD, that can be difficult to distinguish from AD (particularly on SPECT images because of the high normal uptake of the occipital cortex), may have influenced the results. Ferreira et al. studied 20 patients with mild AD and 18 normal controls, showing a similar accuracy for SPECT and PET (68–74 and 68–71%, respectively), highlighting the key role of SPECT in the study of patients with AD (86). In a larger study recently published, Nadebaum et al. evaluated the diagnostic performance of SPECT and PET in 126 patients with MCI and dementia, including amyloid PET information as a reference for the final diagnosis (87). They showed higher sensitivity for PET (75.8 vs. 42.9 for SPECT) but lower specificity (74.3 vs. 82.9% for SPECT). It is important to notice the very low sensitivity reported for SPECT in this study, much lower than expected based on the previous literature. Part of the explanation could be due to the presence of MCI in more than half of the patients included, that usually have more subtle functional alterations more easily recognizable in PET images.

All this data collectively demonstrates that even though there can be a slight advantage in favor of PET in terms of sensitivity, the diagnostic performance of SPECT and PET in AD is fairly similar. **Figure 2** shows the example of two patients clinically referred in which both SPECT and PET allow reaching the diagnosis. It is possible that the differences are more evident in patients with MCI, which can show less perfusion/metabolic abnormalities in comparison with patients with dementia. In patients with MCI a difference in accuracy of about 10% in favor of PET in comparison with SPECT has been described, although more information is needed to finally conclude about the difference in diagnostic performance of both modalities in this clinical scenario. **Table 1** shows a summary of the previously mentioned articles directly comparing SPECT and PET in the same group of patients.

COST-EFFECTIVENESS CONSIDERATIONS FOR SPECT AND PET IN DEMENTIA

The study of cost-effectiveness for the introduction of functional imaging to dementia diagnostic algorithms have showed contradictory results, mainly due to the scarcity of effective treatments to date. McMahon et al. (88, 89) argue against the inclusion of functional imaging, based on the estimation of quality-adjusted life years and the limited efficacy of cholinesterase inhibitors. According to the authors, any diagnostic test, no matter how perfect, would be incapable of reaching adequate cost-effectiveness thresholds using this

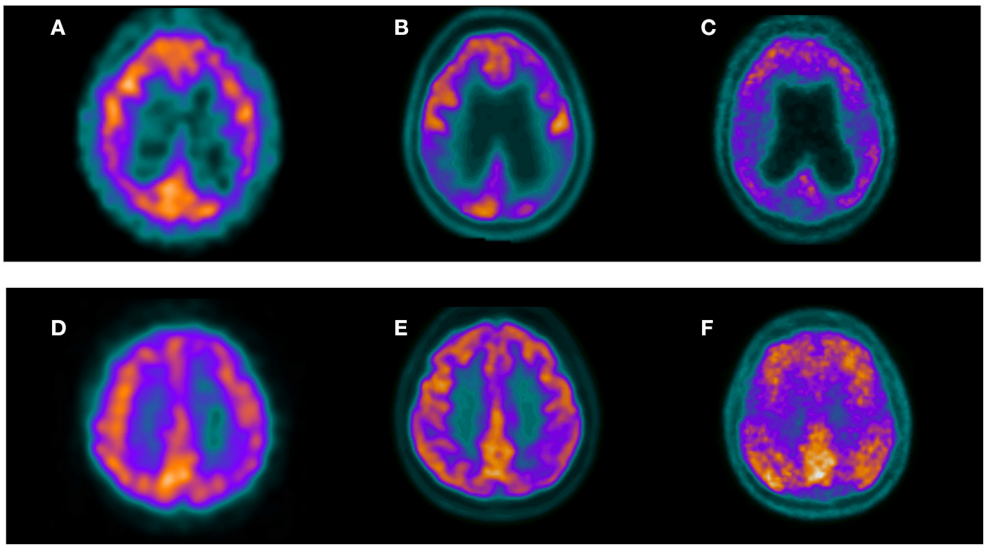


FIGURE 2 | Three selected transaxial slices of the perfusion SPECT, ^{18}F-FDG PET, and ^{11}C-PIB PET of two patients referred for clinical evaluation of cognitive impairment. Superior row corresponds to a 63-year-old female with a mild cognitive impairment. MMSE was 27. Both perfusion SPECT **(A)** and ^{18}F-FDG PET **(B)** showed hypoperfusion/hypometabolism in the bilateral parietal cortex with a typical pattern of AD. Amyloid PET in this patient **(C)** showed significant cortical amyloid deposits. Inferior row shows a 55-year-old female referred for evaluation of probable AD. Both perfusion SPECT **(D)** and ^{18}F-FDG PET **(E)** showed a left posterior parietal hypoperfusion/hypometabolism suggestive of AD. ^{11}C-PIB PET in this patient **(F)** confirmed cortical amyloid deposits.

TABLE 1 | Summary of studies directly comparing SPECT and PET performance in the same group of patients.

References	Subjects	Number of patients	PET sensitivity/ specificity (accuracy)	SPECT sensitivity/ specificity (accuracy)	Comments
Kuwabara et al. (78)	AD, FTD and VD	9 AD, 3 FTD and 5 VD	–	–	Both SPECT and PET identified parietal abnormalities in all AD patients
Messa et al. (79)	Probable AD and normal controls	21 AD, 20 NC	100/-	90/-	
Mielke et al. (80)	Probable AD, vascular dementia and normal controls	20 AD, 12 VD, 13 NC	80/100	80/65	
Nihashi et al. (83)	Probable AD	14 AD	86/97	70/100	No overall differences
Herholz et al. (81)	Probable AD and normal controls	26 AD, 6 NC	–	–	Correlation coefficient of 0.9 between both modalities in temporoparietal and posterior cingulate cortices
Döbert et al. (82)	AD, FTD, VD, Mix and normal controls	9 AD, 1 FTD, 1 VD, 7 mix and 6 NC	91.7/88.9	64.0/84.2	
Ito et al. (84)	Probable AD, MCI due to AD, LBD, FTD	28 AD, 12 MCI, 10 DLB, 5 FTD	77.5–82.5/13.3–40	82.5–87.5/20–33.3	Nearly identical diagnostic performance
Ferreira et al. (86)	Mild AD and normal controls	20 AD, 18 NC	(68–71%)	(68–74%)	
Nadebaum et al. (87)	MCI and dementia	126 patients in total	75.8%/74.3%	42.9%/82.9%	

methodology unless it has a very low cost. Other authors such as Silverman et al. argue in favor of including functional imaging considering that PET can introduce an increase in diagnostic accuracy of 15% with respect to clinical evaluation, resulting in savings per patient that exceed the cost of a PET study in the United States (90). In their study, the authors consider other costs caused by the disease, such as care expenses, which far exceed those of drug therapy. However, it is important to notice that the exclusion of AD in a patient with dementia does not necessarily imply a reduction in the costs of hospitalization and nursing

care, which is fundamentally determined by the functional situation of the patient beyond the etiological diagnosis, since the vast majority of causes of dementia are irreversible. Moulin-Romsee et al. endorsed Silverman's results for the European population. Using the same arguments, they postulate that the diagnostic performance of SPECT in comparison with neuropathological confirmation results in a possible reduction in false diagnoses with respect to conventional algorithms, which is also estimated at 15%, with eventual savings for the health system far superior to the use of PET due to its significantly lower cost (91).

Beyond the discussion of the cost-effectiveness of including functional imaging modalities in the dementia diagnostic algorithm, it seems evident that an earlier or more precise diagnosis will positively affect an already complex situation for the families and the patients suffering from dementia. A more accurate diagnosis will also have important implications for the dementia programs and care systems.

In this context and considering the aforementioned cost-effectiveness dilemmas, the significantly lower cost of SPECT compared to PET (about five times lower in our region) represents a very relevant advantage in favor of the former, particularly in low- and middle-income countries.

AMYLOID IMAGING

Research carried out in the last two decades has made possible to detect beta-amyloid deposits *in vivo* by PET. The first radiopharmaceutical used in patients to reveal amyloid, ^{11}C-PIB, give the way to several ^{18}F-labeled analogs such as florbetapir, florbetaben, and flutemetamol, with considerable advantages in terms of cost and availability due to the longer half-life of ^{18}F (12, 92). These ^{18}F-labeled radiopharmaceuticals have shown a very good correlation with ^{11}C-PIB with high correspondence in visual interpretation (93). High correspondence between ^{11}C-PIB uptake and beta-amyloid deposits in neuropathology has been demonstrated in various studies, and there are also similar reports for ^{18}F radiopharmaceuticals (93, 94).

However, the investigation on the clinical impact of PET with amyloid tracers is still ongoing. A systematic review by Fantoni et al. found that amyloid PET contributed to diagnostic revision in almost a third of cases and demonstrated value in increasing diagnostic confidence and refining management plans (95). Although it is clear that the technique has an important potential impact in clinical management, it is also recognized that a positive amyloid PET alone is not equivalent to a clinical diagnosis of AD. The presence of amyloid pathology in the brain is insufficient by itself to define the cause of cognitive impairment and must be considered in conjunction with other clinical, laboratory, and imaging elements. The existence of comorbidities such as vascular pathology or depression can still have an important influence on the cognitive deterioration observed in an amyloid PET positive patient. Although current evidence suggests that the majority of individuals with MCI who are amyloid PET positive will progress to AD, the proportion is still not defined, and it is not possible to define when this will happen. However, a negative amyloid PET represents a low risk of progression to AD and may provide a more useful clinical information in patients with MCI, particularly in cases where other potential causes of MCI are present. A similar scenario to that of MCI can be presented in the case of patients who meet diagnostic criteria for possible AD, in whom there is an atypical course of deterioration or comorbid conditions capable of confusing the clinical interpretation.

An important limitation of PET with amyloid tracers is the high prevalence of positive studies in asymptomatic older adults, ranging from 10% at 60 to 70 years to 50% between 80 and 90 years (96). This substantially complicates the establishment of a relationship of causality between amyloid deposits and the presence of deterioration in elderly patients. On the other hand, other pathologies such as amyloid angiopathy and LBD can also present positive studies and cannot be differentiated from AD by amyloid imaging alone. Additionally, around 15% of cases of mild to moderate dementia with a phenotype compatible with AD have no or sparse amyloid deposits (97). Likewise, the technique is not useful in the differential diagnosis of numerous causes of dementia that do not have amyloid deposits, such as the different variants of FTD or LBD, in which approximately one third of cases do not present deposits.

Finally, the performance of amyloid PET in comparison with other lower-cost biomarkers has not been explored enough yet, so it is still difficult to define the most appropriate and cost-effective use strategy within the framework of consensus diagnostic algorithms. The association of amyloid PET with tau and neurodegeneration biomarkers is proposed as the most accurate diagnostic alternative, but the high cost of this approach still limits its applicability in clinical practice.

SPECT AND PET IN CLINICAL AND RESEARCH GUIDELINES FOR THE DIAGNOSIS OF DEMENTIA

Since the publication of their first guidelines on brain SPECT in the 1990's, the Society of Nuclear Medicine and Molecular Imaging (SNMMI), the American College of Radiologists (ACR) and the European Association of Nuclear Medicine (EANM) recommended the clinical use of the technique in the diagnosis of dementia (98–100). The recommendations of the neurological societies of the United States and Europe at the beginning of the 2000's also considered SPECT, although not in the routine clinical evaluation, but in specific clinical situations in which there were diagnostic doubts and the technique was expected to provide significant additional information. The American Academy of Neurology in 1996 considered SPECT as a useful imaging modality to support the clinical diagnosis of AD based on level IIB evidence (101). As a general concept, the use of perfusion SPECT is recommended in patients with dementia or cognitive impairment of at least 6 months of evolution in which the etiology remains uncertain after a complete clinical evaluation by an experienced physician (including neurological examination, laboratory studies, CT or MRI, and neuropsychological evaluation), when symptoms do not improve

within a reasonably short follow-up period after the initial evaluation, and it is reasonable to expect that the information provided by the technique will help clarify the diagnosis or guide future treatment. Patients with advanced stage dementia are excluded. These circumstances can occur in the clinical situations listed in **Table 2**. FDG PET can be useful in the same situations as perfusion SPECT.

The approval of the use of FDG PET in dementia by Medicare in 2004 (https://www.cms.gov/medicare-coverage-database), after several negative resolutions, for the differential diagnosis between AD and FTD, has led to the expansion of the use of PET in comparison with SPECT in the United States. This trend is also widespread in high-income countries in Europe. Nowadays, PET is predominantly mentioned in the guidelines, leaving aside SPECT in spite of the important technological advances introduced in the last two decades. The criteria for the diagnosis of AD from NIA-AA consider PET imaging while SPECT is scarcely mentioned (102). The more recent NIA-AA Research Framework for AD emphasizes the importance of biomarkers for the characterization of patients using the A-T-(N) criteria (13), considering PET, MRI, and CSF biomarkers as key players for the study of patients with dementia. Nevertheless, brain SPECT is not mentioned as one of the biomarkers for neurodegeneration, not even as an alternative to PET when it is not available. On the other hand, the recommendations of the NIA-AA for the diagnosis of MCI due to AD recognize the role of SPECT as a biomarker of neurodegeneration (103).

It could be argued that SPECT is not part of the current state of the art in the diagnosis of patients with dementia, given the superior quality of PET images. However, the technique has undergone important technical advances since most of the publications that evaluated its usefulness more than 20 years ago. This is exemplified in **Figure 3**, were typical SPECT images currently available are closer to PET images than old SPECT images obtained in single-head gamma cameras. The review of the diagnostic value of both techniques presented here suggests a much smaller difference in diagnostic performance than that commonly mentioned in the literature, that should be explored in new prospective studies including intra-subject comparison of SPECT and PET using the framework for research in AD as well as clinical follow-up confirmation.

The strategy of performing perfusion/metabolic imaging before amyloid or tau PET can save costs providing a wider spectrum of differential diagnosis of dementia based on the recognition of specific disease patterns and reserving the more complex molecular imaging tools for undetermined cases (**Figures 1**, **2** show examples of this approach). Even with the advent of the new molecular imaging probes, the role of the biomarkers of neurodegeneration is more valid than ever, since abnormal deposits of proteins like amyloid and tau in

TABLE 2 | Clinical situations in which perfusion SPECT or FDG PET can be useful.

Clinical diagnosis of possible AD according to NIA-AA criteria due to atypical clinical presentation, atypical clinical course or coexistence of possible causes.
Clinical diagnosis of persistent or progressive MCI with no clear etiology, especially in the face of coexistence of possible causes.
Early onset progressive dementia (before 65 years of age).
Clinical diagnosis of possible of LBD according to the criteria of the Dementia with Lewy Bodies Consortium.
Differential diagnosis of dementia: to distinguish AD from FTD, LBD, or PD dementia, diagnosis of atypical parkinsonisms, to rule out the association of AD and vascular dementia and to differentiate degenerative dementias from psychiatric pathology.
Persistent cognitive impairment or dementia after brain trauma when MRI does not explain the symptoms.
Low incidence causes of dementia: autoimmune systemic diseases with neuropsychiatric involvement (SLE, Behçet), immune-mediated limbic or extralimbic encephalitis, exposure to neurotoxins, Huntington's disease, Creutzfeld-Jacob disease, HIV encephalopathy, etc.

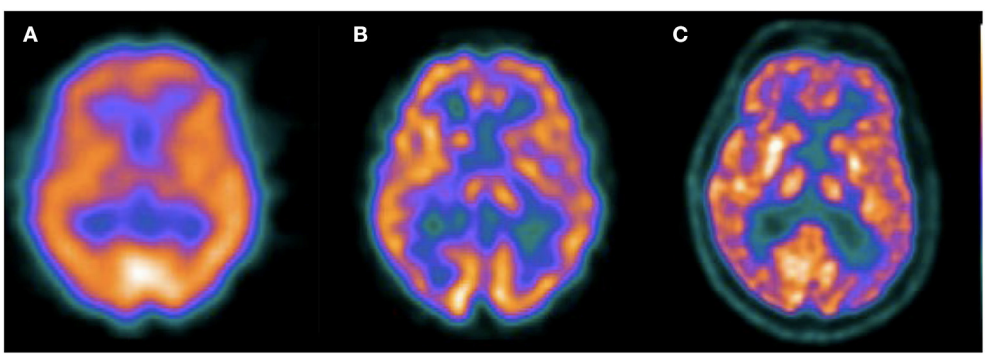


FIGURE 3 | Transaxial slices of perfusion SPECT and ^{18}F-FDG PET of different patients. The first image **(A)** corresponds to a perfusion SPECT acquired in a single head gamma camera in 1998 (Sopha DSX rectangular). The second image **(B)** corresponds to a perfusion SPECT with the same radiotracer (^{99m}Tc-ECD) acquired in 2009 in a two headed gamma camera, without scatter correction (Mediso Nucline SPIRIT DH-V). The third image **(C)** corresponds to a ^{18}F-FDG PET acquired in 2015 (GE Discovery STE). This figure illustrates the significant advances of SPECT image quality in recent years and the comparison with typical ^{18}F-FDG images.

the brain can be asymptomatic for many years and do not represent *per se* the presence of dementia. Neurodegeneration represents the necessary condition that signs the beginning of the clinical disease.

In low- and middle-income countries, brain perfusion SPECT is a valid alternative capable to further reduce the costs of the new diagnostic algorithms. High-cost nuclear biomarkers are more difficult to access in these countries, particularly outside the large cities and in users of public health systems (104, 105). This represents not only a limitation for the correct clinical diagnosis but also for the study of populations that are usually underrepresented in scientific research in the field of dementia. SPECT has much higher availability compared to PET (105) and technetium generators needed for the production of SPECT radiotracers are easily transportable to centers in several countries at much lower cost compared to cyclotron-dependent radiotracers. The search for lower-cost biomarkers has also been one of the priorities highlighted by the Latin American and Caribbean Consortium on Dementia (LAC-CD) in a recent publication (106).

CONCLUSIONS

Although amyloid and tau biomarkers have gained ground in recent years and are the current focus of research, neurodegeneration biomarkers continue to play a key role in the diagnosis of dementia. Despite the trend to use PET instead of SPECT in high-income countries, the differences in diagnostic performance between both techniques are subtle, particularly in patients in the clinical stage of dementia, and SPECT has the advantage of wider availability and significantly lower cost. We conclude that SPECT should still be considered an important tool in clinical practice and research in dementia in low- and middle-income countries.

AUTHOR CONTRIBUTIONS

RF conceived the presented idea. RF and AD wrote the manuscript and contributed to the final version.

REFERENCES

1. Sharp PF, Gemmell HG, Murray AD. *Practical Nuclear Medicine*. 3rd ed. London; New York, NY: Springer (2005). p. 382. Available online at: http://www.loc.gov/catdir/enhancements/fy0662/2004061448-d.html (accessed April 22, 2021).
2. Catafau AM. Brain SPECT in clinical practice. Part I: perfusion. *J Nucl Med*. (2001) 42:259–71.
3. Devous MD. Single-photon emission computed tomography in neurotherapeutics. *NeuroRx*. (2005) 2:237–49. doi: 10.1602/neurorx.2.2.237
4. Sasannezhad P, Juibary AG, Sadri K, Sadeghi R, Sabour M, Kakhki VRD, et al. (99m)Tc-TRODAT-1 SPECT imaging in early and late onset Parkinson's disease. *Asia Ocean J Nucl Med Biol*. (2017) 5:114–9. doi: 10.22038/aojnmb.2017.8844
5. Shih MC, Franco de Andrade LA, Amaro EJ, Felicio AC, Ferraz HB, Wagner J, et al. Higher nigrostriatal dopamine neuron loss in early than late onset Parkinson's disease?–a [99mTc]-TRODAT-1 SPECT study. *Mov Disord*. (2007) 22:863–6. doi: 10.1002/mds.21315
6. Fallahi B, Esmaeili A, Beiki D, Oveisgharan S, Noorollahi-Moghaddam H, Erfani M, et al. Evaluation of 99mTc-TRODAT-1 SPECT in the diagnosis of Parkinson's disease versus other progressive movement disorders. *Ann Nucl Med*. (2016) 30:153–62. doi: 10.1007/s12149-015-1042-y
7. Varrone A, Asenbaum S, Vander Borght T, Booij J, Nobili F, Någren K, et al. EANM procedure guidelines for PET brain imaging using [18F]FDG, version 2. *Eur J Nucl Med Mol Imaging*. (2009) 36:2103–10. doi: 10.1007/s00259-009-1264-0
8. Schöll M, Damián A, Engler H. Fluorodeoxyglucose PET in neurology and psychiatry. *PET Clin*. (2014) 9:371–90. doi: 10.1016/j.cpet.2014.07.005
9. Herholz K. PET studies in dementia. *Ann Nucl Med*. (2003) 17:79–89. doi: 10.1007/BF02988444
10. Nehlig A. Cerebral energy metabolism, glucose transport and blood flow: changes with maturation and adaptation to hypoglycaemia. *Diabet Metabol*. (1997) 23:18–29.
11. Engler H, Damian A, Bentancourt C. PET and the multitracer concept in the study of neurodegenerative diseases. *Dement Neuropsychol*. (2015) 9:343–9. doi: 10.1590/1980-57642015DN94000343
12. Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol*. (2004) 55:306–19. doi: 10.1002/ana.20009
13. Jack CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimer's Dementia*. (2018) 14:535–62. doi: 10.1016/j.jalz.2018.02.018
14. Duthey B. Alzheimer disease and other dementias. *World Heal Organ*. (2013) 6.11:1–74.
15. Salmon DP. Neuropsychology of aging and dementia. *Handb Clin Neurol*. (2008) 88:113–35. doi: 10.1016/S0072-9752(07)88005-5
16. Murray ME, Graff-Radford NR, Ross OA, Petersen RC, Duara R, Dickson DW. Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: a retrospective study. *Lancet Neurol*. (2011) 10:785–96. doi: 10.1016/S1474-4422(11)70156-9
17. Shimizu S, Hirose D, Hatanaka H, Takenoshita N, Kaneko Y, Ogawa Y, et al. Role of neuroimaging as a biomarker for neurodegenerative diseases. *Front Neurol*. (2018) 9:265. doi: 10.3389/fneur.2018.00265
18. Carapelle E, Mundi C, Cassano T, Avolio C. Interaction between cognitive reserve and biomarkers in alzheimer disease. *Int J Mol Sci*. (2020) 21:1–12. doi: 10.3390/ijms21176279
19. Dougall NJ. Systematic review of the diagnostic accuracy of 99mTc-HMPAO-SPECT in dementia. *Am J Geriatr Psychiatry*. (2004) 12:554–70. doi: 10.1097/00019442-200411000-00002
20. Patwardhan MB, McCrory DC, Matchar DB, Samsa GP, Rutschmann OT. Alzheimer disease: operating characteristics of PET - a meta-analysis. *Radiology*. (2004) 231:73–80. doi: 10.1148/radiol.2311021620
21. Nestor PJ, Altomare D, Festari C, Drzezga A, Rivolta J, Walker Z, et al. Clinical utility of FDG-PET for the differential diagnosis among the main forms of dementia. *Eur J Nucl Med Mol Imaging*. (2018) 45:1509–25. doi: 10.1007/s00259-018-4035-y
22. Read SL, Miller BL, Mena I, Kim R, Itabashi H, Darby A. SPECT in dementia: clinical and pathological correlation. *J Am Geriatr Soc*. (1995) 43:1243–7. doi: 10.1111/j.1532-5415.1995.tb07400.x
23. Bonte FJ, Hynan L, Harris TS, White CL. TC-99m HMPAO brain blood flow imaging in the dementias with histopathologic correlation in 73 patients. *Int J Mol Imaging*. (2011) 2011:1–3. doi: 10.1155/2011/409101
24. Jobst KA, Barnetson LPD, Shepstone BJ. Accurate prediction of histologically confirmed Alzheimer's disease and the differential diagnosis of dementia: the use of NINCDS-ADRDA and DSM-III-R criteria, SPECT, X-ray CT, and Apo E4 in medial temporal lobe dementias. *Int Psychogeriatrics*. (1998) 10:271–302. doi: 10.1017/S1041610298005389
25. El Fakhri G, Kijewski MF, Albert MS, Johnson KA, Moore SC. Quantitative SPECT leads to improved performance in discrimination tasks related to prodromal Alzheimer's disease. *J Nucl Med*. (2004) 45:2026–31.

26. Silverman DHS, Chen W, Czernin J, Kowell AP, Gambhir SS, Phelps ME, et al. Positron emission tomography in evaluation of dementia: regional brain metabolism and long-term outcome. *J Am Med Assoc*. (2001) 286:2120–7. doi: 10.1001/jama.286.17.2120
27. Hoffman JM, Welsh-Bohmer KA, Hanson M, Crain B, Hulette C, Earl N, et al. FDG PET imaging in patients with pathologically verified dementia. *J Nucl Med*. (2000) 41:1920–8.
28. Jagust W, Reed B, Mungas D, Ellis W, DeCarli C. What does fluorodeoxyglucose PET imaging add to a clinical diagnosis of dementia? *Neurology*. (2007) 69:871–7. doi: 10.1212/01.wnl.0000269790.05105.16
29. Jagust W, Thisted R, Devous MD, Van Heertum R, Mayberg H, Jobst K, et al. SPECT perfusion imaging in the diagnosis of alzheimer's disease: a clinical-pathologic study. *Neurology*. (2001) 56:950–6. doi: 10.1212/WNL.56.7.950
30. Claus JJ, van Harskamp F, Breteler MMB, Krenning EP, de Koning I, van der Cammen TJM, et al. The diagnostic value of SPECT with Tc 99m HMPAO in alzheimer's disease: a population-based study. *Neurology*. (1994) 44:454–61. doi: 10.1212/WNL.44.3_Part_1.454
31. Silverman DHS, Truong CT, Kim SK, Chang CY, Chen W, Kowell AP, et al. Prognostic value of regional cerebral metabolism in patients undergoing dementia evaluation: comparison to a quantifying parameter of subsequent cognitive performance and to prognostic assessment without PET. *Mol Genet Metab*. (2003) 80:350–5. doi: 10.1016/S1096-7192(03)00139-2
32. Ishii K, Willoch F, Minoshima S, Drzezga A, Ficaro EP, Cross DJ, et al. Statistical brain mapping of 18F-FDG PET in Alzheimer's disease: validation of anatomic standardization for atrophied brains. *J Nucl Med*. (2001) 42:548–57.
33. Hosaka K, Ishii K, Sakamoto S, Sadato N, Fukuda H, Kato T, et al. Validation of anatomical standardization of FDG PET images of normal brain: comparison of SPM and NEUROSTAT. *Eur J Nucl Med Mol Imaging*. (2005) 32:92–7. doi: 10.1007/s00259-004-1576-z
34. Perani D. FDG PET and cognitive symptoms of dementia. *Clin Transl Imaging*. (2013) 1:247–60. doi: 10.1007/s40336-013-0029-8
35. Dukart J, Mueller K, Villringer A, Kherif F, Draganski B, Frackowiak R, et al. Relationship between imaging biomarkers, age, progression and symptom severity in Alzheimer's disease. *NeuroImage Clin*. (2013) 3:84–94. doi: 10.1016/j.nicl.2013.07.005
36. Valotassiou V, Malamitsi J, Papatriantafyllou J, Dardiotis E, Tsougos I, Psimadas D, et al. SPECT and PET imaging in Alzheimer's disease. *Ann Nucl Med*. (2018) 32:583–93. doi: 10.1007/s12149-018-1292-6
37. Huang C, Eidelberg D, Habeck C, Moeller J, Svensson L, Tarabula T, et al. Imaging markers of mild cognitive impairment: multivariate analysis of CBF SPECT. *Neurobiol Aging*. (2007) 28:1062–9. doi: 10.1016/j.neurobiolaging.2006.05.017
38. Hirao K, Ohnishi T, Hirata Y, Yamashita F, Mori T, Moriguchi Y, et al. The prediction of rapid conversion to Alzheimer's disease in mild cognitive impairment using regional cerebral blood flow SPECT. *Neuroimage*. (2005) 28:1014–21. doi: 10.1016/j.neuroimage.2005.06.066
39. Devanand DP, Van Heertum RL, Kegeles LS, Liu X, Hao Jin Z, Pradhaban G, et al. 99m Tc HMPAO SPECT prediction of conversion from mild cognitive impairment to Alzheimer disease. *Am J Geriatr Psychiatry*. (2010) 18:959–72. doi: 10.1097/JGP.0b013e3181ec8696
40. Yuan Y, Gu ZX, Wei WS. Fluorodeoxyglucose-positron-emission tomography, single-photon emission tomography, and structural MR imaging for prediction of rapid conversion to alzheimer disease in patients with mild cognitive impairment: a meta-analysis. *Am J Neuroradiol*. (2009) 30:404–10. doi: 10.3174/ajnr.A1357
41. Frisoni GB, Bocchetta M, Chételat G, Rabinovici GD, De Leon MJ, Kaye J, et al. Imaging markers for Alzheimer disease: which vs. how. *Neurology*. (2013) 81:487–500. doi: 10.1212/WNL.0b013e31829d86e8
42. Yeo JM, Lim X, Khan Z, Pal S. Systematic review of the diagnostic utility of SPECT imaging in dementia. *Eur Archiv Psychiatry Clin Neurosci*. (2013) 263:539–52. doi: 10.1007/s00406-013-0426-z
43. Sjögren M, Gustafson L, Wikkelsö G, Wallin A. Frontotemporal dementia can be distinguished from Alzheimer's disease and subcortical white matter dementia by an anterior-to-posterior rCBF-SPET ratio. *Dement Geriatr Cogn Disord*. (2000) 11:275–85. doi: 10.1159/000017250
44. Mendez MF, Shapira JS, McMurtray A, Licht E, Miller BL. Accuracy of the clinical evaluation for frontotemporal dementia. *Arch Neurol*. (2007) 64:830–5. doi: 10.1001/archneur.64.6.830
45. Nazem A, Tang CC, Spetsieris P, Dresel C, Gordon ML, Diehl-Schmid J, et al. A multivariate metabolic imaging marker for behavioral variant frontotemporal dementia. Alzheimer's Dement Diagnosis. *Assess Dis Monit*. (2018) 10:583–94. doi: 10.1016/j.dadm.2018.07.009
46. Lobotesis K, Fenwick JD, Phipps A, Ryman A, Swann A, Ballard C, et al. Occipital hypoperfusion on SPECT in dementia with Lewy bodies but not AD. *Neurology*. (2001) 56:643–9. doi: 10.1212/WNL.56.5.643
47. Shimizu S, Hanyu H, Kanetaka H, Iwamoto T, Koizumi K, Abe K. Differentiation of dementia with lewy bodies from alzheimer's disease using brain SPECT. *Dement Geriatr Cogn Disord*. (2005) 20:25–30. doi: 10.1159/000085070
48. Minoshima S, Foster NL, Sima AAF, Frey KA, Albin RL, Kuhl DE. Alzheimer's disease versus dementia with Lewy bodies: cerebral metabolic distinction with autopsy confirmation. *Ann Neurol*. (2001) 50:358–65. doi: 10.1002/ana.1133
49. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB consortium. *Neurology*. (2005) 65:1863–72. doi: 10.1212/WNL.65.12.1992-a
50. McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor J-P, Weintraub D, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. *Neurology*. (2017) 89:88–100. doi: 10.1212/WNL.0000000000004058
51. Walker Z, Jaros E, Walker RWH, Lee L, Costa DC, Livingston G, et al. Dementia with Lewy bodies: a comparison of clinical diagnosis, FP-CIT single photon emission computed tomography imaging and autopsy. *J Neurol Neurosurg Psychiatry*. (2007) 78:1176–81. doi: 10.1136/jnnp.2006.110122
52. McKeith I, O'Brien J, Walker Z, Tatsch K, Booij J, Darcourt J, et al. Sensitivity and specificity of dopamine transporter imaging with 123I-FP-CIT SPECT in dementia with Lewy bodies: a phase III, multicentre study. *Lancet Neurol*. (2007) 6:305–13. doi: 10.1016/S1474-4422(07)70057-1
53. Fearnley JM, Lees AJ. Ageing and Parkinson's disease: substantia nigra regional selectivity. *Brain*. (1991) 114:2283–301. doi: 10.1093/brain/114.5.2283
54. Aarsland D, Kurz MW. The epidemiology of dementia associated with Parkinson disease. *J Neurol Sci*. (2010) 289:18–22. doi: 10.1016/j.jns.2009.08.034
55. Walker Z, Gandolfo F, Orini S, Garibotto V, Agosta F, Arbizu J, et al. Clinical utility of FDG PET in Parkinson's disease and atypical parkinsonism associated with dementia. *Eur J Nucl Med Mol Imaging*. (2018) 45:1534–45. doi: 10.1007/s00259-018-4031-2
56. Wenning GK, Litvan I, Tolosa E. Milestones in atypical and secondary Parkinsonisms. *Move Disord*. (2011) 26:1083–95. doi: 10.1002/mds.23713
57. Hellwig S, Amtage F, Kreft A, Buchert R, Winz OH, Vach W, et al. [^{18}F]FDG-PET is superior to [^{123}I]IBZM-SPECT for the differential diagnosis of parkinsonism. *Neurology*. (2012) 79:1314–22. doi: 10.1212/WNL.0b013e31826c1b0a
58. Morbelli S, Esposito G, Arbizu J, Barthel H, Boellaard R, Bohnen NI, et al. EANM practice guideline/SNMMI procedure standard for dopaminergic imaging in Parkinsonian syndromes 1.0. *Eur J Nucl Med Mol Imaging*. (2020) 47:1885–912. doi: 10.1007/s00259-020-04817-8
59. Meyer PT, Hellwig S. Update on SPECT and PET in parkinsonism - Part 1: imaging for differential diagnosis. *Curr Opin Neurol*. (2014) 27:390–7. doi: 10.1097/WCO.0000000000000106
60. Tripathi M, Kumar A, Bal C. Neuroimaging in Parkinsonian disorders. *Neurol India*. (2018) 66(Suppl.):S68–78. doi: 10.4103/0028-3886.226460
61. Nagata K, Saito H, Ueno T, Sato M, Nakase T, Maeda T, et al. Clinical diagnosis of vascular dementia. *J Neurol Sci*. (2007) 257:44–8. doi: 10.1016/j.jns.2007.01.049
62. Lewis DH, Toney LK, Baron JC. Nuclear medicine in cerebrovascular disease. *Semin Nucl Med*. (2012) 42:387–405. doi: 10.1053/j.semnuclmed.2012.06.002
63. Kuhl DE, Metter EJ, Riege WH. Patterns of local cerebral glucose utilization determined in Parkinson's disease by the [^{18}F]fluorodeoxyglucose method. *Ann Neurol*. (1984) 15:419–24. doi: 10.1002/ana.410150504
64. Chui H, Zhang Q. Evaluation of dementia: a systematic study of the usefulness of the American Academy of Neurology's Practice Parameters. *Neurology*. (1997) 49:925–35. doi: 10.1212/WNL.49.4.925

65. Devous MD. Functional brain imaging in the dementias: role in early detection, differential diagnosis, and longitudinal studies. *Eur J Nucl Med*. (2002) 29:1685–96. doi: 10.1007/s00259-002-0967-2
66. Pucci E, Belardinelli N, Regnicolo L, Nolfe G, Signorino M, Salvolini U, et al. Hippocampus and parahippocampal gyrus linear measurements based on magnetic resonance in Alzheimer's disease. *Eur Neurol*. (1998) 39:16–25. doi: 10.1159/000007893
67. Jack CR, Petersen RC, Xu YC, Waring SC, O'Brien PC, Tangalos EG, et al. Medial temporal atrophy on MRI in normal aging and very mild Alzheimer's disease. *Neurology*. (1997) 49:786–94. doi: 10.1212/WNL.49.3.786
68. Knopman DS, DeKosky ST, Cummings JL, Chui H, Corey-Bloom J, Relkin N, et al. Practice parameter: diagnosis of dementia (an evidence-based review): report of the quality standards subcommittee of the american academy of neurology. *Neurology*. (2001) 56:1143–53. doi: 10.1212/WNL.56.9.1143
69. Frisoni GB, Redolfi A, Manset D, Rousseau MÉ, Toga A, Evans AC. Virtual imaging laboratories for marker discovery in neurodegenerative diseases. *Nat Rev Neurol*. (2011) 7:429–38. doi: 10.1038/nrneurol.2011.99
70. Mitchell AJ. CSF phosphorylated tau in the diagnosis and prognosis of mild cognitive impairment and Alzheimer's disease: a meta-analysis of 51 studies. *J Neurol Neurosurg Psychiatry*. (2009) 80:966–75. doi: 10.1136/jnnp.2008.167791
71. Mattsson N, Andreasson U, Persson S, Arai H, Batish SD, Bernardini S, et al. The Alzheimer's Association external quality control program for cerebrospinal fluid biomarkers. *Alzheimer's Dement*. (2011) 7:386–95.e6. doi: 10.1016/j.jalz.2011.05.2243
72. Blennow K. A review of fluid biomarkers for Alzheimer's disease: moving from CSF to blood. *Neurol Therapy*. (2017) 6:15–24. doi: 10.1007/s40120-017-0073-9
73. Ashton NJ, Leuzy A, Karikari TK, Mattsson-Carlgren N, Dodich A, Boccardi M, et al. The validation status of blood biomarkers of amyloid and phospho-tau assessed with the 5-phase development framework for AD biomarkers. *Eur J Nucl Med Mol Imaging*. (2021). doi: 10.1007/s00259-021-05253-y. [Epub ahead of print].
74. Bloudek LM, Spackman DE, Blankenburg M, Sullivan SD. Review and meta-analysis of biomarkers and diagnostic imaging in Alzheimer's disease. *J Alzheimer's Dis*. (2011) 26:627–45. doi: 10.3233/JAD-2011-110458
75. Fink HA, Linskens EJ, Silverman PC, McCarten JR, Hemmy LS, Ouellette JM, et al. Accuracy of biomarker testing for neuropathologically defined Alzheimer disease in older adults with dementia. *Ann Intern Med*. (2020) 172:669–77. doi: 10.7326/M19-3888
76. Morinaga A, Ono K, Ikeda T, Ikeda Y, Shima K, Noguchi-Shinohara M, et al. A comparison of the diagnostic sensitivity of MRI, CBF-SPECT, FDG-PET and cerebrospinal fluid biomarkers for detecting Alzheimer's disease in a memory clinic. *Dement Geriatr Cogn Disord*. (2010) 30:285–92. doi: 10.1159/000320265
77. Silverman DHS, Small GW, Phelps ME. Clinical value of neuroimaging in the diagnosis of dementia. Sensitivity and specificity of regional cerebral metabolic and other parameters for early identification of Alzheimer's disease. *Clin Positron Imaging*. (1999) 2:119–30. doi: 10.1016/S1095-0397(99)00020-5
78. Kuwabara Y, Ichiya Y, Otsuka M, Tahara T, Fukumura T, Gunasekera R, et al. Comparison of I-123 IMP and Tc-99m HMPAO SPECT studies with PET in dementia. *Ann Nucl Med*. (1990) 4:75–82. doi: 10.1007/BF03164600
79. Messa C, Perani D, Lucignani G, Zenorini A, Zito F, Rizzo G, et al. High-resolution technetium-99m-HMPAO SPECT in patients with probable Alzheimer's disease: comparison with fluorine-18-FDG PET. *J Nucl Med*. (1994) 35:210–6.
80. Mielke R, Pietrzyk U, Jacobs A, Fink GR, Ichimiya A, Kessler J, et al. HMPAO SPET and FDG PET in Alzheimer's disease and vascular dementia: comparison of perfusion and metabolic pattern. *Eur J Nucl Med*. (1994) 21:1052–60. doi: 10.1007/BF00181059
81. Herholz K, Schopphoff H, Schmidt M, Mielke R, Eschner W, Scheidhauer K, et al. Direct comparison of spatially normalized PET and SPECT scans in Alzheimer's disease. *J Nucl Med*. (2002) 43:21–6.
82. Döbert N, Pantel J, Frölich L, Hamscho N, Menzel C, Grünwald F. Diagnostic value of FDG-PET and HMPAO-SPET in patients with mild dementia and mild cognitive impairment: metabolic index and perfusion index. *Dement Geriatr Cogn Disord*. (2005) 20:63–70. doi: 10.1159/000085857
83. Nihashi T, Yatsuya H, Hayasaka K, Kato R, Kawatsu S, Arahata Y, et al. Direct comparison study between FDG-PET and IMP-SPECT for diagnosing Alzheimer's disease using 3D-SSP analysis in the same patients. *Radiat Med Med Imaging Radiat Oncol*. (2007) 25:255–62. doi: 10.1007/s11604-007-0132-8
84. Ito K, Shimano Y, Imabayashi E, Nakata Y, Omachi Y, Sato N, et al. Concordance between 99mTc-ECD SPECT and 18F-FDG PET interpretations in patients with cognitive disorders diagnosed according to NIA-AA criteria. *Int J Geriatr Psychiatry*. (2014) 29:1079–86. doi: 10.1002/gps.4102
85. O'Brien JT, Firbank MJ, Davison C, Barnett N, Bamford C, Donaldson C, et al. 18F-FDG PET and perfusion SPECT in the diagnosis of Alzheimer and Lewy body dementias. *J Nucl Med*. (2014) 55:1959–65. doi: 10.2967/jnumed.114.143347
86. Ferreira LK, Rondina JM, Kubo R, Ono CR, Leite CC, Smid J, et al. Support vector machine-based classification of neuroimages in Alzheimer's disease: direct comparison of FDG-PET, rCBF-SPECT and MRI data acquired from the same individuals. *Rev Bras Psiquiatr*. (2018) 40:181–91. doi: 10.1590/1516-4446-2016-2083
87. Nadebaum DP, Krishnadas N, Poon AM, Kalff V, Lichtenstein M, Villemagne VL, et al. A head-to-head comparison of cerebral blood flow SPECT and 18 F-FDG PET in the diagnosis of Alzheimer's Disease. *Intern Med J*. (2020). doi: 10.1111/imj.14890. [Epub ahead of print].
88. McMahon PM, Araki SS, Neumann PJ, Harris GJ, Scott Gazelle G. Cost-effectiveness of functional imaging tests in the diagnosis of Alzheimer disease. *Radiology*. (2000) 217:58–68. doi: 10.1148/radiology.217.1.r00se1358
89. McMahon PM, Araki SS, Sandberg EA, Neumann PJ, Gazelle GS. Cost-effectiveness of PET in the diagnosis of Alzheimer disease. *Radiology*. (2003) 228:515–22. doi: 10.1148/radiol.2282020915
90. Silverman DHS, Gambhir SS, Huang H-WC, Schwimmer J, Kim S, Small GW, et al. Evaluating early dementia with and without assessment of regional cerebral metabolism by PET: a comparison of predicted costs and benefits. *J Nucl Med*. (2002) 43:253–66.
91. Moulin-Romsee G, Maes A, Silverman D, Mortelmans L, Van Laere K. Cost-effectiveness of 18F-fluorodeoxyglucose positron emission tomography in the assessment of early dementia from a Belgian and European perspective. *Eur J Neurol*. (2005) 12:254–63. doi: 10.1111/j.1468-1331.2004.00940.x
92. Arbizu J, García-Ribas G, Carrió I, Garrastachu P, Martínez-Lage P, Molinuevo JL. Recomendaciones para la utilización de biomarcadores de imagen PET en el proceso diagnóstico de las enfermedades neurodegenerativas que cursan con demencia: documento de consenso SEMNIM y SEN. *Rev Esp Med Nucl Imagen Mol*. (2015) 34:303–13. doi: 10.1016/j.remn.2015.03.002
93. Villemagne VL, Doré V, Burnham SC, Masters CL, Rowe CC. Imaging tau and amyloid-? proteinopathies in Alzheimer disease and other conditions. *Nat Rev Neurol*. (2018) 14:225–36. doi: 10.1038/nrneurol.2018.9
94. Vallabhajosula S. Positron emission tomography radiopharmaceuticals for imaging brain beta-amyloid. *Semin Nucl Med*. (2011) 41:283–99. doi: 10.1053/j.semnuclmed.2011.02.005
95. Fantoni ER, Chalkidou A, O'Brien JT, Farrar G, Hammers A. A systematic review and aggregated analysis on the impact of amyloid PET brain imaging on the diagnosis, diagnostic confidence, and management of patients being evaluated for Alzheimer's disease. *J Alzheimer's Dis*. (2018) 63:783–96. doi: 10.3233/JAD-171093
96. Mathis CA, Kuller LH, Klunk WE, Snitz BE, Price JC, Weissfeld LA, et al. *In vivo* assessment of amyloid-β deposition in non-demented very elderly subjects. *Ann Neurol*. (2013) 73:751–61. doi: 10.1002/ana.23797
97. Serrano-Pozo A, Qian J, Monsell SE, Blacker D, Gómez-Isla T, Betensky RA, et al. Mild to moderate Alzheimer dementia with insufficient neuropathological changes. *Ann Neurol*. (2014) 75:597–601. doi: 10.1002/ana.24125
98. Kapucu ÖL, Nobili F, Varrone A, Booij J, Vander Borght T, Någren K, et al. EANM procedure guideline for brain perfusion SPECT using 99mTc-labelled radiopharmaceuticals, version 2. *Eur J Nucl Med Mol Imaging*. (2009) 36:2093–102. doi: 10.1007/s00259-009-1266-y

99. Moonis G, Subramaniam RM, Trofimova A, Burns J, Bykowski J, Chakraborty S, et al. ACR appropriateness criteria® dementia. *J Am Coll Radiol*. (2020) 17:S100–12. doi: 10.1016/j.jacr.2020.01.040
100. Juni JE, Waxman AD, Devous S, Tikofsky RS, Ichise M, Van Heertum RL, et al. Procedure guideline for brain perfusion SPECT using technetium-99m radiopharmaceuticals. *J Nucl Med*. (1998) 39:923–6.
101. American Academy of Neurology. Assessment of brain SPECT report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology. *Neurology*. (1996) 46:278–85. doi: 10.1212/WNL.46.1.278
102. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's Dementia*. (2011) 7:263–9. doi: 10.1016/j.jalz.2011.03.005
103. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging and Alzheimer's Association workgroup. *Alzheimer's Dement*. (2011) 7:270–9. doi: 10.1016/j.jalz.2011.03.008
104. Páez D, Orellana P, Gutiérrez C, Ramirez R, Mut F, Torres L. Current status of nuclear medicine practice in Latin America and the Caribbean. *J Nucl Med*. (2015) 56:1629–34. doi: 10.2967/jnumed.114.148932
105. Paez D, Giammarile F, Orellana P. Nuclear medicine: a global perspective. *Clin Transl Imaging*. (2020) 8:51–3. doi: 10.1007/s40336-020-00359-z
106. Parra MA, Baez S, Sedeño L, Gonzalez Campo C, Santamaría-García H, Aprahamian I, et al. Dementia in Latin America: paving the way toward a regional action plan. *Alzheimer's Dement*. (2020) 17:295–313. doi: 10.1002/alz.12202

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 10 May 2021
doi: 10.3389/fneur.2021.640696

Accuracy of Support-Vector Machines for Diagnosis of Alzheimer's Disease, Using Volume of Brain Obtained by Structural MRI at Siriraj Hospital

Yudthaphon Vichianin[1†], Anutr Khummongkol[2†], Pipat Chiewvit[3], Atthapon Raksthaput[2], Sunisa Chaichanettee[2], Nuttapol Aoonkaew[2] and Vorapun Senanarong[2]*

[1] Department of Radiological Technology, Faculty of Medical Technology, Mahidol University, Bangkok, Thailand, [2] Division of Neurology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, [3] Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

OPEN ACCESS

Edited by:
Christopher Butler,
University of Oxford, United Kingdom

Reviewed by:
Jiu Chen,
Nanjing Medical University, China
Heather Winskel,
Southern Cross University, Australia

***Correspondence:**
Vorapun Senanarong
vorapun.sen@mahidol.ac.th;
vorasenanarong@yahoo.com

[†]These authors share first authorship

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: 11 December 2020
Accepted: 12 March 2021
Published: 10 May 2021

Citation:
Vichianin Y, Khummongkol A, Chiewvit P, Raksthaput A, Chaichanettee S, Aoonkaew N and Senanarong V (2021) Accuracy of Support-Vector Machines for Diagnosis of Alzheimer's Disease, Using Volume of Brain Obtained by Structural MRI at Siriraj Hospital. Front. Neurol. 12:640696. doi: 10.3389/fneur.2021.640696

Background: The determination of brain volumes using visual ratings is associated with an inherently low accuracy for the diagnosis of Alzheimer's disease (AD). A support-vector machine (SVM) is one of the machine learning techniques, which may be utilized as a classifier for various classification problems. This study exploratorily investigated the accuracy of SVM classification models for AD subjects using brain volume and various clinical data as features.

Methods: The study was designed as a retrospective chart review. A total of 201 eligible subjects were recruited from the Memory Clinic at Siriraj Hospital, Thailand. Eighteen cases were excluded due to incomplete MRI data. Subjects were randomly assigned to a training group (AD = 46, normal = 46) and testing group (AD = 45, normal = 46) for SVM modeling and validation, respectively. The results in terms of accuracy and a receiver operating characteristic curve analysis are reported.

Results: The highest accuracy for brain volumetry (62.64%) was found using the hippocampus as a single feature. A combination of clinical parameters as features provided accuracy ranging between 83 and 90%. However, a combination of brain volumetry and clinical parameters as features to the SVM models did not improve the accuracy of the result.

Conclusions: In our study, the use of brain volumetry as SVM features provided low classification accuracy with the highest accuracy of 62.64% using the hippocampus volume alone. In contrast, the use of clinical parameters [Thai mental state examination score, controlled oral word association tests (animals; and letters K, S, and P), learning memory, clock-drawing test, and construction-praxis] as features for SVM models provided good accuracy between 83 and 90%.

Keywords: Alzheimer disease, support vector machine, machine learning, volumetric MRI, Thailand

INTRODUCTION

Alzheimer's disease (AD) is a common condition that is diagnosed in ∼5–7% of the general population (1). Current treatment can improve the quality of life of both Alzheimer's patients and their relatives and caregivers (2). Consequently, a tool that provides high sensitivity and specificity is needed for the accurate diagnosis of this disease.

The current diagnostic tool for AD is the use of clinical criteria, such as DSM-V (3). Despite imaging studies not being included in such criteria, many clinicians have noticed that the size of the brain volume obtained from structural imaging appears to be associated with AD to some extent. Although visual rating of the brain volume is generally used to guide a diagnosis of AD, its interpretation differs vastly among clinicians, and the method lacks specificity and sensitivity (4). It would be beneficial if there was a reliable tool that could interpret imaging results accurately and consistently.

A support-vector machine (SVM), a mathematical function, is designed to classify complex data. This function has the ability to learn the distribution of data and provide a proper classification line (or optimal hyperplane) that is not restricted to a linear fashion (**Figures 1**, **2**).

Several studies have investigated SVM as a diagnostic tool for AD, and a number have shown good levels of accuracy (5–8). However, those results were based on international imaging data obtained from the Alzheimer's Disease Neuroimaging Initiative, which included a different population from the Thai cohort used in the current study. Hence, this study focused on the accuracy of SVM as a diagnostic tool for the Thai population. Moreover, we investigated clinical data in order to determine if it is possible to further increase the accuracy of SVM.

MATERIALS AND METHODS

Study Design

This study was a retrospective, chart review and was approved by the Siriraj Institutional Review Board. Everybody had signed informed consent as part of data registration at the Memory Clinic at Siriraj Hospital. The subjects were recruited by clinical coordinators from the Memory Clinic at Siriraj Hospital. Some normal subjects had brain magnetic resonance imaging scan, which was supported by the Thailand Research Fund. All were living in the community. Their identities (name and identification number) were hidden from the staff.

For the present study, the inclusion criteria consisted of the following: aged 60 years or older, a diagnosis of AD, in accordance with the (9) criteria, and the performance of an MRI brain scan within 1 year of the AD diagnosis. The exclusion criteria were having an untreated psychiatric condition; having a history of stroke (either ischemic or hemorrhagic), CNS infection, drug abuse, epilepsy, severe head trauma, and/or repetitive head trauma; and having been diagnosed with another type of dementia (such as frontotemporal dementia, Parkinson's disease with dementia, Lewy body dementia, vascular dementia, and other secondary dementia).

Subjects

A total number of 201 subjects in this study consists of 101 AD subjects recruited from the memory clinic at Siriraj Hospital, and 100 normal subjects were enlisted from volunteers from the dementia and disability project (10) and caregivers from the memory clinic. These normal controls did not meet the criteria of dementia or mild cognitive impairment. Eighteen subjects were removed due to incomplete MRI data necessary for further analysis.

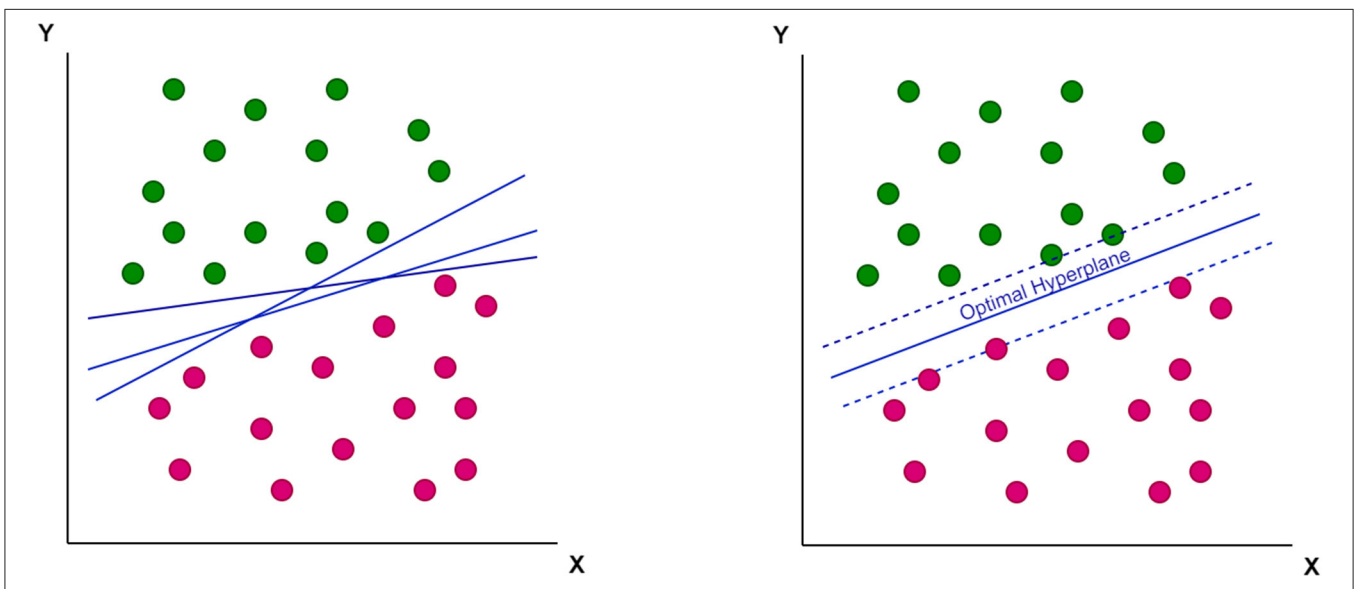


FIGURE 1 | The concept of optimal hyperplane to properly classify the data into two groups.

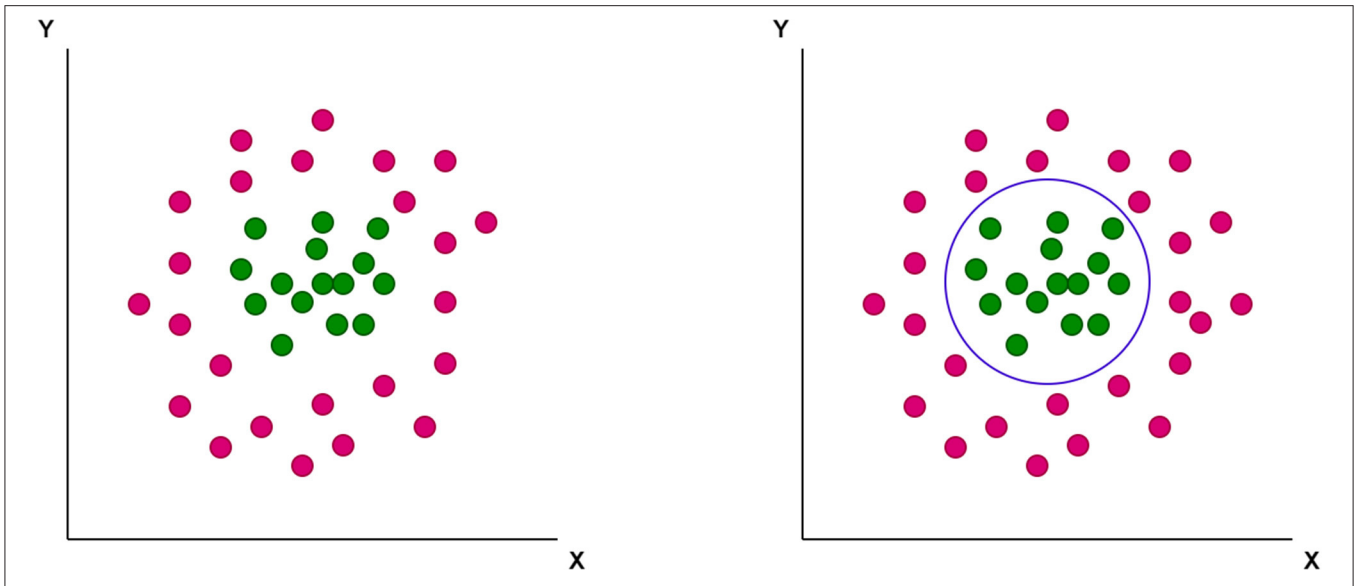


FIGURE 2 | The non-linear optimal hyperplane, which support-vector machine (SVM) can provide as a classification tool.

Eligible 183 subjects then were randomly divided into the training group ($N = 92$ with AD = 46, normal = 46) and testing group ($N = 91$ with AD = 45, normal = 46) for the SVM study using brain volumetry alone. However, due to the subjects' incomplete clinical data, 73 subjects were removed resulting to 55 subjects for the training group (AD = 28, normal = 27) and 55 subjects for the testing group (AD = 27, normal = 28) of the SVM study using a combination of clinical data and brain volumetry. The randomization technique was used for assigning subjects into groups in order to minimize selection bias and ensures against the accidental uncontrolled bias (11) (**Figure 3**).

Clinical Data

The Thai mental state examination (TMSE) (12) is a cognitive assessment modified from the Mini mental status examination. Thai mental state examination consists of seven subdomains: orientation, immediate memory (registration), calculation, attention, language, picture copy, and recalled memory. The total score is 30. The score of <24 is suggestive of having dementia. The higher the TMSE score, the better the cognitive function.

The Neuropsychiatric Inventory (NPI-Q) (13) is used to evaluate neuropsychiatric symptoms of all subjects. The NPI-Q is an informant-based instrument that measures the presence and severity of 12 neuropsychiatric symptoms in patients with dementia and normal controls, and to measure informant distress according to individual neuropsychiatric symptom of patients with dementia.

The cognitive data: the examination scores of TMSE and other neuropsychological assessments, namely, Logical Memory (LM), Controlled Oral Word Association Test—animals (COWA-animals), Controlled Oral Word Association Test—letters K, S, P (COWA-KSP), Clock drawing, and Construction—praxis were used as clinical parameters for further SVM model developments. Neuropsychological evaluation is part of clinical criteria to determine if subjects have dementia.

MRI Data

Whole brain MR (3-Tesla) T1-weighted axial 3D Turbo fast field echo (3D TFE) MR structural images were retrieved from the hospital database [voxel size = 1 × 1 × 1 mm, repetition time (TR) = 7.7 ms, echo time (TE) = 3.6 ms, flip angles = 80, TFE factor = 144, FOV = 230 × 290 mm, matrix = 232 × 288, slice thickness = 1 mm, NSA = 1]. The identities of the patients were subsequently anonymized by the researchers.

Analysis

The MR images were processed using FreeSurfer to seek for brain volumes (14). Brain MR image analysis was performed using the Freesurfer software suite to extract the brain cortical and subcortical brain volume (15).

Because the individuals had different cranial volumes, all specific regions of the brain volume were calculated relative to the whole brain volume, using the following normalization formula:

Specific volume of the brain × 100/intracranial volume

The specific volumes used to develop SVM models comprised of both sides of the hippocampus, nucleus accumbens, amygdala, caudate, thalamus, total white matter volume, total gray matter volume, ventricle volume, and a combination of those values.

The clinical data parameters used for SVM models in this study were the score from various tests including the TMSE, LM, COWA—animals, COWA-KSP, Clock, Construction—praxis, NPI 4, NPI 5, NPI 7, NPI 9, and NPI 12.

The WEKA software suite (available at https://www.cs.waikato.ac.nz/ml/weka/) was utilized in this study for SVM classification. Radial basis function was used to seek for the highest accuracy as suggested in a prior study (15). The SVM models then were trained and tested using the data from the training and testing groups (11). The leave-one-out validation technique was applied due to the small data set. The C and gamma values were adjusted to maximize the accuracy and area

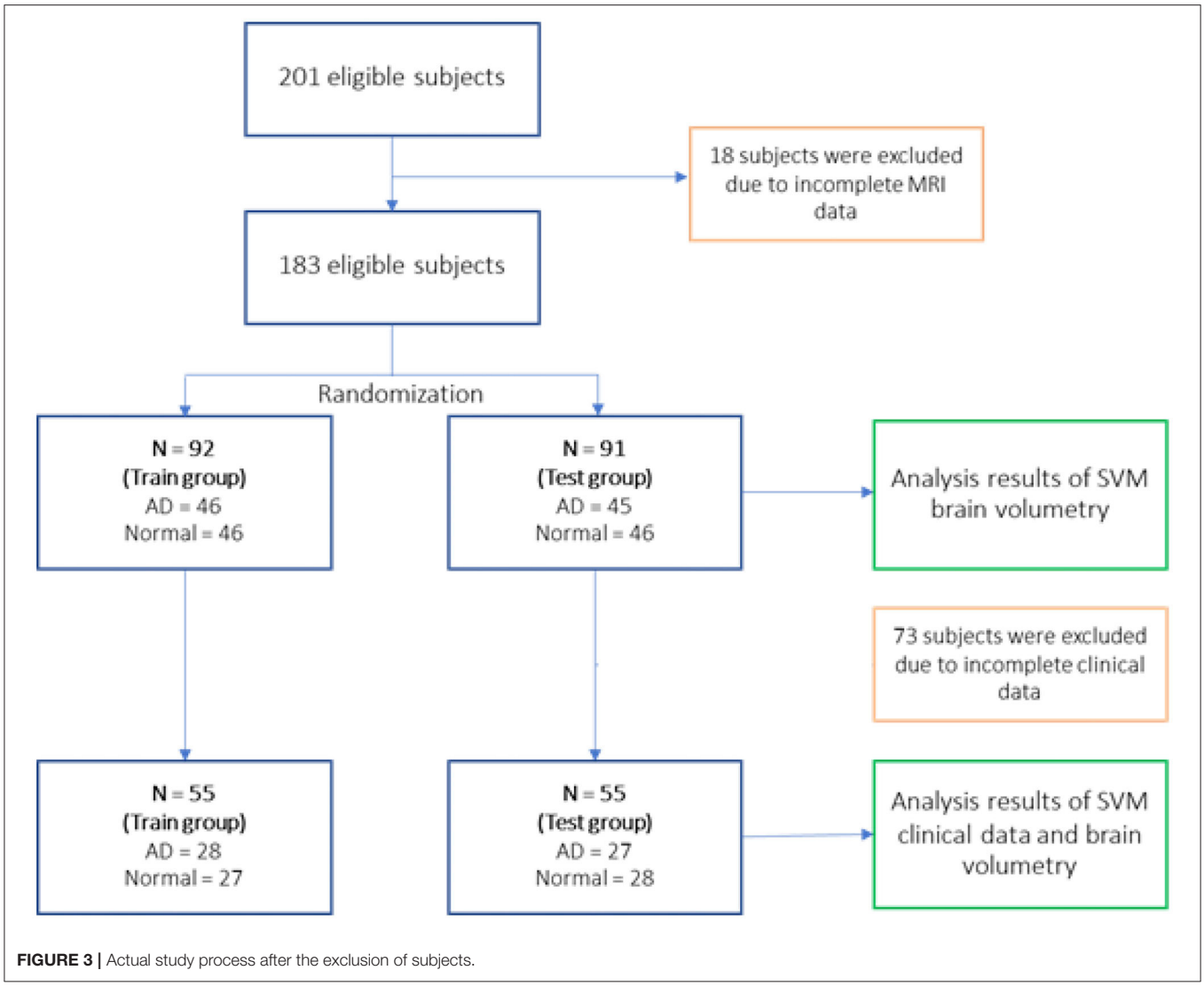


FIGURE 3 | Actual study process after the exclusion of subjects.

under the curve of the ROC for all SVM models as shown in **Table 3**.

The demographic data were analyzed and compared by descriptive statistics, using the unpaired *t*-test or Chi-square-test, according to each variable's type. We considered any p-value < 0.05 as statistically significant. The results were reported as true positive rate (TP rate), false positive rate (FP rate), accuracy, and the area under the curve (AUC) in a receiver operating characteristic curve (ROC) analysis.

RESULTS

An analysis of the demographic data (**Table 1**) revealed an average age of 73.09 years (SD = 7.28) for the AD group, and a lower average of 69.72 years for the normal controlled group, with a significant difference between those averages. Education levels and baseline TMSE scores also differed between the two groups. Even if there are some baseline differences, the randomization method we used with SVM and the leave one out method have something to help to compromise these baseline differences.

As to the descriptive statistical analysis of the brain volumetry of the two groups, only the ventricle volume demonstrated a significant difference, being higher for the AD group (**Table 2**). Other parameters showed no significant differences.

From the SVM modeling performance analysis results in **Table 3**, two models with equally highest accuracy (90.74%) were the model of clinical parameters (TMSE, LM, COWA—animals, COWA-KSP, Clock drawing, and Construction—praxis scores) (item 16 in **Table 3**) and the model of all brain volumetry combined with the scores of TMSE, LM, COWA—animals, COWA-KSP, Clock drawing, and Construction—praxis scores (**Table 3**, item 18).

However, from the results of the ROC analysis, the model consisted of TMSE, LM, COWA—animals, COWA-KSP, Clock drawing, and Construction—praxis scores provided the best performance in the diagnosis of AD with the AUC = 0.96 (**Table 3**, item 18). Other notable high performance

TABLE 1 | Descriptive statistic of demographic data [mean (SD)].

	AD group (*N* = 91)	Normal controlled group (*N* = 93)	*P*-value
Age	73.09 (7.28)	69.72 (6.12)	0.001
Sex			
Male (*N*)	32	40	0.234
Female (*N*)	59	53	
Education (years)	7.40 (5.63)	9.63 (5.67)	0.008
TMSE	21.26 (5.19)	26.83 (2.32)	<0.001
BMI	24.47 (5.00)	24.32 (3.56)	0.906
MAP mmHg	97.38 (13.47)	98.95 (11.52)	0.450
Smoking (*N*)	7	7	0.402
Hypertension (*N*)	31	36	0.942
DM (*N*)	19	13	0.119

AD, Alzheimer's disease; TMSE, Thai Mental State Examination; BMI, body mass index; MAP, mean arterial pressure; DM, diabetes mellitus.

TABLE 2 | Descriptive statistics of brain volumetry.

Volumes	AD group (*N* = 91)	Normal controlled group (*N* = 93)	*p*-value
Ventricle	5.43 (2.48)	4.46 (2.01)	0.004*
Gray matter	48.36 (10.99)	50.07 (5.39)	0.181
White matter	52.71 (7.99)	50.34 (5.76)	0.022*
Nucleus accumbens	0.14 (0.24)	0.16 (0.29)	0.523
Hippocampus	0.34 (0.19)	0.41 (0.22)	0.038*
Amygdala	0.19 (0.18)	0.21 (0.23)	0.431
Caudate	0.31 (0.19)	0.35 (0.19)	0.154
Thalamus	0.56 (0.37)	0.62 (0.33)	0.246

*The values below are calculated from "specific brain volume × 100/intracranial volume". *p < 0.05 = statistical significant; AD, Alzheimer's disease.*

models were found with these parameters: hippocampus with TMSE, LM, COWA—animals, COWA-KSP, clock drawing, and Construction—praxis (AUC = 0.927, **Table 3**, item 17). We also performed analyses on various combinations of features, but those revealed lower accuracies and lower AUC values as shown in **Table 3**.

DISCUSSION

Our study with SVM classification revealed that utilizing the scores of TMSE, LM, COWA—animals, COWA-KSP, Clock drawing, and Construction—praxis can best differentiate AD from normal controlled subjects. Neuropsychiatric symptoms alone could not provide accurate results. The demographic data in this study showed that the individuals in the AD group had a slightly older mean age (73.09 years) than those in the normal control group (69.72 years). Those with AD also had a lower formal educational level, as indicated by their comparatively smaller number of years of schooling. Previous research revealed that individuals with a lower number of years of formal education might have a smaller cognitive reserve. As a consequence, the incidence of AD has been reported to be higher in those individuals with lower education (16).

Previous studies showed that digital health data, cognitive performance such as memory, and neuropsychiatric symptoms can help identify those with dementia from normal subjects (17–21). Some research groups (19) have suggested that a diagnosis of dementia can be made from health recording data.

Despite using the highest accuracy that the SVM could provide, brain volumetry alone provided suboptimal accuracy for the diagnosis of AD. The highest accuracy for brain volumetry was found with the hippocampus region, which reached an accuracy of 62.64%. The inclusion of other regions of the brain did not seem to increase the accuracy level any further. This also reflects previous research findings that the hippocampus volume is associated with AD (22). Given that the mean baseline TMSE score of the AD group was not low, one possibility is that the SVM failed to classify AD accurately using hippocampal volume alone in our study because our AD subjects tended to have a mild-to-moderate degree of severity of the disease. Consequently, the difference in the hippocampal volumes of each group was not pronounced. Individuals in Asian counties are known to have a high prevalence of cerebral small vessel disease, which increases with age (23). This cerebral small vessel disease can cause smaller hippocampal volume in subjects with normal cognition. However, in a recent review of 111 studies, the majority of the studies assessed Alzheimer's disease compared with healthy controls, using AD Neuroimaging Initiative data, support vector machines, and only T1-weighted sequences (24). Accuracy was highest for differentiating Alzheimer's disease from healthy controls and poor for differentiating healthy controls vs. mild cognitive impairment vs. Alzheimer's disease.

Our study with SVM classification suggested that brain volumetry alone seems to be a suboptimal parameter for AD diagnosis; a different situation is found with the clinical parameters. COWA had a high degree of accuracy, especially COWA-KSP (note that KSP come from the letters "กสป" in the Thai language; in English-speaking countries, the letters "F, A, and S" or "C, F, and L" are normally used). These results are consistent with the knowledge that individuals with AD also have executive function impairment of varying severities (25). Word fluency relies on the executive functions that will enable an individual to produce a number of words quickly in a limited time. It follows that COWA might be adapted as a good screening tool for the diagnosis of AD. A combination of other neuropsychiatric tests also afforded a very high degree of accuracy. However, utilizing neuropsychiatric symptoms to aid the diagnosis of AD resulted in poor ROC value in the tested data. This indicated that neuropsychiatric symptoms alone could not differentiate AD from norms or other dementia.

In the previous study, both structural T1-weighted MRI brain studies and neuropsychological measures of individuals were used to train and optimize an artificial intelligence classifier to diagnose mild-AD patients (26). Similar to our study, the classifier was able to distinguish between the two groups before AD definite diagnosis using a combination of MRI brain studies

TABLE 3 | Results of support vector machine (SVM).

	Brain volumetry								Clinical parameters										SVM parameters										
	Hippo	Accumbent	Amygdala	Caudate	Thalamus	White.M	Gray.M	Ventricle	TMSE	LM	COWA-animals	COWA-KSP	Clock	Conpraxis	NPI4	NPI5	NPI7	NPI9	NPI 1–12	Setting		Trained set					Tested set				
																				C	Gamma	*N*	TP rate	FP rate	Accuracy	ROC	*N*	TP rate	FP rate	Accuracy	ROC
1	x																			10	100	92	0.630	0.371	63.050	0.630	91	0.626	0.340	62.637	0.575
2		x																		10	100	92	0.598	0.406	59.783	0.596	91	0.571	0.431	57.143	0.579
3			x																	10	100	92	0.565	0.447	56.521	0.559	91	0.538	0.462	53.846	0.541
4				x																100	1	92	0.565	0.434	56.523	0.565	91	0.549	0.454	54.945	0.526
5					x															100	0.1	92	0.587	0.417	58.660	0.550	91	0.495	0.509	49.451	0.424
6						x														1	100	92	0.641	0.364	64.130	0.590	91	0.571	0.432	57.143	0.488
7							x													1	100	92	0.641	0.364	64.130	0.639	91	0.560	0.444	56.044	0.402
8								x												10	10	92	0.620	0.380	61.957	0.621	91	0.604	0.398	60.440	0.571
9	x						x													10	100	92	0.587	0.416	58.696	0.585	91	0.520	0.473	52.747	0.559
10	x					x	x													100	100	92	0.620	0.381	61.950	0.619	91	0.495	0.505	49.450	0.550
11	x	x	x	x	x	x	x													1	100	92	0.641	0.358	64.130	0.642	91	0.538	0.461	53.846	0.539
12	x	x	x	x	x	x	x	x												100	0.1	92	0.598	0.406	59.783	0.596	91	0.510	0.430	57.143	0.560
13											x		X							100	0.01	55	0.764	0.233	63.640	0.765	54	0.704	0.296	70.370	0.822
14												x								100	0.1	42	0.786	0.267	78.571	0.590	42	0.833	0.181	83.333	0.844
15	x								x											10	0.1	55	0.782	0.218	78.181	0.848	55	0.741	0.259	74.074	0.804
16									x	x	x	x	X	x						100	1	55	0.891	0.109	89.091	0.891	54	0.907	0.093	90.741	0.955
17	x								x	x	x	x	X	x						10	1	55	0.891	0.109	89.091	0.891	54	0.889	0.111	88.889	0.927
18	x	x	x	x	x	x	x	x	x	x	x	x	X	x						100	1	55	0.927	0.073	92.727	0.927	54	0.907	0.093	90.741	0.925
19															x	x	x	x	x	10	10	38	0.842	0.118	84.211	0.862	38	0.737	0.377	73.684	0.475
20															x					10	1	38	0.789	0.411	78.947	0.689	38	0.711	0.711	71.053	0.000
21																x				100	1	38	0.709	0.286	70.909	0.712	38	0.605	0.753	60.526	0.000
22																	x			10	1	38	0.789	0.411	78.947	0.689	38	0.684	0.721	68.421	0.175

Hippo, hippocampus; LM, learning memory; COWA, controlled oral word association test (animals; and letters K, S, P); clock, clock drawing test; NPI4, depression; NPI5, anxiety; NPI7, apathy; NPI9, irritability; TP rate, true positive rate; FP rate, false positive rate; ROC, receiver operating characteristic; curve (stands for AUC—area under the curve—in this table). Blue = main flow; Yellow = subjects excluded; Green = action done to the data.

and specific neuropsychological measures, with 85% accuracy, 83% sensitivity, and 87% specificity.

LIMITATIONS AND FUTURE STUDY

An important limitation was that the severity of the AD of our subjects seemed to be low to moderate. Although, the hippocampus alone was rather a good choice for use as a classification parameter, our study failed to demonstrate that it was. The low education of individuals in our study may play some role on brain volume. The second limitation was that this study did not utilize age-matched group due to the limited number of subject recruitments and the small number of subjects for the SVM training and testing groups. Generalization of the results to clinical use should be done with caution. The third limitation was that, we used dementia subjects from the memory clinic together with normal subjects from the community survey or community study, which could lead to selection bias. When applied to the broader general population, our method of using the SVM might not produce the same degree of accuracy.

Future studies should include a larger sample size in both the training and testing groups. It is known that the Asian population has a prevalence of small vessel disease in the brain. The burden of cerebral small vessel disease can be included to predict the diagnosis of dementia in the future. Exploration with other biomarkers to predict the diagnosis of Alzheimer's disease or prodromal Alzheimer's disease in a Thai cohort could also be done.

CONCLUSIONS

Based on data drawn from the Memory Clinic at Siriraj Hospital, clinical parameters (including TMSE, COWA—animals, COWA-KSP, LM, clock drawing, and Construction—praxis) provided good accuracy (83–90%) using SVM as a classifier. COWA-KSP alone might be the easiest tool to utilize in clinical situations, and it had an accuracy of 83.33% when using the SVM. Our study failed to demonstrate a good degree of accuracy when using brain volumetry alone. The most accurate results were found using the hippocampus alone as a classifier that revealed an accuracy of 62.64%.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by IRB Faculty of Medicine Siriraj Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

VS: research planning, primary investigators of the awarding grants, conducting the field study, data analysis and interpretation of the results, and preparing manuscript. YV and AK: assisted data analysis and interpretation of the results. AR, SC, and NA: conducted field study, assessment of cognition and neuropsychiatricproblems, and preparing the data for statistical analysis. All authors read and approved the final manuscript.

FUNDING

This study was partially funded by Thailand Research Fund (TRF) and Mahidol University 2004–2007 fiscal years for MRI study.

ACKNOWLEDGMENTS

We are thankful to Professor J. L. Cummings for allowing us use NPI questionnaire.

REFERENCES

1. Sosa-Ortiz AL, Acosta-Castillo I, Prince MJ. Epidemiology of dementias and Alzheimer's disease. *Arch Med Res*. (2012) 43:600–8. doi: 10.1016/j.arcmed.2012.11.003
2. Ngandu T, Lehtisalo J, Solomon A, Levälahti E, Ahtiluoto S, Antikainen R, et al. A 2-year multidomain intervention of diet, exercise, cognitive training and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomized controlled trial. *Lancet*. (2015) 385:2255–63. doi: 10.1016/S0140-6736(15)60461-5
3. American Psychiatric Association. *American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*. 5th ed. Arlington: American Psychiatric Association (2013).
4. van de Pol LA, Hensel A, Barkhof F, Gertz HJ, Scheltens P, van der Flier WM. Hippocampal atrophy in Alzheimer disease: age matters. *Neurology*. (2006) 66:236–8. doi: 10.1212/01.wnl.0000194240.47892.4d
5. Barkhof F, Polvikoski TM, van Straaten ECW, Kalaria RN, Sulkava R, Aronen HJ, et al. The significance of medial temporal lobe atrophy: a postmortem MRI study in the very old. *Neurology*. (2007) 69:1521–7. doi: 10.1212/01.wnl.0000277459.83543.99
6. Dukart J, Mueller K, Barthel H, Villringer A, Sabri O, Schroeter M. Meta-analysis based SVM classification enables accurate detection of Alzheimer's disease across different clinical centers using FDG-PET and MRI. *Psychiatry Res Neuroimaging*. (2013) 212:230–6. doi: 10.1016/j.pscychresns.2012.04.007
7. Khedher L, Ramírez J, Górriz J, Brahim A, Segovia F. Early diagnosis of Alzheimer's disease based on partial least squares, principal component analysis and support vector machine using segmented MRI images. *Neurocomputing*. (2015) 151:139–50. doi: 10.1016/j.neucom.2014.09.072
8. Jongkreangkrai C, Vichianin Y, Tocharoenchai C, Arimura H. Computer-aided classification of Alzheimer's disease based on support vector machine with combination of cerebral image features in MRI. *J Phys Conf Series*. (2016) 694:012036. doi: 10.1088/1742-6596/694/1/012036
9. American Psychiatric Association, DSM-5 Task Force (2013). *Diagnostic and Statistical Manual of Mental Disorders: DSM-5®™, 5th ed.* American Psychiatric Publishing, Inc. doi: 10.1176/appi.books.9780890425596

10. Senanarong V, Harnphadungkit K, Poungvarin N, Vannasaeng S, Chongwisal S, Chakorn T, et al. The dementia and disability project in thai elderly: rational, design, methodology and early results. *BMC Neurology*. (2014) 13:3. doi: 10.1186/1471-2377-13-3. Available online at: https://www.researchgate.net/publication/234103449_The_Dementia_and_Disability_Project_in_Thai_Elderly_rational_design_methodology_and_early_results (accessed April 23, 2021).
11. Suresh KP. An overview of randomization techniques: an unbiased assessment of outcome in clinical research. *J Hum Reprod Sci*. (2011) 4:8–11. doi: 10.4103/0974-1208.82352
12. Train the brain forum committee: Thai mental state examination (TMSE). *Siriraj Hosp Gaz*. (1993) 45:359–74.
13. Kaufer DI, Cummings JL, Ketchel P, Smith V, MacMillan A, Shelley T, et al. Validation of the NPI-Q, a brief clinical form of the neuropsychiatric inventory. *J Neuropsychiatry Clin Neurosci*. (2000) 12:233–9. doi: 10.1176/jnp.12.2.233
14. Reuter M, Schmansky NJ, Rosas HD, Fischl B. Within-subject template estimation for unbiased longitudinal image analysis. *Neuroimage*. (2014) 61:1402–18. doi: 10.1016/j.neuroimage.2012.02.084
15. Sarwinda D, Bustamam A. 3D-HOG features-based classification using mri images to early diagnosis of Alzheimer's disease. In: *IEEE/ACIS 17th International Conference on Cumputer and Information Science (ICIS)*. Singapore, (2018). p. 457–62.
16. Rocca WA, Petersen RC, Knopman DS, Hebert LE, Evans DA, Hall KS, et al. Trends in the incidence and prevalence of Alzheimer's disease, dementia, and cognitive impairment in the United States. *Alzheimers Dement*. (2011) 7:80–93. doi: 10.1016/j.jalz.2010.11.002
17. Acostaa I, Borgesb G, Aguirre-Hernandez R, Sosa AL, Prince M. Dementia Research Group. Neuropsychiatric symptoms as risk factors of dementia in a Mexican population: a 10/66 Dementia Research Group study. *Alzheimer Dementia*. (2018) 14:271–9. doi: 10.1016/j.jalz.2017.08.015
18. Lyketsos CH, Lopez O, Jones B, Fitzpatrick AL, Breitner J, DeKosky S. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment. Results from the cardiovascular health study. *JAMA*. (2002) 288:1475–83. doi: 10.1001/jama.288.12.1475
19. Luo H, Lau KK, Wong GHY, Chan W-C, Mak HKF, Zhang Q, et al. Predicting dementia diagnosis from cognitive footprints in electronic health records: a case-control study protocol. *BMJ Open*. (2020) 10:e043487. doi: 10.1136/bmjopen-2020-043487
20. Boustani M, Perkins AJ, Khandker RK, Duong S, Dexter PR, Lipton R, et al. Passive digital signature for early identification of Alzheimer's disease and related dementia. *J Am Geriatr Soc*. (2019) 68:511–8. doi: 10.1111/jgs.16218
21. Bergerona MF, Landsetb S, Tarpin-Bernard F, Ashford CB, Khoshgoftaar TM, Ashford JW. Episodic-memory performance in machine learning modeling for predicting cognitive health status classification. *J Alzheimers Dis*. (2019) 70:277–86. doi: 10.3233/JAD-190165
22. Whitwell JL, Dickson DW, Murray ME, Weigand SD, Tosakulwong N, Senjem ML, et al. Neuroimaging correlates of pathologically defined subtypes of Alzheimer's disease: a case-control study. *Lancet Neurol*. (2012) 11:868–77. doi: 10.1016/S1474-4422(12)70200-4
23. Hilal S, Mok V, Youn YC, Wong A, Ikram MK, Chen CL. Prevalence, risk factors and consequences of cerebral small vessel diseases: data from three Asian countries. *J Neurol Neurosurg Psychiatry*. (2017) 88:669–74. doi: 10.1136/jnnp-2016-315324
24. Pellegrinia E, Ballerinia L, del C. Valdes Hernandeza M, Chappell FM, González-Castro V, Anblagan D, et al. Machine learning of neuroimaging for assisted diagnosis of cognitive impairment and dementia: a systematic review. *Alzheimers Dement (Amst)*. (2018) 10:519–35. doi: 10.1016/j.dadm.2018.07.004
25. Stokholm J, Vogel A, Gade A, Waldemar G. Heterogeneity in executive impairment in patients with very mild Alzheimer's disease. *Dement Geriatr Cogn Disord*. (2006) 22:54–9. doi: 10.1159/000093262
26. Salvatore C, Cerasa A, Castiglioni I, Alzheimer's Disease Neuroimaging Initiative. MRI characterizes the progressive course of AD and predicts conversion to Alzheimer's dementia 24 months before probable diagnosis. *Front Aging Neurosci*. (2018) 10:135. doi: 10.3389/fnagi.2018.00135

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Public Health

ORIGINAL RESEARCH
published: 14 May 2021
doi: 10.3389/fpubh.2021.628700

Dementia Incidence, Burden and Cost of Care: A Filipino Community-Based Study

Jacqueline Dominguez[1,2], Leo Jiloca[3], Krizelle Cleo Fowler[4], Ma. Fe De Guzman[4], Jhozel Kim Dominguez-Awao[2,5], Boots Natividad[4], Jeffrey Domingo[2,4], Jayvee Dyne Dominguez[2,4], Macario Reandelar Jr.[4], Antonio Ligsay[6], Jeryl Ritzi Yu[1], Stephen Aichele[7] and Thien Kieu Thi Phung[8]*

[1] Institute for Neurosciences, St. Luke's Medical Center, Quezon City, Philippines, [2] Institute for Dementia Care Asia, Quezon City, Philippines, [3] Geriatric Center, St. Luke's Medical Center, Quezon City, Philippines, [4] Research and Biotechnology Division, St. Luke's Medical Center, Quezon City, Philippines, [5] Department of Internal Medicine, St. Louis University Hospital, Baguio, Philippines, [6] Section of Clinical Research, St. Luke's Medical Center - College of Medicine, Quezon City, Philippines, [7] Department of Human Development and Family Studies, Colorado State University, Fort Collins, CO, United States, [8] Danish Dementia Research Center, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Background: In the midst of competing priorities and limited resources in low-middle-income countries (LMIC), convincing epidemiological evidence is critical for urging governments to develop national dementia plans. The majority of primary epidemiological studies on dementia are from high income countries (HIC). Implications for developing countries are typically extrapolated from these outcomes through modeling, meta-analyses, and systematic reviews. In this study, we directly assessed the incidence of dementia, disability adjusted life years (DALYs), and cost of care among community-dwelling Filipino elderly.

Methods: This was a follow-up study of the prospective cohort Marikina Memory Ageing Project (MMAP). Baseline assessment was performed in 2011–2012, and follow-up was done in 2015–2016 ($N = 748$ at follow-up). Incident dementia was determined. Disease burden was computed using the incidence rates and DALYs. Both indirect and direct (medical and non-medical) costs of dementia care were computed.

Results: The crude incidence rate was 16 (CI: 13–20) cases per 1,000 person-years (pyr) with 17 (CI: 12–21) per 1,000 pyr for females and 14 (CI: 9–21) per 1,000 pyr for males. Based on this incidence, we project an estimation of 220,632 new cases in 2030, 295,066 in 2040, and 378,461 in 2050. Disease burden was at 2,876 DALYsper 100,000 persons. The economic burden per patient was around Php 196,000 annually (i.e., ∼4,070 USD, or 36.7% of average family annual income in the Philippines). The majority (86.29%) of this care expense was indirect cost attributed to estimated lost potential earning of unpaid family caregivers whereas direct medical cost accounted for only 13.48%.

Conclusions: We provide the first Filipino community-based data on the incidence of dementia, DALYs, and cost of care to reflect the epidemiologic and economic impact of disease. The findings of this study serve to guide the development of a national dementia plan.

Keywords: dementia incidence, cost of care, DALY, LMIC, Filipino

OPEN ACCESS

Edited by:
Huali Wang,
Peking University Sixth Hospital, China

Reviewed by:
Yuping Ning,
Guangzhou Medical University, China
Christopher Butler,
University of Oxford, United Kingdom

****Correspondence:***
Jacqueline Dominguez
jcdominguez@stlukes.com.ph

Specialty section:
This article was submitted to Aging and Public Health, a section of the journal Frontiers in Public Health

Received: *12 November 2020*
Accepted: *12 April 2021*
Published: *14 May 2021*

Citation:
Dominguez J, Jiloca L, Fowler KC, De Guzman MF, Dominguez-Awao JK, Natividad B, Domingo J, Dominguez JD, Reandelar M Jr, Ligsay A, Yu JR, Aichele S and Phung TKT (2021) Dementia Incidence, Burden and Cost of Care: A Filipino Community-Based Study. Front. Public Health 9:628700. doi: 10.3389/fpubh.2021.628700

INTRODUCTION

In the midst of competing priorities and limited resources, low-middle-income countries (LMIC) are projected to have the largest rise in dementia prevalence by 2050 (1, 2). Convincing epidemiological evidence is critical for urging governments to develop national plans to address the dementia epidemic. Large datasets like the 10/66 Dementia Research Group surveys have provided robust data on dementia occurrence in developing countries (3). The estimated prevalence of dementia in Southeast Asia is expected to increase to 12.09 million (236%) by 2050 (1). However, epidemiological studies are lacking in Southeast Asian LMIC countries. The Filipino aging population comprises ∼7% of the country's total population in 2015 and is projected to increase by 11% in 2025 and 16% in 2045 (4). In the Philippines, the estimated number of elderly (60 years and older) will more than double from 9.5 million in 2020 to 19.7 million in 2040 (5). The extent of dementia in the Philippines however has not yet been estimated, and data are lacking. In 2011, we conducted the Marikina Memory and Aging Project (MMAP), a population-based study among Filipino older adults aged 60 years and over which yielded a dementia prevalence of 10.6%. In the study, approximately a quarter (23.2%) were identified to have mild cognitive impairment (MCI) along with an alarmingly high prevalence of cardiovascular risk factors among Filipino older adult men and women, further increasing the risk for developing dementia (6). However, this is not adequately addressed, and dementia is currently not recognized as a major public health issue in the Philippines. This makes the case for establishing epidemiological studies that can increase awareness of the magnitude of the problem and guide government policy in allocating resources to dementia care and prevention, which is especially critical in low-resource health care settings. More specifically, it is essential to have data on burden and cost of care to inform the government of the economic impact of the disease on extended families, who in the Philippines remain the cornerstone of dementia care and of the society. In the current study, we determined the incidence of dementia, disability adjusted life years, and cost of care of dementia among community-dwelling Filipino elderly.

METHODS

Study Design and Setting

This study is a follow-up study of the Marikina Memory and Aging Project (MMAP), which is a population-based cohort study to determine the prevalence of dementia and its associated risk among elderly in Marikina City, Philippines (6). Baseline assessment was done from March 2011 to February 2012 and follow-up assessment from July 2015 to December 2016. All follow-up assessments were conducted door-to-door. All participants provided written informed consent before any assessment was done.

Participants

The MMAP baseline cohort consists of participants randomly selected from the Senior Citizen Registry and is representative of percentages of senior citizens across villages (barangays) in the city of Marikina. The sampling method has been described previously (4). Recruitment was carried out door-to-door, and there were 1,367 participants who completed baseline assessment. For this incidence study, patients with dementia at baseline ($N = 145$) were excluded, leaving an eligible sample of 1,222. Of these, 794 participants (65.0%) were followed-up, among them 46 participants did not complete the evaluation and were excluded from subsequent analysis (**Figure 1**). All participants who were lost to follow-up were traced down to extract reasons for exclusion (as reported by neighbors and family members). The sample size for the current analysis was thus 748, with an average follow-up time of 3.9 years.

Follow-Up Assessment and Case Ascertainment

Data collection, both at baseline and follow-up, used the same methodology of at-home visits, which included informant and patient interviews. Trained nurses gathered socio-demographic and health history information, and a trained psychologist administered the Montreal Cognitive Assessment-Philippines (MoCA-P) (7), Geriatric Depression Scale (GDS) (8), Neuropsychiatric Inventory-Questionnaire (NPIQ) (9), Disability Assessment for Dementia (DAD) (10), and Ascertaining Dementia 8 (AD-8) (11). A neurologist or geriatrician conducted medical history and physical examinations, Clinical Dementia Rating (CDR) (12), and Hachinski Ischemic Scale (HIS) (13). All assessment data were reviewed by the physician and they consulted with each other as necessary to reach a consensus on dementia diagnosis. Dementia diagnosis was based on the DSM-IV-TR criteria; (14) Alzheimer's Disease (AD) on the NINCDS-ADRDA criteria; (15) vascular dementia (VaD) based on the HIS. Other dementia subtypes such as Parkinson's disease dementia (16), Dementia with Lewy Bodies (17), and dementia syndrome of depression (14) were diagnosed based on clinical criteria. Cognitive Impairment No Dementia (CIND) was diagnosed based on a CDR score of 0.5 and not fulfilling DSM-IV criteria for dementia (18). These were the same criteria used during the baseline study. All baseline data for risk factors (i.e., vascular risks like hypertension, diabetes, dyslipidemia and smoking, alcohol consumption, traumatic brain injury, depression, and living arrangement) were collected from the participant or family informant.

Disability-Adjusted Life Years Computation

Data from the study and relevant global literature were used to compute the DALYs using the DALY formula from the WHO. Number of deaths and mean duration of the disease were derived from dementia cases from the prevalence study. The disability weight used was 0.67 according to the WHO Global Burden of Disease in 2004 (19). Based on the Institute of Health Metrics and Evaluation Global Burden of Disease (20), average life expectancy at age 60 was 17 years irrespective of gender, 16 years for males, and 18 years for females. Since this is a global estimate, the researchers assumed that it applies to the Philippine context and also comparability to other similar studies. Note that the standard life expectancy at birth was not used since the population only

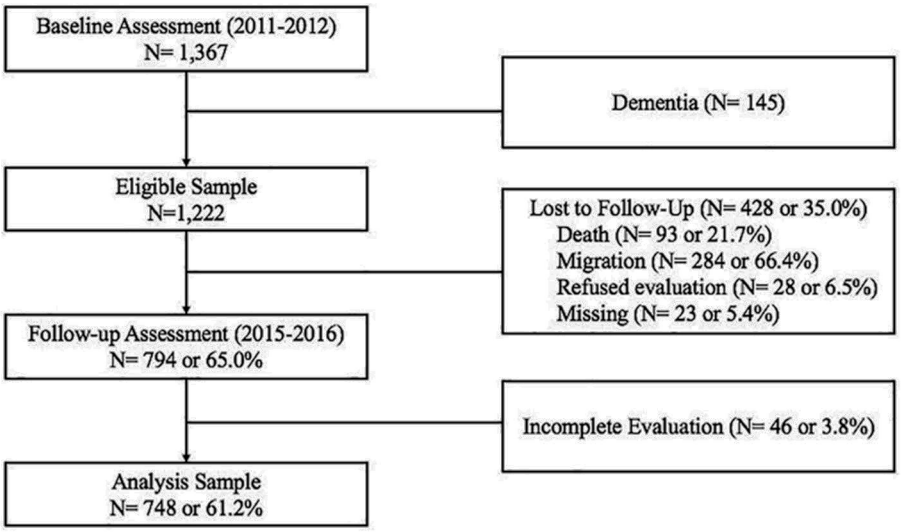


FIGURE 1 | Flow chart of study participants.

included ≥60 years old. Life expectancy at age 60 years was the average number of years that a person at that age is expected to live if age-specific mortality levels remained constant.

Cost of Care

Data was gathered from three groups of informants: (a) patients, relatives, and caregivers; (b) physicians including specialists (i.e., neurologist, geriatrician, and psychiatrist), non-specialists (i.e., family physician and internist), and allied health professionals (physical therapist, occupational therapist, psychologist), and (c) laboratories and drug stores. These groups were all interviewed in order to obtain information about fees and rates of the dementia patients' special needs.

Data Analysis

Analysis was done using SPSS Statistical Program (IBM, ver. 27). Incidence rates per 1,000 person-years (pyr) were computed for each 10-year age interval and by sex. The corresponding 95% confidence intervals were computed based on the Exact Poisson distribution, as is standard practice in reporting incidence rates (21). Univariate statistics (accounts, means, SDs, ranges) and bivariate statistics (correlations) were produced. We assessed differences in socio-demographic variables and medical history related to dementia at follow-up status based on results from Chi-square tests and *t*-tests. Crude odds ratio was also presented to show the association of risk factors and incident dementia. All analyses were evaluated based on a statistical cutoff criterion for significance of 0.05. To compare incidence rates based on sex, rate ratios and their corresponding confidence intervals were calculated.

In terms of the Burden of Disease, the WHO DALY formula [DALY = Years of Life Lost (YLL) + Years Lost due to Disability (YLD)] was used. YLL is the number of deaths multiplied by the standard life expectancy. YLD is the number of incident cases multiplied by mean duration of disease multiplied by disability weight of AD and other dementias.

Cost of care was calculated by adding the direct and indirect costs. Direct medical cost was calculated as the sum of the costs, which included fees for consultations, laboratory assessments, hospital admissions or emergency visits due to problems related to dementia, dementia medications, and aids for mobility and rehabilitation. Direct non-medical costs refer to expense like transportation to and from the hospital for both the caretaker and the patient. Indirect cost used in this study refers to the opportunity cost calculated by the number of days the unpaid caregivers spent taking care of the dementia patient for one entire year multiplied by the daily minimum wage in Marikina City (Php 491.00) (USD 10.91) and then multiplied by the number of unpaid caregivers the patient had. Individual costs were computed per component and aggregated for the two major cost themes (direct vs. indirect). All samples were summarized using the median value.

Ethics

The study was approved by the St. Luke's Institutional Ethics Review Committee (CT-14064).

RESULTS

Dementia Incidence

The incidence rate was 16 (CI: 13–20) cases per 1,000 person-years (pyr). Participants with incident dementia were significantly older at baseline and had lower number of years of education. There was a higher proportion of baseline cognitive impairment (CIND) among those who developed dementia (**Table 1**). This sample mostly comprised females (73.3%). Among subtypes, the majority of cases were Alzheimer's disease (79%) followed by vascular dementia (18.5%) (**Table 2**).

TABLE 1 | Baseline profile of participants with and without incident dementia.

Baseline characteristics	*N*	Incident dementia (*N* = 81)	No dementia (*N* = 667)	Total (*N* = 748)	*p*-value	OR*	95% CI
Age (years, M ± SD; min-max)	748	73.8 ± 8.0 (60.0–99.0)	68.7 ± 5.9 (59.0–90.0)	69.2 ± 6.4	<0.001	N/A	N/A
Years of education (M ± SD)	748	6.1 ± 3.6	8.9 ± 3.8	8.6 ± 3.9	<0.001	N/A	N/A
Male (%)	748	21 (25.9)	179 (26.8)	200 (26.7)	0.884	0.962	0.57–1.63
Female (%)		60 (74.0)	488 (73.2)	548 (73.3)			
With cognitive impairment (*N*, %)	748	39 (48.1)	155 (23.2)	194 (25.9)	<0.001	3.067	1.91–4.92
With vascular risks[δ] (*N*, %)	743	62 (76.5)	470 (71.0)	532 (71.6)	0.296	1.333	0.78–2.29
With hypertension (*N*, %)	711	49 (62.8)	346 (54.7)	395 (55.6)	0.171	1.402	0.86–2.28
With dyslipidemia (*N*, %)	600	16 (25.8)	189 (35.1)	205 (34.2)	0.143	0.642	0.35–1.17
With diabetes (*N*, %)	694	14 (18.2)	107 (17.3)	121 (17.4)	0.855	1.059	0.57–1.96
With smoking history (*N*, %)	735	22 (27.2)	137 (20.9)	159 (21.6)	0.200	1.407	0.83–2.38
With alcohol abuse history (*N*, %)	717	14 (17.5)	112 (17.6)	126 (17.6)	0.985	0.994	0.54–1.83
With TBI[δδ] (*N*, %)	715	2 (2.5)	10 (1.6)	12 (1.7)	0.531	1.626	0.35–7.56
With depression history (*N*, %)	712	36 (44.4)	276 (43.7)	312 (43.8)	0.904	1.029	0.65–1.64
Living alone (*N*, %)	748	5 (6.2)	31 (4.6)	36 (4.8)	0.545	1.35	0.51–3.58
Stroke (*N*, %)	718	9 (11.3)	41 (6.4)	50 (7.0)	0.109	1.849	0.86–3.96
Heart disease** (*N*, %)	726	26 (4.9)	8 (4.2)	34 (4.7)	1.000	0.762	0.23–2.35
Reported physical difficulty[δδδ] (*N*, %)	748	36 (44.4)	151 (22.6)	187 (25.0)	<0.001	2.734	1.70–4.39

Data presented as mean ± standard deviation (SD) or frequency of present risk factors with percentage in the parentheses and p-values obtained using t-tests for independent samples or Pearson's Chi-Square test/Fisher's Exact Test.

**Crude associations and odds ratios are presented.*

***Heart disease includes at least one of the following conditions: heart attack, atrial fibrillation, endarterectomy, bypass, pacemaker, and congestive heart disease.*

[δ]Vascular risks include at least one of the following: hypertension, dyslipidemia, diabetes and smoking history.

[δδ]TBI means traumatic brain injury which may include TBI with brief or extended loss consciousness.

[δδδ]One or more reported physical difficulty in activities of daily living requiring assistance from family.

TABLE 2 | Diagnosis of dementia subtypes in the incident cases.

Diagnosis	Total (%)	Male; *N* (%)	Female; *N* (%)	*p*-value
Alzheimer's disease (AD)	64 (79.0)	12 (57.1)	52 (86.7)	
Vascular dementia (VaD)	15 (18.5)	8 (38.1)	7 (11.7)	
Parkinson's Disease Dementia (PDD)	1 (1.2)	0 (0.0)	1 (1.7)	0.01
Dementia syndrome of depression	1 (1.2)	1 (4.8)	0 (0.0)	
Total	81 (100.0)	21 (100.0)	60 (100.0)	

p-value obtained using Chi-square test for comparison of proportions.

Dementia incidence was higher in females, with 17 (CI: 13–21) per 1,000 pyr compared to 14 (CI: 9–21) per 1,000 pyr for males (**Table 3**). Incidence rates increased with age, except for in males age 80 years and above.

Disability Adjusted Life Years

Mean total disease duration was 3.84 years (3.85 years for males and 3.83 for females). There were 24 recorded deaths, with 14 male and 10 female decedents. Using this number of deaths and the standard life expectancy for Filipinos, years of life lost (YLL) was calculated as 404 years (224 years for males and 180 years for females). Using the incident cases, duration of disease, and disability weights, the years lost due to disability (YLD) was 208 (54 for males and 154 for females). From this information, crude DALYs was estimated as 2,876 years per 100,000 persons, 4,891 per 100,000 persons for males and 2,142 per 100,000 persons for females (**Table 4**).

Cost of Care

The median direct medical cost for dementia care was Php 11,419.03 (USD 237.40) while direct non-medical cost was Php 316.00 (USD 6.57). Total median direct cost was therefore Php 11,016.50 (USD 229.03). Calculating for annual indirect costs accumulated through unpaid caregiving, the median indirect cost was Php 175,565.00 (USD 3,650). The sum of direct and indirect costs (total costs) was Php 188,381.98 (USD 3,916.47) per capita annually (**Table 5**). The majority (93.2%) of this care expense was indirect cost attributed to estimated lost potential earning of unpaid family caregivers whereas direct medical cost accounted for only 6.8%.

Representativeness and Projection

The cohort is demographically representative of senior citizens in the Philippines with respect to age (mean age of 70 years) and years of education (mean of 8.5 years) at study inception in 2015 (14). Geographically, it is representative of Filipino older persons residing in urban and semi-rural areas. The division of urban and rural dwelling in the Philippines was ∼50–50 in 2019 (22).

Dementia incidence was 16 cases per 1,000 pyr (95% CI: 12.7–19.6). Using the calculated incidence rate and projected senior

TABLE 3 | Age and gender-specific incidence rate for dementia (per 1,000 person-years).

Age (in years)	Total (*95% CI)	Female (*95% CI)	Male (*95% CI)	Rate ratio (*95% CI)
60–69	9.13 (5.99–13.38)	7.67 (4.37–12.56)	12.46 (6.33–22.21)	0.62 (0.25–1.55)
70–79	18.78 (13.48–25.52)	19.06 (12.91–27.18)	18.05 (9.17–32.18)	1.06 (0.50–2.44)
80 and above	41.82 (25.92–64.10)	54.80 (33.5–84.94)	7.94 (0.39–39.18)	6.90 (1.09–287.47)
Total	15.86 (12.68–19.62)	16.56 (12.75–21.17)	14.17 (9.00–21.29)	1.16 (0.70–2.02)

**Confidence intervals based on an Exact Poisson Distribution are shown in parentheses.*

TABLE 4 | Data for the computation of disability-adjusted life years.

Variables	Total	Male	Female
Marikina city seniors population (2015)*	21,275	5,684	15,591
Incident cases	81	21	60
Disability weights***	0.67	0.67	0.67
Average (SD) disease duration (in years)**	3.84 (0.30)	3.85 (0.30)	3.83 (0.31)
Number of deaths**	24	14	10
Life expectancy at 60(years)****	17	16	18
Years of life lost$^{\delta}$	404	224	180
Years lost due to disability$^{\delta\delta}$	208	54	154
DALY	612	278	334
DALY ('00000)$^{\delta\delta\delta}$	2,876	4,891	2,142

**Total size was obtained from Marikina City records, male/female distribution was estimated using sample proportions.*
***Obtained from this incidence cohort.*
****As per World Health Organization Global Burden of Disease.*
*****As per Institute of Health Metrics.*
$^{\delta}$Computed as the product of number of deaths and the standard life expectancy at the age of death.
$^{\delta\delta}$Computed as the product of incident cases by duration and disability weight of the condition.
*$^{\delta\delta\delta}$DALY ('00000) is [(YLL+YLD)/population size] * 100,000.*

citizens population, the Philippines has 149,606 new dementia cases in 2020 and will have 220,632 in 2030, 295,066 in 2040, and 378,461 in 2050 (23) (see **Supplementary Table 1a**).

DISCUSSION

This is the first large longitudinal community-based cohort study in the Philippines, first to establish prevalence and subsequently incidence of dementia, providing the first evidence-based data on disease-occurrence and burden. It is a wake- up call for policy makers, as dementia prevalence in the Philippines was shown to be the double of the estimate for South East Asia by World Alzheimer Report 2015. Furthermore, the current study showed that dementia incidence in the Philippines, at 16 per 1,000 pyr, is as high as in East Asia, where studies have shown an incidence rate of 13.50/1,000 pyr (1). This is close to the reported 14.06 per 1,000 pyr of the World Alzheimer Report (1) for LMIC. The projected number of new cases for 2020 in the Philippines makes up one quarter of the annual estimate for the whole South East Asia (1), and that number will increase by 50% in 2030 and 100% in 2040 (see **Supplementary Table 1a**). Using the prevalence rate derived from this cohort in 2011, the Philippines is projected to have total of 1,474,588 dementia cases in 2030, 1,972,067 in 2040 and 2,529,436 in 2050 (see **Supplementary Table 1b**). Clearly, this rapid and marked increase in dementia occurrence will pose a formidable burden on the healthcare system and the financial capacities of affected households. Currently, the Philippines has no social and health policies to address the dementia epidemic. In order to avoid an impending public health crisis, social and health care policy reform is urgently needed.

Consistent with the global trend, dementia incidence in this cohort increased with age, doubling at every 10-year age group. There was no gender-based difference in dementia incidence among younger participants (60–79 years old), but there was a gender difference in dementia incidence among older participants (80 and above). This is consistent with results from a large population cohort from the Netherlands where a striking decrease in incidence was also seen in males aged above 89 and females were more at-risk to develop dementia by 2.61 times (24). Such trends in women across the age groups (i.e., increasing over the years) and the shifting of males (i.e., more cases in the younger age groups then declining) were also present in a community-dwelling Brazilian cohort (25). In a systematic review for dementia studies across the globe on individuals 60 and over residing in the community, the pooled incidence rate (same age and setting) was 17.18 (95%: 13.90–21.23) per 1,000 person-years with estimates for females consistently higher than males (26).

Aside from age, we found lower years of education, presence of cognitive impairment, and reported difficulty with physical function at baseline to be associated with higher incident dementia. Low education is a risk factor with high weighted population attributable fraction (PAF) of dementia and an important target for dementia prevention intervention (27). In this cohort, disparity in education disproportionately affected females (see **Supplementary Table 2**). These latter results indicate that efforts to make early life education equally accessible to all citizens (up to at least a high school diploma, which was recently increased from 10 to 12 years of formal education in the Philippines) may be especially important for dementia prevention (28). Mean follow-up time of 3.9 years is similar to follow-up times from prior cohort studies from high-income countries (29).

Two thirds of the cohort had at least one vascular risk, with males having significantly more, e.g., higher number of strokes, smoking, and alcohol abuse (see **Supplementary Table 2**), consistent with the country's profile. These modifiable lifestyle-related factors such as smoking and alcohol drinking were seen

TABLE 5 | Cost of care of community-based patients with dementia.

Type of cost	Median (in USD*)	25th PCT (in USD*)	75th PCT (in USD*)	Minimum (in USD*)	Maximum (in USD*)
Aggregated direct costs[a]	229.03	62.98	546.09	0.15	2,999.53
Direct medical[b]	237.40	109.08	729.93	0.15	2,999.53
Direct non- medical costs[c]	6.56	3.07	16.32	1.16	28.07
Indirect costs[d]	3,650.00	3,650.00	3,650.00	0.8	18,250.00
Overall costs[e]	3,916.47	1,175.75	4,125.68	30.45	379.42

[a] *Includes Medical and Non-medical cost.*
[b] *Includes salary of caregiver; special diets; drugs; hospitalization costs; and rehabilitative aids.*
[c] *Includes transportation costs to health facilities.*
[d] *Potential earning capacity of unpaid caregivers.*
[e] *Aggregate of direct and indirect costs.*
Individual costs were computed per component, aggregated for the two major cost themes (direct and indirect) then all samples were summarized using median.
**48.1 Php = 1 USD (November 2020).*

to have gender-based differences since males were more likely to have such behaviors (30, 31). However, we did not find baseline vascular risks, stroke, or heart disease to be associated with incident dementia. In this cohort, incident vascular dementia—for which vascular risks, stroke and heart disease are relevant in terms of dementia pathology—was only 18%. This is likely due to the high mortality rate associated with stroke in the Philippines (32). On the other hand, it may also be hypothesized that vascular risks are managed well as Marikina is one of the cities that has a strong health program for its senior citizens. This can be verified in a future follow-up of the cohort.

With improving care for acute stroke, we expect to see more survivors and likely vascular dementia in younger and working populations < 60 years old in the future. The resulting disability will further contribute to increased dementia burden in the population. When incident cases, duration of disease, and disability weights were taken into account in our cohort, the years lost due to disability was 208 and the crude DALY rate was computed to be 2,876 per 100,000 persons (**Table 3**). Using this rate, our calculated DALY was 219,706. This is close to the estimated Philippine DALY value of 230,296 by the Global Burden of Disease (GBD) study 2016 (33). This is double of the estimated DALY for European countries (18). Dementias rank second in the global burden of disease among neurological disorders (34). Traditionally, health statistics and epidemiology place emphasis on mortality rather than disability of a disease entity, resulting in an underestimation of the burden of disabling neurological conditions such as dementia (35). The long-term and progressive disability from dementia is further complicated by a high economic burden in both formal and informal care, largely attributed to unpaid family caregivers in LMIC and to lost opportunity for participation in the labor force. Ironically, there is limited data on the economic costs of dementia in LMIC. This may be due to low priority given to mental health, an absence of trained health economists, and/or inadequate development of mental health services (36). This study revealed that the cost of informal care in the Philippines is exceptionally high, making up 86% of total cost, reflecting the enormous economic strain on the Filipino families. In comparison, the average estimated informal care cost for LMIC is ∼60% (1).

The current healthcare provision system in the Philippines is decentralized, with the Department of Health (DOH) serving as the governing agency and private sectors and local government units providing services to communities (37). The country's national health insurance program, Philippine Health Insurance Corporation (PhilHealth), and other health provision systems such as the Social Security System (SSS) cover for direct medical costs only during hospital admissions (38, 39). Even with government social welfare programs and compensations for medical costs, the affordability of Alzheimer's disease medications remains a challenge in the LMICs. With an affordability index (total number of units purchasable by one's daily income) of 0.8 tablet in the Philippines (40), national health insurance makes little difference in overall economic burden for affected individuals and families. The burden goes beyond direct medical costs because a large proportion of dementia care involves long-term residential care which results in informal costs exceeding formal costs. In our data, the average direct medical cost accounted for only 13.48% while indirect costs of care accounted for 86.29% (**Supplementary Table 3**). The median, minimum and maximum costs are presented in **Table 5**.

Moreover, direct medical cost was undoubtedly underestimated given that the majority of dementia cases in the cohort were diagnosed during the study and were not treated with anti-dementia drugs. There were no dementia-specific support services in place in the community for patients to access. Direct cost was related mainly to emergency hospitalization due to dementia-associated events such as falls, infections, and behavioral disturbances. As noted, overall cost of care was mainly attributed to indirect expenses. A major reason for this is that in the Philippines (and in many other LMIC), informal healthcare cost is driven by cultural factors, such as filial piety and obligatory care (41, 42) which removes family caretakers from the workforce. This is consistent with findings in other neighboring Asian countries where a family member cares for the patient with dementia (92.4% in the Philippines) (43). Indirect cost is further underestimated for caretakers who are

skilled workers and earning higher than minimum wage (i.e., >USD 10.9/day) and who are unable to work while providing care. Thus, the burden appears to be less on the formal healthcare system per se and more on the financial capacities of households. The data presented in our study therefore calls for an urgent need for government efforts to develop a national dementia care plan in line with recommendations of the World Health Organization to increase subsidy for direct costs and include social benefits and formal training for family caregivers.

Although some dementia prediction models developed in high-income countries may be extrapolated to developing countries, country-specific primary data is still very much needed in LMIC (44). This is a key contribution of our study which provides direct, instead of extrapolated, dementia incidence data. This is further strengthened by its use of repeated, longitudinal, and multi-modal assessments (participants were evaluated by a neurologist or geriatrician, and family informants were also interviewed).

LIMITATIONS

One limitation in this study is that about 35% ($N = 475$) of the eligible sample were lost to follow-up or were not included in the analysis due to incomplete data, similar to other LMIC cohorts (45). The main reason was mass migration from the city due to consecutive years of frequent flooding between 2012 and 2014. Nevertheless, analysis for selection bias showed insignificant differences between participants with and without follow-up in terms of age, education and cognitive impairment. Possible bias was only seen in terms of sex as the cohort in the baseline study was proportionally allocated based on residence. Since the subject population in this study is a follow-up of the baseline cohort, it should be noted that mostly males were lost to follow-up (**Supplementary Tables 4a,b**), resulting in the disparate sex distribution reported. Another limitation in this study is the lack of neuroimaging mainly due to high costs in a community-setting of such a sample size. In terms of DALY computation, there are no local data in the Philippines. The estimated life expectancy was therefore derived from the Institute of Health Metrics. Furthermore, there were also no DALY estimates for individual patients, hence we were unable to estimate the 95% confidence interval. For this study, we assumed that the global estimate is applicable to our setting. Lastly, since this is the first community-based cohort study of older adults in the Philippines, the population included was comparatively smaller with fewer risk factors examined than in other 10/66 Dementia Research Group LMIC cohorts. For future follow-up of the cohort, more recently identified risk factors targeted for dementia prevention, such as air pollution (27), a serious problem in LIMCs, will be taken into consideration.

CONCLUSION

We provide the first local community-based data on the incidence of dementia and dementia-related disability adjusted life years and cost of care in the Philippines. Dementia incidence and cost of care was close to estimates in other LMIC. Since informal (family) care is the cornerstone of dementia care in the Philippines, and since educational disparities appeared as a key risk factor for dementia, effective government initiatives for dementia prevention and care should target childhood education for all and assistance for family caregivers. Given the constraints of resource allocation in the LMIC as well as lack of programs geared toward cognitive decline and management of modifiable risk factors for the population of older adults, this study provides data for evidence-based healthcare planning in line with WHO recommendations.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by St. Luke's Institutional Ethics Review Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JaD and LJ conceptualized the research and methodology and acquired funding. JaD, LJ, MD, JD-A, BN, JeD, and JDD were responsible for data collection. KF, MR, and AL conducted the analysis. JaD, KF, and JY wrote the original draft of the manuscript. SA and TP supervised analysis and manuscript organization. All authors contributed to reviewing and editing the manuscript.

FUNDING

This study received funding from the Department of Science and Technology - Philippine Council for Health Research (FP-15001) and Development and St. Luke's Medical Center – Research and Biotechnology Division (No. 15-002).

ACKNOWLEDGMENTS

The study team acknowledges the important contribution of the Marikina Office of Senior Citizens Affairs, barangay local executives, barangay health workers, and the participants with their families to the success of this research.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.628700/full#supplementary-material

REFERENCES

1. Alzheimer's Disease International. *World Alzheimer's Report: The Global Impact of Dementia, an Analysis of Prevalence, Incidence, Cost and Trends*. Alzheimer's Disease International (ADI) (2015). Available online at: https://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf (accessed October 13, 2020).
2. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement.* (2013) 9:63–75.e2. doi: 10.1016/j.jalz.2012.11.007
3. Prince M, Acosta D, Ferri CP, Guerra M, Huang Y, Rodriguez JJL, et al. Dementia incidence and mortality in middle-income countries, and associations with indicators of cognitive reserve: a 10/66 Dementia Research Group population-based cohort study. *Lancet.* (2012) 380:50–8. doi: 10.1016/S0140-6736(12)60399-7
4. Philippine Statistics Authority. *Projected Population, by Age Group, Sex, and by Five-Calendar Year Interval, Philippines: 2010—2045*. (2017). Available online at: https://psa.gov.ph/sites/default/files/attachments/hsd/pressrelease/Table1_8.pdf (accessed October 30, 2017).
5. Ageing Population in the Philippines. *Help Age Network*. Available online at: https://ageingasia.org/ageing-population-philippines/ (accessed November 3, 2020).
6. Dominguez J, Fe de Guzman M, Reandelar M, Thi Phung TK. Prevalence of dementia and associated risk factors: a population-based study in the Philippines. Abe K, editor. *J Alzheimers Dis.* (2018) 63:1065–73. doi: 10.3233/JAD-180095
7. Dominguez JC, Orquiza MGS, Soriano JR, Magpantay CD, Esteban RC, Corrales ML, et al. Adaptation of the montreal cognitive assessment for elderly Filipino patients. *East Asian Arch Psychiatry.* (2013) 23:80–5. doi: 10.1037/t72215-000
8. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res.* (1982) 17:37–49. doi: 10.1016/0022-3956(82)90033-4
9. Kaufer DI, Cummings JL, Ketchel P, Smith V, MacMillan A, Shelley T, et al. Validation of the NPI-Q, a brief clinical form of the neuropsychiatric inventory. *J Neuropsychiatry Clin Neurosci.* (2000) 12:233–9. doi: 10.1176/jnp.12.2.233
10. Gelinas I, Gauthier L, McIntyre M, Gauthier S. Development of a functional measure for persons with Alzheimer's disease: the disability assessment for dementia. *Am J Occup Ther.* (1999) 53:471–81. doi: 10.5014/ajot.53.5.471
11. Galvin JE, Roe CM, Powlishta KK, Coats MA, Muich SJ, Grant E, et al. The AD8: a brief informant interview to detect dementia. *Neurology.* (2005) 65:559–64. doi: 10.1212/01.wnl.0000172958.95282.2a
12. Morris JC. Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. *Int Psychogeriatr.* (1997) 9:173–6. doi: 10.1017/S1041610297004870
13. Rosen WG, Terry RD, Fuld PA, Katzman R, Peck A. Pathological verification of ischemic score in differentiation of dementias. *Ann Neurol.* (1980) 7:486–8. doi: 10.1002/ana.410070516
14. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Text Revision (DSM-IV-TR). Washington, DC: American Psychiatric Association (2000).
15. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology.* (1984) 34:939. doi: 10.1212/WNL.34.7.939
16. Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord.* (2007) 22:1689–707. doi: 10.1002/mds.21507
17. McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor J-P, Weintraub D, et al. Diagnosis and management of dementia with Lewy bodies. *Neurology.* (2017) 89:88–100. doi: 10.1212/WNL.0000000000004058
18. Essink-Bot M-L, Pereira J, Packer C, Schwarzinger M, Burstrom K. Cross-national comparability of burden of disease estimates: the European Disability Weights Project. *Bull World Health Organ.* (2002) 80:644–52. Available online at: https://apps.who.int/iris/handle/10665/268577
19. World Health Organization. *Global Burden of Disease 2004 Update: Disability Weights for Diseases and Conditions*. Geneva: World Health Organization (2004).
20. Wang H, Naghavi M, Allen C, Barber RM, Bhutta ZA, Carter A, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet.* (2016) 388:1459–544. doi: 10.1016/S0140-6736(16)31012-1
21. Gail MH, Benichou J, Armitage PCT. *Encyclopedia of Epidemiologic Methods*. Wiley Reference Series in Biostatistics. West Sussex: John Wiley & Sons (2000).
22. Philippine Statistics Authority. *Updated Projected Mid-Year Population Based on 2015 POPCEN by Five-Year Age Group, Sex, Single-Calendar Year and by Province:2015–2025*. Quezon City: Philippine Statistics Authority (2015).
23. *Population Pyramids of the World From 1950 to 2100*. Available online at: https://www.populationpyramid.net/philippines/2050/ (accessed November 12, 2020).
24. Ruitenberg A, Ott A, van Swieten JC, Hofman A, Breteler MMB. Incidence of dementia: does gender make a difference? *Neurobiol Aging.* (2001) 22:575–80. doi: 10.1016/S0197-4580(01)00231-7
25. Nitrini R, Caramelli P, Herrera E, Bahia VS, Caixeta LF, Radanovic M, et al. Incidence of dementia in a community-dwelling Brazilian population. *Alzheimer Dis Assoc Disord.* (2004) 18:241–6.
26. Stephan Y, Sutin AR, Luchetti M, Terracciano A. Subjective age and risk of incident dementia: evidence from the National Health and Aging Trends survey. *J Psychiatr Res.* (2018) 100:1–4. doi: 10.1016/j.jpsychires.2018.02.008
27. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet.* (2020) 396:413–46. doi: 10.1016/S0140-6736(20)30367-6
28. Satizabal CL, Beiser AS, Chouraki V, Chêne G, Dufouil C, Seshadri S. Incidence of dementia over three decades in the Framingham Heart Study. *N Engl J Med.* (2016) 374:523–32. doi: 10.1056/NEJMoa1504327
29. Roehr S, Pabst A, Luck T, Riedel-Heller S. Is dementia incidence declining in high-income countries? A systematic review and meta-analysis. *Clin Epidemiol.* (2018) 10:1233–47. doi: 10.2147/CLEP.S163649
30. *17.3 Million Filipino Adults Are Current Tobacco Smokers (Final Results from the 2009 Global Adult Tobacco Survey)*. Philippine Statistics Authority (2010). Available online at: https://psa.gov.ph/content/173-million-filipino-adults-are-current-tobacco-smokers-final-results-2009-global-adult (accessed November 4, 2020).
31. *Global Alcohol Report: Philippine Profile*. World Health Organization (2018). Available online at: https://www.who.int/substance_abuse/publications/global_alcohol_report/profiles/phl.pdf?ua=1 (accessed Novemebr 4, 2020).
32. Navarro JC, Baroque AC, Lokin JK, Venketasubramanian N. The real stroke burden in the Philippines. *Int J Stroke.* (2014) 9:640–1. doi: 10.1111/ijs.12287
33. Nichols E, Szoeke CEI, Vollset SE, Abbasi N, Abd-Allah F, Abdela J, et al. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* (2019) 18:88–106. doi: 10.1016/S1474-4422(18)30403-4
34. Feigin VL, Vos T, Alahdab F, Amit AML, Bärnighausen TW, Beghi E, et al. Burden of neurological disorders across the US from 1990-2017. *JAMA Neurol.* (2020) 78:165–76. doi: 10.1001/jamaneurol.2020.4152
35. WHO. *Neurological Disorders: Public Health Challenges*. Geneva, Switzerland: WHO Press (2006).
36. Shah A, Murthy S, Suh G-K. Is mental health economics important in geriatric psychiatry in developing countries? *Int J Geriatr Psychiatry.* (2002) 17:758–64. doi: 10.1002/gps.696
37. Grundy J, Healy V, Gorgolon L, Sandig E. Overview of devolution of health services in the Philippines. *Rural Remote Health.* (2003) 3:220. doi: 10.22605/RRH220
38. Romualdez Jr. A, Rosa J, Flavier J, Quimbo S, Hartigan-Go K, Lagrada L, et al. *The Philippines Health System Review. Vol.1 No.2*. Manila: World Heal Organ Reg Off West Pacific. (2011)
39. Republic of the Philippines Social Security System. Available online at: www.sss.gov.ph (accessed November 8, 2020).

40. Suh G-H, Wimo A, Gauthier S, O'Connor D, Ikeda M, Homma A, et al. International price comparisons of Alzheimer's drugs: a way to close the affordability gap. *Int Psychogeriatr.* (2009) 21:1116–26. doi: 10.1017/S1041610209990086X
41. Win KK, Chong MS, Ali N, Chan M, Lim WS. Burden among family caregivers of dementia in the oldest-old: an exploratory study. *Front Med.* (2017) 4:205. doi: 10.3389/fmed.2017.00205
42. Dominguez JC, Fe P De Guzman M, Esteban RC, Laurilla JG. [P3-489]: in support of a national dementia plan: understanding dementia care in Filipino homes. *Alzheimers Dement.* (2017) 13:P1162–3. doi: 10.1016/j.jalz.2017.06.1708
43. Yang Y-H, Meguro K, Kim S-Y, Shim Y-S, Yu X, Chen CL-H, et al. Impact of Alzheimer's disease in nine Asian countries. *Gerontology.* (2016) 62:425–33. doi: 10.1159/000443525
44. Stephan BCM, Pakpahan E, Siervo M, Licher S, Muniz-Terrera G, Mohan D, et al. Prediction of dementia risk in low-income and middle-income countries (the 10/66 Study): an independent external validation of existing models. *Lancet Glob Heal.* (2020) 8:e524–35. doi: 10.1016/S2214-109X(20)30062-0
45. Peeters G, Almirall Sanchez A, Llibre Guerra J, Lawlor B, Kenny RA, Yaffe K, et al. Risk factors for incident dementia among older Cubans. *Front Public Heal.* (2020) 8:481. doi: 10.3389/fpubh.2020.00481

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 14 May 2021
doi: 10.3389/fneur.2021.610302

Severe Dementia Predicts Weight Loss by the Time of Death

*Aline Maria M. Ciciliati[1], Izabela Ono Adriazola[1], Daniela Souza Farias-Itao[2], Carlos Augusto Pasqualucci[2], Renata Elaine Paraizo Leite[2], Ricardo Nitrini[3], Lea T. Grinberg[2,4], Wilson Jacob-Filho[1] and Claudia Kimie Suemoto[1]**

[1] Discipline of Geriatrics, University of São Paulo Medical School, São Paulo, Brazil, [2] Department of Pathology, University of São Paulo Medical School, São Paulo, Brazil, [3] Department of Neurology, University of São Paulo Medical School, São Paulo, Brazil, [4] Department of Neurology and Pathology, Memory and Aging Center, University of California, San Francisco, San Francisco, CA, United States

Background: Body mass index (BMI) in midlife is associated with dementia. However, the association between BMI and late-life obesity is controversial. Few studies have investigated the association between BMI and cognitive performance near the time of death using data from autopsy examination. We aimed to investigate the association between BMI and dementia in deceased individuals who underwent a full-body autopsy examination.

Methods: Weight and height were measured before the autopsy exam. Cognitive function before death was investigated using the Clinical Dementia Rating (CDR) scale. The cross-sectional association between BMI and dementia was investigated using linear regression models adjusted for sociodemographic and clinical variables.

Results: We included 1,090 individuals (mean age 69.5 ± 13.5 years old, 46% women). Most participants (56%) had a normal BMI (18.5–24.9 kg/m²), and the prevalence of dementia was 16%. Twenty-four percent of the sample had cancer, including 76 cases diagnosed only by the autopsy examination. Moderate and severe dementia were associated with lower BMI compared with participants with normal cognition in fully adjusted models (moderate: $\beta = -1.92$, 95% CI $= -3.77$ to -0.06, $p = 0.042$; severe: $\beta = -2.91$, 95% CI $= -3.97$ to -1.86, $p < 0.001$).

Conclusion: BMI was associated with moderate and severe dementia in late life, but we did not find associations of BMI with less advanced dementia stages.

Keywords: dementia, cognitive decline, body mass index, weight loss, epidemiology, aging

OPEN ACCESS

Edited by:
Christopher Butler, University of Oxford, United Kingdom

Reviewed by:
Jiu Chen, Nanjing Medical University, China
Chandra A. Reynolds, University of California, Riverside, United States

****Correspondence:***
Claudia Kimie Suemoto
cksuemoto@usp.br

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: *25 September 2020*
Accepted: *30 March 2021*
Published: *14 May 2021*

Citation:
Ciciliati AMM, Adriazola IO, Souza Farias-Itao D, Pasqualucci CA, Leite REP, Nitrini R, Grinberg LT, Jacob-Filho W and Suemoto CK (2021) Severe Dementia Predicts Weight Loss by the Time of Death. Front. Neurol. 12:610302. doi: 10.3389/fneur.2021.610302

INTRODUCTION

Dementia affects 46 million people worldwide, and 58% of these people live in low-/middle-income countries (1). Obesity is a known risk factor for dementia, but dementia itself can also affect body weight through changes in appetite and other behavioral problems (2). Body mass index (BMI) is an easy measure to assess nutritional status. Besides, BMI has a strong correlation with total-body and visceral adiposity (3).

In several studies, overweight and obesity evaluated with BMI in midlife (between the fifth and the sixth decades of life) were linked to worse cognitive performance (4–16). However, in older individuals, BMI was not associated with higher dementia risk in some studies,

and even higher BMI values were related to lower dementia risk (9, 11, 15, 17). These unexpected findings could be due to reverse causation, as dementia has an insidious onset and a long and asymptomatic preclinical phase, and the weight loss may be secondary to the cognitive and neuropsychiatric changes that occur early during the disease course (11, 12, 18). Survival bias could be another possible explanation since individuals with higher BMI may not survive until old age to develop dementia symptoms, as they suffer a higher burden of cardiovascular disease (8). Another reason for BMI to be found to be protective against dementia could be the presence of consumptive conditions (e.g., cancer), which lead to weight loss, but were not fully adjusted in previous studies (6, 7, 17, 19). Indeed, the presence of undiagnosed cancer could bias the association between BMI and adverse health outcomes (20). Therefore, we investigated the relationship between BMI near the time of death and cognitive performance in 1,090 deceased individuals submitted to a full-body autopsy, which allowed the detection of undiagnosed cancer.

METHODS

Participants

This study used the Biobank for Aging Studies (BAS) collection from the University of São Paulo Medical School (Brazil). Data were collected at the São Paulo Autopsy Service that receives individuals who died from non-traumatic deaths and required a full-body autopsy to determine the cause of death (21). Trained nurses/gerontologists interviewed family members using a semistructured questionnaire that included sociodemographic variables, clinical history, and functional and cognitive assessments. To ensure data reliability, informants had to have at least weekly contact with the deceased (22). Exclusion criteria for the BAS are individuals with macroscopic cerebral lesions that required brain examination by the pathologist to determine the cause of death or the presence of severe acidosis ($pH < 6.5$) (21).

For this study, we also excluded individuals under 50 years old, those with incomplete data on weight, height, the Clinical Dementia Rating (CDR) scale, or covariates. Body weight was obtained using an electronic scale, and height was measured with a stadiometer with the deceased individuals in the supine position without clothes and shoes (23). All participants underwent a full-autopsy exam. Assessment of the death certificates was carried out to include possible cases of undiagnosed cancer during life. The local ethical committee approved the research (protocol number 04655612.9.0000.0065), and family members of the deceased signed an informed consent document.

Cognitive Evaluation

The CDR is an extensively validated instrument, translated into several languages (24). It is based on clinical symptoms of dementia, not depending on any other psychometric test for its application. It can be applied by non-medical professionals and offers different modes of interpretation, including the possibility of comparative use of a patient's total score over the years (25). It classifies cognitive performance into six categories (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care) through a semistructured interview applied to the individual and an informant. By design, we only used the informant part of the CDR in this study. CDR scores range from 0 (no dementia) to 0.5 (questionable dementia), 1 (mild dementia), 2 (moderate dementia), and 3 (severe dementia) (24). The scoring system is based on individual scores of all categories. Memory was considered the primary category, and others are secondary. It is also possible to compute the total CDR sum of the boxes (CDR-SOB) score by summing the points in each of the six cognitive ability categories (26, 27). The CDR-SOB scores range from 0 to 18.

Covariates

Possible confounders for the association of BMI and CDR were age, sex (male or female), race (White, Black, or Asian), years of education, physical inactivity (defined by <three times of physical activity per week), alcohol use (never consumed any alcohol, current or previous history of alcohol use), current smoking (never smoked, current smoker, or previous use of tobacco), and history of previous medical diagnosis of hypertension, diabetes, coronary heart disease, heart failure, and cancer, which was later compared to death certificates to identify possible non-diagnosed cases during the lifetime.

Statistical Analysis

We compared BMI categories with categorical variables using the chi-square test and continuous variables using one-way ANOVA or the Kruskal–Wallis tests. We hypothesized that dementia presence and severity would determine weight at the time of death. Therefore, we used a linear regression in which the predictor variable was the CDR categories, and the outcome was the measured BMI (**Table 1**). Age, sex, race, education, hypertension, diabetes mellitus, heart failure, dyslipidemia, cancer, sedentary lifestyle, smoking, and alcohol use were considered confounding factors in the association between BMI and CDR. Besides, we performed a sensitivity analysis for this association using the CDR sum of boxes as the outcome. Moreover, since cancer and current smoking could be a strong predictor of BMI (28), we conducted an additional sensitivity analysis excluding participants with these conditions and using adjusted linear models for the same set of covariates.

To explore the diversity of race/ethnicity in our sample, we investigated whether the association between BMI and cognition was different between Black and White participants. For this analysis, we excluded Asians ($n = 35$) and created an interaction term between race and CDR. In addition, we conducted stratified analyses by race for the association between BMI and CDR. Statistical analysis was performed with STATA 15 (StataCorp. 2017, College Station, TX). The level of significance was set at 0.05 in two-tailed tests.

RESULTS

A total of 1,090 participants were included in this study. The final sample consisted mostly of men (55%), with a mean age of 69.5 ± 13.5 years old and median educational attainment of

TABLE 1 | Sociodemographic and clinical characteristics by body mass index (BMI) categories (n = 1,090).

BMI (kg/m^2)	All N = 1,090	<18.5 N = 163	18.5–24.9 N = 569	25–29.9 N = 241	>30 N = 117	p
Age* (years),	69.5	74.5	71.0	65.5	63.3	<0.001
mean (SD)	(13.5)	(13.3)	(13.3)	(12.5)	(12)	
Male†, %	54.5	49.0	59.4	53.1	41.8	0.001
Race†, %						0.055
White	65.4	55.8	66.2	68.4	66.6	
Black	31.3	38.6	30.4	28.2	32.4	
Asian	3.2	5.5	3.1	3.3	0.8	
Education** (years),	4.0	4.0	4.0	4.0	4.0	0.005
median (range)	(0–22)	(0–22)	(0–15)	(0–20)	(0–18)	
Physical inactivity†, %	60.0	80.3	58.3	50.6	58.9	0.572
Hypertension†, %	62.0	42.3	59.2	73.0	80.3	<0.001
Diabetes†, %	30.4	25.1	26.3	36.5	45.2	<0.001
Coronary artery disease†, %	19.8	6.7	18.4	28.6	26.4	<0.001
Heart failure†, %	17.8	6.1	17.7	21.5	27.3	<0.001
Dyslipidemia†, %	12.4	9.8	9.4	19.0	17.0	<0.001
Cancer†, %	24.4	34.3	26.0	17.8	16.2	<0.001
Smoking†, %						0.688
Current	29.0	27.6	30.4	30.22	22.2	
Previous	25.9	29.4	24.7	26.9	24.7	
Never	44.9	42.9	44.8	42.7	52.9	
Alcohol use†, %						0.018
Current	29.2	23.3	29.3	32.7	29.9	
Previous	17.6	24.5	18.1	15.7	7.6	
Never	53.1	52.1	52.3	51.4	61.5	

*One-way ANOVA.
**Kruskal–Wallis test.
†Chi-square test.

4 years (range: 0–22 years). The most frequent clinical conditions were hypertension (62%), diabetes (31%), and physical inactivity (60%) (**Table 1**). The majority of the sample had a normal BMI (52%) with a mean BMI of 23.5 ± 5.5 kg/m^2 (**Figure 1**). The prevalence of cognitive impairment (CDR ≥ 1) was 16%. Approximately 24% of individuals were diagnosed with cancer, and 76 (7%) of the cancers were detected during the autopsy exam only.

We observed that underweight was associated with older age, while obesity (BMI > 30 kg/m^2) was more prevalent in younger individuals. Men had a lower BMI, accounting for almost 60% of malnourished individuals. Higher education level was associated with higher BMI, and Black individuals had, on average, lower BMI than White individuals (**Table 1**). Regarding clinical characteristics, hypertension, diabetes, coronary artery disease, heart failure, and dyslipidemia were associated with overweight and obesity (**Table 1**). Alcohol use was associated with lower BMI levels (**Table 1**).

In the unadjusted model, we did not observe BMI differences among participants with normal cognition, questionable dementia, and mild dementia, while moderate and severe dementia were associated with lower BMI (moderate dementia: $\beta = -2.77$, 95% CI = −4.73 to −0.81, $p = 0.005$; severe dementia: $\beta = -4.47$, 95% CI = −5.49 to −3.45, $p < 0.001$) (**Table 2**). Even after adjusting the analysis for all confounding variables, these associations remained significant. Compared

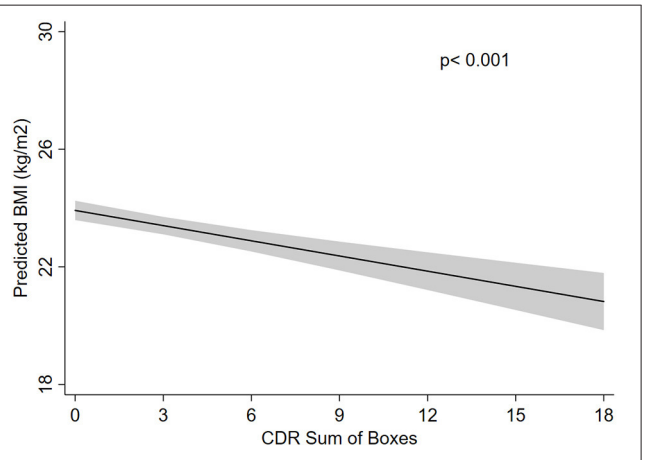


FIGURE 1 | Absolute frequency of participants regarding the Clinical Dementia Rating (CDR) scores and body mass index (BMI) categories.

TABLE 2 | Association between body mass index (BMI) and clinical dementia rating (CDR) categories ($n = 1,090$).

	Crude		Model 1		Model 2	
	β (95% CI)	***p***	**β (95% CI)**	***p***	**β (95% CI)**	***p***
CDR 0.5	−0.89 (−2.53; 0.75)	0.286	−0.41 (−2.01; 1.20)	0.620	−0.84 (−2.39; 0.71)	0.288
CDR 1	−0.65 (−2.54; 1.25)	0.502	0.40 (−1.48; 2.27)	0.678	0.04 (−1.76; 1.84)	0.965
CDR 2	−2.77 (−4.73; −0.81)	0.005	−2.02 (−3.96; −0.09)	0.039	−1.92 (−3.77; −0.06)	0.042
CDR 3	−4.47 (−5.49; −3.45)	<0.001	−3.47 (−4.52; −2.42)	<0.001	−2.91 (−3.97; −1.86)	<0.001

Reference: CDR 0 (without dementia).
CDR 0.5 (questionable dementia), CDR 1 (mild dementia), CDR 2 (moderate dementia), and CDR 3 (severe dementia).
Model 1: linear regression model, adjusted for age, sex, race, and education.
Model 2: linear regression model, adjusted for age, sex, race, education, hypertension, diabetes, coronary artery disease, heart failure, dyslipidemia, cancer, physical inactivity, alcohol use, and smoking.

with participants with normal cognition, participants with moderate dementia had on average 1.92 kg/m^2 of BMI less than participants without dementia ($\beta = -1.92$, 95% CI $= -3.77$ to -0.06, $p = 0.042$). Participants with severe dementia had on average 2.91 kg/m^2 less than those with normal cognition ($\beta = -2.91$, 95% CI $= -3.97$ to -1.86, $p < 0.001$) (**Table 2**). Association between BMI and all covariates is presented in **Supplementary Table 1**. Age, education, heart failure, cancer, and current alcohol use were related to BMI.

We performed two different sensitivity analyses that confirm our finding. We first excluded participants with a cancer diagnosis or current smoking. The exclusion of these participants did not change our results (moderate dementia: $\beta = -2.24$, 95% CI $= -4.48$ to 0.06, $p = 0.044$; severe dementia: $\beta = -3.16$, 95% CI $= -4.52$ to -1.85, $p < 0.001$) (**Table 3**). In another approach, we used the CDR sum of boxes as the exposure variable, and we found on average a 0.178-kg/m^2 decrease in BMI for each 1-unit increase in the CDR sum of boxes in the fully adjusted model ($\beta = -0.178$, 95% CI $= -0.238$ to -0.119, $p < 0.001$) (**Figure 2**).

We also investigated the interaction between race and CDR on BMI values. We did not find a significant interaction between race and CDR ($p = 0.328$). Moreover, we found similar associations between CDR and BMI in White and Black participants in stratified analyses by race, with lower BMI values among participants with severe dementia compared with participants with normal cognition (**Supplementary Table 2**).

DISCUSSION

We found an association of BMI with moderate and severe dementia, suggesting that individuals with more advanced dementia are more likely to have lower body weight by the time of death. We did not find associations between BMI and early dementia stages. When we excluded individuals with cancer and current smokers, moderate and severe dementia were still associated with lower BMI. Moreover, we did not find evidence of interaction between race and cognitive status on BMI.

The relationship between BMI and dementia varies along the life course. In middle-aged adults, obesity was linked to brain atrophy (29), worse cognitive performance, and higher mortality (30, 31). This association may be explained by diverse pathophysiological pathways, including systemic and central nervous system inflammation (32), triggered by the production of hormones like leptin and other inflammatory cytokines (e.g., tumor necrosis factor-α and interleukins) by the adipose tissue. After long-term exposure, inflammation is believed to damage cerebral arteries, raising the risk for vascular dementia and Alzheimer's disease (30, 33–39). In animal models, intestinal microbiota dysbiosis linked to obesity also stimulates the neuroinflammatory response, but human data regarding this hypothesis are still lacking (35).

On the other hand, obesity was not associated with higher dementia risk in late life, while lower BMI was related to higher dementia risk (8, 9, 11, 15). Along with these findings, we found that moderate and severe dementia were related to lower BMI. One possible explanation for the lower BMI to be related to dementia could be reverse causation. Even decades before the dementia diagnosis, deposition of beta-amyloid and tau proteins in the olfactory bulb leads to impaired smelling capacity. In addition, the deposition of beta-amyloid protein on the hypothalamic nuclei is among the earliest neuropathological changes in Alzheimer's disease (36). The impaired smell sensibility can impact food tasting, decreased calorie intake, and lead to weight loss (37, 38). Deposition of beta-amyloid proteins in areas of the brain responsible for energy and hunger regulation can also decrease hormones, like leptin, cholecystokinin, and serotonin. Phosphorylated tau proteins are also linked to the avoidance of high-fat diets, related to higher BMI (39). However, we did not find that early dementia stages were related to lower BMI, only moderate and advanced dementia were associated with lower BMI values. These findings could be caused by neuropsychiatric symptoms that are common among individuals with more advanced dementia stages. Depressive symptoms often include appetite loss and apathy and the absence of motivation or initiative to obtain food and eat (18). Besides, the disturbance of neurons that produce neurotransmitters (e.g., norepinephrine) may result in anxiety and appetite dysfunction (38). Besides, patients with moderate and advanced dementia are at least partially dependent on basic activities of daily life, such as obtaining and cooking food (19). Another crucial factor to consider is dysphagia. A systematic review showed that 57% of patients with advanced dementia had dysphagia, which is an important cause of

TABLE 3 | Association between body mass index (BMI) and clinical dementia rating (CDR) categories, excluding participants with cancer and current smokers ($n = 575$).

	Crude		Model 1		Model 2	
	β (95% CI)	***p***	**β (95% CI)**	***p***	**β (95% CI)**	***p***
CDR 0.5	1.64 (−3.71; 0.42)	0.119	−1.18 (−3.16; 0.80)	0.242	−1.12 (−3.07; 0.83)	0.258
CDR 1	−2.60 (−5.07; 0.14)	0.039	−1.19 (−3.60; 1.22)	0.332	−1.04 (−3.40; 1.32)	0.387
CDR 2	−3.71 (−6.00; −1.42)	0.002	−2.63 (−4.84; −0.42)	0.019	−2.24 (−4.48; −0.06)	0.044
CDR 3	−5.21 (−6.48; −3.94)	<0.001	−3.95 (−5.22; −2.68)	<0.0001	−3.16 (−4.52; −1.85)	<0.0001

Reference: CDR 0 (without dementia).
CDR 0.5 (questionable dementia), CDR 1 (mild dementia), CDR 2 (moderate dementia), and CDR 3 (severe dementia).
Model 1: linear regression model, adjusted for age, sex, race, and education.
Model 2: linear regression model, adjusted for age, sex, race, education, hypertension, diabetes, coronary artery disease, heart failure, dyslipidemia, physical inactivity, and alcohol use.

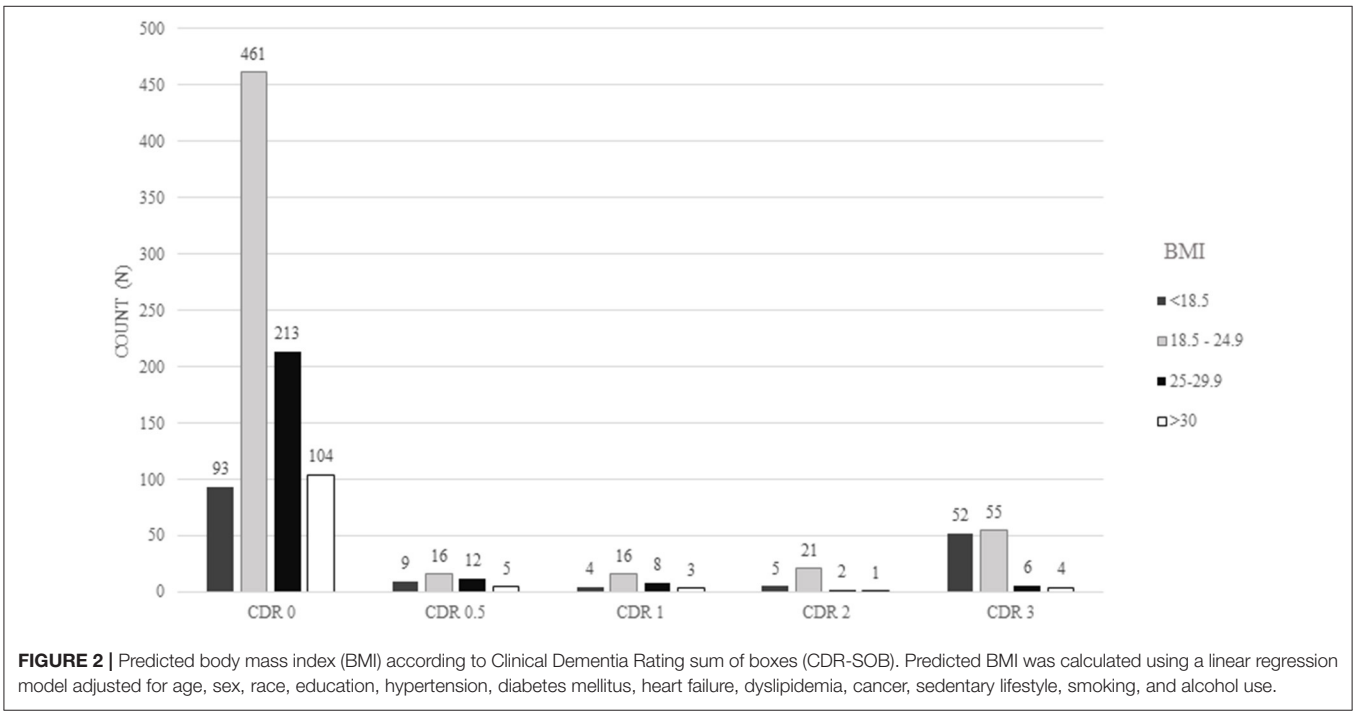


FIGURE 2 | Predicted body mass index (BMI) according to Clinical Dementia Rating sum of boxes (CDR-SOB). Predicted BMI was calculated using a linear regression model adjusted for age, sex, race, education, hypertension, diabetes mellitus, heart failure, dyslipidemia, cancer, sedentary lifestyle, smoking, and alcohol use.

weight loss, malnutrition, dehydration, and additional functional loss (40).

A fundamental aspect of our study is that we could include data from the autopsy examination, while most studies on the association between BMI and dementia used clinical data (8, 9, 12). We were able to detect 76 additional cancer cases, which increased the frequency of neoplasms from 20 to 24% in our sample. The investigation of consumptive diseases like cancer is of paramount importance when studying the effect of BMI on health outcomes. Cancer is associated with severe inflammation and cachexia syndrome that lead to weight loss (41–44). Another strength of our study is that the data were collected at the São Paulo Autopsy Service, a general autopsy service. Therefore, most participants do not have cognitive impairment or have mild symptoms of dementia, which more accurately represent community-dwelling adults regarding dementia prevalence and severity. Another advantage is that this study was conducted in a sample with diverse races compared with other studies based on North American, European, and Asian populations (8, 9, 11, 14). Dementia risk seems to be higher in African Americans compared with non-Hispanic Whites (45). Since Brazil is a multiracial country (46), we were able to explore whether the association between BMI and cognition differed by race. Severe dementia was related to lower BMI in both White and Black participants, but we did not find an effect modification by race in this association.

Nonetheless, our study needs to be considered in light of its limitations. The cross-sectional design does not allow establishing cause–effect relationships. Moreover, despite extensive literature showing a high correlation between BMI and body adiposity (41), we did not directly measure body adipose composition. Instead, we used BMI, which is easy to perform in clinical settings and is correlated with body adiposity (3). Finally, we do not have available information on the neuropathological examination of these cases at this moment.

Our main finding was that individuals with moderate and severe stages of dementia had lower BMI, in agreement with previous studies (4–12, 16). However, no significant association was found with earlier dementia stages. Our study contributes to understanding the association between BMI and dementia at the end of life, including the information of undiagnosed cancer during life that could have contributed to weight loss unrelated to dementia. Further studies are needed to establish the pathophysiology and mechanisms directly leading to weight loss from preclinical to advanced dementia.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of São Paulo's ethical committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AC: Conception and design, data collection, data analysis, drafting, revision and final approval of the version to be published. IA: Conception and design, drafting, revision and final approval of the version to be published. DS, CP, RL, RN, and LG: Revision and final approval of the version to be published. WJ-F: Conception and design, data collection, data analysis, drafting, revision and final approval of the version to be published. CS: Conception and design, data analysis, revision and final approval of the version to be published. All authors contributed to the article and approved the submitted version.

FUNDING

This study received the following grants: FAPESP 06/55318-1, FAPESP 2013/12290-3, and 2017/24066-1 (to DS) and NIH K24AG053435 (to LG).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.610302/full#supplementary-material

REFERENCES

1. Wimo A, Prince M. *Alzheimer's Disease International World Alzheimer Report 2010 The Global Economic Impact of Dementia*. London: Alzheimer's Disease International (2010), p. 56.
2. Müller S, Preische O, Sohrabi HR, Gräber S, Jucker M, Dietzsch J, et al. Decreased body mass index in the preclinical stage of autosomal dominant Alzheimer's disease. *Sci Rep*. (2017) 7:1225. doi: 10.1038/s41598-017-01327-w
3. World Health Organization. WHO Expert Committee on physical status: the use and interpretation of anthropometry: report of a WHO Expert Committee (1995).
4. Gustafson DR, Bäckman K, Joas E, Waern M, Östling S, Guo X, et al. 37 Years of body mass index and dementia: observations from the prospective population study of women in Gothenburg, Sweden. *J Alzheimers Dis*. (2012) 28:163–71. doi: 10.3233/JAD-2011-110917
5. Cova I, Clerici F, Maggiore L, Pomati S, Cucumo V, Ghiretti R, et al. Body mass index predicts progression of mild cognitive impairment to dementia. *Dement Geriatr Cogn Disord*. (2016) 41:172–80. doi: 10.1159/000444216
6. Qizilbash N, Gregson J, Johnson ME, Pearce N, Douglas I, Wing K, et al. BMI and risk of dementia in two million people over two decades: a retrospective cohort study. *Lancet Diabetes Endocrinol*. (2015) 3:431–6. doi: 10.1016/S2213-8587(15)00033-9
7. Whitmer RA, Gustafson DR, Barrett-Connor E, Haan MN, Gunderson EP, Yaffe K. Central obesity and increased risk of dementia more than three decades later. *Neurology*. (2008) 71:1057–64. doi: 10.1212/01.wnl.0000306313.89165.ef
8. Singh-Manoux A, Dugravot A, Shipley M, Brunner EJ, Elbaz A, Sabia S, et al. Obesity trajectories and risk of dementia: 28 years of follow-up in the Whitehall II Study. *Alzheimers Dement*. (2018) 14:178–86. doi: 10.1016/j.jalz.2017.06.2637
9. Kivimäki M, Luukkonen R, Batty GD, Ferrie JE, Pentti J, Nyberg ST, et al. Body mass index and risk of dementia: analysis of individual-level data from 1.3 million individuals. *Alzheimers Dement*. (2018) 14:601–9. doi: 10.1016/j.jalz.2017.09.016
10. Albanese E, Taylor C, Siervo M, Stewart R, Prince MJ, Acosta D. Dementia severity and weight loss: a comparison across eight cohorts. The 10/66 study. *Alzheimers Dement*. (2013) 9:649–56. doi: 10.1016/j.jalz.2012.11.014
11. Suemoto CK, Gilsanz P, Mayeda ER, Glymour MM. Body mass index and cognitive function: the potential for reverse causation. *Int J Obes*. (2015) 39:1383–9. doi: 10.1038/ijo.2015.83
12. Anstey KJ, Cherbuin N, Budge M, Young J. Body mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies: BMI and risk of dementia. *Obes Rev*. (2011) 12:e426–37. doi: 10.1111/j.1467-789X.2010.00825.x
13. Xu WL, Atti AR, Gatz M, Pedersen NL, Johansson B, Fratiglioni L. Midlife overweight and obesity increase late-life dementia risk: a population-based twin study. *Neurology*. (2011) 76:1568–74. doi: 10.1212/WNL.0b013e3182190d09
14. Hassing LB, Dahl AK, Thorvaldsson V, Berg S, Gatz M, Pedersen NL, et al. Overweight in midlife and risk of dementia: a 40-year follow-up study. *Int J Obes*. (2009) 33:893–8. doi: 10.1038/ijo.2009.104
15. Dahl AK, Löppönen M, Isoaho R, Berg S, KivelÃ¤ S-L. Overweight and obesity in old age are not associated with greater dementia risk: (see editorial comments by Dr. David S. Knodman, pp 2349–2350). *J Am Geriatr Soc*. (2008) 56:2261–6. doi: 10.1111/j.1532-5415.2008.01958.x
16. Albanese E, Launer LJ, Egger M, Prince MJ, Giannakopoulos P, Wolters FJ, et al. Body mass index in midlife and dementia: systematic review and meta-regression analysis of 589,649 men and women followed in longitudinal studies. *Alzheimers Dement Diagn Assess Dis Monit*. (2017) 8:165–78. doi: 10.1016/j.dadm.2017.05.007
17. Luchsinger J, Cheng D, Tang M, Schupf N, Mayeux R. Central obesity in the elderly is related to late onset Alzheimer's disease. *Alzheimer Dis Assoc Disord*. (2012) 26:101–5. doi: 10.1097/WAD.0b013e318222f0d4
18. Brodaty H, Heffernan M, Draper B, Reppermund S, Kochan NA, Slavin MJ, et al. Neuropsychiatric symptoms in older people with and without cognitive impairment. *J Alzheimers Dis*. (2012) 31:411–20. doi: 10.3233/JAD-2012-120169
19. Alhurani RE, Vassilaki M, Aakre JA, Mielke MM, Kremers WK, Machulda MM, et al. Decline in weight and incident mild cognitive

impairment: mayo clinic study of aging. *JAMA Neurol.* (2016) 73:439. doi: 10.1001/jamaneurol.2015.4756
20. Banack HR, Kaufman JS, Wactawski-Wende J, Troen BR, Stovitz SD. Investigating and remediating selection bias in geriatrics research: the selection bias toolkit. *J Am Geriatr Soc.* (2019) 67:1970–6. doi: 10.1111/jgs.16022
21. Brazilian Aging Brain Study Group, Grinberg LT, de Lucena Ferretti RE, Farfel JM, Leite R, Pasqualucci CA, et al. Brain bank of the Brazilian aging brain study group—a milestone reached and more than 1,600 collected brains. *Cell Tissue Bank.* (2007) 8:151–62. doi: 10.1007/s10561-006-9022-z
22. Jorm AF. Methods of screening for dementia: a meta-analysis of studies comparing an informant questionnaire with a brief cognitive test. *Alzheimer Dis Assoc Disord.* (1997) 11:158–62. doi: 10.1097/00002093-199709000-00008
23. Nishizawa A, Suemoto CK, Farias-Itao DS, Campos FM, Silva KCS, Bittencourt MS, et al. Morphometric measurements of systemic atherosclerosis and visceral fat: evidence from an autopsy study. *PLoS ONE.* (2017) 12:e0186630. doi: 10.1371/journal.pone.0186630
24. Fagundes Chaves ML, Camozzato AL, Godinho C, Kochhann R, Schuh A, de Almeida VL, et al. Validity of the clinical dementia rating scale for the detection and staging of dementia in Brazilian patients. *Alzheimer Dis Assoc Disord.* (2007) 21:210–7. doi: 10.1097/WAD.0b013e31811ff2b4
25. Isella V. Discriminative and predictive power of an informant report in mild cognitive impairment. *J Neurol Neurosurg Psychiatry.* (2006) 77:166–71. doi: 10.1136/jnnp.2005.069765
26. Morris JC. The clinical dementia rating (cdr): current version and scoring rules. *Neurology.* (1993) 43:2412. doi: 10.1212/WNL.43.11.2412-a
27. O'Bryant SE. Staging dementia using clinical dementia rating scale sum of boxes scores: a Texas Alzheimer's research consortium study. *Arch Neurol.* (2008) 65:1091. doi: 10.1001/archneur.65.8.1091
28. Bowman K, Thambisetty M, Kuchel GA, Ferrucci L, Melzer D. Obesity and longer term risks of dementia in 65–74 year olds. *Age Ageing.* (2019) 48:367–73. doi: 10.1093/ageing/afz002
29. Driscoll I, Gaussoin SA, Wassertheil-Smoller S, Limacher M, Casanova R, Yaffe K, et al. Obesity and structural brain integrity in older women: the women's health initiative magnetic resonance imaging study. *J Gerontol A Biol Sci Med Sci.* (2016) 71:1216–22. doi: 10.1093/gerona/glw023
30. Bischof GN, Park DC. Obesity and aging: consequences for cognition, brain structure, and brain function. *Psychosom Med.* (2015) 77:697–709. doi: 10.1097/PSY.0000000000000212
31. Pedditizi E, Peters R, Beckett N. The risk of overweight/obesity in mid-life and late life for the development of dementia: a systematic review and meta-analysis of longitudinal studies. *Age Ageing.* (2016) 45:14–21. doi: 10.1093/ageing/afv151
32. Jagust W, Harvey D, Mungas D, Haan M. Central obesity and the aging brain. *Arch Neurol.* (2005) 62:1545–8. doi: 10.1001/archneur.62.10.1545
33. Dorrance A, Matin N, Pires P. The effects of obesity on the cerebral vasculature. *Curr Vasc Pharmacol.* (2014) 12:462–72. doi: 10.2174/15701611126661404232224 11
34. Lampe L, Zhang R, Beyer F, Huhn S, Kharabian-Masouleh S, Preusser S, et al. Visceral obesity relates to deep white matter hyperintensities via inflammation. *Ann Neurol.* (2018) 82:194–203. doi: 10.1002/ana.25396
35. Ticinesi A, Tana C, Nouvenne A, Prati B, Lauretani F, Meschi T. Gut microbiota, cognitive frailty and dementia in older individuals: a systematic review. *Clin Interv Aging.* (2018) 13:1497–511. doi: 10.2147/CIA.S139163
36. Ishii M, Iadecola C. Metabolic and non-cognitive manifestations of Alzheimer's disease: the hypothalamus as both culprit and target of pathology. *Cell Metab.* (2015) 22:761–76. doi: 10.1016/j.cmet.2015.08.016
37. Devanand DP. Olfactory identification deficits, cognitive decline, and dementia in older adults. *Am J Geriatr Psychiatry.* (2016) 24:1151–7. doi: 10.1016/j.jagp.2016.08.010
38. Ehrenberg AJ, Suemoto CK, França Resende E de P, Petersen C, Leite REP, Rodriguez RD, et al. Neuropathologic correlates of psychiatric symptoms in Alzheimer's disease. *J Alzheimers Dis.* (2018) 66:115–26. doi: 10.3233/JAD-180688
39. Morley JE. Anorexia of aging: physiologic and pathologic. *Am J Clin Nutr.* (1997) 66:760–73. doi: 10.1093/ajcn/66.4.760
40. Alagiakrishnan K, Bhanji RA, Kurian M. Evaluation and management of oropharyngeal dysphagia in different types of dementia: a systematic review. *Arch Gerontol Geriatr.* (2013) 56:1–9. doi: 10.1016/j.archger.2012.04.011
41. Yavuzsen T, Davis MP, Walsh D, LeGrand S, Lagman R. Systematic review of the treatment of cancer-associated anorexia and weight loss. *Centre Rev. Dissemination.* (2005) 83:1345–50. doi: 10.1093/ajcn/83.6.1345
42. Fearon KC, Voss AC, Hustead DS. Definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. *Am J Clin Nutr.* (2006) 83:1345–50.
43. Langer CJ, Hoffman JP, Ottery FD. Clinical significance of weight loss in cancer patients: rationale for the use of anabolic agents in the treatment of cancer-related cachexia. *Nutrition.* (2001) 17:S1–21. doi: 10.1016/S0899-9007(01)80001-0
44. Hernandez JL, Matorras P, Riancho JA, Gonzalez-Macias J. Involuntary weight loss without specific symptoms: a clinical prediction score for malignant neoplasm. *QJM.* (2003) 96:649–55. doi: 10.1093/qjmed/hcg107
45. Shadlen M-F, Siscovick D, Fitzpatrick AL, Dulberg C, Kuller LH, Jackson S. Education, cognitive test scores, and black-white differences in dementia risk: education, race, and dementia. *J Am Geriatr Soc.* (2006) 54:898–905. doi: 10.1111/j.1532-5415.2006.00747.x
46. IBGE. Coordenação de Trabalho e Rendimento. Pesquisa Nacional por Amostra de Domicílios Contínua 2012/2019. Vol. Complemento F. (2020).

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

BRIEF RESEARCH REPORT
published: 02 June 2021
doi: 10.3389/fneur.2021.628876

Challenges for Diagnostic Clarity for Post-stroke Cognitive Impairment and Behavioural Issues in Middle-Income Countries: Case Studies From Malaysia

Kwong Hsia Yap[1], *Narelle Warren*[2*], *Pascale Allotey*[3] *and Daniel Reidpath*[4]

[1] Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Subang Jaya, Malaysia, [2] School of Social Sciences, Monash University, Clayton, VIC, Australia, [3] International Institute for Global Health, United Nations University, Kuala Lumpur, Malaysia, [4] Health Systems and Population Studies Division, icddr, b, Dhaka, Bangladesh

Following stroke, individuals require ongoing screening, diagnosis and monitoring for cognitive impairment. Services and policies around these vary widely between settings, and reports from many countries highlight persistent under-diagnosis of cognitive impairment in the months and years after stroke. Missed and delayed diagnosis of post-stroke cognitive impairment, including dementia, are important factors in shaping the experiences of people so affected and their family members, especially in low- and middle-income countries. Drawing upon ethnographic research conducted in Malaysia, this article draws upon three case studies to examine the continued health-seeking behaviour after the appearance of salient cognitive and behavioural symptoms that occurred after stroke. Findings highlight the challenges in getting formal diagnostic clarity for cognitive and behavioural symptoms in a rural setting within a middle-income country. No study participants sought help for memory or cognitive problems, partly due to limited lay awareness of cognitive impairment but more significantly due to health service factors. Despite their elevated risk for dementia, participants were not monitored for cognitive impairment during any follow-up care in various health facilities. Furthermore, caregivers' attempts to seek help when behavioural issues became untenable were met with multiple health system barriers. The journey was complicated by the meanings attached to the reactions towards cognitive symptoms at the community level. We suggest that strategies seek to increase the awareness of post-stroke cognitive and behavioural symptoms, and incorporate clear treatment pathways into the long-term care plans of community-dwelling stroke survivors.

Keywords: post-stroke, cognitive impairment, cognitive screening, under-diagnosis, Malaysia

OPEN ACCESS

Edited by:
Mario Alfredo Parra, University of Strathclyde, United Kingdom

Reviewed by:
Eliana Cristina De Brito Toscano, Federal University of Minas Gerais, Brazil
Olusegun Baiyewu, University of Ibadan, Nigeria

***Correspondence:**
Narelle Warren
narelle.warren@monash.edu

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: *13 November 2020*
Accepted: *03 May 2021*
Published: *02 June 2021*

Citation:
Yap KH, Warren N, Allotey P and Reidpath D (2021) Challenges for Diagnostic Clarity for Post-stroke Cognitive Impairment and Behavioural Issues in Middle-Income Countries: Case Studies From Malaysia. Front. Neurol. 12:628876. doi: 10.3389/fneur.2021.628876

INTRODUCTION

Cognitive impairment (CI) is a frequent complication in stroke survivors (1) and predicts post-stroke death, dependency, and institutionalisation (2–4). Cognitive status offers a way to understand the extent of cognitive impairment and is assessed across a continuous spectrum ranging from no cognitive impairment (NCI) to dementia. While cognitive decline may continue

post-stroke, up to 20% of patients with cognitive impairment show improvement (5). While most improvements occur in the first 3 months, recovery may continue for at least the first-year post-stroke. However, stroke survivors can develop delayed dementia beyond the initial 3 months. A registry-based study with mean follow up time of 3.79 years found that, in elderly stroke patients aged above 75 years old, 23.7% developed delayed dementia post-stroke (6). Previous research estimated that 10% of patients had dementia prior to their first stroke, 10% developed dementia after first-ever stroke (7), and approximately one-third experienced dementia following recurrent stroke (8). A 10 - year longitudinal study of people with no stroke at baseline showed that individuals who experienced a stroke during the observation period had faster memory decline than those who remained stroke-free throughout (9). Further, the presence of both post-stroke CI (10) and accelerated post-stroke cognitive decline (11) were independently associated with recurrent stroke. Hence, the recognition of CI in this high-risk group is vital for early intervention and improved management.

The importance of diagnosing and monitoring cognitive impairment after stroke has been repeatedly stressed (12–14). However, reports of under-diagnosis of cognitive impairment remain a common theme in stroke. The onus of the detection of cognitive impairment is often placed in the hands of the healthcare practitioner, and recommendations for post-stroke monitoring emphasises cognitive screening during presentations in hospitals or healthcare facilities. But in reality, health practitioners often miss out on cognitive impairment due to the inherent bias towards physical recovery (in the case of stroke) (15). Delays in the presentation of a person suspected to have cognitive impairment or dementia to health facilities may also play a role, and is commonly attributed to various reasons shaped by the cultural and social environment. This includes: a consideration of memory problems as part of normal ageing (16–18), stigma (17), failure of family members or primary caregivers to recognise symptoms (19–21), and familial disagreements on the symptoms and course of action (17, 20, 22). A timely diagnosis of dementia is beneficial in many ways. Affected individuals and their caregivers or family members can be referred to treatment and support services to enable future planning and better management of disease-related symptoms (23, 24).

Dementia in itself is under-recognised and under-diagnosed in low-and-middle-income countries (LMIC) (25). Contextual factors such as stigma (25), different understandings of disease (26–29), and generally low expectations of abilities in older people (30) contribute to lower awareness and recognition of dementia. LMICs also struggle with limited resources within a health system where acute and other chronic conditions create competing priorities. However, as LMICs are projected to be home for the majority of people living with dementia by 2030 (22), there is a need to better understand how contextual factors interact with health system factors in order to plan for programmes and strategies that will address the underlying issues related to disease recognition and diagnosis.

Malaysia is a middle-income country that is experiencing a demographic transition, edging towards population ageing and increasing prevalence of non-communicable diseases among older adults (31). The Malaysian health system is comprised of both public and private sectors. The majority of the healthcare system is supported by the public sector, with a higher concentration of the private sector in urban areas. In urban areas, where most health facilities (in both private and public sectors) are centred (32), shortages are evident due to the private sector focused on curative services as opposed to long-term chronic care (33). In rural areas, the majority of patients with chronic medical conditions receive their care from the public sector but with less than optimal disease control (34–38). Stroke rehabilitation remains a challenge in Malaysia, where there are there is a shortage in rehabilitation specialists and units (39), and poorly coordinated and fragmented post-stroke care and rehabilitation (40). There is also no information on the experiences of stroke survivors with CI in the community. In this article, we report the continued health-seeking behaviour of three elderly stroke survivors living in the rural community with salient cognitive and behavioural symptoms that occurred after stroke.

MATERIALS AND METHODS

Participants

Participants were recruited as part of a larger ethnographic study on stroke recovery using the South East Asia Community Observatory (SEACO) research platform. SEACO is a demographic and health surveillance system (DHSS) located in the district of Segamat in Johor, the southernmost state of peninsular Malaysia (41). This article focuses on three case studies, drawn from a sub-study of 18 people with stroke and their caregivers. The three participants (two women and one man) sampled for this analysis were aged between 72 and 80 years old. They were all of Malaysian-Chinese descent, and lived in the same village. All three participants lived with their caregivers.

Participation in the study was voluntary and the study was approved by Monash University Human Research Ethics Committee (CF14/315 – 2014000105). A detailed description of the consent process has been previously described (42).

Methodology

The detailed methodology for the ethnographic study has been described elsewhere (42, 43).

Stroke survivors were identified during two annual health data collection rounds conducted by SEACO. Those who reported stroke were then visited, in order to assess their suitability and willingness to be enrolled in the study. A community key informant referred other stroke survivors who were not captured in the annual round to the study team.

Ethnography was chosen as a research approach in order to gain an in-depth insider understanding of people's behaviours and practises, and what they meant to the participants. Ethnographic research draws upon fieldnotes, observations, interviews and even objects, which are triangulated to produce comprehensive and in-depth understandings of the social environment. Through participant observation, researchers can obtain insights into social practises and behaviour that are not readily apparent to the public eye. Compared with some

TABLE 1 | Characteristics of participants in case studies.

Participant	Age	Years since stroke	Household stucture	MoCA score	Comorbidities	Physical condition at enrolment
Mr Pi	72	4	Lived with wife and adult children	10	Diabetes	Left-sided weakness, on wheelchair, needed help with transfers.
Madam Lu	80	1	Lived with husband	8	High blood pressure, high cholesterol, arthritis	Left leg weakness and numbness, needed a walking frame to get around
Madam Nu	78	1	Lived with husband, adult children and grandchildren	19	Atrial fibrillation, high blood pressure, diabetes	Slight left facial droop, slight weakness on left hand, ambulated independently.

other forms of qualitative research, ethnographic research can be more difficult to undertake due to this complexity. The need to spend relatively long periods of time gathering data from different sources, with the goal of producing a detailed account of a particular setting, means it is resource- and time-intensive. Because of this intensive approach, sample sizes are typically smaller. This is reflected in the current study, where the first author (KHY) worked with a small number of individuals in a defined geographic area.

The study was located within a single village, and sought to examine the experiences of Malaysian-Chinese stroke survivors and their health seeking pathways, with a special focus on cognitive decline after stroke. The main study on stroke and CI had 18 participants (42, 43). Three community-dwelling participants with salient cognitive and behavioural symptoms after stroke were sampled from this larger ethnographic study. These participants were selected because a) they had a continuous regular engagement with healthcare facilities and were considered compliant to follow-ups, b) they had responsive caregivers who were willing to participate in the study as informants, and c) they all had salient cognitive and behavioural symptoms observed and reported in detail by their caregivers. Within these cases, we examined the missed opportunities for CI diagnosis.

The case narratives of participants were constructed from in-depth interviews, observations and extensive fieldnotes collected over the span of 1 year (July 2015 to June 2016). Several scales were also administered and rated at the beginning of the study in order to capture the current functional state of participants: *Modified Rankin Scale (mRS)* (44), *Patient Health Questionnaire, 9 items(PHQ-9)* (45), *Montreal Cognitive Assessment (MoCa) basic* (46) and the EuroQol-5D (*EQ5D)* (47) *Visual Analogue Scale (VAS).*

As this study was part of a larger study on stroke, the initial interview typically started with questions on stroke experience, for example, Why did you think stroke happened? How do you think this should be treated? Who did you call to ask for help? What did you think happened? Questions exploring memory concerns were asked subsequently, including How is your memory? Depending on participants' responses, these questions were then followed up with probing questions. These included questions such as: Do you think you have memory problems (or concerns)? Why did you think your memory worsened? Findings on understandings of stroke and CI were reported elsewhere (42, 43).

Subsequently, the researcher explored the choices made by participants and discussed perceptions of stroke, memory (or aspects of cognition) and health. Contextual issues that may have shaped participants' interaction with health services, including uptake, and impact of their actions in health-seeking were also explored.The first author [KHY] lived in the participants' village during the data collection phase, observing how participants lived and how they carried out daily routines. KHY also accompanied participants and their family members during some of their visits to health facilities, and documented her observations though fieldnotes. All participant names in this article are pseudonyms.

FINDINGS

Case 1—Mr Pi

At the time of the study, Mr Pi (72 years old) was 4 years post-stroke and living with his adult daughter (Meijie) and wife (see **Table 1**). He was usually in his wheelchair and could stand but was not able to walk. He was dependent on his family for all aspects of his life, from toileting and transfers to meal preparation, although he could eat on his own. His diabetic medication was also managed by his caregivers. His scope of activities was therefore limited and not high in complexity. He also did not like to talk much after his stroke. At first glance, it would seem that he was a silently compliant person, living peacefully at home, taken care of by his family. However, it was clear that he had cognitive deficits. This was reflected in his cognitive screening, where he only managed 10 out of the maximum 30 points [*via* the Montreal Cognitive Assessment (48) was administered to him as part of the larger study]. He demonstrated challenging behavioural issues, such as fluctuating moods (resulting in temper tantrums), and occasionally intentionally urinated on the walls of his bedroom, which stressed his family. His behaviour was construed as "naughty" but harmless. Meijie felt that, compared to his previous state where he was completely bedbound and on a feeding tube (for the first month post-stroke), his current condition was a lot

better and that he had "stabilised" because he could sit up and could eat well.

Meijie and Mrs Pi monitored Mr Pi's health in the local government health clinic within the village. Still, they had never discussed any of his behavioural issues with the healthcare provider as they did not think that the issues were related to the stroke. Mr Pi's consultations with his healthcare providers were generally short (regular checking of vital signs, blood pressure and blood tests reviews), and not conducive for in-depth discussions regarding Mr Pi's management at home. Especially for chronic stroke survivors like Mr Pi, it was assumed that the carer could manage and that, if they had any issues, caregivers themselves would bring them up with the doctor. On the other hand, Meijie had no expectations that anyone in the health clinic would be able to help her, nor was she able to explicitly verbalise what aspect she wanted help with. Even when explicitly asked if there she desired any help in the care of her father, Meijie responded, "Can't think of anything... [I] just take care of him like this."

Analysis

Meijie's perception of Mr Pi's health was influenced by his previous (poor health) state, and her expectation of a "healthier" body was based on this lower baseline. Because he had put on weight, could sit up on his own, and communicate his likes and dislikes to a certain degree, he was considered "okay." His current state of abilities and behavioural issues were normalised as part of who he was. His family had adjusted to his current state without any expectation of further improvements. This normalisation is similar to findings from India, where the high tolerance of impairments and low expectations for older people was borne out in the low reporting rates or health-seeking for memory issues by their family members (30). Despite regular follow-ups as part of his health management plan, Mr Pi's behavioural and cognitive issues were not detected by his health providers, because his caregivers did not feel that these issues were significant. There was also a lack of monitoring of his cognitive status. Mr Pi was never administered any formal assessments for his cognitive status throughout his care.

Case 2—Madam Lu

At the time of the study, Madam Lu (80 years old) was 1 year post-stroke, and living with her husband, Mr Xing (79 years old) (see **Table 1**). She still had remaining leg weakness and needed to use the walking frame for stability. She had high blood pressure and high cholesterol and was put on medications. Explicit cognitive symptoms were observed in Madam Lu. Her husband managed her medications for her, serving the appropriate doses to her as she would otherwise forget to take them or muddle up the dosage. Both she and her husband were aware of her memory decline, but this was normalised even though she depended on Mr Xing for some, but not all, of her activities of daily living. He did the majority of the household chores. While she used to handle all household chores on her own, by the time of the study, Madam Lu was only able to manage simple tasks in food preparation (plucking vegetables) or folding small items of clothing. Her cognitive issues became more apparent when they shifted into a newly renovated home a few streets away; Madam Lu sometimes became disoriented and asked to be brought to back to her "real home" because she forgot that she had moved. Mr Xing became increasingly puzzled with her behaviour, which included moments when she would ask to die, which he interpreted as evidence that she might be having some mental health issues.

Throughout this time, Madam Lu regularly attended the government health clinic for blood pressure and cholesterol medications but, like Meijie (the caregiver from Case 1), Mr Xing did not bring up these issues to the healthcare provider. Instead, he asked his son to take Madam Lu to the private hospital to consult a psychiatric specialist. Madam Lu, on the other hand, was still preoccupied with her leg weakness. She complained about her leg when her son came to take her to the private hospital; she was brought to the orthopaedic specialist to consult on her leg instead of the psychiatrist. Mr Xing did not want to make a fuss because he felt that the decision-making regarding the choice of health provider lay with his son, who paid for Madam Lu's medical expenses at the private hospital.

This decision to remain silent was borne out negatively over time. One and a half years after her stroke, Madam Lu lost her balance at home and experienced a bad fall, after which she became bedbound. Mr Xing felt that it was because she had forgotten to hold on to her walking frame when making her way to the bathroom, and had therefore lost her balance and fallen. After the incident, Mr Xing simply could not cope alone at home with her, so she was shifted to her son's home to be cared for by him and his family. At that point, her medical care was transferred to the nearest public hospital located in the same town and, from then on, her mental state worsened:

She just sits there and lies down there you know. She is not very spirited you know... she does not really want to talk. The first time when I went to see her, she was sitting there and her eyes were wide open... When people asked her who came to see her, she could still tell [who visited]… The second time when I went to see her... she lay there with her eyes closed. (Mr Xing)

Before she was confined to bed, she was socially active and generally chatty. After her fall, she became very depressed and quickly deteriorated physically and mentally. Mr Xing felt helpless as he watched the deterioration of her mental state, but it was not something that he thought needed management at that time. Madam Lu passed away in her sleep 2 months after she moved to her son's home.

Analysis

Different levels of recognition of the impact of CI meant that participants received varying levels of support to manage their well-being. Earlier recognition and diagnosis of CI and dementia in clinical settings has been advocated because it provided patients and caregivers with earlier support and training to cope at home (38, 39). Mr Xing perceived that there was a need to address her issues and had sought out resources from their son, an external resident. However, due to his lack of understanding of Madam Lu's condition, their son took her to an orthopaedic specialist instead of a professional who could address her psychological and behavioural issues. In the end, because her son provided the resources for her specialist care, Madam Lu

was not able to access services relevant to the needs perceived by Mr Xing. Even though she had been in contact with various healthcare providers, her cognitive issues were not detected in any of the health facilities in either public or private sectors. Again, this points to the lack of monitoring of patients at-risk for dementia by health service providers. Arguably, Mr Xing and Madam Lu's confusion, distress, and helplessness may have been alleviated to a certain degree if the impact of CI was recognised and supported by healthcare providers.

Case 3—Madam Nu

At the time of the study Madam Nu (78 years old) was 1 year post-stroke and lived with her husband, children and grandchildren (see **Table 1**). She had recovered well after stroke and was only left with facial numbness. Her daughter, Huajie, was in charge of the arrangements and transport for Madam Nu's health visits, including regular follow-up visits to the hospital in another town for a heart-related condition. Huajie had noticed that Madam Nu tended to dwell on past memories, and did not always remember what happened more recently. While Madam Nu was aware that her memory had declined, she was unperturbed as the deficits did not interfere with her daily activities. Household chores were done by the younger generation and she usually spent her time watching television.

Huajie became very concerned when Madam Nu's behaviour started to disrupt home life. Madam Nu experienced increasingly frequent periods of poor temper, which created uncomfortable situations for her family members. She would often jump to misconstrued conclusions based on incomplete information, as she had forgotten some of the events that happened in between. Madam Nu's behaviour also caused embarrassment for her family, as some of the storeys she told to her neighbours reflected badly on her family members. Her memory decline not only meant she forgot the small everyday acts of care performed by her family, but also amplified her resistance towards their help or suggestions for activities. Incidents that happened at home were told to other people from a negative angle, with omissions or exaggerations of some details contrary to what really happened. This then strained Madam Nu's relationships with her family members as she created conflicts out of normal everyday interactions.

As the problems with Madam Nu escalated, Huajie tried to suggest a visit to see the psychiatrist, but this was met with intense objection from Madam Nu as she not feel that there was anything wrong with her. She also did not realise that her memory deficits caused some of the misunderstandings that resulted in her suspicion and anger. Huajie then attempted to bring up her mother's behavioural issues with their regular health practitioner at during a follow-up consultation:

I told [the doctor] that my mother's temper is getting worse... [She] keeps scolding people, [so could they recommend] any method or any medication to control her [behaviour]? The doctor just smiled at me. I am not sure if he thought that we were unable to communicate with my mother or that we complain that our mother is not good or because of our socioeconomic status... He did not further ask properly.

Huajie had hoped to get a referral or some suggestions from the doctor to help manage Madam Nu's mood and occasionally erratic behaviour. Her concerns were brushed aside by the attending doctor. Huajie was frustrated with the doctor's reaction, which.she felt reflected an incorrect comprehension of the extent to which she and her family had gone to try and understand Madam Nu.

Analysis

Family members were not always guaranteed any response or helpful advice even when they did report behavioural issues to health providers. Huajie, who finally decided to bring up the matter with Madam Nu's regular healthcare provider after her behavioural symptoms escalated, was dismissed by the doctor. This left Huajie at a loss—she had perceived a need to address such issues, but received no support to do so. In this case, the healthcare provider did not think that the patient needed to be assessed for further management, which resulted in Huajie not having access to appropriate care which was crucial for addressing the Madam Nu's behavioural issues in the home setting.

DISCUSSION

Individuals in this article did not seek help for memory or cognitive problems. Instead, behavioural issues prompted caregivers to seek help. This phenomenon is not surprising and reflected in the same trends found in more well-resourced settings (49). In the current context, health service factors contributed significantly to this phenomenon.

Even though stroke survivors are known to have elevated risk of progressing to dementia, the three study participants were not monitored for cognitive impairment during any follow-up care in various health facilities. According to the participants and their caregivers, none had undergone any form of formal assessment of their cognitive abilities in any of the health facilities they attended, not even during the acute stage of stroke. This was also the case for all participants in the broader study. Contextual issues shaped how they viewed CI, and the obvious emphasis on physical abilities were barriers to the diagnosis of CI or behavioural issues (42). The lack of pathways for stroke after hospitalisation extended to other symptoms, including CI and other psychosocial issues, which increased the difficulties in getting a proper diagnosis. Study participants and their families simply had no clear idea of what to do when faced with these issues, resulting in delays to seeking help from health service providers or not seeking help at all. Families experienced some degree of distress when dealing with the changed behaviour of their loved ones and were stuck in uncertainty. They knew that something was wrong, but could not quite place what this was, and so were not sure of how to go about getting help. This points to the need to implement a care plan or pathway for stroke survivors in which cognitive assessments are routinely undertaken, as per recommendations in international guidelines (50, 51).

The health providers consulted in these three cases did not seem to be picking up distress signals from the family caregiver

when they reported mood and behavioural changes, regardless of the time since stroke, the severity of the CI symptoms, or even reports of mood and behavioural issues. None of these were considered by healthcare providers who were in contact with stroke survivors in the community. In Malaysian settings, behavioural and psychological symptoms significantly contribute to caregiver burden more than the actual cognitive impairment in patients with dementia (52). Therefore, there is a need to strengthen the awareness, knowledge and attitudes of stroke survivors and their caregivers regarding cognitive and behavioural signs, symptoms and changes after stroke—all factors that need attention and reporting. Caregivers should also be educated on the resources and facilities that they can contact when they have doubts about the symptoms or progression of their loved ones. In doing so, caregivers will be able to actively recognise symptoms and make the first step for discussion with healthcare providers, which can lead to suitable treatment or further referrals. The strategies to strengthen awareness need to consider family members' and patients' lay understandings of their condition and the interactions within the households' family structure.

In this paper, we have highlighted the challenges in getting formal diagnostic clarity for cognitive and behavioural symptoms in a rural setting within a middle-income country. We suggest that strategies seek to increase the awareness of post-stroke cognitive and behavioural symptoms, and incorporate clear treatment pathways into the long-term care plans of community-dwelling stroke survivors.

The emphasis of the original study from which the case narratives were extracted from is from the perspective of the stroke survivors and their family units, and focuses less on the perspective of healthcare services providers. One of the reasons for the lack of inclusion of the perspective from healthcare providers is the need for additional layers of ethical and institutional approvals in obtaining formal interviews (especially concerning Ministry of Health employees and facilities). Future studies should include healthcare providers' perspectives in terms of long-term follow up and actual management in the community.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because we are unable to publicly share the data due to restrictions related to ethical approval. We can share other publications and original theses arising from this project. Requests to access the datasets should be directed to NW, narelle.warren@monash.edu.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Monash University Human Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

KY designed the cognitive screening component of the study, and collected and analysed all data. NW, PA, and DR designed the study, obtained funding and ethical approval, and guided the data analysis. All authors contributed to participant recruitment and writing the manuscript.

FUNDING

This research was funded by an Australian Research Council Discovery Project grant DP140101995.

REFERENCES

1. Kalaria RN, Akinyemi R, Ihara M. Stroke injury, cognitive impairment and vascular dementia. *Biochim Biophys Acta BBA—Mol Basis Dis.* (2016) 1862:915–25. doi: 10.1016/j.bbadis.2016.01.015
2. Oksala NKJ, Jokinen H, Melkas S, Oksala A, Pohjasvaara T, Hietanen M, et al. Cognitive impairment predicts poststroke death in long-term follow-up. *J Neurol Neurosurg Psychiatry.* (2009) 80:1230–5. doi: 10.1136/jnnp.2009.174573
3. Pasquini M, Leys D, Rousseaux M, Pasquier F, Hénon H. Influence of cognitive impairment on the institutionalisation rate 3 years after a stroke. *J Neurol Neurosurg Psychiatry.* (2007) 78:56–9. doi: 10.1136/jnnp.2006.102533
4. Jokinen H, Melkas S, Ylikoski R, Pohjasvaara T, Kaste M, Erkinjuntti T, et al. Post-stroke cognitive impairment is common even after successful clinical recovery. *Eur J Neurol.* (2015) 22:1288–94. doi: 10.1111/ene.12743
5. Rasquin SMC, Lodder J, Verhey FRJ. Predictors of reversible mild cognitive impairment after stroke: a 2-year follow-up study. *J Neurol Sci.* (2005) 229–230:21–5. doi: 10.1016/j.jns.2004.11.015
6. Allan LM, Rowan EN, Firbank MJ, Thomas AJ, Parry SW, Polvikoski TM, et al. Long term incidence of dementia, predictors of mortality and pathological diagnosis in older stroke survivors. *Brain.* (2011) 134:3713–24. doi: 10.1093/brain/awr273
7. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. *Lancet Neurol.* (2009) 8:1006–18. doi: 10.1016/S1474-4422(09)70236-4
8. Leys D, Hénon H, Mackowiak-Cordoliani M-A, Pasquier F. Poststroke dementia. *Lancet Neurol.* (2005) 4:752–9. doi: 10.1016/S1474-4422(05)70221-0
9. Wang Q, Capistrant BD, Ehntholt A, Glymour MM. Long-term rate of change in memory functioning before and after stroke onset. *Stroke J Cereb Circ.* (2012) 43:2561–6. doi: 10.1161/STROKEAHA.112.661587
10. Kwon HS, Lee D, Lee MH, Yu S, Lim J-S, Yu K-H, et al. Post-stroke cognitive impairment as an independent predictor of ischemic stroke recurrence: PICASSO sub-study. *J Neurol.* (2020) 267:688–93. doi: 10.1007/s00415-019-09630-4
11. Zheng F, Yan L, Zhong B, Yang Z, Xie W. Progression of cognitive decline before and after incident stroke. *Neurology.* (2019) 93:e20–8. doi: 10.1212/WNL.0000000000007716

12. Levine DA, Galecki AT, Langa KM, Unverzagt FW, Kabeto MU, Giordani B, et al. Trajectory of cognitive decline after incident stroke. *JAMA*. (2015) 314:41–51. doi: 10.1001/jama.2015.6968
13. Melkas S, Jokinen H, Hietanen M, Erkinjuntti T. Poststroke cognitive impairment and dementia: prevalence, diagnosis, and treatment. *Degener Neurol Neuromuscul Dis*. (2014) 4:21–7.
14. Pollock A, St George B, Fenton M, Firkins L. Top ten research priorities relating to life after stroke. *Lancet Neurol.* (2012) 11:209. doi: 10.1016/S1474-4422(12)70029-7
15. Tang EYH, Price C, Stephan BCM, Robinson L, Exley C. Gaps in care for patients with memory deficits after stroke: views of healthcare providers. *BMC Health Serv Res.* (2017) 17:634. doi: 10.1186/s12913-017-2569-5
16. Werner P. Beliefs about memory problems and help seeking in elderly persons. *Clin Gerontol.* (2004) 27:19–30. doi: 10.1300/J018v27n04_03
17. Mukadam N, Cooper C, Livingston G. A systematic review of ethnicity and pathways to care in dementia. *Int J Geriatr Psychiatry.* (2011) 26:12–20. doi: 10.1002/gps.2484
18. Berwald S, Roche M, Adelman S, Mukadam N, Livingston G. Black african and caribbean british communities' perceptions of memory problems: "we don't do dementia." *PLoS ONE.* (2016) 11:e0151878. doi: 10.1371/journal.pone.0151878
19. Feldman L, Wilcock J, Thuné-Boyle I, Iliffe S. Explaining the effects of symptom attribution by carers on help-seeking for individuals living with dementia. *Dement Lond Engl.* (2017) 16:375–87. doi: 10.1177/1471301215593185
20. Innes A, Szymczynska P, Stark C. Dementia diagnosis and post-diagnostic support in Scottish rural communities: experiences of people with dementia and their families. *Dement Lond Engl.* (2014) 13:233–47. doi: 10.1177/1471301212460608
21. McCleary L, Persaud M, Hum S, Pimlott NJG, Cohen CA, Koehn S, et al. Pathways to dementia diagnosis among South Asian Canadians. *Dement Lond Engl.* (2013) 12:769–89. doi: 10.1177/1471301212444806
22. Levkoff S, Levy B, Weitzman PF. The role of religion and ethnicity in the help seeking of family caregivers of elders with Alzheimer's disease and related disorders. *J Cross-Cult Gerontol.* (1999) 14:335–56. doi: 10.1023/A:1006655217810
23. Dubois B, Padovani A, Scheltens P, Rossi A, Dell'Agnello G. Timely diagnosis for alzheimer's disease: a literature review on benefits and challenges. *J Alzheimers Dis.* (2016) 49:617–31. doi: 10.3233/JAD-150692
24. Mijajlović MD, Pavlović A, Brainin M, Heiss W-D, Quinn TJ, Ihle-Hansen HB, et al. Post-stroke dementia—a comprehensive review. *BMC Med.* (2017) 15:11. doi: 10.1186/s12916-017-0779-7
25. Prince MJ, Comas-Herrera A, Knapp M, Guerchet M, Karagiannidou M. *World Alzheimer Report 2016—Improving healthcare for people living with dementia: Coverage, quality and costs now and in the future*. London: Alzheimer's Disease International (2016).
26. Cohen L. *No Aging in India: Alzheimer's, The Bad Family, and Other Modern Things*. Berkeley, CA: University of California Press (1998).
27. Chee YK, Levkoff SE. Culture and dementia: accounts by family caregivers and health professionals for dementia-affected elders in South Korea. *J Cross-Cult Gerontol.* (2001) 16:111–25. doi: 10.1023/A:1010640527713
28. Ikels C. Constructing and deconstructing the self: Dementia in China. *J Cross-Cult Gerontol.* (2002) 17:233–51. doi: 10.1023/A:1021260611243
29. Henderson JN, Henderson LC. Cultural construction of disease: a "supernormal" construct of dementia in an American Indian tribe. *J Cross-Cult Gerontol.* (2002) 17:197–212. doi: 10.1023/A:1021268922685
30. Jacob KS, Kumar PS, Gayathri K, Abraham S, Prince MJ. The diagnosis of dementia in the community. *Int Psychogeriatr.* (2007) 19:669–78. doi: 10.1017/S1041610207005297
31. Tey NP, Siraj SB, Kamaruzzaman SBB, Chin AV, Tan MP, Sinnappan GS, et al. Aging in multi-ethnic Malaysia. *Gerontologist.* (2016) 56:603–9. doi: 10.1093/geront/gnv153
32. Merican MI, bin Yon R. Health care reform and changes: the Malaysian experience. *Asia-Pac J Public Health Asia-Pac Acad Consort Public Health.* (2002) 14:17–22. doi: 10.1177/101053950201400105
33. Ong FS. Health care and long term care issues for the elderly. In: *Health Care in Malaysia—The Dynamics of Provision, Financing and Access.* London and New York, NY: Routledge (2007). p. 170–86.
34. Lee TW, Chan SC, Chua WT, Harbinder K, Khoo YL, Ow Yeang YL, et al. Audit of diabetes mellitus in general practice. *Med J Malaysia.* (2004) 59:317–22. Available online at: http://www.e-mjm.org/2004/v59n3/Audit_of_Diabetes_Mellitus.pdf
35. Mastura I, Zanariah H, Fatanah I, Feisul Idzwan M, Wan Shaariah MY, Jamaiyah H, et al. An audit of diabetes control and management (ADCM). *Med J Malaysia.* (2008) 63(Suppl C):76–7. Available online at: https://www.researchgate.net/publication/24025603_An_Audit_of_Diabetes_Control_and_Management_ADCM
36. Rampal L, Rampal S, Azhar MZ, Rahman AR. Prevalence, awareness, treatment and control of hypertension in Malaysia: a national study of 16,440 subjects. *Public Health.* (2008) 122:11–8. doi: 10.1016/j.puhe.2007.05.008
37. Wong JS, Tan F, Lee PY. The state of lipid control in patients with diabetes in a public health care centre. *Asia-Pac J Public Health Asia-Pac Acad Consort Public Health.* (2007) 19:16–21. doi: 10.1177/101053950701900304
38. Mafauzy M. Diabetes control and complications in private primary healthcare in Malaysia. *Med J Malaysia.* (2005) 60:212–7. Available online at: http://www.e-mjm.org/2005/v60n2/Diabetes_Control.pdf
39. Mohd Nordin NA, Aziz NA, Alkaff SE, Sulong S, Aljunid S. Rehabilitation for patients after stroke in a tertiary hospital: is it early and intensive enough? *Int J Ther Rehabil.* (2012) 19:603–11. doi: 10.12968/ijtr.2012.19.11.603
40. Abdul Aziz AF, Mohd Nordin NA, Abd Aziz N, Abdullah S, Sulong S, Aljunid SM. Care for post-stroke patients at Malaysian public health centres: self-reported practices of family medicine specialists. *BMC Fam Pract.* (2014) 15:40. doi: 10.1186/1471-2296-15-40
41. Partap U, Young EH, Allotey P, Soyiri IN, Jahan N, Komahan K, et al. HDSS profile: the south east Asia community observatory health and demographic surveillance system (SEACO HDSS). *Int J Epidemiol.* (2017) 46:1370–1. doi: 10.1093/ije/dyx113
42. Yap KH, Warren N, Reidpath DD, Allotey P. Understanding cognitive impairment after stroke: stories from a middle-income country. *J Popul Ageing*. (2020). doi: 10.1007/s12062-020-09289-0. [Epub ahead of print].
43. Yap KH, Warren N, Allotey P, Reidpath DD. Understandings stroke in rural Malaysia: ethnographic insights. *Disabil Rehabil.* (2019) 43:1–9. doi: 10.1080/09638288.2019.1624841
44. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke J Cereb Circ.* (1988) 19:604–7. doi: 10.1161/01.STR.19.5.604
45. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9. *J Gen Intern Med.* (2001) 16:606–13. doi: 10.1046/j.1525-1497.2001.016009606.x
46. Julayanont P, Tangwongchai S, Hemrungrojn S, Tunvirachaisakul C, Phanthumchinda K, Hongsawat J, et al. The montreal cognitive assessment-basic: a screening tool for mild cognitive impairment in illiterate and low-educated elderly adults. *J Am Geriatr Soc.* (2015) 63:2550–4. doi: 10.1111/jgs.13820
47. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med.* (2001) 33:337–43. doi: 10.3109/07853890109002087
48. Julayanont P, Tangwongchai S, Hemrungrojn S, Tunvirachaisakul C, Phanthumchinda K, Hongsawat J, et al. The montreal cognitive assessment-basic (MoCA-B): a new mild cognitive impairment screening test for illiterate and low educated elderly. *Alzheimers Dement J Alzheimers Assoc.* (2015) 11:P442–3. doi: 10.1016/j.jalz.2015.06.435
49. Perry-Young L, Owen G, Kelly S, Owens C. How people come to recognise a problem and seek medical help for a person showing early signs of dementia: a systematic review and meta-ethnography. *Dement Lond Engl.* (2018) 17:34–60. doi: 10.1177/1471301215626889
50. Hachinski V, Iadecola C, Petersen RC, Breteler MM, Nyenhuis DL, Black SE, et al. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. *Stroke.* (2006) 37:2220–41. doi: 10.1161/01.STR.0000237236.88823.47
51. Intercollegiate Working Party for Stroke, Stroke Association, Royal College of Physicians of London. *National Clinical Guideline for Stroke.* London: Royal College of Physicians (2016).
52. Rosdinom R, Zarina MZN, Zanariah MS, Marhani M, Suzaily W. Behavioural and psychological symptoms of dementia, cognitive

impairment and caregiver burden in patients with dementia. *Prev Med*. (2013) 57(Suppl):S67–9. doi: 10.1016/j.ypmed.2012.12.025

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

BRIEF RESEARCH REPORT
published: 11 June 2021
doi: 10.3389/fneur.2021.628406

First Symptoms of Primary Progressive Aphasia and Alzheimer's Disease in Brazilian Individuals

Talita Gallas dos Reis[1]*, *Thais Helena Machado*[2], *Paulo Caramelli*[3], *Francisco Scornavacca*[4], *Liana Lisboa Fernandez*[5] and *Bárbara Costa Beber*[1]*

[1] Departamento de Fonoaudiologia, Universidade Federal das Ciências da Saúde de Porto Alegre, Porto Alegre, Brazil,
[2] Departamento de transtornos cognitivos e demências, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil,
[3] Departamento de Clínica Médica—Neurologia, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil,
[4] Departamento de Pediatria, Universidade Federal das Ciências da Saúde de Porto Alegre, Porto Alegre, Brazil,
[5] Departamento de Ciências Básicas da Saúde, Universidade Federal das Ciências da Saúde de Porto Alegre, Porto Alegre, Brazil

OPEN ACCESS

Edited by:
Christopher Butler,
University of Oxford, United Kingdom

Reviewed by:
Petronilla Battista,
Global Brain Health Institute,
United States
Leonardo Caixeta,
Universidade Federal de Goiás, Brazil

***Correspondence:**
Talita Gallas dos Reis
talita18dosreis@gmail.com
Bárbara Costa Beber
barbaracb@ufcspa.edu.br

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: 11 November 2020
Accepted: 06 May 2021
Published: 11 June 2021

Citation:
dos Reis TG, Machado TH, Caramelli P, Scornavacca F, Fernandez LL and Beber BC (2021) First Symptoms of Primary Progressive Aphasia and Alzheimer's Disease in Brazilian Individuals. Front. Neurol. 12:628406. doi: 10.3389/fneur.2021.628406

Background: Primary Progressive Aphasia (PPA) is characterized by progressive language impairment due to focal degeneration of brain areas related to linguistic processing. The detection and differential diagnosis of PPA can be difficult with clinical features that may overlap with features of other neurological conditions, such as Alzheimer's disease (AD). The scientific production on PPA in Latin American patients is still scarce. This study investigated the first symptoms in a Brazilian sample of patients with PPA in comparison with AD patients.

Method: We compared the first symptoms reported by caregivers of people with PPA ($n = 20$; semantic variant $n = 8$, non-fluent variant $n = 7$, logopenic variant $n = 3$, and unclassified cases $n = 2$) and AD ($n = 16$). Data were collected through the application of a structured questionnaire that was presented in an interview format to the caregiver who knew the patient best.

Results: Anomia, paraphasias and motor speech difficulties were the first symptoms capable of differentiating patients with PPA from those with AD, while memory was exclusive of AD. Among the PPA variants, anomia was the initial symptom associated with the semantic variant, while motor speech difficulties were associated with the non-fluent variant. The results are discussed considering the unique cultural and sociodemographic characteristics of this studied population.

Conclusion: This study demonstrated that some of the initial symptoms of PPA patients may be unique to clinical variants of PPA and of AD, and their investigation may be useful for the early and differential diagnosis of this population.

Keywords: aphasia, primary progressive aphasia, Alzheimer's disease, differential diagnosis, signs and symptoms, language

INTRODUCTION

Primary progressive aphasia (PPA) is a neurological syndrome characterized by a progressive and prominent language impairment. It occurs due to neurodegenerative processes in the frontotemporal regions, predominantly in the left hemisphere (1–3). Language impairment should appear relatively isolated, without equivalent changes in other cognitive domains, in addition to the indication of a neurodegenerative condition, in order to confirm a diagnosis of PPA (1, 4, 5). Aphasia should be the most prominent deficit during the early stages of the disease (1). For this reason, the first symptoms must be investigated and described in order to differentiate PPA from other neurological disorders that have a different symptomatic picture in the early stages of the disease, and to perform the differential diagnosis of PPA variants.

There are three variants of PPA, which have specific characterization and diagnostic criteria (1, 3, 6, 7). Semantic variant (svPPA): characterized by fluent spontaneous speech, but with recurrent episodes of anomia and difficulty in understanding isolated words. Subjects may have verbal and semantic paraphasias, generalizations, omissions, in addition to reading and writing difficulties. The clinical condition is due to the involvement of the anterior temporal areas, which may occur in both cerebral hemispheres. Non-fluent/agrammatic variant (nfvPPA): mainly characterized by non-fluent oral expression, and may include apraxia of speech and/or agramatism, with the production of simple and short sentences, slowed speech, errors in articulatory movements, changes in prosody and substitutions of speech sounds. These symptoms result from the involvement of fronto-insular areas of the left hemisphere. Logopenic variant (lvPPA): characterized by difficulty in repeating sentences and finding words at the time of oral communication, including phonological errors in speech. The symptoms in this variant are due to a neurodegeneration at the left temporoparietal junction.

In turn, Alzheimer's disease (AD) is a neurodegenerative disease often diagnosed based on clinical symptoms, which gradually worsens cognitive and behavioral domains, such as learning and memory (8). The main clinical criteria for the diagnosis of dementia due to AD include cognitive and/or behavioral changes that impact the functioning of daily activities and represent a decline from previous levels of functioning (9). The deficits should occur at least in two domains, such as impaired ability to remember new information, impaired reasoning or changes in personality and behavior (9). Common symptoms of AD include impaired ability to acquire or recall new information; impaired judgment and handling of complex activities; involvement of visuospatial skills; involvement of language domains; behavioral changes, such as apathy, hyperactivity (agitation and irritability), psychosis (delusions and hallucinations), and affective symptoms (depression and anxiety) (8, 9).

The characterization of PPA variants can easily be confused with the findings of other neurological disorders, especially with AD. Many cases of PPA are believed to be underdiagnosed, while others still remain without a closed diagnosis or with a long delay to completion (10). Studies have reported that the lvPPA may appear as an initial symptom of AD in atypical cases, being recognized as one of the non-amnestic variants of AD (6). The same occurs with semantic and non-fluent variants, that are mistakenly diagnosed as the behavioral variant of frontotemporal dementia (FTD) (11) without an adequate and accurate characterization. These diagnostic mistakes can be explained both by the common symptomatic characteristics, but also by the similar neuropathological findings of both syndromes.

Studies report that FTD in general (including PPA) in low- and middle-income countries, such as Brazil, have a late diagnosis when compared to AD (12). The delay in receiving the correct diagnosis may be related to the patients' delay in seeking medical care, the delay in the Brazilian public health system in offering care, or even to the difficulties in reaching the correct diagnosis. There is evidence that these patients suffer from diagnostic errors due to the clinicians' difficulty in differentiating the types of dementia during initial manifestations (12). One previous study conducted in Brazil already reported the need for a careful investigation of the first symptoms (12). An in-depth investigation of the initial symptoms is believed to be even more important when patients come to the referral centers at later stages of the disease.

Given these diagnostic difficulties, studies that seek differential diagnoses and characterizations of PPA compared to other disorders, such as AD, are helpful for the accuracy of diagnosis and the best clinical management of these individuals. An important alternative would be the neuropsychological and the speech/language assessments to define the appropriate classification of PPA subtypes, in order to differentiate it from other neurological disorders (11, 13, 14).

However, it is also essential to perform a clinical examination and a comprehensive anamnesis in order to investigate the occurrence of the first symptoms presented by the patient. In addition, language plays a central role in the management of PPA and, therefore, studies that investigate how the syndrome manifests itself in speakers of different languages are of great relevance. Given this context, this study aims to describe the early symptoms of patients with the three variants of PPA, compared with patients with AD, in a sample of Brazilian Portuguese speakers.

MATERIALS AND METHODS

Participants

This is a quantitative, descriptive and cross-sectional study.

The study included a convenience sample of patients with an established diagnosis of PPA (1) or AD (15), according to current diagnostic criteria, who consented to participate in the study by signing the Informed Consent Form (ICF) by the guardian, and who had a family member or caregiver who was familiarized enough with the patient to answer the study questionnaire. The study excluded subjects who did not agree to participate and those who did not have a family member or close caregiver to answer the questionnaire.

All participants were diagnosed by a neurologist who considered information from an interview with patient and caregiver; physical examination; neuropsychological and speech

and language assessment (this only for patients in suspicion of PPA); blood tests; and neuroimaging tests (magnetic resonance imaging—MRI). For some patients, cerebrospinal fluid examination with dosage of biomarkers of AD and functional neuroimaging tests (FDG-PET or SPECT) were also performed. Our sample consisted of patients from both the public and private health systems. The Brazilian public health system does not cover the costs of the cerebrospinal fluid examination AD biomarkers or functional neuroimaging, so such tests were only performed by patients who could afford to pay for these tests privately or had health insurance to cover their costs. A few patients from the public universities had results of AD biomarkers in the cerebrospinal fluid as part of other research protocols.

The study included patients from the Neurology Outpatient Clinic of the Irmandade Santa Casa de Misericórdia de Porto Alegre (ISCMPA), and from the Behavioral and Cognitive Neurology Outpatient Clinic of the Hospital das Clínicas of the Universidade Federal de Minas Gerais (HC-UFMG), in Belo Horizonte.

This study was conducted in line with local ethical standards and was approved by the Research Ethics Committee of the ISCMPA (under no. 3,117,790), and also by the Research Ethics Committee of the HC-UFMG ethics committee (under no. 2,018,855).

Procedures

Data were collected through a structured questionnaire (**Appendix 1**) prepared by the researchers, which was conducted as an interview with the caregiver who had the best knowledge about the patient. The questionnaire was applied in person, or by a previously scheduled telephone call. Participants were informed about the study procedures, then read and signed the informed consent form, and finally answered the interview. When made by telephone call, the ICF was read and agreed to via an online document.

The questionnaire consisted of closed and open questions about personal and sociodemographic information (of patient and caregiver), clinical data, and the description of the first symptoms of the disease presented by the patient. The first symptoms were collected first through an open question, where the respondent had to explain with his/her words how the disease started. The next question was a closed question with a list of symptoms that was read to the respondent and he/she had to confirm if those symptoms occurred at the very beginning of the disease or not. We decided to present this list of symptoms to complement the description made by the respondent in the open question, in case he/she has forgotten any important symptom. This list of symptoms was created by the researchers in order to present the most important symptoms for the detection of PPAs and AD, in a brief way and using a plane language for the participants. The answers in the open question were transcribed and grouped into categories decided upon by consensus by the researchers together with the answers in the closed question.

The questionnaire was administered by one of the researchers who is a speech and language pathologist with expertise in dementia and a Brazilian-Portuguese native speaker. This examiner was not involved in any part of the diagnostic process of our participants, since them were already diagnosed when they were selected to participate of this study. The administration time needed for the questionnaire was about 20 min.

Data Analysis

Pearson's Chi-Squared Test and Fisher's exact test were used to investigate an association between the first symptoms and the participants' diagnosis. Sociodemographic features of the respondents (caregivers of individuals with PPA and AD) were compared using Pearson's Chi-Squared Test and *t*-student test. A significance level of 5% was adopted.

RESULTS

Overall, 20 individuals with PPA and 16 with AD were included in the study. In relation to sex distribution, 50% of the patients who had PPA and 62.5% of the patients who had AD were female. In turn, the mean age of the groups was 68.1 (±7.7) years for patients with PPA and 79.9 (±9.0) for patients with AD. As for the educational level, subjects in the PPA group had an average of 13.5 (±4.3) years of study, while subjects in the group with AD had an average of 5.2 (±4.0) years of study. All participants with PPA and AD were right-handed. Descriptive data for all participants are shown in **Table 1**.

The respondents of our questionnaire were the caregivers of participants with PPA and AD. Among the caregivers with PPA, 70% were female and had an average age of 52.4 (± 15) and an average education of 15.6 (± 1.5). 40% of the caregivers of patients with PPA was composed by spouses, 30% children, 5% brothers and 5% nephews. The caregivers of subjects with AD were mostly women (81.3%), with an average age of 54.1 (± 9.8) and average education of 13.4 (± 2.5). The relationship type of caregivers of people with AD were 75% children, 6.3% spouses and 12.5% son-in-law or daughter-in-law. The characteristics of these respondents were compared and there was no statistically significant difference between age ($p = 0.70$) and sex ($p = 0.94$). Education was significantly higher among caregivers of people with PPA ($p = 0.007$). The type of relationship between the caregiver and the patient were significantly different between the groups ($p = 0.02$), indicating that caregivers of people with PPA were mostly spouses and caregivers of people with AD were children.

At first, the early symptoms reported by the family members/caregivers of the patients were compared between the PPA and AD groups. A statistically significant difference was found for the symptoms of anomia ($p = 0.00$), memory difficulty ($p = 0.00$), speech motor difficulty ($p = 0.00$), and paraphasias ($p = 0.01$). Anomia, speech motor difficulty and paraphasias were predominant in the group with PPA. On the other hand, memory difficulties have been reported only in people with AD. There was no significant difference for behavioral symptoms ($p = 0.08$), agrammatism ($p = 0.69$), temporal/spatial disorientation ($p = 0.19$), executive functioning difficulties ($p = 0.10$), difficulty reading and writing ($p = 0.69$), difficulty repeating ($p = 0.11$), comprehension difficulties ($p = 0.36$), and echolalia ($p = 0.36$).

TABLE 1 | Sociodemographic characteristics of the participants.

	PPA (total) (*N* = 20)	Semantic PPA (*N* = 8)	Logopenic PPA (*N* = 3)	Non-fluent PPA (*N* = 7)	Non-classifiable PPA (*N* = 2)	AD (*N* = 16)
Sex (F)—*N*(%)	10 (50.0)	2 (25.0)	2 (66.7)	4 (57.1)	2 (100)	10 (62.5)
Age—mean (SD±)	68.1 (7.7)	65.0 (8.5)	67.0 (9.6)	72.4 (5.9)	67.0 (2.8)	79.9 (9.0)
Age of first symptoms—mean (SD±)	63.0 (8.6)	59.7 (3.1)	64.0 (6.2)	66.4 (3.3)	63.5 (6.2)	68.8 (8.4)
Educational level—mean (SD±)	13.5 (4.3)	13.9 (3.6)	13.3 (4.6)	13.3 (5.0)	13.0 (8.5)	5.2 (4.0)
Hand dominance (right-handed)—*N* (%)	20 (100)	8 (100)	3 (100)	7 (100)	2 (100)	16 (100)
Race—*N* (%)						
White	18 (90.0)	7 (87.5)	3 (100)	6 (85.7)	2 (100)	10 (62.5)
Mixed	2 (10.0)	1 (12.5)	0 (0)	1 (14.3)	0 (0)	3 (18.8)
Black	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (12.5)
Indigenous	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (6.3)

PPA, primary progressive aphasia; AD, Alzheimer's disease; F, female; SD, standard deviation.

When the early symptoms of the PPA variants were compared, a statistically significant difference was found for anomia ($p = 0.04$) and speech motor difficulty ($p = 0.03$), which were the most frequent in the svPPA and nfvPPA variants, respectively. There was no significant difference for behavioral symptoms ($p = 0.66$), agrammatism ($p = 0.38$), temporal/spatial disorientation ($p = 0.58$), difficulty reading and writing ($p = 0.19$), difficulty repeating ($p = 0.31$), comprehension difficulties ($p = 0.66$), and echolalia ($p = 0.58$). Symptoms related to deficits in memory and executive function were not compared, as they were reported only in the AD group. **Figure 1** shows the percentage of occurrence of each symptom in each group.

DISCUSSION

This study suggests a potential relationship between the early symptoms reported by family members and caregivers close to individuals with PPA and AD, and the diagnosis of these diseases. The results of this study showed that the initial language symptoms, such as anomia and speech difficulties, were significantly associated with the svPPA and nfvPPA variants, respectively; while memory-related symptoms were associated with AD.

The study investigated the early symptoms through a clinical interview with the caregivers of the participants, with no neuropsychological assessment. Nevertheless, the early symptoms that were significantly associated with the svPPA, nfvPPA and AD groups were in line with the neuropsychological descriptions found in the literature (6, 7, 11, 16, 17). A broad review (6) that described the linguistic aspects and anatomical characteristics of the three PPA variants, in addition to the behavioral variant FTD, describes in detail the clinical findings in the variants, confirming that the identification by confrontation is impaired in the svPPA, as well as the articulation and speed of speech have changes in nfvPPA.

The results of this study are in line with the findings of another study (18) that investigated the symptoms of the initial stages and also the pathological analyzes of individuals with FTD, which reported that most of the patients with svPPA reported anomia as one of the first symptoms, and that memory symptoms were rarely reported in patients with frontotemporal changes, such as PPA and behavioral variant FTD. That study (18) also reported that, even in the early stages and with few manifestations, patients with FTD already had changes in the pathological analyzes, and also already reported typical symptoms of the diagnostic criteria of their variants. The authors stressed the importance of evaluating the first clinical symptoms in order to contribute to early diagnosis and favor the prognosis of these individuals.

The results of the present study also indicate that the early symptoms related to memory were significantly associated with patients with AD, while they were not reported in patients with PPA. This finding is in line with the literature, which reports that, initially, the diagnosis of AD requires that at least two cognitive domains—such as memory, learning, reasoning, behavior—must be impaired and must cause significant impairment to the individual's functionality (8, 9).

In this study, the lvPPA was not found to be associated with any initial symptoms described by the sample of participants. This may be explained by three possible reasons. First, it would be due to the fact that the difficulty repeating (1), which is one of the main characteristics of lvPPA, is difficult to perceive and observe by patients and their caregivers, since repetition is not used in common way, and is usually more detectable at a neuropsychological or speech/language examination. Second, the lvPPA is the most recently described variant and there are reports in the literature of the poor reliability of identifying its clinical characteristics (19, 20). The core clinical characteristics of the diagnostic criteria for this variant include symptoms that are not unique to it, such as anomia (which is an important symptom of svPPA) and the difficulty in repeating sentences, which is a symptom that can occur in this variant as well, despite not being one of the diagnostic criteria of nfvPPA (2). In this sense, it was possible to notice that the percentage of occurrence of repetition difficulties in our sample was similar between the lvPPA and nfvPPA groups. Thus, and as already discussed before (11), there may be questions about the diagnostic criteria used in PPAs, and reviewing these criteria may be important for more accurate diagnoses. Butts et al. (11) reported that 31% of a sample of subjects with PPA was not classifiable by the quantitative application of the current diagnostic consensus

FIGURE 1 | Percentages of occurrence of the first symptoms in each group of participants. AD, Alzheimer's disease; PPA, primary progressive aphasia; lvPPA, logopenic variant primary progressive aphasia; svPPA, semantic variant primary progressive aphasia; nfvPPA, non-fluent/agrammatic variant primary progressive aphasia; ncPPA, non-classifiable primary progressive aphasia. *Statistically significant difference for the symptom of "anomia" ($p = 0.00$), when comparing PPA and AD groups. **Statistically significant difference for the symptom of "speech motor difficulty" ($p = 0.00$), when comparing PPA and AD groups. ***Statistically significant difference for the symptom of "paraphasias" ($p = 0.01$), when comparing PPA and AD groups. ****Statistically significant difference for the symptom of "memory difficulty" ($p = 0.00$) reported only in the AD group, when comparing PPA and AD groups. #Statistically significant difference for the symptom of "anomia" ($p = 0.04$) associated with a higher frequency in svPPA, when comparing PPA groups. ##Statistically significant difference for the symptom of "speech motor difficulty" ($p = 0.03$) associated with a higher frequency in nfvPPA, when comparing PPA groups.

criteria (2011) (1), which is in line with Senaha and colleagues (2013) (2), who also reported such difficulties. A recent study (18) also raised the question that, although there are initial symptoms that are referred by several patients, they are not considered diagnostic criteria by the current consensus. This discussion supports the importance of studies in speakers of other

languages, in order to investigate the profile and the occurrence of linguistic manifestations specific to the pattern of each language. Furthermore, the limited sample size of the present study would be the third reason to explain why an association of early symptoms with lvPPA may not have been found.

The first symptoms that were unique in certain groups of this study can be seen as red flags specifically for directing the clinical interview with the patient and caregiver, allowing for a better direction of the investigation. On the other hand, our study did not show a significantly higher occurrence of several other symptoms in any of the groups analyzed. Although the literature indicates the occurrence of these symptoms in the studied disorders, such as the occurrence of behavioral symptoms as inaugural symptoms in PPA (21), this characteristic might not be a red flag of the interview with the patient and the caregiver, despite being extremely relevant for the clinical management.

The analysis and investigation of the first symptoms presented by individuals with PPA is essential for the differential diagnosis of the disorder and for the classification of its variants. Studies that described the concept and diagnostic criteria of PPA (1, 5) emphasize that language deficits must be the main aspects with changes in order to define it as a case of progressive aphasia, while other cognitive domains, such as memory, visuospatial skills, and behavior should remain without significant changes, at least in the first two years of the disease (5). Thus, the identification of the early symptoms that are prevalent in the language domain is essential for a more accurate diagnosis of PPA.

When analyzing the Brazilian context in which this study was carried out, it is known that the diagnosis of patients with PPA is not always carried out accurately, and mistakes and diagnostic errors may occur due to the delay for the patient to reach the reference services (10, 12). Therefore, it is clear that a retrospective investigation of the early symptoms has a more relevant role in this scenario, stressing that a thorough clinical interview should be a priority in monitoring the suspected PPA in this population, contributing to the accuracy of the diagnosis.

All participants in this study were Brazilian Portuguese speakers. However, most scientific knowledge related to PPA is obtained from studies with English speakers. As the PPA is a syndrome centered on language impairment, it is important to emphasize studies that aim to characterize the profile and linguistic manifestations of speakers of other languages, especially in Latin languages, such as Portuguese (10). The unique characteristics of different languages have different perspectives on the development, plasticity and cognitive reserve of specific linguistic networks and, thus, could have different diagnostic criteria, which would apply for each language specifically (16).

It is important to note that the interpretation of our results have to be made considering three important limitations: (I) The sample size of our study, especially the small number of participants with lvPPA. We believe that the results of the lvPPA group are not conclusive due to the sample size. However, we believe it was important not to exclude them from the study in order to call attention to one of the great difficulties to conduct research with this profile of participants in Brazil, which is collecting significant samples from patients with PPA due to the inaccurate and late detection and diagnosis (12). (II) The heterogeneity of sociodemographic characteristics between groups. Participants with PPA and also their caregivers had higher educational level than their peers of the group with AD. Individuals with higher education and better socioeconomic status may tend to seek medical attention sooner in the face of milder and lesser known symptoms, such as the language symptoms of PPA. The caregivers may also notice and report symptoms more accurately. For reasons of study feasibility, most patients with PPA included in this study were from private health services, while those with AD were from public health institutions. As the diagnosis of AD is better known and more easily performed, this type of dementia has a higher frequency of detection in the Brazilian public health system to the detriment of cases of PPA. In turn, although the sample of this study cannot be considered large or expressive, given the reality of Brazilian scientific production on this topic, which is scarce and basically reduced to case studies (10), it can be considered a reasonable sample. (III) Not all participants could perform functional neuroimaging or cerebrospinal fluid examination with dosage of AD biomarkers, due to constraints and because such tests are not covered by the Brazilian public health system.

Finally, the investigation and knowledge of the first symptoms presented by patients with PPA has great potential to assist in the differential diagnosis of the disease variants. This study showed that the symptoms of "anomia" and "speech motor difficulties" are the most frequently reported in svPPA and nfvPPA, respectively; while the symptoms associated with memory are more often related to AD. Further research with larger and even more representative samples may contribute to the description of the profile and clinical symptoms presented by Brazilian Portuguese-speaking patients with PPA.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the committee of the Irmandade Santa Casa de Misericórdia de Porto Alegre (ISCMPA) and Universidade Federal de Minas Gerais (HC-UFMG). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TR: conceived the idea, designed and carried out the study, took lead in writing the manuscript. TM, PC, FS, and LF: contributed to the recruitment of participants and the final manuscript. BB: conceived the idea, designed the study, supervised the study, and reviewed the final manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by Master's Degree scholarship from Coordenação de Desenvolvimento de Pessoal de Nível Superior (CAPES).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.628406/full#supplementary-material

REFERENCES

1. Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, et al. Classification of primary progressive aphasia and its variants. *Neurology.* (2011) 76:1006–14. doi: 10.1212/WNL.0b013e31821103e6
2. Senaha MLH, Caramelli P, Brucki S, Smid J, Takada L, Porto C, et al. Primary progressive aphasia: classification of variants in 100 consecutive Brazilian cases. *Dement Neuropsychol.* (2013) 7:110–21. doi: 10.1590/S1980-57642013DN70100017
3. Mesulam MM. Primary progressive aphasia—a language-based dementia. *N Engl J Med.* (2003) 349:1535–42. doi: 10.1056/NEJMra022435
4. Mesulam MM. Primary progressive aphasia—a dementia of the language network. *Dement Neuropsychol.* (2013) 7:2–9. doi: 10.1590/S1980-57642013DN70100002
5. Mesulam MM. Primary progressive aphasia. *Ann Neurol.* (2001) 49:425–32. doi: 10.1002/ana.91
6. Grossman M. Linguistic aspects of primary progressive aphasia. *Ann Rev Linguist.* (2018) 4:377–403. doi: 10.1146/annurev-linguistics-011516-034253
7. Beber BC. Proposta de apresentação da classificação dos transtornos de linguagem oral no adulto e no idoso. *Distúrb Comum.* (2019) 31:160–9. doi: 10.23925/2176-2724.2019v31i1p160-169
8. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack Jr CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* (2011) 7:263–9. doi: 10.1016/j.jalz.2011.03.005
9. Deardorff WJ, Grossberg GT. Behavioral and psychological symptoms in Alzheimer's dementia and vascular dementia. *Handb Clin Neurol.* (2019) 165:5–32. doi: 10.1016/B978-0-444-64012-3.00002-2
10. Beber BC, Brandão L, Chaves MLF. Alerta à comunidade fonoaudiológica brasileira sobre a importância da atuação científica e clínica na afasia progressiva primária. *CoDAS.* (2015) 27:505–8. doi: 10.1590/2317-1782/20152015081
11. Butts AM, Machulda MM, Duffy JR, Strand EA, Whitwell JL, Josephs KA. Neuropsychological profiles differ among the three variants of primary progressive aphasia. *J Int Neuropsychol Soc.* (2015) 21:429–35. doi: 10.1017/S1355617715000399
12. Beber BC, Chaves MLF. Evaluation of patients with behavioral and cognitive complaints—Misdiagnosis in frontotemporal dementia and Alzheimer's disease. *Dement Neuropsychol.* (2013) 7:60–5. doi: 10.1590/S1980-57642013DN70100010
13. Battista P, Miozzo A, Piccininni M, Catricalà E, Capozzo R, Tortelli R, et al. Primary progressive aphasia: a review of neuropsychological tests for the assessment of speech and language disorders. *Aphasiology.* (2017) 31:1359–78. doi: 10.1080/02687038.2017.1378799
14. Cappa SF, Gorno-Tempini ML. Clinical phenotypes of progressive aphasia. *Future Neurol.* (2009) 4:153–60. doi: 10.2217/14796708.4.2.153
15. American Psychiatric Association. *Manual diagnóstico e estatístico de transtornos mentais: DSM-5*. 5 ed. Tradução: Maria Inês Corrêa Nascimento. Porto Alegre: Artmed; (2014).
16. Tee BL, Gorno-Tempini ML. Primary progressive aphasia: a model for neurodegenerative disease. *Curr Opin Neurol.* (2019) 32:255–65. doi: 10.1097/WCO.0000000000000673
17. Spinelli EG, Mandelli ML, Miller ZA, Santos-Santos MA, Wilson SM, Agosta F, et al. Typical and atypical pathology in primary progressive aphasia variants. *Ann Neurol.* (2017) 81:430–43. doi: 10.1002/ana.24885
18. Kawakami I, Arai T, Shinagawa S, Niizato K, Oshima K, Ikeda M. Distinct early symptoms in neuropathologically proven frontotemporal lobar degeneration. *Int J Geriatr Psychiatry.* (2020) 36:38–45. doi: 10.1002/gps.5387
19. Mesulam MM, Wieneke C, Thompson C, Rogalski E, Weintraub S. Quantitative classification of primary progressive aphasia at early and mild impairment stages. *Brain.* (2012) 135:1537–53. doi: 10.1093/brain/aws080
20. Sajjadi SA, Patterson K, Arnold RJ, Watson PC, Nestor PJ. Primary progressive aphasia: a tale of two syndromes and the rest. *Neurology.* (2012) 78:1670–7. doi: 10.1212/WNL.0b013e3182574f79
21. Caixeta L, Caixeta M. Primary progressive aphasia beginning with a psychiatric disorder. *Clinics.* (2011) 66:1505–8. doi: 10.1590/S1807-59322011000800035

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 14 June 2021
doi: 10.3389/fneur.2021.654143

SENSE-Cog Asia: A Feasibility Study of a Hearing Intervention to Improve Outcomes in People With Dementia

Saima Sheikh[1], Sehrish Tofique[2], Nosheen Zehra[1], Rabia Amjad[2], Maham Rasheed[2], Maria Usman[2], Shanker Lal[2], Emma Hooper[1,3], Jahanara Miah[1], Nusrat Husain[4], Hussain Jafri[5,6], Nasim Chaudhry[2] and Iracema Leroi[7] on behalf of the SENSE-Cog Asia Research Group*

[1] Division of Neuroscience and Experimental Psychology, University of Manchester, Manchester, United Kingdom, [2] Department of Psychiatry, Pakistan Institute of Living and Learning, Karachi, Pakistan, [3] Department of Health, Institute of Health, University of Cumbria, Lancaster, United Kingdom, [4] Division of Global Mental Health, University of Manchester, Manchester, United Kingdom, [5] Department of Health, Alzheimer Pakistan, Lahore, Pakistan, [6] Department of Health, Fatima Jinnah Medical University, Lahore, Pakistan, [7] Department of Psychiatry, Global Brain Health Institute, Trinity College Dublin, Dublin, Ireland

OPEN ACCESS

Edited by:
Agustin Ibanez, Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina

Reviewed by:
Jennifer A. Deal, Johns Hopkins University, United States
Suvarna Alladi, Nizam's Institute of Medical Sciences, India

***Correspondence:**
Iracema Leroi
iracema.leroi@tcd.ie
orcid.org/000-0003-1822-3643

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: *15 January 2021*
Accepted: *07 May 2021*
Published: *14 June 2021*

Citation:
Sheikh S, Tofique S, Zehra N, Amjad R, Rasheed M, Usman M, Lal S, Hooper E, Miah J, Husain N, Jafri H, Chaudhry N and Leroi I (2021) SENSE-Cog Asia: A Feasibility Study of a Hearing Intervention to Improve Outcomes in People With Dementia. Front. Neurol. 12:654143. doi: 10.3389/fneur.2021.654143

Background: There are few evidence-based non-pharmacological interventions adapted for people with dementia (PwD) in lower- and middle-income countries (LMIC). Thus, there is value in culturally adapting existing interventions from other settings. One such intervention for PwD involves hearing rehabilitation, which may improve dementia-related outcomes.

Objective: To culturally adapt and evaluate the feasibility and acceptability of a multi-faceted hearing support intervention to enhance quality of life in PwD for a LMIC setting, Pakistan.

Design: This was a study in three phases: (1) training and capacity building to deliver the study, including Patient and Public Involvement (PPI); (2) cultural adaptation of the intervention; and (3) delivery of a single-group feasibility study with a pre-test post-test design.

Setting: Home-based intervention, in two cities of Pakistan.

Participants: Adults aged $\geq$ 60 with mild-moderate dementia and uncorrected or partially corrected hearing impairment, and their study partners ($n = 14$).

Intervention: An adapted hearing support intervention (HSI) comprising a full assessment of hearing function, fitting of hearing aids, and home-based support from a "hearing support practitioner."

Outcomes: Ratings of the feasibility of the study procedures, and acceptability/tolerability of the adapted intervention were ascertained through questionnaires, participant diaries, therapist logbooks and semi-structured interviews. A signal of effectiveness of the intervention was also explored using a battery of dementia-related outcome measures.

Results: Following cultural adaptation and capacity building for study conduct and delivery, we successfully implemented all intervention components in most participants, which were well-received and enacted by participant dyads. Acceptability

(i.e., understanding, motivation, sense of achievement) and tolerability (i.e., effort, fatigue) ratings and safety of the intervention were within *a priori* target ranges. Recruitment and retention targets required improvement, due to the COVID-19 pandemic outbreak, as well as the lack of a clear clinical diagnostic pathway for dementia in both sites. Areas for future modification were clearly identified, including: the assessment/delivery logistics circuit; procedures for arranging visits; communication among referring clinicians and the study team.

Conclusion: This is the first study in a LMIC of sensory enhancement to improve dementia outcomes. Positive feasibility, acceptability and tolerability findings suggest that a full-scale effectiveness trial, with certain modifications is warranted.

Keywords: dementia, LMICs, hearing impairment, feasibility, acceptability, tolerability

INTRODUCTION

Cognitive decline and dementia are newly emerging as public health priorities in low- and middle-income countries (LMICs) due to aging of the population. In South Asia alone, it is estimated that the number of people who will be living with dementia (PwD) by 2030 will exceed 9 million (1). Approximately one-third of adults over the age of 65 years experiences a disabling hearing loss (2), and in PwD, over 85% are affected (3). Together, cognitive and sensory deterioration can result in a "crucible of co-morbidity" for older people, compounding negative outcomes such as poor quality of life and high caregiver burden (4, 5).

To date, the infrastructure of health and social care services for older people in South Asia is still quite limited (6, 7). However, in contrast to dementia services, hearing services are more developed and there is evidence that improving hearing function in older people represents a potentially reversible cause of cognitive impairment, or, may optimize remaining cognitive and functional ability in people already with dementia (8, 9). Hearing interventions may promote better outcomes for people with cognitive impairment, but consistent evidence for the positive impact is still lacking, highlighting the need for sufficiently powered randomized controlled trials of such interventions on outcomes relevant to people living with dementia (8). As highlighted by recent guidance for up scaling dementia research in Pakistan (10), developing and evaluating low cost, easily accessible interventions for PwD and their families in such low- and middle-income health economies such as South Asia, is essential to support the development of services. Thus, addressing outcomes in dementia by improving hearing is an approach with high potential.

Currently, a large-scale randomized controlled trial (RCT) of a sensory support intervention for PwD is being conducted across clinical sites in five European countries (11, 12), as part of the SENSE-Cog research program (13). The multi-component intervention involves the assessment, management of, and adherence support for hearing and vision deficits in PwD. Early outcomes have indicated that the sensory intervention is pragmatic and feasible (14) and may be effective in improving dementia-related outcomes (15). Thus, SENSE-Cog was deemed a suitable intervention to be evaluated in a South Asian context. However, since the health and care ecosystem in South Asia differs from Europe, and public understanding of dementia and its impact are still developing, it was necessary to undertake an adaptation and feasibility testing program, SENSE-Cog Asia, as a first step, prior to a definitive RCT of effectiveness and implementation.

SENSE-Cog Asia was carried out in three phases, as outlined in **Figure 1**. Phase 1 was conducted to build capacity and capability for applied dementia research in seven sites across Pakistan (Karachi, Rawalpindi, Lahore), India (Mysuru, Bangalore, Chennai), and Bangladesh (Dhaka). We have reported on this work elsewhere (12). Briefly, to develop an integrated capacity and capability building strategy, we established goals embedded within a Theory of Change framework (16), across six domains: people, research integrity and governance, study delivery skills, international collaborative working, patient and public involvement (including awareness raising, addressing social stigma and health literacy), and development of "pathways" (logistics, referrals, links to existing, or developing services).

Additionally, in Phase 1, we developed a network of patient and public involvement (PPI) groups to inform the work and support adaptation of the intervention. The PPI work, which resulted in a network of people with dementia and their families (*SENSE-Cog Asia Research Advisory Team),* involved a variety of public engagement activities reflecting different parts of the Wellcome Trust's "Public Engagement Onion" (17). Each site reported PPI outcomes, including changing attitudes and behavior to dementia and research involvement, best methods to inform participants about the dementia study, sharing knowledge and outcomes, and co-adapting the dementia study protocol to the local context. We also reported on the challenges inherent in introducing a PPI model into LMIC settings where hierarchical social structures predominate, particularly in the context of medical professional-patient relationships.

Phase 2 of SENSE-Cog Asia involved cultural adaptation of the SENSE-Cog hearing and vision intervention, which was originally developed (4) and field tested (11) in Europe over 18-months. Adapting an intervention developed elsewhere into a context with a markedly different language, socioeconomic and cultural context requires modification before it can be systematically evaluated (18). This enhances the relevance of the

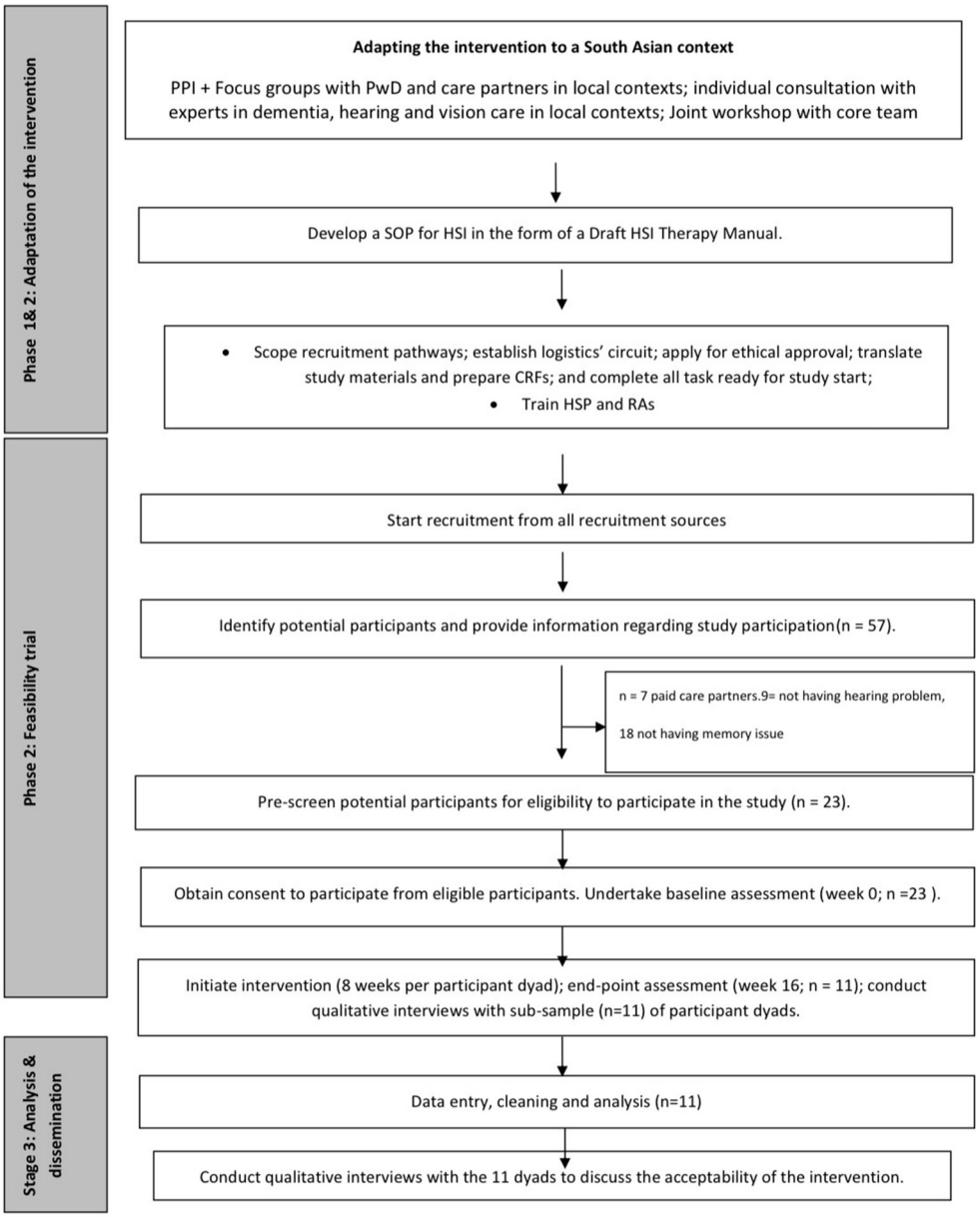


FIGURE 1 | Flowchart of steps in the SENSE-Cog Asia feasibility study.

intervention to the local population and increases the likelihood of implementation and "scale-up" following the evaluation stage.

Finally, Phase 3 of SENSE-Cog Asia was initially designed as a feasibility study of the adapted intervention in all seven sites across South Asia. The original sample size was chosen as 70 dyads (PwD and their care partners) ($n = 7$ dyads from each site). The focus of the study was to develop and test the logistics' circuits of the intervention delivery, other feasibility parameters, and tolerability of the intervention by participants. However, following phase 1 and 2, the COVID-19 pandemic broke out and all research activity stopped. The key challenge in recruitment was due to the local lockdown in participating hospital centers in India and Bangladesh due to the pandemic. However, these sites were also slow to open in the first instance due to delays in obtaining approvals from local sponsors and the bureaucracy around transfer of study funds. Only the sites in Pakistan (Karachi and Lahore), were initiated for the feasibility study. Thus, we chose to follow current guidance regarding contingency planning for dementia research in the COVID-19 pandemic (19) and amended our study protocol accordingly to ensure the safety of our research team and participants. This involved halting further start-up activity in the remaining sites, halting recruitment in the Pakistan sites, and completing as many assessments as possible using remote means. We report

the outcomes of our amended study, SENSE-Cog Pakistan, here. Ethical approval for the amended protocol was obtained from the University of Manchester's Research Ethics Committee 5 [2019-6061- 9196].

OBJECTIVES

The primary objectives of our amended feasibility study, were: (1) to describe the baseline characteristics of PwD with concurrent hearing impairment, and their caregivers in the Pakistan study sites; (2) to evaluate the feasibility of the operational elements; (3) to evaluate the acceptability and tolerability of the adapted intervention for a definitive trial; and (4) to explore the impact of the intervention on PwD and caregiver outcomes.

Ethical Approval

Since the study was conducted in collaboration with UK-based investigators, ethical approval was initially obtained from the University of Manchester's Research Ethics Committee (REC) 5 [2019-6061-9707]. Local approvals were also obtained at each site prior to the study commencing. The investigators at each site ensured that the study protocol and all study-related documentation was approved by the appropriate REC, prior to any participant recruitment. All researchers received training in line with the UK's Good Clinical Practice (GCP) guidelines (20).

Following the COVID-19 restrictions, ethical approval for the amended protocol was obtained from the University of Manchester's Research Ethics Committee 5 [2019-6061- 9196]. The outbreak of pandemic resulted not only in halting further start-up activity in the remaining sites, it also halted recruitment in the two active sites, and the remaining assessments were completed remotely as much as possible using remote means and the amended low risk, non-contact intervention was delivered to the participants who had already consented before the outbreak of the pandemic.

The biggest ethical challenge for the study related to inclusion of PwD in a research protocol when they might not have capacity to consent. Unlike in the UK, where the Mental Capacity Act (2005, amended 2018) has specific legislation to safeguard research participants lacking capacity, none of the three countries involved in the original SENSE-Cog Asia protocol has such legislation. Thus, only participants with capacity were included in the study.

Equitable Partnerships

Since our work involved close collaboration among investigators from multiple regions, ranging from high to very low-income countries, we followed the principles of a "balanced partnership" to ensure equity in our working relationship (10, 21). Power imbalances in international research partnerships can occur, with one partner, usually the partner from the high-income country (HIC), dictating the terms of the collaboration, and the other partner being expected to comply (22–24). This risks the possibility of exploitation and scientific colonialism. In our case, the intervention originated in Europe and was being adapted to South Asian settings, adding to the risk of imbalance. Thus, we strove to ensure equity by: (1) co-developing the study protocol over 6 months via monthly conferences involving all team members; (2) incorporating local solutions for intervention adaptation; (3) ensuring each site's perspectives were included through monthly team meetings; (4) incorporating the feedback from local PPI groups; and (5) sharing of outputs across sites through co-authorship. This approach fostered mutual respect and cooperation amongst team members.

METHODS

Phase 1: Capacity and Capability Building

The methods for Phase 1 are described elsewhere (12, 17).

Phase 2: Cultural Adaptation of the Intervention

Our starting point was the parent form of the intervention, the SENSE-Cog Sensory Support Intervention (SSI), which as was developed and field trialed over an 18-month period (4, 8, 11) and is currently being evaluated in a five-nation definitive RCT in Europe (4). For the South Asian context, it was important to consider local factors such as: (1) language and cultural aspects of participants; (2) availability of resources and services; (3) understanding and awareness of dementia amongst individuals and their caregivers; (4) limited recruitment pathways for clinical dementia research; and (5) limited engagement with dementia clinical research amongst local clinicians and PwD and their families. Thus, we modified the intervention for the South Asian context using a stepwise framework for cultural adaptation including information gathering, preliminary adaptation of the study design, and preliminary testing of the modified intervention (25). The final step, "adaptation refinement" will be guided by the findings of the feasibility study we describe here.

The first step of information gathering involved a rapid literature review of existing psychosocial interventions for dementia in LMICs, followed by PPI consultations with PwD and caregivers in local contexts, individual consultations with local dementia and hearing care professionals, and a joint workshop with core team members of the EU SENSE-Cog RCT team and the local research teams. Findings from this work informed initial modifications of each component of the intervention, as well as aspects of the intervention. In contrast to the European intervention, the culturally adapted intervention, or Hearing Support Intervention (HIS) for South Asia included only hearing support, rather than both hearing and vision support. Additionally, all assessment and outcome rating tools were translated into local languages, and the content of the intervention material was modified to include culturally relevant pictures and activities and take account of literary levels of older participants.

Although the Hearing Support Intervention (HSI) that we developed for the SENSE-Cog Asia trial has core resonances with the European SENSE-Cog SSI, outlined by Regan et al. (11), it differed from the European version in several ways including that we did not specify the make and model of hearing aid that participants would receive and we included dementia awareness education for caregivers (**Table 1**). Moreover, in contrast to the European version of the study, this was as trial targeting a single

TABLE 1 | Similarities and differences between the SENSE-Cog Europe and Asia interventions.

	SENSE-Cog Europe intervention	SENSE-Cog Asia intervention
Nature of sensory loss	Hearing and/or vision	Hearing only
Hearing aids provided	Starkey Muse i2400 Mini BTE	Make/model not specified
Intervention components	Provision of hearing aids/glasses Training and support in using hearing aids/glasses Goal setting Communication training Provision of supplementary sensory devices (e.g., lamp) Referral to support services Supporting social inclusion	Provision of hearing aids Training and support in using hearing aids Goal setting Communication training Dementia awareness training for study partner
Intervention provider	Sensory support therapist	Hearing support practitioner
Duration of intervention	Up to 10 home-based visits	Up to 8 home-based visits
Location of intervention	Participant's home	Participant's home

sensory modality, hearing, only, rather than both hearing and vision. Additionally, the intervention also included dementia education and support for the care partner. This was considered necessary due to the low level of dementia awareness and cognitive health literary of care partners in Pakistan. A complex intervention with multiple parts tailored to the needs of each individual in this context would thus have to include more than just support for hearing impairment. The approach involved these elements being closely aligned and inter-dependent. Finally, our adapted intervention did not include the intervention components relating to social inclusion, referral to support services, as these were limited in the regions in which we worked. We named the intervention provider as a "Hearing Support Practitioner" rather than a "Sensory Support Therapist" to reflect the focus on hearing alone and to ensure that cultural concerns regarding the term "therapist" were avoided.

Phase 3: Feasibility Trial

Study Design and Participants

This was a single arm open-label feasibility and acceptability study including participant dyads (PwD and their caregiver) across two sites in Pakistan. Each dyad received the culturally adapted version of the HSI over an 8-week period, in their own homes. All participants were assessed for capacity to provide informed consent to participate in the study, and if deemed to have capacity, provided written informed consent prior to their inclusion. Researchers were carefully trained to undertake capacity assessments in older and potentially vulnerable people. Additionally, all researchers used a checklist to ensure that the key elements of capacity to consent were present and recorded.

Inclusion/Exclusion Criteria

As outlined in **Table 2**, we included people over the age of 60, with capacity to consent, as per the UK's Mental Capacity Act, 2005 (amended 2018). All participants had to be living at home with symptoms meeting criteria for mild-moderate stage dementia due to Alzheimer disease, vascular dementia or "mixed" Alzheimer and vascular dementia. Where a formal diagnosis of dementia was lacking, we included people with evidence of significant cognitive difficulties (using the informant version of the GP-Cog) and meeting diagnostic criteria based on researcher assessment in consultation with clinical expertise from the PI. All had to have a clinically significant uncorrected or partially corrected (e.g., outdated prescription for hearing aids) mild to moderate hearing loss (worse than 35dBHL at 1,000 Hz and above in the better ear). We did not include people with congenital hearing loss. Study partners were informal caregivers in regular contact with the PwD (at least three times per week).

Recruitment, Screening, and Sample Size

We recruited and screened potential participants from local hospitals (medical and psychiatry outpatient departments) and the community (Alzheimer Pakistan). The agreed sample size in our amended protocol was 21 dyads (PwD and study partner), with seven dyads per site to be recruited over 3 months. This was considered sufficient to evaluate feasibility and tolerability of the intervention and trial protocol. However, due to the outbreak of COVID pandemic, the recruitment was halted at two sites (Karachi and Lahore), and did not begin at one site (Rawalpindi). At the point of study pause, 23 dyads had been screened ($n = 17$ from Karachi, Site A) and ($n = 6$ from Lahore, Site B). Fifteen dyads (65%) met study eligibility criteria and completed baseline assessments (9 dyads from Karachi and six from Lahore). Participant characteristics are outlined in **Table 3**. Of all PwD participants, the mean age of included participants with dementia was of 66.8 ± 5.7 years and 9 (39.1%) were male.

Feasibility Study Procedures

Procedures are shown in **Figure 1**. Following informed consent, we screened potential participants for hearing and cognitive impairment using the Sivantos Siemens Hear Check screener (42) and Urdu-version of the Montreal—Cognitive Assessment MoCA (26), followed by caregiver screening. For those who passed screening, a baseline assessment was undertaken, followed by initiation of the HSI, which was then delivered over eight visits by the HSP in participants' own homes. Dyads kept diaries of each visit, and the HSP kept a logbook detailing visits and dyad responses.

Evaluation Framework

A priori, we established three possible global outcomes for the study, based on a "traffic light" system: (1) proceed to a definitive study; (2) undertake further adaptations and feasibility work; or (3) do not proceed to a definitive study due to lack of feasibility. To ascertain this outcome, we designed an evaluation framework

TABLE 2 | Summary of participant inclusion and exclusion criteria and characteristics.

Inclusion	Age	≥ 60 years
	Domiciliary status	Living at home
	Cognitive impairment	Diagnosed with dementia as per ICD10 criteria due to the following conditions: Alzhemier's disease (AD) (as per NINCDS-ADRDA) or vascular dementia (VAD), or "Mixed" dementia (AD + VAD) OR evidence of cognitive difficulties significant enough to suggest the presence of dementia without having been formally diagnosed as having dementia, both with and without capacity. This will include those with young or later-onset dementia.
	Stage of cognitive function	Dementia in the mild to moderate stage, as indicated by a Montreal Cognitive Assessment score (MOCA) (26) of scale score ≥ 10;
	Hearing or vision impairment or both	Adult acquired hearing Impairment: defined by a bilateral hearing difficulty, indicated by failure of a pure tune hearing screening test in both ears, defined by hearing worse than 35dBHL at 1,000 Hz and above in the better ear, using the Hear Check device;
	Capacity to consent to the study	Has capacity to provide informed consent to participate in the study defined by the UK's Mental Capacity Act (2005)
	Study partner	is aged ≥ 18 years; and an informal caregiver (where providing care is not the person's primary paid role), such as a significant other of the PwD (e.g., a family member or close friend), who is either co-resident or in regular contact (on at least a weekly basis);
Exclusion criteria	Hearing	Congenital hearing impairments or has complete deafness (profound hearing loss) to prevent them from following study procedures;
	General status	Any unstable, acute physical or mental condition that would preclude participation in the study
		Is currently participating in any other trial of a potentially cognitive enhancing intervention, excluding marketed cognitive enhancing medication (cholinesterase inhibitors);

MoCA, Montreal Cognitive Assessment (26).

TABLE 3 | Participant demographic and clinical characteristics at baseline ($n = 15$ Dyads).

Variable	Category	Participants with dementia	Care partner participants
n		15	15
Age (Years)	Mean (SD)	65.2 (5.5)	30.8 (9.9)
	Median (IQR)	64 (8)	29 (10)
	Range	60–80	19–55
Gender	Female	8 (53.3%)	14 (93.3%)
	Male	7 (46.7%)	1 (6.7%)
Duration of cognitive impairment (months)	Median (IQR)	24 (24)	Not Applicable
Duration of memory problems (months)	Range Mean (SD)	4–120 Months 15.53 (2.9)	Not Applicable
Level of cognitive impairment (MoCA Total score)	Median (IQR) Range	15 (5) 10–20	
Normal (score ≥26)	*n* (%)	1 (4.3%)	
Dementia sub-type	Alzheimer's disease	1 (6.7%)	Not Applicable
	Vascular	1 (6.7%)	
	Undiagnosed	13 (86.9%)	
Living status of PwD	Living with spouse	9(60%)	Not Applicable
	Living with family	6 (40%)	
Co-resident with participant with dementia	Yes	Not Applicable	14 (93.3%)
Hours per week spent with PwD	Median (IQR) Range	Not Applicable	168 h (24) 15–168 h

MoCA, Montreal Cognitive Assessment (26); SD, Standard Deviation; IQR, Interquartile Range.

based on a modified version of the ACCEPT framework (43) for feasibility studies, which we have previously used in other studies (44).

Using quantitative measures (**Table 4**) and qualitative interviews with participant dyads, outcomes were captured at baseline, within 1 week of the last intervention visit, and 4–6 weeks after the last intervention visit (for selected measures only). At each HIS visit, the PwD and their study partner completed diaries with in-house Likert-type scales (e.g., rating each aspect of acceptability and tolerability on a scale of 1 = strongly disagree to 5 = strongly agree) with space for free text. Additionally, the HSP completed a logbook and field notes. We also conducted semi-structured interviews, following a topic guide, with dyads who completed the intervention ($n = 11$ dyads), within 1 week of the final intervention visit. The focus of the interviews was on participants' perception, experiences, and acceptance of the HSI. Eight interviews were conducted in Urdu (national language), and two in Punjabi (local language). All the interviews were transcribed into Urdu and analyzed to retain the essence of the themes. Themes were translated into English for reporting and back translated into Urdu to ensure accuracy.

Feasibility of Trial Procedures

These included recruitment rate, suitability of eligibility criteria, execution of the "logistics circuit" for assessment and supply of hearing aids, feasibility of the participant diaries, data collection methods, suitability of the battery of effectiveness measures, and retention. Effectiveness measures for the PwD included ratings of quality of life, mental well-being, neuropsychiatric symptoms, functional ability (dementia and hearing-related), and

TABLE 4 | Outcome assessment measures.

Participant with dementia outcomes		
Quality of life	DEM-QoL (health-related quality of life of people with dementia)	A 28-item questionnaire with options marked on Likert scale from 1 to 4 (a lot/quite a bit/a little/not at all), sum of all items give total score from 28 to 112, where higher score show better quality of life. Item number 1, 3, 5, 6, and 10 were reversed before final scoring (27).
	DEM-QoL-Proxy	A 31-item questionnaire with 4 point Likert scale from "1 to 4" (a lot/quite a bit/a little/not at all). Total of all items give possible score from 31 to 124, higher overall score indicates better quality of life. Item number 1, 4, 6, 8, and 10 were reversed before final scoring. This is answered by carer about PwD (27).
	EQ-5D-5L	This measures five dimensions of health as mobility, self-care, usual activities, pain/discomfort and anxiety/depression) on 5 levels. Five levels of problems (no, slight, moderate, severe, extreme) are marked from 1 to 5 that summed for total score ranging from 5 to 25. Low score indicates no problem in health dimensions. Score measured on Visual Analog Scale (VAS) from 0 to 100, if high indicate the better health state perceived by the patient. EQ-5D-5L-P is a proxy measure (28).
	Short-Form-12 (SF-12)	There are 12 categorical items in this tool. These items measured on liker scale as item 1 from 1 to 5 (excellent, very good, good, fair, and poor), item 2 and 3 from 1 to 3 (limited a lot, limited a little, or not limited at all), item 8 from 1 to 5 (not at all, a little bit, moderately, quite a bit, and extremely), item 9, 10, 11, and 12 from 1 to 6 all of the time, most of the time, a good bit of the time, some of the time, a little of the time, and none of the time). Item 4 to 5 had yes and no options. Two summary scores are reported from the SF-12—a mental component score (MCS-12) and a physical component score (PCS-12). SF-12-P is a proxy measure about PwD answered by caregiver. Higher score indicate better health status (29).
Functional measures	The Hearing Handicap Inventory for the Elderly (HHIE)	A 25 item tool with 3 response categories ("Yes" = 4, "Sometimes" = 2, "No" = 0). Response of all items added to get total score from "0 to 100" that categorized functional impermanent as 0–16: "No functional impermanent," "17–42: Mild to Moderate" and ≥43: Significant. HHIE–P is a proxy measure answered by carer about PwD (30, 31).
	Activities of daily living in the elderly (IADL-EDR)	An 11 item with 3-response category. Each item was rated for its applicability (yes/no), degree of disability (scored from 0 to 2) and causative impairment (cognitive and/or physical) (32).
	Neuropsychiatry inventory (NPI-12)	A 12 domains tool that assess both severity and frequency of Neuropsychiatric symptoms. Severity ranged as "mild, moderate and severe" while frequency as "occasional, often, several times per week and once or more day." Each domain is rated on presence and magnitude of symptoms (frequency × severity). The maximum score per domain is 12, with clinically significant symptoms for a given domain occurring at (frequency × severity) scores ≥4. Total NPI scores range from 0 to 144, higher score for both indicate higher severity and more frequency. It is answered by career about participants (33).
Caregiver outcomes		
Caregiver-related burden and stress	The Family Care giving Role scale (FCR)	Consists of 16 items on a five-point scale from 1 to 5, which are divided into three sub-scales: (1) satisfaction with the caring role, (2) resentment, and (3) anger. A summative score for the items within each sub-scale is calculated and higher scores indicate higher satisfaction with the caring role and greater feelings of resentment and anger (34).
Knowledge and awareness of dementia	Family Attitude Scale (FAS)	A 30 item tool with 5 point scale from "0 to 4" as "Never, Very rarely, Some days, Most days, and Every day." Sum of all items score gave the total score. The FAS was associated with the reported anger, anger expression and anxiety of respondents and found higher among caregivers (35).
	Affiliate Stigma Scale	This instrument has 22 items rated on a 4-point Likert scale with three domains (cognitive = 7 items, affect = 7 items, and behavior = 8 items); a higher score indicates a higher level of affiliate stigma (36).
Participant dyad outcomes		
Psychological aspects	Patient Health Questionnaire−9 (PHQ-9)	A 9-item tool that record responses from 0 to 3 (not at all to nearly every day). Total score of all items categorized as 0–4 none, 5–9 mild; 10–14 moderate; 15–19 major depression moderately sever and >20 depression severe (37).
	Generalized Anxiety Scale-7 (GAD-7)	This has seven items to assess severity of generalized anxiety disorder. The items are scored on 4-point Likert-scale ranging from 0 "not at all" to 3 "nearly every day." Scores 5, 10, and 15 signify cut off points for mild, moderate and severe anxiety, respectively (38).
	The De Jong Gierveld 6-item scale loneliness scale	A 6-item scale with 3 statements about emotional loneliness and 3 about social loneliness. Response categories for each item are "Yes/More or less/No." Negatively worded questions are scored "1" for neutral and positive response while positively worded questions are scored "1" for neutral and negative response. Sum of all items gave possible score range from "0" least lonely to "6" most lonely (39).
Process measures	Satisfaction with Therapy and Therapist Scale-Revised (STTS-R)	A 12-item tool with responses on a Likert scale from "1" strongly disagree to "5" strongly agree. Sum of the all even number items indicates patient's level of Satisfaction With Therapy (ST) and sum of all odd number items score reflects patient's level of Satisfaction With Therapist (SWT); higher the score, greater the level of patient satisfaction. Obtained score may range from 5 to 30 for both categories (40).
	Modified Credibility and Expectancy Questionnaire (MCEQ)	A modified version with six items each with three responses ranges from "1 to 3" (not at all, somewhat, and very). Sum of the score of all items add up to the final score with possible outcome ranging from "6 to 18" (41).

relationship satisfaction. Effectiveness measures for the study partner included ratings of well-being, mental health, caregiving-related burden and stress, and relationship satisfaction. Since this was an open-label study, we did not evaluate randomization and blinding procedures.

Feasibility of the Intervention Components and Implementation

This was assessed by HSP visit completion rates, visit duration and HSP logbook feedback.

Acceptability of the Intervention

The appropriateness of the delivery and receipt of the intervention was determined by percentage dropouts due to non-acceptability and rate of serious adverse events.

Tolerability of the Intervention

This was operationalized by percentage dropouts due to intolerance of the intervention and diary ratings of "effort" and "fatigue." The criterion for "tolerability" was 75% of participants scoring the intervention with the a priori target ranges: $\geq$ 3/5 for "effort" and "fatigue."

Semi structured interviews were also conducted with 10 care-partners who attended the hearing intervention sessions with PwD. Interviews were conducted to evaluate and gather evidence for feasibility of the study.

Data Analysis

Quantitative Analysis

As an initial exploration of a novel intervention, our goal was to observe any signal of change across various outcome measures in the dyad. We examined the change between baseline (pre-intervention) and follow-up (post-intervention) by summarizing the distributions of the outcome measures with measures of central tendency (mean or median) and variability (SD or IQR). The small sample size precluded investigation of associations among outcomes. On initial analysis, the covariates of interest were not heavily skewed and mean and medians were similar, thus, we report mean values here.

Qualitative Analysis

The free text feedback of the participant diaries and SST logbooks, using content analysis (45, 46). The post-intervention semi-structured interviews with the participant dyads, were evaluated using thematic analysis (47) which included familiarization, coding, generating themes, reviewing themes, defining and naming themes. During the familiarization stage, transcripts were read by (ST, AQ), and coding was done to describe the content. Themes were generated by merging codes into a single theme and reviewed among the researchers (ST, MR) to ensure there was accurate representation of the data. Lastly, all themes were defined in order to explain the data. The whole process was supervised by a senior researcher to minimize the bias (NC).

RESULTS

Details of the feasibility of trial procedures and acceptability and tolerability of the intervention are outlined in **Table 5**.

Feasibility of the Trial Procedures

Recruitment and Retention

Over a 6-month period, we enrolled 15 participant dyads across two study sites, giving a rate of 2.8 dyads per month, which was slower than our expected rate of 3.5 dyads per month. Recruitment was slower than expected in Sites A and B, mostly due to the Covid-19 pandemic outbreak, which also prevented Site C from opening. We screened 23 participants dyads across both sites, 15 participant dyads were eligible to be enrolled in the study. Of whom two were excluded following a normal hearing assessment by the audiologist. One participant dyad withdrew consent following the baseline assessments and one participant had an adverse event before the follow-up. At Site A, the reasons for the slow recruitment rate included the retirement of the referring consultant neurologist and a low number of older people with memory complaints attending the local psychiatry outpatient department, which was our main source of recruitment. Additional recruitment was undertaken from community health settings, supported by community workers. At Site B, of the six participant dyads who passed the screening stage, one withdrew due to an unrelated serious adverse event in the PwD after completing the baseline assessment. Reasons for a slower than expected recruitment rate at Site B included: strikes in hospitals, slow approval process for the study from local hospitals, lack of memory clinics and specific services for people with dementia. These factors limited the necessary referral sources. The overall successful screening rate was 65.2%. The retention rate at Site A was 83.3% (one PwD died before second follow-up at site A) and at Site B this was 100%. Screening, baseline and follow up visits were conducted according to the protocol across all sites.

Suitability of Eligibility Criteria

The audiologist did not prescribe hearing aids to two participants who were enrolled in the study. These two participants screened positive on hearing impairment due to conductive hearing loss and the need for surgery. This suggested that refinements to the simple Hear Check hearing screen were needed. All other inclusion/exclusion criteria were considered as appropriate by investigators.

Execution of the Service and Device Logistics' Circuit

Audiologist visits after baseline assessment were mostly carried out according to the timeline mentioned in the protocol (i.e., 71% of participants received their hearing assessment within 2 weeks of the assessment). Nine of the participants received their hearing devices within 2–3 weeks soon after audiologist visit. Two participants received their hearing aid within 5 weeks of the audiology visit because of the adjustments which were recommended due to severe hearing loss.

TABLE 5 | Feasibility of trial procedures.

Parameter and *a priori* evaluation criteria (if applicable)	Findings	Evidence to support finding
Feasibility of study procedures		
Eligibility criteria: 15 participant dyad meet study criteria	Criteria are acceptable except: (1) cognitive score cut-offs may be set too high and exclude PwD who may be appropriate; (2) Hear Check screening cut-off may not be stringent enough.	15 of those screened met inclusion criteria[a]. Two participants who screened positive on hearing impairment using the Hear Check were deemed not clinically suitable for hearing aids on full audiological assessment[a,b]. One participant refused to visit audiologist for full assessment One participant reported an adverse event (not related to study) soon after baseline assessment (before audiologist visit)
Recruitment: • Total target number • Rate	Successful at 11 of 2 sites. Slower than required for a larger trial.	Six at Site A and five at Site B
Retention: ≥10% completed all study procedures	Successful in both sites.	six completed the study in Sites A; five completed in Site B
Screening & baseline process:	Appropriate due to the length of assessment battery.	13 dyads had one visits for screening, 9 dyads had two visits for baseline assessment
Outcome battery administration and suitability:	Outcome rating scales are generally acceptable. Some scales were not suitable for the study population and require revision.	Minimal or no concerns were noted on battery duration and level of difficulty, other than all two sites reporting problems with: Details of the scales are in the table above.
Device logistics circuit:	Broadly feasible; areas for improvement identified.	All participants[a] received the prescribed hearing aids[b]. Delays in assessment for and receipt of hearing aids affected overall study timelines[a].
Participant diary: ≥ 70% completion	Diary activity was feasible for both PwD and study partner.	Out of six participants from site A, five completed their participant diary completely and one participant completed the diary till 3rd session only as sessions done on phone due to COVID-19, and participant refused to fill diary[c] out of five participants from site B, one participant's completed the diary for up to 3 session and two participant's completed the diary over the phone with the research assistant due to COVID[c]
Feasibility of Intervention components and implementation		
HSI: Was the his delivered, received and enacted as intended?	It is feasible, although timeline deviations were evident.	10 participants received a hearing assessment within 2 weeks of baseline[a,b]. One participant's hearing assessment got delayed due to operational issues around audiological assessment 9 participants received their hearing aids within 2–3 weeks and two participants received these within 5 weeks of their audiological assessment. All participants completed intervention component of device skills and knowledge (hearing aids)[b]
Acceptability of the intervention		
Was the hearing Intervention appropriate?	The intervention is acceptable	All 11 participants were willing to use their prescribed aids[b] 0 participant withdrawals due to lack of acceptability
Tolerability of the intervention by participants		
HSI:	The intervention is tolerable	All 11 participants were able to complete their hearing assessment[a,b]. The intervention was completed over a maximum of 12–13 visits

Key PwD, Person with dementia; SP, Study Partner; HSP, Hearing support practitioner; [a]Quantiative data; [b]HSP logbook; [c]Participant dyad diaries.

Usability of Study Materials and Suitability of Effectiveness Battery

All study measures and materials were feasible and acceptable to dyads. A total of 11 dyads completed their screening in one visit and four dyads completed the screening over two visits. Moreover, six dyads completed baseline assessment in one visit and 9 dyads completed this over two visits. There was an impact of COVID- 19 on diary use. Out of the six participants from site A, five completed their participant diary for all sessions while one participant completed the diary for only two session,

as sessions were delivered over phone due to COVID-19, and participant refused to fill the diary. Whereas, at Site B, four participants completed their diaries for all the sessions while for one participant, dairy was completed by the researcher as sessions were delivered over phone due to COVID-19 and participant was unable to complete the diary on his own. There were no missing data on the effectiveness outcome measures.

Feasibility of the Intervention Components and Implementation

We achieved 100% adherence to the study protocol and procedure for HSI at both sites. However, there was an increase in the total number of visits to deliver the intervention mainly due to the outbreak of COVID-19. All dyads completed their intervention over a maximum of 12–13 visits. This included a change from face-to-face to remote delivery of some aspects of the intervention for one dyad at each site due to the pandemic and lock down situation.

Acceptability and Tolerability of the Intervention

At both sites, there were no dropouts or adverse events due to lack of acceptability of the intervention. Adverse events, which were all unrelated to the intervention, included: death due to heart failure ($n = 1$), fall out of bed ($n = 1$), and hospital admission due to fever ($n = 1$).

Exploratory Effectiveness Outcomes

Measuring cognition, the most common primary outcome for dementia trials, was deemed not feasible as our study population had varying levels of literacy. Instead, we based our outcomes on a large-scale consultation exercise of meaningfulness of outcomes of non-pharmacological interventions for people living with dementia. This consultation, which involved multiple lay and professional stakeholders, de-prioritized cognitive outcomes and focused more on quality of life and engagement as important outcomes. Furthermore, according to our hypotheses and previous evidence syntheses (8), we did not anticipate that our intervention would significantly impact on cognitive outcomes but would instead have impact non-cognitive outcomes.

Participants With Dementia

Scores on effectiveness measures at baseline and post-intervention are outlined in **Table 6**. Overall, improvements were seen in several dementia-related outcomes following the intervention, compared to baseline.

Quality of life as assessed by the DEMQOL [health-related quality of life of people with dementia; (27)], showed improvement of mean score from baseline (49.9 ± 4.9) to first follow-up (65.0 ± 10.0), which was maintained at second follow-up (65.3 ±15.9) 4 weeks later. The DEMQOL-proxy, which assessed quality of life of the PwD as perceived by the caregivers, also showed a 15.2 point improvement in score from baseline (61.7 ± 11.7) to post intervention follow up (78.1 ± 7.9) that was also maintained at second follow up point (81.0 ± 11.09) (see **Table 6**). Mean health status, as measured by EQ-5D-5L (28), showed improved quality of life at post intervention with 1.7 point reduction in mean score from baseline to post intervention (i.e. from 14.4 ± 3.7 to 13.5 ± 4.9), while the Visual Analog Scale (VAS) score increased from 42.7 ± 17.2 at baseline to 47.7 ± 18.5 at follow up, suggesting improvement in health status. The EQ-5D-5L Caregiver proxy mean scores (28) at the time of baseline indicated average quality of life. Both summary scores from the Short-Form-12 [SF-12, (29)], the physical component score (PCS-12) and the mental component score (MCS-12), showed improvement PCS and MCS mean scores increased from baseline (26.7 ± 4.9 and 34.0 ± 6.8) to post intervention follow up (29.5 ± 5.2 and 40.0 ± 10.2), respectively.

Functional Measures

Of the 15 participants who completed the baseline measures, 14 (93.3%) had significant impairment and one had mild to moderate impairment on the Hearing Handicap Inventory for the Elderly Screening tool [HHIE; (30, 31)] at baseline, whereas following the intervention, none reported significant impairments on this scale, and two reported moderate impairment, reflecting an overall improvement in hearing-related functional impairment. As shown in **Table 6**, no changes in instrumental activities of daily living [IADL-EDR scale; (32)] were noted including in the sub-components of the scale. Neuropsychiatric symptom load diminished significantly from pre- to post-intervention (29.3 ± 20.1 to 9.8 ± 8.8) on the Neuropsychiatric Inventory [NPI, (33)]. Additionally, the proportion of behavioral domains which were scored in the "clinically significant" range (≥4 on frequency x severity) following the intervention at follow-up one was significantly lower compared to the proportion at baseline. There was a reduction in mean depression scores on the Patient Health Questionnaire−9 (PHQ-9, 44) from baseline (17.6 ± 3.8) to the first post intervention follow up (11.5 ± 3.7) of more than 6 points on the scale, which is greater than the minimally important clinical difference and was maintained at second follow-up (12.3 ± 4.7). On this same measure, severe depression was found among five (33.3%) participants at baseline that was not present in any of the participant post intervention (**Table 6**). Generalized Anxiety Scale-7 [GAD-7, (38)] showed a seven-point reduction in anxiety from baseline (14.2 ± 4.4) to post intervention (6.9 ± 2.9); this improvement was also sustained at second follow up (8.4 ± 4.0). Severity of anxiety also reduced from 10 (66.7%) at baseline to minimal anxiety at post intervention follow up (**Table 6**), as did loneliness scores, as assessed by De Jong Gierveld Loneliness Scale (39).

Caregiver Outcomes

Caregiver measures at baseline and post-intervention are outlined in **Table 7**. Overall, as with the participants with dementia, improvements were seen in a number of outcomes following the intervention, compared to baseline. Caregiver burden and stress reduced from baseline to second follow-up, as by an absolute 5.1-point increase in the satisfaction mean score on the Family Caregiving Role scale [FCR; (34)]. Depression and anxiety improved following the intervention, as shown mean score reduced from baseline (9.4 ± 5.9 and 7.2 ± 5.7) to post intervention (7.7 ± 7.0 and 4.5 ± 3.5) and second

TABLE 6 | Baseline and post-intervention outcome measurements for the Participants with Dementia (PwD).

Outcome domain	Baseline ($n = 15$)	Post-intervention ($n = 11$)	Post intervention difference	2nd Time follow up ($n = 10$)	2nd Follow up difference
Quality of life					
DEM-QoL	49.9 ± 4.9	65.0 ± 10.0	13.2 ± 9.2	65.3 ± 15.9	13.1 ± 18.2
Mean ± SD					
Median (IQR)	49 (5.5)	64 (13)	13 (5.5)	61.5 (13.5)	11 (19)
(Range)	(44–61)	(53–84)	(−2 _30)	(41_96)	(−14_48)
DEM-QOL-proxy					
Mean ± SD	61.7 ± 11.7	78.1 ± 7.9	15.2 ± 17.3	81.1 ± 11.7	14.8 ±17.7
Median (IQR)	64 (17)	76 (8)	6 (28)	85 (15)	11.5 (27.5)
(Range)	(35–78)	(66–94)	(−3_42)	(58–93)	(−10_39)
EQ-5D-5L					
Mean ± SD	14.4 ± 3.7	13.5 ± 4.9	−1.7 ± 4.4	Not applicable	
Median (IQR)	15 (6)	13 (4)	−3 (1.5)		
(Range)	(8–19)	(7–25)	(−5_11)		
VAS Score					
Mean ± SD	42.7 ± 17.2	47.7 ± 18.5	6.8 ± 24.2		
Median (IQR)	45 (20)	50 (12.5)	15 (15)		
(Range)	(5–70)	(10–75)	(−55_25)		
EQ-5D-5L-proxy					
Mean ± SD	13.8 ± 3.7	12.6 ± 4.7	−1.9 ± 3.2	Not applicable	
Median (IQR)	15 (5.5)	12 (7)	−3(2.5)		
(Range)	(7–19)	(6–22)	(−6_4)		
VAS score					
Mean ± SD	53.3 ± 19.6	48.2 ± 12.9	−5.5 ± 25.1		
Median (IQR)	55 (27.5)	50 (17.5)	5 (45)		
(Range)	(20–80)	(25–75)	(−40_30)		
SF-12 PCS					
Mean ± SD	26.7 ± 4.9	29.5 ± 5.2	3.4 ± 6.1	Not applicable	
Median (IQR)	26.4 (5.8)	29.5 (10)	2.7 (8.7)		
(Range)	(19.6–37.5)	(23.2–36.2)	(−6.7_13.9)		
SF-12 MCS					
Mean ± SD	34.0 ± 6.8	40.0 ± 10.2	4.9 ± 9.3	Not applicable	
Median (IQR)	33.6 (5.3)	42.9 (14.8)	6.2 (9.5)		
(Range)	(25.4–50.4)	(22.3–54.2)	(−12.7_21.5)		
Functional measures					
HHIE					
Mean ± SD	66.7 ± 17.9	11.6 ± 10.5	54.5 ± 21.6	Not applicable	
Median (IQR)	70 (30)	8 (8)	56 (24)		
(Range)	(36–92)	(00–32)	(4–80)		
Functional Impairment *n* (%)					
No	0	9 (82%)			
Mild/moderate	1 (6.7%)	2 (18%)			
Significant	14 (93.3%)	0			
IADL-EDR					
CD	9.5 ± 3.0	8.1 ± 3.1	1.0 ±4.8	Not applicable	

(Continued)

TABLE 6 | Continued

Outcome domain	Baseline ($n = 15$)	Post-intervention ($n = 11$)	Post intervention difference	2nd Time follow up ($n = 10$)	2nd Follow up difference
	10 (1.5)	9 (2.5)	0 (4)		
	(2–16)	(1–11)	(−9_9)		
PD	2.4 ± 2.6	3.7 ± 3.8	−1.2 ± 3.0		
Mean ± SD	2 (4)	3 (7)	0 (1.5)		
Median (IQR)	(0–7)	(0–10)	(−9_3)		
(Range)					
NPI-12					
Total Score	29.3 ± 20.1	9.8 ± 8.8	19.5 ± 11.3	7.7 ± 8.5	21.6 ± 11.6
Mean ± SD	22 (21)	8 (18)	14 (25)	8 (13)	16 (24)
Median (IQR)	(8–87)	(0–24)	(−5_70)	(0–27)	(−8_87)
(Range)					
Delusions	1.7 ± 2.7	00	1.7 ± 2.7	00	1.7 ± 2.7
Hallucinations	0.9 ± 2.1	00	0.9 ± 2.1	00	0.9 ± 2.1
Agitation	2.3 ± 2.6	0.5 ± 0.7	1.7 ± 1.9	0.5 ± 0.7	1.8 ± 1.9
Depression	5.5 ± 3.8	1.8 ± 1.8	3.7 ± 2.0	1.6 ± 1.8	3.9 ± 2.0
Anxiety	4.1 ± 3.3	1.1 ± 1.1	2.9 ± 2.3	0.8 ± 1.0	3.3 ± 2.3
Elation	0.9 ± 2.2	00	0.9 ± 2.2	00	0.9 ± 2.2
Apathy	2.3 ± 2.1	0.7 ± 1.0	1.6 ± 1.1	0.9 ± 1.8	1.4 ± 0.3
Disinhibition	1.5 ± 2.5	0.2 ± 0.6	1.3 ± 2.0	0.2 ± 0.6	1.3 ± 2.0
Irritability	3.4 ± 3.5	0.9± 1.6	2.5 ± 1.8	0.8 ± 1.7	2.6 ± 1.8
Aberrant motor behavior	1.3 ± 2.2	1.2 ± 1.7	0.1 ± 0.4	0.5 ± 1.1	0.7 ± 1.1
Sleep	4.2 ± 4.3	2.7 ± 2.9	1.5 ± 1.4	2.0 ± 2.4	2.2 ± 1.9
Appetite	1.2 ± 1.8	0.6 ± 1.1	0.6 ± 0.7	0.3 ± 0.6	0.9 ± 1.2
Mean ± SD					
Psychological aspects					
PHQ-9					
Mean ± SD	17.6 ± 3.8	11.5 ± 3.7	6.0 ± 3.7	12.3 ± 4.7	4.7 ± −5.1
Median (IQR)	18 (5.5)	11 (5)	4 (3.5)	11 (5.8)	3.5 (5.8)
(Range)	(11–23)	(7–18)	(2–14)	(7-21)	(−2_14)
n(%)					
Mild	0	4 (36%)		5 (50%)	
Moderate	3 (20%)	5 (45%)		2 (20%)	
Major	7 (46.7%)	2 (18%)		2 (20%)	
Severe	5 (33.3%)	0		1 (10%)	
GAD-7					
Mean ± SD	14.2 ± 4.4	6.9 ± 2.9	7.1 ± 3.8	8.4 ± 4.0	4.7 ± 4.5
Median (IQR)	15 (5)	6 (4)	7 (6)	9 (6.5)	3.5 (5.5)
(Range)	(6–20)	(2–11)	(2–13)	(2–14)	(−1_13)
n(%)					
None	0	2 (18%)		2 (20%)	
Mild	3 (20%)	6 (55%)		3 (30%)	
Moderate	2 (13.3%)	3 (27%)		5 (50%)	
Severe	10 (66.7%)	0		0	
De Jong Gierveld loneliness scale	4.9 ± 1.1	4.4 ± 1.8	0.7 ±−1.8	Not applicable	
Mean ± SD					
Median (IQR)	5 (2)	5 (1.5)	0 (1.5)		
(Range)	(3–6)	(1–6)	(−1_4)		

(Continued)

TABLE 6 | Continued

Outcome domain	Baseline ($n = 15$)	Post-intervention ($n = 11$)	Post intervention difference	2nd Time follow up ($n = 10$)	2nd Follow up difference
Process measures					
(STTS-R)					
Satisfaction therapy	Not applicable	29.2 ± 1.1 30 (1.5) (27–30)		Not applicable	
Satisfaction Therapist		27.7 ± 1.6			
Mean ± SD		28 (2)			
Median (IQR)		(26–30)			
(Range)					
MCEQ					
Mean ± SD *Median (IQR)* *(Range)*	Not applicable	17.1 ± 1.5 18 (1) (13–18)		Not applicable	

Dem-QOL(-P), dementia quality of life (-Proxy) (27); EQ-5D-5L, EuroQol Five Dimensions Five Levels (28); VAS, Visual Analog Scale (28); SF-12 (-P), 12 Item Short Form Survey (-Proxy) (29); PCS, physical component score (29); MCS, mental component score (29); HHIE, Hearing Handicap Inventory for the Elderly Screening tool (30, 31); IADL-EDR, Instrument of Activities of Daily living in the elderly (32); NPI-12, Neuropsychiatric Inventory 12 (33); PHQ-9, Patient Health Questionnaire-9 items (37); GAD-7, Generalized Anxiety Scale-7itmes (38); STTS-R, Satisfaction with Therapy and Therapist Scale-Revised (40); MCEQ, Modified Credibility and Expectancy Questionnaire (41).

time follow ups (5.0 ± 2.2 and 3.5 ± 1.9) on the PHQ-9 and the GAD-7, respectively. Severe anxiety was found among two (18.2%) caregivers that reduced significantly at both follow ups. In contrast to loneliness scores among participants in dementia, mean loneliness scores increased among caregivers from baseline to follow up (**Table 7**).

Knowledge and awareness of dementia, as reflected by the Family Attitude Scale [FAS; (35)] score among caregivers increased from baseline (37.1 ± 1.9) to post intervention follow up (44.0 ± 16.4), reflecting a possible improvement in attitudes. On the Survey of Attitudes to and Knowledge of Dementia (48) caregivers showed an increase in score from baseline (22.0 ± 3.2) to post intervention follow up (34.5 ± 4.6). Finally, on the Affiliate Stigma Scale (36), initially developed to assess the self-stigma of a caregiver providing care to a family member with a mental illness or intellectual disability and now adapted for dementia, the mean score on all three elements (cognitive, affective and behavior), increased from baseline to post intervention follow up, indicating an increase in caregivers' perceived stigma related to dementia in the person they cared for.

Process Measures

As shown in **Tables 6**, **7**, high levels of satisfaction with both the intervention and the therapist [Satisfaction with Therapy and Therapist Scale-Revised; (40)] were reported by the participant and caregivers, respectively.

Qualitative Findings

As shown in **Table 8**, seven main themes emerged from the thematic analysis of the semi-structured interviews. These were: motivation for participation in the study, views regarding the intervention, impact of the intervention on the participant with dementia and their caregiver, challenges faced due to hearing impairment, understanding of dementia, pathways to care in Pakistan and views regarding the therapist. **Table 8** includes exemplar quotes from participants supporting each theme.

Regarding participants' understanding of dementia, analysis of the interviews suggested that "brain weakness," in terms of memory, and emotional distress were considered part of a dementia syndrome. Participants reported that dementia involved memory impairment and impacted on the ability to undertake basic daily tasks. They recognized that help could be sought from "brain doctors," including psychiatrists; however, participants mentioned barriers in help seeking included the need to undertake household chores, lack of time and encouragement from other family members to take the affected person for appointments, and forgetting to attend appointments.

Caregivers also reported that they gained much knowledge and awareness about dementia and the impact of sensory impairments on the person with dementia's ability to function well. They improved their understanding of hearing aids and felt confident to provide explanations or help others facing same issues. Caregivers also discussed the impact of hearing and memory problem on the mood of the person with dementia and how this fostered family disputes; using hearing aids resulted in improvements in mood and emotional interactions among family members. This echoed the quantitative findings of improved mood, anxiety level and behavioral disturbance seen in the effectiveness outcomes post-intervention.

Participants reported that overall, the intervention was feasible and effective in improving quality of life of the participant dyads. The hearing aids came as a solution to their hearing problem and improved communication, increasing the ability of those with dementia to participate more in daily activities and family interactions. This was reflected in the reduction in loneliness scores in the participants with dementia, as rated

TABLE 7 | Baseline and post-intervention outcome measurements for the caregivers.

Care partner assessment–self administered					
Outcome domain	**Baseline (*n* = 15)**	**Post-intervention (*n* = 11)**	**Post intervention difference**	**2nd Time follow up (*n* = 10)**	**2nd Follow up difference**
Caregiver-related burden and stress					
FCR					
Mean ± SD	51.5 ± 8.5	52.9 ± 8.8	1.6 ± 9.2	55.9 ± 8.2	5.1 ± 8.2
Median (IQR)	50 (9)	51 (4)	0 (10)	54.5 (7.5)	2.5 (7.5)
(Range)	(40–68)	(45–77)	(−17_17)	(44–71)	(−5_21)
Knowledge and awareness of dementia					
FAS *Mean ± SD*	38.9 ± 6.8	44.0 ±16.4	−6.9 ± 17.3	Not applicable	
Median (IQR)	38 (5.5)	40 (6.5)	−3 (5.5)		
(Range)	(25–52)	(33–92)	(−52_14)		
Attitude and knowledge of dementia					
Mean ± SD	22.0 ± 3.2	34.5 ± 4.6	11.8 ± 4.6	Not applicable	
Median (IQR)	23 (3)	35 (8.5)	14 (8)		
(Range)	(14–26)	(27–40)	(4–18)		
Affiliated stigma scale (39)					
Cognitive	2.5 ± 2.0 3 (3.5) (0–6) 2.9 ± 1.9	12.6 ± 2.0 13 (1.5) (7–14) 12.6 ± 2.2	10.5 ± 3.1 11 (4.5) (4–14) 9.8 ± 2.9	Not applicable	
Affective	3 (1.5) (0–7) 2.5 ± 2.6	14 (2.5) (7–14) 15.1 ± 2.4	10 (4) (5–14) 13.0 ± 2.7		
Behavior *Mean ± SD* *Median (IQR)* *(Range)*	2 (2.5) (0–8)	16 (0) (8–16)	14 (2.5) (8–16)		
Psychological aspects					
PHQ-9 *Mean ± SD*	9.4 ± 5.9	7.7 ± 7.0	1.5 ± 7.0	5.0 ± 2.2	4.5 ± 6.0
Median (IQR)	8 (9.5)	5 (4)	1 (7.5)	5 (2.5)	3.5 (3.4)
(Range)	(2–19)	(2–27)	(−9_14)	(1–8)	(−3_18)
n(%)					
None	2 (18.2%)	4 (36.4%)		4 (40%)	
Mild	5 (45.5%)	5 (45.5%)		6 (60%)	
Moderate	2 (18.2%)	1 (9.1%)		00	
Moderately Severe	2 (18.2%)	00		00	
Severe	00	1 (9.1%)		00	
GAD-7					
Mean ± SD	7.2 ± 5.7	4.5 ± 3.5	3.1 ± 5.0	3.5 ± 1.9	4.3 ± 6.3
Median (IQR)	6 (7.5)	3 (2.5)	2 (4)	4 (3)	3 (9)
(Range)	(0–17)	(1–14)	(−4_13)	(1–6)	(−4_14)
n(%)					
None	3 (27.3%)	7 (63.6%)		5 (50%)	
Mild	5 (45.5%)	3 (27.3%)		5 (50%)	
Moderate	1 (9.1%)	1 (9.1%)		0	
Severe	2 (18.2%)	0		0	
De Jong Gierveld loneliness scale					
Mean ± SD	3.6 ± 2.1	4.2 ± 1.7	0.6 ± 2.3	Not applicable	

(Continued)

TABLE 7 | Continued

Care partner assessment–self administered					
Outcome domain	**Baseline (*n* = 15)**	**Post-intervention (*n* = 11)**	**Post intervention difference**	**2nd Time follow up (*n* = 10)**	**2nd Follow up difference**
Median (IQR)	4 (3.5)	3 (2)	2 (3.5)		
(Rage)	(0–6)	(3–8)	(-3–4)		
Process measures					
STTS-R Satisfaction therapy	Not applicable	28.2 ± 2.2 29 (2) (24–30)		Not applicable	
Satisfaction Therapist *Mean ± SD* *Median (IQR)* *(Range)*		27.9 ± 2.3 29 (4) (24–30)			
MCEQ *Mean± SD* *Median (IQR)* *(Range)*	Not applicable	17.2 ± 1.3 18 (2) (14–18)		Not applicable	

FCR, The Family Care giving Role scale (34); FAS, Family Attitude Scal (35); PHQ-9, Patient Health Questionnaire-9 items (37); GAD-7, Generalized Anxiety Scale-7itmes (38); STTS-R, Satisfaction with Therapy and Therapist Scale-Revised (40); MCEQ, Modified Credibility and Expectancy Questionnaire (41).

on the loneliness scale. Finally, caregivers reported that they appreciated the way the HSP delivered the intervention and felt that the mode of delivery was clear and acceptable.

DISCUSSION

This is the first reported study of a sensory support intervention for people living with dementia and their caregivers in a LMIC. Non-pharmacological interventions that are accessible, acceptable and affordable, such as the intervention trialed here, have the potential to positively impact the lives of people with dementia and their families, particularly in settings where resources and health literacy for dementia are low. Here, we demonstrated that a home-based hearing and dementia support intervention is feasible, well-tolerated, and acceptable. We also showed that the study procedures were generally feasible, with some modifications, and that the battery of effectiveness measures, were acceptable to participants, had minimal missing data and showed a signal of change pre- and post-intervention. The carefully adapted intervention activities and material were culturally appropriate and received well by the participants. Thus, our findings suggest that a full-scale effectiveness trial, with certain modifications, is achievable, according to our *a priori* "traffic light" criteria. Additionally, this type of study fits well with the applied dementia research agenda in Pakistan (10).

Key areas requiring modification included the need to improve recruitment rates and referral pathways into the study. Finding appropriate services supporting people with dementia proved challenging since the health and care ecosystem for older people's health, particularly for dementia is still developing. Indeed, it was only in 2019 that the country's first official Memory Clinic was opened in the Punjab, in Lahore (verbal communication). As outlined in the "Roadmap for developing dementia research in Pakistan" (10), undertaking applied dementia research alongside service development is essential to ensure the most appropriate, effective and contextually relevant services are put in place. Thus, for dementia research to develop and provide the necessary evidence-base to improve the lives of people with dementia in Pakistan, services and care pathways for dementia need to develop in parallel.

Interestingly, findings from the qualitative interviews revealed that while aspects of participants' understanding of dementia were present, seeking help and support was not prioritized, and barriers such as household chores and "forgetting the appointment" were cited as reasons for not attending clinics. Advances such as the development of a National Dementia Plan in Pakistan (verbal communication, H. Jafri) may help to raise the profile of dementia and support public understanding of the need to seek help and support for a condition that is outside of the normal aging process.

The first phase of the study involved developing the capacity and capability at an individual and team level. This resulted in upskilling new researchers and fostering a research culture in a LMIC-setting with hither to limited experience in older adult clinical research (49). This stage of the work was crucial to prepare the way for a subsequent definitive intervention. Additionally, part of phase one involved recruiting a PPI group in several study sites. This work reported elsewhere (17), was a key element in supporting the cultural and contextual adaptation of the intervention, which was initially developed in Europe for EU settings, which are markedly different to Pakistan and other South Asian settings. The experience of PPI was also unique, since PPI is not well-known nor practiced beyond certain HIC (mostly English-speaking) countries and, moreover, we involved people with dementia and their caregivers. PPI involving in

TABLE 8 | Qualitative findings.

Main theme	
Motivation behind participation The motivation for most participant dyads to participate in this study was to find a solution of the difficulties associated with hearing and memory impairment. However, due to lack of awareness some participants were initially hesitant to join the study	My mother has hearing impairment and she always gets upset about it. When we try to talk to her, she is unable to hear us. So to make it easier for her we joined the study(PT002) At first I got worried because I was unable to hear what the doctor was saying to me when he came home but she was so nice and dealt with me in such a nice way that made me feel really good later on (PT010)
Reason for participation	
Views regarding Intervention Hearing intervention was perceived as acceptable, feasible, easy to understand and useful by PwD. Dyads took interest in all sessions and reported improvement in PWD. There were no adverse event related to the intervention	It felt good when I realized that you have solved my mother's problems by coming to our house and talking to us and giving us hearing aids. It really feels like most of her problems are resolved. It had made us all so happy (PT01). We were not aware that hearing aids can be so useful and they can make the life of the person with hearing impairment so much easier. In fact not only for them, for all of us. Like for any other illness there is a cure and hearing aids are the cure for hearing impairment. It made us feel good and very happy (PT03). One session got delayed because my mother-in-law was not well, otherwise it was all good (PT06).
Acceptability, feasibility & tolerability	After the intervention she was 100% confident in using them and she used them easily (PT04).
Impact of intervention on PWD Care-partners coded hearing intervention as effective, in improving PWD's quality of life, mood, social relationships and self-concept.	Before getting the hearing aids and the training on how to use them, she used to disturb me all the time even at nights by calling my name very loudly but now she keeps herself busy in different things such as interacting with other people in the family and her friends. She also tries to take care of the loved ones around her. I have even noticed her memory has improved considerably which is making her feel better in herself. The hearing aids you have given are also very advantageous and she is coming back toward life (PT05).
Improved quality of Life	
Improved Self Concept	She started to have an inferiority complex, along with negative thoughts all the time considering hearing impairment as a disability but now that its fixed, my mother's mind stays fresh, she is finding it easy to keep herself busy in doing one thing or another around the house (PT01).
Improved social relations	Due to the hearing impairment she started losing interest in social interaction, because it was very difficult for her to talk to someone, but now this device helps a lot and she started interacting with the people again. She also attend different events and gathering in the family now (PT09).
Improved Mood	She used to be very irritated and angry most of the time but now she stays calm. It makes us happy. I also feel fine most of the time now (PT03). Before the death of my father in law, she used to have chickens and their cage but after he passed away, she removed the cage. The therapist advised a cage and me to get few chickens again for my mother in law. I cannot believe how busy she keeps herself to take care of them now. She even help me taking care of my younger child sometimes (PT05).
Impact of intervention on Care partners Care-partners also coded hearing intervention as a source for improving/increasing their knowledge, attitude and practices toward dementia. Along with overall impact on their mood, quality of life, and care burden.	The therapist taught us really good communication skills. She advised us to make sure there is enough light so the PwD can see our face when we talk to them. She also advised us to keep PwD company as much as we can so their mind is occupied with the conversation. Yes the therapist gave us really useful tips to deal with the PwD (PT01). I used to think that she was doing everything intentionally but the therapist guided me about her problem and advised me that in this age group, people have this problem but the machine (hearing aid) you gave is very useful. I got a lot of relief (PT05). I think I did not have awareness. But now I have a comprehensive guideline that how these things interlink and how to deal with all this (PT10).
Improved knowledge, attitude and Practices	
Mood	No no, as I explained before that my mind becomes like that, I get irritated sometimes. Otherwise their explaining (I am thankful to God) was very good, there was no problem, and everything was fine (PT01).
Quality of Life	He is much better than before. Both me and my husband were so worried before but now it is much better (PT08). I got a lot of knowledge about how to talk with people who have hearing problem and it has given me confidence that I am able to talk to those people and also help them in day to day life (PT09).
Care Burden	The burden of my father's responsibility is less now. Now he takes care of himself and I can focus more on different chores around the house (PT04). Stress which I used to have 24 h is relieved (PT10).
Challenges faced due to hearing problem Hearing problem, highlighted as a main dispute reason between family member and PwD effecting everyone's life with prominent feeling of loneliness in PWD	Before we had to keep repeating ourselves, and she never really liked anything that I do. Always complaining about me doing everything wrong. I have a small kid and there are so many chores around the house, if she call me repeatedly, how am I supposed to finish my work. She always used to call me when I was doing some important chore and then complaining that I don't respond. This was the main reason of our arguments (PT02).
Disputes	
Loneliness	She used to feel very sad, thinking she is becoming a burden and getting stressed about it. Mostly when we try to talk to her, she prefers to stay quiet (PT01).

(Continued)

TABLE 8 | Continued

Main theme	
What is Dementia? Care partners came up with different examples which they were observing in their family member such as forgetting about things, name of the people in the family, not being sure if they had their dinner or not. These were the main symptoms that their brain was getting weak and they are having memory problems. Care-partner's also believed that both memory and hearing problem are interlinked and impacting one another. Knowledge Regarding Dementia	My mother in law always seem to forget if she had her dinner or not. When we had guests over, she asked who those people are although it was her own daughter. She doesn't remember when I came even though I stayed with her 15 days. Like did I come on Wednesday or Thursday, she forgets (PT03). Brain becomes weak so they forget where they put things. This causes stress and depression as well (PT06). Stress is the biggest cause (PT01). I think both things were important and may be if there was no device (hearing aid) we wouldn't come to know what is affecting him as he used to become angry when he can't hear or remember something. I think both things are connected (PT10).
Pathways to care "Neurosurgeons" and "psychiatrists" were highlighted as person to contact for memory issues. Along with lack of family support as hurdle in accessing this. Pathways	People do things like take them to neurosurgeons or psychiatric hospitals because they have a brain problem, puts things somewhere and forgets. (PT01)
Barriers in Pathways to Care	There is either stress or a lot of house chores, that is why we forget, that is why family members avoid taking them to see a doctor. I am talking about myself (PT09).
Views regarding therapist According to the care-partners, sensory support therapist were very cooperative and empathetic. They guided them in such an easier way that it was easy to comprehend and can be understandable to anyone. Feedback about the therapist	The therapist guided us properly and listened to us actively and gave us respect (PT05). She speaks very well, she was very responsible, I mean she empathized our pain (PT08).

this population is still in its nascent phases, even outside LMIC settings (50).

Another key challenge we faced in our study was the Covid-19 pandemic which arrested clinical research in all settings. We had initially planned to conduct our feasibility study in seven sites in three South Asian countries. However, due to the pandemic, we were only able to conduct the study in two sites in Pakistan, resulting in low numbers of participants and findings from only one South Asian country. We were also required to adapt our protocol to minimize face-to-face assessments. Since few of our older participants had access to online or other remote means of communication, we had to undertake telephone assessments. Despite the challenges, we were able to complete the study according to the amended study protocol, achieve an acceptable retention rate of the participants, and glean meaningful results to inform the next stage of our work.

Aside from our main finding that the study procedures and intervention were feasible and acceptable by people with dementia and their caregivers in Pakistan, we also found that the intervention appears to improve quality of life in people with dementia, and may have a role in improving functional ability and reducing behavioral and psychological symptoms associated with dementia. These findings are in line with Dawes et al. (8) and suggest the need of properly powered control trial of similar hearing intervention. A fully powered sample will also help us further understand the mechanisms of the hearing-cognition relationship (51). Moreover, in caregivers, care burden, distress and depression appeared to improve following the intervention. Results from this feasibility study apply to participants with dementia who have cognitive capacity to provide consent. Feasibility and results for participants with more severe dementia is unknown, particularly as the intervention involves hearing aids (not simpler amplification devices).The outcomes were supported by the qualitative findings from our participant dyads. However, contrary to expectation, affiliate stigma appeared to increase following the intervention, likely due to a greater understanding of the condition of the person being cared for. This suggests that care is needed when increasing awareness and educating family members about dementia as being outside the sphere of normal aging. It is important to mention that while interesting, our findings need to be interpreted with significant caution as the sample size was small, the study was uncontrolled, and the intervention and outcome ratings were not blinded. Nonetheless, finding a signal of change is promising and supports the need to further investigate effectiveness in a fully powered sample, with consideration given to implementation in real life settings.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by National Bio Ethics Committee of Pakistan (NBC-389) University of Manchester's Research Ethics Committee 5 [2019-6061-9707]. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SS, IL, and EH designed the study and developed the protocol, including the intervention adaptation, in collaboration with all members of the SENSE-Cog Asia Working Group. SS the study coordinator. IL project lead, prepared first draft of the manuscript, which was then consulted on by the Pakistan SENSE-Cog team. JM led the PPI involvement in the study. The intervention was delivered by MR and MU. Outcome evaluations were undertaken by SL and RA. ST supervised the qualitative part of the study and analyzed the findings. NZ undertook the quantitative analysis. All authors contributed to the final manuscript.

FUNDING

Funding for SENSE-Cog Asia feasibility study was secured from the University of Manchester Research Partner Development/Pump-Priming Grant under Global Clinical Research Fund GCRF(P122809).

ACKNOWLEDGMENTS

We thank all the participants and their families for participating in the study. We also thank all the professionals, researchers who participated in this study and the SENSE-Cog program for permission to adapt the original intervention.

REFERENCES

1. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimer's Dement*. (2013) 9:63–75.e2. doi: 10.1016/j.jalz.2012.11.007
2. World Health Organisation. *Deafness and Hearing Loss*. (2016). Available online at: http://www.who.int/mediacentre/factsheets/fs300/en/ (accessed August 27, 2016).
3. Allen NH, Burns A, Newton V, Hickson F, Ramsden R, Rogers J, et al. The effects of improving hearing in dementia. *Age and Ageing*. (2003) 32:189–93. doi: 10.1093/ageing/32.2.189
4. Leroi I, Pye A, Armitage CJ, Charalambous AP, Constantinidou F, Helmer C, et al. Research protocol for a complex intervention to support hearing and vision function to improve the lives of people with dementia. *Pilot Feasibility Stud*. (2017) 3:38. doi: 10.1186/s40814-017-0176-1
5. Guthrie DM, Davidson JGS, Williams N, Campos J, Hunter K, Mick P, et al. Combined impairments in vision, hearing and cognition are associated with greater levels of functional and communication difficulties than cognitive impairment alone: analysis of interRAI data for home care and long-term care recipients in Ontario. *PLoS ONE*. (2018) 13:e0192971. doi: 10.1371/journal.pone.0192971
6. Shaji S, Bose S, Kuriakose S. Behavioral and psychological symptoms of dementia: A study of symptomatology. *Indian J Psychiatry*. (2009) 51:38–41. doi: 10.4103/0019-5545.44903
7. Sabzwari SR, Azhar G. Ageing in Pakistan-a new challenge. *Ageing Int*. (2011) 36:423–7. doi: 10.1007/s12126-010-9082-z
8. Dawes P, Wolski L, Himmelsbach I, Regan J, Leroi I. Interventions for hearing and vision impairment to improve outcomes for people with dementia: a scoping review. *Int Psychogeriatr*. (2019) 31:203–21. doi: 10.1017/S1041610218000728
9. Heyl V, Wahl HW. Managing daily life with age-related sensory loss: cognitive resources gain in importance. *Psychol Aging*. (2012) 27:510–21. doi: 10.1037/a0025471
10. Leroi I, Chaudhry N, Daniel A, Dunne R, Eman S, Farina N, et al. A roadmap to develop dementia research capacity and capability in Pakistan: A model for low- and middle-income countries. *Alzheimer's Dementia*. (2019) 5:939–52. doi: 10.1016/j.trci.2019.11.005
11. Regan J, Dawes P, Pye A, Armitage CJ, Hann M, Himmelsbachet I, et al. Improving hearing and vision in dementia: protocol for a field trial of a new intervention. *BMJ Open*. (2017) 7:e018744. doi: 10.1136/bmjopen-2017-018744
12. Leroi I, Armitage CJ, Collin F, Frison E, Hann M, Hooper E, et al. A randomised controlled trial of hearing and vision support in dementia: Protocol for a process evaluation in the SENSE-Cog trial. *Trials*. (2020) 21:223. doi: 10.1186/s13063-020-4135-4
13. Welcome to the SENSE-Cog project. Available online at: www.sense-cog.eu (accessed August 27, 2016).
14. Hooper E, Simkin Z, Abrams H, Camacho E, Charalambous AP, Collin F, et al. Feasibility of an intervention to support hearing and vision in dementia: the SENSE-Cog field trial. *J Am Geriatr Soc*. (2019) 67:1472–7. doi: 10.1111/jgs.15936
15. Leroi I, Simkin Z, Hooper E, Wolski L, Abrams H, Armitage CJ, et al. Impact of a home-based hearing and vision intervention for people with dementia: the SENSE-Cog field trial. *Int J Geriatric Psychiatry*. (2019) 35:348–57. doi: 10.1002/gps.5231
16. Vogel I. Review of the use of 'Theory of Change' in international development. *UK Dep Int Dev*. (2012) 24:102. doi: 10.1177/109821400302400102
17. Miah J, Sheikh S, Francis RC, Nagarajan G. Patient and public involvement (PPI) for dementia research in low- and middle-income countries: developing capacity and capability in South Asia. *Front Neurol*. (2021) 12:637000. doi: 10.3389/fneur.2021.637000
18. Bernal G, Jiménez-Chafey MI, Rodríguez MMD. Practice. Cultural adaptation of treatments: A resource for considering culture in evidence-based practice. *Profess Psychol Res Pract*. (2009) 40:361–8. doi: 10.1037/a0016401
19. Mitchell EJ, Ahmed K, Breeman S, Cotton S, Constable L, Ferry G, et al. It is unprecedented: trial management during the COVID_19 pandemic and beyond. *Trials*. (2020) 21:784. doi: 10.1186/s13063-020-04711-6
20. Good Clinical Practice (GCP). Available online at: https://www.nihr.ac.uk/health-and-care-professionals/learning-and-support/good-clinical-practice.htm (accessed August 27, 2016).
21. Bradley M. *North-South Research Partnerships: Challenges, Responses and Trends—A Literature Review and Annotated Bibliography*. Ottawa, ON: Working Paper 1, IDRC Canadian Partnerships Working Paper.
22. Citrin D, Mehanni S, Acharya B, Wong L, Nirola I, Sherchan R, et al. Power, potential, and pitfalls in global health academic partnerships: review and reflections on an approach in Nepal. *Glob Health Action*. (2017) 10:1367161. doi: 10.1080/16549716.2017.1367161
23. Parker M, Kingori P. Good and bad research collaborations: researchers' views on science and ethics in global health research. *PLoS ONE*. (2016) 11:e0163579. doi: 10.1371/journal.pone.0163579
24. Anderson MS, Steneck NH. *Challenges and Tensions in International Research Collaborations. International Research Collaborations: Much to be Gained, Many Ways to get in Trouble*. New York, NY: Routledge (2011). doi: 10.4324/9780203848906

25. Barrera M Jr, Castro FGJ. A heuristic framework for the cultural adaptation of interventions. *Clin Psychol Sci Pract*. (2006) 13:311–6. doi: 10.1111/j.1468-2850.2006.00043.x
26. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. (2005) 53:695–9. doi: 10.1111/j.1532-5415.2005.53221.x
27. Smith SC, Lamping DL, Banerjee S, Harwood RH, Foley B, Smith P, et al. Development of a new measure of health-related quality of life for people with dementia: DEMQOL. *Psychol Med*. (2007) 37:737–46. doi: 10.1017/S0033291706009469
28. EuroQol Group. EuroQol–a new facility for the measurement of health-related quality of life. *Health Policy*. (1990) 16:199–208. doi: 10.1016/0168-8510(90)90421-9
29. Brazier JE, Roberts J. The estimation of a preference-based measure of health from the SF-12. *Med Care*. (2004) 42:851–9. doi: 10.1097/01.mlr.0000135827.18610.0d
30. Ventry IM, Weinstein BE. The hearing handicap inventory for the elderly: a new tool. *Ear Hear*. (1982) 3:128–34. doi: 10.1097/00003446-198205000-00006
31. Newman CW, Weinstein BE. The hearing handicap inventory for the elderly as a measure of hearing aid benefit. *Ear Hear*. (1988) 9:81–5. doi: 10.1097/00003446-198804000-00006
32. Mathuranath PS, George A, Cherian PJ, Mathew R, Sarma PS. Instrumental activities of daily living scale for dementia screening in elderly people. *Int Psychogeriatr*. (2005) 17:461–74. doi: 10.1017/S1041610205001547
33. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. *Neurol Publish Online First*. (1994) 44:2308. doi: 10.1212/WNL.44.12.2308
34. Schofield HL, Murphy B, Herrman HE, Bloch S, Singh B. Family caregiving: measurement of emotional well-being and various aspects of the caregiving role. *Psychol Med*. (1997) 27:647–57. doi: 10.1017/S0033291797004820
35. Kavanagh DJ, O'Halloran P, Manicavasagar V, Clark D, Piatkowska O, Tennant C, et al. The family attitude scale: reliability and validity of a new scale for measuring the emotional climate of families. *Psychiatry Res*. (1997) 70:185–95. doi: 10.1016/S0165-1781(97)00033-4
36. Chang CC, Su JA, Tsai CS, Yen CF, Liu JH, Lin CY. Rasch analysis suggested three unidimensional domains for affiliate stigma scale: additional psychometric evaluation. *J Clin Epidemiol*. (2015) 68:674–83. doi: 10.1016/j.jclinepi.2015.01.018
37. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. (2001) 16:606–13. doi: 10.1046/j.1525-1497.2001.016009606.x
38. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. (2006) 166:1092–7. doi: 10.1001/archinte.166.10.1092
39. de Jong-Gierveld J, Kamphuls F. The development of a rasch-type loneliness scale. *Appl Psychol Measure*. (1985) 9:289–99. doi: 10.1177/014662168500900307
40. Oei TPS, Green AL. The Satisfaction With Therapy and Therapist Scale–Revised (STTS-R) for group psychotherapy: psychometric properties and confirmatory factor analysis. *Profess Psychol*. (2008) 39:435–42. doi: 10.1037/0735-7028.39.4.435
41. Newman MG, Fisher AJ. Expectancy/credibility change as a mediator of cognitive behavioral therapy for generalized anxiety disorder: mechanism of action or proxy for symptom change?. *Int J Cogn Ther*. (2010) 3:245–61. doi: 10.1521/ijct.2010.3.3.245
42. Sivantos Siemens Hearcheck. Available online at: https://www.bestsound-technology.co.uk/nhs/equipment/hear-check/ (accessed August 27, 2016).
43. Charlesworth G, Burnell K, Hoe J, Orrell M, Russell I. Acceptance checklist for clinical effectiveness pilot trials: a systematic approach. *BMC Med Res Methodol*. (2013) 13:78. doi: 10.1186/1471-2288-13-78
44. McCormick SA, Vatter S, Carter LA, Smith SJ, Orgeta V, Poliakoff E, et al. Parkinson's-adapted cognitive stimulation therapy: feasibility and acceptability in Lewy body spectrum disorders. *J Neurol*. (2019) 266:1756–70. doi: 10.1007/s00415-019-09329-6
45. Cavanagh S. Content analysis: concepts, methods and applications. *Nurse Res*. (1997) 4:5–16. doi: 10.7748/nr.4.3.5.s2
46. Krippendorff K. *Content Analysis: An Introduction to Its Methodology*. Newbury: Sage Publications (1980).
47. Vaismoradi, M, Turunen, H, Bondas, T. Content analysis and thematic analysis: Implications for conducting a qualitative descriptive study. *Nurs Health Sci*. (2013) 15:398–405. doi: 10.1111/nhs.12048
48. McParland P, Devine P, Innes A, Gayle V. Dementia knowledge and attitudes of the general public in Northern Ireland: an analysis of national survey data. *Int Psychogeriatr*. (2012) 24:1600–13. doi: 10.1017/S1041610212000658
49. Leroi I, Vaitheswaran S, Sheikh S, et al. Capacity and capability building for applied dementia research in low- and middle-income countries: two exemplars from South Asia. *Ind J Med Res*. (In press).
50. Miah J, Dawes P, Edwards S, Leroi I, Starling B, Parsons S. Patient and public involvement in dementia research in the European Union: a scoping review. *BMC Geriatr*. (2019) 19:220. doi: 10.1186/s12877-019-1217-9
51. Fulton SE, Lister JJ, Bush AL, Edwards JD, Andel R. Mechanisms of the hearing-cognition relationship. *Semin Hear*. (2015) 36:140–9. doi: 10.1055/s-0035-1555117

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 17 June 2021
doi: 10.3389/fneur.2021.629257

Characterization of HIV-Associated Neurocognitive Impairment in Middle-Aged and Older Persons With HIV in Lima, Peru

Monica M. Diaz[1,2,3], *Marcela Gil Zacarías*[4], *Patricia Sotolongo*[5], *María F. Sanes*[4], *Donald J. Franklin*[6,7], *María J. Marquine*[6,7], *Mariana Cherner*[6,7], *Cesar Cárcamo*[3], *Ronald J. Ellis*[6,8], *Serggio Lanata*[9,10] *and Patricia J. García*[3,11]*

[1] Department of Medicine, University of California, San Diego, San Diego, CA, United States, [2] University of California Global Health Institute, San Diego, CA, United States, [3] Facultad de Salud Pública, Universidad Peruana Cayetano Heredia, Lima, Peru, [4] Facultad de Medicina Alberto Hurtado, Universidad Peruana Cayetano Heredia, Lima, Peru, [5] Department of Psychology, Jackson Memorial Hospital, Miami, FL, United States, [6] Human Immunodeficiency Virus (HIV) Neurobehavioral Research Center, University of California, San Diego, San Diego, CA, United States, [7] Department of Psychiatry, University of California, San Diego, San Diego, CA, United States, [8] Department of Neurosciences, University of California, San Diego, San Diego, CA, United States, [9] Weill Institute for Neurosciences, Memory and Aging Center, University of California, San Francisco, San Francisco, CA, United States, [10] Global Brain Health Institute, University of California, San Francisco, San Francisco, CA, United States, [11] School of Public Health, University of Washington, Seattle, WA, United States

OPEN ACCESS

Edited by:
Mario Alfredo Parra, University of Strathclyde, United Kingdom

Reviewed by:
Antonio Giuliano Zippo, Institute of Neuroscience, National Research Council (CNR), Italy
Carlos Jesus Toro-Huamanchumo, Universidad San Ignacio de Loyola, Peru

***Correspondence:**
Patricia J. García
patricia.garcia@upch.pe

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: *14 November 2020*
Accepted: *21 April 2021*
Published: *17 June 2021*

Citation:
Diaz MM, Zacarías MG, Sotolongo P, Sanes MF, Franklin DJ, Marquine MJ, Cherner M, Cárcamo C, Ellis RJ, Lanata S and García PJ (2021) Characterization of HIV-Associated Neurocognitive Impairment in Middle-Aged and Older Persons With HIV in Lima, Peru. Front. Neurol. 12:629257. doi: 10.3389/fneur.2021.629257

Background: With widespread use of antiretroviral medications, people living with HIV (PWH) are living longer worldwide, increasing their risk of developing neurocognitive impairment (NCI). The proportion of Peruvians over age 60 is expected to increase to 25% of the population by 2050, including PWH. Therefore, the problem of aging and NCI, especially in the setting of HIV infection, is uniquely pressing. We sought to study the rates of and risk factors associated with NCI among middle-aged and older PWH in Lima, Peru.

Materials and Methods: Sociodemographic, medical (infectious and non-infectious), and psychiatric comorbidity and laboratory data were collected. We administered a brief neuropsychological battery evaluating seven cognitive domains affected in HIV-associated NCI and a depression screening. Cognitive test raw scores were converted to *T*-scores that were demographically adjusted. Descriptive statistics were performed together with regression (unadjusted and adjusted) analyses to determine potential risk factors for NCI among PWH.

Results: This was a cross-sectional study in which 144 PWH aged ≥40 years attending a large HIV clinic in Lima, Peru, were recruited from September 2019 to March 2020. Mean age was 51.6 ± 7.7 years, and mean years of education were 14.0 ± 3.1 with 15% females. Median [interquartile range (IQR)] current CD4 and nadir CD4 were 554 (371, 723) and 179 (83, 291), respectively, and 10% currently had AIDS. The prevalence of NCI was 28.5%, and many demonstrated difficulty with attention and working memory (70%). One-quarter of PWH had mild depression or worse on Patient Health Questionnaire 9 (PHQ-9 ≥ 5). In bivariate analyses, neither a depression history nor a higher PHQ-9 score correlated with NCI. No other non-communicable medical or psychiatric comorbidity nor HIV characteristic was predictive of NCI. Having a positive lifetime history of hepatitis

B infection, pulmonary tuberculosis, or syphilis increased risk of NCI (PR 1.72; 95% CI 1.04–2.86) in unadjusted analyses, but not in adjusted analyses.

Conclusions: NCI among older Peruvians with HIV was found to be highly prevalent with levels consistent with prior reports of HIV-associated NCI worldwide. Common latent HIV-associated co-infections, including latent syphilis, hepatitis B infection, or pulmonary tuberculosis, may increase the risk of NCI among middle-aged and older PWH in Peru.

Keywords: HIV-associated neurocognitive disorder (HAND), HIV/AIDS & infectious diseases, cognitive impairment, dementia, Latin America, Peru, non-communicable disease

INTRODUCTION

The number of people living with dementia of any cause worldwide in 2015 was estimated at 48 million people, and this figure is expected to rise to 135 million by 2050, with 63% of cases living in low- and middle-income countries (LMICs) (1). With increased access and use of antiretroviral therapy (ART), the life expectancy of people living with HIV (PWH) has markedly increased (2, 3). This represents a breakthrough in the field but also a new challenge due to the increasing prevalence of non-communicable comorbidities, such as diabetes mellitus and hyperlipidemia, associated with aging with HIV including various forms of neurocognitive impairment (NCI) (4, 5). In addition, our understanding of risk factors for NCI has evolved over time during the ART era, with more chronic comorbidities thought to worsen NCI as PWH live longer (6–8). HIV-associated neurocognitive disorder (HAND) is the most common form of NCI among PWH. It presents with varying degrees of neurologic dysfunction (9) and is associated with increased morbidity and mortality (3, 7, 10). Since the introduction of ART, the incidence of HIV-associated dementia, a severe form of HAND, has decreased (11, 12), but the overall prevalence of HAND worldwide remains stable (7, 8). Peru is a country of 32 million people that is undergoing rapid aging. Currently, 3.3 million people are over the age of 60 (13), and it is estimated that by 2050, 25% of the Peruvian population will be over age 60 (1). Therefore, the problem of aging and NCI is uniquely pressing among PWH.

Several studies have reported that the prevalence of HAND in North America and in some European countries exceeds 30% and affects more than 50% of people with Acquired Immune Deficiency Syndrome (AIDS) (7, 8, 14, 15). There is a paucity of research on the prevalence and characterization of HAND in Latin America. Published studies have reported the prevalence of mild neurocognitive disorder, a milder symptomatic form of NCI, in PWH at 20%, and ∼50% have asymptomatic NCI without functional impairment (16, 17). In Peru in particular, there are limited studies addressing NCI among PWH with no studies specifically on middle-aged to older PWH (18, 19). Moreover, there are no standard cognitive screening protocols nor clinical management guidelines for PWH with NCI despite 70,000 PWH living in Peru, with 60% currently having access to ART (20, 21). Cognitive decline in the general population presents significant medical, social, and economic challenges (22), and Peruvian health systems, like those of many Latin American countries, will face challenges with the increasing burden of NCI (1). Documenting the prevalence of HAND and associated risk factors among Peruvians with HIV is the first step in identifying the burden of this disease, which may lead to implementation of public policies that can help PWH living with NCI to improve their quality of life. In this study, we sought to study rates of HIV-related NCI in a group of older Peruvians with HIV living in Lima and determine the risk factors for NCI among PWH.

MATERIALS AND METHODS

This was a cross-sectional study of PWH living in Lima, Peru, in which demographic data were collected and clinical and neurocognitive evaluations were performed. This study was conducted from September 2019 until March 2020. Participants were men and women aged 40 years or older, Peruvian-born, and native Spanish speakers recruited from a large HIV clinic run by a non-governmental organization. All PWH enrolled had a record of a positive ELISA and Western blot tests in their medical chart and had been receiving ART therapy for at least 1 month at the outpatient clinic. All participants had completed at least 6 years of schooling (primary school) and had the ability and willingness to participate in the study and provide informed consent. Individuals with a self-reported history of non-HIV-related neuromedical comorbidities that may cause NCI were excluded by administering to potential participants a screening questionnaire prior to their enrollment. This screening questionnaire included questions about any known non-HIV-related neurological disorder that led to cognitive impairment (e.g., epilepsy or stroke), psychotic disorders (schizophrenia or bipolar disorder), and brain injury with loss of consciousness for more than 30 min without return to premorbid baseline. Those with a current and lifetime substance use disorder according to the *Diagnostic and Statistical Manual of Mental Disorders*-5 (DSM-5) were excluded.

Study Procedures

Eligible patients attending the HIV clinic were identified by study personnel the day prior to their visit if they met the age criteria for enrollment. Nurses and physicians invited these potentially eligible patients to enroll in the study. With the patient's verbal consent, study personnel then contacted the patients by phone and invited them to the clinic for a scheduled study visit. At the study visit, all study procedures were explained to the participant with ample time to answer any questions, and written

informed consent was obtained. Patients were then interviewed and examined by a neurologist (MMD) or a physician research assistant with training in neurological examination and were supervised by the neurologist. Sociodemographic information including age, sex, years of education achieved, occupation, place of birth, and place of current residence was collected. Self-reported past medical history, including history of prior infections [opportunistic (in PWH only) and non-opportunistic] and chronic non-communicable diseases, was also collected and was corroborated with review of the medical chart following the participant's study visit. We also administered an ART adherence questionnaire to all participants. All participants underwent a comprehensive neuromedical assessment including a complete neurological exam. Following the physical examination, a neurocognitive battery was administered to evaluate neurocognitive function, the Pfeffer Activities of Daily Living questionnaire (PFAQ) to determine functional status, and the Patient Health Questionnaire (PHQ)-9 to screen for depression (Section Instruments Utilized).

We obtained the following information from the medical chart: prior and current ART regimens, any adverse events related to ART, corroboration of self-reported past medical history with physician's clinic assessments in the chart. Laboratory data obtained from chart review included any lifetime positive rapid plasma reagin (RPR) test, herpes simplex virus (HSV)-1 antibody test, tuberculosis (TB) sputum test, and hepatitis B surface antigen (HbsAg) test results. We also noted the most recent hemoglobin, creatinine, total cholesterol, and triglyceride levels.

Following the study visit, the results of the neurocognitive battery were normed as described below, and participants and their treating physician were given a summary of their test results. We provided participants with recommendations on healthy living strategies and strategies for prevention of cognitive decline (23). For those in whom NCI was detected, a neurologist (MMD) counseled the participant by phone or in-person visit on their results and NCI prevention strategies, and results were discussed with the treating physician.

Instruments Utilized

Neuropsychological Test Battery

The neuropsychological test battery evaluated seven cognitive domains [abstraction/executive function, motor performance, memory (learning and recall), attention/working memory, verbal fluency/language, speed of information processing, and visuospatial orientation] that are commonly affected in HIV-associated NCI and that have been widely utilized to assess HIV-associated NCI in the United States, in Europe (9, 24, 25), and in Brazil (26). The domains were evaluated using the following tests:

- Abstraction and executive function: Color Trails Test 2 (27);
- Motor performance: Grooved Pegboard (dominant hand) and Grooved Pegboard (non-dominant hand) (28);
- Memory (learning and recall): Hopkins Verbal Learning Test-Revised (HVLT-R)-Total Learning, HVLT-R Delayed Recall (29), and Benson Figure Recall (30);
- Attention and working memory: Weschler Adult Intelligence Scale (WAIS)-3 Digit Span (31);
- Verbal and language fluency: semantic/category fluency (Animal Naming) and letter fluency (PMR) (32);
- Speed of information processing: Color Trails Test 1 (33); and
- Visuospatial orientation: Benson Figure immediate copy (34).

The instruments have been translated, and most have been validated into Spanish by native Spanish speakers and used in several other studies for Spanish speakers in Latin America (35–37). Raw test scores were converted into demographically adjusted *T*-scores (adjusted for age, sex, and education level) for each test. Norms for native Spanish speakers from the Neuropsychological Norms for the US-Mexico Border Region in Spanish (NP-NUMBRS) were applied to all tests when available, including for semantic/category fluency (Animal Naming) (38), letter fluency (PMR) (38), HVLT-R Total Learning and Delayed Recall (39), and Grooved Pegboard (dominant and non-dominant hand) (40). English-speaking norms with similar mean educational levels to that of our study were utilized for those tests for which there were no demographically adjusted Spanish NP-NUMBRS norms available given there are no Spanish-speaker norms for a Peruvian population that were adequate for our population.

Normed *T*-scores were computed for each test, with regression-based adjustments for the effects of age, sex, and educational level. For each test, *T*-scores were converted to deficit scores as follows: $T > 39$ (no worse than −1 standard deviation) was considered normal and assigned a deficit score of 0. *T*-scores below 40 were converted to deficit scores as follows: 35–39 = 1 (mild impairment); 30–34 = 2 (mild to moderate impairment); 25–29 = 3 (moderate impairment); 20–24 = 4 (moderate to severe impairment); and $T < 20 = 5$ (severe impairment). For each domain, an average of the *T*-scores for each test comprising each domain were computed, and this generated a mean *T*-score for each domain. Deficit scores were summed across the test battery and then divided by the total number of individual measures to compute the Global Deficit Score (GDS), a measure of global cognitive impairment. The GDS summarizes the number and severity of neurocognitive deficits across the entire test battery. A GDS cutoff of $\geq$0.50 was used to determine global NCI (7, 41, 42).

Pfeffer Activities of Daily Living Questionnaire (PFAQ)

Subjective cognitive difficulties were assessed using the validated Spanish version of PFAQ (43–45). In the PFAQ, participants rate themselves as having or not having cognitive difficulties in their daily lives on a 4-point scale, in domains of memory, language and communication, sensory perception, motor skills, and higher-level cognitive functions. The score used is the sum of items on which the participants reported experiencing difficulties ranging from normal (0) to dependent (3), for a total of 30 points, with higher scores indicating worse functional status (43). When a caregiver or companion was present during the interview, the questionnaire was corroborated with the caregivers' report with the participants' permission. Employment status was derived from the demographic interview, which collected information on

whether the participant was working and the type of employment (**Supplementary Material 1**).

PHQ-9 for Depression Screening

This is a nine-item questionnaire designed to screen for depression in primary care and other medical settings was administered to all participants as a depression screening measure (46–48). The PHQ-9 scores each of the nine DSM-IV criteria for depression as "0" (not at all) to "3" (nearly every day), addressing somatic (fatigue, appetite, and sleep quality) and non-somatic (suicidal ideation and feelings of guilt) depressive symptoms; higher scores indicate worse depressive symptomatology. The standard cutoff score to identify major depression is 10 or above (46–48). The PHQ-9 has been previously validated in Spanish for use in Peru (49), has been used in other Spanish-speaking populations throughout Latin America and Spain (50–52), and has been validated for use in depression screening in HIV in South Africa (53) (**Supplementary Material 2**).

NCI (or HAND) Diagnosis for PWH

Global cognitive impairment was defined as a GDS score $\geq$0.5, and individual domain cognitive impairment was defined as a domain-averaged T-score <40. HIV-associated NCI diagnoses were assigned according to the Frascati criteria (9). To receive a diagnosis of HIV-associated dementia, participants had to have moderate to severe impairment on neuropsychological testing and require major assistance in activities of daily living based on the PFAQ. Mild neurocognitive disorder was diagnosed when NCI was mild to moderate on neuropsychological testing by GDS score, and difficulties were reported in two Pfeffer areas except that for participants with at least moderate depressive symptomatology on the PHQ-9; three areas were required on the Pfeffer questionnaire. Asymptomatic NCI was defined as mild to moderate impairment without any functional impairment on the Pfeffer questionnaire.

Statistical Analyses

Descriptive statistics were computed with means [standard deviations (SDs)] or medians [interquartile ranges (IQRs)] for all demographic and HIV characteristic continuous variables. Frequencies and percentages were computed for past medical and psychiatric history variables, and to determine the frequency of depressive symptoms, functional dependence and cognitive impairment were used based on defined cutoff points for each test. Univariable (without adjustment for covariates) and multivariable (adjusted for relevant covariates) regression analyses were performed using GLM with link log and family Poisson to obtain unadjusted and adjusted prevalence ratios (PR and aPR, respectively). All covariates [age $\geq$50 years, female sex, educational level of secondary school or less, comorbid conditions (hypertension, hyperlipidemia, anemia, self-reported depression, PHQ-9 score $\geq$ 5, self-reported anxiety, past hepatitis B infection, past TB infection, and past syphilis infection)], current absolute CD4 count <500, nadir CD4 count 51–200, nadir CD4 count <50, detectable plasma viral load, and HIV duration $\geq$5 years) with a $p < 0.10$ in univariable analyses were included as covariates in the multivariable analyses. A $p < 0.05$ was considered statistically significant. All statistical analyses were performed using the JMP Pro® statistical software, version 14.2.0 (SAS Institute Inc., Cary, NC, USA) and STATA (College Station, TX, USA).

Ethical and Institutional Review Board Approvals

The study and instruments were approved by the institutional review boards of Universidad Peruana Cayetano Heredia (Lima, Peru) and Via Libre (Lima, Peru). The institutional review board of the University of California, San Diego (San Diego, CA, USA), exempted the study from review. Written informed consent was obtained from study participants once the research procedure was explained to them, and sufficient time was given for participants to have any questions answered. Participants were not reimbursed for their time.

RESULTS

Demographics and Medical Characteristics

We recruited 144 PWH with a mean age of 51.6 $\pm$ 7.7 years and mean years of education of 14.0 $\pm$ 3.1 (15.2% females). We found that 2/144 (1.4%) have completed up to primary school, 48/144 (33.3%) have completed up to secondary school, 76/144 (52.8%) have had some or completed university or technical school, and 18/144 (12.5%) have completed a post-graduate degree (data not shown). We found that a small proportion of PWH were unemployed (13.0%) (**Table 1**).

Non-communicable comorbidities were common. Less than one third had dyslipidemia (32.6%), 13.7% had hypertension, and very few had diabetes (5%), anemia (10%), or lifetime seizure history (4.3%) (**Table 1**). The most recent mean hemoglobin reported in laboratory analyses was a mean (SD) of 13.9 (1.52), and mean creatinine levels were within the normal range [0.93 (0.17)]. Recent mean total cholesterol levels were 196.2 (46.0), and triglycerides were 170.7 (98.1) (**Table 2**). Alcohol use was more common among PWH (47%), but current cigarette smoking (16.7%), marijuana use (2.8%), and cocaine use (1.4%) were less common (**Table 1**). Self-reported past infectious history (corroborated with chart review) was obtained. Past history of pulmonary TB (15.2%), HSV infection (30.9%), and syphilis (29.5%) was common. All participants with a positive TB history completed treatment, and nearly all who had a history of syphilis per self-report completed treatment (97.2% of those with a syphilis history). Of those participants who had an RPR test in the medical chart, 28/105 (26.7%) had a positive RPR test in the past. Of 92 participants, eight (8.7%) had a positive lifetime TB sputum test (**Table 2**). Prior hepatitis infection was common among PWH with more than one third (35.7%) having had any hepatitis infection in the past (hepatitis A 18.1%, hepatitis B 16.7%, and hepatitis C 1.4%) (**Table 1**). Of those who had an HBsAg test available in their medical chart, 11/100 (11%) had a positive HBsAg. There were five cases of a prior central nervous system (CNS) infection by self-report, including CNS amoebiasis,

TABLE 1 | Demographic and medical characteristics ($N = 144$).

	Median [IQR], Mean (SD), or n (%)
Demographic variables	
Age	51.6 (7.7)
Sex (*n*, % females)	22 (15.2%)
Education (years)	14.0 (3.1)
Unemployed or retired	18 (13.0%)
Past non-infectious medical or psychiatric history[a]	
Hypertension	19 (13.7%)
Hyperlipidemia	46 (32.6%)
Diabetes or prediabetes	7 (5%)
Anemia	14 (10%)
Seizure (ever)	6 (4.3%)
Depression (by self-report)	21 (15.2%)
PHQ-9 total score	3.34 (4.10)
Depression *(PHQ-9 > 4)*	35 (25.2%)
Anxiety (by self-report)	15 (10.9%)
Past infectious medical history[a]	
Pulmonary TB	21 (15.2%)
Completed TB treatment	21 (100%)
Herpes simplex virus	43 (30.9%)
Syphilis	41 (29.5%)
Completed syphilis treatment	35/37 (97.2%)
Any hepatitis type	50 (35.7%)
Hepatitis A	26 (18.1%)
Hepatitis B	24 (16.7%)
Hepatitis C	2 (1.4%)
CNS infection	5 (3.6%)
CNS amoebiasis	1 (20%)
Cryptococcal meningitis	1 (20%)
Herpes encephalitis	1 (20%)
Neurocysticercosis	1 (20%)
CNS toxoplasmosis	1 (20%)
Current substance use[a]	
Alcohol use	68 (47%)
Cigarette smoking	24 (16.7%)
Marijuana use	4 (2.8%)
Cocaine use	2 (1.4%)

[a]*by self-report and corroboration with medical chart whenever possible.*
IQR, interquartile range; SD, standard deviation; TB, tuberculosis.

TABLE 2 | HIV characteristics and laboratory results ($N = 144$).

	Median [IQR], Mean (SD), or n (%)
HIV characteristics	
Current CD4[a]	554 [372–723]
Nadir CD4[b]	179 [83–261]
AIDS history	
HIV infection duration (years)	9.9 (7.1)
On antiretrovirals	144 (100%)
Detectable plasma viral load (>50 copies/mL)	18/126 (14.3%)
Current antiretroviral use ($n = 131$)	
Nucleoside reverse transcriptase inhibitor (NRTI)	
Lamivudine (3TC)	80 (61.1%)
Tenofovir (TDF)	80 (61.1%)
Emtricitabine (FTC)	45 (34.4%)
Zidovudine (AZT)	36 (27.5%)
Abacavir (ABC)	12 (9.2%)
Stavudine (D4T)	1 (0.7%)
Didanosine	0 (0%)
Non-nucleoside reverse transcriptase inhibitors (NNRTI)	
Efavirenz (EFV)	91 (69.5%)
Nevirapine (NVP)	15 (11.5%)
Protease inhibitor	
Lopinavir/ritonavir (Lop/r)	10 (7.6%)
Atazanavir (ATZ)/ritonavir	7 (5.3%)
Darunavir	2 (1.5%)
Integrase inhibitor	
Raltegravir	1 (0.8%)
Dolutegravir	1 (0.8%)
Laboratory analyses (most recent)	
Hemoglobin	13.9 (1.52)
Creatinine	0.93 (0.17)
Total cholesterol	196.2 (46.0)
Triglycerides	170.7 (98.1)
Positive RPR (ever)	28/105 (26.7%)
Hepatitis B surface antigen (ever)	11/100 (11%)
Positive TB sputum test (ever)	8/92 (8.7%)
Any latent HIV coinfection[c]	45/144 (31.3%)

[a]*of 128 participants;* [b]*of 120 participants;* [c]*hepatitis B, tuberculosis, or syphilis prior infections.*
IQR, interquartile range; SD, standard deviation.

cryptococcal meningitis, HSV encephalitis, neurocysticercosis, and CNS toxoplasmosis reported (**Table 1**).

HIV Characteristics

PWH had a mean duration of HIV infection of 9.9 ± 7.1 years, and all participants were currently on ART. On the antiretroviral adherence questionnaire, the large majority of PWH [116/138 (84.1%)] never missed a dose in the past month, and 17/138 (12.3%) missed one to three doses in the past month, and 5/138 (3.6%) missed more than three doses in the past month. PWH had well-controlled HIV infection with a median absolute CD4 count of 554 cells/mm^3 (IQR: 372–732) and a nadir CD4 count of 179 cells/mm^3 (IQR: 83–291). A detectable plasma viral load (>50,000 copies/mm^3) was noted in 14.3% of PWH. The most common non-nucleoside reverse transcriptase inhibitor (NRTI) in current use by the participants were lamivudine [3TC, 80/131 (61.1%)] and tenofovir [TDF, 80/131 (61.1%)]. Of the non-NRTIs, efavirenz was common [91/131 (69.5%)]. Protease inhibitors and integrase inhibitors were rarely used (**Table 2**).

Depression and Functional Assessment Screening Results

Of the self-reported psychiatric history, 15.2% of participants self-reported a current depression diagnosis and 10.9% self-reported anxiety. Depression on the PHQ-9 depression screening

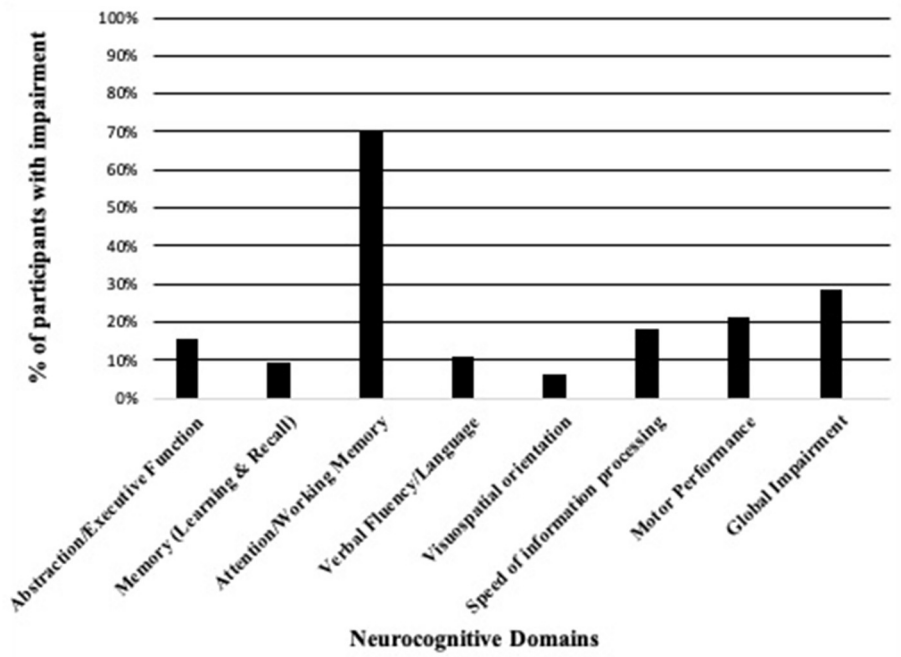


FIGURE 1 | Neurocognitive domain impairment among PWH ($N = 144$).

(defined as PHQ-9 score ≥5) was common, with one quarter of participants screening positive for depression (**Table 1**). To assess functional status, a PFAQ cutoff of ≥9 was used, and we found that there were no participants that met criteria for functional dependence. When the cutoff was set lower (PFAQ total score ≥4), we found that very few had difficulty with independent activities of daily living (2.8%). In unadjusted regression analyses, only self-reported anxiety was a risk factor for depression on PHQ-9 [PR 2.03 (1.08–3.82); $p = 0.047$], but no other demographic, past medical history, or HIV characteristic variable posed an increased risk on depression by PHQ-9 score (data not shown).

Neurocognitive Testing Results

We found that nearly 30% of participants had global NCI and that all participants with global NCI had asymptomatic NCI with no participants having mild neurocognitive disorder or HIV-associated dementia. We found high rates of impairment in the attention and working memory domain (69.9%) and that nearly one fifth of PWH (18.1%) had difficulty with speed of information processing (**Figure 1**, **Table 3**). In unadjusted regression models, HIV infection did not increase risk of NCI [PR 0.99 (0.60–1.63)], but any latent HIV coinfection (including past history of hepatitis B infection, TB infection, or syphilis) increased the risk of NCI [PR 1.72 (1.04–2.86)], and a current CD4 absolute count of <500 cells/mm^3 approached statistical significance [PR 1.64 (0.96–2.8)]. Neither was a statistically significant risk factor associated with NCI in adjusted models [aPR 1.55 (0.81–2.92) for latent coinfection and aPR 1.64 (0.87–3.10) for absolute CD4 count <500 cells] (**Table 4**). In a sub-analysis of PWH (not shown) with an undetectable plasma viral load only ($n = 126$), we found that 28.6% of PWH had NCI, and in the unadjusted regression analyses, the PR of HIV positivity on NCI remained unchanged.

DISCUSSION

In this study, we characterized NCI rates among middle-aged and older PWH living in Lima, Peru, and risk factors for NCI in this population. We found that nearly 30% of PWH had asymptomatic NCI and that no PWH had symptomatic NCI with functional impairment. Among PWH, a risk factor for NCI that was identified was having had a history of latent coinfection, but this was no longer statistically significant in adjusted analyses. Our findings are comparable to previously published findings with comparable NCI rates worldwide.

Several studies have assessed NCI and dementia in geriatric populations in Peru, but none have focused on an older Peruvian population with HIV. In Latin America, eight publications have described HAND prevalence and associated risk factors among PWH aged ≥40 years [seven from Brazil (16, 54–60) one from Mexico (61)], with none from Peru. These studies utilized different neurocognitive screening tools, including the International HIV Dementia Scale (IHDS) (16, 56–58) with HAND prevalence ranging from 37 to 64% using this scale or the Mini Mental State Exam (MMSE) (62) with prevalence ranging from 27 to 37%. (54, 59) Several studies from Brazil reported NCI prevalence specifically among an older age group

TABLE 3 | Neurocognitive and functional status screening results of PWH ($N = 144$).

	Median [IQR], Mean (SD), or n (%)
Functional status screening (PFAQ)	
PFAQ total score	0.46 (1.10)
Functionally dependent *(PFAQ ≥ 9)*	0 (0%)
Some difficulty with IADLs *(PFAQ ≥ 4)*	4 (2.8%)
Neurocognitive test results by cognitive domain (% cognitively impaired)	
Abstraction and executive function	22 (15.3%)
Memory (learning and recall)	13 (9.4%)
Attention and working memory	100 (69.9%)
Verbal fluency and language	15 (10.5%)
Visuospatial orientation	9 (6.3%)
Speed of information processing	26 (18.1%)
Motor	30 (21.0%)
Global impairment*	41 (28.5%)
Asymptomatic neurocognitive impairment	41 (100%)
Mild neurocognitive disorder	0 (0%)
HIV-associated dementia	0 (0%)
Neurocognitive test results by cognitive domain (demographically adjusted T-score, mean ± SD)	
Abstraction and executive function	50.9 (13.8)
Memory (learning and recall)	50.1 (7.9)
Attention and working memory	36.5 (7.6)
Verbal fluency and language	53.6 (11.4)
Visuospatial orientation	51.3 (7.0)
Speed of information processing	48.6 (14.2)
Motor	47.3 (8.8)
GDS	0.42 (0.43)

**Global impairment considered a GDS of ≥0.5.*
IADL, independent activities of daily living; IQR, interquartile range; PFAQ, Pfeffer Functional Assessment Questionnaire; SD, standard deviation.

TABLE 4 | Regression models (unadjusted and adjusted) for risk factors for neurocognitive impairment ($N = 144$).

Variable	Global neurocognitive impairment** Yes, $n = 41$ (28.5%)	
	Unadjusted Prevalence Ratio (95% CI)	Adjusted Prevalence Ratio (95% CI)
≥Age 50 years	1.27 (0.74–2.19)	–
Female sex	1.14 (0.58–2.24)	–
Educational level, secondary school or less	1.21 (0.72–2.03)	–
Hypertension	0.88 (0.40–1.95)	–
Hyperlipidemia	0.85 (0.48–1.52)	–
Anemia	1.24 (0.59–2.64)	–
Depression (self-report)	1.62 (0.91–2.89)	–
Depression (PHQ-9 ≥ 5)	1.54 (0.92–2.59)	–
Anxiety (self-report)	0.91 (0.38–2.20)	–
Current absolute CD4 count<500 (cells/mm^3)	**1.64 (0.96–2.8)***	1.64 (0.87–3.10)
Nadir CD4 51–200 (cells/mm^3)	1.13 (0.64–1.99)	–
Nadir CD4 <50 (cells/mm^3)	1.68 (0.91–3.09)	–
Plasma VL detectable	0.94 (0.42–2.09)	–
HIV duration ≥ 5 years	1.17 (0.65–2.08)	–
Past hepatitis B infection	1.03 (0.52–2.05)	–
Past TB infection	1.67 (0.93–3.00)	–
Past syphilis infection	0.99 (0.56–1.74)	–
Any latent HIV coinfection (hepatitis B, TB, syphilis)	**1.72 (1.04–2.86)**¥	1.55 (0.81–2.92)

**p < 0.10; ¥p < 0.05; **GDS ≥ 0.5.*

of PWH aged ≥50 years with prevalence ranging from 23 to 54%, (16, 54, 57, 59) and in Mexico, a higher prevalence of HAND (66%) among PWH aged ≥50 years was associated with pre-frailty (61). Notably, few studies reported on asymptomatic NCI without impairment in functional status. Among Brazilian PWH with mean age of 42.5 ± 9.1 years, asymptomatic NCI rates were higher than those found in our study (48.3% in the Brazilian study vs. 28.5% in our study) (26, 63). Despite these assessments of HAND from some Latin American countries, prevalence differs depending on the geographic population surveyed and the NCI screening tool utilized and the clinical and demographic characteristics of the group, including immunosuppression, viral suppression, comorbidities, and age.

Only two studies to date have investigated NCI in HIV in Peru. One study utilized a subjective memory complaint questionnaire to determine its utility in identifying NCI in PWH in Peru; however, this sample consisted of PWH who were younger than that of our group (mean age 34.3 years) with a high proportion of alcohol use disorder (41%) and depression (42.5%) (18). Unlike in our study, this study did not assess NCI using objective standardized neurocognitive tests, limiting its utility in objective identification of NCI (18). Another international multisite study from the AIDS Clinical Trials Group included 62 ART-naïve Peruvian PWH (median age 33 and median educational level 12.5 years) (19). Although results were not reported for the Peruvian group, the study reported that across the entire international study, 19% of their population had mild NCI (19). Although the topic of NCI in PWH has been touched on in Peru, it has not been thoroughly studied in an objective manner. Our study is the first to study NCI in a group of middle-aged and older PWH from Peru using an objective multidomain neuropsychological battery.

When comparing our study results to similar studies based in the United States, we found that rates of NCI among PWH in Peru appear to be lower overall. For example, in a multisite study of 1,555 HIV+ adults, 52% of the total sample had NCI (33% of these were asymptomatic NCI, 12% mild neurocognitive disorder, and only 2% with HIV-associated dementia) (7). In another study, Latinos living in the United States had higher rates of NCI compared with non-Latino White PWH (54 vs. 42%), and Latinos tended to perform worse in speed of information processing, working memory, recall, learning, and executive function cognitive domains compared with non-Latino White PWH (37). Latinos living in the United States are heterogeneous from differing racial groups and nationalities and tend to present with worse HIV characteristics (i.e., lower

nadir CD4) or non-communicable comorbidities compared with non-Latino Whites, which may worsen NCI (36, 37). In one study investigating differences in rates of NCI between US Latino and non-Latino Whites, even after adjusting for lower nadir CD4 and other HIV characteristics, Latino PWH in the United States had higher rates of NCI compared with non-Latino White PWH (OR 1.59, CI = 1.13–2.23, $p < 0.01$) (37). Therefore, it is important to consider not only common risk factors and social determinants of health that affect Latino populations with HIV in both Latin America and the United States but also the type of neurocognitive testing norms developed for these populations.

As described earlier, prior studies on HIV-associated NCI in Latin America have demonstrated that NCI and HAND prevalence differs by country depending on the screening instrument utilized. Thus, optimization of an NCI screening instrument validated against a complete neuropsychological battery, the gold standard for diagnosis of HAND (64), is needed but remains a logistical challenge. One study from Brazil, for example, compared the IHDS scale to a brief neurocognitive battery and found that the sensitivity for detection of HAND using standardized cut points of the IHDS was 36% with a specificity of 75%. The top two combinations of neuropsychological tests with the highest sensitivity compared with a gold standard neuropsychological battery were the Trail Making Test A, WAIS-3 Digit Symbol, and HVLT-R Total Recall (sensitivity 91% and specificity 96%) (63). The neuropsychological battery used in the present study included two of these three tests (WAIS-3 Digit Symbol and HVLT-R Total Recall) but replaced the Trail Making Test A with Color Trails Test 1 given a possible preemptive concern of lower literacy in our population. Although our study utilized similar tests to those in the Brazilian study, we did not compare our findings to a gold standard neuropsychological battery; thus, we are unable to report the sensitivity and specificity for detection of HAND of our brief neuropsychological battery. The tests utilized in our battery have been shown to have high sensitivity and specificity in other Brazilian studies with similar sociocultural norms and, thus, may be applicable in our population but may still have limitations (19, 63). Brazil is a Portuguese-speaking country with linguistic factors that may not be generalizable to neurocognitive testing across Spanish-speaking countries in Latin America; therefore, development of a neurocognitive battery specific to each region of Latin America is essential to capture linguistic and sociocultural factors of that region.

We found that few norms have been developed for Spanish speakers living in Peru for the majority of tests we administered; thus, we applied norms for Spanish speakers living in the United States–Mexico border with a similar demographic and sociocultural characteristics and applied norms for English speakers living in the United States when Spanish-speaker norms were unavailable for particular tests. In most prior studies on NCI, applying norms for English speakers or norms collected in Spanish-speaking countries, such as Mexico or Spain, is currently standard clinical practice (65). However, utilizing norms that are not specific to the geographic region of interest may increase the chances of either underclassifying or overclassifying NCI without appropriate demographic adjustment for that region (66). The development of neuropsychological test norms that are representative of the diversity of Latin American populations is urgently needed. This is a key first step toward the development of validated brief cognitive screening tools that can be used in routine clinical HIV care in Lima and other Latin American cities (8, 67).

Risk factors for NCI in PWH are important to consider. Some studies have found that low nadir CD4 and high plasma viral load are strong predictors of NCI among PWH on ART (7). Among ART-naïve PWH, even after treatment for a mean duration of 63 months, NCI persisted among 62.8% of those with NCI prior to treatment (25); like in our study, this study found that HIV characteristics previously associated with NCI in PWH, such as absolute CD4 cell count, plasma viral load, and use of CNS-penetrating drugs, were not associated with persistent neurocognitive deficits; however, the only risk factor that contributed to persistent neurocognitive deficits after initiation of ART was lower educational levels, highlighting the importance of educational level achieved when considering NCI evaluation (25). Our sample was largely educated with 97% of the group having completed at least secondary school, higher than the mean educational level of the general population of Peru (64% female and 75.4% male with at least some secondary schooling) (68). Two thirds of the participants in our study had some university or technical school or a post-graduate degree, likely because study recruitment took place in a specialized multidisciplinary private HIV clinic run by a non-governmental organization, and not a governmental hospital, thus attracting employed patients with higher educational levels. Given the lack of low educational levels in our sample, we did not see an association between educational levels and NCI, which may not be true of rural populations with lower educational levels in Peru. We found no other demographic variable; past medical or psychiatric history increased the risk of NCI. However, having had a latent coinfection (either hepatitis B infection, pulmonary TB, or syphilis) was a risk factor for NCI, but these infections individually did not contribute to cognitive impairment.

Latent coinfections have been described in the literature to contribute to NCI in PWH. According to the World Health Organization Global Tuberculosis report, the incidence of TB/HIV coinfection in Peru is high, with 119 reported cases per 100,000 inhabitants in the general Peruvian population and 7.5 per 100,000 among PWH in Peru (69). One of the most commonly reported active or latent HIV coinfections to worsen NCI is TB. For example, one multinational study that included patients with HIV and active TB found that participants with active TB and HIV performed statistically significantly worse on Grooved Pegboard (motor performance) and finger tapping with the non-dominant hand compared with an HIV+ non-TB group, but sustained ART for 3 years improved cognitive function among ART-naïve PWH (70). Another study from South Africa also found that active multidrug-resistant TB coinfection was associated with significantly lower domain scores in visual attention and task switching (Trail Making Test parts A and B), visual–spatial orientation and executive function (Rey Complex Figure recall), and motor performance (Grooved Pegboard Test) (71), and a similar study found that the prevalence of HAND

among PWH with active multidrug-resistant TB infection was 43.5% (72). The elevated risk of cognitive impairment may be mediated by higher levels of systemic inflammation among those with coinfection as was demonstrated in a study from Zambia, which reported a prevalence of NCI among 55% of HIV+/TB patients, 34% HIV+ non-TB patients, and 14% of HIV-negative controls (73). Worse domain impairment among the HIV+ active TB group (compared with the HIV+ non-TB group) was noted in learning and memory (immediate and delayed recall), working memory, verbal fluency, and speed of information processing, but there were no differences in motor performance and executive function unlike prior studies from South Africa (72, 73). One study from southern India analyzed the effect of latent TB coinfection on NCI and found no difference in NCI prevalence between the HIV+ latent TB group and the HIV+ non-latent TB group; however, it did find that certain inflammatory markers were higher in the HIV+ latent TB group (74). Similar to the findings of this study, our study did not find a relationship between latent TB/HIV+ coinfection on NCI, but the risk of NCI increased when several coinfections were considered simultaneously.

Syphilis is another common coinfection in PWH, and prior syphilis infection was found to be common in our group of PWH (29.5%) but did not independently increase risk of NCI in PWH in our study. The prevalence of syphilis in the Peruvian population is unknown, and the country does not have a government-sponsored syphilis monitoring program; however, in one study, the prevalence of syphilis in Peru was estimated to be 0.5% among men and 0.4% among women (75). Other studies have found that syphilis coinfection may worsen NCI, including one study from the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) cohort, which found that those with prior syphilis infection had a greater number of impaired neuropsychological test domains and a worse GDS score [0.47 (0.46) vs. 0.31 (0.33) in HIV+ non-syphilis patients, $p = 0.03$] (76). Another study demonstrated similar findings with worse neurocognitive performance among PWH with a prior history of syphilis infection; however, this group hypothesized that poor neurocognitive performance predisposes to more frequent acquisition of sexually transmitted infection due to risky behaviors (77). The relationship between syphilis and NCI is unknown, as one study demonstrated that neurosyphilis increases CNS inflammation but does not explain NCI (78). Our study did not find a relationship between past treated syphilis infection and NCI among PWH, but we did find that nearly one third of PWH in our study had syphilis infection, highlighting its prevalence in this population from Peru. Hepatitis B infection is less common compared with TB in Peru but has a prevalence of 0.75 per 100,000 inhabitants (79). Very few studies have investigated the effect of past hepatitis B infection and HIV on NCI as most studies have focused on HIV/HCV coinfection. However, in our study, hepatitis C infection was very rare, and past hepatitis B infection was much more common. Only one study found an increase in impairment of verbal learning and memory among a cohort of HCV and HBV patients without HIV compared to heathy controls (80). Our study demonstrated an increased risk of past infection with pulmonary TB, syphilis, or hepatitis B infection on NCI in unadjusted analyses, but not in adjusted analyses, highlighting the importance of management and treatment of coinfections more prevalent in Latin America to prevent NCI among PWH.

Depression risk is known to be greater in older PWH, yet few studies have reported on depression prevalence among middle-aged and older adult PWH in Latin America, particularly on its effect on NCI (81). The PHQ-9 has been utilized in Latin American populations, including in rural areas of Mexico, suggesting that the internal consistency of the PHQ-9 was good overall and in subgroups of low literacy levels, gender, and age (50). The PHQ-9 has also been validated for use in Peru (49), and studies suggest that those of lower socioeconomic status or from rural areas had lower rates of depression (82). One study from Latin America of 412 Brazilian PWH utilized the Beck Depression Inventory (BDI) for depression screening and found that a BDI score between 13 and 19 points was associated with symptomatic HAND (mild neurocognitive disorder and HIV-associated dementia) (16). Another study of older Brazilian PWH aged $\geq$50 years found that the frequency of mild neurocognitive disorder using the MMSE was 36.5% and that depressive symptoms were present in 34.6% of participants using the BDI-II (59). This study found that depression was a risk factor for greater functional impairment (59), yet our study results do not suggest a relationship between higher PHQ-9 score and NCI among PWH, likely because we did not identify persons with symptomatic HAND or functional impairment. A unified approach to identifying those older PWH at greatest risk for depression is needed by applying culturally appropriate depression screening tools and considering depression screening when evaluating for NCI in older PWH.

Our study has limitations. Firstly, this was a cross-sectional study capturing NCI at one isolated time point during the course of HIV illness and did not capture longitudinal data on cognitive decline. Thus, no inferences can be made on the risk of progressing from asymptomatic NCI to symptomatic forms of HAND (mild neurocognitive disorder or HIV-associated dementia). Second, there are no neuropsychological test norms specific to Lima, Peru; thus, norms for Spanish speakers with similar sociocultural norms were utilized when available (NP-NUMBRS), and English-speaking norms were used for those in which NP-NUMBRS norms were unavailable. Although we adjusted for demographic variables (age, sex, and educational level), without neuropsychological test norms specific to the region of study, NCI may be underestimated or overestimated. Lastly, it is important to note that this study and the neuropsychological battery utilized may not be generalizable to populations of lower literacy or lower educational levels, particularly in rural populations. Participants in our study had a mean educational level of 14 ± 3 years, with the large majority (97%) having completed at least secondary school and two-thirds having had some university or technical school. This figure is much greater than the proportion of Peruvians in the general population across all of Peru with up to secondary school completed (64% female and 75.4% male) (68). Our results may be generalizable to certain regions of Lima with higher educational levels comparable to our population, but they may

not be generalizable to rural populations or other metropolitan areas of Peru and other LAC. Illiteracy and low educational levels are common across Latin America, including Peru, where the illiteracy level is 6% (83), and higher among older adults living in rural areas of Peru compared with urban settings (41.6% rural vs. 12.3% urban), thus limiting the external validity of our results to low-literacy or illiterate populations in Peru and elsewhere in Latin America (84). Lastly, the sample size was not large ($N = 144$), thus limiting conclusions that may be made regarding risk factors of NCI. However, a *post-hoc* power calculation was conducted to determine the power of this study to detect TB as a risk factor of interest for cognitive impairment among PWH. TB was selected as a risk factor for NCI in the *post-hoc* power calculation because of evidence from previous studies that it is a risk factor for cognitive impairment (71, 74); it is a common exposure in Peru (85) and is commonly associated with HIV (86). Given that our secondary aim was to explore risk factors related to NCI, we calculated the power to detect a statistically significant difference in the exposure (TB) when comparing its frequency among those with and without NCI. Given that 21 participants had a history of TB, our study had a power > 80% for a PR of 3.35 or higher.

Despite these limitations, our study is the first to report the rates of NCI among a group of middle-aged and older adult Peruvians with HIV living in the capital city of Lima, utilizing a multidomain objective neurocognitive battery. We have highlighted the need to validate a brief cognitive screening tool that may be generalizable and applicable across the wide spectrum of educational and literacy levels, in order to enhance the external validity of the tool. Neuropsychological test norms specific to Lima, Peru, that account for the sociocultural context and demographics of urban Peru are also key in being able to properly define the rate of NCI seen in an aging HIV population. There is a need for long-term longitudinal data that characterizes whether people with NCI without functional impairment may progress to symptomatic forms with functional impairment and whether cognitive decline should be a concern as PWH age in Peru and throughout Latin America. Demonstrating these aspects of HIV-associated NCI across all of Peru, including in urban and rural areas across the spectrum of educational levels, will allow for the creation of new therapeutic targets and management strategies for HAND in LMICs.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Universidad Peruana Cayetano Heredia (Lima, Peru). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MD study concept and design, data collection, performance of statistical analyses, interpretation of analyses, and drafting of manuscript. MZ study concept and design, data collection, interpretation of analyses, and drafting of manuscript. PS study concept and design, analysis and interpretation, and drafting of manuscript. MS data collection, interpretation of analyses, and drafting of manuscript. DF data management and analyses and drafting of manuscript. MM and MC study concept and design and critical revision of the manuscript for important intellectual content. CC supervised statistical analyses, interpretation of analyses, and critical revision of manuscript. RE and SL study concept and design, interpretation of analyses, and critical revision of the manuscript for important intellectual content. PG study concept and design, interpretation of analyses, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

FUNDING

MD serves as a Fogarty Global Health Trainee and was supported by the Fogarty International Center at the NIH under grant number D43TW009343 and was also supported by the Alzheimer's Disease Resource Center for advancing Minority Aging Research at the University of California, San Diego (P30AG059299, National Institute on Aging). This work was supported by grants from the National Institutes of Health (the HIV Neurobehavioral Research Center (HNRC): P30MH62512, R01MH57266, K23MH105297, P30AG059299, T32MH019934, and P01DA012065). The HIV Neurobehavioral Research Center (HNRC) was supported by center award P30MH062512 from the National Institute of Mental Health.

ACKNOWLEDGMENTS

We would like to thank the nursing staff and administrative staff at Via Libre HIV clinic. We would also like to thank Dr. Robinson Cabello and Mr. Manuel Rouillon, center directors of Via Libre HIV clinic. We would like to thank the research assistants who supported this work, including Marcela Gil-Zacarias, Dr. Maria Fatima Sanes Guevara, Dr. Alex Miguel Vargas Romero, and Ms. Adriana Naranjo Garcia.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.629257/full#supplementary-material

REFERENCES

1. Custodio N, Wheelock A, Thumala D, Slachevsky A. Dementia in latin america: epidemiological evidence and implications for public policy. *Front Aging Neurosci.* (2017) 9:221. doi: 10.3389/fnagi.2017.00221
2. Cardoso SW, Torres TS, Santini-Oliveira M, Marins LMS, Veloso VG, Grinsztejn B. Aging with HIV: a practical review. *Braz J InfectDis.* (2013) 17:464–79. doi: 10.1016/j.bjid.2012.11.007
3. UNAIDS. *HIV and Aging - A Special Supplement to the UNAIDS Report on the Global AIDS Epidemic 2013 - World*. ReliefWeb (2013). Available online at: https://reliefweb.int/report/world/hiv-and-aging-special-supplement-unaids-report-global-aids-epidemic-2013 (accessed May 30, 2020).
4. Sousa RM, Ferri CP, Acosta D, Guerra M, Huang Y, Jacob K, et al. The contribution of chronic diseases to the prevalence of dependence among older people in Latin America, China and India: a 10/66 dementia research group population-based survey. *BMC Geriatrics.* (2010) 10:53. doi: 10.1186/1471-2318-10-53
5. Sheppard DP, Iudicello JE, Bondi MW, Doyle KL, Morgan EE, Massman PJ, et al. Elevated rates of mild cognitive impairment in HIV disease. *J Neurovirol.* (2015) 21:576–84. doi: 10.1007/s13365-015-0366-7
6. Heaton RK, Franklin DR, Ellis RJ, McCutchan JA, Letendre SL, Leblanc S, et al. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *J Neurovirol.* (2011) 17:3–16. doi: 10.1007/s13365-010-0006-1
7. Heaton RK, Clifford DB, Franklin DR, Woods SP, Ake C, Vaida F, et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER study. *Neurology.* (2010) 75:2087–96. doi: 10.1212/WNL.0b013e318200d727
8. Saloner R, Cysique LA. HIV-associated neurocognitive disorders: a global perspective. *J Int Neuropsychol Soc.* (2017) 23:860–9. doi: 10.1017/S1355617717001102
9. Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, et al. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology.* (2007) 69:1789–99. doi: 10.1212/01.WNL.0000287431.88658.8b
10. Ellis RJ, Deutsch R, Heaton RK, Marcotte TD, McCutchan JA, Nelson JA, et al. Neurocognitive impairment is an independent risk factor for death in HIV infection. San Diego HIV neurobehavioral research center group. *Arch Neurol.* (1997) 54:416–24. doi: 10.1001/archneur.1997.00550160054016
11. McArthur JC. HIV dementia: an evolving disease. *J Neuroimmunol.* (2004) 157:3–10. doi: 10.1016/j.jneuroim.2004.08.042
12. Sacktor N, Saylor D, Nakigozi G, Nakasujja N, Robertson K, Grabowski MK, et al. Effect of HIV subtype and antiretroviral therapy on HIV-associated neurocognitive disorder stage in rakai, Uganda. *J Acquir Immune Defic Syndr.* (2019) 81:216–23. doi: 10.1097/QAI.0000000000001992
13. Instituto Nacional de Estadistica e Informatica. *Peru Final Version of OECD Review of Official Statistics and Statistical System*. (2017). Available online at: https://www.inei.gob.pe/media/ocde/English.pdf
14. Tozzi V, Balestra P, Lorenzini P, Bellagamba R, Galgani S, Corpolongo A, et al. Prevalence and risk factors for human immunodeficiency virus-associated neurocognitive impairment, 1996 to 2002: results from an urban observational cohort. *J Neurovirol.* (2005) 11:265–73. doi: 10.1080/13550280590952790
15. Robertson K, Bayon C, Molina JM, McNamara P, Resch C, Muñoz-Moreno JA, et al. Screening for neurocognitive impairment, depression, and anxiety in HIV-infected patients in Western Europe and Canada. *AIDS Care.* (2014) 26:1555–61. doi: 10.1080/09540121.2014.936813
16. Gascón MRP, Vidal JE, Mazzaro YM, Smid J, Nascimento RM, Garcia C, et al. Neuropsychological assessment of 412 HIV-infected individuals in São Paulo, Brazil. *AIDS Patient Care STDS.* (2018) 32:1–8. doi: 10.1089/apc.2017.0202
17. Wright EJ, Grund B, Cysique LA, Robertson K, Brew BJ, Collins G, et al. Factors associated with neurocognitive test performance at baseline: a substudy of the INSIGHT strategic timing of antiretroviral treatment (START) trial. *HIV Med.* (2015) 16:97–108. doi: 10.1111/hiv.12238
18. Weikum D, Shrestha R, Ferro EG, Vagenas P, Copenhaver, Spudich S, et al. An explanatory factor analysis of a brief self-report scale to detect neurocognitive impairment among HIV-positive men who have sex with men and transgender women in Peru. *AIDS Care.* (2017) 29:1297–301. doi: 10.1080/09540121.2017.1322681
19. Robertson K, Jiang H, Kumwenda J, Supparatpinyo K, Evans S, Campbell T, et al. Improved neuropsychological and neurological functioning across three antiretroviral regimens in diverse resource-limited settings: AIDS clinical trials group study a5199, the international neurological study. *Clin Infect Dis.* (2012) 55:868–76. doi: 10.1093/cid/cis507
20. Centro Nacional de Epidemiologia, Prevencion y Control de Enfermedades. *Situación epidemiológica del VIH-Sida en el Perú*. (2018).Available online at: https://www.dge.gob.pe/portal/index.php?option=com_content&view=article&id=656 (accessed June 5, 2020).
21. ONUSIDA. *Perú - Country Factsheets*. Available online at: https://www.unaids.org/es/regionscountries/countries/peru (accessed June 5, 2020).
22. Patel S, Parikh NU, Aalinkeel R, Reynolds JL, Dmello R, Schwartz SA, et al. United States National trends in mortality, length of stay (LOS) and associated costs of cognitive impairment in HIV population from 2005 to (2014). *AIDS Behav.* (2018) 22:3198–208. doi: 10.1007/s10461-018-2128-z
23. Alzheimer's Association. *Can Alzheimer's Disease Be Prevented?* (2020). Available online at: https://www.alz.org/alzheimers-dementia/research_progress/prevention (accessed October 21, 2020).
24. Carey CL, Woods SP, Rippeth JD, Gonzalez R, Moore DJ, Marcotte TD, et al. Initial validation of a screening battery for the detection of HIV-associated cognitive impairment. *Clin Neuropsychol.* (2004) 18:234–48. doi: 10.1080/13854040490501448
25. Tozzi V, Balestra P, Bellagamba R, Corpolongo A, Salvatori MF, Visco-Comandini U, et al. Persistence of neuropsychologic deficits despite long-term highly active antiretroviral therapy in patients with HIV-related neurocognitive impairment: prevalence and risk factors. *J Acquir Immune Defic Syndr.* (2007) 45:174–82. doi: 10.1097/QAI.0b013e318042e1ee
26. de Almeida SM, Ribeiro CE, de Pereira AP, Badiee J, Cherner M, Smith D, et al. Neurocognitive impairment in HIV-1 clade C- versus B-infected individuals in Southern Brazil. *J Neurovirol.* (2013) 19:550–6. doi: 10.1007/s13365-013-0215-5
27. D'Elia LF, Satz P., Uchiyama CL, White T. Color trails test. *PAR.* (1996). https://www.parinc.com/Products/Pkey/77 (accessed October 21, 2020).
28. Merker B, Podell K. Grooved pegboard test. In: Kreutzer JS, DeLuca J, Caplan B, editors. *Encyclopedia of Clinical Neuropsychology*. New York, NY: Springer. (2011). doi: 10.1007/978-0-387-79948-3_187
29. Belkonen S. 2011 Hopkins verbal learning test. In: Kreutzer JS, DeLuca J, Caplan B, editors. *Encyclopedia of Clinical Neuropsychology.* New York, NY: Springer. doi: 10.1007/978-0-387-79948-3_1127
30. Possin KL, Laluz VR, Alcatar OZ, Miller BL, Kramer JH. Distinct neuroanatomical substracts and cognitive mechanisms of figure copy performance in Alzheimer's disease and behavioral fronto-temporal dementia. *Neuropsychologia.* (2011) 49:43–8. doi: 10.1016/j.neuropsychologia.2010.10.026
31. WAIS-III. In: Kreutzer JS, DeLuca J, Caplan B, editors. *Encyclopedia of Clinical Neuropsychology*. New York, NY: Springer (2011).
32. Pena-Casanova J, Quinones-Ubeda S, Gramunt-Fombuena N, Quintana-Aparicio M, Aguilar M, Badenes D, et al. Spanish multicenter normative studies (NEURONORMA Project): norms for verbal fluency tests. *Arch Clin Neuropsychol.* (2009) 24:395–411. doi: 10.1093/arclin/acp042
33. Pontón MO, Satz P, Herrera L, Ortiz F, Urrutia CP, Young R, et al. Normative data stratified by age and education for the neuropsychological screening battery for hispanics (NeSBHIS): initial report. *J Int Neuropsychol Soc.* (1996) 2:96–104. doi: 10.1017/S1355617700000941
34. Tsoy E, Possin KL, Thompson N, Patel K, Garrigues SK, Maravilla I, et al. Self-administered cognitive testing by older adults at-risk for cognitive decline. *J Prev Alzheimer's Dis.* (2020) 7:283–7. doi: 10.14283/jpad.2020.25
35. Mindt MR, Cherner M, Marcotte TD, Moore DJ, Bentley H, Esquivel M, et al. The functional impact of HIV-associated neuropsychological impairment in spanish-speaking adults: a pilot study. *J Clin Exp Neuropsychol.* (2003) 25:122–32. doi: 10.1076/jcen.25.1.122.13634
36. Kamalyan L, Hussain MA, Diaz MM, Umlauf A, Franklin DR, Cherner M, et al. Neurocognitive impairment in Spanish-speaking Latinos living with HIV in the US: Application of the neuropsychological norms for the US-Mexico border region in Spanish (NP-NUMBRS). *Clin Neuropsychol.* (2019) 35:433–52. doi: 10.1080/13854046.2019.1701084
37. Marquine MJ, Heaton A, Johnson N, Rivera-Mindt M, Cherner M, Bloss C, et al. Differences in neurocognitive impairment among HIV-INFECTED

LATINOS IN THE United States. *J Int Neuropsychol Soc.* (2018) 24:163–75. doi: 10.1017/S1355617717000832
38. Marquine MJ, Morlett Paredes A, Madriaga C, Blumstein Y, Umlauf A, Kamalyan L, et al. Demographically-adjusted norms for selected tests of verbal fluency: results from the neuropsychological norms for the US-Mexico Border Region in Spanish (NP-NUMBRS) project. *Clin Neuropsychol.* (2020) 35:269–92. doi: 10.1080/13854046.2020.1762931
39. Diaz-Santos M, Suarez P, Marquine MJ, Umlauf A, Rivera-Mindt M, Artiola I Fortuny L, et al. Updated demographically adjusted norms for the brief visuospatial memory test-revised and hopkins verbal learning test-revised in monolingual spanish speakers from the United States – Mexico Border region. *Arch Clin Neuropsychol.* (2019) 34:1250. doi: 10.1093/arclin/acz029.17
40. Heaton A, Gooding A, Cherner M, Umlauf A, Franklin DR, Rivera-Mindt M, et al. Demographically-adjusted norms for the grooved pegboard and finger tapping tests in Spanish-speaking adults: results from the neuropsychological norms for the U.S.-Mexico Border Region in Spanish (NP-NUMBRS) project. *Clin Neuropsychol.* (2020) 35:396–418. doi: 10.1080/13854046.2020.1713400
41. Carey CL, Woods SP, Gonzalez R, Conover E, Marcotte TD, Grant I, et al. Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV INFECTION. *J Clin Exp Neuropsychol.* (2004) 26:307–19. doi: 10.1080/13803390490510031
42. Heaton RK, Miller SW, Taylor MJ, Grant I. *Revised Comprehensive Norms for an Expanded Halstead-Reitan Battery: Demographically Adjusted Neuropsychological Norms for African American and Caucasian Adults*. Lutz, FL: Psychological Assessment Resources, Inc. (2004).
43. Pfeffer RI, Kurosaki TT, Harrah CHJ, Chance JM, Bates D, Detels R, et al. A survey diagnostic tool for senile dementia. *Am J Epidemiol.* (1981) 114:515–27. doi: 10.1093/oxfordjournals.aje.a113217
44. Herrera P MS, Saldías P, Testa N. [Validation of a brief screening test to assess functional capacity in Chilean older people]. *Rev Med Chil.* (2014) 142:1128–35. doi: 10.4067/S0034-98872014000900006
45. Quiroga L P, Albala B C, Klaasen P G. Validación de un test de tamizaje para el diagnóstico de demencia asociada a edad, en Chile. *Rev méd Chile.* (2004) 132:467–78. doi: 10.4067/S0034-98872004000400009
46. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* (2001) 16:606–13. doi: 10.1046/j.1525-1497.2001.016009606.x
47. Levis B, Benedetti A, Thombs BD. Accuracy of patient health Questionnaire-9 (PHQ-9) for screening to detect major depression: individual participant data meta-analysis. *BMJ.* (2019) 365:l1476. doi: 10.1136/bmj.l1476
48. Spitzer RL. Validation and utility of a self-report version of PRIME-MDThe PHQ primary care study. *JAMA.* (1999) 282:1737. doi: 10.1001/jama.282.18.1737
49. Calderón M, Gálvez-Buccollini JA, Cueva G, Ordoñez C, Bromley C, Fiestas F. Validación de la versión peruana del PHQ-9 para el diagnóstico de depresión. *Rev Peru Med Exp Salud Publica.* (2012) 29:578–79. doi: 10.1590/S1726-46342012000400027
50. Arrieta J, Aguerrebere M, Raviola G, Flores H, Elliott P, Espinosa A, et al. Validity and utility of the patient health questionnaire (PHQ)-2 and PHQ-9 for screening and diagnosis of depression in rural Chiapas, Mexico: a cross-sectional study: PHQ-9 validity for depression diagnosis. *J Clin Psychol.* (2017) 73:1076–90. doi: 10.1002/jclp.22390
51. Muñoz-Navarro R, Cano-Vindel A, Medrano LA, Schmitz F, Ruiz-Rodriguez P, Abellan-Maeso C, et al. Utility of the PHQ-9 to identify major depressive disorder in adult patients in Spanish primary care centres. *BMC Psychiatry.* (2017) 17:291. doi: 10.1186/s12888-017-1450-8
52. Wulsin L, Somoza E, Heck J. The feasibility of using the Spanish PHQ-9 to screen for depression in primary care in honduras. *Prim Care Companion J Clin Psychiatry.* (2002) 4:191–5. doi: 10.4088/PCC.v04n0504
53. Cholera R, Gaynes BN, Pence BW, Bassett J, Qangule N, Macphail C, et al. Validity of the patient health questionnaire-9 to screen for depression in a high-HIV burden primary healthcare clinic in Johannesburg, South Africa. *J Affect Disord.* (2014) 167:160–6. doi: 10.1016/j.jad.2014.06.003
54. Sereia AL, Junior MS, Domiciano TP, Shimauti E, Pupulin ART. Mini mental state examination and evaluation of factors associated with cognitive decline in HIV/AIDS-infected people. *Acta Sci Health Sci.* (2012) 34:193–8. doi: 10.4025/actascihealthsci.v34i2.12687
55. Araujo ML, Duarte W, Oliveira ACP de, Polo MR, Marcondes LA, Alves RM, et al. Is the telomere length associated with neurocognitive disabilities in HIV-1-infected subjects? *Revista do Instituto de Medicina Tropical de Sáo Paulo*. (2018). Available online at: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0036-46652018005000207&lng=en&nrm=iso&tlng=enhttp://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=cagh&AN=20193122783http://wa4py6yj8t.search.serialssolutions.com/?url_ver=Z39.88-2004
56. Pinheiro CAT, Mattos Souza LD de, Motta JV dos S, Kelbert EF, Martins CSR, Souza MS, et al. Aging, neurocognitive impairment and adherence to antiretroviral therapy in human immunodeficiency virus-infected individuals. *Braz J Infect Dis.* (2016) 20:599–604. doi: 10.1016/j.bjid.2016.09.006
57. Pinheiro CAT, Souza LDM, Motta JVS, Kelbert EF, Souza MS, Martins CSR, et al. Depression and diagnosis of neurocognitive impairment in HIV-positive patients. *Braz J Med Biol Res.* (2016) 49:e5344. doi: 10.1590/1414-431x20165344
58. Troncoso FT, Conterno L de O. Prevalence of neurocognitive disorders and depression in a Brazilian HIV population. *Rev Soc Bras Med Trop.* (2015) 48:390–8. doi: 10.1590/0037-8682-0034-2015
59. Filho SMMF, de Melo HRL. Frequency and risk factors for HIV-associated neurocognitive disorder and depression in older individuals with HIV in northeastern Brazil. *Int Psychogeriatr.* (2012) 24:1648–55. doi: 10.1017/S1041610212000944
60. Robertson K, Kumwenda J, Supparatpinyo K, Jiang JH, Evans S, Campbell TB, et al. A multinational study of neurological performance in antiretroviral therapy-naïve HIV-1-infected persons in diverse resource-constrained settings. *J Neurovirol.* (2011) 17:438–47. doi: 10.1007/s13365-011-0044-3
61. Zamudio-Rodriguez A, Belaunzaran-Zamudio PF, Sierra-Madero JG, Cuellar-Rodriguez J, Crabtree-Ramirez BE, Alcala-Zermeno JL, et al. Association between frailty and HIV-associated neurodegenerative disorders among older adults living with HIV. *AIDS Res Hum Retroviruses.* (2018) 34:449–55. doi: 10.1089/aid.2017.0100
62. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* (1975) 12:189–98. doi: 10.1016/0022-3956(75)90026-6
63. de Almeida M, Kamat R, Cherner M, Umlauf A, Ribeiro CE, de Pereira AP, et al. Improving detection of HIV-associated cognitive impairment: comparison of the international HIV dementia scale and a brief screening battery. *J Acquir Immune Defic Syndr.* (2017) 74:7. doi: 10.1097/QAI.0000000000001224
64. Carroll A, Brew B. HIV-associated neurocognitive disorders: recent advances in pathogenesis, biomarkers, and treatment. *F1000Res.* (2017) 6:312. doi: 10.12688/f1000research.10651.1
65. Morlett Paredes A, Gooding A, Artiola i Fortuny L, Rivera-Mindt M, Suarez P, Scott TM, et al. The state of neuropsychological test norms for Spanish-speaking adults in the United States. *Clin Neuropsychol.* (2020) 35:236–52. doi: 10.1080/13854046.2020.1729866
66. Arango-Lasprilla JC. Commonly used neuropsychological tests for spanish speakers: normative data from Latin America. *NeuroRehabilitation.* (2015) 37:489–91. doi: 10.3233/NRE-151276
67. The Mind Exchange Working Group, Antinori A, Arendt G, Grant I, Letendre S, Muñoz-Moreno JA, et al. Assessment, diagnosis, and treatment of HIV-associated neurocognitive disorder: a consensus report of the mind exchange program. *Clin Infect Dis.* (2013) 56:1004–17. doi: 10.1093/cid/cis975
68. INEI, Instituto Nacional de Estadisticas e Informatica. *PERÚ: Indicadores del Índice de Desigualdad de Género referidos a participación política, empleo y educación, según departamento* 2018 (2018). Available online at: https://www.inei.gob.pe/estadisticas/indice-tematico/brechas-de-genero-7913/ (accessed October 29, 2020).
69. World Health Organization. *World Health Organization, Global Tuberculosis Report.* Peru (2020). https://www.who.int/teams/global-tuberculosis-programme/global-tuberculosis-report-2020 (accessed October 30, 2020).
70. Robertson KR, Oladeji B, Jiang H, Kumwenda J, Supparatpinyo K, Campbell TB, et al. Human immunodeficiency virus type 1 and tuberculosis coinfection in multinational, resource-limited settings: increased neurological dysfunction. *Clin Infect Dis.* (2019) 68:1739–46. doi: 10.1093/cid/ciy718

71. Ramlall S, Lessells RJ, Naidu T, Mthembu SS, Padayatchi N, Burns JK, et al. Neurocognitive functioning in MDR-TB patients with and without HIV in KwaZulu-Natal, South Africa. *Trop Med Int Health.* (2020) 25:919–27. doi: 10.1111/tmi.13444
72. Tomita A, Ramlall S, Naidu T, Mthembu SS, Padayatchi N, Burns JK. Neurocognitive impairment risk among individuals with multiple drug–resistant tuberculosis and human immunodeficiency virus coinfection: implications for systematic linkage to and retention of care in tuberculosis/human immunodeficiency virus treatment. *J Nerv Ment Dis.* (2019) 207:307–10. doi: 10.1097/NMD.0000000000000962
73. Hestad KA, Chinyama J, Anitha MJ, Ngoma NS, McCutchan JA, Franklin DR Jr, et al. Cognitive impairment in zambians with HIV infection and pulmonary tuberculosis. *J Acquir Immune Defic Syndr.* (2019) 80:110–7. doi: 10.1097/QAI.0000000000001880
74. LaVergne S, Umlauf A, McCutchan A, Heaton R, Benson C, Kumarasamy N, et al. Impact of latent tuberculosis infection on neurocognitive functioning and inflammation in HIV-infected and Uninfected South Indians. *J Acquir Immune Defic Syndr.* (2020) 84:430–6. doi: 10.1097/QAI.0000000000002368
75. Cárcamo CP, Campos PE, García PJ, Hughes JP, Garnett GP, Holmes KK. Prevalences of sexually transmitted infections in young adults and female sex workers in Peru: a national population-based survey. *Lancet Infect Dis.* (2012) 12:765–73. doi: 10.1016/S1473-3099(12)70144-5
76. Marra CM, Deutsch R, Collier AC, Morgello S, Letendre S, Gelman B, et al. Neurocognitive impairment in HIV-infected individuals with previous syphilis. *Int J STD AIDS.* (2013) 24:351–5. doi: 10.1177/0956462412472827
77. Wallace MR, Heaton RK, McCutchan JA, Malone JL, Velin R, Nelson J, et al. Neurocognitive impairment in human immunodeficiency virus infection is correlated with sexually transmitted disease history. *Sex Transm Dis.* (1997) 24:398–401. doi: 10.1097/00007435-199708000-00003
78. Ho EL, Maxwell CL, Dunaway SB, Sahi SK, Tantalo LC, Lukehart SA, et al. Neurosyphilis increases human immunodeficiency virus (HIV)-associated central nervous system inflammation but does not explain cognitive impairment in HIV-infected individuals with syphilis. *Clin Infect Dis.* (2017) 65:943–8. doi: 10.1093/cid/cix473
79. Peru Ministerio de Salud. *Centro Nacional de Epidemiologia, Prevención y Control de Enfermedades – MINSA (*) Hasta la SE 5 del* 2018 (2018). Available online at: http://www.dge.gob.pe/portal/docs/vigilancia/sala/2018/SE05/hepatitisb.pdf (accessed October 30, 2020).
80. Karaivazoglou K, Assimakopoulos K, Thomopoulos K, Theocharis G, Messinis L, Sakellaropoulos G, et al. Neuropsychological function in Greek patients with chronic hepatitis C. *Liver Int.* (2007) 27:798–805. doi: 10.1111/j.1478-3231.2007.01486.x
81. Carmo Filho A do, Fakoury MK, Eyer-Silva W de A, Neves-Motta R, Kalil RS, Ferry FR de A. Factors associated with a diagnosis of major depression among HIV-infected elderly patients. *Rev Soc Brasil Med Trop.* (2013) 46:352–4. doi: 10.1590/0037-8682-1228-2013
82. Villarreal-Zegarra D, Cabrera-Alva M, Carrillo-Larco RM, Bernabe-Ortiz A. Trends in the prevalence and treatment of depressive symptoms in Peru: a population-based study. *BMJ Open.* (2020) 10:e036777. doi: 10.1136/bmjopen-2020-036777
83. The World Bank. *The World Bank. Literacy Rate, Adult Total (% of people ages 15 and above).* UNESCO Institute for Statistics (uis.unesco.org) (2018). https://data.worldbank.org/indicator/SE.ADT.LITR.ZS?locations=ZJ-PE
84. Instituto Nacional de Estadística e Informática. Perú: Crecimiento y Distribución de la Población 2017. In: Aponte FC, editor. *Censos Nacionales 2017: XII de Población y VII de Vivienda.* Lima: PRIMEROS RESULTADOS (2018). p. 15–6.
85. Brooks-Pollock E, Becerra MC, Goldstein E, Cohen T, Murray MB. Epidemiologic inference from the distribution of tuberculosis cases in households in Lima, Peru. *J Infect Dis.* (2011) 203:1582–9. doi: 10.1093/infdis/jir162
86. Mollel EW, Maokola W, Todd J, Msuya SE, Mahande MJ. Incidence rates for tuberculosis among HIV infected patients in Northern Tanzania. *Front Public Health.* (2019) 7:306. doi: 10.3389/fpubh.2019.00306

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 24 June 2021
doi: 10.3389/fneur.2021.641217

Romanian GPs Involvement in Caring for the Mental Health Problems of the Elderly Population: A Cross-Sectional Study

Raluca Sfetcu[1,2]*, *Daciana Toma*[3], *Catalina Tudose*[4] and *Cristian Vladescu*[2,5]

[1] Psychology Department, "Spiru Haret" University, Bucharest, Romania, [2] The Center for Health Services Assessment and Research, National School of Public Health, Management and Professional Development, Bucharest, Romania, [3] National Society for Family Medicine, Bucharest, Romania, [4] Psychiatry Department, University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania, [5] Public Health Department, Faculty of Medicine, "Titu Maiorescu" University, Bucharest, Romania

OPEN ACCESS

Edited by:
Christopher Butler, University of Oxford, United Kingdom

Reviewed by:
Judith Aharon Peretz, Rambam Health Care Campus, Israel
Elisa De Paula Franca Resende, Federal University of Minas Gerais, Brazil

***Correspondence:**
Raluca Sfetcu
raluca.sfetcu@hotmail.com

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: *13 December 2020*
Accepted: *31 May 2021*
Published: *24 June 2021*

Citation:
Sfetcu R, Toma D, Tudose C and Vladescu C (2021) Romanian GPs Involvement in Caring for the Mental Health Problems of the Elderly Population: A Cross-Sectional Study. Front. Neurol. 12:641217. doi: 10.3389/fneur.2021.641217

The mental health of the elderly is a matter of increased concern in the context of an aging population since currently only a small fraction of this population is receiving adequate care. The provision of treatment in primary care by the General Practitioners (GPs) has been proposed for over a decade as a potential solution, as services offered by GPs are more accessible, less susceptible to stigma, and have a more comprehensive view of the other health care problems that the elderly might suffer from. In this study, we explored the perception of Romanian GPs regarding their practice and roles in caring for the mental health of the elderly as well as the willingness to increase their future involvement in the management of dementia and other mental health problems. Data was collected via an online questionnaire structured on four dimensions: (1) GPs' sociodemographic profile and practice characteristics, (2) GPs assessment of the services available for elderly with mental health problems, (3) GPs current involvement in mental health care for different categories of problems, and (4) factors that might influence the future involvement of GPs in providing care for elderly with mental health problems. The survey was sent via the member mailing lists of the National Society for Family Medicine. Results show that GPs are currently limited by prescribing possibilities, available resources and knowledge in the area, but they are willing to expand their role in the areas of early recognition and prevention of mental health problems as well as providing disease management and collaborative care. An improved communication with mental health care professionals, a better access to resources and having more financial incentives are the three most important categories for GPs to increase their involvement. In conclusion, increasing the access to personal and professional resources and setting up functional communication channels with specialized mental health care could motivate GPs to provide timely mental health support to elderly patients.

Keywords: mental health, primary care, elderly, roles, barriers

INTRODUCTION

The mental health of elderly is of increasing concern in an aging population context, with 20% of adults aged 55 and over suffering from a mental disorder of which most commonly reported are anxiety disorders, severe cognitive impairment, and mood disorders. Nevertheless, the majority of this population does not receive the services they need, with 70% of older adults not seeking help from a mental health professional for their mental health problems (1, 2). This represents an especially important issue in light of the accumulated knowledge that all mental health disorders adversely affect physical health. Studies show that untreated depression in the elderly who also suffer from heart disease can negatively affect the outcome of the somatic condition (3). However, currently depression is still widely under detected in older people, with only one in six elderly people with depression actually discussing their symptoms with the GP and less than half of them receiving adequate treatment (4). The situation was found to be similar for elderly suffering from anxiety disorders (5, 6) and in Low and Middle Income Countries (LMIC) the treatment gap is estimated to be even higher (7). Despite the obvious impact that untreated mental health problems might have (8), the gaps in the provision of services for elderly still exist due to factors such as: the stigma surrounding mental illness and mental health treatment; denial of problems; access barriers; fragmented and inadequate funding for mental health services; lack of collaboration and coordination among primary care, mental health, and aging services providers; gaps in services; and the lack of adequate professional and paraprofessional staff trained in the provision of geriatric mental health services (9).

Since ∼70% of the population seeks health care in primary care settings (10) and General Practitioners (GPs) are frequently the gatekeepers to specialized mental health services (11), they could play an important role in addressing this detection and treatment gap.

Recent research conducted in Indonesia and other LMICs show that GPs supported by nurses in primary care clinics could effectively manage mild to moderate mental health issues commonly found among primary care patients and that they provide non-stigmatizing mental health care within community context, helping to reduce the mental health Treatment Gap (12, 13). While the idea of increasing the involvement of GPs in the treatment of the elderly with mental health problems is at least a decade old, it has been suggested that the feasibility of such an approach must be tested in each country (12).

In Romania such an approach has not been yet tested, although previous efforts to increase the knowledge of GPs in the area of mental health care have been made (14). GPs are currently reimbursed mainly on capitation, with very few fee-for services, none of them for mental health care (15) and they have limited capacity in the prescription of drugs for mental health disorders. They are generally being asked to continue the prescriptions initiated by psychiatrists for a limited period of time (usually up to 3 months) after which a new prescription from the psychiatrist is needed (16). The current legislation also limits the initiation and continuation of the treatment for dementia to specialists such as psychiatrists, neurologists, and geriatricians; these are the main providers of care either in hospitals or outpatient services as no specialized services are currently available for the elderly with mental health problems (17). The official role of the GPs for this type of diagnosis is to identify patients and refer them to the specialists. However, access to specialized services can be difficult in many regions of the country and—when available—these might not meet the actual needs which can result in multiple consultations (18).

In this context, we aimed to explore the views of Romanian GPs on their current role, on factors that deter them from playing a more active role as well as on the specific areas where they would be willing to intensify their involvement in the mental health care of the elderly. Through this study we aim to understand how GPs perceive the services currently provided to elderly with dementia and other mental health problems, their current place within the mental health care system as well as enabling and hindering factors for a further expansion of their role. We hope our results will be used to inform future health care policies in this area.

METHODS

Study Design

This is a cross-sectional survey-based, observational study on the perceived current and future role of GPs in the area of the mental health care of the elderly.

Participants

The selection of participants was opportunistic. The questionnaire was made available in a digital format and a link was posted by one of the authors on the internal communication channels of the national GPs professional society [i.e., National Society of Family Doctors (NSFD)]. The announcement was available online for 2 weeks in May 2018 and resulted in 65 completed questionnaires. Around 4,000 GPs from all over the country are subscribed to the NSFD communication group where the announcement was posted; however due to individual message viewing preferences pre-set by GPs, we cannot estimate the actual number of members who have actually seen our announcement and we cannot give an estimate of the actual response rate.

Instruments

The questionnaire was constructed by the research team, based on a selective review of the literature (19–27), as further indicated below. The structure of the questionnaire reflects our goal to cover different aspects that might influence the current and future role of GPs in providing mental health service to elderly population while keeping the response time around 15 min (no financial incentive was provided to respondents for their participation). We have tested and refined the questionnaire by asking four key experts (three GPs and one psychiatrist) to fill in the form and make suggestions for improvement, wherever necessary.

The questionnaire covers four dimensions: (1) GPs' sociodemographic profile and practice characteristics, (2)

GPs assessment of the services available for elderly with mental health problems, (3) GPs current involvement in mental health care for different categories of problems, and (4) factors that might influence the future involvement of GPs in providing care for elderly with mental health problems. It includes categorical or continuous items, with 4- or 5 point Likert-scale questions. Elderly population was defined as people aged 65 years old and over.

(1) *GPs' sociodemographic profile and practice characteristics*; this dimension included five questions.

As demographic variables, age, and sex were surveyed, as well as the place of the GP office. For the location of the practice, the answer options were "big city," "suburbs," "small town," and "rural area" (these categories were dichotomized into urban (big cities, suburbs, and small town) and rural (mixed urban-rural and rural) areas). In terms of the characteristics of the practice we have asked GPs about their practice setting (whether working alone, with other GPs, with other medical specialties or with GPs and other medical specialties in a shared space) as well as how they estimate their workload to be (working below capacity, at capacity or above capacity). These items have been taken over and adapted from the QUALICOPC study (19, 20).

(2) *GPs assessment of the services available for elderly with mental health problems*; two questions were used to assess how GPs perceive the current provision of services for the elderly.

The first question asked the GPs to rate on a four point Likert scale the availability, diversity, continuity and the global quality of the mental health care services currently available to elderly (21, 22) and the second asked them to rate on five point Likert scale the degree to which different categories of services currently available to elderly with mental health problems respond to their needs. The services included were: General Practitioners, Outpatient psychiatric services, Outpatient neurologic services, Outpatient geriatric services Community Mental Health Center, Day centers, Psychiatric hospitals, Psychiatric departments in general hospitals, Geriatric departments in general hospitals, Neurologic departments in general hospitals, Residential centers, Nursing homes, Memory centers, Home care services, and Palliative care services.

The second question was developed by the authors to reflect the structure of the current provision of services for the elderly in Romania.

(3) *GPs as first contact for psycho-social problems and their current involvement in the initiation and treatment of mental health care for different categories of patients*; this dimension included two questions.

The first referred to the extent to which seven different categories of patients contact the GP as first health care provider (e.g., Man aged 68 with neurocognitive problems (e.g., dementia), Woman aged 70 with anxiety and depression problems, etc.) with the answer categories "almost always," "usually," "occasionally," or "seldom/never."

The second inquired about the involvement of the GP in the initiation and treatment of anxiety disorders, depression, personality disorders, schizophrenia, Parkinson disease, Alzheimer disease, and other neurodegenerative disorders.

(4) *Enabling and hindering factors for GPs future involvement in providing care for elderly with mental health problems*; this dimension included three subsections.

One addressed the barriers that prevent GPs for assuming a more active role in caring for the mental health problems of the elderly and included the following six categories: access to specialized services (4 items), communication with mental health care providers (6 items), personal and professional resources (3 items), patient related factors (2 items), financial related factors (4 items), and competencies (11 items). The list of factors has been created by the authors, based on previous research conducted in this area (21–23, 26, 27).

The second subsection asked about GPs willingness to get involved in different areas of mental health care for the elderly population such as: early recognition and prevention (1 item), self-management and e-health interventions (2 items), diagnosis and treatment (7 items), disease management and collaborative care (2 items), and relapse prevention, rehabilitation, and participation (2 items). This section was developed based on the stepped care model (24).

The last question prompted GPs to self-assess their abilities to provide care for anxiety disorders, depression, personality disorders, schizophrenia, Parkinson disease, Alzheimer disease, and other neurodegenerative disorders both in the current context as well as in an ideal context, where the current barriers would be removed.

Data Analysis

Data were analyzed using descriptive statistics for all included variables (frequencies, percentages, means, and standard deviations). We have also performed a correlation analysis of the different areas of care that GPs would be willing to get involved in with the categories of factors indicated as barriers. To perform the analysis, we have used the Statistical Package for the Social Sciences (SPSS) for Mac, version 20.0.

Ethical Issues

The ethical approval was obtained from the "Spiru Haret University" ethical review board and the protocol was determined to be exempt. No harm was anticipated to the survey respondents. The consent letter was placed directly within the survey, before the actual survey questions. At the end of the consent letter, participants had to provide their consent to participate in the study.

RESULTS

GPs' Sociodemographic Profile and Practice Characteristics

Participants to this study were 65 General Practitioners (GPs), having an average age of 51.6 years (SD = 10.6) and living in

TABLE 1 | General practitioner (GP) characteristics and aspects of their practice and interprofessional collaboration.

Demographic data (*N* = 65)	*N* (%)
Gender	
Male	5 (7.7)
Female	58 (89.2)
Where is the practice located	
Big (inner) city	42 (64.6)
Suburbs	1 (1.5)
(Small) town	7 (10.8)
Mixed urban-rural	3 (4.6)
Rural	12 (18.5)
Practice setting	
Working alone	30 (46.2)
With other GPs in a shared space	20 (30.8)
With other medical specialties in a shared space	13 (20.0)
With GPs and other medical specialties in a shared space	2 (3.1)
Workload	
I still have time	10 (15.4)
I work at my capacity level	22 (33.8)
I work above my capacity level	33 (50.8)

TABLE 2 | GPs' perception of mental health care services for the elderly in terms of availability, diversity, continuity, and global quality.

GPs' perception of mental health care services for the elderly in terms of *N* = 65	Poor and very poor *N* (%)	Good and very good *N* (%)
Availability (Number)	56 (86.2)	9 (13.8)
Diversity	58 (89.2)	6 (9.2)
Continuity	54 (83.1)	11 (16.9)
Global quality	48 (75.4)	14 (21.5)

22 counties in Romania (32 from Bucharest, three each from Bihor, Dolj and Prahova, two each from Calarasi, Ilfov, Satu Mare, Teleorman, Tulcea and Valcea and one from Arad, Bacau, Botosani, Braila, Brasov, Cluj, Galati, Gorj, Hunedoara, Ialomita, Iasi, Vrancea). The majority (89.2%) were female practicing in a big city (64.6%) in an individual office or together with other GPs (77%). Half of the participants reported working above their capacity level, with an average size of the practice population of 2032 (SD = 728) patients on the list (see **Table 1**). The demographic structure of our sample is similar to ones included in other studies, a WHO report on the structure and provision of primary care in Romania reporting an average age of 49.5 years and 80% of respondents being female (28).

GPs Assessment of the Services Available for Elderly With Mental Health Problems

When asked about the mental health services for elderly people with mental health problems, the vast majority of participants have indicated that these are poor or very poor in terms of diversity (89.2%), availability (86.2%) and continuity (83.1). For the global quality of the services, a slightly higher number of participants (i.e., 21.5%) are of the opinion that the services are of good or very good quality (see **Table 2**).

TABLE 3 | GP's assessment of the degree to which services available to elderly with mental health problems respond to their needs.

How well are the following services responding to the mental health care needs of the elderly (*N* = 65)	Not at all or to a low degree *N* (%)	Some degree *N* (%)	High or very high degree *N* (%)
General practitioners	6 (9.2)	29 (44.6)	30 (46.2)
Outpatient psychiatric services	10 (15.4)	22 (33.8)	33 (50.8)
Outpatient neurologic services	14 (21.5)	27 (41.5)	24 (36.9)
Outpatient geriatric services	23 (35.4)	12 (18.5)	7 (10.8)
Community mental health center	25 (38.5)	22 (33.8)	15 (23.1)
Day centers	34 (52.3)	14 (21.5)	9 (13.8)
Psychiatric hospitals	26 (40.0)	19 (29.2)	18 (27.7)
Psychiatric departments in general hospitals	23 (35.4)	22 (33.8)	15 (23.1)
Geriatric departments in general hospitals	28 (43.1)	15 (23.1)	14 (21.5)
Neurologic departments in general hospitals	27 (41.5)	23 (35.4)	13 (20.0)
Residential centers	28 (43.1)	19 (29.2)	4 (7.7)
Nursing homes	32 (49.2)	17 (26.2)	10 (15.4)
Memory centers	22 (33.8)	16 (24.6)	10 (15.4)
Home care services	30 (46.2)	18 (27.7)	10 (15.4)
Palliative care services	27 (41.5)	20 (30.8)	8 (12.3)

TABLE 4 | Reported categories of patients who contact their GP as the first health care provider for different mental health care problems.

First option (contact for *N* = 65)	*Rarely* *N* (%)	*Frequently* *N* (%)
Man aged 28 with a first convulsion	44 (67.7)	21 (32.3)
Anxious man aged 45	9 (13.8)	56 (86.2)
Woman aged 50 with psychosocial problems	12 (18.5)	53 (81.5)
Woman aged 70 with anxiety and depression problems	1 (1.5)	64 (98.5)
Man aged 52 with alcohol addiction problems	32 (49.2)	33 (50.8)
Woman aged 75 with moderate memory problems	4 (6.2)	61 (93.8)
Man aged 68 with neurocognitive problems (e.g., dementia)	7 (10.8)	58 (89.2)

A more detailed image of how the performance of different services is perceived by the GPs, shows that outpatient psychiatric services meet the mental health needs of the elderly in a high or very high degree (50.8%). GPs are following closely (46.2%), being the second most responsive professional category followed by neurologic outpatient services (36.9%), psychiatric hospitals (27.7%) and community mental health centers (23.1%). The mental health needs of the elderly are addressed in a moderate way by inpatient psychiatric, neurologic and geriatric services and poorly by residential care, nursing homes, home care, memory centers, day centers or palliative care services (for details, see **Table 3**).

TABLE 5 | Involvement in initiation and treatment of different mental health problems.

Current involvement for the following categories	*Rarely* *N* (%)	*Frequently* *N* (%)
Anxiety disorders	17 (26.2)	48 (73.8)
Depression	31 (47.7)	34 (52.3)
Personality disorders	53 (81.5)	12 (18.5)
Schizophrenia	58 (89.2)	7 (10.8)
Parkinson disease	51 (78.5)	14 (21.5)
Alzheimer disease	49 (75.4)	16 (24.6)
Other neurodegenerative disorders	49 (75.4)	16 (24.6)

GPs Current Involvement in Mental Health Care

A high number of GPs (81.5–98.5%) report that patients with psychosocial problems, anxiety, depression, memory problems and other neurocognitive problems are frequently contacting them, as their first health care provider. Elderly female patients with anxiety and depression problems are the category for which the GPs are almost exclusively the first health care provider (i.e., 98.5%). The next most frequent categories are elderly males and females with memory problems and/or other neurocognitive problems (**Table 4**).

These results are also confirmed by the high frequency of cases where GPs initiate or provide treatment for mental health problems, anxiety disorders being the most mentioned category (i.e., 73.8%) followed by depression (52.3%). The involvement of GPs in the treatment of patients with Alzheimer disease or other neurodegenerative problems is reported by only one in four GPs to be a frequently occurring practice. The involvement in treating serious mental illness is also reported only by a few GPs (10.8% for Schizophrenia and 18.5% for personality disorders; see **Table 5**).

Enabling and Hindering Factors for GPs Involvement in Providing Care for Elderly With Mental Health Problems

The main barrier to getting involved in the treatment of elderly with mental health problems that was mentioned by the participants to our study is the communication with mental health care providers (psychiatrists, psychologists, members of community mental health care teams), followed by the limited access to specialized mental health care services (i.e., difficulty in accessing specialized resources, a scarcity of mental health care workers, inadequate support and communication among stakeholders or a lack of critical mental healthcare resources). The third category of factors perceived as playing an important role, is represented by financial related factors (i.e., inadequate level of remuneration, increased bureaucracy to get reimbursed, investments of education and lack of financial motivation). Mean scores for all categories measured are presented in **Table 6**. While all factors are perceived as being important, the lowest mean score is corresponding to the category of personal and professional resources. Nevertheless, when looking at individual factors, the limited possibility to prescribe medication is reported by over half of the participants to be in a very high degree a barrier to their involvement in treating the mental health problems of the elderly. Other individual factor for which GPs agreed that play a very high role were the uncertainty of the diagnosis (44.6%), a lack of support from mental healthcare teams (43.1%), the bureaucracy to get reimbursed (41.5%), the inadequate level of remuneration (40.0%) and the lack of explicitness in the roles of different healthcare professionals (e.g., GPs, psychiatrists, psychologists) in managing mental conditions. Scores for all individual factors are included in **Appendix A**).

TABLE 6 | Categories of factors that represent barriers to getting involved in the management of mental health problems of the elderly population.

Categories of factor that represent barriers to mental health care	Mean (*SD*)
(F1) Access to specialized services	3.75 (.94)
(F2) Communication with mental health care providers	3.85 (.80)
(F3) Personal and professional resources	3.40 (1.05)
(F4) Patient related factors	3.50 (1.03)
(F5) Financial related factors	3.72 (1.04)
(F6) Competencies	3.56 (.80)

TABLE 7 | Willingness of GPs to get involved in different areas of mental health care of the elderly population.

Areas of mental health care (elderly population)	Mean (*SD*)
Early recognition and prevention[a]	4.30 (.91)
Self-management and e-health interventions	3.68 (1.07)
Diagnosis and treatment[b]	3.80 (.85)
Disease management and collaborative care[c]	4.03 (1.00)
Relapse prevention, rehabilitation and participation[d]	3.80 (1.05)

[a]Correlates with F2 (0.05 level); [b]Correlates with F3 (.05 level); [c]Correlates with F2 (.01 level) and with F1, F3, and F5 (0.05 level); [d]Correlates with F2 and F3 (0.05 level).

While GPs are reporting above average interest to get involved in all areas of mental health care for the elderly, they would be willing to invest more effort into early recognition and prevention of mental health problems as well as providing disease management and collaborative care (i.e., referring to other health care providers and continuing care initiated in secondary care). The least interesting area for GPs was the one focusing on providing support for self-management or prescribing e-health interventions (for details, see **Table 7** and **Appendix B**).

To identify which factor might have an influence on the willingness of GPs to get involved in different areas of care we have run a correlation analysis between the six categories of factors discussed above (see **Table 6**) and the five areas of mental health care of the elderly population. Our results show a positive correlation between the area of "early recognition and prevention" and the scores obtained for the "communication with mental health providers" indicating that a better communication with the mental health providers

TABLE 8 | Self-assessment of GPs abilities to provide care for different categories of mental health problems in the current context and in an ideal context.

Categories	Current context YES [*N* (%)]	Ideal Context YES [*N* (%)]	Increase %
Anxiety disorders	57 (87.7)	62 (95.4)	7.7
Depression	46 (70.8)	58 (89.2)	18.4
Personality disorders	6 (9.2)	20 (30.8)	21.6
Schizophrenia	5 (7.7)	15 (23.1)	15.4
Parkinson disease	20 (30.8)	37 (56.9)	26.1
Alzheimer disease	22 (33.8)	40 (61.5)	27.7
Other neurodegenerative disorders	14 (21.5)	30 (46.2)	24.7

would improve the willingness of GPs to get involved in "early recognition and prevention" (significant at 0.05 level). Similarly, we have found significant corelation between the area of "diagnosis and treatment" and "the level of personal and professional resources" (0.05 level). For the area of "disease management and collaborative care" we have found correlations with "communication with mental health providers" (0.01 level) as well as with the "access to specialized services" and "the level of personal and professional resources" (0.05 level). Finally, the area of "relapse prevention, rehabilitation and participation" correlates with "communication with mental health providers" and "the level of personal and professional resources" (0.05 level).

A last set of questions we have asked the GPs was addressing their ability to manage the mental health problems of the elderly in context of the existing barriers as well as in an ideal context, where most of these barriers would be removed. As expected, the current ability was assessed to be the highest for anxiety and depression and the lowest for the severe mental illnesses (schizophrenia and personality disorders). For Parkinson and Alzheimer diseases the current ability was estimated as low, with just one in three GPs believing that they would have the skills needed to manage this category of problems (see **Table 8**). However, these are the same diseases for which GPs expect the highest increase in ability, in the scenario where more resources would be available to them (26.1 and 27.7%, respectively).

DISCUSSION

The aim of this study was to shed light on how GPs perceive the services currently provided to elderly with mental health problems, their place within the care system as well as the enabling and hindering factors for a possible future expansion of their role. We have discovered that GPs have an accurate understanding of the existent gap in the provision of mental health care for the elderly in terms of the number, the diversity and the continuity of the available services. For each of these dimensions over 75% of the participants estimate that the current provision is poor or very poor. These percentages are very high by comparison with data from other countries, a similar study from Canada indicating a dissatisfaction with the overall quality of the mental health care system of only 45% (diversity: 46%, continuity: 54%, and availability: 65%) (21). GPs also believe that services that are best meeting the needs of the elderly are provided in psychiatric and neurologic outpatient settings, psychiatric hospitals and by GPs themselves. Taking into consideration the fact that these are the most widespread institutional and human resources in Romania (17), it is highly probable that the majority of mental health services provided to the elderly is indeed taking place in these four main types of services.

The majority of the GPs in our sample (81.5–98.5%) report being frequently the first health care provider for patients with psychosocial problems, anxiety, depression, memory problems, and other neurocognitive problems. However, we have found that not all of these GPs initiate or provide treatment for anxiety disorders (73.8%) or depression (52.3%). As GPs in Romania play a gatekeeping role (29), these results are to be expected and are consistent with a recent study who shows that GPs are the first point of care for 66% of adults with anxiety problems and for 84% of elderly with memory problems (30). The same study indicates that GPs are involved in the treatment of follow-up of the depression in the general population in 74% of cases. These differences might indicate that GPs are less confident or are less motivated to treat the depression of the elderly than treating depression in adults (31), or they might even view it as "justifiable depression" (32). However, this aspect should be adequately investigated in future research.

One of the categories of factors that might have an impact on the decision to get involved in the care of elderly with mental health problems is represented by the lack of communication with mental health care providers. These findings are reinforced by results of Butu et al. (30), where 55% of the Romanian GPs investigated have reported to have rarely or never asked advice from a psychiatrist or have met them face to face. Our results are also similar with those of studies conducted in other countries which highlight that, in general, GPs are willing to initiate and provide treatment for mental health problems if they would have better collaborative relationships with mental health specialists (33–35). For example, a study conducted in France found out that a minority of GPs had a satisfactory relationship with private psychiatrists (49.5%) and public psychiatrists (36). As many different models of collaboration and communication have been proposed in the literature, an in-depth analysis of what is the best form of direct communication with other professionals and what represents an optimized referral process would increase the understanding of this issue. As virtual communication methods are rapidly expanding and cost-effective interventions for improving the collaboration between GPs and other specialists could be easily developed, this is also a timely exploration.

Having access to specialized mental health resources and a more advantageous financing model for services provided by GPs can also incentivize GPs for providing treatment to elderly with mental health problems. These findings are not specific for Romania, as access to specialized resources, the inadequate methods of remuneration and lack of financial incentives for GPs to manage mental disorders are frequently mentioned in the literature as hindering factors (26, 31). The need for the development of evidence-based resources for older people with

mental health problems within primary care was recognized as a highly needed intervention (32). However, due to the differences in how health care systems are organized, solutions must be developed locally and in close collaboration with all actors involved. The future exploration of these issues should include qualitative research with GPs, psychiatrists and representatives of financing bodies.

In terms of the skills GPs need in order to provide mental health services to an elderly population, the strong areas are represented by depression and anxiety disorders. For the rest of diagnostic categories, the percentages of GPs reporting a good level of skills is rather low. However, in an ideal context where current barriers would be surpassed, the GPs expect an increase of these skills of up to 25%, which represent an encouraging result. Previous studies also highlight the fact that GPs are well-positioned to address MHP in their older patients because of (a) their long-lasting bond with their older patients, (b) their holistic view of the patient, and (c) the easy low-threshold access they offer, but the lack of knowledge, skills, and confidence in their skills can substantially impair detection as well as treatment (33). In Romania, interventions for increasing the skills of GPs have been implemented in the last decades but these were project based and did not lead to systemic changes in the initial training of GPs, in the Continuing Medical Education (CME) programs or in the financial incentive structure. Connecting the training with financial incentives have proved to be successful strategies to increase mental health services provision, as demonstrated by the "Better Outcomes" program implemented in Australia between 2000 and 2007 and should be included in future interventions (37).

Despite the above discussed barriers, GPs are reporting an above average interest to get involved in all areas of mental health care for the elderly. However, they would be willing to invest more effort into early recognition and prevention of mental health problems as well as providing disease management and collaborative care. These results indicate that increasing the access to personal and professional resources and setting up functional communication channels with specialized mental health care could increase the willingness of GPs to provide timely mental health support to a larger number of elderly populations. One additional factor to be considered when planning for the involvement of GPs in the treatment of mental health problems of the elderly is their limited time availability, as mental health care can be time consuming and half of our participants have reported already working above their capacity level (22).

Taking into consideration the limited number of participants as well as the opportunistic method used for sampling them, the results of this study should be used with caution. The fact that we have not distributed the questionnaire directly but we have used the communication channels of the National Society for Family Medicine for their regular contact with members might have played a role in the decision of GPs whether to take part in the research or not, even before opening the email (were more information about the study was included). This might be a possible explanation for the low response rate. Also, as GPs had the possibility to self-register for this study it is also likely that GPs with a higher interest for the topic have answered the questionnaire. Despite the limitations and biases associated with this data collection method, it was the only available method of reaching a large number of GPs without violating the data protection rules applicable at the moment of data collection. Despite these limitations, our results can be used to inform future studies with representative samples, which are much needed by decision makers for development of future strategies.

CONCLUSIONS

Our study has found that communication with other mental health care professionals, access to resources and financial incentives are the three most important factors which influence their involvement in providing mental health care for the elderly. While still limited by prescribing possibilities, available resources and knowledge in the area, GPs are willing to expand their role in the areas of early recognition and prevention of mental health problems as well as in providing disease management and collaborative care. Increasing the access to personal and professional resources and setting up functional communication channels with specialized mental health care could motivate GPs to provide timely mental health support to elderly patients. Strategies in the area of service development should also take into consideration the development of adequate financing mechanisms and financial incentives. Future research should focus on the aspects such as: comparative analyses between the willingness of GPs to initiate and provide treatment for mental health care problems to the elderly population by comparison with the general/adult population, understanding what optimal communication with other specialists and an optimized referral process should look like, and preferred method of providing access to specialized mental health resources (e.g., training, best practice/guidelines, and other types of tools).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of the Spiru Haret University. The patients/participants provided their online consent to participate in this study.

AUTHOR CONTRIBUTIONS

RS, DT, CT, and CV: conceptualization and writing—review and editing. RS, DT, and CT: methodology. RS: writing—original

draft preparation. All authors have read and agreed to the published version of the manuscript.

ACKNOWLEDGMENTS

The authors wish to thank Dr. Oana Sever Cristian and Dr. Marina Parcalabu for their contribution to the development of the questionnaire, to Anca Vlad for support in data collection and to the faculty of the REMASTER Research Training: Socio-Economic Determinants of Mental Health Services Delivery in South-Eastern Europe for the grant offered by the University of California, Berkeley in 2014 (1D43TW009122-01).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.641217/full#supplementary-material

REFERENCES

1. Bartels SJ, Gill L, Naslund JA. The Affordable Care Act, Accountable Care Organizations, and Mental Health Care for older adults: implications and opportunities. *Harv Rev Psychiatry.* (2015) 23:304–19. doi: 10.1097/HRP.0000000000000086
2. Byers AL, Arean PA, Yaffe K. Low Use of mental health services among older Americans with mood and anxiety disorders. *Psychiatr Serv.* (2012) 63:66–72. doi: 10.1176/appi.ps.201100121
3. De Hert M, Dekker JM, Wood D, Kahl KG, Holt RIG, Möller H-J. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). *Eur Psychiatry J Assoc Eur Psychiatr.* (2009) 24:412–24. doi: 10.1016/j.eurpsy.2009.01.005
4. Craig R, Mindell J. *Health Survey for England 2005: The Health of Older People* New York, NY: Springer-Verlag (2007).
5. Beekman AT, Bremmer MA, Deeg DJ, van Balkom AJ, Smit JH, de Beurs E, et al. Anxiety disorders in later life: a report from the Longitudinal Aging Study Amsterdam. *Int J Geriatr Psychiatry.* (1998) 13:717–26. doi: 10.1002/(SICI)1099-1166(1998100)13:10<717::AID-GPS857>3.0.CO;2-M
6. de Beurs E, Beekman AT, van Balkom AJ, Deeg DJ, van Dyck R, van Tilburg W. Consequences of anxiety in older persons: its effect on disability, well-being and use of health services. *Psychol Med.* (1999) 29:583–93. doi: 10.1017/S0033291799008351
7. Kohn R, Saxena S, Levav I, Saraceno B. The treatment gap in mental health care. *Bull World Health Organ.* (2004) 82:858–66. doi: 10.1590/S0042-96862004001100011
8. Zivin K, Wharton T, Rostant O. The economic, public health, and caregiver burden of late-life depression. *Psychiatr Clin North Am.* (2013) 36:631–49. doi: 10.1016/j.psc.2013.08.008
9. Tucker S, Baldwin R, Hughes J, Benbow S, Barker A, Burns A, et al. Old age mental health services in England: implementing the National Service Framework for Older People. *Int J Geriatr Psychiatry.* (2007) 22:211–7. doi: 10.1002/gps.1662
10. Summergrad P, Kathol RG. *Integrated Care in Psychiatry: Redefining the Role of Mental Health Professionals in the Medical Setting*. New York, NY: Springer Science & Business (2014). p. 245.
11. Todman J, Law J, MacDougall A. *Attitudes of GPs towards Older Adults Psychology Services in the Scottish Highlands.* (2011). Available online at: https://www.rrh.org.au/journal/article/1496/ (cited February 10, 2020).
12. Anjara SG, Bonetto C, Ganguli P, Setiyawati D, Mahendradhata Y, Yoga BH, et al. Can General Practitioners manage mental disorders in primary care? A partially randomised, pragmatic, cluster trial. *PLoS One.* (2019) 14:e0224724. doi: 10.1371/journal.pone.0224724
13. Spagnolo J, Champagne F, Leduc N, Rivard M, Melki W, Piat M, et al. Building capacity in mental health care in low- and middle-income countries by training primary care physicians using the mhGAP: a randomized controlled trial. *Health Policy Plan.* (2020) 35:186–98. doi: 10.1093/heapol/czz138
14. Katschnig H, Ciumageanu M, Ghenea D, Sfetcu R. The Mental Health Twinning Projects of the European Commission (2007 - 2009). *Rev Rom Psihiatr.* (2008) 10:67–70. doi: 10.6084/m9.figshare.14754297.v1
15. Radu C-P, Chiriac DN, Vladescu C. Changing patient classification system for hospital reimbursement in Romania. *Croat Med J.* (2010) 51:250–8. doi: 10.3325/cmj.2010.51.250
16. Vladescu C, Astarastoae V, Scîntee SG. A health system focused on citizen's needs. Romania. Financing, organization and drug policy. Solutions (II). *Rev Rom Bioetică.* (2010) 8:106–15. doi: 10.6084/m9.figshare.14754369.v1
17. Lungu C, Panait CL, Mihai A, Sfetcu R. Institutional and human resources currently available to elderly people with mental health problems. *Manag Health.* (2017) 21:16–9. doi: 10.6084/m9.figshare.14754387.v1
18. Burns A, Robert P, editors. *Dementia Care: International Perspectives*. Oxford, NY: Oxford University Press (2019). 400 p.
19. Schäfer WLA, Boerma WGW, Kringos DS, De Ryck E, Greß S, Heinemann S, et al. Measures of quality, costs and equity in primary health care instruments developed to analyse and compare primary care in 35 countries. *Qual Prim Care.* (2013) 21:67–79.
20. Schäfer WLA, Boerma WGW, Kringos DS, De Maeseneer J, Gress S, Heinemann S, et al. QUALICOPC, a multi-country study evaluating quality, costs and equity in primary care. *BMC Fam Pract.* (2011) 12:115. doi: 10.1186/1471-2296-12-115
21. Fleury M-J, Bamvita J-M, Farand L, Tremblay J. Variables associated with general practitioners taking on patients with common mental disorders. *Ment Health Fam Med.* (2008) 5:149–60.
22. Fleury M-J, Imboua A, Aubé D, Farand L, Lambert Y. General practitioners' management of mental disorders: a rewarding practice with considerable obstacles. *BMC Fam Pract.* (2012) 13:19. doi: 10.1186/1471-2296-13-19
23. Fleury M-J, Bamvita J-M, Aube D, Tremblay J. Clinical practice settings associated with GPs who take on patients with mental disorders. *Healthc Policy.* (2010) 5:90–104. doi: 10.12927/hcpol.2010.21785
24. Hermens ML, Muntingh A, Franx G, van Splunteren PT, Nuyen J. Stepped care for depression is easy to recommend, but harder to implement: results of an explorative study within primary care in the Netherlands. *BMC Fam Pract.* (2014) 15:5. doi: 10.1186/1471-2296-15-5
25. Boerma WGW, Bohlken E, Kerkhoven VdH. *Profiles of General Practice in Europa: An International Study of Variation in the Tasks of General Practitioners*. Utrecht: NIVEL (2003).
26. Fleury M-J, Imboua A, Aubé D, Farand L. Collaboration between general practitioners (GPs) and mental healthcare professionals within the context of reforms in Quebec. *Ment Health Fam Med.* (2012) 9:77–90.
27. Jaruseviciene L, Sauliune S, Jarusevicius G, Lazarus JV. Preparedness of Lithuanian general practitioners to provide mental healthcare services: a cross-sectional survey. *Int J Ment Health Syst.* (2014) 8:11. doi: 10.1186/1752-4458-8-11
28. World Health Organization. *Evaluation of Structure and Provision of Primary Care in Romania*. (2012). 110 p.
29. Sfetcu R, Ungureanu M. An overview of mental health in Romania. In: *Mental Health in Central and Eastern Europe, Vol. 7, World Scientific Series in Global Health Economics and Public Policy*. (2019). p. 141–74. Available online at: https://www.worldscientific.com/doi/abs/10.1142/9789811205644_0006 (cited April 30, 2020).

30. Butu A, Tomoaia-Cotisel A, Olsavszky V. Are Romanian family doctors ready for Health 2020? *Manag Health*. 18:17–20. Available online at: http://journal.managementinhealth.com/index.php/rms/article/viewFile/314/955
31. Collins KA, Wolfe VV, Fisman S, DePace J, Steele M. Managing depression in primary care: community survey. *Can Fam Physician Med Fam Can.* (2006) 52:878–9.
32. Burroughs H, Lovell K, Morley M, Baldwin R, Burns A, Chew-Graham C. "Justifiable depression": how primary care professionals and patients view late-life depression? A qualitative study. *Fam Pract*. (2006) 23:369–77. doi: 10.1093/fampra/cmi115
33. Adriaenssens J, Benahmed N, Ricour C. Improving mental healthcare for the elderly in Belgium. *Int J Health Plann Manage.* (2019) 34:e1948–60. doi: 10.1002/hpm.2858
34. Lucena RJM, Lesage A. Family physicians and psychiatrists. Qualitative study of physicians' views on collaboration. *Can Fam Physician.* (2002) 48:923–9.
35. Althubaiti N, Ghamri R. Family physicians' approaches to mental health care and collaboration with psychiatrists. *Cureus.* 11:e4755. doi: 10.7759/cureus.4755
36. Younes N, Gasquet I, Gaudebout P, Chaillet M-P, Kovess V, Falissard B, et al. General Practitioners' opinions on their practice in mental health and their collaboration with mental health professionals. *BMC Fam Pract.* (2005) 6:18. doi: 10.1186/1471-2296-6-18
37. Harrison CM, Britt HC, Charles J. Better Outcomes or Better Access - which was better for mental health care? *Med J Aust.* (2012) 197:170–2. doi: 10.5694/mja12.10555

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 25 June 2021
doi: 10.3389/fneur.2021.628489

Watching TV and Cognition: The SPAH 2-Year Cohort Study of Older Adults Living in Low-Income Communities

*Laís Fajersztajn[1], Vanessa Di Rienzo[2,3], Carina Akemi Nakamura[2,4] and Marcia Scazufca[2,4]**

[1] Laboratório de Poluição Ambiental, Departamento de Patologia, Faculdade de Medicina (FMUSP), Universidade de São Paulo, São Paulo, Brazil, [2] Faculdade de Medicina (FMUSP), Universidade de São Paulo, São Paulo, Brazil, [3] Universidade São Judas Tadeu, São Paulo, Brazil, [4] Laboratório de Investigação Medica (LIM) 23, Faculdade de Medicina, Instituto de Psiquiatria, Hospital das Clinicas HCFMUSP, Universidade de São Paulo, São Paulo, Brazil

OPEN ACCESS

Edited by:
Christopher Butler, University of Oxford, United Kingdom

Reviewed by:
Jie Liu, Rutgers, The State University of New Jersey, United States
Yingyun Gong, Nanjing Medical University, China

***Correspondence:**
Marcia Scazufca
scazufca@gmail.com

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: *12 November 2020*
Accepted: *02 June 2021*
Published: *25 June 2021*

Citation:
Fajersztajn L, Di Rienzo V, Nakamura CA and Scazufca M (2021) Watching TV and Cognition: The SPAH 2-Year Cohort Study of Older Adults Living in Low-Income Communities. Front. Neurol. 12:628489. doi: 10.3389/fneur.2021.628489

Watching TV is a highly prevalent leisure activity among older adults and, in many cases, the only leisure option of those living in low-income communities. While engaging in leisure activities have proven to protect older adults from cognitive decline, the effects of watching TV on cognition of this population is controversial in the literature. This study investigated the impact of watching TV on global cognitive function, immediate memory, verbal fluency, risk of dementia of amnestic mild cognitive impairment (aMCI) in a cohort of older adults residents of socioeconomically deprived areas of São Paulo, Brazil. We used data from the São Paulo Aging & Health Study (SPAH). Participants aged 65 years or over, with no dementia diagnosis at baseline and who completed the 2-year follow-up assessment were included in this study (n = 1,243). Multivariable linear regression models were performed to assess the effect of watching TV on global cognitive function, immediate memory and verbal fluency. Multivariable logistic regression models were used to evaluate the risk of developing dementia and aMCI. Models were controlled by cognitive performance at baseline, sociodemographic characteristics and functional status. Cognitive performance at baseline and follow-up were similar. Thirty-one participants were diagnosed with dementia, and 23 with aMCI 24 months after inclusion in the study. Watching TV did not show any positive or negative effect on global cognitive function, immediate memory, verbal fluency, risk of dementia and risk of aMCI. It is good news that watching TV did not predict the decline in cognition in elders. However, it is essential to increase opportunities for other leisure activities for low-income and low-educated older adults if we do consider that leisure activities protect cognition decline in older adults. In the coming decades, developing countries will experience the highest burden of dementia and more than fun, public policies to promote leisure activities might be a strategy to alleviate this burden shortly.

Keywords: dementia, mild cognitive impairment, older adults, leisure activities, low-income, television, cognitive dysfunction

INTRODUCTION

More than 28 million Brazilians -or 13% of the country's population- are aged 60+, and the size of this age group is projected to double in the coming decades (1). The Brazilian elderly population has been exposed to socioeconomic adversities throughout their life course (2, 3). Most of the Brazilian elders have minimum or no formal education, had semi-skilled or non-skilled occupations throughout their lives, are poorer than the average adult population of the country and were raised in rural areas before moving to large cities during the second half of the 20th century (4). It means that they are at a higher risk of developing cognitive related health problems (2, 5). Currently, as many as 6 million Brazilians older adults cannot read or write (6). These characteristics influence the type of leisure activity performed by them.

By 2050, Latin America will host more than 17 million dementia cases (7), and strategies to reduce the burden of cognitive impairment in the region are badly needed. One possible response is to reduce social inequalities by improving modifiable risk factors for cognitive decline, such as education, quality of occupation and socioeconomic status. Social, physical and intellectual leisure activities have shown to reduce the risk of cognitive impairment (8–14) and dementia in older adults (9, 10, 15, 16), but the ability to perform these activities is affected by socioeconomic difficulties faced during the life course (17–19).

Although watching TV is an everyday leisure activity among older adults (20) worldwide, the effects of this activity on their cognition are controversial in the literature. There is no consensus in the literature of to which extent watching TV is a cognitively demanding activity or what type of activity is watching TV (e.g., is it a recreational activity?) (21–23). Longitudinal studies in Europe and the US suggest that excessive hours watching TV impairs cognition somehow (24, 25). Some studies didn't see a longitudinal effect (26, 27). However, one large study in Asia found a protective effect (11).

To date, little (28) is known of the potential protective effects of leisure activities among Latin American populations, particularly from low-income communities, where leisure activities significantly differ from those performed by older adults in high income countries. The low purchase power, restricted mobility and low literacy of this population are factors that restrict their leisure options. In this context, watching TV becomes an essential and almost the only leisure activity available to most Brazilians older adults. In Brazil, watching TV is the most frequent leisure option of 93% of the adults aged 60+ (29).

Given the importance of watching TV as a leisure activity among older adults from low-income communities and the lack of empirical data on its effect on cognition in these population, we examined the association between watching TV and incidence of amnesic mild cognitive impairment (aMCI) and dementia in a 2-year cohort study of older adults residents of socioeconomically deprived areas of São Paulo, Brazil. We also examined the association between watching TV and changes in global cognitive function, immediate memory, verbal fluency in the same population.

MATERIALS AND METHODS

This study is part of the São Paulo Aging & Health Study (SPAH), a large 2-year population-based cohort study of older adults from low-income areas of São Paulo, Brazil (2, 30).

Participants

SPAH enrolled 2,072 community-dwellings aged 65+ that lived in socioeconomically deprived areas of the district of Butantã, in São Paulo, Brazil. The recruiting method was knocking on the door of all households within the 66 pre-defined census sectors (the smallest administrative areas) between 2003 and 2005. The census sectors selected a priori were those with the lowest Human Development Index, including large informal settlements and shantytowns. Follow-up occurred 24 months after enrollment, between 2005 and 2007. Trained interviewers conducted the baseline and follow-up assessments at participants' home, using the SPAH protocol. More details of recruitment procedures are described elsewhere (2, 3, 30).

Participants without dementia at baseline and who could complete the follow-up assessment were included in this study. Socioeconomic and demographic information (age, gender, marital status, schooling, occupation, and personal income) of all participants were collected at baseline assessment. We used the 12-item World Health Organization Disability Assessment Schedule (WHODAS 2.0) to assess functional status (31). The WHODAS 2.0 is a questionnaire that evaluates six areas of life: mobility (moving and getting around), life activities (domestic responsibilities, leisure, work, and school), cognition (understanding and communicating), self-care (hygiene, dressing, eating, and staying alone), participation (joining in community activities), and getting along (interacting with other people). The score ranges from 0 to 48, and the higher the score, the more severe is the disability.

The study received ethics approval from the Brazilian National Committee for Ethics and Research (CONEP-Brazil), and all participants provided written informed consent before enrollment in the study.

Outcomes

The five clinical outcomes in this study are global cognitive function, immediate memory, verbal fluency, risk of dementia and risk of amnestic mild cognitive impairment (aMCI).

Global Cognitive Function

We used thecognitive score (COGSCORE) validated by the 10/66 Dementia Research Group to evaluate global cognitive function. The score is based on the Community Screening Instrument for Dementia (CSD-I) (32), an instrument developed for low educated and illiterate populations (33) and validated for use in Brazil (34). The global cognitive function includes memory, abstract thinking, language, praxis, space and temporal orientation dimensions. Higher scores indicate more severe impairments.

Immediate Memory

We evaluate immediate memory by asking participants to memorize a list of 10 words adapted from the Consortium to

Establish a Registry for Alzheimer's Disease (CERAD) battery (35). The total score is based on the number of recalled words, thus maximum score possible is 10 representing the best immediate memory.

Verbal Fluency

We used animal naming to evaluate verbal fluency. This test is part of the CERAD battery (35) and the CSI-D (32). First, we asked the participant to name items from another category (dressing). After this test, the participant was asked to name all animals he/she could remember during 1 min. Each animal named equals one point. Higher scores indicate better performance on the task.

Dementia

The diagnosis of dementia followed the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (36). It was based on the protocol developed by 10/66 Dementia Research Group for population-based studies in developing countries (34). Detailed description can be found elsewhere (2, 30).

Amnestic Mild Cognitive Impairment

This study used two conditions to determine the Amnestic Mild Cognitive Impairment diagnosis (aMCI): absence of dementia and memory impairment (37). We considered an individual with memory impairment if his/her total score in the memory test was at least 1.5 standard deviation (SD) below the study population's mean. The memory test score was based on four items of the cognitive dimension of the Community Screening Instrument for Dementia (CSD-I) (32). Participants were required to recall the interviewer's name, repeat three standardized words, recall these words and repeat stories. Scores are positively associated with memory performance.

Predictor Variable

The predictor variable was time spent watching TV assessed by asking "How many hours per day you watch TV?" We collected this information at baseline using the Brazilian version of the 'Involvement in Activities' questionnaire (IA). The IA was developed to evaluate engagement in activities in diverse communities and was used in the United States and Nigeria (38). The Brazilian version of the IA was validated in Brazil by the SPAH group in collaboration with the authors who developed the questionnaire. The test-retest reliability of the IA included 70 participants. They were re-assessed with an interval of 3–4 weeks. The reliability of the question about hours spent watching TV was high (0.63).

Statistical Analysis

We used multivariable linear regression to examine the association between watching TV at baseline and global cognitive function, immediate memory and verbal fluency at 2-year follow-up. Two models were built for each outcome. In the first models, we entered hours watching TV adjusting for the corresponding baseline score. Then, we extended these models by adjusting for sociodemographic characteristics (age, gender, marital status, schooling, occupation, and personal income) and function status (second models).

To investigate the impact of watching TV on the risk of dementia and aMCI, we performed two multiple logistic regression models for each outcome variable. We adjusted the first models for sociodemographic characteristics and functional status at baseline. We then extended the models for risk of dementia and the model for aMCI adjusting for global cognitive function at baseline amnestic aMCI at baseline, respectively. We present the 95% confidence interval (CI) for all analysis and set statistical significance at 5%.

Statistical significance was set at 5% for all analysis. We performed the analyses with the software STATA 9.0.

RESULTS

A total of 1,243 subjects without the dementia diagnosis at baseline who completed the 2-year follow-up assessment were included in this study. Participants were most females (61%), with a mean age of 72 years, mainly not employed (73%), low educated (89% with up to 3 years of schooling) and with a low socioeconomic background (only less than one third had a personal monthly income of more than US$246). Participants' characteristics at baseline are presented in **Table 1**. The median functional status score was 2.8 (IQR = 0–72.2). Watching TV was reported by 87% of participants with a median of 2 h per day (IQR = 0–12). Thirteen percent of the participants reported never watching TV ($n = 165$). Among those whom reported watching TV, 22.2% watched up to an hour/day ($n = 276$); 22.7% watched up to 2 h/day ($n = 282$); 14.9% watched up to 3 h/day ($n = 185$); 11.3% watched up to 4 h/day ($n = 141$); 7.4% watched up to 5 h/day ($n = 92$); and 8.2% watched 6 h/day or more ($n = 102$).

The cognitive performance of participants was similar between baseline and follow-up assessments (**Table 2**). At follow-up, mean global cognition function, immediate memory, and verbal fluency scores were 27.1 ± 4.3, 3.2 ± 1.3, and 12.8 ± 4.5. Watching TV showed no association with any cognitive outcome when controlling only by the cognitive performance at baseline or in combination with sociodemographic characteristics and functional status (**Table 3**).

Thirty-one participants were diagnosed with dementia during the follow-up assessment. No association between watching TV and the risk of developing dementia in 2 years was observed in the two models. Amnestic—was identified in 23 participants 2 years after the baseline assessment, and watching TV also showed no effect on preventing or increasing the risk of developing this condition (**Table 4**).

DISCUSSION

In our study, hours per day watching TV did not impact positively or negatively the global cognitive function, immediate memory or verbal fluency of older adults after 2 years. Watching TV did not increase the risk or protect participants of developing dementia or aMCI after 2 years of the initial assessment.

Despite being such a common leisure activity among older adults (20)—and frequently the only leisure option for low-income and low-educated older adults-, not many studies

investigated the isolated effect of watching TV on cognition (11, 24, 25, 27, 39) and the findings are controversial.

Our results are in accordance with an English (27) and a French study (26). In the English cohort study (n = 6,359 older adults aged 65 or over, 2-year follow-up) (27), more time watching TV was associated with poorer global cognition at baseline, but not with changes after 2 years. There is no specific information about the educational and socioeconomic status of the population in the English cohort. Our study also enrolled 65+ individuals for the same follow-up period. The Frenchstudy (26) enrolled 2,579 adults aged between 45 and 60 years old and found that more time watching TV was associated with worse executive function at baseline, but not with verbal memory. All participants in the French study were over 60 years old and no changes were observed after 6 years. Compared to the French study, ours enrolled adults with higher ages (65+ vs. 60+ years old) but a shorter follow-up (2 vs. 6 years).

Different from our results, three studies found that excessive hours watching TV impairs at least one domain of cognition (24, 25, 39). One of the studies is a large English cohort (n = 3,662, 6 years of follow-up) (24), where more hours watching TV was associated with a decline in verbal memory but not in semantic fluency. A possible reason why our results differ from theirs are differences in the population studied. While the English study enrolled adults aged 50+, we enrolled adults aged 65+. Unlike the English study, ours enrolled low-income older adults for whom watching TV is the main leisure activity (more likely exposed). The elders in our study also have less formal education, resulting in fewer opportunities to be exposed to highly cognitive stimulus that would compensate the passiveness of watching TV. The follow-up period in the English study was three times larger. The other two studies that found an association between watching TV and cognitive impairment are less robust. One is a European cross-sectional study (39), and the other is a case-control study (135 cases and 331 controls) (25) that investigated the incidence of Alzheimer Disease in the US.

One study, however, found a protective effect (11). The result of this study differs from the others in the literature and ours. It is a large Chinese cohort (n = 6,586, 6 years follow-up), where watching TV was associated with a lower risk of

TABLE 1 | Sociodemographic and functional characteristics of the participants of the study (n = 1,243).

Baseline characteristics	
Age (years), mean ± SD*	71.7 ± 5.8
Gender (female), *n* (%)	763 (61.4)
Schooling (years), *n* (%)	
None	401 (32.3)
1–3	701 (56.4)
4 and over	141 (11.3)
Marital status (married), *n* (%)	574 (46.2)
Occupation (employment), *n* (%)	
None	910 (73.2)
Partial time	221 (17.8)
Full time	112 (9.0)
Personal income, *n* (%)	
up to 1 MW*[a]	276 (22.2)
>1–1.5 MW*[a]	251 (20.2)
>1.5–3 MW*[a]	346 (27.8)
> 3 MW*	370 (29.8)
Functional status (WHODASII), median (IQR)	2.8 (0–72.2)
Watching TV, median (IQR)	2 (0–12)

IQR, interquartile range; MW, minimum wage; SD, standard deviation.
[a]At the time of the study, the Brazilian monthly minimum wage was US$85.

TABLE 2 | Mean and standard deviation of the cognitive performance of the participants at baseline and follow-up (n = 1,243).

	Baseline	**Follow-up**
Global cognitive function (CSI-D)	27.7 ± 3.4	27.1 ± 4.3
Immediate memory (10 words list–CERAD)	3.0 ± 1.3	3.2 ± 1.3
Verbal fluency (animal naming–CERAD)	12.9 ± 4.3	12.8 ± 4.5

CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CSI-D, Community Screening Instrument for Dementia.

TABLE 3 | Multivariable regression models of cognition performance at follow-up on watching TV (hours/day) adjusting by the corresponding cognition metric at baseline (model 1); and adding sociodemographic characteristics and functional status at baseline (model 2).

	Model 1 (n = 1,243)		**Model 2 (n = 1,243)**	
	Coefficient (95% CI*)	***p*-value**	**Coefficient (95% CI*)**	***p*-value**
Global cognitive function	0.30 (−2.90, 3.50)	0.90	0.60 (−2.60, 3.80)	0.70
Immediate memory	0.02 (−0.01, 0.05)	0.20	0.01 (−0.02, 0.05)	0.40
Verbal fluency	−0.02 (−0.10, 0.07)	0.60	−0.02 (−0.10, 0.07)	0.70

CI, confidence interval.

TABLE 4 | Logistic regression models of the risk of dementia and amnestic mild cognitive impairment on watching TV (hours/day), sociodemographic characteristics and functional status at baseline (model 1); and adding baseline global cognitive function for dementia relative risk and the corresponding baseline score for amnestic mild cognitive impairment (model 2).

	Model 1 (n = 1,243)		**Model 2 (n = 1,243)**	
	OR* (95% CI*)	***p*-value**	**OR* (95% CI*)**	***p*-value**
Dementia relative risk	0.81 (0.64, 1.02)	0.05	0.82 (0.63, 1.04)	0.08
Amnestic mild cognitive impairment	1.00 (0.82, 1.21)	0.97	1.02 (0.84, 1.24)	0.80

CI, confidence interval; OR, odds ratio.

cognitive decline (11). These authors argue that the difference in their results might be because their population is low educated (<6 years of education), and watching TV could act as a cognitive stimulus for them. If this is true, we would expect that watching TV would protect the brain of our population, given that 89% of the population of our study have up to 3 years of schooling.

An open question in the literature is if watching TV in later life could be a cognitive stimulus. If this is true, more time watching TV would build resilience and protect the brain. However, this is not what we observed in our cohort of low-income elders exposed to watching TV as their main leisure activity in adult life. It is likely that the type of program watched, not measured by our study, plays a vital role in the effect of watching TV on cognition. For example, watching a soap opera result in different a more passive stimulus for the brain, compared to watching an educational documentary on a novel subject (40). Indeed, preferring to watch soap operas and talk shows over documentaries, news, sports and other programs was associated with worse performance in cognitive tests in a cross-sectional study (40). Not accounting for the type of program watched is a limitation of our study. However, all longitudinal studies investigating the impacts of watching TV on the cognition of older adults have the same limitation (21, 24, 26, 27). They focus on the frequency of watching TV and do not account for the type of TV program. The only study that accounted for the kind of TV program is a smaller cross-sectional study (40). Given the low-income and low educational level of the population in our study, we can speculate that the programs watched were more similar to the soap opera than the documentary. By the time of the research, cable TV and the internet were not widely available.

Our study is the first study to evaluate the impacts of watching TV on the cognition of older adults living in socioeconomically deprived areas of South America. Although our study has a shorter follow-up period (2 years) compared to most of the prospective studies on the topic literature [ranging from 2 to 9 years follow-up (24, 26, 27, 41)], it is the only prospective study investigating the incidence of dementia.

The average Brazilian older adult is poor, low educated and with reduced leisure options compared to elder populations in developed countries, where most of the studies on healthy aging take place. In developed countries, the most frequent leisure activities among older adults seem to be reading, enrolling in courses, visiting museums, theater, or movies (42–44). In Brazil, the most frequent leisure activities are less complex: watching TV and listening to the radio (29). These activities are not likely to have the same protective effect on cognition as more complex activities might have. Another important reason for not engaging in other leisure activities is purchase power. Mobility might play a role given 35% of Brazilians aged 60+ reported difficulties walking in streets, and 4% reported never living the house (29).

Watching TV is a highly popular leisure activity among the population studied and among other older adults living in socially deprived urban areas of Latin America and other underserved regions. For most of these older adults watching TV is the only leisure option. The good news supported by our data is that watching TV did not predict a decline in cognition, as pointed out by a Chinese cohort (11). Thus, our data do not support advocacy against watching TV among low-income and low-educated older adults. However, in our study, watching TV did not protect from cognitive decline either.

The literature shows that leisure activities can prevent cognitive decline in older adults (16, 45) and should be encouraged through public policies. Thus, it is imperative to increase other leisure activities beyond watching TV for low-income and low-educated older adults. Leisure activities that they can engage in and benefit from.

Performing different types of activities, rather than always the same activity, seems to play a role in preserving cognitive function (46), another strong point to support the promotion of leisure activities for older adults of socially deprived areas. In the coming decades, developing countries will experience the highest burden of dementia and more than entertainment, public policies to promote leisure activities might be a strategy to alleviate this burden shortly.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Brazilian National Committee for Ethics and Research (CONEP-Brazil). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

VD and MS designed the study, supervised data collection, planned and carried out the statistical analyses, and reviewed drafts the paper. MS drafted the paper. LF and CN contributed to the interpretation of the results and drafting of the paper. All authors approved the final version of the manuscript and agreed to be accountable for the content of the work.

FUNDING

This study was funded by Wellcome Trust, UK (GR066133MA); Conselho Nacional de Desenvolvimento Científico e Tecnológico, Brazil partially supported MS (307579/2019-0); Fundação de Amparo à Pesquisa do Estado de São Paulo, Brazil (FAPESP) supported CN (2018/19343-9).

ACKNOWLEDGMENTS

We thank Prof. Paulo R. Menezes for helping with the acquisition of funding and providing comments on an earlier draft of this paper. We also thank all staff that contributed to the data collection.

REFERENCES

1. IBGE. *Projeção da População 2018: número de habitantes do país deve parar de crescer em 2047*. (2018). Available online at: https://agenciadenoticias.ibge.gov.br/agencia-sala-de-imprensa/2013-agencia-de-noticias/releases/21837-projecao-da-populacao-2018-numero-de-habitantes-do-pais-deve-parar-de-crescer-em-2047#:~:text=A%20popula%C3%A7%C3%A3o%20total%20projetada%20para,(228%2C4%20milh%C3%B5es) (accessed June 10, 2021).
2. Scazufca M, Menezes PR, Araya R, Di Rienzo VD, Almeida OP, Gunnell D, et al. Risk factors across the life course and dementia in a Brazilian population: results from the São Paulo Ageing & Health Study (SPAH). *Int J Epidemiol.* (2008) 37:879–90. doi: 10.1093/ije/dyn125
3. Scazufca M, Seabra CA. São Paulo portraits: ageing in a large metropolis. *Int J Epidemiol.* (2008) 37:721–3. doi: 10.1093/ije/dym154
4. Lima-Costa MF, Barreto S, Giatti L, Uchôa E. Desigualdade social e saúde entre idosos brasileiros: um estudo baseado na Pesquisa Nacional por Amostra de Domicílios. *Cad Saúde Pública.* (2003) 19:745–57. doi: 10.1590/S0102-311X2003000300007
5. Lloyd-sherlock P. Old age, migration, and poverty in the shantytowns of São Paulo, Brazil. *J Dev Areas.* (1998) 32:491–514.
6. IBGE. *PNAD Contínua 2018: educação avança no país, mas desigualdades raciais e por região persistem.* (2019). Available online at: https://agenciadenoticias.ibge.gov.br/agencia-sala-de-imprensa/2013-agencia-de-noticias/releases/24857-pnad-continua-2018-educacao-avanca-no-pais-mas-desigualdades-raciais-e-por-regiao-persistem (accessed June 10, 2021).
7. International A-AsD. *World Alzheimer Report 2015. The Global Impact of Dementia: an Analysis of Prevalence, Incidence, Costs and Trends*. London: Alzheimer's Disease International (ADI) (2015).
8. Iwasa H, Yoshida Y, Kai I, Suzuki T, Kim H, Yoshida H. Leisure activities and cognitive function in elderly community-dwelling individuals in Japan: a 5-year prospective cohort study. *J Psychosom Res.* (2012) 72:159–64. doi: 10.1016/j.jpsychores.2011.10.002
9. Wang HX, Xu W, Pei JJ. Leisure activities, cognition and dementia. *Biochim Biophys Acta.* (2012) 1822:482–91. doi: 10.1016/j.bbadis.2011.09.002
10. Yates LA, Ziser S, Spector A, Orrell M. Cognitive leisure activities and future risk of cognitive impairment and dementia: systematic review and meta-analysis. *Int Psychogeriatr.* (2016) 28:1791–806. doi: 10.1017/S1041610216001137
11. Zhu X, Qiu C, Zeng Y, Li J. Leisure activities, education, and cognitive impairment in Chinese older adults: a population-based longitudinal study. *Int Psychogeriatr.* (2017) 29:727–39. doi: 10.1017/S1041610216001769
12. Wilson R, Bennett D, Bienias J, Mendes de Leon C, Morris M, Evans DA. Cognitive activity and cognitive decline in a biracial community population. *Neurology.* (2003) 61:812–6. doi: 10.1212/01.WNL.0000083989.44027.05
13. Hoang TD, Reis J, Zhu N, Jacobs DR, Launer LJ, Whitmer RA, et al. Effect of early adult patterns of physical activity and television viewing on midlife cognitive function. *JAMA Psychiatry.* (2016) 73:73–9. doi: 10.1001/jamapsychiatry.2015.2468
14. Ghisletta P, Bickel JF, Lovden M. Does activity engagement protect against cognitive decline in old age? Methodological and analytical considerations. *J Gerontol B Psychol Sci Soc Sci.* (2006) 61:P253–61. doi: 10.1093/geronb/61.5.P253
15. Wilson RS, Mendes De Leon CF, Barnes LL, Schneider JA, Bienias JL, Evans DA, et al. Participation in cognitively stimulating activities and risk of incident Alzheimer disease. *JAMA*. (2002) 287:742–8. doi: 10.1001/jama.287.6.742
16. Fabrigoule C, Letenneur L, Dartigues JF, Zarrouk M, Commenges D, Barberger-Gateau P. Social and leisure activities and risk of dementia: a prospective longitudinal study. *J Am Geriatr Soc*. (1995) 43:485–90. doi: 10.1111/j.1532-5415.1995.tb06093.x
17. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. *Lancet.* (2017) 390:2673–734. doi: 10.1016/S0140-6736(17)31363-6
18. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the lancet commission. *Lancet.* (2020) 396:413–46. doi: 10.1016/S0140-6736(20)30367-6
19. Kivimäki M, Batty GD, Pentti J, Shipley MJ, Sipilä PN, Nyberg ST, et al. Association between socioeconomic status and the development of mental and physical health conditions in adulthood: a multi-cohort study. *Lancet Public Health.* (2020) 5:e140–9. doi: 10.1016/S2468-2667(19)30248-8
20. Depp CA, Schkade DA, Thompson WK, Jeste DV. Age, affective experience, and television use. *Am J Prev Med.* (2010) 39:173–8. doi: 10.1016/j.amepre.2010.03.020
21. Wilson R, Barnes L, Aggarwal N, Boyle P, Hebert LE, Mendes de Leon C, et al. Cognitive activity and the cognitive morbidity of Alzheimer disease. *Neurology*. (2010) 75:990–6. doi: 10.1212/WNL.0b013e3181f25b5e
22. Wang; H-X, Karp; A, Winblad; B, Fratiglioni L. Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: a longitudinal study from the kungsholmen project. *Am J Epidemiol.* (2002) 155:1081–7. doi: 10.1093/aje/155.12.1081
23. Carlson MC, Parisi JM, Xia J, Xue QL, Rebok GW, Bandeen-Roche K, et al. Lifestyle activities and memory: variety may be the spice of life. The women's health and aging study II. *J Int Neuropsychol Soc.* (2012) 18:286–94. doi: 10.1017/S135561771100169X
24. Fancourt D, Steptoe A. Television viewing and cognitive decline in older age: findings from the english longitudinal study of ageing. *Sci Rep.* (2019) 9:2851. doi: 10.1038/s41598-019-39354-4
25. Lindstrom HA, Fritsch T, Petot G, Smyth KA, Chen CH, Debanne SM, et al. The relationships between television viewing in midlife and the development of Alzheimer's disease in a case-control study. *Brain Cogn.* (2005) 58:157–65. doi: 10.1016/j.bandc.2004.09.020
26. Kesse-Guyot E, Charreire H, Andreeva VA, Touvier M, Hercberg S, Galan P, et al. Cross-sectional and longitudinal associations of different sedentary behaviors with cognitive performance in older adults. *PLoS ONE.* (2012) 7:e47831. doi: 10.1371/journal.pone.0047831
27. Hamer M, Stamatakis E. Prospective study of sedentary behavior, risk of depression, and cognitive impairment. *Med Sci Sports Exerc.* (2014) 46:718–23. doi: 10.1249/MSS.0000000000000156
28. Dias EG, Andrade FB, Duarte YA, Santos JL, Lebrao ML. Advanced activities of daily living and incidence of cognitive decline in the elderly: the SABE Study. *Cad Saude Publica.* (2015) 31:1623–35. doi: 10.1590/0102-311X00125014
29. Abramo FP, SESCSP, Nacional S. *Idosos no Brasil: Vivências, desafios e expectativas na 3ª idade.* (2007). Available online at: https://fpabramo.org.br/publicacoes/publicacao/idosos-no-brasil-vivencias-desafios-e-expectativas-na-3a-idade/ (accessed June 10, 2021).
30. Scazufca M, Menezes PR, Vallada HP, Crepaldi AL, Pastor-Valero M, Coutinho LM, et al. High prevalence of dementia among older adults from poor socioeconomic backgrounds in São Paulo, Brazil. *Int Psychogeriatr.* (2008) 20:394–405. doi: 10.1017/S1041610207005625
31. Rehm; J, Üstün; TB, Saxena; S, Nelson; CB, Chatterji; S, Ivis; F, et al. On the development and psychometric testing of the WHO screening instrument to assess disablement in the general population. *Int J Methods Psychiatr Res.* (1999) 8:110–22. doi: 10.1002/mpr.61
32. Hall KS GS, Emsley CL, Ogunniyi AO, Morgan O, Hendrie HC. Community screening interview for dementia (CSI 'D'); performance in five disparate study sites. *Int J Geriatr Psychiatry.* (2000) 15:521–31. doi: 10.1002/1099-1166(200006)15:6<521::AID-GPS182>3.0.CO;2-F
33. Jorm AFD-J. Neurotic symptoms and subjective well-being in a community sample: different sides of the same coin? *Psychol Med.* (1990) 20:647–54. doi: 10.1017/S0033291700017165
34. Prince M, Acosta D, Chiu H, Scazufca M, Varghese M. Dementia diagnosis in developing countries: a cross-cultural validation study. *Lancet.* (2003) 361:909–17. doi: 10.1016/S0140-6736(03)12772-9
35. Welsh KA, Butters N, Mohs RC, Beekly D, Edland S, Fillenbaum G, et al. The consortium to establish a registry for Alzheimer's disease (CERAD): V. A normative study of the neuropsychological battery. *Neurology.* (1994) 44:609–14. doi: 10.1212/WNL.44.4.609
36. Association AP. *Diagnostic and Statistic Manual of Mental Disorders*. DSMV-IV Donnelley & Sons Company (1994).
37. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund L, et al. Mild cognitive impairment–beyond controversies, towards a consensus: report of the international working group on mild cognitive impairment. *J Intern Med.* (2004) 256:240–6. doi: 10.1111/j.1365-2796.2004.01380.x

38. Hendrie H, Osuntokun B, Hall K, Ogunniyi A, Hui S, Unverzagt F, et al. Prevalence of Alzheimer's disease and dementia in two communities: Nigerian Africans and African Americans. *Am J Psychiatry.* (1995) 152:1485–92. doi: 10.1176/ajp.152.10.1485
39. Da Ronch C, Canuto A, Volkert J, Massarenti S, Weber K, Dehoust MC, et al. Association of television viewing with mental health and mild cognitive impairment in the elderly in three European countries, data from the MentDis_ICF65+ project. *Mental Health Physical Activity.* (2015) 8:8–14. doi: 10.1016/j.mhpa.2014.11.002
40. Fogel J, Carlson MC. Soap operas and talk shows on television are associated with poorer cognition in older women. *Southern Med Assoc.* (2006) 99:226–33. doi: 10.1097/01.smj.0000198270.52240.93
41. Dos Santos Matioli MNP, Suemoto CK, Rodriguez RD, Farias DS, da Silva MM, Leite REP, et al. Diabetes is not associated with Alzheimer's disease neuropathology. *J Alzheimers Dis.* (2017) 60:1035–43. doi: 10.3233/JAD-170179
42. Aartsen MJ, Smits CH, van Tilburg T, Knipscheer KC, Deeg DJ. Activity in older adults: cause or consequence of cognitive functioning? A longitudinal study on everyday activities and cognitive performance in older adults. *J Gerontol.* (2002) 57B:153–62. doi: 10.1093/geronb/57.2.P153
43. Agahi N, Ahacic K, Parker MG. Continuity of leisure participation from middle age to old age. *J Gerontol.* (2006) 61B:S340–6. doi: 10.1093/geronb/61.6.S340
44. Dodge HH, Kita Y, Takechi H, Hayakawa T, Ganguli M, Ueshima H. Healthy cognitive aging and leisure activities among the oldest old in Japan: Takashima Study. *J Gerontol A Biol Sci Med Sci.* (2008) 63:1193–200. doi: 10.1093/gerona/63.11.1193
45. Wang JYJ, Zhou DHD, Li J, Zhang M, Deng J, Gao MTC, et al. Leisure activity and risk of cognitive impairment: the Chongqing aging study. *Neurology.* (2006) 66:911–3. doi: 10.1212/01.wnl.0000192165.99963.2a
46. Lee S, Charles ST, Almeida DM. Change is good for the brain: activity diversity and cognitive functioning across adulthood. *J Gerontol B Psychol Sci Soc Sci.* (2020) 6:gbaa020. doi: 10.1093/geronb/gbaa020

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 07 July 2021
doi: 10.3389/fneur.2021.629325

Performance of the Rowland Universal Dementia Assessment Scale for the Detection of Mild Cognitive Impairment and Dementia in a Diverse Cohort of Illiterate Persons From Rural Communities in Peru

Nilton Custodio[1,2,3]*, *Rosa Montesinos*[2,3,4], *Monica M. Diaz*[5,6], *Eder Herrera-Perez*[2,3,7], *Kristhy Chavez*[2,3], *Carlos Alva-Diaz*[8], *Willyams Reynoso-Guzman*[1,2,3], *Maritza Pintado-Caipa*[1,2,3,9], *José Cuenca*[3,4,10,11], *Carlos Gamboa*[2,3,10] and *Serggio Lanata*[12,13]

[1] Servicio de Neurología, Instituto Peruano de Neurociencias, Lima, Peru, [2] Unidad de diagnóstico de deterioro cognitivo y prevención de demencia, Instituto Peruano de Neurociencias, Lima, Peru, [3] Unidad de Investigación, Instituto Peruano de Neurociencias, Lima, Peru, [4] Servicio de Rehabilitación, Instituto Peruano de Neurociencias, Lima, Peru, [5] Department of Neurology, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States, [6] Unidad de epidemiología, ITS y VIH, Facultad de Salud Pública y Administración, Universidad Peruana Cayetano Heredia, Lima, Peru, [7] Grupo de investigación Molident, Universidad San Ignacio de Loyola, Lima, Peru, [8] Facultad de Ciencias de la Salud, Universidad Científica del Sur, Lima, Peru, [9] Atlantic Fellow, Global Brain Health Institute, University of California, San Francisco, San Francisco, CA, United States, [10] Servicio de Neuropsicología, Instituto Peruano de Neurociencias, Lima, Peru, [11] Carrera de Psicología, Facultad de Ciencias de la Salud, Universidad Privada del Norte, Lima, Peru, [12] Department of Neurology, University of California, San Francisco, San Francisco, CA, United States, [13] Global Brain Health Institute, University of California, San Francisco, San Francisco, CA, United States

OPEN ACCESS

Edited by:
Christopher Butler, University of Oxford, United Kingdom

Reviewed by:
Samantha K. Holden, University of Colorado, United States
Rufus Olusola Akinyemi, University of Ibadan, Nigeria

***Correspondence:**
Nilton Custodio
ncustodio@ipn.pe

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: *14 November 2020*
Accepted: *14 June 2021*
Published: *07 July 2021*

Citation:
Custodio N, Montesinos R, Diaz MM, Herrera-Perez E, Chavez K, Alva-Diaz C, Reynoso-Guzman W, Pintado-Caipa M, Cuenca J, Gamboa C and Lanata S (2021) Performance of the Rowland Universal Dementia Assessment Scale for the Detection of Mild Cognitive Impairment and Dementia in a Diverse Cohort of Illiterate Persons From Rural Communities in Peru. Front. Neurol. 12:629325. doi: 10.3389/fneur.2021.629325

Background: The accurate diagnosis of neurocognitive disorders in illiterate Peruvian populations is challenging, largely owing to scarcity of brief cognitive screening tools (BCST) validated in these diverse populations. The Peruvian version of the Rowland Universal Dementia Assessment Scale (RUDAS-PE) is a BCST that relies minimally on educational attainment and has shown good diagnostic accuracy in an urban illiterate population in Peru, yet its psychometric properties in illiterate populations in rural settings of the country have not been previously investigated.

Objectives: To establish the diagnostic accuracy of the RUDAS-PE compared to expert clinical diagnosis using the Clinical Dementia Rating (CDR) Scale in healthy and cognitively impaired illiterate persons living in two culturally and geographically distinct rural communities of Peru.

Methods: A cross-sectional, population-based study of residents ≥ 50 years of age living in the Peruvian rural communities of Santa Clotilde and Chuquibambilla. A total of 129 subjects (76 from Santa Clotilde and 53 from Chuquibambilla) were included in this study. Gold standard diagnostic neurocognitive evaluation was based on expert neurological history and examination and

administration of the CDR. Receiver operating characteristics, areas under the curve (AUC), and logistic regression analyses were conducted to determine the performance of RUDAS-PE compared to expert gold standard diagnosis.

Results: Compared to gold standard diagnosis, the RUDAS-PE was better at correctly discriminating between MCI and dementia than discriminating between MCI and controls in both sites (97.0% vs. 76.2% correct classification in Chuquibambilla; 90.0% vs. 64.7% in Santa Clotilde). In Chuquibambilla, the area under the curve (AUC) of the RUDAS to discriminate between dementia and MCI was 99.4% (optimal cutoff at <18), whereas between MCI and controls it was 82.8% (optimal cutoff at <22). In Santa Clotilde, the area under the curve (AUC) of the RUDAS to discriminate between dementia and MCI was 99.1% (optimal cutoff at <17), whereas between MCI and controls it was 75.5% (optimal cutoff at <21).

Conclusions: The RUDAS-PE has acceptable psychometric properties and performed well in its ability to discriminate MCI and dementia in two cohorts of illiterate older adults from two distinct rural Peruvian communities.

Keywords: cognition, dementia, education, literacy, mild cognitive impairment, RUDAS, cultural factors

INTRODUCTION

The neurocognitive disorders, which include mild neurocognitive disorder (mild cognitive impairment, MCI) and major neurocognitive disorder (dementia) (1), are among the most prevalent age-related disorders worldwide and lead to substantial morbidity and mortality (2, 3). In Latin America, the prevalence of all forms of dementia is expected to rise from 7.8 million in 2013 to 27 million by the year 2050 (4, 5). Among the known modifiable risk factors for the neurocognitive disorders, low educational attainment appears to be both an independent risk factor for dementia (6) as well as a marker of poor prognosis, particularly in mid- to low-income regions such as Latin America (7–9).

In Peru, 6.0% of the population is illiterate and 20.0% of Peruvians who are able to receive formal education do not advance beyond elementary school (10). The highest illiteracy rates of the country are observed in rural populations, where up to 43.0% of adults report elementary school as their highest level of education (compared to 16.0% in urban settings) (11); among older adults (those $\geq$ 60 years of age) living in rural communities, 41.6% are illiterate (compared with 12.3% in urban settings) (11). Therefore, early, accurate diagnosis of neurocognitive disorders in rural Peruvian communities with low educational attainment represents a critical first step toward the proper allocation of resources for the care of these vulnerable older adults (12).

A significant barrier to the early, accurate diagnosis of older adults with neurocognitive disorders in rural Peruvian communities with low educational attainment relates to the fact that the majority of cognitive tests available to screen for cognitive impairment have been developed in relatively highly educated subjects from urban settings. Several popular brief cognitive screening tools (BCST) have been adapted and validated in Spanish-speaking illiterate or low literacy populations, including the Mini Mental State Exam (MMSE), Cognitive State Test (COST), Montreal Cognitive Assessment (MOCA), and the Memory Alteration Test (M@T). Yet, all of these BCSTs have important limitations, most notably their poor ability to discriminate between MCI and dementia cases, as well as their poor ability to help detect different etiologies (or types) of dementia (13–16).

The Rowland Universal Dementia Assessment Scale (RUDAS) was developed to address the limitations commonly encountered when using BCSTs to evaluate neurocognitive disorders in vulnerable populations. It is minimally influenced by educational attainment and measures a wide range of cognitive domains, hence it is promising for the detection of different types of dementia in sociodemographically diverse populations (17). Our group has validated the Peruvian version of the RUDAS (RUDAS-PE) in low literacy and illiterate populations in the capital city of Lima, Peru (18–20), where RUDAS-PE was useful in differentiating MCI from dementia with high sensitivity (89.0%) and specificity (93.0%) (21). In the present study we expand on this body of knowledge by testing the performance of the RUDAS-PE in two culturally distinct cohorts of illiterate subjects from two rural communities in Peru. We hypothesize that, owing to its low reliance on subject educational attainment, the RUDAS-PE will perform well in these study populations compared to gold standard diagnosis.

METHODS

Participants

This study was approved by the ethics committee of the Institute of Tropical Medicine "Daniel Alcides Carrión" of the Universidad Nacional Mayor de San Marcos with approval number CIEI-2018-021. Participants and their study partners were asynchronously recruited from two geographically and culturally distinct rural communities of Peru: Santa Clotilde

(January to September 2019) and Chuquibambilla (September 2019 to February 2020). Rurality was defined based on a population-density international classification system used by the World Bank (22). Santa Clotilde lies along the Napo River in the Peruvian Amazon region of the department of Loreto, near the border with Ecuador and Colombia; Chuquibambilla is located in the highlands of southern Peru in the district of Pangoa within the department of Junín. Santa Clotilde is located 10 h from the urban center of Iquitos and is accessible only by boat, whereas Chuquibambilla is located 1 h from the urban center of Satipoand is accessible by land.

In both sites, we recruited illiterate Spanish-speaking monolingual or bilingual (with $\geq$ 5 years of experience speaking Spanish) individuals who were $\geq$ 50 years of age at the time of enrollment. Illiteracy was determined using guidelines established by the Peruvian National Institute of Statistics: First, subjects were asked, *How many years of school did you attend?* Those who reported more than 1 year of formal education were excluded. Those who reported never attending school or completing <1 year of formal schooling were asked, *Are you able to read and write?* Those who reported being able to read and/or write were excluded.

We excluded individuals with history of: (1) physical limitations that might interfere with the neurocognitive evaluation, including hearing loss and uncorrected visual impairment [particularly problems with color discrimination, as assessed by the Dvorine color discrimination screening test (23)], (2) large vessel stroke, (3) developmental disabilities affecting cognitive performance, (4) neurocognitive deficits due to severe head trauma, (5) severe/poorly controlled psychiatric illness (depression, addiction disorder, bipolar disorder, schizophrenia, etc.), and (6) advanced neurocognitive impairment defined as severe compromise of activities of daily living regardless of etiology (i.e., stroke, Parkinson's Disease, traumatic brain injury), to the extent that the individual is fully dependent on caregivers and thus unable to participate in cognitive testing. In addition, we excluded individuals who reported taking any of the following medications within 7 nights prior to the assessment: opioid analgesics, decongestants, antispasmodics, anti-emetics, anti-cholinergics, anti-arrhythmics, anti-depressants, anti-psychotics, anti-anxiety and anti-epileptic medications such as valproate, phenobarbital, phenytoin, carbamazepine and levetiracetam.

All participants in this study were recruited from community health centers located in Santa Clotilde (one main clinic and three small satellite clinics) and Chuquibambilla (one main clinic). Recruitment occurred via simple random sampling in partnership with staff at each clinic. The outreach and recruitment process was as follows: (1) study approval was obtained from the directors of each of the community health centers; (2) primary care providers disseminated pertinent study information via existing communication streams (i.e., flyers, radio, face-to-face encounters between the patient and their provider); (3) individuals interested in participating in our study were flagged and the research team was informed of their upcoming clinical appointment dates; (4) the research team responsible for consenting and evaluating patients were present on site during the day of their scheduled clinical appointments; (4) participants were consented on site and were evaluated during the day of their clinical appointment. Attempts to minimize referral bias were made by random sampling of participants who presented to the clinic for their regular care.

All interested participants who met inclusion and exclusion criteria were consented verbally and fingerprints were used in lieu of signatures on the consent form. Each participant's family member or partner (spouse, close relative or friend) was also consented. Once consented and enrolled, each participant underwent an expert gold standard clinical diagnostic evaluation and administration of the RUDAS-PE by blinded team members as described below.

Neurocognitive Measures

Clinical Diagnostic (Gold Standard) Evaluation

All participants included in this study underwent a gold standard diagnostic evaluation by trained and experienced health professionals from the "Instituto Peruano de Neurociencias" (IPN), located in Lima, Peru, which specializes in the care and clinical research of persons with neurocognitive disorders. The evaluating team included neuropsychologists [JC, CG], a neurologist with sub-specialty training in dementia [NC], and a neuro-rehabilitation specialist with experience in the evaluation and management of patients with dementia [RM]. These health professionals have formal training and experience in the administration and interpretation of various BCSTs and the Clinical Dementia Rating (CDR) scale. Given that, to our knowledge, this is the first neurocognitive health study conducted in these rural Peruvian communities and therefore there is no validated gold standard of diagnosis, for this study the diagnostic gold standard was based on an expert neurological examination and results from the CDR scale (24).

The CDR is a well-validated, semi-structured interview of the individual and a reliable informant or collateral source (e.g., family member, close relative or friend) used to characterize six domains of cognitive and functional performance: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care (24). Among its advantages, the CDR offers a global clinical assessment independently from other psychometric tests, does not require a baseline assessment, and has good inter-evaluation reliability, concurrent validity, and predictive validity; among its relative disadvantages, it takes approximately 30 min to administer and requires experienced clinical judgement in order to accurately obtain pertinent information (24–26).

In accordance with published research studies showing that the CDR can accurately distinguish MCI from dementia (25), for this study we assigned subjects with a CDR = 0 to the "control" group, subjects with CDR = 0.5 to the "MCI" group (26), and subjects with CDR = 1 or 2 to the "dementia" group. Cases in which the CDR was unclear were resolved via a multidisciplinary consensus meeting.

Peruvian Version of the Rowland Universal Dementia Assessment Scale (RUDAS-PE)

The RUDAS-PE takes approximately 10 min to administer and includes six cognitive domains, starting with immediate memory

TABLE 1 | Demographic characteristics and brief cognitive test performance by study group in Chuquibambilla, Junín, and Santa Clotilde, Loreto. 2019.

	Chuquibambilla					Santa Clotilde				
	Control (*n* = 20)	MCI (*n* = 22)	Dem (*n* = 11)	*P*-value Control vs. MCI	*P*-value MCI vs. Dem	*P*-value Control vs. Dem	Control (*n* = 16)	MCI (*n* = 18)	Dem (*n* = 42)	*P*-value Control vs. MCI	*P*-value MCI vs. Dem	*P*-value Control vs. Dem
Female (%)	10 (50.0)	12 (52.4)	6 (54.5)	0.51	0.64	0.55	7 (43.7)	10 (55.6)	6 (50.0)	0.37	0.53	0.52
Age in years, mean (SD)	69.2 (6.5)	67.6 (4.7)	71.9 (4.6)	0.60	**0.00**	0.09	71.3 (7.5)	67.6 (3.3)	73.8 (5.5)	0.16	**0.00**	0.31
RUDAS-PE score, mean (SD)	23.0 (1.9)	20.8 (1.6)	14.9 (1.8)	**0.00**	**0.00**	**0.00**	22.63 (2.68)	20.72 (1.74)	15.17 (1.64)	**0.01**	**0.00**	**0.00**

MCI, mild cognitive impairment; Dem, Dementia; SD, standard deviation; RUDAS-PE, rowland universal dementia assessment scale, Peruvian version. Bold values mean $p < 0.05$.

registration, followed by visuospatial orientation, motor praxis, visuospatial construction, judgment, recent episodic memory and language. It produces a maximum score of 30, where a low score denotes poor cognitive performance. The Spanish version of the RUDAS-PE can be found as a **Supplementary Material** to this article.

The study personnel who administered the RUDAS-PE were a resident physician in geriatrics from *Universidad Peruana Cayetano Heredia (UPCH)* Medical School [KC] and a certified practicing neurologist [WR], both of whom who had been previously trained in administering the RUDAS-PE and other BCSTs following previously reported procedures (21) as part of their training experience at the IPN. These evaluators (KC and WR) were blinded to the results of the gold standard clinical diagnostic evaluation.

Statistical Analyses

Following the assignment of the study groups (control, MCI and dementia), the performance scores on the RUDAS-PE of individuals within each group were reviewed in order to carry out statistical analyses of the cohort demographic characteristics and the psychometric properties of the RUDAS-PE. The 95% confidence intervals were calculated, and significance level was set at 0.05. All analyses were completed using STATA software (version 12.0).

Descriptive statistics were obtained from cohorts in each of the two study sites (Chuquibambilla and Santa Clotilde), and compared by pairing cognitive groups with one another (controls, MCI and dementia). *T*-tests (for discrete variables) and Chi Square (for categorical variables) were then calculated.

RUDAS-PE scores and relationships between demographic and clinical characteristics (age, sex, city access, occupation, hypertension, diabetes, myocardial infarction, sedentary lifestyle and smoking) were modeled by adjusting polynomial curves to generate estimated means. We used a second-degree model that suppressed covariate centering, and variables were selected using backwards stepwise regression (backwards elimination) using a significance level of 0.05. Standardized beta coefficients (β) were reported to describe the strength of the association between each predictor and the RUDAS-PE score.

Internal consistency was evaluated using Cronbach's alpha coefficient. Sequential cognitive domains were removed from the RUDAS-PE to evaluate coefficient changes. Convergent validity was evaluated using Spearman correlation coefficient comparisons between RUDAS-PE total scores and scores on individual cognitive domains compared with CDR total scores. Logistic regression (logit) was performed for each pair of study groups (dementia/MCI, MCI/control and dementia/control) using a two-variable model with the final diagnosis as the dependent variable and the RUDAS-PE as the independent variable. Discriminant validity was determined by measuring the average total score of the RUDAS-PE and each of its domains within the three groups (controls, MCI and dementia). These were compared using means of independent samples *t*-test, calculation of the area under the curve (AUC) and Receiver Operating Characteristics (ROC) curves. In addition, we determined the percentage of correctly classified individuals

and calculated multivariate analyses of variance (MANOVA). Diagnostic accuracy was evaluated by *post-hoc* analysis means used to calculate ROC curves and ROC plots. These were adjusted according to certain cut-off points allowing calculation of AUC values. In addition to calculating diagnostic accuracy, sensitivity, specificity, positive predictive values, negative predictive values, positive likelihood ratios (LR+) and negative likelihood ratios (LR) were calculated for different cut-off points for the RUDAS-PE in both regions. The maximum values of these measurements were the selection of the sensitivity, specificity and predictive value cut-off points.

RESULTS

Demographics and Descriptive Statistics

A total of 129 subjects (53 from Chuquibambilla, 76 from Santa Clotilde) were included in this study Nearly 40.0% were female with similar proportions across the three groups (controls, MCI, dementia) in both sites (**Table 1**). The mean age of the participants from Chuquibambilla was 69.6 ± 5.3 years and 70.9 ± 5.4 years in Santa Clotilde. The MCI group was younger than the dementia group in both sites, but there were no statistically significant age differences between the control and MCI group at both sites.

Dementia groups at both sites demonstrated lower performance on the RUDAS-PE compared to the other groups (MCI and controls); moreover, participants with MCI performed worse than controls at both sites. The participants with dementia in the Chuquibambilla site performed worse on the RUDAS-PE compared to participants with MCI, with controls performing the best of all groups. In Santa Clotilde, a similar pattern was observed in RUDAS-PE scores across groups (**Table 1**). No statistically significant differences were found between the two study sites.

We performed an additional analysis to test performance on the RUDAS-PE per neurocognitive domain in MCI and control groups of illiterate persons in rural settings compared with illiterate persons in urban settings (from Ventanilla, in Lima, Peru), and found that rural illiterate individuals performed worse in motor praxis and visuospatial construction **(Table 2)**. **Figure 1** shows examples of the types of difficulties most residents of Santa Clotilde demonstrated when asked to copy the cube. Conversely, the sample of participants with MCI and controls from Ventanilla performed significantly worse than the sample from Chuquibambilla within the memory domain (**Table 2**).

Internal Consistency

The Cronbach's alpha coefficient for RUDAS-PE among rural illiterate older adults from both sites was 0.6 (0.5 in Chuquibambilla and 0.6 in Santa Clotilde). The internal consistency by study group in Chuquibambilla was 0.5 in the control group, 0.6 in MCI group and 0.5 in the dementia group. In the Santa Clotilde cohort, the Cronbach's alpha coefficient was 0.5 in the control group, 0.4 in the MCI group and 0.6 in the dementia group. When a cognitive domain evaluated in the RUDAS-PE was sequentially removed, the overall Cronbach's alpha coefficient did not increase, and the value decreased instead. For this reason, all domains contributed positively to the RUDAS-PE and were shown to be consistent within the test.

Construct Validity

Spearman correlations were obtained between RUDAS-PE compared with CDR scores. The correlation between RUDAS-PE and CDR scores was 0.9 (SD 0.03; 95% CI) for the cohort [0.9 (SD 0.06; 95% CI) for Chuquibambilla and 0.9 (SD 0.1; 95% CI)] for Santa Clotilde.

Discriminant Validity

For each study site, the ROC curve and an AUC for the RUDAS-PE were calculated for the following three study group comparisons: (1) control vs. MCI, (2) control vs. dementia, and (3) MCI vs. dementia. **Figure 2A** shows the RUDAS-PE ROC curve (AUC=0.82) to discriminate between MCI and controls in Chuquibambilla. **Figure 2B** shows the RUDAS-PE ROC curve (AUC = 0.75) to discriminate between MCI and controls in Santa Clotilde. **Figures 3A,B** show the RUDAS-PE ROC curves for Chuquibambilla and Santa Clotilde to discriminate MCI and dementia, with AUCs of 0.99 and 0.99, respectively.

Diagnostic Accuracy

In the Chuquibambilla site, the optimal cut-off score on the RUDAS-PE to differentiate controls from the MCI group was 22 (sensitivity of 85.0%, specificity of 68.2%), with a high proportion of false positives (24.0%); the optimal cut-off score to differentiate participants with MCI from those with dementia was 18 (sensitivity of 100.0%, specificity of 90.9%) with a low proportion of false positives (3.0%). In the Santa Clotilde group, the optimal cut-off score on the RUDAS-PE to differentiate controls from MCI was 21 (sensitivity of 81.3%, specificity of 50.0%), but with a high proportion of false positives (35.0%); the optimal cut-off score to discriminate between MCI and dementia on the was 17 (sensitivity of 100.0%, specificity of 75.0%) with a 10.0% false positive rate (**Table 3**).

DISCUSSION

To our knowledge, this is the first community-based study of the RUDAS-PE in illiterate persons living in rural settings of Peru, and also the first such study that tests the performance of RUDAS-PE in distinguishing between MCI and dementia. Our study results point to three main findings: (1) compared to expert clinical diagnosis, the RUDAS-PE was superior at discriminating between persons with MCI and persons with dementia than discriminating between persons with normal cognition and persons with MCI; (2) in both analyses (controls vs. MCI and MCI vs. dementia), the discriminatory abilities of the RUDAS-PE tended to be relatively weaker in the rural community of Santa Clotilde compared to the discriminatory abilities observed in the rural community of Chuquibambilla, thus suggesting that sociocultural factors unique to each community may influence cognitive testing performance among illiterate persons; and (3) compared to illiterate persons living in the highly urban Peruvian capital city of Lima, illiterate persons living in both rural communities in our study performed significantly worse

TABLE 2 | Performance on the Peruvian version of the Rowland Universal Dementia Assessment Scale (RUDAS-PE) by cognitive domain among control and MCI groups from rural and urban illiterate Peruvian communities.

Rudas, cognitive domains	Chuquibambilla control + MCI ($n = 42$)	Santa Clotilde control + MCI ($n = 34$)	Ventanilla control + MCI ($n = 124$)	*P*-value chuquibambilla vs. ventanilla	*P*-value Santa Clotilde vs. ventanilla
Visuo-spatial orientation	4.3 (0.8)	4.4 (0.8)	4.4 (0.5)	0.42	0.66
Praxis	1.0 (0.7)	1.0 (0.8)	1.6 (0.5)	**0.00**	**0.00**
Visuospatial construction	0.2 (0.4)	0.2 (0.4)	0.7 (0.6)	**0.00**	**0.00**
Judgment	1.8 (0.9)	1.7 (1.1)	1.9 (0.8)	0.38	0.28
Memory	7.0 (1.2)	6.7 (1.2)	6.3 (1.3)	**0.00**	0.09
Language	7.5 (0.7)	7.6 (0.7)	7.3 (0.8)	0.09	0.10

MCI, mild cognitive impairment; SD, standard deviation. Data presented as mean (SD). Bold values mean $p < 0.05$.

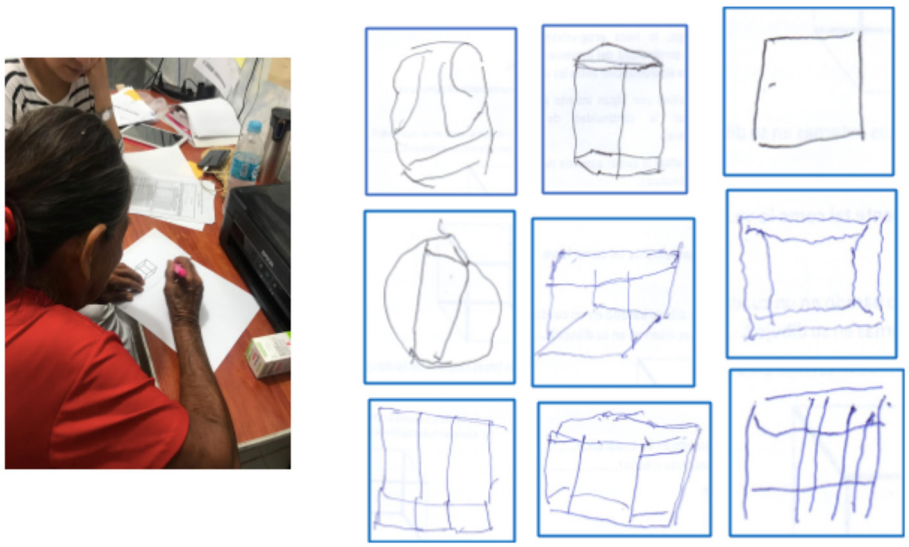
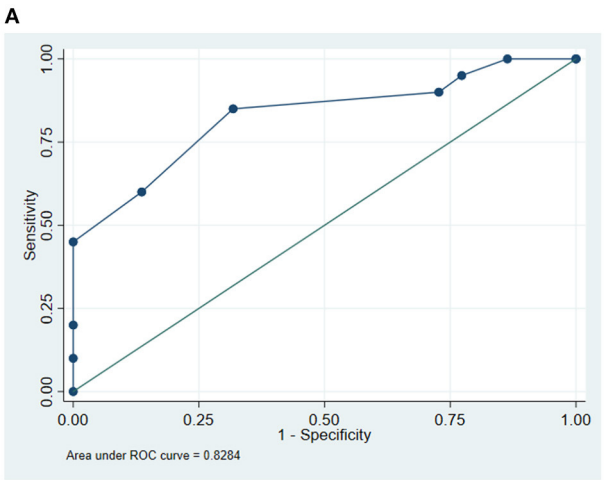


FIGURE 1 | Examples of common errors in drawing the cube in the visuo-spatial construction domain in illiterate individuals from the Santa Clotilde. Note absence of three-dimensionality and distorted angles.

on the domains of motor praxis and visuospatial construction on the RUDAS-PE, suggesting that unspecified sociocultural factors present in urban environments may influence performance on the RUDAS-PE in illiterate persons.

The first RUDAS validation study for Spanish-speakers was carried out among a sample of low literacy subjects in Santiago de Compostela, La Coruña, Spain (20) for an optimal dementia cut-off point of 21/22 (sensitivity of 94.9%, specificity of 75.0%). The same authors also performed a comparative analysis between the MMSE and RUDAS for dementia screening in a different Spanish cohort with low literacy and found that the best cut-off point for the RUDAS was 21/22 (sensitivity of 94.3%, specificity of 72.6%) (19). These results are similar to those obtained in our cohort from Chuquibambilla, with a cut-off point of 22 (sensitivity of 85.0%, specificity of 68.2%), but the values were lower for the cohort from Santa Clotilde, with a cut-off point of 21 (sensitivity of 81.3%, specificity of 50.0 and 64.7% of correctly classified) for a cut-off point of 21. This regional difference in the performance of the RUDAS-PE is noteworthy because it suggests the existence of yet unspecified environmental and cultural factors that may influence performance on the RUDAS-PE among illiterate persons. Indeed, the Santa Clotilde community is more geographically isolated that the Chuquibambilla community and is therefore considered to be "more rural"; moreover, these two communities embody their own distinct cultural practices, which may have also directly impacted performance on the RUDAS-PE in subjects from both communities. We believe these findings shed light on the importance of conducting further studies seeking to understand the potentially significant influence that sociocultural factors, even those at play within a country, have on cognitive testing performance.

It is important for all health professionals, especially those caring for vulnerable populations, to diagnose persons with neurodegenerative diseases early in their illness (mild neurocognitive disorder, or MCI) rather than late (major neurocognitive disorder, or dementia). Indeed, early diagnosis of neurodegenerative disease leads to better patient outcomes, including early initiation of pharmacologic and



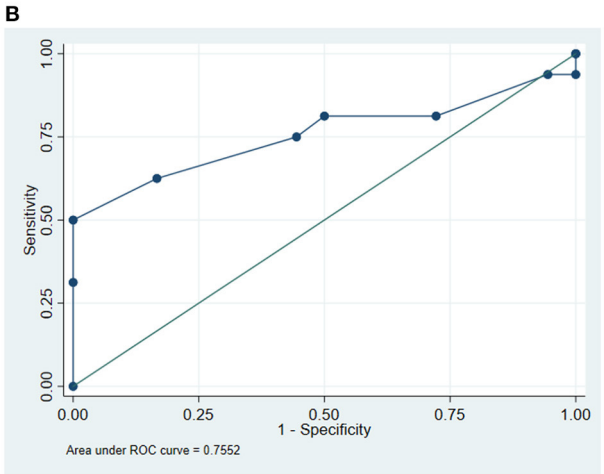
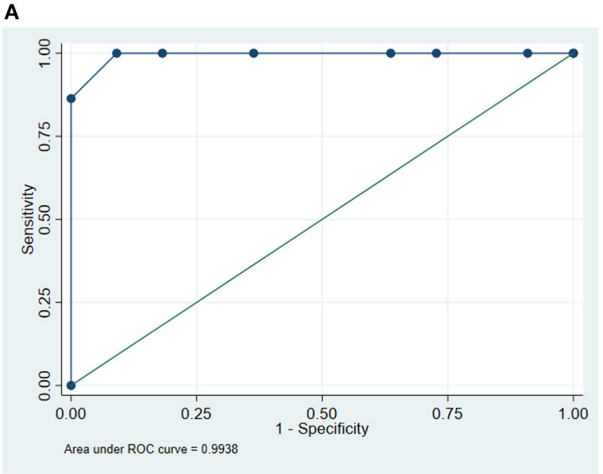


FIGURE 2 | Receiver-operating characteristic (ROC) curve for the Peruvian version of the Rowland Universal Dementia Assessment Scale (RUDAS-PE) for discrimination between mild cognitive impairment (MCI) and control groups. Chuquibambilla, Junín. **(B)** Receiver-operating characteristic (ROC) curve for the Peruvian version of the Rowland Universal Dementia Assessment Scale (RUDAS-PE) for discrimination between mild cognitive impairment (MCI) and control groups. Santa Clotilde, Loreto.



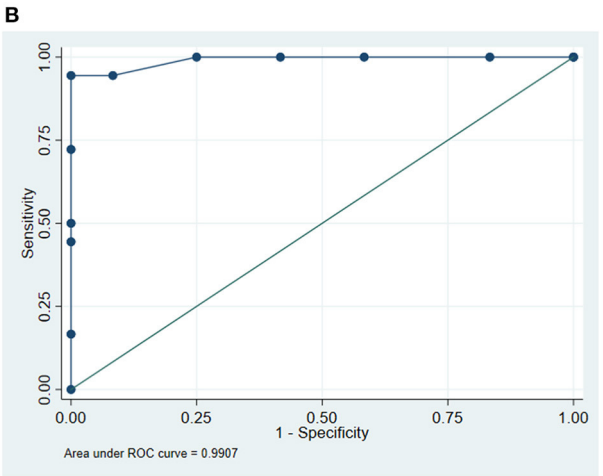


FIGURE 3 | Receiver-operating characteristic (ROC) curve for the Peruvian version of the Rowland Universal Dementia Assessment Scale (RUDAS-PE) for discrimination between mild cognitive impairment (MCI) and dementia groups. Chuquibambilla, Junín. **(B)** Receiver-operating characteristic (ROC) curve for the Peruvian version of the Rowland Universal Dementia Assessment Scale (RUDAS-PE) for discrimination between mild cognitive impairment (MCI) and dementia groups. Santa Clotilde, Loreto.

non-pharmacologic symptomatic therapies, early management of key modifiable risk factors, as well as early family education and planning for long-term care (27). In this regard, in our study, the RUDAS-PE showed promise in discriminating between controls and MCI, with the cut-off score in Santa Clotilde being one point lower than in Chuquibambilla (21 and 22, respectively). Of note, both cut-off scores were lower than the RUDAS-PE cut-off score obtained in our previously reported findings in an urban illiterate population in Lima, Peru (23) (21). Similarly, the specificity, percentage of correctly classified groups and the AUC for the RUDAS-PE was lower in the Santa Clotilde cohort (S = 50.0%; CC = 64.7%; AUC = 0.75) compared to Chuquibambilla (sensitivity [S] = 68.2%: correctly classified [CC] = 76.2% AUC = 0.8284). In turn, these were lower compared to those obtained among urban illiterate persons of Lima (S = 93.3%: CC = 91.1%; AUC = 0.98) (21). These results are difficult to compare with previously published studies, since most of them compare controls with persons with dementia, not MCI, and have been conducted in urban, higher-income populations; but again, these findings suggest that there are important cultural and environment factors to consider when assessing illiterate populations with mild cognitive changes in rural communities of Peru.

It is important to highlight that the screening utility of different BCST is dependent on the expected baseline rates of cognitive impairment in the population being sampled. Our study results suggest that a cut-off point of 21/22 is optimal for MCI screening and a cut-off point of 17/18 is optimal for dementia screening when the RUDAS-PE is used in illiterate

TABLE 3 | Cut-off points and diagnostic performance for the Peruvian version of the Rowland Universal Dementia Assessment Scale (RUDAS-PE) to discriminate between controls and participants with mild cognitive impairment (MCI) and dementia in Chuquibambilla, Junín and Santa Clotilde, Loreto.

Diagnostic performance	Discrimination between controls and participants with MCI		Discrimination between participants with MCI and dementia	
	Chuquibambilla	Santa Clotilde	Chuquibambilla	Santa Clotilde
Optimal cutoff point	22	21	18	17
Sensitivity, %	85.0	81.3	100.0	100.0
Specificity, %	68.2	50.0	91.0	75.0
Correctly classified, %	76.1	64.7	97.0	90.0
Likelihood ratio +	2.67	1.63	11.00	4.00
Likelihood ratio –	0.22	0.38	0.00	0.00
AUC (95% CI)	0.83 (0.81–0.84)	0.76 (0.74–0.78)	0.99 (0.98–1.00)	0.99 (0.98–1.00)

MCI, mild cognitive impairment; AUC, area under the curve; CI, confidence interval.

persons form rural communities where the expected baseline rates of MCI and dementia are 17.7% and 32.3%, respectively (28). Whereas cut-off points of 23 and 19 may be optimal for predicting the presence or absence of MCI and dementia, respectively, in illiterate persons living in the city of Lima, where expected baseline rates of cognitive impairment differ (21, 29).

We found that compared to illiterate persons from the city of Lima our study subjects performed significantly worse on the domains of motor praxis and visuospatial construction on the RUDAS-PE. Previous studies have shown that low educational attainment is associated with poor performance in alternating hand movements and cube copying (30, 31). Similarly, many assessments of praxis, such as buccofacial movements, fine alternating movements of fingers, imitation of non-sensical movements, coordinated movement of both hands, line cancellation, and motor impersistence tasks tend to be more challenging for illiterate persons compared to highly educated professionals (32, 33). Furthermore, previous studies have shown that illiterate persons struggle with cube-drawing and reproduction of three-dimensional figures (34). Compared to highly educated persons, illiterate persons have been show to struggle to copy figures (cube, house, intersecting pentagons, complex Rey-Osterrieth figure), recognize superimposed figures, interpret a map, and draw a floor plan of a room (35). Thus, illiterate persons may be at a clinically significant disadvantage when undergoing cognitive testing, beyond that which would be expected based merely on their reading and writing skills. Several hypotheses have been postulated to explain this observation, including: (1) unfamiliarity with both the content and the test procedure itself ("testwiseness"), given that neuropsychological test formats are reminiscent of a school assignment rather than real-life activities; (2) lack of school-acquired strategies (explicit or implicit) for organizing and retaining information such as problem-solving skills, concentration, accurate expression of knowledge within an allotted time, and being internally motivated to perform well on tests; and (3) the potential effects of longstanding socioeconomic poverty in brain development. Regarding the latter point, it has been proposed that early deprivation of basic health and welfare needs (such as housing, nutrition, and health care) leads to chronic stress, dysfunction of the. hypothalamic-pituitary-adrenal axis, eventually leading to impairments in brain development and functioning (33). Our study findings add to this overall body of literature, but also introduce the possibility that the observed differences in neuropsychological testing performance observed in illiterate persons may be modified by unidentified "urban" factors, such as greater exposure to, and familiarity with, three-dimensional visual stimuli as a result of living in large cities.

Our study has important limitations. First, it was not powered to obtain more precise estimates of validity parameters and decrease the tendency of misclassifications. Second, there is a risk of random variation in participation rates despite attempts to minimize participation bias across the two study sites, which may have led to different reported rates of cognitive impairment between the two groups; however, the primary objective of our study was to determine the feasibility and validity of the RUDAS-PE in illiterate persons and not to establish the prevalence of cognitive impairment in these Peruvian communities. Third, given the cross-sectional design of the study (i.e. no longitudinal ascertainment of cognition) and lack of validated neuropsychological tests for Peruvian illiterate persons from rural settings, there is a probable tendency toward erroneous classifications of our study groups (controls, MCI and dementia); however, to compensate for this weakness we relied on previously trained and experienced clinicians to ascertain our study groups using expert neurological diagnosis and the CDR, which has been previously shown to accurately distinguish healthy controls, from MCI and dementia (25). Furthermore, the evaluating clinicians were blinded to the results of the RUDAS-PE. This procedure was followed to prevent incorporation of biases and overestimation of diagnostic accuracy for the RUDAS-PE assessments. Still, clinical diagnosis may be less accurate than when standardized neuropsychological assessment are included, as well as brain imaging. On the other hand, it should be noted that primary care physicians and geriatricians in Peru usually do not utilize comprehensive neuropsychological testing or neuroimaging when evaluating older adults with cognitive impairment, procedures that are usually performed only at specialized memory centers and academic institutions.

Therefore, our study design is more reflective of the approach used in primary care when evaluating illiterate persons with cognitive impairment, and our study results suggest that the RUDAS-PE may be a good, briefer alternative to the GDS. Fourth, participants included in this study were from rural Peruvian communities that were fluent in Spanish and did not include Peruvians who speak native languages such as Quechua or Aymara. Therefore, the results or our study are reflective of the performance of the RUDAS-PE in Spanish-speaking illiterate rural Peruvians, and further studies are needed to determine influence of indigenous culture and bilingualism on the RUDAS-PE.

CONCLUSIONS

We present the first study assessing the neurocognitive health of rural illiterate persons living in two culturally and geographically distinct regions of Peru. The RUDAS-PE was found to adequately distinguish MCI from dementia in our study. Diagnosing persons with neurodegenerative disease early in their illness (i.e., in MCI stages) is crucial in order to implement supportive therapies in a timely manner, intervene on modifiable risk factors for dementia early on in the disease course, and counsel family members on expectations of disease course promptly. Our study results suggest the existence of cultural and environmental factors that may influence performance on the RUDAS-PE among illiterate persons. Indeed, we believe it's important for researchers to account for the significant cultural and environmental diversity that exists within Latin America, even within Latin American countries, when developing and testing BCSTs in vulnerable populations in the region. Finally, we found that our study participants performed worse in motor praxis (alternating hand movements) and visuospatial construction (copy of the cube drawing), compared to the performance of urban illiterate individuals in Lima, Peru. These results further emphasizes the existence of "urban" factors other than educational level, such as test-taking familiarity, lack of school-acquired problem-solving skills and the potential role of chronic poverty on brain development, all of which influence the testing performance of illiterate persons from rural settings.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institute of Tropical Medicine Daniel Alcides Carrión of the Universidad Nacional Mayor de San Marcos. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

MD was funded by the Fogarty International Center (D43TW009343) and the National Institute on Aging, San Diego Resource Center for advancing Alzheimer's Research in Minority Seniors (5P30AG059299).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.629325/full#supplementary-material

REFERENCES

1. Sachdev PS, Blacker D, Blazer DG, Ganguli M, Jeste DV, Paulsen JS, et al. Classifying neurocognitive disorders: the DSM-5 approach. *Nat Rev Neurol*. (2014) 10:634–42. doi: 10.1038/nrneurol.2014.181
2. Prince M, Ali G-C, Guerchet M, Prina AM, Albanese E, Wu Y-T. Recent global trends in the prevalence and incidence of dementia, and survival with dementia. *Alzheimers Res Ther*. (2016) 8:23. doi: 10.1186/s13195-016-0188-8
3. Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, et al. Defeating Alzheimer's disease and other dementias: a priority for European science and society. *Lancet Neurol*. (2016) 15:455–32. doi: 10.1016/S1474-4422(16)00062-4
4. Baez S, Ibáñez A. Dementia in Latin America: An Emergent Silent Tsunami. *Front Aging Neurosci*. (2016) 8:253. doi: 10.3389/fnagi.2016.00253
5. Bupa, and Alzheimer's Disease International. *Dementia in the Americas: Current and Future Cost and Prevalence of Alzheimer's Disease and Other Dementias*. Chapel Hill, NC: Bupa and Alzheimer's Disease International (2013).
6. Sharp ES, Gatz M. Relationship Between Education and Dementia: An Updated Systematic Review. *Alzheimer Disease & Associated Disorders*. (2011) 25:289–304. doi: 10.1097/WAD.0b013e318211c83c
7. Prince M, Acosta D, Ferri CP, Guerra M, Huang Y, Llibre Rodriguez JJ, et al. Dementia incidence and mortality in middle-income countries, and associations with indicators of cognitive reserve: a 10/66 Dementia Research Group population-based cohort study. *Lancet*. (2012) 380:50–8. doi: 10.1016/S0140-6736(12)60399-7
8. Paddick S-M, Longdon A, Gray WK, Dotchin C, Kisoli A, Chaote P, et al. The association between educational level and dementia in rural Tanzania. *Dement neuropsychol*. (2014) 8:117–25. doi: 10.1590/S1980-57642014DN82000006
9. Qiu C, Bäckman L, Winblad B, Agüero-Torres H, Fratiglioni L. The influence of education on clinically diagnosed dementia incidence and mortality data from the kungsholmen project. *Arch Neurol*. (2001) 58:2034. doi: 10.1001/archneur.58.12.2034
10. The World Bank. The World Bank. *Literacy rate, adult total* (% of people ages 15 and above). UNESCO Institute for Statistics (uis.unesco.org). (2018). Available online at: https://data.worldbank.org/indicator/SE.ADT.LITR.ZS?locations=ZJ-PE (accessed October 16, 2020).
11. Aponte FC, editor. Instituto Nacional de Estadística e Informática. *Crecimiento y Distribución de la Población, 2017 PRIMEROS RESULTADOS*. Lima: Instituto Nacional de Estadística e Informática (2018).
12. Gianella C, Pesantes MA, Ugarte-Gil C, Moore DAJ, Lema C. Vulnerable populations and the right to health: lessons from the Peruvian

Amazon around tuberculosis control. *Int J Equity Health*. (2019) 18:28. doi: 10.1186/s12939-019-0928-z
13. Paddick S-M, Gray WK, McGuire J, Richardson J, Dotchin C, Walker RW. Cognitive screening tools for identification of dementia in illiterate and low-educated older adults, a systematic review and meta-analysis. *Int Psychogeriatr*. (2017) 29:897–929. doi: 10.1017/S1041610216001976
14. Scazufca M, Almeida OP, Vallada HP, Tasse WA, Menezes PR. Limitations of the Mini-Mental State Examination for screening dementia in a community with low socioeconomic status: results from the Sáo Paulo Ageing & Health Study. *Eur Arch Psychiatry Clin Neurosci*. (2009) 259:8–15. doi: 10.1007/s00406-008-0827-6
15. Parra MA. Overcoming barriers in cognitive assessment of Alzheimer's disease. *Dement Neuropsychol*. (2014) 8:95–8. doi: 10.1590/S1980-57642014DN82000002
16. Maestre GE. Assessing dementia in resource-poor regions. *Curr Neurol Neurosci Rep*. (2012) 12:511–9. doi: 10.1007/s11910-012-0300-9
17. Storey JE, Rowland JTJ, Basic D, Conforti DA, Dickson HG. The Rowland Universal Dementia Assessment Scale (RUDAS): a multicultural cognitive assessment scale. *Int Psychogeriatr*. (2004) 16:13–31. doi: 10.1017/S1041610204000043
18. Custodio N, Montesinos R, Lira D, Herrera-Perez E, Chavez K, Hernandez-Córdova G, et al. Validation of the RUDAS in Patients With a Middle-Level Education in Lima, Peru. *Am J Alzheimers Dis Other Demen*. (2019) 34:513–22. doi: 10.1177/1533317519869709
19. Mateos-Álvarez R, Ramos-Ríos R, López-Moríñigo JD. Comparative analysis between the MMSE and the RUDAS for dementia screening in low educated people in a Spanish psychogeriatric clinic. *The European Journal of Psychiatry*. (2017) 31:119–26. doi: 10.1016/j.ejpsy.2017.06.003
20. Ramos-Ríos R, Mateos-Álvarez R, López-Moríñigo JD. Cribado de demencia en una población con un bajo nivel de instrucción. Validación de la versión española del RUDAS (Rowland Universal Dementia Assessment Scale) en una muestra asistencial.:11.
21. Custodio N, Montesinos R, Lira D, Herrera-Perez E, Chavez K, Reynoso-Guzman W, et al. Validation of the RUDAS for the identification of dementia in illiterate and low-educated older adults in Lima, Peru. *Front Neurol*. (2020) 11:374. doi: 10.3389/fneur.2020.00374
22. World Bank Group, Peru. Systematic Country Diagnostic. (2017). Available online at: http://documents1.worldbank.org/curated/en/919181490109288624/pdf/Peru-SCD-final-3-16-17-03162017.pdf (accessed October 16, 2020).
23. Dvorine I. Dvorine color discrimination screening test*. *Optom Vis Sci*. (1948) 25:130–3. doi: 10.1097/00006324-194803000-00006
24. Morris JC. The Clinical Dementia Rating (CDR) : Current version and scoring rules. *Neurology*. (2013) 43:2412–4. doi: 10.1212/WNL.43.11.2412-a
25. Huang H, Tseng Y, Chen Y, Chen P, Chiu H. Diagnostic accuracy of the clinical dementia rating scale for detecting mild cognitive impairment and dementia: a bivariate meta-analysis. *Int J Geriatr Psychiatry*. (2020) 36:239–51. doi: 10.1002/gps.5436
26. Woolf C, Slavin MJ, Draper B, Thomassen F, Kochan NA, Reppermund S, et al. Can the clinical dementia rating scale identify mild cognitive impairment and predict cognitive and functional decline? *Dement Geriatr Cogn Disord*. (2016) 41:292–302. doi: 10.1159/000447057
27. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. (2020) 396:413–46. doi: 10.1016/S0140-6736(20)30367-6
28. Radford K, Mack HA, Draper B, Chalkley S, Daylight G, Cumming R, et al. Prevalence of dementia in urban and regional Aboriginal Australians. *Alzheimers Dement*. (2015) 11:271–9. doi: 10.1016/j.jalz.2014.03.007
29. Custodio N, García A, Montesinos R, Escobar J, Bendezú L. Prevalencia de demencia en una población urbana de Lima-Perú: estudio puerta a puerta. *An Fac med*. (2013) 69:233. doi: 10.15381/anales.v69i4.1110
30. Chaaya M, Phung TKT, El Asmar K, Atweh S, Ghusn H, Khoury RM, et al. Validation of the Arabic Rowland Universal Dementia Assessment Scale (A-RUDAS) in elderly with mild and moderate dementia. *Aging Ment Health*. (2016) 20:880–7. doi: 10.1080/13607863.2015.1043620
31. Nielsen TR, Vogel A, Gade A, Waldemar G. Cognitive testing in non-demented Turkish immigrants–comparison of the RUDAS and the MMSE. *Scand J Psychol*. (2012) 53:455–60. doi: 10.1111/sjop.12018
32. Ostrosky-Solis F, Ardila A, Rosselli M, Lopez-Arango G, Uriel-Mendoza V. Neuropsychological test performance in illiterate subjects. *Arch Clin Neuropsychol*. (1998) 13:645–60. doi: 10.1093/arclin/13.7.645
33. Kosmidis MH. Challenges in the neuropsychological assessment of illiterate older adults. *Lang Cogn Neurosci*. (2017) 33:373–86. doi: 10.1080/23273798.2017.1379605
34. Nielsen TR, Jørgensen K. Visuoconstructional abilities in cognitively healthy illiterate Turkish immigrants: a quantitative and qualitative investigation. *Clin Neuropsychol*. (2013) 27:681–92. doi: 10.1080/13854046.2013.767379
35. Julayanont P, Ruthirago D. The illiterate brain and the neuropsychological assessment: From the past knowledge to the future new instruments. *Appl Neuropsychol Adult*. (2018) 25:174–87. doi: 10.1080/23279095.2016.1250211

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

HYPOTHESIS AND THEORY
published: 22 July 2021
doi: 10.3389/fneur.2021.684524

Air Pollution: A Neglected Risk Factor for Dementia in Latin America and the Caribbean

Nathália Villa dos Santos[1,2], Victor Yuji Yariwake[1], Karina do Valle Marques[3], Mariana Matera Veras[1] and Laís Fajersztajn[1]*

[1] Laboratório de Poluição Ambiental, Departamento de Patologia, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil, [2] Departamento de Saude Ambiental, Faculdade de Saude Publica, Universidade de São Paulo, São Paulo, Brazil, [3] Departamento de Cirurgia, Universidade Federal de Uberlandia, Uberlândia, Brazil

The risk of dementia and Alzheimer's disease in Latin America and the Caribbean (LAC) rises with increasing age and polluted air. Currently, at least 172 million people breathe unhealthy levels of air pollution in LAC countries. Several cohort studies have indicated that air pollution increases the risk of developing dementia and neurodegenerative diseases, but the mechanisms underlying the association are still not clear. Air pollution causes and aggravates five established risk factors for dementia (obesity, hypertension, stroke, diabetes mellitus, and heart diseases) and is linked to three other risk factors (physical inactivity, cognitive inactivity, and depression). Some of these risk factors could be mediating the association between air pollution and dementia. Reducing the risks for dementia is crucial and urgently needed in LAC countries. There is room for improving air quality in many urban areas in the LAC region and other low- and middle-income countries (LMICs), a routealready explored by many urban areas in developing regions. Moreover, reducing air pollution has proved to improve health outcomes before. In this article, we propose that despite the ongoing and valid scientific discussion, if air pollution can or cannot directly affect the brain and cause or aggravate dementia, we are ready to consider air pollution as a potentially modifiable risk factor for dementia in LAC and possibly in other LMICs. We suggest that controlling and reducing current air pollution levels in LAC and other LMIC regions now could strongly contribute.

Keywords: air pollution, particulate matter, dementia, Alzheimer, Latin America, low-and-middle income countries, developing countries

OPEN ACCESS

Edited by:
Agustin Ibanez, Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina

Reviewed by:
Ju Yeon Kim, Soongsil University, South Korea
Ahmed M. Sarki, Aga Khan University, Uganda
Octavio Jiménez-Garza, University of Guanajuato, Mexico

****Correspondence:***
Nathália Villa dos Santos
nathavillia@gmail.com

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: *23 March 2021*
Accepted: *21 June 2021*
Published: *22 July 2021*

Citation:
Santos NVd, Yariwake VY, Marques KdV, Veras MM and Fajersztajn L (2021) Air Pollution: A Neglected Risk Factor for Dementia in Latin America and the Caribbean. Front. Neurol. 12:684524. doi: 10.3389/fneur.2021.684524

INTRODUCTION

Despite the ongoing and valid scientific discussion about whether air pollution can or cannot directly affect the brain, and cause or aggravate dementia, in this article, we propose that we are ready to consider air pollution as a modifiable risk factor for dementia in Latin America and the Caribbean (LAC), and in other low- and middle-income countries (LMICs). We argue that controlling and lowering current air pollution levels in these regions could strongly contribute to reducing the high burden of dementia cases that has been projected for these countries. We base our argument on the following findings: 1) air pollution causes and/or aggravates at least five of

the established risk factors for dementia (i.e., obesity, hypertension, stroke, diabetes mellitus, and heart diseases), 2) reducing air pollution has been proven to lower some of these risks, and 3) there is room for improving air quality in many urban LAC areas and other LMICs, a path already explored in many urban developing regions. First, we will introduce the topic and our hypothesis. In the following subsections, we will discuss how air pollution causes obesity, hypertension, stroke, diabetes mellitus, and heart diseases, and how these conditions can lead to dementia. We will also discuss the potential relations between air pollution and three other risk factors for dementia, for which evidence is less robust (physical inactivity, cognitive inactivity, and depression). Finally, we will discuss the evidence supporting the idea that air pollution can directly cause dementia. In the discussion, we will address why controlling air pollution should be used as a risk reduction strategy to tackle the burden of dementia in the LAC region and LMICs.

AIR POLLUTION AS A MODIFIABLE RISK FACTOR FOR DEMENTIA IN LATIN AMERICA AND THE CARIBBEAN

Dementia

Dementia is an expensive disease with no cure to date, and its estimated global cost has already exceeded 1 trillion dollars. This is an extraordinarily high number for LMICs, a region that will concentrate 68% of the dementia cases by 2050 (1).

The burden of dementia in LAC countries is high and will continue to rise. By 2050, the region will have more than 17 million dementia cases, a 4-fold increase in 35 years (1). The average world increase for the same period will be three times lower (1). Other reports have described how rapid demographic changes, a higher prevalence of risk factors for dementia in the population, and other specific issues have made dementia prominent in the LAC region (2–4). Risk reduction is a crucial public health response to dementia (5), one that is urgently needed in the LAC countries. Our message is that air pollution could figure among the risk reduction strategies in LAC.

Air Pollution

Air pollution is a complex mixture of particles and gases in the air. Its composition varies depending on the emission source and prevailing weather conditions (6). Fine particulate matter [PM with an aerodynamic diameter of $\leq$2.5 μm (PM2.5)] is frequently presented as an indicator of exposure to air pollution in health studies (7, 8), including studies on the effects of air pollution on dementia (9–14). Rather than a single pollutant, PM2.5 reflects different sources of air pollution in the atmosphere. Because of the tiny particle size, PM2.5 can penetrate the lung barrier and enter the blood system. No matter its composition, PM is considered carcinogenic (15). The most frequent gas used to indicate exposure to air pollution in studies investigating the effects of air pollution on dementia is nitrogen dioxide (NO_2), a marker of vehicle exhaust (11–14, 16). Some specific heavy metals, such as lead and cadmium, can trigger neurodegenerative processes and dementia (17). Widely used in industrial and agricultural activities, heavy metals are present in the soil and water and can affect the air, too. Once in the air, they become a major occupational health concern and a threat to the surrounding population. It is crucial to identify the sources of heavy metal air pollution and prevent hazard exposures.

Air pollution is ubiquitous and unevenly distributed (18–20), but it can be reduced. From a global perspective, pollution levels are higher in LMICs (20), the ones that will concentrate approximately 80% of dementia cases in the coming years (1). This makes tackling air pollution a relevant strategy to promote equity in brain health. The unequal distribution of air pollution is also true at smaller scales. Within the same city, those living closer to high traffic roads breathe worse air quality than those living further away. The same goes for those of lower socioeconomic status (21–23).

In 2015, air pollution caused 7.6% of the total global deaths and 4.2% of the total global disability-adjusted life-years (DALYs), a measure of loss in quality of life (7). This estimation was based on the risk for selective cardiovascular (CVD) and respiratory diseases, with no cognitive impairment burden included. It is reasonable to assume that a great part of this burden could be reduced just by lowering levels of air pollution. Indeed, some studies have used natural experiments to show that not only does bad air quality impair health, but also good air quality improves it (24–27). In other words, reducing air pollution can reduce global premature mortality and enhance the quality of life.

Air Pollution in Latin America and the Caribbean

Air pollution in LAC countries does not receive much attention on the global stage (19, 20). This is probably because, when compared with Africa, Asia, and the Middle East, air pollution in this region is not very high (18). However, between 1990 and 2013, particulate pollution increased in parts of the LAC territory (18). If one considers the current knowledge on pollution control and the performance of high-income countries, the decreases in the air pollution levels in LAC countries have been modest. From a public health perspective, the slight reduction in pollution in some regions of LAC has been offset by population growth (7). Although levels of fine particulate matter were decreasing since 2010 in some of the larger LAC cities, such as São Paulo and Bogotá, the current trends point towards an increase (28). At least 172 million people breathe unhealthy levels of air pollution in the LAC region, according to a recent estimation including 100,000 urban residents (29). The total number of LAC residents breathing bad air is higher if we include the rural residents, and remember that the LAC population is nearly 65 times larger than the population used in this estimate. Some rural LAC areas are highly polluted (18) because of wildfires (intentional or not) (30, 31), preharvest sugar cane burning (32, 33), and the more frequent use of wood for cooking and heating (34). At least 172 million LAC residents could reduce their risk for several diseases if air quality improved.

Hypothesis

Reducing the risk of dementia in LAC countries is urgent. The World Health Organization (WHO) strongly recommends that countries take national actions to lower well-established risk factors for dementia at the individual and population levels (5). These risk factors include obesity, hypertension, stroke, diabetes mellitus, heart disease, physical inactivity, poor diet, alcohol abuse, tobacco use, cognitive inactivity, depression, and isolation (5, 35–37). At least five of these risks can be caused or aggravated by breathing bad air quality. This means that controlling air pollution through policies and regulations could help reduce the burden of dementia. This is particularly relevant in LAC countries, where cases will increase, and pollution control is not typically stringent. Large urban areas of the most populated LAC territories, such as São Paulo and Mexico City, present poor air quality far above the health safety levels recommended by the WHO. Both these metropolitan regions rank among the global cities with the highest traffic intensity indexes. Reducing traffic intensity is an example of a pollution control policy that has already been successfully adopted in other large urban areas in Europe, for example.

Recently, mechanistic studies have suggested that air pollution particles can cross the olfactory barrier and reach directly the brain (38). Once in the brain, these particles could trigger neuroinflammation (39, 40) and exaggerated protein misfolding, leading to dementia (9, 40–42). This evidence is still in its early stages and is not yet robust. However, a growing number of epidemiological studies in Europe (11, 13, 16, 43), North America (9, 12, 14, 44–46), and Asia (10) are showing that living in highly polluted areas increases the risk of dementia. Some studies suggest that the link is driven by cardiovascular alterations caused by air pollution (13, 14), but the direct effect pathway was not ruled out. The hypothesis that the association between air pollution and dementia is mediated by cardiovascular disease and metabolic syndrome is reasonable since air pollution is known to cause and aggravate cardiovascular conditions. Nevertheless, the scientific community does not seem to be ready to affirm that air pollution affects the brain and causes dementia (47). Studies in the field are susceptible to a wide range of biases, from the selection of dementia cases to the characterization of long-term exposure to air pollution for each participant. This might explain why air pollution has not yet been included in the list of established and potentially modifiable risk factors for dementia (35–37). We suggest that it is important to change this perspective and consider air pollution a risk factor for dementia, to reduce the burden of the disease in LAC countries. Furthermore, this should be done posthaste. We are not alone. In August 2020, for the first time, a report on dementia prevention listed air pollution as a modifiable risk for the condition (48).

INDIRECT ASSOCIATIONS: CHRONIC DISEASES LINKED TO DEMENTIA AND AIR POLLUTION

Air pollution causes and/or aggravates obesity, hypertension, stroke, diabetes mellitus, and heart diseases. These are all established risk factors for dementia (35–37). Air pollution has also been linked to three other established risk factors for dementia (i.e., physical inactivity, cognitive inactivity, and depression), but the evidence is weaker. In this section, we will discuss these links.

Obesity, Diabetes Mellitus, and Physical Inactivity

Approximately 302 million adults living in the LAC region are overweight, and more than 100 million are obese (49). By the year 2030, overweight and obesity are expected to affect 50% of men and 60% of women in Latin America (50). The countries with the highest prevalence of obesity are El Salvador and Paraguay for females, and Uruguay and Chile for males (51).

Overweight and obesity can be reversed and prevented. Air pollution is linked to metabolic disorders (52). For this reason, safe air quality is among the actions that may reduce the burden of overweight and obesity, alongside healthy diets and physical exercise. Various mechanisms underlie the link between air pollution and increased body weight. Air pollution can cause metabolic dysfunction by increasing oxidative stress in adipose tissue (53) and inflammation. Besides this, liver cells can accumulate more lipids, and skeletal muscles may use less glucose. Obesity is a significant health challenge, as it substantially increases the risk for diseases, such as type 2 diabetes mellitus, fatty liver disease, stroke, and dementia (54). More recently, obesity has been identified as a risk factor for Alzheimer's disease due to hyperglycemia (55). Air pollution can indirectly affect body weight, thus, increasing the risk of other chronic diseases.

Air pollution also prevents people from engaging in regular physical activity, resulting in sedentary behavior (56, 57). Significant levels of air pollution have been negatively associated with physical activity due to decreased lung function, high blood pressure, and other cardiovascular and respiratory symptoms that impair exercise capacity and performance (56, 57).

Cardiovascular and Cerebrovascular Diseases

Epidemiological and observational studies have deepened the knowledge we have about air pollution and its effects on human health (58). Cardiovascular diseases and high blood pressure have been associated with short and long term exposure to air pollution, generated by inflammation, oxidative stress, and arterial remodeling (58, 59).

There are two main types of exposure to air pollution. The first is acute exposure, defined as short-term exposure or a slow but brief increase in pollutant concentrations that may vary in a single day or over several days. Chronic or long-term exposure is exposure to air pollutants over several months or years. Acute exposure to air pollution can result in a similar acute event, such as a thrombosis-induced stroke (60), a rapid rise in blood pressure, or cardiac arrhythmia. Chronic exposure to air pollution can have a direct effect on the brain, triggering and/or furthering neurodegeneration (61) or silent ischemic injuries (62).

Short-term exposure to air pollution can induce vasoconstriction, rupture of atheromatous plaques through inflammatory processes, and cause oxidative stress and thrombin activation. Regarding PM2.5 concentrations, these may cause reduced blood flow in the brain, and ozone can induce cardioembolic strokes, affect heart rate variability, and stimulate atrial fibrillation. On the other hand, chronic exposure can manifest clinically as recurrent strokes provoked by the genesis and progression of atheromas and myocardial infarction (63).

Exposure to air pollution can trigger changes in the cardiovascular system, and these effects can develop acutely, with increased atherosclerosis accelerating the response to chronic disease. Air pollution has also been related to lowering the density of high-density lipoproteins (HDL) due to oxidative stress and inflammation. These processes can cause changes in the structure and function of HDL, resulting in pro-atherogenic or dysfunctional HDL (64). Furthermore, air pollution has been correlated with an increased risk for ventricular arrhythmias and increased ventricular electrical instability, highlighting the potential link between air pollution and sudden cardiac deaths (65).

High concentrations of air pollutants may be correlated with the risk for angina and acute myocardial infarction. Short-term exposure to PM2.5 at levels of 10 mg/m^3 or higher contributes to acute coronary syndromes, especially in patients with preexisting heart disease. The effects are more severe after long-term exposure to traffic (66, 67). Recent studies have suggested that even modest increases in airborne pollutants can trigger an increase in blood pressure in a few hours (68) and affect heart rate variability, vascular tone, and blood coagulation, as well as promote atherosclerosis (69). Even short-term exposure to air pollution has been associated with increased cardiovascular issues and deaths from myocardial ischemia, arrhythmia, and heart failure (59, 70, 71).

Hypertension and heart disease are the main diseases that affect the population worldwide (72). Several studies have indicated that air pollution is a risk factor for hypertension, heart disease (73, 74), and stroke (72, 73).

Research has produced some evidence regarding the association between hypertension, changes in blood pressure, and exposure to PM2.5 and PM10 (particles with an aerodynamic diameter of_or greater than 10 μm). Results indicated that long-term exposure to a 10-μg/m^3 increase in PM10 and PM2.5 is significantly associated with higher systolic and diastolic blood pressure, in addition to a greater risk of hypertension (74). The hypertensive effects of air pollution were more pronounced among men, smokers, drinkers, individuals with a high-fat diet, and those with a high level of physical activity (75).

Elderly patients demonstrate a more apparent association between high blood pressure and cognitive decline when the former condition first arises in middle age. Hypertension can promote changes in the structure and function of the brain through remodeling cerebral vessels. This can lead to disruptions in cerebral self-regulation, reductions in cerebral perfusion, and limitations in the brain's ability to clear potentially harmful proteins, such as β-amyloid (76). Moreover, hypertension disrupts the structure and function of brain blood vessels and can lead to ischemic damage in the white matter that is critical for cognitive function, thus, favoring the development of neurodegenerative diseases (77).

In the case of cerebrovascular diseases, exposure to air pollution particles has also been associated with neuroinflammation (78). The first evidence of neuroinflammation caused by the inhalation of pollution was published in a study involving dogs that had been exposed to significant concentrations of ozone, PM, and other pollutants. Researchers detected inflammation in the brain of the animals with endothelial damage (79). Other *in vivo* studies have shown that PM can stimulate inflammatory and oxidative responses in the CNS (80, 81). Mice exposed to diesel inhalation showed acceleration in the development of Alzheimer's disease characteristics (82), and activated microglial and inflammatory responses. These animal studies demonstrated signs of cellular damage associated with air pollution (83, 84).

AIR POLLUTION, DEPRESSION, AND COGNITIVE INACTIVITY

Studies have shown that exposure to air pollution may be associated with more frequent incidence of depression, anxiety, and cognitive inactivity, especially in people who suffer from concomitant chronic diseases (85). Another study has shown that increases in air pollution may lead to the onset of depressive symptoms among the elderly (41). The pathogenesis may involve oxidative stress and generalized inflammation induced by PM. The pathomechanisms have been linked to vascular lesions and neurodegenerative disorders (86). As a result, these processes may cause or exacerbate the symptoms of depression (87).

TOXICITY MECHANISMS OF AIR POLLUTION

Exposure to contaminated external air is considered an environmental risk factor that promotes brain aging; in contrast, the effects of air pollution on the central nervous system (CNS) are not broadly recognized. Air pollution can cause various neurological disorders as a result of nervous system inflammation and oxidative stress. Damage to neuronal cells caused by fine dust, especially in fetuses and infants, can cause permanent brain damage or lead to neurological disease in adulthood. Epidemiological studies have reported that the risk of developing dementia and Alzheimer's disease is increased by exposure to fine particulates (60).

The role of air pollution in causing metabolic dysfunction is already known (53). The mechanisms by which air pollutants affect the body systems are intimately related to the type and size of inhaled pollutants. The size, load, chemical composition, and propensity to form aggregates determine a pollutant's ability to cross the lung and the blood barrier. The large-diameter PM (PM10) cannot be transported directly into the blood circulation and require neural or proinflammatory responses to mediate

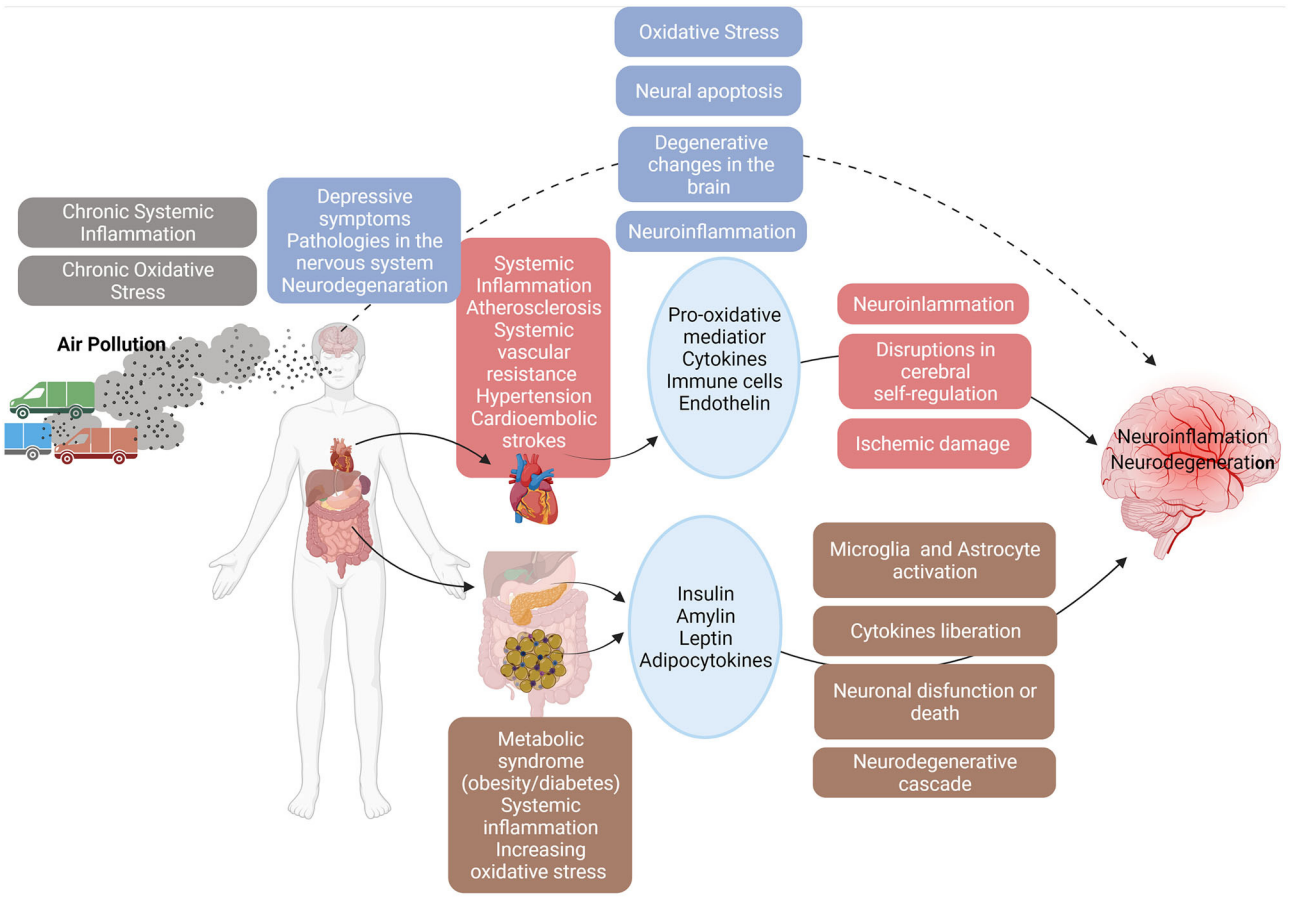


FIGURE 1 | The toxicity mechanisms: air pollution acts directly in brain and indirectly in cardiovascular diseases and metabolic syndromes causing neuroinflammation and neurodegeneration. Created with BioRender.com.

extrapulmonary actions, whereas the ultrafine or soluble PM that constitutes smaller particles can enter the bloodstream directly.

In **Figure 1**, we show the plausible mechanisms of how air pollution affects the human health leading to neurologic impairments highlighting the increased oxidative stress and the pronounced inflammatory responses associated with cardiovascular diseases and metabolic syndromes.

The toxic effects of pollution on cardiovascular diseases are also known (58, 59). The first response caused by inhalation of air pollutants is characterized by the release of pro-oxidative/inflammatory mediators (cytokines, activated immune cells, or platelets) and/or vasoactive mediators (endothelin) in the systemic circulation. Particle inhalation can trigger systemic inflammation, atherosclerosis, and endothelial dysfunction, resulting in increased systemic vascular resistance and hypertension. It is worth noting that the duration of exposure, the levels of co-pollutants, and patient sensitivity are factors that determine subsequent responses (70, 71).

In the second path of action, air pollutants accumulate in the respiratory tree. This can directly stimulate the lung's nervous reflexes, leading to an autonomic imbalance that subsequently favors vasoconstriction (70, 71). In the third pathway, metallic particles and ultrafine PM are inhaled. These can pass through the alveolar and capillary membrane, reach the circulatory system, and cause damage to vasomotor regulation (58, 70, 71, 88).

The direct or indirect effects of air pollution can be associated with stroke and dementia risks. Direct damage can be caused by neuroinflammation and neurodegeneration leading to neurodegenerative diseases (38). Magnetite findings in the magnetic resonance images of human brains exposed to air pollution explain the direct relationship between PM air pollution and AD (89). The indirect mechanism of air pollution in the cerebrovascular system causes stroke, vascular dementia, or other types of dementia. This may be mediated by certain effects on the cardio-neuro-vascular system, such as atherosclerosis, plaque formation and rupture, endothelial dysfunction, cardiac arrhythmia, hypertension, and activated thrombin (90, 91).

By itself, the obesity–diabetes–dementia connection occurs through inflammation and oxidative stress in the brain, caused by systemic inflammation. It is characterized by increased levels of systemic inflammatory mediators (cytokines) that cross the blood–brain barrier (BBB) and metabolic mediators

released by adipose tissue and the pancreas (leptin, insulin, and amylin) that play additional important roles in mediating central nervous system inflammation and neuronal regulation (92), and leading to activation of microglia and astrocytes, inducing the release of cytokines and oxidants. This inflammatory microenvironment causes neuronal dysfunction or death and creates a neurodegenerative cascade.

In obesity and diabetes, there is evidence that exposure to PM 2.5 alters endothelial function, increasing serum levels of tumor necrosis factor alpha (TNF-a), as well as higher levels of interleukin-6 (IL-6), resistin, and leptin (93). Furthermore, Gasparotto et al. (94) investigated oxidative damage and inflammation in different brain regions of obese rats exposed to coal ash, and the results showed that obese rats that inhaled coal ash were more affected by oxidative damage with subsequent inflammation in the hippocampus. This type of damage can lead to chronic neurodegeneration (94).

There are many mechanisms through which air pollutants may cause pathologies in the nervous system, such as nervous system inflammation, oxidative stress, microglial cell activation, protein condensation, and cerebral vascular barrier disorders, but how these mechanisms occur is still unclear (60). The main components of air pollution, PM2.5, as well as the compounds absorbed on their surfaces arrest cell cycles and cause neural apoptosis. These effects, together with the oxidative stress and gene expression alteration induced by these particles, may lead to degenerative changes in the brain (95). Substances found in smog may also cause systemic inflammation with an increased number of active immune cells producing proinflammatory cytokines that pass through the BBB via active transport. As a result, the migration of monocytes to the central nervous system is intensified, aggravating the neuroinflammation process (96).

DIRECT ASSOCIATION: AIR POLLUTION AND DEMENTIA

Higher prevalence of neurodegenerative diseases will certainly come along with population aging. Taking dementia as a reference, the higher increase will occur in LMICs (97).

Air pollution represents an important source of premature mortality and morbidity globally (98) but unevenly distributed across the Globe, since household and outdoor air pollution concentrations are higher in developing countries (20). Adverse effects of air pollution on human health have been mostly attributed to cardiorespiratory events. However, recent studies provide evidence that other health conditions may be influenced by exposures to airborne contaminants, including central neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and mood disorders (99–101).

A series of studies conducted in Mexico demonstrated the usefulness of autopsies in exploring the links between air pollution and cerebral damage (38, 81, 87–89, 102). Thus, a study combining precise measures of exposure, collected cerebral tissues, and autopsy materials could provide important information about the role of air pollution in the development of neurodegenerative diseases.

Other researchers investigated the distribution of the alpha-emitting radon progeny 210-Polonium (^{210}Po) in the olfactory epithelium, olfactory bulb, frontal lobe, and lung tissues of cadavers in São Paulo, Brazil (103). The findings showed that the olfactory bulbs presented higher concentrations of ^{210}Po in comparison with other tissues. The higher concentrations of ^{210}Po in olfactory bulbs suggest that this is a major path entryway for transporting radon progeny from nasal tissues to the central nervous system.

In children, respiratory inflammation is recurrent, especially in the nasal epithelium (99). This leads to changes in the nasal mucous membranes, causing the breakdown of the nasal epithelial barrier and facilitates the passage of xenobiotics into the systemic circulation and the brain. Such damage causes neuroinflammation and the breakdown of the BBB and can affect the olfactory bulb, prefrontal cortex, and brain stem. In patients with apolipoprotein E4, it can significantly accelerate olfactory decline, attention, and short-term memory contributing to neurodegeneration and the progress of Alzheimer's disease (80, 104, 105).

DISCUSSION

The burden of dementia in LAC is high and will increase (1). Reducing dementia risks is crucial and urgently needed in this region. Reducing the levels of air pollution has been shown to improve health outcomes (24–26, 106). Several parts of the LAC region experience bad air quality, and some areas will see an increasing trend in air pollution levels in the coming years (18, 28). At least 172 million LAC inhabitants breathe unhealthy levels of air pollution (29), but there is room to improve their air quality. A better air quality in the region could reduce their risk of developing dementia.

Air pollution control and regulations in LAC countries are not robust (107) and could be improved. Official ground-level information on pollutants is rare (107), and only eight countries have set National Air Quality Standards for fine particulates (108), all above the level recommended by the World Health Organization (109). Three countries in the LAC region were studied in a systematic review on interventions to improve air quality (106), but the reported policies have had little to no success in improving pollution levels. In Ecuador, government action during highly polluted periods effectively reduced the levels of particulate pollution by 20% (110). Although this is a positive policy that will prevent peaks in air pollution, it provides little to no aid in managing the hazards of long-term exposure to polluted air. In Chile, reducing the number of buses alone was not effective in reducing pollution (111). The reported reforms in the public transportation systems in Mexico City and Santiago resulted in a large number of cars and higher levels of pollution (112). Despite the scarcity of documented reports in the literature, the region has had successful experiences controlling air pollution. A proof is the reduction in fine particulate pollution after 2010 in São Paulo and Bogotá (18). At least in São Paulo, the better air quality is mostly attributed to a national pollution control program in Brazil that set progressively more stringent

standards to reduce vehicular emission of new models and the large scale of ethanol and biodiesel enforced by law (113). The targets and deadlines of the Brazilian pollution control program were postponed in different occasions along the years. It is important to notice that the improvement in air quality was achieved for some, but not all, pollutants in the air. The control of secondary pollutants (pollutants formed in the atmosphere, not directly emitted from a source, such as fine particulates) remain a challenge, and despite the improvement in air quality, pollution levels in São Paulo do not yet conform to the WHO's safety recommendations (113). Pollution control and management in São Paulo and in LAC need to be more aggressive to achieve the air pollution safety levels recommended by the WHO. A discussion on possible interventions to improve air quality and health outcomes can be found elsewhere (106).

As explained in detail in previous sections of this manuscript, air pollution causes and aggravates five established risk factors for dementia (obesity, hypertension, stroke, diabetes mellitus, and heart diseases) and has been linked to three others physical inactivity, cognitive inactivity, and depression (35–37). CVD and diabetes mellitus (DM) are the leading causes of mortality and morbidity in the LAC region, resulting in almost 1 million deaths. In 2016, 18.4 million DALYs were lost to cardiovascular disease (114, 115). For diabetics, there were 195,000 deaths, and 8.5 million DALYs were lost in 2016 (114–117). In 2019, these numbers improved by 1% for both diseases (114). The prevalence of these risk factors is higher in LAC countries when compared with the world and other LMICs. The population attributable fractions (PAF) for hypertension is 9% in the LAC region vs. 2% around the world, 6% in China, and 4% in India. The obesity numbers show a similar situation: 8% in the LAC territory vs. 1% around the world, 6% in China, and 3% in India. For diabetes, the LAC PAF is 3% vs. 1% around the world, and 2% in China and India (118). Fifty-six percent of the dementia cases in LAC countries could be avoided if individual risk factors were eliminated. That proportion is higher than in China (49%) and India (41%) (118).

Reducing air pollution could attenuate the prevalence of these established risk factors in the population and, therefore, lower the high burden of dementia in the region. Indeed, two recent cohort studies in Europe (13) and North America (14) have suggested that cardiovascular diseases mediate the association between air pollution and dementia. No similar studies regarding LAC countries were found. However, there is no reason to speculate that cardiovascular disease triggered by air pollution would not culminate in dementia in the LAC population.

As we mentioned in the *Introduction* section, it is plausible to think that air pollution may directly cause dementia. The body of evidence on air pollution and dementia is growing rapidly, with many relevant studies published recently (13–16). Further studies will collaborate to elucidate if air pollution can enter the brain and cause dementia. Nevertheless, whether the agency is direct or indirect, it is clear that air pollution has been associated with dementia, and it is reasonable to expect that reductions in air pollution would help decrease the burden of this disorder.

Given the urgent need to lower the burden of dementia in LAC countries, we recommend implementing strategies to reduce air pollution levels and related risks. We base our argument on the findings that (1) air pollution causes and/or aggravates at least five of the established risk factors of dementia (obesity, hypertension, stroke, diabetes mellitus, and heart diseases), (2) reducing air pollution has been shown to reduce some of these risks, and (3) there is room for improving the air quality in many urban LAC areas and other LMICs. These improvements are already being explored by several urban centers in developing regions with proven health benefits for their population. Although we will just be possible to estimate the real impact of reducing the levels of air pollution in LAC in the burden of dementia in the future, there is no reported side effect for breathing better air quality.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

LF designed the study, reviewed the literature, and wrote the manuscript. NVS and MMV reviewed he literature and wrote the manuscript. VYY interpreted and synthetize the data and revised the manuscript. KVM updated the literature review and revised the manuscript. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

FUNDING

This research was funded by the São Paulo Research Foundation (FAPESP), grant #16/22793-0.

REFERENCES

1. International A-AsD. *World Alzheimer Report 2015. The Global Impact of Dementia: an Analysis of Prevalence, Incidence. Costs and Trends*. London: Alzheimer's Disease International (ADI). (2015).
2. Custodio N, Wheelock A, Thumala D, Slachevsky A. Dementia in Latin America: epidemiological evidence and implications for public policy. *Front Aging Neurosci.* (2017) 9:221. doi: 10.3389/fnagi.2017.00221
3. Ibanez A, Parra MA, Butlerfor C, Latin A, the Caribbean Consortium on D. The latin america and the caribbean consortium on dementia (LAC-CD): from networking to research to implementation science. *J Alzheimers Dis.* (2021) 82:S379-S394. doi: 10.3233/JAD-201384
4. Parra MA, Baez S, Allegri R, Nitrini R, Lopera F, Slachevsky A, et al. Dementia in latin America: assessing the present and envisioning the future. *Neurology.* (2018) 90:222–31. doi: 10.1212/WNL.0000000000004897
5. Organization WH. *Global Action Plan on the Public Health Response to Dementia 2017–2025*. Geneva: World Health Organization. (2017).

6. Adams DR, Ajmani GS, Pun VC, Wroblewski KE, Kern DW, Schumm LP, et al. Nitrogen dioxide pollution exposure is associated with olfactory dysfunction in older U.S. adults. *Int Forum Allergy Rhinol.* (2016) 6:1245–52. doi: 10.1002/alr.21829
7. Cohen AJ, Brauer M, Burnett R, Anderson HR, Frostad J, Estep K, et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study (2015). *Lancet.* (2017) 389:1907–18. doi: 10.1016/S0140-6736(17)30505-6
8. Forouzanfar MH, Afshin A, Alexander LT, Anderson HR, Bhutta ZA, Biryukov S, et al. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet.* (2016) 388:1659–724. doi: 10.1016/S0140-6736(16)31679-8
9. Cacciottolo M, Wang X, Driscoll I, Woodward N, Saffari A, Reyes J, et al. Particulate air pollutants, APOE alleles and their contributions to cognitive impairment in older women and to amyloidogenesis in experimental models. *Transl Psychiatry.* (2017) 7:e1022. doi: 10.1038/tp.2016.280
10. Jung CR, Lin YT, Hwang BF. Ozone, particulate matter, and newly diagnosed Alzheimer's disease: a population-based cohort study in Taiwan. *J Alzheimers Dis.* (2015) 44:573–84. doi: 10.3233/JAD-140855
11. Carey IM, Anderson HR, Atkinson RW, Beevers SD, Cook DG, Strachan DP, et al. Are noise and air pollution related to the incidence of dementia? A cohort study in London England. *BMJ Open.* (2018) 8:e022404. doi: 10.1136/bmjopen-2018-022404
12. Chen H, Kwong JC, Copes R, Hystad P, van Donkelaar A, Tu K, et al. Exposure to ambient air pollution and the incidence of dementia: a population-based cohort study. *Environ Int.* (2017) 108:271–7. doi: 10.1016/j.envint.2017.08.020
13. Grande G, Ljungman PLS, Eneroth K, Bellander T, Rizzuto D. Association between cardiovascular disease and long-term exposure to air pollution with the risk of dementia. *JAMA Neurol.* (2020) 77:801–9. doi: 10.1001/jamaneurol.2019.4914
14. Ilango SD, Chen H, Hystad P, van Donkelaar A, Kwong JC, Tu K, et al. The role of cardiovascular disease in the relationship between air pollution and incident dementia: a population-based cohort study. *Int J Epidemiol.* (2020) 49:36–44. doi: 10.1093/ije/dyz154
15. Cancer IAfRo. *Air Pollution and Cancer France.* World Health Organization. (2013). Report No.: 978-92-832-2166-1.
16. Oudin A, Forsberg B, Adolfsson AN, Lind N, Modig L, Nordin M, et al. traffic-related air pollution and dementia incidence in northern sweden: a longitudinal study. *Environ Health Perspect.* (2016) 124:306–12. doi: 10.1289/ehp.1408322
17. Huat TJ, Camats-Perna J, Newcombe EA, Valmas N, Kitazawa M, Medeiros R. Metal toxicity links to alzheimer's disease and neuroinflammation. *J Mol Biol.* (2019) 431:1843–68. doi: 10.1016/j.jmb.2019.01.018
18. Brauer M, Freedman G, Frostad J, van Donkelaar A, Martin RV, Dentener F, et al. Ambient air pollution exposure estimation for the global burden of disease 2013. *Environ Sci Technol.* (2016) 50:79–88. doi: 10.1021/acs.est.5b03709
19. Fajersztajn L, Saldiva P, Pereira LAA, Leite VF, Buehler AM. Short-term effects of fine particulate matter pollution on daily health events in Latin America: a systematic review and meta-analysis. *Int J Public Health.* (2017) 62:729–38. doi: 10.1007/s00038-017-0960-y
20. Fajersztajn L, Veras M, Barrozo LV, Saldiva P. Air pollution: a potentially modifiable risk factor for lung cancer. *Nat Rev Cancer.* (2013) 13:674–8. doi: 10.1038/nrc3572
21. Martins MCH, Fatigati FL, Ve'spoli TC, Martins LC, Pereira LAA, Martins MA, et al. Influence of socioeconomic conditions on air pollution adverse health effects in elderly people: an analysis of six regions in Sa∼o Paulo, Brazil. *J Epidemiol Community Health.* (2004) 58:41–6. doi: 10.1136/jech.58.1.41
22. Hajat A, Diez-Roux AV, Adar SD, Auchincloss AH, Lovasi GS, O'Neill MS, et al. Air pollution and individual and neighborhood socioeconomic status: evidence from the Multi-Ethnic Study of Atherosclerosis (MESA). *Environ Health Perspect.* (2013) 121:1325–33. doi: 10.1289/ehp.1206337
23. Hajat A, Hsia C, O'Neill MS. Socioeconomic disparities and air pollution exposure: a global review. *Curr Environ Health Rep.* (2015) 2:440–50. doi: 10.1007/s40572-015-0069-5
24. Laden F, Schwartz J, Speizer FE, Dockery DW. Reduction in fine particulate air pollution and mortality: extended follow-up of the harvard six cities study. *Am J Respir Crit Care Med.* (2006) 173:667–72. doi: 10.1164/rccm.200503-443OC
25. Clancy L, Goodman P, Sinclair H, Dockery DW. Effect of air-pollution control on death rates in Dublin, Ireland: an intervention study. *Lancet.* (2002) 360:1210–4. doi: 10.1016/S0140-6736(02)11281-5
26. Rich DQ, Kipen HM, Huang W, Wang G, Wang Y, Zhu P, et al. Association between changes in air pollution levels during the Beijing Olympics and biomarkers of inflammation and thrombosis in healthy young adults. *JAMA.* (2012) 307:2068–78. doi: 10.1001/jama.2012.3488
27. Yinon L, Thurston G. An evaluation of the health benefits achieved at the time of an air quality intervention in three Israeli cities. *Environ Int.* (2017) 102:66–73. doi: 10.1016/j.envint.2016.12.025
28. Gómez Peláez LM, Santos JM, de Almeida Albuquerque TT, Reis NC, Andreão WL, de Fátima Andrade M. Air quality status and trends over large cities in South America. *Environ Sci. Policy.* (2020) 114:422–35. doi: 10.1016/j.envsci.2020.09.009
29. Gouveia N, Kephart JL, Dronova I, McClure L, Granados JT, Betancourt RM, et al. Ambient fine particulate matter in Latin American cities: levels, population exposure, and associated urban factors. *Sci Total Environ.* (2021) 772:145035. doi: 10.1016/j.scitotenv.2021.145035
30. Jacobson Lda S, Hacon Sde S, de Castro HA, Ignotti E, Artaxo P, Saldiva PH, et al. Acute effects of particulate matter and black carbon from seasonal fires on peak expiratory flow of schoolchildren in the Brazilian Amazon. *PLoS ONE.* (2014) 9:e104177. doi: 10.1371/journal.pone.0104177
31. Marlier ME, Bonilla EX, Mickley LJ. How do Brazilian fires affect air pollution and public health? *Geohealth.* (2020) 4:e2020GH000331. doi: 10.1029/2020GH000331
32. Matsuda M, Braga ALF, Marquezini MV, Monteiro MLR, Saldiva PHN, de Santos U. Occupational effect of sugarcane biomass burning on the conjunctival mucin profile of harvest workers and residents of an adjacent town-A Brazilian panel study. *Exp Eye Res.* (2020) 190:107889. doi: 10.1016/j.exer.2019.107889
33. Cancado JE, Saldiva PH, Pereira LA, Lara LB, Artaxo P, Martinelli LA, et al. The impact of sugar cane-burning emissions on the respiratory system of children and the elderly. *Environ Health Perspect.* (2006) 114:725–9. doi: 10.1289/ehp.8485
34. Maas A, Kothe H, Centeno IP, Leiva MJG, Dalhoff1 K. Prevalence of chronic bronchitis and respiratory health profile of a population exposed to wood smoke in Nicaragua. *J Health Pollut.* (2020) 10:1–9. doi: 10.5696/2156-9614-10.26.200607
35. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. *Lancet.* (2017) 390:2673–734. doi: 10.1016/S0140-6736(17)31363-6
36. Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol.* (2011) 10:819–28. doi: 10.1016/S1474-4422(11)70072-2
37. International AsD. From plan to impact Progress towards targets of the Global action plan on dementia (2018). London: Alzheimer's Disease International (ADI) (2018).
38. Maher BA, Ahmed IA, Karloukovski V, MacLaren DA, Foulds PG, Allsop D, et al. Magnetite pollution nanoparticles in the human brain. *Proc Natl Acad Sci USA.* (2016) 113:10797–801. doi: 10.1073/pnas.1605941113
39. Block ML, Elder A, Auten RL, Bilbo SD, Chen H, Chen JC, et al. The outdoor air pollution and brain health workshop. *Neurotoxicology.* (2012) 33:972–84. doi: 10.1016/j.neuro.2012.08.014
40. Cacciottolo M, Morgan TE, Saffari AA, Shirmohammadi F, Forman HJ, Sioutas C, et al. Traffic-related air pollutants (TRAP-PM) promote neuronal amyloidogenesis through oxidative damage to lipid rafts. *Free Radic Biol Med.* (2020) 147:242–51. doi: 10.1016/j.freeradbiomed.2019.12.023
41. Calderon-Garciduenas L, Kavanaugh M, Block M, D'Angiulli A, Delgado-Chavez R, Torres-Jardon R, et al. Neuroinflammation, hyperphosphorylated tau, diffuse amyloid plaques, and down-regulation of the cellular prion

protein in air pollution exposed children and young adults. *J Alzheimers Dis.* (2012) 28:93–107. doi: 10.3233/JAD-2011-110722
42. Calderon-Garciduenas L, Reynoso-Robles R, Perez-Guille B, Mukherjee PS, Gonzalez-Maciel A. Combustion-derived nanoparticles, the neuroenteric system, cervical vagus, hyperphosphorylated alpha synuclein and tau in young Mexico City residents. *Environ Res.* (2017) 159:186–201. doi: 10.1016/j.envres.2017.08.008
43. Oudin A, Segersson D, Adolfsson R, Forsberg B. Association between air pollution from residential wood burning and dementia incidence in a longitudinal study in Northern Sweden. *PLoS ONE.* (2018) 13:e0198283. doi: 10.1371/journal.pone.0198283
44. Chen H, Kwong JC, Copes R, Tu K, Villeneuve PJ, van Donkelaar A, et al. Living near major roads and the incidence of dementia. Parkinson's disease, and multiple sclerosis: a population-based cohort study. *Lancet.* (2017) 389:718–26. doi: 10.1016/S0140-6736(16)32399-6
45. Kulick ER, Elkind MSV, Boehme AK, Joyce NR, Schupf N, Kaufman JD, et al. Long-term exposure to ambient air pollution, APOE-epsilon4 status, and cognitive decline in a cohort of older adults in northern Manhattan. *Environ Int.* (2020) 136:105440. doi: 10.1016/j.envint.2019.105440
46. Kulick ER, Wellenius GA, Boehme AK, Joyce NR, Schupf N, Kaufman JD, et al. Long-term exposure to air pollution and trajectories of cognitive decline among older adults. *Neurology.* (2020) 94:e1782–e92. doi: 10.1212/WNL.0000000000009314
47. Weuve J. Are we ready to call exposure to air pollution a risk factor for dementia? *Neurology.* (2020) 94:727–8. doi: 10.1212/WNL.0000000000009318
48. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet.* (2020) 396:413–46. doi: 10.1016/S0140-6736(20)30367-6
49. FAO, OPS, WFP y UNICEF. *Panorama de la seguridad alimentaria y nutrición en América Latina y el Caribe 2019*. Santiago. 136 (2019). Licencia: CC BY-NC-SA 3.0 IGO.
50. Aschner P. *Obesity in Latin America BT-Metabolic Syndrome: A Comprehensive Textbook*. Ahima RS, editor. Cham: Springer International Publishing. (2014) p. 1–8.
51. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet.* (2014) 384:766–81. doi: 10.1016/S0140-6736(14)60460-8
52. Rao X, Patel P, Puett R, Rajagopalan S. Air pollution as a risk factor for type 2 diabetes. *Toxicol Sci.* (2015) 143:231–41. doi: 10.1093/toxsci/kfu250
53. Mullins J, Bharadwaj P. Effects of Short-Term Measures to Curb Air Pollution: Evidence from Santiago, Chile. *Am J Agric Econ.* (2014) 97:1107–34.
54. Blüher M. Obesity. global epidemiology and pathogenesis. *Nat Rev Endocrinol.* (2019) 15:288–98. doi: 10.1038/s41574-019-0176-8
55. Xue J, Ideraabdullah FY. An assessment of molecular pathways of obesity susceptible to nutrient, toxicant and genetically induced epigenetic perturbation. *J Nutr Biochem.* (2016) 30:1–13. doi: 10.1016/j.jnutbio.2015.09.002
56. An R, Ji M, Yan H, Guan C. Impact of ambient air pollution on obesity: A systematic review. *Int J Obes.* (2018) 42:1112–26. doi: 10.1038/s41366-018-0089-y
57. Croft DP, Zhang W, Lin S, Thurston SW, Hopke PK, Masiol M, et al. The association between respiratory infection and air pollution in the setting of air quality policy and economic change. (2019). *Ann Am Thorac Soc.* 16:321–30. doi: 10.1513/AnnalsATS.201810-691OC
58. Sanidas E, Papadopoulos DP, Grassos H, Velliou M, Tsioufis K, Barbetseas J, et al. Air pollution and arterial hypertension. A new risk factor is in the air. *J Am Soc Hypertens.* (2017) 11:709–15. doi: 10.1016/j.jash.2017.09.008
59. Jalaludin B, Cowie C. Particulate air pollution and cardiovascular disease - It is time to take it seriously. *Rev Environ Health.* (2014) 29:129–32. doi: 10.1515/reveh-2014-0031
60. Kim H, Kim WH, Kim YY, Park HY. Air Pollution and Central Nervous System Disease: A Review of the Impact of Fine Particulate Matter on Neurological Disorders. *Front Public Health.* (2020) 8:575330. doi: 10.3389/fpubh.2020.575330
61. Béjot Y, Reis J, Giroud M, Feigin V. A review of epidemiological research on stroke and dementia and exposure to air pollution. *Int J Stroke.* (2018) 13:687–95. doi: 10.1177/1747493018772800
62. Calderon-Garciduenas L, Mora-Tiscareno A, Ontiveros E, Gomez-Garza G, Barragan-Mejia G, Broadway J, et al. Air pollution, cognitive deficits and brain abnormalities: a pilot study with children and dogs. *Brain Cogn.* (2008) 68:117–27. doi: 10.1016/j.bandc.2008.04.008
63. Kim Y, Myung W, Won H-H, Shim S, Jeon HJ, Choi J, et al. Association between air pollution and suicide in South Korea: a nationwide study. *PLoS ONE.* (2015) 18 10:e0117929. doi: 10.1371/journal.pone.0117929
64. Jianping L, Changping Z, Hongbing X, D. BR, Shengcong L, Tieci Y, et al. Ambient air pollution is associated with HDL (high-density lipoprotein) dysfunction in healthy adults. *Arterioscler Thromb Vasc Biol.* (2019) 39:513–22. doi: 10.1161/ATVBAHA.118.311749
65. Folino F, Buja G, Zanotto G, Marras E, Allocca G, Vaccari D, et al. Association between air pollution and ventricular arrhythmias in high-risk patients (ARIA study): a multicentre longitudinal study. *Lancet Planet Heal.* (2017) 1:e58–64. doi: 10.1016/S2542-5196(17)30020-7
66. Mishra S. Is smog innocuous? Air pollution and cardiovascular disease. *Indian Heart J.* (2017) 69:425–9. doi: 10.1016/j.ihj.2017.07.016
67. Tonne C, Melly S, Mittleman M, Coull B, Goldberg R, Schwartz J. A case-control analysis of exposure to traffic and acute myocardial infarction. *Environ Health Perspect.* (2007) 115:53–7. doi: 10.1289/ehp.9587
68. Cai Y, Zhang B, Ke W, Feng B, Lin H, Xiao J, et al. Associations of short-term and long-term exposure to ambient air pollutants with hypertension: a systematic review and meta-analysis. *Hypertension.* (2016) 68:62–70. doi: 10.1161/HYPERTENSIONAHA.116.07218
69. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* (2012) 380:2224–60. doi: 10.1016/S0140-6736(12)61766-8
70. Brook RD. Cardiovascular effects of air pollution. *Clin Sci (Lond).* (2008) 115:175–87. doi: 10.1042/CS20070444
71. Mills NL, Donaldson K, Hadoke PW, Boon NA, MacNee W, Cassee FR, et al. Adverse cardiovascular effects of air pollution. *Nat Clin Pract Cardiovasc Med.* (2009) 6:36–44. doi: 10.1038/ncpcardio1399
72. Wellenius GA, Schwartz J, Mittleman MA. Air pollution and hospital admissions for ischemic and hemorrhagic stroke among medicare beneficiaries. *STROKE.* (2005) 36:2549–53. doi: 10.1161/01.STR.0000189687.78760.47
73. Yang BY, Guo Y, Bloom MS, Xiao X, Qian Z (Min), Liu E, et al. Ambient PM1 air pollution, blood pressure, and hypertension: Insights from the 33 Communities Chinese Health Study. *Environ Res.* (2019) 170:252–9. Available from:. doi: 10.1016/j.envres.2018.12.047
74. Li N, Chen G, Liu F, Mao S, Liu Y, Liu S, et al. Associations between long-term exposure to air pollution and blood pressure and effect modifications by behavioral factors. *Environ Res.* (2020) 182:1–8. doi: 10.1016/j.envres.2019.109109
75. Sun Q, Hong X, Wold LE. Cardiovascular effects of ambient particulate air pollution exposure. *Circulation.* (2010) 121:2755–65. doi: 10.1161/CIRCULATIONAHA.109.893461
76. Iadecola C, Yaffe K, Biller J, Bratzke LC, Faraci FM, Gorelick PB, et al. Impact of hypertension on cognitive function: a scientific statement from the American heart association. *Hypertension.* (2016) 68: e67–e94. doi: 10.1161/HYP.0000000000000053
77. Calderón-Garcidueñas L, Reed W, Maronpot RR, Henríquez-Roldán C, Delgado-Chavez R, Calderón-Garcidueñas A, et al. Brain inflammation and Alzheimer's-like pathology in individuals exposed to severe air pollution. *Toxicol Pathol.* (2004) 32:650–8. doi: 10.1080/01926230490520232
78. Calderón-Garcidueñas L, Leray E, Heydarpour P, Torres-Jardón R, Reis J. Air pollution, a rising environmental risk factor for cognition, neuroinflammation and neurodegeneration: The clinical impact on children and beyond. *Rev Neurol.* (2016) 172:69–80. doi: 10.1016/j.neurol.2015.10.008
79. Calderón-Garcidueñas L, Torres-Jardón R, Kulesza RJ, Park S-B, D'Angiulli A. Air pollution and detrimental effects on children's brain. The need for

a multidisciplinary approach to the issue complexity and challenges. *Front Hum Neurosci.* (2014) 8:613. doi: 10.3389/fnhum.2014.00613
80. Calderon-Garciduenas L, Reynoso-Robles R, Vargas-Martinez J, Gomez-Maqueo-Chew A, Perez-Guille B, Mukherjee PS, et al. Prefrontal white matter pathology in air pollution exposed Mexico City young urbanites and their potential impact on neurovascular unit dysfunction and the development of Alzheimer's disease. *Environ Res.* (2016) 146:404–17. doi: 10.1016/j.envres.2015.12.031
81. Hullmann M, Albrecht C, van Berlo D, Gerlofs-Nijland ME, Wahle T, Boots AW, et al. Diesel engine exhaust accelerates plaque formation in a mouse model of Alzheimer's disease. *Part Fibre Toxicol.* (2017) 14:35. doi: 10.1186/s12989-017-0213-5
82. Morgan TE, Davis DA, Iwata N, Tanner JA, Snyder D, Ning Z, et al. Glutamatergic neurons in rodent models respond to nanoscale particulate urban air pollutants in vivo and in vitro. *Environ Health Perspect.* (2011) 119:1003–9. doi: 10.1289/ehp.1002973
83. Dimakakou E, Johnston HJ, Streftaris G, Cherrie JW. Exposure to environmental and occupational particulate air pollution as a potential contributor to neurodegeneration and diabetes: a systematic review of epidemiological research. *Int J Environ Res Public Health.* (2018) 15:1704. doi: 10.3390/ijerph15081704
84. Ravi M, Paul E. Stroke mortality associated with living near main roads in england and wales. *Stroke.* (2003) 34:2776–80. doi: 10.1161/01.STR.0000101750.77547.11
85. Lim Y-H, Kim H, Kim JH, Bae S, Park HY, Hong Y-C. Air pollution and symptoms of depression in elderly adults. *Environ Health Perspect.* (2012) 120:1023–8. doi: 10.1289/ehp.1104100
86. Anisman H, Hayley S. Inflammatory factors contribute to depression and its comorbid conditions. *Sci Signal.* (2012) 5:pe45. doi: 10.1126/scisignal.2003579
87. Wei H, Feng Y, Liang F, Cheng W, Wu X, Zhou R, et al. Role of oxidative stress and DNA hydroxymethylation in the neurotoxicity of fine particulate matter. *Toxicology.* (2017) 380:94–103. doi: 10.1016/j.tox.2017.01.017
88. Dockery DW, Pope CA. Acute respiratory effects of particulate air pollution. *Annu Rev Public Health.* (1994) 15:107–32. doi: 10.1146/annurev.pu.15.050194.000543
89. Juha P, Annette P, Gerard H, Pekka T, Bert B, Jeroen de H, et al. Particulate air pollution and risk of ST-segment depression during repeated submaximal exercise tests among subjects with coronary heart disease. *Circulation.* (2002) 106:933–8. doi: 10.1161/01.CIR.0000027561.41736.3C
90. Graber M, Mohr S, Baptiste L, Duloquin G, Blanc-Labarre C, Mariet AS, et al. Air pollution and stroke. A new modifiable risk factor is in the air. *Rev Neurol.* (2019) 175:619–24. doi: 10.1016/j.neurol.2019.03.003
91. Sahathevan R, Brodtmann A, Donnan GA. Dementia, stroke, and vascular risk factors a review. *Int J Stroke.* (2012) 7:61–73. doi: 10.1111/j.1747-4949.2011.00731.x
92. Shalev D, Arbuckle MR. Metabolism and memory: obesity, diabetes, and dementia. *Biol Psychiatry.* (2017) 82:e81–3. doi: 10.1016/j.biopsych.2017.09.025
93. Baron AD, Steinberg HO, Chaker H, Leaming R, Johnson A, Brechtel G. Insulin-mediated skeletal muscle vasodilation contributes to both insulin sensitivity and responsiveness in lean humans. *J Clin Invest.* (1995) 96:786–92. doi: 10.1172/JCI118124
94. Gasparotto J, Chaves PR, da Boit Martinello K, Silva Oliveira LF, Gelain DP, Fonseca Moreira JC. Obesity associated with coal ash inhalation triggers systemic inflammation and oxidative damage in the hippocampus of rats. *Food Chem Toxicol.* (2019) 133:110766. doi: 10.1016/j.fct.2019.110766
95. D'Mello C, Le T, Swain MG. Cerebral microglia recruit monocytes into the brain in response to tumor necrosis factoralpha signaling during peripheral organ inflammation. *J Neurosci.* (2009) 18 29:2089–102. doi: 10.1523/JNEUROSCI.3567-08.2009
96. Calderon-Garcidueñas L, Osorno-Velazquez A, Bravo-Alvarez H, Delgado-Chavez R, Barrios-Marquez R. Histopathologic changes of the nasal mucosa in southwest Metropolitan Mexico City inhabitants. *Am J Pathol.* (1992) 140:225–32.
97. Sleeman KE, de Brito M, Etkind S, Nkhoma K, Guo P, Higginson IJ, et al. The escalating global burden of serious health-related suffering: projections to 2060 by world regions. age groups, and health conditions. *Lancet GlobHealth.* (2019) 7: e883–92. doi: 10.1016/S2214-109X(19)30172-X
98. Richard B, Chen H, Szyszkowicz M, Fann N, Hubbell B, Pope CA, Apte JS, et al. Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter. *Proc Natl Acad Sci USA.* (2018) 115:9592–97. doi: 10.1073/pnas.1803222115
99. Gładka A, Rymaszewska J, Zatoński T. Impact of air pollution on depression and suicide. *Int J Occup Med Environ Health.* (2018) 31:711–721. doi: 10.13075/ijomeh.1896.01277
100. Kilian J, Kitazawa M. The emerging risk of exposure to air pollution on cognitive decline and Alzheimer's disease - Evidence from epidemiological and animal studies. *Biomed J.* (2018) 41:141–62. doi: 10.1016/j.bj.2018.06.001
101. Shou Y, Huang Y, Zhu X, Liu C, Hu Y, Wang H. A review of the possible associations between ambient PM2.5 exposures and the development of Alzheimer's disease. *Ecotoxicol Environ Saf.* (2019) 174:344–52. doi: 10.1016/j.ecoenv.2019.02.086
102. Calderon-Garciduenas L, Gonzalez-Maciel A, Reynoso-Robles R, Kulesza RJ, Mukherjee PS, Torres-Jardon R, et al. Alzheimer's disease and alpha-synuclein pathology in the olfactory bulbs of infants, children, teens and adults </=40 years in Metropolitan Mexico City. APOE4 carriers at higher risk of suicide accelerate their olfactory bulb pathology. *Environ Res.* (2018) 166:348–62. doi: 10.1016/j.envres.2018.06.027
103. Villa N, Leticia C, Zilli V. Levels of Polonium-210 in brain and pulmonary tissues : Preliminary study in autopsies conducted in the city of Saõ Paulo, Brazil. *Sci. Rep.* (2020). 10:180. doi: 10.1289/isee.2020.virtual.P-0612
104. Calderón-Garcidueñas L, Mora-Tiscareño A, Franco-Lira M, Zhu H, Lu Z, Solorio E, et al. Decreases in short term memory, IQ, and altered brain metabolic ratios in urban Apolipoprotein ε4 children exposed to air pollution. *J Alzheimers Dis.* (2015) 45:757–70. doi: 10.3233/JAD-142685
105. Calderon-Garciduenas L, Serrano-Sierra A, Torres-Jardon R, Zhu H, Yuan Y, Smith D, et al. The impact of environmental metals in young urbanites' brains. *Exp Toxicol Pathol.* (2013) 65:503–11. doi: 10.1016/j.etp.2012.02.006
106. Burns J, Boogaard H, Polus S, Pfadenhauer LM, Rohwer AC, van Erp AM, et al. Interventions to reduce ambient air pollution and their effects on health: An abridged Cochrane systematic review. *Environ Int.* (2020) 135:105400. doi: 10.1016/j.envint.2019.105400
107. Riojas-Rodríguez H SdSA, Texcalac-Sangrador JL, Moreno-Banda GL. Air pollution management and control in Latin America and the Caribbean: implications for climate change. *Rev Panam Salud Publica.* (2016) 40:150–9. doi: 10.1289/isee.2016.4675
108. Green J SS. Air Quality in Latin America: An Overview. Clean Air Institute. (2013).
109. World Health Organization. Regional Office for Europe. (2006) . Air quality guidelines: global update 2005: particulate matter, ozone, nitrogen dioxide and sulfur dioxide. World Health Organization. Regional Office for Europe. Available online at: https://apps.who.int/iris/handle/10665/107823
110. Mullins J, Bharadwaj P. Effects of Short-Term Measures to Curb Air Pollution: Evidence from Santiago, Chile. *Am J Agric Econ.* (2014) 97:1107–34. doi: 10.1093/ajae/aau081
111. Gramsch E, Le Nir G, Araya M, Rubio MA, Moreno F, Oyola P. Influence of large changes in public transportation (Transantiago) on the black carbon pollution near streets. *Atmos Environ.* (2013) 65:153–63. doi: 10.1016/j.atmosenv.2012.10.006
112. Gallego F, Montero J-P, Salas C. The effect of transport policies on car use: evidence from Latin American cities. *J Public Econ.* (2013) 107:47–62. doi: 10.1016/j.jpubeco.2013.08.007
113. Andrade MdF, Kumar P, de Freitas ED, Ynoue RY, Martins J, Martins LD, et al. Air quality in the megacity of São Paulo: evolution over the last 30 years and future perspectives. *Atmos Environ.* (2017) 159:66–82. doi: 10.1016/j.atmosenv.2017.03.051
114. Sisa I, Abeyá-Gilardon E, Fisberg RM, Jackson MD, Mangialavori GL, Sichieri R, et al. Impact of diet on CVD and diabetes mortality in Latin America and the Caribbean: a comparative risk assessment analysis. *Public Health Nutr.* (2020) 2016:2577–91. doi: 10.1017/S1368980020000646
115. GDB Results Tool 2021. *University of Washington Institute of Health Metrics and Evaluation.* (2021).

116. Barceló A, Aedo C, Rajpathak S, Robles S. The cost of diabetes in Latin America and the Caribbean. *Bull World Health Organ.* (2003) 81:19–27.
117. Diabetes TL. Obesity prevention in Latin America: Now is the time. *Lancet Diabetes Endocrinol.* (2014) 2:263. doi: 10.1016/S2213-8587(14) 70079-8
118. Mukadam N, Sommerlad A, Huntley J, Livingston G. Population attributable fractions for risk factors for dementia in low-income and middle-income countries: an analysis using cross-sectional survey data. *Lancet Glob Health.* (2019) 7:e596–e603. doi: 10.1016/S2214-109X(19) 30074-9

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

CLINICAL TRIAL
published: 23 July 2021
doi: 10.3389/fneur.2021.651826

Effects of an Enhanced Training on Primary Care Providers Knowledge, Attitudes, Service and Skills of Dementia Detection: A Cluster Randomized Trial

Xiaozhen Lv[1,2], *Mei Zhao*[3], *Tao Li*[1,2], *Changzheng Yuan*[4], *Haifeng Zhang*[1,2], *Chengcheng Pu*[1,2], *Zhiying Li*[1,2], *Na Zhang*[5], *Xin Yu*[1,2] *and Huali Wang*[1,2]*

[1] Beijing Dementia Key Lab, Dementia Care & Research Center, Peking University Institute of Mental Health (Sixth Hospital), Beijing, China, [2] NHC Key Laboratory of Mental Health, National Clinical Research Center for Mental Disorders, Beijing, China, [3] Academic Unit for Psychiatry of Old Age, Department of Psychiatry, The University of Melbourne, Parkville, VIC, Australia, [4] Department of Big Data in Health Science, School of Public Health, School of Medicine, Zhejiang University, Hangzhou, China, [5] Psychological Department, Beijing Anzhen Hospital, Capital Medical University, Beijing, China

OPEN ACCESS

Edited by:
Bao-Liang Zhong,
China University of Geosciences
Wuhan, China

Reviewed by:
Hui-Jie Li,
Chinese Academy of Sciences
(CAS), China
Xiu-Jun Liu,
Wuhan Mental Health Center, China

***Correspondence:**
Huali Wang
huali_wang@bjmu.edu.cn

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: *11 January 2021*
Accepted: *28 June 2021*
Published: *23 July 2021*

Citation:
Lv X, Zhao M, Li T, Yuan C, Zhang H, Pu C, Li Z, Zhang N, Yu X and Wang H (2021) Effects of an Enhanced Training on Primary Care Providers Knowledge, Attitudes, Service and Skills of Dementia Detection: A Cluster Randomized Trial. Front. Neurol. 12:651826. doi: 10.3389/fneur.2021.651826

Background: Effective training programs for primary care providers (PCPs) to support dementia detection are needed, especially in developing countries. This study aimed to investigate the effect of an enhanced training on the competency and service of PCPs for dementia detection.

Methods: We conducted a cluster randomized trial in Beijing, China. Community healthcare centers (CHCs) located in Fengtai or Fangshan District were eligible. The enrolled CHCs in each district were randomly assigned to the standard or the enhanced training group at a 1:1 ratio. PCPs serving older adults in enrolled CHCs were eligible to participate. The standard training group received three-hour didactic lectures, three monthly supervisions, 3 months of online support and dementia screening packages. The enhanced training group additionally received three monthly face-to-face supervisions and 3 months of online support. The participants became aware of their group membership at the end of the standard training. The knowledge, attitudes, service, and skills regarding dementia detection were assessed using questionnaires and submitted dementia detection records, respectively.

Results: A total of 23 and 21 CHCs were randomly assigned to the standard and the enhanced training group, respectively, and 58 participants from 20 CHCs assigned to the standard training group and 48 from 16 CHCs assigned to the enhanced training group were included in the final analysis (mean age 37.5 years, and 67.0% women). A significant increase in the knowledge score was found in both groups, but the increase was similar in the two groups ($P = 0.262$). The attitude score remained stable in both groups, and no between-group difference was found. Compared with the baseline, both groups reported an increase in dementia detection service, especially the enhanced training group (24.1% to 31.0% in the standard training group and 14.6% to 45.8% in the enhanced training group). The completion rate and accuracy of submitted dementia detection

records in the enhanced training group were both significantly higher than those in the standard training group (both $P < 0.001$).

Conclusion: The enhanced training had similar effect on the knowledge of PCPs comparing with the standard training, but was better on continuous service and skills of PCPs related to dementia detection.

Trial registration: www.ClinicalTrials.gov, identifier: NCT02782000. Registration date: May 2016. The trial was completed in July 2017.

Keywords: dementia detection, primary care providers, training, knowledge, attitudes, service, cluster randomized trial

INTRODUCTION

Timely dementia detection is critical if dementia patients are to receive effective interventions and plan accordingly (1, 2). Primary care providers (PCPs) are usually the first clinicians to whom older adults report dementia symptoms; therefore, they are on the front line in timely dementia detection (1, 3, 4). Many PCPs have limited knowledge (e.g., do not recognize early signs of dementia), negative attitudes (e.g., doubtful about the benefits of early diagnosis and treatment) and a lack of skills (e.g., not familiar with dementia screening tools) related to dementia detection in most countries and regions (5–7), which prevents them from detecting and managing dementia in a timely manner (4, 8, 9). Therefore, improving the competency of PCPs regarding dementia detection is imperative worldwide, especially in China, due to its large number of older adults and dementia patients (10, 11), high rate (93.1%) of undetected dementia (12) and limited education and training on dementia detection for PCPs (13).

Training of PCPs plays an important role in timely dementia detection. Previous studies have shown some positive effects of educational intervention on PCPs' knowledge, attitudes, competence, confidence, practice and health care outcomes regarding dementia detection but there is no consistency across studies (14–18). Caution is needed to apply these results to other settings due to the heterogeneity of the intervention components, training methods, expertise of trainees and trainers and methodological robustness across these studies (14, 15). Moreover, the majority of evidence has originated from developed regions, and the required training content and feasible delivery methods in developing countries may differ from those in developed countries (19). To improve the competency of PCPs in dementia detection in developing countries, an effective and feasible dementia detection training program for PCPs is urgently needed.

Our previous pilot study revealed that PCPs' knowledge regarding dementia detection and self-reported dementia screening practice improved after training (20). To provide more reliable evidence on this topic, we conducted the present trial involving 44 community health service centers (CHCs) in Beijing, China. A cluster randomization was chosen for practical reasons and to prevent contamination by communication among PCPs. It aimed to evaluate the effect of an enhanced training on the knowledge, attitudes, provided dementia screening service and skills related to dementia detection of PCPs and to explore the satisfaction and reactions of trainees to the training.

Abbreviations: PCPs, primary care providers; CHCs, community healthcare centers; AD8, Eight-item Interview to Differentiate Aging and Dementia; CDT, Clock Drawing Test.

MATERIALS AND METHODS

Study Design

This study was a cluster randomized trial conducted in CHCs in Fangshan and Fengtai Districts, Beijing, China between August 2016 and July 2017. Little dementia detection training was provided in these areas. CHCs are the primary care units of the national health system, and are the foundation of providing primary health care services to residents who are living in their jurisdictions. Collaborating with the Fangshan and Fengtai Health Commissions, the CHCs in these two districts, as long as the leader of the CHC agreed to participate the program, were all eligible. We enrolled 24 of 24 CHCs in Fangshan District and 20 of 23 CHCs in Fengtai District.

The enrolled CHCs in each district were randomly assigned at a 1:1 ratio to the standard or the enhanced training group using a series of computer-generated random numbers by a researcher. The present trial consisted of two phases lasting for 6 months. In the first phase, both the standard and the enhanced training group received three-hour didactic lectures, three monthly face-to-face supervisions, and 3 months of online support and dementia screening toolkits. In the second phase, the enhanced training group received an additional three monthly supervisions and 3 months of online support, whereas the standard training group received no more training or support, except dementia screening toolkits. The participants became aware of their group membership at the end of the first phase.

This trial was conducted with the approval of the Ethics Committee of Peking University Sixth Hospital (2016-Lunshen-7). All participants provided written informed consent after the randomization of the enrolled CHCs.

Participants

After agreeing to attend the program, the leader of each enrolled center sent the information of the training program to the PCPs. The PCPs working at these selected sites were invited to participate in the study and attended voluntarily. The participant inclusion criteria were as follows: (1) the majority of their

patients were older adults; (2) they had access to WeChat (the most popular social media platform in China, which supports online live chats and classrooms for reviewing slides); and (3) they continued working at their current institution for at least 6 months after enrollment. The exclusion criteria were as follows: (1) refusal to complete the questionnaire for assessing the training effect and (2) involvement in another dementia-related study. The final number of participants was determined by the leader of each CHC.

Intervention

Based on previous studies of dementia detection training (3, 19) and our pilot study (20), a multidisciplinary expert team of geriatric psychiatrists (XY and HW), experts in the field of dementia prevention (HW, TL and XL) and educators (HW and TL) developed the training program that included didactic lectures, supervisions, online support and dementia screening packages to train and support PCPs involved in dementia detection. All four trainers (TL, CP, ZL and NZ) were registered psychiatrists with experience in dementia detection, diagnosis, treatment and education. Before the intervention, the supervisor of the program (HW) reviewed all training slides, and a special workshop for trainers was held to unify the training format.

In the first phase, two groups both received standard training consisting of (1) didactic lectures and exercises: we informed the participants about the prevalence, symptoms, prevention, detection, treatment and referral of dementia through a 50-min lecture, and then we introduced two dementia screening tools [Eight-item Interview to Differentiate Aging and Dementia (AD8) and Clock Drawing Test (CDT)] through a 35-min lecture and guided participants in exercises based on the screening tools; (2) three monthly face-to-face supervisions: the first supervision was provided 1 month after the lectures, and another two were subsequently provided. Each supervision lasted approximately 90 min and followed a uniform format, which was organized into 3 components: review of the key points of the last lecture, a 45-min lecture on dementia symptoms/diagnosis procedure/standard treatment, and case analysis and discussion; (3) 3 months of online support: using the WeChat application, the training slide was uploaded to the online classroom after each lecture for participants to review at any time; in addition, we provided online counseling support about training content, dementia screening and referral in real time through an online discussion group in WeChat or by telephone; and (4) a screening package: a dementia screening package, including training materials, dementia screening and referral records, a referral information card and educational material about dementia for the public, was offered to each trainee at the beginning of the intervention, and these materials were replenished as needed during the study.

In the second phase, the enhanced training group continued receiving three monthly supervisions (in a similar format to that of the first three supervisions, with the lecture introducing dementia differential diagnosis/treatment safety/prevention progress) and 3 months of online support during this period. The standard training group did not receive any intervention during this period, except for the screening toolkit.

The lectures and supervisions were provided at the Center for Continuing Medical Education of each district. During supervision periods, the participants in the included centers, which were assigned to the same group and located in the same district (Fangshan or Fengtai District), received supervision simultaneously. All interventions and procedures for participants from Fangshan District were repeated for those from Fengtai District. To improve their adherence, we provided all participants an opportunity to obtain continuing medical education credit points for attending the training, which was mandatory for all medical workers in China. No other reimbursement was offered for participating in the trial or providing dementia screening services.

Outcome Assessment

Outcome measures were classified according to Kirkpatrick's model for the evaluation of training interventions (21): (1) the participants' knowledge about, attitudes toward and skills in dementia screening; (2) dementia screening and referral service provided by the participants; and (3) participants' satisfaction with and reaction to the program.

The knowledge score, as the primary outcome, consisted of theoretical and practical knowledge, and was assessed using 13 true-false questions, 13 multiple-choice questions (including the etiology, symptoms, screening, diagnosis, treatment, prevention, prognosis, and referral of dementia), and three case analyses (about the evaluation and referral of suspected dementia patients). This score ranged from 0 to 45, with higher scores denoting greater knowledge.

Attitude was assessed using 10 true-false questions about dementia screening and referral, with scores ranging from 0 to 10, and higher scores denoting a more positive attitude. The dementia screening and referral of patients with suspected dementia provided by the participants was assessed by asking whether they provided these services in the past month, and the number of dementia screening and referral records submitted by PCPs at the end of the trial.

Skills in dementia screening and referral were assessed according to the submitted records, with the completion rate and accuracy of the AD8 and CDT, and the referral suggestions. The completion rates of the AD8, CDT and the referral suggestions were calculated with the number of completed AD8s (all items and total score of AD8 completed), CDTs (total score graded) and the referral suggestions (suggestion given) divided by the number of submitted records, respectively. The accuracy of the AD8s was assessed by the number of AD8s with the correct total score (comparing the total score given by the participants with the total score calculated based on all items) divided by the number of completed AD8s. Similarly, the accuracy of the CDTs was calculated as the number of CDTs with the correct total score (comparing the total score graded by the participants with the total score graded by researchers based on the figure drawn by the screening object) divided by the number of completed CDTs. The accuracy of referral suggestions was assessed according to the number of correct referral suggestions (comparing the referral suggestions given by the participants with the recommended

suggestions based on the AD8 and CDT total scores) divided by the number of completed management suggestions.

The satisfaction and reaction of the participants were evaluated using a separate survey, which addressed whether the training program was useful for their clinical practice, their advice for improving the training program, and the advantages and disadvantages of dementia detection in their practice.

All the assessments were examined in exactly the same way for the two groups. Except for the participants' skills and feedback evaluated at the end of the trial, other assessments were conducted at baseline and at the end of the trial. Demographic characteristics of the participants, including sex, age, occupation, education and years of working, were collected at baseline. The questionnaire used for assessing the knowledge, attitudes and self-reported service was shown in supplementary **The Questionnaire**.

Sample Size

According to our previous pilot study (20), we estimated that at a 1:1 ratio, with a sample of 32 clusters (CHCs) with an average of 4 participants in each cluster, the study would have 95% power to detect a difference of 3 points (standard deviation of 4) in knowledge score (the primary outcome) between the two groups, with an intracluster correlation of 0.05 and a two-sided significance level of 0.05. Considering up to a 15% loss to follow-up, the number of clusters was increased to 38, and 152 participants were needed.

Statistical Analysis

The data are presented as the means and standard deviations, medians and interquartile ranges, and counts and percentages for normally distributed variables, non normally distributed variables, and categorical variables, respectively. Between-group differences in baseline characteristics were analyzed with Student's *t* test or the Wilcoxon rank-sum test for continuous variables and chi-square test or Fisher's exact test for categorical variables.

Modified ITT analyses were conducted. Analyses of the difference between the two groups in the change in knowledge and attitude scores and dementia screening and referral between baseline and the end of the intervention were performed on data from the participants who underwent the assessments both at baseline and at the end of the intervention, no matter whether they completed the entire intervention. Analysis of dementia screening and referral skills was performed based on the submitted screening records at the end of the trial. Analysis of the satisfaction and reaction of the participants was conducted on data from the participants who completed the survey at the end of the intervention.

We used paired *t* tests to examine the changes in the knowledge score and attitude score before and after the intervention in each group, respectively. We used paired chi-square tests to examine the proportion of dementia screening and referral provided by the participants before and after the intervention in each group, respectively. We used a generalized linear mixed model to examine the differences in the change in

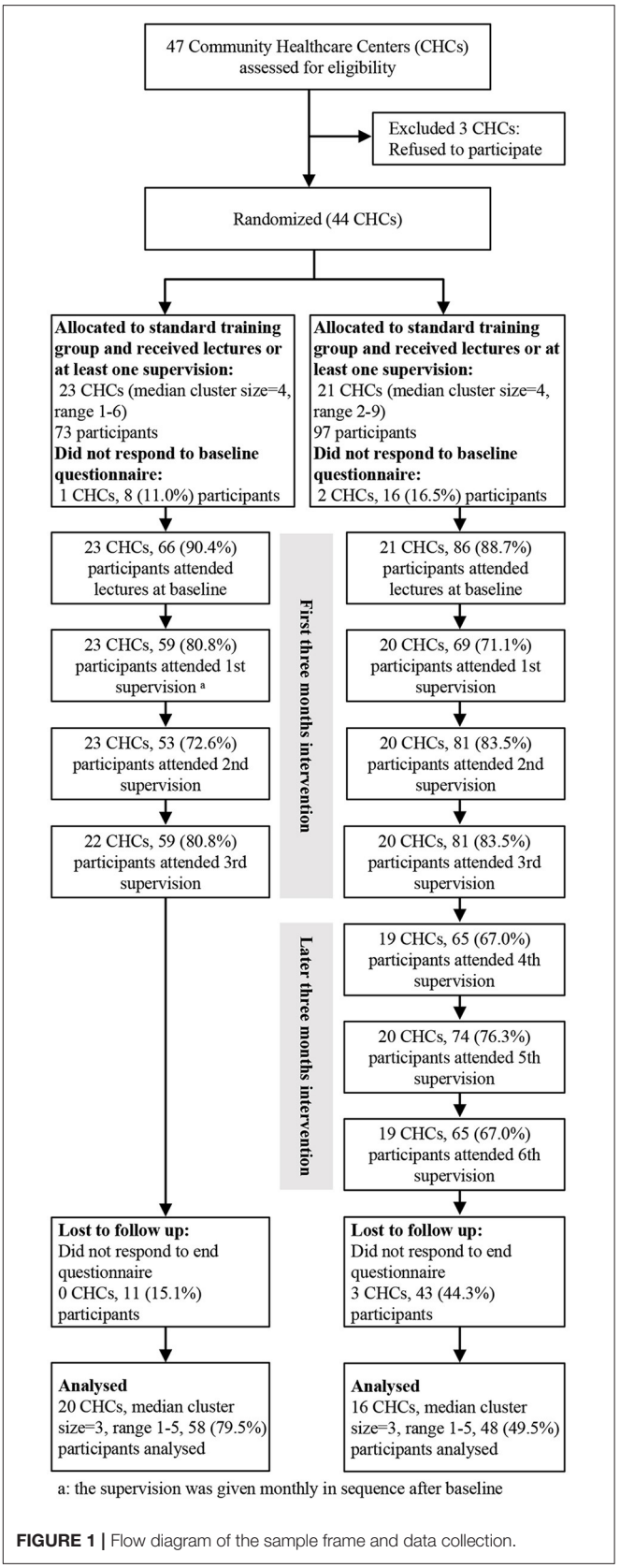


FIGURE 1 | Flow diagram of the sample frame and data collection.

knowledge score, attitude score and the proportion of provided dementia screening and referral of the two groups between baseline and the end of the intervention. Cluster (CHC) was treated as a random effect, and intervention, measure time, and intervention-measure time interaction were treated as fixed effects, with age as a covariate. To evaluate the need to adjust for site, education, occupation and working experience, models included a term for the interaction with the study group (the standard or the enhanced training group). A $P < 0.05$ was considered to indicate a significant interaction. Since all the $P > 0.15$ for interaction, the final model did not adjust for site, education, occupation or working experience. We used chi-square tests to examine the differences in dementia screening and referral skills between the two groups. The participants' reaction was thematically analyzed.

A two-sided $P < 0.05$ was considered statistically significant. All analyses were performed with SAS 9.4.

RESULTS

Participant Flow and Baseline Characteristics

The recruitment started in July 2016 and follow-up ended in July 2017 at the end of the trial. A total of 44 out of 47 CHCs in Fangshan and Fengtai Districts agreed to participate in the trial, and 23 and 21 CHCs were assigned to the standard and enhanced training groups, respectively. Initially, 73 PCPs from the 23 CHCs in the standard training group and 97 from the 21 CHCs in the enhanced training group entered the trial. During the intervention, the attrition rates in the standard and enhanced training group were 18.8% and 23.3%, respectively, and no between-group difference was found ($P = 0.126$). At the end of the trial, participants in the enhanced training group were more likely lost to follow-up than those in the standard training group (44.3 vs. 15.1%). Finally, a total of 58 (79.5%) participants from 20 CHCs in the standard training group and 48 (49.5%) from 16 CHCs in the enhanced training group completed both the baseline and the last assessment and were included in the analysis (**Figure 1**).

The median (P_{25}-P_{75}) cluster size was 3 (2–4). The average age of the participants was 37.5 years, and 67.0% were female. The majority of the participants were physicians (73.6%) and had a bachelor's degree or above (66.6%). The median (P_{25}-P_{75}) years of working was 10 (6–16). Except for age, the characteristics of the participants between the two groups did not differ significantly (**Table 1**). The characteristics of the participants lost to follow-up were similar to those included in the analysis; the except was education, namely, those with lower education level were more likely to be lost to follow-up than those with higher education level ($P = 0.006$). The CONSORT 2010 checklist of information of the study was shown in supplementary **The CONSORT checklist**.

Comparison of Changes in Dementia-Related Knowledge and Attitudes

The knowledge score at the end of the intervention was significantly higher than that at baseline in each group (P both <0.001). However, the change in the knowledge score between baseline and the end of the intervention in the enhanced training

TABLE 1 | Baseline characteristics of the participants.

	Total ($n = 106$)	Standard training group ($n = 58$)	Enhanced training group ($n = 48$)	*P*
Number of clusters (community healthcare centers)	36	20	16	-
Average cluster size, persons, median (25th, 75th percentile)	3 (2, 4)	3 (1, 4)	3 (2, 4)	0.845
Location[a]				0.143
Fangshan District	58 (54.7)	28 (48.3)	30 (62.5)	
Fengtai District	48 (45.3)	30 (51.7)	18 (37.5)	
Age[b], years, mean (standard deviation)	37.5 (7.6)	35.5 (6.9)	39.8 (7.8)	0.004
Sex[a]				0.372
Male	35 (33.0)	17 (29.3)	18 (37.5)	
Female	71 (67.0)	41 (70.7)	30 (62.5)	
Occupation[a]				0.764
Physician	78 (73.6)	42 (72.4)	36 (75.0)	
Nurse	28 (26.4)	16 (27.6)	12 (25.0)	
Education[a,c]				0.473
Junior college or lower	33 (33.3)	17 (30.4)	16 (37.2)	
Bachelor or above	66 (66.6)	39 (69.6)	27 (62.8)	
Years of work[d], median (25th, 75th percentile)	10 (6, 16)	8.5 (6, 15)	10 (5, 18)	0.519

[a] *Data are expressed as counts (percentages).*
[b] *Six participants (4 from the standard and 2 from the enhanced training group) did not report.*
[c] *Seven participants (2 from the standard and 5 from the enhanced training group) did not report.*
[d] *Ten participants (4 from the standard and 6 from the enhanced training group) did not report.*

TABLE 2 | Changes in knowledge, attitudes, and provided service related to dementia detection from baseline to the end of the intervention.

	Baseline		End of the intervention		Difference between baseline and the end of the intervention		Comparison of the change between two groups	
	Standard training group ($n = 58$)	Enhanced training group ($n = 48$)	Standard training group	Enhanced training group	Standard training group	Enhanced training group	P^c	P^d
Knowledge score, points[a]	32 (29, 35)	31 (28, 34)	37 (32, 38)	36 (33, 38)	3.5 (−0.3, 7.3)	4.0 (2.0, 7.0)	0.293	0.218
Theoretical knowledge	21 (18, 23)	21 (18, 23)	24 (23, 25)	25 (23, 27)	3.0 (1.0, 5.0)	4.0 (2.3, 5.0)	0.085	0.098
Practical knowledge	11 (10, 12)	11 (10, 12)	13 (9, 14)	11 (10, 12)	1.0 (−2.3, 3.0)	0.0 (−1.0, 1.0)	0.845	0.847
Attitude score, points[a]	8 (8, 9)	8 (7, 9)	9 (7, 9)	8 (8, 9)	0.0 (−1.0, 1.0)	0.0 (−1.0, 1.0)	0.872	0.675
Self-reported dementia screening or referral service in the past month[b]							0.028	0.045
No	44 (75.9)	41 (85.4)	40 (69.0)	26 (54.2)	-	-		
Yes	14 (24.1)	7 (14.6)	18 (31.0)	22 (45.8)	-	-		
Proportion of participants submitting dementia screening records at the end of the study[b]							0.129	0.028
No	-	-	34 (58.6)	21 (43.7)	-	-		
Yes	-	-	24 (41.4)	27 (56.3)	-	-		
Number of submitted records[a]	-	-	15 (6, 46)	27 (11, 55)	-	-	0.138	0.088
Period using records[b]	-	-						
1st−3rd month	-	-	22 (91.7)	27 (100.0)	-	-	0.216	0.196
4th−6th month	-	-	3 (12.5)	14 (51.9)	-	-	0.003	0.002

[a] *Data are expressed as median (25th−75th percentile).*
[b] *Data are expressed as counts (percentages).*
[c] *Unadjusted.*
[d] *Adjusted for age.*

group was similar to that in the standard training group (4.0 vs. 3.5, $P = 0.218$) (**Table 2**).

The attitude score of participants in both groups remained positive and stable after the intervention, and no significant difference in the change in attitude score between the two groups was found ($P = 0.675$) (**Table 2**).

Comparison of the Change in Provided Service and Submitted Records

Compared with baseline, both groups reported an increase in dementia screening and referral services after the intervention, especially the enhanced training group [24.1% to 31.0% in the standard training group ($P = 0.302$) and 14.6% to 45.8% in the enhanced training group ($P = 0.003$)]. The increase in the enhanced training group was higher than that in the standard training group ($P = 0.045$), although the difference was close to non significant (**Table 2**).

At the end of the trial, a total of 51 (48.1%) participants submitted 1,845 copies of dementia screening and referral records. The participants in the enhanced training group were more likely to use records than those in the standard training group ($P = 0.028$). Additionally, the median number of submitted records in the enhanced training group was greater than that in the standard training group, although the difference was non significant (**Table 2**).

Among those participants who submitted records, the participants in each group had a high tendency to use the records (91.7% in the standard training group and 100% in the enhanced training group) during the first 3 months of the study period, and no difference was found between the two groups. In contrast, the proportion of participants who used records during the later 3 months in the enhanced training group was significantly higher than that in the standard training group ($P = 0.002$), although both proportions significantly decreased compared with those during the first 3 months (both $P < 0.001$) (**Table 2**). Additionally, during the online support period, the questions asked by both the training groups were mainly focused on referring the suspected cases for further assessment and diagnosis.

Comparison of Dementia Screening and Referral Skills

Except for the CDT, the completion rates of the AD8, referral suggestions and whole record in the enhanced training group were significantly higher than those in the standard training group (**Table 3**).

According to those completed records, except for the AD8, the accuracies of CDT, referral suggestions and the whole record in the enhanced training group were significantly higher than those in the standard training group (**Table 3**).

TABLE 3 | Comparison of the dementia detection skills between the standard and the enhanced training groups according to submitted records[a].

	Standard training group ($n = 661$)	Enhanced training group ($n = 1184$)	*P*
AD8[b]			
Not complete	272 (41.1)	216 (18.2)	<0.001
Complete	389 (58.9)	968 (81.8)	
Correct	383 (98.5)	958 (99.0)	0.432
Wrong	6 (1.5)	10 (1.0)	
Clock drawing test			
Not complete	144 (21.8)	287 (24.2)	0.232
Complete	517 (78.2)	897 (75.8)	
Correct	391 (75.6)	760 (84.7)	<0.001
Wrong	126 (24.4)	137 (15.3)	
Referral suggestions			
Not complete	318 (48.1)	396 (33.4)	<0.001
Complete	343 (51.9)	788 (66.6)	
Correct	160 (63.7)	586 (82.8)	<0.001
Wrong	91 (36.3)	122 (17.2)	
Total			
Not complete	440 (66.6)	583 (49.2)	<0.001
Complete	221 (33.4)	601 (50.8)	
Correct	113 (51.1)	452 (75.2)	<0.001
Wrong	108 (48.9)	149 (24.8)	

[a] *Data are expressed as counts (percentages).*
[b] *AD8: Eight-item Interview to Differentiate Aging and Dementia.*

Satisfaction and Reaction at the End of the Intervention

A total of 23 (39.7%) participants in the standard training group and 17 (35.4%) participants in the enhanced training group completed reaction and satisfaction surveys at the end of the study. Most participants considered the program efficient and useful for their practice (82.4% in the enhanced training group and 95.7% in the standard training group). Most of the participants said the lectures were easy-to-understand (94.1% in the enhanced training group and 91.3% in the standard training group). The most common suggestion for improving the training content was to introduce more dementia cases in detail in an easy-to-understand way. The participants in both groups indicated the need to add interaction and communication with the trainers during practice and mentioned video-based or online training as a supplement to face-to-face supervision. The participants in the standard training group, rather than the enhanced training group, emphasized the need to learn more about dementia diagnosis, treatment and care skills. No harm or unintended effect was reported during the intervention.

The familiarity between the residents and PCPs and the large aging population in communities were considered advantages for dementia detection, whereas the lower awareness of residents of dementia and the participants' busy clinical practice were the main barriers. Related policy support or incentives from the administration were considered necessary for the implementation of dementia detection.

DISCUSSION

In this cluster randomized trial, we found that the 3-month standard training and the 6-month enhanced training both had significant effects on improving PCPs' dementia detection-related knowledge and screening as well as referral services. Additionally, the improvement of the service in the enhanced training group was greater than that in the standard training group. Our results suggested that the participants' attitudes toward dementia detection were quite positive before training and remained stable after training. Enhanced training tended to improve the use of dementia screening and referral records. Compared with the standard training group, the enhanced training group had a significantly higher completion rate of the AD8 and referral suggestions and higher accuracy of CDT and referral suggestions. Most participants in both groups considered the training easy-to-understand and useful for their practice. Interaction during practice and online training may be an effective supplement to face-to-face supervision.

In this study, we found that PCPs' knowledge regarding dementia detection at the end of the intervention in each group improved significantly compared with that before training. Likewise, in France, a 2 h group educational meeting supporting the use of brief neuropsychological tools was associated with greater confidence in dementia diagnosis among clinicians (18). Shaji et al. (22) and Ramos-Cerqueira et al. (23) reported that community health workers in India and Brazil could identify dementia patients with reasonable accuracy after a few hours of training. These results clearly indicated that delivering appropriate training for PCPs may serve as an effective modality to enhance their competency regarding dementia detection. Moreover, our findings suggested that PCPs in each group provided more dementia detection services after training, especially the enhanced training group. Similarly, evidence from a cluster randomized trial in the UK showed that decision support systems and workshop formats are effective in improving dementia detection in primary care but not a CD-ROM tutorial compared with the standard training group that received no training intervention (17). However, the study from France showed that a 2 h group educational meeting was not associated with an overall increase in newly identified dementia cases (18). These conflicting results of service change among different training programs may be attributed to the differences in training content, duration, mode of delivery and support. The variety of the participants' professional backgrounds and their clinical settings may also be important reasons for these inconsistent results. Additionally, our results indicated that the enhanced training group provided more services and had better skills related to dementia detection than the standard training group, which suggests that sustainable supervision and support may be required to ensure continuous service and to master skills related to dementia detection.

Although we found that most participants in both groups knew more about and had a positive attitude toward dementia detection at the end of the intervention, our results also showed that nearly 60% of the participants did not provide dementia screening or referral services in the month before the end of the

study. Given that the use of a self-administered questionnaire survey may result in inaccurate reports on changes in practice (24), the present study additionally used dementia screening records to evaluate the effect of training on practice. Similarly, we found that approximately half of the participants probably did not use the dementia screening and referral record during the entire study period. Accordingly, Wang et al. (16) reported that basic knowledge and positive attitudes may not ensure health professionals' demonstration of a person-centered approach in dementia care. This inconsistency among knowledge, attitude and related service may imply that the implementation of dementia detection in primary care probably requires more support or conditions, in addition to the improvement of PCPs' related competency. Surr et al. (14) argued that health and social care workforce education should be conceptualized as a complex system, and the individual, meso-, and macrolevels must be considered in understanding learning processes. The feedback of the participants also suggested that enhancing the public's awareness of dementia, modifying PCPs' clinical practice, and providing related support from the administration were important for dementia detection. Of note, the scale and number of older adults served by each included center may not influence the improvement of the participants' skills and dementia detection service, due to CHCs' responsibility for primary health care and the lack of dementia detection service in CHCs in China.

Regarding the training method adopted, previous studies (14–18) used a variety of delivery methods, although predominantly face-to-face learning was often employed alongside other methods. Learning through a written resource (either hard copy or online) or purely classroom-based training consistently yielded no or weak effects on knowledge gains, whereas a combination of theory (through classroom-based learning) and practice (in-service learning) was more likely to produce positive results in improving staff confidence, competency or self-efficacy (14). The adoption of a specific tool or structured method may strongly support participants in adapting their behavior and changing their practice (14). The present program not only provided didactic lectures and exercises but also involved monthly face-to-face supervision, online support, and screening toolkits, which supported the participants in translating what was learned in the classroom to dementia detection practice. The results of our study verified that multiple training methods may be required with respect to dementia detection training. Smith (25) argued that learners had a reduced requirement for a proximal guide/facilitator and a greater need for interaction and construction as their expertise grew. The participants in our study similarly highlighted the need for interaction and communication with trainers during practice.

Strengths and Limitations

Rather than comparing training with no training, we compared two different training groups against each other. Our results provide evidence for understanding which program is effective and optimal for delivering dementia detection training programs in primary care. Moreover, we used parallel groups, and cluster randomized design in each research district, which minimized contamination and the potential impact of different districts and maximized the comparability of the two groups. Additionally, this study combined didactic lectures, exercises, monthly face-to-face supervision, online support with social media and screening toolkits targeted at improving PCPs' competency and service in dementia detection. The multiple facets of training methods adopted in this study may provide a meaningful reference for other similar education programs in this informational era.

This study has several limitations. First, the participants were not randomly selected from those who provided services to older adults in enrolled CHCs, and they may not be representative of those who chose not to participate in the study. The present study was conducted in Beijing, a first-tier city in China. The participants' professional background and the supporting conditions in their clinical practice may differ from those of PCPs in less developed regions. The sample included in the analysis was smaller than expected. In brief, multicenter trials, especially those in rural areas, may be needed before generalizing the training program to diverse areas. Second, this study explored the possible advantages and disadvantages of implementing dementia detection in primary care according to the participants' feedback, and the questions asked by the participants during the online support period were not quantitatively recorded. The development of an effective way to motivate the participants to translate their knowledge of and attitudes toward dementia detection into dementia detection practice warrants further study. Third, due to limited resources, the perspective of the elderly individuals who received dementia detection services and the potential impact of the improvement in the participants' dementia detection competency on older adults' health outcomes were not evaluated in the present study. Forth, the drop-out rate in this trial was relatively high, especially the enhanced training group, due to the schedule conflict between their routine work and the training program. Fifth, regarding the relatively small sample size and high drop-out rate, those, who completed the assessments both at baseline and at the end of the intervention, were included in the final analysis, rather than all of those who were randomly assigned to the two groups.

CONCLUSION

This study indicated that most PCPs recognized the importance of dementia detection, and that 3 months of standard training may be sufficient to improve their knowledge, whereas 6 months of enhanced training was better on the continuous practice and mastery of skills related to dementia detection. The implementation of dementia detection during primary care practice may also require support from the awareness of residents, in addition to adequate competency of practitioners. This trial may serve as a reference for researchers, clinical educators, and policy specialists to inform the development of PCPs' education in the dementia detection sector, with the aim of improving dementia service.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Peking University Sixth Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XL, XY, and HW designed the study. XL, MZ, TL, HZ, CP, ZL, NZ, and HW designed and implemented the intervention and collected and managed the data. XL and MZ scored the clock drawing test. XL and CY performed the statistical analyses. XL drafted the manuscript. All the authors had full access to all the data, contributed to the interpretation of the results, provided intellectual input to the manuscript and approved the final version of the manuscript.

FUNDING

This work was funded by the Capital's Funds for Health Improvement and Research (CFH2020-3-4114, CFH2016-4-4116), the National Natural Science Foundation of China (No. 82003539) and the National Key R&D Program of China (2017YFC1311100, 2018YFC1314200). The funding agency had no role in the design of the study; in the collection, analysis or interpretation of the data; or in the writing, approval of the manuscript or decision to submit the manuscript for publication.

ACKNOWLEDGMENTS

We appreciate the staff and participants of the study sites and the engagement of Fangshan and Fengtai Health Commissions, Beijing. Additionally, we thank the project coordinators (Dongli Yang, Wenyan Zhang, Zhixin Li, Na Li, Han Li and Yu Zhang) for their kind support during the study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.651826/full#supplementary-material

REFERENCES

1. Prince M, Bryce R, Ferri C. *World Alzheimer Report 2011: The Benefits of Early Diagnosis and Intervention*. London: Alzheimer's Disease International (2011) p. 1–72.
2. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. *Lancet (London, England).* (2017) 390:2673–734. doi: 10.1016/S0140-6736(17)31363-6
3. Galvin JE, Sadowsky CH. Practical guidelines for the recognition and diagnosis of dementia. ***J** Am **Board** Fam **Med**.: JABFM.* (2012) 25:367–82. doi: 10.3122/jabfm.2012.03.100181
4. Prince M, Comas-Herrera A, Knapp M, Guerchet M, Karagiannidou M. *World Alzheimer Report 2016: Improving Healthcare for People Living with Dementia. Coverage, Quality and Costs Now and in the Future*. London: Alzheimer's Disease International (2016) p. 1–140.
5. Wang Y, Xiao LD, Luo Y, Xiao S-Y, Whitehead C, Davies O. Community health professionals' dementia knowledge, attitudes and care approach: a cross-sectional survey in Changsha, China. *BMC Geriatr.* (2018) 18:122. doi: 10.1186/s12877-018-0821-4
6. Pathak KP, Montgomery A. General practitioners' knowledge, practices, and obstacles in the diagnosis and management of dementia. *Aging Ment Health.* (2015) 19:912–20. doi: 10.1080/13607863.2014.976170
7. Pucci E, Angeleri F, Borsetti G, Brizioli E, Cartechini E, Giuliani G, et al. General practitioners facing dementia: are they fully prepared? *Neurol Sci.* (2004) 24:384–9. doi: 10.1007/s10072-003-0193-0
8. Aminzadeh F, Molnar FJ, Dalziel WB, Ayotte D, A. review of barriers and enablers to diagnosis and management of persons with dementia in primary care. *Can Geriatr J CGJ.* (2012) 15:85–94. doi: 10.5770/cgj.15.42
9. Wilkinson D, Sganga A, Stave C, O'Connell B. Implications of the facing dementia survey for health care professionals across Europe. *Int J Clin* Pract Suppl. (2005) (146):27–31. doi: 10.1111/j.1368-504X.2005.00484.x
10. Prince M, Wimo A, Guerchet M, Ali G, Wu Y, Prina M. *World Alzheimer Report 2015: The Global Impact of Dementia: An analysis of prevalence, incidence, cost and trends*. London: Alzheimer's Disease International (2015) p. 1–87.
11. Huang Y, Wang Y, Wang H, Liu Z, Yu X, Yan J, et al. Prevalence of mental disorders in China: a cross-sectional epidemiological study. *The Lancet Psychiatry.* (2019) 6:211–24. doi: 10.1016/S2215-0366(18)30511-X
12. Chen R, Hu Z, Chen RL, Ma Y, Zhang D, Wilson K. Determinants for undetected dementia and late-life depression. *Br J Psychiatry.* (2013) 203:203–8. doi: 10.1192/bjp.bp.112.119354
13. Chen Z, Yang X, Song Y, Song B, Zhang Y, Liu J, et al. Challenges of dementia care in China. *Geriatrics.* (2017) 2:7. doi: 10.3390/geriatrics2010007
14. Surr CA, Gates C, Irving D, Oyebode J, Smith SJ, Parveen S, et al. Effective dementia education and training for the health and social care workforce: a systematic review of the literature. *Rev Educ Res.* (2017) 87:966–1002. doi: 10.3102/0034654317723305
15. Perry M, Draskovic I, Lucassen P, Vernooij-Dassen M, van Achterberg T, Rikkert MO. Effects of educational interventions on primary dementia care: A systematic review. *Int J Geriatr Psychiatry.* (2011) 26:1–11. doi: 10.1002/gps.2479
16. Wang Y, Xiao LD, Ullah S, He GP, De Bellis A. Evaluation of a nurse-led dementia education and knowledge translation programme in primary care: A cluster randomized controlled trial. *Nurse Educ Today.* (2017) 49:1–7. doi: 10.1016/j.nedt.2016.10.016
17. Downs M, Turner S, Bryans M, Wilcock J, Keady J, Levin E, et al. Effectiveness of educational interventions in improving detection and management of dementia in primary care: cluster randomized controlled study. *BMJ (Clinical research ed).* (2006) 332:692–6. doi: 10.1136/bmj.332.7543.692

18. Rondeau V, Allain H, Bakchine S, Bonet P, Brudon F, Chauplannaz G, et al. General practice-based intervention for suspecting and detecting dementia in France: A cluster randomized controlled trial1. *Dementia*. (2008) 7:433–50. doi: 10.1177/1471301208096628
19. Xu L, Hsiao HY, Denq W, Chi I. Training needs for dementia care in China from the perspectives of mental health providers: who, what, and how. *Int Psychogeriatr*. (2017):1–12. doi: 10.1093/geroni/igx004.1720
20. Hu LL, Wang HL, Lv XZ, Ma WX Li WX, Yu X. Effects of the training of community doctors on the skills of early recognition of Alzheimer Disease. *Chinese Gen Pract*. (2015) 18:2697–700. doi: 10.3969/j
21. Kirkpatrick D. Great Ideas Revisited. Techniques for evaluating training programs revisiting kirkpatrick's four-level model. *Training and Development*. (1996) 50:54–9.
22. Shaji KS, Arun Kishore NR, Lal KP, Prince M. Revealing a hidden problem. An evaluation of a community dementia case-finding program from the Indian 10/66 dementia research network. *Int J Geriatr* ***Psychiatry***. (2002) 17:222–5. doi: 10.1002/gps.553
23. Ramos-Cerqueira AT, Torres AR, Crepaldi AL, Oliveira NI, Scazufca M, Menezes PR, et al. Identification of dementia cases in the community: a Brazilian experience. *J Am Geriatr Soc*. (2005) 53:1738–42. doi: 10.1111/j.1532-5415.2005.53553.x
24. Singer E. Subjective evaluations as indicators of change. *J Health Soc Behav*. (1978) 18:84–90. doi: 10.2307/2955400
25. Smith PJ. Workplace Learning and Flexible Delivery. *Rev Educ Res*. (2003) 73:53–88. doi: 10.3102/00346543073001053

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Neurology

ORIGINAL RESEARCH
published: 23 July 2021
doi: 10.3389/fneur.2021.643480

Dementia Prevalence, Comorbidities, and Lifestyle Among Jatinangor Elders

Paulus Anam Ong[1], Febby Rosa Annisafitrie[1], Novita Purnamasari[1], Chandra Calista[1], Noveline Sagita[2], Yulia Sofiatin[3] and Yustiani Dikot[4]*

[1] Department of Neurology, Hasan Sadikin Hospital, Universitas Padjadjaran, Bandung, Indonesia, [2] Department of Neurology, Immanuel Hospital, Maranatha Christian University, Bandung, Indonesia, [3] Department of Public Health, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia, [4] Department of Neurology, Faculty of Medicine, Achmad Yani University, Bandung, Indonesia

Introduction: Research on dementia prevalence and the potentially related risk factors from Indonesia is scarce. We sought to identify the prevalence of dementia, health risk factors, and lifestyle in Jatinangor elders.

Methods: A total of 686 participants completed questionnaires on lifestyle, health risk factors, and cognitive and functional tests from September 2013 to December 2013. We determined the prevalence of dementia; and the associations between health, leisure activities, dietary pattern, and dementia were analyzed using logistic regression.

Results: The prevalence of dementia was 29.15%. The risk factors differed between age groups. Those aged 60–74 years and who have a lower education level, lower occupational attainment, and less active intellectual and recreational activities were associated with higher dementia risk. Those aged > 75 years living in a rural area and who take less fruit were associated with a higher risk of dementia.

Conclusions: The prevalence of dementia in Jatinangor is high. The identified modifiable risk factors are a potential target for intervention and valuable for designing public health policies.

Keywords: dementia, LMIC, lifestyle, prevalence Jatinangor Indonesia, comorbidities

OPEN ACCESS

Edited by:
Kirsten Bobrow, University of California, San Francisco, United States

Reviewed by:
Chaur-Jong Hu, Taipei Medical University, Taiwan
Yao Yao, Peking University, China
Francisca S. Rodriguez, Helmholtz Association of German Research Centers (HZ), Germany

****Correspondence:***
Paulus Anam Ong
anam_ong@yahoo.com

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: *18 December 2020*
Accepted: *22 June 2021*
Published: *23 July 2021*

Citation:
Ong PA, Annisafitrie FR, Purnamasari N, Calista C, Sagita N, Sofiatin Y and Dikot Y (2021) Dementia Prevalence, Comorbidities, and Lifestyle Among Jatinangor Elders. Front. Neurol. 12:643480. doi: 10.3389/fneur.2021.643480

INTRODUCTION

An increase in people living with dementia (PWD) is one of the inevitable aging population consequences. Worldwide, there are ∼50 million PWD in 2015, and this number is projected to increase to 152 million by 2050, rising particularly in low-income and middle-income countries (LMICs), where approximately two-thirds of PWD live (1). Like other countries, Indonesia was estimated to have a rapid increase of PWD, from 1.2 million in 2015 to 1.9 million in 2030, and this figure will reach 3.9 million in 2050 (2). The large number of PWD will cause serious healthcare and socioeconomic impacts if not anticipated.

Currently, there are no disease-modifying agents for dementia. Therefore, implementing evidence-based preventive strategies can mitigate the socioeconomic impact of dementia. Evidence of decline in the prevalence of dementia in high-income countries (HICs) indicated that dementia might, at least partially, be preventable by reducing the prevalent risk factors (3, 4). Moreover, increasing evidence suggests that lifestyle activities that optimize the use of compensatory cognitive

strategies (5) and healthy dietary patterns might help preserve cognition in late life (6). A recent scientific paper was even more optimistic, targeting about 40% of dementia prevention by managing risk factors throughout the life span (7).

Finding from HICs may not be necessarily applicable directly in LMICs, the region with different sociodemographic and risk factors. Therefore, prevention programs that focus on local contexts and modifiable risk factors are needed to design effective interventions and appropriate public health policies. It is especially true for Indonesia, a middle-income country with large numbers of elders and limited healthcare resources, to apply nationwide established preventive measures. The present study sought to identify the modifiable risk factors for dementia, focusing on sociodemographic, health, and lifestyle risk factors, including leisure activities and dietary patterns.

METHODS

Setting and Study Design

We used a cross-sectional study design and collected information from elders aged ≥ 60 years and their caregivers between September 2013 and December 2013 to examine the prevalence and determinants of dementia. The data collection consisted of sociodemographic characteristics (age, gender, education, living area, and marital status), socioeconomic status (best occupation and monthly income), health factors [hypertension, cholesterol, diabetes, body mass index (BMI), and depression], lifestyle including leisure activities (cognitive, social, recreational, physical activities), and dietary pattern, as well as cognitive and functional status assessments. All data were obtained in one seat by 15 trained, third-year medical school students and five neurology residents for field neurological examination consultation. Blood samples were drawn on another day. All participants gave written consent. The Medical Ethics Committee of Universitas Padjadjaran Bandung, Indonesia, approved this study protocol.

Participants

This epidemiology study was done in the Sumedang Regency of West Java province, the most densely populated province in Indonesia. We selected Jatinangor from the total 22 districts as the representative of the Sumedang Regency, considering its accessibility from Universitas Padjadjaran. Jatinangor is located on the slope of Manglayang Mountain. Most of the villagers worked as farmers, employees in the plantation, or civil servants and had a total population of 113,913 people (8). Villages Cilayung and Cipacing were selected to represent the 12 villages, based on the village's status, such as self-made and self-sufficiency villages, respectively. A self-sufficiency village (suburban) has higher welfare, a higher proportion of professional vs. labor, and more self-employment workers than a self-made village (rural area). Cilayung village was selected from seven self-made villages, and Cipacing village was selected from a total of five self-sufficiency villages by stratified random sampling based on data from the sub-village registry.

We involved all families with an elder (age ≥ 60 years) listed in the cadres' registration from the two selected villages.

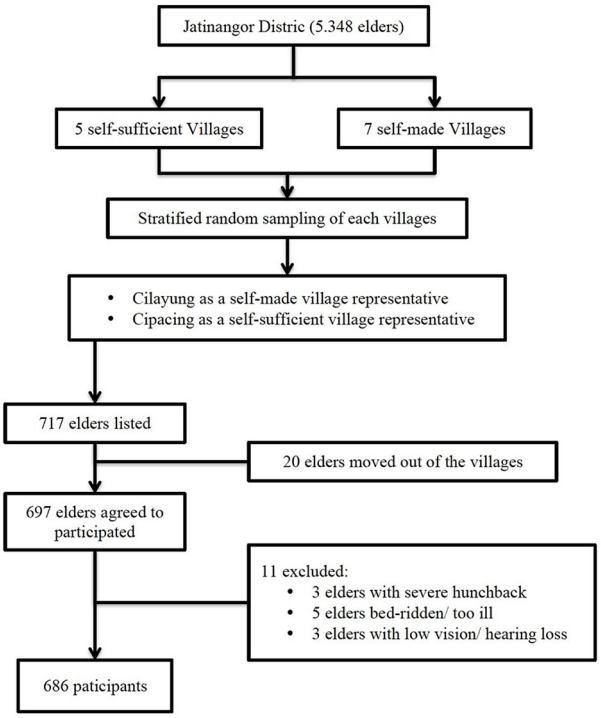


FIGURE 1 | Flowchart describing flow of the participant recruitment in the study.

Meetings with local cadres were held according to village meeting schedules. Meetings with elders and their caregivers, explaining our research aims, participation, consequences, and ethical issues, and their willingness to participate was listed in coordination with cadres. Written consent was obtained from the elders or caregivers on the day of the interview commencement. From the total of 717 elders listed, 20 elders moved out of the villages, and the remained 697 elders agreed to participate (97.2% participation rate). Eleven elders were excluded, including three persons with a severe hunchback, whose BMI could not be measured; five bedridden elders; and three other elders with severe low vision and hearing loss. In this research, we obtained 686 participants. The number of participants exceeded the minimum sampling requirement determined with Slovin's formula, $n = N/[1 + N\ (e)^2]$ (9, 10), where n is the sample size, N is the population size, and e is the margin error. In this study, $N = 5{,}348$ (population aged ≥ 60 years in Jatinangor), $e = 0.08$, and the minimum number of participants $n = 5{,}348/[1 + 5{,}348\ (0.05)^2] = 372$ participants. Refer to **Figure 1** for the detailed participant recruitment flowchart.

Measures

We applied the National Institute on Aging/Alzheimer's Association (NIA-AA) criteria for dementia of all-cause, which requires a severe cognitive decline complained by an individual or a reliable informant, confirmed with an objective cognitive test, which interferes with daily living activities in the

absence of delirium or other mental disorders (11). We used the Abbreviated Mental Test (AMT) (12), considering it was brief, used successfully in an extensive stroke cohort registry, and performed well in our local studies (13). A study done in Singapore reported no differences in diagnostic performance regarding the area under the curve between the Mini-Mental State Examination (MMSE) and AMT in diagnosing dementia among elders in Singapore. However, they found a trend of better diagnostic performance of AMT in patients with lower educational levels (0–6 years) and MMSE for those with higher levels of education (14). Therefore, considering most participants' low education level in our study population, we decided to use AMT for dementia cognitive screening with the cutoff score based on age category and education level as suggested by the previous study (14). For participants aged 60–74 years, we used a cutoff score of 7/8 for those with <6 years of education and a score of 8/9 for those with >6 years of education. For participants aged >75, we used a cutoff score of 5/6 for those with <6 years of education and a score of 8/9 for those with education >6 years (15). The AD8 was used to confirm the decline of cognitive function reported by an informant or caregiver, with a score ≥ 2 indicating cognitive impairment (14). We used the Katz Activities of Daily Living (16) and Lawton Instrumental Activities of Daily Living to assess functional declines (17).

Health Factors

Hypertension was defined as a blood pressure ≥ 140/90 mmHg measured at the upper arm. Depression was diagnosed using the Geriatric Depression Scale (GDS), with a cutoff score of ≥9 indicating depression (18). Diagnosis of diabetes mellitus was made if the fasting plasma glucose is 126 mg/dl or higher. Dyslipidemias was considered high risk if triglyceride ≥ 200 mg/dl and/or high-density lipoprotein (HDL) cholesterol level < 40 mg/dl. Triglyceride and HDL were used as indicators of dyslipidemia, as they are part of a metabolic syndrome and cardio-metabolic risk factors (19, 20). BMI characteristic was based on WHO classification.

Lifestyle Factors

We adapted the classification of late-life leisure activities validated among the elderly in Hong Kong (21) used in CLASSA, a study coordinated by the Asian Society Against Dementia (ASAD). Leisure activities were categorized into physical, intellectual, social, and recreational categories. The participation of each activity from a category was summed and considered as a category activity. Participants were considered less active in a category if the activity of the category was below the mean of the total sample category activity, and vice versa with active participants in a category.

We used the food frequency questionnaire to examine dietary patterns, which consisted of seven categories of frequency: never or less than once/month, sometimes one to three times/month, once/week, three to four times/week, once/day, twice/day, and three times/day. Accompanied by their caregivers, subjects were asked to report their intake frequency on standard dietary, categorized as protein (eggs, meat, fish, and beans), carbohydrate (rice, noodles, bread, tubers, and flour), fruits, and vegetables. We also assessed local customary food, such as tofu/tempeh, instant noodles, and salted fish. A food intake was categorized as "non-frequent" if the frequency is below the total sample's median frequency and vice versa with active participants in a category.

Data Analyses

We use descriptive statistics to compare the baseline characteristics of participants with and without dementia. Missing data were found in risk factor variables, 0–14% in sociodemographics, 0.3% in leisure activities, and 13–16% in the main dietary pattern. Being not accompanied by children (work in the city or abroad), participants living alone or cared for by neighbors contributed to some of the missing data. The mean substitution was used to handle missing values, and there was no significant statistic changing compared with analysis using original data on all substituted variables (22). Mean substitutions data can be seen in the **Supplementary Tables**. The leisure activity questionnaire was validated in several cities in Asia, including Bandung City in Indonesia; however, still there were no applicable activities such as visiting painting fairs, cinemas, music lounges, and libraries for the village setting. Though not much in quantity, they might also be sources of the difference in the number of recorded frequencies and examiners' errors.

Blood-based variables, such as plasma glucose and lipid profile, were obtained only in 57% due to refusal of participants/caregivers, including fear of blood taking, and chores like farming and selling in the morning. Binary logistic regression was applied to examine associations between potential risk factors and dementia. Univariable models were run for each potential risk factor separately, with adjustment for sex and education. The multivariable models included age, sex, education, and all risk factors in the univariable models. As data showed that the associations between lifestyle activities and dementia varied within age groups, the findings will be presented for the total sample and separately analyzed for the younger age group (60–74 years) and older age group (≥75 years). All the above data analyses were performed using the software IBM® SPSS 20.

RESULTS

Demographic Characteristics of Participants

Six hundred eighty-six participants (296 male and 390 female) participated in this study. Two hundred participants (29.15%) fulfilled the criteria of dementia, which were found in 22.11% of elders in the suburban area and 39.42% of elders in the rural area. Participants with dementia were significantly older, had lower education, and were more likely to be female and single ($p < 0.001$) than those with no dementia. They had a lower socioeconomic status, such as lower occupational attainment and monthly income ($p < 0.001$). Moreover, they had worse health parameters such as more likely to be an active smoker ($p < 0.023$), with lower cognition, higher depression rate, more likely to be underweight ($p < 0.001$), and higher stroke event, but with a lower frequency of HDL < 40 mg/dl. Regarding lifestyle, this group was less active in all categories of leisure activities ($p < 0.001$), and they took less fruit ($p < 0.001$) (**Table 1**).

TABLE 1 | Baseline characteristics of participants with and without dementia in Jatinangor cross-sectional study ($n = 686$).

	n	No dementia (*n* = 486)	Dementia (*n* = 200)	*p*-value
Age (M ± SD)	686	68.29 ± 6.57	72.99 ± 7.21	<0.001
Sex (*n*, %)	686			<0.001
Male		232 (47.7)	64 (32.0)	
Female		254 (52.3)	136 (68.0)	
Education (M ± SD)	661	6.070 ± 3.08	3.605 ± 3.36	<0.001
Living area (*n*, %)	686			<0.001
Suburban		317 (65.2)	90 (45.0)	
Rural area		169 (34.8)	110 (55.0)	
Income (*n*, %)	598			<0.001
≥Monthly minimum wage		125 (25.7)	29 (14.5)	
<Monthly minimum wage		99 (20.4)	30 (15.0)	
No income		205 (42.2)	110 (55.0)	
Marital status (*n*, %)	629			<0.001
Still married		327 (67.3)	93 (46.5)	
Single (never married/divorced)		120 (24.7)	89 (44.5)	
Occupational class (*n*, %)	590			<0.001
Professional		134 (27.6)	28 (14.0)	
Not working		94 (19.3)	66 (33.0)	<0.001
Laborer		67 (13.8)	24 (12.0)	
Housewife		128 (26.3)	49 (24.5)	
Hypertension (*n*, %)	665	265 (54.5)	124 (62.0)	0.14
Stroke (*n*, %)	686	8 (1.6)	9 (4.5)	0.05
Diabetes (*n*, %)	391	34 (7.0)	16 (8.0)	0.74
Triglyceride > 200 mg/dl (*n*, %)	391	27 (5.6)	8 (4.0)	0.44
HDL < 40 mg/dl (*n*, %)	391	53 (10.9)	12 (6.0)	0.04
BMI characteristics (*n*, %)	648			0.000
Normal		276 (56.8)	106 (53.0)	
Underweight		74 (15.2)	56 (28.0)	
Overweight		98 (20.2)	14 (7.0)	
Obese		20 (4.1)	4 (2.0)	
Smoking status (*n*, % active smoker)	506	169 (34.8)	52 (26.0)	0.02
Depression (*n*, %)	676	18 (3.7)	22 (11.0)	<0.001
Cognitive score AMT (M ± SD)	638	8.26 ± 1.34	4.53 ± 1.74	<0.001
Leisure activities (*n*, %)	684			
Intellectually less active		312 (64.2)	174 (87.0)	<0.001
Socially less active		228 (46.9)	131 (65.5)	<0.001
Recreationally less active		235 (48.4)	138 (69.0)	<0.001
Physically less active		411 (84.6)	188 (94.0)	<0.001
Less active (total leisure activity)				<0.001
Dietary Intake (*n*, % non-frequent)				
Carbohydrate intake	602	209 (43.0)	99 (49.5)	0.07
Protein intake	602	191 (39.3)	87 (43.5)	0.24
Vegetable intake	597	214 (44.0)	89 (44.5)	0.72
Fruit intake	579	302 (62.1)	143 (71.5)	0.001
Salted fish intake	523	109 (22.4)	42 (21.0)	0.75
Instant noodle intake	537	177 (36.4)	80 (40.0)	0.25
Tempe (fermented soybean) intake	530	177 (36.4)	65 (32.5)	0.50

Non-parametric variables were compared using the Mann–Whitney test. Categorical variables are described as numbers and percentages, and groups were compared using the chi-squared test and Cramer's V test.

M, mean; n, number of participants with available data; SD, standard deviation; HDL, high-density lipoprotein; BMI, body mass index; AMT, Abbreviated Mental Test.

In the total sample, univariable model showed statistical significance in risk factors of age, education level, living area, marital status, stroke, diabetes mellitus, underweight or overweight, depression, all categories of leisure activities, and non-frequent fruit intake (**Table 2**). In the multivariable model, the association remained significant in risk factors for age (>75 vs. 60–74 years: OR = 2.75, 95% CI = 1.70–4.4.6), marital status (single, never married/divorced vs. still married: OR = 1.72, 95% CI = 1.03–2.84), occupation (not working vs. professional: OR = 2.18, 95% CI = 1.04–4.61), BMI characteristic (overweight vs. normal: OR = 0.39: 95% CI = 0.18–0.82), intellectual activities (less active vs. active: OR = 2.85, 95% CI = 1.60–5.08), recreational activities (less active vs. active: OR = 2.19, 95% CI = 1.39–3.46), and fruit intake (non-frequent vs. frequent: OR = 2.02, 95% CI = 1.09–3.72) (**Table 3**).

In the younger age group (60–74 years), statistically significant univariable association with dementia was found for risk factors living area, marital status, occupation attainment, underweight/overweight, depression, all categories of leisure activities, and fruit intake (**Table 2**). In the multivariable model, the association with dementia remained significant in risk factors for occupational attainment (not working vs. professional: OR = 2.98, 95% CI = 1.21–7.31; labor vs. professional: OR = 3.65, 95% CI = 1.29–10.30), BMI (overweight vs. Normal: OR = 0.39, 95% CI = 0.17–0.90), intellectual activities (less active vs. active: OR = 2.67, 95% CI = 1.42–4.99), recreational activities (less active vs. active: OR = 2.12, 95 CI = 1.267–3.57), and total categories of leisure activities (less active vs. active: OR = 2.21, 95% CI = 1.42–3.44) (**Table 3**).

In the older age group (>75 years), a univariable association with dementia was found in risk factors sex, living area, and intellectual, recreational, and total categories of leisure activities (**Table 2**). In the multivariable model, association with dementia was found in living area (suburban vs. rural: OR = 2.52, 95% CI = 1.04–6.16) and fruit intake (non-frequent vs. frequent: OR = 4.62, 95% CI = 1.18–18.02) (**Table 3**).

DISCUSSION

Prevalence of Dementia

The prevalence of dementia among Asian countries in 2012 varied from 0.03 to 33.2% (23). A study from Singapore showed

TABLE 2 | Univariable associations between potential risk factors and dementia in the total sample ($n = 686$) and stratified by age.

	Total sample		60–74 years		≥75 years	
	OR	**95% CI***	**OR**	**95% CI***	**OR**	**95% CI***
Age						
60–74 years	1					
≥75 years	3.76	2.54–5.57				
Sex						
Male	1		1		1	
Female	1.52	0.93–2.50	1.34	0.86–2.08	5.04	2.48–10.25
Education						
≥7 years of education	1		1		1	
0–6 years of education	1.80	1.11–2.92	1.11	0.64–1.91	2.28	0.54–9.64
Living area						
Suburban	1		1		1	
Rural	2.26	1.58–3.24	2.22	1.42–3.46	2.10	1.00–4.37
Income						
≥Minimum wage	1		1		1	
<Minimum wage	1.24	0.65–2.36	2.13	1.07–4.23	1.39	0.39–4.93
No income	1.69	0.97–2.94	2.13	1.07–4.23	1.40	0.50–3.92
Marital status						
Still married	1		1		1	
Single (never married/divorced)	2.31	1.54–3.45	1.75	1.06–2.90	1.72	0.69–4.27
Occupational class						
Professional	1		1		1	
Not working	2.43	1.33–4.45	2.87	1.33–6.21	1.01	0.28–3.66
Laborer	1.97	0.97–4.02	2.91	1.20–7.06	0.63	0.15–2.60
Housewife	1.57	0.68–3.64	2.15	0.69–6.67	1.41	0.20–9.86
Hypertension	1.26	0.88–1.79	1.08	0.71–1.67	1.38	0.66–2.91
Stroke	3.77	1.20–11.84	3.07	0.80–11.74	8.18	0.71–93.37
Diabetes	0.95	2.71–7.86	1.16	0.50–2.80	0.54	0.14–2.01
Triglyceride > 200 mg/dl (*n*, %)	0.81	0.33–2.02	0.67	0.25–1.86	1.93	0.10–35.88
HDL < 40 mg/dl (*n*, %)	0.60	0.29–1.23	0.78	0.36–1.70	0.44	0.07–2.78
BMI characteristics						
Normal	1		1		1	
Underweight	1.87	1.21–2.86	2.07	1.21–3.55	1.36	0.59–3.14
Overweight	0.33	0.17–0.63	0.46	0.23–0.93	0.20	0.03–1.11
Obese	0.46	0.15–1.40	0.54	0.15–1.94	1.04	0.05–20.38
Smoking status	1.30	0.66–2.54	1.01	0.46–2.20	5.17	0.62–43.86
Depression	2.53	1.25–5.11	3.75	1.63–8.66	1.09	0.33–3.61
Leisure activities						
Intellectually less active	3.50	2.61–5.68	2.96	1.70–5.16	3.09	1.01–9.46
Socially less active	2.04	1.43–2.91	1.79	1.16–2.77	1.52	0.71–3.28
Recreationally less active	2.99	2.06–4.34	2.43	1.56–3.79	2.38	1.05–5.41
Physically less active	3.26	1.63–6.49	2.40	1.11–5.18	3.70	0.70–19.57
Less active (total leisure activity)	3.16	2.19–4.58	2.67	1.71–4.16	2.75	1.26–6.01
Dietary intake						
Non-frequent Carbohydrate intake	1.32	0.92–1.90	1.55	0.98–2.45	0.81	0.38–1.71
Non-frequent protein intake	1.16	0.81–1.67	1.24	0.79–1.94	0.69	0.32–1.44
Non-frequent fruit intake	2.17	1.31–3.59	2.02	1.09–3.74	2.55	0.91–7.21
Non-frequent vegetable intake	1.02	0.70–1.47	0.99	0.62–1.57	1.03	0.50–2.16

OR, odds ratio; 95% CI, 95% confidence interval; HDL, high-density lipoprotein; BMI, body mass index.
**Associations were adjusted for sex and education.*

TABLE 3 | Multivariable models for the total sample ($n = 686$) and stratified by age.

	Total sample		60–74 years		≥75 years	
	OR	**95% CI***	**OR**	**95% CI***	**OR**	**95% CI***
Age						
60–74 years	1					
≥75 years	2.75	1.70–4.46				
Sex						
Male	1		1		1	
Female	1.45	0.84–2.51	1.14	0.61–2.14	2.33	0.73–7.42
Education						
≥7 years of education	1		1		1	
0–6 years of education	0.52	0.27–1.00	0.45	0.22–0.91	1.81	0.26–12.72
Living area						
Suburban	1		1		1	
Rural	1.89	1.20–2.97	1.65	0.97–2.83	2.52	1.032–6.16
Income						
≥Minimum wage	1		1		1	
<Minimum wage	0.96	0.46–2.01	0.93	0.38–2.28	0.98	0.22–4.36
No income	1.36	0.54–3.39	1.38	0.44–4.27	1.28	0.21–7.69
Marital status						
Still married	1		1		1	
Single (never married/divorced)	1.71	1.03–2.84	1.53	0.85–2.276	2.80	0.89–8.877
Occupational class						
Professional	1		1		1	
Not working	2.18	1.03–4.60	2.98	1.21–7.31	1.02	0.22–4.65
Laborer	2.19	0.94–5.10	3.65	1.29–10.30	0.23	0.03–1.93
Housewife	1.89	0.64–5.56	2.43	0.68–8.71	0.87	0.06–12.43
Hypertension	1.12	0.73–1.73	1.10	0.66–1.81	1.29	0.52–3.20
Stroke	3.34	0.63–17.65	1.88	0.29–12.15		
Diabetes	1.24	0.53–2.86	1.61	0.58–4.49	0.67	0.15–3.05
Triglyceride > 200 mg/dl	1.37	0.48–3.93	1.09	0.36–3.29		
HDL < 40 mg/dl	0.50	0.21–1.18	0.64	0.26–1.60	0.30	0.02–4.15
BMI characteristics						
Normal	1		1		1	
Underweight	1.30	0.78–2.19	1.49	0.80–2.80	1.25	0.48–3.26
Overweight	0.39	0.18–0.82	0.40	0.17–0.91	0.38	0.06–2.43
Obese	0.87	0.26–2.93	0.80	0.21–3.09	0.49	0.02–11.44
Smoking status	1.39	0.60–3.19	1.14	0.45–2.88	2.04	0.20–20.16
Depression	1.52	0.64–3.57	2.54	0.90–7.15	0.69	0.16–2.90
Leisure activities						
Intellectually less active	2.85	1.60–5.08	2.66	1.42–4.10	3.73	0.81–17.03
Socially less active	1.38	0.89–2.13	1.53	0.92–2.53	1.06	0.41–2.74
Recreationally less active	2.19	1.39–3.46	2.11	1.26–3.56	2.44	0.87–6.79
Physically less active	2.05	0.99–4.25	1.87	0.83–4.20	2.57	0.45–14.65
Less active (total leisure activity)	2.21	1.42–3.44	2.20	1.32–3.66	2.21	0.84–5.80
Dietary intake						
Non-frequent carbohydrate intake	1.13	0.74–1.74	1.30	0.78–2.15	1.03	0.43–2.45
Non-frequent protein intake	0.80	0.52–1.25	0.94	0.56–1.57	0.56	0.23–1.39
Non-frequent fruit intake	2.02	1.10–3.72	1.74	0.88–3.47	4.62	1.18–18.02
Non-frequent vegetable intake	0.96	0.62–1.50	0.62	0.57–1.62	1.03	0.43–2.45

*Multivariable models include age, sex, and education, plus all risk factors with ORs < 0.75 or >1.40 in the univariable models (**Table 2**).*
OR, odds ratio; 95% CI, 95% confidence interval; HDL, high-density lipoprotein; BMI, body mass index.

that the prevalence was significantly higher among Indians (1.9%) compared with Malays (1.6%) and Chinese (1.2%) (24). A recent meta-analysis on the prevalence of dementia in six developing countries (Brazil, India, Jamaica, Kenya, Mexico, and South Africa) showed that the prevalence was 2–9% (25). A higher prevalence of dementia was reported recently from our province of Yogyakarta, 20.1%, varying from 13.9% in the city to 16.8–29.4% in other regencies (26). In the present study, the prevalence of dementia was 29.15, 22.11% of elders in the suburban area, and 39.42% of elders in the rural area. This result was consistent with the abovementioned report from Yogyakarta (26). Differences in dementia diagnosis methods and demographic, socioeconomic, and risk factors may cause variation in the prevalence of dementia. Both studies from our country used local validated cognitive tests (MMSE and AMT), with AD8 as informant report of cognitive decline, and utilized ADL/IADL score for detecting functional decline.

Moreover, many participants living in rural areas with low economic status might contribute to the higher prevalence in our country than in other countries mentioned above. The present study showed that, compared with those residing in suburban, participants living in rural areas were significantly older and had lower education levels and lower occupational attainment (more likely to be not working and less likely to be professionals). These participants were less active in leisure activities, including physical training, social involvement, recreation and relaxation, and cognitive stimulation than were their counterpart elders in suburban. Association between work, social engagement, and mental stimulation has been reported in a previous study (27). Furthermore, the participants took fewer fruits, which are rich in antioxidants and good for cognition (6). These findings further enrich our insight that aside from education level and occupation attainment, as reported in a previous study (28), less engagement in leisure activities and poor dietary patterns may also associate with a higher risk of dementia.

Risk Factors Associated With Dementia

In the present study, the risk factors associated with dementia included demographic, socioeconomic, and health factors and lifestyle, including leisure activities and dietary patterns. We found differences in the numbers and types of risk factors associated with dementia between the younger age group (60–74 years) and the older age group (>75 years). The younger group had more risk factors, including demographic, socioeconomic (occupation attainment), and health factors (BMI) and lifestyle, such as intellectual and recreational activities. Meanwhile, living in rural areas and lifestyles such as less fruit intake were the only risk factors in the older group.

Age-Dependent Risk Factors for Cognitive Decline/Dementia

Most cardiovascular factors will lose their impact on cognitive decline at an older age than at a younger age, as reported in previous studies (29, 30). Midlife hypertension is a known risk factor for developing dementia and Alzheimer's disease in late life until 74 years (31, 32). However, it is protective against dementia at ages over 85 years (33, 34). It is noteworthy that low blood pressure can be a consequence of neurodegenerative disease; therefore, low blood pressure may be an early sign of dementia onset (34, 35). High cholesterol in late life can indicate a better nutritional status and better overall health, and therefore, it was associated with less cognitive decline (36, 37). Several possible mechanisms may explain the abovementioned phenomena (38). Risk factors may occur across the life span, and they take time to affect health in general and the brain in particular. Midlife may be the most critical period for the accumulation of these risk factors. Other chronic conditions, such as lifestyle, may occur during old age and cause "weakening" of the measured associations between vascular risk factors and dementia (39).

Moreover, individuals in old age often have dementia with mixed pathology, which is challenging to identify since certain risk factors may be relevant to specific pathology (40). Mortality bias should also be put into consideration. Old age dementia individuals with vascular risk factors may have a higher mortality rate than those younger, either with or without dementia. A recent report from a large cohort study from Europe has demonstrated the independent association of poor cognitive performance and higher mortality. The mortality was significantly higher in those with old age and comorbidities, such as heart attack, stroke, and diabetes, and lower socioeconomic class (41). Therefore, fewer risk factors will be found in old age compared with younger age groups.

Lifestyle Factors

Leisure Activities

Leisure activity can be defined as the voluntary use of free time for activities outside the daily routine. The protective effect of mental activity on cognitive decline has been consistently reported in observational and interventional studies (21). In the present study, we found a significant association between all categories of leisure activities in the younger age group; meanwhile, only cognitive and recreational activities in the older age group were associated with dementia risk after controlling sex and education. However, as we controlled all health factors, only the cognitive and recreational activities remained related to the risk of dementia in the younger age group, but not in the older age group. Engagement in cognitive activities (such as book reading, playing board games, writing, and playing a musical instrument) and recreational activities (such as listening to music and radio, and shopping) seemed to protect the brain from dementia in this study population. A previous longitudinal study demonstrated that all three activities engaged, namely, cognitive, physical, and social, contribute equally to decreasing dementia risk (42). The exact protective mechanism of leisure activities is unknown. Hypothetically, leisure activities improve cognitive reserve, allowing more efficient, adaptive, and plastic neuronal processing to better cope with progressing dementia pathology (43). Physical movement and social activities can also promote cerebral blood flow and psychological well-being effects and reduce the inflammation process in the brain (44, 45).

Dietary Pattern

In a recently published meta-analysis study, the risk of cognitive impairment and dementia was reduced by 20% for a higher

consumption of fruit and vegetables (6). In that study, fruit consumption or in combination with vegetable, but not vegetable consumption, was associated with the protection of cognitive impairment. This protective effect was significant only in participants age over 65 years and not in those younger (6). This age-specific effect of fruit take was similar to our findings, which showed that less fruit take was associated with a higher risk of dementia in older age group (≥75 years), but not in the younger age group (60–74 years). Both fruits and vegetables are rich in antioxidants such as carotenoids, α- and γ-tocopherol, and folate, which can protect the brain from free radical scavengers, hyper-homocysteinemia, and cognitive impairment (46).

None of the participants consumed alcohol in the present study, so we could not evaluate the effect of alcohol drinking on cognitive impairment. We did not find any association between dementia and the consumption of our traditional food tofu and tempeh, often consumed with salted fish or instant noodles, as well as the rarely consumed fish, in both age groups, as was reported by previous studies (47–50).

Health Factors

In the present study, stroke was more prevalent in the dementia group than those without dementia ($p < 0.05$). Stroke tripled the risk of dementia (OR = 3.77, 95% CI = 1.2–11.86) in the univariable model after controlling for sex and education. Similar association studies also reported from other LMICs (51) and HICs (52). A recent study showed the age-specific effect of stroke on dementia, particularly in the younger age group (38). Stroke is the leading health problem in Indonesia since it occupied the first rank of cause of death in our national basic health research (RISKESDAS) in 2013 and 2018, which is 7 and 10.9%, respectively (53, 54). The small cases of stroke detected in the present study could be due to the under-recognition by participants and caregivers. The subtle motor symptoms of cerebral small vessel disease, such as lacunar infarction, were challenging to detect (55). Current evidence on post-stroke dementia showed that aside from stroke severity, the cognitive impairment after stroke also depends on the interaction between the inflammatory process after stroke and the existence of neurodegenerative pathologies, especially beta-amyloid (52, 56).

BMI analysis in the univariable model showed that, in the younger age group, underweight was associated with an increased risk of dementia (OR = 2.07, 95% CI = 1.21–3.56), and overweight was associated with lower risk dementia (OR = 0.46, 95% CI = 0.23–0.94). This finding should be interpreted carefully since it may be confounded by a long period (two to three decades) of preclinical dementia bodyweight loss. Therefore, the association between BMI and dementia is likely attributable to two different processes, a harmful effect of higher BMI, observable in the extended follow-up study, and a reverse-causation impact, which makes a higher BMI appear protective when the follow-up period is short (57).

In the present study, we did not find any significant relationship between hypertension, diabetes, and dyslipidemias with dementia. It did not mean that these risk factors did not play a role in the decline of cognitive function. As discussed before, the risk factors occur across the life span (most critically, midlife), accumulating the impact on the brain. Chronic conditions, such as leisure activities, stroke, BMI, and nutrition, might have overlapped (in the same group) and cumulatively "weakened" the measured associations between these vascular risk factors and dementia (39). Also, the non-linear association is challenging to be investigated in our cross-sectional study design. Moreover, the present study is underpowered with a limited sample size to examine these associations, even after doing age group analysis. A recent systematic review demonstrated that higher blood pressure was associated with a higher risk of cognitive decline in people without dementia and stroke (58).

Furthermore, the increase of 24-h ambulatory blood pressure variability was associated with lower cognitive function in elderly hypertension with well-controlled blood pressure (59). Higher daytime systolic blood pressure was associated with a 3.73 risk of dementia and a 10.54 risk of MRI finding of subcortical vascular dementia (60). All these data highlight the need for the early management of these risk factors, particularly the blood pressure, even in the absence of clinical hypertension to prevent the risk of cognitive decline typically associated with aging.

Implication of the Study

The present study has demonstrated that both lifestyle and risk factors were associated with the risk of dementia in the district of Jatinangor, Sumedang Regency, in Indonesia. Findings that less engagement in leisure activities and poor dietary patterns are associated with a higher risk of dementia may open up new intervention opportunities for the elders and encourage primary prevention of dementia that started from a younger age. The fact that stroke associates reciprocally with dementia shed the hope that intervention of risk factors after stroke (secondary stroke prevention) and management of risk factors since a younger age (primary stroke prevention) may also reduce the prevalence of dementia in the future. The significance of multiple risk factors in our multivariate model suggests the additive effects on dementia risk. They imply the importance of multidomain intervention targeting all risk factors, alongside the improvement of socioeconomic status, as an integrated action in public policy on dementia prevention programs. We recommend large-scale research to obtain nationwide dementia prevalence and associated risk factors to design an effective and efficient national dementia prevention strategy in the future.

Strengths and Limitation of This Study

Several limitations are worthy to be mentioned in the present study. The nature of a cross-sectional study design would not allow us to determine the causalities between variables firmly. Our finding may be underpowered, reflected in the wide confidence interval and the insignificancy of statistical analyses, especially in variables based on blood tests. Participants of the present study were recruited from suburban and rural areas; therefore, the current findings may be more relevant for the lower socioeconomic status population. Food registry and leisure activities were based on the recall of memory. A self-report by participants with cognitive decline may confound the associations. However, most of the caregivers were present and confirmed answers given by participants. This study's added value included multiple potential risk factors, including socioeconomic, health, and lifestyle factors with broad spectrums

of leisure activities and dietary patterns, which might not be explored together before. At the same time, we may have missed other nutritional components, nutrients, and cognitive intervention.

CONCLUSION

The prevalence of dementia in the present study is high. The risk factors associated with dementia are age-dependent. The younger group (60–74 years) has more risk factors, including lower education, lower occupational attainment, and less intellectual and recreational activities. The risk factors for the older age group (>75 years) are living in a rural area and less fruit intake. Identifying these modifiable lifestyle risk factors is crucial for designing effective interventions and determining public health policies for future dementia prevention in Indonesia.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The Medical Ethics Committee of Universitas Padjadjaran Bandung, Indonesia approved this study design and protocol. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

PO, CC, NS, YS, and YD were responsible for the study design. FA and NP were responsible for the data analyses. PO was responsible for drafting the manuscript. All authors contributed to interpreting the findings, provided critical feedback on drafts of the manuscript, and approved the final manuscript.

FUNDING

This study was partially supported by The Working Group of Neurobehavior, Indonesia Neurological Association, Bandung Branch, and PT, Dexa Medica Indonesia.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.643480/full#supplementary-material

REFERENCES

1. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement.* (2013) 9:63–75.e2. doi: 10.1016/j.jalz.2012.11.007
2. Prince MJ. *World Alzheimer Report 2015: The Global Impact of Dementia: An Analysis of Prevalence, Incidence, Cost and Trends.* London: Alzheimer's Disease International (ADI) (2015).
3. Matthews FE, Arthur A, Barnes LE, Bond J, Jagger C, Robinson L, et al. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the cognitive function and ageing study I and II. *Lancet.* (2013) 382:1405–12. doi: 10.1016/S0140-6736(13)61570-6
4. Langa KM, Larson EB, Crimmins EM, Faul JD, Levine DA, Kabeto MU, et al. A comparison of the prevalence of dementia in the United States in 2000 and 2012. *JAMA Intern Med.* (2017) 177:51–8. doi: 10.1001/jamainternmed.2016.6807
5. Hall C, Lipton R, Sliwinski M, Katz M, Derby C, Verghese J. Cognitive activities delay onset of memory decline in persons who develop dementia. *Neurology.* (2009) 73:356–61. doi: 10.1212/WNL.0b013e3181b04ae3
6. Jiang X, Huang J, Song D, Deng R, Wei J, Zhang Z. Increased consumption of fruit and vegetables is related to a reduced risk of cognitive impairment and dementia: meta-analysis. *Front Aging Neurosci.* (2017) 9:18. doi: 10.3389/fnagi.2017.00018
7. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet.* (2020) 396:413–46. doi: 10.1016/S0140-6736(20)30367-6
8. Sumedang BPSK. *Kecamatan Jatinangor Dalam Angka 2018.* (2018). Available online at: https://sumedangkab.bps.go.id/publication/2013/09/26/132cee05fc38cd51cbb0cead/kecamatan-jatinangor-dalam-angka-2013.html (accessed May 23, 2021).
9. Almeda JV, Capistrano TG, Sarte GMF. *Elementary Statistics.* Quezon City: University of the Philippines Press (2010).
10. Arjuna T, Soenen S, Hasnawati RA, Lange K, Chapman I, Luscombe-Marsh ND. A cross-sectional study of nutrient intake and health status among older adults in Yogyakarta Indonesia. *Nutrients.* (2017) 9:1240. doi: 10.3390/nu9111240
11. McKhann GM, Knopmanc DS, Chertkow H, Hymanf BT, Jack Jr. CR, Kawash CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* (2011) 7:263–9. doi: 10.1016/j.jalz.2011.03.005
12. Hodkinson HM. Evaluation of a mental test score for assessment of mental impairment in the ederly. *Age Ageing.* (1972) 1:233–8. doi: 10.1093/ageing/1.4.233
13. Putra DKA, Putrawan IB, Purnami NKR. Hubungan status Gizi Dengan Status Kognisi Pada Lansia di Panti Sosial Tresna Werdha Wana Seraya Denpasar. *Jurnal Medika Udayana.* (2020) 9:15–8. doi: 10.36085/avicenna.v15i2.948
14. Galvin JE, Roe CM, Powlishta KK, Coats MA, Muich SJ, Grant E, et al. The AD8: a brief informant interview to detect dementia. *Neurology.* (2005) 65:559–64. doi: 10.1212/01.wnl.0000172958.95282.2a
15. Sahadevan S, Lim PiPJ, Tan NJL, Chan SP. Diagnostic performance of two mental status tests in the older Chinese: influence of education and age on cut-off values. *Int J Geriatr Psychiatry.* (2000) 15:234–41. doi: 10.1002/(SICI)1099-1166(200003)15:3<234::AID-GPS99>3.0.CO;2-G
16. Katz Activities of Daily Living (ADL) Index. In: Michalos AC, editor. *Encyclopedia of Quality of Life and Well-Being Research.* Dordrecht: Springer Netherlands (2014). p. 3465.
17. Graf C. The Lawton instrumental activities of daily living (IADL) scale. *Medsurg Nurs.* (2009) 18:315–6.
18. Sheikh JI, Yesavage JA. Geriatric depression scale (GDS): recent evidence and development of a shorter version. *Clin Gerontol.* (1986) 5:165–73. doi: 10.1300/J018v05n01_09

19. Moro E, Gallina P, Pais M, Cazzolato G, Alessandrini P, Bittolo-Bon G. Hypertriglyceridemia is associated with increased insulin resistance in subjects with normal glucose tolerance: evaluation in a large cohort of subjects assessed with the 1999 World Health Organization criteria for the classification of diabetes. *Metabolism.* (2003) 52:616–9. doi: 10.1053/meta.2003.50102
20. Alberti KGM, Zimmet P, Shaw J. The metabolic syndrome - a new worldwide definition. *Lancet.* (2005) 366:1059–62. doi: 10.1016/S0140-6736(05)67402-8
21. Wang H-X, Xu W, Pei J-J. Leisure activities, cognition and dementia. *Biochim Biophys Acta.* (2012) 1822:482–91. doi: 10.1016/j.bbadis.2011.09.002
22. Kang H. The prevention and handling of the missing data. *Korean J Anesthesiol.* (2013) 64:402–6. doi: 10.4097/kjae.2013.64.5.402
23. Catindig J-AS, Venketasubramanian N, Ikram MK, Chen C. Epidemiology of dementia in Asia: insights on prevalence, trends and novel risk factors. *J Neurol Sci.* (2012) 321:11–6. doi: 10.1016/j.jns.2012.07.023
24. Sahadevan S, Saw SM, Gao W, Tan LC, Chin JJ, Hong Cy, et al. Ethnic differences in Singapore's dementia prevalence: the stroke, Parkinson's disease, epilepsy, and dementia in Singapore study. *J Am Geriatr Soc.* (2008) 56:2061–8. doi: 10.1111/j.1532-5415.2008.01992.x
25. Farina N, Ibnidris A, Alladi S, Comas-Herrera A, Albanese E, Docrat S, et al. A systematic review and meta-analysis of dementia prevalence in seven developing countries: a STRiDE project. *Global Public Health.* (2020) 15:1878–93. doi: 10.1080/17441692.2020.1792527
26. Suriastini NW, Turana Y, Supraptilah B, Wicaksono TY, Mulyanto ED. Prevalence and Risk Factors of Dementia and Caregiver's Knowledge of the Early Symptoms of Alzheimer's Disease. *Aging Med Healthcare.* (2020) 11:60–6. doi: 10.33879/AMH.2020.065-1811.032
27. Marioni RE, Proust-Lima C, Amieva H, Brayne C, Matthews FE, Dartigues J-F, et al. Social activity, cognitive decline and dementia risk: a 20-year prospective cohort study. *BMC Public Health.* (2015) 15:1–8. doi: 10.1186/s12889-015-2426-6
28. Karp A, Kåreholt I, Qiu C, Bellander T, Winblad B, Fratiglioni L. Relation of education and occupation-based socioeconomic status to incident Alzheimer's disease. *Am J Epidemiol.* (2004) 159:175–83. doi: 10.1093/aje/kwh018
29. Legdeur N, Heymans MW, Comijs HC, Huisman M, Maier AB, Visser PJ. Age dependency of risk factors for cognitive decline. *BMC Geriatr.* (2018) 18:187. doi: 10.1186/s12877-018-0876-2
30. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol.* (2005) 4:487–99. doi: 10.1016/S1474-4422(05)70141-1
31. Duron E, Hanon O. Hypertension, cognitive decline and dementia. *Arch Cardiovasc Dis.* (2008) 101:181–9. doi: 10.1016/S1875-2136(08)71801-1
32. Kivipelto M, Helkala E-L, Hänninen T, Laakso MP, Hallikainen M, Alhainen K, et al. Midlife vascular risk factors and late-life mild cognitive impairment: a population-based study. *Neurology.* (2001) 56:1683–9. doi: 10.1212/WNL.56.12.1683
33. Li G, Rhew IC, Shofer JB, Kukull WA, Breitner JC, Peskind E, et al. Age-varying association between blood pressure and risk of dementia in those aged 65 and older: a community-based prospective cohort study. *J Am Geriatr Soc.* (2007) 55:1161–7. doi: 10.1111/j.1532-5415.2007.01233.x
34. Ruitenberg A, Skoog I, Ott A, Aevarsson O, Witteman JC, Lernfelt B, et al. Blood pressure and risk of dementia: results from the Rotterdam study and the Gothenburg H-70 Study. *Dement Geriatr Cogn Disord.* (2001) 12:33–9. doi: 10.1159/000051233
35. Skoog I, Nilsson L, Persson G, Lernfelt B, Landahl S, Palmertz B, et al. 15-year longitudinal study of blood pressure and dementia. *Lancet*. (1996) 347:1141–5. doi: 10.1016/S0140-6736(96)90608-X
36. Mielke MM, Zandi P, Sjögren M, Gustafson D, Östling S, Steen B, et al. High total cholesterol levels in late life associated with a reduced risk of dementia. *Neurology.* (2005) 64:1689–95. doi: 10.1212/01.WNL.0000161870.78572.A5
37. Weverling-Rijnsburger AW, Blauw GJ, Lagaay AM, Knock DL, Meinders AE, Westendorp RG. Total cholesterol and risk of mortality in the oldest old. *Lancet.* (1997) 350:1119–23. doi: 10.1016/S0140-6736(97)04430-9
38. Peeters G, Almirall Sanchez A, Llibre Guerra J, Lawlor B, Kenny RA, Yaffe K, et al. Risk factors for incident dementia among older Cubans. *Front Public Health.* (2020) 8:481. doi: 10.3389/fpubh.2020.00481
39. Bullain SS, Corrada MM. Dementia in the oldest old. *Continuum.* (2013) 19:457. doi: 10.1212/01.CON.0000429172.27815.3f
40. Nelson PT, Head E, Schmitt FA, Davis PR, Neltner JH, Jicha GA, et al. Alzheimer's disease is not "brain aging": neuropathological, genetic, and epidemiological human studies. *Acta Neuropathol.* (2011) 121:571–87. doi: 10.1007/s00401-011-0826-y
41. Hayat SA, Luben R, Dalzell N, Moore S, Hogervorst E, Matthews FE, et al. Understanding the relationship between cognition and death: a within cohort examination of cognitive measures and mortality. *Eur J Epidemiol.* (2018) 33:1049–62. doi: 10.1007/s10654-018-0439-z
42. Karp A, Paillard-Borg S, Wang H-X, Silverstein M, Winblad B, Fratiglioni L. Mental, physical and social components in leisure activities equally contribute to decrease dementia risk. *Dement Geriatr Cogn Disord.* (2006) 21:65–73. doi: 10.1159/000089919
43. Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. *J Int Neuropsychol Soc.* (2002) 8:448–60. doi: 10.1017/S1355617702813248
44. Scarmeas N, Zarahn E, Anderson KE, Habeck CG, Hilton J, Flynn J, et al. Association of life activities with cerebral blood flow in Alzheimer disease: implications for the cognitive reserve hypothesis. *Arch Neurol.* (2003) 60:359–65. doi: 10.1001/archneur.60.3.359
45. Seeman TE. Social ties and health: the benefits of social integration. *Ann Epidemiol.* (1996) 6:442–51. doi: 10.1016/S1047-2797(96)00095-6
46. Ebly EM, Schaefer JP, Campbell NR, Hogan DB. Folate status, vascular disease and cognition in elderly Canadians. *Age Ageing.* (1998) 27:485–91. doi: 10.1093/ageing/27.4.485
47. Xu X, Xiao S, Rahardjo TB, Hogervorst E. Tofu intake is associated with poor cognitive performance among community-dwelling elderly in China. *J Alzheimers Dis.* (2015) 43:669–75. doi: 10.3233/JAD-141593
48. Hogervorst E, Sadjimim T, Yesufu A, Kreager P, Rahardjo T. High tofu intake is associated with worse memory in elderly Indonesian men and women. *Dement Geriatr Cogn Disord.* (2008) 26:50–7. doi: 10.1159/000141484
49. Ginting E, Arcot J. High-performance liquid chromatographic determination of naturally occurring folates during tempe preparation. *J Agric Food Chem.* (2004) 52:7752–8. doi: 10.1021/jf040198x
50. Bakre AT, Chen R, Khutan R, Wei L, Smith T, Qin G, et al. Association between fish consumption and risk of dementia: a new study from China and a systematic literature review and meta-analysis. *Public Health Nutr.* (2018) 21:1921–32. doi: 10.1017/S136898001800037X
51. Ojagbemi A, Owolabi M, Bello T, Baiyewu O. Stroke severity predicts poststroke delirium and its association with dementia: longitudinal observation from a low income setting. *J Neurol Sci.* (2017) 375:376–81. doi: 10.1016/j.jns.2017.02.039
52. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. *Lancet Neurol.* (2009) 8:1006–18. doi: 10.1016/S1474-4422(09)70236-4
53. Kemenkes RI. *Riset kesehatan dasar (Riskesdas) 2013*. Jakarta: Kemenkes RI. (2013). p. 259.
54. *Kementerian Kesehatan Republik Indonesia. Hasil Utama Riskesdas 2018*. Jakarta: Kementerian Kesehatan Bagian Penelitian dan Pengembangan Kesehatan (2018).
55. Harris S, Kurniawan M, Rasyid A, Mesiano T, Hidayat R. Cerebral small vessel disease in Indonesia: lacunar infarction study from Indonesian Stroke Registry 2012–2014. *SAGE Open Med.* (2018) 6:2050312118784312. doi: 10.1177/2050312118784312
56. Thiel A, Cechetto DF, Heiss W-D, Hachinski V, Whitehead SN. Amyloid burden, neuroinflammation, and links to cognitive decline after ischemic stroke. *Stroke.* (2014) 45:2825–9. doi: 10.1161/STROKEAHA.114.004285
57. Kivimäki M, Luukkonen R, Batty GD, Ferrie JE, Pentti J, Nyberg ST, et al. Body mass index and risk of dementia: analysis of individual-level data from 1.3 million individuals. *Alzheimers Dement.* (2018) 14:601–9. doi: 10.1016/j.jalz.2017.09.016
58. Forte G, De Pascalis V, Favieri F, Casagrande M. Effects of blood pressure on cognitive performance: a systematic review. *J Clin Med.* (2019) 9:34. doi: 10.3390/jcm9010034

59. Yildirim E, Ermis E, Allahverdiyev S, Ucar H, Yavuzer S, Yavuzer H, et al. Relationship between blood pressure variability and cognitive function in geriatric hypertensive patients with well-controlled blood pressure. *Aging Clin Exp Res.* (2020) 32:93–8. doi: 10.1007/s40520-019-01141-6
60. Shim YS, Shin HE. Impact of the ambulatory blood pressure monitoring profile on cognitive and imaging findings of cerebral small-vessel disease in older adults with cognitive complaints. *J Hum Hypertens.* (2021). doi: 10.1038/s41371-021-00490-y

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Neurology

HYPOTHESIS AND THEORY
published: 26 July 2021
doi: 10.3389/fneur.2021.658705

HIV Associated Neurocognitive Disorders Subsidence Through Citalopram Addition in Anti-retroviral Therapy (HANDS-CARE): A Concept Note

*Akin Ojagbemi**

Department of Psychiatry, World Health Organization Collaborating Centre for Research and Training in Mental Health, Substance Abuse and Neuroscience, College of Medicine, University of Ibadan, Ibadan, Nigeria

There is a pressing need to effectively manage HIV Associated Neurocognitive Disorders (HAND) in sub-Saharan Africa (SSA) where the burden is among the highest in the world. Contemporary approaches based on the use of Highly Active Antiretroviral Therapy (HAART) alone are inadequate interventions for HAND, especially in SSA where there is limited availability of the required combinations of HAART for effective central nervous system penetration and where many currently prescribed agents, including efavirenz, have neurotoxicity as a major drawback. This article reviews data supporting the rationale for additive citalopram in antiretroviral therapy as a latent approach to abate HAND. It proposes the conduct of a HIV Associated Neurocognitive Disorders Subsidence through Citalopram addition in *A*nti-*R*etroviral therapy (HANDS-CARE) pilot feasibility trial (RCT) to assess whether the adjunctive use of citalopram, a widely prescribed serotonergic antidepressant, will lead to a meaningful improvement in neurocognitive functioning and quality of life in patients with HAND who are receiving HAART. A preliminarily feasible and efficacy-suggesting HANDS-CARE trial could generate statistical, clinical and operational data necessary to design and conduct a future definitive RCT. If successful, this intervention will be applicable to resource-limited settings as well as developed countries. Effective management of HAND will improve the quality of life of HIV patients, and reduce the cost of managing the disease.

Keywords: acquired immunodeficiency syndrome, HIV associated dementia, antidepressants, low and middle income countries, HIV and AIDS

OPEN ACCESS

Edited by:
Agustin Ibanez, Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina

Reviewed by:
William Keith Gray, Northumbria Healthcare NHS Foundation Trust, United Kingdom
Pablo Toro, Pontificia Universidad Católica de Chile, Chile

***Correspondence:**
Akin Ojagbemi
drakinjagbemi@yahoo.com; aa.ojagbemi@ui.edu.ng

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: *26 January 2021*
Accepted: *18 June 2021*
Published: *26 July 2021*

Citation:
Ojagbemi A (2021) HIV Associated Neurocognitive Disorders Subsidence Through Citalopram Addition in Anti-retroviral Therapy (HANDS-CARE): A Concept Note. Front. Neurol. 12:658705. doi: 10.3389/fneur.2021.658705

INTRODUCTION

Countries in Sub-Saharan Africa (SSA) account for two-thirds of all People Living with Human Immunodeficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (PLWHA) (1, 2). Previously considered a death sentence, the introduction of increasingly potent combinations of Highly Active Antiretroviral Therapy (HAART) has prolonged survival and reduced morbidity (3, 4). However, this success has not translated to reduction in the global burden of some complications of HIV infection, for example, dementia and other neurocognitive disorders (5, 6).

HIV Associated Neurocognitive Disorders (HAND) are multifactorial complications resulting from the direct affectation of the central nervous system (CNS) by HIV (7). It occurs on a spectrum that includes HIV associated

asymptomatic neurocognitive impairment (ANI), HIV associated mild neurocognitive disorder (MND) and HIV associated dementia (HAD) (5), and has been reported at every stage of HIV/AIDS, including in aviremic treated patients and those with minimal immune-suppression (8). The occurrence of HAND has been linked to functional limitation and poor quality of life (9), which in turn increases dependence and suffering in affected individuals. It is also associated with reduced adherence to HAART (9), thus compromising the effectiveness of HAART, and increasing mortality and the risk of HIV transmission. The prevalence among PLWHA in high income countries may reach up to 50% (9). However, rates of well-over 60% have been frequently reported in some African populations (10).

The Burden of HAND in Sub-Saharan Africa

About 11.3 million HIV/AIDS patients in SSA are reported to be affected by HAND (10, 11), with approximately half of those affected reported to have either symptomatic MND or HAD (12). Given suggestions that the above estimates are conservative (13), the burden of HAND in SSA is likely to rank among the highest of any region in the World.

There are several reasons for the high rates of HAND in sub-Saharan Africa. Firstly, the region has the highest HIV/AIDS burden in the world (2). Secondly, patients in many parts of SSA frequently present with relatively advanced infection characterized by severe immune-suppression (14), a situation which has been shown to directly predispose PLWHA to HAND (9). Thirdly, while HAART is the main approach to the management of HAND (15), the available antiretroviral agents in most of SSA are limited. Notably, efavirenz, one of the most commonly prescribed agents in the region (8), has neurotoxicity as a major drawback.

A fourth reason for an escalation of the burden of HAND in SSA a is major depression. This psychiatric disorder is intrinsic to the process of HIV/AIDS and HAND (16, 17), including through the reduction of adherence to HAART (18). Major depression has a fairly increased and stable prevalence at every point in the spectrum of the disease (at risk individuals, asymptomatic infected, AIDS syndrome, and HAND syndrome) (16, 17). Evidence suggests that major depression may sometimes be the first symptom of HAND, or may confound its diagnosis and outcome (16, 17). Major depression may also be more prevalent in socio-economically disadvantaged settings globally (19), and because of the extensive overlap between depression symptoms and those of HIV/AIDS and HAND, the psychiatric disorder may go unrecognized and untreated in these settings (20).

CONTEMPORARY AND LATENT APPROACHES TO THE MANAGEMENT OF HAND

Some of the commonly proposed strategies for the management of HAND include the early initiation of HAART (15), and the use of combinations of HAART which, by possessing higher assumed CNS Penetrating Effectiveness (CPE) scores (21, 22), are thought to have an advantage of better CNS penetration. The use of higher doses of available agents has also been suggested as a feasible strategy in settings, such as those in SSA where there is only a limited combination of HAART (23).

The rationale for the above suggested strategies is based on the observation that, whereas the blood brain barrier may hinder CNS penetration of HAART (24), a higher concentration of HAART is required for the inhibition of macrophage replication within the brain when compared with the concentration required for T- lymphocytes (25). Despite this supposition, the outlined strategies for the management of HAND in contemporary practice have important limitations. First, therapeutic failures have been widely observed with the use of HAART for the treatment of HAND (9). Some reports have also suggested that up to a quarter of PLWHA experience new neurocognitive impairments after initiation of HAART (26). Second, it remains unclear whether the use of antiretroviral agents with higher CPE scores confer actual and unique advantages or whether early introduction of HAART benefit HAND prospectively in the medium to longer term (27). Given these limitations, it would appear that HAART alone is an inadequate intervention for HAND.

A third limitation of the use of HAART for the management of HAND is the question of potential neurotoxicity of many of the available combinations, including efavirenz, a widely prescribed antiretroviral drug globally. These problems are amplified in resource poor settings like Nigeria, where HAART initiation is often delayed and the available antiretroviral agents are limited. Therefore, there is an urgent need to discover interventions that can prevent or mitigate HAND globally, but especially in resource limited SSA settings like Nigeria.

THE ROLE OF ANTIDEPRESSANTS IN HIV/AIDS AND HAND

Emerging evidence from *in-vitro*, human plasma, and cerebrospinal fluid (CSF) studies suggest that serotonergic antidepressants may modulate the pathogenesis of HIV/AIDS and HAND in several possible ways. First, serotonergic antidepressants are known to reduce HIV viral replication in both the CSF and plasma (28, 29). Secondly, serotonergic antidepressants, especially citalopram, have been shown to prevent CNS macrophage infection in *in-vitro* studies (28, 30). Thirdly, serotonergic antidepressants are known to boost the activity of Natural Killer (NK) cells (31). Natural Killer (NK) cells play important roles in the host defense against the HIV virus by producing an HIV suppressive factor which, in turn, prevents viral entry into healthy cells (31). In addition, these cells have been shown to bring about both cytolytic and non-cytolytic destruction of infected cells (32). An additional mechanism is through the immune boosting potentials of serotonergic antidepressants. This is via the immune-modulatory properties of prolactin. The secretion of this hormone is increased in PLWHA treated with some classes of serotonergic antidepressants (33). The secretion of prolactin in patients using serotonergic antidepressants occurs through the inhibition of dopamine, a neurotransmitter that inhibits

prolactin secretion (34). It is noteworthy that the above listed effects of serotonergic antidepressants are independent of the depression status of PLWHA (29).

Key information synthesized from 4 previous trials of antidepressants for HAND is summarized in **Table 1**. Of the 4 previous trials, 1 was non-randomized (36). The remaining 3 were randomized controlled trials (RCT) (35, 37, 38). All trials included adult HIV seropositive patients with evidence of cognitive impairment and a stable antiretroviral regimen for between 6 and 12 weeks. A RCT of oral paroxetine, the only prior study of a selective serotonine re-uptake inhibitor (SSRI) to reduce HAND (37), demonstrated improvement in total and item-specific neuropsychological battery scores. An open label trial of oral lithium (36) also demonstrated improvement in both total and item-specific neuropsychological battery scores. Two RCTs of monoamine oxidase inhibitors (35, 38) demonstrated improvements in some items, but not total score, of a neuropsychological test battery.

Specific Effect of Serotonergic Antidepressants in Abating HAND

The specific mechanism that underlies the effectiveness of serotonergic antidepressants in ameliorating HAND is yet unclear. However, as HAND is a complication resulting from the direct affectation of the CNS by HIV (7), it would be feasible that the use of an agent that can potentially prevent viral replication (in the CSF and plasma), healthy macrophage infection, and cause the destruction of infected cells may be a latent strategy to prevent and treat HAND.

Other hypotheses may include:

1. As both HAND and depression are sub-cortical complications of HIV/AIDS (39), it is feasible that both have overlapping origins.
2. Serotonergic antidepressants may potentiate the effect of HAART, which is currently the mainstay in the management of HAND, by increasing uptake of antiretroviral molecules in PLWHA (29).
3. HIV infected persons who are on serotonergic antidepressants, but not on HAART, have been shown to be less likely to have detectable CNS RNA (30, 40), thus, it would be reasonable to postulate that this class of antidepressants have an independent effect of reducing CNS RNA levels in PLWHA.

In addition to the above listed hypotheses, the particular observation of independent reduction of brain RNA levels in PLWHA by citalopram, sertraline and trazodone (30) would suggest that it is difficult to simply ascribe the benefit of the antidepressants on CNS RNA suppression to the effect of the drugs in improving uptake or adherence to HAART.

Unique Potential of Citalopram in Abating HAND

Among available serotonergic antidepressants, citalopram is the most attractive to investigate in the effort to abate HAND. This is because, apart from the benefits listed above for the broader categories of serotonergic antidepressants, and which have also been specifically demonstrated for citalopram (30, 41), the molecule may have the lowest interaction with available HAART.

Certain individual components of the commonly used HAART, such as Protease Inhibitors (PI) and the Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI), interact with the Cytochrome P450 by either inhibiting (e.g., ritonavir) or inducing (e.g., nevirapine and efavirenz) the enzyme system in the liver (42). These interactions result in variability in the bio-availability of serotonergic antidepressants metabolized via the same enzyme system (Cytochrome P450), and result in serotonergic toxicity in some cases (40, 42). The interaction between SSRI and Cytochrome P450 occur mostly due to the 2D6 and 3A4 iso-enzymes of the cytochrome system (43–45). However, not all SSRIs are metabolized by both iso-enzymes. For instance, while drugs such as fluoxetin, fluvoxamine, and paroxetine are primarily metabolized through the 2D6 iso-enzyme, sertraline is metabolized through 3A4 (43, 45). Using any of these drugs in combination with a PI, for example, may still result in an increase in their concentration and hence toxicity (42).

Citalopram and its S-enantiomer, escitalopram, are not significantly affected by the action of PIs on the 2D6 and 3A4 isoenzymes (42, 45, 46). Citalopram in particular, is metabolized by a different iso-enzyme of the cytochrome P450 system, the 2C19 (43). Among the more commonly used HAART, only efavirenz has been demonstrated, but not consistently (47), to have a modest to minimal, substrate dependent, mixed inhibition and inducer activity on 2C19 (47, 48). Given the above evidence, it would appear that the 2C19 iso-enzyme is mostly un-affected by a majority of available anti-retroviral agents. For this reason, citalopram and escitalopram are now regarded as the two SSRIs of first choice in patients with HIV/AIDS (48). Apart from this advantage of citalopram (i.e., metabolism is dependent on the 2C19 iso-enzyme of the cytochrome system, and not 2D6 and 3A4), the molecule may also be better tolerated in HIV/AIDS patients since it lacks many of the side effects of the older antidepressants (46, 49).

A "HANDS-CARE" STRATEGY TO REDUCE HIV ASSOCIATED NEUROCOGNITIVE DISORDERS

The potential effectiveness of adjunctive citalopram in the treatment of HAND has not been systematically investigated in a randomized controlled trial (RCT). Proposed in this review is a pilot phase 2 (proof of concept) pragmatic single center RCT, HIV Associated Neurocognitive Disorders Subsidence through Citalopram addition in Anti-Retroviral therapy (HANDS-CARE). The proposed proof of concept HANDS-CARE study could generate statistical, clinical and operational data necessary to design and conduct a future definitive RCT assessing whether the adjunctive use of citalopram, a widely prescribed serotonergic antidepressant, will lead to a meaningful improvement in neurocognitive functioning and quality of life in patients with HIV associated neurocognitive impairment while receiving

TABLE 1 | Previous trials of antidepressants for HAND.

References	Study design	Number of participants	Intervention	Duration	Control intervention	Outcome measures	Measure of effect	Effect
Dana consortium	Randomized double-blind	36	Oral deprenyl monoamine oxidase inhibitor (MAOI)	10 weeks	Placebo	Neuropsychological battery test scores	Analyses of variance	1. RAVLT delayed recall 2. Cal CaP reaction time **Authors' conclusion:** deprenyl treatment is associated with cognitive improvement in subjects with mild HIV-associated cognitive impairment
Sacktor et al. (35)	Randomized double-blind	14	Transdermal selegiline MAOI	10 weeks	Placebo	Neuropsychological battery test scores	Analyses of covariance	1. RAVLT delayed recall 2. Grooved Pegboard test **Authors' conclusion:** Selegilline resulted in improved performance in two neuropsychological tests
Letendre et al. (36)	Single-arm, open-label	8	Oral Lithium	12 weeks	Not applicable	Neuropsychological test battery	Paired t-test	Global deficit scores **Authors' conclusion:** Lithium resulted in improved neuropsychological performance
Sacktor et al. (37)	Randomized double-blind	22	Oral paroxetin	24 weeks	Placebo	Neuropsychological test battery	Generalized linear regression models	1.Summary score 2. Cal CAP reaction time, 2. Timed Gait **Authors' conclusion**: Paroxetine was associated with improvement in a summary neuropsychological test measure and in several neuropsychological tests

RAVLT, Rey Auditory Verbal Learning Test; Cal Cap, California Computerized Assessment Package reaction time test.

HAART in Nigeria. If successful, this intervention will be applicable to Nigeria and other resource-limited settings and exportable to more-resourced developed countries.

Importance and Rationale

Nigeria is the most populous country in Africa (About 200 million people) and may have the largest number of persons with HIV/AIDS (50). The burden of HAND in Nigeria is likely to rank among the highest in the world (3 million people in 2010) (51, 52) because of the massive HIV/AIDS burden, late presentation of patients with relatively advanced infection, and a limited range of available combinations of anti-retroviral agents. Therefore, the need to effectively manage HAND is especially pressing in the country setting. Accordingly, the data generated from the proposed HANDS-CARE proof of concept study will broadly influence the care of HIV patients and shape the design of future trials on HAND and other neuropsychological conditions. The normative data from the proposed study could also be used for future research and training well into the foreseeable future.

Specific Questions That Could Be Addressed by a HANDS-CARE Proof of Concept Study

This proposed HANDS-CARE proof of concept study could address the following questions:

1) What are the age, gender and education specific norms for neuropsychological functioning in the Nigerian sample of PLWHA?
2) What are the means, standard deviations, and effect sizes, derived from a Standard neuropsychological battery, necessary to determine the appropriate sample size for a definitive RCT?
3) What magnitude of change in relevant single or composite neuropsychological measures is clinically significant (e.g., linked to improvement or worsening of quality of life?)
4) What is the magnitude of change in neuropsychological measures that can be expected from citalopram in HAND patients? And whether this is likely to achieve the threshold of clinical relevance determined in Question 3 above?
5) What are the logistical, programmatic, and operational needs to implement the anticipated definitive citalopram RCT in Nigeria?

How the Answers to These Questions Will Be Useful in Informing the Design of a Fully Powered RCT

The datasets outlined in the questions above and the operational preparedness for a large HANDS-CARE RCT is currently unavailable in Nigeria. The importance of each question proposed to the design of a future RCT is as follows:

1. *Ascertainment of age, gender and education specific norms for neuropsychological functioning in the Nigerian sample of PLWHA*: This could allow for a precisely defined cognitive impairment by the local norms. Without this foundational dataset, it will be impossible to conduct a rigorous neuropsychological evaluation of HAND in Nigeria. Previous Nigerian studies of cognitive functioning in HIV/AIDS have either relied on neuropsychological tests which were not previously validated for the setting (53), or measures and norms validated for Alzheimer's dementia (54). Data from outside Nigeria are also scant and, more importantly, are suboptimal given important cultural differences and variable literacy levels. A critical advantage of the HANDS-CARE pilot study, therefore, is that it could use measures and tools that are culturally enriched and adapted to the Nigerian context and presented in English and Yoruba, the local language of over 50 million people in South-Western Nigeria.
2. *Ascertainment of the means, standard deviations, and effect sizes, derived from a standard neuropsychological battery*: This is required to determine the sample size that should power a robust larger multicenter HANDS-CARE RCT.
3. *Ascertainment of the magnitude of change in relevant single or composite neuropsychological measures that will be clinically significant*: This data could be essential to assign clinical meaning to neuropsychological changes caused by any specific HAND intervention. The data could also help determine the sample size to appropriately power a definitive HANDS-CARE RCT, and other future studies. The answer to this question is currently unknown.
4. *Ascertainment of the magnitude of change in neuropsychological measures that could be expected from citalopram in patients with HAND*: The information could help determine whether conducting a definitive large citalopram study is a worthwhile venture. A positive result could justify a large HANDS-CARE RCT, while a negative result will save tremendous resources from being committed to a potentially futile large RCT.
5. *Logistical, programmatic, and operational experience gained from the pilot RCT*: Considerations here could include strategies for subject recruitment, research personnel training, and the development of clinical research forms.

POTENTIAL HANDS-CARE PROOF OF CONCEPT STUDY DESIGN

A few details to a potential HANDS-CARE proof of concept study with possible participants and procedure are briefly outlined below. An innovative study design could be utilized in two phases;

1. *A cross-sectional study to address the following questions:*
   (a) What are the age, gender and education specific norms for neuropsychological functioning in the Nigerian sample of PLWHA?
   (b) What are the means, standard deviations, and effect sizes, derived from a Standard neuropsychological battery, necessary to determine the appropriate sample size for a definitive RCT?
   (c) What magnitude of change in relevant single or composite neuropsychological measures is clinically significant, e.g., linked to improvement or worsening of quality of life?

2. *A feasibility 24 weeks double blind RCT of a flexible-dose, 20–40 mg/day of citalopram plus HAART, vs. standard treatment of HIV/AIDS with HAART alone.* This phase will address the following questions:

   (a) What is the magnitude of change in neuropsychological measures that can be expected from citalopram in HAND patients? And whether this is likely to achieve the threshold of clinical relevance determined in Question 3 above?
   (b) What are the logistical, programmatic, and operational needs to implement the anticipated definitive citalopram RCT in Nigeria?

The total duration of the HANDS-CARE pilot project could be 24 months (3 months to set up logistics and ethics, 6 months cross-sectional study participants recruitment, evaluation and data analyses, 12 months RCT participants recruitment and follow-up, and 3 months data analyses and dissemination).

Proposed Approach to HANDS-CARE Phase I

A potential cross-sectional study.

Potential target population: We could enroll adult (≥18 years old) HIV seronegative subjects from the general outpatient clinic.

Overview: Neurologically healthy, HIV seronegative participants could have a one-time comprehensive neuropsychological assessment. They could be screened for good health using a full physical and neurological examination, a HIV serostatus examination, a detailed history, and assessments of functional status.

Potential inclusion criteria:

1. Subjects≥ 18 years of age,
2. Ascertained to be neurologically healthy after a neurological examination, a detailed history, and assessments of functional status.
3. Ascertained to be HIV-seronegative after a HIV serostatus examination

Potential estimate of sample size: Eight strata could be utilized; defined by sex (2 levels), age (2 levels), and years of education (2 levels). Based on a previous calculation using the t-distribution (55), it is determined that enrolling 30 participants per stratum could result in a width of 0.746 standard deviation for the 95% Confidence interval of the stratum specific mean, thus we could enroll a total of 240 healthy participants for the eight strata.

Potential measurements: Study participants could be administered neuropsychological tests covering the five domains stipulated in the National Institute of Mental Health-sponsored diagnostic (Frascati) criteria (5): verbal fluency (semantic verbal fluency test), executive function (WAIS-R digit symbol test), speed of information processing (Color trails test), verbal learning (Hopkins verbal learning test-revised), and motor speed (Timed gait and grooved pegboard tests). Neuropsychological testing could also include the International HIV dementia scale.

An assessment of activities of daily living, quality of life, and depression could also be included. Validated (in the proposed study population) measures such as the Barthel index, W.H.O quality of life brief version (WHOQOL-BREF), and 9-item patient health questionnaire (PHQ-9), respectively, could be used for these assessments. All test instruments could be translated to the local Yoruba language in Nigeria so that subjects who are Yoruba-only speakers can be assessed in the Yoruba language.

Proposed HANDS-CARE Phase 2

A potential feasibility 24 weeks double blind RCT of a flexible-dose, 20–40 mg/day of citalopram plus HAART, vs. standard treatment of HIV/AIDS with HAART alone.

Target population: we could enroll subjects who are at least 18 years old, confirmed to be HIV-1 infected, and have been suppressed on efavirenz based HAART (plasma 20 copies/mL) for 3 months.

Potential inclusion criteria:

1. Adult HIV/AIDS patients
2. Suppressed on HAART for a minimum period of 3 months
3. Have no evidence of clinical depression or other major mental, physical or neurological co-morbidities,
4. Meets Fracati criteria for HAND (5), defined according to the population specific norms (established in phase I), could be enrolled.

Potential randomization scheme: HANDS-CARE phase 2 participants could be randomly assigned to intervention and standard treatment groups in a 1:1 ratio. A total of 12 participants (six in each arm) could be enrolled.

Proposed measurements: HANDS-CARE phase 2 participants could be assessed at baseline, using the phase I neuropsychological measures and norms, followed up at 4 weeks for the presence of emergent adverse events (A.E). Repeat neuropsychological and A.E evaluations could be conducted at weeks 12 and 24.

Primary endpoint for efficacy: This could be a statistically significant improvement from baseline to week 24 (for the citalopram arm) in the composite neuropsychological test score.

Secondary end points: Could be a statistically significant change in individual neuropsychological scores. Additional measures could include a change in CD4 count, HIV viral load, adherence to HAART, functioning, weight gain, depression, and quality of life. Safety end points could be the frequency and nature of A.E and retention rate in study.

Potential mediators of outcome: Could include demographic characteristics, years of formal education, income, nadir CD4 count, hepatitis C serostatus, alcohol and psychoactive substance use, history of hypertension diabetes or stroke, previous history of depression, baseline severity of cognitive impairment and functional disability, adherence to regimen, presence of mild/sub-threshold depression symptoms at baseline, insomnia, and neuropathic pain. These variables will be assessed and controlled for.

CONCLUSION

Trials evaluating the effectiveness of citalopram as a cheap, safe and readily available adjunctive treatment for HAND are currently needed, and will be especially applicable to resource-poor settings, such as those in SSA, where there is a limited availability of the required variety of HAART combinations with

sufficient CNS penetrating effectiveness to target neuro-cognitive complications. Efficient management of HAND will improve the quality of life of HIV patients, and reduce the cost of management of HIV/AIDS in both resource poor and rich settings.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

AO conceived the idea and study design, prepared the materials, wrote and approved the manuscript drafts.

ACKNOWLEDGMENTS

Ibadan Cohort on NeuroAIDS (ICON) study group.

REFERENCES

1. United Nations Development Programme. *Sustainability and Equity: A Better Future for All*. New York, NY: United Nations Organization (2011).
2. The Joint United Nations Programme on HIV/AIDS. *Progress Report 2011: Global HIV/AIDS Response*. New York, NY: United Nations Organization (2011).
3. Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet*. (2008) 372:293–9. doi: 10.1016/S0140-6736(08)61113-7
4. Nsanzimana S, Remera E, Kanters S, Chan K, Forrest JI, Ford N, et al. Life expectancy among HIV-positive patients in Rwanda: a retrospective observational cohort study. *Lancet Glob Health*. (2015) 3:e169–77. doi: 10.1016/S2214-109X(14)70364-X
5. Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, et al. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*. (2007) 69:1789–99. doi: 10.1212/01.WNL.0000287431.88658.8b
6. Foley JM, Wright MJ, Gooding AL, Ettenhofer M, Kim M, Choi M, et al. Operationalization of the updated diagnostic algorithm for classifying HIV-related cognitive impairment and dementia. *Int Psychogeriatr*. (2011) 23:835–43. doi: 10.1017/S1041610210002085
7. Ho DD, Rota TR, Schooley RT, Kaplan JC, Allan JD, Groopman JE, et al. Isolation of HTLV-III from cerebrospinal fluid and neural tissues of patients with neurologic syndromes related to the acquired immunodeficiency syndrome. *New Engl J Med*. (1985) 313:1493–7. doi: 10.1056/NEJM198512123132401
8. Kelly CM, van Oosterhout JJ, Ngwalo C, Stewart RC, Benjamin L, Robertson KR, et al. HIV associated neurocognitive disorders (HAND) in Malawian adults and effect on adherence to combination anti-retroviral therapy: a cross sectional study. *PLoS ONE*. (2014) 9:e98962. doi: 10.1371/journal.pone.0098962
9. Heaton RK, Clifford DB, Franklin DR Jr, Woods SP, Ake C, et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. *Neurology*. (2010) 75:2087–96. doi: 10.1212/WNL.0b013e318200d727
10. Nakku J, Kinyanda E, Hoskins S. Prevalence and factors associated with probable HIV dementia in an African population: a cross-sectional study of an HIV/AIDS clinic population. *BMC Psychiatry*. (2013) 13:126. doi: 10.1186/1471-244X-13-126
11. Wright EJ, Nunn M, Joseph J, Robertson K, Lal L, Brew BJ. NeuroAIDS in the Asia Pacific Region. *J Neurovirol*. (2008) 14:465–73. doi: 10.1080/13550280802235932
12. Eaton P, Lewis T, Kellett-Wright J, Flatt A, Urasa S, Howlett W, et al. Risk factors for symptomatic HIV-associated neurocognitive disorder in adults aged 50 and over attending a HIV clinic in Tanzania. *Int J Geriatr Psychiatry*. (2020) 35:1198–208. doi: 10.1002/gps.5357
13. Robbins RN, Remien RH, Mellins CA, Joska JA, Stein DJ. Screening for HIV-associated dementia in South Africa: potentials and pitfalls of task-shifting. *AIDS Patient Care STDS*. (2011) 25:587–93. doi: 10.1089/apc.2011.0154
14. Wong MH, Robertson K, Nakasujja N, Skolasky R, Musisi S, Katabira E, et al. Frequency of and risk factors for HIV dementia in an HIV clinic in sub-Saharan Africa. *Neurology*. (2007) 68:350–5. doi: 10.1212/01.wnl.0000252811.48891.6d
15. Ellis RJ, Badiee J, Vaida F, Letendre S, Heaton RK, Clifford D, et al. CD4 nadir is a predictor of HIV neurocognitive impairment in the era of combination antiretroviral therapy. *Aids*. (2011) 25:1747–51. doi: 10.1097/QAD.0b013e32834a40cd
16. Nakasujja N, Skolasky RL, Musisi S, Allebeck P, Robertson K, Ronald A, et al. Depression symptoms and cognitive function among individuals with advanced HIV infection initiating HAART in Uganda. *BMC Psychiatry*. (2010) 10:44. doi: 10.1186/1471-244X-10-44
17. Nath A, Schiess N, Venkatesan A, Rumbaugh J, Sacktor N, McArthur J. Evolution of HIV dementia with HIV infection. *Int Rev Psychiatry*. (2008) 20:25–31. doi: 10.1080/09540260701861930
18. Adejumo O, Oladeji B, Akpa O, Malee K, Baiyewu O, Ogunniyi A, et al. Psychiatric disorders and adherence to antiretroviral therapy among a population of HIV-infected adults in Nigeria. *Int J STD AIDS*. (2016) 27:938–49. doi: 10.1177/0956462415600582
19. Simpson SM, Krishnan LL, Kunik ME, Ruiz P. Racial disparities in diagnosis and treatment of depression: a literature review. *Psychiatr Q*. (2007) 78:3–14. doi: 10.1007/s11126-006-9022-y
20. Voss J, Portillo CJ, Holzemer WL, Dodd MJ. Symptom cluster of fatigue and depression in HIV/AIDS. *J Prev Interv Community*. (2007) 33:19–34. doi: 10.1300/J005v33n01_03
21. Carvalhal A, Gill MJ, Letendre SL, Rachlis A, Bekele T, Raboud J, et al. Central nervous system penetration effectiveness of antiretroviral drugs and neuropsychological impairment in the Ontario HIV Treatment Network Cohort Study. *J Neurovirol*. (2016) 22:349–57. doi: 10.1007/s13365-015-0404-5
22. Letendre S, Marquie-Beck J, Capparelli E, Best B, Clifford D, Collier AC, et al. Validation of the CNS Penetration-Effectiveness rank for quantifying antiretroviral penetration into the central nervous system. *Arch Neurol*. (2008) 65:65–70. doi: 10.1001/archneurol.2007.31
23. Habib AG, Yakasai AM, Owolabi LF, Ibrahim A, Habib ZG, Gudaji M, et al. Neurocognitive impairment in HIV-1-infected adults in Sub-Saharan Africa: a systematic review and meta-analysis. *Int J Infect Dis*. (2013) 17:e820–31. doi: 10.1016/j.ijid.2013.06.011
24. Pardridge WM. Targeting neurotherapeutic agents through the blood-brain barrier. *Arch Neurol*. (2002) 59:35–40. doi: 10.1001/archneur.59.1.35
25. Aquaro S, Calio R, Balzarini J, Bellocchi MC, Garaci E, Perno CF. Macrophages and HIV infection: therapeutical approaches toward this strategic virus reservoir. *Antiviral Res*. (2002) 55:209–25. doi: 10.1016/S0166-3542(02)00052-9
26. Robertson K, Jiang H, Kumwenda J, Supparatpinyo K, Evans S, Campbell TB, et al. Improved neuropsychological and neurological functioning across three antiretroviral regimens in diverse resource-limited settings: AIDS Clinical Trials Group study a5199, the International Neurological Study. *Clin Infect Dis*. (2012) 55:868–76. doi: 10.1093/cid/cis507
27. Nichols SL, Bethel J, Kapogiannis BG, Li T, Woods SP, Patton ED, et al. Antiretroviral treatment initiation does not differentially alter neurocognitive functioning over time in youth with behaviorally acquired HIV. *J Neurovirol*. (2016) 22:218–30. doi: 10.1007/s13365-015-0389-0

28. Benton T, Lynch K, Dube B, Gettes DR, Tustin NB, Ping Lai J, et al. Selective serotonin reuptake inhibitor suppression of HIV infectivity and replication. *Psychosomat Med.* (2010) 72:925–32. doi: 10.1097/PSY.0b013e3181f883ce
29. Tsai AC, Weiser SD, Petersen ML, Ragland K, Kushel MB, Bangsberg DR. A marginal structural model to estimate the causal effect of antidepressant medication treatment on viral suppression among homeless and marginally housed persons with HIV. *Arch Gen Psychiatry.* (2010) 67:1282–90. doi: 10.1001/archgenpsychiatry.2010.160
30. Letendre SL, Marquie-Beck J, Ellis RJ, Woods SP, Best B, Clifford DB, et al. The role of cohort studies in drug development: clinical evidence of antiviral activity of serotonin reuptake inhibitors and HMG-CoA reductase inhibitors in the central nervous system. *J Neuroimmune Pharmacol.* (2007) 2:120–7. doi: 10.1007/s11481-006-9054-y
31. Oliva A, Kinter AL, Vaccarezza M, Rubbert A, Catanzaro A, Moir S, et al. Natural killer cells from human immunodeficiency virus (HIV)-infected individuals are an important source of CC-chemokines and suppress HIV-1 entry and replication in vitro. *J Clin Invest.* (1998) 102:223–31. doi: 10.1172/JCI2323
32. Tomescu C, Mavilio D, Montaner LJ. Lysis of HIV-1-infected autologous CD4+ primary T cells by interferon-alpha-activated NK cells requires NKp46 and NKG2D. *Aids.* (2015) 29:1767–73. doi: 10.1097/QAD.0000000000000777
33. Orlander H, Peter S, Jarvis M, Ricketts-Hall L. Imipramine induced elevation of prolactin levels in patients with HIV/AIDS improved their immune status. *West Indian Med J.* (2009) 58:207–13.
34. Fitzgerald P, Dinan TG. Prolactin and dopamine: what is the connection? A review article. *J Psychopharmacol.* (2008) 22(2 Suppl.):12–9. doi: 10.1177/0269216307087148
35. Sacktor N, Schifitto G, McDermott MP, Marder K, McArthur JC, Kieburtz K. Transdermal selegiline in HIV-associated cognitive impairment: pilot, placebo-controlled study. *Neurology.* (2000) 54:233–5. doi: 10.1212/WNL.54.1.233
36. Letendre SL, Woods SP, Ellis RJ, Atkinson JH, Masliah E, van den Brande G, et al. Lithium improves HIV-associated neurocognitive impairment. *AIDS.* (2006) 20:1885–8. doi: 10.1097/01.aids.0000244208.49123.1b
37. Sacktor N, Skolasky RL, Moxley R, Wang S, Mielke MM, Munro C, et al. Paroxetine and fluconazole therapy for HIV-associated neurocognitive impairment: results from a double-blind, placebo-controlled trial. *J Neurovirol.* (2018) 24:16–27. doi: 10.1007/s13365-017-0587-z
38. The Dana Consortium on the Therapy of HIV Dementia and Related Cognitive Disorders. A randomized, double-blind, placebocontrolled trial of deprenyl and thioctic acid in human immunodeficiency virus associated cognitive impairment. *Neurology.* (1998) 50:645–51. doi: 10.1212/WNL.50.3.645
39. Baker LM, Paul RH, Heaps-Woodruff JM, Chang JY, Ortega M, Margolin Z, et al. The effect of central nervous system penetration effectiveness of highly active antiretroviral therapy on neuropsychological performance and neuroimaging in hiv infected individuals. *J Neuroimmune Pharmacol.* (2015) 10:487–92. doi: 10.1007/s11481-015-9610-4
40. Ances BM, Letendre SL, Alexander T, Ellis RJ. Role of psychiatric medications as adjunct therapy in the treatment of HIV associated neurocognitive disorders. *Int Rev Psychiatry.* (2008) 20:89–93. doi: 10.1080/09540260701877670
41. Evans DL, Lynch KG, Benton T, Dube B, Gettes DR, Tustin NB, et al. Selective serotonin reuptake inhibitor and substance P antagonist enhancement of natural killer cell innate immunity in human immunodeficiency virus/acquired immunodeficiency syndrome. *Biol Psychiatry.* (2008) 63:899–905. doi: 10.1016/j.biopsych.2007.08.012
42. Repetto MJ, Petitto JM. Psychopharmacology in HIV-infected patients. *Psychosomat Med.* (2008) 70:585–92. doi: 10.1097/PSY.0b013e3181777190
43. Feucht CL, Weissman SB. Psychiatric and antiretroviral agents: associated drug-interactions. *TEN.* (2000) 2:69–73.
44. Greenblatt DJ, von Moltke LL, Harmatz JS, Shader RI. Drug interactions with newer antidepressants: role of human cytochromes P450. *J Clin Psychiatry.* (1998) 59(Suppl. 15):19–27. doi: 10.1097/00004714-199910001-00003
45. Spina E, Santoro V, D'Arrigo C. Clinically relevant pharmacokinetic drug interactions with second-generation antidepressants: an update. *Clin Ther.* (2008) 30:1206–27. doi: 10.1016/S0149-2918(08)80047-1
46. Currier MB, Molina G, Kato M. Citalopram treatment of major depressive disorder in Hispanic HIV and AIDS patients: a prospective study. *Psychosomatics.* (2004) 45:210–6. doi: 10.1176/appi.psy.45.3.210
47. Avery LB, VanAusdall JL, Hendrix CW, Bumpus NN. Compartmentalization and antiviral effect of efavirenz metabolites in blood plasma, seminal plasma, and cerebrospinal fluid. *Drug Metab Dispos.* (2013) 41:422–9. doi: 10.1124/dmd.112.049601
48. Xu C, Desta Z. In vitro analysis and quantitative prediction of efavirenz inhibition of eight cytochrome P450 (CYP) enzymes: major effects on CYPs 2B6, 2C8, 2C9 and 2C19. *Drug Metab Pharmacokinet.* (2013) 28:362–71. doi: 10.2133/dmpk.DMPK-12-RG-124
49. Freudenreich O, Goforth HW, Cozza KL, Mimiaga MJ, Safren SA, Bachmann G, et al. Psychiatric treatment of persons with HIV/AIDS: an HIV-psychiatry consensus survey of current practices. *Psychosomatics.* (2010) 51:480–8. doi: 10.1016/S0033-3182(10)70740-4
50. United Nations Development Programme (UNDP). *The Rise of the South: Human Progress in a Diverse World*. New York, NY: The United Nations Development Programme (UNDP) (2013).
51. Yakasai AM, Gudaji MI, Muhammad H, Ibrahim A, Owolabi LF, Ibrahim DA, et al. Prevalence and correlates of HIV-associated neurocognitive disorders (HAND) in Northwestern Nigeria. *Neurol Res Int.* (2015) 2015:486960. doi: 10.1155/2015/486960
52. Robertson K, Liner J, Hakim J, Sankale JL, Grant I, Letendre S, et al. NeuroAIDS in Africa. *J Neurovirol.* (2010) 16:189–202. doi: 10.3109/13550284.2010.489597
53. Akolo C, Royal W, 3rd, Cherner M, Okwuasaba K, Eyzaguirre L, Adebiyi R, et al. Neurocognitive impairment associated with predominantly early stage HIV infection in Abuja, Nigeria. *J Neurovirol.* (2014) 20:380–7. doi: 10.1007/s13365-014-0254-6
54. Salawu FK, Bwala SA, Wakil MA, Bani B, Bukbuk DN, Kida I. Cognitive function in HIV-seropositive Nigerians without AIDS. *J Neurol Sci.* (2008) 267:142–6. doi: 10.1016/j.jns.2007.10.013
55. Baune BT, Renger L. Pharmacological and non-pharmacological interventions to improve cognitive dysfunction and functional ability in clinical depression–a systematic review. *Psychiatry Res.* (2014) 219:25–50. doi: 10.1016/j.psychres.2014.05.013

Conflict of Interest: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

SYSTEMATIC REVIEW
published: 28 July 2021
doi: 10.3389/fneur.2021.628520

Systematic Review Estimating the Burden of Dementia in the Latin America and Caribbean Region: A Bayesian Approach

Yawen Xiang[1,2†], Kimberly Vilmenay[3†], Adrienne N. Poon[1,4], Shant Ayanian[4], Christopher F. Aitken[5] and Kit Yee Chan[1,6] on behalf of the Global Health Epidemiology Reference Group (GHERG) and the Global Dementia Prevention Program (GloDePP)*

[1] Centre for Global Health, Usher Institute, University of Edinburgh, Edinburgh, United Kingdom, [2] Edinburgh Medical School, College of Medicine and Veterinary Medicine, University of Edinburgh, Edinburgh, United Kingdom, [3] College of Medicine, Howard University, Washington, DC, United States, [4] Department of Medicine, School of Medicine and Health Sciences, George Washington University, Washington, DC, United States, [5] Department of Economics, Edinburgh Business School, Heriot-Watt University, Edinburgh, United Kingdom, [6] Nossal Institute for Global Health, Melbourne School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia

OPEN ACCESS

Edited by:
Ching-Kuan Liu,
Kaohsiung Medical University Hospital, Taiwan

Reviewed by:
Mattia Siciliano,
University of Campania Luigi Vanvitelli, Italy
Gustavo C. Roman,
Houston Methodist Research Institute, United States

***Correspondence:**
Kit Yee Chan
k.chan@ed.ac.uk

[†] These authors share first authorship

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: 12 November 2020
Accepted: 09 June 2021
Published: 28 July 2021

Citation:
Xiang Y, Vilmenay K, Poon AN, Ayanian S, Aitken CF and Chan KY (2021) Systematic Review Estimating the Burden of Dementia in the Latin America and Caribbean Region: A Bayesian Approach. Front. Neurol. 12:628520. doi: 10.3389/fneur.2021.628520

Background: The global burden of dementia has increasingly shifted to low- and middle-income regions that lack essential data for monitoring epidemiological progression, and policy and planning support. Drawing upon data that have emerged since the last known estimates published in 2015, this study aims to update dementia estimates in the Latin America and Caribbean (LAC) region for the years 2020, 2030, and 2050 through the application of a recently validated Bayesian approach for disease estimates useful when data sources are scarce.

Methods: A comprehensive parallel systematic review of PubMed, EMBASE, PsycINFO, Global Health, and LILACS was conducted to identify prospective population-based epidemiological studies on dementia published in English from 2013 to 2018 in LAC. English and non-English data cited by a recent review on dementia estimates in LAC were also examined for additional data. A Bayesian normal-normal hierarchical model (NNHM) was developed to estimate age-specific and age-adjusted dementia prevalence in people aged 60+. Using age-specific population projections from the UN, the total number of people affected by dementia for the years 2020, 2030, and 2050 were estimated.

Results: 1,414 studies were identified, of which only 7 met the inclusion criteria. The studies had 7,684 participants and 1,191 dementia cases. The age-standardized prevalence of all forms of dementia in LAC was 8% (95% CI: 5–11.5%) in people aged 60+. The estimated prevalence varied with age, increasing from 2.5% (95% CI: 0.08–4.0%) in the 60-69 age group, to 9.4% (95% CI: 5.4–13.2%) in the 70–79 age group and 28.9% (95% CI: 20.3–37.2%) in the ≥80 age group. The number of people age 60 and older living with dementia in LAC in 2020 was estimated at 6.86 (95% CI: 4.3–9.8) million, 9.94 (95% CI: 6.16–14.15) million in 2030, and 19.33 (95% CI: 12.3–13.6) million in 2050.

Conclusion: We project an upward disease trajectory for dementia in LAC countries. The projection is likely an underestimation of the true dementia burden given the underrepresentation of rural and socio-economically deprived populations. More research is urgently needed to improve the accuracy of disease estimates, guide clinicians to improve evaluations for earlier recognition of dementia, and support the development of effective policies for improving dementia prevention, diagnosis and clinical management in LAC's diverse and aging communities.

Keywords: dementia, Latin America and the Caribbean (LAC), burden of dementia, low- and middle-income countries (LMICs), Bayesian approach

INTRODUCTION

Dementia is an age-related neurocognitive disorder that has become a leading cause of morbidity and mortality in later life. In 2015, there were an estimated 47 million dementia cases globally, costing an estimated US$818 billion (1). With the number of dementia cases worldwide projected to double every 20 years, this cost is estimated to rise to US$2 trillion by 2030. The increasing majority of this burden has been shifting to low- and middle-income countries (LMICs) that have been undergoing drastic demographic and health transitions. In Latin America and the Caribbean (LAC), the average life expectancy has increased by almost 20 years since 1960 (2). The population aged 60 years and over grew by 6.6 times during this period (from 12.7 to 84.9 million) and is projected to increase to 190 million by 2050 (3). As the population experiences longer health expectancy than prior generations, the risk of dementia and prevalence may both increase.

Previous studies that estimated the prevalence of dementia in LAC have been conducted as part of larger multi-regional dementia prevalence estimates (1, 4–6). An issue with using a global model for estimating regional estimates is that countries with better health informatics infrastructures tend to have more complete data and may disproportionately influence the model, and shield the LAC specific data from being relevant. Furthermore, using LAC specific data would account for population variability in terms of genomics, quality of life and education, which are known to affect dementia, thus making the conclusions stronger in terms of applicability for the LAC area. The lack of a standalone model that can estimate the burden of dementia based on LAC data is perhaps due to the historical dearth of data in LMICs. The most recent replicable systematic review of PubMed identified only 14 quality studies published between 1990 and 2013 that contained original data on the prevalence of dementia in LAC (1). Moreover, that meta-analysis estimated a high prevalence of 8.34% for people aged 60 and over – second only to North Africa/Middle East (8.7%). This high prevalence poses a considerable challenge to health and economic systems which lack both the ability to adequately diagnose dementia but also the availability of public and private grants in order to do so (7). The evidence for dementia in LAC is likely to have expanded since this prior estimate. An updated review and estimates are thus timely and pertinent.

To make the best use of the scarce data, in recent years, modelers have turned away from the traditional frequentist analytic approach in favor of Bayesian methods which are considered more suitable for meta-analyzing small datasets [k $\geq$ 2 (6)]. By allowing historical data (prior estimates) to be incorporated into current estimates (8, 9), Bayesian methods also improve the consistency between current and prior estimates (10). Establishing an optimal approach for applying Bayesian methods to prevalence estimates is an area of ongoing study. To this end, Poon et al. (11) recently updated estimates of the burden of dementia for the South-East Asia region using two Bayesian approaches and confirmed the estimates using a traditional frequentist approach. The study showed that results using all three approaches were comparable, though Bayesian stands as a more promising methodology for improving estimates for severely limited datasets. One of these approaches, the Bayesian Bayesmeta algorithm, uses a newer, simpler and open source software that could give opportunities for researchers in low resource settings to participate in disease estimates without paying software subscriptions (12). Given the novelty of this approach, results would benefit from further validation.

The overall aim of this study is to provide an updated estimate of the prevalence of dementia for LAC with improved accuracy. By way of a comprehensive systematic review of a larger number of academic and non-academic databases, we aim to identify data that has emerged from the LAC region since 2013. The total number of dementia cases in LAC will be estimated for the years 2020, 2030, and 2050. The study will also explore the newer Bayesian Random-Effects Meta-Analysis (Bayesmeta) in R (13) against the more established Bayesian JAGS algorithm (14). It is hoped that the updated estimates will help draw attention to the growing burden of dementia in LAC as part of a global trend. This study can generate evidence-based burden estimates that are key for informing policy and healthcare-planning and a knowledge base to support clinicians for earlier identification and management of dementia.

METHODS

Search Strategy

Systematic parallel searches were conducted by YX and KV using PubMed, EMBASE, Global Health, PsycINFO and LILACS, and the gray literature. In order to capture the broadest number

of studies during the search process, we used the United Nations M49 standard definition of LAC which provides a broad definition of the geographical region of LAC (15). This includes all countries south of the United States, West of the Atlantic Ocean, east of the Pacific Ocean, and north of Antarctica; resulting in a total of 52 countries. The overall search terms were "(Dementia or Alzheimer*) AND (prevalence OR incidence OR morbidity OR mortality OR "burden of disease" OR "disease burden" OR Epidemiology) AND ("Latin America" OR Caribbean OR "Central America" OR [names of each included countries separated by an "OR"]) adapted to the syntax requirements of the specific database (see **Supplementary Material 1** for details). Google Scholar and hand searches were used to identify any relevant gray literature. Additionally, non-English data cited in a recent review by Nitrini et al. were hand-searched for additional data (7).

Inclusion and Exclusion Criteria

We included only studies that: (i) were prospective and population-based; (ii) contained original data on incidence, prevalence and/or mortality of dementia; (iii) used internationally recognized diagnosis of dementia [i.e., Diagnostic and Statistical Manual of Mental Disorders (DSM) (16) or International Classification of Diseases criteria for dementia (ICD) (17), National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria for Alzheimer's disease (NINCDS-ADRDA) (18), National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences criteria for vascular dementia (NINDS-AIREN) (19) and the 10/66 Dementia Diagnostic Algorithm] (20); and (iv) published between 2013 and December 2018.

Within the systematic review process from the databases, we excluded: (i) duplicates within and between the databases; (ii) studies with no original numerical estimates (e.g., reviews, viewpoints); (iii) studies of LAC populations outside of LAC; (iv) non-human studies; (v) studies with no clear denominator or inappropriate standardized rates; (vi) studies of non-community-based populations (e.g., nursing homes) and (vii) non-English language studies.

Quality Assessment

Quality assessment was conducted by YX and KV using a modified version of the Joanna Briggs Institute (JBI) Critical Appraisal checklist for prevalence studies (**Supplementary Material 2**).

Data Extraction and Analysis

For each eligible study, the following data were extracted: (i) study country of origin; (ii) sampling method; (ii) screening tool(s); (iii) diagnostic tool(s); (iv) sample size (denominator); and (v) the number of dementia cases (numerator) and/or unweighted dementia prevalence. Where available, we also extracted incidence data, mortality data, prevalence data by urban vs. rural population, age group, gender and types of dementia.

Using the Bayesmeta package of R (version 3.5.2) (12, 13), a Bayesian normal-normal hierarchical model (NNHM) was used to estimate age-specific and age-adjusted dementia prevalence in people aged 60 and above. The prior prevalence estimates published by Prince and Wimo (1) for the age groups 60–69, 70–79, and 80 and over were used in this model, alongside the newly extracted data from the current study.

The foremost step was to sort the number of screened participants and the number of people with dementia (PWD) identified from each study into 10-year group bins. Any participant over the age of 80 was allocated into an "80 and over" bin. Our variance was then set to 0.09^2, 0.15^2, and 0.3^2 for age groups 60–69, 70–79, and 80 and over, respectively. To account for the variability in prevalence estimates with increasing age, the variance was widened in each subsequent group due to the reduction in sample sizes in the older age groups. Prevalence was then pooled for groups 60–69, 70–79, and 80 and over, and 95% credible intervals were calculated.

To test the sensitivity of the Bayesmeta package, we used the Just Another Gibbs Sampler (JAGS) (14), an open source algorithm used often in Bayesian analysis, to generate 3 Markov chain Monte Carlo (MCMC) chains. These MCMC chains produced disease burden estimates for each of the allotted age group bins highlighted above using a similar NNHM model. Using age-specific population projections from the United Nations Development Program (UNDP) (3), the total number of people affected by dementia for the years 2020, 2030, 2050 were estimated.

RESULTS

The searches yielded a total of 1,414 articles; 1,082 after removing duplicates. Of the remaining articles 1,041 articles were further excluded based on the title and abstract relevance and 41 full-text articles were then analyzed based on our set inclusion/exclusion criteria, study design and use of case definitions. Of these, only 7 studies met all inclusion criteria and were retained for meta-analysis (see **Supplementary Material 2** for quality assessment using JBI). Our reading of Nitrini et al.'s recent review on the current trends and challenges of dementia in LAC (7) yield two systematic reviews that incorporated dementia data from LAC in English and Spanish; i.e., Nitrini et al. (21) and Sanchez et al. (22). Neither of these reviews yielded further studies that met our inclusion criteria (see **Supplementary Material 3** for detail). The number of participants in the retained studies was 7,684 with all studies having recruited more female participants than male participants: the proportion of female participants ranged from 55.8 to 74.4%. The range of participants in the included studies varied from 301 participants (23) to 1,898 (24). **Figure 1** illustrates the selection process.

As **Table 1** illustrates, the majority of the studies (four) were conducted in South America (25, 26, 29), two were based in the Caribbean (23, 24), and one in Central America (27). With the exception of the Central American study, all studies had adopted a 2-stage design that involved initial screening by field workers

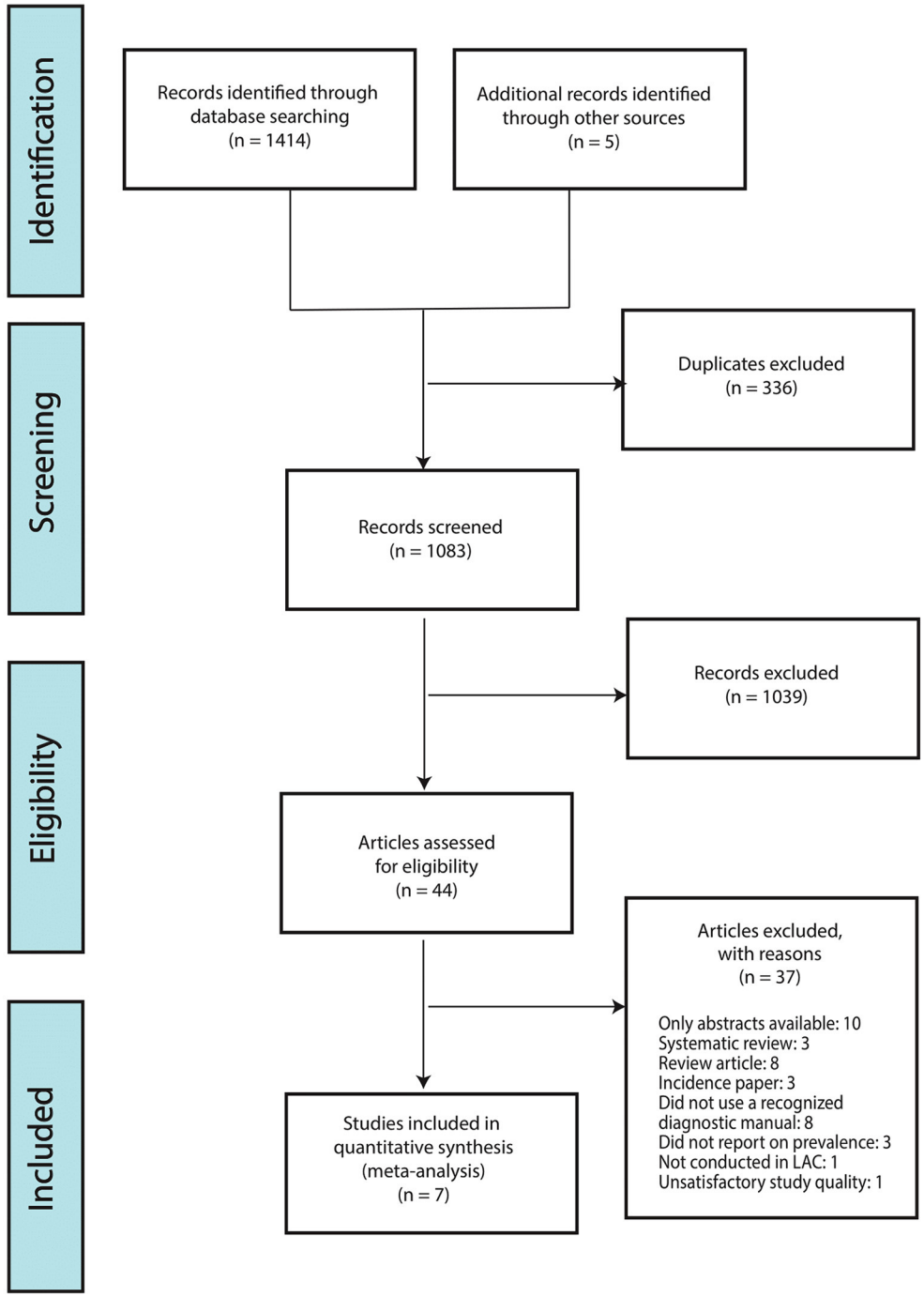


FIGURE 1 | PRISMA of study selections.

and case confirmation by medical specialists (see **Table 1**). All studies reported the prevalence of dementia and were cross-sectional in design. None of the studies reported incidence or mortality of dementia. **Supplementary Materials 4** provides results of our assessment that shows the retained studies are of high quality.

Prevalence Estimates

Based on Bayesian NNHM estimates, the prevalence of dementia for people aged 60 and above in LAC was 8% (95% Credible Interval: 5–11.5%). As expected, the prevalence of dementia increased with age, from 2% (1–4%) for the 60–69 age group to almost 30% (29%, 20–37%) for the 80 and over

TABLE 1 | Characteristics of the retained studies.

References	Region/Country	Sample size and Response rate (%)	Participants traits	Sample selection	Participant recruitment	Study design	Screening tools	Outcome ascertainment
Davis et al. (24)	Trinidad, Caribbean	2,378 approached 1,898 analyzed (79.8%)	44% Male 56% Female >70 years old	Comprehensive cross-sectional survey from nationally representative sample	Random and proportional sampling	Single-phase cross-sectional survey	10/66 Community Screening Instrument for Dementia	10/66 short dementia diagnostic algorithm
Eldemire-Shearer et al. (23)	Jamaica, Carribean	340 approached 301 analyzed (88.5%)	42.5% Male 57.5% Female >60 years old	National representative cross-sectional survey	Random sampling of 340 from a nationally representative cohort	2-stage design cross-sectional study*	MMSE	DSM-IV MRI classification
Pedraza et al. (25)	Bogotá, Columbia, South America	1,263 approached 1235 analyzed (97.8%)	25.6% Male 74.4% Female >50 years old	Community dwelling elderly population	Consecutive sampling	2-stage design cross-sectional study*	MMSE SMCQ MoCA	DSM-IV
Cesar et al. (26)	Tremembé, Brazil, South America	738 approached 630 analyzed (85.4%)	37% Male 63% Female >60 years old	Representative of the region in terms of socioeconomic and cultural levels	Random sampling	Single-phase cross-sectional survey	MMSE BCSB	NIA-AA
Bartoloni et al. (27)	Suburban area of Buenos Aires, Argentina, South America	2,437 approached 1795 analyzed (73.7%)	44.2% Male 55.8% Female >60 years old	Seven slums in Matanza Riachuelo	Consecutive sampling by door to door survey	2-stage design cross-sectional study*	MMSE	DSM-IV
Velázquez-Brizuela et al. (28)	Metropolitan area of Guadalajara, Jalisco, Mexico, Central America	1,142 analyzed (NA)	36.2% Male 63.8% Female >60 years old	Representative of the region	Multistage and proportional random sampling	2-stage design cross-sectional study*	MMSE	DSM-IV
Correa Ribeiro et al. (29)	Rio de Janeiro, Brazil, South America	769 eligible 736 screened 683 analyzed (95.7%)	29.1% Male 70.9% Female >65 years old	Clients of private health care plan, older than 65 years of age	Random sampling from client pool	2-stage design cross-sectional study*	MMSE	DSM-IV, ICD-10, NINCDS-ADRDA, NINDS-AIREN

**Two-stage cross-sectional study involving: 1. Screening (MMSE) by trained fieldworkers; and 2. Case confirmation by psychiatrists.*
Mini-Mental State Examination (MMSE); Montreal Cognitive Assessment (MoCA); Subjective memory complaints questionnaire (SMCQ); Brief Cognitive Screening Battery (BCSB); the International Classification of Diseases (ICD); the Diagnostic and Statistical Manual of Mental Disorders (DSM); National Institute on Aging and Alzheimer's Association also published diagnostic guidelines (NIA-AA); National Institute of Neurological Disorders and Stroke Association criteria for vascular dementia (NINDS-AIREN); National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria for Alzheimer's disease (NINCDS-ADRDA).

age group (**Table 2**). Apart from the 70–79 age group, our prevalence estimates are closely comparable to those of Prince and Wimo (1). The sensitivity test using the classical MCMC found similar results, supporting the validity of our estimates (**Supplementary Material 5**).

Of the seven studies, two reported breakdowns of prevalence by sex (26, 29). No studies reported prevalence by rural vs. urban areas, and two provided prevalence breakdowns by dementia subtypes (23, 29). Unfortunately, their combined sample sizes were too small to allow analysis by any of these variables.

Burden Estimates

By applying the UNDP population projection (3), the number of dementia cases for people aged 60 and above in LAC is estimated at 6.86 (95% Credible Interval: 4.3–9.8) million, 9.94 (CI: 6.16–14.15) million in 2030, and 19.33 (CI: 12.3–13.6) million in 2050. **Table 2** provides the breakdown of the case number by 10-year age groups for the years 2020, 2030, and 2050. As expected, people over the age of 80 had the highest burden of dementia, from 3.6 (CI: 2.5–4.7) million in 2020 to 5.3 (CI: 3.7–6.8) million in 2030 to 12 (CI: 8.3–15.3) million in 2050. This age group is also predicted to take up an increasing proportion of the overall dementia cases from 53% in 2020 and 2030, to 62% in 2050.

DISCUSSION

This study updated the estimates of the burden of dementia in LAC using the latest epidemiological data from the region. To our knowledge, this is the first comprehensive systematic review that has exclusively focused on modeling the prevalence of dementia in LAC. Our results confirmed a high dementia prevalence of 8% in LAC, and a substantial (2.8-fold) increase in the number of dementia cases over the next three decades. The results also indicate that an increasing majority of the cases will fall upon the oldest (≥80) age group. This will place tremendous strains on the already fragile local health and social systems, as well as families and individuals.

While the cost of dementia might seem low in monetary terms in LMICs relative to HICs, the lack of publicly funded formal

TABLE 2 | Pooled age-specific and age-standardized prevalence and number of PWD in LAC for the years 2015, 2020, 2025, 2030, and 2050.

Age	Pooled prevalence (CI 95%)		Number of PWD in LAC from our estimates (thousands)		
	Prince and Wimo (1)	Our estimates	2020	2030	2050
60–69	0.02	0.02 (0.01–0.04)	942 (471–1,884)	1,239 (620–2,478)	1,729 (864–3,457)
70–79	0.07	0.09 (0.05–0.13)	2,266 (1,259–3,273)	3,399 (1,889–4,910)	5,591 (3,106–8,076)
≥80	0.21	0.29 (0.20–0.37)	3,647 (2,515–4,653)	5,299 (3,654–6,761)	12,014 (8,286–15,329)
≥60	0.08	0.08 (0.05–0.115)	6,855 (4,245–9,811)	9,938 (6,163–14,149)	19,334 (12,256–26,862)

ADI (2015) provided prevalence estimates in 5-year age groupings. In this study, the mean of two age groups were taken to represent the prevalence estimates in 10-year age groupings (e.g., the prevalence was 0.015 for people aged 60–64 and 0.026 for people aged 65–69, therefore the prevalence of people aged between 60–69 was determined to be the mean of the two estimates, 0.0205.). The ADI 2015 estimates were used as a comparison for our Bayesian estimation.
Pooled prevalence from ADI (2015) are provided here for comparison.

assistance means the majority of the cost is borne by families (1, 30). Women often bear the role of the informal caregivers both within the family as well as in hired help. In Brazil, for instance, the cost of informal care (including costs associated with carers' loss in economic productivity) represents approximately three times the minimum wage, making it out of reach for the majority of people with dementia (7). The increase in the proportion of dementia cases in the oldest age group is also particularly problematic in light of decreasing family sizes, especially in urban areas (31). Elderly living with dementia often suffers from a number of associated comorbid conditions, requiring an increase in the number of providers, specialized care and healthcare spending to meet the unique clinical challenges of this group. Further burdens may include additional medications, assistance with activities of daily living including feeding, reductions in mobility, and pressure sores. Moreover, an increase in dementia cases in this age group could see an increase in the burden of care falling upon other elderly family members who themselves require assistance. Individuals living with severe dementia may rely more heavily on healthcare in long-term care facilities and eventually hospice (7). The infrastructure and support for such facilities may need policy makers to consider their expansion to meet demands for an aging population with dementia. Additional support to train providers and community members is needed for early identification of dementia. The role of interventions is also largely unknown, but available treatment options may be useful in earlier stages.

Alarmingly, the high prevalence reported in our study is a likely underestimation of the true prevalence of dementia in LAC. Risk factors of dementia, including illiteracy, low educational attainment, hypertension, obesity and diabetes, have been shown to disproportionately affect socio-economically deprived populations (32). LAC is one such region markedly affected by widespread socio-economic inequalities. Eleven LAC countries are amongst the top 30 nations with the worst Gini scores (33), while an estimated 23.3% of the population still live under poverty [<$5.50 a day (34)]. Illiteracy and low education attainment, in particular, are key drivers of dementia in LAC (7). One study in LAC found that the prevalence of dementia may be doubled in the illiterate population relative to the literate population (20). Illiteracy is particularly prevalent amongst LAC's elderly population (21.1%) (35), especially in indigenous populations and populations in rural areas (7). Yet, these populations are not represented in the studies identified for our current model, and are likely to have skewed our results toward an underestimation of the true burden of dementia in LAC.

The lack of data representativeness is largely a manifestation of the lack of research investment in the region resulting in data scarcity. Despite the comprehensiveness of our searches, only seven new cross-sectional studies from six of LAC's 52 countries/territories were identified. These studies together form a small sample of <8,000 people for a region with more than 70 million people over the age of 60 (3). Data scarcity is not an issue unique to the LAC region, but applies to most LMIC regions. One of the most comprehensive global dementia prevalence reviews did not identify any primary study from Central Europe, Australasia, South Asia and Southeast Asia published after 2010 (1). Another well-conducted global review included no study published after 2010 from Eastern Europe, Central Europe, Central Asia and Oceania. In the same review, only four studies published after 2010 were included for the estimate for the Middle East and Africa (6). The only known exception was our systematic review and meta-analysis on the epidemiology of dementia in China (1990–2010) using Chinese databases (i.e., CNKI and WanFang) (36). Our review returned 12,642 publications, of which 89 studies met the inclusion criteria. In total, 340,247 participants were assessed, and 9,900 were diagnosed with dementia. However, even with this relatively large number of studies, the research was still skewed toward urban and more developed parts of China, and did not sufficiently represent the diverse population of the country.

The lack of research investment also reflects a missed opportunity to capitalize on the unique populations (genetic clusters, low literacy, multilingual, multi-ethnic) offered by LAC, which could significantly enhance our understanding of the roles various population characteristics could play in the progression and risk factors of disease development (37). In addition, the lack of longitudinal studies that monitor incidence, mortality and the environmental and biological

risk factors of dementia in the region complicates efforts to adequately understand the rising dementia cases in the region for developing contextually appropriate ways to effectively reduce risks.

A number of strengths and limitations of this study merits further mention. We have aimed to validate the Bayesmeta approach for data projections in the setting of data scarcity in this as well as our prior work (11). However, despite this paper being the second attempt at validating the Bayesmeta package with a separate JAGS algorithm, we have not contrasted the results of the two algorithms using inferential statistics. Furthermore, performing a systematic validation of the Bayesmeta package for use in meta-analysis is also needed, but is outside the scope of this paper. Due to limited resources, we were unable to conduct a full systematic review of non-English publications that contain dementia estimates in the LAC region – a limitation also observed in previous systematic reviews (1, 4) that have produced the currently accepted dementia estimates of LAC for the Alzheimer' Disease International (ADI) and the WHO. This limitation could have potentially reduced the number of studies identified for the region. To reduce the number of non-English studies we might have missed, we evaluated the studies cited by a recent review of dementia in LAC by Nitrini et al. (7) which included the two systematic reviews of English and non-English studies on the subject. Despite the 4-year overlap these reviews and the current study, no new data that met our inclusion criteria were identified. This gives us the confidence that any non-English studies that we might have missed are restricted to the 2-year period between 2017 and 2018. To give an indication on how many papers we might have missed for this 2-year period, we calculated the average number of non-English papers published per year that met our inclusion criteria to be 0.12 (see **Supplementary Material 3**). Thus, any data we might have missed is likely to be marginal and unlikely to have affected our current estimates. To further minimize the chance of missing valuable data, future reviews should strive to incorporate non-English studies when possible. Another limitation of our study is that our analyses were confined by the limited data reported in the studies used for our model. For example, the absence of case breakdowns by sex and dementia subtypes in the original papers has prevented the generation of sex-specific and subtype-specific estimates. This is a well-known issue in the burden of disease area. To maximize the value of the scarcely funded research, future publications of epidemiological studies on dementia should adopt standardized guidelines specifically designed to ensure more precise, consistent and transparent reporting. The adoption of two guidelines would also greatly assist global health researchers to better appraise the quality of studies, extract more relevant information and improve regional burden estimates (38–40). The first is the *Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)* guidelines developed in 2007 for the accurate and complete reporting of observational epidemiological studies (38, 39). The second is the *Standards of Reporting of Neurological Disorders (STROND) Checklist*, in which Bennett et al. (40) which provides future guidance on the steps toward full and consistent reporting of neuro-epidemiological studies for the purpose of the burden of disease-type studies such as the current study.

CONCLUSION

The results of this systematic review suggest that the LAC region is on an upward disease trajectory in terms of burden of dementia. There is a need for more dementia and dementia subtype epidemiological research in this region, especially from the less resourceful countries, in order to accurately estimate dementia prevalence and the health needs of a varied and diverse population. There is a need for greater globalization of knowledge with a greater emphasis placed on the amount and quality of evidence produced. With the trend of demographic aging in the coming decades, the prevalence and burden of dementia will continue to increase. This will have serious implications for the economy, healthcare systems and the communities in LAC. In particular, there may be additional burdens placed on caregivers and strain on healthcare facilities to meet demands of an aging population. Despite the comprehensive scope of our review, rural and socio-economically deprived populations, including indigenous, illiterate and low-literacy populations were underrepresented in these data. This is likely to have skewed our results toward underestimating the true burden in this region. Such information is paramount for guiding clinical practice, which will allow not only for improved evaluations in early dementia diagnosis but also guide the development of effective policies for improving dementia prevention, diagnosis and clinical management in LAC's aging communities.

DATA AVAILABILITY STATEMENT

The original contributions generated for the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

KC and YX conceptualized the paper. YX and KV carried out the systematic review. YX, CA, and SA performed the analytic calculations. YX, KV, AP, and KC wrote the manuscript with input from all authors. All authors have discussed the results and reviewed the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.628520/full#supplementary-material

REFERENCES

1. Prince M, Wimo A. *World Alzheimer Report 2015 - The Global Impact of Dementia*. Alzheimer's Disease International (ADI) (2015). Available online at: https://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf (accessed May 29, 2021).
2. Bank W. *Life Expectancy at Birth, Total (Years) - Latin America & Caribbean*. Available online at: https://data.worldbank.org/indicator/SP.DYN.LE00.IN?locations=ZJ (accessed September 29, 2020).
3. United Nations. *World Population Prospects: The 2019 Revision*. New York, NY: United Nations (2019).
4. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement.* (2013) 9:63–75.e2. doi: 10.1016/j.jalz.2012.11.007
5. Prince M, Jackson J. *World Alzheimer Report 2009*. Alzheimer's Disease International (ADI) (2009). Available online at: https://www.alz.co.uk/research/files/WorldAlzheimerReport.pdf (accessed May 29, 2021).
6. Nichols E, Szoeke CEI, Vollset SE, Abbasi N, Abd-Allah F, Abdela J, et al. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: a systematic analysis for the global burden of disease study 2016. *Lancet Neurol.* (2019) 18:88–106. doi: 10.1016/S1474-4422(18)30403-4
7. Nitrini R, Barbosa MT, Dozzi Brucki SM, Yassuda MS, Caramelli P. Current trends and challenges on dementia management and research in Latin America. *J Glob Health.* (2020) 10:10362. doi: 10.7189/jogh.10.010362
8. Seide SE, Röver C, Friede T. Likelihood-based random-effects meta-analysis with few studies: empirical and simulation studies. *BMC Med Res Methodol.* (2019) 19:16. doi: 10.1186/s12874-018-0618-3
9. Higgins JPT, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. *J R Stat Soc Ser A Stat Soc.* (2009) 172:137–59. doi: 10.1111/j.1467-985X.2008.00552.x
10. Spiegelhalter DJ. Incorporating Bayesian ideas into health-care evaluation. *Stat Sci.* (2004) 19:156–74. doi: 10.1214/088342304000000080
11. Poon AN, Xiang Y, Zavalishina Y, Ayanian S, Aitken CF, Procter A, et al. Systematic review estimating the burden of dementia in the WHO Southeast Asia Region using Bayesian and frequentist approaches. *J Glob Health.* (2020) 10:020701. doi: 10.7189/jogh.10.020701
12. Team RC. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: Team RC (2013).
13. Röver C. Bayesian Random-Effects Meta-Analysis Using the bayesmeta R Package. *J Stat Softw*. (2020) 93:1–51. doi: 10.18637/jss.v093.i06
14. Plummer M. JAGS: a program for analysis of Bayesian models using Gibbs sampling. In: *Proceedings of the 3rd International Workshop on Distributed Statistical Computing*. Vienna, Austria (2003)
15. UNSD. *Standard Country or Area Codes for Statistical Use*. New York, NY: UNSD (2020).
16. Association AP. *Diagnostic and statistical manual of mental disorders (DSM-5®)*. Washington, DC: American Psychiatric Pub (2013).
17. World Health Organization (WHO). *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines.* (1992). Available online at: https://icd.who.int/browse10/2019/en (accessed September 28, 2020).
18. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack Jr CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* (2011) 7:263–9. doi: 10.1016/j.jalz.2011.03.005
19. Román GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, et al. Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. *Neurology.* (1993) 43:250. doi: 10.1212/WNL.43.2.250
20. Prince MJ, De Rodriguez JL, Noriega L, Lopez A, Acosta D, Albanese E, et al. The 10/66 Dementia Research Group's fully operationalised DSM-IV dementia computerized diagnostic algorithm, compared with the 10/66 dementia algorithm and a clinician diagnosis: a population validation study. *BMC Public Health.* (2008) 8:219. doi: 10.1186/1471-2458-8-219
21. Nitrini R, Bottino CM, Albala C, Custodio Capuñay NS, Ketzoian C, Llibre Rodriguez JJ, et al. Prevalence of dementia in Latin America: a collaborative study of population-based cohorts. *Int Psychogeriatr.* (2009) 21:622–30. doi: 10.1017/S1041610209009430
22. Sánchez SS, Abanto J, Sanchez-Boluarte A, Boluarte-Carbajal A, Sanchez-Coronel D, Custodio-Capuñay N, et al. Frequency and associated factors of amnestic mild cognitive impairment at four senior citizen clubs in Lima, Peru. *Dement Neuropsychol.* (2019) 13:321–8. doi: 10.1590/1980-57642018dn13-030009
23. Eldemire-Shearer D, James K, Johnson P, Gibson R, Willie-Tyndale D. Dementia among older persons in jamaica: prevalence and policy implications. *West Indian Med J.* (2018) 67:1–8. doi: 10.7727/wimj.2017.133
24. Davis G, Baboolal N, Mc Rae A, Stewart R. Dementia prevalence in a population at high vascular risk: the Trinidad national survey of ageing and cognition. *BMJ Open.* (2018) 8:e018288. doi: 10.1136/bmjopen-2017-018288
25. Pedraza OL, Montes AMS, Sierra FA, Montalvo MC, Muñoz Y, Díaz JM, et al. Mild cognitive impairment (MCI) and dementia in a sample of adults in the city of Bogotá. *Dement Neuropsychol.* (2017) 11:262–9. doi: 10.1590/1980-57642016dn11-030008
26. Cesar KG, Brucki S, Takada LT, Nascimento LFC, Gomes C, Almeida M, et al. Prevalence of cognitive impairment without dementia and dementia in Tremembé, Brazil. *Alzheimer Dis Assoc Disord.* (2016) 30:264–71. doi: 10.1097/WAD.0000000000000122
27. Bartoloni L, Blatt G, Insua I, Furman M, González MA, Hermann B, et al. A population-based study of cognitive impairment in socially vulnerable adults in Argentina. The Matanza Riachuelo study preliminary results. *Dement Neuropsychol.* (2014) 8:339–44. doi: 10.1590/S1980-57642014DN84000006
28. Veláz-Brizuela IE, Ortiz GG, Ventura-Castro L, Árias-Merino ED, Pacheco-Moisés FP, Macías-Islas MA. Prevalence of dementia, emotional state and physical performance among older adults in the metropolitan area of Guadalajara, Jalisco, Mexico. Umegaki H, editor. *Curr Gerontol Geriatr Res.* (2014) 2014:387528. doi: 10.1155/2014/387528
29. Correa Ribeiro PC, de Souza Lopes C, Alves Lourenço R. Prevalence of Dementia in elderly clients of a private health care plan: a study of the FIBRA-RJ, Brazil. *Dement Geriatr Cogn Disord.* (2013) 35:77–86. doi: 10.1159/000345984
30. Villalobos Dintrans P. Informal caregivers in Chile: the equity dimension of an invisible burden. *Health Policy Plan.* (2019) 34:792–9. doi: 10.1093/heapol/czz120
31. Garcia A, Bucher-Maluschke JSNF, Pérez-Angarita DM, Vargas-Velez YE, Pereira FN. Couple and family relationships in Latin American social comparative studies. *Interpersona An Int J Pers Relationships.* (2016) 10:109–24. doi: 10.5964/ijpr.v10i2.259
32. Mukadam N, Sommerlad A, Huntley J, Livingston G. Population attributable fractions for risk factors for dementia in low-income and middle-income countries: an analysis using cross-sectional survey data. *Lancet Glob Heal.* (2019) 7:e596–603. doi: 10.1016/S2214-109X(19)30074-9
33. World Bank. *Gini Index*. Available online at: https://data.worldbank.org/indicator/SI.POV.GINI (accessed September 28, 2020).
34. Bank W. *LAC Equity Lab: Poverty - Poverty Rate*. Available online at: https://www.worldbank.org/en/topic/poverty/lac-equity-lab1/income-inequality/income-distribution (accessed September 28, 2020).
35. UNESCO. *Literacy Rates Continue to Rise from One Generation to the Next*. UIS Fact Sheet No. 45 | September 2017 (2017). Available online at: http://uis.unesco.org/sites/default/files/documents/fs45-literacy-rates-continue-rise-generation-to-next-en-2017_0.pdf (accessed September 28, 2020).
36. KY, Wang W, Wu JJ, Theodoratou E, Deary IJ, Car J, Middleton L, et al. The burden of Alzheimer's disease and other forms of senile dementias in China between 1990 and 2010. *Lancet.* (2013) 381:2016–23. doi: 10.1016/S0140-6736(13)60221-4
37. Parra MA, Baez S, Allegri R, Nitrini R, Lopera F, Slachevsky A, et al. Dementia in Latin America. *Neurology.* (2018) 90:222–31. doi: 10.1212/WNL.0000000000004897
38. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, for the STROBE initiative. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. (2007) 370:1453–57. doi: 10.1016/S0140-6736(07)61602-X

39. Vandenbroucke JP, Von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. *PLoS Med.* (2007) 4:e297. doi: 10.1371/journal.pmed.0040297
40. Bennett DA, Brayne C, Feigin VL, Barker-Collo S, Brainin M, Davis D, et al. Development of the standards of reporting of neurological disorders (STROND) checklist: a guideline for the reporting of incidence and prevalence studies in neuroepidemiology. *Eur J Epidemiol.* (2015) 30:569–76. doi: 10.1007/s10654-015-0034-5

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Neurology

ORIGINAL RESEARCH
published: 13 August 2021
doi: 10.3389/fneur.2021.662253

Virtual Support in Dementia: A Possible Viable Strategy for Caregivers

Ceres Ferretti, Ricardo Nitrini and Sonia M. D. Brucki*

Cognitive and Behavioral Neurology Group, Faculty of Medicine, Hospital das Clínicas, University of São Paulo, São Paulo, Brazil

Background: In the last 10 months, due to the Covid-19 pandemic, several studies have shown that health education and virtual support strategies for caregivers of patients with dementia, in the management of home care, can be viable. Low and middle income countries, in particular, have sought to use these means to reduce the daily burden of caregivers, through virtual meetings of education and support.

Objectives: To present the feasibility of a pilot study on the use of a support action contemplated by the Caad Project–indirect costs of dementia–from HC-FMUSP.

Methods: Observational study in which 93 caregivers were invited to participate in virtual meetings on a frequency of three times/week, lasting 1 h each.

Results: Of the 93 invited family members, and after 3 months, 42 answered eight questions about the effectiveness of the action. High percentages of positive responses regarding program satisfaction ranged from 86 to 100%.

Conclusion: This study showed results of a very simple intervention that suggests that it is possible to offer caregivers of patients with dementia a program that can be used in primary care, in order to understand the difficulty of caregivers in their daily care of patients with dementia, with daily management guidelines on a case-by-case basis, in addition to promoting the implementation of an education strategy about the importance of knowing, and recognizing anatomophysiological changes in the aging process and its implications for the rupture of the imaginary line that involves senescence and senility. This allows the caregiver to feel able to protect his patient and himself by preventing the emergence of common diseases in this age group. Further studies are needed to explore this type of non-pharmacological support.

Keywords: dementia, support virtual, education health, nursing, care, caregiver

OPEN ACCESS

Edited by:
Suvarna Alladi, Nizam's Institute of Medical Sciences, India

Reviewed by:
Gustavo C. Roman, Houston Methodist Research Institute, United States
Gabriele Sani, Università Cattolica del Sacro Cuore, Italy

****Correspondence:***
Ceres Ferretti
cereseloah@gmail.com

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: *31 January 2021*
Accepted: *02 July 2021*
Published: *13 August 2021*

Citation:
Ferretti C, Nitrini R and Brucki SMD (2021) Virtual Support in Dementia: A Possible Viable Strategy for Caregivers. Front. Neurol. 12:662253. doi: 10.3389/fneur.2021.662253

INTRODUCTION

Never, in history, has there been a greater need for adaptation and social change than that seen today. The world is perplexed, facing the biggest health crisis of all time amid the pandemic caused by COVID-19. Low-, middle-, and high-income countries (LMIC) find themselves totally unprepared, both economically and socially, to prevent more people every day from becoming infected and requiring hospital support and beds in high complexity services, which are simply not available to all those in need. Doctors and nurses on the frontline are suffering the mental impact of

the pandemic, while also themselves vulnerable to contamination and exposed to a life-threatening situation (1, 2). A recent study presented alarming data related to the number of people affected by the new coronavirus pandemic, which has surpassed 10.5 million people infected worldwide (3). Today, we remain perplexed by the worsening of this scenario as epidemiological reports present even more alarming figures showing how the second wave of COVID-19 is already plaguing Europe and the USA, each with 52,593,188 and 32,210,817 confirmed cases, respectively. Thus, the mark of more than 155,665,214 million cases globally has been reached, ∼2% of the world population, with 3,250,648 related deaths (4).

For Latin American countries, the pandemic involving the new coronavirus has had an even more negative impact, due to the limited resources available regarding the health system and society as a whole. These factors meant the global health crisis has taken on a much greater dimension, as it affects thousands of people who do not have equal access to health services (5). At this time, Brazil is concerned over the soaring number of cases signaling the beginning of the second wave. Current data confirm more than 14,930,183 cases of infection by the disease and over 414,399 related deaths (4, 6). Researchers and health professionals are striving for science to prevail and for protection and prevention measures to be adopted by all, a challenge that has proven far from easy. The country has many cultural differences and socio-economic inequalities that facilitate the spread of the virus since not all regions and populations adhere to the health and hygiene measures recommended by the WHO (5, 7). In some cases, this is because the physical conditions and housing preclude adherence, while for others, there is resistance to adopting the necessary measures, such as the use of the main protective equipment, the face mask. In any event, most societies are committed to finding ways to prevent further spread of the disease. For 10 months, we have been following the alarming devastation caused by a virus about which very little is known, yet forces thousands of people to remain isolated in their homes (8). Never before have so many nations come together in an attempt to reduce the number of victims and attenuate the social and financial impact that have led to the crash in the world economy (9). Everyone is unanimous in stating that only the vaccine can have a positive impact and even though doubts remain about possible immunity, scientists agree this is the only way to control the spread and restore community life. This "new normal" seems to be the best alternative until we are sure, as occurred for the H1N1 flu epidemic, that we will indeed achieve immunity, albeit temporary or permanent (9). Some chronic non-communicable diseases (CNCDs), such as dementia with different etiologies, require coping strategies be developed in LMICs, given the clinical course of patients and high morbidity associated with these processes (3, 4). Virtual support programs seem promising and simple, low-cost non-pharmacological interventions have shown positive results (10). This pilot study sought to determine the utility of a virtual non-pharmacological education and support program for caregivers of dementia patients.

Evidence in the literature clearly shows that multi- and interdisciplinary non-pharmacological approaches are always the first line of care for patients with functional and behavioral complaints (11–13). Alternatively, combined therapy (14) can also be useful, and professionals involved in caring for people with dementia and their families need to be well-prepared with regard to their knowledge on the peculiarities encountered in the progression of different types dementia, with a view to proposing and developing an effective care plan on a case-by-case basis (12) and following guidelines addressing the disease in a focused and individualized way, meeting the inherent needs at each stage (**Figure 1**).

FIGURE 1 | Dependencies associated with the evolution stages of Ferretti (2020). *IADL, Instrumental activities daily living; **, ADL, activities daily living.

One of the basic and essential responsibilities in nurse training is the work that involves health promotion and disease prevention, i.e., health education (15). The WHO has highlighted this initiative as a key goal, especially in low- and middle-income nations (16). In addition to the care given at each stage of dementia, the pandemic situation with the new coronavirus requires that everyone be protected. Some of the most vulnerable groups need special attention and care, namely, elderly people aged 60–65 years or older with CNCDs, such as dementia. Institutional care at all levels of public or private health strives to find a way to keep these individuals at home, in the safest possible way (9). The average age of this group is ∼74 years, and their caregivers, many of them elderly, also need attention and care (17). The social isolation imposed by the pandemic makes it more difficult to attend outpatient follow-up consultations, and thus, a distance monitoring strategy may be useful. The objective of this study is to demonstrate the potential feasibility of a follow-up study with adjusted methodology for cost-effectiveness analysis, and we would like to clarify that this was the first virtual support model in our service.

We believe that this pilot study can stimulate other studies and will bring us more robust and consistent results for proposing partnerships for conducting collaborative studies of effectiveness in our country and in other countries as well. It is very important to comment here that despite our economic and social barriers, we understand that some low- and middle-income countries live with extreme economic and social inequalities that, at times, do not allow access to technologies that enable strategies such as the one presented in this work.

Even so, we believe that it is possible to create and or expand this kind of strategies with the participation of the health system, study centers, and neighborhood associations and improve existing actions in the primary care network with human and material resources that meet the needs of the population with these and other proposals that lead to health promotion and disease prevention actions, aiming at quality of life for patients

with dementia and their caregivers and reduction of direct costs for the health system.

METHOD

An observational pilot study was conducted involving non-pharmacological support interventions and online education to assist caregivers of dementia patients during the current pandemic. In fact, there are some important gaps in this section. However, in this pilot work, our main intention was to show that a virtual support for caregivers can make it possible to obtain positive results with education actions for the management with dementia at a distance. Our proposal was to identify whether there is a possibility to mitigate the direct social costs and the indirect costs of family caregivers. The intervention sought to help caregivers regarding their doubts and needs for information on health and disease management for patients followed at the HC-FMUSP Outpatient Clinic for Cognitive and Behavioral Neurology.

Procedures

Potential participants were contacted by phone and 93 family caregivers were included. All participants were explained that due to social distancing measures, an educational and support activity would be provided, initially consisting of three weekly meetings each lasting 1 h. Two of the sessions would be conducted via virtual group meetings and one session would be to clear up doubts via WhatsApp messages. The messages received from caregivers via WhatsApp were monitored by the study coordinator, a specialist nurse in dementia. If an urgent/emergency issue was identified, a doctor in the group was contacted immediately to advise on the best approach; otherwise, the family member waited until a designated online meeting for the response. These meetings were structured as follows:

1. Mondays: Theme "Health Education." Each system of the body was conceptualized separately, from an anatomic-functional perspective, along with the changes typical of senescence and the main diseases, with emphasis on advice for their prevention.
2. Fridays: Guidance on needs raised by the caregivers regarding the patient or themselves.
3. WhatsApp: Employed whenever caregiver deemed necessary where, in this case, the issues were first screened by the coordinator for urgency/emergency status and immediate response. If deemed non-urgent, caregivers waited until the next meeting on a specific day (Fridays).

After 3 months of online monitoring (Aug/Oct), an anonymous questionnaire was sent, also online, by agreement with the participating caregivers. The survey contained eight questions to collect information on the degree of satisfaction of caregivers in relation to the support offered. The study was part of the CAAD Project, approved by the Ethics and Research Committee of the Hospital das Clínicas of the Faculty of Medicine of the University of São Paulo under permit number 31041620.2.1001.0068 on November 5, 2020.

RESULTS

Of the total sample of caregivers ($N = 93$), only 45% ($n = 42$) answered the form sent containing the following questions: Q1. Do you think your daily life has improved after you started participating in the virtual meetings? Q2. Are you satisfied with the subjects of the virtual meetings? Q3. Do you now feel more secure with the support you are receiving? Q4. Are you practicing social isolation as recommended? Q5. Complies with health and hygiene measures aimed at preventing COVID-19 (hand washing, use of masks and alcohol gel, etc.)? Q6. Has the guidance given during the virtual meetings been useful? Q7. Did you feel welcome? Q8. Would you like this support to continue after the pandemic? The level of satisfaction among participants on questions 5 to 8 (100%) was high. On questions 2 to 4, the level of satisfaction ranged from 86 to 93%, while 7.1% of caregivers were dissatisfied with the program on each question. For one question (number 1), 86% of caregivers reported satisfaction with the program, 7.1% dissatisfaction, and 7.1% no change (**Figure 2**). **Tables 1**, **2** show the descriptive analysis of frequencies before and after the virtual program, and **Table 3** shows the percentage improvement of difficulties to the caregivers after intervention model. Finally, **Table 4** presents a Cochran model, a non-parametrical statistical analysis, used to show a global improvement of difficulties founded after the virtual support interventions.

DISCUSSION

The study findings suggest that simple and very low-cost measures enabled the quality of non-pharmacological care to be maintained at this critical time via virtual support. Particularly during the current pandemic, everyone needs to be protected, while some more vulnerable groups need special attention and care, i.e., the elderly aged 60–65 years or older and those with CNCDs, such as dementia. A previous study published a few years ago explored the difficulties observed in low- and middle-income countries and showed that solutions can be found without the need for large investments when economic and social resources are limited (18), a finding corroborated by this pilot study. The training of professionals and of informal (family and friends) and formal (hired) caregivers on providing care has been discussed as an effective strategy that can prevent the onset of comorbidities and thus reduce healthcare costs for the State and the family (17, 18). In Brazil, for some years now, some isolated strategies have been employed that have proven the effectiveness of education programs in dementia, involving the use of printed support material at psychoeducational meetings, later delivered to caregivers or sent by email to those unable to attend face-to-face support meetings (19, 20). These studies have shown that patients and caregivers monitored in specialized services benefit from counseling measures and support groups focused on individualized needs, conferring numerous benefits in terms of both functional and behavioral aspects of patients with dementia, alleviating the burden of caregivers (21, 22).

These support materials, such as management and educational manuals that focus on information inherent to health promotion

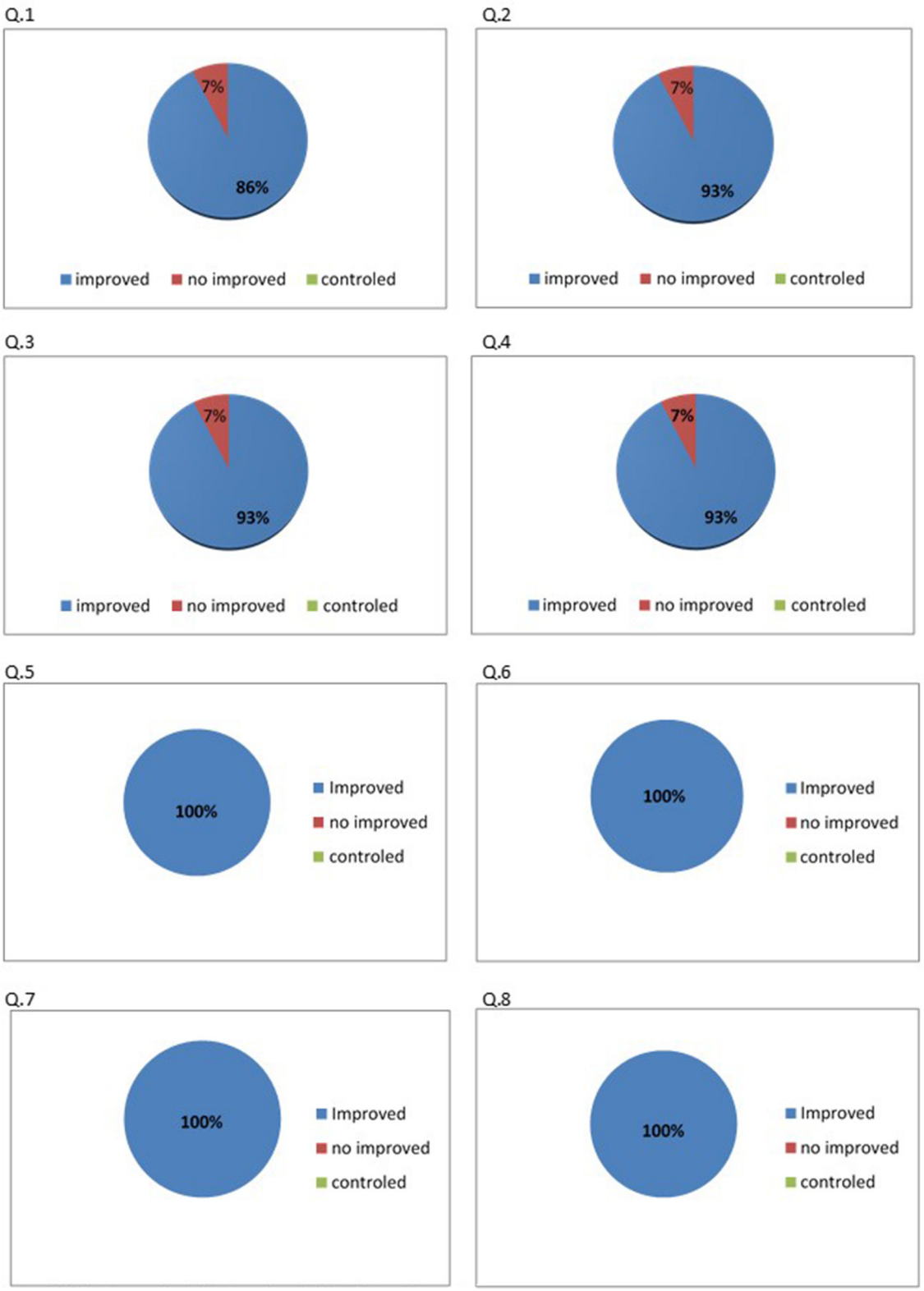


FIGURE 2 | Preliminary results of virtual meetings GNCC-Support. Ferretti et al. (2020).

TABLE 1 | Frequencies of caregiver difficulties before the virtual support program.

	Values	
	*0	#1
$Q.2**B	42	0
$Q.3**B	42	0
$Q.1**B	42	0
$Q.4**B	42	0
$Q.5**B	42	0
$Q.6**B	42	0
$Q.7**B	42	0
$Q.8**B	42	0

*$Q, Question; *0, difficulties of managements; **B, Before; #1 is considered as without difficulties.*

TABLE 2 | Frequencies after the virtual support program.

	Values	
	0**	1#
*Q.2	6	36
*Q.3	6	36
*Q.1	12	30
*Q.4	6	36
*Q.5	0	42
*Q.6	0	42
*Q.7	0	42
*Q.8	0	42

**Q, Question; **0, difficulties of managements; #1 is considered as without difficulties.*

TABLE 3 | Percentage improvement data after the virtual support program.

***N* = 42**	**Improved (*n*)**	**%**	**Controlled (*n*)**	**%**
&Q.1	36	86	3	14
Q.2	39	93	3	7
Q.3	39	93	3	7
Q.4	39	93	3	7
Q.5	42	100	0	0
Q.6	42	100	0	0
Q.7	42	100	0	0
Q.8	42	100	0	0

&Q.1–Q.8, Questions.

and disease prevention, are very useful in the primary healthcare network, helping both professionals and caregivers in the appropriate management of dementia, and their content can be delivered in person or remotely. Whether offered to lay caregivers or health professionals, the language of the content need only be adapted to the level of understanding of the participant. Good results can be obtained from non-pharmacological actions aimed at non-cognitive changes, activities of daily living, and caregiver stress (19, 21).

TABLE 4 | Cochran model for global improvement of difficulties after virtual support.

Test statistics			
N	**[a]Cochran's**	***df***	***p***
42	56,609	7	#0.000

#$p \leq 0.001$.
[a]Cochran's test.

During this pandemic, several publications have shown results corroborating the effectiveness of virtual support, while others have noted their shortcomings (10, 23, 24). However, evidence on the socio-economic difficulties of low- and middle-income countries increasingly points to the use of strategies of this type. This is especially true when social distancing guidelines need to be observed more rigorously, when virtual interventions have proven to be excellent support measures, allowing clarifying of doubts, better organization of time spent on patient care, and prevention of problems related to the mental health of caregivers, who feel supported, albeit at a distance, by the professionals involved in the virtual support program (25). In a recent study, over 40% of caregivers reported clinically diagnosed depression, on average, 24 months after engaging in caregiving (17).

The burden on caregivers of dementia patients has always been high. In Brazil, the same study showed an average duration of 373 h (SD = 251.29 h) of informal patient care provision for basic activities of daily living, instrumental activities of daily living, supervision, and loss of productivity, translating to an average monthly monetary loss for the direct caregiver of US$118 (SD US$149.87), based on the February/2016 BRL–USD exchange rate (17).

In this pilot project, our positive expectations were confirmed, encouraging us to discuss and organize the methods to provide for the continuity of the program after the pandemic, as desired by the participating family members. It is now necessary to contextualize and confirm, by means of cost-effectiveness studies, that nursing interventions providing guidance on disease prevention in aging and on how, when, and why to adhere to certain individually prescribed procedures can improve the quality of life of patients and family members. This approach, especially amid the present health crisis, can cater to the needs of this high-risk group, which is more vulnerable to complications if infected by the new coronavirus, in societies still unprepared for this situation, such as Brazil. Currently, there are an estimated 1.5–1.7 million people living with dementia in Brazil and about 9 million in Latin America as a whole (25). Among all Latin American countries, Chile has proved the most compliant with the WHO proposals regarding the guidelines contained in the World Dementia Plan (16, 26). The Chilean model can contribute greatly to other Latin American countries still in the process of developing their national dementia plans. Despite the economic, social, and humanitarian difficulties, and in view of inequalities in LIMCs, as a social action, discussions should be encouraged among researchers working in diagnosis and treatment of dementias. This initiative could pave the way for a

major forum in which each country can discuss its health policies and present suggestions that lead to a consensus for practical, objective, low-cost, and well-informed decision-making. This can provide the basis for a "pilot" intervention project involving all participating countries, whose results can be analyzed after 18 months, when its feasibility could then be discussed.

Recently, our Research Center at the Hospital of Clinics of the Faculty of Medicine of the University of São Paulo and other research centers technically supported, at the municipal level, the Alzheimer Law—number 17,547 approved on January 12, 2021. This Law primarily advocates a center of assistance, study, and research dedicated to early diagnosis, treatment, monitoring, and training of professionals and family members made by specialists. Our expectation is that this action may, in the future, be replicated throughout Brazil.

Until such initiatives can be implemented, education, and support strategies like that presented in this report can be useful in LMICs.

Economic and social difficulties that already existed in Brazil are now aggravated by the pandemic. At present, 14 million unemployed Brazilians are relying on assistance from government and NGOs, without any other source of income. The economic scenario is one of an annual increase in inflation of (IPCA) 4.31%, exceeding Brazil's Central Bank target for 2020 of 4%, a GDP that shows signs of recovery (7.7%), but insufficient to restore the economy in the country (27), and points to the need in public health for different ways of facilitating the delivery of information that can improve survival for patients with NCDs, and their caregivers, helping them maintain the quality of life of this group.

Finally, it may be useful to reflect that, if results (in terms of cost effectiveness) of a follow-on study prove promising for the groups involved, namely, a study group and control group (on waiting list), then perhaps:

(a) Many elderly caregivers can be spared the mobility difficulty of seeking non-pharmacological guidance in care units, even after the pandemic.
(b) Through health promotion and disease prevention efforts, health education can also reduce the pressure on emergency services with complaints that can be avoided by adequate guidance from the caregiver. Examples include cases of recurrent UTI admission for inadequate hygiene, dehydration as a result of low fluid intake, or constipation due to bad eating habits, low fluid intake, and inadequate diet.

Solutions that require little or no additional investment for these families likely to be implemented in the primary care network, as is the case with the online support system reported, need to be further explored and, given their accessibility, considered for adoption by primary care health systems of LMICs.

Managing modifiable risk factors is a measure that lends itself to online education programs. The preliminary findings observed in this study allow us to envisage that in the near future, some non-pharmacological support interventions online may be even more effective than face-to-face measures considering the context of dementia. In addition, the mobility difficulties encountered by family members to access referral centers, often to clarify doubts easily resolved remotely, may be overcome. Moreover, the burden generated not only by commuting, but also through formal work hours lost that, in many cases, are also online or informal, by the people who live with the patient, can expose these caregivers to several factors that negatively impact their socioeconomic and emotional status (18).

CONCLUSION

The results of this very simple intervention suggest the utility of a program for caregivers of dementia patients in primary care. The intervention allowed a better understanding of the difficulties faced by caregivers in their daily care of dementia patients with daily management guidance given on a case-by-case basis. The program also promoted the implementation of an education strategy on the importance of understanding and recognizing anatomical and physiological changes in the aging process and their implications for the invisible line between senescence and senility. This empowers the caregiver to feel able to protect both the patient and themselves by preventing the emergence of common diseases in this age group.

Further studies are needed to explore this type of non-pharmacological support, which could prove to be an excellent and economical alternative for reducing direct and indirect costs related with dementia in LMICs. The new post-pandemic online support project provides for a longitudinal, cost-effective follow-up study that will prove the effectiveness of the non-pharmacological approach to nursing and that can control the emergence of common diseases in this age group, by reducing comorbidities and contributing to a healthy life throughout the life cycle. We envisage ongoing studies comparing these results and further demonstrating the potential for Latin America to reduce the direct and indirect burden on family members, promoting a more egalitarian and humanized social approach.

LIMITATIONS

This is a low-cost strategy and can be an excellent possibility for professional and family interaction, increasing trust between them, which can lead to the construction of an economic and social model to support our society and other Latin American countries. The limitation of this pilot study is its design. At this point, we only intend to show through this pilot study a real and low-cost possibility for LMIC like Brazil. However, we performed a small descriptive analysis and also applied a non-parametric model to verify if this virtual assistance model was effective. We hope, in the near future, to expand this work to other Brazilian centers, so that we can compare the results obtained between us.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics and Research Committee of Hospital das Clinicas, Faculty of Medicine, University of São Paulo. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

ACKNOWLEDGMENTS

We extend our thanks to RN and SB for their participation and support in carrying out this work and to all the family members of patients monitored at the Outpatient Clinic for Cognitive Neurology and Behavior at the HC-FMUSP, who kindly agreed to contribute to carrying out this study.

REFERENCES

1. OPAS/OMS. *Folha Informativa Covid-19*. Available online at: www.paho.org/pt/covid19 (accessed on December 14, 2020).
2. Archer SL. Providing care for the 99.9% during the COVID-19 pandemic: how ethics, equity, epidemiology, and cost per QALY inform healthcare policy. *Healthc Manage Forum*. (2020) 33:239–42. doi: 10.1177/0840470420939854
3. WHO Coronavirus Disease (Covid−19). *Dashboard Data*. (2020). Available online at: https://covid19.who.int/table (accessed December 14, 2020).
4. Nitrini R, Barbosa MT, Dozzi Brucki SM, Yassuda MS, Caramelli P. Current trends and challenges on dementia management and research in Latin America. *Glob Health*. (2020) 10:00362. doi: 10.7189/jogh.10.010362
5. Ministério da Saúde. Secretaria de vigilância em saúde. boletim epidemiológico especial, doença pelo coronavírus COVID-19. *Semana Epidemiology*. 43. Available online at: https://covid.saude.gov.br (accessed December 13, 2020).
6. World Health Organization. *Coronavirus Disease (COVID-19) Pandemic*. Available online at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019?gclid=EAIaIQobChMIss-_88rN7QIVkYKRCh1ITwwsEAAYASAAEgIj7PD_BwE (accessed 13 December, 2020).
7. Bianchetti A, Bellelli G, Guerini F, Marengoni A, Padovani A, Rozzini R, et al. Improving the care of older patients during COVID-19 pandemic. *Aging Clin Exp Res*. (2020) 32:1883–8. doi: 10.1007/s40520-020-01641-w
8. NEBRICS—Núcleo de Estudos do BRICS. *Os BRICS e a COVID-19: Combate à Pandemia e Cooperação Internacional*. Available online: https://www.ufrgs.br/nebrics/os-brics-e-a-covid-19-combate-a-pandemia-e-cooperacao-internacional/ (accessed December 12, 2020).
9. Domingues RB, Mantese CE, da Silva Aquino E, Fantini FGMM, do Prado GF, Nitrini R. Telemedicine in neurology: current evidence. *Braz Acad Neurol*. (2020) 78:816–26. doi: 10.1590/0004-282X20200131
10. Rokstad AMM, Døble BS, Engedal K, Kirkevold Ø, Benth JŠ, Selbaek G. The impact of dementia ABC educational programme on competence in person-centred dementia care and job satisfaction of care staff. *Int J Older People Nurs*. (2016) 12:1–10. doi: 10.1111/opn.12139
11. Ferretti CEL. Intervenção de enfermagem nas doenças neurodegenerativas. In: Koizume MS, Diccini S, editors. *Enfermagem em Neurociência, Fundamentos para a Prática Clínica*. São Paulo: Atheneu (2006).
12. Ferretti CEL. Avaliação de enfermagem e estratégias facilitadoras. In: Brucki SMD, Nitrini R, editors. *Diagnóstico e Cuidadaos de Pacientes Com Comprometimento Cognitivo: Equipe Multidisciplinar*. São Paulo: Omnifarma (2015).
13. Caramelli P, Bottino CMC. Tratando os sintomas comportamentais e psicológicos da demência. *Conferên Clín*. (2003) 56(2):2007. doi: 10.1590/S0047-20852007000200002
14. Espinheira MO. *Papel do Enfermeiro em Educação em Saúde*. Available online at: www.secad.artmed.com.br/blog/enfermagem/0-papel-do-enfermeiro-na-educação-em-saude (accessed October 11, 2020).
15. WHO. *Global Action Plan in the Public Health Response to Dementia 2017-2025*. Geneva: WHO (2021).
16. Ferretti C, Sarti FM, Nitrini R, Ferreira FF, Brucki SMD. An assessment of direct and indirect costs of dementia in Brazil. *PLoS ONE*. (2018) 13:e0193209. doi: 10.1371/journal.pone.0193209
17. Prince M, Graham N, Brodaty H, Rimmer E, Varghese M, Chiu H, et al. Alzheimer's disease international's 10/66 dementia research group – one model for action research in developing countries. *Int J Geriatr Psychiatry*. (2004) 19:178–81. doi: 10.1002/gps.1059
18. Ferretti C. Alterações anatomofisiológicas do envelhecimento e doenças comuns da Terceira idade. In: *Manual de Enfermagem Geriátrica e Gerontológica*. São Paulo (1997).
19. Brucki SMD, Ferretti C, Nitrini R. Manual para cuidadores da doença de alzheimer. In: *Ceredic – Centro de Referência em Distúrbios Cognitivos*. Faculdade de Medicina da Universidade de São Paulo.
20. Ferretti, C, Bertolucci PHF, Minett TSC. Behavior disorders and subjective burden among caregivers of demented patients. *Dement Neuropsychol*. (2007) 2:190–5. doi: 10.1590/s1980-57642008dn10200012
21. Brodaty H, Draper BM, Low LF. Behavioral and psychological symptoms of dementia: a seven-tired model of service delivery. *MJA*. (2003) 178:231–4. doi: 10.5694/j.1326-5377.2003.tb05169.x
22. Gately ME, Tickle-Degnen L, Trudeau SA, Ward N, Ladin K, Moo LR. Caregiver satisfacytion with video telehealth home safety evaluation for dementia. Int J Telerehabil. (2020) 35–42. doi: 10.5195/ijt.2020.6337
23. Armstrong MJ, Alliance S. Virtual support groups for informal caregivers of individuals with dementia. A scoping review. *Alzheimer Dis Assoc Disord*. (2019) 33:362–9. doi: 10.1097/WAD.0000000000000349
24. Egan KJ, Pinto-Bruno ÁC, Bighelli I, Berg-Weger M, van Straten A, Albanese E, et al. Online training and support programs designed to improve mental health and reduce burden caregivers of people with dementia: a systematic review. *J Am Med Dir Assoc*. (2018) 19:200–6.e1. doi: 10.1016/j.jamda.2017.10.023
25. Alzheimer's Association. *Facts and Figures*. Chicago: Alzheimer's Association (2020).
26. Universidad de Chile. *Policy Paper Demencias*. Santiago: Universidad de Chile (2019).
27. *Instituto Brasileiro de Geografia e Estatística—IBGE*. (2020). Available online at: http://www.ibge.gov.br

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Public Health

PERSPECTIVE
published: 24 August 2021
doi: 10.3389/fpubh.2021.662364

The Social Housing Crisis and the Barriers to Developing Dementia-Friendly Communities in Chile

Daniel A. Jiménez [1,2,3*†] *and Francisca Cancino-Contreras* [4†]

[1] Department of Neurological Sciences, Faculty of Medicine, University of Chile, Santiago, Chile, [2] Department of Neuroscience, Faculty of Medicine, University of Chile, Santiago, Chile, [3] Servicio de Neurología, Hospital Salvador, Santiago, Chile, [4] Francisca Cancino-Contreras, Facultad de Arquitectura, Diseño y Construcción, Universidad de las Américas, Providencia, Chile

Interaction with living place and neighbourhood is one of the cornerstones for creating dementia-friendly communities (DFC). Chile has one of the largest proportions of older adults in Latin America and is currently facing an increase in the number of people with dementia. In this context, the Chilean government has launched a national strategy that involves actions in the health and social care system, including the promotion of DFC. From a multisectoral approach, social and environmental aspects involving engagement with local communities and access to social connections and services are directly related to urban policies. This perspective article focuses on urban aspects of social housing policy, such as placement, networks, affordability and the relationship between subsidy structure and adequate housing provision in a country with a qualitative housing deficit of around 1,200,000 units and where a large proportion of people with dementia and their families live in poverty. We identified several barriers to delivering appropriate environments for people living with dementia in relation to a two-fold problem: (a) the social housing subsidy displaces caregivers and/or older adults to satellite towns where social connections and access to services and urban equipment are lost; and (b) people resisting displacement live in overcrowded neighbourhoods where dementia is a common problem. In both scenarios, a detrimental environment and social conditions directly affect the quality of life of elderly people living with dementia and their caregivers.

Keywords: dementia-friendly communities, Chile, social housing, dementia, neighbourhood

OPEN ACCESS

Edited by:
Geeske Peeters, Radboud University Nijmegen Medical Centre, Netherlands

Reviewed by:
Kate O'Loughlin, The University of Sydney, Australia
Louise Lafortune, University of Cambridge, United Kingdom

***Correspondence:**
Francisca Cancino-Contreras francisca.cancino.contreras@edu.udla.cl

† These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Aging and Public Health, a section of the journal Frontiers in Public Health

Received: *01 February 2021*
Accepted: *28 July 2021*
Published: *24 August 2021*

Citation:
Jiménez DA and Cancino-Contreras F (2021) The Social Housing Crisis and the Barriers to Developing Dementia-Friendly Communities in Chile. Front. Public Health 9:662364. doi: 10.3389/fpubh.2021.662364

INTRODUCTION

Chile has one of the largest proportions of older adults (over 60 years of age) in Latin America and is currently facing an increase in the prevalence of dementia and other non-communicable chronic diseases (1). The rapid ageing of Chile's population has been driven by an increase in life expectancy—currently 82.4 years for females and 76.5 for males—and a sustained decline in the fertility rate that mirrors trends in developed countries (2). The increase in the proportion of elderly people has been accompanied by a rise in the number of people with dementia to around 200,000 in 2020, a figure expected to surpass 500,000 by 2050 (3). This figure is especially concerning for a country with almost 20 million people requiring urgent attention from the public and private sectors.

In 2015, the Chilean government launched the first National Plan for Dementia, upgrading the disease to a national priority (4). The biopsychosocial model proposed comprised actions in the health sector and in other areas, including the promotion of dementia-friendly communities (DFC). However, there are no clear definitions or guidelines for the implementation of these communities in the Chilean context. This perspective article considers housing as the primary component for the development of healthy communities and neighbourhoods, focusing on the urban aspects of social housing policy, such as placement, networks, affordability, and the relationship between the subsidy structure and adequate housing provision for people living with dementia in Chile.

CARING FOR PEOPLE LIVING WITH DEMENTIA IN CHILE

In Chile, as in most Latin American countries, people living with dementia, along with their caregivers, are struggling silently against inadequate support and the economic cost of treating the disease (5). Patients and families feel abandoned by a broken health and social care system, relying on unspecialised support from relatives and neighbours. Some 97% of people with dementia live in a family member's home, and in over 70% of cases are cared for by a female caregiver, generally daughters or spouses (6). Informal care delivered by family members who are inactive in the labour market increases indirect costs in lower socio-economic status groups (7). This scenario contrasts with the situation in high-income countries, where up to 50% of people living with dementia reside in care homes (8).

In this context and following recommendations by the World Health Organization (WHO) and Alzheimer's Disease International (9), the Chilean government, headed by Michelle Bachelet, delivered the first Plan for Dementia in 2015 (4). This national strategy was developed by an intersectoral work group comprising—in recognition of the wide range of medical and social assistance concerned—stakeholders from civil society, academics, clinicians, and decision-makers involved in dementia care. The result was the enactment of the National Plan for Dementia in 2017. This policy guideline encompasses actions for dementia in the health sector and in other areas, including the promotion of DFC and age-friendly cities in the long term (10).

The Chilean plan's DFC approach prioritises action to create awareness, reduce stigma and foster dementia-friendly environments. The strategy considers multi-sectoral collaboration for the design and construction of new infrastructure and public spaces to provide physical environments for social participation by people living with dementia. It is expected that the Ministry of Health, along with the Ministry of Housing and City Planning and the National Service for the Older People will coordinate multidisciplinary work with universities, scientific societies, municipalities, media and civil society towards creation of a dementia-friendly environment. However, no details have been provided about the initiative and there is no specific budget or investment for this specific goal.

FRAMING DEMENTIA-FRIENDLY COMMUNITIES IN CHILE

The concept of DFC has recently been embraced by dementia researchers and policymakers to ensure a better life for people with dementia and their families. However, there are a variety of perspectives on the concept, indicating constant reconsideration of the issue (11). For instance, the WHO defines DFC as an approach that normalises dementia in society. This is aligned with Alzheimer's Disease International, which emphasises empowerment, self-confidence and participation in meaningful activities as the defining attributes of DFC (12). Nevertheless, local initiatives in the UK and Australia have defined DFC based on the responsiveness of the physical and social environment of a person with dementia to preserve access to local facilities and their social networks (13, 14). As there is no single model for developing DFC nor a template for expected outcomes, the definition must be interpreted in the social and physical context in which these communities are developed.

Although the creation of dementia-friendly environments is beginning to gain interest in Latin America and the Caribbean, most countries that include efforts to develop DFC in their national strategies have prioritised raising awareness of dementia over interventions in the physical environment. For example, educational, social and awareness events have taken place in Argentina, Brazil and Costa Rica, led mainly by local Alzheimer's associations and with far less government involvement (15). Increased awareness and understanding of dementia remains a major concern in the region and one of the outcomes of any DFC (12). However, the ageing process that many low- and middle-income countries are already experiencing will reveal the need for a more comprehensive approach in which both the social and physical environment are seen as essential to the formation of ageing- and dementia-friendly societies.

The definitions of community as applied to the development of DFC remain diverse and may constitute a space, a social environment or even an organisation or virtual community (11, 16). In the case of Chile, where most patients with dementia live in the family home, neighbourhoods play a key role in promoting well-being and quality of life for people living with dementia and their families. Although the impact of the neighbourhood has been largely ignored by the biomedical model, epidemiological evidence supports its role as an additional determinant of health that modulates potential risk factors at the individual level. Neighbourhoods that support active ageing may reduce dementia risk factors, while unfavourable environmental features such as low green space availability and poor access to local services might have the opposite effect (17–19).

In this perspective, we recognise that the dementia-friendly community approach requires not only a social and educational intervention but also urban and environmental adaptation. This is mainly because a community is based on a space—a territory in which there are socio-spatial relations that maintain bonded networking. Temporality is considered a key element here because it allows neighbours to identify and include themselves within collective history (20). This means that members of the community are aware of who is part of it and broadly

comprehend the situation in which participants are related to them. These bonds, based on time and location, are especially important in low-income contexts, where survival relies on the social networking that sustains everyday life through practises of collaboration and solidarity. Women have a key role here, as the structural division of labour pushes them to undertake work involved in social reproduction (21).

In this sense, a community represents a safe space that can offer diverse networks rich enough to facilitate support when needed. Regarding dementia, we consider at least three urban features to be important and require special attention in relation to the development of DFC. The first is secure housing tenancy. It is generally agreed that insecurities in housing tenancy could drive both mental and physical health issues for householders (22, 23). The second feature is provision of public care infrastructure that is well-distributed across cities. Here, specialised centres could help in providing not only medical but also educational support to make neighbours aware of the needs of people with dementia (11). The third feature is the adaptation to these special requirements of not only housing units but also the urban environment as a whole in order to render neighbourhoods inhabitable by and bearable for those who live with dementia, especially in terms of safe mobility (24, 25) and urban equipment.

THE IMPACT OF DISPLACEMENT AND FORCED EVICTION ON PEOPLE LIVING WITH DEMENTIA

Given that spatial injustice inflicting disproportionate damage on vulnerable population (26), older people and especially those suffering from physical and mental disabilities should be among the groups to receive priority attention from urban and healthcare policies. "Ageing in place," or the ability to remain rooted in one's own home and community rather than in a residential home, regardless of age and income, is preferred by most older people (27).

For older people with dementia and their families, the concept of place goes far beyond houses and encompasses a community based on a neighbourhood that can be mobilised to improve adaptation and self-management. Yet the term is elusive in public policy and there is a tendency to treat place simply as a home instead of a socially interconnected system, despite growing evidence for the contribution of integrated neighbourhoods and communities to well-being in old age (28). This social interaction is crucial to allowing older people to maximise their well-being despite chronic medical conditions and thus to establishing a new definition of health from a social perspective (29).

The aspiration of ageing in a familiar environment is under threat from evictions—a global phenomenon related to gentrification occurring in both developing and developed countries (30) and affecting mainly poor and vulnerable communities (31, 32). The negative consequences of displacement for people with dementia can be predicted based on evidence that reveals the impact of an abrupt change in the usual physical and social environment. For example, the transition to a nursing home represents a challenging experience for patients, associated with loss of home, neighbourhoods and daily contact with close family members, and may result in poorer mental and physical health (33, 34). Similarly, changes in the usual environment of older people with dementia, such as prolonged hospitalisation, increase the risk of delirium, an acute and life-threatening attention and cognitive disorder that leads to loss of independence and increased morbidity and mortality (35, 36). As such, displacement of older people with dementia to an unfamiliar neighbourhood is likely to harm well-being and behaviour.

BARRIERS TO DFC IN RELATION TO THE CHILEAN HOUSING CRISIS

Chilean legislation does not consider housing as a right. Instead, it is covered by the right to property, which views housing as a market-tradable commodity (37). In other words, access to housing is dependent on the financial resources of each individual or family. Further, land was deregulated in 1979, giving total control of urban development to the market (38). Together, this has led to a constant rise in prices and speculation in terms of housing stock and its construction (39, 40), increasing social inequality (41), segregation (42, 43) and exclusion (44, 45).

The state does not have the power to directly manage the housing deficit, which has recently reached 497,560 housing units (46). The role of the state is limited to the delivery of subsidies through various programmes focused on demand. As a result, social housing remains excluded from more established, central urban areas due to land prices (47). As a result, people living in poverty have been constantly displaced from their neighbourhoods to areas lacking in urban infrastructure, services, and amenities.

The subsidy programmes consist of quarterly contests during which funds are allocated depending on the vulnerability score of applicants (48). Level of vulnerability is measured parametrically using a tool called the Household Social Registry (HSR, *Registro Social de Hogares*). The instrument classifies individuals by percentage based on the situation of their family group, addressing factors such as their educational level, housing condition, total income, physical and mental health, and access to social security. Importantly, the HSR awards more credits to people who care for others, especially elderly people who are completely dependent upon them (49). This means that informal and unpaid caregivers to the elderly are more likely to be categorised within the most vulnerable socio-economic section of society, thus increasing their likelihood of receiving public funds over people who care for children and teenagers.

With this in mind, it is concerning that more than 1.3 million people in Chile declare themselves to work as unpaid carers of a relative. Some 97% of these caregivers are women (50), and their situation has a considerable negative impact on their educational and career trajectories. As such, there is a strong connection between this unpaid female labour and the percentage of women who apply for and receive housing subsidies, a figure which today stands at 81% (51). It could be said there is some

recognition on the part of the HSR of the vulnerability of caregivers engaged in unpaid labour. However, this is not to say that subsidies necessarily cover the special needs of housing programme beneficiaries, especially in terms of their disabilities and/or mental health conditions.

As mentioned previously, one aspect used to measure vulnerability is the health situation of the individual and their capacity for independence from the householder. The survey offers six selectable options concerning health condition, plus five relating to activities that could be completed by the individual, for example, whether they are able to be alone in public spaces. However, it not possible to relate answers with a particular diagnosis beyond evident conditions such as blindness or physical impairments. For example, the options presented in the survey fail to differentiate between mental issues and psychiatric problems, and people often struggle to answer the question. As such, data is not collected specifically about people living with dementia, their degree of vulnerability, or their socio-economic situation. Indeed, dementia could be confused with other conditions, obscuring valuable data needed to effect material improvements to the environment. We interpret this as a lack of political will to address and improve the situation, a view reinforced by the meagre 0.06% of central government budget that is assigned to elderly programmes (52), among which the amount available to dementia programmes is unclear and unstable.

As we have observed through our ethnographic experience of working with women's housing committees, this obscuring of people's health conditions has at least three potential side effects for people living with dementia. Generated by a social housing policy that we consider to constitute a threat to dementia sufferers, these side effects are (a) the double vulnerabilisation of people, whereby applicants attempt to achieve the figures needed to receive subsidies, thus exposing family members to risky conditions in the process; (b) the displacement of caregivers—with or without their respective dementia sufferer—from their original neighbourhoods to underdeveloped satellite settlements; and (c) the tendency for overcrowding through the construction of informal and dangerous house extensions as people struggle to maintain their network of care and avoid eviction by the housing market or state subsidies.

The first of these risks is directly related to the healthcare system. The HSR awards higher scores to those whose healthcare coverage is provided by the public system (49). This creates a dilemma for families who cannot afford to buy or rent a home but whose members are affiliated with the private health system, which is far more expensive and effective than the public system. It is common for families in this situation to opt to expose themselves to poorer healthcare coverage, thus doubling their initial condition of vulnerability. This state of affairs can persist throughout the housing application process, which frequently lasts more than 5 years.

The second risk stems from the fact that, as indicated earlier, an important condition for creating dementia-friendly communities concerns allowing people to reside in the place with which they are most familiar. Subsidy beneficiaries tend to be displaced from their original neighbourhoods to urban peripheries (53), causing a two-fold problem. First, if the caregiver is displaced, their continued care work could be rendered unfeasible by long commutes. The effect of this on people living with dementia could be substantial, as extra effort would be involved in comprehending an unexpectedly changed relationship with the caregiver. A second problem would arise if both sufferer and caregiver are displaced, resulting in the loss of the community network which sustains them.

This situation requires additional psychological effort on the part of the dementia sufferer, which, as mentioned above, would also affect their quality of life, as they must come to understand and navigate an entirely new environment. In addition, urban peripheries in Chile lack social services and urban amenities, exposing people with dementia to loss of access to healthcare facilities and stress generated by long journeys. Furthermore, it is recognised that caregivers tend to receive frequent support from various people involved in their care network, all of whom live in the same neighbourhood. Displacement would mean loss of this essential support and potential psychological, social and economic impacts as displaced people find themselves paying for all of the assistance and services previously provided by neighbours and relatives.

The third risk is the phenomenon of overcrowding, related to the housing affordability crisis and job insecurity (54) triggered by the transformation of spatial design in both residential and urban areas. Here, kinship is a crucial factor, as householders receive relatives into their homes in order to save them from homelessness or displacement. However, this involves informal deconstruction/reconstruction of housing spaces in order to adapt to growing occupant numbers. The process has several detrimental effects on the quality of life of inhabitants, mostly associated with precarious and often extremely risky adaptations to homes (55). Healthcare and sanitary risks are high, and the COVID-19 pandemic has exacerbated the situation due to the challenges of maintaining physical and social distance (56). This has a direct impact on elderly people who find themselves in disrupted environments and new undefined social relations of co-dependency—conditions that also tend to increase instances of domestic violence (57).

CONCLUSION AND RECOMMENDATIONS

The rapid ageing of Chile's population over the last few decades has emphasised the need for protection of the elderly and older people living with dementia. The dynamics of dementia care in Chile depend on the socio-spatial connections established during the sufferer's lifetime, and ageing in place is thus a cornerstone for the implementation of dementia-friendly communities. Nevertheless, housing shortages driven by constant price rises associated with speculation and the subsidiary housing model expose poor and vulnerable communities to the negative consequences of displacement.

From a public health perspective, we recommend a review of current housing and land policy in view of the considerable impact of urban areas on the physical and mental well-being

and care of people, especially those with disabilities. The recently initiated constitutional process provides key political momentum for this, and it is hoped that improvements will be made to the development of healthcare and urban spaces, moving from the subsidiary model to the politics of distribution and recognition.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

DJ and FC-C: article concept and design, literature research, drafting of the manuscript, critical revision, and final approval of the manuscript. Both authors contributed to the article and approved the submitted version.

ACKNOWLEDGEMENTS

We thank the members of the *Kintun* programme for families with dementia and the EAGIS team from the *Movimiento de Pobladoras y Pobladores en Lucha* for their valuable insights.

REFERENCES

1. Organization PAH. *Health in the Americas+*. Washington DC: Organization PAH (2017).
2. World Health Organization. *World Health Statistics 2020: Monitoring Health for the SDGs, Sustainable Developments Goals*. Geneva: World Health Organization (2020).
3. Fuentes P, Albala C. An update on aging in dementia in Chile. *Dement Neuropychol.* (2015) 8:317–22. doi: 10.1590/S1980-57642014DN84000003
4. Ministerio de Salud. *Documento preliminar para la elaboración del Plan Nacional para las demencias*. Santiago: Ministerio de Salud (2015).
5. Custodio N, Wheelock A, Thumala D, Slachevsky A. Dementia in Latin America: epidemiological evidence and implications for public policy. *Front Aging Neurosci.* (2017) 9:221. doi: 10.3389/fnagi.2017.00221
6. Slachevsky A, Budinich M, Miranda-Castillo C, Núñez-Huasaf J, Silva J, Muñoz-Neira Cea. The CUIDEME study: determinants of burden in Chilean primary caregivers of patients with dementia. *J Alzheimer's Dis.* (2013) 35:297–306. doi: 10.3233/JAD-122086
7. Hojman D, Duarte F, Ruiz-Tagle J, Budnich M, Delgado C, Slachevsky A. The cost of dementia in an unequal country. The case of Chile. *PLoS ONE.* (2017). 12:1–17. doi: 10.1371/journal.pone.0172204
8. Toot S, Swinson T, Devine MCD, Orrell M. Causes of nursing home placement for older people with dementia: a systematic review and meta-analysis. *Int Psychogeriatrics.* (2017) 29:195–208. doi: 10.1017/S1041610216001654
9. World Health Organization. *Dementia: A Public Health Priority*. Geneva: WHO (2012).
10. Ministerio de Salud. *Plan Nacional de Demencia*. Santiago: Ministerio de Salud (2017).
11. Lin SY. 'Dementia-friendly communities' and being dementia friendly in healthcare settings. *Curr Opin Psychiatry.* (2017) 30:145–50. doi: 10.1097/YCO.0000000000000304
12. Alzheimer Disease International. *Dementia Friendly Communities Key Principles*. London: Alzheimer Disease International (2016). p. 16.
13. Cramton J, Dean J, Eley R. *Creating Dementia-Friendly York*. York: Joseph Rowntree Foundation (2012). p. 68.
14. Moore B, Pritchard-Wilkes V, Miles S, Sweeney R, Billin ABE. *Dementia-Friendly Housing Guide*. London: Alzheimer's Society 2020 (2017).
15. Alzheimer's Disease International. *Dementia Friendly Communities Global Developments*. London: Alzheimer's Disease International (2017).
16. Rahman S, Swaffer K. Asset-based approaches and dementia-friendly communities. *Dementia.* (2018) 17:131–7. doi: 10.1177/1471301217751533
17. Yen I, Michael Y, Perdue L. Neighborhood environment in studies of health of older adults. A systematic review. *Am J Prev Med.* (2009) 37:455–63. doi: 10.1016/j.amepre.2009.06.022
18. Wu Y, AM P, Jones A, Barnes L, Matthews F, Brayne C. Community environment, cognitive impairment and dementia in later life: results from the cognitive functions and ageing study. *Age Ageing.* (2015) 44:1005–11. doi: 10.1093/ageing/afv137
19. Ward R, Clarck ACS, Graham B, Kullberg A, Manji K. The lived neighborhood: understanding how people with dementia engage with their local environment. *Int Psychogeriatrics.* (2018) 30:867–80. doi: 10.1017/S1041610217000631
20. Unger D, Wandersman A. The importance of neighbors: the social, cognitive, and affective components of neighboring. *Am J Commun Psychol.* (1985) 13:139–69. doi: 10.1007/BF00905726
21. Fraser N. Crisis of care? On the social-reproductive contradiction of contemporary capitalism. In Bhattacharya T, editor. *Social Reproduction Theory: Remapping Class, Recentering Oppresion*. London: Pluto Press (2017). p. 21–36.
22. Kavanagh A, Aitken Z, Baker E, LaMontagne A, Milner A, Bentley R. Housing tenure and affordability and mental health following disability acquisition in adulthood. *Soc Sci Med.* (2016) 9:225–32. doi: 10.1016/j.socscimed.2016.01.010
23. Bentley R, Pevalin D, Baker E, Mason K, Reeves A, Beer A. Housing affordability, tenure and mental health in Australia and the United Kingdom: a comparative panel analysis. *Housing Stud.* (2016) 31:208–22. doi: 10.1080/02673037.2015.1070796
24. Bister M, Klausner M, Niewöhner J. The cosmopolitics of 'niching'. Rendering the city habitable along infrastructures of mental health care. In: Blok A, Farías I, editors. *Uban Cosmopolitics. Agencements, Assemblies, Atmospheres*. New York, NY: Routledge (2016). p. 187–205.
25. Jirón P, Carrasco JA, Rebolledo M. Observing gendered interdependent mobility barriers using an ethnographic and time use approach. *Transportacion Research Part.* (2020) 140:204–14. doi: 10.1016/j.tra.2020.08.018
26. Fainstein S. Urban Planning and Social Justice. In Gunder M, Madanipour A, Watson V, editors. *The Routledge Handbook of Planning Theory*. New York, NY: Routledge (2017).
27. Wiles JLA, Guberman N, Reeve JAR. The meaning of "ageing in place" to older people. *Gerontologist.* (2012) 52:357–66. doi: 10.1093/geront/gnr098
28. Van Dijk H, Cramm J, Birnie E, Nieboer A. Effects of an integrated neighborhood approach on older people's (health-related) quality of life and well-being. *BMC Res Notes.* (2016) 9:1–10. doi: 10.1186/s13104-016-2254-5
29. Huber M, André Knottnerus J, Green LVDHH, Jadad A, Kromhout D, al e. How should we define health? *BMJ.* (2011) 343:1–3. doi: 10.1136/bmj.d4163
30. Lees L, Bang Shin H, López-Morales E. *Planetary gentrification: Polity*. Cambridge; Malden, MA: John Wiley & Sons (2016).
31. du Plessis J. The growing problem of forced evitions and the crucial importance of community-based, locally appropriate alternatives. *Environ Urban.* (2005) 17:123–34. doi: 10.1630/0956247053633692
32. Speer J. Urban makeovers, homeless encampments, and the aesthetics of displacement. *Soc Cult Geogr.* (2019) 20:575–95. doi: 10.1080/14649365.2018.1509115
33. Sury L, Burns K, Brodaty H. Moving in: adjustment of people living with dementia going into nursing home and their families. *Int Psychogeriatr.* (2013) 25:867–76. doi: 10.1017/S1041610213000057
34. Scocco P, Rapattonoi M, Fantoni G. Nursing home institutionalization: a source of eustress or distress for the elderly? *Int J Geriatr Psychiatry.* (2006) 21:281–7. doi: 10.1002/gps.1453

35. Oh E, Fong T, Hshieh T, Inouye S. Delirium in older persons: advantages in diagnosis and treatment. *JAMA*. (2017) 318:1161–174. doi: 10.1001/jama.2017.12067
36. Fong T, Davis D, Growdon M, Albuquerque A, Inouye S. The interface between delirium and dementia in elderly adults. *Lancet Neurol.* (2015) 14:823–32. doi: 10.1016/S1474-4422(15)00101-5
37. Ríos Sdl. El Derecho a la Vivienda y las Declaraciones Constitucionales. *Revista INVI.* (2008) 23:127–47. Available online at: https://revistateoriadelarte.uchile.cl/index.php/INVI/article/view/62264
38. De Mattos C. Globalización, negocios inmobiliarios y mercantilización del desarrollo urbano. Producción inmobiliaria y reestructuración metropolitana en América Latina. (2008) 11.
39. Vergara-Perucich F, Aguirre-Nuñez C. Housing prices in unregulared markets: study on verticalised dwellings in santiago of chile. *Buildings.* (2020) 10:6. doi: 10.20944/preprints201910.0036.v1
40. López-Morales E. *A Multidimensional Approach to Urban Entrepreneurialism, Financializacion, and Gentrification in the High-Rise Residential Market of Inner Santiago Chile*. Bingley: Emerald Group Publishing Limited (2016).
41. López V. Desigualdad programada. El impacto de los programas de vivienda social en base a subsidio en Chile. *Revista CIS.* (2019) 16:55–75. Available online at: https://redib.org/Record/oai_articulo2502087-desigualdad-programada-el-impacto-de-los-programas-de-vivienda-social-en-base-a-subsidio-en-chile
42. Ruiz-tagle J. La persistencia de la segregación y la desigualdad en barrios socialmente diversos: un estudio de caso en La Florida, Santiago. *EURE.* (2016) 42:81–108. doi: 10.4067/S0250-71612016000100004
43. Hidalgo R, Paulsen A, Santana L. El neoliberalismo subsidiario y la búsqueda de justicia e igualdad en el acceso a la vivienda social: el caso de Santiago de Chile (1970–2015). *Andamios.* (2016) 13:57–81. doi: 10.29092/uacm.v13i32.525
44. Ureta S. To move or not to move? Social exclusion, accessibility and daily mobility among the low-income population in Santiago, Chile. *Mobilities.* (2008) 3:269–89. doi: 10.1080/17450100802095338
45. López-Morales E. Gentrification in Santiago, Chile: a property-led process od dispossession and exclusion. *Urban Geogr.* (2015) 37:1109–31. doi: 10.1080/02723638.2016.1149311
46. Fundación Vivienda. Modifica la Ley General de Urbanismo y Construcciones estableciendo una reserva de suelo urbano destinada a viviendas de bajo valor. Valparaiso: Fundación Vivienda (2019).
47. Tapia R. Vivienda social en Santiago de Chile: análisis de su comportamiento locacional, período 1980–2002. *Revista INVI.* (2011) 26:105–31. doi: 10.4067/S0718-83582011000300004
48. Minvu DS. *N°49 de 2011 que aprueba reglamento del programa Fondo Solidario de Elección de Vivienda*. Chile: Ministry of Housing and Urbanism (2012).
49. MIDESOC. Orientaciones al RSH N°8: Cálculo de la Calificación Socioeconómica. Santiago: Ministerio de Desarrollo Social; (2019). Available online at: http://www.registrosocial.gob.cl/docs/Orientaciones-complementarias-N8_c%C3%A1lculo-CSE_VF.pdf (accessed January 31, 2021).
50. INE. *Banco de datos de la Encuesta Nacional del Empleo*. Santiago: INE(2020).
51. MINVU. *Estudio MINVU revela que el 72% de los beneficiarios de subsidios son mujeres*. Santiago (2019). Available online at: https://www.minvu.cl/noticia/agenda-ministerial/estudio-minvu-revela-que-72-de-los-beneficiarios-de-subsidios-son-mujeres/ (accessed August 08, 2021).
52. DIPRES. *Ley de Presupuestos año 2021*. Santiago (2021). Available online at: https://www.dipres.gob.cl/597/articles-213661_doc_pdf.pdf (accessed January 31, 2021).
53. Zunino HM, Hidalgo R. Spatial and socioeconomic effects of social housing policies implemented in neoliberal Chile: the case of Valparaiso. *Urban Geogr.* (2009). 30:514–42. doi: 10.2747/0272-3638.30.5.514
54. DESUC. *Estudio Factores que influyen en el allegamiento interno y externo*. Santiago: DESUC (2017).
55. Sugranyes A, Rodríguez A. El problema de la vivienda de los con techo. In: Sugranyes A, Rodríguez A, editors. *Los con techo. Un desafío para la política de vivienda social*. Santiago: Ediciones SUR (2005). p. 101–22.
56. Vergara-Perucich F, Correa-Parra J, Aguirre-Núñez C. The spatial correlation between the spread of COVID-19 and vulnerable urban areas un Santiago of Chile. *Crit Housing Anal.* (2020) 7:21–35. doi: 10.13060/23362839.2020.7.2.512
57. Greenberg NE, Wallick A, Brown LM. Impact of COVID-19 pandemic restrictions on community-dwelling caregivers and persons with dementia. *Psychol Trauma.* (2020) 12:S220–1. doi: 10.1037/tra0000793
58. Ingold T. *Being Alive: Essays on Movement, Knowledge and Description*. London: Taylor & Francis (2011).
59. Murray C, Vos T, Lozano R, Naghavi M, Flacman A, Michaud C. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a sistematic analysis for the Global Burden of Diseases Study. *Lancet.* (2012) 380:2197–223. doi: 10.1016/S0140-6736(12)61689-4

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

REVIEW
published: 25 August 2021
doi: 10.3389/fneur.2021.683131

Memory Clinics and Day Care Centers in Thessaloniki, Northern Greece: 30 Years of Clinical Practice and Experience

Magda Tsolaki[1,2,3,4], Marianna Tsatali[1], Mara Gkioka[1,2], Eleni Poptsi[1], Anthoula Tsolaki[1,2], Vasileios Papaliagkas[1,5], Irene-Maria Tabakis[1], Ioulietta Lazarou[2], Marina Makri[1,2], Dimitrios Kazis[4], Sotirios Papagiannopoulos[4], Andreas Kiryttopoulos[2], Efrosyni Koutsouraki[2] and Thomas Tegos[2]*

[1] Greek Association of Alzheimer's Disease and Related Disorders (GAADRD), Thessaloniki, Greece, [2] 1st University Department of Neurology UH "AHEPA", School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece, [3] Laboratory of Neurodegenerative Diseases, Center for Interdisciplinary Research and Innovation (CIRI - AUTh) Balkan Center, Buildings A & B, Aristotle University of Thessaloniki, Thessaloniki, Greece, [4] 3rd University Department of Neurology "G. Papanikolaou" Hospital, Faculty of Health Sciences, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece, [5] Department of Biomedical Sciences International Hellenic University, Thessaloniki, Greece

OPEN ACCESS

Edited by:
Rufus Olusola Akinyemi, University of Ibadan, Nigeria

Reviewed by:
Georgios Ponirakis, Weill Cornell Medicine-Qatar, Qatar
Sirel Karakaş, Doğuş University, Turkey

***Correspondence:**
Marianna Tsatali
mtsatali@yahoo.gr

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: *19 March 2021*
Accepted: *25 June 2021*
Published: *25 August 2021*

Citation:
Tsolaki M, Tsatali M, Gkioka M, Poptsi E, Tsolaki A, Papaliagkas V, Tabakis I-M, Lazarou I, Makri M, Kazis D, Papagiannopoulos S, Kiryttopoulos A, Koutsouraki E and Tegos T (2021) Memory Clinics and Day Care Centers in Thessaloniki, Northern Greece: 30 Years of Clinical Practice and Experience. Front. Neurol. 12:683131. doi: 10.3389/fneur.2021.683131

Background: This review describes the diagnostic and interventional procedures conducted in two university memory clinics (established network of G. Papanikolaou Hospital: 1988–2017 and AHEPA hospital: 2017–today) and 2 day care centers (established network of DCCs: 2005–today) in North Greece and their contribution in the scientific field of dementia. The aims of this work are (1) to provide a diagnosis and treatment protocol established in the network of memory clinics and DCCs and (2) to present further research conducted in the aforementioned network during the last 30 years of clinical practice.

Methods: The guidelines to set a protocol demand a series of actions as follows: (1) set the diagnosis criteria, neuropsychological assessment, laboratory examinations, and examination of neurophysiological, neuroimaging, cerebrospinal fluid, blood, and genetic markers; and (2) apply non-pharmacological interventions according to the needs and specialized psychosocial interventions of the patient to the caregivers of the patient.

Results: In addition to the guidelines followed in memory clinics at the 1st and 3rd Department of Neurology and two DCCs, a database of patients, educational programs, and further participation in international research programs, including clinical trials, make our contribution in the dementia field strong.

Conclusion: In the current paper, we provide useful guidelines on how major and minor neurocognitive disorders are being treated in Thessaloniki, Greece, describing successful practices which have been adapted in the last 30 years.

Keywords: memory, dementia, day care centers, educational programs, Alzheimer association, neurology departments, non-pharmacological interventions

INTRODUCTION

Dementia has been described as a clinical syndrome caused by neurodegeneration (Alzheimer's disease, Lewy body, and frontotemporal dementia being the most common pathologies) or as a secondary syndrome (vascular, metabolic, hormonal, and infectious dementia), characterized by progressive deterioration in cognitive ability, behavior, and capacity for independent living (1). Typically, it is a condition that usually affects older people (2, 3). Because of a longer life expectancy along with the lack of efficient therapeutic strategies, dementia is increasingly becoming a major public health problem. According to Alzheimer Disease International, it has been estimated that 35.6 million people were living with dementia worldwide in 2010, with the numbers expected to almost double every 20 years up to 65.7 million in 2030 (1). In Greece, there are almost 196,000 people living with dementia, while in 2050 this number is going to increase to 356,000. Moreover, family caregivers are estimated at 400,000 all over the country. Few studies have been conducted so far concerning the prevalence of dementia and mild cognitive impairment (MCI) in Greece (4–7), but the latest data revealed that the overall prevalence of dementia is 5.0%, with 75.3% of the cases attributed to Alzheimer's disease (8).

Thessaloniki, located in northern Greece, is the second biggest city of the country with high contribution in dementia research and clinical practice. The memory and dementia network in Thessaloniki, which started with the so-called Outpatient Memory and Dementia Clinic (3rd Department of Neurology), which was established in 1988 at "G. Papanikolaou" General Hospital (established network 1988–2017). Years later and specifically in 1995, Professor Magda Tsolaki, with the cooperation of dementia experts, founded the Association of Alzheimer's Disease and Related Disorders (GAADRD) which is responsible for 2 day care centers (DCCs) in Thessaloniki. Since 2005, the team of experts had the opportunity to expand the network and establish in total four DCCs in several cities across Greece (Thessaloniki, Volos, Chania, and Athens). At the end of 2017, the memory and dementia network was established to the Outpatient Memory and Dementia clinic (1st Department of Neurology) at "AHEPA" University Hospital till today. The aforementioned network between memory clinics and DCCs offer medical treatment, psychological support, and non-pharmaceutical interventions to beneficiaries who range from no cognitive impairment (NCI), subjective cognitive impairment (SCI), MCI, and dementia. Additionally, many projects and clinical trials are also being implemented with the collaboration of several dementia scientists abroad. Moreover, a large electronic database containing the information of all patients has been developed for clinical purposes. Consequently, the memory and dementia network provides high-quality diagnostic, treatment, and support services to individuals affected by major or minor neurocognitive impairment and their caregivers or family members in North Greece. Given that this initiative constitutes a significant part of global research groups, the memory and dementia network works in line with high standards provided worldwide.

The goals of this work are (1) to provide a diagnosis and treatment protocol established in memory clinics and DCCs and (2) to present further research conducted in the last 30 years of clinical practice.

SETTING

Memory Clinics

The current memory clinic network includes the outpatient memory clinic of a university general hospital (AHEPA), where the initial diagnosis and follow-up assessments patients as well as education of students, including academic lectures and staff meetings, take place. The outpatient clinic operates once per week under the umbrella of the general hospital and health ministry. It consisted of a neurologist, nurses, medical students, and psychologists offering services of full screening, diagnosis, and medical treatment. Patients who visit the memory clinic, for any reason, follow the screening/diagnostic protocol, and after giving out the results and prescription of medication, they are recommended to visit a DCC for further benefits according to their needs, such as non-pharmaceutical interventions. Moreover, the research and academic team developed a new postgraduate program in 2020 (master's degree) entitled "Neuroscience and Neurodegenerative Diseases," and therefore professionals who work on the dementia field provide new treatment horizons both in beneficiaries as well as in the research field.

Alzheimer Hellas DCCs

GAADRD is a non-governmental organization and member of European as well as international organizations such as Alzheimer Europe and Alzheimer Disease International. It consists of neurologists, psychiatrists, general practitioner, psychologists, biologists, social workers, physical trainers, physiotherapists, and nurses who have been specially trained and educated. The DCCs under the umbrella of GAADRD are prototype and perfectly organized centers offering diagnosis and several non-pharmacological programs for the beneficiaries, namely: (a) programs of cognitive training for people with MCI and people with dementia (PwD) of first stages and (b) cognitive stimulation programs for people with mild and moderate stage of dementia. The participants attend cognitive training or stimulation programs for one or several days per week, following a protocol according to their needs, such as cognitive deficits, mood disorders, and functionality problems. The entrance to the group is determined by a psychologist who is an expert in non-pharmaceutical programs. Each program duration is almost a year. Furthermore, there are also prevention programs to minimize the conversion of SCI to MCI and dementia as well as those delivered to NCI healthy older adults who are at risk of developing dementia due to family history or other relevant health problems. Furthermore, psychotherapeutic programs are also provided to caregivers in order to support them during their caregiving role. Additionally, in the last 15 years, 1-h lectures are conducted every week, including the most recent developments in the research of neurodegenerative diseases as well as many educational projects for caregivers

TABLE 1 | Screening tools.

Screening tools	Domain	Greek cutoff scores
Clinical dementia rating (CDR)[a,b] (9)	Global cognition	Translation and adaptation to Greek (study under preparation)
Global deterioration scale (GDS)[a,b] (10)	Global cognition	(11)
Mini mental state examination MMSE (MMSE)[a,b] (12)	Global cognition	(13)
Montreal cognitive assessment (MoCA)[a,b] (14)	Global cognition	(15)
Hindi mental state examination (HMSE)[a,b]	Global cognition for illiterates	Translation and adaption to Greek (study under preparation) (16)
Alzheimer's disease assessment scale cognitive subscale [ADAS-Cog, (10)][b] (17)	Global cognition	(18)
Confusion assessment method (CAM)[a] (19)	Delirium	Translation and adaption to Greek (study under preparation)
Cognitive decline questionnaire (SCDQ)[a,b] (20)	SCI	Translation and adaption to Greek (study under preparation)
Memory alternation test (MAT)[a,b] (21)	SCI	(Lazarou et al. under revision)

[a] *Tools included in the neuropsychological assessment of memory clinic.*
[b] *Tools included in the neuropsychological assessment of day care centers.*

all over Greece. Finally, GAADRD has organized 12 national conferences, one Alzheimer Europe Conference (2003), and one Alzheimer Disease Conference (2010). GAADRD also contributed to the national observatory for dementia in Greece (2013) and one Satellite AAIC Athens Conference (2021) and has also organized DCCs all over Greece and Egypt. Since 2001, GAADRD has been a member of the European Alzheimer Disease Consortium (EADC).

DIAGNOSTIC METHODS

The diagnostic procedure officially takes place in DCCs or in outpatient memory clinics. All patients who visit the outpatient memory clinics are screened for cognitive deficits with a neuropsychological battery (**Tables 1, 2**), while laboratory examinations, neurophysiological and neuroimaging examination, and genetic markers are also conducted (**Table 3**). The memory clinic's services are used as "a hub" of patients diagnosed with a cognitive disorder. Subsequently, some of them, if they need it, are referred to DCCs for further neuropsychological assessments (**Table 2**) and psychological support and to attend non-pharmaceutical programs. Vice versa, patients who visit a DCC for the first time after diagnosis may visit the memory clinic to undertake specialized examinations.

The diagnostic procedures are delivered to PwD, MCI, as well as SCI as detailed below.

TABLE 2 | Further neuropsychological assessment.

Neuropsychological assessment	Domain	Greek cutoff scores
Rivermead behavioral memory test (RBMT)[a] (22)	Memory	(23)
Rey auditory–verbal learning test (RAVLT)[b] (24)	Verbal learning	(25)
Boston naming test (BNT)[b] (26)	Language	(27)
Boston diagnostic aphasia examination (BDAE; subtests of narrative writing, repetition, phonemic correlation, and reading comprehension of sentences[b] (28)	Language	(29)
Verbal fluency test[b]	Language	(30)
Rey figure complex test (copy, immediate, and free delayed recall and recognition trial)[b] (31)	Visuospatial ability	(32)
Stroop test[b] (33)	Executive function, processing speed and attention functions	Greek cutoff scores derived from Tsolaki et al. (18), Zalonis et al. (34)
Trail making test A and B (TMT-B)[b] (35)	Executive function, processing speed and attention functions	(36)
Wechsler adult intelligence scale (WAIS-FSIQ) digit span (forward and backward digit span)[b] (37)	Short-term memory and working memory	Translation and adaption to Greek (study under preparation)
Digit symbol substitution (DSST)[b] (37)	Working memory, learning	(38)
Instrumental activities of daily living (IADL)[b] (39)	Independent living capacity	(40)
Functional rating scale for symptoms of dementia (FRSSD)[a,b] (41)	Independent living capacity	Translation and adaption to Greek (study under preparation)
Functional cognitive assessment scale (FUCAS)[a,b] (42)	Independent living capacity	(42)
Neuropsychiatric inventory (NPI)[a,b] (43)	Behavioral disorders	(44)
Geriatric depression scale (GDS)[a,b] (45)	Depression	(46)
Short anxiety screening test (SAST)[a,b] (47)	Anxiety	(48)
Perceived Stress Scale (PSS)[b] (49)	Anxiety	(50)

[a] *Tools included in the neuropsychological assessment of memory clinic.*
[b] *Tools included in the neuropsychological assessment of day care centers.*

Dementia

Criteria

The inclusion criteria for dementia are (a) diagnosis of major neurocognitive impairment of any etiology according to DSM-V criteria (76), (b) MMSE total score $\leq$23, (c) stages 4 and 5 of the disease according to the Global Deterioration Scale (GDS) (10), and (d) absence of anxiety and depression evaluated by the same scales employed for the two previous groups.

TABLE 3 | Further examinations (neurochemical and biomarkers).

	Domain	Greek cut off score	Cut off scores
Laboratory examinations			
Regular blood test examination[a,b]	Medical view of patient	(51)	
Cerebrospinal fluid examination[a,b]	Identify markers for AD/other dementias, MCI, or healthy	(52)	(52–54)
Neurophysiological and neuroimaging markers			
Auditory event-related potentials (AERPs)[a,b]	Identify markers for AD/other dementias, MCI, or healthy	(55, 56)	
Electroencephalography (EEG)[a,b]	Identify markers for AD/other dementias, MCI, or healthy	(57–60)	(54, 61)
HD-EEG recordings (GES 300-256 HCGSN)[b]	Identify markers for AD/other dementias, MCI, or healthy	(62–66)	
MRI[a,b]	Identify markers for AD/other dementias, MCI, or healthy		(67–70)
Genetic markers			
APOE genotyping[a]	Identify markers for AD/other dementias, MCI, or healthy	(71, 72)	
Other genes[a] ADRA2B TPEM2 (R47H) ABCA1	Identify mutation for early AD	(73)	(74, 75)

[a] *Diagnosis procedures followed in outpatient memory clinics.*
[b] *Diagnosis procedures followed in day care centers.*

Neuropsychological Assessment

The most common types of dementia are Alzheimer's disease (AD) and vascular dementia, while frontotemporal dementia (FTD) and Lewy body dementia are less common. The neuropsychological evaluation lasts approximately 2 h, divided into two different face-to-face sessions to obtain the best performance from the participants by reducing the possibility of them getting tired. These tests are administered by a neuropsychologist consisting of screening tools, detection of memory, orientation, and language disorders, and tests of visuospatial ability, attention, executive function, and working memory ability as well as neuropsychiatric symptoms and independent living capacity (**Tables 1, 2**).

Mild Cognitive Impairment

Criteria

MCI is a transitional state between normal aging and dementia. The inclusion criteria are (a) diagnosis of MCI according to Petersen (77), excluding other pathologies not associated with dementia according to the Diagnostic and Statistical Manual of Mental Disorders, DSM-5 (76), (b) Mini Mental State Examination (MMSE) total score $\geq$26, (c) stage 3 of the disease according to the GDS, and (d) 1.5 standard deviation (SD) below the normal mean according to age and education in at least one cognitive domain according to the utilized neuropsychological tests.

Neuropsychological Tests

In order to identify older adults with MCI, all the psychometric tools used for dementia detection are also administered in MCI using different cutoff scores (**Tables 1**, **2**).

Subjective Cognitive Impairment Criteria and Tests

To determine SCI, we apply the Subjective Cognitive Decline Questionnaire (SCDQ) (20) and Memory Alternation Test (MAT) (21), which hold excellent reliability and sensitivity for discriminating those with SCI from NCI and MCI patients (**Tables 1**, **2**).

Laboratory Examinations

Regular Blood Test Examination

Blood tests are performed in all patients. Routine blood test includes hematological (complete blood count, hematocrit, and hemoglobulin) and biochemical (glucose, cholesterol, *etc.*), rapid plasma reagin, as well as thyroid-stimulating hormone, and the levels of homocysteine, folic acid, vitamin D, and B12, which are correlated with cognitive impairment. Some patients who participate in clinical trials or clinical research projects, further blood tests or serum tests are performed to identify biological markers or risk genes which are possibly implicated in AD (78, 79).

Cerebrospinal Fluid Examination

Cerebrospinal fluid (CSF) samples are taken by lumbar puncture at the L3/L4 or L4/L5 interspace. The samples are stored at 80°C until further examination. CSF-Aβ42 is determined using a sandwich ELISA [INNOTEST β amyloid (1–39, 76, 77) (Lazarou et al. under revision) Innogenetics, Ghent, Belgium-−96 tests]. CSF-total tau levels are determined using the INNOTEST hTau-Antigen sandwich ELISA−96 tests (Innogenetics, Ghent, Belgium) and INNOTEST Phospho TAU protein at threonine-181hyperphosphorylated-tau–96 tests as well. The CSF Fas levels are determined with the human sAPO-1/Fas ELISA (Bender MedSystems, Vienna, Austria).

Neurophysiological and Neuroimaging Markers

Auditory Event-Related Potentials

Auditory event-related potentials (AERPs) are sensitive neurophysiological biomarkers of MCI and AD using a simple discrimination task, the so-called oddball paradigm. In this task, two stimuli are presented in a random series, with one of the two less frequently, i.e., the odd ball. A series of binaural

tones at 70 dB sound pressure level with 10-ms rise/fall and 100-ms plateau time is presented to all subjects. The auditory stimuli are presented in a random sequence with target tones of 2,000 Hz occurring 20% of the time and standard tones of 1,000 Hz occurring 80% of the time at a rate of 0.5 Hz. The subject is required to distinguish between the two tones by responding to the target (*e.g.*, mentally counting) and not responding to the standard (79). The patients must pay attention in distinguishing the tones in order for the examination to be as accurate as possible.

The ERP activity is recorded at the Fz and Pz electrode sites of the 10–20 system using gold-plated electrodes affixed with electrode paste and tape, referred to as linked earlobes at the A1 A2 sites with a forehead ground and impedance at the lowest possible level. For all recordings, the electrode impedances are below 5 kΩ, and they are checked periodically during the recording session. For artifact suppression, an AC filter function was performed. For the purpose of reduced impedance, a special type of paste is used (Elefix Nihon-Kohden, EEG paste Z-401 CE). The AERPs are analyzed by means of Neuropack 4 (Nihon-Kohden, Tokyo).

Electroencephalography

Electroencephalography (EEG) activity is acquired in a resting state with a 19-channel Nihon Kohden. Neurofax J 921A EEG system at electrodes Fp1, Fp2, F7, F3, F z, F4, F8, T3, C3, Cz, C4, T4, T5, P3, P z, P4, T6, O1, and O2 of the international 10/20 system [43]. EEG data is sampled at 500 Hz, and the electrode impedance is kept lower than 5 kΩ. The signals are digitized with Neurofax EEG-1200, ver. 01–93. The patients are sitting in a comfortable armchair in a quiet room. They are instructed to remain calm, with their eyes closed, for 5 min and then open their eyes. During the pre-processing state, the EEG signal is bandpass-filtered at 0.5–50 Hz, with a notch filter at 50 Hz. These data are assessed in a qualitative way by neurologists, and quantitative analysis is performed by neurophysiologists and engineers.

Additionally, the HD- EEG EGI 300 Geodesic EEG system (GES 300), which uses a 256-channel Hydro-Cel Geodesic Sensor Net (HCGSN) (EGI Eugene, OR), is also implemented in order to investigate the ERP components and multiple network properties. Using this particular EEG system, it has been revealed that the amplitude of visual N170 ERP can differentiate SCI and MCI from the healthy older adults during a task which assessed the emotional processing of facial stimuli (62). This system is used in participants of clinical studies.

MRI

In agreement with radiology departments, brain MRI scans (mostly in 1.5 Tesla) are performed in most patients with cognitive disorders. Each MRI examination consists of the following sequences: T1W (±IV contrast), T2W, FLAIR, DWI/ADC, and 3D T2 FLAIR for volumetry. In some cases, T2*/SWI sequences are also included.

Genetic Markers

APOE Genotyping

APOE alleles and different mutations are also tested if patients or family members desire to know about the genetic predisposition. The blood samples used for genotyping are collected in ethylenediaminetetraacetic acid-containing receptacles. DNA is extracted from peripheral blood using the QIAamp Blood DNA purification kit (Qiagen Inc, USA). To determine the APOE genotype, part of the APOE gene (228 bp) containing both polymorphic sites (amino acid positions 112 and 158) is amplified by PCR analysis using the following primers: forward: 5′-GGCACGGCTGTCCAAGGAGCTGCA-3′ and reverse: 5′-GCCCCGGCCTGGTACACTGCCAG-3′, according to the method described in Koutroumani et al. (73).

TREM2

TREM 2 examination is performed to patients who desire to know if there is any mutation for the early onset of AD. DNA is extracted from peripheral blood. The mutation of TREM2 (c.140G>A/p.Arg47His) is amplified by PCR analysis. For the PCR, Platinum™ II Hot-Start PCR Master Mix (Thermo Fisher Scientific) was used. Primer sequencing, forward: AACACATGCTGTGCCATCC and reverse: CCCAGGATCCCTGAGAGC, was according to Sanger, using the BigDye terminator v3.1 cycle sequencing kit. Electrophoresis followed in an automated genetic analyzer SeqStudio (Applied Biosystems). The diagnosis is based on comparison with the referral sequence NM_018965.

INTERVENTIONS

Interventions Applied in MCI, SCD, and Healthy Older Adults

Healthy older adults and people with SCI and MCI have the following cognitive and physical trainings. Many of the interventions are published here (80–86).

Physical Exercise

The program gives emphasis on fundamental dexterities such as stability, movement, handling, functional ability, and general fitness. Therefore, the program consists of aerobic, strength, flexibility, balance, and mobility exercises two to three times per week. It helps people maintain their good health state, improve their physical and functional abilities and their cognitive function through kinetic stimulations, and additionally sustain or decrease the development of dementia symptoms.

Memory and Executive Function Program

This program aims to improve the central executive system of working memory based on Baddeley's model. The main goal is to teach the patient three different coding strategies—double coding, hierarchical processing, and reducing speed—in order to remember a specific number of words presented at the beginning of each session.

Cognitive Training by Using Famous Paintings

The program aims to enhance cognitive functions such as attention, visual, and verbal memory and semantic memory

and trigger the emotions and imagination of the participants through structured tasks, including famous paintings. They are specifically encouraged to answer questions about art crafts, write a story about the content, and recall significant elements of these paintings at the end of each session. It also gives them the chance to learn about masterpieces of painting and express their emotions toward art.

English Language Training

The program aims to improve verbal memory, attention, perception, speech production, comprehension, and learning ability, in general, by learning English as a second language. Specifically, the participants are provided with structured language tasks such as reading and writing as well as listening to simple dialogues between native speakers.

Greek Monuments

It is a cognitive training program using the history of ancient monuments. It aims to improve cognitive skills such as attention, memory, perception, creativity, speech, socialization, and orientation during the sessions. It includes audiovisual material about the history of Thessaloniki, while discussion and relevant exercises followed. Actual visits to these monuments followed as a way to improve the social life of older adults, decreasing at the same time any feelings of loneliness.

Educational TV

The program aims to enhance attention skills, working memory, and written speech. The participants watch an educational video for 20 min, which include various themes (health, ecology, history, arts, astronomy, philosophy, etc.). After that, the video is divided into smaller sections (to make it easier for the participants to remember), and a therapist asks them about the content. At the same time, the participants make comments about their knowledge in a specific topic while also completing some pencil-and-paper tasks.

Computer Exercises

This program aims to improve working memory, attention, language, and visuospatial functions, including several computerized memory exercises. Each participant has a touchscreen and performs the exercises in front of him/her. It does not require knowledge of computers. There are five levels of difficulty in each exercise consisting of the following categories: (1) visual–spatial exercises, (2) speech exercises, (3) numerical exercises, (4) reasonable exercises, and (5) memory exercises.

Computer Learning

The goal of the program is to promote the learning process, as well as executive functions, and is mainly delivered to high-level participants. The learning modules are the following: (1) usability and familiarity with a PC—Microsoft Windows XP, (2) Word Processor—Microsoft Office Word 2007, (3) Internet use—Internet Explorer, and (4) using accounts—Microsoft Office Excel 2007.

Reality Orientation

The program aims to improve language skills, memory, and attention as well as enhance the quality of life, social skills, and mood. It is comprised of paper-and-pencil tasks. At first, all participants read a specific article and are encouraged to remember it, summarize it, and answer specific questions regarding the content. Thus, they are given tasks focused on language functions, including naming, comprehension, semantic memory, and verbal fluency.

RHEA: Cognitive Training by Using Kinetic Instructions

This program enhances the visuospatial abilities, attention, executive function, and language skills *via* the execution of motion instructions. Each session consists of five visuomotor and verbal–kinetic tasks, including visual and verbal kinetic stimuli, respectively. During the tasks, the participants are encouraged to use personal strategies toward executing and completing the tasks.

Cognitive Control Training via the Execution of Dual Task

The cognitive control training *via* the execution of dual task has as a basic aim the enhancement of cognitive abilities such as the switch of attention, inhibition, and working memory as well as other attention abilities such as divided and sustained attention. During the program, the participants divide their attention in two tasks using paper and pencil. There are also given stimuli of daily life, such as sounds, puzzles, cards, supermarket products, etc.

Attention Training

The attention training aims to enhance attention, executive function, and visual–verbal memory. The program includes teaching of memory strategies and adapt levels of difficulty. Each session consists of 10 cognitive tasks including visual selective attention, working memory and switched attention, shifting of visuospatial attention, and a dual task. The tasks are ecologically valid and derived from activities of daily living (ADL) scale, such as the shopping list and searching in a telephone catalog.

Language Intervention

Language intervention aims to enhance the vocabulary, including 10 tasks of semantic expression of language (three tasks), semantic comprehension of language (three tasks), and phonemic expression of language (four tasks), whereas each set of cognitive tasks has three levels of difficulty. The tasks are ecologically valid, as they are derived from ADL scale.

Prospective Memory

The program aims to enhance the executive function components, such as working memory and verbal fluency as well as prospective memory (PM). It consists of three tasks in each session: (a) an event-based task (non-focal PM task), (b) a time-based task, and (c) a combination task (the intention should be executed after a specific period of time and if a specific cue appeared). The tasks include occupation with puzzles, watching videos, listening to music, doing handcrafts, reading newspapers, making shopping lists, *etc*.

Memory Strategies

Cognitive Training of Memory Through Learning of Strategies

The aim of the program is to improve the cognitive and functional performance of the older adult participants with MCI. At the beginning, the participants are taught a variety of internal memory strategies, which include "method of loci," "keywords," "visual imagery," "association," "categorization," and so forth. As long as they are taught, the participants are encouraged to use internal strategies in aspects of their everyday life, such as memory for numbers, appointments, events which are going to happen in the near future, and names of individuals and places, so that the transmission of knowledge can succeed.

Traveling in Greece

In this program, the participants see pictures of several places in the country. They are asked to answer specific questions in order to practice their working memory function, as well as attention abilities, and improve their verbal fluency performance. Afterwards, all participants present a favorite place among those they have previously seen, and a brief description of the place and personal experiences are followed. Finally, a discussion between all group members takes place.

Mental Imagery and Relaxation Techniques

The intervention aims to reduce the anxiety of the participants and help them explore their thoughts and feelings through the interpretation of symbolic mental images. The program includes three relaxation techniques: (a) progressive muscle relaxation, (b) breathing exercises, (c) autogenic relaxation and mental imagery as a cognitive rehabilitative technique. Environmental conditions, including soothing music and fragrant essence, are applied.

Interventions Applied in People With Dementia

Patients with mild and moderate dementia have the following cognitive and physical training: physical exercise, language intervention, RHEA program, and reality orientation are administered also to PwD based on their physical and cognitive capability.

Cognitive Training Using Old Greek Movies

In the current program, parts of Greek movies are presented. One of the main goals of the program is mood improvement because of the pleasant content of these movies. After watching the movie, structured exercises, including memory, attention, and recall, followed. Additionally, the participants are encouraged to share the experiences they may have about the content of the movies.

Cognitive Empowerment Using Music Stimuli

The program aims to improve long-term memory, attention, and oral and written language and help them to reduce stress levels and enhance their mood. The participants listen to musical stimuli, and afterward they try to remember facts and experiences related to that song; finally, they perform written exercises about the lyrics.

Dance and Drama Therapy

The patients are encouraged to dance and play different roles in order to enhance their executive function abilities, such as planning, step sequence, accuracy, and abstract thinking. This program combines cognitive training *via* psychotherapy techniques, such as dance and drama, and aims to (a) enhance attention, executive function, and verbal and visual memory and (b) deal with the psychological needs of the patients, such as anxiety, depression, apathy, or irritability.

Peter Pan: Cognitive Training Through Toy Therapy

This program utilizes toys in order to enhance auditory and visual selective attention, dual-task abilities, working and episodic memory, and language and visuospatial abilities. Executive function and attention abilities are trained using toys, such as dolls, puzzles, plastic letters, plastic animals, and fruits—for example, the participants have to collect plastic fruits and categorize them according to season, color, or size. They were then asked to find words beginning with the first letter of the fruit that they had collected.

Psychosocial Activities

Apart from the cognitive training or cognitive stimulation programs applied in PwD and MCI, there are also provided leisure activities and psychotherapeutic sessions for the participants. These activities are as follows: (1) a choir group including PwD and MCI which aims to enhance the mood and self-esteem of a patient, (2) a painting group and an art therapy group which both aim to the expression of feelings and emotions and mental health improvement through painting or other kinds of art, and (3) Gestalt psychotherapy which is applied on patients with MCI**.** The aim of this psychotherapeutic procedure is the mental health improvement and the reduction of anxiety and mental deficits in general.

Interventions Applied to Caregivers

There is available published work for caregivers in the some studies (87–91).

Psycho-Educational Groups

The aim of the psychoeducational program is to provide information to caregivers regarding the disease and the level of functionality of the patient, in addition to the guidelines for more effective care. Education helps caregivers in making difficult decisions concerning the care and the treatment of their beloved. Caregivers also learn to be flexible in the negotiation of alternative solutions. There is also an online group which satisfies the needs of caregivers who cannot benefit from the face-to-face health support services due to health issues, transportation (due to COVID pandemic-related reasons), or time.

Family Psychological Support

Family psychological support aims to help the whole family of people with dementia face and cope with the disease and reduce negative feelings and sense of burden.

TABLE 4 | Clinical trials.

Clinical trial name	Main objectives	Results	Sponsors
Rivastigmine [Alzheimer's disease (AD) treatment]	Identifying clinical efficacy and safety of rivastigmine for patients with dementia of Alzheimer's type	Rivastigmine was found to be beneficial in patients with mild and moderate AD, mainly in cognitive function and ADL. However, further research should shed light on how to minimize its adverse effects (92)	Department of Clinical Geratology Radcliffe Infirmary, Oxford 6HE, UK/1999–2000
SB-742457 (AD treatment)	A Double-blind, controlled phase II study of a 5-HT6 receptor antagonist, SB-742457, in patients with mild to moderate AD to identify its safety and efficacy	SB-742457 was generally safe and well-tolerated and may be efficacious in AD (93)	GlaxoSmithKline, Uxbridge, Middlesex, UK. Gareth.C.Maher-Edwards@gsk.com/2005–2007
AVA105640 (AD treatment)	A 24-week, double-blind, randomized, parallel-group study to investigate the effects of rosiglitazone (extended release tablets), donepezil, and placebo as monotherapy on cognition and overall clinical response in APOE ε4-stratified subjects with mild to moderate AD	APOE epsilon 4 non-carriers exhibited cognitive and functional improvement in response to rosiglitazone, whereas APOE epsilon 4 allele carriers showed no improvement, and some decline was noted (94)	GlaxoSmithKline R&D Ltd/2006–2008 (+extensions)
Memantine [treatment for dementia, Parkinson's disease (PD), Lewy bodies (LBD)]	An international double-blind study of memantine in patients with dementia, PD and LBD	Memantine seems to improve the global clinical status and behavioral symptoms of patients with mild to moderate LBD and might be an option for the treatment of these patients (95)	Lundbeck/2007–2009
Donepezil (AD treatment)	Efficacy and safety of donepezil. A multicenter double-blind study about the effectiveness and side effects of donepezil in patients with mild to moderate AD (DON-1-97-001)	Donepezil treatment is effective in everyday clinical practice, showing significantly improved cognition, social behavior, and activity in patients with mild to moderate AD (96)	Not available/2008–2010
Galantamine (AD treatment)	Effects and safety of galantamine. A multicenter 2-year, randomized, placebo-controlled study in mild to moderate AD change to galantamine. An international outcome survey in dementia—GAL-ALZ-401 (IOSID)	Galantamine slowed the functional as well as cognitive decline in patients with Alzheimer's disease (97)	Janssen Research Foundation, Beerse, Belgium/2008–2014
Ladder (treatment for AD)	The effect on cognitive performance of Lu AE58054 (idalopirdine), a selective 5-HT6 receptor antagonist, was assessed in donepezil-treated patients with moderate AD	Idalopirdine significantly improved cognition in donepezil-treated patients with AD in moderate stage (98)	Lundbeck/2009–2011
NCT01549834 (treatment for AD)	A randomized, double-blind, placebo-controlled multicenter study investigated the efficacy and safety of ABT-126 in subjects with mild to moderate AD who were taking stable doses of acetylcholinesterase inhibitors (AChEIs)	The efficacy profile of ABT-126 did not warrant further development as add-on therapy to AChEIs to treat mild to moderate Alzheimer's disease (99)	AbbVie Inc., North Chicago, Illinois/2012–2013 (+extensions)
Nilvad (AD treatment)	A European multicenter double-blind placebo-controlled phase III trial of nilvadipine in mild to moderate AD	Pharmacological intervention in AD. The results do not suggest the benefit of nilvadipine as a treatment in a population spanning mild to moderate Alzheimer disease. Future clinical trials of nilvadipine should be restricted to mild and very mild AD patients (100)	FP7/2012–2017
Masitinib (AD treatment)	A multicenter, double-blind, placebo-controlled, randomized, parallel-group phase III study to evaluate the safety and efficacy of masitinib in patients with mild to moderate Alzheimer's disease	The drug appeared to halt cognitive decline, with the treatment group, on average, notching slight improvements on the ADAS-Cog and ADCS-ADL. In addition, fewer patients on the drug, than on placebo, progressed to severe dementia (101)	AB Science/2013–2020
BI 425809 (treatment for AD)	A multicenter, double-blind, parallel-group, randomized controlled study to investigate the efficacy and safety of orally administered BI 425809 during a 12-week treatment period compared to placebo in patients with cognitive impairment due to AD	No results available; ongoing study (102)	Boehringer Ingelheim/2018–2021

(Continued)

TABLE 4 | Continued

Clinical trial name	Main objectives	Results	Sponsors
Micoil (treatment for MCI)	A randomized clinical trial of Greek high phenolic early harvest extra virgin olive oil in mild cognitive impairment	Long-term intervention with extra virgin olive oil or MP-EVOO was associated with a significant improvement in cognitive function compared to MeDi, independent of the presence of APOE ε4 (103, 104)	GAADRD, World Olive Center for Health (WOCH)-Yanni's Olive Grove Company providing the Early Harvest EVOO, Potidea Chalkidiki, Greece 2018–2020
Olive oil leaves—golden (treatment for MCI)	A single-blind, Randomized Clinical study designed to investigate the Olive Oil Leaves' efficacy to modify treatment and prevention for MCI patients (2019–2021)	No result available; ongoing study (105)	Yanni's Olive Grove Company/2019–2021
Teamentia (treatment for MCI)	Management of mild cognitive impairment patients with Greek mountain tea—Teamentia. A double-blind, randomized clinical study designed to investigate the efficacy of Greek mountain tea as a disease course-modifying treatment for MCI	No result available; ongoing study (106)	Aristotle University of Thessaloniki/2019–2021
NEURO-TTRansform	A study to evaluate the efficacy and safety of AKCEA-TTR-LRx in participants with hereditary transthyretin-mediated amyloid polyneuropathy	No result available; ongoing study (107)	Ionis Pharmaceuticals, Inc. Akcea Therapeutics 2020/2024

Support Groups

Support groups aim to help the caregivers to be effective in their role and build up the necessary psychological skills to deal with difficult aspects of the disease and feelings of anger, loneliness, loss, and helplessness. During the support group, caregivers can develop new approaches of interpreting the situation they are dealing with and adapt more realistic targets and more effective pressure and anxiety management strategies.

Dyadic Intervention: "Writing Our Couples' Life Book"

The participants are couples, where one partner has been diagnosed with MCI or mild dementia. Based on narrative therapy principles, dyadic intervention helps the couple re-narrate and rewrite their story, including dementia in their common life. Moreover, communication techniques are presented to couples in order to improve their communication skills.

Support Group for Grief

It refers to those who experience grief due to the loss of their patient. This group aims to help them accept the reality of loss, manage their emotions, and adapt the new cycle of life.

Relaxation Intervention

It aims to reduce the anxiety level and manage psychosomatic symptoms using relaxation techniques and mental imagery which lead to a deep relaxation of the body and mind. Relaxation intervention helps caregivers to develop their well-being and decrease stress levels.

FURTHER ACTIONS IN CONTRIBUTION TO THE FIELD OF DEMENTIA

Development of a Dementia Database: Empedocles Electronic Health Record

Due to the huge amount of data of patients, the creation of a health database was crucial. Thus, an electronic health record (her) system, called Empedocles, was developed in 2016. Software developers, neurologists, psychologists, and other experts worked together to create the database which meets the needs of patients and experts, providing flexibility for different environments and clinical workflows. Empedocles is compliant with the (EU) 2016/679 General Data Protection Regulation by design. The EHR stores the following data on the patients: (1) personal information and demographic characteristics (including geospatial data), (2) medical history, triggers, and risk factors, (3) diagnosis, (4) medication, (5) neurophysiological examination, (6) dental examination, (7) neuropsychological assessment, (8) hematological and biochemical test results, (9) genetic and CSF results, (10) diagnostic neuroimaging test results, (11) perforation results, and (12) assessment of the mental health of caregivers. Currently, Empedocles EHR is hosted on a server at the Aristotle University of Thessaloniki and serves about 132 active users daily. It stores over 5,200 parameters, which can be repeatedly saved in each patient examination. Empedocles has amassed data for over 19,000 patients examined from 1988 till today (visits in memory clinics and DCCs), with more than 45,000 neuropsychological examinations. The database is continually updated and improved following both the requirements of end-users and society. During the COVID-19 pandemic, the functionalities of Empedocles were adapted so that the neuropsychological assessments could be applied from a distance (e.g., via telephone or Skype).

Clinical Trials

Memory clinic has been participated in several clinical trials to test new drugs for dementia during the last 30 years. The most indicative are provided in **Table 4**.

Studies/Projects

Memory clinic and DCCs have also participated in several research studies and international projects the last 30 years. The most indicative are provided in **Table 5**.

TABLE 5 | Research studies and projects.

Project name, main role, objective	Aims	Main results	Call
MIRAGE (participant) Genetic markers "A multi-institutional research in Alzheimer's genetic epidemiology"	The goal was to identify genetic and non-genetic risk factors for AD. There were collected data on medical and family history and demographic and lifestyle information, drawing of blood for DNA and analysis, and capturing of data from MRI to evaluate the association between vascular and genetic risk factors and AD in families including Caucasians, African Americans, and Japanese Americans	It has been shown that the E4 variant of apolipoprotein E (APOE) is the strongest AD risk factor identified thus far. Moreover, some vascular risk factors are more prevalent in African American and Japanese American populations than in Caucasians (108)	NIH/2002–2008
ENIR (participant) Biomarkers in MRI "Foresight study for the development of a European neuroimage repository"	The goal was to investigate the scientific needs in relation to the development of a large and shared European multidimensional repository of MRI images of normal brains and brains with different neurodegenerative disorders [AD, Parkinson's disease (PD), etc.] completed by clinical, genetic, and neuropsychological data	Identification of standardized procedures and practical implications and processing and storage of neuroimages by means of a coordinated approach to the setting up of a devoted research infrastructure, making the best use of the already existing repositories, in view of their increased integration toward the development of the future European infrastructure (109)	FP6, 2002–2006
ICTUS (participant) Management of AD "The impact of treatment with anticholinesterase inhibitors (AChE I) on Europeans with AD"	The goals were to find clinical evidence for the global efficacy of AChE I and to develop a picture of the natural history of AD. These outcomes would provide a fundamental insight into the progression and treatment of AD, aiding in the formulation of European guidelines	It was a prospective 2-year observational study which coordinates the centralization of patient data available within the individual centers of the study. The primary outcome measure was a deterioration of one level on the clinical dementia rating scale (110)	FP5/2003–2006
DESCRIPA (participant) *Biomarkers in MCI patients* "DEvelopment of Screening guidelines and clinical CRIteria for Predementia Alzheimer's disease"	The goals were to develop the diagnostic criteria for pre-dementia AD in a clinical setting and the development of screening guidelines for pre-dementia AD in the general population	Screening guidelines and clinical criteria for AD were developed. The clinical criteria were based on a prospective cohort study of non-demented subjects from a memory clinic. The screening guidelines were based on a meta-analysis of prospective population-based cohort studies in Europe (111)	FP5/2003–2010
InnoMed /AddNeuroMed Biomarkers of AD "Innovative medicines in Europe"	AddNeuromed is part of InnoMed, being a cross-European study, designed to find biomarkers or tests for AD. The AD biomarkers are useful for accurate and earlier diagnosis, for prediction of progressing to disease or for more rapid deterioration, and for monitoring the progression of disease	Development of plasma markers. Identification of a range of markers including CFH and A2M, both of which have been independently replicated. Conclusions: (1) collaboration is essential; (2) design is paramount and combining modalities, such as imaging and proteomics, may be informative; (3) animal models are valuable in biomarker research; and (4) plasma markers are feasible (112)	FP6/IMI 2006–2008
EDAR (participant) Biomarkers of AD "Cerebrospinal fluid (CSF) differences in different types of dementia"	Its goal was to develop and validate new biomarkers for AD and to develop an assay for the measurement of beta amyloid oligomers in CSF and plasma	Ultra-sensitive assays were developed to measure oligomers *in vivo*. To validate the assay for beta amyloid oligomers, CSF and plasma were repeatedly collected in subjects with AD, other types of dementia, and MCI and in control subjects (113)	FP6 2007–2010
En-NOHSHS (primary investigator) Management of cognitive impairment via new technologies "An ambient intelligence system for the monitoring, empowerment, and disease evolution prediction for patients with MCI"	Its goal is the exploration and integration of environmental factors as well as the effect of activities of daily living with medical and biological factors in order to monitor and predict AD/MCI disease progression and evolution	The system used IT-based tools (including also 3D gaming environments) in order to address specific cognitive and physical/motor parameters and ADL factors within AD and MCI domain to improve their diagnosis, evaluating their variations along the progress of the AD and its different steps and supporting the stimulation/training of the patient affected by the disease (114)	"COLLABORATION" 2009–2011
LLM (participant) Management of AD *via* new technologies "Long-lasting memories"	Its goal is the development of an integrated ICT platform which combines state-of-the-art cognitive exercises with physical activity in the framework of an advanced ambient assisted living environment	By combining cognitive exercises and physical activity, LLM delivers an effective countermeasure against age-related cognitive decline, thus actively improving the quality of life of the elderly and significantly prolonging the time that they can remain independent at home while respecting ethical and legal boundaries (115)	FP6 2009–2012

(Continued)

TABLE 5 | Continued

Project name, main role, objective	Aims	Main results	Call
PHARMACOG (participant) Multiple biomarkers of AD "Prediction of cognitive properties of new drug candidates for neurodegenerative diseases in early clinical development"	Its goal is to provide the tools needed to define more precisely the potential of a drug candidate, reduce the development time of new medicines, and thus accelerate the approvals of promising new medicines	It developed a matrix of biomarkers which can be used to study the effect of a drug candidate both in animals and humans and has the potential to predict the success of future drugs more accurately in the early stages of drug development. It also found a better way to stratify patients with early signs of AD, which may lead to more definitive clinical trials. At least one biotech company is already using the results of Pharma-Cog to test a promising new drug candidate (116)	IMI/2010–2015
Dem@Care (participant) Management of cognitive impairment *via* new technologies "Dementia ambient care multi-sensing monitoring for intelligent remote management and decision support"	Using biosensors, it contributes to the timely diagnosis, assessment, maintenance, and promotion of self-independence of PwD by deepening the understanding of how the disease affects their everyday life and behavior	Positive impact regarding the implementation of a multi-parametric closed-loop remote management solution that affords adaptive feedback to the PwD while including clinicians into the remote follow-up, enabling them to maintain a comprehensive view of the health status and progress of the affected person (117)	FP7/ 2011–2015
ASPAD (principal investigator) Management of MCI patients and support care givers *via* new technologies "Exploring the potential of programming tasks to benefit patients with MCI"	Its goals were the computerized exercises and support groups through the Internet. Exploration of the potential of robot programming tasks to benefit patients with MCI when implemented as a form of cognitive training with the use of user-friendly tangible interface	Available evidence encourages further investigation of the impact of programming tasks on MCI patients, as a cognitive training and assessment tool, in relation to important mental skills (such as analysis and planning) and cognitive processes such as attention (118)	"EXCELLENCE, ESPA"-2012
BIOMARK-APD (participant) Biomarkers for AD and PD	Its goal was to improve the clinical use of body fluid markers for the diagnosis and prognosis of AD and PD. The objective was to standardize the assessment of existing assays and to validate novel fluid biomarkers for AD and PD	(1) New and better assays to test the new and better biomarker candidates; (2) certified reference materials that can be used to harmonize assays that are used to measure the different biomarkers were developed. A virtual biobank with 8,600 subjects and varying diagnoses from 21 local biobanks was also created. A website has been launched to enable sample requests from the central biobank and virtual biobank and standardized assays (119, 120)	JPND/2012–2016
CBP (participant) Diagnosis of cognitive impairment *via* new technologies (EEG) "Cognitive brain signal processing lab"	Its goal was to advance the state of the art in vector field tomography (VFT) by exploiting the new methodology in 2D and extending its theory to 3D. Subsequently, the goal was to apply 3D-VFT to high-density EEG data to solve the inverse EEG problem and determine the active states of the brain to understand the cognitive process	The project not only advanced the state of the art in VFT on its own but also served as a tool to understanding cognitive processes in the brain and, in particular, cognitive vision through different experimental scenarios and among different experimental groups[a]	EXCELLENCE, ESPA/2013–2015
HARC (participant) Education of European physicians "Healthy aging research centers"	Its goal was the development of research focusing on major areas relevant to active and healthy aging: novel approaches to improve well-being in the elderly; pathogenesis and prevention of neurodegenerative, respiratory, cardiovascular and kidney diseases; and molecular basis of aging	It allowed for the enhanced integration of research consortium and extended collaboration with international partners, resulting in achieving significant progress in research (121)	FP7/2013–2016
ARCHIMIDIS (participant) " MCI and diabetes mellitus (DM)"	Its goal was to assess the cognitive function of DM and MCI patients with neurophysiological and neuropsychological measures and seek for possible correlations	No difference in the AERP characteristics and the neuropsychological performance between the groups. The higher cognitive functions of DM patients as assessed with ERPs and neuropsychological tests are affected in a similar way with that of MCI patients; this supports the existence of common pathophysiological mechanisms between the two diseases (122)	ESPA/2014–2016

(Continued)

TABLE 5 | Continued

Project name, main role, objective	Aims	Main results	Call
ehcoBUTLER (participant) Management of MCI patients *via* new technologies "A global ecosystem for the independent and healthy living of elder people with mild cognitive impairment"	It is a multidisciplinary study approach, designed to test the socio-economic benefits from the deployment of an innovative and user-led ICT platform with both leisure and care apps to promote the independence and quality of life and good health of elderly people.	The outcomes of this ongoing project will determine any relevant changes in cognition, mood, quality of life, activities of daily living, and quality of patient–carer relationship after 4 months and 1-year follow up of intervention in a cross-sectional group comparison (123)	Horizon 2020/2015–2016, interrupted and started again 2019–2022
Serious Games-AD GAMING (participant) Management of cognitive impairment via new technologies "Development of a training program for the improvement of the quality of life of PwD"	Its aim is to improve the technological skills of PwD, their families and caregivers, thus allowing them to use Serious Games (SGs) with the purpose of improving their quality of life	The practitioners and care partners found the SG training platform useful and were excited about the prospect of using it to support the well-being of PwD[b]	ERASMUS +/2016–2018
ALTOIDA (participant) Management of cognitive impairment *via* new technologies "A revolutionary assessment test for cognitive impairment. Cognitive biomarker for AD"	It was designed to evaluate the performance of the ALTOIDA™ System as a tool to assist physicians in diagnosing AD in real-world clinical settings. It tests the functional and cognitive aptitude of a patient, via a self-learning (ML) algorithm	Accurate assessment in <10 min; higly validated cognitive assessment for patients over 62 years old. Report on brain patterns of certain neurologic conditions such as cognitive impairment and AD. These data should only be used as additional information to add to the diagnostic impression of the primary physician[c] (124)	Altoida 2016–2020
iCONNECT Education of students *via* new technologies "Intergenerational CONtact between studeNts and people with dementia through CreaTive education"	Its goal is the development of innovative practices in supporting the social engagement of higher educational institutions in promoting via intercultural and intergenerational support the social inclusion of older people with dementia	The only published output is regarding the needs analysis[d]	Erasmus+/2017–2020
RECage (participant) Management of BPSDs "Special medical care unit for patients with BPSD (SCU-B)"	Its goal is to assess the short- and long-term effectiveness of the SCU for people with dementia and BPSD toward alleviating BPSD and improving the quality of life of patients with dementia and their caregivers	This is a 3-year ongoing prospective study where 500 persons will be enrolled (125)	Horizon/2018–2023
STORY2REMEMBER (participant) Education of healthcare professionals "Drama and storytelling in dementia care"	Its goal is to improve the quality of life of both PwD and their caregivers and to improve the skills of healthcare professionals skills through training with methodology of drama and storytelling	A training handbook was produced as a final product for professionals to deliver the experiential workshops to PwD based on storytelling and creative drama techniques. The program had a positive impact to the well-being of PwD and their caregivers as well as positively benefiting professionals working in dementia care settings (126)	Erasmus+/2018–2021
BRIDGE (participant) Management of AD *via* new technologies "An intergenerational approach using serious games for PwD"	Its goal is to develop a set of prototypes Serious Games (physical, digital, and phygital) acting on cognitive and behavioral symptoms of dementia, involving also younger and older people	Prototype games entitled: next destination, flea market, find the word, bird-watching, emotions, the directors, blooming flowers, speciatite—tested during a series of workshops. The web platform containing massive open online courses on the methodology of the game-creation workshops and the final eight selected serious games is the final result[e,f]	Erasmus+/2018–2021
E.LSoM.C.I (participant) Management of MCI *via* teaching "A European intervention with English lessons using songs for people with MCI"	Its goal is to teach English language to people with MCI using songs as the main tool of the teaching process. It is based on innovative teaching approaches, places great emphasis on verbal communication, creates a positive environment in class, reduces stress, and encourages learners to learn step by step naturally and pleasantly	It is an ongoing program; thus, so far it has prepared a methodological guide that provides trainers with a lesson plan for each lesson and many teaching aids, such as songs, images, flashcards, Powerpoint presentations, and videos as well as interactive activities such as role playing, chain drills, and games	Erasmus+/2020–2023

(Continued)

TABLE 5 | Continued

Project name, main role, objective	Aims	Main results	Call
RADAR-AD (participant) Management of AD *via* new technologies "Remote assessment of disease and relapse—Alzheimer's disease"	Its main aim is to explore how mobile and digital technologies—such as smart phones, wearables, and home-based sensors—can be used in AD assessment and care and to measure disability progression associated with AD	It is an ongoing program with no results published yet. Technological techniques might help to detect AD earlier. Mobile technology also allows a more personalized approach to AD treatment and care so that PwD can live independently for longer. It will also identify "digital biomarkers" (electronic signals that give information about a person's health status) for AD, creating new perspectives for the development of treatments against this progressive condition (127, 128)	Horizon 2020/IMI-EFPIA/2019–2022
VRADA (participant) Management of MCI *via* new technologies and physical exercise "A virtual reality (VR) app for physical and cognitive training of older people with MCI: mixed methods feasibility study"	Its goal is to design and test the acceptability, usability, and tolerability of an immersive VR platform that allows older people with MCI symptoms to simultaneously practice physical and cognitive skills on a dual task	The findings suggest that VRADA is an acceptable, usable, and tolerable system for physical and cognitive training of older people with MCI and university students. Randomized controlled trial studies are needed to assess the efficacy of VRADA as a tool to promote physical and cognitive health in patients with MCI. The program is ongoing[g]	ESPA/2018–2021

[a] *http://cbp.iti.gr/.*
[b] *https://adgaming.ibv.org/en/training-content/.*
[c] *https://altoida.com/.*
[d] *https://www.iconnectdementia.eu/.*
[e] *https://projectbridge.eu/the-serious-game/.*
[f] *http://bridgecourses.uowm.gr/.*
[g] *http://ikee.lib.auth.gr/record/329332.*

CONCLUSIONS

All the above-mentioned efforts have the following as targets:

- To provide a protocol of a holistic evaluation of cognitive status through clinical examination, an extended neuropsychological assessment, and biomarkers like blood tests, CSF, genetic tests, and MRI scans.
- To detect cognitive disorder as early as possible and carry out a differential diagnostic procedure to identify their etiologies.
- Plan the future care and provide advice to patients and their caregivers with respect to medical, psychological, legal, ethical, and social issues.
- Provide direct support to patients and caregivers by means of counseling, discussions with caregivers, and therapeutically oriented workgroups (e.g., memory training groups)
- Support families either at our day centers or at their homes
- Contribution to the dementia research and clinical field through funded projects and a plethora of studies conducted in DCC's and Outpatient Memory Clinics.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

REFERENCES

1. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metanalysis. *Alzheimers Dement.* (2013) 9:63–75. doi: 10.1016/j.jalz.2012.11.007
2. Sousa RM, Ferri CP, Acosta D, Albanese E, Guerra M, Huang Y, et al. Contribution of chronic diseases to disability in elderly people in countries with low and middle incomes: a 10/66 Dementia Research Group population-based survey. *Lancet.* (2009) 374:1821–1830. doi: 10.1016/S0140-6736(09)61829-8
3. Prince M, Ferri CP, Acosta D, Albanese E, Arizaga R, Dewey M, et al. The protocols for the 10/66 dementia research group population-based research programme. *BMC Public Health.* (2007) 7:165. doi: 10.1186/1471-2458-7-165
4. Tsolaki M, Fountoulakis C, Pavlopoulos I, Chatzi E, Kazis A. Prevalence and incidence of Alzheimers disease and other dementing disorders in Pylea, Greece. *Am J Alzheimers Dis Other Dement.* (1999) 14:138–48. doi: 10.1177/153331759901400308
5. Tsolaki M, Kakoudaki T, Tsolaki A, Verykouki E, Pattakou V. Prevalence of mild cognitive impairment in individuals aged over 65 in a rural area in North Greece. *Adv Alzheimers Dis.* (2014) 3:11–9. doi: 10.4236/aad.2014.31002
6. Argyriadou S, Melissopoulou H, Krania E, Karagiannidou A, Vlachonicolis I, Lionis C. Dementia and depression: two frequent disorders of the aged in primary health care in Greece. *Fam Pract.* (2001) 18:87–91. doi: 10.1093/fampra/18.1.87
7. Tsolaki M, Gkioka M, Verykouki E, Galoutzi N, Kavalou E, Pattakou-Parasyri V. Prevalence of dementia, depression, and mild cognitive impairment in a rural area of the island of Crete, Greece. *Am J Alzheimers Dis Other Demen.* (2017) 32:252–64. doi: 10.1177/1533317517698789
8. Dardiotis E, Kosmidis MH, Yannakoulia M, Hadjigeorgiou GM, Scarmeas N. The hellenic longitudinal investigation of aging and diet (HELIAD):

rationale, study design, and cohort description. *Neuroepidemiology.* (2014) 43:9–14. doi: 10.1159/000362723
9. Morris JC. The clinical dementia rating (cdr): current version and. *Young.* (1991) 41:1588–92.
10. Reisberg B, Ferris SH, de Leon MJ, Crook T. The global deterioration scale for assessment of primary degenerative dementia. *Am J Psychiatry.* (1982) 1136–9. doi: 10.1037/t48466-000
11. Mougias AA, Christidi F, Kontogianni E, Skaltsounaki E, Politis A, Politis A. Patient-and caregiver-related factors associated with caregiver assessed global deterioration scale scoring in demented patients. *Curr Gerontol Geriatr Res.* (2018) 2018:9396160. doi: 10.1155/2018/9396160
12. Folstein MF, Folstein SE, McHugh PR. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* (1975) 12:189–98. doi: 10.1016/0022-3956(75)90026-6
13. Fountoulakis K, Tsolaki M, Chatzi E, Kazis A. Mini mental state examination (MMSE). A validation study in demented patients from the elderly Greek population. *Am J Alzheimers Dis.* (2000) 15:342–7. doi: 10.1177/153331750001500604
14. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc.* (2005) 53:695–9. doi: 10.1111/j.1532-5415.2005.53221.x
15. Poptsi E, Moraitou D, Eleftheriou M, Kounti-Zafeiropoulou F, Papasozomenou C, Agogiatou C, et al. Normative data for the montreal cognitive assessment in Greek older adults with subjective cognitive decline, mild cognitive impairment and dementia. *J Geriatr Psychiatry Neurol.* (2019) 32:265–74. doi: 10.1177/0891988719853046
16. Tsolaki M, Iakovidou V, Navrozidou H, Aminta M, Pantazi T, Kazis A. Hindi mental state examination (HMSE) as a screening test for illiterate demented patients. *Int J Geriatr Psychiatry.* (2000) 15:662–4. doi: 10.1002/1099-1166(200007)15:7<662::AID-GPS171>3.0.CO;2-5
17. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry.* (1984) 141:1356–64. doi: 10.1176/ajp.141.11.1356
18. Tsolaki M, Fountoulakis K, Nakopoulou E, Kazis A, Mohs RC. Alzheimer's Disease assessment scale: the validation of the scale in Greece in elderly demented patients and normal subjects. *Dement Geriatr Cogn Disord.* (1997) 8:273–80. doi: 10.1159/000106644
19. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method: a new method for detection of delirium. *Ann Intern Med.* (1990) 113:941–8. doi: 10.7326/0003-4819-113-12-941
20. Rami L, Mollica MA, García-Sanchez C, Saldaña J, Sanchez B, Sala I, et al. The subjective cognitive decline questionnaire (SCD-Q): a validation study. *J Alzheimers Dis.* (2014) 41:453–66. doi: 10.3233/JAD-132027
21. Rami L, Molinuevo JL, Sanchez-Valle R, Bosch B, Villar A. Screening for amnestic mild cognitive impairment and early Alzheimer's disease with M@T (memory alteration test) in the primary care population. *Int J Geriatr Psychiatry.* (2007) 22:294–304. doi: 10.1002/gps.1672
22. Wilson B, Cockburn J, Baddeley A, Hiorns R. The development and validation of a test battery for detecting and monitoring everyday memory problems. *J Clin Exp Neuropsychol.* (1989) 11:855–70. doi: 10.1080/01688638908400940
23. Efklides A, Yiultsi E, Kangellidou T, Kounti F, Dina F, Tsolaki M. Wechsler memory scale, rivermead behavioral memory test, and everyday memory questionnaire in healthy adults and alzheimer's patients. *Euro J Psychol Assess.* (2002) 18:63. doi: 10.1027//1015-5759.18.1.63
24. Schmidt M. *Rey Auditory Verbal Learning Test: A Handbook*. Los Angeles, CA: Western Psychological Services (1996).
25. Messinis L, Tsakona I, Malefaki S, Papathanasopoulos P. Normative data and discriminant validity of rey's verbal learning test for the Greek adult population. *Arch Clin Neuropsychol.* (2007) 22:739–52. doi: 10.1016/j.acn.2007.06.002
26. Kaplan EF, Goodglass H, Wintraub S. *The Boston Naming Test. Experimental Edition*. Philadelphia, PA: Lea & Febiger (1983).
27. Patricacou A, Psallida E, Pring T, Dipper L. The Boston naming test in Greek: normative data and the effects of age and education on naming. *Aphasiology.* (2007) 21:1157–70. doi: 10.1080/02687030600670643
28. Goodglass H, Kaplan E. *The Assessment of Aphasia and Related Disorders*. Philadelphia, PA; Boston, MA: Lea & Febiger (1972).
29. Tsantali E, Tsolaki M, Efklides A, Kiosseoglou G, Pita G. Validation of the Boston diagnostic aphasia examination test in Greek elderly population. *Encephalos.* (2001) 38:146–66.
30. Kosmidis MH, Vlahou CH, Panagiotaki P, Kiosseoglou G. The verbal fluency task in the Greek population: normative data, and clustering and switching strategies. *J Int Neuropsychol Soc.* (2004) 10:164–72. doi: 10.1017/S1355617704102014
31. Rey A. L'examen psychologique dans le cas d'encephalopathie traumatique. *Arch Psychol.* (1941) 28:286–340.
32. Tsatali M, Emmanouel A, Gialaouzidis M, Avdikou K, Stefanatos C, Diamantidou A, et al. Rey complex figure test (RCFT): norms for the Greek older adult population. *Appl Neuropsychol Adult.* (2020) 1–9. doi: 10.1080/23279095.2020.1829624
33. Jensen AR, Rohwer WD. The stroop color – word test: a review. *Acta Psychol.* (1966) 25:36–93. doi: 10.1016/0001-6918(66)90004-7
34. Zalonis I, Christidi F, Bonakis A, Kararizou E, Triantafyllou NI, Paraskevas G, et al. The stroop effect in Greek healthy population: normative data for the stroop neuropsychological screening test. *Arch Clin Neuropsychol.* (2009) 24:81–8. doi: 10.1093/arclin/acp011
35. Partington JE, Leiter RG. Partington's pathway test. *Psychol Serv Center Bull.* (1949) 1:9–20. doi: 10.1037/t66320-000
36. Zalonis I, Kararizou E, Triantafyllou NI, Kapaki E, Papageorgiou S, Sgouropoulos P, et al. A normative study of the trail making test A and B in Greek adults. *Clin Neuropsychol.* (2008) 22:842–50. doi: 10.1080/13854040701629301
37. Wechsler D. *Manual for the Wechsler Adult Intelligence Scale*. Washington, DC: Psychological Corp (1955).
38. Tsatali M, Poptsi E, Moraitou D, Agogiatou C, Bakoglidou E, Gialaouzidis M, et al. Discriminant validity of the WAIS-R digit symbol substitution test in subjective cognitive decline, mild cognitive impairment (amnestic subtype) and Alzheimer's disease dementia (ADD) in Greece. *Brain Sci.* (2021) 11:881. doi: 10.3390/brainsci11070881
39. Finlayson M, Mallinson T, Barbosa VM. Activities of daily living (ADL) and instrumental activities of daily living (IADL) items were stable over time in a longitudinal study on aging. *J Clin Epidemiol.* (2005) 58:338–49. doi: 10.1016/j.jclinepi.2004.10.008
40. Theotoka I, Kapaki E, Vagenas V, Ilias I, Paraskevas GP, Liappas I. Preliminary report of a validation study of instrumental activities of daily living in a Greek sample. *Percept Motor Skills.* (2007) 104:958–60. doi: 10.2466/pms.104.3.958-960
41. Hutton JT. Alzheimer's disease. In: Rakel RE, editor. *Conn's Current Therapy*. Philadelphia, PA: W.B. Saunders (1990). p. 778–81.
42. Kounti F, Tsolaki M, Kiosseoglou G. Functional cognitive assessment scale (FUCAS): a new scale to assess executive cognitive function in daily life activities in patients with dementia and mild cognitive impairment. *Hum Psychopharmacol.* (2006) 21:305–11. doi: 10.1002/hup.772
43. Cummings JL. The neuropsychiatric inventory: assessing psychopathology in dementia patients. *Neurology.* (1997) 48:10–6. doi: 10.1212/WNL.48.5_Suppl_6.10S
44. Politis AM, Mayer LS, Passa M, Maillis A, Lyketsos CG. Validity and reliability of the newly translated hellenic neuropsychiatric inventory (H-NPI) applied to Greek outpatients with Alzheimer's disease: a study of disturbing behaviors among referrals to a memory clinic. *Int J Geriatr Psychiatry.* (2004) 19:203–8. doi: 10.1002/gps.1045
45. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatric Res.* (1982) 17:37–49. doi: 10.1016/0022-3956(82)90033-4
46. Fountoulakis KN, Tsolaki M, Iacovides A, Yesavage J, O'hara R, Kazis A, et al. The validation of the short form of the geriatric depression scale

(GDS) in Greece. *Aging Clin Exp Res.* (1999) 11:367–72. doi: 10.1007/BF03339814
47. Sinoff G, Ore L, Zlotogorsky D, Tamir, A. Short anxiety screening test—a brief instrument for detecting anxiety in the elderly. *Int J Geriatr Psychiatry.* (1999) 14:1062–71. doi: 10.1002/(SICI)1099-1166(199912)14:12<1062::AID-GPS67>3.0.CO;2-Q
48. Grammatikopoulos IA, Sinoff G, Alegakis A, Kounalakis D, Antonopoulou M, Lionis C. The short anxiety screening test in Greek: translation and validation. *Ann Gen Psychiatry.* (2010) 9:32. doi: 10.1186/1744-859X-9-1
49. Cohen S, Kessler RC, Gordon LU, editors. *Measuring Stress: A Guide for Health and Social Scientists*. Oxford: Oxford University Press on Demand (1997).
50. Andreou E, Alexopoulos EC, Lionis C, Varvogli L, Gnardellis C, Chrousos GP, Darviri C. 2011 perceived stress scale: reliability and validity study in Greece. *Int J Environ Res Public Health*. (2011) 8:3287–98. doi: 10.3390/ijerph8083287
51. Tsolaki M. Clinical workout for the early detection of cognitive decline and dementia. *Euro J Clin Nutr*. (2014) 68:1186–91. doi: 10.1038/ejcn.2014.189
52. Marizzoni M, Ferrari C, Babiloni C, Albani D, Barkhof F, Cavaliere L, et al. CSF cutoffs for MCI due to AD depend on APOEε4 carrier status. *Neurobiol Aging.* (2020) 89:55–62. doi: 10.1016/j.neurobiolaging.2019.12.019
53. Albani D, Marizzoni M, Ferrari C, Fusco F, Boeri L, Raimondi I, PharmaCog Consortium. Plasma Aβ 42 as a biomarker of prodromal alzheimer's disease progression in patients with amnestic mild cognitive impairment: evidence from the PharmaCog/E-ADNI study. *J Alzheimers Dis*. (2019) 69:37–48. doi: 10.3233/JAD-180321
54. Galluzzi S, Marizzoni M, Babiloni C, Albani D, Antelmi L, Bagnoli C, et al. Clinical and biomarker profiling of prodromal Alzheimer's disease in workpackage 5 of the innovative medicines initiative PharmaCog project: a 'European ADNI study'. *J Intern Med*. (2016) 279:576-591. doi: 10.1111/joim.12482
55. Papaliagkas V, Kimiskidis V, Tsolaki M, Anogianakis G. Usefulness of event-related potentials in the assessment of mild cognitive impairment. *BMC Neurosci.* (2008) 9:107. doi: 10.1186/1471-2202-9-107
56. Papaliagkas VT, Anogianakis G, Tsolaki MN, Koliakos G, Kimiskidis VK. Progression of mild cognitive impairment to Alzheimer's disease: improved diagnostic value of the combined use of N200 latency and β-amyloid (1–42) levels. *Dement Geriatr Cogn Disord.* (2009) 28:30–5. doi: 10.1159/000229023
57. Tsolaki A, Kazis D, Kompatsiaris I, Kosmidou V, Tsolaki M. Electroencephalogram and Alzheimer's disease: clinical and research approaches. *Int J Alzheimers Dis.* (2014) 2014:349249. doi: 10.1155/2014/349249
58. Iliadou P, Kladi A, Frantzidis CA, Gilou S, Tepelena I, Gialaouzidis M, et al. The pattern of mu rhythm modulation during emotional destination memory: comparison between mild cognitive impairment patients and healthy controls. *J Alzheimers Dis.* (2019) 71:1201–15. doi: 10.3233/JAD-190311
59. Dimitriadis SI, Laskaris NA, Bitzidou MP, Tarnanas I, Tsolaki MN. A novel biomarker of amnestic MCI based on dynamic cross-frequency coupling patterns during cognitive brain responses. *Front Neurosci.* (2015) 9:350. doi: 10.3389/fnins.2015.00350
60. Dimitriadis SI, Tarnanas I, Wiederhold M, Wiederhold B, Tsolaki M, Fleisch E. Mnemonic strategy training of the elderly at risk for dementia enhances integration of information processing via cross-frequency coupling. *Alzheimers Dement Transl Res Clin Intervent.* (2016) 2:241–9. doi: 10.1016/j.trci.2016.08.004
61. Jovicich J, Babiloni C, Ferrari C, Marizzoni M, Moretti DV, Del Percio C, et al. Two-year longitudinal monitoring of amnestic mild cognitive impairment patients with prodromal Alzheimer's disease using topographical biomarkers derived from functional magnetic resonance imaging and electroencephalographic activity. *J Alzheimers Dis*. (2019) 69:15–35. doi: 10.3233/JAD-180158
62. Lazarou I, Adam K, Georgiadis K, Tsolaki A, Nikolopoulos S, Tsolaki M. Can a novel high-density EEG approach disentangle the differences of visual event related potential (N170), elicited by negative facial stimuli, in people with subjective cognitive impairment? *J Alzheimers Dis.* (2018) 65:543–75. doi: 10.3233/JAD-180223
63. Lazarou I, Georgiadis K, Nikolopoulos S, Oikonomou VP, Tsolaki A, Kompatsiaris I, et al. A novel connectome-based electrophysiological study of subjective cognitive decline related to Alzheimer's disease by using resting-state high-density EEG EGI GES 300. *Brain Sci.* (2020) 10:392. doi: 10.3390/brainsci10060392
64. Tsolaki AC, Kosmidou V, Kompatsiaris IY, Papadaniil C, Hadjileontiadis L, Adam A, et al. Brain source localization of MMN and P300 ERPs in mild cognitive impairment and Alzheimer's disease: a high-density EEG approach. *Neurobiol Aging.* (2017) 55:190–201. doi: 10.1016/j.neurobiolaging.2017.03.025
65. Tsolaki A, Kosmidou V, Hadjileontiadis L, Kompatsiaris IY, Tsolaki M. Brain source localization of MMN, P300 and N400: aging and gender differences. *Brain Res.* (2015) 1603:32–49. doi: 10.1016/j.brainres.2014.10.004
66. Tsolaki AC, Kosmidou VE, Kompatsiaris IY, Papadaniil C, Hadjileontiadis L, Tsolaki M. Age-induced differences in brain neural activation elicited by visual emotional stimuli: a high-density EEG study. *Neuroscience.* (2017) 340:268–278. doi: 10.1016/j.neuroscience.2016.10.059
67. Ten Kate M, Redolfi A, Peira E, Bos I, Vos SJ, Vandenberghe R, et al. MRI predictors of amyloid pathology: results from the EMIF-AD Multimodal biomarker discovery study. *Alzheimers Res Ther.* (2018) 10:100. doi: 10.1186/s13195-018-0428-1
68. Marizzoni M, Ferrari C, Jovicich J, Albani D, Babiloni C, Cavaliere L, et al. Predicting and tracking short term disease progression in amnestic mild cognitive impairment patients with prodromal Alzheimer's disease: structural brain biomarkers. *J Alzheimers Dis*. (2019) 69:3–14. doi: 10.3233/JAD-180152
69. Khan W, Giampietro V, Banaschewski T, Barker GJ, Bokde AL, Büchel C, et al. A multi-cohort study of ApoE ε4 and Amyloid-β effects on the hippocampus in Alzheimer's disease. *J Alzheimers Dis.* (2017) 56:1159–74. doi: 10.3233/JAD-161097
70. Lombardi G, Crescioli G, Cavedo E, Lucenteforte E, Casazza, G, et al. Structural magnetic resonance imaging for the early diagnosis of dementia due to Alzheimer's disease in people with mild cognitive impairment. *Cochrane Database Syst Rev.* (2020) 3:CD009628. doi: 10.1002/14651858.CD009628.pub2
71. Giannouli V, Tsolaki M. APOE ε4 allele and financial capacity performance in mild Alzheimer's disease: a pilot study. *J Alzheimers Dis Rep.* (2021) 5:93–7. doi: 10.3233/ADR-200254
72. Tsolaki AC, Gatzima O, Daniilidou M, Lazarou E, Bamidis PD, Verykouki E, et al. Prevalence of apolipoprotein E polymorphisms in Alzheimer's disease, mild cognitive impairment, and healthy elderly: a Northern Greece study. *Neurodegenerat Dis.* (2018) 18:216–24. doi: 10.1159/000491764
73. Koutroumani M, Daniilidou M, Giannakouros T, Proitsi P, Liapi D, Germanou A, et al. The deletion variant of α2b-adrenergic receptor is associated with decreased riskin Alzheimer's disease and mild cognitive impairment. *J Neurol Sci.* (2013) 328:19–23. doi: 10.1016/j.jns.2013.02.003
74. Wollmer MA, Sleegers K, Ingelsson M, Zekanowski C, Brouwers N, Maruszak A, et al. Association study of cholesterol-related genes in Alzheimer's disease. *Neurogenetics.* (2007) 8:179–88. doi: 10.1007/s10048-007-0087-z
75. Lupton MK, Proitsi P, Lin K, Hamilton G, Daniilidou M, Tsolaki M, et al. The role of ABCA1 gene sequence variants on risk of Alzheimer's disease. *J Alzheimers Dis.* (2014) 38:897–906. doi: 10.3233/JAD-131121
76. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*. American Psychiatric Pub (2013). doi: 10.1176/appi.books.9780890425596
77. Petersen RC. Mild cognitive impairment. *Continuum.* (2016) 22:404–18. doi: 10.1212/CON.0000000000000313
78. Tzekaki EE, Tsolaki M, Pantazaki AA, Geromichalos G, Lazarou E, Kozori M, et al. Administration of the extra virgin olive oil (EVOO) in Mild cognitive impairment (MCI) patients as a therapy for preventing the progress to AD. *Hellen J Nucl Med.* (2019) 22:181.
79. Squires K, Petuchowski S, Wickens C, Donchin E. The effects of stimulus sequence on event related potentials: a comparison of visual and auditory sequences. *Percept Psychophys.* (1977) 22:31–40. doi: 10.3758/BF03206077

80. Tsolaki M, Kounti F, Agogiatou C, Poptsi E, Bakoglidou E, Zafeiropoulou M, et al. Effectiveness of nonpharmacological approaches in patients with mild cognitive impairment. *Neurodegenerat Dis.* (2011) 8:138–145. doi: 10.1159/000320575
81. Kounti F, Bakoglidou E, Agogiatou C, Lombardo NBE, Serper LL, Tsolaki M. RHEA,* a nonpharmacological cognitive training intervention in patients with mild cognitive impairment: a pilot study. *Topics Geriatr Rehabil.* (2011) 27:289–300. doi: 10.1097/TGR.0b013e31821e59a9
82. Kosta-Tsolaki M, Poptsi E, Aggogiatou C, Kounti F, Zafeiropoulos S, Markou N. Computer-Based cognitive training versus paper and pencil training: which is more effective? A randomized controlled trial in people with mild cognitive impairment. *JSM Alzheimers Dis Relat Dement.* (2017) 4:1032.
83. Papasozomenou C, Poptsi E, Tabaki EM, Tsolaki M. The operation of the day care centre of alzheimer hellas" saint helen" and of the memory clinic of papanikolaou general hospital from 2007 to 2017. *Hellen J Nucl Med.* (2017) 20:136–45.
84. Poptsi E, Lazarou I, Markou N, Vassiloglou M, Nikolaidou E, Diamantidou A, et al. A comparative single-blind randomized controlled trial with language training in people with mild cognitive impairment. *Am J Alzheimers Dis Other Dement*. (2019) 34:176–87. doi: 10.1177/1533317518813554
85. Mouzakidis C, Garopoulou V, Poptsi E, Antonopoulos A, Markou N, Tambaki, et al. Scientific planning of physical exercise protocols to prevent Dementia in elderly. The "fitness alzheimer mobility exercise"(FAME) project. A roadmap. *J Phys Activ Nutrit Rehabil*. (2019) 573–79.
86. Poptsi E, Tsatali M, Agogiatou C, Bakoglidou E, Batsila G, Dellaporta D, et al. Longitudinal cognitive and physical training effectiveness in MCI, based on the experience of the alzheimer's hellas day care centre. *J Geriatr Psychiatry Neurol*. (2021) 8919887211016057. doi: 10.1177/089198872110016057
87. Karagiozi K, Papaliagkas V, Giaglis G, Papastavrou E, Pattakou V, Tsolaki M. Combined intervention for caregivers of patients with dementia: a randomized controlled trial. *Int J Acad Res Psychol.* (2014) 1:77–95. doi: 10.46886/IJARP/v1-i1/1203
88. Karagiozi K., Margaritidou P, Makri M, Toumpalidou M, Egkiazarova M, Kosta-Tsolaki, et al. Interventions for Caregivers of people with dementia in Greece. *J Family Med.* (2017) 4:1125.
89. Toumpalidou M, Egkiazarova M, Iordan AR, Tsolaki M. Forgiveness as an intervention among caregivers of dementia patients: case report. *J Fam Med.* (2017) 4:1127. doi: 10.26420/jfammed.2017.1127
90. Karagiozi K., Margaritidou P., Tsatali M, Makri M, Apostolidis H, Dimitriou T, et al. Comparison of onsite versus online psycho education groups and reducing caregiver burden. *Clin Gerontol.* (2021) 1–11. doi: 10.1080/07317115.2021.1940409
91. Marki M, Sourgouni E, Tsatali M, Tsolaki M. Feelings experienced by informal caregivers of patients with dementia, from the moment of diagnosis until the beginning of psychotherapy. *J Family Med.* (2021) 8:1–7. doi: 10.26420/jfammed.2021.1248
92. Birks J, Grimley Evans J, Iakovidou V, Tsolaki M. Rivastigmine for Alzheimer's disease. *Cochrane Database Syst Rev*. (2000) CD001191. doi: 10.1002/14651858.CD001191
93. Maher-Edwards G, Zvartau-Hind M, Hunter AJ, Gold M, Hopton G, Jacobs G, et al. Double-blind, controlled phase II study of a 5-HT6 receptor antagonist, SB-742457, in Alzheimer's disease. *Curr Alzheimer Res.* (2010) 7:374–85. doi: 10.2174/156720510791383831
94. Risner ME, Saunders AM, Altman JFB, Ormandy GC, Craft S, Foley IM, et al. Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease. *Pharmacogenom J.* (2006) 6:246–54. doi: 10.1038/sj.tpj.6500369
95. Emre M, Tsolaki M, Bonuccelli U, Destée A, Tolosa E, Kutzelnigg A, et al. Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. (2010) 9:969–77. doi: 10.1016/S1474-4422(10)70194-0
96. Boada-Rovira M, Brodaty H, Cras P, Baloyannis S, Emre M, Zhang R, et al. Efficacy and safety of donepezil in patients with Alzheimer's disease. *Drugs Aging*. (2004) 21:43–53. doi: 10.2165/00002512-200421010-00004
97. Wilcock GK, Lilienfeld S, Gaens E. Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. *BMJ*. (2000) 321:1445. doi: 10.1136/bmj.321.7274.1445
98. Wilkinson D, Windfeld K, Colding-Jørgensen E. Safety and efficacy of idalopirdine, a 5-HT6 receptor antagonist, in patients with moderate Alzheimer's disease (LADDER): a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Neurol.* (2014) 13:1092–9. doi: 10.1016/S1474-4422(14)70198-X
99. Florian H, Meier A, Gauthier S, Lipschitz S, Lin Y, Tang Q, et al. Efficacy and safety of ABT-126 in subjects with mild-to-moderate Alzheimer's disease on stable doses of acetylcholinesterase inhibitors: a randomized, double-blind, placebo-controlled study. *J Alzheimers Dis.* (2016) 51:1237–47. doi: 10.3233/JAD-150978
100. Lawlor B, Segurado R, Kennelly S, Olde Rikkert MG, Howard R, Pasquier F, et al. Nilvadipine in mild to moderate Alzheimer disease: a randomised controlled trial. *PLoS Med*. (2018) 15:e1002660. doi: 10.1371/journal.pmed.1002660
101. NIH. *Masitinib in Patients With Mild to Moderate Alzheimer's Disease.* (2020). Available online at: https://www.clinicaltrials.gov/ct2/show/NCT01872598
102. Alzforum. *Positive Phase 2 Results Claimed for Masitinib in Alzheimer's.* Available online at: https://www.alzforum.org/news/research-news/positive-phase-2-results-claimed-masitinib-alzheimers
103. Tsolaki M, Lazarou E, Kozori M, Petridou N, Tabakis I, Lazarou I, et al. A Randomized clinical trial of greek high phenolic early harvest extra virgin olive oil in mild cognitive impairment: the MICOIL pilot study. *J Alzheimers Dis.* (2020) 78:801–17. doi: 10.3233/JAD-200405
104. Tzekaki EE, Tsolaki M, Pantazaki AA, Geromichalos G, Lazarou E, Kozori M, et al. The pleiotropic beneficial intervention of olive oil intake on the Alzheimer's disease onset via fibrinolytic system. *Exp Gerontol.* (2021) 150:111344. doi: 10.1016/j.exger.2021.111344
105. ICH Good Clinical Practice Network. *Management of Dementia With Olive Oil Leaves.* Available online at: https://ichgcp.net/cs/clinical-trials-registry/NCT04440020
106. NIH. *Management of Mild Cognitive Impairment Patients With Greek Mountain Tea - TEAMENTIA (TEAMENTIA).* Available online at: https://clinicaltrials.gov/ct2/show/NCT04435509
107. NIH. *NEURO-TTRansform: A Study to Evaluate the Efficacy and Safety of AKCEA-TTR-LRx in Participants With Hereditary Transthyretin-Mediated Amyloid Polyneuropathy*. Available online at: https://clinicaltrials.gov/ct2/show/NCT04136184
108. NIH. MIRAGE: *Multi-Institutional Research in Alzheimer's Genetic Epidemiology*. Available online at: https://www.clinicaltrials.gov/ct2/show/NCT00239759
109. European Commission. *Foresight Study for the Development of an European NeuroImage Repository*. Available online at: https://cordis.europa.eu/project/id/26036/reporting
110. European Commission. *The Impact of Treatment With Acetylcholinesterase Inhibitors on Europeans With Alzheimers Disease*. Available online at: https://cordis.europa.eu/project/id/QLK6-CT-2002-02645
111. Descripa. *DESCRIPA Study Early Diagnosis of Alzheimer's Disease*. Available online at: http://www.descripa.eu/publications.html
112. Lovestone S, Francis P, Kloszewska I, Mecocci P, Simmons A, Soininen H, et al. AddNeuroMed-the European collaboration for the discovery of novel biomarkers for Alzheimer's disease. *Ann N Y Acad Sci.* (2009) 1180:36–46. doi: 10.1111/j.1749-6632.2009.05064.x
113. EDAR. *EDAR Study Biomarkers for Alzheimer's Disease*. Available online at: http://www.edarstudy.eu/
114. Votis K, Segkouli S, Drosou A, Tzovaras D, Tsolaki M. An ambient intelligence system for the monitoring, empowerment, and disease evolution prediction for patients with mild cognitive impairment. In: Bamidis PD, Tarnanas I, Hadjileontiadis L, Tsolaki M, editors. *Handbook of Research on Innovations in the Diagnosis and Treatment of Dementia*. IGI Global (2015). p. 225–39. doi: 10.4018/978-1-4666-8234-4.ch012
115. European Commission. *Project Description*. Available online at: https://cordis.europa.eu/project/id/238904

116. Alzheimer Europe. *PharmaCog*. Available online at: https://www.alzheimer-europe.org/Research/PharmaCog
117. Demacare. *The Dem@Care Project: Dementia Ambient Care Multi-Sensing Monitoring for Intelligent Remote Management and Decision Support*. Available online at: https://demcare.eu/
118. Demetriadis S, Tsiatsos T, Sapounidis T, Tsolaki M, Gerontidis A. Exploring the potential of programming tasks to benefit patients with mild cognitive impairment. In: *PETRA '16: Proceedings of the 9th ACM International Conference on PErvasive Technologies Related to Assistive Environments*. Thessaloniki (2016).
119. JPND Research. *BIOMARKAPD*. Available online at: https://www.neurodegenerationresearch.eu/initiatives/annual-calls-for-proposals/closed-calls/biomarkers-transnational-call/results-of-biomarker-call/biomarkapd/
120. Reijs BLR, Teunissen CE, Goncharenko N, Betsou F, Blennow K, Baldeiras I, et al. The central biobank and virtual biobank of BIOMARKAPD: a resource for studies on neurodegenerative diseases. *Front Neurol*. (2015) 6:216. doi: 10.3389/fneur.2015.00216
121. Komisja Europejska. *Final Report Summary - HARC (Healthy Ageing Research Centre)*. Available online at: https://cordis.europa.eu/project/id/316300/reporting/pl
122. Papaliagkas V, Gkioka M, Mousiolis A, Chatzidimitriou M, Skepastianos P, Tsolaki M, et al. Neurophysiological study of alzheimer's disease and diabetes mellitus type 2 patients. Is there a common link? *J Adv Med Res*. (2021) 10–15. doi: 10.9734/jammr/2021/v33i1230935
123. Vanova M, Irazoki E, García-Casal JA, Martínez-Abad F, Botella C, Shiells KR, et al. The effectiveness of ICT-based neurocognitive and psychosocial rehabilitation programmes in people with mild dementia and mild cognitive impairment using GRADIOR and ehcoBUTLER: study protocol for a randomised controlled trial. *Trials*. (2018) 19:100. doi: 10.1186/s13063-017-2371-z
124. NIH. *Evaluation of a Computerized Complex Instrumental Activities of Daily Living Marker (NMI) (AltoidaML)*. Available online at: https://clinicaltrials.gov/ct2/show/NCT02843529
125. Poptsi E, Tsolaki M, Bergh S, Cesana BM, Ciccone A, Fabbo A, et al. Rationale, design, and methodology of a prospective cohort study for coping with behavioral and psychological symptoms of dementia: the RECage project. *J Alzheimers Dis*. (2021) 80:1–15. doi: 10.3233/JAD-201215
126. Petridou N, Tsolaki M, Vasile A, Tudose C, Gadalean DA, Wyman D, et al. Story2Remember: using drama and storytelling in dementia care. In: *Alzheimer's Association International Conference*. Thessaloniki (2020).
127. IMI. *Remote Assessment of Disease and Relapse – Alzheimer's Disease*. Available online at: https://www.imi.europa.eu/projects-results/project-factsheets/radar-ad
128. Stavropoulos TG, Lazarou I, Diaz A, Gove D, Georges J, Manyakov NV, et al. Wearable devices for assessing function in Alzheimer's disease: a european public involvement activity about the features and preferences of patients and caregivers. *Front Aging Neurosci*. (2021) 13:43135. doi: 10.3389/fnagi.2021.643135

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Neurology

ORIGINAL RESEARCH
published: 26 August 2021
doi: 10.3389/fneur.2021.629048

Literacy Level and Executive Control in Healthy Older Peruvian Adults

Marcio Soto-Añari[1], Norman López[2], Claudia Rivera-Fernández[3], Verónica Belón-Hercilla[1] and Sara Fernández-Guinea[4]*

[1] Laboratorio de Neurociencia, Departamento de Psicología, Universidad Católica San Pablo, Arequipa, Peru, [2] Universidad de la Costa, Barranquilla, Colombia, [3] Universidad Nacional de San Agustín de Arequipa, Arequipa, Peru, [4] Departamento de Psicología Experimental, Facultad de Psicología, Universidad Complutense de Madrid, Madrid, Spain

OPEN ACCESS

Edited by:
Christopher Butler, University of Oxford, United Kingdom

Reviewed by:
Maria Paula Foss, University of São Paulo, Brazil
Lambros Messinis, Aristotle University of Thessaloniki, Greece
Vera U. Ludwig, University of Pennsylvania, United States
Pablo Luis Martino, Universidad Nacional de Rosario, Argentina
Tanu Wadhera, Dr. B. R. Ambedkar National Institute of Technology Jalandhar, India

***Correspondence:**
Marcio Soto-Añari
msoto@ucsp.edu.pe

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: *13 November 2020*
Accepted: *30 July 2021*
Published: *26 August 2021*

Citation:
Soto-Añari M, López N, Rivera-Fernández C, Belón-Hercilla V and Fernández-Guinea S (2021) Literacy Level and Executive Control in Healthy Older Peruvian Adults. Front. Neurol. 12:629048. doi: 10.3389/fneur.2021.629048

Introduction: Early-life educational experiences are associated with cognitive performance in aging. Early literacy seems to improve executive control mechanisms, however, it is not clear whether early education would still be an advantage in countries like Peru, where access to and quality of education is highly variable.

Aim: Our objective was to analyze the association of literacy level with executive control factors.

Method: We evaluated 93 healthy older adults with a clinical protocol that included the Mini-Mental State Examination, the Geriatric Depression Scale and Global Dementia Staging. We also used a neuropsychological executive function battery which included the Trail-Making Test parts A and B, the Stroop Test, phonological and semantic verbal fluency tasks, Forward and Backward Digits, Numbers and Letters of the Wechsler Scale, and the Go/No-Go task. We used a principal component analysis for the dimensional reduction of the variables. To measure the level of literacy we used the word accentuation test (WAT).

Results: We observed statistically significant correlations between the principal components (PCs) of working memory, cognitive flexibility and inhibitory control with the WAT scores. Furthermore, we observed that processing speed and WAT predict the scores on PCs factors better than years of education and age.

Conclusions: Literacy level correlates more closely with better cognitive performance than years of education and thus, might improve executive control factors that could compensate and protect against brain changes in cognitive decline and dementia.

Keywords: literacy level, executive control, aging, neuropsychology, dementia, education

INTRODUCTION

The rapid aging of the population is one of the most serious issues worldwide in this century (1). An estimated 2.1 billion people will be elderly by 2050. Eighty percentage will live in low- and middle-income countries, such as most Latin-American countries, and a high percentage will be illiterate, have difficulty in accessing education or have received poor quality education (1). This scenario will bring an increase in diseases and health disorders such as dementia (2), for which a low educational level is one of the main risk factors (3, 4), along with a low literacy level.

Early-life educational experiences have an important effect on cognition throughout development (5). The pioneering studies of Manly et al. (6, 7), demonstrated that literacy level was a more reliable predictor of cognitive decline in ethnic minorities and immigrants than years of education. Later studies confirmed these findings (8, 9). Therefore, the literacy level achieved, including not only the ability to read and write but also the competent use of information, seems to modulate the cognitive response in older adults with different ethnicities, through basic and complex cognitive mechanisms (10).

This modulation has been associated with basic attentional mechanisms such as processing speed, which is known as an important factor influencing cognition in aging (11) and executive control (12), which includes working memory, inhibitory control and cognitive flexibility (13). These mechanisms are activated in normal (14, 15) and pathological (16) cognitive aging to better cope with physiological changes or task demands (12, 17).

These executive control mechanisms are activated during a complex or novel task, or when processing resources are reduced, as in pathological aging (18). They activate brain processing networks that compensate for changes (19, 20). Other studies have suggested that these compensatory activations are not always positive, because it seems to have a threshold above which they could be rather inefficient, thus reflecting a greater level of deterioration (21).

Literacy level has been assessed through asking subjects to read low-frequent words, classically used for the estimation of premorbid IQ (22). It is assumed that the pronunciation of these words is associated with the literacy level achieved and that this in turn is correlated with IQ (23). For this, the Word Accentuation Test (WAT) has been used for Spanish speakers (24). This has shown itself to be useful in studies with neuropsychiatric populations for the measurement of premorbid IQ (25, 26) and suitable for evaluating educational quality where education is not homogeneous (27).

Previous studies in Peru have shown that older adults with higher reading level scores performed better in executive functions and memory tasks (28). This study concludes that higher literacy levels might reflect a higher quality education received early in life.

These early-life educational experiences (exposure to quality content), also promote the implementation of mechanisms for regulating cognition, such as executive control, which are associated with cognitive reserve and brain resilience mechanisms in later-life (29). Consequently, it seems that limited years of education is not the only risk factor for neurodegenerative diseases, but also low literacy level. Thus, our objective is to analyze the association of literacy level with executive control factors in normal aging. In addition, we analyze the effect of processing speed, years of education and age on executive control. We hypothesize that higher scores in the Word Accentuation Test will predict better performance in executive control tasks, which will be independent of age, years of education, and processing speed. These results will permit us to identify the influence of educational quality on the dynamics of cognition in older adults.

METHODS

Participants

The initial sample consisted of 121 older adults from public and private senior citizen clubs in the city of Arequipa, Peru. The participants were selected according to the following criteria: not having a history of neurological or psychiatric disease and not having major visual or auditory problems. Besides we excluded participants with Mini-Mental State Examination scores below 27 points if they had more than 7 years of schooling, below 23 points for those with 4–7 years of schooling and below 21 points for those with 1–3 years of schooling; following the used by Custodio & Lira (30). Finally, we excluded participants with scores above 6 points on the Yesavage Geriatric Depression Scale (31) and above 2 points on Reisberg's Global Dementia Staging (32). The final sample was made up of 93 healthy older adults (see **Table 1**).

Instruments

We used a paper and pencil neuropsychological battery to test various components of executive control. Working memory was assessed with the raw scores of Forward and Backward Digits, as well as of Numbers and Letters from the III Wechsler Scale (33). For cognitive flexibility, we used the raw scores (time) of Trail Making Test B (TMT-B) (34) and the total number of words with "P" (phonological fluency) and animals (semantic fluency) named in 60 s (35). Inhibitory control was evaluated with the Word-Color subtest and interference scores of Stroop Test (36) and the Go/No-Go subtest of the Frontal Assessment Battery (FAB) (37).

Likewise, we evaluated processing speed as a basic attention mechanism that modulates cognition in aging (11). For that purpose, we used the raw scores of Trail Making Test A (time) (TMT-A) (38) and Word and Color subtests of the Stroop Test (36), accordingly the proposal of Perea et al. (39), along with the raw scores of the Digit Symbol subtest from the Wechsler scale (WAIS IV).

Literacy level was measured through the Word Accentuation Test (WAT) (24). We used the Ecuadorian version (26), which showed good internal consistency as well as good test-retest reliability. This test requires the subject to read aloud some low-frequency words presented visually, written in capital letters without an accent mark. The subjects were asked to read the word correctly and mark the tonic accent. We used the 30-item version.

Procedure

Two sessions of approximately 50 min each were carried out over a period of 2–3 weeks. The assessments were carried out in 2 phases. In the first one, a clinical screening protocol was applied to all subjects, excluding those who did not meet the inclusion criteria. In the second phase, the subjects were administered the neuropsychological battery.

Statistical Analysis

We performed a Principal Component Analysis (PCA) to reduce the neuropsychological factors and identify executive control and processing speed components. To obtain PCA components, we transformed Direct scores of individual tests into Z scores for

TABLE 1 | Sociodemographic, clinical and cognitive characteristics of the final sample ($N = 93$), according to the WAT score.

	WAT scores		
	≤24 points $N = 52$	>24 points $N = 41$	*P* value
Age, mean (SD)	73.42 (8.20)	70 (7.38)	0.064
Education (years), mean (SD)	10.41 (3.84)	13.82 (3.45)	0.000*
Sex			
Male, n (%)	6 (5.45)	12 (7.13)	0.422∧
Female, n (%)	31 (47.69%)	34 (52.03%)	
MMSE, M (DS)	25.20 (4.43)	28.10 (1.52)	0.001*
Geriatric Depression Scale M (SD)	5.39 (2.95)	5.13 (2.93)	0.075
Global Dementia Staging M (DS)	1.43 (0.48).	1.17 (0.47)	0.091
Executive control			
Working memory M (DS)	−0.40 (0.94)	0.41 (0.84)	<0.000**
Cognitive Flexibility M (DS)	−0.52 (0.73)	0.47 (0.91)	<0.000**
Inhibitory Control M (DS)	−0.51 (0.89)	0.33 (0.92)	<0.000**

WAT, word accentuation test; MMSE, Mini Mental State Examination; M, Media; SD, Standard Deviation.
*$p < 0.05$.
**$p < 0.001$.
^*Chi2.*
**t student.*

standardized data. The number of principal components (PCs) extracted was prespecified using the standard eigenvalues >1 criterion. Top contributors of each rotated PC were defined as those with a factor loading > 0.5.

We used the median obtained in the word accentuation test (Me = 24) to split the participants into two groups (lower score ≤ 24 and higher score > 24) according with Manly et al. (6). Afterwards, Pearson bivariate correlation tests were performed between the PCs found with the WAT score. Finally, we performed a linear regression analysis, in which the PCs were analyzed as dependent variables and the age factor, years of education, WAT scores and composite index of the processing speed factor were the independent variables. The processing was performed using the statistical software SPSS version 24.

Ethical Aspects

This study is part of a follow-up research project about the impact of literacy level on cognition in preclinical and clinical phases of dementia and was reviewed and approved by the Ethics Committee of the Research unit of San Pablo Catholic University (Acta N° 012.CEDI.UCSP.2020). All participants gave written informed consent in accordance with the declaration of Helsinki.

RESULTS

Demographic, Clinical and PC Information on the Participants

The sociodemographic, clinical and PC data (**Supplementary Material**) of the sample are presented in **Table 1**. Participants with WAT scores below and above 24 points do not differ significantly in age and sex, but they do in years of education and MMSE (see **Table 1**). The PCs obtained were inhibitory control (Word-Color and Interference subtests of Stroop Test), cognitive flexibility (TMT-B, semantic [animal] and phonological [letter P] fluency task) and working memory (Forward and Backward Digits and Numbers and Letters). These components explained 72.9% of the variance. In addition, their scores differ significantly between the groups.

Associations Between Composite Factors and WAT Score

Pearson bivariate correlation tests showed significant correlations between PC scores of working memory ($r = 0.527$, $p < 0.000$); cognitive flexibility ($r = 0.521$, $p < 0.000$) and inhibitory control ($r = 382$, $p < 0.000$) with the WAT scores across participants (see **Figure 1**).

Linear Regression for Principal Components of Executive Control

We performed the linear regression analysis using the composite factor of working memory as the dependent variable and the composite index of processing speed, years of education and age as independent variables. We observed that the WAT and processing speed scores significantly predict the working memory scores and explain 52.7% (adjusted R^2) of the variability in the scores, while years of education and age did not predict working memory scores (see **Table 2**).

In the case of the cognitive flexibility, we observed that WAT scores, age and processing speed significantly predict the factor scores. In addition, these factors explain 62.3% (adjusted R^2) of the variability (see **Table 3**).

Finally, we observed that processing speed and WAT scores predict the inhibitory control factor scores. Similarly, these factors explain 26% (adjusted R^2) of the variations in the factor (see **Table 4**).

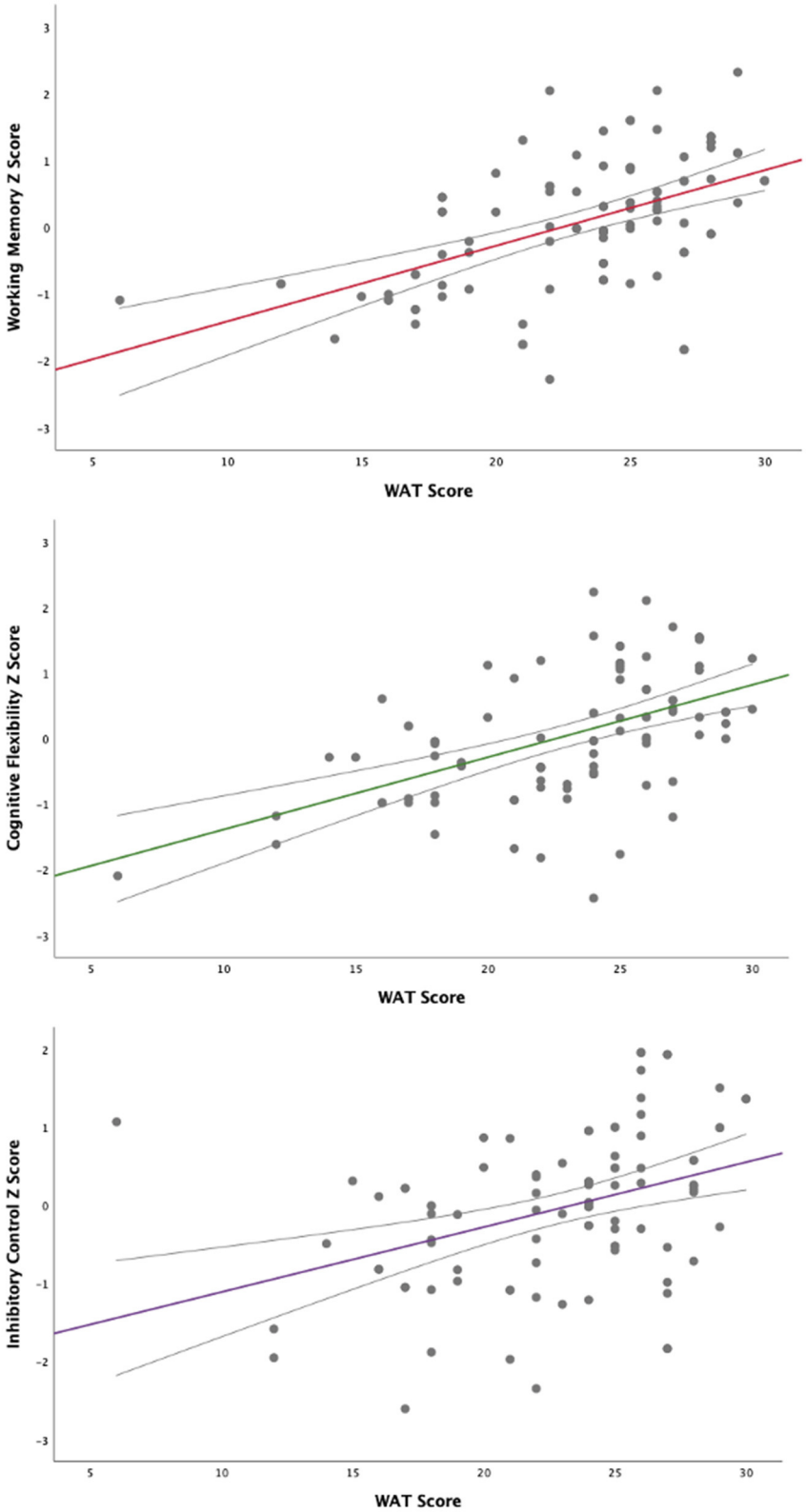


FIGURE 1 | Correlations of executive control PCs with the WAT score.

TABLE 2 | Linear regression of years of education, age, processing speed and WAT with working memory factor as DV.

Model	Predictors	USC B	SE	SC beta	*t* value	*p*	95% CI for B	
							Lower	Upper
Multivariable	Education (years)	0.038	0.024	0.154	1.547	0.125	−0.011	0.086
	Age	0.003	0.010	0.025	0.309	0.758	−0.017	0.023
	Processing speed	0.465	0.086	0.469	5.401	<0.001	0.294	0.635
	WAT	0.068	0.017	0.318	3.927	<0.001	0.034	0.103

WAT, word accentuation test; CI, Confidence Interval; USC B, Unstandarized beta; SE, Standard error; SC, Standardized.
$R^2 = 0.527$.

TABLE 3 | Linear regression of years of education, age, processing speed and WAT with cognitive flexibility factor as DV.

Model	Predictors	USC B	SE	SC beta	*t* value	*p*	95% CI for B	
							Lower	Upper
Multivariable	Education (years)	0.029	0.022	0.121	1.314	0.192	−0.015	0.073
	Age	−0.035	0.010	−0.283	−3.695	<0.001	−0.054	−0.016
	Processing speed	0.357	0.080	0.360	4.461	<0.001	0.198	0.515
	WAT	0.070	0.016	0.330	4.349	<0.001	0.038	0.102

WAT, word accentuation test; CI, Confidence Interval; USC B, Unstandardized beta; SE, Standard error; SC, Standardized.
$R^2 = 0.623$.

TABLE 4 | Linear regression of years of education, age, processing speed and WAT with inhibitory control factor as DV.

Model	Predictors	USC B	SE	SC beta	*t* value	*p*	95% CI for B	
							Lower	Upper
	Education (years)	−0.002	0.032	−0.009	−0.069	0.945	−0.066	0.062
Multivariable	Age	−0.024	0.014	−0.191	−1.770	0.080	−0.052	0.003
	Processing speed	0.233	0.116	0.229	2.014	0.047	0.003	0.463
	WAT	0.065	0.023	0.301	2.826	0.006	0.019	0.112

WAT, word accentuation test; CI, Confidence Interval; USC B, Unstandardized beta; SE, Standard error; SC, Standardized.
$R^2 = 0.260$.

DISCUSSION

This study examined the association of literacy level with executive control factors in normal aging by using the word accentuation test (WAT). Our results showed better scores in working memory, cognitive flexibility and inhibitory control in subjects who performed better on the WAT. In addition, we found that scores on this measure, together with the processing speed, better predict executive control scores. These results confirm our hypothesis that literacy level is a better predictor of executive control than years of education or age.

Predictors of Scores in Executive Control

Our results show that subjects with better WAT scores exhibit a greater capacity to retain and manipulate information (working memory). These results have been confirmed in other studies (40, 41), where working memory, modulated by education, is associated with cognition during aging. This suggests that perhaps formal education strengthens the ability to select, update, and manipulate information available in the working memory, through the promotion of progressively more complex activities in classroom settings, autonomous learning and improvement curricula.

In addition, we found that WAT scores predict performance on inhibitory control measures. Thus, people with higher WAT scores and faster processing speed show a greater ability to inhibit powerful and/or automatic stimuli. Similar results have been found by de Bruin et al. (42) and Hull et al. (43). Their studies showed that inhibitory control is modulated by processing speed and the type of task used for its assessment. Some tasks are more demanding than others and therefore require more inhibitory control mechanisms to be carried out correctly.

Likewise, we found higher scores for the cognitive flexibility factor when the WAT score is higher, and performance is better predicted by this, together with age and processing speed, as has been reported in research by Gallen et al. (12). We observed that participants who are younger and those with higher literacy (higher WAT scores) have a greater capacity to change attentional and mental sets (44). This is a fundamental aspect in accomplishing complex cognitive tasks (45).

These results could help us to understand the importance of executive control mechanisms in brain and cognitive aging, showing a bigger impact in the case of low-quality education. As a result, we would observe a weakening in mechanisms associated with brain resilience, like white matter integrity and cortical thinning, which could contribute to cognitive decline in the following years (46) and cognitive reserve (47) used to compensate for cognitive changes with an alternative network or better processing strategy. Therefore, people with low literacy levels could perform worse on tasks and have a greater risk of cognitive impairment and dementia.

Literacy Level, Executive Control and Education

Literacy level allows us to explain the scores on the executive control tasks. Nonetheless, it should be noted that processing speed is a mechanism with a significant effect on adult cognitive performance (11, 48). Our data show that the measurement and analysis of literacy level (educational quality) and processing speed can more clearly explain cognitive changes in older adults than years of education. That is, exposure to quality content or being exposed to a more enriching education might make the execution of general processing tasks and those that involve executive control more efficient.

If individuals with a more efficient processing capacity faces a neurodegenerative event, they can generate brain and cognitive compensatory strategies that minimize the impact of the pathology (49–52) and reduce the risk of cognitive impairment or dementia. This could help to achieve satisfactory aging, through the implementation of cognitive reserve mechanisms (53), and thus protect against neurodegenerative pathology. This is an aspect we might not see in subjects with low literacy levels.

This first look at studying the literacy level in Peru can help us to explain the cognitive and behavioral variants observed in older adults who have different scores and performances despite having the same years of education. We consider that literacy level is a more accurate measure than years of education when assessing the effect of formal education on cognition and, consequently, as a protective factor for the development of neurodegenerative pathologies. This is particularly important in settings such as Peru where the quality of education is highly variable, educational quality statistics are below international standards (54) and where the education received depends on socioeconomic status and area of residence (55).

Limitations

Our findings are interesting, but they are not without limitations. As we do not have a group of subjects with a clinical diagnosis (mild cognitive impairment or mild Alzheimer's), we cannot establish a point of comparison with impairment at the executive and cognitive level derived from the WAT score. Furthermore, since it is a cross-sectional study, we cannot precisely establish the protective factor of literacy level. We need to carry out longitudinal studies to estimate the level of protection participants have against deterioration. Furthermore, the Socio-Economic Status (SES) and Intelligence Quotient (IQ) have not been considered in the present study and could be associated with the results obtained (56). The impact of SES on cognition could be mitigated by years of schooling, literacy level, and other environmental factors (57), so they need to be evaluated in future research. Finally, as we do not have a standardized WAT test in Peru, we used the Ecuadorian version. Despite similarities between Andean nations in many aspects (e.g., culturally, educational, etc.), it is necessary to validate the WAT in the Peruvian context.

Conclusions

We can conclude that literacy level, measured through the WAT, is significantly correlated with executive control processes in elderly people in Peru. One interpretation of this is that higher educational quality in young age (as indicated by literacy scores in older age) favor a better development of executive control over the life span.

In this context, we consider that in Peru it is not only illiterate people who have a higher risk of developing dementia, but also adults with lower scores in literacy level and quality of education measures. Consequently, there is a need to develop programs aimed at improving educational quality from the early years of education. This is in addition to the implementation of cognitive intervention programs that favor cognitive mechanisms such as attention and executive function among our adults.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Research unit of San Pablo Catholic University (Acta N° 012.CEDI.UCSP.2020). Written informed consent to participate in this study was provided by the patients/participants.

AUTHOR CONTRIBUTIONS

MS-A: designed the study, performed the statistical analysis and the preparation, and final approval of the manuscript. NL: participated in the statistical analysis and in the preparation and final revision of the manuscript.

CR-F and VB-H: analyzed the data and participate in the preparation and final revision of the manuscript. SF-G: designed the study and revised and approved the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.629048/full#supplementary-material

REFERENCES

1. United Nations, Department of Economic and Social Affairs, Population Division. World Population Prospects. (2019)
2. Parra MA, Baez S, Allegri R, Nitrini R, Lopera F, Slachevsky A, et al. Dementia in Latin America: Assessing the present and envisioning the future. *Neurology*. (2018) 90:222–31. doi: 10.1212/WNL.0000000000004897
3. Arce Rentería M, Vonk J, Felix G, Avila JF, Zahodne LB, Dalchand E, et al. Illiteracy, dementia risk, and cognitive trajectories among older adults with low education. *Neurology*. (2019) 93:e2247–56. doi: 10.1212/WNL.0000000000008587
4. Nitrini R, Bottino C, Albala C, Santos S, Custodio N, Ketzoian C, et al. Prevalence of dementia in Latin America: a collaborative study of population-based cohorts. *Int Psychogeriat*. (2009) 21:622–30. doi: 10.1017/S1041610209009430
5. Mantri S, Nwadiogbu C, Fitts W, Dahodwala N. Quality of education impacts late-life cognition. *Int J Geriatr Psychiatry*. (2019) 34:855–62. doi: 10.1002/gps.5075
6. Manly J, Touradji P, Tang M, Stern Y. Literacy and memory decline among ethnically diverse elders. *J Clini Exp Neuropsychol*. (2003) 25:680–90 doi: 10.1076/jcen.25.5.680.14579
7. Manly J, Schupf N, Tang M, Stern Y. Cognitive decline and literacy among ethnically diverse elders. *J Geriatr Psychiatry Neurol*. (2005) 18:213–17 doi: 10.1177/0891988705281868
8. Gamaldo AA, Sardina AL, Corona RT, Willingham K, Migoyo RV, Andel RA. The association between educational parameters and a cognitive screening measure in older blacks. *Int Psychogeriatr*. (2018) 30:311–22. doi: 10.1017/S1041610217001107
9. Sisco S, Gross AL, Shih RA, Sachs BC, Glymour MM, Bangen KJ, et al. The role of early-life educational quality and literacy in explaining racial disparities in cognition in late life. *J Gerontol B Psychol Sci Soc Sci*. (2015) 70:557–67. doi: 10.1093/geronb/gbt133
10. UNESCO. Replantear la educación. 'Hacia un buen común mundial? (2015) Available online at: http://unesdoc.unesco.org/images/0023/002326/232697s.pdf
11. Salthouse TA. Trajectories of normal cognitive aging. *Psychol Aging*. (2019) 34:17–24. doi: 10.1037/pag0000288
12. Gallen CL, Turner GR, Adnan A, D'Esposito M. Reconfiguration of brain network architecture to support executive control in aging. *Neurobiol Aging*. (2016) 44:42–52. doi: 10.1016/j.neurobiolaging.2016.04.003
13. Friedman NP, Miyake A. Unity and diversity of executive functions: Individual differences as a window on cognitive structure. *Cortex*. (2017) 86:186–204. doi: 10.1016/j.cortex.2016.04.023
14. Park DC, Reuter-Lorenz P. The adaptive brain: aging and neurocognitive scaffolding. *Annu Rev Psychol*. (2009) 60:173–96. doi: 10.1146/annurev.psych.59.103006.093656
15. Turner G, Spreng N. Executive functions and neurocognitive aging: dissociable patterns of brain activity. *Neurobiol of Aging*. (2012) 33:826e1–826e13. doi: 10.1016/j.neurobiolaging.2011.06.005
16. Schroeter ML, Vogt B, Frisch S, Becker G, Barthel H, Mueller K, et al. Executive deficits are related to the inferior frontal junction in early dementia. *Brain*. (2012) 135:201–15. doi: 10.1093/brain/awr311
17. Isingrini M, Angel L, Fay S, Taconnat L, Lemaire P, Bouazzaoui B. Age-related differences in the reliance on executive control in working memory: role of task demand. *PLoS ONE*. (2015) 10:e0145361. doi: 10.1371/journal.pone.0145361
18. Colangeli S, Boccia M, Verde P, Guariglia P, Bianchini F, Piccardi L. Cognitive reserve in healthy aging and Alzheimer's Disease: A meta-analysis of fMRI studies. *Am J Alzheimers Dis Other Demen*. (2016) 31:443–9. doi: 10.1177/1533317516653826
19. Cabeza R, Albert M, Belleville S, Craik F, Duarte A, Grady CL, et al. Maintenance, reserve and compensation: the cognitive neuroscience of healthy ageing. *Nat Rev Neurosci*. (2018) 19:701–10. doi: 10.1038/s41583-018-0068-2
20. Daselaar S, Iyengar V, Davis S, Eklund K, Hayes S, Cabeza R. Less wiring, more firing: low-performing older adults compensate for impaired white matter with grater neural activity. *Cerebral Cortex*. (2013) 25:983–90. doi: 10.1093/cercor/bht289
21. Pusil S, López ME, Cuesta P, Bruña R, Pereda E, Maestú F. Hypersynchronization in mild cognitive impairment: the 'X' model. *Brain*. (2019) 142:3936–50. doi: 10.1093/brain/awz320
22. Bright P, Jaldow E, Kopelman MD. The National Adult Reading Test as a measure of premorbid intelligence: a comparison with estimates derived from demographic variables. *J Int Neuropsychol Soc*. (2002) 8:847–54. doi: 10.1017/S1355617702860131
23. Lezak MD, Howieson DB, Bigler ED, Tranel D. Neuropsychological Assessment. 5th ed New York: Oxford University Press. (2012).
24. Gonzales Montalvo J. *Creación y validación de un test de lectura para el diagn3stico del deterioro mental en el anciano. Tesis doctoral*. Madrid: Universidad Complutense de Madrid (1991).
25. Sierra, N, Torralva, T, Roca, M, Manes, F, Burin, D. Estimación de la inteligencia premórbida en deterioro cognitivo leve y moderado y en déficit ejecutivo. *Revista Neuropsicologia Latinoamericana*. (2010) 2:25–32.
26. Pluc, G, Almeida-Meza P, Gonzalez-Lorza A, Muñoz-Ycaza RA, Trueba, AF. Estimación de la Función Cognitiva Premórbida con el Test de Acentuación de Palabras. *Rev Ecuat Neurol*. (2017) 26:226–34. Available online at: http://scielo.senescyt.gob.ec/scielo.php?script=sci_arttext&pid=S2631-25812017000200226&lng=es.
27. Contador I, Bermejo-Pareja F, Del Ser T, Benito-León J. Effects of education and word reading on cognitive scores in a community-based sample of Spanish elders with diverse socioeconomic status. *J Clin Exp Neuropsychol*. (2015) 37:92–101. doi: 10.1080/13803395.2014.989819
28. Soto-Añari M, Flores G, Fernández-Guinea S. Nivel de lectura como medida de reserva cognitiva. *Revista de neurología*. (2013) 56:79–85. doi: 10.33588/rn.5602.2012402
29. Stern Y, Chételat G, Habeck C, Arenaza-Urquijo EM, Vemuri P, Estanga A, et al. Mechanisms underlying resilience in ageing. *Nat Rev Neurosci*. (2019) 20:246. doi: 10.1038/s41583-019-0138-0
30. Custodio, N, Lira, D. Adaptación peruana del Mini-mental State Examination (MMSE). Rev invest UNMSN. *Anales de la Facultad de Medicina*. (2014) 75:69. doi: 10.15381/anales.v75i1.6951
31. De la Torre Maslucan J, Shimabukuro Maeki R, Varela Pinedo L, Krüger Malpartida H, Huayanay Falconí L, Cieza Zevallos J, et al. Validación de la versión reducida de la escala de depresión geriátrica en el consultorio externo de geriatría del Hospital Nacional Cayetano Heredia. *Acta méd. peruana [Internet]*. (2006) 23:144–7. Available online at: http://www.scielo.org.pe/scielo.php?script=sci_arttext&pid=S1728-59172006000300003&lng=es.
32. Reisberg B, Ferris S, de León M, Crook T. The global deterioration scale for assessment of primary degenerative dementia. *Am J Psychiat*. (1982) 139:1136–9 doi: 10.1176/ajp.139.9.1136
33. Wechsler D. Escala de inteligencia para adultos, versión III. TEA ediciones: Madrid. (1997).
34. Hobert M, Niebler R, Meyer S, Brochmann K, Becker C, Huber H, et al. Poor trail making test performance is directly associated with altered dual task

prioritization in the elderly – baseline results from the TREND study. *PLOS ONE*. (2011) 6:e27831. doi: 10.1371/journal.pone.0027831
35. Olabarrieta-Landa L, Rivera D, Galarza-del-Angel J, Garza MT, Saracho CP, Rodríguez W, et al. Verbal Fluency Tests: Normative data for the Latin American Spanish speaking adult population. *Neuro Rehabilitation*. (2015) 37:515–61. doi: 10.3233/NRE-151279
36. Rivera D, Perrin PB, Stevens LF, Garza MT, Weil C, Saracho CP, et al. Stroop color-word interference test: Normative data for the Latin American Spanish speaking adult population. *Neuro Rehabilitation*. (2015) 37:591–624. doi: 10.3233/NRE-151281
37. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a frontal assesment battery at bedside. *Neurology*. (2000) 55:1621–26. doi: 10.1212/WNL.55.11.1621
38. Arango-Lasprilla JC, Rivera D, Aguayo A, Rodríguez W, Garza CT, Saracho CP, et al., Trail Making Test: Normative data for the Latin American Spanish speaking adult population. *Neuro Rehabilitation*. (2015) 37:639–61. doi: 10.3233/NRE-151284
39. Perea MV, García R, Cañas M, Ladera V. Velocidad de procesamiento de la información en la enfermedad de Alzheimer. *Revista chilena de neuro-psiquiatría*. (2019) 57:228–37. doi: 10.4067/S0717-92272019000300228
40. Pliatsikas C, Veríssimo J, Babcock L, Pullman MY, Glei DA, Weinstein M, et al. Working memory in older adults declines with age, but is modulated by sex and education. *Q J Exp Psychol (Hove)*. (2019) 72:1308–27. doi: 10.1177/1747021818791994
41. Adrover-Roig D, Sesé A, Barceló F, Palmer A. Latent variable approach to executive control in healthy aging. *Brain Cogn*. (2012) 78:284–99. doi: 10.1016/j.bandc.2012.01.005
42. de Bruin A, Sala SD. Effects of age on inhibitory control are affected by task-specific features. *Q J Exp Psychol (Hove)*. (2018) 71:1219–33. doi: 10.1080/17470218.2017.1311352
43. Hull R, Martin R. Beie, M, Lane D, Hamilton C. Executive function in older adults: a structural equation modelling approach *Neuropsychology*. (2008) 22:508–22. doi: 10.1037/0894-4105.22.4.508
44. Friedman N, Miyake A, Young S, DeFries J, Corley R. Hewitt J. *Individual difrerences in executive functions are almost entirely genetic in origin J Exp Psychol Gen*. (2008) 137:201–25. doi: 10.1037/0096-3445.137.2.201
45. López N, Véliz A, Soto-Añari M, Ollari J, Chesta S, Allegri R. Efectos de un programa combinado de actividad física y entrenamiento cognitivo en pacientes chilenos con Alzheimer leve. *Neurología Argentina*. (2015) 73:131–9. doi: 10.1016/j.neuarg.2015.04.001
46. Vemuri P, Lesnick TG, Knopman DS, Przybelski SA, Reid RI, Mielke MM, et al. Amyloid, vascular, and resilience pathways associated with cognitive aging. *Ann Neurol*. (2019) 86:866–77. doi: 10.1002/ana.25600
47. Bettcher BM, Gross AL, Gavett BE, Widaman KF, Fletcher E, Dowling NM, et al. Dynamic change of cognitive reserve: associations with changes in brain, cognition, and diagnosis. *Neurobiol Aging*. (2019) 83:95–104. doi: 10.1016/j.neurobiolaging.2019.08.016
48. Craik F, Bialystok E. Cognition through the lifespan: mechanisms of change. *TRENDS in Cognitive Science*. (2006) 10:131–9. doi: 10.1016/j.tics.2006.01.007
49. Skouras S, Falcon C, Tucholka A, Rami L, Sanchez-Valle R, Lladó A, et al. Mechanisms of functional compensation, delineated by eigenvector centrality mapping, across the pathophysiological continuum of Alzheimer's disease. *Neuroimage Clin*. (2019) 22:101777. doi: 10.1016/j.nicl.2019.101777
50. Daselaar S, Cabeza R. Age-related changes in hemispheric organization. En Cabeza, R., Nyberg, L. y Park, D. (Eds). Cognitive neurosciences of aging: linking cognitive and cerebral aging. London: Oxford University press. (2005) p. 325–35. doi: 10.1093/acprof:oso/9780195156744.003.0014
51. Davis S, Dennis N, Daselaar S, Fleck M. Cabeza, R. Que PASA The posterior anterior shift in aging. *Cereb cortex*. (2008) 22:1201–9. doi: 10.1093/cercor/bhm155
52. Reuter-Lorenz P, Park D. How does it STAC Up? Revisiting the Scaffolding Theory of Aging and Cognition. *Neuropsychol Rev*. (2014) 24:355–70. doi: 10.1007/s11065-014-9270-9
53. Stern Y, Arenaza-Urquijo EM, Bartrés-Faz D, Belleville S, Cantilon M, Chetelat G, et al. Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. *Alzheimers Dement*. (2020) 16:1305–11. doi: 10.1016/j.jalz.2018.07.219
54. Ministerio de Educación. Oficina de medición de la calidad de los aprendizajes. Evaluación PISA. MINEDU. (2018). Available online at: http://umc.minedu.gob.pe/wp-content/uploads/2020/10/PPT-PISA-2018_Web_vf-15-10-20.pdf
55. Beltrán A, Seinfeld J. Hacia una educación de calidad: la importancia de los recursos pedagógicos en el rendimiento escolar. Lima: Universidad del Pacífico. (2011)
56. Hackman DA, Farah MJ, Meaney MJ. Socioeconomic status and the brain: mechanistic insights from human and animal research. *Nat Rev Neurosci*. (2010) 11:651–9. doi: 10.1038/nrn2897
57. Piccolo L.dR, Arteche AX, Fonseca RP, Rodrigo Grassi-Oliveira R, Salles JF. Influence of family socioeconomic status on IQ, language, memory and executive functions of Brazilian children. *Psicol. Refl. Crít*. (2016) 29:23. doi: 10.1186/s41155-016-0016-x

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Public Health

ORIGINAL RESEARCH
published: 06 September 2021
doi: 10.3389/fpubh.2021.676518

Thyroid Dysfunction, Vitamin B12, and Folic Acid Deficiencies Are Not Associated With Cognitive Impairment in Older Adults in Lima, Peru

Monica M. Diaz[1,2], *Nilton Custodio*[3,4,5]*, *Rosa Montesinos*[4,5,6], *David Lira*[3,4,5], *Eder Herrera-Perez*[5,7], *Maritza Pintado-Caipa*[3,4,5,8], *Jose Cuenca-Alfaro*[4,5,9,10], *Carlos Gamboa*[4,5,9] and *Serggio Lanata*[11,12]

[1] Department of Neurology, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States, [2] Facultad de Salud Pública y Administración, Universidad Peruana Cayetano Heredia, Lima, Peru, [3] Servicio de Neurología, Instituto Peruano de Neurociencias, Lima, Peru, [4] Unidad de Diagnóstico de Deterioro Cognitivo y Prevención de Demencia, Instituto Peruano de Neurociencias, Lima, Peru, [5] Unidad de Investigación, Instituto Peruano de Neurociencias, Lima, Peru, [6] Servicio de Rehabilitación, Instituto Peruano de Neurociencias, Lima, Peru, [7] Grupo de investigación Molident, Universidad San Ignacio de Loyola, Lima, Peru, [8] Atlantic Fellow, Global Brain Health Institute, University of California, San Francisco, San Francisco, CA, United States, [9] Servicio de Neuropsicología, Instituto Peruano de Neurociencias, Lima, Peru, [10] Carrera de Psicología, Facultad de Ciencias de la Salud, Universidad Privada del Norte, Lima, Peru, [11] Department of Neurology, University of California, San Francisco, San Francisco, CA, United States, [12] Global Brain Health Institute, University of California, San Francisco, San Francisco, CA, United States

OPEN ACCESS

Edited by:
Maira Okada de Oliveira, University of São Paulo, Brazil

Reviewed by:
Maria Niures P. Matioli, Guilherme Alvaro Hospital, Brazil
Ophir Keret, Rabin Medical Center, Israel

***Correspondence:**
Nilton Custodio
ncustodio@ipn.pe

Specialty section:
This article was submitted to Aging and Public Health, a section of the journal Frontiers in Public Health

Received: *05 March 2021*
Accepted: *12 August 2021*
Published: *06 September 2021*

Citation:
Diaz MM, Custodio N, Montesinos R, Lira D, Herrera-Perez E, Pintado-Caipa M, Cuenca-Alfaro J, Gamboa C and Lanata S (2021) Thyroid Dysfunction, Vitamin B12, and Folic Acid Deficiencies Are Not Associated With Cognitive Impairment in Older Adults in Lima, Peru. Front. Public Health 9:676518. doi: 10.3389/fpubh.2021.676518

Background: Reversible etiologies of cognitive impairment are common and treatable, yet the majority of mild cognitive impairment (MCI) and dementia research in Latin America has focused on irreversible, neurodegenerative etiologies.

Objective: We sought to determine if thyroid dysfunction and vitamin B12 and folate deficiencies are associated with cognitive disorders among older adults with memory complaints in Lima, Peru.

Methods: This was a retrospective review of patients who presented for cognitive evaluations to a multidisciplinary neurology clinic in Lima, Peru from January 2014 to February 2020. We included individuals aged ≥60 years, native Spanish-speakers, with at least a primary school educational level and a complete clinical assessment. Patients had either subjective cognitive decline (SCD), MCI, or dementia. One-way ANOVA and multiple logistic regression analyses were performed.

Results: We included 720 patients (330 SCD, 154 MCI, and 236 dementia); the dementia group was significantly older [mean age SCD 69.7 ± 4.1, dementia 72.4 ± 3.7 ($p = 0.000$)] and had lower folate levels than SCD patients. The MCI group had higher free T3 levels compared with SCD patients. Those with lower TSH had greater dementia risk (OR = 2.91, 95%CI: 1.15–6.86) but not MCI risk in unadjusted models. B12 deficiency or borderline B12 deficiency was present in 34% of the dementia group, yet no clear correlation was seen between neuropsychological test results and B12 levels in our study. There was no association between MCI or dementia and thyroid hormone, B12 nor folate levels in adjusted models.

Conclusion: Our findings do not support an association between metabolic and endocrine disorders and cognitive impairment in older Peruvians from Lima despite a high prevalence of B12 deficiency. Future work may determine if cognitive decline is associated with metabolic or endocrine changes in Latin America.

Keywords: dementia, metabolic disorder, thyroid dysfunction, vitamin B12, folic acid, Peru

INTRODUCTION

The risk of mild cognitive impairment (MCI) and dementia is known to increase exponentially with age (1–3). Worldwide, the number of people aged 65 years or older has risen from 6% in 1990 to 9% in 2019, and this figure is expected to double by the year 2050 (4). Following these demographic trends, the prevalence of dementia in Latin America (LA) is expected to rise to 27 million people by the year 2050 (5, 6).

Both reversible and irreversible etiologies of dementia and MCI exist (7, 8), yet the clinical evaluation of older adults with cognitive impairment in LA is often hindered by lack of access to skilled clinicians with resources and training needed to diagnose dementia appropriately and a limited consensus on the best approaches for evaluation and diagnosis (9). Further adding to this diagnostic challenge, the medical literature on dementia in LA has mostly focused on irreversible, neurodegenerative etiologies such as Alzheimer's disease (AD), whereas relatively little emphasis has been placed on reversible or treatable etiologies, especially metabolic and endocrine disorders known to cause cognitive impairment (10–13).

Guidelines published by the American Academy of Neurology (AAN) recommend screening for certain metabolic and endocrine disorders, such as B12 and folic acid (or folate) deficiencies and thyroid dysfunction, when evaluating a person with cognitive impairment (14). The prevalence of these and other potentially reversible causes of dementia is as high as nearly 20% in one study of patients recently diagnosed with dementia from Brazil (15); thus, screening for these relatively common and potentially treatable conditions in LA may be of value, particularly in regions with poor nutritional status and lack of mandatory vitamin fortification. Serum laboratory analyses of potentially reversible etiologies of dementia, such as thyroid hormone, vitamin B12 and folate levels are cost-effective, highly-accessible and may identify potentially treatable etiologies of cognitive impairment in LA (15–17).

Vitamin B12 deficiency is common in older adults and potentially treatable (18). Particularly among those with MCI and dementia, low levels of vitamin B12 may worsen cognition among older adults with ApoE4 allele or with depression (19). Additionally, folate deficiency, arising from insufficient dietary folate or gut malabsorption, leading to high serum levels of the amino acid homocysteine, has been linked to dementia (11, 20, 21). One systematic review found that a folate supplemented diet led to improved cognition in mouse models (21), however, another review found that folic acid supplementation did not improve cognition in older adults (22). Thus, the role of folate in improving cognition is conflicting. Identifying folate or vitamin B12 deficiency and homocysteine levels in patients with a major neurocognitive disorder, such as dementia, may help reverse or improve the cognitive impairment associated with these conditions. Thyroid hormone dysfunction, particularly clinical hyperthyroidism and chronic hypothyroidism, is also associated with increased dementia risk (23, 24), yet in LA, few studies have investigated this relationship (25, 26) and no study has investigated this relationship in Peru. Therefore, metabolic and endocrine disorders, such as thyroid hormone and vitamin deficiencies are important to consider when evaluating both (i) persons without an existing dementia diagnosis presenting for an initial consultation for cognitive complaints, and (ii) older adults who have a diagnosis of dementia, given medical management of these hormonal or metabolic alterations may help reverse or prevent further cognitive decline (27).

To our knowledge, no research studies have explored associations between metabolic and endocrine disorders and cognitive impairment in Peru, and only a few studies have explored these associations in other countries in the region. Therefore, we present a retrospective, cross-sectional study characterizing serum levels of thyroid hormone, vitamin B12 and folate among older adults presenting to a multidisciplinary neurology clinic in Lima, Peru for an initial consultation for cognitive complaints, diagnosed as either subjective cognitive decline, having MCI, or dementia. We hypothesize that metabolic and endocrine disorders are associated with cognitive impairment in older adults living in Lima, Peru.

METHODS

Study Design

We conducted a retrospective review of medical records of all patients who presented for an initial consultation for a cognitive complaint to a multidisciplinary neurology clinic of the Instituto Peruano de Neurociencias (IPN) in Lima, Peru from January 2014 to February 2020. The protocol was approved by the institutional review board of the Hospital Nacional Docente Madre Niño San Bartolomé.

Participants

All patients evaluated at IPN undergo a standard evaluation that includes data collection of demographic (age, sex, and years of education), clinical (including functional evaluation), and neurological characteristics and findings, cognitive and a complete neuropsychiatric evaluation, followed by serum laboratory analyses and neuroimaging.

Inclusion Criteria

We included individuals 60 years of age or older who were native Spanish-speakers, completed at least 6 years of primary school education and who had a complete clinical assessment (demographic data; clinical, neurological, cognitive, neuropsychiatric evaluations and testing; serum laboratory analyses and neuroimaging).

Exclusion Criteria

We excluded patients with an educational levels < 4 years and those with a history of substance abuse or addiction, chronic recurrent depression, chronic renal failure, HIV infection, neurological sequelae of severe traumatic brain injury, as well as any medical condition that could affect their performance on cognitive testing (auditory or visual difficulties, severe dementia impeding ability to complete cognitive testing, hydrocephalus, arachnoid cyst, brain tumors, motor sequelae of cerebrovascular disorders or traumatic sequelae). We also excluded those with who did not complete brief cognitive screening. We also excluded patients receiving treatment for thyroid dysfunction and vitamin B12 or folic acid supplementation at the time of study entry. All patients with a period of longer than 30 days between the first and second phases of the clinical evaluations were also excluded (**Figure 1**).

Study Procedures

Clinical evaluations of patients presenting to our clinics for evaluation of cognitive complaints are performed in three successive consecutive phases as follows: (1) screening phase to determine which patients are cognitively-impaired; (2) determination of the etiology of cognitive impairment; and (3) final classification of the subtype of disease. In the screening phase, data from a structured clinical interview and clinical examination (including functional independence) were collected to determine general demographic and clinical characteristics, medication history at the time of assessment, and past medical and mental health history. Medications known to have an effect on cognition were collected, including opioid analgesics, decongestants, anti-spasmodics, anti-emetics, anti-cholinergics, anti-arrhythmics, anti-depressants, anti-psychotics, anti-anxiety, or anti-epileptic medications. Due to the effect of vascular or depressive risk factors on thyroid hormone levels (28), as well as cognitive impairment and dementia (29), we collected the following data: anthropometric data (weight, height, waist and hip circumference), number of depressive symptoms, self-reported history of transient ischemic attack (TIA)/stroke, heart disease (self-reported history of myocardial infarction, atrial fibrillation, digitalis use, or angina pectoris), hypertension (self-reported history, or diastolic blood pressure [DBP] $\geq$ 95 mmHg and systolic blood pressure [SBP] $\geq$ 160 mmHg at study visit), diabetes mellitus (self-reported or use of diabetic medication) and physical activity level [defining regular exercise as that which induces frequent sweating at least 1 day per week, as previously described (30)].

In the first phase (screening phase), we applied the Pfeffer Functional Activities Questionnaire (PFAQ) (31) and two brief cognitive screening tests, the Mini Mental State Examination (MMSE) (32) and the INECO Frontal Screening (IFS) exam (33). MMSE and IFS were administered to all study subjects; while PFAQ was administered to the caregivers/chaperones accompanying each patient to the clinic visit. In the second phase, patients were evaluated using serum laboratory tests (vitamin B12, folic acid, free T3 [fT3] and free T4 [fT4], and ultra-sensitive Thyroid Stimulating Hormone [TSH] levels), and neuroimaging (CT scan or MRI of the brain). In this phase, all patients also underwent a complete neuropsychological test battery administered by a licensed neuropsychologist. The neuropsychological battery included the following tests: Rey Auditory Verbal Learning Test, Logical Memory Subtest of Weschler Memory Scale-Revised, Trail Making Test A and B, Rey-Osterrieth Complex Figure Test, Boston Naming Test, Wisconsin Card Sorting Test, Letter-Number (subtest of the Weschler Adult Intelligent Scale-III), Digit Span and Clinical Dementia Rating (CDR) scale, as has previously been described (34). Neuropsychiatric symptoms were assessed by means of the Neuropsychiatric Inventory (NPI). We used NPI-12, a clinical informant interview surveying the following behavioral disturbances: delusions, hallucinations, agitation/aggression, irritability, depression, anxiety, euphoria, disinhibition, aberrant motor behavior, apathy, sleep, and appetite and was administered by two trained professionals. With a maximum of 144 points, the NPI-12 delivers a total symptom score based on frequency and severity of each subdomain. According to the criteria-based rating scheme, the severity of each manifestation was classified into four grades (from 1 to 3; 0 if absent), and the frequency of each manifestation was also classified into five grades (from 1 to 4; 0 if absent). The NPI score (severity x frequency) was calculated for each manifestation (range of possible scores: 0–12). The presence of a symptom was expressed as an NPI subset score >0 (35).

Finally, in the third phase, a diagnosis of MCI or dementia was made based on clinical impression and the results of the complete neuropsychological evaluation, blood tests and neuroimaging, based on previously published criteria for diagnosing major and minor neurocognitive disorders in the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) (36).

All assessments in the first phase were administered by a study neurologist or geriatrician who was blinded to the neuropsychological testing results that were administered by the neuropsychologists. Diagnostic classification disagreements among the evaluators was resolved by consensus among the study team members comprised of neurologists, geriatricians and neuropsychologists. Individuals who presented with cognitive complaints but had normal results on all brief cognitive tests and had normal scores on the PFAQ and CDR were classified as having subjective cognitive decline (SCD) (37, 38). Thus, all participants included were assigned to one of three groups based on the above evaluations and clinical consensus: SCD, MCI or dementia group. For those who had dementia, we further characterized them by sub-type of dementia including: (1) vascular dementia [defined as a cognitive syndrome caused by vascular cognitive impairment due to cerebrovascular disease with manifestations of cognitive impairment exceeding those observed in normal aging; vascular dementia is the final stage

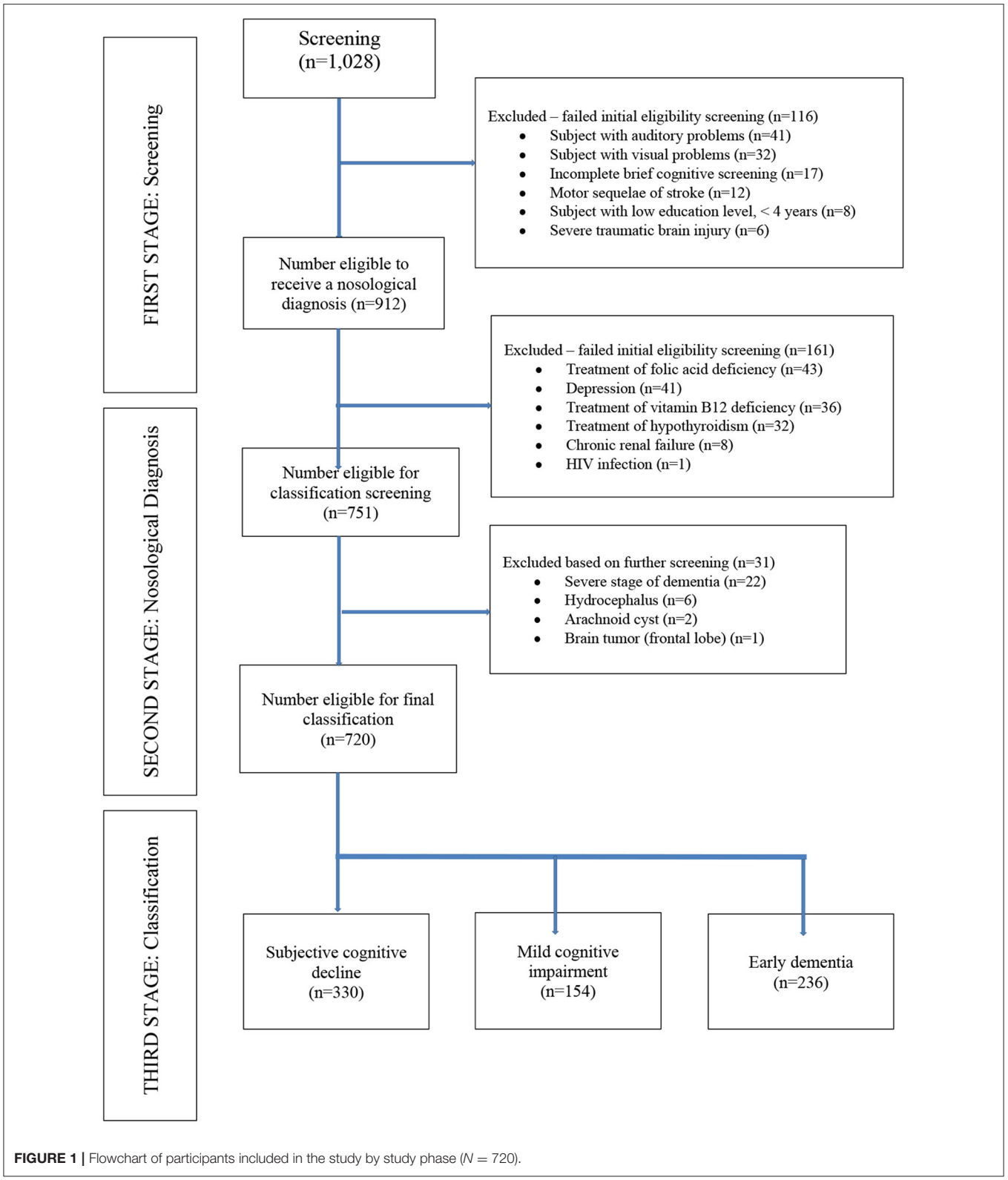


FIGURE 1 | Flowchart of participants included in the study by study phase ($N = 720$).

of vascular cognitive impairment (39)]; (2) frontotemporal dementia (40); (3) mixed dementia [requires the existence of a typical AD and dementia related to cerebrovascular disease, as previously described (41, 42)]; (4) Dementia with Lewy bodies (43); or (5) AD (utilizing criteria published by McKhann et al. (44), by evidence of progressive cognitive decline on serial

evaluations based on information from informants and cognitive testing by either formal neuropsychological evaluation (34).

Cognitive and Functional Assessments

The brief cognitive screening tests applied in this study included the Peruvian Spanish adaptation of the MMSE and the validated Spanish version of the IFS. The MMSE and IFS were selected given their utility among persons with educational levels of at least primary school and have been used widely among Spanish-speaking older adults (45). Moreover, the Peruvian Spanish version of the MMSE has been found to be highly sensitive and specific when comparing dementia vs. SCD (sensitivity 91%, specificity 75%) and dementia vs. MCI (sensitivity 87%, specificity 75%) among Peruvians living in Lima, Peru (46, 47). The MMSE is a brief cognitive screening tool that evaluates orientation (in time and space), immediate recall (or 3-word recall), attention and calculation, delayed recall, language (naming, repetition, reading, writing, performing verbal commands) and constructive praxis. We used the Peruvian version, modified from the Buenos Aires, Argentina version (32), and is administered in about 10 min, on average, and is based on a maximum score of 30 with a score <26 indicating cognitive impairment in a Peruvian population with >7 years of education (48) (**Supplementary Material 1**). The IFS is a screening test that uses eight sub-tests to assess executive function, with a maximum of 30 points, including motor programming (3 points), conflicting instructions (3 points), motor inhibitory control (3 points), backward digit span (6 points), verbal working memory (2 points), spatial working memory (4 points), abstraction capacity (3 points), verbal inhibitory control (6 points), where lower scores indicate poorer cognitive performance. The maximum score on the IFS is 30, and a score <23 indicates cognitive impairment in a Peruvian population with >10 years of education (33) (**Supplementary Material 2**). Functional assessment was completed using the PFAQ, which includes 11 questions assessing activities of daily living (ADLs), including an additional question on ability of the patient to take their own medications correctly. The maximum score on the PFAQ is 33, and a score >7 indicates functional impairment (49) (**Supplementary Material 3**).

Laboratory Analyses

A blood sample (3–5 ml of blood) was collected intravenously from the upper limb of the participants who were fasting for at least 12 h. Serum levels of folic acid < 3 ng/ dL and vitamin B12 < 80 pg/mL were considered deficient. A low cut-off of <80 pg/mL, previously utilized in other published studies (50, 51), was selected to ensure that any relationships detected between vitamin B12 levels and cognitive status were accurate. Of note, homocysteine and methylmalonic acid levels are unavailable in the laboratory where these laboratory results were obtained. Thyroid dysfunction was evaluated with measurements of levels of TSH, fT3, and fT4. According to verified laboratory reference ranges, the normal serum levels of TSH, fT3 and fT4 were 0.55–4.78 mIU/l, 3.50–6.50 pmol/l, and 11.50–22.70 pmol/l, respectively. Laboratory cut-offs for hypothyroidism were TSH level > 4.78 mIU/l, fT4 < 11.50 or fT3 < 3.50 pmol/l, and hyperthyroidism were TSH level <0.55 mIU/l, fT4 > 22.70 or fT3 > 6.50 pmol/l. Based on thyroid hormone levels, patients were classified into four categories: subclinical hyperthyroidism (low serum TSH with normal levels of fT3 and fT4), euthyroidism (TSH, fT3, and fT4 at normal values), subclinical hypothyroidism (elevated serum TSH with normal levels of fT3 and fT4) and clinical hypothyroidism (elevated serum TSH with low levels of fT3 and/or fT4), based on previously published criteria (52).

Statistical Analysis

Descriptive statistics were performed comparing demographics, brief cognitive screening and laboratory results of each cognitive group against one another (subjective cognitive decline-MCI, subjective cognitive decline-dementia, MCI-dementia) applying Chi-square (for categorical variables) or Analysis of One-Way Variance (ANOVA) for continuous variables. Bonferroni corrections were applied to adjust for these multiple comparisons. Participants were also divided into five quintiles based on lowest to highest TSH levels to allow for a logistic regression analysis to be performed using the fifth (or highest) quintile as the reference group. Logistic regression was used to assess the association of thyroid dysfunction with MCI and dementia (univariable logistic regression analyses were performed and multivariable logistic regression analyses adjusted for age, sex and BMI). Linear regression models comparing thyroid function, vitamin B12 and folate levels to MMSE and IFS scores, adjusted for age, sex, years of education and body mass index, were completed. For analyses in which vitamin B12 and folate levels were the dependent variables, conditional multiple logistic regression analyses were applied to obtain the odds ratios (OR) and *p*-value for any trends in the models. The first model was a crude model without variable adjustment. In the second model (adjusted model) the analyses were adjusted for regular exercise [utilized as a marker of cardiovascular health, a known risk factor for cognitive impairment (29)]. In the third model, where Vitamin B12 level was the dependent variable, any value >2,000 pg/mL was considered an outlier and excluded from the model. We also completed a sub-analysis of exploring the effect of folate and Vitamin B12 levels on AD. All calculated *P*-values were unpaired and two-tailed with differences considered significant at $p < 0.05$. Data were evaluated using 95% confidence intervals using STATA software (version 12.0).

RESULTS

Per the study protocol, we reviewed the electronic medical record system of IPN and found 1,028 patients eligible for screening from which 720 clinical records were obtained between January 2014 to February 2020 that met inclusion criteria (**Figure 1**). Of these, 330 patients were diagnosed with SCD, 154 patients with MCI and 236 patients with dementia (146 AD, 45 vascular dementia, 18 mixed dementia, 10 dementia associated with Parkinson's Disease, 10 behavioral variant frontotemporal dementia, 4 primary progressive aphasia, and 3 dementia with Lewy bodies). Of the entire sample, vitamin B12 deficiency was present in 21% ($n = 151$), thyroid dysfunction in 7% ($n = 50$) and folic acid deficiency in 1.7% ($n = 12$). Other risk factors

TABLE 1 | Demographic, cognitive, and metabolic characteristics of the sample by cognitive stage**.

Characteristics	SCD ($n = 330$)	MCI ($n = 154$)	Dementia ($n = 236$)	*P*-value (SCD vs. MCI)	*P*-value (MCI vs. D)	*P*-value (SCD vs. D)
Age, years (mean ± SD)	69.65 ± 4.13	70.26 ± 3.51	72.42 ± 3.66	0.416	**0.021**	**0.000**
Female, n (%)	171 (51.8%)	74 (48%)	121 (51.3%)	0.078	0.129	0.563
Education, years (mean ± SD)	12.71 ± 3.11	11.68 ± 3.16	11.16 ± 2.27	0.087	0.217	0.061
BMI, kg/m^2 (mean ± SD)	22.59 ± 6.5	23.2 ± 5.4	22.48 ± 4.9	0.142	0.235	0.636
MMSE, score (mean ± SD)	25.61 ± 1.5	22.18 ± 2.1	17.79 ± 2.2	**0.000***	**0.000***	**0.000***
IFS, score (mean ± SD)	26.73 ± 1.3	21.12 ± 1.2	15.12 ± 1.9	**0.000***	**0.000***	**0.000***
PFAQ, score (mean ± SD)	2.11 ± 1.33	4.21 ± 1.18	15.19 ± 2.63	**0.003**	**0.000***	**0.000***
CDR, score (mean ± SD)	0.47 ± 0.19	0.81 ± 0.27	1.58 ± 0.69	**0.015**	**0.011**	**0.002**
NPI, score (mean ± SD)	7.1 ± 0.29	8.2 ± 1.41	13.8 ± 4.37	**0.001**	**0.003**	**0.000***
B12 pg/ml (mean ± SD)	364.25 ± 65.4	404.20 ± 123.6	356.46 ± 36.4	0.162	0.092	0.813
Folic Acid ng/dl (mean ± SD)	9.3 ± 4.4	9.4 ± 3.7	8.2 ± 2.8	0.621	0.072	**0.024**
Free T3 pmol/L (mean ± SD)	4.4 ± 0.6	4.7 ± 0.6	4.4 ± 0.3	**0.032**	0.117	0.472
Free T4 pmol/L (mean ± SD)	15.3 ± 1.2	15.1 ± 0.9	14.9 ± 2.2	0.296	0.158	0.172
TSH mU/L (mean ± SD)	2.0 ± 1.0	2.1 ± 1.3	1.9 ± 1.3	0.359	0.084	0.168

BMI, body mass index; CDR, Clinical Dementia Rating scale; D, dementia; IFS, INECO Frontal Screening; NPI, Neuropsychological Inventory; MCI, mild cognitive impairment; MMSE, Mini Mental State Examination; PFAQ, Pfeffer Activities of Daily Living Questionnaire; SCD, subjective cognitive decline.

*$p<0.001$.

Instituto Peruano de Neurociencias, 2014–2020.

***One-way ANOVA (continuous variables) or Chi-square (categorical variables) were performed.*

The bold values mean that the p-value < 0.05.

for cognitive impairment included medications known to have an effect on cognition in 9% ($n = 64$), hepatitis B/C in 3% ($n = 21$), any history of traumatic brain injury in 2% ($n = 14$). The MCI and dementia groups were each older compared with the subjective cognitive decline (SCD) group, with no differences in sex or educational level between the groups. Mean ± SD of thyroid hormone levels (fT4, fT3, and TSH), vitamin B12 and folate levels were within normal range for all three cognitive groups (**Table 1**). Both MMSE and IFS scores were lower in the dementia and MCI groups, compared with the SCD group ($p = 0.000$ for both comparisons; **Table 1**). The mean PFAQ score for the dementia group was 15.19 ± 2.63; the mean CDR score for the dementia group was 1.58 ± 0.69, and the mean score for the NPI was 13.8 ± 4.37 in the dementia group; all were significantly greater in the dementia group compared with both the MCI and SCD groups individually (**Table 1**).

Comparative Analyses Between Serum Thyroid Hormone With Demographic and Cognitive Characteristics

Of 720 participants in this study, 670 (93%) had normal thyroid function, 18 (2.5%) had hypothyroidism, 23 (3.2%) had subclinical hypothyroidism, and 9 (1.3%) had subclinical hyperthyroidism (**Table 2**). Higher levels of fT3 were observed among the MCI group compared with the SCD group ($p = 0.032$), but not among the dementia group compared with the SCD group ($p = 0.472$). There were no statistically significant differences in fT4 or TSH levels between the groups (**Table 1**). No statistically significant association was found between serum thyroid hormone levels, age, BMI, years of education and cognitive test results in the MCI group (**Supplementary Table 4**). However, fT3 levels were inversely associated with age in the dementia group ($\gamma = -0.31$, $p < 0.05$; **Supplementary Table 4**). Serum TSH levels were inversely associated with MMSE and IFS scores in the dementia group ($\gamma = -0.21$, $p < 0.05$; $\gamma = -0.32$, and $p < 0.05$, respectively; **Table 3**), but no other significant associations in the MCI and SCD groups (**Table 3**). There were no significant associations between fT3 and fT4 levels and dementia, MCI nor SCD independently (**Table 3**). Compared with the fifth (Q5, or highest) quintile, participants in the lowest (Q1) and second (Q2) lowest TSH quintiles had greater risk of dementia (**Table 4**), but no statistically significant associations were noted between TSH quintiles and MCI (**Table 4**) nor SCD risk (**Table 4**). fT4 levels were inversely associated with years of education in the SCD group ($\gamma = -0.35$, $p < 0.05$; **Supplementary Table 4**).

Compared with the normal thyroid function group, we found no significant association between MCI and thyroid dysfunction both in the univariate analysis (**Table 2**) and in the multivariate analysis after adjustment for age, sex, years of education, and BMI (OR = 0.71, 95% CI: 0.11–4.36; OR = 1.13, 95% CI: 0.24–7.92; OR = 0.37, 95% CI: 0.07–1.28, respectively). Similarly, we found no association between thyroid dysfunction and dementia in the multivariate model (OR = 1.31, 95% CI: 0.39–4.51; OR = 1.18, 95% CI: 0.12–6.43; OR = 1.13, 95 % CI: 0.13–5.36, respectively).

Comparative Analyses Between Serum Folate and Vitamin B12 Levels With Demographic and Cognitive Characteristics

Of all participants, 151 had vitamin B12 deficiency (28% with SCD, 32.5% with MCI, 49% of these with dementia), however there were no statistically significant differences between those in the vitamin B12 deficiency group and those in the normal B12

TABLE 2 | Demographic, clinical, and cognitive characteristics of participants with normal thyroid function and thyroid dysfunction.

Characteristic	Hypothyroidism ($n = 18$)	Subclinical hypothyroidism ($n = 23$)	Normal thyroid function ($n = 670$)	Subclinical hyperthyroidism ($n = 9$)	*P*-value*
SCD, *n* (%)	5 (27.8%)	5 (21.7%)	176 (26.3%)	1 (11.1)	0.875
MCI, *n* (%)	3 (16.7%)	5 (21.7%)	145 (21.6%)	5 (55.5%)	0.956
Dementia, *n* (%)	10 (55.5%)	13 (56.5%)	349 (52.1%)	3 (33.3%)	0.862
Age, years (mean ± SD)	65.6 ± 8.8	63.4 ± 9.1	62.2 ± 8.3	64.1 ± 8.9	0.068
Education, years (mean ± SD)	11.7 ± 3.5	10.8 ± 3.6	11.1 ± 2.9	10.2 ± 2.9	0.456
Female, *n* (%)	9 (50%)	13 (56.5%)	352 (52.5%)	5 (55.5%)	0.403
BMI, kg/m^2 (mean ± SD)	23.1 ± 2.3	23.2 ± 3.1	22.9 ± 2.9	23.3 ± 2.6	0.856
MMSE score (mean ± SD)	21.3 ± 4.5	20.8 ± 8.1	20.9 ± 7.6	22.1 ± 5.1	0.435
IFS score (mean ± SD)	22.7 ± 2.3	20.2 ± 1.9	23.1 ± 1.3	20.8 ± 2.2	0.135

BMI, body mass index; IFS, INECO frontal screening; MCI, mild cognitive impairment; SCD, subjective cognitive decline; MMSE, Mini Mental State Examination.
**One-way ANOVA (continuous variables) or Chi-Square (categorical variables) performed between normal thyroid function and thyroid dysfunction groups (hypothyroidism + subclinical hypothyroidism + subclinical hyperthyroidism).*
Instituto Peruano de Neurociencias, 2014–2020.

group in any of the groups (**Table 5**). A total of 12 participants had folic acid deficiency in the cohort (25% SCD, 42% MCI, and 33% dementia). Given the small number of participants with folic acid deficiencies, comparisons between groups were not possible.

Lower serum folate concentrations were observed in the dementia group compared to those who had SCD ($p = 0.024$), but no differences in Vitamin B12 levels were observed between the groups (**Table 1**). Serum B12 and folate levels were each inversely associated with age in the dementia group ($\gamma = -0.35$, $p < 0.05$; $\gamma = -0.43$, $p < 0.05$, respectively; **Supplementary Table 5**). There were no statistically significant associations between age, BMI, years of education and vitamin B12 nor folic acid levels within the MCI and SCD groups (**Supplementary Table 5**). No significant associations were observed between serum vitamin B12 and folate levels with MMSE and IFS scores (**Table 3**; **Supplementary Table 5**). When stratifying vitamin B12 levels by three groups (deficient, <80 pg/mL; indeterminate, 81–200 pg/mL; normal, >200 pg/mL) we found that there were no significant differences in vitamin B12 status in the MCI group, but vitamin B12 deficiency and indeterminate levels of Vitamin B12 were both associated with dementia compared with normal B12 levels. Most patients had normal vitamin B12 levels in the SCD group and more patients in the dementia group had vitamin B12 deficiency (**Supplementary Table 6**). We completed a sub-analysis comparing the effect of folate levels and vitamin B12 levels on having a diagnosis of AD ($n = 146$) vs. SCD and found no significant effect of either folic acid levels or vitamin B12 levels stratified by quintiles in adjusted models; data not shown. Serum folate concentrations were inversely associated with cognitive impairment in the unadjusted model when comparing 5th vs. 1st quintiles. However, after additional adjustment for regular exercise, this association was no longer significant (**Table 6**).

DISCUSSION

To our knowledge, this is the first study that seeks to determine associations between endocrine and metabolic disorders and cognitive impairment in Peru, and one of the few in the LA region. In this cross-sectional study of 720 patients older than 60 years of age presenting to a specialized center in Lima for an initial evaluation of cognitive complaints, we found that patients with a diagnosis of dementia had lower folate levels and patients with MCI had higher fT3 levels, when compared with a group of patients with SCD but no objective evidence of dementia. Importantly, the mean and standard deviations of thyroid hormone levels, vitamin B12 and folate levels were within the normal range in all three groups. Despite this, we found that those in the lowest TSH quintiles had a dementia risk of nearly 3 times when compared with the SCD group in unadjusted models. However, we found no statistically significant associations between cognitive impairment and thyroid dysfunction, serum B12 or folic acid deficiencies after controlling for relevant covariates. We did, however, find that vitamin B12 deficiency and indeterminate levels of vitamin B12 were more prevalent in the dementia group, however, the causation of dementia cannot be determined based on these analyses. Thus, some of our findings do not strongly support the notion that these metabolic or endocrine disorders are important independent contributors to cognitive impairment in older Peruvians from Lima. However, our finding those with the lowest TSH levels had a greater dementia risk compared with the SCD group suggests a possible association between hyperthyroidism and cognitive impairment in our population.

Thyroid dysfunction is of particular importance given iodine deficiency is prevalent in many low- and middle-income countries, and can lead to thyroid dysfunction. In Latin America and the Caribbean, 10% of the general population of adults and children have insufficient iodine intake, and in Peru 11.8% (95% CI: 10.9–12.7%) have iodine deficiency (53) increasing their risk of developing a thyroid disorder. The prevalence of thyroid dysfunction among older adults from different regions of LA and its relationship to cognitive function is largely unknown. Similar to findings in our study, one study of Brazilians younger than 65 years of age found no relationship between subclinical thyroid

status and cognitive function, but lower TSH was statistically associated with worse performance on executive function tests in extensively adjusted analyses (25). Another cross-sectional study of Brazilians older than age 65 noted a relationship between subclinical hyperthyroidism and all-cause dementia, but these analyses were only adjusted for age, not for other confounding factors such as the demographic variables that were accounted for in our study (age, sex, educational attainment, and regular exercise) (26). Similar to findings from these studies, our unadjusted results support the notion that lower TSH levels are associated with a greater risk of cognitive impairment, but after adjusting for covariates this association was weaker. Therefore, our study findings suggest that among older Peruvians from Lima with cognitive complaints, thyroid dysfunction does not represent a strong risk factor for cognitive impairment and other factors such as age or cardiovascular health may be more important contributors., however, further research is needed to determine the pathophysiological mechanisms underlying existing associations between cognitive impairment and thyroid dysfunction that were not uncovered in the present study.

Our study found that vitamin B12 deficiency was more common in the dementia group, however, there was no association between vitamin B12 deficiency and cognitive impairment (MCI + dementia combined) in unadjusted and adjusted multivariable analyses. More than 20% of the study population and nearly half of the dementia group was vitamin B12 deficient. The prevalence of vitamin B12 deficiency found in our study is high, but similar to that reported in another study on women with pre-eclampsia in Peru with 19% of the cohort having vitamin B12 deficiency (considered in that study to be a level <178.5 pg/mol) (54) and it was 9% in one international study of people with HIV in low- and middle-income countries (55). Several reasons for the high prevalence of B12 deficiency in our group, particularly in the dementia group, are possible. People with dementia have poor nutritional status prevalent in Latin America (56), which may be due to less meat ingestion (due to high costs, difficulty with chewing due to poor or no dentition) and lower absorption of vitamin B12 in older age (57), likely leading to a higher prevalence of B12 deficiency in our study population.

Although the findings of our study found no significant correlation between vitamin B12 deficiency and cognitive test scores in the dementia group after adjustment for relevant covariates, vitamin B12 deficiency was more common in the dementia group compared with the MCI and SCD. Other studies conducted in LA have found associations between vitamin B12 and folate levels and cognitive dysfunction in both unadjusted and adjusted analyses. In LA, B12 deficiency has been reported to be common with 17.4% (95%CI: 13.4–21.4%) of elderly Brazilians having B12 deficiency (58). Two studies, both from Brazil, have investigated the relationship between B12 and cognition and found that subjects with lower vitamin B12 levels have a greater risk of cognitive decline (59) and perform poorly on executive function tests in adjusted analyses (60). These studies were performed in a population of adults older than age 80, hence, our study population may have been too young to detect this association. In a study from Chile, investigators found that the

TABLE 3 | Comparison of free T3, free T4, TSH, vitamin B12, and folic acid with scores on brief cognitive tests* among patients with dementia, mild cognitive impairment and subjective cognitive decline.

Variable	Dementia group						MCI group						SCD group					
	MMSE			IFS			MMSE			IFS			MMSE			IFS		
	β (SE)	*P*-value	95% CI for β	β (SE)	*P*-value	95% CI for β	β (SE)	*P*-value	95% CI for β	β (SE)	*P*-value	95% CI for β	β (SE)	*P*-value	95% CI for β	β (SE)	*P*-value	95% CI for β
Free T3**	−0.23 (0.19)	0.072	−0.65 to 0.35	−0.15 (0.88)	0.089	−0.56 to 0.29	−0.09 (0.23)	0.085	−0.03 to 0.11	−0.06	0.082	−0.02 to 0.21	0.17 (0.61)	0.071	0.06 to 0.31	0.11 (0.29)	0.091	0.07 to 0.57
Free T4	−0.15 (0.37)	0.145	−0.46 to 0.25	−0.21 (0.71)	0.092	−0.43 to 0.16	−0.10	0.071	−0.07 to 0.21	−0.10	0.127	−0.06 to 0.35	−0.06 (0.81)	0.164	0.02 to 0.24	−0.21 (0.17)	0.252	0.07 to 0.49
TSH	−0.32 (0.24)	**0.010**	−1.49 to 0.16	−0.37 (0.97)	**0.004**	−3.26 to 0.73	−0.37 (0.19)	0.081	−0.92 to 0.58	−0.32 (0.72)	0.086	−0.13 to 0.62	−0.27 (0.19)	0.092	−1.49 to 0.52	−0.23 (0.48)	0.082	−1.26 to 0.49
Vitamin B12	0.03 (0.16)	0.062	0.01 to 0.21	0.09 (0.32)	0.074	0.05 to 0.42	0.07 (0.22)	0.095	0.02 to 0.15	0.10 (0.27)	0.146	0.04 to 0.33	0.12 (0.23)	0.213	0.04 to 0.69	0.19 (0.61)	0.084	0.06 to 0.61
Folic acid	0.05 (0.38)	0.060	0.03 to 0.52	0.12 (0.21)	0.082	0.07 to 0.34	0.08 (0.44)	0.083	0.02 to 0.41	0.21 (0.19)	0.077	0.09 to 0.42	0.13 (0.56)	0.087	0.07 to 0.46	0.21 (0.49)	0.273	0.09 to 0.49

IFS, INECO Frontal Screening; MCI, mild cognitive impairment; MMSE, Mini Mental State Examination; SE, standard error; SCD, subjective cognitive decline; TSH, thyroid stimulating hormone.

Linearity test: Pearson correlation coefficient, r = 0.8; p = 0.033; coefficient of determination, $R^2 = 0.66$.

**Linear regression models adjusted for age, sex, years of education, and body mass index.*

***Normal serum free T3, 3.50–6.50 pmol/l; normal serum free T4 11.50–22.70 pmol/l; normal serum TSH, 0.55–4.78 mIU/l; vitamin B12 deficiency <80 pg/mL; normal folic acid levels, ≥3 ng/ dL.*

Instituto Peruano de Neurociencias, 2014–2020.

The bold values mean that the p-value < 0.05.

TABLE 4 | Regression analyses* of serum TSH levels (in quintiles) and risk of dementia, mild cognitive impairment, and subjective cognitive decline.

Variable**	Dementia				MCI				SCD			
	β (SE)	*P*-value	OR (β)	95% CI for OR (β)	β (SE)	*P*-value	OR (β)	95% CI for OR (β)	β (SE)	*P*-value	OR (β)	95% CI for OR (β)
TSH (1)	1.03 (0.46)	**0.021**	2.91	1.15–6.86	0.81	0.069	1.47	(0.83–3.21)	0.66 (0.41)	0.128	1.39	0.59–4.18
TSH (2)	0.89 (0.37)	**0.032**	2.63	1.09–6.31	0.63	0.072	1.23	(0.56–3.41)	0.59 (0.71)	0.073	1.33	0.51–4.93
TSH (3)	0.56 (0.37)	0.271	1.62	0.60–3.87	0.61	0.456	1.12	(0.82–4.51)	0.49 (0.37)	0.124	1.28	0.46–4.17
TSH (4)	0.45 (0.42)	0.319	1.56	0.65–2.97	0.26	0.092	1.83	(0.74–3.47)	0.51 (0.36)	0.092	1.15	0.53 to 3.71

β, beta; OR, odds ratio; CI, confidence interval; SE, standard error; TSH, thyroid stimulating hormone.
Linearity test: Pearsons correlation coefficient, $r = 0.7$; $p = 0.016$; coefficient of determination, $R^2 = 0.74$.
***Logistic regression models adjusted for age, sex, years of education, and body mass index.*
***Fifth quintile is the reference group.*
Quintiles: Q1: 0.26–1.12 mIU/L; 1.13–1.33 mIU/L; Q3: 1.34–1.86 mIU/L; Q4: 1.87–4.25 mIU/L; Q5: 4.26–28.5 mIU/L.
Instituto Peruano de Neurociencias, 2014–2020.
The bold values mean that the p-value < 0.05.

TABLE 5 | Demographic, clinical, and cognitive characteristics of participants with normal levels of vitamin B12 and vitamin B12 deficiency*.

Characteristic	Vitamin B12 deficiency (*N* = 151)	Intermediate Vitamin B12 status (*N* = 96)	Vitamin B12 normal (*N* = 473)	*P***	*P****
SCD, *n* (%)	28 (18.5%)	15 (15.6%)	236 (49.9%)	0.079	0.064
MCI, *n* (%)	49 (32.5%)	37 (38.5%)	156 (32.9%)	0.863	0.091
Dementia, *n* (%)	74 (49%)	44 (45.8%)	81 (17.2%)	0.066	0.072
Age, years (mean ± SD)	64.8 ± 7.2	66.3 ± 6.4	65.4 ± 5.1	0.143	0.317
Education, years (mean ± SD)	10.5 ± 3.2	10.9 ± 2.9	11.3 ± 2.9	0.633	0.734
Female, *n* (%)	78 (51.7%)	52 (54.2%)	239 (50.5%)	0.625	0.691
BMI, kg/m^2 (mean ± SD)	22.5 ± 3.1	22.9 ± 2.7	23.4 ± 3.2	0.726	0.811
MMSE score (mean ± SD)	21.5 ± 4.3	23.4 ± 3.9	21.2 ± 5.6	0.628	0.158
IFS score (mean ± SD)	22.9 ± 2.1	21.6 ± 3.3	20.6 ± 3.1	0.319	0.097

BMI, body mass index; IFS, INECO Frontal Screening; MCI, mild cognitive impairment; MMSE, Mini Mental State Examination; SCD, subjective cognitive decline.
**Vitamin B12 deficiency (<80 pg/mL); indeterminate Vitamin B12 status (81–200 pg/mL); normal Vitamin B12 (>200 pg/mL).*
***One-way ANOVA (continuous variables) or Chi-square (categorical variables) for normal vitamin B12 group vs vitamin B12 deficiency group.*
****One-way ANOVA (continuous variables) or Chi-square (categorical variables) for normal vitamin B12 group vs. intermediate vitamin B12 group.*
Instituto Peruano de Neurociencias, 2014–2020.

risk of cognitive impairment increased with an increase in serum folate, but only in the setting of low vitamin B12 levels (61). The findings of our study cannot determine whether causation (whether vitamin B12 deficiency may have preceded onset of dementia, or whether B12 deficiency may lead to worse cognitive impairment in people with existing dementia), thus, further longitudinal work investigating causation is required.

In our study, serum folate concentrations were inversely associated with cognitive impairment in crude analyses, but not after additional adjustment. The relationship between folate levels and cognitive impairment in LA has also mostly been studied in Brazil, where lower serum folate levels were found among subjects with dementia of the AD type compared to MCI and controls in adjusted analyses (62). In our study, folate levels were lower in the dementia group compared with a group of patients with SCD. It is possible that persons with dementia could develop poor nutritional habits leading to vitamin B12 and folate deficiencies, but in our study the majority of participants had normal folate levels suggesting adequate micronutrient nutritional intake. Moreover, it is important to note that mandatory folate fortification in wheat flour is now standard practice in Peru (63), which likely accounts for the low prevalence (1.7%) of folate deficiency in the population studied. In addition, our study took place in a private neurology clinic in Lima, Peru, which likely represents patients of higher socioeconomic status with lower risk of nutritional deficiencies leading to vitamin deficiencies. However, despite lower folate levels in the dementia group in our study, there was no association between MMSE nor IFS scores with folate levels.

Possible explanations for a link between folate deficiency and cognitive dysfunction include impaired methylation reactions in the brain and insufficient methyl groups that are required for the synthesis of myelin, neurotransmitters, and membrane phospholipids (64). Deficiencies of cofactors involved in methionine and homocysteine metabolism (such as folate, vitamin B12, and vitamin B6) can result in hyperhomocysteinemia, and folate plays a crucial role in the methionine-homocysteine cycle (65). Several studies demonstrate that folate supplementation can affect cognitive function by diminishing serum homocysteine levels (66). Low

TABLE 6 | Odds ratio (OR) for the prevalence of cognitive impairment by quintiles of serum folic acid and vitamin B12 concentrations. Instituto Peruano de Neurociencias, 2014–2020.

Variable*	MCI + D	SCD	Prevalence of cognitive impairment			
			Crude model		Adjusted model[b]	
	$N = 390$	$N = 330$	OR (95% CI)	*P*-value[a]	OR (95% CI)	*P*-value[a]
Folic acid (ng/dL)				**0.021**		0.098
Q1	128	56	1.00 (reference)		1.00 (reference)	
Q2	90	89	0.49 (0.21–1.02)		0.51 (0.17–1.23)	
Q3	90	89	0.34 (0.16–0.96)		0.36 (0.15–1.16)	
Q4	82	96	0.33 (0.14–0.79)		0.41 (0.17–1.08)	
B12[c] (pg/mL)				0.113		0.216
Q1	109	68	1.00 (reference)		1.00 (reference)	
Q2	93	77	0.66 (0.31–1.59)		0.77 (0.33–1.98)	
Q3	101	77	0.71 (0.31–1.73)		0.95 (0.37–2.35)	
Q4	74	95	0.49 (0.22–1.17)		0.58 (0.24–1.43)	

CI, confidence interval; Q, Quintile; D, dementia; MCI, mild cognitive impairment; OR, odds ratio; SCD, subjective cognitive decline.

Linearity test: Pearsons correlation coefficient, $r = 0.7$; $p = 0.027$; coefficient of determination, $R^2 = 0.69$.

**Fifth quintile is the reference group; Quintiles: Folic acid: Q1: 0.7–9.5 ng/dL; Q2: 9.6–18.4ng/dL; Q3: 18.5–27.3 ng/dL; Q4: 27.4–36.2 ng/dL; Q5: 36.3–45.1 ng/dL; Vitamin B12: Q1:43–210 pg/mL; Q2: 211–378 pg/mL; Q3: 379–546pg/mL; Q4: 547–714pg/mL; Q5: 715–879 pg/mL.*

[a]*p-values for linear trend; conditional logistic regression analysis.*

[b]*Adjusted model was adjusted for regular exercise by conditional multiple logistic regression analysis.*

[c]*Removed 13 outliers with serum vitamin B12 levels ≥ 2,000 pg/mL.*

homocysteine is also an independent risk factor for altered endothelial and hemostatic function (67). Due to lack of availability of homocysteine levels in routine clinical practice in Peru, we did not measure homocysteine levels, which may have mediated the lack of effect of vitamin B12 deficiency on dementia risk (11, 20). For example, a study from China found that elevated serum homocysteine levels were associated with increased AD risk, but higher vitamin B12 and folate levels were protective factors (20). Therefore, vitamin B12 and folate are not sufficient on their own to explain a possible etiology of reversible dementias, highlighting the importance of measuring these other levels in parallel with vitamin B12 and folate levels.

Our study has limitations. First, this is a cross-sectional retrospective study preventing the establishment of causal relationships and temporal associations. A prospective, longitudinal study with multiple measurements of serum metabolic levels over time would allow for correlation with neurocognitive changes, particularly with treatment initiation of a newly-detected metabolic disorder. Secondly, we excluded participants who were receiving treatment for a known previously diagnosed thyroid disorder or B12 or folate deficiency; thus, our results may not be generalizable to those with a known metabolic disorder already receiving treatment at baseline. In addition, we did not measure homocysteine or methylmalonic acid levels which may be the mediators of vitamin B12 deficiency in certain cases. Next, this was a convenience sample of Spanish-speaking generally healthy older adults attending a multi-disciplinary specialized neurological center in an urban setting, thus, limiting the external validity and generalizability of these study results to the general population of Peru, particularly rural communities that may experience a higher prevalence of nutritional deficiencies and may not have access to a specialized clinic. In addition, our population is not representative of the entire Peruvian population as many patients in our cohort had at least a high school or secondary school level education, excluding populations of lower education and non-native Spanish speakers. Next, because the screening phase of our study used brief cognitive screening tools whose scores may be influenced by factors such as educational level, there may have been initial group misclassification of the SCD group. Moreover, the SCD group was a group of persons with memory complaints but with normal results on cognitive testing, which may have been explained by existing subclinical metabolic disorders that may not have manifested as a clinical cognitive disorder. However, group assignment into dementia or MCI was completed in a systematic fashion using results from the complete neuropsychological test battery, and any group disagreement was resolved by consensus between the study team. Despite these limitations, we present the first study on metabolic disorders and cognitive impairment conducted in a well-characterized population with a large sample size ($N = 720$) of older Peruvians using a standardized evaluation protocol including patients with both dementia and MCI.

CONCLUSIONS

Our results indicate that metabolic and endocrine disorders (thyroid dysfunction, B12, and folic acid deficiency) are not associated with dementia or MCI cross-sectionally in a population of older adults with cognitive complaints from Lima, Peru. Our study results add to existing evidence from other regions of LA which indicate that these disorders may not be significantly associated with cognitive impairment in the region despite a high prevalence of vitamin B12 deficiency found in our study. We found that B12 deficiency or borderline deficiency was present in more than one-third of those with dementia in our study population, however, no clear association was found between vitamin B12 levels and neuropsychological test results. Our study results may demonstrate that cognitive symptoms were likely a result of neurodegenerative disorders (such as AD, for example) and that potentially reversible metabolic and endocrine causes may be an incidental comorbidity. Because our study is cross-sectional, we are unable to determine if thyroid dysfunction, B12 or folate deficiencies are incidental or may relate directly to cognitive decline. Our study has emphasized that without longitudinal measurements of metabolic alterations and correlation with cognitive decline over time, it remains important to check thyroid function, vitamin B12, and folate levels during first-time consultation for cognitive impairment. Future

work may investigate metabolic dysfunction longitudinally and its role in cognitive decline over time, particularly in LA where a greater burden of nutritional deficiencies may lead to metabolic disorders.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Hospital Nacional Docente Madre Niño San Bartolomé. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MD: study concept and design, analysis and interpretation, and drafting of manuscript. NC: study concept and design, drafting of manuscript, and critical revision of the manuscript for important intellectual content. RM and DL: study concept and design, drafting of manuscript, critical revision of the manuscript for important intellectual content, and major role in acquisition of data. EH-P: statistical analyses and interpretation of results, drafting of manuscript. MP-C, JC-A, and CG: critical revision of the manuscript for important intellectual content, major role in acquisition of data. SL: study concept and design, critical revision of the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

FUNDING

The authors disclosed receipt of the following financial support for the research, authorship, and publication of this article: MD was supported by the Fogarty International Center of the National Institutes of Health under (Grant Number D43TW009343) and the University of California Global Health Institute and the National Institute on Aging San Diego Resource Center for advancing Alzheimer's Research in Minority Seniors (5P30AG059299). NC and RM were supported by National Institute of Health (5R01AG057234-02).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.676518/full#supplementary-material

REFERENCES

1. Prince M, Ali G-C, Guerchet M, Prina AM, Albanese E, Wu Y-T. Recent global trends in the prevalence and incidence of dementia, and survival with dementia. *Alzheimers Res Ther.* (2016) 8:23. doi: 10.1186/s13195-016-0188-8
2. Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, et al. Defeating Alzheimer's disease and other dementias: a priority for European science and society. *Lancet Neurol.* (2016) 15:455–532. doi: 10.1016/S1474-4422(16)00062-4
3. Lipnicki DM, Crawford J, Kochan NA, Trollor JN, Draper B, Reppermund S, et al. Risk factors for mild cognitive impairment, dementia and mortality: the sydney memory and ageing study. *J Am Med Dir Assoc.* (2017) 18:388–95. doi: 10.1016/j.jamda.2016.10.014
4. United Nations. *World Population Ageing.* (2019). Available online at: https://www.un.org/en/development/desa/population/publications/pdf/ageing/WorldPopulationAgeing2019-Highlights.pdf (accessed June 21, 2020).
5. Baez S, Ibáñez A. Dementia in Latin America: an emergent silent tsunami. *Front Aging Neurosci.* (2016) 8:253. doi: 10.3389/fnagi.2016.00253
6. Bupa and Alzheimer's Disease International. *Dementia in the Americas: Current and Future Cost and Prevalence of Alzheimer's Disease and Other Dementias*. (2013).
7. Day GS. Reversible dementias. *Continuum (Minneap Minn).* (2019) 25:234–53. doi: 10.1212/CON.0000000000000688
8. Muangpaisan W, Petcharat C, Srinonprasert V. Prevalence of potentially reversible conditions in dementia and mild cognitive impairment in a geriatric clinic. *Geriatr Gerontol Int.* (2012) 12:59–64. doi: 10.1111/j.1447-0594.2011.00728.x
9. Parra MA, Baez S, Allegri R, Nitrini R, Lopera F, Slachevsky A, et al. Dementia in Latin America: assessing the present and envisioning the future. *Neurology.* (2018) 90:222–31. doi: 10.1212/WNL.0000000000004897
10. Luthra NS, Marcus AH, Hills NK, Christine CW. Vitamin B12 measurements across neurodegenerative disorders. *J Clin Mov Disord.* (2020) 7:3. doi: 10.1186/s40734-020-00085-8
11. Ma F, Wu T, Zhao J, Ji L, Song A, Zhang M, et al. Plasma homocysteine and serum folate and vitamin B12 levels in mild cognitive impairment and Alzheimer's disease: a case-control study. *Nutrients.* (2017) 9:725. doi: 10.3390/nu9070725
12. Bavarsad K, Hosseini M, Hadjzadeh M, Sahebkar A. The effects of thyroid hormones on memory impairment and Alzheimer's disease. *J Cell Physiol.* (2019) 234:14633–40. doi: 10.1002/jcp.28198
13. Doets EL, Ueland PM, Tell GS, Vollset SE, Nygård OK, Van't Veer P, et al. Interactions between plasma concentrations of folate and markers of vitamin B12 status with cognitive performance in elderly people not exposed to folic acid fortification: the Hordaland Health Study. *Br J Nutr.* (2014) 111:1085–95. doi: 10.1017/S000711451300336X
14. American Academy of Neurology. *Diagnosis of Dementia, Guideline Detail, American Academy of Neurology*. (2001). Available online at: https://www.aan.com/Guidelines/home/GuidelineDetail/42 (accessed July 31, 2020).
15. Bello VME, Schultz RR. Prevalence of treatable and reversible dementias: a study in a dementia outpatient clinic. *Dement Neuropsychol.* (2011) 5:44–7. doi: 10.1590/S1980-57642011DN05010008
16. Issac TG, Soundarya S, Christopher R, Chandra SR. Vitamin B12 deficiency: an important reversible co-morbidity in neuropsychiatric manifestations. *Indian J Psychol Med.* (2015) 37:26–9. doi: 10.4103/0253-7176.150809
17. Tripathi M, Vibha D. Reversible dementias. *Indian J Psychiatry.* (2009) 51(Suppl 1):S52–S5. Available online at: https://www.indianjpsychiatry.org/text.asp?2009/51/5/52/44861
18. Lindenbaum J, Rosenberg IH, Wilson PW, Stabler SP, Allen RH. Prevalence of cobalamin deficiency in the Framingham elderly population. *Am J Clin Nutr.* (1994) 60:2–11. doi: 10.1093/ajcn/60.1.2
19. Vogiatzoglou A, Smith AD, Nurk E, Drevon CA, Ueland PM, Vollset SE, et al. Cognitive function in an elderly population: interaction between vitamin B12 status, depression, and apolipoprotein E ε4: the Hordaland Homocysteine Study. *Psychosom Med.* (2013) 75:20–9. doi: 10.1097/PSY.0b013e3182761b6c
20. Meng H, Li Y, Zhang W, Zhao Y, Niu X, Guo J. The relationship between cognitive impairment and homocysteine in a B12 and folate deficient

population in China: a cross-sectional study. *Medicine.* (2019) 98:e17970. doi: 10.1097/MD.0000000000017970
21. Montgomery SE, Sepehry AA, Wangsgaard JD, Koenig JE. The effect of S-adenosylmethionine on cognitive performance in mice: an animal model meta-analysis. *PLoS One.* (2014) 9:e107756. doi: 10.1371/journal.pone.0107756
22. Malouf M, Grimley EJ, Areosa SA. Folic acid with or without vitamin B12 for cognition and dementia. *Cochrane Database Syst Rev.* (2003) 4:1–29. doi: 10.1002/14651858.CD004514
23. George KM, Lutsey PL, Selvin E, Palta P, Windham BG, Folsom AR. Association between thyroid dysfunction and incident dementia in the atherosclerosis risk in communities neurocognitive study. *J Endocrinol Metab.* (2019) 9:82–89. doi: 10.14740/jem588
24. Aubert CE, Bauer DC, da Costa BR, Feller M, Rieben C, Simonsick EM, Yaffe K, Rodondi N, the Health ABC Study. The association between subclinical thyroid dysfunction and dementia: the Health, Aging and Body Composition (Health ABC) Study. *Clin Endocrinol.* (2017) 87:617–26. doi: 10.1111/cen.13458
25. Szlejf C, Suemoto CK, Santos IS, Lotufo PA, Haueisen Sander Diniz MF, Barreto SM, et al. Thyrotropin level and cognitive performance: baseline results from the ELSA-Brasil Study. *Psychoneuroendocrinology.* (2018) 87:152–8. doi: 10.1016/j.psyneuen.2017.10.017
26. Benseñor IM, Lotufo PA, Menezes PR, Scazufca M. Subclinical hyperthyroidism and dementia: the São Paulo Ageing & Health Study (SPAH). *BMC Public Health.* (2010) 10:298. doi: 10.1186/1471-2458-10-298
27. Jager CA, Oulhaj A, Jacoby R, Refsum H, Smith AD. Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: a randomized controlled trial: Treatment of mild cognitive impairment. *Int J Geriatr Psychiatry.* (2012) 27:592–600. doi: 10.1002/gps.2758
28. Martin SS, Daya N, Lutsey PL, Matsushita K, Fretz A, McEvoy JW, et al. Thyroid function, cardiovascular risk factors, and incident atherosclerotic cardiovascular disease: the Atherosclerosis Risk in Communities (ARIC) study. *J Clin Endocrinol Metab.* (2017) 102:3306–15. doi: 10.1210/jc.2017-00986
29. Wang W, Norby FL, George KM, Alonso A, Mosley TH, Gottesman RF, et al. Association of carotid intima-media thickness and other carotid ultrasound features with incident dementia in the ARIC-NCS. *J Am Heart Assoc.* (2021) 10:e020489. doi: 10.1161/JAHA.120.020489
30. Tolppanen A-M, Solomon A, Kulmala J, Kåreholt I, Ngandu T, Rusanen M, et al. Leisure-time physical activity from mid- to late life, body mass index, and risk of dementia. *Alzheimers Dement.* (2015) 11:434–43.e6. doi: 10.1016/j.jalz.2014.01.008
31. Custodio N, García A, Montesinos R, Escobar J, Bendezú L. Prevalencia de demencia en una población urbana de Lima-Perú: Un estudio puerta a puerta. *Anal Facul Med.* (2008) 69:233–8. doi: 10.15381/anales.v69i4.1110
32. Custodio N, Lira D. Adaptación Peruana del Mini Mental State Examination (MMSE). *Anal Facul Med.* (2014) 75:69. doi: 10.15381/anales.v75i1.6951
33. Custodio N, Herrera-Perez E, Lira D, Roca M, Manes F, Báez S, et al. Evaluation of the INECO frontal screening and the frontal assessment battery in Peruvian patients with Alzheimer's disease and behavioral variant Frontotemporal dementia. *eNeurologicalSci.* (2016) 5:25–9. doi: 10.1016/j.ensci.2016.11.001
34. Custodio N, Lira D, Herrera-Perez E, Montesinos R, Castro-Suarez S, Cuenca-Alfaro J, et al. Memory alteration test to detect amnestic mild cognitive impairment and early Alzheimer's dementia in population with low educational level. *Front Aging Neurosci.* (2017) 9:278. doi: 10.3389/fnagi.2017.00278
35. Kaufer DI, Cummings JL, Christine D, Bray T, Castellon S, Masterman D, et al. Assessing the impact of neuropsychiatric symptoms in Alzheimer's disease: the Neuropsychiatric Inventory Caregiver Distress Scale. *J Am Geriatr Soc.* (1998) 46:210–5. doi: 10.1111/j.1532-5415.1998.tb02542.x
36. Sachdev PS, Blacker D, Blazer DG, Ganguli M, Jeste DV, Paulsen JS, et al. Classifying neurocognitive disorders: the DSM-5 approach. *Nat Rev Neurol.* (2014) 10:634–42. doi: 10.1038/nrneurol.2014.181
37. Jessen F, Amariglio RE, Buckley RF, van der Flier WM, Han Y, Molinuevo JL, et al. The characterisation of subjective cognitive decline. *Lancet Neurol.* (2020) 19:271–8. doi: 10.1016/S1474-4422(19)30368-0
38. Miebach L, Wolfsgruber S, Polcher A, Peters O, Menne F, Luther K, et al. Which features of subjective cognitive decline are related to amyloid pathology? Findings from the DELCODE study. *Alzheimers Res Ther.* (2019) 11:66. doi: 10.1186/s13195-019-0515-y
39. Custodio N, Montesinos R, Alva-Diaz C, Pacheco-Barrios K, Rodriguez-Calienes A, Herrera-Pérez E, et al. Diagnostic accuracy of brief cognitive screening tools to diagnose vascular cognitive impairment in Peru. *Int J Geriatr Psychiatry.* (2021). 2:1–10. doi: 10.1002/gps.5531
40. Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain.* (2011) 134:2456–77. doi: 10.1093/brain/awr179
41. Custodio N, Montesinos R, Lira D, Herrera-Pérez E, Bardales Y, Valeriano-Lorenzo L. Mixed dementia: a review of the evidence. *Dement Neuropsychol.* (2017) 11:364–70. doi: 10.1590/1980-57642016dn11-040005
42. Chui HC, Victoroff JI, Margolin D, Jagust W, Shankle R, Katzman R. Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. *Neurology.* (1992) 42:473–80. doi: 10.1212/WNL.42.3.473
43. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology.* (2005) 65:1863–72. doi: 10.1212/01.wnl.0000187889.17253.b1
44. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CRJ, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* (2011) 7:263–9. doi: 10.1016/j.jalz.2011.03.005
45. Scazufca M, Almeida OP, Vallada HP, Tasse WA, Menezes PR. Limitations of the Mini-Mental State Examination for screening dementia in a community with low socioeconomic status: results from the São Paulo Ageing & Health Study. *Eur Arch Psychiatry Clin Neurosci.* (2009) 259:8–15. doi: 10.1007/s00406-008-0827-6
46. Custodio N, Lira D, Herrera-Perez E, Nuñez del Prado L, Parodi J, Guevara-Silva E, et al. The memory alteration test discriminates between cognitively healthy status, mild cognitive impairment and Alzheimer's disease. *Dement Geriatr Cogn Disord Extra.* (2014) 4:314–21. doi: 10.1159/000365280
47. Custodio N, Duque L, Montesinos R, Alva-Diaz C, Mellado M, Slachevsky A. Systematic review of the diagnostic validity of brief cognitive screenings for early dementia detection in spanish-speaking adults in Latin America. *Front Aging Neurosci.* (2020) 12:270. doi: 10.3389/fnagi.2020.00270
48. Custodio N, Alva-Diaz C, Becerra-Becerra Y, Montesinos R, Lira D, Herrera-Pérez E, et al. [Performance of cognitive brief test in elderly patients with dementia in advanced stage living in an urban community of Lima, Peru]. *Rev Peru Med Exp Salud Publica.* (2016) 33:662–9. doi: 10.17843/rpmesp.2016.334.2549
49. Quiroga P, Albala C, Klaasen G. Validación de un test de tamizaje para el diagnóstico de demencia asociada a edad, en Chile Validation of a screening test for age associated cognitive impairment, in Chile. *Rev Méd Chile.* (2004) 67–478. doi: 10.4067/s0034-98872004000400009
50. Kim S, Choi BY, Nam JH, Kim MK, Oh DH, Yang YJ. Cognitive impairment is associated with elevated serum homocysteine levels among older adults. *Eur J Nutr.* (2019) 58:399–408. doi: 10.1007/s00394-017-1604-y
51. Jatoi S, Hafeez A, Riaz SU, Ali A, Ghauri MI, Zehra M. Low vitamin B12 levels: an underestimated cause of minimal cognitive impairment and dementia. *Cureus.* (2020) 12:e6976. doi: 10.7759/cureus.6976
52. Persani L, Brabant G, Dattani M, Bonomi M, Feldt-Rasmussen U, Fliers E, Gruters A, Maiter D, Schoenmakers N, van Trotsenburg ASP. 2018 European Thyroid Association (ETA) guidelines on the diagnosis and management of central hypothyroidism. *Eur Thyroid J.* (2018) 7:225–37. doi: 10.1159/000491388
53. de Benoist, Bruno. *Iodine Status Worldwide. WHO Global Database on Iodine Deficiency.* (2004). Available online at: https://apps.who.int/iris/bitstream/handle/10665/43010/9241592001.pdf?sequence=1 (accessed January 24, 2021).
54. Sanchez SE, Zhang C, Rene Malinow M, Ware-Jauregui S, Larrabure G, Williams MA. Plasma folate, vitamin B(12), and homocyst(e)ine

concentrations in preeclamptic and normotensive Peruvian women. *Am J Epidemiol.* (2001) 153:474–80. doi: 10.1093/aje/153.5.474
55. Shivakoti R, Christian P, Yang W-T, Gupte N, Mwelase N, Kanyama C, et al. Prevalence and risk factors of micronutrient deficiencies pre- and post-antiretroviral therapy (ART) among a diverse multicountry cohort of HIV-infected adults. *Clin Nutr.* (2016) 35:183–9. doi: 10.1016/j.clnu.2015.02.002
56. Brito A, Mujica-Coopman MF, López de Romaña D, Cori H, Allen LH. Folate and vitamin B12 status in latin America and the Caribbean: an update. *Food Nutr Bull.* (2015) 36:S109–S18. doi: 10.1177/0379572115585772
57. Marsman D, Belsky DW, Gregori D, Johnson MA, Low Dog T, Meydani S, et al. Healthy ageing: the natural consequences of good nutrition-a conference report. *Eur J Nutr.* (2018) 57:15–34. doi: 10.1007/s00394-018-1723-0
58. Oliveira Martinho K, Luiz Araújo Tinôco A, Queiroz Ribeiro A. PREVALENCE AND FACTORS ASSOCIATED WITH VITAMIN B12 DEFICIENCY IN ELDERLY FROM VIÇOSA/MG, BRASIL. *Nutr Hosp.* (2015) 32:2162–8. doi: 10.3305/nh.2015.32.5.9648
59. da Rosa MI, Beck WO, Colonetti T, Budni J, Falchetti ACB, Colonetti L, et al. Association of vitamin D and vitamin B(12) with cognitive impairment in elderly aged 80 years or older: a cross-sectional study. *J Hum Nutr Diet.* (2019) 32:518–24. doi: 10.1111/jhn.12636
60. Senger J, Bruscato NM, Werle B, Moriguchi EH, Pattussi MP. Nutritional status and cognitive impairment among the very old in a community sample from southern Brazil. *J Nutr Health Aging.* (2019) 23:923–9. doi: 10.1007/s12603-019-1230-x
61. Castillo-Lancellotti C, Margozzini P, Valdivia G, Padilla O, Uauy R, Rozowski J, et al. Serum folate, vitamin B12 and cognitive impairment in Chilean older adults. *Public Health Nutr.* (2015) 18:2600–8. doi: 10.1017/S1368980014003206
62. Almeida CC, Brentani HP, Forlenza OV, Diniz BS. Redução dos níveis séricos de ácido fólico em pacientes com a doença de Alzheimer. *Rev Psiquiatr Clín.* (2012) 39:90–3. doi: 10.1590/S0101-60832012000300004
63. Food Fortification Initiative. *Enhancing Grants for Healthier Living.* Available online at: https://www.ffinetwork.org/americas (accessed January 24, 2021).
64. Calvaresi E, Bryan J. B vitamins, cognition, and aging: a review. *J Gerontol Ser B Psychol Sci Soc Sci.* (2001) 56:P327–P39. doi: 10.1093/geronb/56.6.P327
65. Miller AL. The methionine-homocysteine cycle and its effects on cognitive diseases. *Altern Med Rev.* (2003) 8:7–19. doi: 10.1007/978-3-322-81541-5_2
66. Sun Y, Lu C-J, Chien K-L, Chen S-T, Chen R-C. Efficacy of multivitamin supplementation containing vitamins B6 and B12 and folic acid as adjunctive treatment with a cholinesterase inhibitor in Alzheimer's disease: a 26-week, randomized, double-blind, placebo-controlled study in Taiwanese Patients. *Clin Ther.* (2007) 29:2204–14. doi: 10.1016/j.clinthera.2007.10.012
67. Stott DJ, MacIntosh G, Lowe GD, Rumley A, McMahon AD, Langhorne P, et al. Randomized controlled trial of homocysteine-lowering vitamin treatment in elderly patients with vascular disease. *Am J Clin Nutr.* (2005) 82:1320–6. doi: 10.1093/ajcn/82.6.1320

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 06 September 2021
doi: 10.3389/fneur.2021.612416

Evaluating a Memory Clinic Using the RE-AIM Model. The Experience of the "Memory and Neuropsychiatry Clinic" in Hospital Del Salvador, Chile

Tomas Leon[1,2], *Loreto Castro*[1], *Franco Mascayano*[3,4], *Brian Lawlor*[2] and *Andrea Slachevsky*[1,5,6,7]*

[1] Memory and Neuropsychiatric Clinic, Neurology Department, Del Salvador Hospital and University of Chile School of Medicine, Santiago, Chile, [2] Department of Psychiatry and Global Brain Health Institute, Trinity College, Dublin, Ireland, [3] Mailman School of Public Health, Columbia University, New York, NY, United States, [4] Department of Psychiatry, New York State Psychiatric Institute, New York, NY, United States, [5] Geroscience Center for Brain Health and Metabolism (GERO), Santiago, Chile, [6] Neuropsychology and Clinical Neuroscience Laboratory (LANNEC), Physiopathology Department, Instituto de Ciencias Biomedicas (ICBM), Neurosciences and East Campus Neuroscience Departments, University of Chile School of Medicine, Santiago, Chile, [7] Neurology Unit, Department of Medicine, Clinica Alemana, Universidad del Desarrollo, Santiago, Chile

The development of healthcare services for dementia is key to improving access to care and post-diagnostic support for people living with dementia. Memory Units have emerged as a new healthcare service composed of multidisciplinary teams with the goal of improving diagnosis and/or management of dementia patients. The main objective of this study was to describe and evaluate the Reach and Effectiveness of a Memory Unit in a public hospital in Chile, using the RE-AIM model, a multi-component model that allows for the evaluation of the implementation of ongoing healthcare programs. Regarding "R" (Reach): from March 2018 up to June 2019, a total of 510 patients were referred and assessed. Most patients came from primary care (51.9%) and from outpatient services at the Hospital Salvador (39.2%), particularly from the Neurology (63.3%) and Psychiatry (16.0%) departments. We estimated that our Memory Unit assessed 5.39% of all of the dementia patients living in the area of referral. With respect to "E" (Effectiveness): 419 patients are still being followed up at the Memory Unit. Ninety-one patients (18%) were discharged. Of these, 55 (66%) were referred to primary healthcare, 28 (31%) to other outpatient services, 9 (10%) to a specialized mental healthcare center, and 9 (10%) to a daycare center. Due to the short period of time that the Memory Unit has been operating, no other RE-AIM dimensions could be evaluated at this juncture. To our knowledge, this is the first implementation study of a Memory Unit in Latin America, and the first using the RE-AIM model. Although cultural differences worldwide might play a role in the lack of international guidelines, the publication of the experience of the first year of this unit in Chile could inform new countries about this process. Ongoing challenges include continuing to collect data to complement the RE-AIM evaluation and developing a protocol that can be adopted elsewhere in Chile and Latin America. Further studies are needed to assess the benefits of a Memory Unit in comparison to regular care and to develop a model that assures continuity and coordination of care for people with dementia.

Keywords: memory clinic, public health, Latin America, RE-AIM, implementation

OPEN ACCESS

Edited by:
Kit Yee Chan,
University of Edinburgh,
United Kingdom

Reviewed by:
Tamlyn Watermeyer,
Northumbria University,
United Kingdom
Macarena Hirmas,
Universidad del Desarrollo, Chile

***Correspondence:**
Andrea Slachevsky
andrea.slachevsky@uchile.cl

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: *30 September 2020*
Accepted: *30 July 2021*
Published: *06 September 2021*

Citation:
Leon T, Castro L, Mascayano F, Lawlor B and Slachevsky A (2021) Evaluating a Memory Clinic Using the RE-AIM Model. The Experience of the "Memory and Neuropsychiatry Clinic" in Hospital Del Salvador, Chile. Front. Neurol. 12:612416. doi: 10.3389/fneur.2021.612416

INTRODUCTION

Dementia is a syndrome composed of impairment in one or more cognitive domains (e.g., memory, language, orientation, and decision-making) that affects everyday day functioning and independent living. The main causes of dementia include Alzheimer's disease, vascular dementia, and other neurodegenerative disorders (1). The prevalence of dementia in Chile is 1.06%, which means that over 200,000 individuals are living with dementia in the country. If we consider the impact that dementia has on relatives and friends, one can estimate that over 800,000 people are dealing with the consequences of this condition in Chile (2). In those 60 years old and older, the prevalence was 7.0% (women 7.7%; men 5.9%) and was higher in rural than in urban samples (10.3 vs. 6.3%) (3). There is no information on the possible underdiagnosis of dementia in Chile or in Latin America. A recent PRISMA systematic review on diagnosis of dementia only found one Latin America, with no information on underdiagnosis (4).

Chile's population is aging and consequently there is a projected increase in the incidence and prevalence of dementia. It has been estimated that over half a million people will have dementia by 2050 (5, 6). However, the health system is not prepared to tackle the challenge of increasing numbers of people with dementia, with inadequate numbers of dementia specialists, a lack of primary care training in dementia, and low numbers of daycare centers (7–9). There are few studies on the costs of dementia in Chile; however, it has been reported that families with a person living with dementia spend over 1,400 US dollars per month on care, mainly due to indirect costs. This cost is greater for poorer families (10, 11).

Therapies to cure or modify the course of dementia have been unsuccessful so far. Therefore, the main goals of dementia care are to (1) develop preventive strategies, (2) provide timely diagnosis, and (3) provide care and interventions that improve the quality of life of the person with dementia and their caregivers (12).

Due to the complexity of dementia, a comprehensive and holistic multidisciplinary approach is needed. There is evidence that a collaborative care model with a focus on primary care improves several outcomes. For the person with dementia, a collaborative care model results in fewer ER visits and acute hospitalizations (13), an improvement in neuropsychological symptoms (14), and cognitive symptoms (15), earlier diagnosis (16), and better satisfaction with care (17). For caregivers, such a model can improve depressive symptoms (14), decreased burden (18), and result in higher satisfaction with care (17), shorter waiting times and a reduction in time to diagnosis (19, 20).

In this context, the WHO recommends that countries should develop Dementia Plans as a multidisciplinary and multilevel response to tackle the many challenges posed by dementia. At the moment, 28 countries around the world have implemented Dementia Plans, mostly in high-income countries, with only three in Latin America (Costa Rica, Cuba and Chile) (6).

In 2017, the Ministry of Health launched *The Chilean National Plan of Dementia* (hereafter, "the Plan") for Chile (21) and began its implementation. The plan proposes a model of coordinated care for people with dementia and their caregivers across a continuum from primary care to specialized Memory Units (MU) (22).

MU, also known as Memory Clinics or memory assessment services, were first established in the USA in the 1970 s to provide diagnostic, treatment, and research in dementia (23). MU consist of multidisciplinary teams, bringing together professionals such as neurologists, geriatricians, psychiatrists, psychologists, neuropsychologists, occupational therapists, speech therapists, and nurses (24). MU have been proposed as a more comprehensive service at no extra cost compared to traditional community mental health teams (25); however, there is still a dearth of data supporting the cost-effectiveness of MU as part of the dementia care system (26). Therefore, more research is needed regarding the analysis of the health economic aspects and the implementation of MU.

MU also have a role in providing education and provide training about dementia to primary care, with the goal of improving diagnostic and treatment capacity in primary care settings (27). There have been several reports on the implementation of MU worldwide (28–30) with positive outcomes for patients and caregivers (31), establishing MU as an acceptable and effective form of dementia care (26, 32–34).

A number of MU have been established in Latin America, in private and/or universities centers, mainly in the capital and/or main cities of Argentina, El Salvador, Brazil, and Peru. However, to our knowledge, there is no MU implemented in a network of care facilities within the public system. Additionally, there is little available information on the setup and implementation approaches for such services that can be used as a basis for the development of new MU (35). Although there have been some efforts to develop quality standards for MU (36, 37), these exist mainly in high-income countries (HIC) and are therefore not necessarily applicable to the Chilean population and other low- and middle-income countries (LMIC).

In the context of the Chilean plan, MU are at the level of specialized care in secondary health facilities, based in the main hospitals across the country, one in Santiago (the nation's capital) with the others located in Osorno and Magallanes, regional capitals. Their purpose is to assess people with dementia and their caregivers whose health needs cannot be managed by primary care teams or in community centers for people with dementia, and/or that require evaluation by a dementia specialist (e.g., young-onset, atypical and complex cases with severe and/or treatment resistant symptoms).

An evaluation of the implementation of MU is crucial to inform the development of the Plan and to guide the creation of new units. Such an evaluation should be guided by models that characterize and help understand the implementation processes. One such model is RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance), which has been used extensively to plan, evaluate, and report the implementation of healthcare programs and services (38). The RE-AIM model allows for describing both implementation and dissemination processes, including the design and evaluation of specific interventions, as well as the identification of barriers and facilitators for the implementation of a health service, program,

or intervention (39). The model is particularly useful to assess the implementation of health services and policies in real-world settings; it can be easily adjusted to different contexts and populations, and it has been recognized as one of the most flexible and compelling models to translate research into practice by stakeholders (http://www.re-aim.org/).

The RE-AIM model considers the following components represented by each of its letters: Reach, Effectiveness, Adoption, Implementation, and Maintenance. Reach refers to the number or proportion of potential beneficiaries that are receiving the service. Effectiveness is the impact of the different interventions offered by a patient-level program. Adoption considers the number of institutions or clinical professionals that are willing to adopt the program and use it regularly. Implementation refers to whether the program is being offered as expected or according to a particular manual, like a clinical guideline or a protocol. Finally, Maintenance is expressed at two levels: institutional (the degree to which the program is part of the regular services of a clinic) and individual (the long-term effects on people enrolled in the program) (38). To our knowledge, this is one of the few attempts to evaluate the implementation of a memory assessment service in a low- to medium-income country and the first in a South American country.

OBJECTIVE

The main objective of this study was to describe and evaluate the Reach and Effectiveness of a Memory Unit, the "Memory and Neuropsychiatry Clinic" (CMYN for its acronym in Spanish), in the Hospital Salvador (hereafter "the hospital"), a public hospital in Santiago Chile, using the RE-AIM model.

METHODOLOGY

The methodology is divided into the following sections: Ethics, Study design, and Population including composition and internal functioning of CMYN, Data collection techniques and instruments, and Data analysis. In our study, only the "R" (Reach) and "E" (Effectiveness) components were analyzed. Other dimensions will be described in future papers.

Ethics

In accordance with local legislation and institutional requirements, our study has been reviewed by the Research in Human Beings Ethic Committee of the Universidad de Chile's Medical School and was determinate that ethical approval was not required for this study on human participants. Neither written informed consent from the participants was required to participate in this study in accordance with the national legislation and the institutional requirements.

Study Design and Population

To properly evaluate CMYN, some context of its history and context is needed. CMYN was established in late 2017 and began to assess patients in March 2018 in the outpatient part of the hospital, where historically the complex dementia patients had been treated, and where all the medical and non-medical specialists are based.

The Chilean Health System is divided into public and private systems, with the public system caring for over 80% of the population, especially older people. The public system has a pyramidal model of care whereby most of the specialists are hospital based and each hospital receives referrals from several areas. Hospital Del Salvador receives referral from several areas across the capital, one of which is called Peñalolen. Peñalolen is an urban area with over 240,000 inhabitants and its public health system is composed of six primary care centers, one mental health center and a daycare center for dementia. A detailed description of the Chilean health system can be found here (40).

As the Plan was in a pilot stage, it was initially decided that CMYN would only assess referrals from the primary care centers of Peñalolen, where according to the Plan, services and supports for dementia care were implemented in primary care centers as well as the provision of a Kintun, i.e., a daycare for dementia, that has been described elsewhere (8). However, since the hospital is a referral center for eight other communes in the eastern metropolitan area, CMYN quickly extended its services to patients from this larger area, regardless of whether they have facilities for dementia care within the primary care centers.

Study Design

Our study describes the performance of CMYN, evaluating the Reach and the Effectiveness under the RE-AIM model.

Population

The MU and its multidisciplinary team and specific program for dementia care received referrals from 20 primary care centers, with only six of them located in Peñalolen. CMYN receive patients mainly from primary care, referred under the diagnosis of "dementia" (confirmed) or "suspected dementia." We also received patients from other areas of the Hospital that could be referred under any diagnosis.

Variable/Intervention

CMYN is a multidisciplinary team of medical and non-medical specialists in dementia comprising two neurologists, two psychiatrists, a clinical psychologist, two neuropsychologists, a nurse, an occupational therapist, a speech and language therapist, and a social worker. CMYN performs several functions, including clinical evaluation and external consultation for patients with dementia and their caregivers requiring evaluation at a specialist care level, with established criteria for referral (see **Table 1**), management, continuity of care, and case coordination with primary care, together with research and teaching.

The clinical interventions of CMYN were organized into different programs for people with dementia and their caregivers, characterized by (i) being time-limited, (ii) addressing unresolved problems after evaluation in other healthcare centers, and (iii) encouraging referral to other services in <3 months. Assessments at CMYN were organized into three programs: (1) diagnostic, (2) biopsychosocial, and (3) communication (described in **Table 2**), with a team leader for each program that organizes the medical and non-medical evaluation needed

TABLE 1 | Criteria for referral to specialist care according to the Plan.

Criteria	Rapid evaluation needed	Diagnosis problems	Treatment problems	Communication or swallow problems	Caregiver burden
	1. Convulsions 2. Rapid onset of cognitive impairment 3. History of recent falls, after emergency department evaluation	1.- Cognitive impairment including the following: 1.1.- Behavioral symptoms as an early symptom 1.2 Late onset psychiatric disorders 1.3.- Motor impairment as an early symptom 1.4.- Hallucinations and delirium as an early symptom 1.5 Cognitive fluctuations 1.6- Communication problems as an early symptom 1.7.- Neurological focal signs 2.- Rapid onset dementia (<6 months) 3.- Young onset dementia (<65 years) 4.- Subjective cognitive impairment with normal cognitive screening but impaired function	1.- Behavioral and psychological symptoms of dementia, after primary care interventions	1.- Swallow disorder 2.- Nasogastric tube complications 3.- Young onset dementia with communication disorders	1.- Caregiver with significant burden, after primary care and mental health interventions

and being able to refer to any professional both in CMYN and the Hospital.

In exceptional circumstances, some patients were treated despite not assigned to one of the aforementioned programs, either for clinical, administrative or other reasons. These patients were kept in medical treatment, or with other professionals, according to their needs and for the time that was required. At the end of the assessment and care process, a report was created, summarizing the interventions offered, as well as making suggestions for ongoing care in the other parts of the network.

Additionally, the MU professionals train care teams from primary care centers in the diagnosis and treatment of patients with cognitive impairment and dementia. These training sessions are held every week by members of the MU and are usually delivered by a medical professional and an allied healthcare professional.

Data Collection

Data collection has been a priority for CMYN since its inception, bearing in mind the importance of generating data that could be used to replicate and validate its implementation for use by policymakers.

To obtain accurate and more complete data, the CMYN data collection process has had to go beyond the basic clinical paper-based record system available in the hospital and has progressively developed its own electronic database. First, data were registered in an online data chart and subsequently on an electronic health registry.

The data collection was set up as follows:

1.-Registry of data: A data chart was created using Google drive, allowing it to be completed and reviewed from any device by professionals that registered data in real-time on diagnosis, treatment and referrals.

2.- The registered data were doubled checked for accuracy: First, the data of the electronic registry were compared with the paper medical record; then, our electronic registry was compared with the hospital electronic registry.

CMYN's nurse also obtained information about the dementia patients seen in Peñalolen's primary care, both referred and not referred to MU. Unfortunately, there was no reliable and systematic registry of dementia in primary care centers locate in the areas that were not part of the Dementia Plan.

To ensure patient privacy, both the electronic registry and the Google drive was protected by password, available only to CMYN's professionals. Also, for analysis, only anonymized demographic and clinical data were extracted.

Data Analysis

The data collected from patients and clinicians were analyzed using descriptive statistics in SPSS. To compare differences between areas of referral and the discharge rates, chi-square was used.

RESULTS

As mentioned above, we will present only the analysis for the two first dimensions of the RE-AIM model. For Reach and Effectiveness, we provide a general evaluation regarding the performance of CMYN in each of these dimensions based on information regularly collected by healthcare professionals and interviews with key informants (e.g., patients and caregivers).

TABLE 2 | Programs of CMYN.

Program	Objective	Components	Professionals	Referral criteria
Diagnostic	Making a diagnosis	Complete multidisciplinary evaluation: • Medical history • Neuropsychological assessment • Occupational therapist assessment • Blood samples • Neuroimaging • Others (as required) *Post diagnosis, there are several sessions with a clinical psychologist and social worker to help to cope with the diagnosis*	All: • Neurologist (leader) • Neuropsychologist • Clinical psychologist • Social worker Per request • Psychiatrist • Occupational therapist • Speech and language therapist	• Diagnostic evaluation • Early-onset dementia.
Biopsychosocial	Comprehensive treatment to manage symptoms related to the dementia syndrome	Multidisciplinary intervention based on the DICE (describe, investigate, create, and evaluate) model (41) • Psychopharmacological interventions • Psychological interventions for the caregiver • Occupational therapy interventions • Social worker interventions	All • Psychiatrist (leader) • Clinical psychologist • Occupational therapist • Social worker Per request • Speech and language therapist • Nurse	• Patients with severe neuropsychiatric symptoms • Caregivers with severe caregiver burden
Communication and swallowing	Evaluation and treatment of alterations in communication and/or swallowing.	Evaluation and treatment by a speech-language therapist	Speech and language therapist	• Primary Progressive aphasia • Communications and/or swallowing issues*

**Most of the existing care networks do not have access to a speech therapist; the majority of patients that need a service are referred to this program.*

Reach

Reached Patients

This dimension corresponds to the number or proportion of potential beneficiaries that are receiving the services offered by CMYN. From March 2018 up to June 2019, the *Reach* of CMYN was a total of 510 patients.

When analyzing the reached patients, most of them came from primary care (51.9%), mainly from Peñalolen (33.9% of all the patients), the pilot area of the Plan where there are specific resources for the care of people with dementia (PwD) and their families, case management, and a mandatory registry of all dementia cases. Another large group of patients came from other outpatient services of the Hospital (39.2%), particularly from the Departments of Neurology (63.3%) and Psychiatry (16.0%) of the Hospital. Eighteen percent of all the patients were referred from primary care centers of the other seven areas of the health network of the Hospital del Salvador. Only 6.2% of the patients assessed came from other secondary care outpatient services.

Percentual Reach

To know the percentage of patients reached by CMYN of the possible patients, some analysis is required.

In Peñalolen, 36,593 persons over 60 years are enrolled in Primary Care Centers and 120,656 in the other areas (https://degi.saludoriente.cl/degidssmo/biodemografico.php). Although dementia is not an exclusive disease of older adults, with 10% cases occurring in people under the age of 60 years, it is more common in older individuals. Considering an estimated prevalence of dementia in Chile of 7.0% in people older than 60 years old, 2,500 persons could have dementia in primary care centers in Peñalolen and 8,500 from other areas (3, 6, 42). In June 2019, 862 cases with suspected dementia (68% woman and 51% over 80 years old) were being followed up in Peñalolen's primary care center (43).

From March 2018 to June 2019, 113 cases with suspected dementia were referred from Peñalolen to CMYN, representing 5.3% of the estimated PwD of Peñalolen. The number of cases with suspected dementia in follow-up in primary care centers outside Peñalolen is not available. These centers have referred, in the same period, 304 cases of suspected dementia patients to CMYN, corresponding to <1% of PwD living in the areas of these centers.

Effectiveness

National Plan of Dementia

One of the objectives of the National Plan of Dementia was to improve the diagnosis and referral rates for patients with dementia. According to the Peñalolen's primary care mental

health coordinator, in the pre-Plan era, before 2018, the number of patients for follow-up with a diagnosis of suspected dementia was about 100. This number increased to over 800 from 2018 until mid-2019 (43). Considering the prevalence of dementia in Chile (3), we can estimate that at least 60% of PwD have not received a diagnosis. As mentioned before, based on our estimations, the MU has interacted with nearly 5% of PwD from the Peñalolen area.

CMYN Memory Unit

During the period between March 2018 and June 2019, 510 patients were referred to CMYN (143 from Peñalolen and 367 from the other areas). Ninety-one (17.8%) of the referred patients were discharged: 24 (26.3%) from the discharged came from Peñalolen and 67 (73.6%) from the other areas. There was no significant difference between the area of precedence and the rate of discharges (16.78% of patients from Peñalolen were discharged and 18.25% from those of the other areas, chi-square test: χ^2 (1, $N = 510) = 0.15$, $p = 0.69$].

Of these 91 patients, 60 (65.93%) were referred back to primary care and 31 (34.06%) to another outpatient services at the Hospital del Salvador, mainly to Neurology and Psychiatry. Of the 91 discharged patients, 9 (10%) were also referred to a specialized mental health outpatient center, and another 9 (10%) were instructed to attend the KINTUN Daily Care Center aimed to support to people with dementia and their families.

A diagnostic of subjective cognitive complaint, or mild cognitive impairment, or cognitive complaint associated with a psychiatric disorder was made in 64 (70.4%) of the discharged patients. The diagnosis of dementia was confirmed in 24 (26.7%) that were referred to continue follow-up. Lastly, three patients (3.3%) were discharged against medical advice.

DISCUSSION

Our analysis on the implementation of CMYN with the Reach (number of patients) and the Effectiveness (impact on those patients) showed that the Plan reached a significant number of patients with CMYN reaching over 500 patients, with a novel and multidisciplinary approach to dementia care.

We will discuss the following key points (i) the utility of the RE-AIM to evaluate CMYN implementation; (ii) the number of patients under follow-up, (iii) comparison between CMYN and other MU worldwide, and (iv) barriers for the creations of new MU in Chile.

The Utility of the RE-AIM to Evaluate CMYN Implementation

There are several models available to evaluate the implementation of health services and programs (44–46). Among them, RE-AIM is recommended to evaluate the implementation of health services that are still in a developmental stage and provides several other advantages to fulfill the goal of our study: it represents an easy and approachable methodology and enables us to analyze parts of the model (e.g., Reach and Effectiveness) even if the other parts are not available. The advantage of using this model is its capacity to evaluate the ongoing implementation process of CMYN and to improve and complete the evaluation as the program develops in the areas that we already analyzed as well on the other components. Our study suggests that the RE-AIM is a suitable model to evaluate the reach and effectiveness of MU and contributes to providing insight that facilitates the sharing of experiences on the setup and implementation of MU. The use of the RE-AIM model to evaluate CMYN is a unique aspect of this study. While some programs for older people have been evaluated using RE-AIM (47, 48), to the best of our knowledge, this model has not used previously to evaluate the creation of MU or the implementation of a national plan of dementia. This is probably associated to low awareness among clinicians of the need to evaluate the implementation of MU in a systematic way (44).

The Number of Patients Being Followed Up

Our results suggest that the Plan increased the number of cases diagnosed with suspected dementia in primary care in Peñalolen from under 100 patients to over 800, suggesting that over a third of the elderly population with dementia in that area were diagnosed (43). Nevertheless, because of the lack of diagnostic confirmation of most of the cases seen at the primary care level, we were not able to calculate the exact number of PwD diagnostic in primary care, especially considering the high rate of misdiagnosis generally reported in primary healthcare (49).

Interestingly, based on our estimates, nearly 5% of all PwD of Peñalolen were referred to CMYN. That is signifiable low, especially compared with the international guidelines, like the standards from UK, that suggest that at least 66% of the dementia patients should be diagnosed by memory services (50). However, literature also suggest that referrals to MU increase significantly over the years, as MU are progressive more known among clinicians and services coordinators (50, 51). This number should be also analyzed in the context of our referral criteria, since they are different from the ones in other MU; for example, UK memory assessment services aim to evaluate all dementia patients, while our referral criteria, presented in **Table 1**, were atypical cases, young-onset dementia, difficult to diagnose or treat.

CMYN was able to discharge only 18% of their patients. This is not concordant with the objective of returning patents to primary care after clarification of their diagnosis and/or achieving remission of their presenting symptoms. This result can be in part explained by the relative short follow-up of our study. It is likely that more patients will be discharged over time. Nevertheless, this result suggests the existence of barriers to discharge patients from MU to primary care.

Possible barriers to discharge were that some of the medication could be prescribed and delivered only at the specialist care in MU, caregiver's resistance to discharge to primary care, and the need for longitudinal evaluations for a precise diagnosis. These barriers are similar to those reported in other studies (52, 53). One of them is the lack of specialized teams in primary care, but definitely not the only one, since most of the patients referred from primary healthcare from Peñalolen were not discharged, even having some facilities to dementia care in their primary care centers. Indeed, the rate of discharged patients from Peñalolen did not differ significantly from patients from other areas.

Future studies need to explore the low rate of discharges and possible barriers in more detail, exploring not only the discharge but also the re-entry to CMYN, since the lack of continuity of care for PwD has been associated with readmission and other poor health outcomes (54, 55), and therefore Peñalolen's patients might have fewer readmission to CMYN.

Our results also shows that even with the reported increase in reach in primary care (43), there is still a significant underdiagnosis of dementia in primary healthcare, with <50% of PwD being diagnosis according to our estimations. This is similar to the international experience (49, 56–58).

Therefore, there is a need for specific actions to improve awareness of cognitive disorders in both clinicians and the general population to increase access to opportune diagnosis and the quality of diagnostic at primary healthcare. Although frequently described in the literature (49), we can estimate the rate of misdiagnosis in primary care. On one hand, as discussed previously, the rate of referral from primary healthcare is low. On the other hand, all the referred patients from primary care came under the diagnosis of dementia to CMYN, and in over 90% of them, the diagnosis was either confirmed or is still under evaluation. Studies are needed to analyze the quality of diagnosis in primary healthcare.

One of the MU's objective is the continuous training of primary care in various aspects of dementia, including diagnosis. Our results suggest that MU need to improve its training techniques, implementing effective schemes to increase awareness and diagnosis of dementia in primary care, as has been done elsewhere (59, 60).

Comparison Between CMYN and Other MU Worldwide

Our preliminary data are consistent with previous reports suggesting that MU are an alternative for dementia care. Although the evidence is still scarce (33), most studies show that MU deliver benefits for patients (61), caregivers (62), clinicians and health systems (63) with better outcomes than treatment as usual (25). However, as mentioned above, the data available on cost-effectiveness of MU is contradictory (26). Also, research on the implementation of MU needs to consider the existence of different models of MU that are not limited to high-income countries and big cities (29). There are reports of experiences of successful MU in low- to middle-income patients (64) and in rural areas, using telehealth evaluations (23). Other MU have been established in primary care instead of specialized care settings (65) and can be composed mainly of nurses that can assess and manage specific symptoms (66, 67). Some MU treat and manage different types of dementia such as frontotemporal dementia (68). CMYN is based in secondary care and has established a novel model of treatment for Chile, with multidisciplinary treatment sorted into several programs aimed to deal with specific issues in dementia care such as diagnosis and treatment, with a continuous support for primary care. Furher research is needed to study if this new model generates better outcomes than treatment as has been done before in Chile and is more cost-effective.

Barriers for the Creations of New MU in Chile

We have identified several barriers, mainly related to the creation of multidisciplinary teams, coordination of care, funding, and health policy, to the creation of MU in Chile.

In Chile, there is no history and tradition of multidisciplinary teams operating in specialized care settings. Traditionally, PwD have been treated only by the neurologist or geriatrician using a biomedical and mainly pharmacological approach, with little or no interaction with other medical or non-medical health professionals. The implementation of a multidisciplinary team to tackle dementia might be seen as unnecessary.

At a coordination level, the lack of facilities for care of PwD at primary care centers, well-defined primary and specialist care referral pathways and processes, and a shared EHR, as mentioned above, are barriers to the implementation of MU due to problems with developing effective referral and discharge processes for the PwD from MU to primary care centers patients (69). Also, training and education in primary care are critical to improve referral and discharge and assure continuity of care in primary healthcare (70). Regarding prescription delivery, the creation of a joined-up service could facilitate the medication continuity in the transition from specialist care to primary based. That is one of the changes, among others, needed toward building capacity for dementia care in primary care, as it has been suggested elsewhere (71, 72).

At a funding level, a fee-for-service (FFS) payment model in healthcare is a barrier to care based on multidisciplinary teams. Supervision, management and discussion of cases, and coordination of care are not reimbursed in FFS (73). Indeed, current evidence suggests that value-based payment models are more suitable for MU (19).

At the health policy level, the main barrier is the lack of continuity of health policy regarding dementia in Chile. The plans for dementia care changes along the different governments as well as the priority of dementia among other health conditions. Hence, the funding for the creation of MU, daycare centers, and training program is not guaranteed to remain stable over the years.

LIMITATIONS

The main limitation of our study was the lack of information before and after the MU interventions in most of the areas. Our results suggest that the implementation of Plan increased the number of cases with suspected dementia diagnosed by GPs at primary care in Peñalolen. Nevertheless, we did not have more reliable information on the care of PwD before the implementation of MU to evaluate change in the navigation pathway at the whole health network associated with the implementation of the Dementia Plan and MU. The lack of availability of this information is mainly explained by the configuration of the Chilean health system: primary care is separated from secondary care with respect to data registry, clinical guidelines, and administration.

Another limitation is the availability of data. There is no shared EHR either between areas of the hospital or primary care. It is very difficult with the current registries to map the journey of a PwD across health systems. We need to create a shared dementia registry using EHR that would enable better tracking, evaluation, and care for PwD, as has been described elsewhere (74).

We were not able to evaluate the AIM (adoption, implementation, maintenance) components of the RE-AIM model, mainly due to the early phase of the implementation of the National Plan of Dementia and CMYN.

To evaluate adoption, other centers need to replicate the interventions made in our MU. Although there have been some informal discussions regarding adoption of our MU model in other hospitals, this has not occurred yet.

To evaluate implementation in the RE-AIM model, as described above, a clinical guideline is required prior to the start of the program to evaluate if the program follows it. This is not possible, due to the fact that the Chilean Ministry of Health has neither specified the organization of MU nor provided a manual or protocol for the creation of MU. Hence, a challenge, for CMYN, is to design a manual for the implementation of MU based on our experience.

Finally, to evaluate maintenance over the years, more time is required and due to the short time CMYN has been operating, we are not yet able to evaluate this phase.

CONCLUSION

A collaborative care model for dementia has been recommended, integrating primary care, specialist care, and national policies on dementia (20, 75, 76) and has been proven to be cost-effective (77). MU have been proposed as a significant part of the dementia care strategies. Due to the increasing prevalence of dementia, WHO currently recommends that the majority of dementia patients should be treated in primary care in coordination with secondary care and only the more complex patients should be referred to MU (78). MU clinics are recommended even in low-income countries (28, 79). The implementation of the Plan was a significant step forward for dementia care in Chile (40). However, in the Plan, there are no recommendations or guidelines on how to organize MU and how to interact with primary care.

As a result, even if the three MU in Chile have the same objective, they present significant differences in terms of human resources, health programs, and links with primary and secondary care. Even though it is important for the MU to adapt to local reality, there is also the need for harmonized practices between teams. With a common practice, it is easier to improve quality of care, gather evidence for further implementation of MU, and develop research, as has been recommended elsewhere (35, 69, 80).

To our knowledge, there are no guidelines in Latin America on how to implement MU. Although cultural differences and differences in healthcare organization worldwide might play a role in the lack of international guidelines, the publication of the evaluation of the first year of CMYN generates some useful information and creates a model of intervention that could be helpful not only for the expansion of MU across Chile but also for any Latin American country looking to implement a national dementia plan.

Further studies are needed to assess the contribution of MU in comparison to regular care in the Chilean health system, as it has been proven elsewhere (81) and to develop a model of care that assures continuity and coordination of care in the health sector, avoiding discontinuation of care when the case is transferred from primary to secondary care and back.

Also, it is important to keep a constant process of evaluation and improvement in all health services to both evaluate the efficacy and sustainability of the intervention and use that information to generate better interventions. The lack of health registry hampers the evaluation of a health program (82), since it makes it harder to gather standardized data for analysis.

Finally, in dementia care, there is a need for a constant process of adaptation due to the heterogeneity of patients (83–85), their caregivers (10), and their needs (86). However, there is also a heterogeneity for clinical and administrative reasons, the quality and quantity of resources, the assigned population to each hospital (as happened to CMYN), and the different professionals' background and experience.

Therefore, a clinical protocol should always be fluid and adaptable, looking to create a tailor-made intervention for each reality. Research should focus on enhancing the knowledge on how to implement MU, aiming to create profiles of cases and guidelines to respond using evidence-based interventions that are both effective and sustainable.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Electronic record of clinical interventions. Requests to access these datasets should be directed to tileon@uc.cl.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

TL and AS: conception. TL, AS, LC, and FM: design. LC and TL: analysis. TL, AS, BL, and FM: interpretation. TL, LC, FM, BL, and AS: draft manuscript and substantial manuscript revision. All authors contributed to the article and approved the submitted version.

FUNDING

AS is supported by ANID/FONDAP/15150012, MULTI-PARTNER CONSORTIUM TO EXPAND DEMENTIA RESEARCH IN LATIN AMERICA (ReDLat), supported by

the National Institutes of Aging of the National Institutes of Health under award number R01AG057234, an Alzheimer's Association grant (SG-20-725707-ReDLat), the Rainwater Foundation, and the Global Brain Health Institute. The content is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health, Alzheimer's Association, Rainwater Charitable Foundation, or Global Brain Health Institute.

REFERENCES

1. Chertkow H, Feldman HH, Jacova C, Massoud F. Definitions of dementia and predementia states in Alzheimer's disease and vascular cognitive impairment: consensus from the Canadian conference on diagnosis of dementia. *Alzheimers Res Ther.* (2013) 5:S2. doi: 10.1186/alzrt198
2. Russ TC, Murianni L, Icaza G, Slachevsky A, Starr JM. Geographical variation in dementia mortality in Italy, New Zealand, and chile: the impact of latitude, vitamin D. Air pollution. *Dement Geriatr Cogn Disord.* (2016) 42:31–41. doi: 10.1159/000447449
3. Fuentes P, Albala C. An update on aging and dementia in Chile. *Dement Neuropsychol.* (2014) 8:317–22. doi: 10.1590/S1980-57642014DN84000003
4. Pelegrini LNC, Mota GMP, Ramos CF, Jesus E, Vale FAC. Diagnosing dementia and cognitive dysfunction in the elderly in primary health care: a systematic review. *Dement Neuropsychol.* (2019) 13:144–53. doi: 10.1590/1980-57642018dn13-020002
5. Nitrini R, Bottino CM, Albala C, Custodio Capunay NS, Ketzoian C, Llibre Rodriguez JJ, et al. Prevalence of dementia in Latin America: a collaborative study of population-based cohorts. *Int Psychogeriatr.* (2009) 21:622–30. doi: 10.1017/S1041610209009430
6. Custodio N, Wheelock A, Thumala D, Slachevsky A. Dementia in latin america: epidemiological evidence and implications for public policy. *Front Aging Neurosci.* (2017) 9:221. doi: 10.3389/fnagi.2017.00221
7. Olavarria L, Mardones C, Delgado C, Slachevsky Ch A. Chilean healthcare professionals perception of knowledge about dementia. *Rev Med Chil.* (2016) 144:1365–8. doi: 10.4067/S0034-98872016001000019
8. Gajardo J, Aravena JM, Budinich M, Larrain A, Fuentes P, Gitlin LN. The Kintun program for families with dementia: from novel experiment to national policy (innovative practice). *Dementia.* (2020) 19:488–95. doi: 10.1177/1471301217721863
9. Gitlin LN, Fuentes P. The Republic of Chile: an upper middle-income country at the crossroads of economic development and aging. *Gerontologist.* (2012) 52:297–305. doi: 10.1093/geront/gns054
10. Slachevsky A, Budinich M, Miranda-Castillo C, Nunez-Huasaf J, Silva JR, Munoz-Neira C, et al. The CUIDEME study: determinants of burden in chilean primary caregivers of patients with dementia. *J Alzheimers Dis.* (2013) 35:297–306. doi: 10.3233/JAD-122086
11. Hojman DA, Duarte F, Ruiz-Tagle J, Budnich M, Delgado C, Slachevsky A. The cost of dementia in an unequal country: the case of Chile. *PLoS ONE.* (2017) 12:e0172204. doi: 10.1371/journal.pone.0172204
12. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. *Lancet.* (2017) 390:2673–734. doi: 10.1016/S0140-6736(17)31363-6
13. Boustani MA, Sachs GA, Alder CA, Munger S, Schubert CC, Guerriero Austrom M, et al. Implementing innovative models of dementia care: the healthy aging brain center. *Aging Ment Health.* (2011) 15:13–22. doi: 10.1080/13607863.2010.496445
14. Callahan CM, Boustani MA, Unverzagt FW, Austrom MG, Damush TM, Perkins AJ, et al. Effectiveness of collaborative care for older adults with Alzheimer disease in primary care: a randomized controlled trial. *JAMA.* (2006) 295:2148–57. doi: 10.1001/jama.295.18.2148
15. LaMantia MA, Alder CA, Callahan CM, Gao S, French DD, Austrom MG, et al. The aging brain care medical home: preliminary data. *J Am Geriatr Soc.* (2015) 63:1209–13. doi: 10.1111/jgs.13447
16. Richters A, Nieuwboer MS, Olde Rikkert MGM, Melis RJF, Perry M, van der Marck MA. Longitudinal multiple case study on effectiveness of network-based dementia care towards more integration, quality of care, and collaboration in primary care. *PLoS ONE.* (2018) 13:e01 98811. doi: 10.1371/journal.pone.0198811
17. Lee L, Hillier LM, Harvey D. Integrating community services into primary care: improving the quality of dementia care. *Neurodegener Dis Manag.* (2014) 4:11–21. doi: 10.2217/nmt.13.72
18. Thyrian JR, Hertel J, Wucherer D, Eichler T, Michalowsky B, Dreier-Wolfgramm A, et al. Effectiveness and safety of dementia care management in primary care: a randomized clinical trial. *JAMA Psychiatry.* (2017) 74:996–1004. doi: 10.1001/jamapsychiatry.2017.2124
19. Heintz H, Monette P, Epstein-Lubow G, Smith L, Rowlett S, Forester BP. Emerging collaborative care models for dementia care in the primary care setting: a narrative review. *Am J Geriatr Psychiatry.* (2020) 28:320–30. doi: 10.1016/j.jagp.2019.07.015
20. Duru OK, Ettner SL, Vassar SD, Chodosh J, Vickrey BG. Cost evaluation of a coordinated care management intervention for dementia. *Am J Manag Care.* (2009) 15:521–8.
21. G.d.C. *Ministerio de Salud, Plan Nacional de Demencia*, Santiago: Ministery of Health (2017).
22. Burns A, Robert P, Group IS. Dementia care: international perspectives. *Curr Opin Psychiatry.* (2019) 32:361–65. doi: 10.1097/YCO.0000000000000511
23. Morgan DG, Crossley M, Kirk A, D'Arcy C, Stewart N, Biem J, et al. Improving access to dementia care: development and evaluation of a rural and remote memory clinic. *Aging Ment Health.* (2009) 13:17–30. doi: 10.1080/13607860802154432
24. Jolley DJ, Benbow SM. Role of cholinesterase inhibitors in dementia care: memory clinics and cholinesterase inhibitors have their place. *BMJ.* (2006) 333:602. doi: 10.1136/bmj.333.7568.602-b
25. Rubinsztein JS, Girling D, Brayne C. CMHTs provide follow-up for patients with dementia and behavioural and psychological symptoms of dementia in both service models. *BJPsych Bull.* (2015) 39:205. doi: 10.1192/pb.39.4.205a
26. Meeuwsen E, Melis R, van der Aa G, Goluke-Willemse G, de Leest B, van Raak F, et al. Cost-effectiveness of one year dementia follow-up care by memory clinics or general practitioners: economic evaluation of a randomised controlled trial. *PLoS ONE.* (2013) 8:e79797. doi: 10.1371/journal.pone.0079797
27. Lee L, Kasperski MJ, Weston WW. Building capacity for dementia care: training program to develop primary care memory clinics. *Can Fam Physician.* (2011) 57:e249–52.
28. Jolley D, Moniz-Cook E. Memory clinics in context. *Indian J Psychiatry 51 Suppl.* (2009) 1:S70–6.
29. Cheung G, Strachan J. A survey of memory clinics in New Zealand. *Australas Psychiatry.* (2008) 16:244–7. doi: 10.1080/10398560701852131
30. Banerjee S. A narrative review of evidence for the provision of memory services. *Int Psychogeriatr.* (2015) 27:1583–92. doi: 10.1017/S1041610215000149
31. Hailey E, Hodge S, Burns A, Orrell M. Patients' and carers' experiences of UK memory services. *Int J Geriatr Psychiatry.* (2016) 31:676–80. doi: 10.1002/gps.4380
32. Meeuwsen EJ, Melis RJ, Van Der Aa GC, Goluke-Willemse GA, De Leest BJ, Van Raak FH, et al. Effectiveness of dementia follow-up care by memory clinics or general practitioners: randomised controlled trial. *BMJ.* (2012) 344:e3086. doi: 10.1136/bmj.e3086
33. Melis RJ, Meeuwsen EJ, Parker SG, Olde Rikkert MG. Are memory clinics effective? The odds are in favour of their benefit, but conclusive evidence is not yet available. *J R Soc Med.* (2009) 102:456–7. doi: 10.1258/jrsm.2009.090259
34. Frederiksen KS, Cooper C, Frisoni GB, Frolich L, Georges J, Kramberger MG, et al. A European academy of neurology guideline on medical management issues in dementia. *Eur J Neurol.* (2020) 27(10):1805–1820. doi: 10.1111/ene.14412
35. Parra MA, Baez S, Allegri R, Nitrini R, Lopera F, Slachevsky A, et al. Dementia in Latin America: assessing the present and envisioning the future. *Neurology.* (2018) 90:222–31. doi: 10.1212/WNL.0000000000004897

36. Draskovic M, Vernooij-Dassen M, Verhey F, Scheltens P, Rikkert MO. Development of quality indicators for memory clinics. *Int J Geriatr Psychiatry.* (2008) 23:119–28. doi: 10.1002/gps.1848
37. Doncaster E, McGeorge M, Orrell M. Developing and implementing quality standards for memory services: the memory services national accreditation programme (MSNAP). *Aging Ment Health.* (2011) 15:23–33. doi: 10.1080/13607863.2010.519322
38. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. *Am J Public Health.* (1999) 89:1322–7. doi: 10.2105/AJPH.89.9.1322
39. Gaglio B, Shoup JA, Glasgow RE. The RE-AIM framework: a systematic review of use over time. *Am J Public Health.* (2013) 103:e38–46. doi: 10.2105/AJPH.2013.301299
40. Thumala D, Kennedy BK, Calvo E, Gonzalez-Billault C, Zitko P, Lillo P, et al. Aging and health policies in chile: new agendas for research. *Health Syst Reform.* (2017) 3:253–60. doi: 10.1080/23288604.2017.1353844
41. Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. *BMJ.* (2015) 350:h369. doi: 10.1136/bmj.h369
42. González F, Massad C, Lavanderos F, Albala C, Sanchez H, Fuentes A, et al. *Estudio Nacional De la Dependencia En Las Personas Mayores*. Santiago: SENAMA (2009).
43. Carla R, Peñalolen APS. *Experiencia Plan Nacional de Demencias UM Hospital del Salvador*. Santiago: Presented as a Oral Communication at the XXIII National Congress of Geriatric Medicine and Gerontology (2019).
44. Tabak RG, Khoong EC, Chambers DA, Brownson RC. Bridging research and practice: models for dissemination and implementation research. *Am J Prev Med.* (2012) 43:337–50. doi: 10.1016/j.amepre.2012.05.024
45. Sales A, Smith J, Curran G, Kochevar L. Models, strategies, and tools. Theory in implementing evidence-based findings into health care practice. *J Gen Intern Med.* (2006) 2(Suppl. 21):S43–9. doi: 10.1111/j.1525-1497.2006.00362.x
46. Nilsen P. Making sense of implementation theories, models and frameworks. *Implement Sci.* (2015) 10:53. doi: 10.1186/s13012-015-0242-0
47. Anderson KA, Weber KV. Auto therapy: using automobiles as vehicles for reminiscence with older adults. *J Gerontol Soc Work.* (2015) 58:469–83. doi: 10.1080/01634372.2015.1008169
48. Murphy K, Liu WW, Goltz D, Fixsen E, Kirchner S, Hu J, et al. Implementation of personalized music listening for assisted living residents with dementia. *Geriatr Nurs.* (2018) 39:560–5. doi: 10.1016/j.gerinurse.2018.04.001
49. Bradford A, Kunik ME, Schulz P, Williams SP, Singh H. Missed and delayed diagnosis of dementia in primary care: prevalence and contributing factors. *Alzheimer Dis Assoc Disord.* (2009) 23:306–14. doi: 10.1097/WAD.0b013e3181a6bebc
50. E.B. Claudelle Abhayaratne. *Suzanna Greally, Sinead Rogers, Memory Services National Accreditation Programme Standards for Memory Services.* 7th Ed. London: Royal College of Psychiatrists' Centre for Quality Improvement (2020).
51. Chen Y, Lebouvier T, Skrobala E, Volpe-Gillot L, Huvent-Grelle D, Jourdan N, et al. Twenty-year trends in patient referrals throughout the creation and development of a regional memory clinic network. *Alzheimers Dement.* (2020) 6:e12048. doi: 10.1002/trc2.12048
52. Kable A, Chenoweth L, Pond D, Hullick C. Health professional perspectives on systems failures in transitional care for patients with dementia and their carers: a qualitative descriptive study. *BMC Health Serv Res.* (2015) 15:567. doi: 10.1186/s12913-015-1227-z
53. Stockwell-Smith G, Moyle W, Marshall AP, Argo A, Brown L, Howe S, et al. Hospital discharge processes involving older adults living with dementia: An integrated literature review. *J Clin Nurs.* (2018) 27:e712–25. doi: 10.1111/jocn.14144
54. Chenoweth L, Kable A, Pond D. Research in hospital discharge procedures addresses gaps in care continuity in the community, but leaves gaping holes for people with dementia: a review of the literature. *Australas J Ageing.* (2015) 34:9–14. doi: 10.1111/ajag.12205
55. Amjad H, Carmichael D, Austin AM, Chang CH, Bynum JP. Continuity of care and health care utilization in older adults with dementia in fee-for-service medicare. *JAMA Intern Med.* (2016) 176:1371–8. doi: 10.1001/jamainternmed.2016.3553
56. Connolly A, Gaehl E, Martin H, Morris J, Purandare N. Underdiagnosis of dementia in primary care: variations in the observed prevalence and comparisons to the expected prevalence. *Aging Ment Health.* (2011) 15:978–84. doi: 10.1080/13607863.2011.596805
57. Aminzadeh F, Molnar FJ, Dalziel WB, Ayotte D. A review of barriers and enablers to diagnosis and management of persons with dementia in primary care. *Can Geriatr J.* (2012) 15:85–94. doi: 10.5770/cgj.15.42
58. Cannon P, Larner AJ. Errors in the scoring and reporting of cognitive screening instruments administered in primary care. *Neurodegener Dis Manag.* (2016) 6:271–6. doi: 10.2217/nmt-2016-0004
59. Mason A, Liu D, Kasteridis P, Goddard M, Jacobs R, Wittenberg R, et al. Investigating the impact of primary care payments on underdiagnosis in dementia: a difference-in-differences analysis. *Int J Geriatr Psychiatry.* (2018) 33:1090–7. doi: 10.1002/gps.4897
60. Liu D, Green E, Kasteridis P, Goddard M, Jacobs R, Wittenberg R, et al. Incentive schemes to increase dementia diagnoses in primary care in England: a retrospective cohort study of unintended consequences. *Br J Gen Pract.* (2019) 69:e154–63. doi: 10.3399/bjgp19X701513
61. Park MH, Smith SC, Chrysanthaki T, Neuburger J, Ritchie CW, Hendriks AAJ, et al. Change in health-related quality of life after referral to memory assessment services. *Alzheimer Dis Assoc Disord.* (2017) 31:192–9. doi: 10.1097/WAD.0000000000000190
62. Park MH, Smith SC, Hendriks AAJ, Black N. Caregiver burden and quality of life 2 years after attendance at a memory clinic. *Int J Geriatr Psychiatry.* (2019) 34:647–56. doi: 10.1002/gps.5060
63. Park L, Kouhanim C, Lee S, Mendoza Z, Patrick K, Gertsik L, et al. Implementing a memory clinic model to facilitate recruitment into early phase clinical trials for mild cognitive impairment and Alzheimer's disease. *J Prev Alzheimers Dis.* (2019) 6:135–8. doi: 10.14283/jpad.2019.8
64. Alladi S, Shailaja M, Mridula KR, Haritha CA, Kavitha N, Khan SA, et al. Mild cognitive impairment: clinical and imaging profile in a memory clinic setting in India. *Dement Geriatr Cogn Disord.* (2014) 37:113–24. doi: 10.1159/000354955
65. Lee L, Hillier LM, Stolee P, Heckman G, Gagnon M, McAiney CA, et al. Enhancing dementia care: a primary care-based memory clinic. *J Am Geriatr Soc.* (2010) 58:2197–204. doi: 10.1111/j.1532-5415.2010.03130.x
66. Barton C, Merrilees J, Ketelle R, Wilkins S, Miller B. Implementation of advanced practice nurse clinic for management of behavioral symptoms in dementia: a dyadic intervention (innovative practice). *Dementia.* (2014) 13:686–96. doi: 10.1177/1471301213519895
67. Clevenger CK, Cellar J, Kovaleva M, Medders L, Hepburn K. Integrated memory care clinic: design, implementation, initial results. *J Am Geriatr Soc.* (2018) 66:2401–7. doi: 10.1111/jgs.15528
68. Grinberg A, Lagunoff J, Phillips D, Stern B, Goodman M, Chow T. Multidisciplinary design and implementation of a day program specialized for the frontotemporal dementias. *Am J Alzheimers Dis Other Demen.* (2007) 22:499–506. doi: 10.1177/1533317507308780
69. World Health Organization. *Continuity and coordination of care: a practice brief to support implementation of the WHO Framework on integrated people-centred health services.* Geneva: World Health Organization (2018). Available online at: https://apps.who.int/iris/handle/10665/274628
70. Lang L, Clifford A, Wei L, Zhang D, Leung D, Augustine G, et al. Prevalence and determinants of undetected dementia in the community: a systematic literature review and a meta-analysis. *BMJ Open.* (2017) 7:e011146. doi: 10.1136/bmjopen-2016-011146
71. Daliri S, Bekker CL, Buurman BM, Scholte Op Reimer WJM, van den Bemt BJF, Karapinar-Carkit F. Barriers and facilitators with medication use during the transition from hospital to home: a qualitative study among patients. *BMC Health Serv Res.* (2019) 19:204. doi: 10.1186/s12913-019-4028-y
72. Foulon V, Wuyts J, Desplenter F, Spinewine A, Lacour V, Paulus D, et al. Problems in continuity of medication management upon transition between primary and secondary care: patients' and professionals' experiences. *Acta Clin Belg.* (2019) 74:263–71. doi: 10.1080/17843286.2018.1483561
73. Naylor M, Keating SA. Transitional care. *Am J Nurs.* (2008) 108:58–63; quiz 63.
74. Simon KC, Yucus C, Castle J, Chesis R, Lai R, Hillman L, et al. Building of EMR tools to support quality and research in a memory disorders clinic. *Front Neurol.* (2019) 10:161. doi: 10.3389/fneur.2019.00161

75. Morgan RO, Bass DM, Judge KS, Liu CF, Wilson N, Snow AL, et al. A break-even analysis for dementia care collaboration: partners in dementia care. *J Gen Intern Med.* (2015) 30:804–9. doi: 10.1007/s11606-015-3205-x
76. French DD, LaMantia MA, Livin LR, Herceg D, Alder CA, Boustani MA. Healthy aging brain center improved care coordination and produced net savings. *Health Aff.* (2014) 33:613–8. doi: 10.1377/hlthaff.2013.1221
77. Rosa TD, Possin KL, Bernstein A, Merrilees J, Dulaney S, Matuoka J, et al. Variations in costs of a collaborative care model for Dementia. *J Am Geriatr Soc.* (2019) 67:2628–33. doi: 10.1111/jgs.16076
78. World Health Organization. *Dementia: a public health priority*. World Health Organization, Alzheimer's Disease International (2012). Available online at: https://apps.who.int/iris/handle/10665/75263
79. Prince M, Livingston G, Katona C. Mental health care for the elderly in low-income countries: a health systems approach. *World Psychiatry.* (2007) 6:5–13.
80. Tan ZS, Jennings L, Reuben D. Coordinated care management for dementia in a large academic health system. *Health Aff.* (2014) 33:619–25. doi: 10.1377/hlthaff.2013.1294
81. Meeuwsen EJ, Melis RJ, Meulenbroek O, Rikkert MG, Group AD-ES. Comparing content of dementia care after diagnosis: memory clinics versus general practitioners. *Int J Geriatr Psychiatry.* (2014) 29:437–8. doi: 10.1002/gps.4064
82. Krysinska K, Sachdev PS, Breitner J, Kivipelto M, Kukull W, Brodaty H. Dementia registries around the globe and their applications: a systematic review. *Alzheimers Dement.* (2017) 13:1031–47. doi: 10.1016/j.jalz.2017.04.005
83. Seelaar H, Rohrer JD, Pijnenburg YA, Fox NC, van Swieten JC. Clinical, genetic and pathological heterogeneity of frontotemporal dementia: a review. *J Neurol Neurosurg Psychiatry.* (2011) 82:476–86. doi: 10.1136/jnnp.2010.212225
84. Qiu Y, Jacobs DM, Messer K, Salmon DP, Feldman HH. Cognitive heterogeneity in probable Alzheimer disease: clinical and neuropathologic features. *Neurology.* (2019) 93:e778–90. doi: 10.1212/WNL.0000000000007967
85. Kazui H, Yoshiyama K, Kanemoto H, Suzuki Y, Sato S, Hashimoto M, et al. Differences of behavioral and psychological symptoms of dementia in disease severity in four major dementias. *PLoS ONE.* (2016) 11:e0161092. doi: 10.1371/journal.pone.0161092
86. Curnow E, Rush R, Maciver D, Gorska S, Forsyth K. Exploring the needs of people with dementia living at home reported by people with dementia and informal caregivers: a systematic review and meta-analysis. *Aging Ment Health.* (2021) 25(3):397–407. doi: 10.1080/13607863.2019.1695741

Author Disclaimer: The contents of this publication are solely the responsibility of the authors and do not represent the official views of the sponsors.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer MH declared a shared affiliation, with no collaboration, with one of the authors AS to the handling Editor at time of review.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Neurology

ORIGINAL RESEARCH
published: 18 October 2021
doi: 10.3389/fneur.2021.661269

Validation of ICMR Neurocognitive Toolbox for Dementia in the Linguistically Diverse Context of India

Mansi Verma[1], Manjari Tripathi[1], Ashima Nehra[2], Avanthi Paplikar[3], Feba Varghese[3], Suvarna Alladi[3,4], Jwala Narayanan[5], R. S. Dhaliwal[6], Meenakshi Sharma[6], Aralikatte Onkarappa Saroja[7], Faheem Arshad[3], Gollahalli Divyaraj[4], Amitabha Ghosh[8], Tejaswini S. Manae[3], Shailaja Mekala[4], Ramshekhar N. Menon[9], Roopa Hooda[1], Gowri K. Iyer[4], J. Sunitha[9], Rajmohan Kandukuri[4], Subhash Kaul[4], Arfa Banu Khan[10], Robert Mathew[11], Ranita Nandi[8], M. V. Padma[1], Apoorva Pauranik[12], Subasree Ramakrishnan[3], Lekha Sarath[9], Urvashi Shah[13], P. N. Sylaja[9], Ravi Prasad Varma[9] and Yeshaswini Vishwanath[5] on behalf of the ICMR-NCTB Consortium*

[1] Department of Neurology, All India Institute of Medical Sciences, New Delhi, India, [2] Clinical Neuropsychology, Neurosciences Centre, All India Institute of Medical Sciences, New Delhi, India, [3] Department of Neurology, National Institute of Mental Health and Neurosciences, Bengaluru, India, [4] Department of Neurology, Nizam's Institute of Medical Sciences, Hyderabad, India, [5] Department of Neurology, Manipal Hospitals, Bengaluru, India, [6] Indian Council of Medical Research, New Delhi, India, [7] Department of Neurology, Jawaharlal Nehru Medical College, KLE Academy of Higher Education and Research, Belagavi, India, [8] Cognitive Neurology Unit, Apollo Gleneagles Hospital, Kolkata, India, [9] Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, India, [10] Department of Psychiatry, KAHER's Jawaharlal Nehru Medical College and Research Center, Belagavi, India, [11] Department of Neurology, Government Medical College, Alappuzha, India, [12] Department of Neurology Mahatma Gandhi Mission Medical College, Indore, India, [13] Department of Neurology, King Edward Memorial Hospital, Mumbai, India

OPEN ACCESS

Edited by:
Sudeshna Das,
Massachusetts General Hospital and Harvard Medical School, United States

Reviewed by:
Arun Bokde,
Trinity College Dublin, Ireland
Atanu Biswas,
Bangur Institute of Neurosciences, India

***Correspondence:**
Manjari Tripathi
manjaritaiims@gmail.com

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: 30 January 2021
Accepted: 16 September 2021
Published: 18 October 2021

Citation:
Verma M, Tripathi M, Nehra A, Paplikar A, Varghese F, Alladi S, Narayanan J, Dhaliwal RS, Sharma M, Saroja AO, Arshad F, Divyaraj G, Ghosh A, Manae TS, Mekala S, Menon RN, Hooda R, Iyer GK, Sunitha J, Kandukuri R, Kaul S, Khan AB, Mathew R, Nandi R, Padma MV, Pauranik A, Ramakrishnan S, Sarath L, Shah U, Sylaja PN, Varma RP and Vishwanath Y (2021) Validation of ICMR Neurocognitive Toolbox for Dementia in the Linguistically Diverse Context of India. Front. Neurol. 12:661269. doi: 10.3389/fneur.2021.661269

Objectives: The growing prevalence of dementia, especially in low- and middle-income countries (LMICs), has raised the need for a unified cognitive screening tool that can aid its early detection. The linguistically and educationally diverse population in India contributes to challenges in diagnosis. The present study aimed to assess the validity and diagnostic accuracy of the Indian Council of Medical Research-Neurocognitive Toolbox (ICMR-NCTB), a comprehensive neuropsychological test battery adapted in five languages, for the diagnosis of dementia.

Methods: A multidisciplinary group of experts developed the ICMR-NCTB based on reviewing the existing tools and incorporation of culturally appropriate modifications. The finalized tests of the major cognitive domains of attention, executive functions, memory, language, and visuospatial skills were then adapted and translated into five Indian languages: Hindi, Bengali, Telugu, Kannada, and Malayalam. Three hundred fifty-four participants were recruited, including 222 controls and 132 dementia patients. The sensitivity and specificity of the adapted tests were established for the diagnosis of dementia.

Results: A significant difference in the mean (median) performance scores between healthy controls and patients with dementia was observed on all tests of ICMR-NCTB. The area under the curve for majority of the tests included in the ICMR-NCTB ranged from 0.73 to 1.00, and the sensitivity and specificity of the ICMR-NCTB tests ranged from 70 to 100% and 70.7 to 100%, respectively, to identify dementia across all five languages.

Conclusions: The ICMR-NCTB is a valid instrument to diagnose dementia across five Indian languages, with good diagnostic accuracy. The toolbox was effective in overcoming the challenge of linguistic diversity. The study has wide implications to address the problem of a high disease burden and low diagnostic rate of dementia in LMICs like India.

Keywords: dementia, Alzheimer's disease, vascular dementia, neuropsychological assessment, cross cultural validation, India, ICMR-NCTB

INTRODUCTION

Dementia, a neurocognitive syndrome that affects the ability to perform everyday activities, has become a major health crisis worldwide, and research priorities that are aimed at reducing its global disease burden are a priority (1, 2). There has been a significant rise in the numbers of elderly people with dementia, especially in developing regions of the world (3–5). Of the 47 million people living with dementia globally, about 63% of these currently live in low- and middle-income countries (LMICs) (5–7). These figures are projected to further increase to 82 million by 2030 and 152 million by 2050, particularly in China, India, and Latin America (2, 8, 9). In India itself, there are at least 5.29 million people living with dementia currently, and this number is expected to double by 2035 (6). The prevalence of undetected dementia is also significantly high globally. It is estimated to be currently at 61.7%, with India and China having a higher proportion compared to Europe and the USA (10).

There are various barriers to the diagnosis of dementia in LMICs. Major factors include low awareness, inadequate healthcare resources, and scarcity of diagnostic tools that are culturally and linguistically valid (1, 8, 11). As a result, both under-detection and overdiagnosis of dementia are possible (11, 12). Hence, it is important that reliable diagnostic tools and instruments are developed that are culturally, educationally, and linguistically valid and can help in early and accurate diagnosis (12, 13). Additionally, the use of diagnostic tests that can be harmonized with future global studies is crucial. There have been some efforts toward developing comprehensive neuropsychological test batteries for use in various languages such as 10/66 global dementia studies (14), the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery (15), the NIMHANS neuropsychological battery for the elderly (16), the Spanish English Neuropsychological Assessment Scales (SENAS) (17), and the international harmonization standards proposed by the National Institute of Neurological Disorders and Stroke (NINDS) and the Canadian Stroke Network (CSN) (18, 19). However, except for the studies by 10/66 dementia research groups, majority have been conducted in the developed world.

A significant amount of variance has been detected in the prevalence rate of dementia in India, a country with a large and diverse population (6, 7, 20–25). Variability in sociodemographic factors; genetic, protective, and risk factors; and methodological factors could account for these differences. To unravel the complex nature of dementia, research priorities to examine such large variations in dementia detection should be set, particularly in LMICs (26).

Variability in dementia-screening instruments and the use of different diagnostic methods and criteria contribute significantly to regional variability in reported dementia prevalence. To accurately establish the incidence or prevalence rates of dementia that are comparable across diverse populations, it is crucial that diagnostic instruments are harmonized by developing standardized procedures that are sensitive toward linguistic, educational, and cultural variability in populations (3). Additionally, efforts should also be made to increase the availability and ease of accessibility of these diagnostic instruments across the societies that are limited in resources. Another major barrier to effective management is a delay in early detection and treatment due to the scarcity of skilled professionals. Training more personnel on standardized diagnostic tools will also be necessary for effective management. These challenges exist not only for the diagnosis, treatment, and care of dementia but also for a majority of other mental health conditions (27).

To overcome these major barriers, a multidisciplinary group of neurologists, neuropsychologists, speech and language pathologists, and experts from related fields collaborated on a project funded by the Indian Council of Medical Research (ICMR) (http://icmr.nic.in). The efforts put forth by the group focused upon development, adaption, and validation of a comprehensive cognitive and functional test, the ICMR-Neurocognitive Toolbox (ICMR-NCTB) protocol, in five Indian languages (Hindi, Bengali, Telugu, Kannada, and Malayalam) with sensitivity toward different literacy levels across India (28). This test battery was developed to screen and diagnose dementia and mild cognitive impairment in the early stages, across the country (29), and to be suitable for conducting global collaborative research in cognitive disorders (28). The ICMR-NCTB has been validated for the diagnosis of MCI in the Indian context and demonstrated a good sensitivity of 81.1% and specificity of 88.8% to diagnose all-cause MCI (29). The usefulness of the ICMR-NCTB to diagnose dementia in the context of India requires to be established (30). In the background of a high burden of dementia due to Alzheimer's disease (AD) and vascular dementia (VaD) in India, the present study aimed to determine the validity of the ICMR-NCTB for the diagnosis of dementia in the context of linguistic heterogeneity in India.

METHODS

The ICMR established a collaboration between six academic institutions representing different linguistic states of India to develop and validate a cognitive test battery, to diagnose dementia in a standardized manner. Six centers that participated in this study are (1) Nizam's Institute of Medical Sciences (NIMS), Hyderabad, for Telugu and Hindi (the coordinating center); (2) All India Institute of Medical Sciences (AIIMS), Delhi, for Hindi; (3) Sri Chitra Tirunal Institute of Medical Science and Technology (SCTIMST), Trivandrum, for Malayalam; (4) National Institute of Mental Health and Neurosciences (NIMHANS) and Manipal Hospital, Bangalore, for Kannada; (5) Jawaharlal Nehru Medical College, Belgaum, for Kannada; and (6) Apollo Gleneagles, Kolkata, for Bengali. A multidisciplinary expert group collaborated toward the development of the ICMR Neurocognitive Toolbox (ICMR-NCTB) in five Indian languages (Hindi, Bengali, Telugu, Kannada, and Malayalam), to standardize the diagnosis of dementia in India (28).

The adaptation and validation involved a systematic process that included a review of existing international and national efforts at standardizing dementia diagnosis to identify culturally appropriate tests for the Indian context, adaptation for its use in five Indian languages and for both literates and illiterates, and validation in a cohort of individuals with normal cognition, mild cognitive impairment, and dementia across the multiple centers. This process has been detailed in an earlier report (28).

The ICMR-NCTB consisted of a range of tests that evaluate the major cognitive domains: (a) tests of cognition for the various domains of attention-executive functions: Trail Making Test A & B (TMT A & B) (31) and Category Fluency (32); memory: Verbal Learning Test—Total Learning and Delayed Recall (VLT—TL & DR) (33) and Modified Taylor Complex Figure Test—Delayed Recall (MTCF—DR) (34); and language (Picture Naming Test-PNT) and visuospatial skills (Modified Taylor Complex Figure test—Copy); and (b) questionnaires on behavior and functional activities: Geriatric Depression Scale (GDS) (35), Instrumental Activities of Daily Living—Elderly (IADL-E) (36), Neuropsychiatric Inventory (NPI) (37), Informant Questionnaire on Cognitive Decline in Elderly (IQCODE) (38), and RAND Short Form Health Survey (RAND SF-36) (39). A uniform protocol for the diagnosis of normal cognition and dementia due to neurodegenerative diseases was followed in all five centers (28).

Patients were recruited from out-patient services of neurology, geriatric, and internal medicine clinics of the participating hospitals, and healthy controls were randomly drawn from senior citizen centers, community outreach services, and healthy relatives of patients in the clinics. The detailed demographic, cognitive, and medical history of participants was collected to determine the eligibility for participation. Participants who fulfilled the following inclusion criteria for healthy controls were recruited: individuals >40 years and consented to participate; individuals with no history of head injury, infections, stroke, and other neurological, systemic, medical, or psychiatric disorders that can cause cognitive impairment; and those with no significant hearing or visual impairments that could interfere with the testing. A standard and harmonized case record form was used to collect sociodemographic information and neurocognitive and functional data.

An experienced cognitive neurologist evaluated all subjects, and experienced psychologists administered the gold standard tests on all the participants. Participants without any subjective cognitive complaints and scored normally on Addenbrooke's Cognitive Examination-III (ACE-III), Clinical Dementia Rating (CDR), Rey Auditory Verbal Learning Test (RAVLT), and Color Trails Test (CTT) were considered as healthy controls (28, 29). Participants with dementia were diagnosed based on clinical evaluation and the presence of impaired cognitive functions, as indicated by their scores on ACE-III (40) and CDR (28, 41). The dementia diagnosis was done based on the standard DSM-IV criteria (42). Patients were further classified into dementia subtypes: AD was diagnosed in patients who fulfilled the NIA-AA criteria for probable and possible AD (43), vascular dementia was diagnosed in patients who fulfilled the NINDS-AIREN criteria (44), and FTD was diagnosed based on the criteria by Rascovsky et al. (45). Persons diagnosed to have MCI were excluded from this study. The diagnosis of MCI was made based on the modified Petersen criteria (46). The recruited participants were subsequently administered with the complete ICMR-NCTB by a team of psychologists and clinicians who were blind to the diagnosis. The research ethics committee of all the participating centers approved the study, and consent was obtained from all the participants and their family caregivers.

Statistical Analysis

To compare the demographic data and neuropsychological test scores of patients with dementia and controls, an independent sample *t*-test for normally distributed continuous data or Mann—Whitney *U*-test for non-normal data, $\chi 2$ tests or Fisher's exact tests for categorical data, and trend test for ordinal data were used as appropriate. The test scores were represented in mean and standard deviation except TMT A & B scores, which is represented in median and interquartile range due to variability in the scores in the dementia group. The external validity of the battery was determined by the receiver operating curve (ROC) using the area under the curve (AUC). The optimum cutoff scores were established with corresponding sensitivity and specificity levels. All statistical analyses were performed using SPSS Statistics for Windows, version 23.0.

RESULTS

A total of 1,141 participants were recruited that included 991 controls and 185 patients with dementia. After matching the groups for age, education, and gender, 354 participants (222 controls and 132 patients with dementia) were included for further analysis. The patients were diagnosed as Alzheimer's disease (AD), vascular dementia (VaD), and frontotemporal Dementia (FTD): AD−65, VaD−45, and FTD−22. The mean age of the healthy controls and patients with dementia was 65 years and 66 years, respectively. Participants were from

both urban and rural backgrounds: 71% were controls and 77% of patients were urban dwellers. Out of 132 patients with dementia, 61 (46.30%) reported to have very mild dementia, 47 (35.60%) mild dementia, 18 (13.60%) moderate, and 6 (4.50%) severe on the Clinical Dementia Rating Scale (CDR). Because of the heterogeneity in demographic characteristics in the overall cohort, language-wise analysis was conducted (Hindi: controls−40, dementia−20; Bengali: controls−45, dementia−29; Telugu: controls−45, dementia−33; Kannada: controls−57, dementia−15; and Malayalam: controls−35, dementia−35). The demographic characteristics and cognitive test scores on ACE-III of healthy controls and patients with dementia are presented in **Table 1.** Both healthy controls and dementia patient groups were matched for age, education, and gender in all the language groups. Healthy controls performed significantly better on ACE-III than patients with dementia [$t_{(330)} = 18.87$, $p < 0.001$) in all the five language groups.

A significant difference in the mean (median) scores between healthy controls and patients with dementia was observed on all the tests of ICMR-NCTB (**Table 2**). Dementia patients took more time on TMT A & B and scored lower on category fluency than healthy controls in five Indian languages, which is indicative of significant impairment in their attention and executive functioning (*TMT A*—Hindi: $U = 187$, $n = 45$ $p = 0.194$; Bengali: $U = 185$, $n = 72$, $p < 0.001$; Telugu: $U = 149.50$, $n = 65$, $p < 0.001$; Kannada: $U = 127.50$, $n = 47$, $p < 0.001$; Malayalam: $U = 166$, $n = 66$, $p < 0.001$), *TMT B*—Hindi: $U = 235$, $n = 45$ $p = 0.862$; Bengali: $U = 577$, $n = 70$, $p = 0.832$; Telugu: $U = 214.40$, $n = 61$, $p = 0.003$; Kannada: U = 90.50, $n = 43$, $p = 0.482$; Malayalam: $U = 143.50$, $n = 65$, $p < 0.001$), and *category fluency*—Hindi: $t_{(55)} = 4.46$, $p < 0.001$; Bengali: $t_{(67)} = 5.32$, $p < 0.001$, Telugu: $t_{(74)} = 6.61$, $p < 0.001$; Kannada: $t_{(70)} = 9.15$, $p < 0.001$; Malayalam: $t_{(68)} = 9.09$, $p < 0.001$). Similarly, patients with dementia performed poorly on PNT, VLT (total learning and delayed recall), and MTCF copy and delayed recall compared to healthy controls, suggesting difficulties in language, memory, and visuospatial abilities (*PNT*—Hindi: $t_{(53)} = 9.49$, $p < 0.001$; Bengali: $t_{(55)} = 6.07$, $p < 0.001$; Telugu: $t_{(56)} = 4.85$, $p < 0.001$; Kannada: $t_{(53)} = 12.05$, $p < 0.001$; Malayalam: $t_{(68)} = 6.68$, $p < 0.001$), *VLT (total learning and delayed recall)*—Hindi: $t_{(55)} = 6.16$, $p < 0.001$; Bengali: $t_{(70)} = 5.42$, $p < 0.001$, Telugu: $t_{(74)} = 4.68$, $p < 0.001$; Kannada: $t_{(70)} = 4.64$, $p < 0.001$; Malayalam: $t_{(68)} = 7.69$, $p < 0.001$), and *MTCF copy and delayed recall* (Hindi: $t_{(45)} = 5.04$, $p < 0.001$; Bengali: $t_{(51)} = 10.29$, $p < 0.001$, Telugu: $t_{(76)} = 5.23$, $p = 0.024$; Kannada: $t_{(39)} = 5.46$, $p < 0.001$; Malayalam: $t_{(61)} = 10.99$, $p < 0.001$).

The ROC revealed that the majority of the ICMR-NCTB tests had good discriminating power in differentiating cognitively impaired participants from the normal healthy group across five languages (see **Table 3**) (*TMT A*: AUC: 0.79-0.99, CI: [0.69, 1.00]; *TMT B*: AUC: 0.74-0.98, CI: [0.60, 1.00]; *Category Fluency Animal*: AUC: 0.77-0.99, CI: [0.59, 1.00]; *Verbal Learning Test Delayed Recall:* AUC: 0.79-0.94, CI: [0.67, 0.99]; *Verbal Learning Test Total Recall:* AUC: 0.89-0.98, CI: [0.76, 1.00]; and *Picture Naming Test*: AUC: 0.81-1.00, CI: [0.69, 1.00]). The ROC analysis for the MTCF test could not be done due to small sample size, as individuals with <7 years of education and severe cases of dementia were not able to perform the task. The tests of ICMR-NCTB showed high sensitivity and the specificity at optimal cutoff scores, suggesting the ability of the tests to diagnose dementia in five Indian languages, namely, Hindi, Bengali, Telugu, Kannada, and Malayalam (**Table 4**; **Figures 1**, **2**).

DISCUSSION

In the present study, we assessed the diagnostic accuracy of the tests included in the ICMR Neurocognitive Toolbox in detection of dementia, across five Indian languages (Hindi, Bengali, Telugu, Kannada, and Malayalam). The ICMR-NCTB in all the five Indian languages met standardized test requirements, which indicates that the test adaption and standardization were successful across languages. This study confirms the utility of majority of the tests included in the ICMR-NCTB as effective instruments for the diagnosis of dementia, particularly with a relatively high sensitivity and specificity in a linguistically diverse context. Overall, the ICMR-NCTB appears promising in terms of validity based upon standard criteria for evaluating a dementia diagnostic test in the Indian context (28, 47).

Dementia is one of the most important independent contributors to disability in elderly especially in low- to middle-income countries (LMICs) where the resources to diagnose and manage dementia are limited. While specialized services for dementia are increasingly available in high-income countries, such facilities are lacking in LMICs. In addition, primary care physicians in developing countries do not receive suitable training to diagnose dementia and its subtypes. The gap in the diagnosis of dementia is further widened by the cross-cultural differences in understanding dementia due to linguistic and educational diversity. Therefore, a valid test battery that can be applied by clinicians and neuropsychologists in diagnosing dementia is crucial in the linguistically and educationally diverse Indian context.

The development and validation of a comprehensive NCTB protocol for the diagnosis of dementia, harmonized in five different languages, was an important facet of this study. It was established by following a common methodology that was applied on a large cohort consisting of persons with diverse linguistic profiles, which enabled it to be effectively utilized to detect cognitive deficits in early stages of dementia and help in reducing the variability in clinical diagnosis in hospitals and clinics across India. The main finding in our study was that the tests included in the ICMR-NCTB were found to be sensitive and specific in the identification of dementia in LMICs in all of the five Indian languages.

The external validity of each individual test included in the ICMR-NCTB was determined by the receiver operating curve (ROC) using the area under curve (AUC), and optimum cutoff scores were established with corresponding sensitivity and specificity levels.

Our study showed that the Trail Making Test-A, a test of attention, included in the ICMR-NCTB accurately differentiated patients with dementia from healthy control participants with high sensitivity ranging from 71 to 93% and specificity ranging

TABLE 1 | Demographic profile of Hindi, Bengali, Telugu, Kannada, and Malayalam speaking healthy controls and dementia.

Language and diagnosis	N	Age (years) mean (SD)	Gender (male, female) %	Years of education mean (SD)	ACE-III mean (SD)
Hindi—controls	40	57.10 (6.25)	67.5, 32.5	14.03(3.40)	86.37 (7.53)
Hindi—dementia	20	61.00 (9.06)	55.0, 45.0	13.15(2.98)	56.33 (19.45)
Bengali—controls	45	66.27 (6.18)	71.1, 28.9	11.62(4.28)	88.62 (7.24)
Bengali—dementia	29	67.03 (10.47)	65.5, 34.5	12.21(3.74)	57.69 (16.11)
Telugu—controls	45	66.29 (3.93)	66.7, 33.3	14.20(4.14)	93.62 (4.13)
Telugu—dementia	33	65.55 (8.56)	54.5, 45.5	13.03(5.32)	70.52 (19.02)
Kannada—controls	57	64.47 (3.10)	40.4, 59.6	12.00(3.49)	87.77 (7.59)
Kannada—dementia	15	67.20 (9.11)	46.7, 53.3	11.67(4.25)	37.20 (21.51)
Malayalam—controls	35	68.91 (5.39)	65.7, 34.3	12.71(2.56)	92.09 (4.08)
Malayalam—dementia	35	70.11 (5.91)	77.1, 22.9	11.50(2.59)	66.43 (13.15)

SD, standard deviation; ACE-III, Addenbrooke's Cognitive Examination.
Missing values: ACE-III (controls, patients)—Hindi (2, 5), Bengali (8, 0), Telugu (6, 0), Kannada (0, 0), Malayalam (1, 0).

from 81 to 100% at the optimal cutoff points ranging from (>) 74 to 144 across the five Indian languages. Similarly, the Trail Making Test-B, a test of executive function, also accurately differentiated the patient group from healthy individuals with sensitivity and specificity ranging from 70 to 100% and 71to 89%, respectively, at optimal cutoff points ranging from (>) 180 to 298 across languages. Few moderate and severe patients with dementia were not able to complete the Trail Making Test due to the typical decline in attention and executive functions that are evident in the later stages of the disease (48).

Category fluency (animals) showed high sensitivity (86-100%) and specificity (74-98%) at optimal cutoff points ranging from 8 to 11, except in Bengali where the sensitivity of the category fluency task was moderate (66%) with good specificity (83%) at an optimal cutoff point of 11. This finding is in agreement with the verbal fluency test included in the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery which showed higher sensitivity (75%) and specificity (74%) at an optimal cutoff point of <17 for the category fluency task (15). The lower category fluency cutoff score in the ICMR-NCTB compared to CERAD neuropsychological battery might be due to the inclusion of moderate and severe dementia patients. The NIMHANS Neuropsychological Battery for the Elderly demonstrated good discriminability for the animal fluency task (AUC = 0.99, 95% CI [0.96, 0.99]) (16) that was comparable to the discriminability findings of category fluency (AUC = 0.77-0.99, 95% CI [0.58, 1.00]) findings of our study.

The episodic memory tests of the ICMR-NCTB (verbal learning test—TL and verbal learning test—DR) accurately differentiated patients with dementia from the healthy control group, which is consistent with the criteria to diagnose majority of dementia subtypes including AD (49) that highlight episodic memory impairment in patients with dementia. The verbal learning test-DR showed high sensitivity and specificity ranging from 71 to 90% and 83 to 91%, respectively, with optimal cutoff points ranging from 2 to 3, and the verbal learning test-TL showed a sensitivity of 71-100% and specificity of 80-95% at optimal cutoff points ranging from 11 to 16. The high discriminability of the episodic memory tests of ICMR-NCTB compares well with the word list DR (sensitivity = 94%, specificity = 85%, cutoff = 5) and word list learning (sensitivity = 90%, specificity = 83%, cutoff = 17) of CERAD neuropsychological battery (15). The cutoff scores of verbal learning test are consistent with studies done in LMICs like Brazil. A Brazilian epidemiological study derived a cutoff score of 3 in the literate group and 1 in the illiterate group for delayed recall of a word list test from the CERAD neuropsychological battery (50). A different study from India also established a cutoff score of 3 for the delayed verbal memory test (33), from Kolkata cognitive screening battery, which is also consistent with our study. The word list-delayed recall (AUC = 0.99; 95% CI [0.97, 0.99]) of NIMHANS neuropsychological battery for the elderly revealed the highest discriminability (16), which is comparable with the verbal learning test DR (AUC = 0.79-0.94; 95% CI [0.67, 0.99]).

The Picture Naming Test included in the ICMR-NCTB showed high sensitivity (71-100%) and specificity (73-100%) at optimal cutoff points ranging from 69 to 81 (maximum score = 90), which compares favorably well with the naming test of CERAD neuropsychological battery with a sensitivity of 68% and specificity of 76% at an optimal cutoff point of 12 (maximum score = 15) (15).

The high sensitivity and specificity of the majority of the tests included in the ICMR-NCTB for diagnosing dementia favorably compares to that of other cognitive test batteries such as the Spanish and English Neuropsychological Assessment Scales (SENAS) (51) battery with 80% sensitivity and specificity for a combination of word list learning and object naming to diagnose dementia. The sensitivity of the diagnostic algorithm against clinically diagnosed dementia in the widely used 10/66 pilot samples was 94%, and the specificity was 97% in people with high education and 93% in individuals with low education (52), which is comparable with the sensitivity and specificity of the ICMR-NCTB tests.

Tests included in the NINDS-CSN battery include Animal Naming Test (ANT), Wechsler Adult Intelligence Scale (WAIS)

TABLE 2 | ICMR-NCTB test scores of healthy controls and patients with dementia in Hindi, Bengali, Telugu, Kannada, and Malayalam.

Language and diagnosis	Attention and executive functions			Episodic memory			Language	Visuospatial functions
	Trail Making Test (TMT) A in seconds Median [IQR]	Trail Making Test (TMT) B in seconds Median [IQR]	Category Fluency (animals) Mean (SD)	Verbal Learning Test Delayed Recall Mean (SD)	Verbal Learning Test Total Learning Mean (SD)	Modified Taylor Complex Figure Test (MTCF)—Delayed Recall Mean (SD)	Picture Naming Test (PNT) Mean (SD)	Modified Taylor Complex Figure Test (MTCF)-Copy Mean (SD)
Hindi—controls	68.00 [41.00]	162.00 [62.00]	9.53 (2.75)	5.05 (1.93)	17.21 (4.06)	15.42 (6.74)	88.51 (4.03)	34.88 (1.82)
Hindi—dementia	89.50 [121.00]	180.00 [300.00]	5.58 (3.85)	1.11 (1.66)	8.68 (6.33)	4.70 (6.95)	49.31 (25.35)	19.57 (13.46)
Bengali—controls	71.00 [41.00]	203.00 [139.00]	15.65 (4.02)	4.72 (1.93)	19.49 (4.56)	15.39 (5.38)	81.55 (7.28)	33.85 (2.19)
Bengali—dementia	151.00 [83.00]	300.00 [300.00]	9.90 (4.95)	1.55 (1.88)	13.24 (5.12)	2.45 (3.46)	65.07 (14.53)	12.86 (12.77)
Telugu—controls	60.51[25.00]	160.00[77.00]	14.38 (3.73)	5.35 (2.14)	18.85 (3.86)	18.61 (6.78)	86.07 (3.94)	34.95 (1.71)
Telugu—dementia	90.5[38.8]	200.00[93.00]	8.75 (3.53)	2.65 (2.84)	8.39 (8.24)	9.33 (8.84)	63.80 (27.03)	33.97 (38.16)
Kannada—controls	70.00 [31.00]	157.00 [91.00]	12.11 (4.09)	4.23 (1.91)	17.02 (2.48)	20.03 (8.06)	83.80 (5.18)	34.69 (1.89)
Kannada—dementia	359.00 [240.5]	618.00 [310.00]	2.20 (1.61)	1.66 (1.87)	7.33 (5.12)	2.71(4.79)	35.07 (24.53)	9.14 (11.55)
Malayalam—controls	79.00 [39.00]	205.00 [69.00]	14.43 (2.27)	4.60 (1.79)	18.09 (3.00)	17.40 (6.59)	79.31 (5.89)	35.16 (1.55)
Malayalam—dementia	175.00 [154.00]	413.00 [288.00]	8.11 (3.43)	0.97 (1.93)	11.26 (4.31)	2.74 (3.72)	61.68 (13.93)	20.15 (13.74)

IQR, interquartile range; SD, standard deviation.

Missing values.

Hindi: TMT A and B: controls: 13, patients: 10; category fluency (animals): controls: 1, patients: 1; VLT: controls: 0, patients: 4; PNT: controls: 2, patients: 3; MTCF: controls: 5, patients: 9.

Bengali: TMT A and B: controls: 4, patients: 12; category fluency (animals): controls: 5, patients: 0; VLT: controls: 2, patients: 0; PNT: controls: 7, patients: 0; MTCF: controls: 21, patients: 0.

Telugu: TMT A and B: controls: 14, patients: 12; category fluency (animals): controls: 1, patients: 1; VLT: controls: 0, patients: 2; PNT: controls: 15, patients: 5; MTCF: controls: 5, patients: 9.

Kannada: TMT A and B: controls: 19, patients: 1; PNT: controls: 17, patients: 15; MTCF: controls: 21, patients: 8.

Malayalam: TMT A and B: Controls: 4, Patients: 4; MTCF: Controls: 4, Patients: 2.

TABLE 3 | Area under curves of ICMR-NCTB tests across five languages.

Test	Hindi	Bengali	Telugu	Kannada	Malayalam
Attention and executive functions					
Trail Making Test (TMT) A (seconds)	AUC = 0.79 CI: [0.69, 0.98]	AUC = 0.92 CI: [0.85, 0.99]	AUC = 0.82 CI: [0.69, 0.94]	AUC = 0.99 CI: [0.98, 1.00]	AUC = 0.89 CI: [0.81, 0.97]
Trail Making Test (TMT) B (seconds)	AUC = 0.87 CI: [0.72, 1.00]	AUC = 0.88 CI: [0.79, 0.97]	AUC = 0.74 CI: [0.60, 0.87]	AUC = 0.98 CI: [0.95, 1.00]	AUC = 0.95 CI: [0.89, 1.00]
Category fluency (animals)	AUC = 0.77 CI: [0.58, 0.95]	AUC = 0.86 CI: [0.76, 0.97]	AUC = 0.89 CI: [0.81, 0.98]	AUC = 0.99 CI: [0.97, 1.00]	AUC = 0.93 CI: [0.87, 0.99]
Episodic memory					
Verbal Learning Test Delayed Recall	AUC = 0.92 CI: [0.81, 1.00]	AUC = 0.87 CI: [0.76, 0.98]	AUC = 0.79 CI: [0.67, 0.93]	AUC = 0.83 CI: [0.72, 0.91]	AUC = 0.94 CI: [0.88, 0.99]
Verbal Learning Test Total Recall	AUC = 0.90 CI: [0.76, 1.00]	AUC = 0.89 CI: [0.81, 0.98]	AUC = 0.86 CI: [0.75, 0.97]	AUC = 0.98 CI: [0.95, 1.00]	AUC = 0.90 CI: [0.83, 0.98]
Language					
Picture Naming Test (PNT)	AUC = 0.98 CI: [0.95, 1.00]	AUC = 0.92 CI: [0.82, 0.99]	AUC = 0.81 CI: [0.69, 0.92]	AUC = 1.00 CI: [1.00, 1.00]	AUC = 0.93 CI: [0.87, 0.99]

AUC, area under curve; CI, confidence interval.

TABLE 4 | Optimal cutoff scores and the respective sensitivity and specificity of ICMR-NCTB tests for diagnosis of dementia across five languages.

Test	Hindi	Bengali	Telugu	Kannada	Malayalam
Attention and executive functions					
Trail Making Test (TMT) A (seconds)	Cutoff: > 95 Sensitivity: 71.43 Specificity: 81.48	Cutoff: > 105 Sensitivity: 92.30 Specificity: 88.40	Cutoff: > 74 Sensitivity: 75.00 Specificity: 85.40	Cutoff: > 144 Sensitivity: 92.90 Specificity: 100.00	Cutoff: > 115 Sensitivity: 75.76 Specificity: 83.87
Trail Making Test (TMT) B (seconds)	Cutoff: > 204 Sensitivity: 90.00 Specificity: 77.80	Cutoff: > 298 Sensitivity: 88.20 Specificity: 82.90	Cutoff: > 180 Sensitivity: 70.00 Specificity: 70.70	Cutoff: > 267 Sensitivity: 100.00 Specificity: 89.20	Cutoff: > 290 Sensitivity: 90.30 Specificity: 87.10
Category Fluency (animals)	Cutoff: ≤ 8 Sensitivity: 89.50 Specificity: 73.70	Cutoff: ≤ 11 Sensitivity: 65.52 Specificity: 82.50	Cutoff: ≤ 8 Sensitivity: 100.00 Specificity: 97.50	Cutoff: ≤ 8 Sensitivity: 100.00 Specificity: 80.70	Cutoff: ≤ 11 Sensitivity: 85.70 Specificity: 94.30
Episodic memory					
Verbal Learning Test Delayed Recall	Cutoff: ≤ 3 Sensitivity: 89.50 Specificity: 84.20	Cutoff: ≤ 2 Sensitivity: 82.80 Specificity: 90.70	Cutoff: ≤ 3 Sensitivity: 71.00 Specificity: 84.40	Cutoff: ≤ 2 Sensitivity: 73.30 Specificity: 82.50	Cutoff: ≤ 2 Sensitivity: 82.86 Specificity: 88.57
Verbal Learning Test Total Recall	Cutoff: ≤ 11 Sensitivity: 78.90 Specificity: 94.70	Cutoff: ≤ 16 Sensitivity: 75.80 Specificity: 83.70	Cutoff: ≤ 16 Sensitivity: 87.10 Specificity: 80.00	Cutoff: ≤ 14 Sensitivity: 100.00 Specificity: 87.70	Cutoff: ≤ 13 Sensitivity: 71.40 Specificity: 94.30
Language					
Picture Naming Test (PNT)	Cutoff: ≤ 81 Sensitivity: 93.70 Specificity: 97.40	Cutoff: ≤ 77 Sensitivity: 86.20 Specificity: 73.70	Cutoff: ≤ 73 Sensitivity: 71.40 Specificity: 73.30	Cutoff: ≤ 69 Sensitivity: 100.00 Specificity: 100.00	Cutoff: ≤ 74 Sensitivity: 88.60 Specificity: 82.90

digit symbol coding, Trail Making Test A & B, Boston Naming Test (BNT), Rey—Osterrieth Complex Figure Test (RCFT) copy, Verbal Learning Test-delayed recall, and RCFT-delayed recall (53), which is very similar to the range of tests included in the ICMR-NCTB. Z-scores were derived, and the external validity evaluated by AUC for the 60-min protocol of the NINDS-CSN battery was 0.88 [95% (CI), 0.81, 0.95]. Although a direct comparison of ICMR-NCTB with NINDS-CSN battery cannot be made, the AUC of ICMR-NCTB tests ranged from 0.73 to 1.00, which indicates a good discriminating power in diagnosing dementia, similar to NINDS-CSN battery.

An important feature of the study is that it is unique in comprehensively addressing the validity of each neuropsychological test included in the ICMR toolbox in a linguistically, educationally, and culturally heterogeneous population. A further strength of the ICMR-NCTB is that tests for all major cognitive domains of attention/executive function, language, memory, and visuospatial functions are incorporated and optimum cutoff points with corresponding

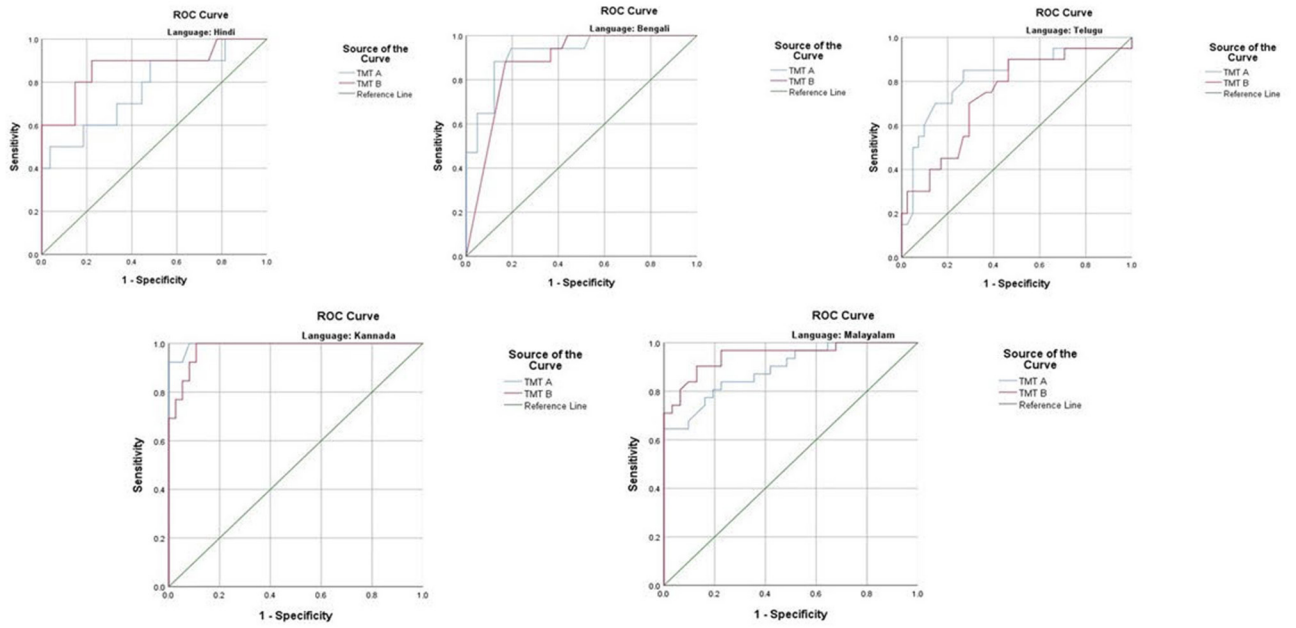


FIGURE 1 | Receiver operating curve (ROC) of Trail Making Test (A and B) in diagnosing dementia across five languages.

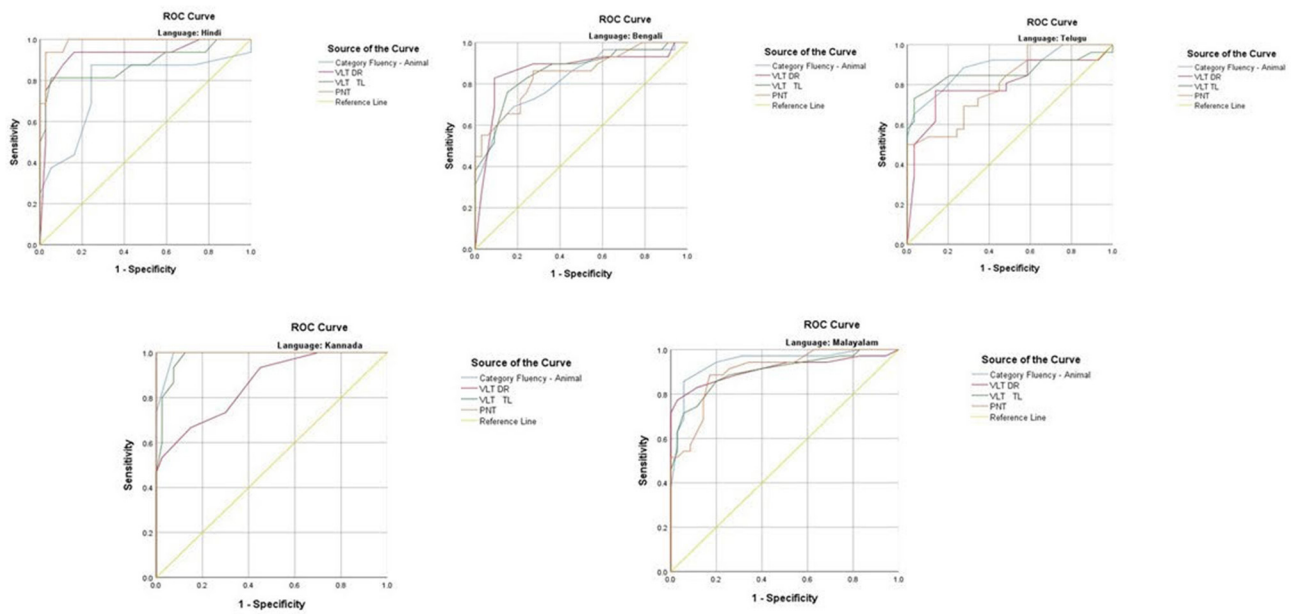


FIGURE 2 | Receiver operating curve (ROC) of Category Fluency-Animal, Verbal Learning Test: Delayed Recall and Total Learning (VLT DR and VLT TL), and Picture Naming Test (PNT) in diagnosing dementia across five languages.

sensitivity and specificity of various cognitive domains in five Indian languages are provided separately. This is crucial for the diagnosis of dementia subtypes: AD, VaD, and FTD that have characteristic cognitive profiles. While AD is a disorder of memory especially in the early stages (54), VaD is characterized by prominent executive dysfunction (55) and frontotemporal dementia syndromes present with language and/or executive function impairment (56). The advantage of inclusion of tests of all major cognitive domains in the ICMR-NCTB is reflected in the relatively high diagnostic sensitivity and specificity of majority of the cognitive domains in this dementia cohort consisting of multiple subtypes. While the study has established successful discriminability between dementia and controls across all tests, the most efficacious combination of measures discriminating healthy controls from patients with dementia is yet to be determined.

There were certain limitations identified. (i) The study was conducted in a literate population, and patients with dementia studied were relatively young. (ii) We had a relatively small sample in the Kannada dementia group which might be one of the reasons for the high sensitivity and specificity of ICMR-NCTB tests in Kannada. (iii) Differing proportions of dementia subtypes in our dementia cohort might have led to the differences in ages across dementia patients in five language groups. (iv) We did not have enough numbers for establishing diagnostic validity separately for subtypes of dementia. (v) For clinical and research generalizability, the test battery will need to be adapted to the illiterate group and in larger numbers in the future. (vi) The findings of the current study are applicable to dementia cohorts seen in memory clinics and specialized centers only as the study was conducted in academic medical centers. (vii) There was a variation in the cutoff scores across languages for the Modified Taylor Complex Figure test (MTCF) copy and delayed recall tests, as the sample size was not adequate due to the inability of the low-educated participants and advanced dementia patients to perform the test. Therefore, the MTCF test could not be validated in the current study and the tool might not be applicable for the low literate population in the Indian context. This is planned during the next phase of the study, in larger and more diverse clinical and community populations to further validate the ICMR-NCTB.

To conclude, we were successfully able to validate a cognitive test battery in five different languages that is harmonized culturally and linguistically to diagnose dementia in India. The high specificity and sensitivity of the tests included in the ICMR-NCTB highlight its ability to detect dementia across languages. Our study thus establishes a benchmark for dementia research in India and will prove to be an invaluable tool for clinical practice and for multicentric preventive and therapeutic research in a socio-linguistically diverse context.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available upon request, without undue reservation. Requests to access the datasets should be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Research Ethics Committee of Nizam's Institute of Medical Sciences, Hyderabad; All India Institute of Medical Sciences Ethics Committee, Delhi; Institutional Ethics Committee, Apollo Gleneagles Hospital, Kolkata; Ethics Committee of Manipal Hospital, Bengaluru; and Institutional Ethics Committee, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Kerala. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MV contributed toward project implementation, data collection, analyses, and manuscript writing. MT, AN, and SA contributed toward tool development and adaptation, project implementation, data collection, analyses, and manuscript writing. APap contributed data collection, data analyses, and manuscript writing. FV contributed toward statistical and data analyses. RD, MS, AS, AG, RNM, GI, RM, JN, SR, PS, and RV contributed toward tool development and adaptation, project implementation, data collection, analyses, and manuscript editing. APau, MP, US, and SK are expert panelists who contributed toward tool development and adaptation, project implementation, and manuscript editing. FA, GD, TM, SM, RH, JS, RK, AK, RN, LS, and YV contributed toward project implementation, data collection, and manuscript editing. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the Indian Council for Medical Research under Grant [SWG/Neuro/32/2017-NCD-1].

ACKNOWLEDGMENTS

We would like thank the following individuals for their expertise extended toward the project: J. S. Chopra, S. K. Das, Prabhakar S., Narendra K. Arora, Anand Krishnan, M. Gourie-Devi (ICMR scientific experts), Prathiba Karanth, Sunil Kumar Ravi, and Annamma George. We would also like to thank the following people/organizations for providing us with permission to use and adapt the tests wherever required: John R. Hodges for ACE-III, SangYun Kim for Trail Making Test-B&W, Anitha M. Hubley for MTCF, and P. S. Mathuranath for PNT.

REFERENCES

1. Prince M, Wimo A, Guerchet M, Ali GC, Wu YT, Prina M. *Alzheimer's Disease International: World Alzheimer Report 2015: The Global Impact of Dementia: An Analysis of Prevalence, Incidence, Cost and Trends 2015.* London: Alzheimer's Disease International (2019).
2. Shah H, Albanese E, Duggan C, Rudan I, Langa KM, Carrillo MC, et al. Research priorities to reduce the global burden of dementia by 2025. *Lancet Neurol.* (2016) 15:1285-94. doi: 10.1016/S1474-4422(16)30235-6
3. Prince M. Dementia in developing countries. A consensus statement from the 10/66 Dementia Research Group. *Int J Geriatr Psychiatry.* (2000) 15:14-20. doi: 10.1002/(sici)1099-1166(200001)15:1<14::aid-gps70>3.0.co;2-8
4. Sousa RM, Ferri CP, Acosta D, Albanese E, Guerra M, Huang Y, et al. Contribution of chronic diseases to disability in elderly people in countries with low and middle incomes: a 10/66 Dementia Research Group population-based survey. *Lancet.* (2009) 374:1821-30. doi: 10.1016/S0140-6736(09)61829-8

5. Sosa-Ortiz AL, Acosta-Castillo I, Prince MJ. Epidemiology of dementias and Alzheimer's disease. *Arch Med Res.* (2012) 43:600-8. doi: 10.1016/j.arcmed.2012.11.003
6. Shaji KS, Jotheeswaran AT, Girish N, Srikala Bharath AD, Meera Pattabiraman and Mathew Varghese. *The Dementia India Report: Prevalence, Impact, Costs and Services for Dementia*. New Delhi: Alzheimer's & Related Disorders Society of India (ARDSI) (2010)
7. Das SK, Pal S, Ghosal MK. Dementia: Indian scenario. *Neurol India.* (2012) 60:618. doi: 10.4103/0028-3886.105197
8. Llibre Rodriguez JJ, Ferri PC, Acosta D, Guerra M, Huang Y, Jacob KS, et al. Prevalence of dementia in Latin América, India, and China: a population-based crosssectional survey. *Lancet.* (2008) 372:464-74. doi: 10.1016/S0140-6736(08)61002-8
9. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and meta-analysis. *Alzheimers Dement.* (2013) 9:63-75. doi: 10.1016/j.jalz.2012.11.007
10. Lang L, Clifford A, Wei L, Zhang D, Leung D, Augustine G, et al. Prevalence and determinants of undetected dementia in the community: a systematic literature review and a meta-analysis. *BMJ Open.* (2017) 7:e011146. doi: 10.1136/bmjopen-2016-011146
11. Chandra V, Ganguli M, Ratcliff G, Pandav R, Sharma S, Gilby J, et al. Studies of the epidemiology of dementia: comparisons between developed and developing countries. *Aging Clin Exp Res.* (1994) 6:307-21. doi: 10.1007/BF03324258
12. Ganguli M, Ratcliff G, Chandra V, Sharma S, Gilby J, Pandav R, et al. A Hindi version of the MMSE: the development of a cognitive screening instrument for a largely illiterate rural elderly population in India. *Int J Geriatr Psychiatry.* (1995) 10:367-77. doi: 10.1002/gps.930100505
13. Hall KS, Hendrie HC, Brittain HM, Norton JA, Rodgers DD, Prince CS, et al. The development of a dementia screening interview in 2 distinct languages. *Int J Methods Psychiatr Res*. (1993) 3:1–28.
14. Sosa AL, Albanese E, Stephan BC, Dewey M, Acosta D, Ferri CP, et al. Prevalence, distribution, and impact of mild cognitive impairment in Latin America, China, and India: a 10/66 population-based study. *PLoS Med.* (2012) 9:e1001170. doi: 10.1371/journal.pmed.1001170
15. Sotaniemi M, Pulliainen V, Hokkanen L, Pirttilä T, Hallikainen I, Soininen H, et al. CERAD-neuropsychological battery in screening mild Alzheimer's disease. *Acta Neurol Scand.* (2012) 125:16-23. doi: 10.1111/j.1600-0404.2010.01459.x
16. Tripathi R, Kumar JK, Bharath S, Marimuthu P, Varghese M. Clinical validity of NIMHANS neuropsychological battery for elderly: a preliminary report. *Indian J Psychiatry.* (2013) 55:279. doi: 10.4103/0019-5545.117149
17. Mungas D, Reed BR, Crane PK, Haan MN, González H. Spanish and English neuropsychological assessment scales (senas): further development and psychometric characteristics. *Psychol Assess.* (2004) 16:347. doi: 10.1037/1040-3590.16.4.347
18. Hachinski V, Iadecola C, Petersen RC, Breteler MM, Nyenhuis DL, Black SE, et al. National Institute of Neurological Disorders and Stroke—Canadian stroke network vascular cognitive impairment harmonization standards. *Stroke.* (2006) 37:2220-41. doi: 10.1161/01.STR.0000237236.88823.47
19. Zhang ZX, Zahner GE, Roman GC, Liu XH, Wu CB, Hong Z, et al. Socio-demographic variation of dementia subtypes in China: methodology and results of a prevalence study in Beijing, Chengdu, Shanghai, and Xian. Neuroepidemiology. (2006) 27:177-87. doi: 10.1159/000096131
20. Rajkumar S, Kumar S, Thara R. Prevalence of dementia in a rural setting: a report from India. *Int J Geriatr Psychiatry.* (1997) 12:702-7. doi: 10.1002/(sici)1099-1166(199707)12:7<702::aid-gps489>3.0.co;2-h
21. Chandra V, Ganguli M, Pandav R, Johnston J, Belle S, DeKosky ST. Prevalence of Alzheimer's disease and other dementias in rural India: the Indo-US study. *Neurology.* (1998) 51:1000-8. doi: 10.1212/WNL.51.4.1000
22. Vas CJ, Pinto C, Panikker D, Noronha S, Deshpande N, Kulkarni L, et al. Prevalence of dementia in an urban Indian population. *Int Psychogeriatr.* (2001) 13:439. doi: 10.1017/S1041610201007852
23. Raina SK, Razdan S, Pandita KK. Prevalence of dementia in ethnic Dogra population of Jammu district, North India: a comparison survey. *Neurol Asia.* (2010) 15:65-9.
24. Saldanha D, Mani MR, Srivastava K, Goyal S, Bhattacharya D. An epidemiological study of dementia under the aegis of mental health program, Maharashtra, Pune chapter. *Indian J Psychiatry.* (2010) 52:131. doi: 10.4103/0019-5545.64588
25. Farina N, Hughes LJ, Griffiths AW, Parveen S. Adolescents' experiences and perceptions of dementia. *Aging Mental Health.* (2020) 24:1175-81. doi: 10.1080/13607863.2019.1613343
26. Alladi S, Hachinski V. World dementia: one approach does not fit all. *Neurology.* (2018) 91:264-70. doi: 10.1212/WNL.0000000000005941
27. Ali GC, Ryan G, De Silva MJ. Validated screening tools for common mental disorders in low and middle income countries: a systematic review. *PLoS ONE.* (2016) 11:e0156939. doi: 10.1371/journal.pone.0156939
28. Iyer GK, Paplikar A, Alladi S, Dutt A, Sharma M, Mekala S, et al. Standardising dementia diagnosis across linguistic and educational diversity: study design of the Indian council of medical research-neurocognitive tool box (ICMR-NCTB). *J Int Neuropsychol Soc.* (2019) 12:1-5. doi: 10.1017/S1355617719001127
29. Menon RN, Varghese F, Paplikar A, Mekala S, Alladi S, Sharma M, et al. Validation of Indian council of medical research neurocognitive tool box in diagnosis of mild cognitive impairment in India: lessons from a harmonization process in a linguistically diverse society. *Dement Geriatr Cogn Disord*. (2020) 49:355–64. doi: 10.1159/000512393
30. Kalaria RN, Maestre GE, Arizaga R, Friedland RP, Galasko D, Hall K, et al. Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. *Lancet Neurol.* (2008) 7:812-26. doi: 10.1016/S1474-4422(08)70169-8
31. Kim HJ, Baek MJ, Kim S. Alternative type of the trail making test in nonnative English-speakers: the trail making test-black and white. *PLoS ONE.* (2014) 9:e89078. doi: 10.1371/journal.pone.0089078
32. Lezak MD, Howieson DB, Loring DW, Fischer JS. *Neuropsychological Assessment*. Oxford University Press (2004).
33. Das SK, Banerjee TK, Mukherjee CS, Bose P, Biswas A, Hazra A, et al. An urban community-based study of cognitive function among non-demented elderly population in India. *Neurol Asia.* (2006) 11:37-48.
34. Hubley AM. The modified Taylor complex figure: a comparable measure to the Rey-Osterrieth figure. *Arch Clin Neuropsychol.* (1999) 8:734. doi: 10.1016/S0887-6177(99)80225-X
35. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res.* (1982) 17:37-49. doi: 10.1016/0022-3956(82)90033-4
36. Mathuranath PS, George A, Cherian PJ, Mathew R, Sarma PS. Instrumental activities of daily living scale for dementia screening in elderly people. *Int Psychogeriatr.* (2005) 17:461. doi: 10.1017/S1041610205001547
37. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. *Neurology.* (1994) 44:2308. doi: 10.1212/WNL.44.12.2308
38. Jorm AF, Korten AE. Assessment of cognitive decline in the elderly by informant interview. *Br J Psychiatry.* (1988) 152:209-13. doi: 10.1192/bjp.152.2.209
39. Ware JE, Snow KK, Kosinski M, et al. *SF-36 Health Survey Manual and Interpretation Guide*. Boston, MA: New England Medical Center; The Health Institute (1993).
40. Mekala S, Paplikar A, Mioshi E, Kaul S, Divyaraj G, Coughlan G, et al. Dementia diagnosis in seven languages: the Addenbrooke's cognitive examination-III in India. *Arch Clin Neuropsychol.* (2020) 35:528-38. doi: 10.1093/arclin/acaa013
41. Morris JC. Current vision and scoring rules the clinical dementia rating (CDR). *Neurology*. (1993) 43:2412–4. doi: 10.1212/wnl.43.11.2412-a
42. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th Ed. Washington, DC: American Psychiatric Association (1994).
43. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack Jr CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* (2011) 7:263-9. doi: 10.1016/j.jalz.2011.03.005
44. Román GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, et al. Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. *Neurology.* (1993) 43:250. doi: 10.1212/WNL.43.2.250

45. Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain.* (2011) 134:2456-77. doi: 10.1093/brain/awr179
46. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med.* (2004) 256:183-94. doi: 10.1111/j.1365-2796.2004.01388.x
47. Gifford DR, Cummings JL. Evaluating dementia screening tests—methodological standards to rate their performance. *Neurology.* (1999) 52:224-227. doi: 10.1212/WNL.52.2.224
48. Kuzmickiene J, Kaubrys G. Specific features of executive dysfunction in Alzheimer-type mild dementia based on Computerized Cambridge Neuropsychological Test Automated Battery (CANTAB) Test results. *Med Sci Monit.* (2016) 22:3605. doi: 10.12659/MSM.900992
49. Dubois B, Feldman HH, Jacova C, DeKosky ST, Barberger-Gateau P, Cummings J, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS—ADRDA criteria. *Lancet Neurol.* (2007) 6:734-46. doi: 10.1016/S1474-4422(07)70178-3
50. Takada LT, Caramelli P, Fichman HC, Porto CS, Bahia VS, Anghinah R, et al. Comparison between two tests of delayed recall for the diagnosis of dementia. *Arquivos de Neuro-psiquiatria.* (2006) 64:35-40. doi: 10.1590/S0004-282X2006000100008
51. Mungas D, Reed BR, Farias ST, Decarli C. Criterion-referenced validity of a neuropsychological test battery: equivalent performance in elderly Hispanics and non-Hispanic Whites. *J Int Neuropsychol Soc.* (2005) 11:620. doi: 10.1017/S1355617705050745
52. Stewart R, Guerchet M, Prince M. Development of a brief assessment and algorithm for ascertaining dementia in low-income and middle-income countries: the 10/66 short dementia diagnostic schedule. *BMJ Open.* (2016) 6:e010712. doi: 10.1136/bmjopen-2015-010712
53. Chen X, Wong A, Ye R, Xiao L, Wang Z, Lin Y, et al. Validation of NINDS-CSN neuropsychological battery for vascular cognitive impairment in Chinese stroke patients. *BMC Neurol.* (2015) 15:1-6. doi: 10.1186/s12883-015-0270-z
54. Mori E, Yoneda Y, Yamashita H, Hirono N, Ikeda M, Yamadori A. Medial temporal structures relate to memory impairment in Alzheimer's disease: an MRI volumetric study. *J Neurol Neurosurg Psychiatry.* (1997) 63:214-21. doi: 10.1136/jnnp.63.2.214
55. Moorhouse P, Song X, Rockwood K, Black S, Kertesz A, Gauthier S, et al. Executive dysfunction in vascular cognitive impairment in the consortium to investigate vascular impairment of cognition study. *J Neurol Sci.* (2010) 288:142-6. doi: 10.1016/j.jns.2009.09.017
56. Harciarek M, Cosentino S. Language, executive function and social cognition in the diagnosis of frontotemporal dementia syndromes. *Int Rev Psychiatry.* (2013) 25:178-96. doi: 10.3109/09540261.2013.763340

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

BRIEF RESEARCH REPORT
published: 19 November 2021
doi: 10.3389/fneur.2021.599378

Two Sides of the Same Coin: Fluid Intelligence and Crystallized Intelligence as Cognitive Reserve Predictors of Social Cognition and Executive Functions Among Vulnerable Elderly People

Natalia Salas[1], *Josefina Escobar*[2] *and David Huepe*[2]*

[1] *Facultad de Educación, Psicología y Familia, Universidad Finis Terrae, Santiago, Chile,* [2] *Center for Social and Cognitive Neuroscience, School of Psychology, Universidad Adolfo Ibáñez, Santiago, Chile*

OPEN ACCESS

Edited by:
Christopher Butler, University of Oxford, United Kingdom

Reviewed by:
Prasanta Panigrahi, Indian Institute of Science Education and Research Kolkata, India
Chemin Lin, Chang Gung Memorial Hospital, Taiwan

***Correspondence:**
David Huepe
david.huepe@uai.cl

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: *27 August 2020*
Accepted: *14 October 2021*
Published: *19 November 2021*

Citation:
Salas N, Escobar J and Huepe D (2021) Two Sides of the Same Coin: Fluid Intelligence and Crystallized Intelligence as Cognitive Reserve Predictors of Social Cognition and Executive Functions Among Vulnerable Elderly People. Front. Neurol. 12:599378. doi: 10.3389/fneur.2021.599378

The concept of cognitive reserve –CR– postulates two forms that prevent cognitive impairment: neural reserve and neural compensation. Both have been primarily linked to the protective role played by genetic factors, educational level, occupation or socioeconomic status. Though it is true that it has been related to executive functions, so far very little attention has been paid to its predictive capacity with other variables more related to social cognition and psychosocial adaptation. Considering socially vulnerable contexts with reduced cultural capital and educational levels, the neural reserve function would be the most relevant and best predictor of aspects related to social cognition and executive functions. We suggest that variables such as fluid and crystallized intelligence influence social cognition and executive functions. This study included a sample of 27 participants over 60 years old from varied contexts of social vulnerability. The procedure included data collection using various cognitive measures. Results show that elderly people with high intelligence—mainly fluid intelligence—have better executive functions, emotional recognition and theory of mind. These results focus on cognitive reserve and its importance because they show that elderly people in vulnerable contexts who strengthen these aspects protect themselves against the deterioration of cognitive skills. This study is the first preliminary research to present a relationship between cognitive reserve and social cognition factors in elderly subjects. Fluid intelligence functions as a highly related factor to protect the performance of executive functions, along with other social-cognitive factors relevant to facilitating the conditions of social adaptation.

Keywords: cognitive reserve, fluid intelligence, crystallized intelligence, social cognition, executive functions

INTRODUCTION

The concept of cognitive reserve –CR– (1, 2) involves two forms of protective actions. The first, known as the neural reserve, states that pre-existing brain networks that are more efficient or have a greater capacity may be less modifiable. On the other hand, it can operate as a neural compensation system where alternative networks can compensate for the disruption of pre-existing pathology networks. Thus, CR has mainly been linked to the protective role of education, occupation, or socio-economic status against cognitive impairment and very little attention has been paid to its moderating role, among other variables like social cognition, since it not only incorporates environmental aspects but also intrinsic body actions [concept differs "brain reserve capacity" - BRC - of (3)]. Epidemiological evidence suggests that individuals with higher fluid intelligence (FI), education, occupational level, or participation in leisure activities have a lower risk of developing Alzheimer's disease (AD) and other neurodegenerative diseases (2). According to the above, we wanted to know which of these components, considered part of the cognitive reserve, better predict social adaptation capabilities. So far, no studies are known to have tested this question. SC and EF refer to the quality of life in terms of social and relational activities, as well as the subjective well-being of an individual in a given context, which, in turn, is a crucial skill for proper development and adaptation in contexts of social vulnerability. This concept includes multiple dimensions such as social behavior, emotional regulation and the development of social habits (4, 5). Psychosocial functioning represents an ecological approach to everyday adaptation and cognitive contexts interrelating cognition and emotion (6). We suggest that variables such as fluid intelligence (FI) and crystallized intelligence (CrI), as part of CR, influence social cognition (SC), emotional recognition (ER), and executive functions (EF) in vulnerable contexts.

Some Aspects on Elderly Chileans and Vulnerable Contexts

Chile has 2.8 million people 60 years of age and older [16.2% of the total Chilean population; (7)]. According to the Chilean National Health Survey 2009–2010 (8), prevalence of cognitive impairment in this group was 10.4% and it rises rapidly with advancing age (12.8% for people 70–79 years old and 20.9% for 80 years and over). Moreover, this prevalence is much higher among older adults living in contexts of social and economic vulnerability and with low educational levels; 39% had some degree of disability. From a socioeconomic standpoint, 44% of disabled people in Chile belong to low socioeconomic sectors. Older adults account for 44.3% of disabled people, with a high percentage having low levels of education [69.6% according to (9)]. The same trend was seen in the educational level, where prevalence of cognitive impairment was 5.6 times higher among less educated adults than among those with higher educational levels (8). Disability to perform in daily life among the elderly has the same distribution by socioeconomic and educational levels; which means that the poorest and least educated have a higher prevalence of disability to perform in everyday life (9). There is also a high prevalence of depression in Chile (17.5% according to the latest National Health Survey ENS Chile from 2009 to 2010), especially so among older adults (10) in vulnerable conditions (11). This is relevant, given the association between depression and development of dementia (12), for example. Among diseases associated with cognitive impairment, in Chile Alzheimer's disease is the leading cause of dementia in older adults. Its incidence increases with age (1–2% of the people aged 60 years, 3–5% of people 70, in 15–20% of people 80 years and one-third or half of those over 85). Its clinical course generally begins with failures in recent memory and ends with total dependence (13). Chilean authorities consider factors such as low education and low levels of culture (low-income patients from vulnerable and rural contexts) to be social determinants of this kind of disease (14). Social vulnerability is understood as a set of social characteristics that put a group of people who live in contexts of lower economic resources and at high risk of falling into poverty in a situation of structural, material and personal inequality (15, 16). Typically, these populations have low cultural and educational capital, limited access to goods and services, lower quality of social benefits (health, education, housing), higher levels of social deprivation, more impoverished social environments, and unsafe neighborhoods, effectively lowering the quality of life of their inhabitants compared to the general population (17, 18). For example, it is known that environments of lower social capital or poverty are more likely to be exposed to higher toxins and pollutants, crime and traffic and have fewer chances to participate in physical activities, less access to healthy food, greater likelihood of living in chaotic homes, more violence and lower parental sensitivity (19). Thus, exposure to multiple stressors, that is, various risk factors, has greater side-effects on cognitive abilities than exposure to a single risk (20, 21).

Cognitive Reserve and Social Cognition as Associated Factors to Psychosocial Adaptation (PSA)

The term psychosocial adaptation (PSA) refers to quality of life in terms of social and relational activities. This concept includes multiple dimensions such as social behavior, emotional regulation, and the development of social habits (4, 5). PSA represents an ecological approach to everyday and cognitive-contextual adaptation, in which cognition and emotion are interrelated (6). Within PSA, social cognition (SC), fluid, and crystalized intelligence (FI; CrI) play a highly significant part, particularly in decision-making, emotional processing, and the way we relate to others (empathy and theory of mind). Research suggests that the prefrontal cortex plays a major role in such adaptability, given its involvement in the flexibility of behavior, executive functions (EF), FI and SC (22, 23). It should be noted that not all EF are related to FI (24–26). Similarly, SC tasks and FI (27, 28) or mental flexibility have been associated with this area (29, 30). Damage or alterations in the frontal lobe have direct implications on these functions, resulting

mainly in maladaptive behaviors. SC includes the ability to make decisions, emotional processing, the ability to understand others' intentions and to develop in the social world (31). Studies in this line have shown that the social context exerts a profound influence on SC (32, 33). Meanwhile, FI has been defined as the ability to think logically and solve problems in new situations, regardless of the acquisition of knowledge. This reflects the ability to reason and think abstractly, in contrast to what is called crystallized intelligence (CrI) (34), which depends on cultural and academic learning. From a neuroanatomical viewpoint, FI has been associated with frontal lobe functions (27). Injuries in this area affect the performance of these cognitive abilities (28, 35) and studies that have measured FI with functional neuroimaging have shown activation of frontal areas (36, 37). FI has been linked as a protective factor for mental health, violent conditions and PSA (38). On the other hand, CrI is known as the ability to use skills, knowledge, and experience (39), relying on accessing information from long-term memory. As McGrew (40) establishes, it "is primarily a store of verbal or language-based declarative (knowing what) and procedural (knowing how) knowledge acquired through the investment of other abilities during formal and informal educational and general life experiences" (p. 5). According to this, CrI is indicated by a person's depth and breadth of general knowledge, vocabulary, and the ability to reason using words and numbers. As such it is also viewed as the product of educational and cultural experience in interaction with FI. One relevant element is that it changes with age (41, 42). For example, research on individuals over the age of 60 showed that many abilities indeed show average decline rates (43–45). Thus, given the description of SC, FI and CrI, this gains relevance as protective factors in aging, in addition to cognitive reserve (CR). In this sense, the CR can be defined as "differences in cognitive processes as a function of lifetime intellectual activities and other environmental factors that explain differential susceptibility to functional impairment in the presence of pathology or other neurological insult" [(46) p. 502]. CR acquires importance since it proposes two forms of protective actions (1, 2). Neural reserve refers to pre-existing brain networks that are more efficient or have a greater capacity but are less susceptible to change. It can also operate like an alternative neural network that compensates for the disruption of pre-existing pathology networks. Despite the fact that CR has mainly been linked to the protective role in everyday activities, as well in education, work, or socio-economic status against cognitive impairment (47), literature on SC shows that very little attention has been paid to its moderating role. It has even been suggested that there is no relationship (48, 49). This is interesting, considering that it incorporates environmental aspects as well as intrinsic body actions [concept differs "brain reserve capacity" (BRC) of (3)]. Epidemiological studies have shown that individuals with higher FI, educational and occupational levels or leisure-related activities have a lower risk of developing AD and other neurodegenerative diseases (2). In the same way, SC has been associated with positive outcomes in aging. On the one hand, factors such as positive life events and social support, have proven to influence and increase survival rates in patients with dementia compared to subjects living in poor conditions (50). Similarly, Fratiglioni et al. (51) have found that the construction of social networks with poor or limited support increased the risk of dementia by 60% and that there is a link between variables such as isolation, feelings of social isolation, educational level, among other lifestyles, that accelerate or delay the occurrence dementia (52, 53). These can be seen as protective factors, but with an active role (1) based on neural networks. On the other hand, evidence from epidemiological research suggests that higher FI, high educational and occupational levels (better jobs), being active in leisure activities or larger social networks, have a lower risk of developing, for example, Alzheimer's disease (AD) or dementia (54, 55). Therefore, we understand that people with better social adaptability, given their greater social cognition, will be more resistant to neurodegenerative diseases, either due to the existence of a more functional network or a larger brain capacity to involve alternative networks. There are known risks factors for neurodegenerative diseases such as genetic or medical conditions, other neurological pathologies, or brain injuries. Nevertheless, the role of social variables have been studied less formally and are less understood, especially considering only individual factors (56). One possible hypothesis about the relationship between CR and FI is that other protective social and cultural factors could modulate the adaptation process, benefiting from the social and cognitive conditions that people possess, such as social support and social networks, demographic aspects, educational level, among others. Although the concepts of CR, CrI and FI differ in important respects, they are complementary as opposed to competing. Accordingly, the study of social factors as predictors of the delay or acceleration of neurodegenerative diseases is essential and we sought to fill a gap in previous research by conducting a study to find the relationship between fluid intelligence (FI) and crystallized intelligence (CrI), and as complementary factor with cognitive reserve (CR), as well as their relationship to social cognition (SC), emotional recognition (ER) and executive function (EF) in older adults in socially vulnerable contexts. In addition, we want to go into greater depth and answer the question of which of these two types variables (FI or CrI) better predicts social adaptive capacity. We suggest that FI and CrI, are associated with aspects of SC, such as emotional recognition and theory of mind (ToM), in addition to EF; and could strength cognitive process that are crucial for CR. All these aspects could influence the processes of social adaptation and thus the possibility to the adjustment of the elderly in vulnerable contexts. CR is often estimated using proxy variables for lifetime exposures and cognitive activity: years of education, measures of crystallized intelligence, such as vocabulary or knowledge, literacy level, number of intellectually stimulating leisure activities, degree of occupational complexity, and socioeconomic status are all commonly used to create an estimate of CR (1). According to the above, FI and Crl are variables that we propose to use as a synthetic way to explain a broader construct of CR (since both variables are components of CR).

METHODS

Participants

All twenty-seven participants in this study were in healthy conditions, over 60 years old ($M = 66.44$, $SD = 6.59$; 55.6% male) and recruited from contexts of social vulnerability. Given that they come from contexts of high social risk (poverty and insecurity), they are participants who are very difficult access. They come from families currently participating in a Chilean Social Security Program—CSPP—implemented by the Chilean Ministry of Social Development. All participants signed an informed consent, following the protocol of the Declaration of Helsinki. Participation was voluntary, protecting participants' anonymity. The following exclusion criteria were considered: individuals with visual and/or hearing impairment that prevents them from performing the various tasks and measurements in the study; and a psychiatric or neurological background representing an impediment to the evaluation of the protocol, assessed in an initial interview.

MEASURES AND PROCEDURE

The procedure included direct telephone contact, with the help CSPP agencies, and data collection by members of the program, who had been previously trained in the measures taken. A house for neighborhood meetings (local area) was the setting for data collection and the interview considered a research assistant to complete the instruments. The study protocol included: Executive functions (EF), measured with INECO Frontal Screening –IFS- (57, 58), a brief tool that evaluates EF through different domains: programming tasks Motorboat; conflictual instructions, inhibitory verbal control, abstraction, back span of digits for working memory space, and Go / No Go testing. It is a very sensitive instrument and has been tested in patients with frontal and neuropsychiatric disorders and injuries. To measure Fluid and crystallized intelligence (FI and CrI), we used the Wechsler Adult Intelligence Scale III (WAIS-III) (59) and ran two subtests, progressive matrices and vocabulary. We obtained a total score for each subtest from each scale. The progressive matrices represent FI and from vocabulary test, we calculated CrI. Additionally, years of education also was used as a proxy for CrI (as a second variable) and Theory of Mind (ToM) was measured with Reading the Mind in the Eyes Test (60, 61). This battery evaluates ToM, through 28 pictures of faces of people where only the area around the eyes is visible;. Emotional recognition was tested with the Mini-Sea (62). This instrument is built around two subtests: (a) a facial emotion recognition test (from Ekman pictures; scored from 0 to 15) in which participants must identify which emotion is being expressed; and (b) a shortened version of the Faux Pas recognition test (63) to evaluate emotional recognition. Inhibitory verbal control was measured because it could be linked to emotional regulation and adaptation (64, 65). For that purpose, we used the Hayling Test (66), consisting in two parts: (a) concentrated attention, verbal initiation, processing speed and the strategy of a well-succeeded search for automated words; and (b) EF components, such as verbal inhibition and planning (the individual must inhibit the content of the sentence).

Statistical Analysis

We obtained descriptive statistics (central trend and dispersion measurements) and subsequently calculated Pearson's correlation coefficients to evaluate the independency between variables. A Kolgomorov-Smirnov Test was conducted to test for normal distribution. We worked with p level of < 0.05 (two-tailed) to confirm bivariate correlations. In addition, we quantified the evidence to support the alternative hypothesis by computing a Bayes factor for the specific effect of crystallized and fluid intelligence on: (a) EF score; (b) total emotional recognition score; (c) ToM; and (d) inhibitory verbal control. Bayes factor analysis for each prediction will yield very strong evidence to support the alternative expected effect on main interest variables when BF10 $>$ 30 and $\leq$ 100; strong when BF10 $>$ 10 and $\leq$ 30; and moderate evidence if it is between BF10 $>$ 3 and BF $\leq$ 10 [assuming a uniform distribution of priors; see (67, 68)].

RESULTS

Descriptive statistics are shown in **Table 1**, where one can see that almost all the scores for each test are above the median point of the maximum obtained for its scale (with de exception of inhibitory verbal control and CrI). In **Figure 1**, Cognitive reserve (CR) variables –FI and CrI—show associations with social and cognitive variables. The most important effect found was between FI and ToM ($r = 0.56$, $p < 0.01$; $BF_{10} = 34.48$, very strong evidence) and next with executive functions ($r = 0.42$, $p < 0.05$; $BF_{10} = 4.59$, moderate evidence), inhibitory verbal control ($r = 0.42$, $p < 0.05$; $BF_{10} = 4.42$, moderate evidence)

TABLE 1 | Mean, standard deviations, median and minimum-maximum for each interest variable.

	Executive function	Emotional recog.	ToM	Inhibitory verbal control	Crystallized intell (years education)	Crystallized intell (vocab.)	Fluid intelli.
Mean	17.72	19.65	7.593	16.44	6.852	21.00	8.593
Std. deviation	4.163	5.321	2.606	11.28	3.870	7.514	3.153
Median	18.00	20.50	8.00	14.00	6.00	20.00	8.00
Minimum	9.00	9.00	2.00	1.00	0.00	9.00	4.00
Maximum	25.00	29.00	12.00	41.00	16.00	35.00	16.00

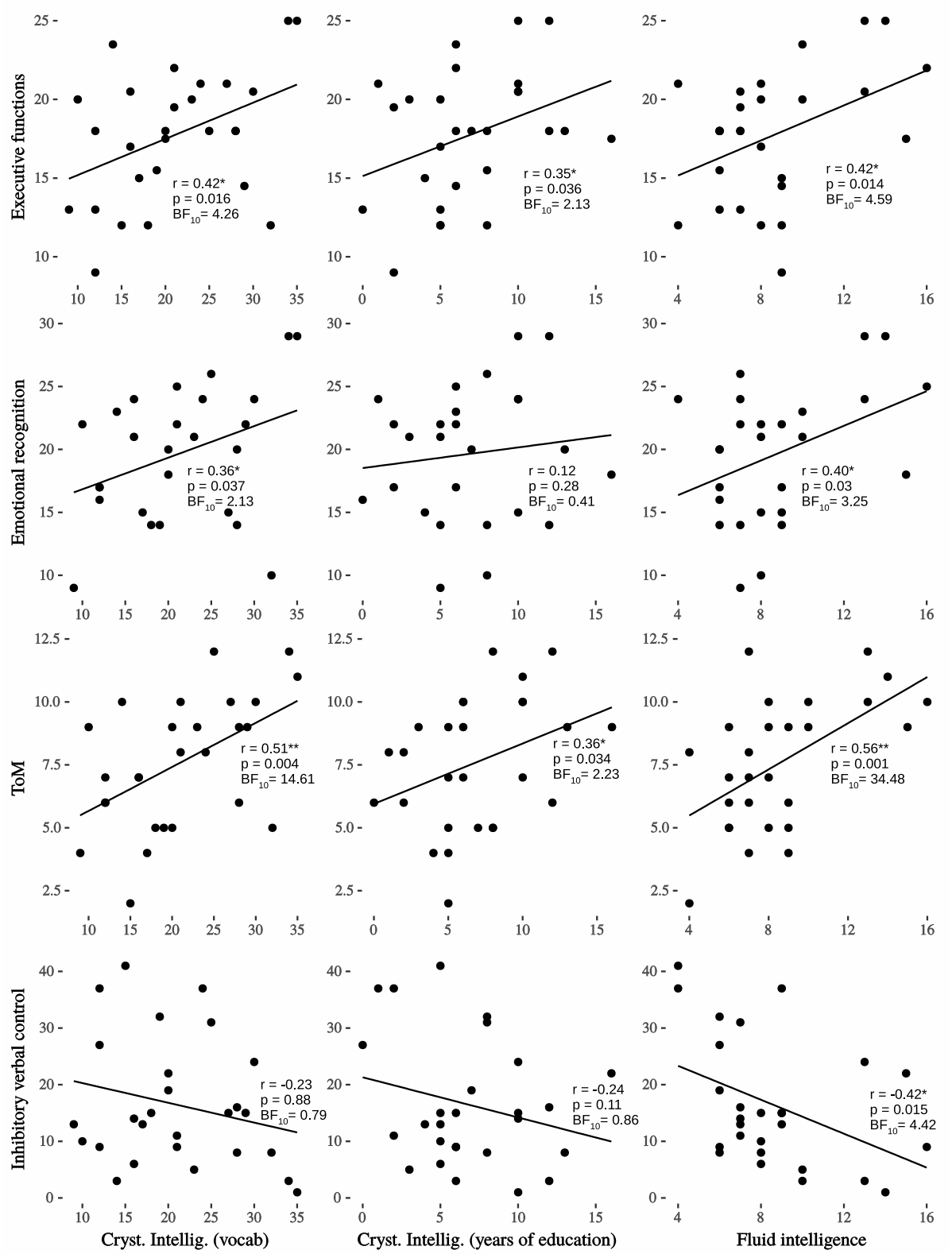


FIGURE 1 | Regression lineal, Pearson's r and Bayesian factor between crystallized and fluid intelligence on interest variables. Very strong evidence between fluid intelligence and ToM; moderate evidence with executive functions, inhibitory verbal control and emotional recognition; strong evidence between crystallized intelligence (vocabulary) and ToM; moderate evidence between crystallized intelligence (vocabulary) and executive functions; $^{*}p < 0.05$; $^{**}p < 0.01$.

and emotional recognition ($r = 0.40$, $p < 0.05$; $BF_{10} = 3.25$, moderate evidence). On the other hand, and taking the Bayes factor into account, only crystallized intelligence (vocabulary) was significantly associated with ToM ($r = 0.51$, $p < 0.01$; $BF_{10} = 14.61$, strong evidence) and executive functions ($r = 0.42$, $p < 0.05$; $BF_{10} = 4.26$, moderate evidence). On the other hand, it is known that fluid intelligence and age are variables typically that have been inversely associated (15, 41, 69, 70). Before age 50 ability such as processing speed, memory, and reasoning begins to decline (71). To control the effect of the age, we calculate partial correlation for each variable of the interest, adjusting for age. Outcomes show that all correlations remained statistically significant (one-tailed): FI – FE, $r = 0.41$, $p = 0.019$; FI – ToM, $r = 0.56$, $p = 0.001$; FI – Emotional recognition, $r = 0.35$, $p = 0.043$; and inhibitory verbal control, $r = -0.40$, $p = 0.021$.

CONCLUSION AND FUTURE DIRECTIONS

This study shows that elderly individuals living in vulnerable contexts in Chile and with high intelligence -mainly fluid intelligence- have better executive functions, emotional recognition and theory of mind (ToM). This is the first preliminary research to present a relationship between cognitive reserve (CR), social cognition (SC) and executive function (EF) in elderly subjects who live in vulnerable contexts. As seen in the results, FI functions as a factor highly related to the improvement of EF shown by the subjects measured, along with other SC factors relevant in the probability of enhanced psychosocial adaptation (PSA). These results focus on cognitive reserve (IF and CrI connected to SC) and their possible protective effects in vulnerable contexts. We can say that older people in vulnerable contexts who strengthen these aspects (through CR) protect the deterioration of some cognitive and social abilities (72–74). Social interactions that promote the resolution of everyday situations (that is, FI) allow the brain to continue with the demands it has become accustomed to since birth. The exercise of cognitive aspects and the use of cognitive functions such as attention, memory and planning to solve day-to-day dilemmas function as protective factors in vulnerable contexts. This could also be because these contexts present multiple challenges that are approached from social and cognitive abilities and which generate greater social adaptation. Furthermore, social contact skills are essential for collaborative work and the joint construction of learning (75). Elderly people who adapt and continue learning use CR as a key element. This study invites us to review social and health policies regarding the promotion of programs for the elderly that favor autonomy and continuity in decision-making by the elderly. Activities that favor the continuity of establishing relationships with others, which allow elderly people to face the resolution of daily dilemmas, seem to be key and should be informed to those health professionals who attend to them.

Further studies that relate cultural and social factors associated with neurodegenerative diseases are needed, but not just as mere descriptors. On the other hand, SC should be increasingly considered in research on neurodegenerative diseases, not only as a potential early marker, but also as a key factor to understanding how it can moderate and slow the disease manifests itself on a day-to-day basis. Fluid intelligence must be revealed in its protective role, especially from its educational potential, in the sense that learning instances in the elderly should be highly promoted. The same way, SC and EF appear to be relevant factors to improving adaptive capacities, particularly in vulnerable contexts. There is a need to methodologically bridge the study of PSA skills between external individual characteristics (social and cultural factors) and internal (genetic or hereditary predisposition) based on the concept of "CR," upon an active (neural networks) point of view.

Regarding the limitations of the present study, we can mention the small sample and the need for additional measurements to evaluate social adaptation. However, given the difficulty of access, and despite the small number of participants, it was still possible to robustly demonstrate the expected effects. In favor of this argument, other research types have been published with sample sizes similar to the present study (76–78). On the other hand, social adaptation was also considered through the protocol study that considered inclusion criteria associated with a population normally adapted to daily life.

In conclusion, this study has researched the positive effectiveness that CR has on SC and EF from an ecological perspective. Our results show that FI is the most relevant variable for predicting how elderly people adapt and function in their social environments.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Universidad Adolfo Ibáñez, Chile. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NS and DH participated in the development of the study, in data collection and analysis, in writing and editing the manuscript, and in giving final approval. JE worked on editing the language and made important contributions to the manuscript and made final comments. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by grants from National Scientific and Technological Research Commission (ANID/FONDECYT Regular No. 1201486 to DH and ANID/FONDECYT Iniciación No. 11190565 to JE). The funders had no role in the decision to publish, or preparation of the manuscript.

REFERENCES

1. Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. *J Int Neuropsychol Soc.* (2002) 8:448–60. doi: 10.1017/S1355617702813248
2. Stern Y. Cognitive reserve and Alzheimer disease. *Alzheimer Dis Assoc Dis.* (2006) 20:112–7. doi: 10.1097/01.wad.0000213815.20177.19
3. Satz P. Brain reserve capacity on symptom onset after brain injury: a formulation and review of evidence for threshold theory. *Neuropsychology.* (1993) 7:273. doi: 10.1037/0894-4105.7.3.273
4. Bishop AJ, Marteau TM, Hall S, Kitchener H, Hajek P. Increasing women's intentions to stop smoking following an abnormal cervical smear test result. *Prev Med.* (2005) 41:179–85. doi: 10.1016/j.ypmed.2004.09.046
5. Cox KS, Wilt J, Olson B, McAdams DP. Generativity, the Big Five, and psychosocial adaptation in midlife adults. *J Person.* (2010) 78:1185–208. doi: 10.1111/j.1467-6494.2010.00647.x
6. Wilson BA. Neuropsychological rehabilitation. *Annu Rev Clin Psychol.* (2008) 4:141–62. doi: 10.1146/annurev.clinpsy.4.022007.141212
7. Instituto Nacional de Estadistica I. *Censo de Población y Vivienda.* (2017). Available online at: https://redatam-ine.ine.cl/redbin/RpWebEngine.exe/Portal?BASE=CENSO_2002&lang=esp (accessed October 6, 2021)
8. Ministerio de Salud de Chile. *Encuesta Nacional de Salud ENS Chile 2009-2010.* (2010). Available online at: http://web.minsal.cl/portal/url/item/bcb03d7bc28b64dfe040010165012d23.pdf (accessed October 6, 2021).
9. Fondo Nacional de la discapacidad. *Primer Estuido Nacional de la Discapacidad en Chile*. Ministerio de Desarrollo Social y Familia, Gobierno de Chile (2005). Available online at: https://www.senadis.gob.cl/pag/136/1196/resultados_endisc_i (accessed October 6, 2021).
10. von Mühlenbrock F, Gómez R, González M, Rojas A, Vargas L, von Mühlenbrock C. Prevalencia de depresión en pacientes mayores de 60 años hospitalizados en el Servicio de medicina interna del hospital militar de santiago. *Rev Chil Neuro Psiquiatría.* (2011) 49:331–7. doi: 10.4067/S0717-92272011000400004
11. Ministerio de Salud de Chile. *Plan Nacional De demencia 2017.* (2017). Available online at: http://www.minsal.cl/wp-content/uploads/2017/11/PLAN-DE-DEMENCIA.pdf (accessed October 6, 2021).
12. Snowden MB, Atkins DC, Steinman LE, Bell JF, Bryant LL, Copeland C, et al. Longitudinal association of dementia and depression. *Am J Geriatric Psychiatry.* (2015) 23:897–905. doi: 10.1016/j.jagp.2014.09.002
13. Donoso A. La enfermedad de Alzheimer. *Rev Chil Neuro Psiquiatría.* (2003) 41:13–22. doi: 10.4067/S0717-92272003041200003
14. Servicio Nacional del Adulto Mayor. *Estudio Nacional de la Dependencia en las Personas Mayores.* (2010). Available online at: http://www.senama.cl/filesapp/EstudioNacionalde%0ADependenciaenlasPersonasMayores.pdf (accessed October 6, 2021).
15. Chaudhuri S. *Assessing Vulnerability to Poverty: Concepts, Empirical Methods and Illustrative examples*. New York, NY: Department of Economics; Columbia University (2003). Available online at: http://www.econdse.org/wp-content/uploads/2012/02/vulnerability-assessment.pdf (accessed October 6, 2021).
16. Henoch, P. *Vulnerabilidad Social. Más allá de la Pobreza*. Serie Informe Soc, (2010) 128. Available online at: https://archivos.lyd.org/other/files_mf/SISO-128-Vulnerabilidad-social-mas-alla-de-la-pobreza-PHenoch-Agosto2010.pdf (accessed October 6, 2021).
17. Neely-Prado A, Navarrete G, Huepe D. Socio-affective and cognitive predictors of social adaptation in vulnerable contexts. *PLoS ONE.* (2019) 14:1–23. doi: 10.1371/journal.pone.0218236
18. Ministerio de Desarrollo Social. *Informe de Desarrollo Social 2015*. Gobierno de Chile (2015). Available online at: http://www.desarrollosocialyfamilia.gob.cl/pdf/upload/IDS_INAL_FCM_3.pdf (accessed October 6, 2021).
19. Evans GW, Kim P. Childhood poverty and young adults' allostatic load: the mediating role of childhood cumulative risk exposure. *Psychol Sci.* (2012) 23:979–83. doi: 10.1177/0956797612441218
20. Evans GW, Kim P. Multiple risk exposure as a potential explanatory mechanism for the socioeconomic status–health gradient. *Ann N Y Acad Sci.* (2010) 1186:174–89. doi: 10.1111/j.1749-6632.2009.05336.x
21. Evans GW, Li D, Whipple SS. Cumulative risk and child development. *Psychol Bull.* (2013) 139:1342–96. doi: 10.1037/a0031808
22. Van Horn JD, Irimia A, Torgerson CM, Chambers MC, Kikinis R, Toga AW. Mapping connectivity damage in the case of phineas gage. *PLoS ONE.* (2012) 7:e37454. doi: 10.1371/journal.pone.0037454
23. Waters-Wood SM, Xiao L, Denburg NL, Hernandez M, Bechara A. Failure to learn from repeated mistakes: persistent decision-making impairment as measured by the iowa gambling task in patients with ventromedial prefrontal cortex lesions. *J Int Neuropsychol Soc.* (2012) 18:927–30. doi: 10.1017/S135561771200063X
24. Ardila A. Is intelligence equivalent to executive functions. *Psicothema.* (2018) 30:159–164.
25. Friedman NP, Miyake A, Corley RP, Young SE, DeFries JC, Hewitt JK. Not all executive functions are related to intelligence. *Psychological Science.* (2006) 17:172–9.
26. van Aken L, Kessels RPC, Wingbermühle E, van der Veld WM, Egger JIM. Fluid intelligence and executive functioning more alike than different? *Acta Neuropsychiatrica.* (2016) 28:31–7.
27. Duncan J, Burgess P, Emslie H. Fluid intelligence after frontal lobe lesions. *Neuropsychologia.* (1995) 33:261–8. doi: 10.1016/0028-3932(94)00124-8
28. Roca M, Parr A, Thompson R, Woolgar A, Torralva T, Antoun N, et al. Executive function and fluid intelligence after frontal lobe lesions. *Brain.* (2010) 133:234–47. doi: 10.1093/brain/awp269
29. Larquet M, Coricelli G, Opolczynski G, Thibaut F. Impaired decision making in schizophrenia and orbitofrontal cortex lesion patients. *Schizop Res.* (2010) 116:266–73. doi: 10.1016/j.schres.2009.11.010
30. Shamay-Tsoory SG, Aharon-Peretz J, Perry D. Two systems for empathy: a double dissociation between emotional and cognitive empathy in inferior frontal gyrus versus ventromedial prefrontal lesions. *Brain.* (2009) 132:617–27. doi: 10.1093/brain/awn279
31. Blakemore SJ, Winston J, Frith U. Social cognitive neuroscience: where are we heading? *Trends Cogn Sci.* (2004) 8:216–22. doi: 10.1016/j.tics.2004.03.012
32. Chung YS, Barch DM. The effect of emotional context on facial emotion ratings in schizophrenia. *Schizop Res.* (2011) 131:235–41. doi: 10.1016/j.schres.2011.05.028
33. Rankin KP, Salazar A, Gorno-Tempini ML, Sollberger M, Wilson SM, Pavlic D, et al. Detecting sarcasm from paralinguistic cues: anatomic and cognitive correlates in neurodegenerative disease. *NeuroImage.* (2009) 47:2005–15. doi: 10.1016/j.neuroimage.2009.05.077
34. Cattell RB. The theory of fluid and crystallized general intelligence checked at the 5–6 year-old level. *Brit J Educ Psychol.* (1967) 37:209–24. doi: 10.1111/j.2044-8279.1967.tb01930.x
35. Woolgar A, Parr A, Cusack R, Thompson R, Nimmo-Smith I, Torralva T, et al. Fluid intelligence loss linked to restricted regions of damage within frontal and parietal cortex. *Proc Natl Acad Sci USA.* (2010) 107:14899–902. doi: 10.1073/pnas.1007928107
36. Bishop S, Fossella J, Croucher C, Duncan J. COMT val158met genotype affects recruitment of neural mechanisms supporting fluid intelligence. *Cerebral Cortex.* (2008) 18:2132–40. doi: 10.1093/cercor/bhm240
37. Duncan J, Seitz RJ, Kolodny J, Bor D, Herzog H, Ahmed A, et al. A neural basis for general intelligence. *Science.* (2000) 289:457–60. doi: 10.1126/science.289.5478.457
38. Huepe D, Roca M, Salas N, Canales_Johnson A, Rivera_Rei AA, Zamorano L, et al. Fluid intelligence and psychosocial outcome: from logical problem solving to social adaptation. *PLoS ONE.* (2011) 6:e24858. doi: 10.1371/journal.pone.0024858
39. Cattell RB. Theory of fluid and crystallized intelligence: a critical experiment. *J Educ Psychol.* (1963) 54:1. doi: 10.1037/h0046743
40. McGrew KS. CHC theory and the human cognitive abilities project: standing on the shoulders of the giants of psychometric intelligence research. *Intelligence.* (2009) 37:1–10. doi: 10.1016/j.intell.2008.08.004
41. Horn JL, Cattell RB. Age differences in fluid and crystallized intelligence. *Acta Psychol.* (1967) 26:107–29. doi: 10.1016/0001-6918(67)90011-X
42. Belsky J. *The Psychology of Aging: Theory, Research, and Interventions*. Pacific Grove, CA: Brooks/Cole Pub. Co (1990).
43. Finkel D, Reynolds CA, McArdle JJ, Pedersen NL. Age changes in processing speed as a leading indicator of cognitive aging. *Psychol Aging.* (2007) 22:558. doi: 10.1037/0882-7974.22.3.558

44. Singer T, Verhaeghen P, Ghisletta P, Lindenberger U, Baltes PB. The fate of cognition in very old age: six-year longitudinal findings in the Berlin aging study (BASE). *Psychol Aging.* (2003) 18:318. doi: 10.1037/0882-7974.18.2.318
45. Whalley LJ, Deary IJ, Appleton CL, Starr JM. Cognitive reserve and the neurobiology of cognitive aging. *Ageing Res Rev.* (2004) 3:369–82. doi: 10.1016/j.arr.2004.05.001
46. Barulli D, Stern Y. Efficiency, capacity, compensation, maintenance, plasticity: emerging concepts in cognitive reserve. *Trends Cogn Sci.* (2013) 17:502–9. doi: 10.1016/j.tics.2013.08.012
47. Stern Y. Cognitive reserve. *Neuropsychologia.* (2009) 47:2015–28. doi: 10.1016/j.neuropsychologia.2009.03.004
48. Lavrencic LM, Churches OF, Keage HAD. Cognitive reserve is not associated with improved performance in all cognitive domains. *Appl Neuropsychol Adult.* (2018) 25:473–85. doi: 10.1080/23279095.2017.1329146
49. Lavrencic LM, Kurylowicz L, Valenzuela MJ, Churches OF, Keage HAD. Social cognition is not associated with cognitive reserve in older adults. *Aging Neuropsychol Cogn.* (2016) 23:61–77. doi: 10.1080/13825585.2015.1048773
50. Orrell M, Butler R, Bebbington P. Social factors and the outcome of dementia. *Int J Geriatric Psychiatry.* (2000) 15:515–20. doi: 10.1002/1099-1166(200006)15:6<515::AID-GPS147>3.0.CO;2-U
51. Fratiglioni L, Hui-Xin W, Ericsson K, Maytan M, Winblad B. Influence of social network on occurrence of dementia: a community-based longitudinal study. *Lancet.* (2000) 355:1315. doi: 10.1016/S0140-6736(00)02113-9
52. Eshkoor SA, Hamid TA, Nudin SSH, Mun CY. The effects of social support, substance abuse and health care supports on life satisfaction in dementia. *Soc Indic Res.* (2014) 116:535–44. doi: 10.1007/s11205-013-0304-0
53. Holwerda TJ, Deeg DJH, Beekman ATF, van Tilburg TG, Stek ML, Jonker C, et al. Feelings of loneliness, but not social isolation, predict dementia onset: results from the Amsterdam study of the elderly (AMSTEL). *J Neurol Neurosurg Psychiatry.* (2014) 85:135–42. doi: 10.1136/jnnp-2012-302755
54. Bennett DA, Schneider JA, Tang Y, Arnold SE, Wilson RS. The effect of social networks on the relation between Alzheimer's disease pathology and level of cognitive function in old people: a longitudinal cohort study. *Lancet Neurol.* (2006) 5:406–12. doi: 10.1016/S1474-4422(06)70417-3
55. Crooks VC, Lubben J, Petitti DB, Little D, Chiu V. Social network, cognitive function, and dementia incidence among elderly women. *Am J Public Health.* (2008) 98:1221–7. doi: 10.2105/AJPH.2007.115923
56. Andrew MK, Rockwood K. Social vulnerability predicts cognitive decline in a prospective cohort of older Canadians. *Alzheimer Dementia.* (2010) 6:319–25. doi: 10.1016/j.jalz.2009.11.001
57. Ihnen J, Antivilo A, Muñoz-Neira C, Slachevsky A. Chilean version of the INECO frontal screening (IFS-Ch): psychometric properties and diagnostic accuracy. *Dementia Neuropsychol.* (2013) 7:40–7. doi: 10.1590/S1980-57642013DN70100007
58. Torralva T, Roca M, Gleichgerrcht E, Lopez P, Manes F. INECO frontal screening (IFS): a brief, sensitive, and specific tool to assess executive functions in dementia–CORRECTED VERSION. *J Int Neuropsychol Soc.* (2009) 15:777–86. doi: 10.1017/S1355617709990415
59. Wechsler D. *WAIS-III: Wechsler Adult Intelligence Scale*. 3rd editors. San Antonio, TX: Psychological Corporation (Spanish adaptation: WAIS-III: Escala Wechsler para adultos. Madrid: TEA 1998) (1997).
60. Baron-Cohen S, Wheelwright S, Hill J, Raste Y, Plumb I. The "Reading the Mind in the Eyes" test revised version: a study with normal adults, and adults with asperger syndrome or high-functioning autism. *J Child Psychol Psychiatry Allied Disc.* (2001) 42:241–51. doi: 10.1111/1469-7610.00715
61. Brüne M, Brüne-Cohrs U. Theory of mind—evolution, ontogeny, brain mechanisms and psychopathology. *Neurosci Biobehav Rev.* (2006) 30:437–55. doi: 10.1016/j.neubiorev.2005.08.001
62. Bertoux M, Delavest M, de Souza LC, Funkiewiez A, Lépine, J.-P., et al. Social cognition and emotional assessment differentiates frontotemporal dementia from depression. *J Neurol Neurosurg Psychiatry.* (2012) 83:411–6. doi: 10.1136/jnnp-2011-301849
63. Stone VE, Baron-Cohen S, Knight RT. Frontal lobe contributions to theory of mind. *J Cogn Neurosci.* (1998) 10:640–56. doi: 10.1162/089892998562942
64. Carlson SM, Wang TS. Inhibitory control and emotion regulation in preschool children. *Cogn Dev.* (2007) 22:489–510. doi: 10.1016/j.cogdev.2007.08.002
65. Rydell A-M, Berlin L, Bohlin G. Emotionality, emotion regulation, and adaptation among 5-to 8-year-old children. *Emotion.* (2003) 3:30. doi: 10.1037/1528-3542.3.1.30
66. Burgess PW, Shallice T. *The Hayling and Brixton Tests*. St. Edmonds: Thames Valley Test Company Bury (1997).
67. Albert J. *Bayesian Computation With R*. New York, NY: Springer Science & Business Media (2009).
68. Ortega A, Navarrete G. Bayesian hypothesis testing: an alternative to null hypothesis significance testing (NHST) in psychology and social sciences. *Bayes Inference*. (2017) 12:235–53. doi: 10.5772/intechopen.70230
69. Salthouse TA. Localizing age-related individual differences in a hierarchical structure. *Intelligence.* (2004) 32:541–61. doi: 10.1016/j.intell.2004.07.003
70. Schubert AL, Hagemann D, Löffler C, Frischkorn GT. Disentangling the effects of processing speed on the association between age differences and fluid intelligence. *J Intellig.* (2020) 8:1–20. doi: 10.3390/jintelligence8010001
71. Bugg JM, Zook NA, DeLosh EL, Davalos DB, Davis HP. Age differences in fluid intelligence: contributions of general slowing and frontal decline. *Brain Cogn.* (2006) 62:9–16. doi: 10.1016/j.bandc.2006.02.006
72. Arcara G, Mondini S, Bisso A, Palmer K, Meneghello F, Semenza C. The relationship between cognitive reserve and math abilities. *Front Aging Neurosci.* (2017) 9:429. doi: 10.3389/fnagi.2017.00429
73. Evans IEM, Llewellyn DJ, Matthews FE, Woods RT, Brayne C, Clare L, et al. Social isolation, cognitive reserve, and cognition in healthy older people. *PLoS ONE.* (2018) 13:e0201008. doi: 10.1371/journal.pone.0201008
74. Vance DE, Roberson AJ, McGuinness TM, Fazeli PL. How neuroplasticity and cognitive reserve protect cognitive functioning. *J Psycho Nurs Mental Health Serv.* (2010) 48:23–30. doi: 10.3928/02793695-20100302-01
75. Singer T, Seymour B, O'doherty J, Kaube H, Dolan RJ, Frith CD. Empathy for pain involves the affective but not sensory components of pain. *Science.* (2004) 303:1157–62. doi: 10.1126/science.1093535
76. Ciccarelli N, Monaco MR, Lo, F.usco D, Vetrano DL, Zuccal,à G, et al. The role of cognitive reserve in cognitive aging: what we can learn from Parkinson's disease. *Aging Clin Exp Res.* (2018) 30:877–80. doi: 10.1007/s40520-017-0838-0
77. Héron M, Le Faou A-L, Ibanez G, Métadieu B, Melchior M, et al. Smoking cessation using preference-based tools: a mixed method pilot study of a novel intervention among smokers with low socioeconomic position. *Addic Sci Clin Practice.* (2021) 16:1–10. doi: 10.1186/s13722-021-00254-6
78. Tziakouri A, Tsangari H, Michaelides C. Assessment of the effect of erenumab on efficacy and quality-of-life parameters in a cohort of migraine patients with treatment failure in cyprus. *Front Neurol.* (2021) 12:687697. doi: 10.3389/fneur.2021.687697

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Neurology

ORIGINAL RESEARCH
published: 28 March 2022
doi: 10.3389/fneur.2022.769360

Facilitators and Barriers to Dementia Assessment and Diagnosis: Perspectives From Dementia Experts Within a Global Health Context

Alissa Bernstein Sideman[1,2,3*], *Tala Al-Rousan*[2,4], *Elena Tsoy*[2,5], *Stefanie D. Piña Escudero*[2,5], *Maritza Pintado-Caipa*[2,6], *Suchanan Kanjanapong*[2,7], *Lingani Mbakile-Mahlanza*[2,8], *Maira Okada de Oliveira*[2,9,10], *Myriam De la Cruz-Puebla*[11,12,13,14,15], *Stelios Zygouris*[2,16], *Aya Ashour Mohamed*[2,17], *Hany Ibrahim*[11,18], *Collette A. Goode*[5], *Bruce L. Miller*[2,5], *Victor Valcour*[2,5] and *Katherine L. Possin*[2,5*]

[1] Philip R. Lee Institute for Health Policy Studies, University of California, San Francisco, San Francisco, CA, United States, [2] Global Brain Health Institute, University of California, San Francisco, San Francisco, CA, United States, [3] Department of Humanities and Social Sciences, University of California, San Francisco, San Francisco, CA, United States, [4] Herbert Wertheim School of Public Health, University of California, La Jolla, CA, United States, [5] Department of Neurology, Memory and Aging Center, University of California, San Francisco, San Francisco, CA, United States, [6] Research Department, Peruvian Institute of Neurosciences, Lima, Peru, [7] Division of Geriatrics, Department of Preventive Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, [8] Department of Psychology, Faculty of Social Sciences, University of Botswana, Gaborone, Botswana, [9] Cognitive and Behavioral Neurology Unit, Hospital das Clinicas, University of São Paulo, São Paulo, Brazil, [10] Hospital Santa Marcelina, São Paulo, São Paulo, Brazil, [11] Global Brain Health Institute, Trinity College Dublin, Dublin, Ireland, [12] Neurosciences Institute, Autonomous University of Barcelona, Barcelona, Spain, [13] Cognition and Brain Plasticity Unit, University of Barcelona, Barcelona, Spain, [14] Bellvitge Institute for Biomedical Research, Barcelona, Spain, [15] Technical University of Ambato, Tungurahua, Ecuador, [16] Centre for Research and Technology Hellas/Information Technologies Institute, Thessaloniki, Greece, [17] Department of Neurology, Ain Shams University, Cairo, Egypt, [18] Geriatric Medicine Department, Ain Shams University, Cairo, Egypt

OPEN ACCESS

Edited by:
Görsev Yener,
Izmir University of Economics, Turkey

Reviewed by:
Ladson Hinton,
UC Davis Health, United States
Deniz Yerlikaya,
Dokuz Eylul University, Turkey

***Correspondence:**
Alissa Bernstein Sideman
Alissa.bernstein@ucsf.edu
Katherine L. Possin
Katherine.possin@ucsf.edu

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: 01 September 2021
Accepted: 25 January 2022
Published: 28 March 2022

Citation:
Bernstein Sideman A, Al-Rousan T, Tsoy E, Piña Escudero SD, Pintado-Caipa M, Kanjanapong S, Mbakile-Mahlanza L, Okada de Oliveira M, De la Cruz-Puebla M, Zygouris S, Ashour Mohamed A, Ibrahim H, Goode CA, Miller BL, Valcour V and Possin KL (2022) Facilitators and Barriers to Dementia Assessment and Diagnosis: Perspectives From Dementia Experts Within a Global Health Context. Front. Neurol. 13:769360. doi: 10.3389/fneur.2022.769360

Objectives: Dementia poses one of the greatest global health challenges, affecting 50 million people worldwide. With 10 million new cases each year, dementia is a growing burden, particularly in low- and middle-income countries (LMIC). This study aimed to identify the facilitators and barriers to providing quality dementia assessment and care in LMICs from a global health perspective.

Methods/Design: A qualitative semi-structured interview study with 20 dementia expert healthcare providers from 19 countries. To be included, providers had to: practice dementia assessment or care in LMICs where the population over age 60 is projected to more than double by 2050 and be recognized as a leading dementia expert in the region based on position, research publications, and/or policy leadership. Interviews were analyzed by a multidisciplinary team of researchers using thematic analysis.

Results: Barriers to dementia assessment and care included stigma about dementia, poor patient engagement in and access to healthcare, inadequate linguistic and cultural validation, limited dementia capable workforce, competing healthcare system priorities, and insufficient health financing. Facilitators included the rise in dementia awareness campaigns, dementia training for general practitioners, availability of family support and family caregivers, and national and international collaborations including coordinated policy efforts and involvement in international research initiatives.

Conclusions: Findings from this study provide insights for prioritizing dementia assessment and care capacity-building in LMICs as a global health priority and for tailored public health approaches to strengthen dementia assessment and care at the individual, community, national, and multi-national levels.

Keywords: dementia, global health, dementia experts, qualitative study, cognitive assessment

KEY POINTS

- This study used qualitative semi-structured interviews to understand and characterize the assessment and care of dementia in low- and middle-income countries from the perspective of expert healthcare providers and leaders in dementia research and policy.
- We identified four major thematic domains, and within these domains characterized facilitators and barriers based on a social-ecological model of health.
- While much of the literature focuses on dementia care in high-income countries, these findings demonstrate the challenges and strengths that exist to dementia assessment and care from the perspective of dementia experts from a broader global view.
- Based on these findings, we provide recommendations using a social-ecological model for taking a tailored public health approach to strengthening dementia care at the individual, community, national, and policy levels.

INTRODUCTION

Dementia is a costly disease impacting patients, families, and societies, and is a major and growing global health challenge due to population aging. In 2015, Alzheimer's Disease International (ADI) reported that there were over 9.9 million new cases of dementia each year worldwide, implying one new case every 3.2 seconds (1). Of these cases, 58% of lived in LMIC, and this is expected to rise to 68% in 2050 due to changing demographics and healthcare infrastructure (1, 2). These countries are expected to face major challenges to ensure that their health and social systems are prepared to meet the increasing dementia care needs associated with this demographic shift.

Research has demonstrated that people with dementia and their caregivers are not receiving services of the type and quality that they need and there are wide variations in detecting dementia globally (3). Pragmatic, realistic strategies and policies that address key facilitators and barriers to quality dementia care are crucially needed (4, 5). Within the countries experiencing the most rapid growth in the aging population, dementia care experts who are providing clinical services on the ground as well as leading research and policy initiatives could provide a critical perspective to inform the development of National Dementia Plans and brain health diplomacy initiatives (6).

The purpose of this study was to identify facilitators and barriers to meeting dementia care needs that are common across countries experiencing a rapid increase in the aging population. Our approach was to collect insights from in-depth interviews with leading regional dementia experts who are working to address gaps in dementia care through their clinical work, research, and/or policy work. Knowledge gained in these expert interviews may offer insight for developing national and international strategies and interventions.

Social-Ecological Model

The social-ecological model is a framework that suggests people's experiences are shaped by interactions among individual, interpersonal, institutional, community, and policy factors (7). Following analysis of our data, we identified the social-ecological model as an approach to organizing our findings, as it can be used to provide a way of understanding how both social and structural factors shape dementia assessment and care approaches in global health settings. A social-ecological model has been used in prior studies to understand attitudes about dementia, access to dementia care, and dementia awareness (8–10). The model is dynamic in that some findings may fall into more than one category. We demonstrate ways components of the model can collectively guide efforts to improve dementia care globally by either developing new interventions or building on strengths and approaches that already exist.

METHODS

Design

We conducted a qualitative study based on interviews with dementia experts from different regions of the world, focused primarily on those in LMICs. Interviewers from our multidisciplinary team had expertise in global health, social science, neurology, and neuropsychology. Interviewers were trained as part of their Global Brain Health Institute fellowship by the first author, a medical anthropologist with 15 years of qualitative research experience. The study was conducted in accordance with the Consolidated Criteria for Reporting Qualitative Research (COREQ) reporting guidelines (**Supplementary Materials, Appendix 1**).

Participants and Setting

We selected experts in dementia diagnosis and care using purposeful sampling (11), which involved identifying and interviewing individuals who are knowledgeable about dementia. Inclusion criteria were: (1) dementia experts in countries with projected growth of the population aged 60 years or older of over 100% between 2017 and 2050 based on United Nations Department of Economic and Social Affairs Population Division estimates (12); (2) established expertise in dementia diagnosis

and care, including the following disciplines: geriatric medicine, geriatric psychiatry, neurology, neuropsychology, and psychiatry; (3) currently involved in clinical practice and training; and (4) recognition as a leading national dementia expert based on role, publications, and/or policy leadership. We first identified a list of possible participants based on recommendations from professional networks, local Alzheimer's Associations, and multi-national studies. We then contacted experts by email to invite them to participate in the study. We contacted a total of 26 experts and 20 responded and agreed to participate. We conducted interviews from August 2019 through November 2020. All participants provided oral informed consent. This study was approved by the Institutional Review Board at the University of California, San Francisco.

Data Collection

Our multidisciplinary team developed a pre-interview survey (Supplementary materials, **Appendix 2**) and a semi-structured interview guide (Supplementary materials, **Appendix 3**). Study instruments were reviewed by the team, and then piloted with a neurologist. The interview covered the following domains: (1) expert and national context; (2) process for diagnosing dementia; (3) facilitators and barriers to dementia diagnosis and care; (4) needs to improve dementia diagnosis and care. While the interview guide included structured questions, the interviews were open-ended, meaning that interviewers were able to ask follow-up questions, request examples, and expand on topics as long as all key domains of the interview guide were covered. Once an expert was identified, we sent the survey *via* a password-protected online platform and scheduled an interview. Interviews were conducted in English or the expert's native language, based on their preference, by trained researchers (AS, ET, SE, MP-C, SK, TA-R, LM-M, MdO, MlCP, SZ, AM, and HI) *via* secure videoconferencing, and lasted approximately 1 h. They were digitally recorded and transcribed. If the interview was not conducted in English, it was translated for analysis.

Data Analysis

We used inductive and deductive thematic analysis to analyze the data and identify key themes through an iterative process using ATLAS.ti. A team of 3–5 coders inductively coded 5/20 transcripts, meeting regularly to review the codes. We discussed and resolved discrepancies in coding and developed a codebook based on consensus. The codebook was reviewed by the first, second, and senior authors. The first author then used this codebook to code the remaining transcripts (15/20). When new codes emerged, they were reviewed by the team during regular meetings and added to the codebook. Disagreements were discussed and resolved. We reached thematic saturation when no new codes emerged, though we continued to code all transcripts. The team then identified themes based on the codes and themes were deductively organized based on the social-ecological framework, our overarching theoretical model. We reviewed the data for each theme and identified the most illustrative quotations to incorporate into the manuscript and tables.

RESULTS

Participants

We provide characteristics of the 19 countries represented by our 20 research participants in **Table 1** and demographic and practice characteristics of our sample in **Table 2**. Ten participants were neurologists, four were neuropsychologists, three were geriatricians, two were psychiatrists, and one was a geriatric psychiatrist.

Barriers and Facilitators According to a Social Ecological Model Framework

Respondents identified key barriers and facilitators to dementia assessment and care (**Figure 1**, **Tables 3** and **4**). We present these by Social-Ecological (SE) factor. For each barrier and facilitator we provide a description of the theme and one or two exemplary quotations in the text. Additional quotations from a range of participants are presented in the tables. We found more agreement among experts around barriers to dementia diagnosis than we did around facilitators, but indicate in the text when a topic raised was a major theme endorsed by many participants or a minor theme endorsed by fewer participants.

Barriers

Individual and Interpersonal Factors

Theme 1: Stigma and Lack of Awareness and Knowledge About Dementia

Every respondent reported major challenges related to either stigma or a lack of knowledge and awareness about dementia in the general population. Some of the issues related to awareness that they identified included seeing dementia as part of normal aging, denial of the disease, and ageism. Many felt that more education would remedy this lack of awareness. For a few participants, stigma emerged in relationship to cultural beliefs about cognitive impairment, such as beliefs about symptoms of dementia being connected to witchcraft. The issue of stigma and awareness was exemplified by a geriatrician from Latin America who discussed the relationship between stigma and discrimination,

> *Geriatrician, Latin America: One of the main barriers is that there is stigma in this country. When families find out that their loved one is sick, they do not make it public. . . discrimination toward people with brain diseases is a serious cultural problem.*

Furthermore, while most experts referred to stigma when talking about the general population, representing a major theme, some also noted that there was a lack of awareness about dementia among clinicians, as well, particularly general practitioners. For those that identified this theme among clinicians, the sense of stigma and lack of awareness involved clinicians avoiding fields that focus on dementia, lack of expertise, lack of time or ability to gain expertise, or disinterest. Those that identified this issue related to awareness felt that lack of awareness created barriers to good dementia care.

A geriatrician in Africa articulated this challenge of lack of awareness among healthcare providers.

TABLE 1 | Characteristics of the 19 countries represented by experts in the study[a].

World region	Country	Projected growth (%) (2)[b]	Literacy rate (%) (13)[c]	Mean years of school (13) [d]	Rural residence (%) (13)[e]	GDPPC (USD) (13)[e]	Gini index (14)[f]	Linguistic diversity index (15)[g]
Africa	Botswana	264	40	ND	31	$8,259	53.3	0.444
Africa	Kenya	247	57	ND	73	$1,711	40.8	0.901
Africa	Ghana	185	51	ND	44	$2,202	43.5	0.805
Americas	Brazil	235	79	8.0	13	$8,921	53.9	0.032
Americas	Colombia	237	83	8.5	19	$6,651	50.4	0.030
Americas	Ecuador	208	73	8.8	36	$6,345	45.4	0.264
Americas	Mexico	244	81	8.9	20	$9,698	45.4	0.135
Americas	Nicaragua	276	56	ND	41	$2,029	46.2	0.081
Americas	Peru	219	79	9.7	22	$6,947	42.8	0.376
Asia	India	203	45	ND	66	$2,016	37.8	0.930
Asia	Indonesia	223	74	8.2	45	$3,894	39.0	0.846
Asia	Kyrgyzstan	220	97	ND	64	$1,281	27.7	0.670
Asia	Taiwan	204	ND	ND	ND	ND	ND	ND
Asia	Thailand	208	79	8.5	50	$7,274	36.4	0.753
Europe	Greece	157	95	10.3	21	$20,324	34.4	0.175
Europe	Spain	166	95	10.3	20	$30,524	34.7	0.438
Middle East	Egypt	195	33	9.0	57	$2,549	31.5	0.509
Middle East	Jordan	270	91	ND	9	$4,248	33.7	0.484
Middle East	UAE	779	69	12.5	13	$43,005	32.5	0.777

GDPPC, gross domestic product per capita; ND, no data; UAE, United Arab Emirates. [a]Adapted from Tsoy et al. (16). [b]Projected growth of population aged 60 and above between 2017 and 2050. [c]Literacy rate among population aged 65 and above; reference year: 2013 (Botswana), 2015 (Nicaragua, Thailand, UAE), 2017 (Ecuador, Egypt), 2018 (Brazil, Colombia, Greece, India, Indonesia, Jordan, Kenya, Kyrgyzstan, Mexico, Peru, Spain). [d]Mean years of formal schooling among adults aged 25 and above; reference year: 2016 (Greece), 2017 (Ecuador, Egypt), 2018 (Brazil, Colombia, Indonesia, Mexico, Peru, Spain, Thailand, UAE). [e] Rural residence among adults aged 25 and above; reference year: 2018 (all). [f]Gini index measures the deviation of the actual income distribution from a hypothetical perfectly equal distribution with values ranging from 0 (perfect equality) to 100 (perfect inequality); reference year: 2010 (Jordan), 2011 (India), 2014 (Nicaragua, UAE), 2015 (Botswana, Kenya), 2017 (Egypt, Greece, Spain), 2018 (Brazil, Colombia, Ecuador, Indonesia, Kyrgyzstan, Mexico, Peru, Thailand). [g]Linguistic diversity index is based on the population of each language spoken in the country as a proportion of the total population with values ranging from 0 (no diversity, everyone has the same primary language) to 1 (total diversity, no two people have the same primary language); reference year: 2009 (all).

Geriatrician, Africa: Healthcare providers… are still not interested to know how to diagnose. They are interested to know about [dementia]. They think it is the hot topic they cannot touch. We need to remove this stigma from the healthcare providers themselves.

Theme 2: Late Presentation

Another prominent theme identified in the majority of interviews was the issue of late presentation, where patients show up at the doctor when they already have severe dementia and when it is more challenging to address their needs. In some interviews, late presentation was connected to lack of awareness, while in others, the experts discussed issues such as access to care or the lack of expertise among general practitioners to diagnose dementia until later stages in the disease. In an example where late presentation was connected to a lack of awareness, a neurologist in our study explained.

Neurologist, Africa: By the time patients present, it's rather late… by the time people come, they are often moderately advanced to advanced. There are some problems with that because people have lost the ability now to, say, for example, execute a will.

Organizational and Institutional Factors

Theme 3: Competing Health System Priorities

At the organizational and institutional levels, nearly all experts noted the challenge of competing health systems priorities. Some examples provided of competing priorities included the health of younger people or pregnant women. Others suggested that dementia was not a priority because of a focus on infectious and other treatable diseases. In these discussions of competing priorities, many participants noted that these other health issues often take precedent over the aging population, which some explained shaped decisions about resource allocation. Two experts in our study exemplified these challenges:

Psychiatrist, Latin America: In our country these needs are not a priority because there are the needs of children, of pregnant women. There is still no clear recognition of all the emergent needs that we are facing with the population's aging… there are other problems that are a priority, like extreme poverty. When people are worried about what will they have to eat that day, or what their children are going to eat, they do not prioritize memory issues.

Neurologist, Asia: We are grappling with infections and we are grappling with so many other treatable problems that

TABLE 2 | Participant demographics and practice characteristics.

Region	***n***
Demographic information (*n* = 20)	
Africa	4
Asia	6
Europe	2
Central/South America	6
Middle East	2
Gender	
Female	9
Male	11
Primary specialty	
Geriatric medicine	3
Geriatric psychiatry	1
Neurology	10
Neuropsychology	4
Psychiatry	2
Years in clinical practice	***Mean (SD)***
	21.3 (10.8)
Practice Characteristics*	
Expert Practice Setting**	***n***
Public institution	8
Private institution	9
Teaching hospital	13
Research institution or university	8
Day Care Center	1
% time dedicated to the following activities	***Mean % (SD)***
Patient care	39 (20)
Research	25 (18)
Teaching & mentoring	22 (14)
Administration	11 (9)
Other	2 (7)
Number of patients newly diagnosed with MCI or Dementia per month at expert's practice	***Mean (SD)***
	25 (19)

** One provider did not provide responses to all non-demographic questions. **Some providers indicated working in multiple practice settings.*

probably dementia would be marginalized when it comes to healthcare.

Theme 4: Limited Dementia Capable Workforce

Many of the challenges raised by participants in our study centered around the healthcare workforce. Respondents from every region noted limited personnel and human resources required to address dementia diagnosis and care, including lack of neuropsychologists and neurologists. Some articulated this issue by providing an estimate of number of neurologists available across the entire population. A psychiatrist articulated a theme that was echoed by many of the experts in our study,

Psychiatrist, Asia: There are practically no specialists who work in this area. . . .there is no prestige in working with dementia, there are no gerontologists in the whole country. . . in [[largest medical school in the country]] the topic of dementia gets 2 h of teaching.

Most participants also noted a need for more training focused on dementia, especially among general practitioners. Some respondents felt that working in dementia was not a popular choice for clinicians in their setting, which is related to the issues above regarding awareness and stigma among healthcare personnel, while another expert related this to concerns about lack of prestige for those who choose to work with the aging population.

Community Factors

Theme 5: Social Determinants of Health

At the community level, barriers identified fell within a framework of social determinants of health, such as lack of access to healthcare and geographic, socioeconomic and educational disparities. Access issues most participants raised included both lack of access and differential access to dementia-specific healthcare. Reasons that emerged across interviews included cost and lack of specialists, as noted above. Nearly every expert reported geographic differences between rural and urban areas, or differential access based on public vs. private healthcare systems. A neurologist illustrated this issue of both urban and rural differences, as well as access to specialty hospitals.

Neurologist, Middle East: Half of the country is in the cities, and the other half are living like [[Bedouins]] and all that, so they're living in the rural areas. They have access to primary care, but not more than that, not secondary or tertiary hospitals.??

Related to dementia specialty care, some experts identified a lack of access to key tools needed to do a diagnostic workup. These included lack of access to neuroimaging, cognitive assessment tools, imaging, and biomarker testing, with most experts reporting a lack of standardized approach to dementia care.

Neurologist, Europe: If you are lucky you will have access to a center that has a memory clinic. The majority of patients do not get this type of attention.

Others noted disparities due to socioeconomic, and educational factors, which included inadequate testing and validation in patients' languages and cultures. For example,

Neuropsychologist, Latin America: For the population that has very low socioeconomic conditions...accessing a specialized diagnosis, like the one we do here in our fourth level hospital, is very difficult. They do not come easily, almost never. . . the way we diagnose, it does not include illiterate patients. Those with low education do not come to our center.

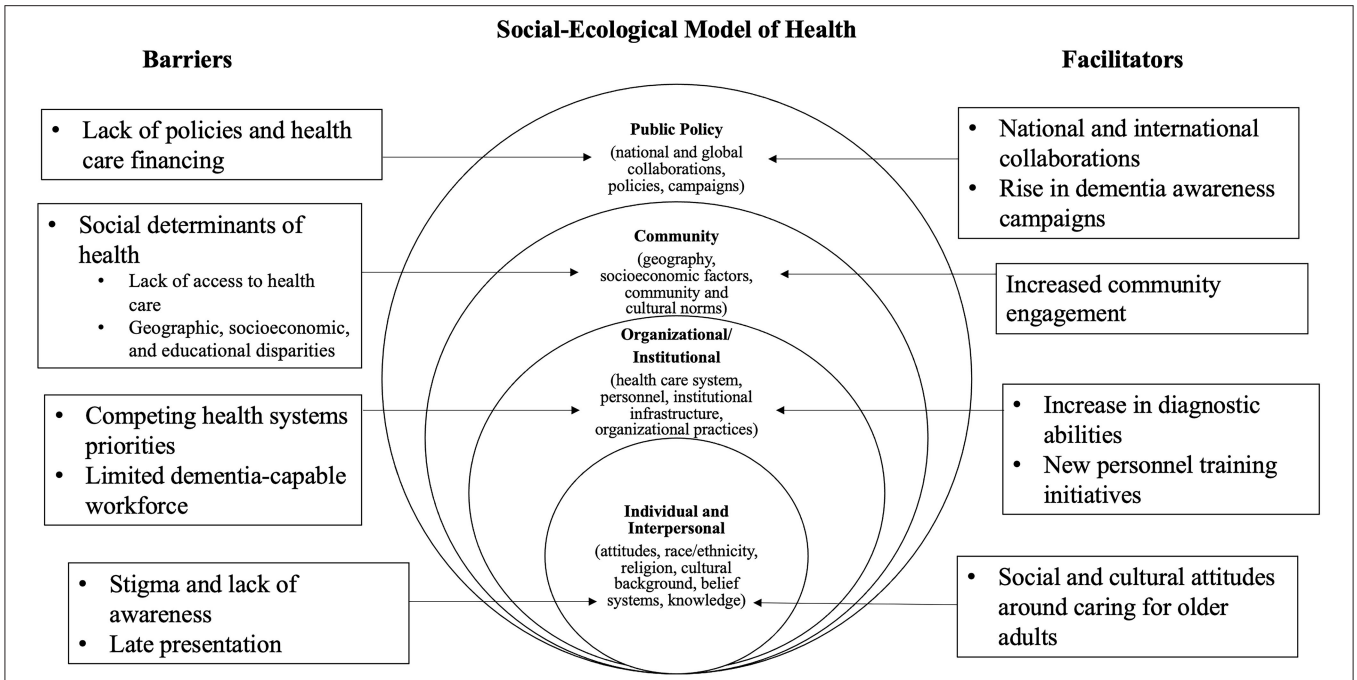


FIGURE 1 | Social ecological model of health.

Public Policy Factors

Theme 5: Lack of Policies and Healthcare Financing Emphasizing Dementia

Finally, at the public policy level, most experts identified lack of policy and healthcare financing as significant barriers, particularly regarding implementing new plans. Some experts discussed the lack of financing for training in specialties related to dementia, while others focused on the cost of care or the lack of financing for research related to dementia. In some cases, policies and plans existed on paper with no plan for implementation, as exemplified by a neurologist:

> *Neurologist, Africa: We have a National Dementia Plan, but, for its implementation, resources and stakeholder support is needed. We need bigger and more global efforts.*

Facilitators

Individual and Interpersonal Factors

Theme 1: Social and Cultural Infrastructure Around Caring for Older Adults and Those With Dementia

Some participants noted strengths of the social and cultural systems in their countries, for example, respect for the elderly, or availability of caregivers and family networks to support people with dementia, though these strengths were not identified by the majority of participants. In some cases they connected the lack of a public care infrastructure with the need for families to be so involved, while in others they spoke of the culture of caring for older adults. A neurologist explained the role of the family structure as a strength in dementia care,

> *Neurologist, Asia: One thing which is very, very strong in our sector is that our family structure helps us in the management post-diagnosis...we don't have dementia care centers...our dementia care system is the center of the patient's home.*

Organizational and Institutional Factors

Theme 2: Increase in Diagnostic Abilities

There was wide variation across sites in what is included in the diagnostic workup, which has been explored in a previous paper by our group (16). For a few experts, this involved adopting new guidelines and standardized protocols for diagnostic assessment. Others referred directly to new diagnostic tests in use, the availability of neuropsychological testing, and new technology available such as MRI machines or biomarker testing. One neurologist exemplified these changes,

> *Neurologist, Europe: Now we have at the hospital a Lumipulse machine and the cerebrospinal fluid biomarker determination is…routinely tested at the hospital. Before, the cost of this biomarkers had to be covered by research. Now, they are covered by the national health care system.*

Theme 3: New Personnel Training Initiatives

Related to the above theme, in many of the discussions about the increase in diagnostic abilities, the experts connected these abilities to the more recent increase in personnel able to conduct diagnostic assessments, such as neuropsychologists. In some settings, new training programs were developed to build capacity. Some noted an increase in providers able to do dementia diagnosis over the last 5–10 years. Many of these initiatives

TABLE 3 | Barriers to dementia assessment and care.

Theme by social-ecological domain	Description	Exemplary quotes
Individual and interpersonal factors		
Stigma and lack of awareness and knowledge about dementia in the population and among healthcare providers	Dementia being seen as normal aging, denial of the disease, ageism, stigma around dementia	• ***Geriatrician, Africa:*** *I think the most important issue relating to the stigma in the Arabic word for dementia. This is a major barrier. The Arabic word for dementia is kharaf, okay? Kharaf means losing your mind. So still, physicians and some of the official translating groups, they use the word kharaf, which is like insane.* • ***Psychiatrist, Central America:*** *I believe that we need education for both the general population and health personnel. I believe that these are the two main barriers and that education would be the way to address this lack of awareness of the probem both in the population and in health personnel.* • ***Neurologist, Middle East:*** *People are in denial. They resist being sick. It's part of the culture. They deny, they resist it with all their power until everything falls down.*
Late presentation	Underdiagnosis, misdiagnosis, delayed diagnosis	• ***Neurologist, Asia:*** *The problem is [they] come when they are in the late onset…the family just thinks it's normal for the elderly to forget. But, if the patient has a behavioral problem, it's the problem for the family…So, when come to the doctor, usually, you know, the patient hopes that the doctor will give them one pill to fix everything, you know, a potion.* • ***Neurologist, Middle East:*** *I see that the family takes their family member late to the doctor…They deny that they have any problems.* • ***Neurologist, Africa:*** *Our health-seeking behaviors for most things, and especially things that have to do with cognition, we wait until the problem is a glaring one before we think, Oh, maybe I should go see the doctor. So, it is coming to the hospital late. It's even by, again, I mentioned this earlier, the health professional identifying the problem late, when it's already full-blown, and then thinking, Oh, maybe I should refer now.*
Organizational/institutional factors		
Competing health systems priorities	Communicable diseases, maternal health, infant health, hunger, poverty	• ***Neurologist, Africa:*** *The healthcare system is not set up in a way to take into account these kinds of non-communicable diseases. We are still too basic. We are still in the communicable disease phase. That's where all our focus, public health and so on, it is based. We are moving slightly toward non-communicable diseases, but it's still extremely basic. So hypertension, diabetes, heart disease. Diseases of the nervous system are very, very low down on the priority list of the government, the policy makers, and so on.??* • ***Psychiatrist, Asia:*** *Psychiatric and mental health areas are financed in this country based on the leftover principle. In other words, if there is some money left in the healthcare budget, it would rather be spent on gynecology, obstetrics, or cardiology services…Recently, our [[Minister of Health]] even expressed a wish to release patients with psychiatric disorders from acute wards to free up beds for observation of patients with infectious diseases, for example.* • ***Neurologist, India:*** *Dementia affects the geriatric group. Now we are grappling with infections and we are grappling with so many other treatable problems that probably dementia would be marginalized when it comes to healthcare.*
Limited dementia capable workforce	Lack of providers, lack of training (particularly for general practitioners/primary care), lack of focus on dementia in the healthcare workforce	• ***Neuropsychologist, Africa:*** *So, it there's one neurologist who's based in the north of the country, another who's based in the south of the country, and then myself who's the only neuropsychologist. So, there's really a lack of personnel and human resources. There's a lack of training. For example, even nurses, you know, they have very little training about how to identify dementia, how to treat dementia or anything like that* • ***Neuropsychologist, Europe:*** *Across [[European country]] I do not think there are well-trained professionals…there are no professionals – neuropsychologists in [these] places unfortunately. They are not aware of these techniques. It's something unknown to them.* • ***Neurologist, South America:*** *Psychiatrists in [[South American country]] have no training, they only assess behavioral symptoms.*
Community factors		
Social determinants of health Lack of access or differential access to healthcare • Geographic, socioeconomic, and educational disparities	Access to healthcare in general, specialty care, or affordable care Geographic, socioeconomic, education, literacy, culture, language	• ***Neurologist, Middle East:*** *The general neurologist, there were like maybe two in the government hospital, two or three total more than 5 years ago. Maybe two or three at most. And you have about five or six million people population, with absence] of access to the government hospital. So there was no way they can treat these patients. There is no way. Maybe the one who has certain connections, the one that has powerful friends, there is no way you can treat that whole amount of patients*

(Continued)

TABLE 3 | Continued

Theme by social-ecological domain	Description	Exemplary quotes
		• ***Neurologist, Europe:*** *It will all depend on the resources that the referral center that you were assigned to has… If you are lucky you will have access to a center that has a memory clinic, and I insist, the majority of the patients do not get this type of attention. Regarding memory clinics, there are a lot of inequities regarding neuropsychological testing and biomarker access.*
Public policy		
Lack of policies and healthcare financing emphasizing dementia	Financing, policies	• ***Geriatrician, Latin America:*** *Another barrier is the economical one, and there is where we come into the game. As we know, this is a disease for which the treatment is extremely expensive. At least here in [[country]] the cost can be around $150 to $300 dollars per month if patches or any type of drug for Alzheimer is used.* • ***Neurologist, Africa:*** *Is there a national policy to try and help with dementia? I do not think we have reached that point yet.* • ***Neurologist, Europe:*** *A major reason for these inequities is that the capacity of getting funding that each center has is tremendously unequal.* • *Geriatrician, Africa: MSPKR: Financing research for elderly health care like dementia is still, unfortunately, not of the priorities of the finance of research…I think it should be part of the local and international communities to put dementia care at the priorities of the financing.*

were enabling better use of cognitive tests and increased training in dementia.

> *Neurologist, Latin America: The fact is that in the past there were not even dementia classes in the medical course… today geriatrics has a course in dementia, psychiatry has a course in dementia and in universities there is a course in dementia...It increases visibility…this I think is positive…it is giving more importance to the theme.*

Community Factors

Theme 4: Increased Community Engagement

Some interview participants noted an increase in community engagement around caring for the elderly and specifically around those with cognitive impairment. Those that articulated this theme shared ways in which members of the community were getting involved to increase community engagement, for example, by participating in creating a dementia care plan, increasing awareness about dementia through neighborhood participation, or becoming involved in implementing assessments. A neurologist explained,

> *Neurologist, Asia: We are trying to include more people that are in the community into the dementia care plan. So, once this chief in the village should be included when we try to discuss policy to try to increase dementia awareness.*

A geriatrician in our study explained the way former caregivers of people with Alzheimer's disease were getting involved in his setting by learning by volunteering and learning how to implement cognitive tests:

> *Geriatrician, Latin America: We also have other kind of volunteers that are not professionals. They have been caregivers of patients with Alzheimer. We have a very solid group of people whose parents passed away and are now volunteering to teach other caregivers how to take care of patients. At the same time, they are receiving training on how to detect Alzheimer. We have provided them all with a training that I call ABC. This is basic training in which they learn to administer the Minimental or the mini cognitive tests. They can administer them in their neighborhoods, in their families or in their communities. When we make the detection campaigns, they come with us.*

Public Policy Factors

Theme 5: Rise in Dementia Awareness and Awareness Campaigns

Most respondents noted that there have been changes in awareness over the last 10 years even amidst an atmosphere of stigma around the disease. For example, many participants reported an increase in awareness campaigns and media initiatives. A few reported the increase in awareness among healthcare personnel, for example, primary care physicians who were more aware of when to refer patients, or the development of memory care sites that could accept referrals.

> *Geriatrician, Latin America: Media is covering this topic. Five years ago, they did not. I think that within the millennium development objectives, the benefit that has been obtained is that the [country's] population is more aware about the disease. People know a little more about alarm symptoms and would be willing to [go] to a center that offers them help.*

Others noted the increase in awareness at the population level, which is connected to the theme discussed above about the increase in community engagement.

> *Psychiatrist, Asia: Normalization used to be the case in the past. Like, in the 90s, everyone used to think that forgetfulness is a part of normal aging, it is expected. But now, particularly in [[region of country]], there are increasing social efforts about awareness of dementia, with the help of primary care physicians, psychiatrists, and neurologists; so other medical professionals are largely aware of what dementia is.*

TABLE 4 | Facilitators to dementia assessment and care.

Theme by social-ecological domain	Description	Exemplary Quotes
Individual and interpersonal factors		
Social and cultural attitudes around caring for older adults	Cultural infrastructure around caring for older adults; Caregiver/family/patient support available for people with dementia/older adults	• ***Neurologist, Asia:*** *So I think in most areas, [the] care model is a bit like as a family unit, meaning that – one thing to note that in Taiwan, almost 90 percent of our patients are never institutionalized during the dementia disease process. It's a very stigmatic thing regarded as the son and daughter failed the parents…in a more rural area, they might take care as a village…the whole village, all the elders that are healthy would take care of the elders that are less healthy, or the village would take care of them. So you do not own a particular elder – you own every elder.* • ***Psychiatrist, Africa:*** *What I can say is working well is care because of the sculpture of our family system. You know, we tend to care for our own, so we tend to do – you know, if your grandmother has dementia or your great aunt has dementia, chances are that they will never go without care because we care for our own at home. So, I think that's the good thing.*
Organizational/institutional factors		
Increase in diagnostic abilities	Increase in specialists, more testing available, more technology available (but mostly focused on specialty centers)	• ***Geriatrician, Asia:*** *20 years ago, physicians who went oversea came back to adapt and validate various cognitive tests in [Asian country] versions. Most work were confined in specialized fields [like neurology]. Even among neurologists or psychiatrists, there were a few who took interest in dementia. Ten years ago, people grew more interested in dementia. There have been more tests and research which combine clinical and biomarkers such as CSF biomarker, PET Scan. The past 5 years, I feel that cognitive assessment moved to a larger circle of medicine. It is talked about and put in the undergraduate curriculum. Family physicians talk about it. Other disciplines also cares more about it. [The ministry] supports public screen program and referral track. Systems are linked and have become more supportive.* • ***Neurologist, Middle East:*** *The number of physician neurologists were less than 10 five years ago. Now we are about 60, so that's a big improvement. Now, patients are getting much more accessibility to neurologists. They did not have that luxury before.* • ***Neurogeriatrician, South America:*** *In these last 5 years, more trained neuropsychology professionals have arrived. Now there is more knowledge of the tests.*
New personnel training initiatives	Increased initiatives to train more clinicians in dementia-specific topics	• ***Geriatrician, Asia:*** *20 years ago…most work [was] confined in specialized field [like neurology]. Even among neurologists or psychiatrists, there were a few who took interest in dementia. 10 years ago, people grew more interest in dementia. There have been more tests and research…the past 5 years, I feel the cognitive assessment move to a larger circle of medicine. It is talked about and put in undergraduate curriculum. Family physicians talk about it. Other disciplines also care more about it. [The ministry] supports public screen program and referral track. Systems are linked and become more supportive.?* • ***Neurologist, Latin America:*** *In the past there were not even dementia classes in the medical course, this appeared later, I was one of the initiators, today the geriatrics has a course in dementia, psychiatry has a course in dementia and in universities there is a course in dementia. We have a course on dementia at congresses. It increases visibility. This occurs at our university and also at other universities. [This university] is a knowledge generating center, and this is spreading and all doctors end up knowing more dementia. And this is very important.*
Community factors		
Increased community engagement	Community engagement or dissemination of knowledge about dementia	• ***Neurologist, Asia:*** *At least the few areas that I work at, they can approach the chief of the community center. So you usually have a chief, like a village chief…there would be this person that's like responsible for the community, and then organize events, like be responsible for the local community center. So question, and you ask them, right - okay, so who is 65 and above in your community, and who do you think has a concern of a cognitive kind?*
Public policy factors		
Rise in dementia awareness and awareness campaigns	Media, change in awareness, increased community engagement	• ***Neurologist, Africa:*** *I think there has been an attempt from our side, also, as neurologists, to try and help people to understand this condition, and I think that has helped medical students, newly qualified doctors, residents in training, and physicians to be more aware of this diagnosis.*
National and international collaborations	Coordinated policy efforts and involvement in international research initiatives, collaborations, research support, international training, and new initiatives/new policies	• ***Psychiatrist, Latin America:*** *We collaborate with the national Alzheimer's Association and the national Alzheimer's Federation. We participated in many of their activities directed toward family members and the general public. Also, in radio and television campaigns directed at to general public, for example, in September.*

Theme 6: National and International Collaborations

Some experts in our study suggested that there has been an increase in both national and international collaborations around dementia. While these collaboration took different forms depending on the country, some examples that participants provided included coordinated policy efforts, involvement in international research initiatives, international training, and new policy initiatives. Some examples of the approaches to building collaborations both nationally or internationally included the creation of national dementia plans, collaborations with associations or NGOs, international research consortiums, and national health surveys.

DISCUSSION

In this study, we identified facilitators and barriers to dementia assessment and care based on the experiences of dementia experts in global health settings. Prior global health studies in dementia have focused on the epidemiology of dementia (1), emphasizing identifying disease frequencies across regions, and have looked at risk factors such as education, socioeconomic status, and access to healthcare (17). Other work has focused on cognitive testing, and its cultural or linguistic applicability (16, 18). Our findings are confirmatory of many issues raised in prior studies, including the 2021 World Alzheimer's Report (19). These include challenges such as limited access to healthcare resources, including lack of clinicians, the limited primary care infrastructure, and the need for more clinicians skilled in dementia diagnosis; challenges doing diagnostic testing in populations with low education; cultural factors; the role of comorbid conditions; and costs of doing dementia diagnosis. However, we also note that our qualitative approach to interviewing dementia experts in the global health context is unique, and using their voices to illustrate previously-identified issues provide more nuance and gives voice to the on-the-ground perspectives. Furthermore, while other studies have looked primarily at challenges and barriers, we also present facilitators and strengths that emerged in our interviews, though others have noted similar opportunities as we found, such as improving medical education and the need to build more public awareness. Our study used a qualitative approach to gain the global perspective of experts who are on-the-ground in health systems.

In 2013, the G8 summit committed to focus on dementia as a global health priority, and emphasized the importance of a multi-sectorial approach to addressing dementia, particularly in LMICs. Our findings identify challenges that cross multiple sectors, while strengths identified indicate a multi-sectorial approach to addressing the challenge of dementia. We identified the following key areas based on our results: (1) raising dementia awareness while building on social and cultural strengths; (2) building dementia care workforce capacity across the health system, including generalists, given disparities in access to specialty care; and (3) building and strengthening international collaborations to support the integration of new tools, policies, and approaches to address gaps in dementia assessment and care.

Raising Dementia Awareness While Building on Social and Cultural Strengths

Awareness (17, 20, 21), knowledge (22), and stigma are commonly cited barriers to dementia prevention, treatment, and care in the global health context (17, 23, 24). Findings from our study also reinforced these challenges. We similarly identified the need for more dementia awareness to address issues around stigma or seeing dementia as part of normal aging (21) that may result in late presentation, as many research participants suggested. However, we also identified social and cultural strengths, such as approaches to caring for older adults and ways that cultural leaders have been engaged, that may provide a foundation for more effective community-based work building dementia awareness. Supporting this approach, previous work in both epidemiological and clinical research has emphasized the importance of recognizing diversity in sociocultural factors across cultures and societies, and how these shape people's understanding of dementia and prevention and care management interventions (20). Tailored interventions that center the experiences and voices of local communities as well as geopolitical and social contexts are needed to develop awareness and produce a more targeted response in LMICs (9, 25).

Furthermore, we found that the need for dementia awareness extended to generalist healthcare providers. Focusing awareness campaigns on non-expert healthcare personnel is an important next step for improving dementia care globally. However, we also found that experts *did* identify improvements in dementia awareness over the last 10 years, offering examples of new educational campaigns, media approaches, and community outreach that set the stage for building more widespread understanding of dementia.

Building Dementia Care Workforce Capacity Across the Health System, Including Generalists, Given Disparities in Access to Care

In our study, most participants identified the need for a more robust dementia care workforce and reported challenges that exist around lack of training and capacity to diagnose and care for people with dementia. Although much of the literature on the dementia care workforce focuses on HICs (26), recent work has discussed the need for "task shifting" in the global health setting-the concept of moving dementia-related tasks from expert health providers to health workers with less training, such as community health workers (27, 28). These types of workforce solutions can help to address the need for dementia capable providers (13). Furthermore, much work has emphasized the role of primary care providers in dementia care in HICs, including the barriers faced as well as attitudes about dementia care (14, 15, 29, 30). Given the disparities we identified in access to specialty care, building dementia care capacity among generalist clinicians may improve dementia care more broadly in LMICs. Emphasis is needed on incentives to bring generalists the education and training they need to do dementia-capable work with patients (31). Finally, challenges around training go hand-in-hand with the need for feasible dementia assessment tools (16). Work

is needed to develop the healthcare infrastructure related to dementia assessment tools that can be easily used and interpreted by generalists (16).

Building and strengthening international collaborations to support the integration of new approaches, tools, and policies to improve dementia assessment and care globally.

Experts in our study noted deficiencies in national policies around dementia. However, many also identified the development of international collaborations as a strength that can be built on. International collaborations and global coordination is important both for inclusiveness in research to ensure representative research cohorts, as well as to address the unequal impact of dementia across the globe (32). A key example is Alzheimer's Disease International's coordination of the development of national dementia care plans and writing annual reports about dementia in LMIC. Other international consortiums are also working to set research priorities, improve diagnosis and care, and both address and record global challenges related to dementia care (2).

Limitations

This study has several limitations. (1) We were unable to sample from all LMICs meeting the inclusion criteria, though we had regional representation. (2) We relied on interviews with one to two neurology experts from each country sampled, and therefore cannot generalize these results. More work and a larger sample are needed. (3) Participants in our study were not asked specifically about the different levels of the social ecological model, as the model was used as a way to organize inductive findings of our exploratory study. It is possible the experts would have identified additional barriers an facilitators if the interview had been conducted in a systematic way using this model. (4) We limited our interview to dementia experts, though we asked about challenges in non-expert settings. Future work is needed with broader representation of generalists, community health workers, and other informants in these settings to identify whether their perceptions are consistent with expert perspectives and to identify additional facilitators and barriers. (5) Finally, this study was not designed to compare and contrast differences across countries, and particularly did not look at differences between MIC and LICs. Future work would sample from more LICs and conduct a comparative analysis.

Future Directions

Findings from this study provide insights for prioritizing dementia assessment and care capacity-building in LMICs as a global health priority. We also identified ways that tailored public health approaches can strengthen dementia assessment and care at the individual, community, national, and multi-national levels.

DATA AVAILABILITY STATEMENT

The raw qualitative data is not available publicly due to the need to protect the privacy of interviewees, who did not consent to have transcripts of their interviews shared. However, the authors may make summary data available on a case-by-case basis as allowed by human subjects policies. Requests to access the data should be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of California San Francisco. Written informed consent from the participants was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

ABS designed and conceptualized study, analyzed and interpreted the data, drafted and revised the manuscript for intellectual content, obtained funding, and major role in the acquisition of data. TA-R designed and conceptualized study, analyzed and interpreted the data, and revised the manuscript for intellectual content. ET, SP, MP-C, SK, LM-M, MO, and MD designed and conceptualized study, major role in the acquisition of data, revised the manuscript for intellectual content. SZ, AA, and HI had major role in the acquisition of data and revised the manuscript for intellectual content. CG had major role in acquisition of data and manuscript preparation. BM revised the manuscript for intellectual content. VV designed and conceptualized study and revised the manuscript for intellectual content. KP designed and conceptualized study, obtained funding, and revised the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by the Global Brain Health Institute, the UCSF Population Health & Health Equity Scholars Program, the National Institute on Aging (K01AG059840-01A1), the National Heart, Lung, and Blood Institute (K23HL148530), and the National Institute of Neurological Disorders and Stroke (UG3NS105557-01).

ACKNOWLEDGMENTS

We are grateful to the participants in this study for sharing their experiences and knowledge.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.769360/full#supplementary-material

REFERENCES

1. Prince MJ, Wimo A, Guerchet MM, Ali GC, Wu YT, Prina M. *World Alzheimer Report 2015. The global impact of dementia: An analysis of prevalence, incidence, cost and trends. Alzheimer's Disease International.* London (2015) 87.
2. Parra MA, Butler S, McGeown WJ, Brown Nicholls LA, Robertson DJ. Globalising strategies to meet global challenges: the case of ageing and dementia. *J Glob Health*. 9. doi: 10.7189/jogh.09.020310
3. Lang L, Clifford A, Wei L, Zhang D, Leung D, Augustine G, et al. Prevalence and determinants of undetected dementia in the community: a systematic literature review and a meta-analysis. *BMJ Open.* (2017) 7:e011146. doi: 10.1136/bmjopen-2016-011146
4. Bieber A, Nguyen N, Meyer G, Stephan A. Influences on the access to and use of formal community care by people with dementia and their informal caregivers: a scoping review. *BMC Health Serv Res.* (2019) 19:88. doi: 10.1186/s12913-018-3825-z
5. Broda A, Bieber A, Meyer G, Hopper L, Joyce R, Irving K, et al. Perspectives of policy and political decision makers on access to formal dementia care: expert interviews in eight European countries. *BMC Health Serv Res.* (2017) 17:518. doi: 10.1186/s12913-017-2456-0
6. Dawson WD, Bobrow K, Ibanez A, Booi L, Pintado-Caipa M, Yamamoto S, et al. The necessity of diplomacy in brain health. *Lancet Neurol.* (2020) 19:972–4. doi: 10.1016/S1474-4422(20)30358-6
7. Lawton MP. Social ecology and the health of older people. *Am J Public Health.* (1974) 64:257–60. doi: 10.2105/AJPH.64.3.257
8. Parke B, Hunter KF, Strain LA, Marck PB, Waugh EH, McClelland AJ. Facilitators and barriers to safe emergency department transitions for community dwelling older people with dementia and their caregivers: a social ecological study. *Int J Nurs Stud.* (2013) 50:1206–18. doi: 10.1016/j.ijnurstu.2012.11.005
9. Zeng F, Xie WT, Wang YJ, Luo HB, Shi XQ, Zou HQ, et al. General public perceptions and attitudes toward Alzheimer's disease from five cities in China. *J Alzheimers Dis.* (2015) 43:511–8. doi: 10.3233/JAD-141371
10. Lian Y, Xiao LD, Zeng F, Wu X, Wang Z, Ren H. The experiences of people with dementia and their caregivers in dementia diagnosis. *J Alzheimer's Dis.* (2017) 59:1203–11. doi: 10.3233/JAD-170370
11. Palinkas LA, Horwitz SM, Green CA, Wisdom JP, Duan N, Hoagwood K. Purposeful sampling for qualitative data collection and analysis in mixed method implementation research. *Adm Policy Ment Health.* (2015) 42:533–44. doi: 10.1007/s10488-013-0528-y
12. United Nations Department of Economic and Social Affairs Population Division. *World Population Ageing 2019 (ST/ESA/SER.A/444).* Department of Economic and Social Affairs, United Nations, New York, Unites States (2020). Available online at: https://www.un.org/development/desa/pd/sites/www.un.org.development.desa.pd/files/files/documents/2020/Jan/un2019worldpo_pulationageing_report.pdf (accessed July 1, 2019).
13. Oliveira D, Deckers K, Zheng L, Macpherson H, Ishak WS, Silarova B. The career development of early- and mid-career researchers in dementia should be a global priority: a call for action. *Aging Ment Health.* (2021) 26:439–41. doi: 10.1080/13607863.2021.1875193
14. Hinton L, Franz CE, Reddy G, Flores Y, Kravitz RL, Barker JC. Practice constraints, behavioral problems, and dementia care: primary care physicians' perspectives. *J Gen Intern Med.* (2007) 22:1487–92. doi: 10.1007/s11606-007-0317-y
15. Bernstein A, Rogers KM, Possin KL, Steele NZ, Ritchie CS, Miller BL, et al. Primary care provider attitudes and practices evaluating and managing patients with neurocognitive disorders. *J Gen Intern Med.* (2019) 34:1691–2. doi: 10.1007/s11606-019-05013-7
16. Tsoy E, Sideman AB, Piña Escudero SD, Pintado-Caipa M, Kanjanapong S, Al-Rousan T, et al. Global perspectives on brief cognitive assessments for dementia diagnosis. *J Alzheimers Dis.* (2021) 82:1001–13. doi: 10.3233/JAD-201403
17. Nitrini R, Barbosa MT, Dozzi Brucki SM, Yassuda MS, Caramelli P. Current trends and challenges on dementia management and research in Latin America. *J Glob Health*. (2020) 10. doi: 10.7189/jogh.10.010362
18. Prince M, Acosta D, Chiu H, Scazufca M, Varghese M. Dementia diagnosis in developing countries: a cross-cultural validation study. *Lancet.* (2003) 361:909–17. doi: 10.1016/S0140-6736(03)12772-9
19. World Alzheimer Report. *Journey Through the Diagnosis of Dementia.* Alzheimer's Disease International, London, United Kingdom (2021). Available online at: https://www.alzint.org/u/World-Alzheimer-Report-2021.pdf (accessed February 7, 2022).
20. Alladi S, Hachinski V. World dementia: one approach does not fit all. *Neurology.* (2018) 91:264–70. doi: 10.1212/WNL.0000000000005941
21. Cations M, Radisic G, Crotty M, Laver KE. What does the general public understand about prevention and treatment of dementia? A systematic review of population-based surveys. *PLoS ONE.* (2018) 13:e0196085. doi: 10.1371/journal.pone.0196085
22. Cahill S, Pierce M, Werner P, Darley A, Bobersky A, A. systematic review of the public's knowledge and understanding of Alzheimer's disease and dementia. *Alzheimer Dis Assoc Diso.* (2015) 29:255–75. doi: 10.1097/WAD.0000000000000102
23. Amado DK, Brucki SMD. Knowledge about Alzheimer's disease in the Brazilian population. *Arq Neuropsiquiatr.* (2018) 76:775–82. doi: 10.1590/0004-282x20180106
24. Lawlor B. The local and global imperative to raise public awareness and knowledge about dementia. *Arq Neuropsiquiatr.* (2018) 76:729–30. doi: 10.1590/0004-282x20180118
25. Warren LA, Shi Q, Young K, Borenstein A, Martiniuk A. Prevalence and incidence of dementia among indigenous populations: a systematic review. *Int Psychogeriatr.* (2015) 27:1959–70. doi: 10.1017/S1041610215000861
26. Pickett J, Bird C, Ballard C, Banerjee S, Brayne C, Cowan K, et al. A roadmap to advance dementia research in prevention, diagnosis, intervention, and care by 2025. *Int J Geriatr Psychiatry.* (2018) 33:900–6. doi: 10.1002/gps.4868
27. Alam RB, Ashrafi SA, Pionke JJ, Schwingel A. Role of community health workers in addressing dementia: a scoping review and global perspective. *J Appl Gerontol.* (2021) 40:1881–92. doi: 10.1177/07334648211001190
28. Joshi R, Alim M, Kengne AP, Jan S, Maulik PK, Peiris D, et al. Task shifting for non-communicable disease management in low and middle income countries – a systematic review. *PLoS ONE.* (2014) 9:e103754. doi: 10.1371/journal.pone.0103754
29. Bernstein A, Rogers KM, Possin KL, Steele NZ, Ritchie CS, Kramer JH, et al. Dementia assessment and management in primary care settings: a survey of current provider practices in the United States. *BMC Health Serv Res.* (2019) 19:919. doi: 10.1186/s12913-019-4603-2
30. Grober E, Wakefield D, Ehrlich AR, Mabie P, Lipton RB. Identifying memory impairment and early dementia in primary care. *Alzheimer's Dementia.* (2017) 6:188–95. doi: 10.1016/j.dadm.2017.01.006
31. Surr CA, Gates C, Irving D, Oyebode J, Smith SJ, Parveen S, et al. Effective dementia education and training for the health and social care workforce: a systematic review of the literature. *Rev Educ Res.* (2017) 87:966–1002. doi: 10.3102/0034654317723305
32. Sexton C, Snyder HM, Chandrasekaran L, Worley S, Carrillo MC. Expanding representation of low and middle income countries in global dementia research: commentary from the Alzheimer's association. *Front Neurol.* (2021) 12. doi: 10.3389/fneur.2021.633777

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: frontiersin.org/about/contact

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership