COGNITIVE, PSYCHOLOGICAL, AND PSYCHIATRIC CONSEQUENCES OF THE CORONAVIRUS (COVID-19) PANDEMIC IN THE POPULATION OF OLDER PERSONS WITH COGNITIVE IMPAIRMENT, DEMENTIA, AND/OR NEUROPSYCHIATRIC DISORDERS

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Editorial: Cognitive, Psychological, and Psychiatric Consequences of the Coronavirus (COVID-19) Pandemic in the Population of Older Persons With Cognitive Impairment, Dementia, and/or Neuropsychiatric Disorders

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Editorial on the Research Topic

Cognitive, Psychological, and Psychiatric Consequences of the Coronavirus (COVID-19) Pandemic in the Population of Older Persons With Cognitive Impairment, Dementia, and/or Neuropsychiatric Disorders

INTRODUCTION

The COVID-19 pandemic has created an unprecedented crisis throughout the world, which has led to emergency measures to control the rates of SARS-CoV-2 infection and a relocation of healthcare resources to monitor, diagnose, and treat COVID-19. Although there has been an understandable concern that older individuals, particularly men and those with preexisting comorbidities, have a higher risk of COVID-19 disease complications and mortality (1), older individuals have also faced wider risks related to their long-term health and well-being in relation to public health measures that were initiated at the start of the pandemic to control infection rates.

During 2020, in the first wave of the pandemic, most countries devised public health measures that had the primary aim to decrease rates of infection and reduce the burden of COVID-19 on already stretched healthcare systems, including social distancing, lockdowns, quarantines, and reduction of non-urgent medical services, among others. Although there was an understandable urgency to control the pandemic, the short- and long-term risks of these measures were unknown and there was concern that older persons, especially those with noncommunicable diseases such as dementia disorders, may be at particularly high risk of negative outcomes associated with these measures, particularly psychological effects, psychiatric symptoms, and declining health due to reduced access to healthcare.

It is well established that prevention can be useful for reducing cognitive deterioration, both primary (to prevent cognitive impairment) and secondary prevention (to slow down ongoing cognitive decline). Guidelines on dementia prevention by the World Health Organization (2) and Lancet Commission (3, 4) describe 12 modifiable risk factors, including physical activity, appropriate nutrition, social support and social interactions, and cognitive stimulation as important measures for reducing cognitive decline. During the current COVID-19 crisis, where many countries have been using isolation and lockdown procedures, it is likely that these protective factors are compromised, particularly in older persons with or without mental disorders and those at risk of developing dementia, which may cause a cascade of events leading to cognitive impairment.

In this Research Topic, we aimed to investigate how the COVID-19 pandemic has affected older people, especially those with cognitive impairment, from a range of perspectives to help establish factors associated with poor physical, cognitive, and mental health. One important focus of the current Research Topic was to examine how the pandemic has affected older individuals in different living situations, including those who live alone, residents in Long-Term Care Facilities (LTCF), and those receiving support from family and other informal caregivers. It is important to note that the studies in this Research Topic mostly collected data during 2020, mainly during the first wave of COVID-19. Therefore, the insights relate only to this time period. The Research Topic is comprised of 44 contributions on a wide range of themes that address how the pandemic has affected the lives of older people from multiple perspectives, including 29 original articles, 5 reviews, 9 opinion and perspective articles, and a study protocol (Porcari et al.), as summarized below.

PSYCHOLOGICAL AND NEUROLOGICAL EFFECTS IN PATIENTS WITH COVID-19

Several papers highlighted the psychological effects of COVID-19 in both the acute phase of the disease and post-infection. A scoping review of 85 articles published between 2019 and May 19th 2020 (Wenting et al.) described that the neurological manifestations of COVID-19 vary from mild (e.g., loss of taste and smell, dizziness, headache) to severe (e.g., ischemic stroke, encephalitis). The authors suggested that underlying mechanisms of central nervous system (CNS) involvement could be both direct (neurotropic) and indirect (as a result of thrombotic complication, inflammatory consequences, hypoxia, blood pressure dysregulation). In their hypothesis and theory article, Panariello et al. proposed possible mechanisms underlying neuropsychiatric manifestations in COVID-19 that appear to develop in patients with and without pre-existing neurological disorders. In a sample of older COVID-19 patients with psychosis in North Italy, Rozzini et al. reported that delirium, particularly the hypokinetic form, is related to a high risk of mortality in patients with COVID-19, especially in the presence of dementia. In the observed patients, 43% exhibited hypokinetic delirium with lethargy and confusion, of whom half died.

THE EFFECTS OF THE COVID-19 PANDEMIC ON THE GENERAL POPULATION AND HEALTHY OLDER PEOPLE

Several studies in the Research Topic focused on identifying how lifestyle and health-related behaviors of older individuals changed during the pandemic, with a mixture of both positive and negative changes. These results are important, since many of these are risk factors for cognitive decline and are modifiable (Lehtisalo et al.), such as smoking, obesity, depression, physical inactivity, infrequent social contact, and excessive alcohol consumption (4).

Ongoing epidemiological studies with pre-pandemic measures have provided useful insights into intra-individual changes that have occurred in older persons as a result of the pandemic. In a population-based study in the Czech Republic, involving participants from the Kardiovize study (5),Novotný et al. observed increased stress levels and more severe depressive symptoms in participants during the COVID-19 lockdown compared to baseline levels measured before the lockdown. This increase in mental distress was more severe in women and was associated with illness perception, personality characteristics such as feelings of loneliness, and several lifestyle components (e.g., nutrition, sleep quality, exercise etc.). Individuals who perceived COVID-19 as emotionally threatening exhibited the highest increase in stress levels and severity of depressive symptoms. Although this increase in mental distress was present in all ages, cross-sectionally the older age group showed the lowest levels of mental distress prior to and during the lockdown. Several cross-sectional surveys reported similar symptoms in the general population during the first wave of the pandemic. In Greece, Parlapani et al. found that a large percentage of individuals reported moderate to severe depressive (81.6%) and anxiety (84.5%) symptoms, as well as sleep disturbances (37.9%) and suicidal ideation (37.9%) during the first wave of the COVID-19 pandemic. The analyses highlighted that women had a significantly higher level of COVID-19 related fear, severe depressive symptoms, sleep disturbances, and higher levels of intolerance of uncertainty. Moreover, participants living alone showed higher level of loneliness; intolerance of uncertainty was found as a predictor of sense of loneliness. Similarly, in the UK (Robb et al.) a survey revealed that 12.8% of cognitively healthy older adults reported increased depressive symptoms and 12.3% had increased anxiety. These symptoms were higher in women, younger participants, people who were single, widowed, or divorced, as well as those who were living alone. Further, individuals who reported having little sleep and expressed feelings of loneliness were more likely to feel more depression and anxiety symptoms.

A Spanish study on persons aged 60 and over (Rodríguez-González et al.) reported that although more than two thirds of participants had an open space at home, 65.7% did less physical activity and only one third continued doing activities to promote healthy aging. There was a higher presence of negative feelings during quarantine in participants who did not have open spaces at home. The authors also observed that greater scores on resilience were negatively correlated with age and negative feelings, and positively correlated with the size of the social network and positive feelings.

An Italian study on community-dwelling people at increased risk of dementia (e.g., subjective cognitive decline and MCI) (Di Santo et al.) reported negative lifestyle changes that are potentially harmful to future cognitive decline. More than one third reduced their physical activity during the pandemic and nearly 70% reported an increase in idle time. Individuals also reported a decrease in adherence to the Mediterranean diet and more than a third reported weight gain. About one fifth were depressed, and this was significantly associated with living alone or having a poor relationship with cohabitants, low sleep quality, and not owing a pet. More than a quarter (27.2%) reported that they had often felt sad, depressed, or downcast so much since the start of the lockdown that nothing could cheer them up. Community-dwelling people at increased risk of cognitive decline were also the focus of a Finnish population-based survey (Lehtisalo et al.), where a mixture of positive and negative lifestyle changes were observed during the pandemic. Although about one third reported a decrease in physical activity a large proportion of people were able to keep up healthy eating habits, with many increasing their vegetable and fruit consumption. Self-rated health and quality of life generally remained stable, but 21% reported more feelings of loneliness and 15% felt that their memory had been getting worse during the pandemic. Older people and those living alone seemed more susceptible to loneliness and negative changes. In contrast, Bidzan-Bluma et al. found that older people (aged 60+) in a Polish and German population study rated their quality of life, life satisfaction, sleep quality, and well-being during the pandemic higher than younger people. Further, they experienced lower levels of trait anxiety. However, the authors noted that the older participants were generally financially stable and had high education (>60% with university education), which may have influenced the results. Similarly, Rossi et al. reported that age moderates the mediating effect of resilience in the relationship between COVID-19-related stressful events and depressive and anxiety symptoms and perceived stress in an Italian sample. Older adults (age 60+) reported lower levels of depressive symptoms, anxiety, and stress than younger persons, and had higher levels of resilience. The authors suggested that resilience in older adults is less influenced by stressful events, and this could be one of the reasons accounting for the better mental health outcomes observed in the older age group during the pandemic.

After performing a search of the existing literature, Fontes et al. proposed some intervention and preventive measures to mitigate and reduce the risk of psychological and psychiatric disorders in older persons. They proposed expanding telehealth services for older people and their relatives (for answering questions about psychological and psychiatric symptoms and establishing contact to monitor and access medication and non-pharmacological adjuvant therapy) and using telepsychiatry as a screening and assessment tool. They also emphasized the needed to prepare training materials for healthcare on good mental health practices during the pandemic and to offer educational materials for individuals to increase awareness of interacting and caring for older relatives.

In a perspective paper, Lozupone et al. reinforced the importance of correct assessment of social frailty in terms of the prevention of late-life neuropsychiatric disorders, particularly in the COVID-19 era. One study also examined how COVID-19 affected patients after recovery; Janiri, Kotzalidis, et al. reported a higher frequency of psychological distress in patients aged over 60 after the acute phase of illness, which in turn may be associated with impaired emotional regulation and higher scores on depressive and cyclothymic temperaments. A literature review (Manca et al.) reported evidence from 8 papers showing that different neuropsychiatric symptoms emerged and/or worsened in older adults with and without dementia as a consequence of COVID-19 infection. Further, a study by Banerjee and Rao conducted in India on older individuals with transgender identity, revealed that they were at increased emotional and social risks during the COVID-19 pandemic, particularly marginalization, the dual burden of "age" and "gender," and multi-faceted survival threats (physical, emotional, financial). Social rituals, spirituality, hope, and acceptance of "gender dissonance" emerged as the main coping factors.

RESIDENTS IN LONG-TERM CARE FACILITIES DURING THE PANDEMIC

de Girolamo et al. reported higher mortality rates in LTCF residents in Northern Italy when compared to expected values of mortality rates among the older general population living in the community; mortality increased about four times during the pandemic when compared to previous years. Other adverse events were also seen during the pandemic in these settings; Lombardo et al. found that one third of LTCFs participating in their study reported at least one adverse event (defined as any harm or injury resulting from medical care or the failure to provide care), during March 24 to May 5 2020. Several factors were associated with the occurrence of adverse events in these facilities, including having a higher bed capacity (more than the median of 60 beds), increased use of psychiatric drugs, physical restraint measures, residents hospitalized due to flu-like symptoms, and being located in specific geographic areas (i.e., North-West, North-East Italy). The pandemic was also shown to affect visitors to LTCFs; an online survey in Ireland (O'Caoimh et al.) reported that many LTCF visitors experienced poor psychological and emotional well-being during the COVID-19 lockdown. Further, visitors of residents with cognitive impairment showed significantly lower well-being than those without.

THE EFFECT OF COVID-19 LOCKDOWNS AND QUARANTINE ON PATIENTS WITH MILD COGNITIVE IMPAIRMENT (MCI) AND DEMENTIA DISORDERS

Many articles in this Research Topic highlighted that the pandemic affected individuals with dementia disorders, MCI, and other conditions, particularly with regard to behavioral and neuropsychiatric symptoms. In a systematic review, Simonetti et al. observed that neuropsychiatric symptoms of dementia (especially apathy, anxiety, and agitation) during COVID-19 appear to arise from pandemic-related social restrictions, while Manca's et al. review highlighted that that delirium, agitation, and apathy were the symptoms most commonly detected in older adults during the pandemic, especially in people with dementia. An Italian multisite study in 87 memory clinics (Cagnin et al.) reported a rapid increase of Behavioral and Psychological Symptoms of Dementia (BPSDs) in ∼60% of dementia patients. The pattern of BPSDs varied according to dementia type, disease severity, and sex; anxiety and depression were associated with Alzheimer's Disease, mild to moderate dementia severity, and being female, whereas patients with dementia with Lewy bodies had a significantly higher risk of worsening hallucinations and sleep disorders. Frontotemporal dementia was associated with wandering and appetite changes. Overall, irritability, apathy, agitation, and anxiety were the symptoms that were most frequently reported to worsen during the pandemic, while sleep disorders and irritability were the most reported new symptoms. Similar behavioral symptoms were observed in community-dwelling patients with dementia in an Argentinian study; Cohen et al. reported increased anxiety, insomnia, depression, and a worsening of gait disturbances during the pandemic in these patients. Anxiety, depression, and insomnia were more common in individuals with mild compared to severe dementia. Family members also reported an increased use of psychotropic drugs to control behavioral symptoms in the dementia patients (specifically a 20% increase for antipsychotics, 15% for benzodiazepines, 6% for hypnotics, and 10% for antidepressants).

A study conducted in an Alzheimer Center in the Netherlands (van Maurik et al.) showed that 44% of patients with cognitive impairment were concerned about faster cognitive decline. Both patients with symptomatic cognitive impairment and cognitively normal patients (i.e., with subjective cognitive decline) reported an increase of one or more psychological symptoms as a result of the pandemic-related measures. Caregivers reported an increase in patients' apathy (54%), a change in sleeping behavior (48%), increased repetitive behavior (34%), and patient aggression (30%). Social isolation and reporting one or more psychological symptoms were determinants for worries for faster cognitive decline.

A Japanese study provided important insight into the situation faced by patients with dementia or MCI who live alone (Hashimoto et al.). Most patients who lived alone did not limit their outings or activities during the COVID-19 outbreak, whereas more than half of the patients who lived with their families reduced their frequency of going out. The researchers used an original questionnaire to caregivers and/or patients to evaluate how the patient's current state compared to the prepandemic period. When asked "Did the COVID-19 outbreak increase the patients' mental stress?," patients with dementia or MCI reported significantly less mental stress than caregivers, regardless of living conditions.

PATIENTS WITH PARKINSON'S DISEASE, DOWN SYNDROME, AND TUMORS

An Italian study (Baschi et al.) on patients with PD, MCI, or both (PD-MCI), showed a worsening of cognitive, behavioral (both pre-existing and new), and motor symptoms during the COVID-19 lockdown, particularly those with PD and MCI. Compared to PD patients without cognitive impairment, PD-MCI were more like to decline in Instrumental Activities of Daily Living functions. Further, they had higher frequencies of all NPI symptoms except appetite/eating disturbances and a significantly higher frequency of cognitive impairment, fatigue, and speech problems. These symptoms resulted in an increased caregiver burden in about a quarter of cases. Similarly, Janiri, Petracca, et al. reported that a quarter of PD outpatients with lifetime psychiatric symptoms showed a worsening of psychiatric symptomatology during the COVID-19 outbreak, especially depression and insomnia. Lifetime pre-existing delusions, having received antipsychotics, and not having received mood stabilizers were associated with subjective worsening of psychiatric symptomatology due to the COVID-19 pandemic.

Villani et al. investigated Italian adults with Down Syndrome using an analysis comparing pre- and post-lockdown evaluations. After the lockdown period there was a significant worsening in social withdrawal, instrumental activities of daily living, and depression together with a significant improvement in aggressive behavior. Büssing et al. reported lower well-being among tumor patients living in Germany, especially in the younger population. More than half were worried about being infected and having a complicated disease course. Patients noticed changes in their attitudes and behaviors because of the pandemic-related restrictions, including worrying reflections and loneliness, interest in spirituality, and intense relationships.

CAREGIVER BURDEN DURING THE PANDEMIC

Early in the pandemic, there was a significant disruption to healthcare and formal care services due to the potential risk of SARS-CoV-2 infection in staff and patients, as well as a redistribution of healthcare budgets to focus on COVID-19 diagnosis, prevention, and treatment. Consequently, informal caregivers, particularly those of patients with dementia and other neurocognitive disorders, were often relied on to counterbalance the reduction of formal services, which may negatively affect their health and well-being. In a Dutch study on pre-dementia memory clinic patients (van Maurik et al.), care was discontinued during the COVID-19 pandemic for three quarters of symptomatic patients, and this was strongly associated with caregiver burden. More than half of caregivers reported a higher caregiver burden, which was also associated with psychological and behavioral problems, and almost one third reported a need for more support. An Italian multisite study (Cagnin et al.) found stress-related symptoms in two-thirds of dementia patient caregivers during COVID-19 and, in China, Li et al. reported a high prevalence of anxiety and depressive symptoms among caregivers. Being female was an independent risk factor for experiencing anxiety symptoms while pre-existing mental disorders increased the risk of depressive symptoms. In Brazil (Penteado et al.), a study on patients with neurocognitive disorders and Down syndrome reported that clinically relevant neuropsychiatric symptoms had a significant impact on caregiver distress during the COVID-19 pandemic. Apathy, aberrant motor behavior, sleep disorders, and psychoses contributed most to an increase in caregiver burden. Interestingly, interventions may help to reduce the risk of caregiver burden, as reported by a study in Northern Italy (Cravello et al.) on patients with dementia or cognitive decline whose related caregivers had attended a structured family support course before the COVID-19 lockdown. After lockdown, the patients did not have a worsening of neuropsychiatric symptoms and, although their functional abilities declined, their caregivers experienced a decrease in caregiver burden in comparison to the pre-lockdown period. This provides promising insight into how comprehensive family support interventions that teach, train, and aid caregivers of patients with cognitive disorders can reduce caregiver burden even in negative periods such as the COVID-19 pandemic.

EFFECTS OF THE COVID-19 PANDEMIC ON CLINICAL ACTIVITIES AND HEALTHCARE

During the first year of the pandemic, there was a rapid change in routine clinical activities for non-urgent medical conditions, due to public health restrictions and the potential risk of SARS-CoV-2 infection in both patients and healthcare professionals. In the first wave, cancellations in dental healthcare (43%), home aid (30%), and rehabilitative services (53%) were reported in a Finnish population-based survey of older persons at risk of cognitive decline. Cohen et al. reported that rehabilitation services had been discontinued due to the lockdown in most community-dwelling dementia patients in their Argentinian study. Further, Spalletta et al. reported a substantial decrease in scheduled appointments in an Italian Memory Clinic in March–April 2020 compared to the same period in 2019 due to the Government's restrictive measures. They estimated that many patients with dementia and cognitive disorders missed crucial appointments (66.7% of patients who were due to have first appointments and 77.4% with follow-up appointments), resulting in a delay in initial diagnosis and initiation of treatment. Korsnes et al. described that most of the patients at the Department of Old Age Psychiatric 24-h unit in Norway welcomed the strict measures that were applied in the clinic (including a visitation ban for inpatients and a reduction in outpatient consultations). Interestingly, many individuals reported that they were not very scared of getting COVID-19 and many did not believe that they would die if they were infected. On the other hand, employees were concerned about how the COVID-19 crisis would influence their health and well-being at work.

In a perspectives article, D'Cruz and Banerjee expressed concerns regarding the care of persons living with dementia in India, discussing that they face dual risks due to both age and cognitive decline, which are accentuated by the pandemic. The authors suggested that pandemic control in India can be best achieved when persons living with dementia are made part of, and advocates for, care rather than mere recipients. Through interviews with dementia care physicians in Southern India, Banerjee et al. outlined the major concerns and barriers to care of persons with dementia during the pandemic. Although an overarching theme was that telemedicine is the future of dementia care in India most participants perceived ambiguity related to newly-released national telepsychiatry guidelines.

TEMPORARY CARE FACILITIES, REMOTE ASSESSMENT, AND DIGITAL SOLUTIONS FOR HEALTHCARE DURING AND AFTER THE PANDEMIC

COVID-19 heightened the need for remote assessment of older people, especially as they have a higher risk of COVID-19 complications and thus, have often been encouraged to adhere strictly to social distancing measures. Owens, Hindus et al. provided recommendations from a Patient Advisory board of a European project that included a set of prioritized functional domains sensitive to the early stages of Alzheimer's Disease and a set of remote measurement technologies capable of targeting them. A review of the existing literature (Owens, Ballard, et al.) highlighted several challenges for remote memory clinics related to internet access, computer skills, limited evidence base, and regulatory and data protection issues. The authors suggested that digital biomarkers collected remotely may have significant potential for diagnosis and symptom management in older adults and proposed a framework and pathway for how technologies can be implemented to support remote memory clinics. Sousa Alves et al. conducted a systematic review of pre-pandemic home-setting psychoeducation interventions for behavioral changes in dementia, to identify potential solutions for the COVID-19 era. They observed that most of the psychosocial and psychoeducational interventions described were person-centered strategies based on the cognitive-behavioral approach or informational tools to enhance care providers' knowledge of dementia. Most studies achieved successful results in handling BPSD and mood-anxiety symptoms of care providers, contributing to an overall improvement in dyad life quality. They concluded that low-cost techniques, tailored to the dyad well-being, with increasing use of technology through friendly online platforms and application robots, can be an alternative to conventional assistance during COVID-19 Pandemic.

Debas et al. reported their experience from a temporary care facility for institutionalized patients with major neurocognitive disorder and BPSDs during the SARS-CoV-2 pandemic in Canada. Due to their expertise as a multidisciplinary team specialized in BPSD management, they were asked to support staff in the temporary care facility who had little experience in dementia care. This had a positive impact on non-professionals' sense of effectiveness in addressing patients' neuropsychiatric symptoms.

Keng et al. provided recommendations on how to address challenges faced by individuals with BPSD and their caregivers during the pandemic with a proactive approach: implementing infection control strategies, monitoring the long-term biological and psychosocial effects of COVID-19 in patients with BPSDs, using evidence-based structured psychosocial and biological interventions through innovative means such as virtual and individualized care to manage BPSD, use of structured and algorithmic models of care, and appropriate use of psychosocial interventions across healthcare settings.

Soares et al. gave recommendations on telemedicine as an important alternative method of assistance for BPSD management. They discussed how telemedicine can expand access to clinical resources and link healthcare providers with patients and their caregivers, thereby overcoming the reductions in face-to-face appointments and providing a balance between the need for both social distancing and specialized consultation. They also described how it can help caregivers by providing guidance on non-pharmacological measures to control symptoms that are adapted to the new social distancing and lockdown scenarios.

Although many articles discussed the benefits of digital medicine tools, Martins Van Jaarsveld importantly discussed the increased negative effects that the digital divide is having in the older population during the COVID-19 pandemic. The digital divide refers to the uneven distribution of technological access and skill across ages, where older people have less access and lower proficiency in using technologies than younger adults. The authors explored the increased negative effects that the digital divide is having on the older population during the COVID-19 pandemic, while highlighting the need for increased attention and resources to improve digital literacy in the elderly. Intriguingly, this technological chapter clarifies that one of the few positive effects of the pandemic has been the acceleration of the application of telemedicine and digital medical and health tools.

THE IMPACT OF THE PANDEMIC ON ONGOING RESEARCH

In the first wave of the pandemic, many ongoing research activities with human participants were halted to reduce face-to-face contact between participants and research staff. Through an anonymous self-administered online survey, McGoohan et al. investigated the willingness of PD patients and carers to resume clinical research and their opinion on adaptations to trials in light of COVID-19. The majority of respondents were positive about the continuation of non-COVID-19 related research as long as certain safety measures were in place, including using personal protective equipment, and research staff having regular tests for COVID-19 and traveling by car rather than public transport. Almost all (94%) indicated a willingness to complete assessments virtually, but telephone calls were the preferred method for remote follow-up compared to video call or online surveys. Thirty-nine percent of participants said they would feel more comfortable taking part in research if they did not have to visit a clinical setting, 8% preferred clinic settings, and the remainder were happy with either option. Regular and supportive communication from the research team was seen as important for maintaining the psychological well-being of participants while taking part in trials.

DISCUSSION

Countries are now facing their 2nd and 3rd waves of COVID-19. Although vaccination programmes are ongoing globally, periodical restrictions to reduce the rates of SARS-CoV-2 infection are being implemented; thus, results found in the first wave may be useful for providing better insights for the future. As the papers in the current Research Topic show, the restrictions may adversely affect older individuals in different ways. Nevertheless, the original research papers presented here predominantly analyzed data from the first wave of the pandemic in 2020 and the findings must be interpreted in light of this.

Many authors highlighted rising psychological effects of COVID-19 and the consequent restrictive measures adopted worldwide in patients with and without neurocognitive disorders. The emergence of new neuropsychiatric symptoms and a rapid increase of pre-existing symptomatology were reported at different stages of cognitive impairment, from both patients and caregivers, together with an increased use of psychotropic drugs. Furthermore, patients with symptomatic cognitive impairment or subjective cognitive complaints showed increased concerns about faster cognitive decline, with social isolation and reporting of one or more psychological symptoms considered as determining factors. It will be important to identify whether the neuropsychiatric symptoms that were often seen in patients with cognitive impairment and dementia in the first wave of the pandemic still increased in subsequent waves or whether people found better coping strategies over time.

The rapid negative change in routine clinical activities for non-urgent medical conditions during the pandemic affected not only patients' care access and monitoring but also increased caregiver burden. Apathy, aberrant motor behavior, sleep disorders, and psychosis increased in dementia patients and contributed to an increase in caregiver burden. Nevertheless, a comprehensive family support intervention on caregivers of patients with dementia was reported to reduce caregiver burden even in negative periods such as the COVID-19 pandemic. Furthermore, telemedicine and improving digital health literacy, together with psychosocial and psychoeducational person-centered interventions, were proposed as effective alternatives to manage patients' and caregivers' care during the pandemic emergency. It is essential to assess how effective such strategies have been for older individuals and whether they are sustainable in the post-pandemic era. Importantly, patient preferences and health equity must be considered, especially in relation to the digital divide that affects the older population.

This Research Topic also highlighted how the pandemic affected healthier older persons, in terms of lifestyle factors, among others. The "Dementia prevention, intervention, and care: 2020" report of the Lancet Commission (4) highlighted

12 modifiable factors risk factors that are estimated to account for around 40% of worldwide dementias, which consequently could theoretically be prevented or delayed. It is imperative to investigate what effect the pandemic-related changes in health and lifestyle behaviors will have on the future prevalence of dementia disorders. Further, intervention strategies to increase healthy lifestyle behaviors and promote social and cognitive stimulation during the ongoing pandemic need to be evaluated to identify which interventions are more successful at achieving behavior change in the short- and medium-term.

Studies in this Research Topic repeatedly demonstrated that the effects of the pandemic were particularly marked in individuals who live alone (Di Santo et al.; Lehtisalo et al.; Novotný et al.; Robb et al.; etc). As we move forward, it is crucial that people who have a higher risk of negative outcomes such as these are targeted for interventions to help them during future phases of the pandemic. Further, cross-country comparisons are needed to assess how lifestyle and health behaviors differed globally during the pandemic, depending on the various public health measures. Collaborative research and data harmonization between different study groups may play an essential role. For example, the World-Wide FINGERS network (6), a global network of trials that aim to prevent dementia and cognitive decline through risk factor modification, launched the WW-FINGERS SARS-CoV-2 Survey in multiple countries, to explore how the pandemic has affected risk factors for dementia, while accounting for country-specific strategies to contain the spread of the infection.

The progression of the pandemic is still unclear; we need to await long-term evidence concerning how long immunity persists after vaccination against COVID-19 and whether this differs between individuals according to individual characteristics (e.g., age, sex, ethnicity, etc). There is also uncertainty about SARS-CoV-2 Variants of Concern, and whether these may undermine current public health and vaccination strategies. Further, access to vaccination has not been equal for all countries; due to issues in production and supply, some low- and middle-income countries might have lower vaccination coverage than higher-income settings. Given all these uncertainties, it is likely that countries around the globe will need to periodically impose infection control measures to protect the population from COVID-19 and reduce the burden on healthcare systems. Thus, healthcare services need to plan strategies to deal with the emerging needs of older persons, patients with cognitive impairment and dementia, and those with psychological and neuropsychiatric symptoms. Initiatives need to deal with the screening, treatment, and monitoring of such symptoms during the ongoing pandemic as well as identifying strategies to deal with the rapid progression of cognitive and behavioral symptoms faced many individuals with pre-existing cognitive impairment, whose care has been significantly disrupted during the pandemic.

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OPINION
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Impacts of the SARS-CoV-2 Pandemic on the Mental Health of the Elderly

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INTRODUCTION

According to the World Health Organization (WHO), SARS-CoV-2 has infected approximately 17 million people worldwide, and almost 670,000 have died from complications of the disease (1). Hence, countries around the world have implemented social distancing measures to reduce the spread of the virus. Coronavirus coping strategies have profoundly changed social dynamics, given the adverse effects on people's mental health (2) and their psychosocial impact (3). Due to higher morbidity and mortality (4, 5) and potential previous mental illnesses (6), the elderly population should be given more considerable attention, considering they must adhere more appropriately and for more extended periods to preventive measures (7). However, despite these studies, the psychiatric impact of COVID-19 on the elderly population still lacks more significant theoretical support, since few reports are describing psychiatric symptoms associated with the pandemic (5). Given the above, this paper is intended to illustrate and correlate the mental, psychiatric, and psychological consequences for the elderly during the COVID-19 pandemic.

MATERIALS AND METHODS

The authors searched in three electronic databases: PubMed (NCBI), Science Direct, and Google Scholar. They used the following search terms with adjustments and variants:

1 "COVID-19" OR "SARS-CoV-2" (Medical Subject Headings – (MeSH term)) AND
2 "Elderly people" (keywords) OR "Aged" (MeSH term) AND
3 "Mental health" (MeSH term) OR "Mental health disorders" (keywords).

Papers were chosen using the following criteria: at least a combination of two terms described in the search strategy; approach on the psychiatric impact of the COVID-19 pandemic on the elderly and original papers with the full text available. An additional search was also carried out on websites and available documents relevant to the theme but which did not previously fit the search.

DISCUSSION

Vulnerability of the Elderly

Older people are among the most vulnerable and high-risk groups during epidemics (7, 8), as they often have associated comorbidities (4). The incidence of systemic hypertension in people who are over 60 years old ranges between 45.5 and 63.1%, that of diabetes mellitus is around 16.8 and 26.8% (9, 10), heart failure accounts for 3.8%, and COPD is found in 23.7% (9, 10). These diseases can potentially affect the prognosis of patients with COVID-19, as there may be damage to vascular structures, impaired lung function, and even reduced immunity (11). Also, the elderly naturally have a relatively less effective immune system than young people and are more susceptible to developing critical illnesses (8, 11). Thus, the elderly population can be considered at high risk of disease progression and death from COVID-19. Therefore, the very notion of vulnerability, previous comorbidities such as heart failure, and chronic obstructive pulmonary disease that increase the risk of depression, anxiety disorders, and functional limitations caused by these comorbidities can be significant stressors for the psychological distress of this population.

Another factor that increases the vulnerability of the elderly is limited access to healthcare services. Although they use it more frequently and have higher rates of hospitalizations compared to younger people (12) due to their cardiovascular comorbidities and cognitive and psychotic disorders (2, 8, 9, 11, 13), according to van Gaans and Dent (14), the elderly still face problems in accessing healthcare services. This problem may be due to uneven geographical and spatial distribution of healthcare services, insufficient availability, and difficulty obtaining information. These aspects contribute to a weakness that can be aggravated by financial and health crises, in which there are cuts and reduced spending on healthcare (14). This, in turn, generates concerns and anxiety about the future (15). Thus, it is reasonable to assume that the pandemic's economic crisis will also affect the mental health of the elderly while significantly reducing their mental healthcare.

Another essential issue to be outlined is that the elderly are subject to social distancing, affecting their psychological and psychiatric status. Most older people have little means of socializing with other people, some being restricted to community centers and religious temples (16, 17). These places may be inaccessible due to lockdowns, which generates feelings of social and psychological isolation in this age group (16, 17). Also, visits to nursing homes have been restricted or even banned, making interaction with family members more difficult and exacerbating nursing homes' isolation feelings (18). These are worrying facts because they can be triggers (7) for previous psychiatric disorders (8, 13, 18), as they limit therapeutic adherence, amplify negative symptoms, and reinforce self-destructive tendencies from a view of "I am not necessary (…), I have been forgotten (…), I am alone and lonely." Considering today's demographic transition around the world, which points to clear population aging, especially in developing countries where psychiatric care is limited, the elderly's mental health of the elderly and their vulnerability factors become a concern in global public health (7, 17).

Mental Disorders in the Elderly During the Pandemic

During the COVID-19 epidemic, lack of interaction and social distancing exacerbate psychological disorders and increase the risk of depression and anxiety in the elderly (16, 17). Meng et al. (8) showed that about 37.1% of the elderly had experienced depression and anxiety during the pandemic. In addition to isolation, fear and stress contribute to the onset and exacerbation of pre-existing mental health disorders. People with obsessive-compulsive disorder have higher chances of experiencing obsessive thoughts due to precautionary measures (19). However, there is a lack of consensus concerning these data. A cross-sectional study carried out in China found that 33% of people show anxiety disorders, and about 20% show depressive symptoms. Still, it argued that these data should be lower in more advanced age groups (20).

A robust predictive factor for psychiatric comorbidities is dementia, which is common with advancing age (2, 18). Subjects with dementia and cognitive impairment have limited access to accurate information and facts about the pandemic (18). Also, they may not correctly follow recommendations to reduce the spread of COVID-19 (such as hygiene and precautionary measures), because they cannot remember procedures or understand important information (3, 18). Social distancing effects are also reflected in people with dementia due to withdrawal from important non-pharmacological therapies to treat comorbidities, such as social activities, physical exercises, and group therapies (2). Possible trauma resulting from these changes can further accelerate cognitive decline. As subjects with dementia are more likely to have cardiovascular disease and diabetes (2), it can be assumed that this group is at an even higher risk of morbidity and mortality from COVID-19.

Like dementia, psychosis requires special attention. Social distancing measures can increase psychotic patients' stress, just like precautions related to disease spread have been associated with increased paranoia (13). The excess of information can also intensify paranoid symptoms, generating suspicions regarding healthcare (3). In this case, patients with psychosis are less motivated to comply with recommended measures (13), leading them to avoid social distancing and quarantine measures (3). Findings show that COVID-19 has been associated with a 25% increase in the incidence of psychotic outbreaks cases (13, 21). In the elderly, there has also been an increase in the risk of schizophrenia, as the mean age for patients newly diagnosed with schizophrenia changed from 39 to 50 years (21). The severity of symptoms and steroid administration seem to contribute to the onset of psychotic symptoms (12). Similarly, there are reports of recent psychosis in infected individuals, and SARS-CoV-2 may have a neuropathogenic mechanism that would trigger these symptoms (5, 13).

Suggested Proposals

Because of the crisis caused by the pandemic, intervention and preventive measures must be implemented to mitigate and reduce the risk of psychological impact and psychiatric disorders in the elderly (6, 8, 17, 22), namely:

a. Expanding telehealth services for the elderly/their family members to answer questions about symptoms, establishing contact to monitor access/medication administration and suggest non-pharmacological adjuvant therapy (e.g., cognitive-behavioral therapy sessions that can be attended online) (7, 17);
b. Using telepsychiatry as a screening tool for cases of elderly people with mild/moderate psychiatric disorders, and an assessment tool for cases requiring hospitalization/strict monitoring, such as psychoses (2, 17);
c. Preparing training materials for health professionals based on past experiences to qualify them to provide care and act as multipliers of good mental health practices in the pandemic (7, 21);
d. Offering advertisement and educational materials to make people aware of the need to interact/care and respect their elderly relatives, the need to maintain regular contact online/through the telephone (3) during the pandemic, and health promotion measures to fight COVID-19 and mental health disorders (8);
e. Introducing social security measures to fight the economic exclusion of these individuals (15, 22).

CONCLUSION

With the spread of COVID-19, health authorities, governments, and the civil society must deeply reflect on the issue in an attempt to offer equity of care and formulate emergency public policies to deal with the short and long term psychiatric effects of the pandemic, especially in the most vulnerable groups: children, mental patients, refugees, indigenous people, quilombolas (Afro-Brazilian residents of settlements created by escaped slaves), people with chronic non-communicable diseases and, of course, the elderly.

AUTHOR CONTRIBUTIONS

JGJ, WHAF, and CACV designed the review, developed the inclusion criteria, screened titles and abstracts, appraised the quality of included papers, and drafted the manuscript. MSVG, CGLS, and CACV reviewed the methodological protocol and inclusion criteria and provided substantial input to the manuscript. JGJ, WHAF, CACV, CGLS, and MSVG reviewed the study protocol.

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Intolerance of Uncertainty and Loneliness in Older Adults During the COVID-19 Pandemic

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Objective: The COVID-19 pandemic imposed a psychological burden on people worldwide, including fear and anxiety. Older adults are considered more vulnerable during public health emergency crises. Therefore, the aim of the present study was to investigate the psychological response of older adults during the acute phase of the pandemic in Greece.

Method: This cross-sectional study was part of a larger three-day online survey. A total of 103 participants over the age of 60 fulfilled inclusion criteria. The survey included sociodemographic questions and six psychometric scales: the Fear of COVID-19 Scale (FCV-19S), the Brief Patient Health Questionnaire (PHQ-9) depression scale, the Generalized Anxiety Disorder scale (GAD-7), the Athens Insomnia Scale (AIS), the Intolerance of Uncertainty Scale (IUS-12), and the De Jong Gierveld Loneliness Scale (JGLS).

Results: A significant proportion of the participants reported moderate to severe depressive symptoms (81.6%), moderate to severe anxiety symptoms (84.5%), as well as disrupted sleep (37.9%). Women reported significantly higher levels of COVID-19–related fear, more severe depressive symptoms and sleep disturbances, as well as higher levels of intolerance of uncertainty. Participants living alone showed higher levels of loneliness. Intolerance of uncertainty was shown to modulate levels of loneliness.

Conclusions: During the quarantine, attention was promptly drawn upon the risks related with older people's loneliness. Studies identifying factors that may contribute to loneliness during a public health emergency facilitate the implementation of supportive interventions. Preparedness to address and manage older people's loneliness may limit this deleterious emotional response during the pandemic, as well as at the post-COVID-19 phase.

Keywords: COVID-19, older adults, loneliness, intolerance of uncertainty, depression, anxiety

INTRODUCTION

The World Health Organization (WHO) declared COVID-19, the disease associated with the novel "Severe Acute Respiratory Syndrome Coronavirus 2" SARS-CoV-2, a "Public Health Emergency of International Concern" on January 30 (1), and a "pandemic" on March 11, 2020 (2). In Greece, the first confirmed COVID-19 case was reported on February 26. While the number of COVID-19 positive cases was constantly increasing, restriction measures were stepwise introduced. After 695 COVID-19 confirmed cases and 17 COVID-19–related deaths had been reported, a 6-week national lockdown was imposed on March 23 (3).

The COVID-19 pandemic induced worry (4), fear (5), anxiety, and depressive symptoms (6), as well as insomnia (7). Older adults are considered more vulnerable during public emergency crises (8). Their vulnerability is linked with the age-related compromised physical state, increased prevalence of chronic health conditions and other disabilities, cognitive abilities' decline, as well as the potential presence of adverse psychosocial conditions (9). Similarly, the COVID-19 pandemic affected older people in many different aspects. Fear of contracting the virus and fear of death impinged on older people (10), since increased age is a risk factor for severe disease due to compromised immune system function and the higher prevalence of risk conditions for severe COVID-19, such as hypertension, diabetes mellitus, cardiovascular, and respiratory diseases (11); around 66% of people over the age of 70 were shown to suffer from at least one chronic medical condition (12). The case fatality ratio was estimated at 1.4% for people under the age of 60, at 4.5% for people over 60, whereas at 13.4 for people over 80 (13). During the pandemic, around 95% of COVID-19–related deaths in Europe, 80% of fatal COVID-19 cases in the United States, and 80% of fatal cases in China involved patients over the age of 60 to 65 (14). By June 1, 2020, 76.5% of the 179 COVID-19–related deaths in Greece involved patients over the age of 65 (15). Despite the emphasis placed by WHO on the older residents of long-term care facilities (16), a great number of COVID-19–related deaths was reported in care homes in countries severely affected by the pandemic. Although official records were not always complete and accurate, available data suggested that between the middle of April and the beginning of May, 67% of total COVID-19–related deaths in Spain and 37% of total COVID-19–related deaths in France involved residents in care homes; death numbers in care homes in the United Kingdom were the greatest since 1993 (17), while roughly one out of five COVID-19–related deaths in the United States was recorded in nursing homes (14).

The older high-risk group for severe COVID-19 illness was also in danger of having to cope with ageism, a term coined by Dr. Robert Butler to broach the matter of discrimination against older people and the common use of stereotypes (18), since ageism may involve age discrimination in health care as well (19). During the pandemic and in face of medical equipment shortage, age was a criterion that may have been applied in ventilator triage policies, in such "if patients have similar expected incremental increases in survival, triage decisions may include consideration of patient age based on the principle that people should have the opportunity to live as much of the normal human life cycle as possible"; "in the event that there are ties in priority scores between patients, life-cycle considerations will be used as a tiebreaker, with priority going to younger patients, who have had less opportunity to live through life-stages" (20). Despite criticism against such policies (21), healthcare professionals in countries severely affected by the pandemic were forced to prioritize younger over older patients due to the healthcare system's overload with COVID-19 patients (22).

Furthermore, measures to preserve resources for the management of the pandemic, such as suspension and/or postponement of health services for non-emergent conditions unrelated to COVID-19 (23), posed a risk to older people's physical health (10), since older adults are more likely to suffer from chronic conditions requiring regular doctor visits and long-term medication (14). Similarly to other countries, the guidelines by the Hellenic National Public Health Organization (24) to restrict virus spread in hospitals included canceling all non-emergent outpatients' visits and surgical procedures. In addition, fear of retracting the virus may have been associated with decreased hospital visits and hospitalizations for other conditions. Although there have been no official data on hospital visits at the emergency departments for COVID-19–unrelated reasons, there were anecdotal records of markedly decreased visit numbers in all departments (25). Altogether, older people's chronic health issues were in danger of being lower-prioritized, due to the necessity of placing emphasis on containing the pandemic (26).

A pandemic is a worldwide health emergency crisis associated with fear (27), an "emotional reflex" related with collective memories of former deadly infectious diseases (28). Fear of the unknown (29) and worry (30) are emotions related to Intolerance of Uncertainty (IU), a characteristic originally conceptualized as the cognitive, emotional, and behavioral responses to uncertainty in everyday situations (29, 31). Throughout the years, researchers provided more definitions, in an effort to describe this concept more accurately (29). Individuals with high IU consider the possibility of a negative event as unacceptable and threatening (32), are prone to worry about unpredictable, future negative events and tend to perceive uncertain and ambiguous situations as threatening (33). Two dimensions were incorporated in the concept of IU, prospective and inhibitory IU (34); prospective IU represents the cognitive dimension, that is, cognitive assessments of threat related with unforeseeable events and desire for foreseeable events; inhibitory IU represents the behavioral dimension, that is, behavioral inhibition or "paralysis" due to uncertainty (35). Lately, IU has been conceptualized as an individual feature, a trait, reflecting negative beliefs about uncertainty and, according to Carleton (36), the incapacity to bear the response "triggered by the perceived absence of salient, key, or sufficient information". This tendency toward negative perceptions and responses to uncertain circumstances was associated with worry (37) and anxiety-related disorders (33). On the other side, "state" IU may also emerge in response to uncertain stimuli, on the ground of high or normal trait IU, or as part of emotional disorders (33) that may have emerged during the COVID-19 pandemic (38). Moreover, IU was found to be a predictor of COVID-19–related fear (39).

Social-physical distancing and quarantine, the main strategies implemented to prevent the spread of COVID-19 (40), were related with psychological distress, depression, anxiety, insomnia, and social detachment (41). The latter imposed a great psychological burden particularly on dependent older people living alone and/or receiving home care by family members, friends, caregivers or social services. Although prompted by empathy and fear for the high-risk community members' safety (42), physical distancing was associated with reduced home visits, disruption of regular care provision, and focus on only basic needs. Still, the fragile health condition of very old people may be affected by inadequate nutrition, lack of personal and home hygiene, restriction of physical exercise, and irregular supervision of medication intake. Moreover, lack of social contacts contributes to cognitive decline, which, in turn, may lead to risky behavioral disturbances (25). In addition, common socialization channels for older people, such as meeting centers and churches, were locked down. As a result, restriction measures deprived older adults of the opportunity to socialize with their peers, compromising psychological well-being by bringing on isolation, a condition posing a great risk for depression, anxiety (43), as well as loneliness (10).

"Loneliness" is a term encompassing a wide range of definitions, among which, "a subjective perception of a negative emotional state related with the divergence between desired and existing relations with others" (44). According to Weiss (45), loneliness may be emotional or social. Emotional loneliness, a subjective experience, is related with the absence of a desirable close and affectionate bonding with a person, absence of someone to turn to. Social loneliness, an objective condition, involves lack of contacts, social networks and the sense of belonging to a smaller or wider circle of people. Therefore, the term "loneliness" encompasses both qualitative and quantitative aspects of relationships (46, 47). In older adults, loneliness was related with depression, anxiety, increased risk of further social dysconnectivity (48), poor global sleep satisfaction (49), and deterioration of cognitive functions (50). Moreover, it was observed that lonely older adults engage in unhealthy practices, such as smoking, alcohol consumption, and less physical activity, which compromise physical health (44, 51); loneliness was associated with increased risk of coronary heart disease and deterioration of cardiovascular diseases (52), a well acknowledged risk factor for severe COVID-19 (53). Altogether, loneliness was shown to have an impact on older people's mental health, physical health and overall well-being (44, 51). Therefore, loneliness remains an issue of significant research interest in older adults.

In 2018, people over the age of 65 represented one fifth of the European Union population, an increase of 2.6% compared with 10 years earlier. Greece offered the second highest share of people over 65 years in the total population (21.8%) after Italy (22.6%). In 2018, the old-age dependency ratio (OADR; an index used to investigate the level of support offered to older people by the working population, defined as the number of old-age dependents over the age of 65 per 100 persons of working ages 20–64) was estimated at 34.1% in Greece, that is, around three working age people for every person aged over 65 (54); in 2019, the OADR raised at 37% and is expected to reach a 75% by 2050, placing Greece within the 10 countries with the highest OADR worldwide (55).

Altogether, the population is ageing all over the world, a "longevity revolution". By 2050, one out of six individuals worldwide will exceed the age of 65, compared with 2019 data indicating that 1 out of 11 exceeded the age of 65. People will have a 90% chance of surviving up to the age of 65 in countries with high life expectancy. In most developed countries, the proportion of older adult life will correspond to one quarter of total life time (55). Moreover, the chronological age may not always be identical with the biological age (56). According to the latest Eurostat data, women and men at the age of 65 are expected to live an average of 9.5 years in good health. Specifically, in Greece, both women and men at the age of 65 are expected to live in good health until the age of 72.7 (57). Since health expectancy has been prolonged, older people may remain active and contribute to the family and societal life in multiple manners. During the COVID-19 pandemic, retired health professionals were called upon to support the overloaded healthcare system in many countries, including Italy (58), Spain (59), the United Kingdom (60), and the United States (61).

Taking into account that older adults comprise a significant proportion of the population, may continue to retain an active role in society (62), and may be more vulnerable during public health emergencies (9), older adults remain a significant research population. Therefore, this study focused on an older Greek population during the COVID-19 crisis. Taking available literature into account, the study aimed to investigate the psychological impact of COVID-19, that is, fear, depressive and anxiety symptoms, as well as sleep disturbances, on older individuals. Furthermore, the study focused on loneliness during the COVID-19 pandemic, and investigated whether fear of COVID-19, depressive and anxiety symptoms, insomnia, and IU were potential predictors of loneliness.

METHODS

Study Population and Design

A non-standard, though widely accepted cutoff threshold to define an older population in developed countries is the age of 60. The definition of "old" is also related with one's employment-retirement status; in the majority of countries the retirement age ranges from 60 to 65 years (63). In Greece, three out of four employees retire by the age of 61 (64). Taken together, the present study included older adults over the age of 60.

This cross-sectional study was part of a larger online survey (3,029 participants) targeting the Greek general population. The survey, created via Qualtrics online survey software (65), was distributed through the social media and was available online for a period of three days, three weeks after a national lockdown had been imposed in Greece. Information about the study's scope and usefulness was provided in the survey's homepage. Before taking the survey, respondents were requested to formally consent to their participation. Acceptance to participate was a prerequisite for study inclusion. Participation was voluntary and anonymous.

Initially, 120 consenting participants fulfilling the age criterion completed the survey (3.96% of the original sample). Among these, 17 (5 males and 12 females) reported that they suffered from a pre-existing psychiatric disorder during the last 6 months, for which they received psychiatric medication (including antidepressants, antipsychotics, tranquilizers, and hypnotics). These participants were excluded from the analysis. As a result, a total of 103 participants (3.4% of the original sample) entered the study.

Ethical approval was received from the Scientific Committee of the General Hospital "Papageorgiou" Review Board.

Measures

At first, the survey included basic sociodemographic questions, including age, gender, residential area, living status, and educational level. Consequently, respondents completed the following psychometric scales:

1. The Greek version of the Fear of COVID-19 Scale (FCV-19S) (38, 66). The scale is a reliable and valid unidimensional self-report tool, recently developed to facilitate research during the COVID-19 pandemic. The scale assesses COVID-19–related fear independent of gender and age. It consists of seven items, e.g., item 1, "I am most afraid of coronavirus-19"; item 4, "I am afraid of losing my life because of coronavirus-19"; item 7, "My heart races or palpitates when I think about getting coronavirus-19". Each item is rated on a 5-point Likert-type scale as follows: 1 = strongly disagree; 2 = disagree; 3 = neither agree nor disagree; 4 = agree; 5 = strongly agree. The total score ranges between 7 and 35. Higher scores reflect greater fear of COVID-19.
2. The Greek version of the Brief Patient Health Questionnaire (PHQ-9) depression scale (67, 68). The scale constitutes the 9-item depression module from the complete Patient Health Questionnaire (PHQ). It is a self-report tool used for the diagnosis of major depression and subthreshold depression in the general population (69), assessing depressive symptoms' severity over the past two weeks. Each of the nine items (e.g., item 1, "Little interest or pleasure in doing things") is rated on a 4-point severity scale (0 = not at all; 1 = several days; 2 = more than half the days; 3 = nearly every day). The total score ranges between 0 and 27. Symptoms' severity is assessed based on the following cutoff scores: 0–4 = minimal or none; 5–9 = mild; 10–14 = moderate; 15–19 = moderately severe; 20–27 = severe (the cutoff point of 10 or greater may indicate a clinically significant condition).

   The last item of PHQ-9 exploring suicidal ideation (item 9: Over the last two weeks, how often have you been bothered by thoughts that you would be better off dead or of hurting yourself in some way?) was shown to be a strong predictor of suicide attempts regardless of age (70), and was therefore separately analyzed (item 9 score > 0) to investigate the prevalence of suicidal ideation in the present sample.
3. The Greek version of the Generalized Anxiety Disorder scale (GAD-7) (71, 72). The scale was proven a useful self-administered tool for the assessment of anxiety symptoms' severity over the past two weeks. Each of the seven items (e.g., item 1, "Feeling nervous, anxious or on edge") is rated on a 4-point severity scale (0 = not at all; 1 = several days; 2 = more than half the days; 3 = nearly every day). The total score ranges between 0 and 21. Symptoms' severity is assessed based on the following cutoff scores: 0–5 = mild; 6–10 = moderate; 11–15 = moderately severe; 15–21 = severe (the cutoff point of 10 or greater may indicate a clinically significant condition).
4. The Athens Insomnia Scale (AIS) (73). The scale is an 8-item instrument originally developed in Greek to evaluate sleep duration and quality according to the International Classification of Diseases, 10th Revision, criteria. The first five items explore sleep induction, awakenings during the night, final awakening, total sleep duration, and sleep quality, while the last three items explore day-time well-being, physical and mental functioning, as well as sleepiness. Each item is rated on a 4-point severity scale ranging from 0 (no considerable sleep disturbances) to 4 (serious/intense sleep disturbances). The total score ranges from 0 to 32; higher scores reflect more severe sleep difficulties. The cutoff score of 10 was proposed for usage in the general population (positive predictive value of about 90%) and was applied in this study to distinguish non-insomniacs from insomniacs (74).
5. The Greek version of Intolerance of Uncertainty Scale (IUS-12) (35, 75). The scale is a 12-item instrument, derived from the original 27-item IU questionnaire (31). It assesses reactions to ambiguous conditions, uncertainty and forthcoming events. The scale displayed strong psychometric properties, was accepted as a transdiagnostic assessment tool for trait IU (76), and demonstrated a two-factor structure, evaluating prospective IU (7-item subscale; sum of items 1, 2, 4, 5, 8, 9, and 11; e.g., item 1: "Unforeseen events upset me greatly"), and inhibitory IU, related with avoidance (5-item subscale; sum of items 3, 6, 7, 10, and 12; e.g., item 3: "Uncertainty keeps me from living a full life"). Each item is rated on a 5-point Likert-type scale ranging from 1 (not at all characteristic of me) to 5 (entirely characteristic of me). The total score ranges between 12 and 60. Higher scores indicate greater levels of IU. The Greek version's Confirmatory Factor Analysis resulted in the following parameters: chi-square goodness of fit test = χ^2 (54) = 1176.40, $p < .001$, RMSEA = 0.09, 90% CI = [0.08, 0.09], CFI = 0.86, TLI = 0.83, and SRMR = 0.05. Convergent validity was established by correlating IUS-12 with GAD-7 [(r_p = 0.58, $p < .001$, 95% CI (0.56, 0.61)]. The items for IUS-12 had a Cronbach's alpha coefficient based on standardized items of 0.90.
6. The Greek version of the De Jong Gierveld Loneliness Scale (JGLS) (46, 77). This is a 6-item measure, the short version of the original 11-item De Jong Gierveld Loneliness Scale (78), consisting of two subscales, a 3-item subscale assessing

emotional loneliness (e.g., item 1, "I experience a general sense of emptiness") and a 3-item subscale assessing social loneliness (e.g., item 4, "There are plenty of people I can rely on when I have problems"). Each question may be answered with "yes", "more or less" or "no". To rate the items, the "more or less" and "yes" answers are scored with one on the negatively worded questions, that is, items 1, 2, and 3 assessing emotional loneliness. On the contrary, on the positively worded items, that is, items 4, 5, and 6 assessing social loneliness, the "more or less" and "no" answers are scored with one. The total score for both emotional and social loneliness ranges from 0 to 3; the total loneliness score ranges from 0 (least lonely) to 6 (most lonely). The Greek version's Confirmatory Factor Analysis resulted in the following parameters: chi-square goodness of fit test = χ^2 (9) = 20.04, p = .018, RMSEA = 0.12, 90% CI = [0.05, 0.19], CFI = 0.91, TLI = 0.85 and SRMR = 0.08. Convergent validity was established by correlating JGLS with PHQ-9 [(r_p = 0.31, p <.001, 95% CI (0.12, 0.47)]. The items for JGLS had a Cronbach's alpha coefficient based on standardized items of 0.70.

Data Analysis

Data and parameter estimates were presented as numbers (N) and percentages (%) or as mean values (M) and standard deviations (SD). Independent samples t-tests and one-way analyses of variance (ANOVA), with Bonferroni Correction were performed to explore participants' differences regarding the main psychometric scales. Chi-squared cross-tabulation was used to identify significant differences among the severity categories of fear, anxiety, and depression.

Linear regression analysis was performed to calculate the associations of loneliness (dependent variable) with IU, depressive and anxiety symptoms (independent variables).

Statistical analyses were performed by the IBM Statistical Package for Social Sciences (SPSS), Version 26.0.

RESULTS

The study included 40 male and 63 female participants. The majority of survey respondents were urban residents (80.6%), lived together with their family or a caregiver (78.6%) and had a university degree (45.6%) (**Table 1**).

Females reported significantly higher levels of COVID-19–related fear (p = .012), more severe depressive symptoms (p = .018) and more severe sleep disturbances (p = .043). Furthermore, females showed higher levels of IU (p = .022) compared with males. Specifically, females showed higher levels of prospective IU (M = 19.73, SD = 4.95) compared with males (M = 16.97, SD = 4.72), and this difference was statistically significant (t = −2.759, df = 97, p = .007). Although females showed higher levels of inhibitory IU (M = 14.07, SD = 4.36) than males (M = 12.64, SD = 3.70), this difference was not statistically significant (t = −1.686, df = 98, p = .95). Lastly, females and males did not differ with regard to anxiety symptoms' severity and loneliness (**Table 1**).

Participants living alone showed higher levels of loneliness (p = .004) compared with participants living together with their family or a caregiver. On the contrary, there were no statistically significant differences in the levels of COVID-19–related fear, depressive and anxiety symptoms' severity, sleep difficulties, as well as IU between participants living alone and participants living together with their family or a caregiver (**Table 2**).

A significant proportion of the participants reported moderate to severe depressive symptoms (81.6%), moderate to severe anxiety symptoms (84.5%), as well as disrupted sleep (37.9%) (**Table 3**). Moreover, a total of 35 participants (33.9%; 12 males and 23 females) reported suicidal ideation based on PHQ-9 item 9 (score > 0), while 70% of the male and 63.5% of the female participants did not report any suicidal thoughts.

Linear regression analysis was performed to identify significant predictors of loneliness. AIS and FCV-19S did not enter the model as their correlation with JGLS was non-significant (p >.05). The highest correlation of JGLS was with IUS-12 (r = .335, p <.01) and the lowest with anxiety (r = .263, p <.05). All needed transformation was completed before the analysis and relevant statistical assumptions were met.

The results of the analysis revealed that the linear combination of IUS-12, PHQ-9, and GAD-7 accounted for a significant amount of variance of loneliness [R^2 = 0.14, F(3,89) = 4.93, p = .003]. Further examination of the beta weights on each scale indicated that IUS-12 score significantly predicted JGLS score [B = 0.05, t(89) = 2.33, p = .022)]. On the contrary, PHQ-9 and GAD-7 scores failed to present significance as predictors of the JGLS score [B = 0.04, t(89) = 0.71, p = .482; B = 0.02, t(89) = 0.28, p = .778] (**Table 4**).

DISCUSSION

The awareness that increased age is a risk factor for COVID-19–related mortality, together with the restriction of family and social contacts due to quarantine measures, had a psychological impact on older adults during the pandemic (79). Although a study of a Chinese population reported that adults over the age of 60 displayed the highest COVID-19 peritraumatic distress index (80), other studies of different Chinese populations showed that the prevalence of posttraumatic stress symptoms (81) and the severity of depressive and anxiety symptoms (6) were not differentiated based on age. Moreover, a study of a Spanish population observed that adults over the age of 65 reported less severe depressive and anxiety symptoms compared with younger adults under the age of 35 (82). Altogether, further research is required to explore the differences in the psychological impact of COVID-19 between younger and older adults.

According to previous community-based studies, published between 2005 and 2018, the prevalence of moderate to severe depressive symptoms in Greek adults over the age of 60 ranged from 30% to 46% (83–89), depending on sample size and differences in study groups and assessment methods. This

TABLE 1 | Participants' sociodemographic and clinical characteristics.

Sociodemographic characteristics	Overall (n = 103)		Male (n = 40)		Female (n = 63)			
Age	M	SD	M	SD	M	SD	p	
	69.85	5.26	70.87	5.84	69.2	4.79	>.001	
Residential area	N	%	N	%	N	%	p	
Urban	83	80.6	31	79.5	52	83.9	>.001	
Small City	5	4.9	1	2.6	4	6.5		
Rural	13	12.6	7	17.9	6	9.7		
Living with	N	%	N	%	N	%	p	
Family/caregiver	81	78.6	33	82.5	48	76.2	>.001	
Alone	20	19.4	6	15	14	22.2		
Education	N	%	N	%	N	%	p	
Elementary school	6	5.8	2	5.3	4	6.3	>.001	
Middle school	2	1.9	0	0	2	3.2		
High school	25	24.3	13	34.2	12	19		
University	47	45.6	14	36.8	33	52.4		
MSc	14	13.6	6	15.8	8	12.7		
PhD	7	6.8	3	7.9	4	6.3		
Clinical characteristics	M	SD	M	SD	M	SD	t-test	Cohen's d
FCV-19S	18.48	5.32	16.75	5.43	19.54	5.01	t = −2.551, df = 93, p = .012	.53
PHQ-9	13.68	4.22	12.45	3.74	14.46	4.35	t = −2.407, df = 101, p = .018	.65
GAD-7	13.21	4.67	12.61	4.83	13.59	4.58	p > .001	
AIS	12.79	3.84	11.83	3.44	13.40	43.99	t = −2.05, df = 101, p = .043	.041
IUS-12	31.75	8.58	29.33	7.79	33.29	8.76	t = −2.331, df = 101, p = .022	.54
JGLS	2.35	1.64	2.23	1.57	2.43	1.70	p > .001	

FCV-19S, Fear of COVID-19 Scale; PHQ-9, Brief Patient Health Questionnaire Depression Scale; GAD-7, Generalized Anxiety Disorder scale; AIS, Athens Insomnia Scale; IUS-12, Intolerance of Uncertainty Scale; JGLS, De Jong Gierveld Loneliness Scale; M, mean; SD, Standard Deviation.

TABLE 2 | Clinical characteristics in relation with living status.

Clinical characteristics	Living with				t-test	Cohen's d
	Family/caregiver		Alone			
	M	SD	M	SD		
FCV-19S	18.65	5.37	17.94	5.37	$t_{(92)}$ = −.480, p = .606	–
PHQ-9	13.47	3.74	14.60	5.36	$t_{(100)}$ = 1.064, p = .245	–
GAD-7	13.32	4.66	12.56	5.09	$t_{(91)}$ = −.578, p = .502	–
AIS	12.67	3.75	13.35	4.40	$t_{(99)}$ =.703, df=99, p=.483	–
IUS-12	31.49	8.54	32.70	8.99	$t_{(100)}$ = .560, p = .620	–
JGLS	2.09	1.55	3.25	1.71	$t_{(99)}$ = 2.932, p = .004	.71

FCV-19S, Fear of COVID-19 Scale; PHQ-9, Brief Patient Health Questionnaire Depression Scale; GAD-7, Generalized Anxiety Disorder scale; AIS, Athens Insomnia Scale; IUS-12, Intolerance of Uncertainty Scale; JGLS, De Jong Gierveld Loneliness Scale; M, mean; SD, Standard Deviation.

study showed that roughly 8 out of 10 older adults reported moderate to severe depressive and anxiety symptoms. Therefore, current results indicated that during the COVID-19 pandemic, the prevalence of depressive/anxiety symptoms may have increased. Furthermore, around 3 out of 10 participants reported insomnia.

Greece continues to belong among the countries with the lowest suicide rates (5 suicide deaths/100,000 population in a year versus an average suicide rate of 11.3 in European Union countries in 2014) (90, 91). It has been suggested that suicide rates may increase during the COVID-19 pandemic (92). Older adults, especially the ones suffering from depression, may be more vulnerable to suicide during a health crisis (93). According to current results, 34% of the participants reported suicidal ideation, based on the last PHQ-9 item, a finding potentially reflecting the pressure experienced during the imposed lockdown.

There was evidence that the psychological impact of COVID-19 was greater in women compared with men, that is, women expressed more worry (4) and showed more severe depression, anxiety (6), psychological distress (80), and insomnia (7). Based on current results, older women showed significantly higher levels of COVID-19–related fear, more severe depressive symptoms and greater sleep difficulties compared with older men. On the contrary, severity of anxiety symptoms was not differentiated based on gender. Therefore, it may be postulated that although older women were shown to report altogether more worry, as well as more severe depressive and anxiety symptoms compared with older

TABLE 3 | Participants' grouping according to psychometric scales' cutoff scores.

	Overall		Male		Female		x^2	df	p	Vcramer
	N	%	N	%	N	%				
Depressive symptoms										
Mild	18	17.5	10	25	8	12.9	4.604	3	.203	.203
Moderate	45	43.7	18	45	27	43.5				
Moderately severe	31	30.1	11	27.5	20	32.3				
Severe	8	7.8	1	2.5	7	11.3				
Total	102	99.1	40	100	62	100				
Anxiety symptoms										
Mild	3	2.9	2	5.9	1	1.8	3.91	3	.270	.270
Moderate	28	28.2	11	32.4	17	30.9				
Moderately severe	33	32	15	44.1	18	32.7				
Severe	25	24.3	6	17.6	19	34.5				
Total	89	87.4	34	100	55	100				
Insomnia										
Absent	64	62.1	30	75	34	54.0	4.6	1	.038	.032
Present	39	37.9	10	25	29	46.0				
Total	103	100	40	100	63	100				

TABLE 4 | Linear regression with IUS-12, PHQ-9, and GAD-7 predicting JGLS.

Variable	B	SE	95% CI	β	t	p
(Intercept)	–0.16	0.67	[–1.49, 1.16]	0.00	–0.24	.809
IUS-12	0.05	0.02	[0.01, 0.10]	0.28	2.33	.022
PHQ-9	0.04	0.06	[–0.08, 0.17]	0.11	0.71	.482
GAD-7	0.02	0.06	[–0.10, 0.13]	0.04	0.28	.778

IUS-12, Intolerance of Uncertainty Scale; PHQ-9, Brief Patient Health Questionnaire Depression Scale; GAD-7, Generalized Anxiety Disorder scale; JGLS, De Jong Gierveld Loneliness Scale.

men (94), the novel COVID-19 circumstances imposed similar levels of anxiety on both genders.

This study also explored IU in older individuals, using a gender invariant scale (95). According to the results, women showed higher levels of IU compared with men; this difference was particularly significant with regard to prospective IU, reflecting more cognitive assessments of threat regarding unforeseeable events and more desire for predictability (35), a finding related with the fact that women tend to worry more than men (96). Still, there is only limited information about gender differences in IU, suggesting that although women tend to worry more than men, IU levels are not significantly different based on gender (97). There is also limited evidence that individuals over the age of 65 show lower levels of IU compared with younger individuals (98), supporting the theory that ageing may modify personality characteristics (99). Older people's better emotional regulation and maturation through long-term experience with unforeseeable and ambiguous situations may attenuate trait IU, alleviating worry in older ages (98). Still, to the best of our knowledge, gender-related differences in IU in older individuals have not been reported yet. Further research of IU in older women and men is warranted, since it was suggested that IU constitutes a transdiagnostic mechanism contributing to a variety of psychological symptoms, with a more pronounced involvement in the manifestation of anxiety and depressive symptoms (100). Moreover, during the COVID-19 pandemic, IU was related with higher fear of COVID-19 (39), insomnia (7), and less positivity (101).

Anecdotal statements of gradually increasing loneliness in older people over the past decades were not supported by longitudinal studies. Becoming older is misguidedly identified as becoming lonelier. Loneliness affects younger adults as well. The highest prevalence of loneliness was observed over the age of 80 (47), while loneliness was shown to increase with age only over the age of 80 (102). Therefore, the relatively low loneliness levels observed in this study may be explained by the sample's lower mean age. Moreover, old age alone is not a sufficient condition for the manifestation of loneliness, since there are more contributors to loneliness, such as not living together with a spouse/partner and limited socialization (103).

Evidence of gender differences in loneliness is inconclusive. Reports of increased loneliness in women compared with men were provided by studies using another tool, the UCLA loneliness scale, or one item indicators, and not the DeJong-Gierveld scale, applied in this study. Moreover, gender alone may not be an independent factor predicting loneliness in older individuals (102–104). Similarly, the current results did not support gender-related differences in loneliness.

Attention was promptly drawn upon the risks related with older people's social isolation during the quarantine (10). The magnitude of the pandemic's psychological impact on older adults is related with sociocultural factors mediating older people's family and social connectedness (105, 106). According to Reher's work (2004), the center and north of Europe was characterized by weaker, while the Mediterranean by stronger family ties (107). The grade of familialism was shown to increase from North to South Europe; Greece was shown to be a country with strong familistic attitudes toward older people compared with other European countries (108). The living status followed the same "North to South" pattern, that is, the proportion of older people living alone was lower in South Europe (109). According to Eurostat, an average of 32.1% of older adults in Europe live alone, whereas in Greece, only about one out of four older adults lives alone (57) Although living alone does not necessarily equate loneliness (110), it was proven a strong predictor of loneliness (111). Similarly, this study showed that living alone was related with higher levels of loneliness in older adults.

Furthermore, having children (104), as well as being a member of a joint family were related with less loneliness, since "family" offers older people security, comfort, connectedness, and support. Loneliness was not shown to be a major issue for older members of an extended family, being collectively taken care of by other family members (112). The strong family bonds in Greece date back to the "Golden Age" of Pericles (fifth century BC). In Ancient Greece, "geroboskia" or "gerotrophia", that is, providing care for older people, was a sacred duty performed by family members. Moreover, severe penalties were imposed on offspring refusing to provide care for their older parents. As a result, at that time, there were no public facilities for the care of older people (113). Ancient Greeks' practices toward older people were a legacy to the next generations. During the following centuries, family members remained the traditional caregivers for older people in Greece. Moreover, in the beginning of the 20th century, Greek families were organized in an extended form, not only embracing older family members, but also placing them on top of the family hierarchy. Patriarchal authority exercised by older males involved decisions on financial matters and the future spouses of children and grandchildren, while matriarchal authority exercised by older women involved organization of housework. Lately, the development of nuclear families disempowered older people, weakening their position in society (114). However, strong bonds between the younger and the older family members are maintained. Residential proximity is often pursued between parents and at least one of the adult children. The strong family values render "family" a core component of the Greek society. Altogether, the Greek society is still governed by a moral duty toward its older members. Moreover, the article 1485 of the Greek Civil Code imposes a legal duty as well, obligating adult children to take care of their parents (115).

Although depression and anxiety were shown to contribute to loneliness (48), the current results highlighted the modulating effect of IU on severity of loneliness. This study was conducted three weeks after a national lockdown had been imposed in Greece. The family network remains a cornerstone in the care and welfare of older adults in Greece. Uncertainty about the duration of the quarantine and the necessity to maintain physical distancing from family and friends may have intensified loneliness. The fact that the Greek sociocultural background nurtures the moral obligation to provide support and emotional care to older people may elevate older Greeks' expectations and needs from their family. Therefore, loneliness may be easier to experience, when expectations are not fully met (47). In addition, older adults support their adult children in everyday routine. Grandparents in Greece take care of their grandchildren to facilitate working mothers (115). Caring for a grandchild was shown to expand older people's social network and to reduce loneliness (116, 117). Restriction measures and isolation deprived older people of the opportunity to contribute to their family and therefore to retain the sense of a significant societal role and connectedness. Families kept their older members in safety, away from the virus, and managed alone. This new situation may have raised older people's uncertainty about the importance of their family role and their societal position, contributing to loneliness. Lastly, restriction measures compelled older people to become more involved in technology. Older people are more reluctant with the Internet use. In Greece, only about 4% of people within the age range of 65–74 use the Internet (118). The necessity to get acquainted with the Internet technology and to develop new skills, for instance use of online bill pay, potentially raised older people's uncertainty. The need to undertake new responsibilities may have led to a sense that instead of being taken care of, older people were left to manage on their own.

To the best of our knowledge, up to date there have been no published studies of older adults during the COVID-19 crisis in Greece. This study investigated the psychological impact of COVID-19 on older people during the acute phase of the pandemic. According to the results, the majority of study participants manifested moderate to severe depressive and anxiety symptoms, women carried a heavier psychological burden, and intolerance of uncertainty modulated loneliness severity. Studies identifying factors that may have contributed to loneliness during the COVID-19 pandemic facilitate the implementation of supportive interventions. Older individuals show a preference for goals and environments with minimal negative emotional load, that is, a protective, "stable" surrounding, alleviating uncertainty (119). Restriction measures and disruption of daily routine was a significant source of uncertainty during the COVID-19 pandemic. Therefore, any form of regular care, such as delivering groceries and medical supplies to older people regardless of their ability to provide for themselves or not, signifies care and ensures brief, but frequent meetings. This approach restores some daily routine, mitigates uncertainty, and may therefore alleviate related feelings of loneliness. Limiting exposure to information overload by the media is another remedy to relief uncertainty (10). Introducing older people to online technology enhances social contacts (120), while frequent telephone contacts and involvement of older people in decision-making about family matters nurture a sense of connectedness, which was shown to promote older adults' well-being during the previous SARS outbreak in 2003 (121). Among a variety of other policies and programs (21), the initiative taken by the Doctors of the World/Médecins du Monde-Greece to support isolated older adults over the age of 60 (122), as well as various national telephone psychosocial support services aimed to provide assistance and psychological care to older Greeks in need during the pandemic.

Still, the present study had some limitations. The cross-sectional design did not allow investigation of causal relationships. Results were based on self-report tools, and may therefore suffer from bias. Moreover, despite the attempts to focus respondents' attention on the COVID-19–related impact (the survey's headline was "The psychological burden related with the COVID-19 pandemic crisis"; the survey's homepage included a description of the study's scope), and although participants with pre-existing psychiatric disorders were excluded from the analysis, it cannot be ruled out that study results may have reflected, at least partially, pre-existing psychological symptoms. Furthermore, due to the strict restriction measures, the study was conducted through an online survey distributed by the social media, which are used only by 2.3–5.5% of adults over the age of 65 in Greece (123). Consequently, the sample was relatively small, while less educated and socially disadvantaged older adults may not have been adequately represented. Lastly, online surveys suffer from the so-called "volunteer-effect". Therefore, responders' characteristics may differ substantially from non-responders, limiting results' generalizability (124).

Conclusively, the COVID-19 pandemic crisis unveiled a lack of sufficient data on the older population (14), a significant proportion of the total population in many countries that should not be overlooked. Healthy ageing does not solely involve physical health attainment, but also nurture of psychological resources (125). This crisis may offer the opportunity to address issues related with more efficient care for older adults during public health crises (21). As a result, awareness and therefore preparedness to assess and address loneliness in older adults may rise during the post-pandemic period, allowing the development of management strategies to eliminate this deleterious emotional response (126).

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This study involving human participants was reviewed by the Scientific Committee of the General Hospital "Papageorgiou" Review Board, Thessaloniki, Greece. Ethical approval was received prior to data collection. Before entering the online-survey, respondents were requested to indicate their consent. The study was anonymous.

AUTHOR CONTRIBUTIONS

EP and VH contributed equally to this study. EP contributed to intellectual input and data interpretation, and wrote the first draft of the manuscript. VH contributed to study's conception and design, as well as to data management interpretation. VN contributed to data management and literature search. KS, MA, AG, and TS contributed to literature search and paper editing. ID supervised the study and contributed to the final revision of the manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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COVID-19 Neurological Manifestations and Underlying Mechanisms: A Scoping Review

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Background: In the Corona Virus Disease 2019 (COVID-19) pandemic, the primary problem is respiratory-related, but there also is increasing evidence of central nervous system (CNS) involvement. This study aims to summarize the literature on neurological manifestations of COVID-19, underlying mechanisms of CNS involvement and cognitive consequences.

Methods: A scoping review was conducted with multiple searches in PubMed, PsycInfo, and CINAHL databases. Full text articles in English were included if they involved humans with COVID-19. The search was updated twice, the latest on 19 May 2020.

Results: After screening 266 records and cross referencing, 85 articles were included. The articles were case studies, opinion papers, letters to editors, and a few observational studies. No articles were found regarding cognitive consequences in COVID-19 patients. All reported on neurological manifestations and/or underlying mechanisms of CNS involvement in COVID-19.

Conclusion: Neurological manifestations of COVID-19 vary from mild (e.g. loss of taste and smell, dizziness, headache) to severe (e.g. ischemic stroke, encephalitis). Underlying pathways are suggested to be both indirect (as a result of thrombotic complication, inflammatory consequences, hypoxia, blood pressure dysregulation), and direct (neurotropic properties of the virus). Since most articles were opinion papers and no studies have been conducted on cognitive consequences, further research is warranted.

Keywords: Corona Virus Disease 2019, neurological, neurotropic, cognitive, scoping review

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INTRODUCTION

The recent outbreak of Corona Virus Disease 2019 (COVID-19) caused by the Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) led to the current pandemic, which is characterized by ominously high infection rates. By the end of May, over 4.8 million people have been infected and over 323,000 deceased worldwide due to COVID-19 (1). To stop the devastating impact of COVID-19, scientists are in a race to find a cure or vaccine for the virus.

SARS-CoV-2 is primarily transmitted between people through respiratory droplets. It can bind to the angiotensin-converting enzyme 2 (ACE2) receptor in the lungs. After which most people develop mild symptoms, such as coughing or fever. However, the disease can lead to more severe problems such as pneumonia (2). In the Netherlands, a quarter of all identified patients were admitted to the hospital due to COVID-19. The leading cause of hospital admittance was respiratory failure due to acute respiratory distress syndrome (ARDS) (3, 4).

Although the most prominent symptoms of COVID-19 are respiratory-related, there is also emerging literature on neurological manifestations of the virus. First opinion papers, letters to the editors, and case studies have been published. The primary aim of the current study was to summarize the literature on neurological manifestations due to COVID-19 and its underlying mechanisms. Furthermore, if COVID-19 might lead to neurological tissue damage, then it could lead to impaired cognitive functioning (e.g. memory impairment or attention problems). Therefore, the secondary aim was to summarize the literature on cognitive consequences of COVID-19.

METHODS

Design

A scoping review was used to provide an overview of the relevant literature on neurological and cognitive manifestations in COVID-19 patients (5). Possible mechanisms underlying these manifestations will be presented based on the available evidence. A scoping review was chosen over a systematic review to provide a broader overview of the literature using multiple sources (e.g., opinion papers, letters to the editors, case studies). We used the extended PRISMA checklist for scoping reviews and the following methodological framework: identifying the research question, study selection, charting the data, and reporting the results (5–7).

Data Sources, Search Strategy, and Inclusion and Exclusion Criteria

The databases PubMed, PsycInfo, and CINAHL were searched using a search strategy based on free text terms in Title/Abstract and descriptor terms. Some basic searches were carried out by two authors to identify key terms. The search strategy is provided in the **Supplementary Material**. We included all relevant publications on the neurological manifestations in COVID-19, underlying mechanisms, and cognitive consequences. A limit was placed on year of publication (2019–2020). Animal studies, studies in neonates, and articles without a full text in English were excluded. The search was carried out on 29 April 2020 and updated on 12 May and 19 May 2020.

Study Selection and Charting of the Data

One author independently screened all titles and abstracts. Two authors discussed the included full texts and found a perfect agreement on the included papers. Cross referencing was applied to determine if relevant articles were missing. Two authors reviewed, extracted, and summarized the full text articles. The main topics were analyzed using a qualitative content approach and narratively described. The following themes were determined: neurological manifestations in COVID-19 and its underlying mechanisms. Descriptives were reported from the observational studies.

RESULTS

The first search (29 April) yielded 160 records, the second update (12 May) 206 records, and the final update (19 May) 266 records. A total of 82 full texts were evaluated for inclusion, of which 73 were included. Through cross referencing another twelve articles were identified, which led to the inclusion of 85 papers. **Figure 1** shows the flowchart of this selection process. In this scoping review, all included papers were summarized using a narrative report. An overview of the findings of all articles are described in **Table 1** in the **Supplementary Material**. The 85 articles were 25 opinion papers, 22 case studies, 16 letters to the editor, 13 reviews (11 literature reviews, 1 systematic review, 1 scoping review), 6 observational studies, and 3 comments on other publications.

Neurological Manifestations and Neuropsychological Consequences

Unfortunately, no papers have been reported yet on cognitive consequences of COVID-19, such as memory impairment or attention deficits in COVID-19 patients. However, the literature on neurological manifestations of SARS-CoV-2 is emerging. A few observational studies on neurological symptoms have been conducted in COVID-19 patients. Mao, Wang (8) demonstrate that 36.4% of 214 hospitalized COVID-19 patients had neurological symptoms, varying from dizziness and headache, to cerebrovascular disease. In the COVID-19 intensive care (IC) population neurological symptoms were found in 84 percent of 58 patients included in the study of Helms et al. (9), and 21 percent of 235 patients included in the study of Kandemirli, Dogan (10).

There is a great variety in the type and severity of the neurological manifestations of COVID-19. The first evidence of mild neurological symptoms emerged quickly after the outbreak, such as hyposmia, hypogeusia, headache, dizziness, diplopia, and ophthalmoplegia (11–18). Case studies have been published since February on neurological symptoms as an atypical presentation of COVID-19 (19). To illustrate, a delirium could be a first atypical symptom of COVID-19, especially in the elderly (20–22). Neurological movement disorders have also been reported in COVID-19 cases, such as Guillain-Barré syndrome, Miller Fisher syndrome, polyneuritis cranialis, and ataxia (8, 23, 24). Furthermore, Lu, Xiong (25) found acute symptomatic seizures in 27% of 304 COVID-19 patients with no prior history of seizures. More severe types of brain disease (encephalopathy) have been described as well, such as hypoxic encephalopathy, encephalitis, and stroke (11–13, 26). A retrospective study from Chen, Wu (27) showed that 20% of 113 COVID-19 ICU patients had hypoxic encephalopathy. In

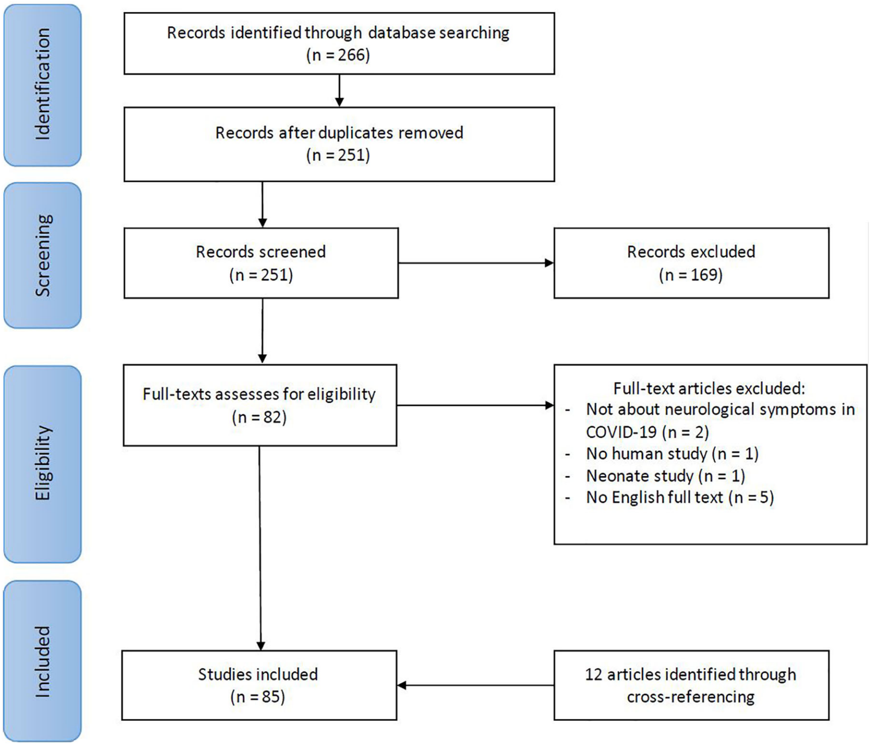

FIGURE 1 | Flowchart article selection procedure.

another study 31% of 184 ICU patients with COVID-19 had thrombotic complications with ischemic strokes (28). Furthermore, acute necrotizing encephalopathy (ANE) is also described in a case report of a COVID-19 patient (29). ANE is a rare disease, which can lead to severe brain damage including hemorrhage. In conclusion, neurological manifestations vary from mild to severe, all summarized in **Figure 2**.

COVID-19 Mechanisms Underlying the Neurological Manifestations

The literature about possible pathways in which COVID-19 can cause neurological manifestations is emerging. Both direct and indirect suggested pathways are summarized in **Figure 2**.

The suggested indirect effects of SARS-CoV-2 on the brain are:

1. Neuro-inflammation: a cytokine storm, induced by the immune system in reaction to the virus, can spread through the body, pass the blood brain barrier, and can cause brain infections or damage nearby neurons and glial cells (20, 30–38).
2. Blood pressure imbalance: since ACE2 regulates blood pressure in the renin angiotensin aldosterone system (RAS), damage of the ACE2 receptor can lead to hypertension or hypotension (30, 38–41).
3. Hypoxia: metabolic disruption, caused by lung damage, can lead to an oxygen deficiency in the brain (30, 32, 37, 38).
4. Thrombosis: thrombotic complications can lead to ischemic strokes (32, 38).

First opinion papers are published in which scientists assume that SARS-CoV-2 can enter the central nervous system CNS (12, 14, 16, 17, 27, 42, 43). It is stated that other coronaviruses have been found to be neurotropic (16, 27, 42, 44). Hereby ACE2, to which the virus is binding to, is assumed also to be present in the brain (42–44). In a case study in two patients, SARS-CoV-2 was not found in the cerebrospinal fluid (CSF) (45). However, two other case studies mentioned presence of the virus in the frontal lobe and CSF (39, 40). Various direct pathways are proposed to which the virus could possibly have a direct effect on the brain. After the virus enters the body *via* the eyes, nose, or mouth, it can bind to ACE2 receptors. The possibility of binding to the ACE2 receptors in the nose and taste buds could explain the possible loss of taste and smell in COVID-19 (16). A neural pathway is suggested, in which the virus enters the CNS along the olfactory pathway penetrating the olfactory bulb in the forebrain (15, 30–32, 34, 35, 46–48). Also, the virus could be transported to the brain *via* the lymphatic system through lymphoid tissue (32, 43, 49). The blood circulation is another supposed pathway. When the virus enters the blood circulation it can be transported to the brain. The virus could possibly pass the blood brain barrier by infecting the endothelial cells (49). Once in the CNS, the virus could possibly enter the cerebrospinal fluid, through which it can spread through the brain (15, 30, 35). The medulla oblongata is

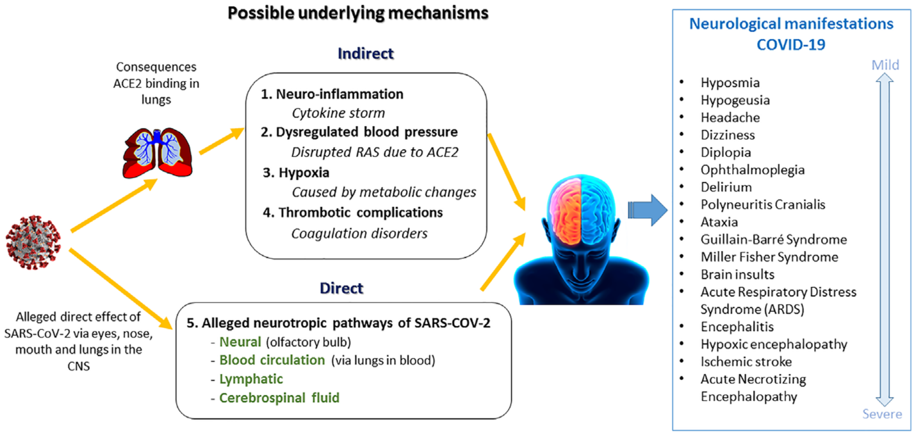

FIGURE 2 | Neurological manifestations of COVID-19 and possible underlying mechanisms.

the primary respiratory control center, located in the lowest portion of the brain stem. It is suggested that damage to the medulla oblongata, caused by direct effects of SARS-CoV-2, can possibly explain respiratory failure in COVID-19 (20, 32, 37, 43, 46, 48, 50–53). Scientists propose that this neurotropic potential of SARS-CoV-2 may account for the difference in respiratory distress in patients (51). However, some researchers believe this is not the case, since recovery of respiratory distress symptoms takes place (32).

DISCUSSION

The aim of the current study was to summarize the literature on neurological manifestations in COVID-19, underlying mechanisms, and cognitive consequences. This scoping review included 85 articles. Neurological manifestations were prominently described with suggestions for underlying mechanisms. The CNS is involved in COVID-19, as neurological manifestations (e.g., consequences of hypoxia and thrombosis) were shown in several case reports and observational studies (7, 8, 25, 53, 54). Suggested pathways of CNS involvement are both direct (neurotropic) and indirect. Since no literature on cognitive consequences of COVID-19 was found yet, previous research on other coronaviruses should be taken into account. A systematic review and meta-analysis on recovered patients of other coronaviruses found that a significant proportion of patients developed a delirium during the acute stage, and almost halve (44%) had a memory impairment post-illness (54). Elderly, people with already existing neurodegenerative diseases, or people with psychiatric comorbidities might be even more at risk for cognitive impairment following COVID-19, due to their cognitive vulnerability. Hereby, since people living with dementia might have difficulties in understanding and remembering the public health information, they are more vulnerable to be infected with COVID-19 (55, 56). In case of co-occurrence of COVID-19 and dementia, delirium could complicate the presentation of dementia (55, 56). Furthermore, as a result of neuro-inflammation that causes or progresses neurodegenerative processes in the brain, it is suggested that COVID-19 could result in a higher incidence of neurodegenerative diseases (30).

A strength of the current study is the use of scoping review methodology to gain insight into the current available evidence on neurological manifestations and underlying mechanisms while using a systematic process with a replicable and transparent approach. To our knowledge, this is the first scoping review on both neurological manifestations, its underlying mechanisms, and cognitive consequences in COVID-19 patients. Some limitations have to be considered as well. No quality appraisal of the studies was taken into account, which is often the case in scoping reviews. Due to the quick rise of literature on COVID-19 new publications might have emerged. The body of literature is fast-growing, which is illustrated by the inclusion of 27 articles after our first search on the 29 April 2020, and the latest update on 19 May 2020 resulting in a total of 85 articles.

THERAPEUTIC IMPLICATIONS

- Clinicians should be vigilant for CNS involvement and possible neurological manifestations of COVID-19.
- Clinicians should be aware of possible neurological and cognitive complaints post-COVID-19, especially in older patients, patients with cognitive impairment and/or psychiatric comorbidity.
- In case of cognitive complaints post-COVID-19 cognitive screening or neuropsychological assessment is recommended.
- In case of complex cognitive of emotional complaints post-COVID-19 it is recommended to involve a psychiatrist or psychologist.

CONCLUSION AND RECOMMENDATIONS

In conclusion, neurological manifestations of COVID-19 vary from mild, such as headache and dizziness, to severe, such as ischemic stroke and encephalitis. Underlying mechanisms of CNS involvement are suggested to be both direct (neurotropic) and indirect (as a result of thrombotic complication, inflammatory consequences, hypoxia, blood pressure dysregulation). Since most articles were opinion papers, further research is warranted.

No literature was found on the cognitive consequences of COVID-19. Therefore, cross sectional and longitudinal studies are needed. Neuropsychological assessment could be used to monitor the course of cognitive functioning after recovering from COVID-19. This should not only be conducted in hospitalized COVID-19 patients, but should also contain community-based studies in adults and children that recovered from COVID-19.

AUTHOR CONTRIBUTIONS

AW and AG carried out abstract screening and full text extraction of the scoping review. The first draft of the manuscript was written by both AW and AG. All other authors contributed to revisions of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00860/full#supplementary-material

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COVID-19 Epidemic in Argentina: Worsening of Behavioral Symptoms in Elderly Subjects With Dementia Living in the Community

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In Argentina, the quality of care that elderly subjects with dementia living in the community received has been deeply affected by COVID-19 epidemic. Our objective was to study to what extend mandatory quarantine imposed due to COVID-19 had affected behavioral symptoms in subjects with dementia after the first 8 weeks of quarantine. We invited family members to participate in a questionnaire survey. The sample consisted of family caregivers ($n = 119$) of persons with AD or related dementia living at home. We designed a visual analog scale to test the level of the burden of care of family members. Items inquired in the survey included type and setting (home or day care center) of rehabilitation services (physical/occupational/cognitive rehabilitation) and change in psychotropic medication and in behavioral symptoms that subjects with dementia experienced before and during the epidemic. Characteristics of people with dementia and their caregivers were analyzed with descriptive statistics using the chi-square tests, $p < 0.01$ was considered significant. Results: The sample included older adults with dementia. Mean age: 81.16 (±7.03), 35% of the subjects had more than 85 years of age. Diagnosess were 67% Alzheimer´s dementia and 26% mixed Alzheimer´s disease (AD). Stages were 34.5% mild cases, 32% intermediate stage, and 33% severe cases as per Clinical dementia Rating score. In 67% of the sample, a family member was the main caregiver. Important findings were increased anxiety (43% of the sample), insomnia (28% of the subjects), depression (29%), worsening gait disturbance (41%), and increase use of psychotropics to control behavioral symptoms. When we compared the frequency of behavioral symptoms within each dementia group category, we found that anxiety, depression, and insomnia were more prevalent in subjects with mild dementia compared to subjects with severe dementia. We analyzed the type and pattern of use of rehabilitation services before and during the isolation period, and we observed that, as a rule, rehabilitation services had been discontinued in most subjects due to the quarantine. We concluded from our analysis that during COVID-19 epidemic there was a deterioration of behavioral symptoms in our population of elderly dementia subjects living in the community. Perhaps, our findings are related to a combination of social isolation, lack of outpatient rehabilitation services, and increased stress of family caregivers. It is

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necessary to develop a plan of action to help dementia subjects deal with the increased stress that this epidemic imposed on them.

Keywords: dementia, behavioral symptoms, COVID-19 epidemic, quarantine, elderly

INTRODUCTION

The World Health Organization declared the COVID-19 epidemic on March 11 (1). A few days later, and with the experience of how the epidemic was affecting countries in Europe and Asia, the Argentinian Government issued an executive order implementing a complete lockdown and isolation of travelers returning from the affected countries (2). Non-essential business was closed, and people were asked to avoid unnecessary travel to maintain social distance and to limit family visits to elderly subjects (2). At the time of writing this communication, quarantine in Buenos Aires had lasted 101 days, the number of deceased people in the entire country had reached 1,245, and the number of infected persons is 59,933 (3). Governments through the world were challenged to deal with both the direct impact of the disease on the health system and the economic, financial, and social consequences of the epidemic. Worldwide health authorities also need to design models of care of chronic conditions not related to COVID-19 in times of this epidemic (3).

Alzheimer`s disease (AD) and related disorders subjects are especially vulnerable to the effects of COVID-19 disease and the imposed quarantine (4, 5). Based on frequent comorbidities and older age, they might be at higher risk for severe illness from COVID-19 (5–7). For example, in Italy, dementia was one of the most frequent comorbidities present in 12% of the deceased COVID-19 patients (8). On the other hand, dementia subjects are also extremely vulnerable to the effects of enforced quarantine (9). They depend strongly on community and social support systems for survival due to the dependence on activities of daily living (10). They may not learn properly the use personal protection elements, such as wearing facial masks, washing hands, and keeping social distance, and may forget to avoid leaving their home unnecessarily. They are probably be less flexible on coping with changing situations and during crisis, and they rely more on family members. However, during this epidemic, family members are trying to limit contact with elderly dementia subjects to decrease as much as possible the risk of coronavirus transmission. While during this epidemic virtual technology is playing a central role in preventing isolation in the general population, this vital resource is sometimes difficult to utilize for dementia subjects due to their difficulties to learn the use of this technology (9–12).

As suggested by the Alzheimer`s International Society, support for subjects living with dementia and their caregivers is mandatory (11). Access to care for family members and dementia subjects in order to deal with a new situation is critical (8) and mitigation strategies to reduce the immediate and long-term impact of this health crisis are needed (4). For example, in Australia, the Health Department quickly realized the need for improved access to mental healthcare services for older people during COVID-19 times (13). While during this epidemic virtual technology is playing a central role in preventing isolation, this vital resource is difficult to utilize on dementia subjects due to their difficulties to learn the use of this technology (9–12).

To prepare a rational plan to mitigate the effects of the epidemic, it is necessary first to identify in our setting the most problematic situations that AD and related dementia subjects are facing. It is also important to determine if enforced isolation imposed specific issues related to the severity of the cognitive disease. We know that AD and related dementia neuropsychiatric symptoms, such as anxiety, depression, sleep difficulties, among others, are extremely frequent with a prevalence ranging from 60 to 80% and usually imposed more troubling on caregivers than the cognitive symptoms (14, 15). Sleep disturbances are reported in at least 30% of subjects with AD. Multifactorial contributors are depression, anxiety, sedentarism, and adverse reactions from medications (17). Standard nonpharmacologic proven strategies to improve these disrupting symptoms and commonly used by caregivers are maintaining a structured routine, reassuring responses, physical exercise, sleep hygiene, and distraction. Most of these strategies are difficult, almost impossible, to implement during the quarantine (16).

Our objective was to measure in our setting the impact of COVID-19 epidemic on the well-being and behavioral symptoms of subjects at different stages of dementia living in the community after the first 8 weeks of enforced isolation.

MATERIALS AND METHODS

Family members of patients of the Aging and Memory Center of FLENI with AD and related disorders were invited to participate in our survey. Two physicians (MJR and GC) of the Aging and Memory Center provided information about study´s aim and distributed the questionnaire survey. Participation was voluntary and anonymous. The survey sample consisted of family caregivers (n = 119) of persons with AD or related dementia living at home.

Survey

The survey had two main sections. The first one included demographics of family members, paid caregivers, and dementia subjects, and the other was composed of questions regarding the challenges of care and management that subjects and relatives experienced during the first 8 weeks of the coronavirus quarantine in our setting. The survey was not intended to replace a medical office visit or to make a clinical diagnosis, and validated tests were not used. Our idea was to study with easy and quick to answer questions the psychological issues that might had occurred during quarantine. A series of questions were designed specifically to screen the onset or worsening of behavioral symptoms (anxiety, insomnia, and depression) or gait disturbances during the quarantine. We specifically asked caregivers the following two questions for each symptom inquired: "Did your relative with dementia experience anxiety before the epidemic?" and "Do your relative with dementia experience anxiety during the epidemic?" In order to study if there was a change in the prescription of psychotropics during quarantine, we asked caregivers specifically the following questions. "During quarantine your relative needed the dose of the following medications to be increased or to be started?" For each of the following medications, we asked one specific question. The list included: antipsychotics (quetiapine/risperidone/olanzapine), anxiolytics (clonazepam, alprazolam, diazepam), non-benzodiazepines hypnotics (zolpidem), and antidepressants (citalopram, escitalopram, sertraline, venlafaxine, fluoxetine, paroxetine, and trazodone). We did not record the exact dose of the psychotropics, but the reported change in the dose of the prescriptions.

A series of questions were made to assess the type and setting of rehabilitation services that subjects where receiving before the epidemic. We inquired specifically if subjects did physical/occupational and cognitive rehabilitation and if it was home based/at a day care center or specialized outpatient center. We then asked if rehabilitation services had been discontinued during the epidemic. We also asked if family members continued or discontinued visiting subjects during the quarantine.

Patients

Patients were seen and studied extensively by a doctor specialized in memory disorders before COVID-19 epidemic. Clinical diagnosis of cognitive disorder syndromes was made based on a detailed workup of history taking, medication review, physical examination, neuroimaging, and neuropsychological tests. Disease severity was based on Clinical Dementia Ration (CDR) (18) score and functionality scales. All subjects had a longitudinal follow up in the memory disorder clinic. Due to the unique feature of isolation and quarantine in long term care facilities, we decided to include in our sample only subjects living in the community and excluded those living at long-term care settings.

Family and Paid Caregivers

We designed a visual analog scale to study the burden of care that family members or paid caregivers experienced before and during the epidemic. The question was: "How much stress from 1 (low) to 3 (severe) do you feel by taking care of your family member with dementia before the quarantine and during quarantine?" We assigned 1 point for low, 2 points for intermediate, and 3 points for severe burden of care. Our intention was to measure the amount of burnout that a family caregiver feels ranges across a continuum from none to an extreme amount of stress. Based on the obtained score, the results were transformed into three categories: low, medium, and high. The next step was to understand the main concerns that family members were dealing with during quarantine in relation to the care of subjects with dementia. We created a list of six different hypothetical situations and asked family members to select the main concern from that list.

Ethics

This study was presented and approved by the Medical Ethics Committee of our center. The participation of this survey was voluntary, and confidentiality of the dyad patient-family member was preserved through all research stages and after. A letter was mailed together with the questionnaire inviting family members to participate in the survey and informing them of the purpose of the research study.

Statistical Analysis

Statistical analyses were made using IBM SPSS 21 software package. The characteristics of people with AD or related dementia and their caregivers were analyzed with descriptive statistics (percentages and means ± standard deviations). Chi-square tests, with $p < 0.01$ were used to test differences between family caregivers of persons in the mild stage and in severe stages of dementia based on CDR (18) score. Behavioral symptoms and covariates were analyzed with Spearman's rank-order correlations. The level of burden of the family caregiver before and during the COVID-19 epidemic was analyzed with paired-samples t tests. To overcome some of the limitations imposed by conventional pretest-posttest self-report measures, the retrospective pretest-posttest design was utilized. We selected this method since it has been shown to reduce response-shift bias, p is convenient to implement and provides comparison data in the absence of "pre" data.

RESULTS

Our work is based on the data of a questionnaire survey collected during the month of May of 2020, after approximately 8 weeks of complete lockdown due to quarantine in Argentina.

Demographics and clinical characteristics of 119 subjects with AD and related dementia and their family members are shown in **Table 1**.

Characteristics of Subjects With Dementia

Baseline demographics were the following: Mean age of subjects with dementia was 81.16 ± 7.03 years (a third of the sample belonged to the eldest-old group of more than 85 years of age), approximately a third were male, and mean number of years of education was 13.26 ± 4.68. The most frequent diagnosis was AD, followed by mixed AD, and then by vascular dementia. The distribution of the staging of dementia was the following: 34% of the sample had mild dementia (CDR 1), 32% had moderate dementia, and 34% had severe dementia with a CDR score of 3.

Our main result was the report by family members of new onset or exacerbation of pre-existing behavioral symptoms in

TABLE 1 | Characteristics of participating caregivers and persons with Alzheimer's disease or related dementia.

Variables	
Part I: Persons with dementia	
Age, mean ± SD	81.16 ± 7.03
<65 years old, n (%)	2 (1.7)
65–85 years old, n (%)	85 (71.4)
≥85 years old, n (%)	32 (26.9)
Gender, male, n (%)	42 (35.3)
Education, mean ± SD	13.26 ± 4.68
Diagnosis, n (%)	
AD	80 (67.2)
Mixed AD	26 (21.8)
Vascular dementia	7 (5.9)
Others	2 (1.7)
CDR, mean ± SD	1.99 ± 0.83
CDR 1, n (%)	40 (34.5)
CDR 2, n (%)	37 (31.9)
CDR 3, n (%)	39 (33.6)
Increased or onset of COVID-19-related anxiety, n (%)	50 (42)
Increased or onset of COVID-19-related insomnia, n (%)	34 (28.6)
Increased or onset of COVID-19-related depression, n (%)	35 (29.4)
Increased gait problems during the COVID-19 pandemic, n (%)	49 (41.2)
Increased or onset of COVID-19-related antipsychotics prescription, n (%)	24 (20.2)
Increased or onset of COVID-19-related benzodiazepines prescription, n (%)	18 (15.1)
Increased or onset of COVID-19-related hypnotics prescription, n (%)	8 (6.7)
Increased or onset of COVID-19-related antidepressants prescription, n (%)	12 (10.1)
Physical therapy, n (%)	
At home	47 (39.5)
Specialized centers or Senior Day Care Center	24 (20.2)
No therapy	48 (40.3)
Occupational therapy, n (%)	
At home	18 (15.1)
Specialized centers or Senior Day Care Center	12 (10.1)
No therapy	89 (74.8)
Cognitive Rehabilitation, n (%)	
At home	21 (17.6)
Specialized centers or Senior Day Care Center	29 (24.4)
No therapy	69 (58)
Discontinued physical therapy during the COVID-19 pandemic, n (%)	47/61 (76.9)
Discontinued occupational therapy during the COVID-19 pandemic, n (%)	21 (91.3)
Discontinued cognitive rehabilitation during the COVID-19 pandemic, n (%)	31/40 (77.5)
Part II: Family caregivers	
Age, mean ± SD	58.61 ± 13.60
<45 years old, n (%)	17 (14.9)
45–65 years old, n (%)	64 (56.1)
65–85 years old, n (%)	30 (26.3)
≥85 years old, n (%)	3 (2.6)
Gender, male, n (%)	32 (28.1)
Education, mean ± SD	17.04 ± 5.15
Level of burden of the family caregiver prior to the pandemic, mean ± SD	1.69 ± 0.67
Low burden, n (%)	51 (42.9)
Medium burden, n (%)	54 (45.4)
High burden, n (%)	14 (11.8)
Level of burden of the family caregiver due to COVID-19, mean ± SD	2.27 ± 0.72
Low burden, n (%)	19 (16)
Medium burden, n (%)	49 (41.2)
High burden, n (%)	51 (42.9)
Discontinued visit to a family member with dementia during the COVID-19 pandemic, n (%)	41 (34.5)
Discontinued paid caregiver with dementia during the COVID-19 pandemic, n (%)	27 (23.7)
Questions about supporting someone with dementia during the coronavirus outbreak, n (%)	
I'm concerned with how to handle disruptive behaviors while we are quarantined at home	32 (31.1)
I'm not sure how I explain the situation to a person with dementia?	11 (10.7)
I'm worried that my relative with dementia may worse during COVID-19 quarantine.	9 (8.7)
I'm worried that the professional caregivers who come in to help us might not be able to come.	13 (12.6)
I need to go outside to pick up supplies for my relative with dementia but I am worried that I might catch the virus	27 (26.2)
I'm concerned that the caregiver is exhausted by the quarantine	11 (10.7)
Part III: Paid caregivers	
Paid caregiver, n (%)	40 (33.6)
Level of burden of the paid caregiver prior to the pandemic, mean ± SD	1.35 ± 0.57
Low burden, n (%)	72 (69.9)
Medium burden, n (%)	26 (25.2)
High burden, n (%)	5 (4.9)
Level of burden of the paid caregiver due to COVID-19, mean ± SD	1.55 ± 0.75
Low burden, n (%)	62 (60.2)
Medium burden, n (%)	25 (24.3)
High burden, n (%)	16 (15.5)

This table represents valid percentage of responses on the questionnaire survey specifically designed for this study. The bold represents p < 0.05.
CDR, clinical dementia rating; AD, Alzheimer's disease.

60.5% of subjects with dementia during the epidemic. Symptoms of anxiety, depression, and sleep disorders were reported in 33, 12.8, and 14.7% of the sample, respectively. Increasing gait difficulties was reported in 40% of the sample. New onset of behavioral symptoms or exacerbation of pre-existing behavioral symptoms had a positive correlation with patient age and with the presence of anxiety reported before the epidemic ($r = 0.228$, $p = 0.017$ and $r = 0.290$, $p = 0.002$, Spearman, respectively) and a negative correlation with the global CDR score ($r = -0.289$, $p = 0.002$, Spearman) and with the following domains of CDR: memory ($r = -0.202$, $p = 0.035$, Spearman), community affairs ($r = -0.236$, $p = 0.013$, Spearman), and home and hobbies ($r = -0.216$, $p = 0.024$, Spearman).

Family members reported an overall increased use of psychotropic medication during the epidemic with the following distribution: 20% increased for antipsychotics, 15% for benzodiazepines, 6% for hypnotics, and 10% for antidepressants.

In **Table 2**, we compared data according to the stages of severity of dementia. We found significant differences in increased behavioral symptoms of anxiety, insomnia, and depression in subjects with mild dementia compared to subjects with a more advanced stage of dementia. These results were showed in **Figure 1**. For psychotropics, we observed a non-significant trend in increased prescription in the mild dementia group (**Table 2**). Walking difficulties didn´t differ significantly according to the disease severity.

Before the epidemic, the most commonly prescribed type of rehabilitation was physical therapy (60% of the sample), followed by cognitive rehabilitation in 42%, and by occupational therapy in a lower percentage (25%) (**Table 1**). As expected, subjects with more severe dementia received home-based physical therapy (**Table 2**). There was a high rate of discontinuation of rehabilitation during the epidemic: 76% discontinued physical therapy, 91% occupational therapy, and 77% cognitive rehabilitation. There was no statistical difference in the rate of discontinuation based on the severity of dementia.

Characteristics of Family Members and Paid Caregivers

In **Table 1**, we showed the demographic characteristics of family members and paid caregivers. The mean age of the family members was 58.61 ± 13.60 years, 26% were older than 65 years of age, and 2% older than 85%. As expected, most family members caring for patients were female. The mean education of the family caregivers was 17.04 ± 5.15 years. Another aspect of care that we wanted to study was the discontinuation of family visits during the COVID-19 epidemic. We found that most family members continued to visit their loved ones during quarantine with a discontinuation rate of only 34%.

Overall, we observed an increased burden of care of family members during the epidemic, independently of the dementia severity. 12% of the family members felt that the burden of care was severe before the epidemic, and this number increased to 42% during the epidemic. Thus, there was a significant difference in the burnout scores before (M = 1.69, SD = 0.67) and during (M = 2.27, SD = 0.72) the COVID-19 epidemic; $t = -8,657$, $p < 0.001$. When we analyzed the reasons for the increased family burnout, we found interesting differences. Relatives of severe dementia subjects were mainly concerned of the possibility of a sick leave of paid caregivers, whereas relatives of subjects with mild dementia were mainly concerned of the risk of COVID-19 transmission when assisting subjects in instrumental activities of daily living.

Before the epidemic, 40% of the sample received care from a paid caregiver. More severe cases tended to receive care from a paid caregiver compared to milder cases. During the epidemic, only 23% of the sample discontinued this service.

DISCUSSION

This is a report of a survey of the well-being and aspects of care of 119 subjects living with dementia in the community and their family caregivers in Argentina during the initial 8 weeks of mandatory isolation due to COVID-19 epidemic.

Our sample was composed of elderly subjects with dementia, a third of those belonged to the very old group of elderly patients, and a third of the sample were men. As expected to this age group, the most frequent diagnosis was AD and followed by mixed AD. The severity of the dementia was evenly distributed, a third had mild disease, a third had intermediate disease, and a third had severe disease.

Overall, we found worsening or new onset of behavioral symptoms of anxiety, depression, and insomnia during the enforced quarantine in subjects with dementia. There was a positive correlation of these symptoms with advanced age and with the presence of anxiety before this epidemic and a negative correlation with the global CDR (18) score, community affairs, and hobbies domain of CDR scale. Other findings were that most family members continued family visits during the epidemic, only a small proportion canceled caregiver paid services, and most rehabilitation services were discontinued during the epidemic.

Our findings are worrisome since behavioral and psychological symptoms associated to dementia are a main cause of deterioration of quality of life for patients and caregivers, institutionalization, disability, increased use of health resources and caregiver stress (15, 16). Longitudinal studies of dementia subjects showed that these symptoms are highly prevalent and persistent over time and can occur at any point in the clinical course of the cognitive process (19, 20). Non-pharmacologic management is consistently recommended in the literature to control these symptoms due, in part, of the modest efficacy and the potential of harm of pharmacologic therapy (16). Caregiver training, keeping the patient active with a structured personalized routine, taking the patient for a walk-in neighborhood are all well-proven strategies to deal with anxiety and agitation in patients with dementia (16). Unfortunately, during enforce isolation, some of these strategies were impossible to implement since Argentinian authorities recommended that high-risk subjects with comorbidities remain at home (2). Most forms of rehabilitation interventions had been cancelled. Home-based interventions were probably cancelled because of fear of letting a health care professional enter patient's home and increasing the risk of spreading the epidemic. Outpatient rehabilitation services had been cancelled as a direct effect of quarantine to avoid unnecessary travel. Evidence from small trials in dementia showed that cognitive training and rehabilitation could improve cognition and decreased psychological symptoms. A recent review of reviews showed that exercise improved performance of daily activities in dementia (21). In our study, most interventions were suspended, and there is probably a relationship with the negative psychological issues found during quarantine and the cancellation of rehabilitation services.

Another main finding of our research was that neuropsychiatric symptoms during quarantine were more frequent in subjects with mild dementia than in advanced dementia cases. One possible explanation for this could be that comparatively, mild dementia subjects might have suffered more radical modification in their lifestyle habits during quarantine

TABLE 2 | Characteristics of participating caregivers and persons with Alzheimer's disease or related dementia according to Global Clinical Dementia Rating score.

Variables	**CDR**			**T/χ2**	***p***
	1	**2**	**3**		
Part I: Persons with dementia					
Age				3.861	0.425
<65 years old	50.00%	0.00%	50.00%		
65–85 years old	38.10%	28.60%	33.30%		
≥85 years old	23.30%	43.30%	33.30%		
Gender, male	24.40%	31.70%	43.90%	3.868	0.145
Education	13.3 ± 4.65	12.06 ± 4.82	14.53 ± 4.43	2.63	0.077
Diagnosis				7.866	0.447
AD	31.30%	32.50%	36.30%		
Mixed AD	42.30%	34.60%	23.10%		
Vascular dementia	42.90%	28.60%	28.60%		
Others	0.00%	0.00%	100.00%		
Increased or onset of COVID-19-related anxiety	35.40%	41.70%	22.90%	5.733	**0.05**
Increased or onset of COVID-19-related insomnia	44.10%	35.30%	20.60%	4.37	**0.037**
Increased or onset of COVID-19-related depression	42.90%	42.90%	14.30%	0.886	**0.012**
Increased gait problems during the COVID-19 pandemic	38.80%	32.70%	28.60%	0.423	0.809
Increased or onset of COVID-19-related antipsychotics prescription	33.30%	33.30%	33.30%	0.098	0.952
Increased or onset of COVID-19-related benzodiazepines prescription	27.80%	33.30%	38.90%	0.796	0.672
Increased or onset of COVID-19-related hypnotics prescription	12.50%	50.00%	37.50%	2.021	0.364
Increased or onset of COVID-19-related antidepressants prescription	41.70%	33.30%	25.00%	0.338	0.845
Physical therapy				13.003	**0.011**
At home	19.60%	30.40%	50.00%		
Specialized centers or Senior Day Care Center	33.30%	37.50%	29.20%		
No therapy	50.00%	30.40%	19.60%		
Occupational therapy				5.595	0.232
At home	11.10%	38.90%	50.00%		
Specialized centers or Senior Day Care Center	41.70%	33.30%	25.00%		
No therapy	38.40%	30.20%	31.40%		
Cognitive Rehabilitation				7.251	0.123
At home	28.60%	33.30%	38.10%		
Specialized centers or Senior Day Care Center	48.30%	37.90%	13.80%		
No therapy	30.30%	28.80%	40.90%		
Discontinued physical therapy during the COVID-19 pandemic	25.50%	36.20%	38.30%	2.802	0.246
Discontinued occupational therapy during the COVID-19 pandemic	14.30%	42.90%	42.90%	4.65	0.098
Discontinued cognitive rehabilitation during the COVID-19 pandemic	29.00%	41.90%	29.00%	1.966	0.374
Part II: Family caregivers					
Age				4.714	0.581
<45 years old	41.20%	17.60%	41.20%		
45–65 years old	32.80%	36.10%	31.10%		
65–85 years old	26.70%	36.70%	36.70%		
≥85 years old	66.70%	0.00%	33.30%		
Gender	31.30%	31.30%	37.50%	0.218	0.897
Education	15.95 ± 4.94	18.39 ± 6.28	16.87 ± 4.10	2.08	0.13
Level of burden of the family caregiver prior to the pandemic				5.377	0.251
Low burden	35.30%	31.40%	33.30%		
Medium burden	40.40%	30.80%	28.80%		
High burden	7.70%	38.50%	53.80%		
Level of burden of the family caregiver due to COVID-19				4,538	0.338
Low burden	47.40%	31.60%	21.10%		
Medium burden	33.30%	25.00%	41.70%		
High burden	30.60%	38.80%	30.60%		
Discontinued visit to a family member with dementia during the COVID-19 pandemic	0.268	0.317	0.415	2.238	0.327
Discontinued paid caregiver with dementia during the COVID-19 pandemic	0.259	0.333	0.407	1.037	0.595

(Continued)

TABLE 2 | Continued

Variables	CDR			T/χ2	*p*
	1	2	3		
Questions about supporting someone with dementia during the coronavirus outbreak					
I'm worried that the professional caregivers who come in to help us might not be able to come.	0.077	0.462	0.462	3.645	**0.05**
I need to go outside to pick up supplies for my relative with dementia but I am worried that I might catch the virus	0.519	0.296	0.185	5.731	**0.02**
Part III: Paid Caregivers					
Paid caregiver	22.50%	27.50%	50.00%	7.784	**0.02**
Level of burden of the paid caregiver prior to the pandemic, mean ± SD				7.464	0.113
Low burden	33.30%	36.20%	30.40%		
Medium burden	26.90%	19.20%	53.80%		
High burden	0.00%	60.00%	40.00%		
Level of burden of the paid caregiver due to COV6ID-19, mean ± SD				3.588	0.465
Low burden	35.00%	35.00%	30.00%		
Medium burden	20.80%	29.20%	50.00%		
High burden	25.00%	31.30%	43.80%		

This table represents valid percentage of responses on the questionnaire survey specifically designed for this study. The bold represents p < 0.05.

than subjects with severe dementia who usually are more homebound and less active.

Anxiety is reported in the literature to be strongly related to impairment of activities of daily living and dependence. In our sample, anxiety was the most frequently behavioral symptom experienced by dementia subjects during quarantine, and it was most frequently suffered by subjects with mild dementia. It is possible that, during quarantine, these subjects had more awareness of epidemic and risks of getting sick and that this knowledge induced more anxiety.

Sleep disturbances are frequent in AD patients and are related to age changes in sleep patterns, medication effects, comorbidity with anxiety, depression, and to the neurodegenerative disease by itself (18). Sleep disorders are disruptive to caregivers and increase the rate of institutionalization and caregiver burnout (22, 23). Strategies to improve sleep quality include sleep hygiene, physical activity during the day, and keeping a structured daily routine (22, 23). These strategies were all compromised during this lockdown period, and sleep difficulties were overall frequent, with even higher prevalence in subjects with mild dementia. Specially in this population, sedentary behavior during quarantine could had impacted on the quality of sleep of subjects with mild dementia

Psychotropic medication use increased during quarantine, independently of the dementia severity. Specifically use of antipsychotics, benzodiazepines, hypnotics, and antidepressants were more frequently prescribed. The first three medications are included in the Beer´s list of potentially inappropriate medication in elderly subjects with dementia (24). These medications have the potential for cognitive decline and increase the risk of falling and confusional state (24). Also, antipsychotics in this vulnerable group increased the risk of worse cardiovascular outcomes and are not currently recommended (25). This increased in use of potentially inappropriate medications in the elderly could cause in the future a deleterious effect on the health status of the subjects in our sample. A medication reconciliation plan once the quarantine ends with an active deprescribing strategy is one possible strategy to mitigate this increased risk.

Another main finding of our study is that there was a deterioration of the quality of walking during the quarantine. Gait impairment is frequent in dementia patients, especially in frail elderly subjects with advanced dementia, and is directly related to the risk of falling and quality of life of the subjects (26, 27). The performance of functional capacities depends on the ability to ambulate (27). Walking deterioration during quarantine is probably multifactorial, including discontinuation of physical and cognitive rehabilitation, deconditioning related to staying at home, and increased use of psychotropics as described above.

Probably, one of the most important learnings of this epidemic is the inclusion of technology for the evaluation and monitoring of our patients at a distance, even in older adults. While technology now is being used to socialize and give emotional support and guidance to caregivers, cognitive and physical exercise can be delivered *via* internet (28). It is true than some individuals may struggle to use this technology (29), by contrast, most caregivers usually can successfully use this resource. A recent published randomized trial of a specialized dementia care program delivered this way to the dyad patient-caregiver showed improved quality of life, decreased caregiver burn out and depression in those assigned to the active intervention (30).

Our study's main limitations are the relatively small size of the sample and the lack of prospectively longitudinal follow-up. Another pitfall is the lack of use of validated instruments to measure caregiver burnout and behavioral and psychological symptoms. We will continue to follow this cohort of subjects to study the health consequences and the real impact after the isolation period, and we will continue our research using validated scales to measure these symptoms.

Our findings, in summary, showed the negative consequences of quarantine in this sample of elderly patients. Individuals with cognitive disorders are especially vulnerable during these times

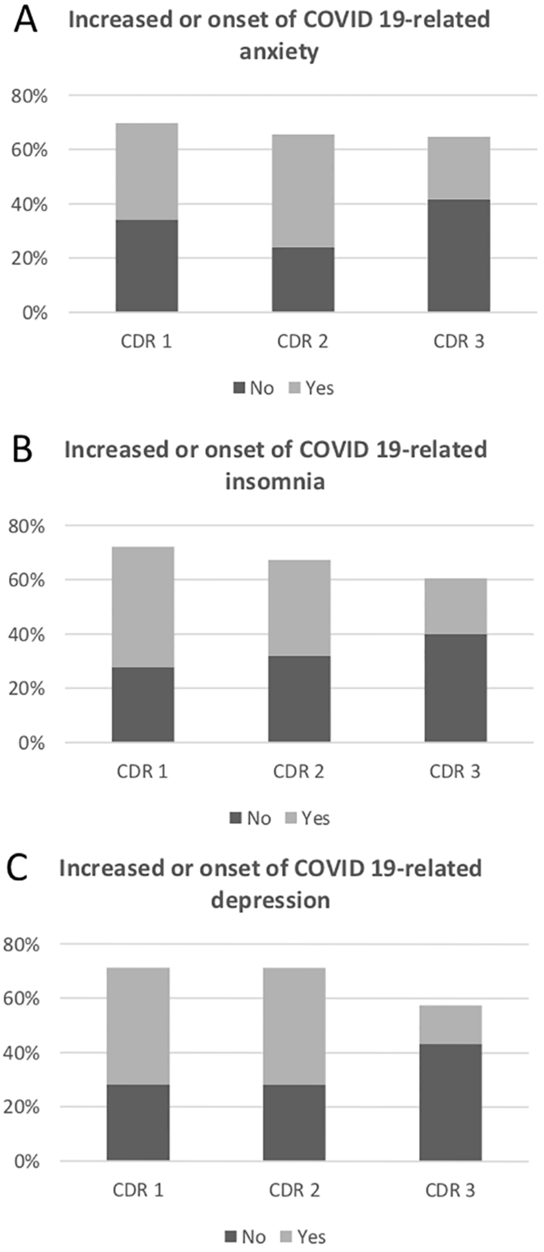

FIGURE 1 | This figure detailing valid percentage of responses on the questionnaire survey specifically designed for this study. **(A)** Percentage of patients with increased or onset of anxiety during quarantine. **(B)** Percentage of patients with increased or onset of insomnia during quarantine. **(C)** Percentage of patients with increased or onset of depression during quarantine.

of isolation and epidemic, their care needs are not met, and social engagement is decreased. Caregivers and patients need more medical attention, support groups, and virtual modalities to deal with worsened behavioral symptoms, caregiver stress and burnout, walking abnormalities, and increased use of psychotropics. In general, most office consults had been cancelled, and caregiver have less contact and guidance with specialized medical teams than before COVID-19. Physical social distance required during the epidemic suspended interventions that subjects with dementia constantly need due to the chronic nature of cognitive decline. Family member's awareness of the potential problems and a mitigation plan of action may help families deal with the negative impact of this natural crisis. Solutions will have to be creative, patient-centered, and flexible to deal with the new changing scenario. More medical counseling, guidance, and presence are needed urgently to help this population deal with new serious health challenges arose during the epidemic. Telehealth visits and telemedicine are a priority, and it must be implemented on a regular basis to provide frequent weekly medical counsel on specific new health issues related to this quarantine. Rehabilitation services also will have to adapt to the new scenario, with reduced occupancy of patients in the same area, among other strategies (31). It is necessary to urgently develop a plan of action to help dementia subjects and family members deal with the increased stress that his epidemic imposed on them.

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 FLENI. Ethics Committee. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

The study was designed and conceived by GC, MR, JC, and RA. Recruitment of participants and data collection were undertaken by GC and MR. Statistical analysis was overseen by RA, and analysis was undertaken by GC and MR. The manuscript was prepared by GC and critically reviewed and approved by all authors.

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Behavioral and Psychological Effects of Coronavirus Disease-19 Quarantine in Patients With Dementia

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Background: In March 2020, the World Health Organization declared a global pandemic due to the novel coronavirus SARS-CoV-2 and several governments planned a national quarantine in order to control the virus spread. Acute psychological effects of quarantine in frail elderly subjects with special needs, such as patients with dementia, have been poorly investigated. The aim of this study was to assess modifications of neuropsychiatric symptoms during quarantine in patients with dementia and their caregivers.

Methods: This is a sub-study of a multicenter nation-wide survey. A structured telephone interview was delivered to family caregivers of patients with diagnosis of Alzheimer disease (AD), dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), and vascular dementia (VD), followed regularly at 87 Italian memory clinics. Variations in behavioral and psychological symptoms (BPSD) were collected after 1 month since quarantine declaration and associations with disease type, severity, gender, and caregiver's stress burden were analyzed.

Results: A total of 4,913 caregivers participated in the survey. Increased BPSD was reported in 59.6% of patients as worsening of preexisting symptoms (51.9%) or as new onset (26%), and requested drug modifications in 27.6% of these cases. Irritability, apathy, agitation, and anxiety were the most frequently reported worsening symptoms and sleep disorder and irritability the most frequent new symptoms. Profile of BPSD varied according to dementia type, disease severity, and patients' gender. Anxiety and depression were associated with a diagnosis of AD (OR 1.35, CI: 1.12–1.62), mild to moderate disease severity and female gender. DLB was significantly associated with a higher risk of worsening hallucinations (OR 5.29, CI 3.66–7.64) and sleep disorder (OR 1.69, CI 1.25–2.29), FTD with wandering (OR 1.62, CI 1.12–2.35), and change of appetite (OR 1.52, CI 1.03–2.25). Stress-related symptoms were experienced by two-thirds of caregivers and were associated with increased patients' neuropsychiatric burden (p<0.0001).

Conclusion: Quarantine induces a rapid increase of BPSD in approximately 60% of patients and stress-related symptoms in two-thirds of caregivers. Health services need to plan a post-pandemic strategy in order to address these emerging needs.

Keywords: behavioral and psychological symptoms, behavioral symptoms, psychological symptoms, quarantine, dementia, caregiver, coronavirus disease, gender

INTRODUCTION

An outbreak of a novel coronavirus (severe acute respiratory syndrome coronavirus 2 -SARS-CoV-2) emerged in Wuhan, China, in late 2019 and spread to Europe in February 2020 with the first infected patient diagnosed in Italy. It has since then spread globally, with over 10 million confirmed cases as of June 30, 2020. SARS-CoV-2 has been identified as the cause of COVID-19, a respiratory illness with heterogeneous systemic and neurological symptoms (1–3). Older adults and subjects with higher comorbidities have the lower prognosis (4) and presence of dementia increases the risk of mortality after COVID-19 (5). For the containment and management of COVID-19, government authorities have introduced mitigation strategies based on measures of lockdowns, travel restrictions, and mass quarantine. Italy was the first European Country to impose a nationwide lockdown on March 13, 2020.

Confinement and isolation have been proven to be highly effective for the control of infectious diseases, including COVID-19 pandemic (6). However, previous outbreaks of SARS and MERS showed that quarantine has a negative effect on mental health, with increased psychiatric symptoms particularly related to stress reactions such as anxiety, depression, and anguish (7). Considering findings from previous outbreaks and preliminary observations during the COVID-19 pandemic, the scientific community has launched an alarm about a possible imminent "pandemic" of psychiatric disorders (8–10). Factors triggering an increase of post-pandemic psychiatric disorders may be multiples. Importance has been given to a direct effect of isolation, with restrictions on movements, impoverishment of social contacts, and affective relationships, perceived loneliness. Anxiety may arise from the rapid need to adapt to new lifestyle and changes of day to day routines. In addition, an increased state of alert due to fear of contagion and grief or even mourning for the loss of family members or friends for COVID-19 may undermine mental health wellbeing (10).

These considerations apply to the general population and very few information is available for the most vulnerable persons in society, such as elderlies and those affected by dementia (11, 12). Individuals with dementia are frail, dependent on caregivers for daily living activities and needing the support of a network of social and health services resources (memory clinics, Alzheimer café, diurnal centers, physiotherapy, etc.). In this scenario, extended lockdown with imposed self-isolation and change or deprivation of usual daily activities may represent a stressor event in both patients and caregivers with high risk to induce anxiety and depression (13). Changes in neuropsychiatric symptoms in subjects with dementia may exacerbate the psychological effects of lockdown in their caregivers, situation which may further worsen patients' behavioral symptoms, acting in a vicious loop of mutual increase of psychiatric burden. Finally, confinement reduces access to physical exercise or even physiotherapy, and movement restriction exacerbates symptoms of dementia (13, 14). In turn, lack of activities and global cognitive and physical stimulation may cause delirium in individuals with dementia, contributing further to morbidity. There is also increase evidence that psychological symptoms due to stressor events can contribute to cognitive decline (15).

A call of action for a plan to evaluate and counteract mental status illnesses in the COVID-19 post-pandemic phase in the general population has been launched (16). However, knowledge on the psychological effects of quarantine in patients with dementia, at higher risk of mental health worsening, is lacking. In this perspective, the aim of this study was to investigate the frequency and type of changes in behavioral and psychological symptoms of dementia (BPSD) during the first month of COVID-19 quarantine in patients with different types of brain diseases leading to dementia and the psychological effects in their caregivers. Factors that may modulate the change in neuropsychiatric symptoms such as disease type and severity, patient's gender, and caregiver's stress were also investigated.

METHODS

This is an observational sub-study nested in a larger multicenter nation-wide survey conducted in Italy between 14 and 24 April

2020 and evaluating the effects of quarantine due to COVID-19 pandemic on cognitive, behavioral, and motor symptoms of patients with dementia, impact of quarantine in family caregivers, and changes of health services devoted to dementia care. Here we report results regarding patients' BPSD changes and caregivers' psychological symptoms.

Study Protocol

Eighty-seven Centers for Cognitive Disorders and Dementia (CDCD) equally distributed among Northern, Center, and Southern Italy were recruited. Invitation to participate in the survey was made through two Italian scientific societies involved in dementia care and research, the Italian Neurological Society for Dementia (SINdem), and the Italian Association of Psychogeriatrics (AIP), to all their participants working in the CDCD. Eighty-nine centers responded positively and two centers were not able to conclude the enrolment and therefore 87 finally participated in the study. Patient's response rate was 98%. Study collaborators of each CDCD were asked to deliver by phone call a semi-structured interview to family caregivers of patients with dementia on regular clinical follow-up. Inclusion criteria were a) a diagnosis of one of the most common forms of dementia including: 1. Alzheimer's disease (AD), 2. dementia with Lewy bodies (DLB), 3. frontotemporal dementia (FTD), and 4. vascular dementia (VD); b) presence of a family caregiver. Exclusion criteria included a diagnosis of mild cognitive impairment and primary psychiatric disorders. The semi-structured interview was administered to family caregivers through a questionnaire divided in two parts, regarding patients' and caregivers' features (**Supplementary Material**). The part related to patients consisted of nine questions regarding modifications of dementia-related symptoms after beginning of quarantine and clinical data on previous physical independence and awareness of current pandemic. In particular, caregivers were asked whether patients had worsened one or more of the following BPSD: irritability, apathy, agitation, anxiety, depression, sleep disturbances, aggressiveness, wandering, appetite change, hallucinations, and delusions. In addition, the onset of new symptoms among the abovementioned BPSD was enquired. A further question about the need of drug treatments modifications due to worsened or new BPSD was administered. The part related to family caregivers explored 16 domains concerning demographic and social characteristics, life style and work changes after quarantine, use of medical care and health services for patients needs, and psychological effects of pandemic. Each center was asked to practice with the telephone-based interview before starting recruiting. A person of the organizing committee was available to solve questions or doubts risen from initial training. No formal harmonized procedure of delivering the interview was planned.

The study was initially approved by the Ethics Committee of the Coordinating Center (University of Torino on April 7, 2020, n.00150/2020) and by the local ethics boards. Participants gave informed consent to the study.

Statistical Analysis

The primary data source consists of all the interviews administered (total sample = 4,913). A sub-sample of patients with BPSD changes (n= 2,929) was extracted, considering patients with BPSD changes having either preexisting and/or new-onset symptoms. The fields with missing values are approximately 0.6% for which no substitution has been made.

EPI Info 7.2 software (EPIINFO ™, CDC, Atlanta, USA) was used for the statistical analysis. Microsoft Excel (Microsoft Office 2019) was used to process the charts. Microsoft Access (Microsoft Office 2019) was used to create the intermediate analysis tables. The analysis of the descriptive frequencies and the crude univariate logistic regression for the preexisting and new BPSD symptoms were performed, stratifying where necessary to control the confounding's. Subsequently, unconditional and matched logistic regressions were performed to assess the dependence on the diagnosis, the degree of disease severity and gender, setting the confidence limits at 95%.

RESULTS

Patients' Demographic and Clinical Characteristics

Data were obtained through interview of 4,913 caregivers of patients with dementia after a mean quarantine period of 47.2 ± 6.4 days. Patients' demographic, social, and clinical characteristics are reported in **Table 1**.

Patients had a diagnosis of AD in 69% of cases, VD in 16%, FTD in 8%, and DLB in 7%. Mean age, disease duration, disease severity, gender type, and geographical distributions of recruiting centers were not different between disease groups.

Neuropsychiatric Symptoms Changes

Caregivers reported BPSD changes (worsening and/or new onset BPSD) in 2,929 patients (59.6%) after 1-month from beginning of quarantine. Worsening of preexisting BPSD was described in 51.9% of cases. The DLB group had the highest frequency of increased BPSD (63.8%), followed by FTD (55.3%), AD (50.5%), and VD (50.3%). Onset of new BPSD was reported in 25.9%, with higher frequency in AD (26.7%) and lower in FTD (21.9%) (**Table 1**).

Patients with DLB and BPSD changes had a wider burden of neuropsychiatric symptoms (considering both worsened and new symptoms) with almost 30% having three or more symptoms, respect to FTD (21%) and AD and VD (both 19%) (**Figure 1**).

The increased burden of BPSD required a modification of drug treatments in 27.6% of patients with BPSD changes. In the multivariate analysis frequency of neuropsychiatric symptoms was not associated with patient's age, gender, type of dementia, severity, and duration of the disease.

As far as the type of BPSD, the most frequently reported worsened BPSD was irritability (40.2%), followed by apathy (34.5%), agitation (30.7%), anxiety (29%), depression (25.1%), and sleep disorder (24%). The less frequently reported BPSD were in the psychotic domain, with both hallucinations and delusions worsened in 10% of cases. Sleep disorder and irritability were the main newly onset BPSD during pandemic

TABLE 1 | Demographic and clinical characteristics of patients affected by dementia.

Patients	Total (n = 4913)	AD (n = 3372)	DLB (n = 360)	FTD (n = 415)	VD (n = 766)
Age (years, mean ± SD)	78.3 ± 8.2	78.3 ± 8	78 ± 7.3	72.3 ± 8.9	81.6 ± 7
Gender, female % (n)	59.7 (2.934)	63.5 (2.140)	42.2 (153)	46.7 (194)	58.4 (447)
Disease duration (years, mean ± SD)	4.5 ± 3.1	4.6 ± 3.1	4.5 ± 3	4.8 ± 3.2	4.1 ± 2.9
Regional distribution in Italy % (n)					
North	32.2 (1582)	26.5 (892)	35.3 (127)	47.5 (197)	47.8 (366)
Center	31.5 (1550)	34.1 (1151)	36.4 (132)	21.2 (88)	23.4 (179)
South/Islands	36.3 (1781)	39.4 (1328)	28.3 (102)	31.3 (130)	28.8 (221)
CDR stage % (n)					
1	25.0 (1222)	24.3 (816)	26.3 (94)	23.4 (96)	28.4 (216)
2	47.8 (2334)	49.2 (1651)	41.9 (151)	48.6 (199)	43.8 (333)
3	27.2 (1325)	26.5 (885)	31.8 (114)	28.0 (115)	27.8 (211)
Worsening of BPSD, yes % (n)	51.9 (2542)	50.5 (1699)	63.8 (229)	55.3 (229)	50.3 (385)
Gender, female % (n)	57.9 (1472)	62.9 (1068)	38.4 (88)	45.4 (104)	55.1 (212)
Onset of new BPSD, yes % (n)	25.9 (1272)	26.7 (901)	23.3 (84)	21.9 (91)	25.6 (196)
Gender, female % (n)	56.7 (722)	59.8 (539)	41.7 (35)	41.8 (38)	56.1 (110)
BPSD-related drug modification, yes % (n)	27,6 (795)	25,9 (505)	33,6 (83)	32,1 (78)	29,1 (129)

AD, Alzheimer's disease; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; VD, vascular dementia; CDR, clinical dementia rating; BPSD, behavioral and psychological symptoms of dementia.

(**Figure 2**). In **Table 2** are reported the prevalence of worsened and new BPSD in the entire patients' sample.

Prevalence of increased BPSD changes (worsened and/or new symptoms) was similar across different classes of disease severity defined by the Clinical Dementia Rating scale (CDR): mild= CDR-1: 55.8%; moderate= CDR-2: 62.3%; severe CDR-3: 58.6%). These results were maintained analyzing separately preexisting and new BPSD. Instead, the type of BPSD changes varied according to disease severity. Frequency distributions of specific BPSD by CDR severity is represented in **Figure 3**. Anxiety was most frequent in patients with mild dementia while agitation and sleep disorder in patients with severe dementia.

Results of the multivariate analyses of neuropsychiatric symptoms in different classes of disease severity showed an increased risk of a wider pattern of BPSD in patients with severe disease, while anxiety was associated with mild disease severity (**Figure 4**).

Profile of Neuropsychiatric Symptoms Changes and Disease Type

Type of dementia was associated with different frequency distribution of specific neuropsychiatric symptoms (**Figure 5**).

Worsening of sleep disorder and hallucinations were more frequent in DLB compared to other types of dementia, while worsening of wandering and change of appetite were more frequently reported in FTD (**Table 2** and **Supplementary Table 1**). Anxiety was more frequently reported in AD and DLB than in FTD and VD. On the contrary, some symptoms increased similarly across disease groups such as apathy.

In the multivariate analyses the risk profiles of increased BPSD were different according to type of dementia (**Figure 6**). Having AD was associated with an increased risk of anxiety, DLB with hallucinations and sleep disorder, and FTD with wandering and change of appetite. On the opposite, AD and FTD had lower risk of worsening hallucinations and FTD and VD to develop worsening of anxiety. No significant associations were found between type of dementia and type of new BPSD.

Profile of Neuropsychiatric Symptoms Changes and Gender

Gender influenced the type of BPSD worsened during quarantine. Symptoms of anxiety and depression were more frequently reported in female patients, while apathy and irritability in male patients ($p<0.05$) as shown in **Figure 7**.

In the multivariate analyses, increased risk of anxiety and depression was significantly associated with female gender, while apathy, irritability, and sleep disorder with male gender (**Figure 7**).

Within the disease group, different frequency of specific neuropsychiatric symptoms was observed in females compared to males. Gender risk of BPSD by disease types showed different associations which are summarized in **Figure 8**. In AD, the risk of increased anxiety and depression was associated with being female patients, while the risk of apathy was associated with male patients. In DLB a higher risk of increased hallucinations was associated with male gender, and sleep disorder.

Caregivers' Psychological Changes

Demographic, social, and psychological data of caregivers are summarized in **Table 3**.

During quarantine a large range of stress-related feelings were reported by 65.9% (n=3,240) of caregivers. Almost 46% had symptoms of anxiety, followed by helplessness (34.2%), anguish (29.3%), irritability (26.4%), abandonment (22%), and depression (18.6%). There were not differences in frequency distribution of caregiver's psychological symptoms across types of dementia.

Being females conferred an increased risk to develop anxiety (OR 1.4, CI 1.3–1.6, $p<0.0001$), anguish (OR 1.5, CI 1.2–1.7, $p<0.0001$), helplessness (OR 1.2, CI 1.1–1.4, $p<0.01$). Among

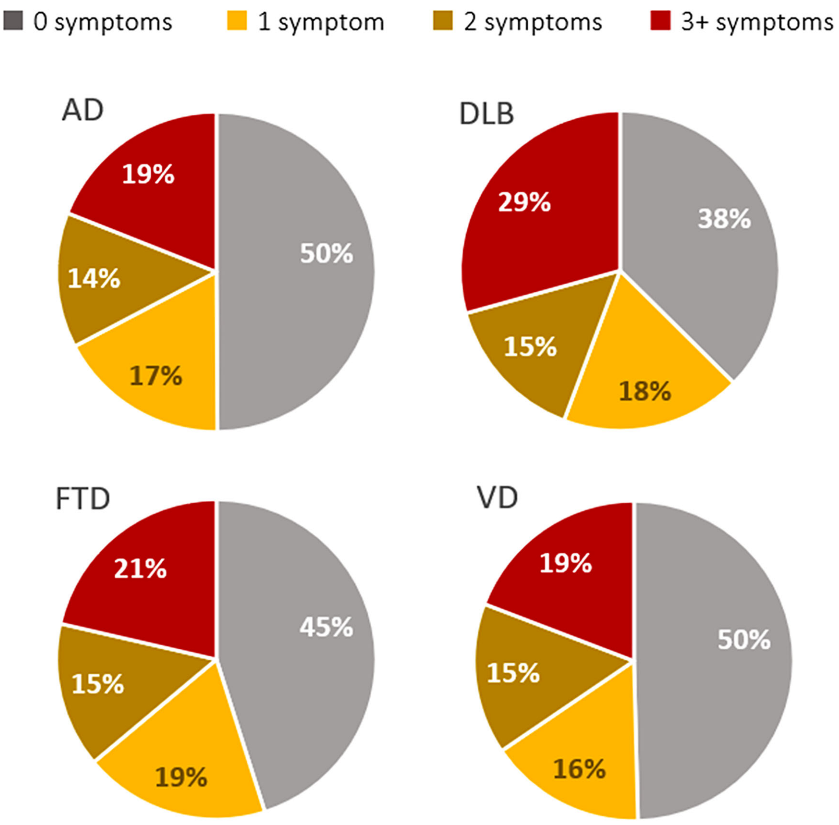


FIGURE 1 | Distribution of classes of behavioral and psychological symptoms (BPSD) burden defined as number of neuropsychiatric symptoms during quarantine divided by disease type.

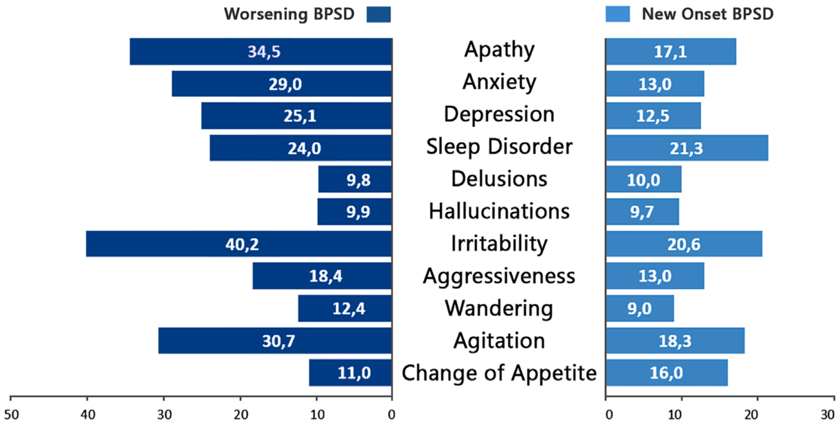


FIGURE 2 | Frequency of behavioral and psychological symptoms (BPSD) worsened (dark blue) and newly ongoing (light blue) in the sample of patients with BPSD changes (worsened and/or new onset, n = 2,929).

social characteristics, living with housemates reduced the caregiver's risk to develop symptoms of depression (OR 1.6, CI 0.5–0.7) and to conflict with the patient (OR 0.7, CI 0.6–0.8) ($p<0.0001$).

Presence of at least one caregiver's stress-related symptom was associated with increased risk of worsened preexisting BPSD (OR 2.6, CI 2.3–13) and onset of new BPSD (OR 1.6, CI 1.4–1.9) ($p<0.0001$).

TABLE 2 | Frequency distribution of worsened preexisting and new behavioral and psychological symptoms of dementia (BPSD) in the entire patients' sample and divided by disease type.

Patients	Total (n = 4,913)	AD (n = 3,372)	DLB (n = 360)	FTD (n = 415)	VD (n = 766)
Worsening, % (n):					
Apathy	17.9	17.8	21.9	19.8	15.5
	(881)	(601)	(79)	(82)	(119)
Anxiety	15.1	15.7	18.6	12.5	12.5
	(744)	(529)	(67)	(52)	(96)
Depression	13.0	12.4	18.0	12.0	14.0
	(640)	(418)	(65)	(50)	(107)
Sleep disorder	12.5	11.5	21.9	13.5	12.0
	(615)	(388)	(79)	(56)	(92)
Delusions	5.1	4.4	10.0	6.3	5.2
	(251)	(149)	(36)	(26)	(40)
Hallucinations	5.1	4.1	18.6	3.4	4.2
	(252)	(139)	(67)	(14)	(32)
Irritability	20.9	20.6	20.2	21.7	22.1
	(1026)	(694)	(73)	(90)	(169)
Aggressiveness	9.6	8.9	10.2	11.1	11.2
	(470)	(301)	(37)	(46)	(86)
Wandering	6.4	6.1	3.9	10.1	7.2
	(315)	(204)	(14)	(42)	(55)
Agitation	16.0	15.0	20.5	19.5	16.2
	(784)	(505)	(74)	(81)	(124)
Change of appetite	5.7	5.3	6.1	8.7	6.0
	(282)	(178)	(22)	(36)	(46)
New onset, % (n)					
Apathy	4.4	4.6	4.4	3.9	4.2
	(218)	(154)	(16)	(16)	(32)
Anxiety	3.4	3.5	3.3	2.4	3.4
	(165)	117)	12)	10)	26)
Depression	3.2	3.5	1.7	1.7	3.5
	(159)	(119)	(6)	(7)	(27)
Sleep disorder	5.5	5.7	3.0	4.6	6.5
	(271)	(191)	(11)	(19)	(50)
Delusions	2.6	2.4	3.3	2.4	3.1
	(127)	(81)	(12	(10)	(24)
Hallucinations	2.5	2.6	2.8	1.4	2.6
	(124)	(88)	(10)	(6)	(20)
Irritability	5.4	5.8	4.2	3.6	5.1
	(263)	(194)	(15)	(15)	(39)
Aggressiveness	3.4	3.4	3.0	3.4	3.7
	(166)	(113)	(11)	(14)	(28)
Wandering	2.3	2.4	1.1	1.9	2.7
	(115)	(82)	(4)	(8)	(21)
Agitation	4.7	5.0	3.9	3.6	4.6
	(233)	(169)	(14)	(15)	(35)
Change of appetite	4.1	4.4	2.8	3.9	3.8
	(203)	(148)	(10)	(16)	(29)

AD. Alzheimer's disease; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; VD, vascular dementia; BPSD, behavioral and psychological symptoms of dementia.

DISCUSSION

In this nation-wide survey performed in Italy after 1 month from the beginning of COVID-19 quarantine an increased burden of neuropsychiatric symptoms was reported in approximately 60% of community-dwelling persons affected by dementia by their family caregivers. Treatment drug modifications were made in 27.6% of these patients. The most frequently reported BPSD were symptoms of the anxiety-affective cluster. Profiles of BPSD changes were influenced by type of dementia, disease severity, and gender. Anxiety and depression were associated with a diagnosis of AD, mild disease severity, and female gender. Having DLB increased the risk of worsening hallucinations and sleep disorder, while FTD increased the risk of aberrant motor behavior and change of appetite. Increased BPSD burden was also associated with manifestation of psychological symptoms of distress in two-thirds of caregivers. To our knowledge this is the first survey assessing the impact of pandemic quarantine on the mental health status of a large population of patients with dementia and their caregivers.

Pandemic Quarantine as Stressor Event

Studies on mental health modifications induced by COVID-19 pandemic in healthy subjects demonstrated increased symptoms of anxiety and depression (17–19). By now very few data are available for persons with special needs and increased fragility as

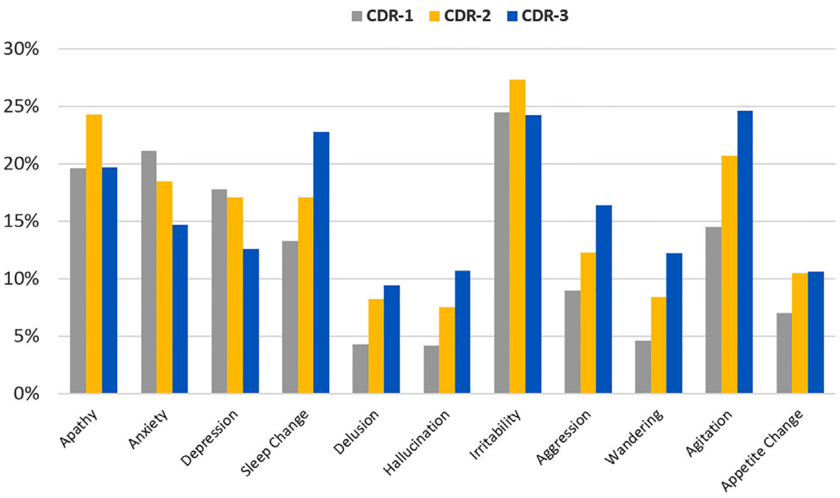


FIGURE 3 | Frequency of neuropsychiatric symptoms in patients with behavioral and psychological symptoms (BPSD) changes (worsened and/or new onset, n=2,929) divided by disease severity defined by Clinical Dementia Rating scale (CDR): mild: CDR-1 gray bar; moderate: CDR-2 orange bar and severe: CDR-3 blue bar.

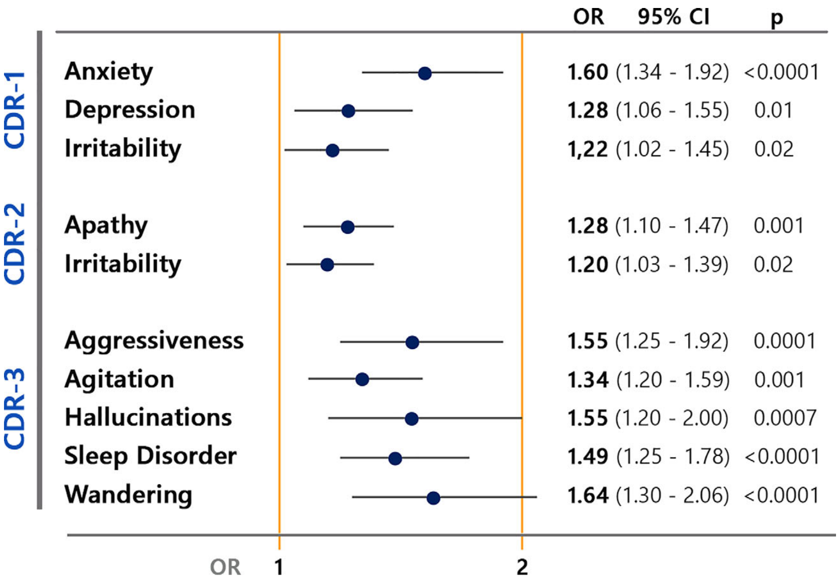


FIGURE 4 | Multivariate analyses of behavioral and psychological symptoms (BPSD) changes associated to disease severity defined by CDR (Clinical Dementia Rating) in mild (CDR-1), moderate (CDR-2), and severe (CDR-3).

patients with dementia (20). A recent study evaluated BPSD changes after 5 weeks of COVID-19 quarantine through the Neuropsychiatric Inventory questionnaire in 40 patients with AD: 20 with MCI and 20 with mild dementia (21). Worsening of BPSD respect to baseline pre-lockdown assessment was reported in 30% of patients and significant changes were found for apathy (in both groups), anxiety in MCI, agitation, and aberrant motor behavior in mild AD. We found a higher prevalence of increased BPSD respect to what has previously been reported. In our study, family caregivers were enquired about any perceived changes of patients' neuropsychiatric symptoms; we did not use a quantitative BPSD assessment and did not compare results with a previous level of BPSD burden. Furthermore, diseases with high risk of behavioral disorders such as FTD and DLB have been included. Therefore, the higher burden of BPSD in our study may be due to different study methodology and inclusion of types of dementia other than AD. On the other hand, our results confirmed the preliminary findings that apathy, agitation,

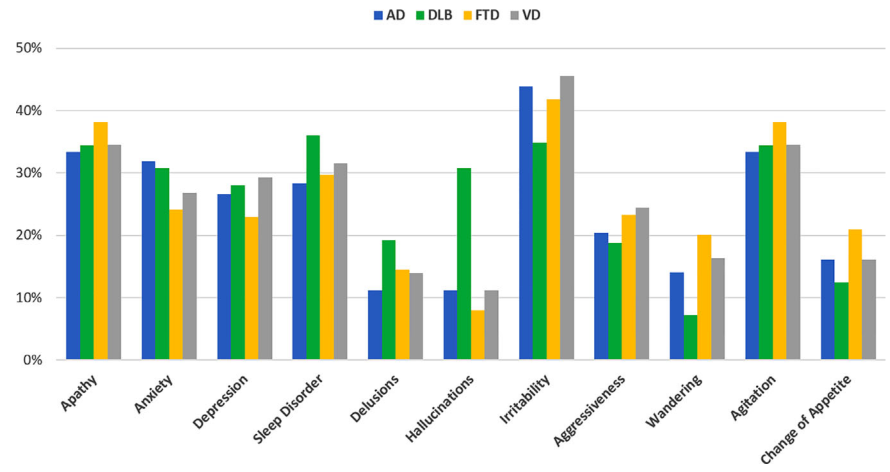
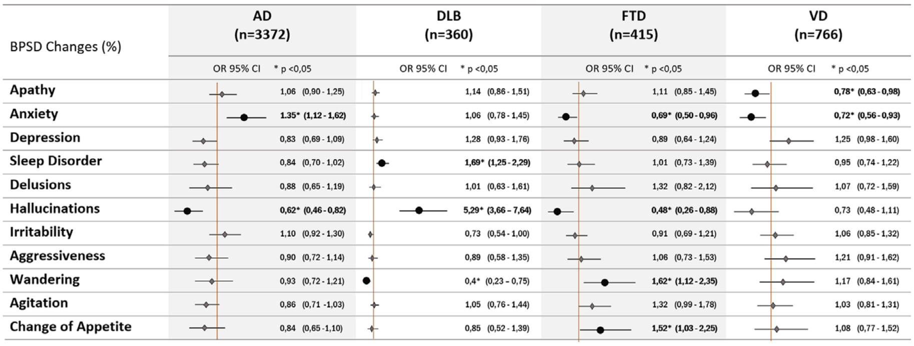
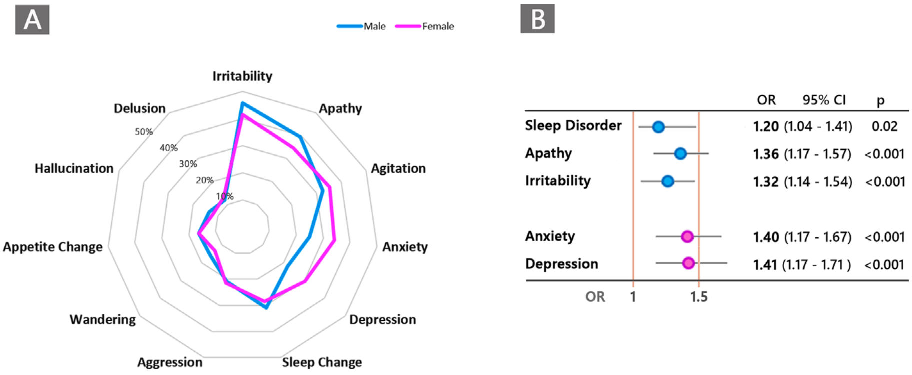


FIGURE 5 | Frequency of neuropsychiatric symptoms in patients with behavioral and psychological symptoms (BPSD) changes (worsened and/or new onset, n=2,929) divided by disease type (blue bar AD, green DLB, yellow FTD, gray VD).



BPSD Changes (%)	AD (n=3372) OR 95% CI * p <0,05	DLB (n=360) OR 95% CI * p <0,05	FTD (n=415) OR 95% CI * p <0,05	VD (n=766) OR 95% CI * p <0,05
Apathy	1,06 (0,90 - 1,25)	1,14 (0,86 - 1,51)	1,11 (0,85 - 1,45)	**0,78* (0,63 - 0,98)**
Anxiety	**1.35* (1,12 - 1,62)**	1,06 (0,78 - 1,45)	**0,69* (0,50 - 0,96)**	**0,72* (0,56 - 0,93)**
Depression	0,83 (0,69 - 1,09)	1,28 (0,93 - 1,76)	0,89 (0,64 - 1,24)	1,25 (0,98 - 1,60)
Sleep Disorder	0,84 (0,70 - 1,02)	**1,69* (1,25 - 2,29)**	1,01 (0,73 - 1,39)	0,95 (0,74 - 1,22)
Delusions	0,88 (0,65 - 1,19)	1,01 (0,63 - 1,61)	1,32 (0,82 - 2,12)	1,07 (0,72 - 1,59)
Hallucinations	**0,62* (0,46 - 0,82)**	**5,29* (3,66 – 7,64)**	**0,48* (0,26 - 0,88)**	0,73 (0,48 - 1,11)
Irritability	1,10 (0,92 - 1,30)	0,73 (0,54 - 1,00)	0,91 (0,69 - 1,21)	1,06 (0,85 - 1,32)
Aggressiveness	0,90 (0,72 - 1,14)	0,89 (0,58 - 1,35)	1,06 (0,73 - 1,53)	1,21 (0,91 - 1,62)
Wandering	0,93 (0,72 - 1,21)	0,4* (0,23 – 0,75)	**1,62* (1,12 - 2,35)**	1,17 (0,84 - 1,61)
Agitation	0,86 (0,71 -1,03)	1,05 (0,76 - 1,44)	1,32 (0,99 - 1,78)	1,03 (0,81 - 1,31)
Change of Appetite	0,84 (0,65 -1,10)	0,85 (0,52 - 1,39)	**1,52* (1,03 - 2,25)**	1,08 (0,77 - 1,52)

FIGURE 6 | Multivariate analyses of worsened neuropsychiatric symptoms associated to disease types (diagnosis of AD, Alzheimer disease; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; VD, vascular dementia).



	OR	95% CI	p
Sleep Disorder	1.20	(1.04 - 1.41)	0.02
Apathy	1.36	(1.17 - 1.57)	<0.001
Irritability	1.32	(1.14 - 1.54)	<0.001
Anxiety	1.40	(1.17 - 1.67)	<0.001
Depression	1.41	(1.17 - 1.71)	<0.001

FIGURE 7 | (A) Graphical representation of frequency distribution of neuropsychiatric symptoms according to male (blue) and female (violet) gender in patients with behavioral and psychological symptoms (BPSD) changes (worsened and/or new onset, n=2,929). **(B)** Type of neuropsychiatric symptoms significantly associated with male gender (blue color) and female gender (violet) in the entire population of patients with dementia.

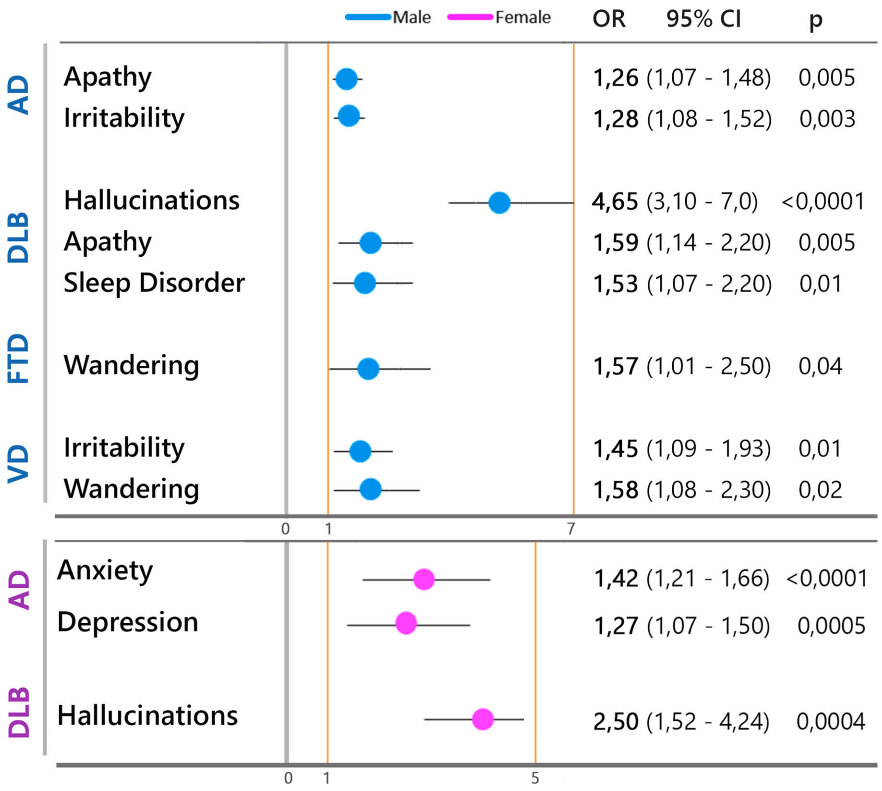


FIGURE 8 | Type of neuropsychiatric symptoms significantly associated with male gender (blue circles) and female gender (violet circles) by disease type.

TABLE 3 | Demographic, social, and psychological characteristics of family caregivers.

Caregivers	Total (n = 4913)	AD (n = 3372)	DLB (n = 360)	FTD (n = 415)	VD (n = 766)
Age (years, mean ± SD)	59.3 ± 13	59.3 ± 13.1	60.7 ± 12.7	59.1 ± 13.6	60 ± 12.4
Gender, female % (n)	53.9 (2649)	51.2 (1724)	66.4 (240)	55.4 (230)	59.4 (455)
Cohabitant caregiver, % (n)	58.9 (2876)	58.1 (1945)	63.5 (228)	69.6 (288)	54.4 (415)
Presence of housemates, % (n)	63.3 (3076)	63.1 (2104)	62.8 (224)	58.8 (241)	67.0 (507)
Degree of kinship, % (n)					
Spouses	36.0 (1739)	35.0 (1160)	43.1 (154)	54.8 (221)	26.9 (204)
Son/daughter	54.5 (2636)	55.5 (1840)	48.7 (140)	37 (149)	62.5 (473)
Others	9.5 (460)	9.5 (318)	8.2 (29)	8.2 (33)	10.6 (80)
Change of conflicts, % (n)					
Increased	22.6 (1105)	21.9 (735)	23.4 (84)	28.7 (119)	21.8 (167)
Decreased	8.0 (394)	8.5 (285)	7.2 (26)	7.0 (29)	7.1 (54)
Concern of patient's health, % (n)	75.1 (3662)	75.2 (2518)	76.6 (272)	74.0 (304)	74.6 (568)
Stress-related feelings (%)					
Anxiety	45.9 (2242)	46.1 (1543)	43.4 (155)	44.2 (182)	47.4 (362)
Depression	18.6 (902)	17.2 (573)	21.3 (76)	24.3 (101)	20.3 (152)
Anguish	29.3 (1422)	28.4 (943)	28.9 (103)	32.1 (133)	32.2 (243)
Irritability	26.4 (1285)	25.3 (843)	30.4 (109)	28.3 (117)	28.5 (216)
Abandonment	22.0 (1072)	21.2 (711)	22.2 (80)	24.8 (102)	23.6 (179)
Helplessness	34.2 (1672)	34.3 (1150)	33.0 (118)	33.7 (139)	34.9 (265)

AD, Alzheimer's disease; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; VD, vascular dementia.

and anxiety are among the most frequently reported worsening symptoms during quarantine in patients with dementia.

In our study we found increased neuropsychiatric symptoms that rely on two different dimensions: those that represent a behavioral reaction to quarantine and those that represent an increased level of those symptoms that are specific in the different types of dementia. Increased symptoms of the anxiety-affective cluster were common (prevalence ≥ 30% for worsened irritability, agitation, and apathy and ≥ 20% of new onset sleep disorder and irritability) and were homogeneously reported across disease types. This finding is in line with many observations of increased psychological symptoms of anxiety and depression during COVID-19 quarantine in healthy subjects and give support to the notion that quarantine acts as a stressor event that induces symptoms similar of those reported in the post-traumatic stress disorder (PTSD) (22–24). Indeed, quarantine due to pandemic involves different social, emotional, psychological, and physical modifications, each one with a potential contribution to increase distress. Quarantine determines social isolation and feeling of loneliness, conditions which have been demonstrated to induce psychiatric and physical alterations in healthy individuals (25, 26). The pandemic in itself can contribute to trigger fear and contagion phobia. In persons with dementia, the increase of anxiety-related BPSD during quarantine may be interpreted as a response to a stressor event and represent a PTSD-like condition. A confirm of such speculation derives from the observation that anxiety and depression increased more in patients with mild to moderate level of severity that could still present a post-traumatic reaction. Patients with dementia have pre-trauma risk factors for the development of PTSD such as increased central nervous system sensitization due to preexisting anxiety and hyperarousal, and lower hippocampal volume (27). Neuroimaging studies showed that the neuro-anatomical correlates of PTSD are decreased volume of the hippocampus and anterior cingulate cortex which are target regions of neuropathology in AD, DLB, and FTD (27). On the other hand, there are emerging evidence of a higher risk to develop cognitive decline in patients with PTSD (15).We could here hypothesize that patients with mild to moderate level of dementia are at higher risk respect to healthy subjects to manifest a variety of anxiety-related symptoms triggered in response to isolations and restrains imposed by quarantine and that this condition may render these patients more vulnerable to the development of a PTSD-like symptomatology. This in turn might potentially worsen the trajectory of cognitive decline.

Pandemic Quarantine as a Model of "Deprivation Syndrome"

In the last years the research field of dementia has invested a lot in demonstrating the value of cognitive, social, and physical stimulation in the prevention of cognitive decline, the modulation of the trajectory of clinical worsening in the early stage of the disease and containment of the neuropsychiatric burden (28–30). Based on the results of these studies many countries have started population programs of multimodal stimulation for persons at risk of dementia or with initial cognitive decline (31). During quarantine any formal and informal cognitive stimulation programs have been suddenly stopped. In addition, informal multidimensional stimulation derived by performances of outdoor day to day routines and maintenance of social contacts have been also markedly reduced for everyone.

Reduction of social contacts, cognitive stimulation, and physical activity can be viewed as a paradigm of "de-stimulation" or even as a model of "deprivation syndrome." The effects of environmental deprivation defined as lack of inputs from the environment have been studied in young and adolescents for which deprivation influences subsequent psychopathology and alters cognitive developmental abilities (32, 33). Translating this term into old-age psychiatry and applying it to the topic of our study, quarantine may be viewed as an ecological experiment on the effects of acute interruption and deprivation of social, cognitive, and physical stimulation. This condition may affect cognitive and physical domains but also neuropsychiatric symptoms, reverting the well-known effects on global health of multidimensional stimulation. Obviously, this condition might be considered a sort of "partial deprivation" as family members continue to play an important, although limited, role on the social interaction with demented subjects. We can hypothesize that increase apathy, observed in approximately 35% of patents with BPSD changes and equally distributed across the disease types, might be a surrogate manifestation of a complex and global interaction of cognitive, physical, and emotional down-regulation. Apathy, in fact, may have a cognitive, emotional, and physical component and each type of apathy has defined neuro-anatomical correlates targeting prefrontal, dorsolateral, and motor cortex other than striatum (34, 35).

Modulators of the Profile of Behavioral and Psychological Symptoms of Dementia Changes

Factors modulating the profile of increased BPSD were disease type, disease severity, and gender. Although worsening of some BPSD such as irritability and apathy are transdiagnostic, the type of neurodegenerative disease confers different risk of specific BPSD changes, such as hallucinations and sleep disorder for DLB or appetite change for FTD. Exposure to stressful events can therefore increase those neuropsychiatric symptoms for which patients with dementia are inherently more vulnerable due to the neuropathology of dementia.

Presence of visual hallucinations and alterations of sleep and wake are specific features of DLB (36). In DLB there is a higher burden of behavioral symptoms than in AD and high frequency of anxiety and depression symptoms (37, 38). On a substrate of a disease targeting the sleep-wake cycle and attentional abilities, the increase of stress-related symptoms may further worsen an efficient sleep pattern and impair attention and reality monitoring checking, with subsequent increase of hallucinations.

As regard as FTD, eating disorders are key symptoms in the diagnosis of the behavioral variant FTD, are disease specific, and are characterized by changes in dietary preferences toward carbohydrates, increased appetite, binge-eating behavior, and altered eating habits (39). We recognize the limit of this study related to the genericity of the question investigating changes of appetite without specifying whether it was a variation of increase or decrease appetite. Aberrant motor behavior may be explained as expression of reduced inhibitory control, lack of adherence to imposed societal rules and poor judgment of risks.

Disease severity was not associated with prevalence of increased BPSD burden (preexisting or new symptoms) but with profile of BPSD changes. We confirmed previous findings from the study by Lara *et al*. that showed increased anxiety in MCI patients and apathy in mild-moderate AD patients after

COVID-19 quarantine (21). Patients with preserved awareness of the traumatic event and with higher limitations respect to pre-pandemic lifestyle may be at higher risk to develop stress-related symptoms. With disease progression, the heterogeneity of BPSD manifestations reflects the increased multifactorial complexity (40, 41).

Gender effect on the type of BPSD has been demonstrated in AD, with females having more frequently psychotic symptoms and depression (42–44), and males presenting more frequently apathy and aggression (45). Different presentations of BPSD according to gender have already been described and most studies report the prevalence of anxiety and depression among female patients. This gender effect is more evident in mild to moderate stage of the disease and disappear in advanced stage (46). Some other authors report different manifestation of BPSD also in advanced stages of disease with males that exhibited more apathy and sexually inappropriate behavior and females exhibiting more anxiety and sadness (47). Our data are in line with these findings confirming that symptoms of depression and anxiety are more prevalent in women, particularly in the mild stages of the disease (43, 46, 48), while apathy and irritability are more prevalent in males (45).

Caregivers Distress and Influence on Behavioral and Psychological Symptoms of Dementia

BPSD are the most stressful aspects strongly reducing quality of life for both patients and caregivers. Anxiety and depression accompany caregivers along the entire disease course (49) and caregiver burden is a well-known socially and scientifically recognized aspect (50). Caregiving burden is known to be higher and heavier for women than men (51). In our study we found an increase prevalence of symptoms of anxiety, feeling of helplessness, and anguish reported by caregivers. Increased concern for patient health and increased familial conflicts were also reported. Presence of housemates reduced the risk of depression and conflicts thus indicating that caregiver burden may be mitigated by contrasting loneliness and supporting needs of caring with a network of helps (52).

We found an association between psychological symptoms of anxiety and depression in caregivers and increased BPSD burden. From the results of our survey we could not address the issue of whether increased BPSD are the cause or consequence of caregiver distress, particularly during quarantine when both counterparts have been exposed to similar stressor conditions.

Strengths and Limitations

This is the first survey addressing prevalence and type of increase in neuropsychiatric symptoms as acute consequence of imposed isolation due to COVID-19 quarantine in a large population of patients affected by dementia. The sample is large, representative of the most frequent forms of dementia and balanced across groups as far as demographic and clinical variables. Considerations drawn from the results of this study could therefore be extended to community-dwelling subjects affected by dementia. Limitations included the lack of standardized assessment using formal neuropsychiatric rating scales and lack of information on previous BPSD severity and type. This was due to the narrative nature of phone-based interview, the organizational constrains due to the emergency setting, and the need to recruit a large sample in a short time to monitor acutely the neuropsychiatric modifications during quarantine. Moreover, the interview was delivered to caregivers and therefore reports could be influenced by their emotional status and level of distress. However, there are studies confirming the reliability of caregivers reporting BPSD in dementia (53). Another limitation is the absence of information on type of drug prescription modification made in more than one-quarter of patients with BPSD changes. This would have been interesting since use of some drugs classes, such as antipsychotics, modify the risk of stroke and mortality and since an untailored therapeutic plan during quarantine could be partially responsible for BPSD worsening.

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 Ethics Committee of the Coordinating Center (University of Torino on April 7, 2020, n.00150/2020). Written informed consent for participation was not required for this study due to lockdown restrictions and in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

IR, AB, CM, AC, LB, CC, and VL designed the study and planned centre recruitment. AC, CM, RL, and AB wrote the report. RL and PP did the statistical analyses. ER, VA, VI, NV, FA, IA, PC, MP, IP, RS, DQ, VG, GL, MF, GT, and CF contributed to the interpretation and discussion of results and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.578015/full#supplementary-material

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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 handling editor declared a shared affiliation with several of the authors, CM, DQ, and GV, at time of review.

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The Influence of Telemedicine Care on the Management of Behavioral and Psychological Symptoms in Dementia (BPSD) Risk Factors Induced or Exacerbated During the COVID-19 Pandemic

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The number of people with dementia worldwide is expected to increase to approximately 1.3 billion in 2050. Almost 90% of patients diagnosed with dementia suffer from behavioral and psychological symptoms of dementia (BPSD). BPSD causes and risk factors are multiple and complex and can be responsible for hospitalizations in long-term institutions, psychiatric hospitalizations and search for health services. Recently, the world imposition of social distance and self-isolation as the best preventive measures for the COVID-19 pandemic has created challenges in the health care and management of this population, which may trigger or aggravate BPSD, and most caregivers are not prepared to address it. In face of this actual social distancing, telemedicine comes to be a tool for improving the management of these acute symptoms and mental care. In this article, we discuss and disseminate recommendations on this important alternative of assistance, especially considering the cases of BPSD. In this context of a pandemic, even patients with BPSD and caregivers require more frequent and updated guidance, considering the difficult context to social distance. Telemedicine can reduce the risk for the development of negative outcomes in mental health precipitated by the reduction of social contact and less access to health services, improving dementia symptom management, mainly BPSD.

Keywords: elderly, behavioral and psychological symptoms in dementia, social isolation, caregiver burden, COVID-19, telemedicine, dementia, BPSD

INTRODUCTION

Dementia, according to the Diagnostic and Statistical Manual of Mental Disorders 5th edition, is a neurocognitive disorder defined as a chronic and gradually developing decline of cognitive functions that results in occupational and social dysfunctions (1). The number of people with dementia worldwide is expected to increase to approximately 1.3 billion in 2050 (2, 3). Even if cognitive symptoms are commonly considered the hallmark feature of dementia, patients usually present a wide variety of "non-cognitive" neuropsychiatric symptoms, and they are important disease manifestations (4, 5). They are termed behavioral and psychological symptoms of dementia (BPSD) and represent a heterogeneous group of non-cognitive symptoms related to disturbed perception, thought content, mood, and behavior.

Throughout the course of the dementia process, the vast majority of patients will develop one or more of these symptoms, which can include agitation, motor disturbance, anxiety, irritability, depression, apathy, disinhibition, hallucinations, delusions, and sleep or appetite disturbances (6–9), and their prevalence may increase from mild to severe dementia (10). Almost 90% of patients suffer from dementia (11), although the etiology and management of dementia are still a challenge, and dementia can be responsible for increased referrals to nursing homes and prolonged periods of hospitalization (12).

A preliminary study rated BPSD in 124 patients with Alzheimer's disease and found that the prevalence of neuropsychiatric symptoms in this population was higher for apathy (51%), dysphoria (50%), and irritability (38%) (11), while another study with 408 patients evaluating a 5-year period prevalence of neuropsychiatric symptoms in dementia found that this was greatest for depression (77%), apathy (71%), and anxiety (62%) (13). The progression of the severity of dementia increases the likelihood of hallucinations while decreasing the odds of depression, and Alzheimer's disease (AD) patients, compared to other dementias, are less likely to present agitation, disinhibition, and depression (14).

Coronavirus disease 2019 (COVID-19) is an infectious respiratory illness caused by SARS-CoV-2, a newly emergent coronavirus that was first identified in Wuhan, China at the end of 2019 (15) and declared a pandemic in March 2020 (16). Recently, the world imposition of social distance and self-isolation as the best preventive measures for COVID-19 has created challenges in health care and management, especially for elderly people (17). In this context, telemedicine, a remote medical practice using telecommunication and information technologies, appeared to be a viable alternative to face-to-face consultations (18).

In this article, we aim to discuss the worsening of BPSD in elderly people with dementia during the pandemic and defend how telemedicine can be an important alternative for the current context.

ELDERLY PEOPLE AND THEIR HIGH RISK FOR SOCIAL ISOLATION

After the outbreak of COVID-19, the increase in the amount of information about the disease and concerns about its implications are impacting global mental health (19). The increase in the number of suspected cases and confirmed patients spread the public worry of being infected. The uncertain future of the pandemic has been exacerbated by the excess of information, sometimes driven by erroneous news reports (20). Sick patients may experience fear of an uncertain prognosis due to the fatal potential of the virus. On the other hand, the general population, especially those who are experiencing quarantine, can feel boredom, loneliness, and anger (21). This situation can be stressful for all people, provoking fear and anxiety about the disease and causing strong emotions in children and adults (22).

In fact, these changes and the fear of the unknown lead to increased psychiatry symptoms in both healthy people and those with pre-existing mental health problems (19). The stress associated with COVID-19 increases the chances of patients with pre-existing mental disorders to relapse or have new episodes. Therefore, it is important to find a balance between distance and social isolation since the loneliness imposed by quarantine can cause harmful psychological effects, especially for the elderly (23).

Elderly people can experience these feelings more intensely. They already have special physical, psychosocial, and environmental vulnerabilities associated with age (24). Case fatality in individuals 65 years or above is higher than that in other populations (25). Their frailty brings the risk of various infections and decreases the immune response; they have more comorbidities and more hospitalizations, increasing the chance of being infected with COVID-19 (26). Knowledge about this vulnerability can increase the effect of the uncertainty and fear of the pandemic, and they may experience the fear of their own death and of losing their loved ones (24).

The known limitations of the elderly in dealing with technology gadgets and sensory and cognitive deficits may make it difficult for them to access updated information about COVID-19 situations, making them victims of misinformation and inadequate precautionary measures to follow (24). Furthermore, self-isolation as a preventive measure can severely affect the elderly whose only social contact is out of home; those who do not have the support of their families or friends and depend on the social support of volunteers or social care could be in additional risk situations, along with those who live alone or isolated (27). Social distancing can be an independent risk factor for depression, anxiety and suicide, especially in places such as nursing care or old-age homes (28). Studies have observed that under these stress factors, the level of anxiety among nursing homes and caregivers increased, and they developed signs of exhaustion and burnout after a month of full lockdown (17).

Beyond age, patients with dementia are more susceptible to morbidity and mortality of the virus because they have more cardiovascular disease, diabetes, and pneumonia compared to the elderly without dementia (29). Other features may increase the risk of contracting COVID-19, such as the difficulties of this population to follow the recommendations from public health to prevent the transmission: correct hand hygiene, maintain physical distance, monitor and report symptoms of the disease and self-isolation by remaining alone at home (15).

In addition to social isolation, elderly people infected with COVID-19 could have experienced other consequences, including hospitalization and behavioral problems. One of the main symptoms of the disease is dyspnea, and the hypoxia generated by COVID-19 can cause delirium, which may complicate the course of dementia, increasing the suffering of the patients and their caregivers, the cost of medical care, and the need for support (17).

Increased demand in the health care system can hinder the access of patients with chronic diseases, such as dementia, to the services, and the fear of being infected during the use of health care settings can impair outpatient follow-up and the use of emergency services if necessary. The workup, diagnosis and clinical follow-up of these patients can be harmed by deviation of resources and professionals to act in combat of pandemic, and those living alone in community may feel loneliness due the social isolation and absence of their group activities (28).

THE PANDEMIC CAN INCREASE RISK FACTORS FOR WORSENING BEHAVIORAL SYMPTOMS

BPSD causes and risk factors are multiple and complex. Factors that contribute to the occurrence of these symptoms can be categorized as follows: factors related to the patient (neurobiological changes—brain lesions and type of dementia, changes in neurotransmission and neuromodulation, acute medical illness—urinary tract infection, pneumonia, dehydration, constipation, unmet needs—pain, sleep problems, fear, pre-existing personality and psychiatric illness); caregiver factors (stress, burden, depression, lack of education about the disease, communication issues) and environmental factors (safety issues, overstimulation or under stimulation, lack of structure or lack of established routines) (8, 9).

BPSD is not well diagnosed, and the treatment is poorly understood. Deciding which aspects constitute a behavioral disorder is extremely subjective and is associated with worse cognition, more severe stages of dementia, high levels of distress both in patients and their caregivers (family members or health professionals), long-term hospitalization, misuse of medications and increased health care costs (6).

Neuropsychiatric manifestations could be divided into three different groups according to the main symptoms presented: affective syndrome, psychological syndrome, and other neuropsychiatric disorders (30). Some studies reveal that there are differences between the occurrences of BPSD over time. In general, hyperactivity and apathy have high persistence and incidence, depression and anxiety have moderate incidence, low or moderate persistence, and psychotic symptoms are less prevalent with a moderate or low incidence (10). This is important for the identification and proper approach by the doctor and caregivers.

The initial management of BPSD is to identify and quantify the symptoms to evaluate the possibility of being secondary to comorbidities such as infection, dehydration, metabolic decompensation, adverse drug effects, and others. Proper treatment of these comorbidities alone can mitigate BPSD. If those are not the causes, non-pharmacological measures have to be instituted. Under normal conditions, environmental adaptations or modifications, the establishment of a specific routine, guidance for caregivers and family members and programs for physical activity, music and light therapy are good strategies for dealing with these symptoms (30). Some of these can be harmed during the pandemic, which can become a problem for non-pharmacologic management of these conditions.

In the actual context, several risk factors (social isolation; pharmacology adherence; caregivers' burden; reduction of nonpharmacologic strategies; lack of medical evaluation; modification of house routine) can arise to trigger or exacerbate BPSD. Elderly people, especially those who are isolated and with cognitive decline or dementia, can become more anxious, irritated, stressed, agitated, and withdrawn during quarantine. Most of the caregivers are not prepared to deal with BPSD, requiring guidance on where and how to get practical help and regular medications.

TELEMEDICINE AS A VIABLE ALTERNATIVE TOOL FOR ELDERLY MENTAL HEALTHCARE

Telemedicine is defined as a tool to provide healthcare at a distance through the use of telecommunications technology (31). The first reference to telemedicine was in 1897, informing the use of telephone calls instead of a personal doctor visit for a bedridden home patient (32). Today, many people have telecommunication devices, such as smartphones, laptops and tablets that could be used as private real-time consultations (33).

Moreover, telemedicine is growing in popularity because of the COVID-19 pandemic context and social distance (34). After all, in addition to social isolation, there are still restrictions on public transport, which also represents a major barrier to access medical care (35). It is an alternative tool that could be more used and enable mental health professionals to keep improving health care during the outbreak (36, 37). Additionally, the elderly are affected by health problems that need frequent monitoring, and telemedicine, by breaking geographical barriers and reducing unnecessary travel, facilitates access and management of all these factors by the caregivers, improving health care (38).

It is important to consider that most elderly people need a caregiver (professionals, family, friends) who must be supported by health services (23) and benefit from telemedicine. Caregivers have many responsibilities in caring for dementia patients, and the convenience and accessibility of telemedicine could help them manage psychosocial issues and even their own support, doubts and early interventions (31).

Therefore, telemedicine is well established in the literature as an alternative balance between social distance and the need for specialized consultation. It can imply cost reduction, relief of the health system, less exposure of the population at risk to infections, continuity of monitoring during the period of social distance and greater articulation between health services and patients/caregivers (31, 37, 39).

This system allows for easy access to a dementia specialist and can assist the patient in maintaining his clinical stability, as well as providing caregivers with sufficient guidance to deal with new symptoms that may appear during the pandemic, relieving stress caused by BPSD. Additionally, it expands access to clinical resources and links health care providers with patients and their caregivers, thereby overcoming the limitations of face-to-face appointments. In addition, telemedicine may reduce hospitalization and emergency department visits (40) and implies higher rates of treatment continuation in dementia patients, which could suggest that telemedicine improves factors that can contribute to slowing the progression of dementia, resulting in better prognosis, reduced hospitalization and visits to urgency/emergency settings (37).

Although psychiatry evaluation is about what we see, nonverbal communication and what is not said (36), mental health is still a specialty that can be well suited to telemedicine programs (31). Studies show that telemedicine has a high level of satisfaction and effectiveness with low cost, is very convenient, and is easily accessible (41). In addition, it provides clinical outcomes equivalent to face-to-face services (31, 37, 39). Telemedicine is not just a replacement for face-to-face appointments; it holds the possibility of new avenues for care delivery, more frequent but shorter encounters, and opportunities for earlier intervention (41) to improve mental health.

TELEMEDICINE CHALLENGES

Studies have listed some problems with telemedicine, such as technically challenged staff (11%), resistance to change (8%), cost (8%), age of patient (5%), and level of education of patient (5%) (31). Additionally, it is important to include visual and hearing problems of elderly people as a difficult factor in handling electronic devices, and we should provide appropriate adjustments to them (33).

There are many platforms to use, but for Brazil's public health reality, due to the low education and social level of our population (especially in our reality—University Hospital), WhatsApp is probably the most accessible mobile app. Even so, we still face some other problems related to infrastructure and population needs, such as: some of them have no smartphone to proceed a video call, poor internet connection, and the need of a caregiver to help with the telecommunication process.

In those cases, we need to lay hands on a simple phone call, but we have been successful considering the pandemics' needs. This tool works well for established patients, or the one we already know, but for the first time, it could be insufficient (36). For a complex or difficult case, we still proceed with a face-to-face consultation, respecting the rules of individual protection.

DISCUSSION

The COVID-19 pandemic has brought important structural and behavioral changes worldwide. For health systems, social distancing has imposed the need for new alternatives for medical care without exposing patients, especially risk groups such as the geriatric population, to possible infections. The elderly have more reason to suffer from this whole situation, both in relation to their biological risk of contracting the disease and to the more restricted social isolation. Those with dementia are at serious risk of losing their effective follow-up, adjusting medications and general orientations when non-pharmacological approaches should be adopted. In addition, the lack of routine and of the others outside therapeutic alternatives can worsen dementia symptoms, especially BPSD.

There are a few reasons why BPSD can worsen during a pandemic, such as social isolation, caregiver stress, sleep disturbances, lack of medical follow-up with medication adjustments, changes in the house routine, risk of infections, and untreated clinical diseases. One of the most important points in the treatment of BPSD is non-nonpharmacological interventions, which involve social and physical contact, such as social and exercise groups. The social isolation imposed by the pandemic suspended these interventions and will also result in decreased social engagement and worse disease progression. It is necessary to create new alternative plans for these patients in this new situation (**Table 1**).

In this context, telemedicine comes as a valid alternative to expand access to clinical resources and links health care providers with patients and their caregivers, thereby overcoming the limitations of face-to-face appointments and being a balance between social distance and the need for specialized consultation.

In contrast to the results found from the latest Kaiser Family Foundation (KFF) Health Tracking Poll (a survey project that provides consistent and up-to-date information on the public's opinions, knowledge and experiences with the U.S. healthcare

TABLE 1 | Recommendations for old age people with cognitive impairment and their caregivers in times of COVID-19 pandemic (42, 43).

1. Public health information can be difficult to understand—Try to transmit the information in a clear and simple way, remembering how to properly do the hygiene measures as many times as necessary and helping the elderly to do it. Using memory aids like pictures or notes can assist in this task; encourage and celebrate the small achievements.
2. Keep in touch with family and friends through electronic devices so that the elderly do not feel so lonely.
3. Look for signs of impaired mental health (is he feeling more anxious? Sad? Confused)? and provide psychological support, encouraging them to talk about any feelings and look for professional help if it is necessary.
4. Changes in routine can be difficult and increase BPSD: try to maintain a routine as similar as before the pandemic, the activities you would usually do around the house and keep to regular meal and bedtimes.
5. Learn simple physical exercises to do at home with the elderly to maintain the mobility. Relaxation and mindfulness are good activities too.
6. Try to promote cognitive stimulation (listen to music, see family photos and try to remember who are in those, discuss special objects); stimulate light activities, like taking care of plants and animals.
7. Take care of a good sleep routine.
8. Create a week schedule and do the plans to maintain the routine.
9. Be sure of the amount of medications and groceries you have at home so that you are safe.
10. Look for the possibilities of medical assistance by telemedicine. Ask all the questions you have; ask for help to manage the symptoms at home and make sure there is enough medication at home.
11. Have easy access to all possible help channels: close family, taxis, phone number, supermarket, medical assistance.

system), that seven out of 10 adults 65 and older (68%) say they have a computer, smartphone or tablet with Internet access at home, but only 11% of this population says they used one of these devices for a teleconsultation; in our services, we have achieved greater adherence to psychogeriatric telemedicine during this pandemic period. During the month of May 2020, we performed 34 teleconsultations through video (WhatsApp) or audio (phone call); 45 were scheduled, only five did not answer the contact, one patient died, two rescheduled because of first appearance in our service, two had wrong schedules, and one was not confirmed. In June and July, we made 43 and 58 consultations, respectively, and the vast majority of them were by teleconsultation. In the same period of last year (May, June and July, 2019), our psychogeriatric service had 51, 42, and 25 scheduled consultations, respectively, 42, 33, and 24 of which were made.

The service flow of our service begins three or four days before the consultation day. Our nurse team has contact with the patient or a caregiver, telling him that he will receive a psychiatric teleconsultation and communicate our orientations for a good interaction (for example, the patient must be with a caregiver at home; they should be in a quiet room; test the connection). Initially, we had a poor adherence level, and this nurse contact was very important to increase it and decrease the time lost to explain these orientations during medical contact. Most of the patients or caregivers were open to this type of medical care and tried to make it work. Important prescription modifications have been made during these pandemic months, such as new depressive episodes, psychotic episodes, or the worsening of BPSD, which probably avoided more severe symptoms. When we have doubts about medical conduct, the patient was scheduled to receive an ambulatory consultation. Nevertheless, some of the caregivers had no compromise with the teleconsultation; by the time of scheduled communication, they were not with the patient. The application of scales for cognitive screening was another important difficulty, which became a limitation. Patients and caregivers had trouble understanding our instructions to download, answer, or perform some scale tasks.

A recent survey study used a television-based telehealth service to support European adults living with mild dementia or mild cognitive impairment and found that those who are using this technology are doing more memory exercises and can help them with cognitive stimulation in this particular situation. Access to these devices may reduce feelings of isolation, and the creation of a specific telephone support line has been described as effective in providing health information and social support to this population (44).

Telemedicine might help reduce the risk for the development of negative mental health outcomes precipitated by a reduction in social contact and less access to health services, improving dementia symptom management, mainly BPSD, and mental care. In addition, it can help caregivers by providing more agile guidance on non-pharmacological measures to control symptoms adapted to the new reality of confinement. Additionally, it allows health support in real time, even at a distance, making possible adequate medication adjustment, when necessary, without exposing the patient and caregiver to risks of infection.

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 authors.

AUTHOR CONTRIBUTIONS

Author contribution study design: KA, WS. Writing the draft: KMA, WS, IS, AL. Integration of the authors' comments: KA, WS, IS, AL. Final manuscript: KA, WS, IS, AL. All authors contributed to the article and approved the submitted version.

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Associations of Social Isolation with Anxiety and Depression During the Early COVID-19 Pandemic: A Survey of Older Adults in London, UK

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The COVID-19 pandemic is imposing a profound negative impact on the health and wellbeing of societies and individuals, worldwide. One concern is the effect of social isolation as a result of social distancing on the mental health of vulnerable populations, including older people. Within six weeks of lockdown, we initiated the CHARIOT COVID-19 Rapid Response Study, a bespoke survey of cognitively healthy older people living in London, to investigate the impact of COVID-19 and associated social isolation on mental and physical wellbeing. The sample was drawn from CHARIOT, a register of people over 50 who have consented to be contacted for aging related research. A total of 7,127 men and women (mean age=70.7 [SD=7.4]) participated in the baseline survey, May–July 2020. Participants were asked about changes to the 14 components of the Hospital Anxiety Depression scale (HADS) after lockdown was introduced in the UK, on 23rd March. A total of 12.8% of participants reported feeling worse on the depression components of HADS (7.8% men and 17.3% women) and 12.3% reported feeling worse on the anxiety components (7.8% men and 16.5% women). Fewer participants reported feeling improved (1.5% for depression and 4.9% for anxiety). Women, younger participants, those single/widowed/divorced, reporting poor sleep, feelings of loneliness and who reported living alone were more likely to indicate feeling worse on both the depression and/or anxiety components of the HADS. There was a significant negative association between subjective loneliness and worsened components of both depression (OR 17.24, 95% CI 13.20, 22.50) and anxiety (OR 10.85, 95% CI 8.39, 14.03). Results may inform targeted interventions and help guide policy recommendations in reducing the effects of social isolation related to the pandemic, and beyond, on the mental health of older people.

Keywords: COVID-19, older adults, anxiety, depression, mental health, social isolation, loneliness

INTRODUCTION

With unprecedented population aging; the consequences of social isolation on the mental wellbeing of older people is emerging as a significant public health concern, now exacerbated by the COVID-19 pandemic (1, 2). Previous studies have reported that social disconnection puts older people at greater risk of depression and anxiety (3). The impact of severe acute respiratory syndrome (SARS) on mental health, within the general public has previously been reported (4), and recent systematic reviews are beginning to highlight the detrimental impact of COVID-19 on mental health among different populations (5–7). Factors exacerbating this risk are less known but vital in informing appropriate targeted intervention and preventative measures.

The United Kingdom (UK) announced COVID-19 lockdown measures on the 23rd March 2020. Lockdown stipulated a ban on nonessential travel, closure of most shops, offices and public spaces, alongside self-isolation and quarantine for those with possible infection and shielding for those deemed extremely vulnerable due to health conditions. These measures have placed many individuals under conditions of complete isolation, especially those living alone. Long periods of social isolation may have a profound negative effect on mental health conditions including depression, anxiety, stress and insomnia (8), may differ as a function of sex and age (5), and may worsen health inequalities, with poorer and marginalized groups at greatest risk (9). Furthermore, social isolation, loneliness and depression have, in turn, been associated with cognitive decline (10, 11) and incident dementia (12, 13) among older people.

A systematic review, conducted in May 2020, sought to identify the psychiatric symptoms or morbidities associated with COVID-19 among those infected, the general population, psychiatric patients and health-care workers (5). They identified 43 studies, the majority of which were conducted within Chinese populations, investigating the impact of COVID-19 on mental health, but not exclusive to the elderly. One Danish study (n=2,458), conducted within the general public, revealed higher scores in anxiety and depression when compared to pre-lockdown (14), especially among females, while a Chinese study (n=333) reported a moderate-to-severe level of subjective stress, anxiety and depression in an initial survey post-lockdown, with no significant changes one-month later (15). Another systematic review and meta-analysis was conducted on studies relating to the mental health impact of COVID-19 on the general public and health workers, up until the 25th May, including 65 studies, again, predominantly from China (7). They reported the prevalence of anxiety and depression among the general population during the pandemic as 33% (28%–30%) and 28% (23%–32%), respectively. Common risk factors for higher psychological impact included being female, having contracted COVID-19, lower socio-economic status, social isolation and spending longer watching COVID-19 related news. Frontline providers of telephone help services such as Lifeline in Australia, have reported dramatic increases in calls from people experiencing anxiety and loneliness (16). The Australian Bureau of Statistics' national Household impacts of COVID-19 survey of 1000 adults found that 28% of women and 16% of men reported feeling lonely as a result of the pandemic, and that this was the most common personal stressor identified (17). Finally, a UK study has published findings on the impact of COVID-19 on mental health before and during the pandemic, in participants of the UK Household Longitudinal Study (aged >16 years, n=17,452) (18). A web-based survey administered between April 23–30th 2020, assessed mental health *via* the 12-item General Health Questionnaire and reported that prevalence of mental health distress rose from 18.9% (17.8, 20.0) in 2018–2019 to 27.3% (26.3, 28.2) in April 2020. Predictors of change were greatest in younger adults, women and people living with children.

Among these studies, the older population is largely underrepresented. We are not aware of any studies in high income countries that have exclusively investigated the impact of social isolation and physical distancing due to COVID-19 restrictions on the mental health of older people. Identifying the key factors that place older people at risk of decline in mental wellbeing is critical in planning appropriate mitigation strategies. Here, we report the effects of social isolation on self-reported changes in levels of depression and anxiety among older people residing within London *via* an online survey. We investigated the effect of sociodemographic factors, health variables and indicators of loneliness and reduced connectivity as risk factors for change in levels of depression and anxiety. As the literature presents consistent evidence for the effect modification of sex in response to social isolation on mental health (14, 19–23), we also explored whether certain risk factors differentially altered responses to social isolation among men and women. Results may inform interventions to prevent or delay the effects of social isolation on worsening mental health in this susceptible older population.

MATERIALS AND METHODS

Study Design and Population

To investigate the associations between social isolation measures, implemented due to the COVID-19 pandemic, and the mental and physical health of an older population, we designed and implemented, on April 29th, 2020, the ongoing longitudinal CHARIOT COVID-19 Rapid Response Study (CCRR). Study participants were recruited from the Cognitive Health in Ageing Register for Interventional and Observation Trials (CHARIOT), comprised of ~40,000 volunteers aged 50 years and over, without known dementia diagnosis and who have consented to be contacted for participation in age-related research (24). CHARIOT has been developed by the School of Public Health at Imperial College London, since 2012, in collaboration with primary care practices and community organizations across London. For the CCRR study, data on symptoms and results of COVID-19 tests, demographic and lifestyle factors, mental and physical health are being collected by repeated six-weekly questionnaire online surveys. In the present analysis we report cross-sectional results from the baseline survey, conducted between 30th April – 8th July 2020. All register volunteers were invited *via* email or post for participation in the CCRR study.

Additional adult members of their household, able to provide consent and who wished to take part in the survey, could do so by contacting the study team. Participants were directed *via* a unique link to the online survey platform, hosted by Qualtrics (Provo, UT, USA), where they were presented with the Participant Information Sheet, then directed to complete an electronic Informed Consent Form. Once the consent form was electronically signed by the participant, the survey was launched. Data collected as a part of this study are anonymized and kept strictly confidential in accordance with the UK General Data Protection Regulations (2016). CCRR was ethically approved by the Imperial College London Joint Research Compliance Office (20IC5942) and by the Health Research Authority (16/EM/0213).

Assessment of Sociodemographic, Health and Lifestyle Factors

Data on general (age, sex, ethnicity, and marital status) demographics, household composition, current occupational status and friend/family contact *via* technology such as skype/zoom/mobile were extracted. Alcohol and smoking behavior, and height/weight for the calculation of body mass index (BMI) were included. Participants were asked to report any medical history *via* checking against a list of comorbidities including vascular factors, cancers, neurological and mental health conditions, arthritis and respiratory disease. Loneliness was measured *via* the following question: "During the period of reduced social contact, have you experienced loneliness (felt isolated, with no companions)", with the following responses; "never", "rarely", "sometimes", "often". The variable used to assess sleep was obtained from the question: "During the period of reduced social contact, have you experienced poor sleep (restless and unable to sleep)", with the following responses; "Not ever", "Less than once a week", "Once or twice a week", "Three or more times a week". The sleep and loneliness questions were obtained from the Imperial College Sleep Quality questionnaire adapted from the Pittsburgh Sleep Quality Index (25) and Centre for Epidemiologic Studies of Depression Scale, for work-free periods (26).

Depression and Anxiety (Outcome)

Depression and anxiety levels were assessed with the Hospital Anxiety and Depression Scale (HADS) which includes 14 questions on feelings related to anxiety and depression (seven items for each), rated on a 4-level Likert scale from "most of the time" to "not at all" or similar responses (27). The widely used HADS has face validity for use in an older population (28), with questions that are easy to relate to and appropriate to the current circumstances of social isolation. After each item, we added a question as to whether participants were experiencing that feeling "more than", "less than" or "the same as" before COVID-19 social distancing restrictions. The categorical outcome variable used in this study was overall improvement, worsening or no change in reported items of anxiety and depression (**Figure 1**). Participants were categorized as either worsened or improved on the depression or anxiety components of HADS if they responded feeling "more than" or "less than" since before lockdown, on four or more of the seven items for depression or anxiety, respectively. All others were categorized as not changed.

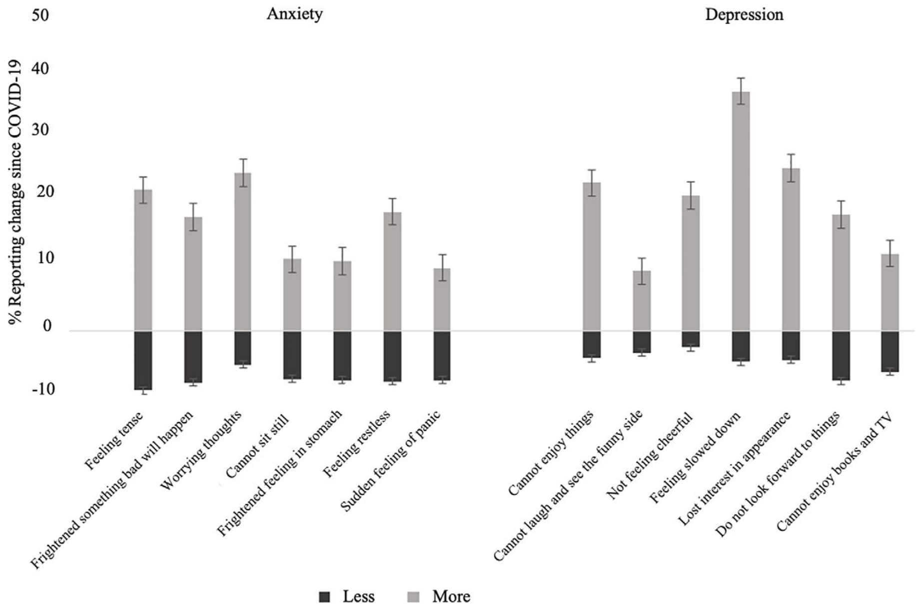

FIGURE 1 | Percent of cohort reporting worsened or improved items of anxiety and depression following COVID-19 social isolation measures. Error bars indicate standard error.

Statistical Analyses

We conducted separate multinomial logistic regression models to assess the association between each of the following factors: sex (men, women), age (continuous, years), marital status (married/partnered, single/widowed/divorced), smoking (no, yes), alcohol consumption (continuous, units per week), sleep quality (not ever, < once per week, 1–2 times per week, ≥3-times per week), feelings of loneliness (never, rarely, sometimes, often), household composition (not living alone, living alone), level of remote friend/family contact *via* technology (daily, 2–6 times per week, ≤ once per week) and their association with risk of change in components of anxiety and depression since lockdown as separate outcomes (worsened, improved, no change). Analyses was initially conducted in men and women combined, followed by sex-stratification. Interaction terms by sex and exposure were included in each model to determine if the effect of exposure on the outcome measure significantly varied as a function of sex. Models were controlled for confounding effects of age and sex (model 1), and additionally for hypertension, hypercholesterolemia, diabetes, cardiovascular disease, chronic obstructive pulmonary disease (COPD) and any mental health conditions, pre-lockdown (model 2). These common chronic conditions were included as subjectively reported poor health is a known risk factor for depression and anxiety (29–31). Less than 7% of data were missing for any one variable; hence, we did not compute missing values. All variables were included in the model as categorical, with the exceptions of age and alcohol consumption. To enhance interpretation of the logistic regression, alcohol consumption was adjusted to represent risk per increase in 3-units of alcohol per week (approximately one glass of wine), and for age, an increase in risk per 5-years. Results are presented as odds ratios (ORs) and 95% confidence intervals (CI). Statistical two-sided significance level was set at 5% ($p<0.05$). All analyses were conducted using IBM SPSS 23 for windows.

RESULTS

Cohort Characteristics

At time of data extraction, a total of 9,314 register participants had read the Participant Information Sheet and were directed to complete the consent form. Of this number, 2,187 (24.5%) participants did not complete consent to join CCRR. The remaining 7,127 were included in this study for baseline data analysis. The response rates from 15,000 emailed invitations and 25,000 postal invitations were approximately 35% and 7.5%, respectively.

Table 1 presents the cohort characteristics. Of the total sample, majority were Caucasian (91.5%) with a mean age 70.6 (SD 7.4) years (range 50-100). Women represented 54.1% of the cohort, 65.5% were married/partnered, and 20.7% were employed. Mean BMI was 25.1 (SD 5.7), 77.1% of men and 50.6% women reported at least one vascular factor, 2.4% of the overall cohort reported a mental health condition, pre-pandemic. Poor sleep ≥3 times per week was reported by 12.3% of men and 20.9% of women. Majority of the cohort reported that they did not smoke (93.6%), and alcohol consumption was low. A higher proportion of men reported feeling lonely "often" and having contact with friends and family ≥3 times per week compared to women; whereas a higher proportion of women reported living alone. A total of 5.5% of participants fell within the abnormal category for anxiety and 2.5% for depression on the HADS questionnaire, according to population norms. Since lockdown, 12.8% of participants reported feeling worse on components of depression on the HADS and 12.3% reported feeling worse on components of anxiety. On the other hand, fewer participants reported feeling improved on components of depression and anxiety (**Figure 1**). There was a substantially higher proportion of women scoring abnormal on the HADS depression and anxiety assessment, and who reported feeling worse in components of anxiety and depression post-lockdown, compared to men.

Association of Age and Sex With Change in Anxiety and Depression

After accounting for the confounding effect of covariates, women compared to men were more than twice as likely to report feeling worse on components of depression (OR 2.46, 95% CI 2.10, 2.89) and anxiety (OR 2.42, 95% CI 2.06, 2.85) on the HADS (**Tables 2**, **3**). Conversely, of those reporting improvements (4.9%), women were more likely to report feeling better in components of anxiety (OR 1.7, 95% CI 1.36, 2.16), relative to men. With every five-year increase in age there was a 19% (OR 0.81, 95% CI 0.77, 0.85) and 22% (OR 0.78, 95% CI 0.75, 0.83) lower risk of reporting feeling worse on components of depression and anxiety, respectively.

Loneliness and Reduced Social Connectivity

Overall, 27.2% of the cohort reported that they felt lonely sometimes or often, more in women (34.8%) than men (17.7%). There was a prominent and dose-response association between loneliness and worsened components of anxiety and depression on the HADS. Individuals reporting that they "often" felt lonely had a 17.24 (95% CI 13.20, 22.50) times higher risk of reporting feeling worse in components of depression and 10.85 (95% CI 8.39, 14.03) times higher risk of reporting feeling worse in components of anxiety, compared to those who never felt lonely (**Tables 2**, **3**). Women were twice as likely to report worsened components of depression as a result of loneliness (OR 19.74, 95% CI 14.28, 27.29) compared to men (OR 11.60, 95% CI 6.86, 19.62), and men were more likely to report worsened anxiety (OR 14.79, 95% CI 8.99, 24.32) than women (OR 9.36, 95% CI 6.92, 1.80) (**Tables 4**, **5**).

Compared to those who reported living with others, those who lived alone were more likely to report feeling worse on components of anxiety (OR 1.89, 95% CI 1.01, 1.40) and depression (OR 1.36, 95% CI 1.16, 1.60) (**Tables 2**, **3**). Findings were augmented among men (**Tables 4**, **5**). The associations were attenuated but remained significant after accounting for the

TABLE 1 | Descriptive statistics within the overall cohort and stratified by sex.

	Overall Cohort	Males	Females
Demographics			
Sex, n (% women)	7,127 (100)	3,114 (43.7)	3,855 (54.1)
Age, mean years, (SD)	70.6 (7.4)	71.3 (7.2)	70.1 (7.5)
Marital status, n, % married/partner	4,668 (65.5)	2457 (78.9)	2210 (57.3)
Ethnicity, n (%)			
Caucasian	6,522 (91.5)	2,900 (93.1)	3,614 (93.7)
African/Caribbean	48 (0.7)	17 (0.5)	31 (0.8)
Asian	195 (2.7)	98 (3.1)	95 (2.5)
Other	192 (2.7)	89 (2.9)	103 (2.7)
Employment status, n (%)			
Employed	1,444 (20.7)	690 (22.2)	754 (19.5)
Retired	4,815 (67.6)	2,179 (70)	2,633 (68.3)
Furloughed/unemployed	403 (5.6)	155 (5)	241 (6.4)
Health and Lifestyle			
BMI, mean (SD)	25.1 (5.7)	26.7 (6.1)	23.9 (5.1)
Normal (<25 kg/m^2), n (%)	1,272 (57.2)	415 (43.9)	855 (67)
Overweight (25-29.9 kg/m^2), n (%)	599 (26.9)	299 (31.6)	300 (23.5)
Obese (≥ 30 kg/m^2), n (%)	352 (15.8)	231 (24.4)	121 (9.5)
Medical history, n (%)			
Hypertension	1,919 (26.9)	1,009 (32.4)	897 (23.3)
Hypercholesterolaemia	1,529 (21.5)	774 (24.9)	743 (19.3)
Arthritis	1,048 (14.7)	352 (11.3)	691 (17.9)
Cardiovascular disease	478 (6.7)	319 (10.2)	154 (4.0)
Type 2 diabetes	456 (6.4)	299 (9.6)	153 (4.0)
Asthma	445 (6.2)	193 (6.2)	250 (6.5)
COPD	198 (2.8)	108 (3.5)	88 (2.3)
Psychiatric diagnosis	173 (2.4)	61 (2.0)	109 (2.8)
Active cancer treatment	114 (1.6)	71 (2.3)	43 (1.1)
Poor sleep, n (%)			
Not ever	1,411 (21.3)	839 (28.3)	571 (15.7)
< once per week	2,501 (37.1)	1,152 (38.9)	1,344 (36.9)
1-2 times per week	1,574 (23.8)	606 (20.5)	966 (26.5)
≥3 times per week	1,125 (17)	365 (12.3)	759 (20.9)
Smoking status, n, % nonsmoker	6,668 (93.6)	2,970 (95.4)	3,693 (95.8)
Alcohol unit's p/w, median (IQR)	8.0 (2.0, 15.0)	10.0 (3.0, 20.0)	6.0 (1.0, 14.0)
Indicators of isolation			
Feeling lonely, n (%)	6,617 (92.8)	2,965 (95.2)	3,643 (94.5)
Not ever	3,245 (49)	1,793 (60.5)	1,449 (39.8)
Rarely	1,573 (23.8)	647 (21.8)	925 (25.4)
Sometimes	1,374 (20.8)	423 (14.3)	947 (26.0)
Often	425 (6.4)	102 (3.4)	322 (8.8)
Household members, n (% living alone)	1,915 (26.9)	571 (18.3)	1,334 (34.6)
Friend/family social media contact, n (%)			
Daily	3,709 (53.7)	1,496 (48.7)	2,249 (59.3)
2-6 times per week	2,415 (35.0)	1,181 (38.5)	1,220 (32.2)
≤ once per week	780 (11.3)	454 (14.8)	320 (8.4)
Mood			
HADS Depression score, n (%)			
Normal	5,114 (90.8)	2,368 (93.7)	2,740 (88.5)
Borderline	375 (6.7)	116 (4.6)	258 (8.3)
Abnormal	142 (2.5)	44 (1.7)	98 (3.2)
HADS Anxiety score, n (%)			
Normal	4,774 (84.8)	2,276 (90.0)	2,495 (80.6)
Borderline	550 (9.8)	162 (6.4)	384 (12.4)
Abnormal	307 (5.5)	90 (3.6)	217 (7.0)
Depression change, n (%)[a]			
Same	5,640 (79.1)	2,689 (84.4)	2,946 (76.4)
Worsened	912 (12.8)	243 (7.8)	668 (17.3)
Improved	108 (1.5)	48 (1.5)	60 (1.6)
Anxiety change, n (%)[a]			

(Continued)

TABLE 1 | Continued

	Overall Cohort	Males	Females
Same	5,432 (76.2)	2,612 (83.9)	2,815 (73.0)
Worsened	880 (12.3)	244 (7.8)	636 (16.5)
Improved	348 (4.9)	124 (4.0)	223 (5.8)

[a]Denotes change in ≥4 items within the seven mood items (each for depression and anxiety).
SD, standard deviations; kg, kilograms; m^2, meters squared; BMI, body mass index; COVID, 2019 coronavirus pandemic; COPD, chronic obstructive pulmonary disease; HADS, Hospital Anxiety and Depression Scale.

confounding effect of self-reported mental health conditions and vascular factors.

Level of remote contact with friends/family *via* technology did not significantly alter risk of reporting feeling worse on components of depression (**Tables 2**, **4**). Compared to individuals who reported daily contact, those reporting 2–6 times of online social contact per week had a 19% (OR 0.81, 95% CI 0.68, 0.95) lower risk of reporting feeling worse on components of anxiety, and, conversely, a 26% (OR 0.74, 95% CI 0.57, 0.94) lower likelihood of reporting feeling improved (**Table 3**). Sex stratified analysis found these results to be augmented and to remain statistically significant among men (**Table 5**).

Single/widowed/divorced individuals had a 1.37 (95% CI 1.17, 1.59) and 1.17 (95% CI 1.00, 1.37) times higher risk of reporting worsened components of depression and anxiety on the HADS, respectively, compared to those who were married/partnered (**Tables 2**, **3**). These associations were augmented among men (**Tables 4**, **5**). There was also a small proportion more likely to report feeling improvement on components of anxiety, following lockdown (OR 1.30, 95% CI 1.03, 1.64), compared to those who are married/partnered, which were augmented among women (**Table 5**).

Sleep, Alcohol, and Smoking

Male smokers were more likely to report feeling worse on components of depression (OR 1.75, 95% CI 0.97, 3.14) and anxiety (OR 1.69, 95% CI 0.95, 3.02) on the HADS compared to nonsmokers (**Tables 4**, **5**). This association was not significant for women. However, of those reporting improvements in components of depression, female smokers were more likely to do so than female nonsmokers, while this association was not statistically significant for men. Alcohol consumption was not associated with a remarkable worsening or improvement in components of anxiety or depression in men. However, a three-unit increase in alcohol consumption per week (approximately one glass of wine) was associated with a 22% (OR 0.78, 95% CI 0.66, 0.93) lower likelihood of reporting improvement in components of depression in women.

Cohort participants who subjectively reported experiencing poor sleep were more likely to report worsened components of

TABLE 2 | Association between sociodemographic factors, health and lifestyle, indicators of isolation and change in components of depression.

Predictor		Worsened, OR [95% CI]		Improved, OR [95% CI]	
	N	Model 1	Model 2	Model 1	Model 2
Sex, ref. Men	6581				
Women		2.43 [2.07, 2.84]***	2.46 [2.10, 2.89]***	1.10 [0.75, 1.62]	1.14 [0.77, 1.69]
Age (years)	6581	0.81 [0.77, 0.85]***	0.81 [0.77, 0.85]***	0.88 [0.76, 1.00]	0.89 [0.78, 1.02]
Marital status, ref. Married/partner	6580				
Single/widow/divorced		1.40 [1.20, 1.63]***	1.37 [1.17, 1.59]***	0.68 [0.43, 1.08]	0.65 [0.41, 1.03]
Smoking status, ref. Nonsmoker	6580				
Smoker		1.50 [1.04, 2.16]*	1.41 [0.97, 2.04]	2.26 [1.03, 4.94]*	2.07 [0.94, 4.57]
Alcohol consumption (units p/w)	6580	1.02 [1.00, 1.04]*	1.01 [1.00, 1.01]*	0.98 [0.66, 1.44]	0.97 [0.95, 0.99]**
Poor sleep, ref. Not ever	6535				
< once per week		2.00 [1.51, 2.64]***	2.00 [1.51, 2.65]***	0.71 [0.43, 1.16]	0.72 [0.44, 1.18]
1-2 times per week		2.85 [2.14, 3.79]***	2.84 [2.13, 3.79]***	0.79 [0.46, 1.36]	0.78 [0.45, 1.35]
≥3 times per week		7.11 [5.37, 9.41]***	6.91 [5.21, 9.15]***	0.80 [0.43, 1.51]	0.75 [0.40, 1.42]
Feeling lonely, ref. Not ever	6535				
Rarely		2.72 [2.16, 3.42]***	2.72 [2.16, 3.43]***	0.61 [0.37, 1.02]	0.62 [0.37, 1.02]
Sometimes		7.22 [5.84, 8.92]***	7.14 [5.78, 8.82]***	0.51 [0.27, 0.94]*	0.49 [0.26, 0.91]*
Often		18.34 [14.09, 23.86]***	17.24 [13.20, 22.50]***	0.97 [0.39, 2.45]	0.77 [0.30, 1.99]
Household members, ref. Not alone	6580				
Live alone		1.36 [1.16, 1.60]***	1.32 [1.12, 1.55]**	0.65 [0.39, 1.07]	0.62 [0.37, 1.02]
Friend/family social media contact, ref. Daily	6534				
2-6 times per week		1.04 [0.89, 1.21]	1.05 [0.90, 1.23]	0.71 [0.49, 1.09]	0.72 [0.47, 1.11]
≤ once per week		1.03 [0.81, 1.32]	0.99 [0.77, 1.27]	0.72 [0.37, 1.41]	0.69 [0.35, 1.36]

*Reference outcome category: No change. p ≤ 0.001***, p ≤ 0.01**, p ≤ 0.05*. Model 1 adjusted for age and sex; Model 2 adjusted for age, sex, hypertension, hypercholesterolemia, type 2 diabetes, chronic obstructive pulmonary disease, cardiovascular disease and mental health conditions prior to lockdown. N; sample size in each multivariable regression model (N did not differ in models 1 and 2).*

TABLE 3 | Association between sociodemographic factors, health and lifestyle, indicators of isolation and change in components of anxiety.

Predictor	*N*	Worsened, OR [95% CI]		Improved, OR [95% CI]	
		Model 1	**Model 2**	**Model 1**	**Model 2**
Sex, ref. Men	6581	2.33 [1.98, 2.73]***	2.42 [0.75, 0.83]***	1.63 [1.30, 2.05]***	1.7 [1.36, 2.16]***
Age (years)		0.79 [0.76, 0.83]***	0.78 [0.75, 0.83]***	0.96 [0.89, 1.04]	0.97 [0.89, 1.04]
Marital status, ref. Married/partner	6581				
Single/widow/divorced	6580	1.20 [1.02, 1.40]*	1.17 [1.00, 1.37]*	1.32 [1.04, 1.67]**	1.30 [1.03, 1.64]*
Smoking status, ref. Nonsmoker					
Smoker	6580	1.25 [0.85, 1.85]	1.16 [0.79, 1.72]	1.39 [0.79, 2.42]	1.36 [0.78, 2.38]
Alcohol consumption (units p/w)		1.01 [0.99, 1.03]	1.00 [1.00, 1.01]	0.99 [0.96, 1.02]	1.00 [0.99, 1.01]
Poor sleep, ref. Not ever	6580				
< once per week	6535	1.80 [1.33, 2.44]***	1.81 [1.34, 2.45]***	0.52 [0.40, 0.68]***	0.53 [0.41, 0.69]***
1-2 times per week		3.52 [2.61, 4.76]***	3.50 [2.59, 4.73]***	0.44 [0.32, 0.60]***	0.43 [0.31, 0.60]***
≥3 times per week		7.90 [5.87, 10.63]***	7.67 [5.69, 10.33]***	0.42 [0.29, 0.62]***	0.41 [0.28, 0.61]***
Feeling lonely, ref. Not ever					
Rarely	6535	1.65 [1.32, 2.07]***	1.65 [1.32, 2.07]***	0.73 [0.55, 0.96]*	0.72 [0.56, 0.96]*
Sometimes		4.77 [3.91, 5.82]***	4.73 [3.87, 5.77]***	0.63 [0.46, 0.88]**	0.62 [0.45, 0.86]**
Often		11.27 [8.75,14.51]***	10.85 [8.39, 14.03]***	0.58 [0.31, 1.10]	0.53 [0.28, 0.99]*
Household members, ref. Not alone					
Live alone	6580	1.89 [1.01, 1.40]*	1.15 [0.98, 1.36]	1.07 [0.83, 1.37]	1.05 [0.82, 1.35]
Friend/family social media contact, ref. Daily					
2-6 times per week	6534	0.79 [0.68, 0.93]**	0.81 [0.68, 0.95]**	0.73 [0.57, 0.93]**	0.74 [0.57, 0.94]*
≤ once per week		0.79 [0.61, 1.02]	0.77 [0.59, 1.00]	0.77 [0.52, 1.13]	0.76 [0.51, 1.11]

Reference outcome category: No change. p ≤ 0.001***, p ≤ 0.01**, p ≤ 0.05*. Model 1 adjusted for age and sex; Model 2 adjusted for age, sex, hypertension, hypercholesterolemia, type 2 diabetes, chronic obstructive pulmonary disease, cardiovascular disease and mental health conditions prior to lockdown. N; sample size in each multivariable regression model (N did not differ in models 1 and 2).

anxiety and depression and less likely to report improvement, in a dose response manner. Those reporting poor sleep ≥3 times per week had a 6.91 (95% CI 5.21, 9.15) and 7.67 (95% CI 5.69, 10.33) times higher risk for reporting feeling worse in components of depression and anxiety, respectively, compared to those who reported an absence of poor sleep (**Tables 2**, **3**). Differences did not vary significantly by sex.

DISCUSSION

We investigated the effect of sociodemographic, health and lifestyle factors, indicators of loneliness and reduced connectivity on subjective feelings of anxiety and depression among an older population. Most people did not report a change on components of anxiety and depression on the HADS, but for those who did

TABLE 4 | Association between sociodemographic factors, health and lifestyle, indicators of isolation and change in components of depression among males and females.

Predictor	Worsened, OR [95% CI]		Improved, OR [95% CI]	
	Male	**Female**	**Male**	**Female**
Age (years)	0.83 [0.75, 0.91]***	0.80 [0.76, 0.85]***	1.10 [0.89, 1.35]	0.78 [0.65, 0.93]**
Marital status, ref. Married/partner				
Single/widow/divorced	1.73 [1.28, 3.34]***	1.26 [1.06, 1.51]**	0.78 [0.36, 1.69]	0.64 [0.36, 1.15]
Smoking status, ref. Nonsmoker				
Smoker	1.75 [0.97, 3.14]	1.24 [0.77, 1.99]	1.17 [0.28, 4.99]	2.95 [1.12, 7.79]*
Alcohol consumption (units p/w)	1.01 [1.00, 1.02]	1.01 [1.00, 1.01]	0.98 [0.96, 1.01]	0.78 [0.66, 0.93]**
Poor sleep, ref. Not ever				
< once per week	2.32 [1.47, 3.69]***	1.82 [1.27, 2.59]***	1.38 [0.66, 3.76]	0.39 [0.20, 0.75]**
1-2 times per week	3.15 [1.93, 5.13***	2.64 [1.84, 3.77]***	1.61 [0.70, 3.70]	0.44 [0.21, 0.90]*
≥3 times per week	7.68 [4.76, 12.39]***	6.33 [4.45, 9.00]***	1.13 [0.38, 3.33]	0.52 [0.24, 1.13]
Feeling lonely, ref. Not ever				
Rarely	2.86 [1.97, 4.16]***	2.68 [2.00, 3.60]***	0.88 [0.43, 1.80]	0.48 [0.24, 0.97]*
Sometimes	7.53 [5.28, 10.74]***	7.17 [5.49, 9.37]***	0.30 [0.07, 1.27]	0.55 [0.27, 1.12]
Often	11.60 [6.86, 19.62]***	19.74 [14.28, 27.29]***	1.59 [0.44, 5.71]	0.46 [0.11, 1.98]
Household members, ref. Not alone				
Live alone	1.61 [1.17, 2.21]**	1.25 [1.03, 1.50]*	0.87 [0.40, 1.88]	0.55 [0.28, 1.06]
Friend/family social media contact, ref. Daily				
2-6 times per week	0.94 [0.70, 1.25]	1.09 [0.90, 1.32]	1.10 [0.60, 2.02]	0.46 [0.24, 0.90]*
≤ once per week	0.78 [0.51, 1.19]	1.13 [0.83, 1.55]	0.69 [0.26, 1.84]	0.82 [0.32, 2.11]

Reference outcome category: No change. p ≤ 0.001***, p ≤ 0.01**, p ≤ 0.05*. Adjusted for age, hypertension, hypercholesterolemia, type 2 diabetes, chronic obstructive pulmonary disease, cardiovascular disease and mental health conditions prior to lockdown.

TABLE 5 | Association between sociodemographic factors, health and lifestyle, indicators of isolation and change in components of anxiety among males and females.

Predictor	**Worsened, OR [95% CI]**		**Improved, OR [95% CI]**	
	Male	**Female**	**Male**	**Female**
Age (years)	0.79 [0.72, 0.87]***	0.78 [0.74, 0.83]***	0.97 [0.85, 1.10]	0.97 [0.88, 1.06]
Marital status, ref. Married/partner				
Single/widow/divorced	1.44 [1.06, 1.97]*	1.09 [0.91, 1.32]	1.20 [0.78, 1.84]	1.34 [1.01, 1.78]*
Smoking status, ref. Nonsmoker				
Smoker	1.69 [0.95, 3.02]	0.91 [0.54, 1.55]	0.88 [0.31, 2.47]	1.71 [0.87, 3.36]
Alcohol consumption (units p/w)	1.00 [0.99, 1.01]	1.01 [0.20, 1.02]	1.00 [0.99, 1.01]	0.99 [0.98, 1.01]
Poor sleep, ref. Not ever				
< once per week	1.39 [0.87, 2.21]	2.10 [1.39, 3.15]***	0.61 [0.40, 0.92]*	0.47 [0.33, 0.66]***
1-2 times per week	3.45 [2.19, 5.44]***	3.66 [2.44, 5.49]***	0.40 [0.22, 0.73]*	0.42 [0.29, 0.63]***
≥3 times per week	7.58 [4.80, 11.98]***	8.07[5.40, 12.05]***	0.63 [0.33, 1.19]	0.33 [0.20, 0.54]***
Feeling lonely, ref. Not ever				
Rarely	2.11 [1.45, 3.08]***	1.43 [1.08, 1.90]**	0.77 [0.48, 1.23]	0.70 [0.50, 0.99]*
Sometimes	5.71 [4.03, 8.08]***	4.21 [3.30, 5.37]***	0.50 [0.25, 1.00]*	0.66 [0.45, 0.95]*
Often	14.79 [8.99, 24.32]***	9.36 [6.92, 1.80]***	0.96 [0.32, 2.82]	0.42 [0.19, 0.91]*
Household members, ref. Not alone				
Live alone	1.52 [1.11, 2.09]**	1.05 [0.86, 1.27]	0.96 [0.59, 1.54]	1.08 [0.81, 1.46]
Friend/family social media contact, ref. Daily				
2-6 times per week	0.66 [0.49, 0.88]**	0.88 [0.72, 1.07]	0.49 [0.32, 0.75]***	0.92 [0.68, 1.25]
≤ once per week	0.55 [0.37, 0.87]*	0.92 [0.67, 1.28]	0.55 [0.31, 0.99]*	0.97 [0.58, 1.62]

*Reference outcome category: No change. $p \leq 0.001$***, $p \leq 0.01$**, $p \leq 0.05$*. Adjusted for age, hypertension, hypercholesterolemia, type 2 diabetes, chronic obstructive pulmonary disease, cardiovascular disease and mental health conditions prior to lockdown.*

report change, it was more likely worsened than improved (**Table 1**). Our results indicate that women, younger age, being single/widowed/divorced, living alone, poor sleep and experiencing loneliness are factors linked with higher risk for reporting worsened components of anxiety and/or depression.

Loneliness and Reduced Social Connectivity

This study demonstrated a significant negative association between subjective loneliness and worsened components of both depression and anxiety, following lockdown. These associations had a dose response effect. Levels of anxiety were exacerbated among men, and depression, among women. Furthermore, descriptive statistics indicated a significant change in loneliness before and after lockdown stipulations, whereby those reporting loneliness "often" prior to lockdown increased from 2% to 20% post-lockdown (data not shown). These findings indicate that an increase in loneliness was most likely due to the circumstances surrounding COVID-19 social isolation and was not pre-existing. Our findings corroborate results from a survey on the impact of COVID-19 on mental health (32), as reported in a recent Lancet Psychiatry position paper, indicating a strong association between social isolation and loneliness with symptoms of depression and anxiety (33). Social isolation and loneliness are strongly associated with anxiety, depression, self-harm and suicide attempts across the lifespan (34–36). Older people may be considered prime candidates for risk of loneliness, owing to the higher likelihood of reduced capacity, frailty and comorbidities, and reduced likelihood to engage with others *via* technology. Our results found that those who were single/widowed/divorced and/or who lived alone were also at increased risk of reporting worsened components of depression and anxiety following COVID-19 lockdown, especially among men. Furthermore, men who engaged in higher levels of friend/family contact *via* technology, reported feeling worse in components of anxiety, perhaps indicating reverse causality. Being widowed or divorced as a risk factor for worsened mental health has been reported in similar COVID-19 general population cohort studies in Spain (n=3,055) (19) and China (n=1,060) (37), although among younger cohorts and without investigating the effect modification of sex. It may be expected that living alone and without a partner are inherently linked with an increased risk of loneliness, especially under circumstances of social and physical distancing. The frequency and mode of social connectivity *via* technology, while under social distancing circumstances, and its link with anxiety and depression has not yet been investigated outside the current study, warranting further attention.

The longer-term consequence of such risk factors as loneliness and reduced social connectivity have been reported elsewhere. Social isolation, depression and apathy have been associated with an increased risk of incident dementia in a circular-causal manner (12, 38). Furthermore, data from the English Longitudinal Study of Ageing reported that incident dementia was independently associated with loneliness, a lower number of close relationships and not being married, and that these findings were in fact independent of depression and without reverse causality (13). Our findings and those reported above, only further highlight the need to promptly tackle both the immediate and longer-term consequence of social isolation on the mental and consequential cognitive health of older adults.

Sleep, Alcohol, and Smoking

A total of 40% of our cohort reported sleep disturbances. This figure exceeds worldwide insomnia prevalence, estimated before the pandemic to be between 3.9% and 22% (39). A study conducted in Greece (n=2,427), following COVID-19 lockdown, detected a similar proportion (37.6%) of the general public experiencing some level of sleep disturbance (40). They also reported that women, living in urban areas, stress surrounding risk of COVID-19 infection, loneliness and severe depressive symptoms were all predictive of insomnia. Therefore, it is not unreasonable to suggest that, in such circumstances, sleep disturbances may be an artifact of reverse or bi-directional causality. It may be expected that personal circumstances surrounding the COVID-19 pandemic will increase levels of stress. Worry and ruminating thoughts provoke cognitive arousal and may disturb cortisol homeostasis, resulting in poorer sleep. Such associations have previously been reported under similar circumstances (41). Furthermore, there is existing evidence that loneliness and poor sleep have a bi-directional relationship (42).

We found that men who reported smoking had an increased risk of reporting worsened components of anxiety and depression. Conversely, among the sub-group of those reporting improved components of depression, females with higher alcohol consumption were 22% less likely to report these improvements. Although no study has yet investigated the associations of smoking and alcohol with risk for depression and anxiety during the COVID-19 pandemic, social isolation has been reportedly associated with unhealthy lifestyle factors, including increased smoking and alcohol consumption (35). In our study, of those who smoke, 24.6% reported that they had increased smoking since lockdown, and of drinkers, 14.7% reported an increase in alcohol consumption, both warranting further investigation. Once again, these observations may be a consequence of reverse or bi-directional causality. Nonetheless, majority of participants report no change in smoking and/or drinking behavior post-lockdown, indicating that perceived worsening in components of depression and/or anxiety may also be linked with this pre-existing behavior. Exploration of longitudinal data will elucidate such inferences.

Age and Sex

Women, compared to men, were more likely to report worsened components of anxiety and depression on the HADS. These findings have been replicated, in varying age-groups and from different countries including the UK (18), Demark (14), Spain (19, 23, 43), Italy (21), Turkey (44) and Iran (20, 22). Furthermore, studies conducted on the effects of stress, have consistently reported women to be at increased risk of developing anxiety and depression (45). Notwithstanding, one recent study reported that associations between depression, stress and insomnia was higher among men surveyed during the COVID-19 pandemic (46), while another study reported no differences related to sex (37), both conducted within Chinese populations. To the best of our knowledge, ours is the first to report the effect modification of sex on the association of key risk factors for depression and anxiety, among older people, during the COVID-19 lockdown. Such findings may elucidate causative variations in risk for mental health decline. Factors including loneliness, being single/widowed/divorced, living alone, remote friend/family contact *via* technology, and alcohol consumption were all contributors to differences between men and women in reported worsening in components of anxiety and depression. These results highlight the importance of investigating specific sociodemographic, health and lifestyle circumstances which augment risk among men and/or women differentially.

In our population of older people, we found that younger age was a risk factor for worsened components of anxiety and depression. To our awareness, only one other study of a much smaller sample (n=236) reported on the associations of COVID-19-related social isolation on mental health among older people exclusively (44), but the authors did not investigate the risk of age. The older age-group is poorly represented within most of reported studies, to date. However, two studies reported lowest risk for anxiety and depression during the earlier stages of COVID-19 lockdown, among a small sub-sample of those >60 years, when compared to younger age-categories, both being within Spanish cohorts (19, 43). Conversely, a Chinese population study, reported that older age increased risk for anxiety and depression (37). Although the effect of COVID-19 on mental health appears to be attenuated by older age, findings within an older sample are scarce and studies have often failed to account for risk factors more commonly affecting older people, such as social isolation and loneliness. Indeed, social disconnection has reportedly put older people at great risk of depression and anxiety (3). Nonetheless, among a healthier older population such as ours, it may also be that with increasing age, older adults are more able to adapt and show higher resilience. To truly understand the relevance of our findings, follow-up data will need to be investigated, and ideally, in comparison with a congruent, younger population.

Limitations

Some study limitations warrant acknowledgment. Firstly, we did not have a measure of anxiety and depression before the COVID-19 social isolation and physical distancing measures were mandated. Thus, we were unable to assess change other than from current and self-reported change. Nonetheless, given the magnitude of observed outcomes, it is not unreasonable to speculate that mental health changes were largely influenced by circumstances surrounding the COVID-19 pandemic and resultant social isolation. Indeed, by comparing the proportion of those reporting worsened components of anxiety and depression against HADS clinical classification (normal, borderline, abnormal), 53% of those who reported worsened depression, and 34% of those who reported worsened anxiety, scored within the normal range on the HADS scale, indicating that lockdown affected mood not only among those with pre-existing disorders, but also in psychologically healthy individuals.

The use of cross-sectional data in this study precludes causal inferences. We are unable to establish the direction of the association between various factors such as changes in alcohol consumption, cigarette smoking, sleep quality, and worsened levels of anxiety or depression. It will be important to investigate repeated measures of modifiable exposures and reported symptoms of depression and anxiety over time. Nonetheless, the CCRR study is ongoing and we endeavor to publish longitudinal findings in due course. Furthermore, we have not yet captured the experiences of those less technologically literate. Wider access to technology may help buffer loneliness and isolation that lead to worsened mental health. Older people, however, are more likely to have limited ability to access technology, most likely representing the more vulnerable of this demographic. We may hypothesize that those who are less able or willing to engage with technology may also present with exacerbated risk factors such as a higher prevalence of comorbidities, and hence, be yet more vulnerable to the effect of social isolation as a result of the pandemic. Similar studies should endeavor to allow administration of surveys *via* a variety of means, such as phone or post, to capture the experience of those across the so-called digital divide. Indeed, the included cohort is a biased and nonrepresentative sample of the wider London population. The CCRR cohort are healthier with fewer comorbidities than would be expected for this age-group, are predominantly Caucasian and living within the West London region, an area typically associated with higher socioeconomic status (24). Finally, we found a strong and convincing link between subjective loneliness and higher risk for reporting worsened levels of anxiety and depression. However, this variable warrants a more in-depth investigation, with loneliness being gathered *via* an existing and validated questionnaire designed to assess a wider spectrum of loneliness indicators, such as both emotional and social, believed to be distinct concepts (47). We have, since, optimized our survey questionnaire to capture such additional data.

Conclusion and Perspectives

The negative impact of COVID-19 on mental health among the general population has been identified as a research priority (1, 2, 6, 33, 48). However, few studies to date have specifically addressed the effect of COVID-19 and consequential social and physical distancing measures on mental wellbeing, specifically among an older population. Findings from this study highlight potentially important clinical and public health implications. We have identified, within an older, UK population, risk factors for the development of anxiety and depression as a result of COVID-19 related social isolation. These factors may inform risk stratification and targeted intervention strategies at both a clinical and community level. We highlight the need to track, identify and implement early interventions among individuals at increased risk of developing loneliness as a result of social isolation. Of the interventions used to combat loneliness and social isolation, effective strategies include those that facilitate engagement in meaningful, satisfying group activities, and psychological interventions to address the maladaptive conditions associated with loneliness (16). As in-person intervention strategies during pandemics may be limited or impossible, the use of technologies, such as apps, may remain an important tool, albeit limited by the digital divide, thus potentially excluding significant numbers of particularly vulnerable older people. These and other adaptive strategies to improve knowledge, awareness and self-coping will be vital in mitigating the risk of loneliness, anxiety and depression in older people.

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 CCRR study was ethically approved by the Imperial College London Joint Research Compliance Office (20IC5942) and by the East Midlands Derby Health Research Authority (16/EM/0213). The participants provided their written informed consent to participate in the study.

AUTHOR CONTRIBUTIONS

CR, CdJ, SA-A, CU-M, and LM conceptualized and designed the study. CR performed the data analyses with SA-A, CdJ, and CR conducted the literature review. CR wrote the manuscript with co-authors. All authors contributed to the article and approved the submitted version.

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Implementing Remote Memory Clinics to Enhance Clinical Care During and After COVID-19

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Social isolation is likely to be recommended for older adults due to COVID-19, with ongoing reduced clinical contact suggested for this population. This has increased the need for remote memory clinics, we therefore review the literature, current practices and guidelines on organizing such remote memory clinics, focusing on assessment of cognition, function and other relevant measurements, proposing a novel pathway based on three levels of complexity: simple telephone or video-based interviews and testing using available tests (Level 1), digitized and validated methods based on standard pen-and-paper tests and scales (Level 2), and finally fully digitized cognitive batteries and remote measurement technologies (RMTs, Level 3). Pros and cons of these strategies are discussed. Remotely collected data negates the need for frail patients or carers to commute to clinic and offers valuable insights into progression over time, as well as treatment responses to therapeutic interventions, providing a more realistic and contextualized environment for data-collection. Notwithstanding several challenges related to internet access, computer skills, limited evidence base and regulatory and data protection issues, digital biomarkers collected remotely have significant potential for diagnosis and symptom management in older adults and we propose a framework and pathway for how technologies can be implemented to support remote memory clinics. These platforms are also well-placed for administration of digital cognitive training and other interventions. The individual, societal and public/private costs of COVID-19 are high and will continue to rise for some time but the challenges the pandemic has placed on memory services also provides an opportunity to embrace novel approaches. Remote memory clinics' financial, logistical, clinical and practical benefits have been highlighted by COVID-19, supporting their use to not only be maintained when social distancing legislation is lifted but to be devoted extra resources and attention to fully potentiate this valuable arm of clinical assessment and care.

Keywords: dementia, cognitive impairment, telemedicine, neuropsychological assessment, geriatric psychiatry and aging, remote measurement technologies

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INTRODUCTION

Cognitive impairment and dementia increase with age and represent major challenges for patients, their families and society. Accurate diagnosis of cognitive impairment, the degree of impairment, such as subjective cognitive decline (SCD), mild cognitive impairment (MCI) and dementia, and underlying aetiologies in older people are important tasks for the healthcare system, requiring;

- collection of history to ascertain subjective cognitive impairment
- any potential impact on function *via* activities of daily living (ADLs)
- mental status examination, including objective assessment of cognition, mood and other psychiatric symptoms that can affect cognition and provide diagnostic information
- medical/neurological examination and biomarker analyses for aetiological diagnosis (1).

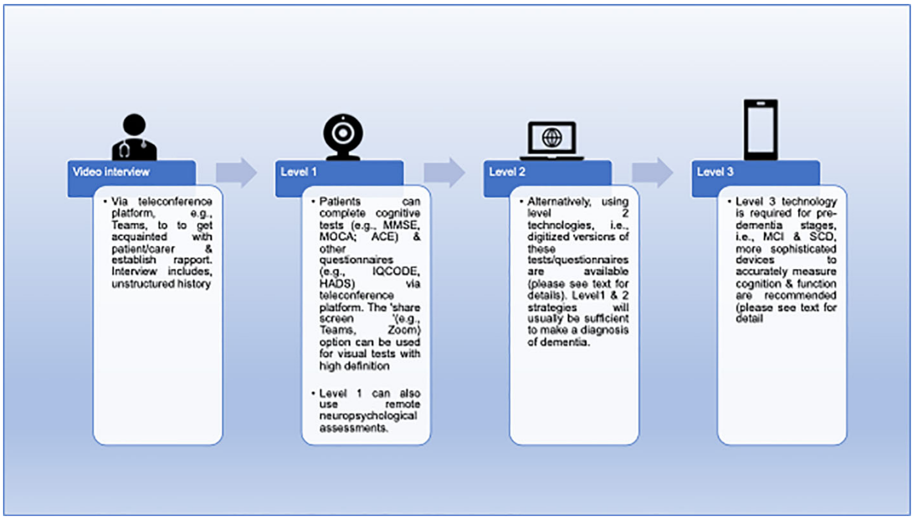
The COVID-19 pandemic has heighted the need for remote offsite (i.e., virtual) cognitive assessment. Older people are at higher risk from COVID-19, due to ongoing age-related psychosocial changes, existing physical and mental health conditions and smaller social networks, on whom they may be reliant. Older adults are therefore particularly recommended to minimize risk of infection by using social distancing measures, yet the importance of a timely diagnosis of dementia remains unchanged, or has arguably increased due to the high association between COVID-19 and dementia (2). In fact, unintended consequences of such distancing may lead to reduced physical and social activity, loneliness and depression - all factors associated with more rapid cognitive and functional decline - compounding the burden on individuals and healthcare services (3). Moreover, there is also the dilemma faced by many patients regarding their concerns about potentially having dementia and wanting to speak to a clinician, offset against concerns of contracting COVID-19 should they allow a clinician into their home or visit a clinic (4). Remote memory assessments can potentially resolve this dilemma and provide an opportunity to re-evaluate how existing methods can be adapted for remote assessment and how digital technology can be used to automate cognitive assessments and data collection.

Memory clinics can use a variety of approaches in this challenging situation. In the UK, regional and national guidelines have been provided (5, 6). At the simplest level, clinicians can use the telephone to interview patients and informants and ask simple questions to get an impression of mental status in addition to history. At a more systematic level, clinicians can employ structured telephone interviews [e.g. Telephone Interview for Cognitive Status (TICS) (7)] or remote versions of standardized assessment scales (e.g. eMontreal Cognitive Assessment [eMOCA (8)], telephone-Mini Mental State Examination [tMMSE (9)]. Finally, fully automated systems and related scalable digital technologies exist to measure cognition and function. **Table 1** lists potential

TABLE 1 | An overview of how remote memory clinics can adapt standardized procedures (level 1), use already standardized remote instruments (level 2) or utilize automated batteries and remote measurement technologies (RMT, level 3).

Domain	Level 1 Adapting standard procedures	Level 2 Standardized instruments	Level 3 Automated batteries/RMTs
Cognition	CDR	eMOCA	Automatic Neuropsychological Assessment Metrics
		MoCA Blind	
	ADCS	tMMSE	CANTAB
	MoCA		Cognitive Assessment of Later Life Status
	MMSE	TAMS	Cognitive Drug Research Computerized Assessment System
			Computerized Neuropsychological Test Battery
			Mezurio
		TICS & TICSM	Mindstreams
			PROTECT
			Touch Panel-Type Dementia Assessment Scale
Function	ADCS-ADL	eAiADL	Altoida Medical Device
	AiADL		Residential Movement Detectors
	DAD		
	ECog		Wearable camera during ADLs
	FAQ	eMMSE	
		TICS	
Mood	NPI	eGAD-7	Mezurio
	PHQ		
Motor	UPDRS ADL section	Home video diary	GAITRite
			Gait Up
			KinetiSense
			Personal KinetiGraph

ADCS, Alzheimer's Disease Cooperative Study; ADCS-ADL, Alzheimer's Disease Cooperative Study-Activity of Daily Living; AiADL, Amsterdam Instrumental Activities of Daily Living Questionnaire; CANTAB, Cambridge Neuropsychological Test Automated Battery; CDR, Clinical Dementia Rating; DAD, Disability Assessment for Dementia; ECog, Everyday Cognition Scale; FAQ, Functional Activities Questionnaire; eGAD-7, electronic General Anxiety Disorder-7; MMSE, Mini Mental State Exam; MoCA, Montreal Cognitive Assessment; NPI, Neuropsychiatric Inventory; PHQ, Patient Health Questionnaire; RMDs, Residential Movement Detectors; TICS, Telephone interview for cognitive status; TICSM, Telephone interview for cognitive status modified; TAMS, Telephone assessed mental state; UPDRS ADL, Activities of Daily Living section of the Unified Parkinson's Disease Rating Scale.



Video interview

- Via teleconference platform, e.g., Teams, to to get acquainted with patient/carer & establish rapport. Interview includes, unstructured history

Level 1

- Patients can complete cognitive tests (e.g., MMSE, MOCA; ACE) & other questionnaires (e.g., IQCODE, HADS) via teleconference platform. The 'share screen '(e.g., Teams, Zoom) option can be used for visual tests with high definition
- Level 1 can also use remote neuropsychological assessments.

Level 2

- Alternatively, using level 2 technologies, i.e., digitized versions of these tests/questionnaires are available (please see text for details). Level1 & 2 strategies will usualy be sufficient to make a diagnosis of dementia.

Level 3

- Level 3 technology is required for pre-dementia stages, i.e., MCI & SCD, more sophisticated devices to accurately measure cognition & function are recommended (please see text for detail

FIGURE 1 | Example of remote memory clinic care pathway. ACE, Addenbrooke's cognitive examination; HADS, Hospital Anxiety and Depression Scale, IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; MCI, mild cognitive impairment; MMSE, Mini Mental State Exam; MoCA, Montreal Cognitive Assessment; SCD, subjective cognitive decline.

remote memory clinic assessments and **Figure 1** provides an overview of how remote memory clinics can stratify these assessments into adapted standardized procedures (level 1), use already standardized remote instruments (level 2) or utilize automated batteries and remote measurement technologies (RMTs, level 3).

While physical examination provides information that cannot easily be captured remotely, the wealth of recent developments of digital devices and technologies represent unique opportunities for more efficient and accurate data collection, which are feasible and acceptable from the user-perspective. Remote memory clinics may also reduce the cost of face-to-face outpatient appointments, while improving the quality and relevance of cognitive monitoring and creating trial-ready cohorts for academic and commercial trials.

Active and passive digital biomarkers of cognitive domains can be collected using smartphones, tablets, personal computers (PCs), wearables and smart home sensors, virtual reality, augmented reality and even video games, that can detect changes in health status and quality of life (QoL), offering a unique opportunity to accurately and continuously track and assess changes in various physiological, motor and psychological domains. However, in terms of accuracy of measurement, acceptability and feasibility, implementation of novel strategies needs to be evidence-based and must comply with regulatory requirements, including data protection. When using adapted traditional tools, there is also some uncertainty about potentially invalidating tests by using smartphones and tablets. The device haptics usually will differ and user-interface interaction differences, as well as video and audio quality or screen size, may impact performance.

Therefore, the aim of this paper is to present a framework for virtual memory clinic assessment. To do this we will review recent practices, guidelines, scientific literature and our own experience of adapting procedures for virtual administration of diagnostic procedures relevant for memory clinics, digital cognitive assessment and RMTs for measuring function *via* ADLs, and other relevant features, such as mood and motor symptoms. Based on our experience of adapting practices for remote clinical assessments during COVID-19, the procedures for history taking, cognitive testing, functional assessment and other relevant assessments will be categorized according the three levels mentioned above:

Level 1: *ad hoc* adaptations of traditional assessments,
Level 2: specific adaptations with psychometric data available
Level 3: automated digital techniques, including RMTs.

METHODS

There have been a handful of systematic reviews of RMT-based cognitive assessment (10, 11), the last of which, to our knowledge, was published in January 2019 (12), which included data until October 2018. A summation of these reviews is included in **Table 2**, along with an update of the field since the last review. A more detailed description of this update and related emerging RMTs is given below in, '*Level 3: cognitive remote measurement technologies for remote memory clinics.*' We carried out a literature review to examine new candidate RMTs for cognitive testing in remote memory clinics since November 2019 until May 2020. Google (https://www.google.co.uk/) and PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) literature were searched using relevant keywords, such as, 'digital cognitive assessment', 'remote digital cognitive assessment', 'remote cognitive assessment', 'self-administered cognitive test' and 'mobile cognitive testing'. Searches were

TABLE 2 | Potential remote measurement technologies for self-administered remote cognitive assessments.

Type of RMT	Examples	Domains tested			Pros	Cons
Online platforms	CANTAB (13)	Attention general memory working memory visual memory	semantic/verbal memory decision making response control	learning reaction time executive function	PCs & laptops are commonly owned by an increasing number of older adults	Limitations in hardware capabilities and internet access
	Cognitive Testing on Computer (14)	Memory processing speed	language skills visuospatial skills	constructional capabilities executive function		
	DETECT (15)	Attention selective memory	working memory information processing speed	executive function		
	GrayMatters (16)	Visual memory		executive function		
	Interactive Voice Response (17)	Declarative memory working memory	short-term memory long-term memory	semantic memory		
	MyCognition (18)	Attention psychomotor speed	working memory episodic memory	executive functioning		People who are non-fluent in English will be unable to use
	PROTECT Battery (including CogPro) (19)	Visual episodic memory spatial working memory working memory	numeric working memory verbal reasoning visual attention	task-switching delayed word recall word recognition		Questions over the generalizability of normative data, given the skewed sample favoring older people with higher levels of computer literacy
	VECP (20)		Visuospatial attention			
Device-based	BrainCheck Memory (21)	Immediate recall delayed recall visual attention	task switching processing speed working memory	visuospatial processing executive function	Devices & smartphones are more portable than computer-based testing.	Devices are easier to lose or damage than PCs or laptops
	Integrated Cognitive Assessment (Cognetivity)	Visual attention task switching reaction time executive functioning	working memory visual function episodic memory	semantic memory spatial memory global cognition		
	Computerized Assessment of MCI (22)	Attention processing speed verbal memory	nonverbal memory functional memory	incidental memory executive function		Visual impairments in the elderly can add to challenge when using a smaller device
	CANTAB Mobile (23)	Visual episodic memory	depression	activities of daily living		
	ClockMe System (24)	Visuospatial skills	constructional capabilities	executive function		
	Cognitive Assessment for Dementia, iPad version (25)	Recall delayed recall	semantic memory working memory	spatial orientation executive function		Non-English speakers may have limited options
	CANS-MCI (26)	Memory Language	spatial capabilities	executive function		
	CRRST (27)		Verbal memory & learning		Apps are readily available from the appropriate vendor	Handheld nature of such devices may be a challenge for those with motor or rheumatological comorbidities
	Mezurio (28)	Visuospatial memory	spatial orientation	visuospatial skills		
	Mobile Cognitive Screening (29)	Attention visual configuration language	memory orientation	calculation executive function		
	NCGG-FAT (30)	Memory Attention	processing speed visuospatial perception	executive function		

(Continued)

TABLE 2 | Continued

Type of RMT	Examples	Domains tested			Pros	Cons
	Neurotrack Memory Health Program (30)	Visual recognition		memory		
	Spatial Delayed Recognition Span Task (31)	Visuospatial working memory				
	Touch Panel-type Dementia Assessment Scale (32)	Immediate recall delayed verbal memory	spatial orientation	spatial recognition		
Wearables	Cognition Kit (33)	Working memory			Can provide passive data collection or short but repeated session of active data collection compared to online platforms & smartphone or tablet-based assessment	Can be expensive
		Can be expensive			Can be collected for all people irrespective of sensory impairments or speech & language difficulties	Are easier to forget to wear/use & misplace
Virtual reality, augmented reality & games consoles	Altoida MD (34)	Visual attention	Orientation	spatial memory	More engaging approach to cognitive assessment & may negate any issues with poor eyesight, speech or language difficulties	Potential additional user interface complexity, additional devices & expense if compatible device must be purchased
	VSM (35)	Visual attention	task switching	executive functioning		
	Nintendo Wii balance board (36)	Spatial orientation				

CANTAB, Cambridge Neuropsychological Test Automated Battery; CANS-MCI, Computer-Administered Neuropsychological Screen for Mild Cognitive Impairment; CRRST, Cued-Recall Retrieval Speed Task; NCGG-FAT, National Centre for Geriatrics and Gerontology Functional Assessment Tool; VECP, Visual Exogenous Cuing Paradigm; VSM, Virtual Super Market.

restricted to studies published in peer-reviewed English-language journals and no age or sample-size restrictions were placed on articles at this stage. Other studies were identified by reviewing relevant bibliographies in original papers and reviews, as well as recent guidelines that were available to us. Conference reports were also included. The initial 732 results were examined by the lead author (AO) for duplications before the authors with experience in memory clinics (CB, CK, KB, JS, LV, DA), clinical neuropsychological testing (MB, SB) and RMT-based clinical research (AO, GL, HB) independently reviewed and reached a consensus on the final 48 eligible articles. There was a particular focus on studies involving neurotypical older adults and MCI. MCI was of interest because, during disease progression, the patient's proficiency to carry out instrumental ADLs will be increasingly impaired, yet remote testing requires self-regulation from the patient in order to comply with testing procedures. Moreover, test logistics may overwhelm the capacity of patients inexperienced with digital technology, and those at the predementia or mild dementia stages are likely to provide better uptake of technology-use than dementia cohorts. Therefore, our focus of RMTs centered on these cohorts to ensure the results were as relevant and applicable to a timely rolling out of a remote memory clinic service as possible. Relevant and accessible journal articles that assessed the use of cognitive assessments that could be deployed offsite from the clinical setting and allowed for test data to be collected by the clinician were considered.

We build these findings around a discussion of our experience of deploying remote assessments and internet-based cognitive testing in clinical practice, collection of health data and RMT assessment of function in elderly people with pre-dementia and dementia in two large ongoing multicentre studies, RADAR-AD and PROTECT and remote assessments during the COVID-19 pandemic, with a view of providing guidance into how remote memory clinics may be realized.

RESULTS

Level 1: *Ad Hoc* Adaptations of Traditional Clinic Assessments

This is the simplest way of adapting to the need for remote assessments. Instruments used in pre-COVID-19 clinical settings are straightforwardly adapted for remote assessment. This has limitations if conducted telephonically as certain items cannot be performed, e.g., visual tasks in the Addenbrookes Cognitive Examination III (ACE III) and the Mini Mental State Exam (MMSE). This necessitates an adjusted score with changes in test validity. However, the benefits of this method are its ease, similarity to a standard clinical interview and simple technology and delivery. The clinician will be familiar and comfortable with this procedure, which requires no technological resources other than a telephone. Such technology is also likely to be accessible and acceptable to older populations.

The application of a standard clinical assessment *via* video call allows the use of tools already familiar to clinicians, as set out above, and can be applied in a manner more akin to the usual clinic. However, the authors experiences of such assessments *via* video is that it can take at least 50% more time. It can also be more challenging for patients due to increased cognitive load for those with attentional depletion, particularly if holding up instructions or images, although screen-sharing pre-prepared images or instructions can mitigate against this. Still, the possibility of underestimating the patients' true cognitive level should always be considered. Mood symptoms can be easily addressed in an interview, with video providing important non-verbal information. Similarly, motor symptoms can be discussed verbally, and video offers the opportunity to observe and assess bradykinesia as well gait, stride, turning and tremor (rest and postural).

The limitations of such an approach includes the lack of standardization and evidence regarding the accuracy of paper-based tests being used in this way. In some cases, one is likely to lose sensitivity and is less likely to detect subtle changes of cognitive and functional decline, particularly in early phases of dementia. However, in cases of dementia with predominant attentional deficits, other cognitive domains may be underestimated due to the increased attentional demands inherent in the situation. Hearing or speech difficulties can add to the challenge. Hence, the clinician should evaluate the combination of sources of bias in each case.

Level 2: Specific Adaptations With Psychometric Data Available

The instructions and content of the electronic version of the Montreal Cognitive Assessment (eMoCA) (8) are identical to the original and it is available as a downloadable app on tablets. Studies comparing the eMoCA vs MoCA are limited, as are those validating the MoCA-Blind, which has also been proposed as a suitable cognitive screening tool for telephone administration. Snowden and colleagues (8) randomly allocated participants to the eMoCA (n=182) or MoCA (n=219) from nine primary care practices. The study concluded between-group significant differences in scores (MoCA group = 26.21, eMoCA group = 24.84) and completion times (MoCA group = 10.3 min, eMoCA group = 15.3 min). However, in a recent smaller-scale study in adults (n=43) presenting with memory concerns (mean age: 72 years), the eMOCA shows convergent validity (*r*=.84) with the original MOCA, indicating the eMOCA does not significantly alter the reliability of the original scale (38).

The MoCA-Blind removes the four visual items included in the original to for patients with visual impairments. Wittich and colleagues (39) report that based on absolute score ranges, the MoCA-Blind achieves poorer sensitivity for MCI (44%) in comparison to the original MoCA (90%) but provides improved sensitivity for Alzheimer's disease (AD) (87%), although this was still inferior to the MoCA (100%). Although the MoCA-Blind has potential for remote use, it has not been designed or validated for these purposes. All versions of the MoCA are currently free to access.

Scores of the telephone version of the MMSE (tMMSE) strongly correlate (*r*=.85) with original MMSE scores across the spectrum of neurotypical to moderately demented participants (40) and the more recent 26-item tMMSE produces scores are even closer (*r*=.88) to in-person MMSE administration in AD (9). The tMMSE involves a three-step action-based response prior to cognitive assessment, which examines memory, attention, recall, orientation and calculation (9).

The Telephone Interview for Cognitive Status (TICS) (7) was designed to examine cognitive status in AD and was proposed as an alternative to the standard MMSE (41), as both have comparable cut point scores. The TICS examines attention, short-term memory, orientation to time and place, sentence repetition, naming to verbal description, immediate recall, word opposites and praxis and has become the most commonly used telephone cognitive assessment (42). The TICS-Modified (TICSM) includes an additional delayed verbal recall component. Both TICS (*r*=.94) and TICSM (*r*=.57) scores correlate with MMSE scores (43). To date, there are several versions of the TICSM that have been developed, including those scored out of 50, 41 and 39. The latter of these versions has developed a norms calculator that corrects for age, education and sex (44). The same study found that this version of the TICSM correlated well with the MMSE (*r*=.70) and ACE-Revised (*r*=.80).

In light of recent restrictions due to COVID-19, psychometric test battery copyrighters and regulators have issued updated guidance's to assist clinicians with resuming administration of test batteries. For example, Pearson's (https://www.pearsonassessments.com/) have issued instructions enabling clinicians to administer their tests remotely, using screen sharing techniques for a limited time. However, this comes with the caveat that tests must not be scanned but rather projected using equipment, such as visualizers. This has allowed clinicians to more easily adapt their administration of tests to computer-based presentations using their current test batteries. The Division of Neuropsychology (DoN) (https://www.bps.org.uk/) has taken this further by providing guidance on how clinicians may be able to facilitate remote, computerized assessments in a standardized fashion.

Remote neuropsychological testing eliminates the need to adapt to online-based platforms that may be unfamiliar to services and create difficulties when needing to re-assess clients that have previously been tested using face-to-face batteries. A recent systematic review and meta-analysis has indicated that neuropsychological assessments administered through videoconferencing produce comparable validity to that of face-to-face testing (45). Remote assessments may also help clinicians access clients who are unable to attend clinics and live in hard-to-reach areas or under conditions that make them anxious at the prospect of a clinician visiting them. To this end, a home-based assessment may introduce an additional level of security and comfort for patients.

The South London and Maudsley memory service has developed a new protocol incorporating videoconferencing in order to complete neuropsychological assessments during COVID-19, involving several extensive pathways to explore the potential for testing clients remotely. All pathways involve separate electronic devices for clients and clinicians, as well as a visualizer for administration of visual tests to maintain social distancing and avoid cross contamination of material. These measures, although helpful in identifying whether remote assessments will work, do result in clinicians having to dedicate additional time to each client they wish to test. Nevertheless, remote assessments using the short form of the Wechsler Abbreviated Scale of Intelligence, Rey Complex Figure and California Verbal Learning have been administered with relative ease. Pearson's argue that clinicians should use two cameras to observe clients during remote assessments and while this would be ideal, it is rarely possible for patients to facilitate this. This disadvantage is evident when patients perform the Rey Complex Figure, as it is not possible to observe the informative strategies that are used when completing this task. Similarly, the Hayling and Brixton test batteries have been administered remotely, with little noticeable disadvantage to patient and clinician. Feedback from clients has been relatively positive with patients feeling that they have performed as they would had the assessment been face to face.

Level 3: Cognitive Remote Measurement Technologies for Remote Memory Clinics

The results of our literature review are listed in **Table 2** and based on our experience of remotely collecting digital biomarkers in neurotypical and cognitively impaired older adults, the authors consensus opinion was to categorize our findings into;

- online platforms
- device-based tests
- wearable RMTs
- virtual and augmented reality and games consoles.

Below we list in more detail, some of the most recent examples since the last review of the literature (12) to bring together the latest additions to the field that can be readily deployed in remote memory clinics.

Online Platforms

Online platforms involving cognitive tests provide a valuable means of carrying out remote cognitive assessments. As PCs pre-date tablets and smartphones, online platforms tended to be the first digital medium through which cognitive tests were digitized and modified for self-assessment. Another benefit is the popularity of PCs and laptops within many homes. However, this may bring inherent limitations in hardware capabilities and internet access, particularly in more remote areas. Also, many older adults may not be able to engage with these platforms, therefore there is a risk of only reaching those who are more able but not necessarily most representative of the general population reducing the generalisability of the normative data and the utility of the assessment tool for clinical purposes.

PROTECT (https://www.protectstudy.org.uk/) is an online longitudinal study of a healthy aging (>50 years) population funded by the National Institute of Health and Research (NIHR) for 25 years with a recruitment target of 50,000 participants (19, 46). The PROTECT cognitive test platform includes, the paired association learning task, self-ordered search, digit span task, grammatical reasoning, trail-making test B (47). There is also the option to use the CogPro system that examines immediate word recall, pattern separation stages 1 and 2, simple reaction time, digit vigilance, choice reaction time, spatial working memory, numeric working memory, delayed word recall and word recognition (48, 49). The PROTECT platform also collects data on demographic characteristics, medical history, psychiatric symptoms, lifestyle, family history of dementia, and instrumental ADLs (50). PROTECT is a versatile, modifiable and long-term platform that offers a bespoke option for remote memory clinics in the UK and is currently also adapted for use in other countries.

MyCognition (https://mycognition.com/) is a new web-based cognitive assessment tool that negates the need for specialist supervision, is designed for self-administration online *via* PC or iPad. MyCognition assesses the five cognitive domains of, attention, psychomotor speed, working and episodic memory and executive functioning using 10 short subtests and has recently been validated against the CANTAB (18), however it is worth noting that the MyCognition has not been validated in any older adults for dementia. MyCognition Quotient total scores correlated with CANTAB total scores and psychomotor speed (r=.604), attention (r=.224) and episodic memory (r=.374) domains correlated with the corresponding CANTAB domains. However, executive function (r=.278) and working memory (r=.229) had limited divergent validity.

Device-Based

Device-based cognitive assessments have the benefit of being agile compared to bulkier computer-based testing. Apps can also be downloaded from the appropriate vendor onto any compatible tablets or smartphones that the patient may already own. However, the portability of such devices does mean that they are easier to misplace or damage, especially as cognitive impairment progresses, and the handheld nature of such devices, may also be a challenge in the presence of any motor symptoms.

The Integrated Cognitive Assessment (ICA, www.cognetivity.com) is a 5-min, self-administered, iPad-based, computerized cognitive assessment. It has been validated in patients with Mild-AD, MCI and multiple sclerosis and licensed as Software as Medical Device (SaMD) (51, 52). The ICA is a rapid image categorization task that measures attentional speed, accuracy and attentional speed and accuracy decay over time. It employs an artificial intelligence algorithm to improve its predictive accuracy by correlating age, gender and handedness with the composite score. The ICA does not demonstrate educational, interpretation bias or a practice effect (51) and integrates with electronic health systems. The use of the ICA aims at early detection, high-frequency monitoring of disease trajectory and response to treatment.

Mezurio [https://mezur.io] is a smartphone app that provides digital biomarkers targeting the cognitive symptoms of MCI by collecting data actively and passively *via* the patient's smartphone with a user-friendly interface involving gamified tasks (28). Mezurio has been used in the PREVENT Dementia study and the UK Alzheimer's Society GameChanger Study (53), with high user-compliance reported. Mezurio adapts to the user's abilities when assessing memory (episodic, semantic, spatial memory), executive functions (attention, planning), verbal free-recall and fluency. Mezurio provides a broad spectrum of cognitive testing well-validated and easily deployable RMT in MCI cohorts.

BrainCheck Memory (https://braincheck.com/individuals/memory) is available on any Apple device and has been modified to detect age-related cognitive decline by measuring immediate and delayed recall, Trail Making Tests A and B, Stroop Test and Digit Symbol Substitution Task. In a recent large cohort study (54) in participants aged >49 years, BrainCheck Memory was administered by research staff, with scores significantly correlating with Saint Louis University Mental Status exam scores, Mini-Mental State Examination (MMSE) scores and MoCA scores. BrainCheck Memory was able to differentiate healthy controls from cognitively impaired participants (p=.02) and BrainCheck Memory composite scores were found to have a sensitivity of 81% and specificity of 94%.

The "Novel Assessment of Nutrition and Ageing" (NANA) touchscreen interface has been tested in 40 neurotypical elderly (mean age: 72 years) care home residents where it was deployed daily (55). Cognitive NANA data produced comparable validity and reliability to standard clinical measures, such as the MMSE, Symbol Digit Modalities Test and Digit Scan tests (55).Winterlight (https://winterlightlabs.com/) is a tablet-based cognitive assessment designed to detect cognitive impairment (56) by examining linguistic markers (57). The Mindmore (https://mindmore.com/) digitized cognitive test battery has been designed to examine global cognition, processing speed and attention, learning and memory (including working memory, executive function and language. Mindmore was recently tested in 81 healthy controls aged 21-85 years and was found to significantly correlate with traditional measures (median r=.53) (58).

The 'Mobile Cognitive Screening' (MCS) Android-based app is comprised of 33 questions over 14 tests examining the cognitive domains of executive functions, orientation, abstraction, arithmetic, memory, language, visual function and attention (29). In a sample of 23 healthy controls (mean age: 82 years) and 14 people with dementia (mean age: 73 years), MCS was able to differentiate MCI and controls participants in the cognitive domains of executive, visual, memory, attention, orientation functions (p=<0.05) [8]. MCS scores also correlated (mean r^2 = .57) with MoCA scores. Although providing interesting findings, the MCS has been tested in a small sample.

Wearables

Wearable sensors have the advantage of providing either passive data collection or short but repeated session of active data collection compared to online platforms and smartphone or tablet-based assessment. This provides an attractive alternative to memory services, who will want to use relatively short and simple measures/platforms. However, wearables can be expensive and are easier to misplace than other digital options.

The CANTAB's n-back task has recently been adapted as part of the Cognition Kit app to be delivered *via* the Apple watch (https://www.apple.com/uk/watch/) in 30 mild-to-moderate depression participants (aged 19-63 years) (34). Participants were required to complete the n-back three times per day, in addition to mood surveys. Adherence, defined by participants completing the n-back as least once daily, was 95% and remained consistent over the 6 weeks of data collection. Daily n-back scores correlated (r=0.37-0.50) with standard cognitive assessments sensitive to depression (spatial working memory, rapid visual information processing).

Virtual Reality, Augmented Reality, and Games Consoles

Virtual reality, augmented reality and games consoles offer a unique and potentially more engaging approach to cognitive assessment and may negate any issues with poor eyesight if a headset or television screen is used. However, with this comes more user complexity, (potentially) additional devices and expense if the patient does not already have a compatible device.

The virtual reality platform, Smart Aging Serious Game (SASG), has recently been trialed in 32 amnestic MCI (aMCI) participants (mean age: 77 years) and 107 healthy controls (mean age: 77 years) (59). The SASG had a sensitivity of 84% and specificity of 74% and was superior than the MoCA, Free and Cued Selective Reminding Test and Trail Making Test for detecting right hippocampal neurodegeneration.

The Altoida Medical Device (https://altoida.com) has received Food and Drug Administration (FDA) class II medical device qualification. It provides digital biomarkers for detection of subtle microerrors in accuracy and micromovements in latency that can help detect if MCI will progress to dementia (35). The app employs a user-friendly augmented reality interface to recreate an advanced ADL in locating a recently concealed item in the immediate environment. Voice data, hands micromovements and microerrors, gait microerrors, posture changes, eye-tracking, visuospatial navigation microerrors data streams during task performance are combined to create the user's Neuro Motor Index (NMI). In participants aged 55-95 years, the NMI provides diagnostic accuracy of 94% in predicting cognitive worsening in amyloid positive individuals who converted to Alzheimer's disease (AD) from MCI after 5 years (60).

Game consoles have also been employed for dual-task paradigms. For example, Leach and colleagues (37) used the Nintendo Wii balance board (https://www.nintendo.co.uk/index.html) to examine sway distance, velocity, area, centroidal frequency and frequency dispersion as a single-task condition and dual-task paradigm in 20 neurotypical elderly care home residents (mean MMSE score = 28.6; mean age 87 years) over 30 days. The dual-task paradigm comprised of combined daily word search tasks administered *via* a tablet simultaneously with use of the Wii balance board. Postural sway related to global cognitive scale scores and poorer performance on the tablet-based daily word search related to a lower cognitive status. Greater variability in sway distance and area, and less variability in centroidal sway were associated with lower scores of single-task and dual-task conditions.

Neuro-World is a set of six mobile games designed to challenge visuospatial short-term memory and selective attention (61). These games allow the player to self-administer the assessment of his/her cognitive impairment level. Game-specific performance data was collected from 12 post-stroke patients at baseline and a three-month follow-up, which were used to train supervised machine learning models to estimate the corresponding MMSE scores, and were demonstrated to have great potential to be used to evaluate the cognitive impairment level and monitor long-term change (62).

Function

Accurately measuring function is crucial to distinguish between levels of cognitive decline (i.e., SCI, MCI and dementia) and also a key outcome in AD trials, especially at the earliest stages. Function is usually measured by self-report or caregiver reports regarding the person with dementia's proficiency in executing basic, instrumental and advanced ADLs. Scales often neglect advanced ADLs, such as social functioning, despite social functioning, loneliness and social isolation's contribution to dementia risk and morbidity (63–65). Indexing advanced ADLs are particularly relevant during the social distancing restrictions related to COVID-19, particularly in those more at risk of social isolation, such as the old and infirm.

Zygouris and colleagues (36) used the Virtual Super Market (VSM) to recreate an instrumental ADL for six healthy and six MCI participants (mean age: 64 years). Time of task completion was significantly longer for MCI participants and VSM scores provided a 92% classification rate for the detection of MCI. Mean VSM scores also significantly correlated with scores on the Functional Cognitive Assessment Scale, Test of Everyday Attention and Rey Osterrieth Complex Figure test.

The use of technology and devices itself has proven to be a valuable ADL for indexing functional decline in MCI, with computer-based behaviors, such as mouse clicks, typing speed and pauses corelating with cognitive scores in MCI and neurotypical users (66). Couth and colleagues identified 21 key technology behaviors sensitive to early cognitive impairment, such as text-based language use, incorrect passwords, mouse movements and difficulty opening correct items (67). Active and passive assessment of function across the full spectrum of basic, instrumental and advanced ADLs using RMTs is the primary purpose of 'Remote Assessment of Disease and Relapse - Alzheimer's disease' (RADAR-AD, https://www.radar-ad.org/) to improve the assessment of functional decline in early-to-moderate AD. RADAR-AD's main aim is the development and validation of technology-enabled, quantitative and sensitive measures of functional decline in AD and to evaluate if these new measures are more precise measures of function in a real-world environment across pre-clinical-to-moderate stages of AD compared to standard clinical rating scales. RADAR-AD's leveraging of RMTs with real-life functional endpoints intends to improve methodologies for monitoring functional decline across the AD spectrum.

Mood Measurement for Remote Memory Clinics

Recent evidence has demonstrated that social disconnectedness, predicts higher perceived social isolation, leading to higher depression and anxiety symptoms among older people (68). The link between mood and sleep is also been well-established (69). Therefore, the potential negative psychological impact of COVID-19 may be compounded further by widely experienced sleep alterations, including disturbances in sleep quality and quantity, which also occur with increasing age and for those with dementia (70, 71).

Patient engagement with active smartphone applications, such as those developed by Remote Assessment of Disease and Relapse (RADAR) base (72, 73) offer a solution for the remote delivery of already validated questionnaires of sleep and mood (e.g., Patient Health Questionnaire, General Anxiety Disorder-7, Pittsburgh Sleep Quality Index). This type of RMT platform has the potential to provide easily accessible information to clinicians remotely, to better inform diagnoses and clinical decision making. This concept has already been developed among people with Major Depressive Disorder (MDD) to explore if longitudinal tracking using RMT can capture information predictive of depressive relapse and other key clinical outcomes (73). RMTs also offer a unique capability to provide continuous objective data, through passive data streaming methods (72). Sleep quality and quantity variables (e.g., duration of sleep and time spent in REM cycles) can be monitored remotely through actigraphy and consumer-wearable activity trackers (74, 75).

Motor Measurement for Remote Memory Clinics

Continuous day-to-day use of wearables are an ideal medium to collect large, well-powered data on motor symptoms, either by passive use of on-body sensors or "little but often" RMT-based active protocols. Wearable sensors for the detection of motor symptoms, such as The Personal KinetiGraph (PKG), have FDA approval and have been deployed and validated in clinical trials (76). Smartwatch-based sensors have been used predominantly in Parkinson's disease (PD) to discriminate essential tremor from postural tremor (77). Other motor fluctuations, such as bradykinesia have been remotely assessed using wearable shoe sensors and watch-like sensors to measure gait patterns (78) and dyskinesia has been analyzed *via* home video recording (79) or using home diaries (80) for some time. Wearable gyroscopes and accelerometer sensors can passively collect data during standardized motor tasks, voluntary movements and ADLs to measure dyskinesia (78), for example, KinetiSense (https://kinetisense.com) wearable triaxial accelerometers and gyroscopes and have found that dyskinesia scores collected from KinetiSense highly correlated with clinician scores (*r*=.86) (81). The GAITRite (https://www.gaitrite.com) system has been employed to examine gait in aMCI (n=15), non-amnestic MCI (n=21) comparative to healthy controls HCs (n=21) to delineate that aMCI had greater gait variability than clinical and healthy controls (82).

Virtual Pathway for Memory Assessment

Outpatient-based remote memory clinics can carry-out further specialist diagnostic investigations to support accurate and timely diagnosis. Patients at risk of dementia can be followed up both remotely and in-clinic, while patients without evidence of a neurodegenerative disease (e.g., dementia biomarker-negative MCI) can be discharged to Primary Care. Patients diagnosed with prodromal dementia can be given the option of remote cognitive and functional assessments, even as part of a research framework, with these patients expected to have an annual face-to-face follow up in-clinic or until transition to clinical dementia (see **Figure 2** for potential pathway). There is also increasing evidence the computerized cognitive training can have positive effects, and these may easily by administered from online testing platforms (47, 83).

DISCUSSION

The COVID-19 pandemic has created major challenges for elderly people with cognitive impairment, as well as for memory clinics tasked with assessing and caring for this group. While the health systems in many countries are slowly moving back to normal, elderly people will still want to, or be expected, to reduce traveling and visiting hospitals for non-urgent causes, and in many countries infection rates are still increasing. Memory clinics therefore must adapt to this new situation and explore and offer new models and pathways for assessment and care. This situation also represents an opportunity to critically assess practices and to explore the many new technologies and methods available to assist clinicians in providing accurate, safe, and user-friendly ways of diagnosing elderly people with cognitive impairment. We have reviewed the literature and other sources, as well as reporting our own experience of deploying remote memory clinics and propose a new pathway that can be implemented immediately in memory clinics, at various levels of complexity.

As the simplest approach, Level 1 involves standard procedures, tests and questionnaires that can be administered by telephone, or, better, using available video-based platforms. While simple and requiring only a telephone, the limitations include that the psychometric characteristics may not immediately translate to this form of administration. At Level 2, we present several standardized measurements and instruments that have been digitized and have provided at least some degree of psychometric validity and reliability. Interestingly, many exciting new technologies are available to test not only cognition, but also

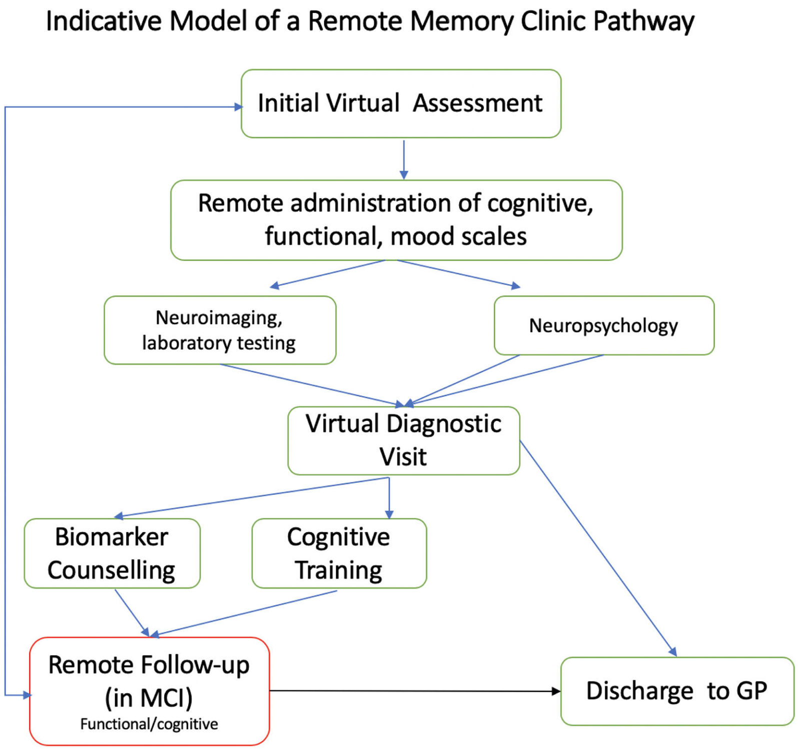


FIGURE 2 | Potential clinical pathway for remote memory clinics. GP, general practitioner; MCI, mild cognitive impairment.

mood and motor symptoms as well as daily functioning (Level 3). We believe that the recent challenges offer an opportunity to embrace new technology, devices, and wearables to accurately diagnose age-related cognitive disorders.

Digital biomarkers collected in remote memory clinics have significant potential for diagnosis and symptom management in older adults during and after COVID-19. Information is collected by RMTs in real-time, at a high frequency level and can also be delivered cost-effectively at a large scale. The collation of both active and passive RMT data in tandem, provides a more enriched clinical picture, while also providing a background of explanatory variables. Reduced participant burden and increased participant engagement are also among the potential benefits. Additionally, the frequency of data collected is incomparable to the momentary data capture currently employed in clinical settings. Such approaches provide accurate and continuous tracking of disease progression. These technologies may also be used to examine if some groups are more responsive than others to treatments. Such methodologies can be easily scaled-up to reach larger populations, including potentially primary care and will have relevance for future pandemics. Therefore, the scope of virtual memory clinics has significant potential to enhance current standards and should remain common practice after COVID-19.

The technologies discussed are particularly well-suited to measure and track cognitive and function and are thus excellent tools for identifying and staging cognitive impairment (i.e., SCD, MCI or dementia). However, an etiological diagnosis, i.e., identifying the disease causing the cognitive impairment, requires additional information. Although remote assessment of mood and motor symptoms, as well as the clinical history, can provide important information, biomarkers such as neuroimaging, cerebrospinal and blood markers and electroencephalogram (EEG) should be available.

Some of these biomarkers can be acquired remotely, such as EEG, sleep monitoring, and collection of saliva, urine and stools for microbiome and other analyses. For example, for the early differentiation of dementia with Lewy bodies (DLB) from AD, RMTs can enrich assessment of neuropsychiatric and dysautonomic symptoms typical in DLB (84) by capturing novel neurophysiological markers of fluctuating cognition (FC), visual hallucinations (VH), apathy or autonomic nervous system (ANS) impairments. By remotely measuring ANS function, RMTs can equip patients with person-specific protocols that complement their daily routines and lifestyle, in addition to integrating their clinical and psychosocial profiles to passively and actively collect objective contextualized data in day-to-day life over numerous timepoints. RMT-based EGG, such as Bytflies (https://www.byteflies.com), has begun to be used in epilepsy (85) and provides well-powered and contextualized data that we are using to remotely examine low-frequency spectral power in DLB (86), as longer EEG recordings in real-world settings will provide more sensitive signatures of brain changes and are more likely to capture acute episodes of FC or VH than lab-based EEG. We are also using RMTs to passively collect remote data on cardiovascular (e.g., orthostatic hypotension, postprandial hypotension) and thermoregulatory (e.g., anhidrosis, compensatory hyperhidrosis) ANS function in potential DLB cases to unmask any dysautonomia indicative of alpha-synucleinopathy. However, these biomarkers have not yet been established as diagnostic markers, thus, collection of diagnostic structural and functional neuroimaging and cerebrospinal fluid markers still requires attending a clinic.

We have provided an update on the landscape of RMT-based cognitive assessments that can be employed with immediate effect due to the urgent need to continue to deliver comprehensive memory clinic care and assessment during COVID-19, as well as a potential pathway for virtual memory assessment. Platforms, such as CANTAB and PROTECT Cognitive Test Battery offer validated and longitudinal follow-up in addition to agile design that allows for the addition of relevant tests. Other platforms, such as Neurotrack Memory Health Program (MHP, https://neurotrack.com/) combines interventions related to physical activity, diet, sleep, stress, social interaction and cognitive engagement but before any of these interventions can be used by the participant, they are required to carry out a visual paired comparison task that includes eye-tracking to provide a baseline sore of visual recognition memory. Neurotrack MHP has recently been validated in a feasibility investigation utilizing a quasi-experimental, single-arm, nonrandomized, longitudinal design in 242 healthy controls aged >51 years (31). MHP is more geared toward overarching health than cognitive testing, underlining how these online batteries can easily adapt interventions, such as cognitive behavioral therapy (CBT). Device-based cognitive assessments, such as Cognetivity and Mezurio are downloadable apps that are particularly targeted to detecting and tracking cognitive impairment. Altoida's gamified augmented reality tasks on tablet or smartphone provides meaningful clinically relevant data and its use in largescale dementia trials makes it an ideal candidate RMT if the patient has access to the requisite hardware. The TICS has been well-validated and tested in the clinical environment (including in our clinics during the COVID-19 pandemic), producing strong construct validity compared to typical pen and paper and neuropsychological tests, aiding diagnosis while remaining a very cost-effective alternative to RMT-based assessments.

Ultimately the main argument for digital transformation in the memory services is being made for us due to COVID-19. Translating conventional pen-and-paper testing has accuracy and acceptability limitations and we believe this paper shows digital biomarkers are currently available and ready for use to this end. However, this will only be accessible for some and a key issue for memory clinics is providing a protocol and complete testing logistics chain involving caregivers or other proximal agents that can be applied to all patients. Long-term monitoring of people with MCI to identify progression to dementia is expensive and implementation of remote memory clinic pathways can provide a cost-efficient way of achieving this. Remote memory clinics can also improve research practices due to the integration of digital data onto electronic patient records that will improve data curation and availability.

A variety of computerized cognitive training interventions are available and there is increasing evidence supporting their efficacy, showing mild to moderate effect sizes in several cognitive domains in older people with MCI and dementia (83). Interestingly, several of the platforms and batteries for digital cognitive testing also offer interventions on the same platform, for example PROTECT (and its inbuilt cognitive test batteries) and MyCognition, which can often be directly tailored to the level of cognitive impairment (47). Given the lack of drug treatments for people with MCI, this is a particularly relevant feature for this group.

Although we argue the case for remote memory clinics, it is important not to neglect patients and carers who are unable to use technology for remote assessment or videoconferencing or have relevant disabilities, such as vision, speech or hearing difficulties, or other healthcare barriers related to race, economic status, disability and location. This also implies that only the more able members of the older adult community will access clinical assessment through this approach. However, arguments against digital solutions are often embedded in stereotyped views about tablet and computer use by older individuals, and there is evidence that the number of older people on line is growing fast and might even increase during COVID-19 (87). There are also limitations to rapport building and risk management should vulnerable clients become distressed during the assessment process. Clinicians should also be advised that facilitating remote testing should involve an additional pre-assessment screen to test suitability of video conferencing that factors in additional time requirements. Neuropsychological test batteries are designed and validated based on a strict set of instructions and protocols, meaning any adaptations or irregularity test administration risks invalidation. This has two major implications for clinicians. Firstly, invalidation may implicate licenses obtained through copyrighters and thus place clinicians in breach of signed agreements. Secondly, changes in administration may invalidate the norms on which scores and interpretations are based. Clinicians must therefore pay careful consideration to the implications of any adaptations for remote assessments as a result of these risks. The DoN caution that although research suggests some neuropsychological test batteries may have good reliability when administered remotely, there are still many measures that have not been assessed under these conditions, meaning the interpretation of such results must be conservative. Consideration must also be given to the risk of test material entering the public domain through remote assessments, thus undermining the validity of the tests themselves. Again, the DoN advised that clinicians must exercise caution when choosing to administer tests remotely and implement procedures that limit the risk of material entering the public domain. A further limitation to services committing to remote assessments is the publishers of tests have given notice that clinicians will need to complete training in order to qualify as registered administrators and the uncertainty regarding how long test manufacturers and licensors intend on allowing clinicians to administer their material remotely. The removal of any permission to share visual material on a computerized device would seriously hinder the potential use of visual tests. This means that, as well as a need for more research, testing the validity of remote assessments, greater flexibility on the part of test manufacturers will also be required. For example, during the COVID-19 pandemic, copyrighters have offered flexibility of how their tests can be administered, allowing the use of visualizers to share images of their tests during video calls for a limited time. It would be very beneficial for the sustainability of remote memory clinics to make such temporary permissions more permanent to allow for the development of more viable remote testing protocols. Patients' lack of experience with RMTs and cognitive impairment present specific challenges, meaning remote memory clinics must be pragmatic (including relevant training for clinicians) and adhere to validated measures. Another consideration proving to be problematic in our experience is working with interpreters. This is already a challenge and will need separate and stratified approaches for both RMT and telephone consultations, as will sensory impairments, data protection, regulatory and feasibility issues. But the many challenges the COVID-19 pandemic has placed on memory services also provides an excellent opportunity to embrace novel technologies and approaches, both for cognitive testing and the tracking of functional status.

Future Implications and Needs

Several platforms and devices show good measurement accuracy in small groups, future research should include confirmatory studies demonstrating diagnostic accuracy in pre-dementia diagnosis in multicentre studies with large and diverse cohorts representative of the general clinic population, as well as sensitivity to change and utility in clinical trials. In addition, comprehensive assessments, including feasibility and acceptability involving user groups, cost-efficacy studies, and ensuring adherence to regulatory requirements are required to enable evidence-based selections and priorities of devices and platforms to be used for virtual memory clinic assessments. The Horizon2020/IMI2-supported RADAR projects (https://www.radar-ad.org, https://www.radar-cns.org/) are good examples for how to achieve this.

CONCLUSIONS

The individual, societal and public/private costs of COVID-19 are high and will continue to rise for some time but the many challenges COVID-19 has placed on memory services also provides an excellent opportunity to embrace novel technologies and approaches. A large number of possible solutions and technologies are available at different levels of sophistication. Remote memory clinics can be cost-effective and can enhance clinical assessment in the old and frail even during current or future social distancing measures. The financial, logistical, clinical and practical benefits of remote memory clinics have therefore been highlighted by COVID-19, supporting their use to not only be maintained when social distancing legislation is lifted but should be devoted extra resources and attention to fully potentiate this valuable arm of clinical assessment and care.

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.

AUTHOR CONTRIBUTIONS

AO and DA: primary authors. CB, CK, HB, GL, KB, JS, SB, and LV: revisions and scientific content of MS. All authors contributed to the article and approved the submitted version.

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SYSTEMATIC REVIEW
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A Systematic Review of Home-Setting Psychoeducation Interventions for Behavioral Changes in Dementia: Some Lessons for the COVID-19 Pandemic and Post-Pandemic Assistance

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Background: Impacts of social isolation measures imposed by COVID-19 Pandemic on mental health and quality of life of older adults living with dementia and their caregivers remain unexplored. Studies have shown that psychoeducational and psychosocial interventions can manage behavioral and psychological symptoms in dementia (BPSD) and reduce the emotional burden on family members when applied in home-setting scenarios.

Method: a comprehensive systematic review of useful interventions for easing the BPSD burden in patients with dementia (PwD) and their caregivers in the context of COVID-19 quarantine was performed from January 2010 to March 2020.

Results: From a total of 187 articles retrieved from electronic databases (MEDLINE, LILACS, Cochrane and SCOPUS), 43 studies were eligible for this review. Most of the psychosocial and psychoeducational interventions described were person-centered strategies based on the cognitive-behavioral approach or informational tools to enhance care providers' knowledge of dementia. Most studies achieved successful results in handling BPSD and mood-anxiety symptoms of care providers, contributing to an overall improvement in dyad life quality.

Conclusion: Evidence from the last few years suggest that low-cost techniques, tailored to the dyad well-being, with increasing use of technology through friendly online platforms and application robots, can be an alternative to conventional assistance during COVID-19 Pandemic. Nevertheless, the world's current experience regarding the duration of the COVID-19 Pandemic and its effects on the cognition, behavior, and life quality of PwD will demand research on preventive and protective factors of dementia and the pursue of efficient interventions in different scenarios.

Keywords: dementia, psychoeducation, psychosocial intervention, caregiver, COVID-19

INTRODUCTION

Dementia is a progressive syndrome and the associated functional decline inevitably leads to increasing dependence on others in different activities of daily living (1, 2). Patients with dementia (PwD) represent a heterogeneous group regarding diagnosis, stages of the disease, and level of functional decline. Behavioral and psychological symptoms in dementia (BPSD) are present at some point in almost 90% of PwD (3, 4), which is related to increased morbidity and mortality, caregiver burden, early institutionalization, and reduced survival (5, 6). One recent estimation of the global costs of dementia in Brazil cited values of US$1,012.35 (7). Although the economic and social impact remains to be further understood, the elevated healthcare costs resulting from the use of higher doses of psychoactive medications and falls, treatment dropouts, and wandering have all been thoroughly described in the literature (8).

A large number of PwD, mostly in moderate and advanced stages, require constant supervision (9). Since they are at the forefront of care, caregivers—family members and professionals, have a strategic role in the PwD quality of life and survival. A model of coping with stress is embedded in multiple stress-based problems, such as lack of social interactions, financial difficulties, frustration, anxiety, reduction of leisure activities, and concerns about the future (10, 11). Therefore, caregivers need professional assistance to cope with dementia, as they are a group particularly vulnerable to emotional burden, depression, and physical exhaustion. (10, 12).

Also, the COVID-19 Pandemic, which started in September of 2019 in Wuhan, the capital city of Hubei Province (China), had a crucial psychosocial impact on the mental health of older adults with pre-diagnosed dementia, especially after social isolation measures such as lock-down, and is still an unexplored topic. Despite dementia's heterogeneity and psychoeducation measures, which are defined as a set of information provided by healthcare professionals that help in understanding the biological and social phenomena involved in the illness process and contribute to delivering higher-quality care in a home setting (13).

Measures directed to the dyad—caregiver and PwD—at home can be of a psychoeducational or psychosocial nature. Psychosocial interventions, defined as a set of techniques developed to use cognitive and behavioral mechanisms to promote the caregiver and PwD psychological well-being, can be associated with psychoeducation. Evidence shows that both measures, when aimed at understanding dementia and managing behavioral changes in a home setting and social isolation, can benefit PwD therapeutically, minimizing complications and reducing the emotional burden on family members during the isolation period, when social contact with specialized services is limited.

Furthermore, evidence has shown that PwD wish to participate in interventions that enhance their well-being, confidence, health, social participation, and human rights. This point highlights a need for improvements in psychosocial research to capture these outcomes (14). The present article aims to discuss psychoeducation measures and brief psychosocial interventions designed in a home setting, based on an integrative literature review, to manage behavioral changes in individuals with dementia and social isolation, which may be useful for the COVID-19 pandemic and post-pandemic assistance.

METHODS

An integrative literature review was conducted to gather and summarize the evidence available from original articles for the issue investigated. This integrative review study included six stages: 1 – formulation of the central research question (theme identification); Step 2 – definition of inclusion and exclusion criteria and literature search; Step 3 – categorization of primary studies (description of data to be extracted from the selected studies); Step 4 – assessment of the studies included; Step 5 – interpretation of results; 6 – knowledge synthesis of the results obtained from the studies assessed (15–17).

The central research question was formulated using the PVO method, where P is the study population (adults over 60 years of age with a diagnosis of dementia); V is the variable (psychoeducation measures), and O is the outcome (BPSD management).

Our review's guiding question was: "Which psychoeducational and psychosocial measures are used for easing the BPSD burden in both PwD and their caregivers in the home setting?" The inclusion criteria were English language articles in the electronic databases (Medical Literature Analysis and Retrieval System Online (MEDLINE), Latin American and Caribbean Health Sciences Literature (LILACS), Cochrane, and SCOPUS); cross-sectional or prospective design; outpatient or population-based samples of adults over 60 years of age with irreversible and progressive dementia (e.g., Alzheimer's disease, vascular dementia; Parkinson's dementia); and non-pharmacological treatment through psychoeducation and psychosocial measures. The exclusion criteria were guidelines, systematic reviews, institutional protocols, psychoeducation measurements in other psychiatric or neurological conditions, and psychosocial intervention in hospitalized patients. The publications were individually searched and selected by two investigators during March and April 2020 and included papers from January 2010–April 2020.

The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (18) were used as a basis for the search and selection of studies (**Supplement Material**). A search strategy was created to conduct searches in the following databases: MEDLINE *via* PubMed from the US National Library of Medicine, LILACS, Cochrane, and SCOPUS with no time restriction. To expand our search, we chose to use a natural controlled language. The following descriptors (bold), synonyms, natural language, and Boolean operators were used to cross-check the databases: MEDLINE (Medical Subject Headings [MeSH]: search strategy – (aged or elderly or old or elder) and (non-pharmacological treatment or psychosocial treatment or ") and ("Alzheimer disease" or Alzheimer's) and ("dementia" or "cognitive dysfunction").

Two investigators independently conducted the literature search and data extraction to minimize selection bias (misinterpretation of results and study design), and any discrepancies were resolved by consensus. We also performed a qualitative rating (see **Supplement Material**) of all selected studies through the Newcastle-Ottawa-Scale score (http://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf).

RESULTS

The study selection process, according to the PRISMA guidelines, is illustrated in **Supplement Material** flow chart. A total of 187 articles were retrieved and read, and from these, only 43 studies were considered eligible for our review. The selected studies are described in **Tables 1**, **2**. The sample sizes ranged from 6 to 555 participants. They were conducted in 16 countries, with the most substantial proportion nested in Europe (n = 23, 53.49%) and United States (n = 10, 23.26%). In contrast, the same ratio (n = 9, 20.93%) was found in Eastern Asia or Oceania, and only one was in Africa (2.32%). No studies were found for Latin America.

Almost all studies (n = 42, 97.67%) employed psychosocial and-or psychoeducational strategies addressing the dyad, and only one used cognitive-behavioral intervention (2.33%) for the caregiver solely (**Table 1**). The majority of investigations (n = 33, 76.74%) were based on randomized controlled trials, as following: 1 interventional study design (2.22%), 1 multiple case (2.22%), 6 longitudinal studies (13.95%), 1 explanatory sequential mixed-method design (2.22%), 1 exploratory design (2.22%), 2 quasi-experimental interventions (4.44%), and 1 controlled clinical trial alternately assigned (2.22%). A few studies used more than one design method.

The studies included in our review evaluated participants with distinct levels of dementia, being most of them (n = 34, 79.07%) focused on mild-moderate dementia. In comparison, 8 (18.60%) other studies investigated mild Alzheimer's disease, and only 1 (2.32%) moderate-severe dementia. Cognitive and functional scores were provided only by a few studies (n = 10, 23.26%). Most caregivers were familiar or informal caregivers (n = 30, 69.76%), albeit professional care providers could be found in the remaining studies (n = 13, 30.23%). For most of the compelled studies, the primary outcome result was evaluating and reducing behavioral disturbances in PwD, such as agitation, restlessness, anxiety (n = 17, 39.53%), including specific interventions for decreasing sleep disturbances (n = 2, 4.65%). Concerning caregivers, the most important outcome was the reduction of burden and stress (n = 21, 48.84%), including the attenuation of depression or other mood symptoms (n = 4, 9.30%). Also, studies aimed at evaluating caregiver wellbeing, quality of life and satisfaction of with caregiving (n = 6, 13.95%); some outcome measures comprised the enhancement of knowledge on dementia through psychoeducation and the development of a sense of competence in dealing with BPSD (n = 9, 20.93%) and reducing guilty and adverse reactions toward PwD (n = 2, 4.65%). Finally, other studies had primary goals evaluating online psychosocial support, including robot-guided psychosocial intervention (n = 3, 6.98%).

The primary interventions are summarized in the following topics.

An Overview of the Psychosocial and Psychoeducational Interventions

Most of the studies of psychosocial and psychoeducational interventions for the field of dementia use an umbrella of techniques, most of them based on cognitive-behavioral therapy (CBT) (19) or a combination of psychotherapy and essential information on dementia (20). Caregivers were generally encouraged to share feelings about dementia such as guilt, loneliness, worry and sadness (20). The majority of studies carried out interventions for dyad (15). Caregivers may learn from CBT to develop self-monitoring of depressive or anxiety symptoms or help PwD do so (4). One study, for instance, employed CBT in PwD at moderate stages (16). The Coping with Caregiver model – CCM (5) articulates cognition and behavior with negative affective states and teaches cognitive-behavioral mood management skills. In one investigation consisting of a 14 h training program with CCM, the intervention group exhibited significantly less depressive symptoms and experienced lower caregiver burden than the control group at the end of study (5). The Residential Care Transition Module (RCTM) consists of a six-session, 4-month psychosocial intervention designed to help families manage their emotional and psychological distress following residential care placement of a cognitively impaired relative (17). Cognitive Stimulation Therapy (CST) is a psychosocial group intervention recommended by the UK NICE guidelines that have shown to improve cognition and quality of life (18). There is some evidence showing the efficacy of CST in apathy and depression-dysphoria (21). Multisensory stimulation (MS) comprises a set of sensory stimuli (visual, auditory, tactile) and controlled environment, following a schedule of reinforcement and has been studied in AD, Huntington's disease (15). Mindfulness-based intervention (MBI) is based on paying attention in a particular way, i.e., at the present moment and non-judgmentally to enhance emotional regulation (22, 23). This meditation method focuses mainly on breath or body and open monitoring of the whole cognitive-affective field (22). One single-blind intervention conducted by Churcher Clarke and colleagues included a 10-session MBI with mild and moderate dementia and found a medium effect size improvement in overall quality of life, but no significant changes in depression or anxiety symptoms (22).

Main Goals of Interventions

Overall, most psychoeducational and psychosocial interventions aimed to enhance care providers' knowledge about the required skills of caregiving and, ultimately, to reduce dementia sufferers' illness deterioration and institutionalization (24, 25). Most studies employed personalized and person-centered strategies (26, 27) designed to fulfill the needs, characteristics and preferences of both PwD and their caregivers (28). As an example, the Person-centered care (PCC), widely recognized concept in dementia research and care and the Dementia Care Mapping (DCM), a method for implementing PCC (29).

Some strategies seek to promote the general well-being and life quality of the dyad (17, 20), such as the case of the Dealing Well with Dementia project, which used the "Dignity Therapy" (30), the Family Intervention (FITT-C) (31) or the Northern Manhattan Caregiver Intervention Project, which addressed the relief of stress symptoms in Hispanic spouses of PwD in NYC (32). In Denmark, a large multicentric study (DAISY) evaluated the effectiveness of a program for outpatients with Alzheimer's disease in 12 months (33, 34). The therapy was based on measures of education, counseling and support for family members (33). Raeanne and colleagues (35) evaluated the efficacy of the Pleasant Events Program (PEP), a 6-week Behavioral Activation intervention designed to reduce CVD risk and depressive symptoms in caregivers. According to the authors, the group receiving PEP intervention had significant reductions in depressive symptoms (p = .039) and negative affect (p = .021) from pre- to post-treatment (35).

Other examples included multiple activities, such as the Pleasant Events Program, in which a protocol comprised physical exercise, occupational therapy and support intervention for the dyad, have also been employed (28). The caregivers were encouraged to learn from cognitive stimulation through specific protocols, by dealing with their stress and anxiety feelings and the daily routine; this was the case of the individual Cognitive Stimulation Therapy (iCST) (36).

The promotion of well-being through dancing was also a therapeutic tool in some studies (37), improving social activity and psychical health. The Project DANCIN (Dance Therapy Intervention) measured in two daily sessions (in a total of 24 sessions) PwD with mild and moderate stages and caregivers who want to include this activity in their daily routine (38). Participants exhibited a set of BPSD assessed by the Dementia Mood Assessment Scale (DMAS-17) (39), including insomnia, agitation, angry outbursts, daytime drowsiness, continually fidgeting and staring at the floor and perseverative questioning (38). PwD and also those showing sensory or auditory deficits could benefit from the dancing sessions (38). Additionally, the absence of dance experience was not a limitation to overall engagement in the PwD group.

The reduction of psychological distress among familiar care providers was pursued by the START Project (Strategies for Relatives Intervention) by developing healthy coping strategies (40). Family member's engagement was reinforced through partnership interventions, as a critical element to reduce behavioral disturbances and enhance well-being in another study (41).

The specific training of staff members showed useful outside metropolitan areas, where memory clinics are not available. One example is the Clinical Antipsychotic Trials of Intervention Effectiveness—CATIE-AD study (n = 421 AD outpatients), which implemented psychoeducation training for GP and non-specialists to the early identification of behavior disturbances, clarifying its main behavior dimensions. A total of 4 distinct clusters have been identified: a) agitation and irritability, b) apathy and eating problems, c) psychosis (delusions and hallucinations, and d) emotion and disinhibition (depression, euphoria and disinhibition) (42).

In other studies, self-monitoring skills were assessed both by the staff and the family member (43). In agitation management, a study aimed at satisfying basic needs proved effective in reducing verbal agitation (44). Improving the patient's food intake and nutritional status is also essential to reduce agitation and improve this group's quality of life (45).

Adopting Tailored Activities

One aspect regarded as crucial to warranty the effectiveness of psychosocial interventions is the provision of tailored activities, particularly for home-dwelling PwD (9, 46). As the caregiver group usually varies from adolescents (including "adult children"), adults, spouses to professional care providers, individualized dyadic interventions shall be designed in any dyadic compositions to reduce the caregiver social strain (47) and improve PwD functional ability (47). One of the strategies credited as successful is the promotion of multiagency discussions, which enable the evaluation and provision of unmet needs (19). Dyadic interventions may also be addressed to the primary health care system (48), and GPs may receive training in psychosocial counseling (49). Another innovative intervention allowed personalized interventions to integrate home and residential care services in Japan (19). Noteworthy, the level of PwD engagement shall consider not only the degree of cognitive decline but the preservation of sensory stimuli (e.g., sight, smell, and touch), since potential sensory dysfunctions may be associated with apathy and isolation (23, 50).

Optimal care also involves adapting the expectations of both professionals and the dyad. In one interesting study conducted by Popham and colleagues (13), the main obstacles to optimal care through the Sheffield Care Environment Assessment Matrix (SCEAM) questionnaire (51). The main themes for the dyad were the lack of social interaction activities, more freedom for PwD to go outside, more freedom to choose what activities they could do according to the program, while health and safety, most of the times involving spatial restriction for the patient to wander, were the strong concern for health professionals (13). The support tool Inlife was launched in the Netherlands, developed explicitly for caregivers and PwD to lower the threshold for asking and support (52) in an ongoing 16-week RCT. Primary outcomes comprised the caregiver's sense of competence and secondary, while secondary outcomes consist of evaluating mood symptoms (anxiety and depression), social network, and feelings of loneliness.

Albeit most studies showed successful results in stimulating PwD, negative results were also reported. One follow-up investigation of 3 years revealed no benefit on the well-being

TABLE 1 | Characteristics of Intervention studies with patients with dementia and caregivers*.

Authors, Year	CountryStudy Design	Outcome measures	Sample Size-Mean Age	Intervention Tool used	Main Results
Arritxabal et al. (1)	Spain Interventional	To evaluate a psychoeducational intervention program centered on the regulation of the emotion among caregivers.	Informal caregivers Intervention: n = 52 (56 ± 13) Control group: n = 32, 54.10 ± 12.30)	Cuestionario de Pensamientos Disfuncionales sobre el Cuidado, CBI, PSQ, PANAS, SWLS, TMMS-24, CES-D, PSS	When compared with the control condition, the experimental group obtained higher scores in positive affect, (subjective well-being, regulation of emotions, and satisfaction with caregiving), but obtained lower values in perceived stress and negative affect. The experimental group showed a significant decrease in dysfunctional thoughts and emotional attention. The control group registered higher levels of psychosocial support and lower satisfaction with caregiving
Boersma et al. (2)	The Netherlands Multiple case study	To perform a process analysis of the implementation of the Veder contact method.	Caregivers: n = 42 (47 ± 10.02)	Focus groups and interview	The reach of the intervention and aspects of implementation-effectiveness facilitated implementation. Both facilitators and barriers were identified. Little effort was put into maintenance: only one nursing home developed a long-term implementation strategy.
Chen et al. (3)	China Randomized controlled trial	To develop an intervention targeted towards improving coping strategies and reducing caregiver burden	Caregivers: n = 46 Intervention group: n = 24 (54.8 ± 15.1), Controls: n = 22 (55.1 ± 11.1)	RMBPC, CBI Chinese version, WCCL-R	Individual psychosocial and education interventions can be beneficial in terms of reducing the caregiver burden.
Clarke et al. (4)	England Randomized controlled	To develop a group-based adapted mindfulness program for people with mild to moderate dementia in care homes	Total = 31 caregivers Group intervention: n = 20 (81.30 ± 9.29) Controls: n = 11 (79.36 ± 9.91) and 28 participants post-test.	MBI manual, CSDD, RAID, QLAD, MMSE, PSS-13, MBAS	There were no significant changes between groups in terms of depression or anxiety.
Dam et al. (5)	The Netherlands Randomized controlled trial	To evaluate the effects of Inlife and its effectiveness and feasibility for caregivers of PwD	Total = 122 caregivers (> 18 years)	PPQ, SSCQ, MSPSS, SSL12-I, LS, LSNS-6, HADS, ICECAP-O, CarerQol, PSS, CRA	The study provided insights into the usability and implementation of online social support interventions in dementia care.
Fossey et al. (6)	United Kingdom Cluster-randomized controlled trial	To use WHELD, or not, in the psychosocial approach for PwD	Total = 47 care home staff within nine care homes in the United Kingdom	WHELD program	Participants attributed effectiveness in using the WHELD approach to both patients and caregivers.
Gaugler et al. (7)	United States Longitudinal	To estimate the effects of comprehensive psychosocial support on spouse caregivers' well-being trajectories related to the nursing home placement transition.	Total = 406 spouse caregivers of community-dwelling persons with Alzheimer's disease Treatment: n = 203 71.55 ± 8.7 Usual care: n = 203 71.03 ± 9.5	ZBI, GDS, Global Deterioration Scale	Longitudinal models found that wives were more likely than husbands to indicate reductions in burden in the months after placement in an institution. Wives also reported more significant decreases in depressive symptoms after placement in an institution when compared with husbands.
Guzmán et al. (8)	United Kingdom Follow up	Monitor individual behavior and mood diaries through DMAS-17	Total: 10 PwD from two care homes and one nursing home Age interval 78–95 years Education: 9–12 years MMSE: 14–26	12-week Dance therapy sessions	A small to medium change was seen in behavioral and mood items, such as energy levels to socialize, increased appetite, mobility, and decreased irritability and depressed appearance.
Jones et al. (9)	Australia Cluster-randomized controlled trial	To explore whether the severity of cognitive impairment and agitation of older PwD predict outcomes in engagement, mood states, and agitation after an intervention with the robotic seal, PARO	N = 138 caregivers (intervention group) Age 84 ± 8.4	Robotic seal PARO, CMAI-SF, RUDAS	In clinical practice, PARO should be restricted to people with low-moderate severity of agitation.

(Continued)

TABLE 1 | Continued

Authors, Year	CountryStudy Design	Outcome measures	Sample Size-Mean Age	Intervention Tool used	Main Results
Karel et al. (10)	Germany Longitudinal Multicomponent training program	To evaluate the feasibility and effectiveness of STAR-VA, an interdisciplinary program to manage behavioral disturbances in nursing-home residents with dementia	Total: 17 community living centers, PwD veterans > 60 years old (n = 71) Caregivers > 18 years old	STAR-VA training program Functional assessment staging tool Cornell Scale for Depression in Dementia Rating Anxiety in Dementia Scale Cohen-Mansfield Agitation Inventory	Behaviors were clustered into six domains: care resistance, agitation, aggression, vocalization, wandering and others. Frequency and severity of agitation and mood symptoms decreased with effect sizes ≥1
Kerssens et al. (11)	United States Longitudinal	To test the usability, feasibility and adoption of the Companion in a home- and community-based setting	Total = 7 dyads of PwD and caregivers PwD: median age 77 (60–88) Caregivers: median age 79 (63–86)	Barthel Index, MMSE, Lawton, CSDD, NPI, CSI, ZARIT	The technology was easy to use, significantly facilitated meaningful and positive engagement and simplified caregivers' daily lives. Caregivers had high expectations of their loved one's ability to regain independence. Care recipients used the system independently but were limited by cognitive and physical impairments.
Matsuzomo et al. (12)	Japan Follow-up Cluster randomized	To investigate the effects of BASE on challenging behavior of home-dwelling PwD	Home caregivers (n = 24) Professionals (n = 49) Controls: n = 70 (84.9 ± 6.7) PwD: n = 141 (83.7 ± 7.1)	BASE program	Significant reduction in BPSD in the intervention group after 6 months as compared with the CG (11.6 to 10.8; P <.05).
Nakanishi et al. (13)	Japan Cluster-randomized controlled trial	To investigate the effect of the BASE program on challenging behavior in home-dwelling PwD	Total = 283 PwD Intervention group: n = 141 Control group: n = 142 Total: n = 95 care professionals Intervention group: n = 46 Control group: n = 49	BASE program	Significantly less challenging behavior in the intervention group compared to the control group follow-up.
Nakanishi et al. (14)	Japan Cluster-randomized controlled study	To identify a key component of the psychosocial dementia care program that is associated with a reduction in challenging behavior	Total: 305 participants PwD: n = 219 (83.8 ± 6.9) Care professionals: n = 86 (45.6 ± 5.3)	NPI-NH, Abbey pain Scale Japanese version, SMQ JV, Barthel Index JV, ATC, SCIDS JV	There was a significant reduction both in challenging behavior and pain from baseline to the follow-up assessment.
Stockwell-Smith et al. (19)	Australia Explanatory sequential mixed-method design	To evaluate the effect of a targeted community-based psychosocial intervention	Total: 88 dyads Care recipient n = 45 > 65 years	Early Diagnosis of Dyadic Intervention	There were no significant between-group differences in either Symptom Management and Support Service self-efficacy.
Van Mierlo et al. (20)	The Netherlands Cluster randomized controlled trial	To evaluate the effectiveness of DEM-DISC on informal caregivers and people with dementia. To investigate its user-friendliness and usefulness among informal caregivers of people with dementia and case managers who provide care coordination and continuity of care in community-dwelling people with dementia. To investigated which facilitating and impeding factors were expected to influence the further nationwide implementation of DEM-DISC.	Total: 73 informal caregivers, 19 randomized case managers, and 41 professional caregivers Experimental group: n = 54 63.0 ± 11.6 Control group: n = 46 60.4 ± 12.7)	MMSE, MDS-care receiver, CANE, Qol-AD, NPI, SSCQ, USE	Informal caregivers who used DEM-DISC for twelve months reported an increased sense of competence than controls. A subgroup of users who frequently accessed DEM-DISC reported more met needs after six months than controls. Overall informal caregivers and case managers judged DEM-DISC as easy to learn and user-friendly.

(Continued)

TABLE 1 | Continued

Authors, Year	CountryStudy Design	Outcome measures	Sample Size-Mean Age	Intervention Tool used	Main Results
Williams et al. (21)	United States Controlled clinical trial	To determine whether video-based coping skills (VCS) training with telephone coaching reduces psychosocial and biological markers of distress in primary caregivers	116 primary caregivers Intervention group: n = 59 (62.1 ± 13.6) Waiting list: n = 57 (59.0 ± 12.8)	PSS, STAI, STAXI, CES-D, MMPI, CGSE, PSQI, Blood pressure (BP) and heart rate (HR) were recorded during stress testing using an automatic blood pressure monitor, Salivettes®,	The group main effect was significant for depressive symptoms and perceived stress, and there was a trend for the group effect for trait anxiety. None of the Group × Visit interactions were significant. A Group × Visit interaction was found for both mean systolic and mean diastolic blood pressure, with a significant group main effect for mean diastolic blood pressure maintained over the six-month follow-up period.

*Tables 1 and 2: references are available at the **Supplementary Material**.*

and delay of cognitive decline in mild and very-mild DA (53). The absence of regular weekly phone support and a lack of homogeneity in patient recruitment, including culturally heterogeneous groups, are significant limitations (53).

Intervention Programs Targeting Home-Dwelling PwD and Caregivers

Evidence has suggested that caregivers living outside metropolitan areas (e.g., in rural areas) are more prone to develop emotional burden and instability in the dyad (54), mostly due to the scarcity of specialized facilities, including a memory outpatient service and the absence or lack of psychosocial counseling. Conversely, similarly to their counterparts in major cities, these subjects may benefit mainly from home-based psychosocial intervention targeting the caregiver's depressive symptoms and burden (55) and short and long term complications associated with BPSD (56). Thus, both low cost and more comprehensive strategies should be favored, especially in times of pandemics. Some experiences have successfully engaged GPs in a psychosocial counseling initiative (41). The adaptation of the protocol "Living Well with Dementia" stimulated the search for psychosocial support among users of the United Kingdom's primary healthcare system (21). One cluster-randomized trial conducted by Nakanishi and colleagues (19) in a local home setting implemented through a 6-month follow the BASE program, a palliative care approach lead by care managers and professional caregivers, which resulted in a significant reduction of challenging BPSD of PwD. The project Staff Training in Assisted Living Residences (STAR-VA) assessed the frequency and intensity of BPSD in veterans PwD in nursing home care (52). In Germany, the Project Future Workshop Dementia (Zukunftswerkstatt Demenz) has followed Family members and PwD in rural areas (57).

Home-based approaches, including a complete set of activities, such as cognitive and physical training combined, may exhibit better results in randomized controlled trials (RCTs) with community-dwelling PwD. The NYU Caregiver Intervention (NYUCI) was designed to provide caregiver support for adult children and prevent residential care placement through 2 years. The term "adult children" is applied to the child or teenager relatives, most of them sons or daughters or grandchildren compelled to assume caregiving duties, including personal hygiene, economy, and safety (58). NYUCI intervention included family counseling, support group referral and *ad hoc* consultation, or a contact control group. Participants of NYUCI were found to be less prone to admit their parents to a residential care setting ($p < 0.05$) and also delayed their parent's time to admission significantly longer (228.36 days) than those of the control group (17).

Interventions Based on Phone Calls and Internet Apps

Internet psychosocial interventions hold considerable promise for meeting the educational and support needs of informal dementia caregivers at reduced costs (52, 59). A number of them have been delivered to support caregivers

TABLE 2 | Characteristics of Intervention studies with patients with dementia and caregivers*.

Authors, Year	CountryStudy Design	Outcome measures	Sample SizeMean age (SD)	Intervention Tool used	Main Results
Bartels et al. (15)	The Netherlands A single-blinded randomized controlled trial	To examine the sustainability of positive intervention effects of the mobile health intervention on caregivers' well-being	Total: n = 76 caregivers (72.1 ± 8.4) Experimental group: n = 26 (71.7 ± 8.4) Pseudo-experimental: n = 24 (71.1 ± 7.3) Control group: n = 26 (73.2 ± 9.4)	SSCQ, PSS, PMS, CES-D, HADS-A, NPI-Q, CDR	The results obtained showed that the intervention "Partner in Sight" can reduce feelings of stress, depressive symptoms and enhance a sense of competence in caregivers.
Brown et al. (16)	United States Randomized controlled trial	To test the efficacy of MBSR program for reducing caregiver stress and enhancing the care giver-recipient relationship	Total: 38 caregivers (MBSR group n = 23, SS group n = 15). Age of participants: 61.14 ± 10.41 (39–88 years)	MBSR program	Caregiver participants in MBSR reported lower levels of stress, tension and anger. The SS intervention highlighted an understanding and acceptance of dementia behaviors, which can help to reduce the perceived burden.
Bruvik et al. (17)	Norway Assessor-blinded multicenter RCT	To describe a multicomponent tailored psychosocial intervention trial design to reduce depressive symptoms in PWD and caregivers	Total: 230 dyads of home-dwelling PWD and a principle family caregiver Intervention group (n = 115): caregiver 64.1 ± 12.2, PwD 78.3 ± 7.5; Control group (n = 115): caregiver 62.9 ± 11.4, PwD 78.5 ± 7.5	CSDD, GDS, RRS Norwegian version, MMSE NV, NPI-Q, PSMS, IADL	The study did not find that a structured, multicomponent and tailored psychosocial intervention program significantly reduced depressive symptoms in PWD or their family caregivers compared to usual care.
Burns et al. (18)	USA, Australia and the UK Randomized controlled trial	To assess whether caregiver interventions can still be successful when anti-dementia drugs are provided to patients	158 dyads divided equally across three centers: Sydney (n = 52), New York (n = 52) and Manchester (n = 54). Sydney: Patients 75.0 mean age (58–89 years), caregivers 71.8 (53–86); Manchester: Patients 72.7 (52–91), caregivers 72.2 (49–88); New York: Patients 73.6 (55–89), caregivers 70.2 (47–88).	MMSE, GDS, BAI, RMBPC, BDI, Stokes Social Network List, WFCS, PMS, EuroQol,	The caregiver intervention was associated with positive results on caregiver depression across all the countries.
Dahlrup et al. (22)	Sweden A quasi-experimental longitudinal cohort study	To examine the effects of a psychosocial intervention for family caregivers in describing symptoms of dementia	Intervention group: n = 129 (61 ± 12.9) Control group: n = 133 (62 ± 12.6) PWD: n = 144 (85 ± 5.9);	MMSE, GBS-scale, The Berger scale, IADL	The family caregivers who underwent psychosocial intervention achieved a better understanding of different symptoms and the behaviors of dementia.
Davis et al. (23)	United States Randomised controlled trial	To study the preliminary efficacy of a telephone intervention (FITT-NH) for improving dementia caregivers' adjustment	Total: 27 caregivers assigned to FITT-NH and 26 to the non-contact control condition. Caregivers in the intervention group: 57.25 ± 10.67 Care recipient: 82.54 ± 5.48 Caregivers in the control group: 61.32 ± 10.46 Care recipient: 82.73 ± 9.05	FITT-NH	Caregivers receiving FITT-NH showed reduced guilt feelings and more staff positive interactions compared to those caregivers with no additional contact.
Den IJssel et al. (24)	The Netherlands Cluster randomized controlled trial	To evaluate the effect of the intervention on nursing staff burnout, job satisfaction, and job demands.	nursing staff: n = 305 (43.5 years ± 12.2)	APID, NPI-Q, CANE Dutch version, UBOS DV, Leiden Quality of Work Questionnaire	The intervention showed no additional improvement in three dimensions of burnout, job satisfaction and job demands.
Gaugler et al. (25)	United States A single-blinded randomized controlled trial	To evaluate the effects of NYUCI-AC on decreases in family and role conflict and increases in perceived social support	Total n = 107 (treatment group n = 54 and control group n = 53). Total: 50.46 ± 8.24 Control: 49.68 ± 9.36 Treatment: 51.23 ± 6.95	NYUCI-AC	Effectiveness in reducing residential long term care placement for persons with ADRD and adult child caregivers' adverse reactions to disruptive behavior problems, and depressive symptoms.
Johannessen et al. (26)	Norway Randomized controlled trial	To investigate the outcome of the study from the perspective of the healthcare professionals	19 health professionals 34–61 years	Psychoeducation of dementia and the management of its symptoms.	The intervention can prevent burnout of the primary caregivers and social isolation and thereby promote health.

(Continued)

TABLE 2 | Continued

Authors, Year	CountryStudy Design	Outcome measures	Sample SizeMean age (SD)	Intervention Tool used	Main Results
Johannessen et al. (27)	Norway Randomized controlled trial	To investigate family caregivers' experiences of a multicomponent psychosocial intervention program	20 family caregivers 50–82 years	Individual qualitative interviews and a psychosocial intervention program	It contributed to reducing the burden and loneliness caused by the disorder.
Koivisto et al. (28)	Finland Randomized controlled trial	To assess the influence of the intervention on AD progression, behavioral symptoms, and HRQoL	236 dyads of home-dwelling persons with AD and their family caregivers (control group n = 152; intervention group n = 84)	CDR-SOB, CERAD-NB, MMSE, ADCS-ADL, NPI, QoL-AD, VAS, BDI, SOC, 12-GHQ, 15D	The present study did not show any long-term effect of the early psychosocial intervention.
Langhammer et al. (29)	Norway Exploratory design	To evaluate whether a combined intervention of physical activity and music therapy could reduce anxiety, restlessness, irritability, and aggression	6 individuals with dementia and signs of frontal lobe problems PwD: n = 6 (75.6 ± 6.52) Caregiver: n = 6 (65.6 years ± 11.9) Mean age of 84.3 years	BVC, NPI-Q, Semi-structured interviews	Implementation of individualized music therapy combined with increased physical activity for eight weeks was a feasible intervention that reduced anxiety, restlessness, irritability, and aggression in the current study.
Liang et al. (30)	New Zealand Pilot block randomized controlled trial	To investigate the affective, social, behavioral, and physiological effects of the companion robot Paro for PwD	30 dyads (PwD and caregivers) PwD age range: 67–98 years Caregivers age range: 30–86 years	Paro	Paro helped improve mood, reduce anxiety, acting as a social stimulus, and increasing communication and cooperation with therapists and staff.
Lord et al. (31)	United Kingdom Randomized controlled trial	To evaluate the dissemination of the program Strategies for Relatives (START)	134 clinical psychologists and 39 admiral nurses -	START, individual interview	The study began the new intervention dissemination process.
McCurry et al. (32)	United States A randomized, controlled trial with blinded assessors	To test the effects of walking, light exposure, and a combination intervention (walking, light, and sleep education) on the sleep of persons with Alzheimer's disease	132 AD participants and their caregivers Walking: 82.2 ± 8.50 Light: 80.6 ± 7.3 NITE-AD: 80.0 ± 8.2 Control: 81.2 ± 8.0	SDI, Actigraph, CSDD, SCQ, MMSE	To test the effects of walking, light exposure, and a combination intervention (walking, light, and sleep education) on the sleep of persons with Alzheimer's disease
McCurry et al. (33)	United States Randomized controlled trial	To investigate the feasibility of implementing a Sleep Education Program (SEP) for improving sleep in an adult family home (AFH) residents with dementia, and the relative efficacy of SEP compared with usual care control	37 adult family home (AFH) staff-caregivers and 47 residents with co-morbid dementia and sleep disturbances. AFH staff-caregivers: 86.6 ± 7.2 Residents: 48.2 ± 9.7	Actigraphy, CSDD, RMBPC, ESS	To investigate the feasibility of implementing a Sleep Education Program (SEP) for improving sleep in an adult family home (AFH) residents with dementia, and the relative efficacy of SEP compared with usual care control
Moyle et al. (34)	New Zealand Randomized controlled trial	To compare a lifelike baby doll intervention for reducing agitation and aggression in older people with dementia in long-term care (LTC)	Total: 35 residents from five LTC facilities (Lifelike Doll n = 18, Usual Care n = 15). Total: 87.8 years ± 8.6 Intervention group: 86.1 ± 8.6 Control 89.7 (8.4)	Semi-structured interview, OERS, CMAI-SF, MMSE, NPI-NH	There was no statistical evidence to support the hypothesis that the lifelike baby doll intervention would reduce residents' anxiety, agitation, and aggression.
Orrell et al. (35)	United Kingdom A single-blind pragmatic randomized controlled trial	To evaluate the effectiveness of a home-based, caregiver-led (iCST) program in (i) improving cognition and QoL for the PwD and (ii) mental and physical health for the caregiver.	A total of 356 dyads iCST group: n = 180 TAU group: n = 176		To evaluate the effectiveness of a home-based, caregiver-led (iCST) program in (i) improving cognition and QoL for the PwD and (ii) mental and physical health for the caregiver.

(Continued)

TABLE 2 | Continued

Authors, Year	CountryStudy Design	Outcome measures	Sample SizeMean age (SD)	Intervention Tool used	Main Results
Pihet et al. (36)	Switzerland Quasi-experimental intervention that followed the TIDieR guidelines	To examine the feasibility and the effects of implementing the program and the participants' use of the trained strategies	26 ICD through service providers in the field of dementia ICD median age of 68 years (*Q1* = 60, *Q3* = 72, *range* 37–86); Patients median age of 77 years (*Q1* = 71, *Q3* = 82, *range* 56–94)	Caregiver's burden 22-items questionnaire, MBP, caregiver's MBP-related distress, Ilfeld short version, VAS	The program resulted in substantial improvements in burden, psychological distress, self-efficacy and the increasing ICD quality of life.
Phung et al. (37)	Denmark Multicentre, randomized controlled rater-blinded trial	36-month follow-up to rate changes in behavioral symptoms and quality of life of both PwD and caregivers in 5 Danish districts	Counseling, psychosocial support; 163 patients to DAISY intervention group and 167 to control group	QoL-AD NPI ADCS-ADL GDS EQ-VAS	The 12-month follow-up study observed positive effects on preventing depressive symptoms and maintaining the quality of life among PwD. No effects were found on the caregiver's quality of life after a 360-month follow-up.
Schall et al. (38)	Germany Randomized, wait-list controlled design	To relieve the sense of isolation experienced by many PwD, as well as the burden on family caregivers	44 PwD Intervention group n = 25, Wait-list control group n = 19). Intervention Group: 75.1 ± 7.70 Wait-list control group: 76.4 ± 8.68	ARTEMIS	ARTEMIS intervention provided positive effects on the emotional well-being and the self-assessment of quality of life in PwD and a reduction in apathy and depressive symptoms.
Shata et al. (39)	Egypt Randomized controlled trial	To develop and evaluate the efficacy of a multicomponent psychosocial intervention program for informal caregivers of persons with NCDs	114 patients (Intervention group n = 55 and control group n = 59) PWD: age range 61 -86 years: 69.29 ± 6.24 years. Total: 48.63 years (12.31); Intervention: 49.35 ± 11.89; Control: 47.97 ± 12.76	MMSE, Caregivers' Dementia-related Knowledge Questionnaire, HDRS Arabic version, TMAS, ZBI, DRKQ	The study provided evidence for the short-term efficacy of a culturally sensitive multicomponent psychosocial intervention program in improving Dementia-related knowledge and the emotional status of informal caregivers of people with NCDs.
Søgaard et al. (40)	Denmark Randomized controlled trial	To investigate the impact of an early psychosocial intervention aimed at patients with Alzheimer's disease (AD) and their caregivers	330 dyads Intervention group n = 163 and control group n = 167.	RUD	An AD intervention may burden the caregiver more than it saves costs in proper health care and institutionalization.
Søgaard et al. (41)	Denmark Randomized controlled trial	To assess the cost-utility of early psychosocial intervention for patients with Alzheimer's disease and their caregivers.	Patients in the intervention group 76 years (**8**), caregivers 65 (13); Patients in the control group 75 (7), caregivers 66 (13) ≥50 years	RUD, EQ-5D, QALY	Psychosocial intervention is unlikely to be cost-effective in a Danish setting because it did not generate additional QALYs, and it led to the higher average usage of informal care.
Tremont et al. (42)	United States Randomized controlled trial	To examine the efficacy of the FITT-C to reduce depressive symptoms and burden in distressed dementia caregivers	250 dyads Caregivers – total sample: ± Intervention group: n = 133 (63.32 ± 12.30) Telephone support: n = 117 62.03 ± 13.75 PwD total sample: 78.06 ± 10.06, Intervention group: 79.22 ± 9.11 Control: 76.74 ± 10.93	FITT-C	The study demonstrated the equivalence of face-to-face and telephone assessments on two of the primary outcome measures (depressive symptoms, perceived burden, and reaction to memory and behavior problems).
Tremont et al. (43)	New England Randomize controlled trial	To examine the efficacy of Telephone Tracking-Dementia (FITT-D) and telephone support (TS) to promote psychoeducation, problem-solving, and a directive approach to behavioral disturbances.	≥50 years Intervention group: caregivers: 65.75 ± 13.71 Care recipient 75.94 ± 9.14; Control caregivers: 61.00 ± 9.60 PwD: 75.29 ± 10.79	FITT-D	Caregivers receiving the FITT-C used community support services more often than those receiving TS (P = .02). FITT-C caregivers had a significantly lower rate of emergency department visits (rate difference 9.5%, P = .048) and hospital stays (rate difference 11.4%, P = .01) over the 6-month course of the intervention than TS caregivers.

Tables 1 and 2: references are available at the **Supplementary Material.*

(60). The types of intervention vary widely, as does the quality of the methods used (46). Person-centered care approaches designed to home settings have been performed using observational tools and practice development cycles, such as the Dementia Care Mapping™ (DCM™) (61). Besides, touch screen technologies, such as the Companion, have offered an exciting opportunity to deliver the psychosocial intervention and monitor BPSD and caregiver distress and represent a promising field of development for the caregiver network (62). The Dementia Digital Interactive Social Chart (DEM-DISC) is an e-advice ICT tool to support customized disease management in dementia. This study aimed to improve and evaluate DEM-DISC, its user-friendliness and usefulness, and investigate future implementation (63). A total of 73 informal caregivers of PwD, supported by 19 randomized case managers. This study demonstrates that using DEM-DISC positively affected the sense of competence and experienced (met) needs of informal caregivers (63). Care providers could also manifest their opinion about the user-friendliness and usefulness of DEM-DISC through telephone interviews.

The "Ability Program" conducted by Realdon and colleagues in RCT lasted six weeks and comprised cognitive, physical activities, and a set of devices measuring and monitoring remotely vital and psychical health parameters (64). Another relevant follow-up intervention was promoted by the FITT-C study, using telephone-based interventions with trained therapists to manage the caregiver´s depression and burden. Those who received the FITT-C along six months tended to seek less medical attention in the urgency and had fewer hospital stays than the control group (65).

DISCUSSION

Our review provided a concise perspective of the last ten years of research on psychoeducational and psychosocial interventions directed to PwD and caregivers. Most studies achieved successful results in handling BPSD and mood-anxiety symptoms of the care provider, leading to an increase in skills related to caring and contributing to an overall improvement of the dyad quality of life. Telephone-based interventions have also shown effectiveness in reducing presential medical consultation and hospitalization. Similarly, studies adapting to friend-technology devices, including robots and remote-monitoring apps, exhibited promising results for promoting knowledge and facilitating decision-making among care providers. The world currently experiences uncertainty on the COVID-19 pandemic duration, and its effects in the cognition, behavior, and quality of life of PwD are yet to be understood. The current review sheds light on this theme, highlighting the potential use of low-cost and high-impact strategies actionable at the home-dwelling during the quarantine and the post-pandemic period.

The existing approaches tend to favor elements of the dyadrelationship differently. Such aspects involve, in summary, caregivers' awareness of what behavioral changes are. These approaches can range from simple monitoring to psychotherapy. Conversely, taking care of restlessness, apathy and other behavioral symptoms is also critical. If applied for the current pandemics, measures to monitor sleep, daily walks, and light exposure can counteract the prolonged quarantine period. Another critical aspect is promoting the caregiver's well-being, by reducing depressive symptoms and burden related to the isolation and permanent contact with PwD. Feelings of being overwhelmed, frustration, and loss of family contact may benefit from regular support and assistance, as demonstrated by telephone-derived interventions (31, 65).

One exciting field of research, for instance, will be the home-based adaptation through technological devices of classic intervention tools, including visual arts (66), museum visitations (61), or artistic, educational workshops (67, 68). The overall adherence and engagement by caregivers to e-devices have shown to be enjoyable and positive (60, 63, 69). Furthermore, technology devices also offer an opportunity for disease management to health assistants (63). In the future, user-friendly ICT solutions may be used to promote self-management by informal caregivers and assist caregivers in finding appropriate care services tailored to their specific situation and needs. Albeit the benefits of computer-based assistive technology have been evidenced, barriers and impediments still threaten the extensive use of these tools, including the inability of partners and care providers to recognize its added value, the lack of potential financial investors and the lack of government support for the development and enhancement of such instruments (63). Possibly, the undetermined duration of pandemics will demand the need for modifying the current protocols and research programs through the emphasis of support group intervention (70) and optimal staff training (13). Future studies will also require personalized protocols to overcome regional challenges, such as the low access of material resources, diversity of school background and the profile of BPSD among PwD.

A multiplicity of factors in primary care may serve as obstacles to optimal primary dementia care, as pointed by previous studies (71), including challenges related to a) the complex biomedical, psychosocial, and ethical nature of the condition; b) the gaps in knowledge, skills, attitudes, and resources of PWD/caregivers and their primary caregivers, thus affecting the active engagement of the latter; and c) the broader systemic and structural barriers negatively affecting the context of dementia care. As previously outlined, from the methods reported in this systematic review, a significant part requires long-term training (i.e., 4–12 weeks) and could not be accessible to a vast parcel of elderlies outside metropolitan areas or modest resource centers (72). Thus, one of the significant challenges is the home-setting adaptation of well-established double-blind, placebo-controlled protocols. In this scenario, both PwD and care providers should be encouraged to influence the organization and living environment of care homes whenever possible (13). Also, some evidence has highlighted the role of ethnicity and cultural background (e.g., Hispanic and Afro-Americans) and the importance of religious coping (73) in the context of psychosocial intervention and recommend the inclusion of ethnic and cultural variables in a more comprehensive program (74, 75). Gender differences, particularly in symptom profile, living condition, and coping style and response, seem to affect the outcome of psychosocial intervention, as highlighted by the literature (76). Another relevant aspect is the educational attainment of PwD (77); interestingly, prior evidence has suggested more significant benefits of cognitive intervention among higher educated patients (77). The importance of continuous follow-up, support, and professional reinforcement, mostly offering help based on the family's needs, has been outlined in previous studies with no benefit of psychosocial interventional (35, 78).

The present work has some limitations that deserve further comment. First, the broad scope of the theme, encompassing studies with multiple methods and outcomes. Second, the difficulty in transposing the current evidence to the real scenario of the COVID-19 pandemics, particularly in different continents and socio-cultural and economic realities. Although there is a vast multiplicity of psychosocial health programs for the old age with dementia and behavioral disturbances, we expect to bring a sum of the well-succeeded initiatives and, through that, global insights directed to best practices of caring for this population. We believe that future programs targeting behavioral disturbances and caregiver mental health issues in dementia shall consider general principles such as those briefly commented in our review.

CONCLUDING REMARKS

Before the COVID-19 epidemy, many studies have invested in evidence-based models targeting the provision of personalized interventions to implement community-based customized dementia care. Conversely, the experience of dealing with social isolation during the pandemic period will demand research on preventive and protective factors of dementia and the pursue of efficient intervention from every perspective, notably the domestic setting. The summary of the evidence from the last ten years suggests that low-cost techniques, tailored to the dyad, with increasing use of technology through friendly online platforms and application robots, can counteract the team's physical absence during the COVID-19 Pandemic. Such techniques should be directed to mood, sleep, and physical exercise, exploring playful music and dance activities. The potential benefits of different programs are substantial: Improve mood in dementia, reduce lack of mobility, decrease social isolation and integrate the outcomes with more general medical support, helping avoid complications and early recognition of delirium and other physical problems. Also, the caregiver's self-monitoring, the further understanding of the PwD symptoms, the development of a sense of competence, well-being, and the treatment of mood changes in caregivers are crucial endpoints. Other aspects still to explore are related to adapting the protocols to distant areas or where the pandemics have increased. The integration of support networks with expertise centers is also essential. Lastly, it is also essential to acknowledge the importance of real-world studies, even when limited by resources and strict bias control. Therefore, the existing studies may provide useful information on the effect size of specific interventions, the optimal number of sessions, participants enrolled in staff supervision in different scenarios. The future investigation, supporting the implementation of evidence-based psychosocial interventions, will help optimizing training programs for caregivers in post-pandemic times.

AUTHOR CONTRIBUTIONS

GA: method design, systematic review of literature and results compilation (including creation of figures and tables), writing of the manuscript (abstract, introduction, methods, results, discussion and conclusions), selection and organization of bibliographic references. MD: method design, systematic review of literature and results compilation (including creation of figures and tables), writing of the manuscript (abstract, introduction, methods, results, discussion and conclusions), selection and organization of bibliographic references. VR: discussion of the theory and method, critical review and text editing. MC: discussion of the theory, critical review and text editing. AV: discussion of the theory and method, writing of the manuscript, critical review and text editing. CC: discussion of theory, writing of the manuscript and critical review. EB: discussion of the theory and method, writing of the manuscript, critical review and text editing.

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SUPPLEMENTARY MATERIAL

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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.

GLOSSARY

BASE	Behavior Analytics & Support Enhancement
PwD	Patients with dementia
BPSD	Behavior and Psychological Symptoms of Dementia
CG	Control Group
DANCE	Dance Therapy Intervention
DMAS-17	Dementia Mood Assessment Scale
WHELD	Well-being and Health for People with Dementia
BASE	Behavior Analytics & Support Enhancement
BPSD	Behavioral and Psychological Symptoms of Dementia
NPI-NH	Neuropsychiatric Inventory—Nursing Home version
SMQ	Short-Memory Questionnaire
ATC	Anatomical Therapeutic Chemical classification
HASK	Hearing Aid Skills and Knowledge test
SENSE-CogGSKTV	SENSE-Cog Glasses Skills and Knowledge Test for Vision
SENSE-Cog FA	SENSECog Functional Assessment
BGSI	Bangor Goal Setting Inventory
SENSE-Cog CM	SENSE-Cog Communications Manual
DEMQOL	Dementia Quality of Life
BADL	Bristol Activities of Daily Living scale
VALV-VFQ	Veterans Affairs Low Vision-Visual Functioning Questionnaire
VALV-VFQS	Veterans Affairs Low Vision-Visual Functioning Questionnaire Spousal rating
HHIE	Hearing Handicap Inventory for the Elderly
HHIES	Hearing Handicap Inventory for the Elderly Spousal rating
NPI	Neuropsychiatric Inventory
RSS	Relationship Satisfaction Scale
12-GHQ	12-item General Health Questionnaire
12-SFHS	Short Form-12 Health Survey
FCR	Family Caregiving Role scale
HAD	Hospital Anxiety and Depression scale
RUD-L	RUD-Lite instrument; EQ-5D-5L, 5-level EuroQol 5-dimension
NPI-NH	Neuropsychiatric Inventory – Nursing Home version
SCIDS	Sense of Competence in Dementia Care Staff
RMBPC	Revised Memory and Behavior Problems Checklist
CBI	Caregiver Burden Inventory
WCCL-R	Revised Ways of Coping Checklist
MBI	Mindfulness-based Interventions
CSDD	Cornell Scale for Depression in Dementia
RAID	Rating Anxiety in Dementia Scale
QLAD	Quality of Life Alzheimer's Disease scale
MMSE	Mini Mental State Examination
PSS-13	Perceived Stress Scale
MBAS	Meditation Breath Attention Scores
CMAI-SF	14-item Cohen-Mansfield Agitation Inventory Short Form
RUDAS	Rowland Universal Dementia Assessment Scale
PPQ	e Program Participation Questionnaire
SSCQ	Short Sense of Competence Questionnaire
MSPSS	Multidimensional Scale of Perceived Support
SSL12-I	Social Support List 12-Interactions
LS	Loneliness Scale
LSNS-6	Lubben Social Network Scale
ICECAP-O	e Investigating Choice Experiments for the Preferences of Older People Capability Measure for Older People
CarerQol	Care Related Quality of Life scale
CRA	Caregiver Reaction Assessment
DEM-DISC	Dementia Digital Interactive Social Chart
MDS	Minimum Dataset
CANE	Camberwell Assessment of Needs for the Elderly
QoL-AD	13-item Quality of Life – AD
EQ5D+c	Health-Related Quality of Life extended with a cognitive dimension

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USE	Usefulness, ease of use, ease of learning and satisfaction questionnaire
CDR-SOB	Clinical Dementia Rating Scale Sum of Boxes
CERAD-NB	Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery
ADCS-ADL	Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory
VAS	Visual Analog Scale; BDI, 21-item Beck Depression Inventory
SOC	29-item sense of coherence scale
HRQoL	The generic health-related quality of life instrument (15D)
BVC	Brøset Violence Checklist
NPI-Q	Neuropsychiatric Inventory– Questionnaire
GBS-scale	The Gottfries-Bråne-Steen scale
ADL	Katz Index of Independence in Activities of Daily Living
SSCQ	The Short Sense of Competence Questionnaire
PSS	The Perceived Stress Scale
PMS	The Pearlin Mastery Scale
CES-D	Center for Epidemiological Studies Depression Scale
HADS-A	Hospital Anxiety and Depression Scale
CDR	Clinical Dementia Rating Scale
MBP	Memory and behavioral problems
Ilfeld short version	Ilfeld Psychiatric Symptoms Index
NYUCI-AC	New York University Caregiver Intervention-Adult Child
GDS	Geriatric Depression Scale
RMBPC	24-item Revised Memory and Behavior Problems Checklist
START	STrAtegies for RelaTives
CMAI	The Cohen-Mansfield Agitation Inventory
EQ-VAS	Self-rated quality of life
CSDD	Cornell Scale for Depression in Dementia
ACE-R	Addenbrooke's Cognitive Examination-Revised
RUD	Resource Utilisation In Dementia Questionnaire
EQ-5D	EuroQoL 5-dimensions
QALY	Quality-Adjusted Life-Year
FITT-NH	Family Intervention: Telephone Tracking-Nursing Home
ZBI	Zarit Burden Interview
NH Hassles	Nursing Home Hassles Scale
RMBC	Revised Memory and Behavior Checklist
FITT-C	Telephone Tracking –Caregiver
FAD	Family Assessment Device
SEQ	Self-Efficacy Questionnaire
PAC	Positive Aspects of Caregiving
CDR	Clinical Dementia Rating
IADL	Instrumental Activities of Daily Living
APID	Appropriate Psychotropic drugs use In Dementia index
NPI-Q	Neuropsychiatric Inventory Questionnaire
CANE	Camberwell Assessment of Need for the Elderly
UBOS	Utrecht Burnout Scale
ADK	Alzheimer's Disease Knowledge test
SF-36	Short-Form Health Survey
SSES	Self-Efficacy Scale
iCST	individual cognitive stimulation therapy
TAU	Treatment As Usual
ADAS-Cog	Alzheimer's Disease Assessment Scale–Cognitive Subscale
QoL-AD	Quality of Life Alzheimer Disease Scale
BADLS	Bristol Activities of Daily Living Scale
QCPR	Quality of the Carer–Patient Relationship Scale
SF-12	Short Form-12 Health Survey
RS-14	Resilience Scale
HDRS	Hamilton Depression Rating Scale
TMAS	Taylor Manifest Anxiety Scale
DRKQ	Dementia Related Knowledge Questionnaire
BAI	Beck Anxiety Inventory
WFCS	The Work–Family Conflict Scale
RRS	Ruminative Responses Scale

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PSMS	Physical Self-Maintenance Scale
ARTEMIS	ART Encounters: Museum Intervention Study
CODEM	Communication Behavior In People With Dementia
OERS	Observed Emotion Rating Scale
NPI-NH	Neuropsychiatric Inventory – Nursing Home Version
MBSR	Mindfulness-based Stress Reduction
SS	Social Support
FAST	Functional Assessment Staging of Alzheimer's Disease
TICS	Telephone Interview for Cognitive Status
AAQ II	10-item Acceptance and Action Questionnaire II
POMS	Profile of Mood States
MOSSF-36	Medical Outcomes Study Short-Form Health Survey
FCIMS	15-item Mutuality scale of the Family Care Inventory.

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SYSTEMATIC REVIEW
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Neuropsychiatric Symptoms in Elderly With Dementia During COVID-19 Pandemic: Definition, Treatment, and Future Directions

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Background: *Neuropsychiatric* symptoms *(NPS)* of dementia, such as anxiety, depression, agitation, and apathy, are complex, stressful, and costly aspects of care, and are associated to poor health outcomes and caregiver burden. A steep worsening of such symptoms has been reported during Coronavirus Disease 2019 (COVID-19) pandemic. However, their causes, their impact on everyday life, and treatment strategies have not been systematically assessed. Therefore, the aim of this review is to provide a detailed description of behavioral and *psychopathological* alterations in subjects with dementia during COVID-19 pandemic and the associated management challenges.

Methods: A PubMed search was performed focusing on studies reporting alterations in behavior and mood and treatment strategies for elderly patients with dementia, in accordance with *PRISMA* guidelines. The following search strategy was utilized: (COVID* OR coronavirus OR "corona vir*" OR SARS-CoV-2) AND (dementia OR demented OR dement* OR alzheimer* OR "pick's disease" OR "lewy body" OR "mild cognitive" OR mild cognitive impairment OR MCI).

Results: Apathy, anxiety and agitation are the most frequently *NPS* during the COVID-19 pandemic and are mainly triggered by protracted isolation. Most treatment strategies rely on pharmacotherapy; technology is increasingly utilized with mixed results.

Conclusions: *NPS* of dementia during COVID-19 appear to arise from social restrictions occurring as a consequence of the pandemic. Implementation of caregiver support and the presence of skilled nursing home staff are required to restore social interaction and adjust technological support to the patients' needs.

Keywords: dementia, COVID-19, apathy, anxiety, agitation, treatment

INTRODUCTION

In late 2019, a new respiratory syndrome, now known as coronavirus disease 2019 (COVID-19), was reported in Wuhan, China (1). The identified cause was a novel coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since then, infection from SARS-CoV-2 has spread globally, officially becoming a pandemic on March 11, 2020 (2).

The increasing mortality rates from SARS-CoV-2 stressed global healthcare systems, prompting the vast majority of countries to adopt extraordinary measures to limit contagion spread *via* the enforcement of social distancing, quarantining of people exposed to the disease, and confinement of the healthy at home except for essential outings (3).

The majority (75%) of people affected by COVID-19 recover without treatment (4). However, mortality increases with age (5) and the presence of comorbidities (6). Among them, dementia is associated with greater risk of death (7). Increased risk of death in elderly patients with dementia impairment may not be solely due to their vulnerability to SARS-CoV-2 infection (8), but may also relate to the cognitive, behavioral and psychological effects of rapid environmental changes brought by the pandemic. Worsening of cognitive impairment in elderly patients with dementia has been reported during the few months following the beginning of the pandemic (2, 3, 9). Impaired comprehension of the public health situation and difficulty following restrictive measures has also been reported (10). More importantly, several authors have described a steep worsening of a plethora of neuropsychiatric symptoms (NPS), including depression, anxiety, anger, agitation, insomnia (11). These complications may increase levels of distress in caregivers and nursing home staff (12), favor contagion (2), and increase risk of self-injury, hospitalization, and death (13). Managing NPS in elderly patients with dementia is particularly challenging during the COVID-19 pandemic in the context of lacking routine infection screening programs (2), isolation from family members who would otherwise visit and monitor the status of their loved ones (14), and a general deficiency in the widespread implementation of non-pharmacological treatments for dementia (15).

Given this stress on healthcare systems and caregivers, systematic description of the psychopathology arising during COVID-19 pandemic in elderly patients with cognitive disorders and possible treatment strategies, are greatly needed to guide management. Therefore, the aim of this review is to describe the behavioral and psychopathological characteristics of elderly patients with dementia during the COVID-19 pandemic and potential interventions.

METHODS

A PubMed search was performed of all literature published before June 19, 2020 using the following terms: (COVID* OR coronavirus OR "corona vir*" OR SARS-CoV-2) AND (dementia OR demented OR dement* OR alzheimer* OR "pick's disease" OR "lewy body" OR "mild cognitive" OR mild cognitive impairment OR MCI). The search was performed by two researchers (GS and CP) independently. Papers included in this review met the following criteria: (i) written in English; (ii) an original article (no review or meta-analyses were allowed); (iii) focused on subjects with dementia of any etiology (e.g. Alzheimer's Disease (AD), Pick Disease, Lewy body disease); (iv) included geriatric populations; (v) reported original data, case series, or case reports, and (vi) provided information of the characteristics and/or recommendations for the management of *NPS* in subjects meeting the aforementioned criteria during COVID-19 pandemic. Exclusion criteria were: (i) reviews and meta-analyses; (ii) editorials, comments, notes or letters without any data and/or recommendations; (iii) studies with aims inconsistent with the scope of the review (e.g. studies investigating behavioral problems in the elderly without cognitive impairment); (iv) studies focusing on non-elderly populations; (v) studies specifically designed to describe the scope and rationale of a multicenter study (defined as "rationale"); (vi): articles without peer-review or in which peer-review process is still pending (defined as "preprint"); (vii) studies not including human subjects (defined as "*in vitro*").

Inclusion and exclusion of papers were based on consensus discussion among the two researchers performing the aforementioned research and the among all authors; unanimity was required for both and was achieved through Delphi rounds. Two rounds were sufficient to reach complete agreement for paper inclusion or exclusion.

This review follows the *P*referred *R*eporting *I*tems for *S*ystematic reviews and *M*eta-*A*nalyses (*PRISMA*) guidelines (16). A *PRISMA* checklist and flowchart as well as detailed results stemming from database searches are shown in the Online Supplement.

RESULTS

The search produced 99 records on June 19, 2020. Dates of publication of such 99 records spanned from 1960 to 2020. A total of 20 papers were eligible following application of the inclusion/exclusion criteria and consensus determination. Eligible studies spanned from March 2020 to June 2020. Therefore, these dates represent the period of enrollment of this research. Reason of exclusion are shown in **Figure 1**. Results are described below according to the type of NPS and treatment issues/strategies.

Symptoms

Mood

Evidence of mood alterations in subjects with dementia during COVID-19 pandemic is mixed. Development of depressed mood, hopelessness and increased suicidal ideation is anecdotally described (13), mainly due to protracted isolation and loss of familial contact due to confinement in homes or in nursing facilities (2). Accordingly, Canevelli and colleagues (15) reported an increase of depressed mood within the first month of

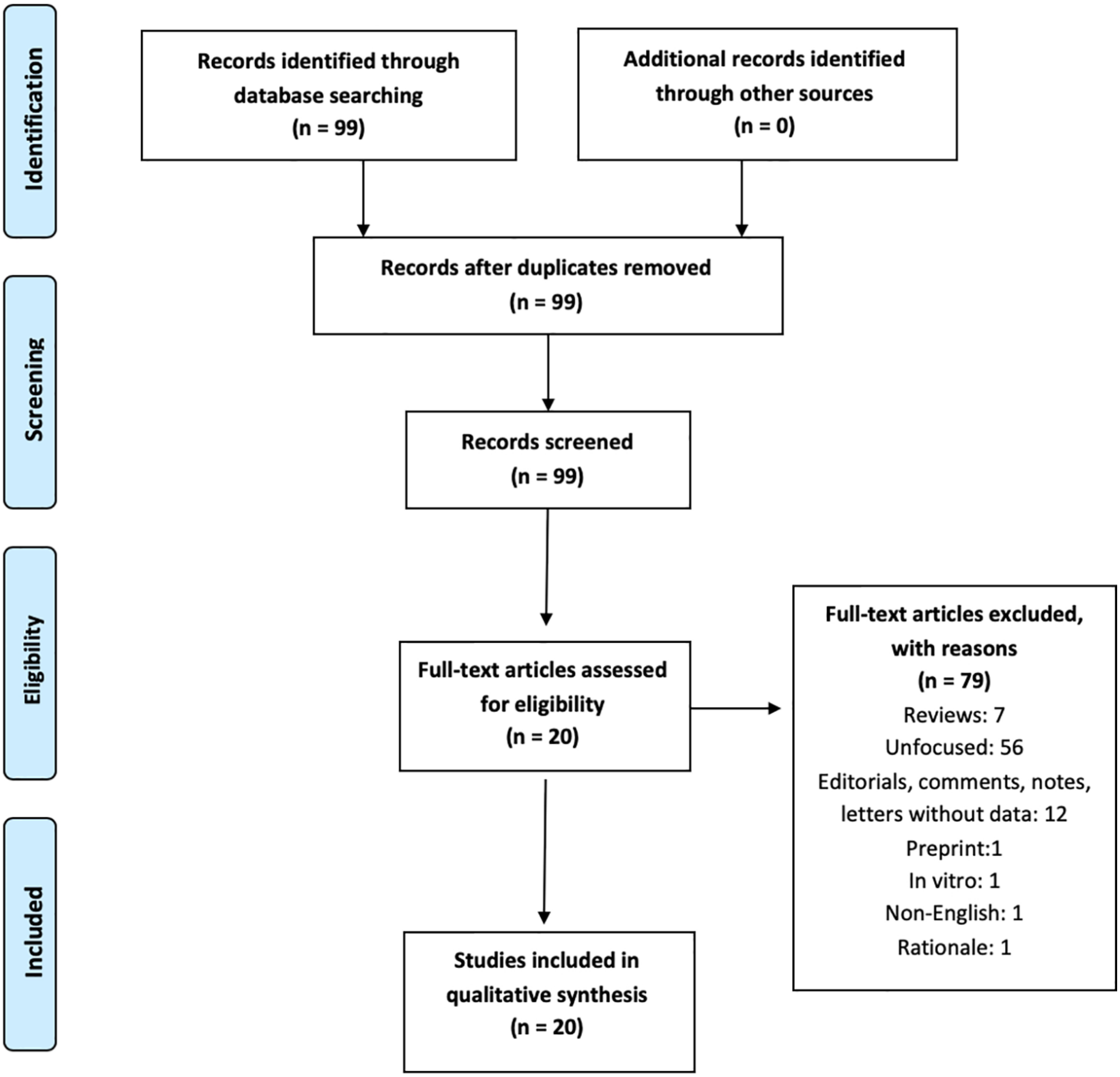

FIGURE 1 | *PRISMA* flowchart of our review's results.

lockdown in an Italian sample of subjects with dementia. On the other hand, in a similar cohort in Spain, no worsening of depression was observed after 5 weeks of home confinement (9). Additionally, increased hopelessness was reported in subjects with AD after interruption of experimental trials on potential disease-modifying drugs. This behavior was induced by the sudden withdrawal of the social support from clinical care staff and their participation in the trial (17). The onset or worsening of elation/euphoric mood was poorly reported, and when it was, the occurrence of it was low (15).

Apathy

Apathy, i.e. a general absence of motivation or interest in activities, appears to be consistently impacted by persistent isolation in subjects with dementia during the COVID-19 pandemic. In a survey of 300 psychologists or healthcare practitioners working in nursing homes, apathy was reported to be the most common behavioral disturbance manifesting from protracted isolation due to COVID-19-related social restriction in subjects with AD (18). Accordingly, Canevelli and colleagues (15) reported that apathy presented in more than 25% of quarantined subjects with dementia within the first month of lockdown in Italy. Apathy also overwhelmingly increased over time, as compared with depressed mood, in subjects with dementia and home confinement (9). Patients with apathy are less likely to initiate behaviors necessary to impede the transmission of the virus, including selfcare and personal hygiene, washing hands, or covering their mouth while coughing (2). Protracted apathy might also lead patients to spend more time in beds, thus increasing the risk of pressure ulcers and hospitalizations (13).

Apathy occurring in the context of altered consciousness was also described as an atypical presentation of the SARS-CoV-2 infection (11). This so-called "apathetic delirium" may supersede classical SARS-CoV-2 infection symptoms and interfere with the early identification of COVID-19 disease (11, 19).

Anxiety

Anxiety and aggression were reported as the main psychopathological manifestations in patients with AD in an Alzheimer's clinic in France during the COVID-19 pandemic (20). During the same period, in a multicenter European study of isolated-at-home subjects with dementia, greater levels of anxiety differentiated those living alone to patients living with at least one family member. This suggests that anxiety is particularly fostered by a reduction in social contact (3). Abrupt withdrawal of social contacts has been also reported to foster anxiety related trauma experiences, which in turn have been found to accelerate cognitive decline and worsen prognosis (2). Anxiety related to isolation also dominated the clinical presentation in a woman affected by early-dementia (21).

Motor Activity

Agitation is another typical behavioral alteration described in confined subjects with dementia (15) during the COVID-19 pandemic. Motor agitation also steeply worsened over time in subjects with AD (9) and high levels of motor agitation and fear were reported in a Dutch survey of patients living in nursing facilities during the pandemic (18). High levels of agitation need to require greater dosages of medication to maintain behavioral control (22). Greater motor activity was also associated with intrusiveness or wandering, which may undermine efforts to maintain isolation, thus increasing the risk of contagion (2). Motor retardation is not reported, at least as an isolated symptom, possibly due to its characterization as a manifestation of apathy or depression (23).

Appetite

Loss of appetite is frequently reported in relation to isolation. In particular, this symptom appears to coincide with social restrictions during COVID-19 pandemic, especially in nursing homes. In these environments, such behavior may persist even when family members were asked to prepare the patient's favorite meal (13). The interruption of activities facilitating feeding and social life (e.g., sharing meal-time in nursing facilities or assistance with eating) induced by the pandemic has been proposed as a factor influencing loss of appetite and malnutrition, especially in the COVID-19 era (13). Loss of appetite and malnutrition may also increase risk of hospitalization.

Circadian Rhythms

Sleep alterations often accompany agitation in isolated subjects with dementia (22). Reduced quality of sleep is reported in subjects living alone compared to subjects not living alone during COVID-19 confinement (3). Importantly, sleep alterations may be particularly dangerous due to their potential to increase the risk of delirium, and accordingly, the risk of mortality (2).

Psychotic Symptoms

Data on psychotic symptoms without alteration of consciousness are infrequently reported during the COVID-19 pandemic. Lara and colleagues (9) reported no changes in hallucination/delusion severity in elderly with dementia after 5 weeks of social isolation. On the other hand, paranoia was associated with rapid changes in social context (i.e. from in-person contacts to video calls) during the quarantine (18).

Treatment Challenges

Pharmacological and Non-Pharmacological Strategies

Some authors provide recommendations aiming to reduce behavioral dyscontrol in subjects with dementia in accordance with recommendations from dementia association guidelines, accounting for limitations caused the pandemic (24). Such guidelines stress implementation of technology to improve mood; maintain daily activities at home (e.g., gardening, cooking, reading, listening to music, physical exercise) to treat apathy; and foster the development of simplified and sequential routines to treat anxiety. However, the shrinkage of support commonly provided by caregivers, nursing home staff, and environmental resources heavily limits the efficacy of these non-pharmacological strategies.

On the other hand, a surge in the dosage of medications commonly needed to treat NPS, such as antipsychotics and mood stabilizers, has been reported (15, 25). For instance, a double dose of loxapine was needed to control behavior of an elderly patient with dementia and severe agitation (26). However, increases in pharmacological treatment strategies during COVID-19 pandemic carries several risks. First, several authors report an inability to increase or change drug dosages due to the disruption of routine assessments, including in-person clinical visits, blood work, or electrocardiograms, or the inability to follow up on adverse events in a timely manner (2).

Moreover, the increased utilization of antipsychotics (specifically without monitoring) may double the risk of death and triple the risk of stroke (27, 28). In order to avoid increasing antipsychotic usage and dosages, physical restraint techniques have been used to control agitation (26). Other specific programs, which included selective, personalized isolation for those who cannot comply with current isolation guidelines, have been described (29, 30). However, behavioral dyscontrol in patients with dementia largely exceeds the resources provided by nursing homes (31), and systematic application of personalized isolation may be difficult to implement.

Use of Electronic Devices

A second theme described in the literature is the management of isolation and prevention of its associated behavioral dyscontrol through the use of technology. In many nursing homes, as well as in personal home settings, the use of electronic devices has been increasingly utilized to maintain patients' social supports and monitor their clinical state by healthcare providers (32). However, the effectiveness of the use of electronic devices in patients with dementia is mixed. Due to the inability of electronic devices to facilitate adequate physical and neurological examinations necessary for diagnosis and follow up, technology platforms may lead to incorrect assessments of cognitive and behavioral statuses in cognitively-impaired elderly (2). Prevalent hearing and vision problems in subjects with dementia may also interfere with interpretation of such assessments (33). Despite some authors advocating for the electronic provision of information on physical exercise, sensory stimulation, reminiscience-based brain health, music therapy, and other creative activities for people with dementia in the home (34), Goodman-Casanova and colleagues (3) found that the implementation of these approaches did not produce behavioral improvements over time. On the other hand, Padala and colleagues (22) reported a case in which depressive symptoms and agitation in a subject with dementia in a nursing home improved after the patient was able to see his family through facetime. In another case report, a woman affected by dementia relieved anxiety by using computer and social media applications (21).

In recognition of the importance of in-person contact and caregiving, the Dutch Alzheimer Association requested permission from the government to allow one visit per patient per day in nursing homes during the early weeks after the lockdown in the Netherlands. While initially denied by the government, visits were subsequently allowed once the number of affected subjects in Netherlands dropped (18).

DISCUSSION

In this review, we described the findings of recent literature on the nature, trajectory, and management strategies of NPS during COVID-19 pandemic in subjects with dementia. Our search indicates that NPS in the COVID-19 era span from inhibition of volition, movement and initiative (i.e., apathy) to severe hyperactivity (i.e., anxiety and agitation) (see **Figure 2**). On the other hand, treatment strategies frequently rely on pharmacological interventions to control behavior. On the other hand, technology is used as a compensatory strategy to counterbalance the drastic lack of non-pharmacological interventions.

Anxiety, agitation and apathy are cardinal behavioral and psychological features of dementia (35). During COVID-19 pandemic, they appear to worsen after protracted isolation due to environmental restrictions. Isolation may foster behavioral disturbances *via* several, partially overlapping mechanisms. Forced separation may interfere with caregiver support, whether the subject lives in his/her house or in nursing homes (24), and leads to poor health monitoring. Loss of interpersonal monitoring may increase the risk of dehydration, infections, and the decompensation of chronic diseases, such as diabetes or hypertension (36). As patients with dementia may show impairments in the interpretation and outward expression of stimuli in their internal *milieu* (37), symptoms related to possible medical conditions, such as pain, may be expressed *via* aberrant arousal and motor responses, i.e., anxiety and agitation (38, 39). Apathy is also known to be exacerbated by acute medical conditions. Worsening of physical status causes rapid acceleration of impairments in cognitive functions. Such decline has been shown to be paralleled with an increase of apathy (40), possibly through progressive prefrontal based circuitry dysfunction (41–43). However, emotional distress might trigger anxiety, agitation or apathy (44, 45). Similarly, sadness and hopelessness have been reported in isolated elderly with dementia (13). Therefore, a more direct, psychological effect of isolation on behavioral and psychological alterations in dementia cannot be excluded.

The available evidence suggests that the management of NPS during COVID-19 should ideally rely on non-pharmacological interventions (46). Non-pharmacological strategies consist of: a)

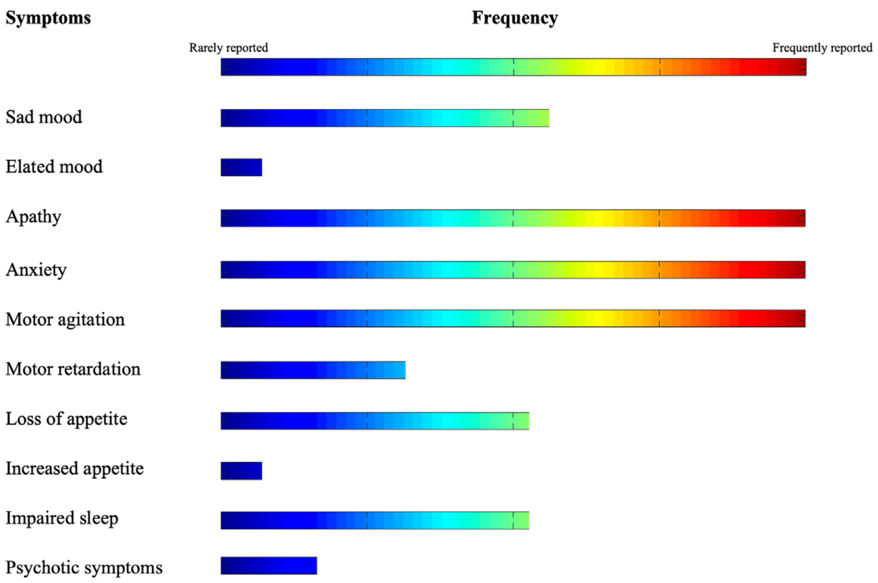

FIGURE 2 | Frequency of *NPS* in elderly with dementia during COVID-19 pandemic.

patient-targeted interventions, including several techniques aimed at reducing stress (47–50); b) caregiver-targeted interventions, which primarily consist of support programs and training to enhance problem solving (51, 52); c) environment-targeted interventions, which include plans aimed to reduce potentially destabilizing aspects of patients' surroundings, such as environmental over- or under-stimulation, safety risks, or a lack of routine (53–55). Unfortunately, environmental changes induced by the COVID-19 pandemic undermines the foundation of all these interventions. Limitation in gatherings impedes activities aimed to enhance social life, autonomy, and cognitive abilities. Furthermore, social contact restrictions minimize caregiving support from patients' relatives or nursing home staff (56). In fact, strict behavioral rules brought by the COVID-19 pandemic (respect for hygiene, the use of masks and the maintenance of social distancing) increase the caregiver's daily workload, with consequential barriers to providing routine support (57). Caregiving, either by family members or nursing home staff, is even more difficult in the context of infection risk. In fact, the social contact required to perform the act of caregiving may n heighten the caregiver's fear of getting sick, being unable to assist family members, and/or of potentially infecting them. Together, these stressors increase the risk of caregiver distress and anxiety (58). Issues in managing the elderly with dementia are present also in nursing home and they are compounded by the inability to quickly provide infrastructure, technology and the skilled staff required to tend to patients' needs during isolation (56). These barriers to the implementation of non-pharmachological strategies may result in the use of pharmacological treatments. However, pharmacotherapy may not be effective for anxiety or sad mood in patients with dementia (59). Pharmacotherapies are also associated with several side effects, such as drowsiness, extrapyramidal symptoms, orthostatic hypotension, (60–63), and higher risk of death (64–66).

The application of technology may be the most realistic solution to address the need for non-pharmacological supporting the cognitively impaired elderly. However, despite some enthusiastic reports (67), findings are generally mixed. One limitation of technological applications is the inability to train caregivers on the use of computer-based support strategies (68) due to lockdown-related restrictions or a lack of skilled staff in nursing homes. Caregivers are required to address the needs of the user and the user's acceptance of technology (14). Acceptability, i.e., the degree of primary users' predisposition to carry out daily activities using the intended device (69), is based on a complex interaction between the subjects' confidence with the technology, the caregiver beliefs, and the time spent in training (70, 71). Without caregiver support or training, patients may not view the device as useful, or the patient may feel stigmatized (72). These issues may have influenced the results of the studies reporting the use of technology to address behavioral dyscontrol during the pandemic (see **Figure 3**).

Therefore, specialized programs and support are needed to address the escalation of behavioral dyscontrol observed in elderly with dementia during the pandemic. Implementation of environmental and caregiver supports are required to facilitate the use of technology. Additionally, services promoting social interaction should be restored as soon as possible.

LIMITATIONS

The urgency to provide a comprehensive review of NPS occurrence and management during the Covid-19 pandemic, in combination with the scarcity of high-quality of studies, led us to include case reports, case series, recommendations or anecdotal reports. Therefore, conclusions drawn from this review should be interpreted with caution. Specifically, factors proposed to cause a surge/worsening of NPS, i.e. blunting of social activities and insufficient caregiving brought by isolation, should be considered as highly speculative. The rapid spread of COVID-19 and the consequential lack of long-term follow-up studies impede a clear disentanglement of the effects of isolation from other possible, co-occurring influences. As stated above, NPS, and specifically apathy, might represent the most relevant symptom of acute COVID-19 infection (11). Additionally, SARS-CoV-2 infection has been proposed to directly induce neurodegeneration, even though specific studies investigating such mechanisms in the elderly, and specifically in those with a well-defined diagnosis of dementia, are absent (73). Therefore, NPS might surge/worsen due to a direct effect of SARS-CoV-2, rather than being an indirect consequence of COVID-19 pandemic-related isolation. Accordingly, the aforementioned issues prompt us to underline the preliminary nature of the treatment paradigms proposed by this review. The effectiveness of antidepressants, methylphenidate, memantine, low dosages of atypical antipsychotic, as well as non-pharmacological interventions in treating NPS has been extensively investigated in subjects with dementia in the pre COVID-19 pandemic era (74–76), whereas evidence supporting recommended strategies during COVID-19 pandemic are still based on limited data. Additional studies with larger sample sizes, longer follow-up durations, or placebo-controlled designs are needed to clearly define the impact of COVID-19 disease on NPS, the cause of the surge in NPS, and appropriate treatment strategies during this time period. Furthermore, the selected studies were unable to provide comparisons of symptoms among different forms of dementia, such as AD or frontotemporal dementia, or different environments, i.e., between subjects living in their house or in nursing homes. Therefore, discussions are limited to subjects with dementia (considered as a whole), and we cannot provide recommendations for specific sub-populations. Finally, the conclusions drawn in this review are biased by the unclear assessments and definitions of social isolation in the selected studies. Social isolation and social functioning should ideally be assessed by combinations of objective and subjective self-report measurements (77). The development of standardized methodologies of assessing social isolation would provide much needed clarity to the study of the behavioral sequelae of pandemic-related social restrictions.

CONCLUSIONS

The COVID-19 pandemic has disrupted everyday life. This interruption of routine activities is particularly dangerous in the cognitively impaired elderly due to their sensitivity to

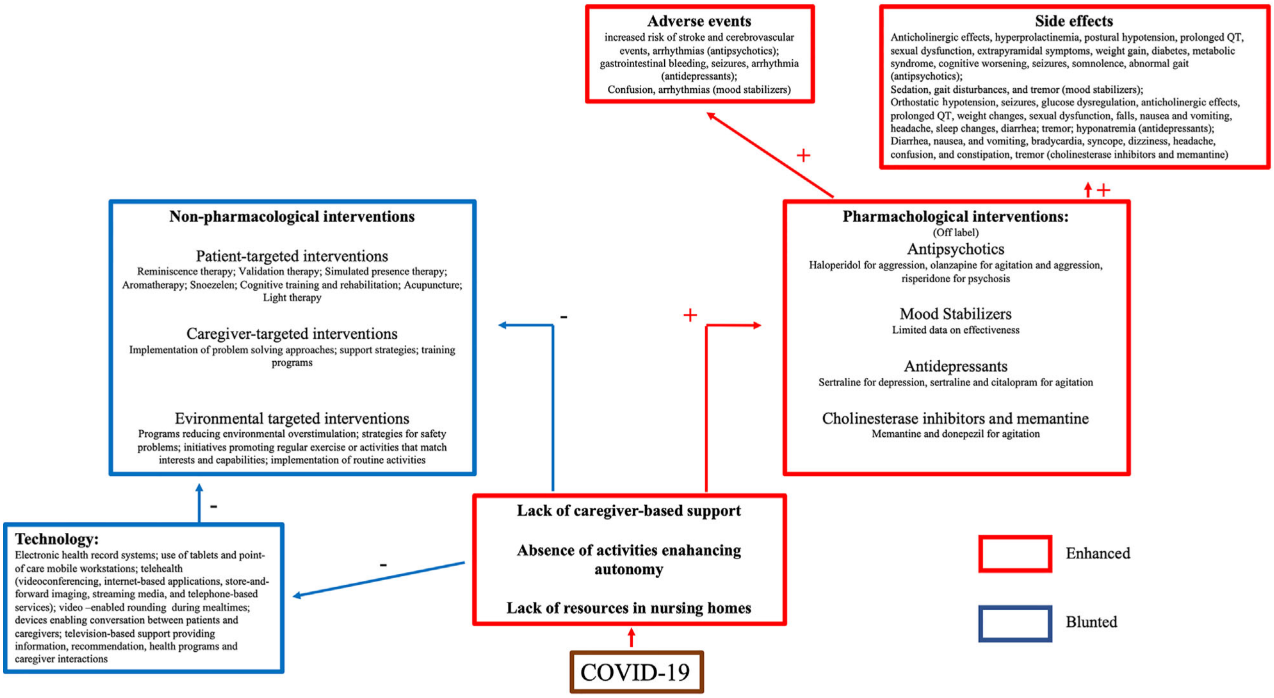

FIGURE 3 | Schematic representation of treatment challenges in patients with dementia during COVID-19 pandemic.

environmental changes. Disruption of routine may lead to the onset/worsening of *NPS* that increase the risk of self-injury, personal distress, COVID-19 contagion, and death. The use of technology may represent a valid alternative to in-person social contact and facilitate non-pharmacological interventions. However, the use of technology is limited by the requirement for a caregiver to customize the technology to the patient's needs.

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.

AUTHOR CONTRIBUTIONS

GS and AS designed the review, all authors were involved in selection of eligible material and in Delphi rounds to reach consensus. AS and CP wrote the *Introduction*, *Methods*, and *Results*, designed the search strategy, gathered eligible material, and supervised the writing of the paper along with RL, LM, FL, and RB. DJ and MCC wrote the *Discussion*. MJ and LM wrote the *Limitations* and *Conclusions*. All authors contributed to the article and approved the submitted version.

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This work is dedicated to the memory of Elvira D'Amico, died on June 16, 2020, after 3 months of isolation in a nursing home.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.579842/full#supplementary-material

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Adverse Events in Italian Nursing Homes During the COVID-19 Epidemic: A National Survey

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Older people living in nursing homes (NHs) are particularly vulnerable in the ongoing COVID-19 pandemic, due to the high prevalence of chronic diseases and disabilities (e.g., dementia). The phenomenon of adverse events (AEs), intended as any harm or injury resulting from medical care or to the failure to provide care, has not yet been investigated in NHs during the pandemic. We performed a national survey on 3,292 NHs, either public or providing services both privately and within the national health system, out of the 3,417 NHs covering the whole Italian territory. An online questionnaire was addressed to the directors of each facility between March 24 and April 27, 2020. The list of NHs was provided by the Dementia Observatory, an online map of Italian services for people with dementia, which was one of the objectives of the implementation of the Italian National Dementia Plan. About 26% of residents in the Italian NHs for older people listed within the Dementia Observatory site had dementia. The objective of our study was to report the frequency of AEs that occurred during the months when SARS-CoV-2 spreading rate was at its highest in the Italian NHs and to identify which conditions and attributes were most associated with the occurrence of AEs by means of multivariate regression logistic analysis. Data are referred to 1,356 NHs that participated in the survey. The overall response rate was 41.2% over a time-period of six weeks (from March 24 to May 5). About one third of the facilities (444 out of 1,334) (33.3%) reported at least 1 adverse event, with a total of 2,000 events. Among the included NHs, having a bed capacity higher than the median of 60 beds (OR=1.57, CI95% 1.17–2.09; p=0.002), an observed increased in the use of psychiatric drugs (OR=1.80, CI95% 1.05–3.07; p=0.032), adopting physical restraint measures (OR=1.97, CI95% 1.47–2.64; p<0.001), residents hospitalized due to flu-like symptoms (OR =1.73, CI95% 1.28–2.32; p<0.001), and being located in specific geographic areas (OR=3.59, CI95% 1.81–7.08; OR = 2.90, CI95% 1.45–5.81 and OR = 4.02, CI05% 2.01–8.04 for, respectively, North-West, North-East

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and Centre vs South, p<0.001) were all factors positively associated to the occurrence of adverse events in the facility. Future recommendations for the management and care of residents in NHs during the COVID-19 pandemic should include specific statements for the most vulnerable populations, such as people with dementia.

Keywords: dementia, adverse events, nursing homes, Long-Term Care Facilities, COVID-19, public health

INTRODUCTION

During the COVID-19 pandemic, NHs in many countries were the among welfare settings most affected by the spread of the SARS-CoV-2 virus (1–4). NHs reported a high number of laboratory-confirmed cases of COVID-19 among residents, along with an increased number of residents deceased or hospitalized due to influenza-like symptoms (5–8). In particular, a national study including 9,395 NHs in the US, reported that 31.4% of the considered facilities had a documented case COVID-19 (9). A national survey involving 1,356 Italian NHs, reported that 29.0% of the facilities had at least one case of COVID-19 (10). At a regional level, in Ontario (Canada), 30.5% of NHs reported outbreaks of COVID-19 (11).

Case fatality rates among NHs residents ranged between 26% and 33.7% (5, 8, 9). In many countries, the number of deaths in NHs accounted for 21% to 50% of all the fatal cases of COVID-19 (12). In Italy, the cumulative incidence of hospitalizations of residents with laboratory-confirmed SARS-CoV-2 infection and with influenza-like symptoms was 1 and 2 per 100 residents, respectively (10).

Older people living in NHs are particularly vulnerable in the ongoing pandemic due to the high prevalence in this population of chronic diseases and disabilities (e.g., dementia). In particular, a systematic review of 74 studies examining the prevalence of psychiatric disorders and psychological symptoms in NHs, reported that a 58% median prevalence of dementia and a 78% prevalence of behavioural disorders among people with dementia (13). Accordingly, stricter guidelines have been defined for such vulnerable populations during the COVID-19 outbreak. Many National Health Authorities had recommended social distancing and limiting the access of visitors in NHs. As a result, older residents lost face-to-face contacts with their family members and caregivers, thus becoming socially isolated (14). These restrictive measures, necessary to avoid or limit the spreading of the infection, also resulted in an increase in behavioural disorders in patients with dementia during the pandemic (15). NHs actively found new means of communication to replace direct contacts, using videocalls and phone-calls. However, this means had a limited impact on residents with dementia, who need physical contact, a massage, and a nearby voice (16).

Hence, it can be assumed that the COVID-19 pandemic had an impact on NHs even beyond the extremely high number of deaths and hospitalizations. The epidemic and the measures adopted to contain its diffusion probably contributed to the occurrence of a wide range of adverse events (AEs) in long term care facilities, and specifically harms or injuries resulting from medical care, including the failure to provide needed care (17). These AEs may be classified in four groups: health care-acquired infections (i.e., catheter-associated urinary tract infection, respiratory infection); events related to residential care (i.e., falls causing injuries, pressure ulcers, confusion/delirium); events related to medication, (i.e., allergic reactions, delirium or other changes in mental status); events related to procedures (17).

The changing contingencies may have triggered negative events involving both residents and health care professionals, with potential important implications in terms of health outcomes, quality of life, and emotional status.

The objective of our study were: (i) to document the frequency of AEs that occurred in Italian NHs during the months in which the virus had its highest spreading rate (from start of February to the start of May); and (ii) to identify the determinants and attributes associated with the occurrence of AEs during the pandemic.

MATERIALS AND METHODS

This national survey involved 3,292 nursing homes, either public or providing services both privately and within the national health system, out of the 3,417 NHs covering the whole Italian territory. We included all the NHs for which we had an available reference contact. The list of NHs was provided by the Dementia Observatory, an online map of Italian services for people with dementia, which was one of the objectives of the implementation of the Italian National Dementia Plan (18, 19). In Italy, the majority of the NHs is located in the northern part of the country, the area that had the highest number of COVID-19 cases when the survey was carried out. In a previous study, we assessed prevalently the phenomenon of mortality and hospitalization during the COVID-19 pandemic in Italian NHs (10).

Data Source

An online questionnaire with a cover letter was addressed to the directors of each NH between March 24 and April 27, 2020. NHs were subsequently also contacted by telephone to provide assistance in completing the questionnaire (about 3300 phone calls were made or received) Some of the NHs were further contacted to solve incongruences in some of the provided data. The 29 items of the online questionnaire were designed to gather information on: (1) the characteristics of the facility, including number of beds, type of structure (public or providing services both privately and within the NHS), number and type of healthcare and social workers (HCSW), residents living in the facilities; (2) the spreading of the infection, including the number of residents who died or were hospitalized due any cause occurred since February 1st, and those who were SARS-CoV-2 positive or had influenza-like symptoms, the number of hospitalizations within the considered time period, and the number of residents and staff members who had a SARS-CoV-2 positive test or influenza-like symptoms when the questionnaire was completed and the presence of positive cases among staff members; (3) the infection prevention and control (IPC) program components and practices for managing patients with suspected or confirmed COVID-19, including presence in the NH of written guidelines, availability of ad-hoc consultation, training for personnel, actions to raise awareness among residents (education of residents), ability to isolate patients, restriction of access for external visitors, and alternative means adopted to guarantee communication between residents and their relatives and caregivers (phone calls, video-calls), monitoring of possible early symptoms (temperature control twice daily), supply of alcohol-based hand sanitizers, and vaccination coverage for influenza. Moreover, the questionnaire included a question on potential difficulties faced during the pandemic; (4) issues potentially related to the epidemic, including use of physical restraint measures, increase in the use of psychoactive drugs (i.e., "Have you noticed an increase in the prescription of psychotropic medications -benzodiazepines, antidepressant or antipsychotic agents, since February 1?"), and AEs occurred since February 1st. (The full questionnaire is available in the **Supplementary Materials**). No information on individual residents and staff members were collected. On February 27, 2020, the Italian Presidency of the Council of Ministers authorized the collection and scientific dissemination of data concerning the COVID-19 epidemics by the INIH and other public health institutions.

Definition of Adverse Events (AEs) and Physical Restraint

AEs were intended as any harm or injury resulting from medical care or to the failure to provide care. The directors of the surveyed NHs could report all the negative events occurring in their facilities involving residents and/or healthcare professionals. For instance, AEs could consist in falls, injuries, emotional suffering and behavioral disorders, delirium, adverse drug events, dehydration, bowel obstruction (17). Physical restraint was defined as "any action or procedure that prevents a person's free body movement to a position of choice and/or normal access to his/her body by the use of any method, attached or adjacent to a person's body that he/she cannot control or remove easily" (20).

Statistical Analysis

We reported a description of the characteristics of the included NHs and of some aspects of their infection control and prevention (ICP) programs. We focused on data from the point 4 of the list reported above.

Descriptive statistics were performed on overall data and by region. Frequencies were used to describe discrete or dichotomous variables; mean and standard deviation (SD) were used for continuous variable, median, and range of values in case of asymmetric distribution. Missing data for the number residents were imputed using the number of beds. No other missing data were imputed. Univariate and multivariate regression logistic models were performed to assess whether some factors were associated to the occurrence of adverse events during the considered time period. We considered as study variables some characteristics of the included NHs (beds capacity, beds to staff ratio, geographical distribution), the difficulties faced during the pandemic, all information gathered on ICP, the spreading of COVID-19 in the NHs. The spreading of COVID-19 was assessed using the number of laboratory-confirmed cases among deceased and hospitalized residents, and among residents and/or staff members within the facility. The occurrence of death and hospitalization among residents with influenza-like symptoms was also investigated, to account for a possible underestimation of COVID-19 cases due to the potential lack of availability of swab tests in such a critical time, as, for example, the first period of the pandemic. All variables resulting as significant at 5% level in the univariate analysis were included in the multivariate model. Moreover, a sensitivity analysis was performed using the negative binomial regression model to assess the association between the number of events and the same considered factors. The exposure variable, i.e., the number of residents per facility, was included in the model.

All data analyses were performed using STATA software, version 14.2 (Stata Corp, College Station, Texas, USA).

RESULTS

This survey was addressed to both public structures and structures providing services both privately and within the NHS. However, 92 private NHs were also listed among the participating facilities and were included in the analyses.

Data are referred to 1,356 NHs that participated in the survey. The overall response rate was 41.2% over a time-period of 6 weeks (from March 24 to May 5). A negative association was observed between the response rate and the attack rate per region from the national surveillance system (20), even if not reaching statistical significance (Spearman's rho= -0.21, p=0.344) (10). Two of the 21 regions (Valle D'Aosta and Basilicata) did not participate in the survey. At March, 24, the day the survey started, the regions where the spreading rate of COVID-19 was higher were Lombardy (303.6 per 100,000), Emilia Romagna (190.3), PA Trento (185.2 per 100,000) and Marche (175.7), while Basilicata was the region with the lowest attack rate (2.8 per 100,000 habitants) (21).

Data Description and Spreading of the Infection in NHs

Overall, 100,806 persons were resident in the NHs participating to the survey (**Table 1**), with 77.2% of them located in the North of Italy. Overall, a mean of 74.7 beds (SD 57.6) per facility was reported, with a range between 8 and 667 beds and a median of

TABLE 1 | Distribution and description of facilities (number of NHs, residents, NHs with number of beds above the median, number of staff members, average number of beds per unit of staff (physicians, nurses, and health care social workers), by Region, and overall.

Italian Regions	NHsn (%)[a]	Residents[b]	NHs with beds above median[c], N (%)	number of staff per facility[d] median [range interquartile]	n. beds to staff ratio, mean ± sd
Piedmont	249 (41.0)	17186	130 (52.2)	26.5 [19–42.5]	2.3 ± 0.7
Lombardy	292 (43.1)	27657	222 (76.0)	42 [28–67]	2.2 ± 1.5
AP Bolzano	4 (10.8)	425	3 (100)	50 [26.5–127]	1.5 ± 0.5
AP Trento	15 (29.4)	1201	15 (100)	50 [46–68]	1.4 ± 0.2
Veneto	148 (28.5)	17902	122 (82.4)	57 [36–83]	1.9 ± 1.4
Friuli V.G.	39 (55.7)	3636	27 (69.2)	35.5 [25–53]	2.1 ± 0.7
Liguria	20 (17.2)	1573	11 (55.0)	25.5 [15–44]	2.4 ± 0.8
Emilia Romagna	128 (46.0)	8200	63 (49.2)	31 [24–45]	1.8 ± 0.7
Tuscany	200 (62.7)	9607	56 (28.0)	26 [17–36]	1.8 ± 1.2
Umbria	16 (38.1)	730	4 (25.0)	26 [13.5–38]	1.6 ± 0.2
Marche	36 (90.8)	1384	7 (19.4)	25 [18–29]	1.4 ± 0.4
Latium	79 (41.1)	4597	38 (48.1)	27.5 [17.5–42.5]	2.1 ± 0.7
Abruzzo	8 (49.0)	447	3 (37.5)	25 [19.5–35.5]	1.9 ± 0.7
Molise	4 (66.7)	233	2 (50.0)	26.5 [21–29]	2.6 ± 0.8
Campania	16 (13.2)	642	4 (25.0)	21.5 [17–27]	2.0 ± 0.5
Apulia	35 (57.4)	2088	18 (51.4)	26 [18–40]	2.0 ± 0.6
Calabria	36 (45.0)	1557	13 (37.1)	25.5 [16–39.5]	1.6 ± 0.4
Sicily	24 (61.5)	1132	7 (29.2)	25 [16.5–38]	1.5 ± 0.4
Sardinia	7 (43.8)	609	6 (85.7)	58 [37–67]	1.5 ± 0.3
North-West	561 (40.0)	46416	363 (64.7)	33 [22–54]	2.2 ± 1.2
North-East	334 (34.9)	31364	230 (69.1)	41.5 [28–68]	1.8 ± 1.1
Centre	331 (55.8)	16318	105 (31.7)	26 [17–36]	1.8 ± 1.0
South and Islands	130 (36.8)	6708	53 (41.1)	25 [18–39]	1.8 ± 0.6
Overall	**1356 (41.2)**	**100806**	**751(55.5)**	**32 [21–51]**	**1.8 ± 1.1**

AP, Autonomous Province.

[a] percentage on the total of NHs in the whole territory.

[b] Residents = people preset at 1st February and new recovered since the 1st March.

[c] median: 60 beds per facility.

[d] staff includes physicians, nurses and health care social workers.

North-West: Piedmont, Veneto, Liguria, Lombardy.

North-East: PA Bolzano, PA Trento, Veneto, Friuli Venezia Giulia, Emilia Romagna.

Centre: Tuscany, Umbria, Marche, Latium.

South and Islands: Abruzzo, Molise, Campania, Apulia, Basilicata, Calabria, Sicily, Sardinia.

60 beds per facility. A huge variability was observed between Regions (**Table 1**). Considering the health care personnel operating in each facility, a median of 2 physicians, 7 nurses, and 24 health care social workers (HSCW) was reported per facility, with 11% of the NHs reporting that they had no physician within the facility. Overall, considering all the three professional figures, the staff included a median of 32 units (median value), corresponding to a mean of 1.8 beds (SD 1.1) per unit of staff.

Along with physicians, nurses, and HCSWs, the staff included also other healthcare professionals such as physiotherapists, psychologists, educators/animators, social workers, who were present respectively in 98.7%, 68.5%, 95.6%, and 45.3% of the NHs, reaching a median of 4 additional professionals (data not shown). Adverse events (AEs) were defined as any unfavorable event (e.g., accidents, confrontations, falls, aggressions) involving staff members, residents, or both staff members and residents. Information on the occurrence of AEs was based on the answers provided to the question if any AE occurred from February 1 to the date questionnaire was completed, and on the actual number of reported AEs, since some discrepancies were observed between the answers to these two questions. After checking for consistency, 14 NHs that answered "Yes" to the first question were recoded as "No" because they reported a number of 0 adverse events for all the types of AEs (involving residents, personnel, or both), while 6 NHs that answered "No" were recoded as "Yes" since they reported the number of events. Overall, one third of the facilities (444 out of 1,334) (33.3%) reported AEs, with a total of 2,000 events (**Table 2**). Most of the events involved only residents (92.1% of all events). An average of 2.1 events per 100 residents were reported, with a geographical trend showing higher values in the North-West area compared to the South and Islands (**Table 2**).

The physical restraint measures applied in the NHs during the period of investigation are reported in **Table 3**.

In this survey, each resident may have received more than one measure of physical restraint. Up to 92.0% (1,221 over 1,327 NHs) of the facilities reported that they had a register and monitored all applied physical restraint measures. A total of 62.1% of the included NHs adopted physical restraints measures (773 out of 1,245). An average of 19 measures per 100 residents was reported, with a total number of 16,802 measures. A huge variability was observed across Regions (**Table 3**).

Overall, 29.0% of the NHs (387 out of 1,326) reported laboratory confirmed cases of COVID-19 among the deceased and/or hospitalized residents or among the staff members and residents living in the NHs when the questionnaire was completed. When considering also influenza like-symptoms the

TABLE 2 | Adverse events occurred between February 1st and the date the questionnaire was completed (between March 24 and May 5).

Italian Regions	NHs with adverse events, N (%)	Number of events	Events among personnel, N (%)	Events among residents, N (%)	Events involving staff and residents, N (%)	Cumulative incidence per 100 residents
Piedmont	76 (31.4)	428	9 (2.1)	404 (94.4)	15 (3.5)	2.6
Lombardy	117 (40.5)	621	11 (1.8)	590 (95.0)	20 (3.2)	2.3
AP Bolzano	0 (0.0)	0	0 (0.0)	0 (0.0)	0 (0.0)	0.0
AP Trento	11 (73.3)	85	0 (0.0)	82 (96.5)	3 (3.5)	8.9
Veneto	48 (33.1)	333	2 (0.6)	291 (87.4)	40 (12.0)	2.0
Friuli V.G.	14 (35.9)	54	0 (0.0)	47 (87.0)	7 (13.0)	1.6
Liguria	8 (40.0)	18	0 (0.0)	17 (94.4)	1 (5.6)	1.3
Emilia Romagna	41 (32.8)	122	4 (3.3)	111 (91.0)	7 (5.7)	1.6
Tuscany	68 (34.5)	176	8 (4.5)	151 (85.8)	117 (9.7)	1.9
Umbria	5 (31.3)	10	0 (0.0)	9 (90.0)	1 (10.0)	1.4
Marche	11 (30.6)	17	0 (0.0)	17 (100)	0 (0.0)	1.4
Latium	28 (36.3)	90	3 (3.3)	80 (88.9)	7 (7.8)	2.0
Abruzzo	1 (12.5)	1	0 (0.0)	1 (100)	0 (0.0)	0.2
Molise	0 (0.0)	0	0 (0.0)	0 (0.0)	0 (0.0)	0.0
Campania	0 (0.0)	0	0 (0.0)	0 (0.0)	0 (0.0)	0.0
Apulia	5 (14.3)	15	0 (0.0)	15 (100)	0 (0.0)	0.7
Calabria	4 (11.1)	11	0 (0.0)	11 (100)	0 (0.0)	0.7
Sicily	5 (20.8)	10	2 (20.0)	7 (70.0)	1 (10.0)	0.9
Sardinia	2 (28.6)	9	1 (11.1)	8 (88.9)	0 (0.0)	1.5
North-West	201 (36.5)	1067	20 (1.9)	1011 (94.8)	6 (3.4)	2.4
North-East	114 (34.8)	594	6 (1.0)	531 (89.4)	57 (9.6)	2.0
Centre	112 (34.6)	293	11 (3.8)	257 (87.7)	25 (8.5)	1.9
South and Islands	17 (13.2)	46	3 (6.5)	42 (91.3)	1 (2.2)	0.7
Overall	**444 (33.3)**	**2000**	**40 (2.0)**	**1841 (92.1)**	**119 (6.0)**	**2.1**

North-West: Piedmont, Veneto, Liguria, Lombardy.
North-East: PA Bolzano, PA Trento, Veneto, Friuli Venezia Giulia, Emilia Romagna.
Centre: Tuscany, Umbria, Marche, Latium.
South and Islands: Abruzzo, Molise, Campania, Apulia, Basilicata, Calabria, Sicily, Sardinia.

TABLE 3 | Physical restraint measures by Region between February 1st and the date the questionnaire was completed (between March 24 and May 5).

Italian Regions	NHs adopting physical restraints, N (%)	Physical restraints, N	Median number [range interquartile]	Number of restraints per 100 residents
Piedmont	147 (64.2)	2260	2 [0–10]	15.3
Lombardy	190 (73.4)	4854	3 [0–21]	20.1
PA Bolzano	1 (25.0)	2	0 [0–1]	0.2
PA Trento	12 (80.0)	321	4 [2–37]	33.4
Veneto	84 (64.1)	3596	2 [0–30]	23.9
Friuli Venezia Giulia	19 (54.3)	342	1 [0–10]	12.0
Liguria	15 (78.9)	361	7 [1–27]	29.9
Emilia Romagna	80 (66.7)	1591	2 [0–15]	21.2
Tuscany	122 (65.6)	2056	3 [0–20]	25.1
Umbria	10 (66.7)	105	2 [0–9]	15.8
Marche	28 (84.8)	322	4 [1–17]	30.8
Latium	21 (27.3)	440	0 [0–1]	11.0
Abruzzo	2 (25.0)	30	0 [0–5]	7.7
Molise	2 (50.0)	6	1 [0–3]	2.4
Campania	3 (20.0)	40	0 [0–0]	8.4
Apulia	19 (59.4)	219	1.5 [0–6.5]	14.5
Calabria	5 (14.7)	17	0 [0–0]	1.2
Sicily	6 (28.6)	101	0 [0–1]	12.1
Sardinia	7 (100)	139	6 [2–26]	15.9
North-West	352 (69.4)	7475	3 [0–17]	18.3
North-East	196 (64.3)	5852	2 [0–20]	21.6
Centre	181 (58.2)	2923	2 [0–15]	21.8
South and Islands	44 (36.4)	552	0 [0–2]	8.8
Overall	**773(62.1)**	**16,802**	**2[0–15]**	**19.1**

pandemic involved 909 out of the 1343 included NHs (67.7%) (10), with an overall cumulative incidence death rate of 9.1 per 100 residents (10). The rate of residents who died with laboratory confirmed COVID-19 was 0.7 per 100 residents, while the rate of residents who died with influenza-like symptoms was 3.1 per 100 residents (10).

Only 5.7% of the considered NHs reported an increase in the use of psychoactive drugs, mainly antipsychotics and benzodiazepine.

Description of Data on IPC Programs Applied in the NHs

When considering aspects of IPC procedures, written guidelines for the appropriate management of residents with COVID-19 were available in 92.9% of the NHs, but 59.4% of the facilities did not receive any ad-hoc consultation for neither the management of patients nor for IPC. No specific training for COVID-19 was provided to staff members in 35.1% of the NHs, while 93.3% of the NHs provided some training on the appropriate use of personal protective equipment (PPE). Moreover, 91.5% of the NHs provided information and raised awareness on COVID-19 among residents.

All the NHs, except for one, suspended all visits from relatives/caregivers to the residents (in agreement with the legislation issued on March 8, 2020), with almost all of them (99.5%) providing alternative means for communication. The most frequently adopted alternative were videocalls (89.6%).

As for the main difficulties faced during the pandemic, 77.2% of the 1259 NHs that answered this question reported a lack of PPE, 52.1% were not able to obtain laboratory tests (data available starting April, 9, thus referring to 541 NHs), 33.8% reported lack of personnel, 26.2% had difficulties in isolating patients with COVID-19, and 12.5% had difficulties in transferring patients to hospitals. A total of 20.9% of the NHs reported they received scarce information on the procedures to be carried out to contain the infection, and 9.8% reported a lack of drugs.

Up to 7.7% of the NHs were not able to isolate residents with suspected or confirmed COVID-19. An in-depth analysis showed that facilities with a lower bed capacity had a higher probability of not being able to isolate residents with confirmed or suspected COVID-19. Specifically, 4.5% of the facilities with more than 60 beds (n=747) were not able to isolate residents compared to 11.6% of NHs with less than 60 beds.

Almost all the NHs (99.9%) provided alcohol-based hand sanitizers to their staff members. Most of the included NHs (79.1%) reported to monitor the temperature among residents and staff members twice a day.

A total of 1045 NHs reported data on influenza vaccination, with an overall median coverage of 95%. Only 16.2% of the NHs reported a coverage lower than 75%.

Association With Adverse Events

As AEs were more frequent in North Italy, the area where the highest number of NHs with high bed capacity were located and where the spreading of COVID-19 was higher, these aspects were further explored to assess their potential association with the occurrence of AEs. Moreover, the beds to staff ratio was also investigated, as a potential proxy of the quality of assistance. The association between AEs and spreading of COVID-19 in the facility was also evaluated, considering the presence of cases of COVID-19 reported among residents (deceased, hospitalized or still living in the facility) and staff members. Furthermore, due to the lack of availability of swab tests in some contexts, in particular during the early phases of the pandemic, information about deceased and hospitalized residents with influenza-like symptoms were also considered. Potential associations with use of physical restraints, difficulties during the pandemic, aspects of IPC, use of alternative means of communication with relatives/caregivers (videocalls, phone calls or other means), and increased use of psychoactive drugs were also explored. In particular, the purpose of this last question was to understand whether there had been an increase in the prescriptions of these categories of drugs from February 1.

Univariate and multivariate logistic models were performed in order to investigate the association among these aspects and the likelihood of occurrence of AEs.

The multivariate analysis showed that facilities with beds capacity higher than the median of 60 beds (OR=1.57,CI95% 1.17–2.09; p=0.002), an observed increase in the use of psychoactive drugs (OR=1.80, CI95% 1.05–3.07; p=0.032), the adoption of physical restraint measures (OR=1.97, CI95% 1.47–2.64;p<0.001), the occurrence hospitalizations of residents with flu-like symptoms (1.73, CI95% 1.28–2.32; p<0.001) and the geographic area (OR=3.59, CI95% 1.81–7.08 for North-West, OR = 2.90, CI95% 1.45–5.81 for North-East and OR = 4.02, CI 95% 2.01–8.04 for Centre vs South, p<0.001) were all positively associated with the occurrence of AEs in the facility. Lack of personnel, difficulties in isolating patients, spreading of COVID-19 within the facility, and presence of residents deceased with influenza-like symptoms, all lost statistical significance in the multivariate models (**Table 4**). The sensitivity analysis conducted on the number of AEs performing the negative binomial model, despite the lack of convergence for some factors, confirmed which factors were associated with AEs and no further factors were identified. All the other variables of ICP not included in **Table 4** resulted non statistically significant in the comparison between NHs and AEs and those not at the univariate analysis.

DISCUSSION

In this study, we observed that one third of the included facilities (33.3%) reported at least one AE, with a total of 2,000 events. Most of the events involved only residents. A geographical trend was observed, with higher values in the North-West area compared to the South and Islands. Overall, 29.0% of the NHs reported at least one laboratory-confirmed case of COVID-19 among residents and staff members. When considering also influenza-like symptoms 67.7% of NHs reported at least one case.

TABLE 4 | Crude and adjusted ORs by univariate and multivariate logistic model, estimating the association with the occurrence of adverse events in nursing home (NHs).

Variables	Crude OR			Adjusted OR[a]		
	OR_{cr}	p-value	95%CI	OR_{adj}[a]	p-value	95%CI
Lack of personnel (Y vs N)	1.38	0.010	1.08–1.77	0.96	0.786	0.71–1.29
Difficulty in isolating (Y vs N)	1.42	0.008	1.09–1.85	1.21	0.227	0.89–1.63
Number of beds (upper vs below the median*)	1.74	<0.001	1.38–2.21	1.57	0.002	1.17–2.09
Increased use of psychoactive drugs (Y vs N)	2.09	0.002	1.31–3.32	1.80	0.032	1.05–3.07
Physical restraints (Y vs N)	2.37	<0.001	1.83–3.08	1.97	<0.001	1.47–2.64
COVID-19 spreading (Y vs N)	1.57	<0.001	1.22–2.01	1.08	0.663	0.77–1.50
Deaths with influenza-like symptoms (Y vs N)	1.66	<0.001	1.32–2.09	1.00	0.990	0.73–1.36
Hospitalization with influenza-like symptoms (Y vs N)	2.10	<0.001	1.66–2.65	1.73	<0.001	1.28–2.32
Geographic Region (vs South)						
North-West	3.78	<0.001	2.21–6.48	3.59	<0.001	1.81–7.08
North-East	3.51	<0.001	2.01–6.14	2.90	0.003	1.45–5.81
Centre	3.45	<0.001	1.97–6.03	4.02	<0.001	2.01–8.04

[a] *Adjusted for all the variables listed in the table.*

**the median of beds per facility was 60 beds.*

The NHs that reported AEs also reported a higher frequency of use of psychoactive drugs and physical restraint when compared to those that did not report any AEs. The strong association between these variables is likely a reflection of a critical context in the daily management of residents. An association between AEs and NHs with a higher number of beds and those with a higher number of residents hospitalized due to flu-like symptoms was also reported. All these variables contributed to define a pattern of the facilities who faced critical situations during the pandemic.

Our study showed that the NHs located in Central Italy and Northern Italy had a higher risk of AEs compared to those in the South-Islands. This trend is not in line with the spread of COVID-19 in Italy, as the most affected regions were those in the Northern area.

This may mean that probably the specific care setting of the NHs, with a large number of residents and part of them requiring an hospitalization, had a higher weight in determining the frequency of conflicts rather than the spreading of COVID-19 in general population.

A study conducted in 2015–2019 on a sample of 330 Italian NHs for older people taken from the Dementia Observatory register, showed that about 26% of residents had dementia (22). A similar frequency was also reported by a systematic review including studies focusing specifically on NHs (13).

Residents with dementia in NHs need a higher level of care than other residents due to a higher number of both non-self-sufficient individuals and people with behavioral disorders. During quarantine, the usual care routine was radically changed and several facilities probably reduced, if not suspended, the set of non-pharmacological treatments. This, along with the suspension of visits from relatives/caregiver, who are often able to calm residents with cognitive impairment, can result in an onset or an increase of behavioral symptoms (23).

The use of technologies such as videocalls or/and calls is likely to be less effective in residents with dementia than in other types of residents (16, 24). However, in our study this variable did not show any association with a lower probability of AEs in NHs.

In our study we did not analyze the different components of adverse events (falls, injuries, emotional suffering and behavioral disorders, delirium, adverse drug events, dehydration, bowel obstruction) and thus were not able to perform any comparison with the pre-pandemic situation.

There are few data published on the frequency of specific AEs in Italian NHs (25–27). However, potentially inappropriate drug prescriptions, an increased risk of falls causing injuries in residents with cognitive impairment, and an high prevalence of behavioral disorders in people with dementia were reported in NHs (13, 25, 28). Overall, it is known that mistakes in medications, falls, delayed or inappropriate interventions, and lacking or inadequate care contribute to AEs. The most commonly identified contributing factors were lack of expertise, lacking or incomplete documentation, failure to work as a team, and inadequate communication (29). These factors may have been more common during the pandemic. Moreover, nurses in NHs can play a relevant role in reporting and reducing adverse events, and a routine monitoring should be considered as a quality and safety indicator (30, 31).

The main strength of our study is reporting the results of a national survey carried out during the most critical phase of the pandemic.

Limitations

Limits are mainly due to a lack of data on persons with dementia and a 41% response rate. In particular, to our knowledge, this is the first study that reports living conditions within a large number of NHs included in the Italian Dementia Observatory in which about 26% of residents had a diagnosis of dementia (22).

In an attempt to characterize the non-response bias in our survey, we observed an inverse correlation between the response rate to the survey across the different regions and the corresponding infection attack rate per region. Moreover, we identified about 53 NHs from news report that did not respond to the survey and had outbreaks of COVID-19 with a consistent number of deaths and a high frequency of people hospitalized due to flu-like symptoms.

We believe that NHs that had problems during the pandemic might have not responded to our survey, and thus the results of this study might probably underestimate AEs and other variables that characterize the level of assistance in a NHs.

We are also aware that the answers provided to our questionnaire may not be accurate (i.e., different understanding of physical restraints, psychotropic medication or AEs by the respondents) nor true, and a validity study was not performed (the administration of a second questionnaire in a sub-sample of NHs). In particular, we could not check whether all respondents to the questionnaire considered all the events included in the definition of adverse events used in literature. We also underlined that for some questions the quantitative data on the pre-COVID-19 period were not available (i.e., the use of psycho-active drugs, adverse events, physical restraint measures). Therefore so, we could not be able to perform any comparisons with the data collected with the survey. Moreover, the wide variability of these data could be explained by a different level of participation in answering to these specific questions.

Future recommendations issued by governmental agencies, scientific societies and public institutions for the management and care of residents in NHs during the COVID-19 pandemic should include specific statements for the most vulnerable populations, such as people with dementia (12, 32–36).

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

On February 27, 2020, the Italian Presidency of the Council of Ministers authorized the collection and scientific dissemination of data concerning the COVID-19 epidemics by the INIH and other public health institutions. Therefore, ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements.

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AUTHOR CONTRIBUTIONS

NV, GO, FD'A, MC, and GL conceived the study. FL and FM worked on statistical aspects of the study. IB, ES, EL, PP, AA, GR, and GB were involved in the organization of the study. The Italian National Institute of Health Nursing Home Study Group performed the study. 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/fpsyt.2020.578465/full#supplementary-material

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Effectively Caring for Individuals With Behavioral and Psychological Symptoms of Dementia During the COVID-19 Pandemic

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The COVID-19 pandemic has significantly affected the elderly and particularly individuals with Alzheimer's disease and related disorders (ADRD). Behavioral and psychological symptoms of dementia (BPSD) are heterogeneous and common in individuals with ADRD and are associated with more severe illness. However, unlike the cognitive symptoms of ADRD that are usually progressive, BPSD may be treatable. Individuals with BPSD are facing unique challenges during the pandemic due to the inherent nature of the illness and the biological and psychosocial impacts of COVID-19. These challenges include a higher risk of severe COVID-19 infection in individuals with BPSD due to their frailty and medical vulnerability, difficulty participating in screening or testing, and adhering to infection control measures such as physical distancing. Further, biological effects of COVID-19 on the brain and its psychosocial impact such as isolation and disruption in mental health care are likely to worsen BPSD. In this paper, we discuss these challenges and strategies to manage the impact of COVID-19 and to effectively care for individuals with BPSD in community, long-term care, or hospital settings during the pandemic. Despite the ongoing uncertainty associated with this pandemic, we can reduce its impact on individuals with BPSD with a proactive approach.

Keywords: Alzheimer's disease and related disorders, behavioral and psychological symptoms of dementia, COVID-19, pandemic, coronavirus, clinical care, clinical research, caregivers

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INTRODUCTION

The COVID-19 pandemic has affected the elderly including those with Alzheimer's disease and related disorders (ADRD), creating numerous challenges to their mental health (1, 2). Behavioral and psychological symptoms of dementia (BPSD) affect the majority of individuals with ADRD (3). BPSD are a group of heterogeneous symptoms that include motor disturbances, disinhibition, hyperactivity, psychosis, euphoria, affective symptoms, apathy, eating disturbances, and night-time behaviors (3, 4). BPSD occur at all stages of cognitive disorders including pre-clinical, mild cognitive impairment, or dementia (5). Furthermore, specific cognitive disorders may present with different BPSD (6–8). BPSD are associated with more rapid cognitive decline and poor functional status (9, 10). BPSD are widely prevalent in residents of long-term care homes (11, 12) where the current pandemic has had the most devastating effect (13). Acutely, BPSD may require emergency room assessment and hospital admission (14), potentially exposing patients to nosocomial COVID-19.

Older age, medical comorbidities, and other risk factors, such as APOE4 (15), which are commonly seen in individuals with BPSD, are also associated with increased risk of severe COVID-19 infection and mortality (16–18). Further, it has been shown that up to 69% of patients with severe COVID-19 infection may present with delirium or encephalopathy (19), which increase mortality rates (20). In the United States, the case fatality rate for those ≥85 years old has been reported to be between 10 and 27%, about 100-fold higher than the rate for those 20–44 years old (18). These studies did not report separately on the subgroups with dementia or BPSD; however up to 40% of elderly ≥85 years old are likely to have ADRD with associated BPSD in a significant proportion (21). Given the association of BPSD with risk factors of both COVID-19 exposure and severity, we expect that those with BPSD are one of the most vulnerable groups and that the pandemic will make their care more challenging.

The recommended treatment approach to BPSD depends on the presenting symptom or the nature of the underlying disorder. However, individualized non-pharmacologic interventions are typically first line, followed by carefully considered pharmacological interventions (22, 23). Furthermore, optimal management of BPSD requires a multidisciplinary collaborative approach between physicians, allied health clinicians, behavioral therapists, and patients' substitute decision makers (24). Standard interventions for BPSD involve close contact between patients and their caregivers (3, 24). During the pandemic, these interventions may require significant adaptation or restriction to be compatible with measures to reduce infection risk including "physical distancing" (25) or "social distancing" (26).

In a 4-year retrospective case-control study of an Alzheimer's Special Care Unit, a higher inherent risk of respiratory infections relative to other units was found (27). Previous experiences of infectious disease outbreaks offer some lessons to balance effective management of BPSD with infection control principles (28–30). However, these interventions are limited in scope and do not capture the unprecedented scale of the current pandemic.

There is a need to understand the impact of the current pandemic on individuals with BPSD across various settings from community living to hospital units. Further, there is an urgent need to implement preventive interventions to protect individuals with ADRD from the COVID-19 infection while effectively managing BPSD. In this paper, we discuss unique challenges faced by individuals with BPSD and their caregivers during the COVID-19 pandemic and provide recommendations on how to address these challenges. Our aim is to address these challenges in individuals experiencing significant BPSD across the spectrum of cognitive decline ranging from pre-clinical to dementia, and across different neurodegenerative disorders.

HIGHER RISK OF COVID-19 INFECTION AND ASSOCIATED MORBIDITY IN INDIVIDUALS WITH BPSD

Risk of COVID-19 Infection and Its Severity

There is increasing interest in the possible association between BPSD and COVID-19 infection (31, 32) and the challenge this may pose for those who care for individuals with BPSD (33). Although the association between BPSD and COVID-19 risk and severity is yet to be established empirically, the literature on this topic is expanding quickly. First, individuals with BPSD experiencing motor disturbances, disinhibition, hyperactivity, and psychosis may place themselves at higher risk of infection by increasing their proximity to others (**Figure 1**). Second, BPSD are associated with increased severity of cognitive impairment which limits the individual's ability to understand, remember, and therefore, adhere to instructions regarding isolation or hand hygiene (9). Third, BPSD are associated with anosognosia, limiting the individual's ability to adjust their behaviors, take necessary precautions, and seek help (34). This poor insight has been shown to increase their care needs and use of support services, which are critical resources during this pandemic (35). Fourth, individuals with BPSD and severe cognitive impairment depend on others for their basic needs which may involve close physical contact and potential exposure to a range of situations including personal care, feeding, and behavioral support for complex activities of daily living (36). Fifth, most health and personal care workers serve many patients or several facilities thus increasing the risk of infection. Sixth, environmental factors, such as shared rooms and physical layout, may limit an individual's ability to isolate. Finally, dementia is associated with frailty, a syndrome of physical symptoms (*i.e.* weight loss, exhaustion, weakness, and inactivity) and functional decline and dysregulation of immune and inflammatory mechanisms (37, 38). This places patients with dementia at a higher risk of infection and mortality when exposed to the virus. Individuals with BPSD are likely to experience even more frailty among those with dementia due to the nature of their symptoms (39).

BPSD such as apathy, affective symptoms, and psychosis may impact the individuals' ability to report symptoms of the infection. Older age has been identified as a risk factor for mortality from COVID-19 infection (17, 18). Furthermore, emerging evidence suggests an association between APOE4, a specific risk factor for Alzheimer's Disease, and the risk and severity of infection (15, 40). Dementia has also been reported as a common comorbidity (12%) in those who have died due to COVID-19 (41) even though it may be under-represented in studies of in-hospital deaths as individuals with severe dementia

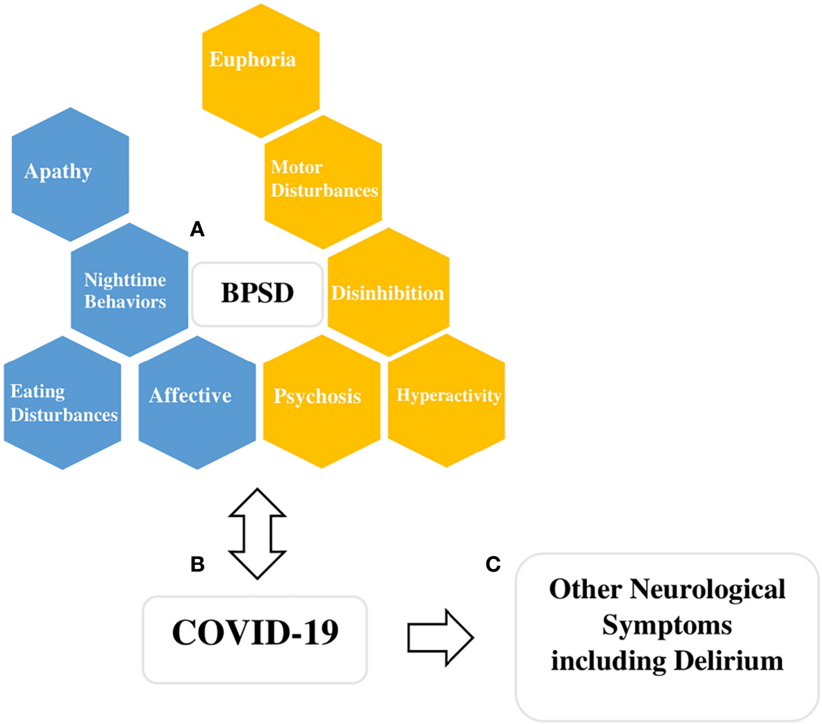

FIGURE 1 | Figure describing potential interactions between COVID-19 and behavioral and psychological symptoms of dementia (BPSD). **(A)** BPSD are clustered here, based on previous consensus, into four main groups (hyperactivity, affective, psychosis, euphoria), and five other symptoms are listed individually (disinhibition, motor disturbances, apathy, night-time behaviors, eating disturbances) (4). Boxes colored gold indicate BPSD symptoms or clusters that may get worse due to the biological or psychological impact of COVID-19, and also the symptoms themselves interfere with infection control precautions and thus increase the chances of spread of COVID-19 infections (*i.e.* individuals with an increased propensity to wander or decreased likelihood of cooperating with isolation). Boxes colored blue indicate symptoms or clusters that are likely to worsen due to the biological or psychosocial impact of the COVID-19 but may not present challenges from infection control perspective (*i.e.* social isolation, loss of scheduled activities and routines). **(B)** COVID-19 and its hypothetical bidirectional relationship with BPSD, emphasizing the risk of more severe COVID-19 infection in individuals with BPSD due to their frailty and medical vulnerability. **(C)** COVID-19 can present with neurological symptoms and delirium due to its biological impact on the brain and nervous system and other systemic effects. Delirium and other neurological symptoms may also mimic BPSD.

may not be transferred to hospital. Individuals with BPSD also have comorbidities that result in a poorer prognosis when they are hospitalized (42, 43). Moreover, medications used in the management of BPSD, such as benzodiazepines and antipsychotics, may increase cardiovascular and respiratory mortality through sedation, cardiac toxicity, or increased risk of aspiration (44). To summarize, the risk of infection and its severity seems to be elevated in individuals with BPSD and their caregivers. Special consideration should be given to individuals with BPSD when planning preventive and therapeutic initiatives for COVID-19, keeping in mind the unique vulnerabilities of this population.

Screening and Testing for COVID-19 in Individuals With BPSD

Specific BPSD such as apathy, affective symptoms, and psychosis, as well as moderate or severe cognitive impairment may result in inadequate participation in screening questionnaires and testing for COVID-19. Consequently, the task of monitoring and screening will fall on family and professional caregivers in the community, or nursing and other allied healthcare workers (HCW) in long-term care homes and inpatient units. Caregivers and HCW need to assess for both typical (upper respiratory symptoms and fever) and atypical presentations of COVID-19, including gastrointestinal and neurological symptoms (17, 45). An acute change in behavior and delirium might be the first manifestation of an underlying infection (20). Hyperactive presentations of delirium may interfere with COVID-19 screening. Clinicians and organizations should employ structured algorithms and routinely include COVID-19 screening in delirium work-up of individuals with BPSD (46). Unfortunately, nasopharyngeal swabs for COVID-19 are invasive and require patient cooperation to obtain an adequate specimen (47, 48). This may pose a challenge in certain individuals with BPSD. Individuals with BPSD who experience agitation/hyperactivity, or disinhibition may have higher false negative rates due to poor compliance when compared to those with apathy or affective symptoms. Thus, continued universal precautions for infection control and aggressive testing may be necessary. Individuals with BPSD living in the community may be unable to access screening and testing for COVID-19 and require support from agencies and primary care providers.

Infection Control Precautions for Individuals With BPSD During COVID-19

Adherence to infection control precautions may be impeded by BPSD (49, 50). Specifically symptoms such as motor disturbances, euphoria, disinhibition, hyperactivity, and psychosis may impair the patients' ability to maintain isolation, stay in one place or wear face masks (**Figure 1**). In such cases, use of behavioral and pharmacological interventions may need to be optimized. It is still important to use the least restrictive measures specific to each situation, such as creating physical barriers or cues by rearranging furniture or changing the layout of common areas to prevent wandering and to restrict movement of individuals to certain areas. In some cases, upholding infection control principles may require the use of chemical restraints (*e.g.* sedative medications in an emergency situation to reduce movement), as well as seclusion, or physical restraints as a last resort. However, these situations require careful examination of ethical, legal, and institutional factors, due to the potential for serious harm (51).

Communicating COVID-19 Risks to Individuals With BPSD and Their Caregivers

Individuals with BPSD may have varying levels of cognitive impairment. Those with more severe cognitive impairment may be unable to appreciate the risks and consequences of the illness for themselves and others. Individuals with milder or non-amnestic cognitive impairment may have some preserved ability to understand and practice basic infection control measures. Nevertheless, communicating the risks of infection is critical to elicit cooperation with infection control measures. Verbal and non-verbal modes of communication should be used, moving from basic to more complicated principles of infection control. Non-verbal measures that have been studied to improve communication between individuals with ADRD and staff include: memory books, visual and motor cues, multi-sensory stimulation Snoezelen interventions, and active listening techniques (*e.g.* making eye contact) (52). The communication needs to be individualized based on personal and environmental factors (50, 53, 54). For example, an individual with psychosis or severe cognitive impairment may not fully comprehend the pandemic but may be directed to wash their hands with frequent reminders. Family caregivers may be reluctant to share information regarding infection risk for fear of aggravating symptoms and should be encouraged and supported. Caregiver based interventions are highly effective for management of BPSD and can help with reducing caregiver stress (55). Several organizations have published helpful resources and run support groups specific to COVID-19 (53, 54). Further, due to shortage of resources to care for patients with COVID-19 infection, individuals with ADRD or BPSD may be triaged to a lower priority, as has occurred in some jurisdictions, sparking ethical considerations (56, 57). The substitute decision makers of individuals with ADRD and BPSD should be involved in these discussions to promote informed choices (2, 58). The presence of BPSD may influence them and lead them to select a palliative approach, without realizing that BPSD is usually treatable and temporary (3, 22).

MANAGING THE BIOLOGICAL AND PSYCHOSOCIAL IMPACT OF COVID-19 ON BPSD

Biological Impact of COVID-19 on BPSD and Considerations for Appropriate Use of Psychopharmacology

Mounting evidence suggests that COVID-19 causes possible neuronal death *via* neuro-inflammatory mechanisms or vascular mechanisms such as hyper-coagulation (59, 60). Early studies from Wuhan, China reported that within days of admission, over 1/3 of patients with COVID-19 had one or more neurologic symptoms (*i.e.* dizziness, headache, impaired consciousness) (45). These findings are now supported in other cohorts (61) with neuropathological (62) and MRI correlates (63). In severe cases, COVID-19 patients are at higher risk of stroke, delirium, and acute encephalopathy, leading to both short and long-term neuropsychiatric sequelae (64, 65) and causing significant problems with management in hospital and ICU settings (66, 67). Individuals with ADRD are particularly vulnerable to neuropsychiatric impact of any systemic illness and are likely to experience even higher rates of delirium and encephalopathy, which can be mistaken for BPSD (20). Increasingly, healthcare organizations and public health entities are including these symptoms in screening algorithms (25). However, given the focus on the respiratory illness associated with COVID-19, its neuropsychiatric manifestations are likely be missed or to be mistaken for pre-existing BPSD. Clinicians should consider new acute neuropsychiatric symptoms or worsening in BPSD to be an indication for COVID-19 testing. Long term neurologic sequelae could also be linked to COVID-19 infection due to neurodegenerative changes associated directly with the virus or indirectly with autoimmune processes. These sequelae could mimic some neurodegenerative syndromes, warranting long-term follow up (68).

Some individuals who experience worsening of BPSD due to COVID-19 may require additional pharmacological interventions. Many of these individuals are already prescribed multiple psychiatric medications and are likely to experience adverse effects related to polypharmacy (69, 70). This situation may worsen further due to lack of access to specialist care, limited resources, and a desire for faster symptom relief in the context of COVID-19 (2). Clinicians should adhere to best practice guidelines: first optimizing non-pharmacological measures, then carefully weighing benefits and risks of pharmacological interventions (71). Algorithms or integrated care pathways may help in treatment planning (23). We suggest a careful review of current medications and considering discontinuation of ineffective medications or those with potential for drug interactions or adverse effects, followed by a sequential trials of safer evidence-based medications (23). Special consideration should be given to the use of benzodiazepines and other sedating medications in concurrent BPSD and COVID-19 given the risk of respiratory depression (72). Similarly, COVID-19 has known cardiac complications including heart failure and arrhythmias (73). Based on this information and in keeping with general principles of treatment in geriatric medicine, we suggest avoiding or exercising extra caution with medications that prolong QTc or have other cardiac adverse effects (74). We advocate for use of an individualized algorithmic approach to pharmacological management of BPSD in each patient with emphasis on monotherapy, measurement based care, and close monitoring for cardiac and other potential adverse effects (23).

Psychosocial Impact of COVID-19 on BPSD and Its Management

We expect an increase in all domains of BPSD (**Figure 1**) in keeping with projected worsening of pre-existing mental health symptoms in the general population (19, 75, 76). First, cancellation of recreational activities and routine disruption are particularly challenging for individuals with BPSD. Second, physical distancing and infection control measures may result in a reduction of visits from family, friends, and caregivers leading to increased social isolation and worsening of affective symptoms, such as anxiety and depressed mood (50, 77). Third, individuals with BPSD who are able to comprehend some aspects of the pandemic may also experience second-hand distress from caregivers (50). Lastly, individuals with BPSD may find it harder to adequately use telecommunications and virtual care tools that may help them cope with the psychosocial impact of the pandemic. As individuals with BPSD live in a variety of settings, we discuss specific measures that can be adapted at each setting.

Home or Community Living

In home environments, family or external caregivers provide support for activities of daily living and management of BPSD. Appointments with physicians and other clinicians may have to be conducted virtually (2). Thus, family caregivers and clinicians should develop an inventory of existing supports for the individual during the pandemic. The goal should be to continue to treat individuals with BPSD at home, where the risk of exposure to COVID-19 is lower, by ensuring that healthy home routines are continued, and unmet needs are identified and addressed (2). Individuals with BPSD and their caregivers should be engaged in discussions regarding protocols for minimizing exposure to COVID-19 during in-person visits. Goals of care and a plan for transfer to primary, secondary, or tertiary care centers should be discussed explicitly with the individuals and their substitute decision makers as applicable.

Long-Term Care Homes (LTCH)

LTCH have been a major focus during this pandemic, given the high morbidity and mortality in these settings (78, 79). Many LTCH face challenges in terms of staff absenteeism due to COVID-19 morbidity, daycare/school closures, or rules preventing staff from working in more than one health facilities. Behavioral support teams and specialist care clinics may not be functioning at their optimal level (80). Furthermore, many LTCH have invoked blanket bans on visitors to their facilities. Although these measures were implemented to protect residents, there is now evidence that such measures lead to increased social isolation and worsening of depression and anxiety (81). As much as possible, LTCH should preserve some programming to prevent decompensation while following universal precautions. For example, audio-video phone conferencing, physical exercises, music, doll therapy, and individualized one-to-one relaxation training can be safely used in residents' personal space (82). When LTCH residents with BPSD experience death of peer residents due to COVID-19, some may benefit from grief counseling or supportive therapy (83). LTCH should also revisit advance directives with residents and their substitute decision makers in view of the pandemic. Residents' wishes regarding code status, transfer to hospital or ICU, and provision of invasive care should be ascertained (84).

Hospital and Other Behavioral Units

At any given time, a significant number of patients affected by dementia and BPSD are admitted to specialized behavioral units or geriatric inpatient units (14, 85). There may be inadequate behavioral and psychosocial interventions due to staff unavailability or diversion towards infection control activities. Many hospitals limit group activities due to infection control. Thus, they need to maximize the individualized one-to-one behavioral interventions either in person or through audio-video technologies, which might in-fact require more staff resources (86). To meet these demands, hospitals may need to redeploy staff from other clinical services such as outpatient clinics, or other services deemed "non-essential". Volunteers may also be able to provide psychosocial support to older inpatients when their engagement is allowed by local policies and directives (87).

Attending to the Needs of Those Working and Caring for Individuals With BPSD

Consistent staffing is critical to provide effective care to individuals with BPSD because the work demands a high degree of familiarity with the individual. The psychological impact of working in LTCH, hospital, or other institutional settings during a pandemic should be recognized and addressed proactively (88). There are many potential sources of stress for HCW including caring for vulnerable and potentially dying residents, keeping abreast of regularly evolving infection control regulations, and worrying about their own health and safety. Frontline HCW involved in the care of patients with COVID-19 have higher risks of mental distress, insomnia, anxiety, and depression (89). Frontline HCW should have support made available, but not mandated (90). Organizations should have clear and widely advertised ways for staff to access timely and confidential professional support and crisis services. Including mental health professionals in planning and supporting teams may be helpful. The overall resilience of HCW raises the hope that the healthcare work force can be preserved with adequate measures (91). Non-HCW, such as family, friends, and informal caregivers, play a critical role in the care of individuals with BPSD and might be experiencing stress due to reduction in the frequency of family visits during the pandemic (92, 93). Thus, efforts should be made to proactively detect and manage caregiver stress among family members and other informal caregivers (93).

CONCLUSIONS

The COVID-19 pandemic is disproportionately impacting the elderly including those with BPSD. Individuals with BPSD and their family or professional caregivers are facing unique challenges due to the inherent nature of the illness and superimposed biological and psychosocial factors related to the COVID-19 pandemic. Certain BPSD may lead to a higher risk of infection, a more severe course of illness, and higher mortality rates. These challenges can be addressed with a proactive approach. It is important to implement infection control strategies for individuals with BPSD across settings such as proactive screening and testing, maintaining a high degree of suspicion for atypical presentations of COVID-19, and instituting timely interventions. Individuals with BPSD and COVID-19 should also be monitored for long term biological and psychosocial effects of COVID-19. BPSD need to be managed during the pandemic using evidence-based structured psychosocial and biological interventions through innovative means such as virtual and individualized care, use of structured and algorithmic models of care, and appropriate use of psychosocial interventions across healthcare settings. Individuals with BPSD and their substitute decision makers should be invited to discuss and make decisions regarding goals of care and end of life care. Efforts should be made to address the psychological health of the frontline HCW and informal caregivers as they are paramount to success in caring for BPSD.

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.

AUTHOR CONTRIBUTIONS

AK: Substantial contributions to the conception or design of the work and the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. EB: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and final approval of the version to be published. AR: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and final approval of the version to be published. TR: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and final approval of the version to be published. BP: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and final approval of the version to be published. BM: Substantial contributions to the conception or design of the work; interpretation of data for the work; revising it critically for important intellectual content; and final approval of the version to be published. SK: Substantial contributions to the conception or design of the work and the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors contributed to the article and approved the submitted version.

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Tumor Patients´ Perceived Changes of Specific Attitudes, Perceptions, and Behaviors Due to the COVID-19 Pandemic and Its Relation to Reduced Wellbeing

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Background: During the COVID-19 pandemic, the Working Group “Prevention and Integrative Oncology” (PRIO) in the German Cancer Society has initiated flash interviews and surveys. One of these stated increasing rates of fears and mental stress of tumor patients. Now we aimed to analyze whether tumor patients did perceive changes in their attitudes and behaviors related to their relationships, awareness of nature and quietness, interest in spiritual issues, or feelings of worries and isolation. A further point of interest was how these perceived changes could be predicted, either by meaning in life, spirituality as a resource to cope, perceived fears and worries, or particularly by their wellbeing.

Materials and Methods: Online survey with standardized questionnaires (i.e., WHO-Five Well-being Index (WHO5), Meaning in Life Questionnaire (MLQ), Spiritual and Religious Attitudes to cope with illness (SpREUK-15), Gratitude/Awe scale (GrAw-7)) among 292 tumor patients (72% men; mean age 66.7 ± 10.8 years; 25% < 60 years, 33% 60-70 years, 41% > 70 years) from Germany between May 6 to June 10, 2020.

Results: Patients´ wellbeing (WHO5) scores were in the lower range (14.7 ± 6.0); 35% scored < 13, indicating depressive states. Wellbeing was significantly higher in older persons and lower in younger ones (F=11.1, p<.0001). Most were irritated by different statements about the danger and the course of the corona infection in the public media (60%), and 57% were worrying to be infected and to have a complicated course of disease. Because of the restrictions, patients noticed changes in their attitudes and behaviors (measured with the 12-item *Perceptions of Change Scale*): 1) *Perception of nature and silence* (Cronbach´s alpha = .82), 2) *Worrying reflections and loneliness* (Cronbach´s alpha = .80), 3) *Interest in spirituality* (Cronbach´s alpha = .91), 4) *Intense relationships* (Cronbach´s alpha = .64). These perceptions of change were similar in women and men, age groups and also with respect to tumor stages. Regression analyses revealed that the factor *Perception of nature and silence* was predicted best by patients´ ability to value and experience the 'wonder' of the present moment (in terms of wondering awe and gratitude) and by patients´ search for meaning in life. The factor *Worrying reflections and loneliness* was predicted best by their search for meaning in life and by feelings of being under pressure because of the Corona pandemic. *Interest in spirituality* was predicted best by search for an access to a spiritual source and by frequency of praying. *Intense relationships* were explained with weak predictive power by patients´ ability to reflect life concerns. Patients´ wellbeing during the Corona pandemic was predicted (R^2 =.57) by a mix of disease and pandemic related stressor, and by available resources (meaning in life and religious trust).

Conclusion: In this study among tumor patients from a secular society the topics meaning in life, having (religious) trust, stable relationships, mindful encounter with nature, and times of reflection were found to be of importance. To overcome tumor patients´ feelings of isolation, depressive states, and insecurity about future perspectives, further support is needed, particularly in their socio-spatial surrounding. These are the domains of psychotherapy and spiritual care. The planned integration of structured access to spiritual care seems to be important, not only for the field of cancer care. As the findings refer to patients´ self-perceptions, longitudinal studies are required to substantiate these perceived changes.

Keywords: tumor patients, elderly, corona pandemic, wellbeing, change of attitudes, spirituality, meaning in life, COVID-19

INTRODUCTION

The COVID-19 pandemic resulted in a societal lockdown in Germany. The public health system has focused on preventive strategies and treatment possibilities for infected patients at ICU and normal hospitals. Most persons in Germany followed the individual and social restrictions and stayed at home. As a consequence, several felt isolated from their friends and relatives, missed the collaborative networks at their job, and had to deal with so much (boring) 'extra time'. Some experienced fears to get in contact with potentially infected persons, avoided direct contact with others, and were allowed to go to the grocery store and pharmacies only. Several patients with chronic diseases and also those with acute illness symptoms avoided going to hospitals or meeting their medical doctors, because they feared potential infection routes.

The Working Group "Prevention and Integrative Oncology" (PRIO) in the German Cancer Society has initiated a series of flash interviews among the stakeholders during the crisis in order to reflect the moment and to develop strategies to be better prepared for next critical situations. These flash interviews have documented increasing rates of fear and mental stress of tumor patients and their physicians during the crisis in April 2020 (1). Main problems were common anxieties regarding delays, therapy breaks or finishing these treatments. A majority of patients reported diffuse fears of the future. Half of the oncologists and nurses were awaiting their own physical and/or mental burdens as a consequence of actual pandemic management. Similar data were reported by Italian colleagues, especially for patients suffering from both cancer and infection (2).

Apart from fears and worries, several persons anecdotally reported that they used the 'extra time' of the lockdown to spend more time outdoors, to perceive nature more intensely, to spend more time with their partner and their children, read more books, etc. - and generally to have more time for themselves. This 'extra time' could be used as a chance to reflect on those matters which may give meaning in life, to reflect what is essential in life, maybe also as a hint to change important aspects of life, to be more aware of nature and people around, and to deal more consciously ('mindfully') with them. Further, some may have experienced that these restricted times allowed them to focus more on their own interests instead on work related duties, and thus some may have enjoyed the 'silence', while others feared this 'silence' because they became aware of their loneliness from which they could be distracted more easily through various duties. These perceived changes of attitudes and behaviors have two directions, internal and external directed changes.

The aim of the study was to analyze whether patients with malignant tumors during the COVID-19 pandemic perceived changes of their attitudes and behaviors related to their relationships, awareness of nature and quietness, interest in spiritual issues, or feelings of worries and isolation. Tumor patients´ higher 'vulnerability' (i.e., worries about the course of their disease, fear of relapse, avoidance of routine visits because of their insecurity about potentially infection routes during the

COVID-19 pandemic) may have resulted in more differentiated views which can be seen as reappraisal coping strategies (3) as part of a 'post traumatic growth' (4, 5) during the Corona pandemic. Therefore, we 1) analyzed which changes tumor patients perceived by themselves during the pandemic using the 12-item version of the *Perceptions of Change Scale* (its validation data are presented to underline the instruments´ quality), 2) described how these perceived changes relate to stressors (i.e., perception of burden either due to tumor symptoms or the Corona pandemic restrictions, worries about getting infected) and resources (i.e., meaning in life, spirituality as a resource, awe/gratitude, wellbeing), and 3) identified which of these independent variables would predict these perceived changes using regression analyses. An additional point of interest was how these changes on the one hand and patients´ stressors and resources on the other hand were related to their wellbeing (as a dependent variable).

MATERIAL AND METHODS

Recruitment of Patients

Patients with malignant tumors were recruited mainly in eight West and East German centers (Solingen, Wetzlar, Bielefeld, München, Herne, Nordhausen, Jena, Dessau) and a Cancer Self Care group within a five-week time span (from May 6 to June 10, 2020). All patients were assured of confidentiality and were informed about the purpose of the study and data protection information at the starting page of the online survey and at page one of the printed version. Most used the online version, while 50 patients (from Solingen and Jena) used a printed version of the questionnaire. By filling in the anonymous questionnaire, patients consented to participate. Neither concrete identifying personal details nor IP addresses were recorded to guarantee anonymity. The study was approved by the IRB of Jena University Clinic (#5497-04/18; amendment from May 5, 2020). We followed the ethical principles of the Helsinki convention.

As a reference sample for self-perceived changes we enrolled putatively healthy persons within the same time span (anonymous online survey). These were recruited *via* snowball sampling in different networks in Germany, i.e., university students and staff, research collaborators, websites of neighbor dioceses, Facebook sites, etc. from June 9 to June 21. As well, all were invited to spread the information about this survey in their personal networks and websites. Participants were assured of confidentiality and were informed about the purpose of the study and data protection information at the starting page of the online survey. There was no specific incentive, and we had no explicit exclusion criteria.

Measures

In the following we will describe the perceived changes as dependent variables and influencing stressors and resources as independent variables.

Perception of Changes

The COVID-19 pandemic and related social and individual restrictions may have changed people's specific attitudes, perceptions and behaviors. To assess which changes due to the Corona pandemic were observed, we formulated 13 statements which cover the following topics: more intense relations, perception of nature, times of quietness, loneliness, worrying reflections, and interest in spiritual issues. The respective items were introduced by the phrase "Due to the current situation…", which referred to the Corona pandemic. Agreement or disagreement was scored on a 5-point scale (0 - does not apply at all; 1 - does not truly apply; 2 - neither yes nor no; 3 - applies quite a bit; 4 - applies very much). The internal consistency of these items will be described in this article. The scores were referred to a 100% level (transformed scale score). Scores > 60% indicate higher agreement (positive attitude/behavior), scores between 40 and 60 indifference, and scores < 40 disagreement (negative attitude/behavior).

A 24-item version of this shortened 12-item version of the *Perceptions of Change Scale* is currently in use (Cronbach´s alpha = .91; 5 factors) in different healthy samples and can be requested for research purposes by the primary author. The short version of this questionnaire is available as **Supplementary Material**.

Spiritual and Religious Attitudes in Dealing With Illness (SpREUK-15)

The SpREUK questionnaire was developed to investigate whether or not patients with chronic diseases living in secular societies rely on spirituality as a resource to cope (6, 7). The instrument relies on essential motifs found in counseling interviews with chronic disease patients (i.e., search for a transcendent source to rely on, having trust/faith, reflection of life and subsequent change of life and behavior).

The 15-item SpREUK questionnaire differentiates 3 factors:

1. *Search* (for support/access) deals with patients´ intention to find or have access to a spiritual/religious resource to cope with illness, and having interest in spiritual/religious issues.
2. *Trust* (in higher source) is a measure of intrinsic religiosity dealing with patients´ conviction to be connected with a higher source which carries through, and to be sheltered and guided by this source – whatever may happen.
3. *Reflection* (positive interpretation of situation/disease) deals with cognitive reappraisal and subsequent attempts to change (i.e., reflect on what is essential in life; hint to change life; chance for development; illness has meaning, etc.)

Some phrasings were moderately adjusted in the sense that the phrasing "my illness" (has made me…) was replaced by "the current situation" (has made me…).

The internal consistency of the SpREUK-15 ranges from Cronbach´s alpha = .86 to .91. The items were scored on a 5-point scale from disagreement to agreement (0 - does not apply at all; 1 - does not truly apply; 2 - neither yes nor no; 3 - applies quite a bit; 4 - applies very much). The scores were referred to a 100% level (transformed scale score). Scores > 60% indicate higher agreement (positive attitude), scores between 40 and 60 indifference, and scores < 40 disagreement (negative attitude).

We added a further item (A37) with the same scoring which asks whether faith is a strong hold in difficult times. This item was used as a differentiating variable.

Spiritual-Religious Self-Categorization

The SpREUK includes two specific items which ask whether persons regard themselves as a spiritual and/or religious person (without defining what these terms may mean). Scores > 2 indicate agreement and scores < 3 indifference or disagreement. Subsequently one can categorize persons who regard themselves as religious and spiritual (R+S+), religious but not spiritual (R+S-), not religious but spiritual (R-S+) and neither religious nor spiritual (R-S-).

Awe and Gratitude (GrAw-7)

To address times of pausing for 'wonder' in specific situations (mainly in nature), we measured feelings of wondering awe and subsequent feelings of gratitude as a perceptive aspect of spirituality with the 7-item Gratitude/Awe scale (GrAw-7) (8). This scale has good psychometric properties (Cronbach's alpha = .82) and uses items such as "I stop and then think of so many things for which I'm really grateful", "I stop and am captivated by the beauty of nature", "I pause and stay spellbound at the moment" and "In certain places, I become very quiet and devout". Thus, awe/gratitude operationalized in this way is a matter of an emotional reaction towards an immediate and 'captive' experience. All items were scored on a 4-point scale (0 - never; 1 - seldom; 2 - often; 3 - regularly), referred to a 100-point scale.

Meaning in Life (MLQ)

Whether respondents were in search of meaning in life or already had found it, was measured with the 10-item Meaning in Life Questionnaire (MLQ) (9). The 5-item Search subscale uses items such as "I am looking for something that makes my life feel meaningful" and "I am always looking to find my life's purpose", and the 5-item Presence subscale items such as "My life has a clear sense of purpose" and "I have discovered a satisfying life purpose." Internal consistence of both subscales is good to very good (Cronbach´s alpha between .81 and .92). Items are scored form 1 (absolutely untrue) to 7 (absolutely true). The higher the MLQ subscale score, the higher the perceived meaning in life is.

Well-Being Index (WHO-5)

To assess participants' well-being, we used the WHO-Five Well-being Index (WHO-5). This short scale avoids symptom-related or negative phrasings, and measures well-being instead of absence of distress (10). Representative items are "I have felt cheerful and in good spirits" or "My daily life has been filled with things that interest me". Respondents assess how often they had the respective feelings within the last two weeks, ranging from at no time (0) to all of the times (5). Here we report the sum scores ranging from 0 to 25. Scores < 13 would indicate rather depressive states.

Perception of Burden

Perceived daily life affections due to disease related symptoms, feelings of being restricted in daily life by the Corona pandemic, and feelings of being under pressure (i.e., stress and fear) due to the Corona pandemic were measured using three visual analogue scales (VAS), ranging from 0 (not at all) to 100 (very strong).

COVID-19 Pandemic Outcomes

Several tumor patients reported that they were "Irritated or unsettled by different statements about the danger and the course of the corona infection in the public media" and that they are "Worrying to be infected with COVID-19 virus and to have complicated course of disease". Both statements were addressed with two single items. Agreement to these statements was scored from not at all, a little, somewhat and very much.

Health Behaviors

Alcohol consumption was scored on a 5-grade scale: never, at least once per month, 2-3 times per month, 1-2 times per week, several times per week. Usage of relaxing drugs, physical activity/sporting, meditation and praying were measured with a 4-grade scale: never, at least once per month, at least once per week, at least once per day.

Statistical Analyses

Descriptive statistics and analyses of variance (ANOVA) of the influencing and outcome variables (wellbeing, stressors, resources and perceived changes), internal consistency (Cronbach's coefficient α) and factor analyses (principal component analysis using Varimax rotation with Kaiser's normalization) of the 12 items of the Perceived Changes Scales as well as first order correlation (Spearman rho) and regression analyses with perceived changes as dependent variables were computed with SPSS 23.0. Given the exploratory character of this study, significance level was set at p <.01. With respect to classifying the strength of the observed correlations, we considered r >.5 as a strong correlation, an r between .3 and .5 as a moderate correlation, an r between .2 and .3 as a weak correlation, and r <.2 as negligible or no correlation.

RESULTS

Description of the Sample

We had basic data of 330 people with tumors, among them a fraction responded only to some basic sociodemographic data but not to the wellbeing and burden questions and subsequent other topics. These were regarded as 'non-responders' (n=38; 12%). These non-responders did not significantly differ from the responders with respect to gender, age, religious affiliations or tumor stage (data not shown). Nevertheless, among the responders (n=292) not all responded to all questionnaire modules.

As shown in **Table 1**, men (72%) and persons living with a partner (80%) were predominating in the sample. Their mean age was 66.7 ± 10.8 [29-92] years (25% < 60 years, 33% 60-70

TABLE 1 | Sociodemographic data of enrolled patients.

	n	% of responders	mean ± SD	range
Gender				
Women	81	28		
men	207	72		
Age (years)	285		66.7 ± 10.8	29-92
<60 years	72	25		
60-70 years	95	33		
>70 years	118	41		
Partner status				
Living with partner	235	80		
Living without partner	57	20		
Tumor localizations				
Larynx	55	17		
Breast	34	10		
Prostate	138	42		
Other	60	18		
(no data)	43	13		
Tumor description				
Primary tumor	196	67		
Relapse	61	21		
Metastases	66	23		
Tumor stage				
Early stages (St. 0-II)	94	32		
Progressive stages (St. III-IV)	124	42		
Unclear stage	74	25		
Treatments intentions				
Curative treatment	82	28		
Palliative treatment	42	14		
No active treatment	30	10		
Already treated effectively	138	47		
COVID-19 tested				
Positively tested	0	0		
Negatively tested	17	6		
No testing	275	94		
Irritated or unsettled by different statements about the danger and the course of the corona infection in the public media			1.7 ± 0.9	0-3
Not at all	30	10		
A little	86	30		
somewhat	102	35		
very much	74	25		
Worrying to be infected with COVID-19 virus and to have complicated course of disease			1.7 ± 1.0	0-3
Not at all	36	13		
A little	88	31		
somewhat	92	32		
very much	70	25		
Religious affiliation				
Christians	175	60		
Other	14	5		
none	103	35		
Spiritual-religious self-categorization				
R+S+	41	16		
R+S-	44	17		
R-S+	16	6		
R-S-	155	61		
n.d.	36	–		
Faith as strong hold in difficult times			1.6 ± 1.5	0-4
Disagreement	131	51		
Undecided	41	16		
Agreement	83	33		
Meditation				
Never	178	69		
At least once per month	32	12		
At least once per week	31	12		
At least once per day	18	7		
Praying				
Never	152	59		
At least once per month	23	9		
At least once per week	34	13		
At least once per day	51	20		
Wellbeing and burden				
Wellbeing (WHO5)	286		14.7 ± 6.0	0-25
WHO5 scores < 13	101	35		
WHO5 scores 13-18	88	31		
WHO5 scores > 18	97	34		
Daily life affection due to symptoms (VAS)	289		39.8 ± 26.4	0-100
Restricted in daily life by corona pandemic (VAS)	274		45.1 ± 26.4	0-100
Under pressure due to corona pandemic (VAS)	289		32.1 ± 28.5	0-100
Meaning in life (MLQ)				
Search	264		16.1 ± 7.8	0-35
Presence	266		26.5 ± 6.4	0-35
Spirituality and Coping (SpREUK-15)				
Search	258		25.5 ± 25.9	0-100
Trust	259		38.8 ± 30.6	0-100
Reflection	260		45.4 ± 25.1	0-100
Awe/Gratitude (GrAw-7)	262		57.4 ± 20.2	0-100

years, 41% > 70 years). Patients with prostate cancer (42%) and larynx tumors (17%) were predominating in the sample. Most had a primary tumor (67%) and a progressive state (42%). A large fraction stated they were already treated effectively (47%).

A majority had a Christian denomination (60%), a few had other religious orientations (5%), while 35% had no religious affiliation. However, most (61%) regarded themselves as neither religious nor spiritual (R-S-) and 33% as religious (R+S+ or R+S-). 33% agreed that their faith is a strong hold in difficult times, 16% were undecided, and 51% disagreed.

The reference sample (n=993) had a mean age of 52.6 ± 11.2 [31-92] and was thus younger; 33% were men and 67% women. 75% were living in a family household, 21% as singles and 4% in living communities. They were from different professions (17% administration, 14% education, 12% economy, 26% medicine, 31% other).

Wellbeing, Meaning in Life and Spirituality in the Sample

In the following we describe external measures which are of relevance to describe patients´ wellbeing, meaning in life and spirituality indicators. These analyses are mostly descriptive (mean values and standard deviations), followed by analyses of variance (ANOVA).

Patients´ wellbeing scores were in the lower range (referring to the general range of the WHO5 scale as depicted in **Table 1**), while their perceived daily life affections due to tumor symptoms, and also feelings of being restricted in daily life the by Corona pandemic or feelings of being under pressure due to the Corona pandemic scored in the lower mid-range, however, with large variance (**Table 1**). Wellbeing was significantly higher in older persons (16.2 ± 5.4) as compared to 60-70 years old patients (14.6 ± 5.9) or younger ones (12.1 ± 5.8) (F(2,278)=11.1, p<.0001; ANOVA).

Most (60%) were somewhat to very much irritated or unsettled by different statements about the danger and the course of the COVID-19 infection in the public media, and 57% were somewhat to very much worrying to be infected with COVID-19 virus and to have a complicated course of disease. However, most were so far not tested for a COVID-19 infection (94%), and 6% were negatively tested. None of the respondents was positively tested, only one person in the non-responder group.

Search for meaning in life (MLQ) scored rather low with respect to the scale´s general range, while most already have found meaning in life and thus scored high on MLQ´s Presence component (**Table 1**). Similarly, SpREUK´s Search for a spiritual source scored rather low with respect to the range and interpretation of scores, while SpREUK´s Trust scored higher (in the lower mid-range); SpREUK´s Reflection scale scored in the mid-range. Similarly, the perception of wondering awe in distinct situations and subsequent perceptions of gratitude (GrAW-7 scale) scored in the mid-range (**Table 1**).

Patients´ Perception of Changes

To better summarize and calculate patients´ perceived changes in attitudes and behavior, an explorative factor analysis of the respective items was performed. A Kaiser-Mayer-Olkin value of .76 (as a measure for the degree of common variance) indicated that the item pool is suited for principal component factor analysis. The item "treating others with more caution" was deleted due to a low factor loading. The 12 remaining items had a good internal consistency (Cronbach´s alpha = .82) and differentiated in four factors that would account for 72% of variance (**Table 2**):

1. *Perception of nature and silence*, with four items and good internal consistency (Cronbach´s alpha = .821): going outdoors more often and perceiving nature more intensely, consciously taking time for silence and enjoying quite times of reflection.
2. *Worrying reflections and loneliness*, with four items and good internal consistency (Cronbach´s alpha = .797): concerned about meaning in life and the lifetime one has, more intense perception of loneliness and feelings of being cut off from life (due to the pandemic restrictions).
3. *Interest in spirituality*, with two items and very good internal consistency (Cronbach´s alpha = .909): praying/meditating

TABLE 2 | Factor and reliability analyses of the 12-item Perceived Changes Questionnaire.

"Due to the current situation I (am) …."	Mean value	SD	Corrected item – scale correlation	Cronbach´s alpha if item deleted (alpha = .820)	Factor loading			
					1	2	3	4
Eigenvalue					4.3	1.9	1,3	1.1
Cronbach´s alpha					.821	.787	.909	.636
Factor 1: Perception of nature and silence								
perceive nature more intensely.	2.64	1.07	.531	.802	.798			
go outdoors much more often.	2.50	1.14	.345	.817	.785			
consciously take more time for silence	2.13	1.13	.610	.795	.750		.300	
enjoy quiet times of reflection.	2.14	1.17	.636	.793	.713		.379	
Factor 2: Worrying reflections and loneliness								
more concerned about the lifetime that I have.	2.32	1.25	.477	.806		.822		
more concerned about the meaning and meaning of my life.	2.14	1.25	.573	.798		.774		
feel cut off from life.	1.58	1.24	.385	.815		.764		
perceive times of loneliness more intensely.	1.96	1.15	.551	.800	.454	.586		
treat others with more caution	3.06	0.97	–	–	–	/	–	–
Factor 3: Interest in spirituality								
pray/meditate more than before.	1.10	1.29	.479	.806			.921	
more interested in religious/spiritual topics.	1.02	1.20	.490	.805			.898	
Factor 4: Intense relationships								
perceive the relationships with my friends more intensely.	2.09	1.09	.263	.823				.852
perceive the relationship with my partner/family more intensely.	2.62	1.06	.334	.817				.804

Principle component analysis (Varimax rotation with Kaiser normalization); rotation is converged in 6 iterations. The four factors explain 71% of variance. Difficulty Index (mean/4) = 0.50; all items are in the acceptable range between 0.2 to 0.8.

/- was deleted due to low factor loading (<0.5).

more than before, and more interest in religious/spiritual topics as a strategy to cope.

4. *Intense relationships*, with two items and acceptable internal consistency (Cronbach´s alpha = .636): more intensive perceptions of relationships with partner/family and with friends

Wellbeing, Perceived Burden and Perceptions of Change Within the Sample

We performed analyses of variance to assess the influence of variables such as tumor stage and treatment intentions on patients' wellbeing, perceived burden and perceptions of change.

Only symptom burden was related to higher tumor stages (Stages III-IV) in trend (37.1 ± 26.2 vs 43.4 ± 26.2; F(1,287)=4.2, p=.042), but not general stress perception due to the COVID-19 pandemic (45.7 ± 24.4 vs 44.6 ± 24.4; F(1,272)=0.1, n.s.) or patients´ wellbeing (14.8 ± 5.8 vs 14.5 ± 6.3; F(1,284)=0.2, n.s.). Patients who were already treated effectively reported higher wellbeing scores than the other patients (13.7 ± 6.0 vs 15.8 ± 5.8; F(1,284)=0.0, p=.003). When patients were treated with a curative intention, their wellbeing was not significantly lower (15.0 ± 5.8 vs 13.7 ± 6.5; F(1,284)=2.5, n.s.), and also palliative treatment intention was not of significant relevance for their wellbeing (14.9 ± 6.0 vs 13.5 ± 5.7; F(1,284)=1.8, n.s.). Instead, palliatively treated patients were in trend more affected by their symptoms (38.2 ± 26.4 vs 49.5 ± 24.6; F(1,297)=6.6. p=.011) and stronger by the restrictions during the lockdown (43.5 ± 25.9 vs 54.6 ± 28.1; F(1,272)=6.0. p=.015).

To analyze differences in perceived changes as dependent variables which are related to sociodemographic (gender, age, partner status) and tumor related variables (tumor stage and treatment intentions) as independent variables, we performed analyses of variance. Here, the most frequently perceived changes were *Perception of nature and silence* and also *Intense relationships* (**Table 3**). Here, experience of nature and more intensive relations with partner/family were most relevant (**Table 2**). Nevertheless, *Worrying reflections and loneliness* were also perceived (particularly being more concerned about the lifetime one has), while *Interest in spirituality* scored lowest. There were no significant differences related to gender and age groups, but a weak impact of living

TABLE 3 | Expression of change perceptions within the sample of tumor patients and a reference sample of healthy persons.

		Perception of nature and silence	Worrying reflections and loneliness	Interest in spirituality	Intense relationships
Reference sample*	mean	58.28	45.78	39.56	62.18
	SD	24.39	23.12	27.68	21.62
Tumor patients	mean	58.88	50.13	26.57	58.98
	SD	22.89	23.85	29.59	23.08
Partner status					
Living without partner	mean	59.38	50.71	27.90	53.35
	SD	21.42	23.61	30.15	25.62
Living with partner	mean	58.76	49.99	26.25	60.34
	SD	23.28	23.96	29.51	22.27
F(1,285-288) values		0.03	0.04	0.14	4.19
p values		n.s.	n.s.	n.s.	.042
Wellbeing (WHO-5)					
Scores < 13	mean	60.28	62.79	31.75	59.22
	SD	23.53	19.53	31.40	22.20
Scores 13-18	mean	59.82	49.57	22.38	61.21
	SD	20.78	22.68	28.19	22.23
Scores > 18	mean	56.23	37.78	24.87	56.44
	SD	23.98	22.85	28.30	24.48
F(2,282-284) values		1.08	32.80	2.58	1.00
p values		n.s.	<.0001	.077	n.s.
SpR self-categorization					
R-S-	mean	54.78	46.40	11.77	57.98
	SD	22.24	23.50	19.07	22.96
R+S+/R+S-/R-S+	mean	61.59	52.06	47.75	58.66
	SD	22.88	22.94	29.21	23.43
F(1,253-254) values		5.60	3.62	141.66	0.05
p values		.019	.058	<.0001	n.s.
Faith as a strong hold					
No	mean	52.83	44.02	9.83	58.02
	SD	22.82	23.89	18.35	24.17
Indifferent	mean	62.65	56.30	28.66	60.67
	SD	18.93	21.62	27.70	20.83
yes	mean	64.33	53.16	50.46	58.99
	SD	22.81	23.15	28.40	22.76
F(2,251-252) values		7.79	6.33	74.68	.021
p values		.001	.002	<.0001	n.s

**Healthy persons recruited in a similar time span (N=993; mean age of 52.6 ± 11.2 [31-92]; 33% men and 67% women).*

with or without a partner on the perception of *Intense relationships* (**Table 3**). Compared to a reference sample of putatively healthy (non-tumor) persons recruited in the same time span, *Perception of nature and silence* scored identically, while *Worrying reflections and loneliness* and *Intense relationships* were in a similar range; in contrast, *Interest in spirituality* scored much lower in tumor patients (**Table 3**). We performed no statistical analyses regarding whether these differences were significantly different or not, as this was not the objective of this study.

In the sample of tumor patients there were no significant differences in these perceptions with respect to their tumor stage (data not shown). However, those who were not treated actively anymore had significantly higher *Worrying reflections and isolation* scores than the others (61.5 ± 18.1 vs 48.8 ± 24.1; F (1,288)=7.7, p=.006).

Patients´ wellbeing was significantly related to the perception of *Worrying reflections and loneliness* which was highest in the group of patients with WHO5 scores < 13, indicating depressive states (**Table 3**).

The spiritual/religious self-categorization had a significant impact on *Interest in spirituality* and *Perception of nature and silence* which scored lowest in R-S- persons. Those who had access to faith as a resource in difficult times had significantly higher *Interest in spirituality*, *Perception of nature and silence*, and *Worrying reflections and loneliness* scores (**Table 3**).

Associations Between Perceptions of Change With Indicators of Wellbeing, Meaning in Life, and Spirituality

Next we performed correlation analyses to assess how the putative stressors and resources (i.e. wellbeing, meaning in life and spirituality) as dependent variables related to the perceptions of changes. The respective ordinal scales are not normally distributed (as tested with the Shapiro-Wilk test) and thus we used the Spearman rho test.

The four perceptions of change factors were moderately interconnected, particularly *Worrying reflections and loneliness* was positively related to *Interest in spirituality* and *Perception of nature and silence* (**Table 4**).

Perception of nature and silence was moderately related to SpREUK´s Reflection and also to awe/gratitude, and weakly with faith as hold, SpREUK´s Trust, and with the frequency of praying (**Table 4**), indicating that both the perceptive and the cognitive aspects of spirituality were related to this experiential factor.

Worrying reflections and loneliness was strongly associated with feelings of being under pressure (i.e. stress/anxiety) because of the Corona pandemic, moderately positively with other indicators of burden and low wellbeing (**Table 4**), and further with SpREUK´s Reflection, MLQ´s Search for meaning in life, and with irritations by different statements about the danger and the course of the COVID-19 infection in the public media, and

TABLE 4 | Correlations between perceived changes and indicators of spirituality, meaning in life, wellbeing and health behaviors.

	Perception of nature and silence	Worrying reflections and loneliness	Interest in spirituality	Intense relationships
Spiritual transformation				
Perception of nature and silence	1.000			
Worrying reflections and loneliness	**.377****	1.000		
Interest in spirituality	**.323****	**.413****	1.000	
Intense relationships	**.358****	.221**	.086	1.000
Spirituality				
Search (SpEUK-15)	.179**	.257**	**.731****	.023
Trust (SpEUK-15)	.240**	.180**	**.678****	.003
Reflection (SpEUK-15)	**.409****	**.315****	**.441****	.224**
Faith as hold in difficult times (A37)	.284**	.222**	**.668****	.008
Awe/Gratitude (GrAw-7)	**.407****	.162**	**.385****	.135
Meditation frequency	.096	.114	**.322****	.023
Praying frequency	.248**	.146	**.630****	-.026
Meaning in life				
Meaning in life - Search	.155	**.447****	.286**	.061
Meaning in life - Presence	.053	-.229**	-.051	.157
Wellbeing				
Wellbeing (WHO-5)	-.052	**-.450****	-.075	-.032
Daily life affections through tumor symptoms (VAS)	.095	**.331****	.088	.059
Daily life restrictions because of Corona pandemic (VAS)	.067	**.419****	.159**	.142
Under pressure (i.e. stress/anxiety) because of Corona pandemic (VAS)	.194**	**.510****	.172**	.196**
Irritated or unsettled by different statements about the danger and the course of the corona infection in the public media?	.152**	**.322****	.044	.098
Worrying to be infected with COVID-19 virus and to have complicated course of disease	.131	**.334****	.080	.044
Current health behaviors				
Relaxing drugs	.088	.164**	.061	-.058
Alcohol consumption	-.164**	-.036	.071	.014
Physical activity/sporting	.088	-.057	-.006	.039

***p<.0001 (Spearman rho); moderate to strong correlations were highlighted (bold).*

also with patients´ worries about their own infection with the virus and to have a complicated course of the disease.

Interest in spirituality was strongly related with SpREUK´s Search and Trust scales and with faith as hold, moderately with other indicators of spirituality, and weakly also with MLQ´s Search for meaning in life (**Table 4**).

Intense relationships was weakly related only to SpREUK´s Reflection scale and with feelings of being under pressure (i.e. stress/anxiety) because of Corona pandemic, but with none of the other variables (**Table 4**).

With respect to health behaviors, physical activity/sporting was not relevantly related to the four change factors (**Table 4**). Alcohol consumption was marginally negatively related to *Perception of nature and silence*, while usage of relaxing drugs was marginally positively associated with *Worrying reflections and loneliness*.

Predictors of Patients´ Perceived Changes

There are several variables which were significantly associated with the changes tumor patients did perceive during the Corona pandemic. To analyze which of these independent variables could be regarded as predictors of perceived changes (as dependent variables), we performed stepwise regression analyses with significantly related variables. The best fitting model for each of the four dependent variables is depicted in **Table 5**.

As shown in **Table 5**, *Perception of nature and silence* was predicted best by awe/gratitude and further by patients' search for meaning in life, with their ability to reflect their life concerns, and with worry about being infected. These four predictors would explain 27% of variance.

Worrying reflections and loneliness was predicted best by patients' search for meaning in life and by feelings of being under pressure because of the Corona pandemic, and further by their ability to reflect, by low wellbeing, and perceived daily life restrictions because of Corona pandemic. These five predictors explain 50% of variance.

Interest in spirituality was predicted best by patients' search for an access to a spiritual source and by frequency of praying, and further by search for meaning in life, perceived daily life restrictions because of the Corona pandemic, and by a spiritual/religious self-categorization. These five predictors explain 66% of variance.

Intense relationships were explained with weak predictive power (R^2=.15) by patients' ability to reflect life concerns, low religious Trust, by presence of meaning in life, and by feelings of being under pressure because of the Corona pandemic. However, living with or without a partner had no significant influence.

Predictors of Patients' Wellbeing

Are these perceived changes contributing to patients' wellbeing? Regression analyses revealed that *Worrying reflections and*

TABLE 5 | Stressors and resources as independent predictors of perceived changes as dependent variables (stepwise regression analyses).

	Beta	T	p
Dependent variable: Perception of nature and silence			
Model 4: F=20.6, p<0.0001; R^2=.27			
(constant)		3.221	.002
Awe/Gratitude (GrAw-7)	.331	5.004	<.0001
Meaning in Life - Search (MLQ)	.155	2.631	.009
Reflection (SpREUK)	.180	2.669	.008
Worrying to be infected with COVID-19 virus and to have complicated course of disease	.123	2.107	.036
Dependent variable: Worrying reflections and loneliness			
Model 5: F=43.8, p<0.0001; R^2=.50			
(constant)		4.180	<.0001
Under pressure (i.e. stress/anxiety) because of Corona pandemic (VAS)	.205	2.855	.005
Meaning in Life - Search (MLQ)	.333	6.542	<.0001
Reflection (SpREUK)	.208	2.268	<.0001
Wellbeing (WHO-5)	-.202	-3.388	.001
Daily life restrictions because of Corona pandemic (VAS)	.139	2.104	.036
Dependent variable: Interest in spirituality			
Model 5: F=84.4, p<0.0001; R^2=.66			
(constant)		-3.099	.002
Search (SpREUK)	.498	8.774	<.0001
Praying	.238	4.369	<.0001
Meaning in Life - Search (MLQ)	.128	3.130	.002
Daily life restrictions because of Corona pandemic (VAS)	.103	2.549	.011
SpR self-categorization	.133	2.206	.028
Dependent variable: Intense relationships			
Model 4: F=9.6, p<0.0001; R^2=.15			
(constant)		3.917	<.0001
Reflection (SpREUK)	.311	4.203	<.0001
Trust (SpREUK)	-.174	-2.389	.018
Meaning in Life - Presence (MLQ)	.172	2.718	.007
Under pressure (i.e. stress/anxiety) because of Corona pandemic (VAS)	.184	2.927	.004

loneliness (Beta = -.51, T = -8.8, p<.0001) and in trend also *Perception of nature and silence* (Beta = .15, T = 2.5, p=.012) would predict wellbeing (as depending variable), albeit with weak predictive power (R^2=.22) The first variable would explain 20% of variance and the second would add 1.8% only and is thus irrelevant.

Adding meaning in life, spirituality as a resource, fears and worries, and age as independent variables to the model resulted in six predictors of wellbeing as dependent variable (R^2=.57), daily life affections due to symptoms (Beta = -.35, T = -7.1, p<.0001; explains 34% of variance), being under pressure due to the Corona pandemic (Beta = -.26, T = -4.7, p<.0001; +12% of explained variance), MLQ´s Presence component (Beta = .17, T = 3.8, p <.0001; +4% of explained variance), religious Trust (Beta = .14, T = 3.2, p<.0001 =.002; +2% of explained variance), *Worrying reflections and loneliness* (Beta = -.22, T = -4.0, p<.0001; +2% of explained variance), and age (Beta = .16, T = 3.5, p=.001; +2% of explained variance). Here, praying, SpREUK´s Search and Reflection scales, and awe/gratitude had no significant influence in this model.

DISCUSSION

This survey among tumor patients who have to cope with the restrictions of the COVID-19 pandemic revealed that a majority was irritated by different statements about the danger and the course of the Corona infection in the public media, and feared their own infection with the COVID-19 virus. Their wellbeing was rather low and their burden in a mid-range, indicating that they felt moderately restricted in their daily life and under pressure by stress and fear. In fact, 35% had WHO5 scores < 13, indicating depressive states. Patients' wellbeing was significantly higher in older persons and low in younger ones. Wellbeing was predicted best by a mix of disease and pandemic related variables, and available resources. Their perceived daily life affections due to symptoms alone explained 34% of variance, feelings of being under pressure due to Corona pandemic added further 12%, having found meaning in life added further 4%, while religious Trust 2% and also, *Worrying reflections and loneliness* and also higher age would add together further 6% of explained variance.

Because of the restrictions, patients noticed changes in their attitudes and behaviors. These refer mainly to more intense relationships with partners, family and friends on the one hand, and a more intense perception of nature with more frequent time outside (related to time for silence and enjoying quiet times of reflection) on the other hand. Nevertheless, worrying thoughts (particularly being concerned about the lifetime one has) and perceptions of loneliness were of relevance, too. In contrast, more interest in spiritual issues was of relevance only for some patients. Faith as a hold in difficult times was stated by 33% of patients analyzed herein; most would regard themselves as R-S- and thus it is comprehensible that this resource is of less relevance to most of them.

The observed perceptions of change were similar in women and men and in the different age groups, and not different with respect to patients' tumor stage. Nevertheless, it is worth mentioning that the few patients (10%) who were not treated actively anymore had significantly higher *Worrying reflections and isolation* scores than the other ones; these are still in contact with their oncologists, but obviously in fear. Compared to a reference sample of healthy persons recruited in the same time span, *Perception of nature and silence* scored identically, while *Worrying reflections and loneliness* were slightly higher and *Intense relationships* were slightly lower in tumor patients compared to the healthy reference sample, but in a similar range; in contrast, *Interest in spirituality* was much lower in tumor patients. Thus, tumor patients (and also healthy persons) perceived similar changes of their attitudes and behaviors, with the exception of *Interest in spirituality*. A reason for this lower interest in spiritual issues in enrolled tumor patients could be the predominance of women in the healthy sample who are generally more spiritually interested than men.

The relevant predictors of the perceived changes of attitudes and behaviors were complex. Pausing to wonder and stand still in silence in specific situations (awe) as an aspect of perceptive spirituality was the best predictor of *Perception of nature and silence*. This means patients became more aware of their surroundings, particularly that they used the time of restriction to go into nature and perceive it more consciously. Related as a predictor was the ability to reflect life concerns, to reflect on what is essential in life, and to change aspects of life. In the same vain was the finding that patients' search for meaning in life was a further predictor. This time-out phase thus encouraged reflection processes and more awareness ('mindfulness').

Search for meaning in life was the best predictor of patients´ *Worrying reflections and loneliness*, which was further predicted by the feeling of being under pressure because of the Corona pandemic. The COVID-19 restrictions obviously left some patients in the situation that they had difficulties in adequately coping and in finding meaning. In fact, the ability to reflect on one's own life concerns was a further predictor, indicating an inner process of clarification and prioritization to cope with these worries and feelings of isolation. Other, yet weaker predictors were low wellbeing, and perceived restrictions of life due to the pandemic.

Although *Interest in spirituality* was relevant only for a fraction of persons, it is nevertheless a relevant resource to cope also in secular societies (6, 11–13). These perceived changes were predicted best by patients´ search for access to a spiritual source and by their frequency of praying. In line with this, searching for meaning in life was an additional (yet weaker) predictor. More relevant as a further predictor was praying (20% of patients were praying at least once per day). Praying means to be in 'communication' with God as an external source of help, to let go fears and worries, to ask for help and to express trust when other resources seem to be less helpful (14–16).

Intense relationships were explained with low predictive power by patients´ ability to reflect their life concerns, and further by low religious Trust (which would underline the aforementioned statement that referring to God might be an 'alternative' when stable partner relations are experienced as less helpful), having found some meaning in life, and feelings to be under pressure (i.e. stress/anxiety) because of Corona pandemic. However, these predictors explain only 15% of variance, and thus we do not consider them to be of central importance; therefore, other unidentified variables might be of relevance.

Gender or age were not of relevance for any of these changes in perceptions. Further, patients´ health behaviors were of marginal relevance only. Of interest was that the usage of relaxing drugs was at least marginally positively associated with *Worrying reflections and loneliness*. This would indicate that for some patients the COVID-19 restrictions were more severe than for others and they required medication. Further, alcohol consumption was marginally negatively related to *Perception of nature and silence*, indicating that the ability to go out and perceive nature and experience times of quietness may prevent alcohol consumption. However, this alcohol consumption was marginally negatively related to more intensive perception of loneliness, and thus it is not a relevant indicator of loneliness.

It is obvious that several tumor patients have changed their attitudes and behavior. These can be seen as indicators of 'posttraumatic growth' (4, 5) due to the Corona lockdown experience. However, are these perceived changes also contributing to their wellbeing? It was striking that 35% of tumor patients had wellbeing scores < 13, 31% had moderate and 34% high wellbeing. In the healthy reference sample recruited in a similar period, we found 28% with scores <13, 39% with moderate wellbeing and 33% with high wellbeing. Thus, also healthy persons are emotionally affected by the Corona pandemic restrictions. The wellbeing groups differ only with respect to tumor patients´ *Worrying reflections and loneliness*. Nevertheless, post-hoc analyses showed that the 'depressive states' patients felt significantly (p<.0001) more affected in their daily life situation by their symptoms (mean 55.1 ± 24.7; F(2,282)=43.4), by the Corona restrictions (mean 59.1 ± 23.7; F(2,267)=36.0), and felt under pressure because of the Corona pandemic (mean 50.3 ± 29.4; F(2,282)=52.1) compared to the other wellbeing groups. Regression analyses revealed that *Worrying reflections and loneliness* and in trend also *Perception of nature and silence* would predict wellbeing to some extent (R^2=.22). Adding meaning in life, spirituality as a resource, fears and worries and age changed the prediction model in as much as now patients´ wellbeing was predicted with stronger power (R^2 =.57) by a mix of disease and pandemic related stressors, and available resources (meaning in life and religious trust).

What are the consequences from these findings for the psycho-oncological support of patients, both in the COVID-19 pandemic (which is not yet 'solved') and also for future difficult situations because of restrictions? – When perception of nature and peaceful silence and wondering awe are a resource for several tumor patients, one has to consider specific offers to experience these, either in a group (to avoid feelings of isolation and loneliness) or individually. These could be guided forest walks (17, 18), also with the option of virtual walks (which could be considered for specific groups at risk) to encourage feelings of inner peace and stress-relief. A further option would be mindful mediation (19, 20), as both individual offers at home and also in group settings; even web-based mindfulness approaches seem to be effective (21). For several patients, their faith was a resource to cope, and thus retreating in monastic contexts to sensitize for the topic of spirituality or consolidate faith might be an option. This would also allow talks with pastoral professionals when phases of religious struggles (22, 23) or spiritual dryness (24, 25) may affect patients´ emotional and spiritual wellbeing. Here, patients´ spiritual needs should be assessed to support them in the requirements they express (26–29). Gonçalves et al. (30) suggested that during the Corona pandemic the "use of spirituality" could be a tool to promote mental health particularly in psychiatric patients. However, in our study with tumor patients most had no specific interest in spiritual or religious issues, but were nevertheless perceiving awe in specific situations. These perceptions could be sensitized by awareness training. In this sample, the experience of awe and gratitude scored significantly higher in women compared to men (F=9.7, p=.002), and thus they might be especially suited.

During the COVID-19 pandemic several patients required intensive care treatment and were isolated from their relatives. Reports from oncologists as well as ICU staff and patients´ relatives underlined that the restrictions (with either no or minimal contact only) were causing mental and spiritual pain on the side of the patients, their relatives, but also on the staffs´ side (1, 31). When it is true that mentally stabilizing and supportive relations with partners, family and friends are that important, one has to consider possibilities to facilitate contacts with the family. Here, digital media facilities to connect isolated patients with their relatives were often used, particularly in such departments. Furthermore, it is necessary to develop ways to remain in personal contact within families during crisis times.

Physicians and psychologists are mostly able to treat depression. However, during the Corona crisis we have to prevent and/or overcome demoralizations of patients, physicians, and their staff (32). Here, an additional planned integration of structured access to spiritual care seems to be important, not only for the field of cancer care.

Limitations

This study was planned as an online survey and thus persons without internet access may not be reached adequately. Nevertheless, some have used to option to fill a concrete (paper-pencil) questionnaire. The sample might not be representative for all tumor patients in Germany, as we recruited in distinct centers related to members of the AG PRIO within the German Cancer Society. However, we enrolled centers from East and West Germany to balance putative differences in socialization and cultural peculiarities.

The untypical predominance of male persons (72%) in such a survey, with specific tumor localizations (i.e., prostate and larynx), can be attributed to our recruiting centers with their specific specialization. Studies enrolling more women with their specific tumor localizations are needed.

Further, we have no information about the reasons of those who have not participated. At least we were able to compare persons who have provided basic socio-demographic data but decided not to finalize the online questionnaire with those who completed the survey. Here, no significant differences with respect to gender, age, religious affiliations or tumor stage were found.

The most important limitation might be that patients´ perceived changes of their attitude and behaviors were assessed 'retrospectively' by themselves. For them, these perceptions are important and for researchers informative to provide additional support. However, longitudinal studies are required to substantiate patients´ perceptions.

Outlook

The majority of patients with malignant tumors are not necessarily hospitalized and not all have access to psychological or pastoral support which may help them to cope with their fears and worries, particularly during the Corona pandemic with its individual and social restrictions. To overcome feelings of isolation, depressive states, and insecurity about future perspectives, further supporting offers are needed, particularly in their socio-spatial surrounding where patients are mostly left alone. In this study among tumor patients from a secular society the topics of meaning in life, having trust, stable relationships, mindful encounter with nature, and times of reflection were important topics. These are the domains of psychotherapy and spiritual care. Particularly in secular societies, non-religious forms of (secular) spirituality are relevant (29). Spirituality, understood in this more broad and open context (33), can be seen as an individual resource for patient's resilience, which is "maintaining self-esteem, providing a sense of meaning and purpose, giving emotional comfort and providing a sense of hope" (34) in personal crisis management. Such spiritual care approaches (27, 35) can be easily incorporated into a more comprehensive treatment and support of tumor patients, particularly in times of pandemic restrictions.

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 Ethic Committee of the Jena University Clinic, Bachstraße 18, 07743 Jena, Germany (#5497-04/18; amendment from May 5, 2020). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

The study was initiated by JB. JH, SW, WG, and JB organized the distribution of the survey. Data analysis was performed by AB. The *Perceptions of Change* scale was developed by AB. The first draft of the manuscript was written by AB and JB. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.574314/full#supplementary-material

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The Effects of COVID-19 and Quarantine Measures on the Lifestyles and Mental Health of People Over 60 at Increased Risk of Dementia

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Background: The lockdown strategies adopted to limit the spread of COVID-19 infection may lead to adopt unhealthy lifestyles which may impact on the mental well-being and future risk of dementia. Older adults with mild cognitive impairment (MCI) or subjective cognitive decline (SCD) may suffer important mental health consequences from measures of quarantine and confinement.

Aims: The study aimed to explore the effects of COVID-19 and quarantine measures on lifestyles and mental health of elderly at increased risk of dementia.

Methods: One hundred and twenty six community-dwelling seniors with MCI or SCD were phone-interviewed and assessed with questions regarding variables related to COVID-19 pandemic, lifestyle changes and scales validated for the assessment of depression, anxiety, and apathy.

Results: The sample included 55.6% patients with MCI and 56 people with SCD. Over 1/3 of the sample reduced their physical activity and nearly 70% reported an increase in idle time. Adherence to the Mediterranean diet decreased in almost 1/3 of respondents and over 35% reported weight gain. Social activities were abolished and 1/6 of participants also decreased productive and mental-stimulating activities. 19.8% were depressed, 9.5% anxious, and 9.5% apathetic. A significant association existed between depression and living alone or having a poor relation with cohabitants and between anxiety and SCD, cold or flu symptoms, and reduction in productive leisure activities.

Conclusions: Seniors with SCD and MCI underwent lifestyle changes that are potentially harmful to their future cognitive decline, even if, with the exception of leisure activities, they do not appear to be cross-sectionally associated with psychiatric symptoms.

Keywords: COVID-19, quarantine, mild cognitive impairment, subjective cognitive decline, lifestyle changes, depression, apathy, anxiety

BACKGROUND

The pandemic emergency linked to the spread of the new coronavirus disease COVID-19, led the Italian Government to adopt extreme measures of social distancing, which paralyzed the economy, the society and the daily life of thousands of people (1). The restrictive rules involved the whole population, with particular emphasis on older people and people with pre-existing medical conditions, since these individuals are extremely at risk of developing a Severe Acute Respiratory Syndrome (SARS), hospitalization, and death. Therefore, the indications contained in the DPCM of the 8th March 2020, made an "express recommendation to all people who are elderly or suffering from chronic or multi-morbid diseases [...] to avoid leaving their home out of cases of strict need (2)."

COVID-19 can have direct and indirect effects on physical and mental health of the aged people. The SARS-CoV-2 virus which causes COVID-19 may affect central and peripheral nervous system (3, 4), having potential effects on the development and progression of neurodegenerative diseases (5). SARS-CoV-2 may also affect the cells of the intestinal mucosa, triggering intestinal inflammation and dysbiosis and potentially causing short and long-term alterations of gut microbiota, which have demonstrated strong associations with, neuroinflammation and neurodegenerative diseases (6, 7).

In order to reduce the spread of infection and optimize the management of the COVID-19 pandemic, some aspects of health management were modified: medical visits, non-urgent surgery and rehabilitative interventions were suspended, reduced, or post-poned; part of the visits were conducted by telephone or with the aid of telematic instruments. These changes may affect the management of elderly patients, who might encounter difficulties related to the modification of their routines and/or to the use of tools with which they are not familiar, and of patients with multiple comorbidities, who need integrated and continuous care, periodic symptoms monitoring, and readjustment of drug treatments. Moreover, elderly people and patients with multimorbidity may not access the medical visits for fear of being infected by COVID-19.

The lockdown measures in Italy led also to the closure of the day centers, offices of voluntary associations, churches, parishes, gyms, elderly universities, and other meeting places for seniors. Social disconnection is a risk factor for incident dementia, determining an increased risk of depression and anxiety for elderly people (8). Retrospective studies on the SARS epidemic in 2003 observed an increase in suicide rates between seniors during the epidemic period (9) and an online survey conducted last February in the regions of south-western China by Lei et al. (10), found that the inhabitants of the areas subjected to quarantine for COVID-19 showed almost double prevalence of depression and anxiety compared to the residents of the regions where isolation measures were not applied. Depression, anxiety and other neuropsychiatric symptoms represent risk factors for the conversion to dementia (11, 12); these symptoms worsen the quality of life of patients, accelerate the progression of the disease and lead to institutionalization and to an increase of health costs (13). Furthermore, lockdown could affect disproportionately the mental health of old people, whom relatives contracted COVID-19, people who live alone and whose only social contacts take place outside home, and people who do not have close relatives or friends and rely on the support of voluntary services or social assistance (14).

It is also important to note that changes in lifestyles, physical activity, and nutritional habits have a significant impact on cardiovascular risk factors (15), that are important predictors of dementia. In fact, it has been estimated that about a third of Alzheimer's disease cases (AD)—the most common form of neurodegenerative disease—is attributable to modifiable risk factors, as low education, smoking, physical inactivity, presence of hypertension, obesity, diabetes, depression (16, 17). Modifiable risk factors play also an important role in the conversion from MCI to dementia (11, 18), therefore, any COVID-19 related changes in lifestyle might affect the progression of cognitive impairment.

Eating habits may change during quarantine due to reduced availability of products, restrictions on access to stores (as, for example, the need to queue outside every store to do groceries), the fear of the possible lack of food which leads to the purchase and the consumption of packaged and preserved food, the reduced intake of fresh foods and the transition to unhealthy foods, such as snacks, and hunger-breakers—which may lead to a weight gain and to a reduced intake of antioxidants (15).

Also a decrease in the amount of time spent being physically active might have negative consequence on cognition and mental health. In a recent literature review, Narici et al. (19) described the impact of sedentariness potentially associated to COVID-19 on human body at the level of muscular, cardiovascular, metabolic, endocrine, and nervous systems and on the basis of several models of inactivity, including bed or couch rest, and reduced number of steps. A few days of sedentary life are enough to induce muscular loss, damage to neuromuscular junction and fibers' denervation (neuromuscular integrity is strictly binded to mitochondrial function), insulin resistance, reduction in aerobic capacity, fat deposition and low-grade systemic inflammation. Indeed, mechanisms involving oxidative processes, neuroinflammation and apoptosis have long been studied under different neurological conditions, as stroke, Alzheimer's disease, Parkinson's disease, multiple sclerosis (MS) and Huntington's disease (HD). Inflammatory processes are known to be closely linked to depression, hypertension, hyperlipidemia, insulin resistance, diabetes mellitus (DM), and obesity, small vessels' diseases and atherosclerosis, which are the main risk factors for the main cerebrovascular and neurodegenerative diseases, including AD (20).

A recently published study reported associations between changes in healthy behaviors and psychological distress in Australian adults during the COVID-19 pandemic: particularly, the more important were the negative changes in physical activity, sleep, smoking and alcohol consumption, the higher was the increasing in depression, anxiety and distress scores (21). No study, until today, inquired associations between changes in lifestyle and mental health issues in older adults at increased risk of dementia.

Many institutional sources, as scientific societies, the World Health Organization (WHO), the Italian Health Ministry, and the National Institute of Health, promoted and shared guidelines and tutorials dedicated to citizens or healthcare workers, in order to promote healthy lifestyles and maintain mental health during the lockdown phase (22–25). Free psychological support services were also provided including the National toll-free number 800.833.833, to meet psychological needs of people under quarantine and reduce the mental distress associated with COVID-19 (26). However, aged people, and in particular those who suffer from cognitive decline, may not have the necessary mental abilities to access these services.

Until today, there are only few studies who evaluated the effects of COVID-19 pandemic and of the quarantine measure on the psychological well-being, and lifestyles of older people and, in particular, of those at risk of cognitive decline.

Two studies observed that older people showed less COVID-19 outbreak-related emotional distress than younger ones, a more optimistic outlook and better mental health (27, 28). On the other hand, these researches enrolled seniors without cognitive impairment. It was observed that the COVID-19 related confinement aggravated the behavioral and psychological symptoms of community-dwelling older adults with mild cognitive impairment (MCI) or mild dementia, with agitation, apathy, and aberrant motor activity being the most affected symptoms (29, 30). A phone-based survey conducted by Goodman-Casanova et al. (31) in order to explore the well-being and the physical and mental health impact in community-dwelling older adults with MCI or mild dementia during the quarantine also showed that 46.1% participants reported negative experiences, such as fear of become infected or infecting family members, frustration and boredom involving not being able to take part in daily activities, loss of usual routine and social isolation. However, this latter did not assess mental health using validated scales and did not investigate whether there were any associations between lifestyle changes and negative experiences.

The aim of this observational study was to evaluate the effects of the COVID-19 outbreak and related infection control measures on the mental health and the lifestyles of older people at risk of dementia. In detail, we aimed to explore and analyse: (1) the reported changes in physical activity, leisure activities, smoking habits, caffeine and alcohol intake, eating behaviors, and in particular adherence to the MD during lockdown; (2) the presence of mental health issues, and in particular of depression, anxiety and apathy, according to validates scales. Another aim of this study was to identify (3) factors occurring during the COVID-19 pandemic which could be associated to the presence of depressive, apathetic, anxious symptoms.

METHODS

Study Design and Description

This cross-sectional observational study included community-dwelling seniors $\geq$ 60 years of age with Mild Cognitive Impairment or Subjective Cognitive Decline who were enrolled in a randomized controlled trial (GR-2013-02356043, co-financed by the Italian Ministry of Health) aimed to assess the effectiveness of a 12-week intervention of cognitive stimulation and/or physical exercise in preventing dementia or cognitive and functional decline. Since GR-2013-02356043 was temporarily suspended due to the restrictions caused by COVID-19 pandemic, from April 21st to May 7th participants were contacted and interviewed by phone by trained psychologists. Due to the exceptional situation, informed consent to the interview and the use of the data collected during the GR-2013-02356043 study was provided orally or by SMS or e-mail. The study and its amendment were approved by the Ethic Committee of the IRCCS Fondazione Santa Lucia of Rome.

Sample Characteristics

Inclusion criteria were: age $\geq$ 60 years; having undergone the last study visit in the preceeding 18 months; absence of a significant functional impairment in the last study visit, that was operationalized as a score $<$ 9 in the Functional Assessment Questionnaire (FAQ) or as a loss $<$ 20% in the Instrumental Abilities of Daily Living (IADL); diagnosis of MCI according to the International Working Group criteria (32) and cognitive impairment operationalized as a MMSE score $\geq$ 20 and $\leq$ 26 (or $\leq$ 28 for participants with 16 or more years of education) or as a score under the normative cut-off in at least one domain-specific cognitive test from an extensive neuropsychological battery (33). Participants with a diagnosis of Subjective Cognitive decline according to the International Working Group on SCD criteria (34), perception of a worsened cognitive efficiency, MMSE $>$ 26 (or $>$ 28 if 16 or more years of education) and absence of impairment in domain-specific neuropsychological scores were also included.

Exclusion criteria were diagnosis of dementia, presence of significant functional impairment, history of cerebrovascular or neurologic disease, drug or alcohol abuse, major psychiatric disease, presence of manifest sensory and motor deficits, contraindications to physical exercise, being unable—according to the caregiver's opinion—to perform the phone interview and inability to provide informed consent.

The Survey

A structured questionnaire was specifically built with Google Forms (Google LLC) by the Epidemiology and Clinical Research Laboratory (LASERC) of IRCCS Fondazione Santa Lucia, in order to facilitate the insertion of data during the telephone interview and minimize the possibility of imputing incorrect data. The survey included 8 sections:

(1) Sociodemographic, anamnestic, lifestyle, and clinical data: information was collected about height, weight, weight changes during quarantine, living conditions (alone, with others), quality of relation with co-habitants (for participants not living alone), house size and presence of external spaces such as balconies and gardens, pet-ownership, possible comorbidities as hypertension, diabetes, cardiovascular diseases and other morbidities, psychiatric diagnoses, pharmacological treatment, quality of sleep, sleep changes since the beginning of the lockdown.

(2) Cognitive status was assessed through a phone version of the Mini Mental State Examination (Itel-MMSE) (35). Itel-MMSE is a validated Italian tool which shows strong correlations with paper-and-pencil MMSE ($r = 0.85$ in the whole sample and $r = 0.77$ in MCI subjects) (36) and it is predictive of domain-specific cognitive test performances (37). A regression equation allows to convert Itel-MMSE scores into MMSE (36) score. Participants who scored ≤ 17 were excluded from further analyses, since it was not possible to ascertain that they were not too cognitively compromised to appropriately understand and answer the questions.

(3) The Functional Assessment Questionnaire (FAQ) (38), the Basic Activities of Daily Living (BADL) and the Instrumental Activities of Daily Living (IADL) (39) were administered to evaluate functional independence. A FAQ cut-point of 9 was adopted to define the presence of clinically relevant functional impairment (40, 41) while IADL and BADL have no cut-off scores.

(4) COVID-19 and health: participants were asked to specify if they received a diagnosis of COVID-19, pneumonia, influenza, or if they had cold or flu symptoms since the 1st of February; if they contacted emergency numbers and/or their GP in presence of respiratory or any other kind of symptoms; if isolation was recommended to them; if they underwent oropharyngeal swab; if they were hospitalized for COVID-19 or other respiratory disease; if they knew people who got infected with SARS-CoV-2; if they had had any contact with people who got infected with SARS-CoV-2; if infected people were hospitalized/received intensive care/died due to COVID-19; presence of any changes, due to COVID-19, in the services they received by the health system, municipality, voluntary associations and other institutions.

(5) The emotional impact of the COVID-19 pandemic: participants were asked the reason why they started auto-isolation (ministerial decree, coming back from a "red zone," personal decision before the decree, other); to quantify the impact of quarantine on their daily routine (none/slight/moderate/extreme); to specify changes of greater impact; the frequency and reasons for leaving home during the quarantine; engagement and frequency of violations of restrictive norms; the possibility of talking about their feelings and delegating some needs to relatives/friends/neighbors, to quantify any concerns about COVID-19 epidemic (none/slight/moderate/extreme), time they spent in informing and talking about the pandemic, concerns related to the influence of the pandemic on their health and their's family members'; presence/absent of persistent sadness, irritability and disengagement. Validated questionnaires were also used: the Geriatric Depression Scale-5-item (GDS-5) (42); the Apathy Evaluation Scale (AES) and the General Anxiety Disorder-7 (GAD-7) (43) were administered to screen depression, apathy and anxiety symptoms, respectively:

   a. The GDS-5 is a short questionnaire investigating satisfaction with life, social withdrawal, feelings of emptiness/boredom, helplessness, and worthlessness. A point is assigned to the presence of each of these 5 items, resulting in a global GDS-5 score ranging from 0 to 5, with a cut-off score of 2.
   b. The 18 questions of AES inquire 3 domains of apathy (decrease in goal-directed behaviors, reduction of goal-related thoughts, emotional indifference). Each item is scored on a 4-point Likert Scale, with overall AES scores ranging from 18 to 72, with a cut-off score of 38. Higher scores reflect more severe apathy.
   c. The GAD-7 is a 7-item self-rated scale which describes the most salient diagnostic features of Generalized Anxiety Disorder (GAD). Each item is rated on a 4-point Likert Scale (0 = not at all to 3 = nearly every day). A cut-off score of 10 provides the best sensitivity and specificity for GAD diagnosis.

Other questions included the impact of information about COVID-19 on their feelings; having felt the need to consult freely available psychological services; having contacted the freely available psychological services; and whether they actually did.

(6) Physical activity was assessed with a modified version of the "International Physical Activity Questionnaire—short form" (IPAQ-SF) (44). IPAQ-SF records the individual's activity according to four intensity levels: (1) vigorous-intensity activity, such as aerobics, (2) moderate-intensity activity, such as leisure cycling, (3) walking, and (4) sitting or laying. The time spent in each activity level can be converted into Metabolic Equivalent of Task (MET) values, to obtain an index of the amount of the individual's total energy expenditure. A cut-point of 600 MET/week, roughly corresponding to 150 min of moderate intensity activity, was adopted to classify participants as physically active/inactive. Participants were asked to evaluate their physical activity levels via IPAQ during the last week before the phone call and during the last week before the lockdown.

(7) Food habits were assessed using the Mediterranean Diet Adherence Screener (MEDAS) (45), a 14-item questionnaire requesting participants to report food habits (consumption of olive oil and greater consumption of white meat, compared to red meat) and frequency of 11 consumption/amount of 12 main foods related to the Mediterranean Diet. Each of the 14 MEDAS items is assigned a score of 0 or 1, according to predetermined criteria. The maximum overall score is 14. Participants who obtained a MEDAS score < 9 were classified as non-adherent to the Mediterranean diet. Participants were also asked to provide information about any changes dietary changes consequent to the lockdown, on tobacco, alcohol, and caffeine consumption and changes in consumption since the beginning of the lockdown were also inquired.

(8) A self-report questionnaire was created to investigate participation in 16 cognitively stimulating leisure activities or hobbies. Social and leisure activities were grouped following the classification adopted in the Kungsholmen Project (46). Mental stimulating activities consisted of reading books/newspapers, doing puzzle games like

crosswords, card solitaires, sudoku, or others; singing; keeping informed about—or attending—economic, social, politic, or other news or events. Social activities included traveling; going to the cinema, theater concerts, or art exhibitions; playing cards/games with other people; volunteering/charitable activities; meeting relatives and friends. Productive activities included housekeeping, cooking, bricolage, collecting; writing; knitting or embroidery; painting, drawing or photographing; gardening; others. Recreational activities included watching television, movies, concerts, or theatral plays on the internet and listening to music.

Statistical Analyses

Data were collected, preserved and analyzed in compliance with the applicable privacy rules. All the data were tabulated in a Google Sheet file.

The statistical analyses were performed with IBM SPSS ver. 20 (IBM, Chicago, IL, USA). GDS-5, GAD-7, AES, IPAQ, and MEDAS scores where dichotomized according to the previously described cut-points. A first description of the epidemiological characteristics of the sample was provided—data are represented as absolute frequencies and percentages (%) for categorical variables, as average ± standard deviation for continuous normally distributed variables or as median and interquartile range [IQR] for continuous not normally distributed variables; the Shapiro–Wilk test was performed in order to evaluate the normality of distributions.

The Pearson or Spearman correlation coefficients were then calculated in order to evaluate the correlation between continuous variables. Chi square test was used to assess the association between categorical variables. The McNemar test was calculated to inquire the difference between categorical variables before and after the COVID-19 lockdown. *T*-Test and McNemar *U*-test were performed to verify the presence of any difference between groups in continuous scores. Significance was set for a $p < 0.05$.

Univariate logistic regression analyses were performed to evaluate the association of variables—i.e., age, instruction, sex, group (MCI vs. SCD), Itel-MMSE score, pluripathologies, overweight, weight changes, smoking, changes in smoking habits, alcohol consumption, changes in alcohol consumption, caffeine, increased caffeine intake, living alone, quality of relationship with cohabitants, symptoms of cold or flu, knowing people with covid-19, leaving home at least once a week, personal decision to start quarantine, perceived impact of quarantine (high-moderate vs. fair-absent), presence of balcony/garden in their home, extent of concerns regarding COVID-19 pandemic, time taken to inquire about COVID-19, time taken to talk about COVID-19, extent of concerns for their health or that of their family members, IPAQ at least 600 MET/week, IPAQ decreased physical activity, adherence to the Mediterranean diet according to MEDAS score, dietary changes, variation in leisure activities—with the presence of depression in GDS-5, apathy in AES and anxiety in GAD-7. The association between being/not being anxious or apathetic or depressed was also assessed.

Finally, variables found to be statistically significant (at $p < 0.1$) in the univariate analyses were included in conditional multiple logistic models in order to determine the continuous or categorical variables which independently associated with the presence of depression, anxiety or apathy.

Ethical Aspects

The study protocol was prepared in full application of Good Clinical Practice (GCP) guidelines for observational studies and of the Declaration of Helsinki for clinical trials in humans. The study was approved by the Ethic Committee of the IRCCS Fondazione Santa Lucia. Researchers made phone contact in respect of individual autonomy, and in compliance with current privacy regulations.

RESULTS

Sociodemographic and Clinical Characteristics of the Sample

One-hundred seventy-six seniors at risk were contactable, who had been evaluated at LASERC in the previous 18 months. Five of them (2.84%) were unavailable and 40 (22.73%) refused to be interviewed; according to the caregiver's opinion, 3 (1.70%) were unable, due to cognitive impairment, to complete the interview. Therefore, 128 seniors were interviewed. Two of them (1.56%) were excluded from subsequent analyses because they had obtained an Itel-MMSE score < 17. The final sample therefore consisted of 126 participants (71.59% of the interviewable seniors at risk) aged between 60 and 87 years (mean age = 74.29 ± 6.51 years); the sample was mainly composed of females (81.00%) and included 70 (55.55%) patients with MCI and 56 people with SCD (**Table 1A**). The interviewees obtained a median Itel-MMSE score of 21 (IQR = 2) and a median FAQ score of 0 (IQR = 1) No differences were observed between the cognitive and functional scores of participants who, in the last visit, were classified as MCI or SCD (**Table 1B**). Although the entire sample, with the exception of one interviewee, was generally independent in carrying out the instrumental activities of daily life, 5.55% of the respondents reported they needed to be helped in some higher cognitive-demanding tasks or to delegate.

Clinical Characteristics

One hundred and one participants (96.03%) have at least one comorbidity among hypertension (53.97%), hyperlipidemia (49.21%), diabetes (10.32%), cardiovascular diseases (31.75%), musculoskeletal disorders (16.67%), thyroid dysfunction (28.57%), autoimmune diseases (7.14%), pre-existing respiratory illnesses (8.73%) or others (31.75%); 72.23% aged people had multi-morbidity; 105 (91.27%) regularly assumed one or more medicines. Although a slightly higher number of seniors with MCI had clinical complaints, there were no statistically significant differences in the proportions of SCD or MCI participants with clinical conditions and with multicomorbidity (**Table 1C**).

One hundred and three participants (81.75%) reported good/fair sleep quality; 7 (5.55%) reported a deterioration in sleep quality after the start of the lockdown, with no statistically

TABLE 1 | Sociodemographic, clinical, cognitive, and functional characteristics of the sample, divided by diagnosis.

	SCD	MCI	Total
A. Demographics			
Cases	56 (44.4)	70 (55.6)	126 (100)
Females	47 (83.9)	55 (78.6)	102 (81.0)
Age (years)	74.39 ± 6.38	74.20 ± 6.66	74.29 ± 6.51
Education (years)			
B. Cognitive and functional status			
MMSE score (last visit)	*27.55 [3.07]*	*26.78 [2.10]*	*27.30 [2.40]*
Itel-MMSE score	21.50 [1.50]	21.00 [2.00]	21.00 [2.00]
FAQ score	0.00 [0.50]	0.00 [2.00]	0.00 [1.00]
C. Clinical data			
Overweight/obesity	25 (44.6)	37 (52.9)	62 (49.2)
Hypertension	27 (48.2)	41 (58.6)	68 (54.0)
Hyperlipidemia	28 (50.0)	34 (48.6)	62 (49.2)
Diabetes	5 (8.9)	8 (11.4)	13 (10.3)
Cardiovascular dis.	13 (23.2)	27 (38.6)	40 (31.7)
Musculoskeletal dis.	10 (17.9)	11 (15.7)	21 (16.7)
Thyroid dis.	14 (25.0)	22 (31.4)	36 (28.6)
Autoimmune dis.	2 (3.6)	7 (10.0)	9 (7.1)
Pre-existing respiratory dis.	3 (5.4)	8 (11.4)	11 (8.7)
Other dis.	11 (19.6)	14 (20.0)	25 (19.8)
2 or more comorbidities	38 (67.9)	54 (77.1)	92 (73.0)
Regular drug consumption	52 (92.9)	63 (90.0)	115 (91.3)
Poor sleep quality	47 (83.9)	56 (80.0)	103 (81.7)
Worsened sleep	3 (5.4)	4 (5.7)	7 (5.6)
D. Living conditions			
Lived alone	15 (26.8)	21 (30.0)	36 (28.6)
Absence of external openings at home	9 (16.1)	10 (14.3)	19 (15.1)
Poor relation with cohabitants	9 (22.0)	6 (12.2)	15 (16.7)
Had pets	8 (14.3)	20 (28.6)	28 (22.2)

Results are reported as absolute frequencies and percentages (in brackets) for categorical variables, as average ± standard deviation for continuous normally distributed variables or as median and interquartile range [IQR] for continuous not normally distributed variables. In italics, the statistically significant differences between participants with SCD and MCI, with p-level < 0.05, are reported.

TABLE 2 | Clinical information regarding the health of the participants and their acquaintances, and data concerning the quarantine and facilities available during it.

	SCD	MCI	Total
A. COVID-19 and health status			
Cold or flu symptoms	17 (30.4)	12 (17.1)	29 (23.0)
Referred to the physician/emergency services	5 (29.4)	1 (8.3)	6 (20.7)
Insulation recommended	1 (20.0)	0 (0.0)	1 (16.7)
Received COVID-19 diagnosis	0 (0.0)	0 (0.0)	0 (0.0)
New drugs prescription	*8 (14.5)*	*2 (2.9)*	*10 (8.0)*
B. COVID-19 among known people			
Knew COVID-19 cases	4 (7.1)	7 (10.0)	11 (8.7)
Had physical contact with them	1 (25.0)	2 (40.0)	3 (33.3)
Friends/relatives hospitalized for COVID-19	1 (25.0)	2 (40.0)	3 (33.3)
Friends/relatives dead for COVID-19	1 (25.0)	1 (20.00)	2 (22.2)
High/moderate distress associated with it	2 (50.0)	2 (40.0)	4 (44.4)
C. Quarantine			
Started spontaneously	15 (26.8)	20 (28.6)	35 (27.8)
Of high/moderate impact on daily routine	48 (85.7)	52 (74.3)	100 (79.4)
Violated for unauthorized reasons	4 (7.1)	4 (5.7)	8 (6.3)
Determined changes in living conditions	5 (9.1)	2 (2.9)	7 (5.6)
D. Facilities			
Home delivery from volunteers	2 (3.6)	0 (0.0)	2 (1.6)
Called COVID-19 related numbers	0 (0.0)	0 (0.0)	0 (0.0)
Had someone to turn to for help	50 (89.3)	67 (95.7)	117 (92.9)
Had someone to talk with about his/her feelings	55 (98.2)	65 (94.2)	120 (96.0)

Results are reported as absolute frequencies and (percentages). In italics, the statistically significant differences between participants with SCD and MCI, with p-level < 0.05, are reported.

significant differences between MCI and SCD participants (**Table 1C**).

Living Conditions

Thirty-six participants (28.57%,) lived alone, while the remainder shared their home with one or more co-habitants (in 95.55% of cases, spouses and/or children); 4.8% declared that they had changed their living situation in order to deal with the quarantine, by welcoming relatives into their home or by moving to their relatives' houses (**Table 2C**); one participant with SCD reported that he had gone to live alone, to avoid the transmission of the infection to his relatives. The relationship with the cohabiting people was declared good or fair from the clear majority of the sample, with only 2 cases reporting a poor relationship. Nineteen aged ones (15.08%) stated that their houses did not have a garden, a terrace or any other type of external opening that would allow them to go outside without leaving home.

Twenty-eight participants (22.22% of the sample, 6 of them living alone) had one or more pets (in 100% of cases dogs or cats). No differences were reported by participants with SCD or MCI regarding living conditions (**Table 1D**).

COVID-19 and Health Status

Twenty-nine (23.01%) had cold or flu symptoms since the second half of february, and 6 (20.69% of the symptomatics) contacted the doctor and/or emergency numbers; 2 of them (33.33%) received diagnosis of flu. Isolation was recommended to 1 participant, who did not undergo oropharyngeal swab. Two asymptomatic seniors (1.59% of the sample) swabbed, with negative results, in order to undergo day-hospital interventions. Therefore, none of the participants were diagnosed with COVID-19. Ten seniors (7.94%) were prescribed new medicines during the COVID-19 emergency, in 8 (80%) cases medicines to treat cold or flu, in one case melatonin and in one lorazepam due to sleep disturbances and anxious symptoms that emerged after the lockdown. Significantly more seniors with SCD received new drug prescriptions than participants with MCI (**Table 2A**).

Eleven participants (8.73%) stated that they knew people who had contracted COVID-19 (**Table 2B**). Three 3 of the COVID-19 cases were hospitalized and 2 died during hospitalization. Four of the participants who knew or had contact with COVID-19 cases (36.36%) experienced symptoms such as soreness (2 cases, one of which also experienced difficulty breathing), running nose (1 participant), anxious symptoms such as tachycardia and tightness in the chest (1 respondent). Two of these 11 participants had physical contact with confirmed cases of COVID-19 and one with a suspected case of COVID-19 (**Table 2B**). None of the three cases was hospitalized or died and none of the 3 participants who had close contact with a confirmed/suspected case experienced flu-like or anxious symptoms.

The stress associated with knowing and/or having been in contact with a person affected by COVID-19 was assessed as moderate/high by 4/11 seniors (36.36%) and as low/absent by 3 (27.27%); 4 participants did not know how to answer, as they claimed to be unable to discriminate the amount of stress that was specifically associated with this condition from to the overall stress associated with the pandemic (**Table 2B**).

The COVID-19 Related Quarantine

Ninety-two interviewees (73.02%) stated that they had started quarantine following the ministerial decree or after returning from a "red zone" (1 case); More than a quarter participants (26.98%) declare that they started the isolation spontaneously, before the official regulation (**Table 2C**).

Only 2 seniors (1.59%) declared that the Government provisions had had no effect on their daily routine. For everyone else, the lockdown had a big (33.33%), moderate (46.03%), or slight (18.25%) impact (**Table 2C**).

Slightly more than a responder in 10 (11.90%) reported that they never left home during the quarantine. The others went outside daily or almost daily (23.02%), several times a week (19.84%), once a week (20.63%), several times a month (17.46%) or less frequently (7.14%), for reasons permitted by the Ministerial Decree. Eight seniors (6.35%) admitted having violated the quarantine for unauthorized reasons such as meeting other people (37.50% of violations), leaving home beyond the allowed distance (50.00%) or others (25.00%) (**Table 2C**).

None of the interviewees stated that, before the COVID-19 emergency, they had received any type of home assistance from the Health System or the Municipality, or from voluntary associations. Two participants (1.60% of the 125 respondents) received facilities created to deal with the consequences of the pandemic (home delivery of medicines and groceries from volunteers). 117 (92.86%) seniors reported having other people available to whom they can ask for help in case of need, 7 (5.55%) claimed that they had no need to seek outside help and 2 (1.59%) admitted that they had no one to turn to, even if they needed (**Table 2D**).

One-hundred and twenty elders at risk (96.00% of 125 responders) reported that they had someone to turn to (family members, friends or other people) when they needed to talk about their feelings; 123 participants (98.40%) reported that they perceived no need having recourse to the free psychological public support services that were available to deal with the emotional impact of the pandemic; 2 seniors with SCD stated that they would have resorted to them, however they did not (**Table 2D**).

TABLE 3 | Lifestyles, behaviors and emotional state during quarantine, divided by diagnosis.

	SCD	MCI	Total
A. Lifestyles during quarantine			
Smoke	8 (14.3)	10 (14.3)	18 (14.3)
Alcohol	23 (41.1)	33 (47.1)	56 (44.4)
Caffeine	45 (80.4)	61 (87.1)	106 (84.1)
Low physical activity (< 600 MET/week)	23 (41.1)	37 (52.9)	60 (47.6)
Low adherence to MeDi diet	22 (40.0)	31 (44.3)	53 (42.4)
B. Daily leisure activities during quarantine			
Passive recreational	54 (98.2)	69 (98.6)	123 (98.4)
Mind-stimulating	40 (72.7)	56 (80.0)	96 (76.8)
Productive	48 (87.3)	61 (87.1)	109 (87.2)
Social	2 (3.6)	4 (5.7)	6 (4.8)
C. Time spent for COVID-19			
Time spent informing on media < 30 min/day	15 (26.8)	22 (31.4)	37 (29.4)
< 2 h/day	19 (33.9)	19 (27.1)	38 (30.2)
2+ h/day	22 (39.3)	29 (41.4)	51 (40.5)
Time spent talking about it < 30 min/day	36 (64.3)	44 (62.9)	80 (63.5)
< 2 h/day	12 (21.4)	15 (21.4)	27 (21.4)
2+ h/day	8 (14.3)	11 (15.7)	19 (15.1)
High/moderate influence of news on feelings	42 (75.0)	47 (68.1)	89 (71.2)
D. Psycho-emotional status			
Spontaneously declared high/moderate concern	46 (83.6)	58 (82.9)	104 (83.2)
Spontaneously declared being sad/depressed	17 (30.4)	17 (24.6)	34 (27.2)
Spontaneously declared being nervous/irritable	20 (35.7)	18 (25.7)	38 (30.2)
Spontaneous declared loss of interest	8 (14.3)	10 (14.3)	18 (14.3)
GDS-5 $\geq$ 2	13 (23.2)	12 (17.1)	25 (19.8)
GAD-7 $\geq$ 10	*9 (16.1)*	*3 (4.3)*	*12 (9.5)*
AES $\geq$ 38	3 (5.4)	9 (12.9)	12 (9.5)

Results are reported as absolute frequencies and (percentages). In italics, the statistically significant differences between participants with SCD and MCI, with p-level < 0.05, are reported.

Lifestyles, Behaviors, and Emotional Status During Quarantine

Lifestyles

Eighteen seniors (14.3%) were smokers (15.82 ± 7.86 cigarettes/day on the average). A third of them declared having smoked a higher number of cigarettes than before, since the beginning of the quarantine, while 2 reported having smoked less (Graph 1 reports percentages referred to the valid cases, i.e., participants who answered the question about smoke). Nobody started or stopped smoking after the lockdown. Non-significant differences were observed among MCI and SCD participants in the proportion of smokers (**Table 3A**) or of people who reported any variation in smoke (Chi-2, 1 df $= 0.11$ $p = 0.744$).

Fifty-six interviewees (44.4%) reported regular alcohol consumption (**Table 3A**), on average 1.15 ± 0.69 alcoholic units (AU) per day during quarantine. During the lockdown, 7.0% of drinkers increased their alcohol consumption, 12.4% decreased it—among them, 2 (28.6%) declared having stopped drinking alcohol (Graph 1). Two participants declared having started drinking ½ glass of wine per day. Non-significant differences were observed among MCI and SCD participants in the proportion of drinkers (**Table 3A**) or of people who reported any variation in alcohol consumption (Chi-2, 1 df $= 1.80$ $p = 0.180$).

One-hundred and six participants (84.1%) reported drinking coffee or tea (**Table 3A**), on average 2.09 ± 1.02 cups/day. During the lockdown, caffeine consumption remained stable for most of them (84.9%), while 6.6% declared having increased and 8.5% stated having decreased the number of cups of coffee/tea per day (Graph 1 reports percentages referred to valid cases). Nobody started or stopped drinking caffeine during the lockdown. Non-significant differences were observed among MCI and SCD participants in the proportion of caffeine consumers (**Table 3A**) or of people who reported any variation in caffeine consumption (Chi-2, 1 df $= 0.76$ $p = 0.384$).

Forty-six participants (36.5% of valid cases and 43.4% of those that before the lockdown reached the recommended threshold of 600 MET/week) declared having decreased their physical activity to < 600 MET/week, since the start of the lockdown; 69.60% of the sample reporting an increase in the time spent sitting or laying down (idle time). At the moment of the interview, half (52.4%) of the sample did not reach that threshold, with no significant differences between MCI and SCD participants (**Table 3A**), while, before the lockdown, only 25 interviewee (19.8%) had scored < 600 MET/week. McNemar's test determined that there was a statistically significant difference in the pre- and post-quarantine proportions of participants above /below the recommended 600 MET/week threshold ($p < 0.001$). Non-significant differences were observed between MCI and SCD participants (**Table 3A**) in the proportions of people who reported any variation in physical activity (Chi-2, 2 df $= 1.75$ $p = 0.416$). However, 5 of the 25 respondents who, before the lockdown did not reach the recommended threshold of 600 MET/week, increased their physical activity levels to over 600 MET/week during quarantine, and 6 of them reported a decrease in idle time.

Forty-seven participants (37.6% of 125 respondents) reported that the quarantine had caused some changes in their nutritional habits. Of these, 19.2% reported to eat in higher amounts, 31.9% to eat more sweets, 12.8% to use more frequently preserved or frozen foods, 8.5% to have a less varied menu, 14.9% to eat in an unregulated or unhealthy way, 6.4% to eat more regularly/healthily, 2.5% to eat less, 17.0% other. However, 57.6% of the sample obtained MEDAS scores indicative of adequate adherence to the Mediterranean diet (**Table 3A**). Non-significant differences were observed among MCI and SCD participants in the proportion of people with adequate adherence to MD (**Table 3A**) or of people who reported any variation in dietary habits (Chi-2, 2 df $= 0.75$ $p = 0.688$).

During the quarantine, 35.7% of the sample reported having gained weight, and 11.1% declared having lost weight (Graph 1). At the moment of the interview, almost half of the participants (49.2%) were overweight or obese; and 2.4% were underweight. Non-significant differences were observed among MCI and SCD participants in the proportion of people with overweight/obesity (**Table 3A**) or of people who reported any weight change (Chi-2, 2 df $= 0.82$ $p = 0.663$).

One hundred and twenty-five participants completed the evaluation of the leisure activities (**Table 3B**). As expected, the whole sample declared having reduced their social activities since the start of the quarantine. However, 11.2% of the participants reported that they still engaged in social activities such as meeting with other people keeping the safety distance (mainly neighbors) or attending groups on online platforms at least once at week, without differences between SCD and MCI responders in the proportion of people engaging in social activities (**Table 3A**). The 58.1, 45.2, and 55.2% of the sample reported an increase in the time spent engaging in recreational, mind-stimulating and productive activities, respectively, while 5.6, 16.1, and 16.8%, respectively, declared carrying out these activities less frequently than before the lockdown. At the time of the interview, 76.8 and 96.0% of the interviewees, respectively, reported to practice mental activities at least daily and productive activities at least weekly. Non-significant differences were observed among MCI and SCD participants in the proportion of people which engaged in these activities (**Table 3B**) or of people who reported any variation in them (Recreational: Chi-2, 2 df $= 2.29$ $p = 0.318$; Mind-stimulating: Chi-2, 2 df $= 2.81$ $p = 0.245$; Productive: Chi-2, 2 df $= 0.36$ $p = 0.834$).

Variations in lifestyles after the lockdown in valid cases (i.e., in the participants who answered each question) are shown in Graph 1. Variables with * are reversed, so that red represents a potentially negative change in health and/or on the risk of dementia, and blue represents a positive one.

Behaviors

The estimated time spent in searching information about COVID-19 in the media was < 30 min/day for 37 (29.4%) participants; < 2 h/day for 38 (30.2%); and 2 or more h/day for 51 (40.5%). The estimated time spent in talking about COVID-19 with other people was < 30 min/day for 80 (63.5%) participants; < 2 h/day for 27 (21.4%); and 2 or more hours/day for 19 (15.1%). According to 19 seniors (15.2% of 125 respondents), the news about the coronavirus that they received from the media (TV, radio, newspapers, social networks, and others), had a great influence on their feelings. 56.0, 23.2, and 5.6%, respectively, reported that they were enough, little or not at all influenced by these informations (**Table 3C**).

Psycho-Emotional Consequences

The most important changes with the greatest emotional impact associated with the lockdown concerned the inability to meet children, grandchildren or other family members (41.3%) or friends (19.1%); attend meeting places, cinema, theater or dance hall (29.4%); leaving home, going out for a walk (24.6%); carry out the usual physical activity outside home or at the gym (23.8%); get help from a domestic worker (14.3%); cancellation of medical visits or physiotherapy treatments (5.6%); absence of human contact (5.6%); others (33.3%). Seven participants (5.6%) reported no substantial changes.

Forty people (31.8%) rated their level of concern associated with the COVID-19 pandemic as high, 64 (50.8%) as moderate, 16 (12.7%) as low and 5 (4.0%) as absent. Main concerns included the possibility of contracting COVID-19 (55.0%); the possibility that some family member fell ill with COVID-19 (53.3%); worries regarding the effect of the pandemic on their own health (50.8%) or on the health of their family members (35.8%) (e.g., difficulty in receiving adequate and timely treatment for their comorbidities due to the emergency); concerns about the personal/family economic or working situation (34.2%); concerns for the socio-economic future of the Nation (38.3%); other (19.1%).

The 11.1% of the sample declared themselves very concerned about their health or their family's health; 48.4, 23.8, and 16.7%, respectively, declare themselves quite, slightly and not at all worried.

More than a quarter participants (27.0%) declared themselves not worried at all that their health or their family's health may worsen during the pandemic; 45.2, 23.8, and 4.0%, respectively, declare themselves slightly, quite, and very concerned.

Thirty-four interviewees (27.2% of 125 respondents) declared that, since the start of the lockdown they had often felt sad, depressed, downcast, so much so that nothing could cheer them up. When evaluated with GDS-5, 25 (19.8%) participants obtained a score $\geq$ 2 (**Table 3D**). Depression was significantly associated with living alone or being in a poor relationship with cohabitants, low sleep quality and not owing a pet (**Table 4**).

Thirty-eight seniors (30.2% of the sample) reported feeling often irritated, nervous and getting angry easily. When evaluated with GAD-7, 47 (37.3%) participants scored $\geq$ 5 and 12 (9.5%) obtained scores indicative of at least moderate anxiety (**Table 3D**). Anxiety resulted associated with SCD, having had cold/flu symptoms, reduction in productive activities, and with high time spent searching information about COVID-19 on the media (**Table 4**).

Eighteen interviewees (14.3%) reported having lost interest in many of their activities, hobbies, or friends/relatives since the beginning of the quarantine; 12 (9.5%) participants were categorized as apathetic according to AES (**Table 3D**). Apathy associated significantly with living alone or being in a poor relationship with cohabitants, having had cold of flu symptoms, non-adherence to MD and reduction in productive activities.

Multivariable Logistic Regression Analyses

In the multivariable logistic regression analyses (**Table 1**), depression resulted significantly associated with living alone or having a poor relation with cohabitants (OR: 2.79, 95% CI: 1.20–6.49); anxiety associated significantly with the presence of Subjective Cognitive Decline (OR: 4.39, 95% CI: 1.03–18.69, **Table 1A**), having had cold or flu symptoms (OR: 4.01, 95% CI: 1.13–14.24, **Table 1B**), and with a reduction in productive activities (OR: 4.41, 95% CI: 1.10–17.76). No significant associations were observed with apathy for variable that associated in the univariate analyses, when included in the multiple conditional model (**Table 1C**).

DISCUSSION

During COVID-19 outbreak, quarantine demonstrated an effective measure to prevent the further spread of the infection. However, it had negative effects that may hamper the psycho-physical well-being of people who are quarantined and it determined changes in lifestyles which might be associated with an increased future risk of dementia. To our knowledge, this is among the first studies evaluating the impact of the COVID-19 lockdown on lifestyle changes among seniors at increased risk of dementia and to analyse the association between variables related with the COVID-19 pandemic and depression, anxiety and apathy in this population.

Quarantine implied that over a third of the sample reduced their physical activity levels from over 600 MET/week to < 600 MET/week. In addition, nearly 70% of the sample reported an increase in time spent sitting or lying down. Adherence to the Mediterranean diet also decreased in almost a third of respondents and over 35% reported weight gain. Minor changes were observed with respect to smoking or drinking alcohol or caffeine. As widely expected, the sample completely reduced social activities, but, at the same time, nearly 60% of seniors reported an increase in time spent in passive recreational activities, such as watching television or listening to the radio. Conversely, one in six elderly people at risk of dementia also decreased production and mental-stimulating activities (**Figure 1**) even if most of the sample, especially people with MCI, engaged in daily mental-stimulating activities. Changes toward increased sedentary lifestyle, overweight, unhealthy diet and lower engagement in non-passive recreational activities can increase the risk of dementia, since these variables have been consistently associated in middle age with a subsequent increased incidence of Alzheimer's disease and other dementias (16). An association, although weaker and non-invariable, also exists with an increased risk of dementia in people with MCI (11, 18) and recent evidence indicate that poor social interactions, small social networks, and low level of physical activity are correlated with depressive symptoms in community-dwelling seniors with MCI (47).

If it is true that the changes implied by the quarantine may be temporary and their effects lower compared to long-lasting lifestyles, it is equally conceivable that, at the end of the lockdown phase, many people will not return to their pre-pandemic "normal routine." Unhealthy lifestyles adopted during lockdown could be maintained despite the reopening—for example, it is possible that people who before the lockdown used to go to the gym to exercise and who during quarantine stopped their training, will not start again, because of the fear of contagion or other reasons—similarly to what reported about MERS (Middle East Respiratory Syndrome), where it was observed that psychological difficulties associated to quarantine

TABLE 4 | Univariate and multivariate analyses of factors which resulted associated with depression, anxiety and apathy.

	Univariate analysis				Multivariate analysis			
	OR	**95% CI inf**	**95% CI sup**	***p***	**OR**	**95% CI inf**	**95% CI sup**	***p***
A. Depression								
Alone or poor relation	4.19	1.64	10.68	0.003	*2.79*	*1.20*	*6.49*	*0.017*
Poor sleep quality	2.70	0.99	7.35	0.047	1.85	0.80	4.29	0.154
No pets	8.77	1.13	66.67	0.038	0.16	0.02	1.20	0.075
B. Anxiety								
Subjective cognitive disorder	4.28	1.10	16.64	0.036	*4.39*	*1.03*	*18.69*	*0.05*
Cold/flu symptoms	3.96	1.17	13.41	0.027	*4.01*	*1.13*	*14.24*	*0.03*
Reduction in productive activities	3.26	0.86	12.36	0.082	*4.42*	*1.10*	*17.76*	*0.04*
Time spent searching information	3.30	0.94	11.63	0.063	2.45	0.71	8.45	0.16
C. Apathy								
Alone or poor relation	5.14	1.32	20.06	0.018	3.73	0.96	14.45	0.057
Cold/flu symptoms	3.96	1.17	13.41	0.023	2.56	0.81	8.09	0.110
Non-adherence to MD	3.02	0.86	10.63	0.085	2.76	0.83	9.21	0.099
Reduction in productive activities	4.33	1.22	15.32	0.023	2.66	0.82	8.68	0.105

In italics, the variables statistically associated with each psychological disorder in the multivariate analysis are reported, with p-level < 0.05. OR, odds ratio; 95% CI, 95% confidence interval; inf, inferior; sup, superior.

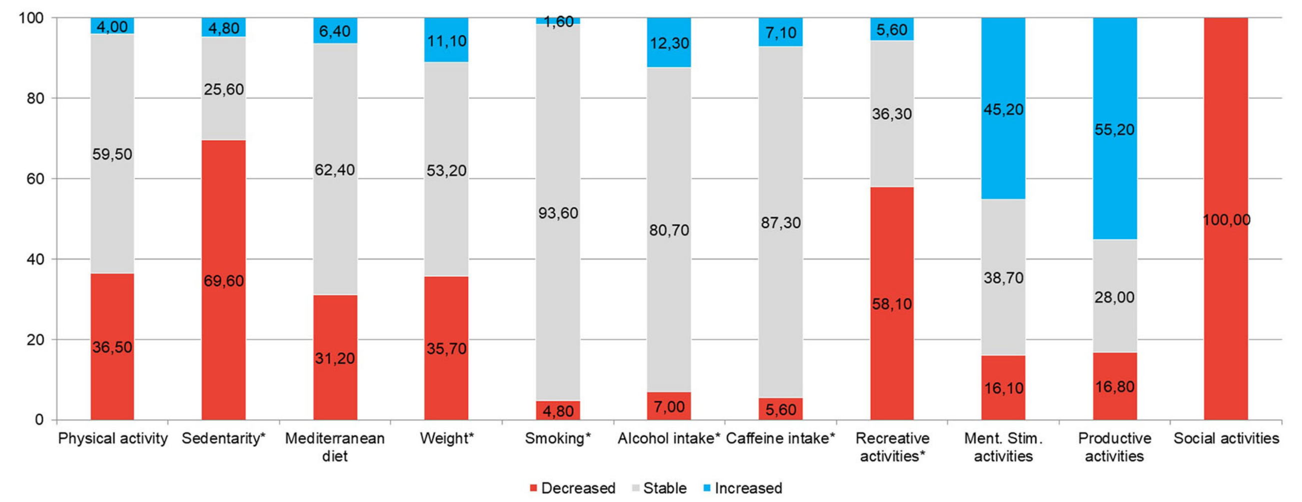

FIGURE 1 | Lifestyle changes after the lockdown. The variable with * are reversed, so that red represents a potentially negative variation on health and/or on future risk of dementia, and blue represents a positive one.

persisted for 4–6 months beyond the end of the restrictions in almost half of the people (48). Therefore, the use of quarantine as a measure of public health must consider the potential acute and chronic psychological effects of this procedure. In addition, the early assessment of the consequences of this measure on health conditions of the population at risk of dementia and the study of the strategies to limit this effect are particularly important (30).

Eighteen seniors of our sample (14.29%) were smokers. A third of them declared having smoked a higher number of cigarettes than before, since the beginning of the quarantine, while only 2 reported having smoked less. Moreover, most of our participants who, in the pre-quarantine were physically active, reduced time spent engaging in physical activity. Our results are in agreement with a recent web-based cross-sectional study (49) which showed an increased number of cigarettes per day among those who were smokers, and are in disagreement with those from a recent survey conducted by Di Renzo et al. (50) that showed reduced smoking habits and increased physical activity after the COVID-19 lockdown in a high proportion of Italian responders: authors hypothesized that their this results might be due to the fear, in Italians, of increased risk of respiratory distress and mortality from COVID-19 associated with smoke (51). Their sample was mainly composed of younger respondents without cognitive impairment. It has been hypothesized that people with cognitive decline may not be fully aware of the risks associated with the pandemic, and therefore less likely to adopt coping strategies. On the other hand, the proportion of smokers between participants with MCI and SCD in our sample is largely overlapping, so our results our results cannot be solely attributable to a lack of risk awareness. It is possible that the observed differences with respect to that survey are attributable to age differences in risk perceptions. Accordingly, the recent survey of Bruine de Bruin (28) observed that the fear of contracting the virus or of health consequences of the COVID-19 pandemic appears to decrease with increasing age.

Nevertheless, also a consistent part of our participants still implemented coping strategies such as increasing physical activity levels, improving their nutritional style, engaging in cognitively stimulating or productive activities, reducing smoking. Moreover, different from Di Renzo et al. (50), only 14.89% of our respondents reported greater tendency to eat unhealthy after the lockdown (less than half compared to 35.08% of their sample). However, this higher percentage may again reflect age differences: in fact, they reported higher appetite increase in younger people while our sample is made up of seniors $\geq$ 60 years of age. It has been shown that the adoption of healthy behaviors during quarantine may be useful to fight against the mental and physical consequences of COVID-19 quarantine, especially in older people. Our study did not reveal any association between lifestyle factors and GDS-5, GAD-7 scores o AES in our sample. Therefore, at least in the short term, maintaining an active lifestyle seems not to be protective against cognitive decline, depression or anxiety. However, we must consider the cross sectional nature of our study, which is a limitation that does not allow us to draw any definitive conclusions. It is therefore plausible that in the long term the seniors who engaged in active lifestyles will have a slower progression of their cognitive decline and a lesser probability that their mental health status will worsen.

Although Bruine de Bruin et al. (28) observed that older people experience less negative emotions than younger ones, we found that, since the start of the lockdown, thirty-four participants reported that they often felt so much sad, depressed or downcast that nothing could cheer them up. The 19.84% of our interviewees had a GDS-5 score indicative of depressive symptoms. Our results, showing a significant association between depression and living alone or having a poor relationship with the cohabitants, are in contrast with a recent cross-sectional study based on a national online survey in Spain conducted by García-Fernandez et al. (27) which did not show any relationship between loneliness and increase of depression in older adults. However, our results are consistent with another study conducted by phone-interviewing elders with MCI (31) and with the hypothesis that quarantine period affects mental health of older people who live alone and whose only social contacts take place outside home (14). Therefore, our results suggest that particular attention should be placed on social isolation for older people living alone or having bad relationships with family-members.

In our study, 30.16% reported feeling often irritated, nervous and getting angry easily. The scores obtained in GAD-7, showed that 37.30% of the participants scored $\geq$ 5 (mild anxiety) and 9.52% obtained scores indicative of clinically significant anxiety. These results are consistent with the study by Bruine de Bruin et al. (28). We found a significant association between anxiety and perceiving SCD: this could mean that people with SCD are more concerned about their cognitive status and their health, showing increased awareness. Increased anxiety is also associated with the presence of flu symptoms: considering their higher vulnerability, older people perceive the risk of contracting the virus and the manifestation of flu or COVID-19 symptoms, e.g., fever or cold, which inevitably increases the concern of a probable contagion. On the other hand, it is equally possible that anxious people are overly focused on their symptoms and emphasize signs of cognitive decline that are part of normal aging and physical symptoms of negligible severity. In fact, none of our participants had such severe flu or respiratory symptoms that they required hospitalization or performing the oropharyngeal swab. In addition, we found an association between anxiety and reduced productive leisure activities: we hypothesized that, probably, these people could not get away from their worries. However, it is also possible that the impossibility of dedicating to some productive activities, which were carried out outside the home before the lockdown, led to greater levels of anxiety. Again, the cross-sectional nature of the study does not allow us to verify any causal associations.

In a recent study, Beatriz Lara et al. (30) interviewed MCI and mild AD patients 5 weeks after the start of the lockdown by using the Neuropsychiatric Inventory (NPI) and the EuroQol-5D who were evaluated with the same scales a month before the lockdown. In both groups, symptoms related to apathy increased after a few weeks: comparing the presence of these symptoms before and after lockdown, they found that both in MCI and in AD patients apathy increased, although they did not observe changes in their quality of life. We found that 14.29% of the participants reported having lost interest in many of their activities, hobbies, or friends/relatives since the beginning of the quarantine; while 9.52% participants were categorized as apathetic according to AES. Univariate analyses revealed a significant association between apathy and no adherence to Mediterranean Diet, decrease of time in productive leisure activities, living alone or having a poor relation with relatives, however these associations lost significance in the multiple model.

Although a not negligible percentage of the sample reported the presence of psychiatric symptoms and/or of emotional consequences of the lockdown on their feelings, almost the whole sample did not feel any need to resort to the free psychological support services that were made available to counteract the emotional impact of the pandemic. The only two participants who thought to recurr to a call-center, desisted from doing so. Two seniors instead turned to their GP, who prescribed pharmacological treatments. This has possible implications regarding the strategies adopted at the public level to counteract the possible psycho-emotional consequences of the pandemic in elderly people at risk of dementia: although not in any way conclusive, the data available to us indicate that seniors with MCI or SCD tend to not think about and to not resort to call center services or unknown professionals in case of emotional distress, perhaps because they do not remember having this opportunity, perhaps because they prefer to turn to their known and trusted physicians or perhaps because they find themselves uncomfortable talking about their difficulties by phone instead of through a face-to-face conversation. In anticipation of a possible second wave of COVID-19 it would be advisable to strengthen the capacity of GP offices to take care of the psychological well-being of elderly patients.

Limits

Beyond the cross-sectional nature of the study and the limited sample size, that warrants making any conclusive inference, participants were recruited among elderly that were included in a prevention programme, whose aim was reducing the risk to develop dementia, while we do not have any data about elderly who were not interested in taking part in the study. Moreover, almost a third of selected did not participate to the phone interview. Therefore, we should not overlook the presence of a potential selection bias. Furthermore, our sample includes only people with subjective or objective cognitive decline, not considering healthy elderly subjects who are aware to have no difficulties or MCI subjects not completely aware of their difficulties. For this reasons, our data may not be representative of over-60 population. However, GR-2013-02356043 recruited a more representative community-based sample of general population than a clinical sample of people pertaining to clinics or departments to assess cognitive disorders.

Another major limitation of our study is that we obtained data through telephone interviews with people with MCI, who might present memory or judgment deficits that do not make them reliable witnesses. Unfortunately, the danger of contagion warranted against conducting face-to-face interviews. In any case, we excluded all GR-2013-02356043 participants who had obtained an MMSE score below 24 in their last visit, subjects with an Itel-MMSE score < 17 and those unable to be interviewed according to their caregivers' judgment. Moreover, the data obtained from our sub-sample of participants with SCD are substantially consistent with those with MCI. This indicates that our participants with MCI may be adequately informative.

CONCLUSIONS AND FUTURE DIRECTIONS

People at increased risk of dementia underwent changes in their lifestyles that are potentially harmful for their cognitive and mental health. In particular, increased levels of sedentary lifestyle, which together with a less healthy diet led to weight gain in over a third of the sample, less social interaction, and greater engagement in passive recreational activities. However, even if, with the exception of productive leisure activities, increased smoke, alcohol or caffeine consumption, unhealthy diet, physical inactivity or time spent watching TV seem not be cross-sectionally related with mental health issues, it is possible that they have long-term effects. Further follow-ups will help us verify this hypothesis. The future directions should therefore focus on reducing loneliness, and on psychoeducational interventions, involving the patients and their caregivers to relieve anxiety associated with the onset of new respiratory symptoms, enhance awareness, healthy behaviors and reduce family conflicts, promoting the active listening, and mutual support between family members. Furthermore, one possible intervention is that of promoting a major awareness of the patients about the psychological help they may receive in case of need, since in our survey, elderly have never referred to *ad-hoc* services as the psychological help desk.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Due to the exceptional situation, informed consent to the interview and the use of the data collected during the GR-2013-02356043 study was provided orally or by SMS or e-mail. The study and its amendment were approved by the Ethic Committee of the IRCCS Fondazione Santa Lucia of Rome.

AUTHOR CONTRIBUTIONS

SD, FF, and BF study project and questionnaire construction. SD database creation and data-analysis. FF, BF, AM, and SS data collection. SD, FF, BF, AM, and SS manuscript drafting. SD manuscript completion. All authors contributed to the article and approved the submitted version.

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Older People Living in Long-Term Care Facilities and Mortality Rates During the COVID-19 Pandemic in Italy: Preliminary Epidemiological Data and Lessons to Learn

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Background: Long-Term Care Facilities (LTCF) in Italy have been particularly affected by the COVID-19 pandemic, especially in terms of mortality rates of older residents. However, it is still unclear the actual extent of this situation. The aim of this manuscript is to assess the extent of mortality rates of older adults in LTCF during the pandemic across different regions of Italy, compared to the previous years and to older general population not resident in LTCF.

Methods: We extracted and analyzed data collected by three Italian institutions (i.e., Italian Statistician Institute ISTAT, Italian N.I.H, Milan Health Unit) about the number of deaths among older people living in the community and among LTCF residents during the pandemic and the previous years. We also compared the observed mortality rate among LTCF residents in each Italian Region with the corresponding expected number of deaths of the general older adult population to obtain an observed/expected ratio (O/E ratio).

Results: During the pandemic, about 8.5% ($N = 6{,}797$) of Italian older adults residents in LTCF died. Findings resulting from the O/E ratio suggest that LTCF residents (in particular in the Lombardy Region) show higher mortality rates when compared to expected values of mortality rates among the older general population living in the community. Furthermore, we found that the risk of death among LTCF residents increased about 4 times during the pandemic when compared to the previous years.

Conclusions: Mortality rates in LTCF were high during the pandemic, especially in Lombardy. Possible causes of higher mortality rates in LTCF and suggestions for specific targeted interventions are discussed.

Keywords: long-term care facilities, older people, mortality rate, COVID-19, risk factors

INTRODUCTION

Italy is one of the countries most violently affected by the Coronavirus-Disease 19 (COVID-19) pandemic and outbreak. As of July 22nd, 244,708 persons (median age 61 years) were known to have contracted the infection and 34,126 (13.9%) died (1). A recent review on COVID-19 pandemic highlights the urgent need to give appropriate attention to the more sensitive population groups, including children, healthcare workers, and older individuals (2). In particular, older adults deserve specific attention as they are at higher risk of both contracting COVID-19 (3, 4) and of negative prognosis or death due to it (3–8).

The higher predisposition of older adults to COVID-19 and their negative prognosis seem to be due to preexisting chronic comorbidities [e.g., hypertension, diabetes, cardiovascolar diseases; (8)] and to an higher likelihood of developing clinical complications after having contracted the virus [probably due to higher predisposition to contract bacteric infection, and to changes in pulmonary anatomy; (7)]. A specific vulnerable subgroup is represented by older adults with dementia, since they may have cognitive deficits which may limit their understanding and memory of safeguard procedures, which may lead, in turn, to an higher risk of infection (9).

However, the link between age, disability, and COVID-19 risk of mortality is still unclear and needs further clarification. Indeed, despite the increasing evidence about the role of age in affecting the risk of contracting the COVID-19 virus and mortality risk, a recent study, investigating the association between frailty and in-hospital mortality due to COVID-19 in the UK and Italy, found that disease outcomes of older adults were better predicted by frailty than either age or comorbidity (10). Long-Term Care Facilities (LTCF) for older people have been particularly affected by the pandemic in terms of number of infections and mortality rates (11). Indeed, COVID-19 related deaths in LTCF residents represented 30–60% of all COVID-19-related deaths in many European countries (11). Despite the public health relevance of this issue, only a few articles have specifically addressed the problem of COVID-19 among LTCF residents (12–14), and so far none of them has been conducted in Italy. Thus, the toll of deaths of older adults in these facilities still remains to be clarified.

The aim of this manuscript is to analyze the mortality rates of older adults in LTCF across different regions of Italy, compared to older general population not resident in LTCF during the COVID-19 outbreak; we will also explore mortality rates of Milan LTCF residents during the outbreak compared to the previous 4 years. This analysis may provide important insights to prevent, control and mitigate future pandemics within LTCF, to allocate appropriate resources (in terms of manpower and equipments) to allow these facilities control and mitigation, to identify specific at risk populations for psychological suffering (e.g., healthcare workers in LTCF, relatives of patients who died) during the post-pandemic phase, and to target specific psychological and medical interventions.

METHODS

We extracted, analyzed, and compared data collected by the Italian National Health Institute (N.I.H.), the National Statistical Institute (ISTAT), and the Milan Health Unit.

Data about deaths among LTCF at the time of COVID-19 has been collected by the Italian N.I.H. through a brief online survey (15), started on March 24th, targeting 3,420 public or private LTCF (reimbursed by the National Health Institute or by municipalities) included in the "*Dementia Registry*." The survey was conducted with a 29-item questionnaire aimed at assessing the consequences of pandemic and the procedures and behaviors adopted to reduce the risk of COVID-19 contagion. The survey was firstly e-mailed to the Directors of facilities and followed then to additional phone calls (∼3,042) to solicitate a reply. LTCF located in Basilicata and Valle d'Aosta regions did not reply to the N.I.H. survey and, for this reason, were excluded from the analyses.

As of April 14th, 2020, 3,276 LTCF (92.6% of the total) have been contacted, and 1,082 answered, that is 33.0% of the total sample. In the 1,082 participating LTCF (5 did not report this information), there were 80,131 residents as of February 1st, 2020, with an average of 74 residents for each facility (range 7–632). Lombardy LTCF were hosting the largest number of both residents ($N = 23{,}594$) and LTCF ($N = 678$). The ratio between the number of LFCT and total residents provide us the average number of number of beds of each facilities in Lombardy ($N = 35$).

Mortality rates of LTCF residents have been compared to mortality rates of specific age groups of the general population, regularly collected by the National Statistical Institute (ISTAT) and freely accessible on the ISTAT website (16).

Furthermore, we extracted data from a recent report of the Milan Health Unit (17) reporting data on mortality rates among about 16,000 residents (aged >70) of 162 LTCF located in the Province of Milan during the first 4 months of 2020 compared to the previous 4 years. The report also compared mortality rates of LTCF residents with the general population aged over 70 years, living in the same catchment area.

Statistical Analysis

Since age-specific mortality rates in LTCF surveyed in the N.I.H. report (15) were not available, we accessed a ISTAT report (18), showing the age structure of the overall population resident in LTCF to estimate residents' mean age: that is, 73 years considering the midpoint of each age category or 77 years as the oldest possible mean age, considering the upper end of each age category.

Based on this estimate, we compared national mortality rates for each Italian Region in the age categories 70–74 and 75–79 to the number of LTCF residents in the corresponding Regions, to obtain the corresponding expected number of deaths. Expected deaths in each Italian Region were calculated multiplying the number of residents by the age-specific mortality rates of the Italian population of the same Region (75–79 years and 70–74 years columns). Then, we compared the observed with the

TABLE 1 | Number of deaths recorded in LTCF, mortality rates in older population groups, expected deaths, and Observed/Expected ratio.

	Living in nursing homes			Mean age: 77 years			Mean age: 73 years		
Region*	**Residents****	**Observed deaths (O)**	**Mortality rate (per 100 residents)**	**ISTAT 75–79 mortality rate (%)**	**Expected deaths (E)**	**O/E**	**ISTAT 70–74 mortality rate (%)**	**Expected deaths (E)**	**O/E**
1. Lombardy	23,594	3,045	12.9	4.76	1,123	2.71	2.66	627	4.85
2. Piemonte	8,729	684	7.8	5.02	438	1.56	2.90	253	2.70
3. Liguria	1,128	82	7.3	5.05	57	1.44	2.90	33	2.51
4. Veneto	16,815	1,093	6.5	4.67	785	1.39	2.69	453	2.41
5. Emilia-Romagna	7,137	520	7.3	4.65	332	1.57	2.73	195	2.67
6. Trentino Alto Adige	1,538	127	8.3	4.43	68	1.87	2.49	38	3.32
7. Friuli V.G.	2,936	174	5.9	4.85	142	1.22	2.86	84	2.07
8. Tuscany	7,399	465	6.3	4.59	340	1.37	2.66	197	2.36
9. Lazio	3,913	147	3.8	5.21	204	0.72	3.02	118	1.25
10. Umbria	664	30	4.5	4.53	30	1.00	2.46	16	1.84
11. Marche	511	33	6.5	4.50	23	1.43	2.45	13	2.63
12. Abruzzo e Molise	638	71	11.1	4.97	32	2.24	2.94	19	3.78
13. Calabria	1,309	42	3,2	5,43	71	0,59	3,22	42	1,00
14. Campania	512	33	6.4	6.18	32	1.04	3.66	19	1.76
15. Puglia	1,866	89	4.8	5.11	95	0.93	2.89	54	1.65
16. Sardegna	526	65	12.4	4.84	25	2.55	2.87	15	4.31
17. Sicilia	916	73	8.0	5.97	55	1.34	3.36	31	2.37

Basilicata and Valle d'Aosta did not provided reply to the N.I.H. survey and were excluded from the analyses. Data from Molise were aggregated with those of the neighboring region Abruzzo. Data from the two autonomous provinces of Bolzano and Trento were aggregated and presented as "Trentino Alto Adige".

Residents up to February 1st, 2020 and new admissions as from March 1st, 2020.

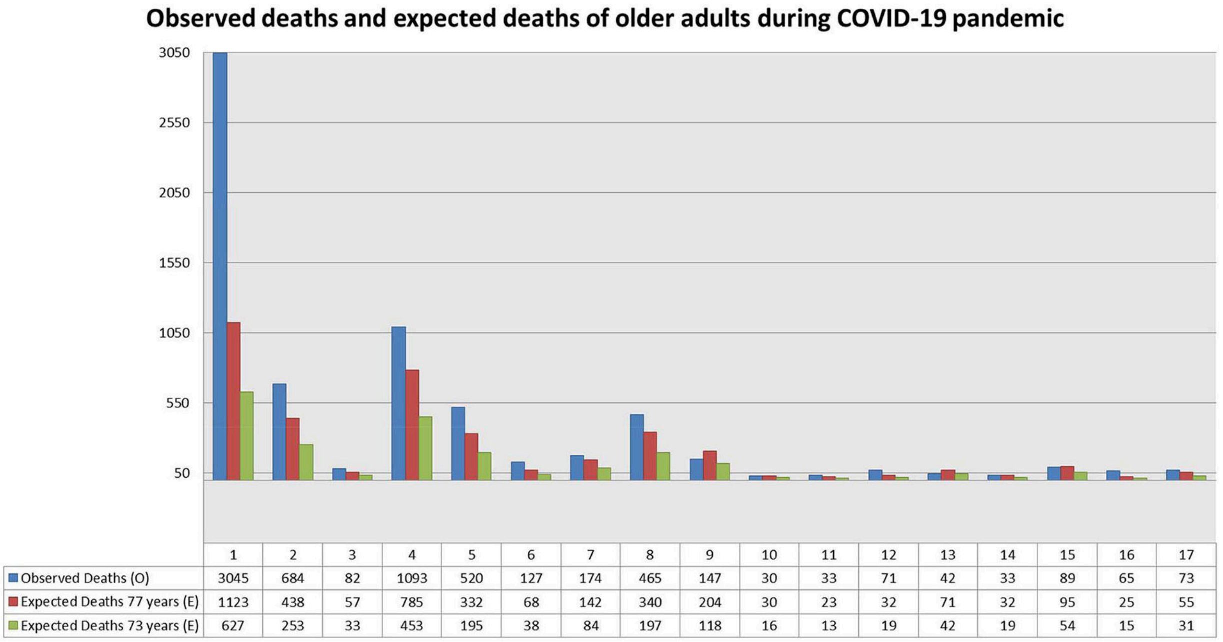
expected number of deaths to obtain an Observed/Expected ratio (O/E ratio).

Finally, we extracted data reported in the Milan Health Unit report (17) to compare mortality rates recorded in the first 4 months of 2020 in 162 LTCF with average mortality rates recorded in the same facilities in the 4 previous years (2016–2019) during the same period (i.e., from 1st January to 28th April).

RESULTS

The N.I.H. survey shows that during the pandemic, 8.5% ($N = 6{,}797$) of Italian older adults residents in LTCF died. **Table 1** shows the number of total deaths recorded among the 1,082 LTCF participants to the N.I.H. survey, and the corresponding mortality rates per 100 residents over 2 months (65 days) starting from February, 1st. As shown in **Table 1**, there is a marked difference in mortality rates between different Regions, with Lombardy showing the highest rate (12.9) and others, including neighboring Regions, showing remarkably lower rates; the mean of the rates shown in the 4th column of **Table 1** is 7.0 and the standard deviation is 2.5. **Table 1** also shows the number of expected deaths in the same period according to two hypothesized residents' mean age: 77 years and 73 years. If we consider a residents' mean age of 77 years, therefore applying the 75–79 age-specific rates of the national population (5th column of **Table 1**), the ratios of observed to expected deaths (O/E) for all Regions (but four, Lazio, Umbria, Calabria and Puglia) were >1, suggesting an higher mortality among LTCF residents. The highest ratio was found in Lombardy: in this Region, observed deaths were about three times those expected; in Sardegna we found a similar value (2.6), while in Abruzzo-Molise the O/E ratio was 2.1. On the other hand, assuming a mean age of 73 years for expected deaths (therefore applying the rates shown in the 8th column of **Table 1**), this leads to much higher values of O/E ratios; in this case, deaths observed in subjects living in Lombardy LTCF were almost five times than those expected, and in all Regions (but two, Lazio and Calabria) the O/E ratio was 1.5 or greater. **Figure 1** provides a graphical overview of the observed and expected deaths in each Italian region.

Figure 2 is based on data collected by the Milan Health Unit (17); it compares daily mortality rates among LTCF residents from January 1, 2020 up to April 30, 2020 with mean daily mortality rates for years 2016–2019 for all subjects aged 70 and older living in the same facilities. It is noticeable the excess of deaths after March 1, 2020: in the 2 months March-April 2020 there has been a 4-fold excess of deaths compared to the same period of the previous years, with a peak in April. Overall there has been an excess of over 2,550 deaths in the period January-April 2020, and most of this excess is concentrated in the period March 1—April 30. The increase in overall risk from January 1 to April 30 was a value of 2, while in the



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
🟦 Observed Deaths (O)	3045	684	82	1093	520	127	174	465	147	30	33	71	42	33	89	65	73
🟥 Expected Deaths 77 years (E)	1123	438	57	785	332	68	142	340	204	30	23	32	71	32	95	25	55
🟩 Expected Deaths 73 years (E)	627	253	33	453	195	38	84	197	118	16	13	19	42	19	54	15	31

FIGURE 1 | Observed deaths in LTCF residents and expected deaths at 77 and 73 years. Old age groups of the Italian general population by Regions. For the numbering of different Regions, see numbers in **Table 1**.

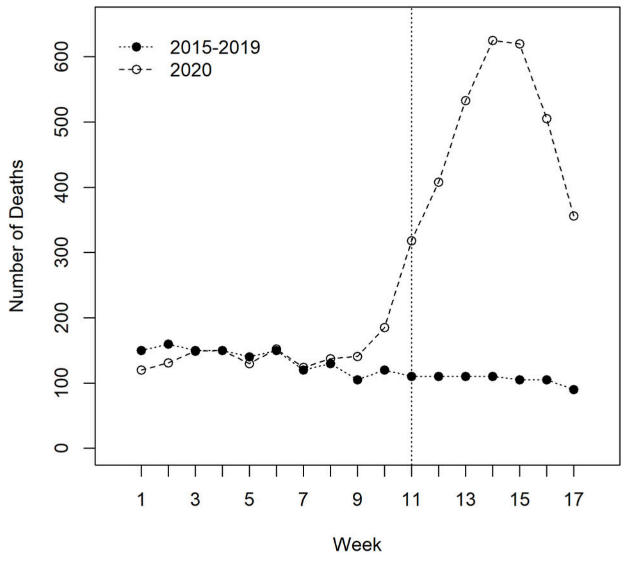


FIGURE 2 | Weekly number of deaths between residents in Long-Term Care Facilities of the "ATS Città Metropolitana di Milano" (Health Protection Agency of Milan) between 1/1/2020 and 28/4/2020 compared with the mean number of deaths of residents during the corresponding periods of 2015–2019. Week number 1 starts on January 1 and ends on January 7, and so on up to week number 17, which starts on April 22 and ends with April 28. A clear increase in the number of deaths is evident from week number 11 (which starts on March 11). The peak was observed during the week number 14 (which starts on April 1). Source: "Valutazione degli eccessi di mortalità nel corso dell'epidemia Covid-19 nei residenti delle Rsa" ATS di Milano, 11th June 2020.

period from March 1 to April 30 (when the risk excess was also visible in the general population) the increase in risk of death increases to ∼4 times the reference mortality values for 2016–2019.

DISCUSSION

In this epidemiological report comparing mortality rates of Italian community-dwelling older people with those of LTCF residents during the COVID-19 pandemic we found that during the COVID-19 pandemic, mortality in LTCF was higher than expected, using the general population as the reference group; interestingly, the excess of mortality we found in the N.I.H. sample (which was a convenience sample, including only 33% of the initial target sample) was very similar to the rate found by the Milan Health Unit including all 162 LTCF located in the Milan City, with a 2-fold increase in the period January-April and a 4-fold increase in the period March-April compared to the previous years. Furthermore, according to ISTAT (19), in March and April 2020 the analysis of general mortality rates leads to an estimated number of 45,186 deaths in excess compared to the same period of 2015–2019; among them, 28,282 (63%) might be considered due to COVID-19 according to reports of the Integrated Surveillance system. Mortality rates were different across LTCF in various Regions, with Lombardy being the Region with the highest mortality rate. Moreover, mortality rates among LTCF residents in the province of Milan (one of the areas most violently hit by the pandemic) were much higher compared to the mean rates found in the previous 4 years in the same facilities.

Why Are Residents in LTCF at Higher Risk of Death During the COVID-19 Pandemic?

Data regarding mortality rates in LTCF is noteworthy. According to the Epidemiological Office of the Lombardy Region (20), the official annual mortality rate in Lombardy LTCF was 21.0 deaths per 100 residents both in 2017 and in 2018; this rate equals to 3.7 deaths per 100 residents in a 65-day period (the same timespan covered by the N.I.H. survey). At odds with these findings, we found a mortality rate of 12.9 per 100 LTCF residents in Lombardy in the recent COVID-19 survey, that is about 4 times as those recorded in 2017 and in 2018. Very similar findings have been found in the Milan Health Unit epidemiological study. This marked discrepancy among mortality rates clearly suggests that the COVID-19 pandemic is responsible for the increased mortality rate. In this perspective, the excess of mortality in LTCF compared to the general population cannot be explained only by a higher proportion of chronic diseases among LTCF residents. In fact, multimorbidity, geriatric syndromes, dementia, frailty, malnutrition, and disability, despite being disproportionately more common among LTCF residents, should not be considered as the leading cause of death, but, as most, as predisposing factors. Among them, frailty has been recently recognized to play a key role in heightening the risk of death due to COVID-19, more than age or comorbidity (10).

Moreover, the Milan Health Unit study shows that the mortality excess was visible also comparing residents during the 2020 pandemic with residents of the same facilities in previous years.

There are several tentative explanations for the increased mortality among older people in LTCF. Acute disorders in older people do not always present with the typical symptoms found among younger people, indirectly suggesting that the recognition of COVID-19 infections in LTCF residents might be challenging (21). This represents an important problem for the infection control. Moreover, standardized protocols for the evaluation and management of COVID-19 among LTCF residents have been missing for many weeks since the start of the pandemic, therefore leading to wide variations in the management of older patients living in LTCF. The lack of imaging facilities, the shortage of laboratory facilities and consultants (such as specialists in infectious diseases and respiratory care) in LTCF has represented a further obstacle to the safe management of infected patients. Moreover, not all LTCF are staffed with dedicated physicians on site and geriatricians, among facility physicians, are an exception rather than the rule (22).

Prevention of COVID-19 transmission was likely to be another factor affecting mortality rates in LTCF. Though we do not have official data about this, laboratory tests have been routinely available nor for LTCF residents and health care personnels, making difficult the separation between COVID-19 positive and negative subjects, and probably contributing to spread the infection. The shortage of Personal Protective Equipments (PPE) for physicians, nurses and health-care workers, repeatedly broadcasted, may have been an additional risk factor.

Variation in Mortality Rates Across Different Regions

The huge difference in LTCF mortality rates among Italian Regions also deserves a comment. Lombardy was the Region that paid the highest toll of deaths in these facilities. It is possible that specific healthcare policies in this Region may have, at least partially, contributed. In the first days after the development of the pandemic, hospitals were overcrowded and some patients were transferred to LTCF, with obvious consequences for the risk of infection spread. Another possible explanation may have to do with the virulence of the COVID-19 virus. A recent study has shown that, soon after starting of the pandemic, the virus has mutated and that European, North American and Asian strains coexisted, each of them characterized by a different mutation pattern (23). Accordingly, it may be hypothesized that some genetic mutations, if present, might be correlated with different COVID-19 related mortality rates.

In addition, the number of LTCF beds per capita, controlling for the proportion of adults aged 75 and older and population density, has been recently found to be significantly associated with COVID-19 mortality rates (24). These findings suggest that structural features of LTCF might have affected the impact of the infection on mortality rates. In Lombardy the average number of LTCF beds in each facility is about 35, and this number is higher compared to other Italian Regions (e.g., Emilia-Romagna region has a mean of 20 beds for each LTCF): we may therefore suppose that the higher likelihood of death in Lombardy LTCF may be explained, among other reasons, also by the higher concentration of older people, with heightened risks of spread, and heavier problems in patients' management.

CONCLUSIONS AND IMPLICATIONS

These findings provide some insights for preventing, controlling, and mitigating future possible epidemics within LTCF, for better allocating specific funds in the case of emergencies, for allowing facilities most hit to relieve after the pandemic, and for identifying specific at-risk populations groups.

A priority is to ensure an easy and rapid access to appropriate testing for the identification of COVID-19 cases among LTCF residents and healthcare workers. Another priority is to make available standardized, clear procedures for the consistent management of epidemics in LTCF. Unfortunately, both these points have not been achieved so far (25).

It is also necessary to support health personnel and rescuers, often highly distressed. This need has been largely neglected so far and needs a proper reflection. Specific targeted psychological interventions should be oriented to healthcare staffs of LTCF, relatives of older people who died because of COVID-19, as well as to other older people who survived to COVID-19 and are still living in LTCF. Exposure to complex grief for these vulnerable groups should be taken into consideration and specifically targeted. The analyses presented here should be considered preliminary and largely descriptive. The N.I.H. survey on LTCF is still ongoing, and results reported here come from ∼1/3 of the total sample. There are several limitations which should be taken into account. Firstly, age-specific mortality rates in LTCF were not reported in the N.I.H. report and were based on ISTAT data. Furthermore, no information about previous health conditions, comorbidity or causes of death of LTCF residents were included in the N.I.H. report. Data on age-specific mortality rates and comorbidities are available only for the general older population. Age-specific mortality rates among older subjects COVID-19 positive were 9.8% among 60–69 years old, 24.2% among 70–79 years old, 29.0% among 80–89 years old and 24.7% among those aged 90 years old and over (26). Furthermore, in an analysis of 4,942 death certificates (based on 31,573 reports received by the Integrated National Surveillance System for COVID-19 as of 25 May 2020), ISTAT (27) has estimated that COVID-19 was the direct cause of death in 89% of SARS-CoV-2 positive deaths. The proportion of deaths in which COVID-19 was the direct cause of death varies according to age, reaching a proportion as high as 92% among the 60–69 year-old people (with quite similar values among older classes: 90% among 70–79 year-old and 88% among 80 and older). The most frequent contributory causes of death associated with COVID-19 were hypertension (18% of deaths), diabetes mellitus (16%), ischemic heart disease (13%), and cancer (12%).

While we acknowledge that data regarding age-specific mortality, comorbidities and cause of death of older residents would allow a more specific and deep assessment of the impact of COVID-19 pandemic in Italian LTCF, unfortunately the lack of this data in the original N.I.H. report makes additional analyses or conclusions impossible. We may only assume that LCTF residents are older (>70 years old), are not totally autonomous and exhibit comorbidities which may increase the likelihood of both contracting the virus and having a negative prognosis. However, the comparison of mortality rates in LTCF during the pandemic with those in previous years (2016–2019) allows us to assume that the significant increase in mortality rates in LTCF during the pandemic may have been triggered by the COVID-19, independent of pre-existing specific comorbidities. Future targeted investigations should address these limitations in order to increase our knowledge in this area.

Despite the above mentioned limitations, available data is significant as shows a trend and points to the urgent need of appropriate measures to be taken to stop, or reduce, the increased mortality rates among very frail subjects, such as those living in LTCF. The high mortality rates observed among LTCF residents during the COVID-19 pandemic has triggered a debate about the overall organization and management of these facilities, about patient-staff ratios, about healthcare personnel's skills and, more in general, about resources allocated by the Italian healthcare system in this sector. Even if a unique model of LCTF organization and management cannot be implemented in all Italian Regions for administrative and political reasons, it is clear that it is necessary to allocate more resources for the care of frail patients, especially in LTCF (28). The "hospital-centered" health system in which the LCTF acts as a passive actor has proven to be totally unsuitable for the proper management of emergencies such as the COVID-19 pandemic (29). For this reason, models of care in LCTFs will need to be reformulated in a more personalized way, while the role of primary care and long-term care will be more and more important in future health systems. It would be desirable that more geriatricians will be employed in LTCFs and that continuing geriatric education will become a mandatory requisite for all LCTF healthcare staff.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. Data are available on request to the corresponding author.

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 for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

GG had the initial idea and wrote the first draft. GG and RM collected the data. RM analyzed the data. All authors carefully reviewed, discussed, and contributed to various draft of the manuscript. All authors approved the final manuscript.

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REVIEW
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The Impact of COVID-19 Infection and Enforced Prolonged Social Isolation on Neuropsychiatric Symptoms in Older Adults With and Without Dementia: A Review

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Background: The sudden and drastic changes due to the Coronavirus Disease 19 (COVID-19) pandemic have impacted people's physical and mental health. Clinically-vulnerable older people are more susceptible to severe effects either directly by the COVID-19 infection or indirectly due to stringent social isolation measures. Social isolation and loneliness negatively impact mental health in older adults and may predispose to cognitive decline. People with cognitive impairments may also be at high risk of worsening cognitive and mental health due to the current pandemic. This review provides a summary of the recent literature on the consequences of COVID-19, due to either viral infection or social isolation, on neuropsychiatric symptoms in older adults with and without dementia.

Methods: A search was conducted in PubMed and Web of Science to identify all relevant papers published up to the 7th July 2020. Two independent assessors screened and selected the papers suitable for inclusion. Additional suitable papers not detected by literature search were manually added.

Results: Fifteen articles were included: 8 focussed on the psychiatric symptoms caused by the COVID-19 infection and 7 investigated the impact of social isolation on older adults' neuropsychiatric symptoms. Four studies included older adults without dementia and 11 included patients with cognitive impairment mainly due to Alzheimer's disease. All studies found that different neuropsychiatric symptoms emerged and/or worsened in older adults with and without dementia. These changes were observed as the consequence of both COVID-19 infection and of the enforced prolonged conditions of social isolation. Cases were reported of viral infection manifesting with delirium at onset in the absence of other symptoms. Delirium, agitation and apathy were the symptoms most commonly detected, especially in people with dementia.

Conclusion: The available evidence suggests that the COVID-19 pandemic has a wide negative impact on the mental well-being of older adults with and without dementia.

Viral infection and the consequent social isolation to limit its spreading have a range of neuropsychiatric consequences. Larger and more robustly designed studies are needed to clarify such effects and to assess the long-term implications for the mental health of older adults, and to test possible mitigating strategies.

Keywords: Alzheimer's disease, neuropsychiatric, COVID-19, social isolation, delirium, mental health, ageing

INTRODUCTION

The current pandemic of *Coronavirus Disease 2019* (COVID-19) has brought abrupt and pervasive changes in our lives that go beyond the infection itself and its consequences on the physical and mental health of those infected. In fact, of equal relevance are the psycho-social consequences generated by the measures put in place worldwide by governments to limit the spreading of COVID-19 and by the traumatic course of events experienced by all those directly involved in this crisis. The biologically-mediated effects of COVID-19 infection have been shown to be multifaceted. Among the many clinical manifestations a variety of neuropsychiatric symptoms (1) and delirium (2) have been observed in patients with severe COVID-19 infection, even in the absence of any other symptoms/signs. Likewise, the psycho-social impact of this pandemic on the mental health of the general population, as well as of frontline workers and people with pre-existing psychiatric conditions, has been extensively documented (3).

Since the beginning of the pandemic, particular concerns have been raised to protect the most clinically vulnerable people in our society, including older adults (i.e., above 60 years old). Analyses carried out using clinical data accumulated over the first half of 2020 and prognostic prediction models clearly show that older adults are particularly vulnerable to COVID-19 infection (4), especially if they are affected by comorbidities such as Alzheimer's disease (AD) (5). The mental well-being of people with dementia who are socially isolating is also considered to be at extremely high risk and a thorough clinical management of this population is regarded as a top priority, especially for those living in care homes, since up to 98% of them present with neuropsychiatric symptoms (6, 7). In fact, a significant association between social isolation and both mental health (8) and levels of cognitive abilities (9) has already been observed in older adults and appears to be mediated by loneliness, i.e., the subjective perception of social isolation. Moreover, greater loneliness has also been found to be significantly associated with reduced brain volume in areas in the left medial temporal lobe involved in memory and harshly affected by AD (10). Consistently, two recent meta-analyses suggested that both poor social engagement/isolation (e.g., living alone, having a limited social network, low frequency of social contact, or inadequate social support) (11) and loneliness (12) may significantly increase the likelihood of developing dementia. Therefore, a suddenly and drastically impoverished social environment may be particularly detrimental to older people, and may contribute to worsen neurological ageing and neurodegeneration-related processes.

However, many of the questions sparked around the potential detrimental effects of the current pandemic on neuropsychiatric manifestations in older adults still remain unanswered. To address this theoretical gap, the scientific community has been very active in the timely attempt to collect clinical data from the populations of interest. As a result of such hectic efforts, however, the relevant findings are quite scattered at time of writing (July 2020). For this reason, the aim of this review was to summarise the initial wealth of knowledge provided by papers published in the first half of 2020 that reported original data on the effects of the COVID-19 pandemic, both biological (i.e., in individuals who have contracted the virus) and psycho-social (i.e., due to social isolation), on neuropsychiatric symptoms (i.e., behavioural and psychological issues related to the realm of mental health) in older adults with and without dementia. To provide an overview of these two distinct, but inter-connected theoretical aspects, we have included a graphical framework of reference (**Figure 1**).

METHODS

A systematic literature search was carried out in two online databases, PubMed and Web of Science, to identify equally studies within the remit of medicine and social sciences. A series of keywords regarding the three main factors investigated were used in order to capture all relevant papers: (1) "COVID-19" and "COVID19" for the COVID-19 infection; (2) "dementia," "mild cognitive impairment," "neurodegeneration," "Alzheimer's disease," "older adults," "ageing" and "aging" for the populations of interest; (3) "neuropsychiatric," "psychiatric," "behavioural," "behavioral," "neurobehavioural," "neurobehavioral" and "delirium" for the specific symptoms. No date-of-publication interval time limits were set for the literature search, but only papers published up to 7th July 2020 (last day of literature search) were eventually included. All publications found were initially screened to identify papers reporting original data, with no restrictions regarding the type of article (e.g., letters and commentaries were included, as long as they presented novel data on the topic of interest). The abstracts of these were reviewed by two independent assessors (MDM and RM) to select all relevant papers to be retained. The exclusion criteria were the following: (1) manuscripts not in English, (2) studies on populations other than those of interest (e.g., children, adolescents, young/middle-aged adults, medical personnel, or general samples of participants not including a distinctive group of older adults), (3) studies focussed on disease and treatment mechanisms, (4) studies investigating other clinical or social/psycho-social aspects of no relevance to this review and (5) non-clinical studies exploring subsidiary topics (e.g., health

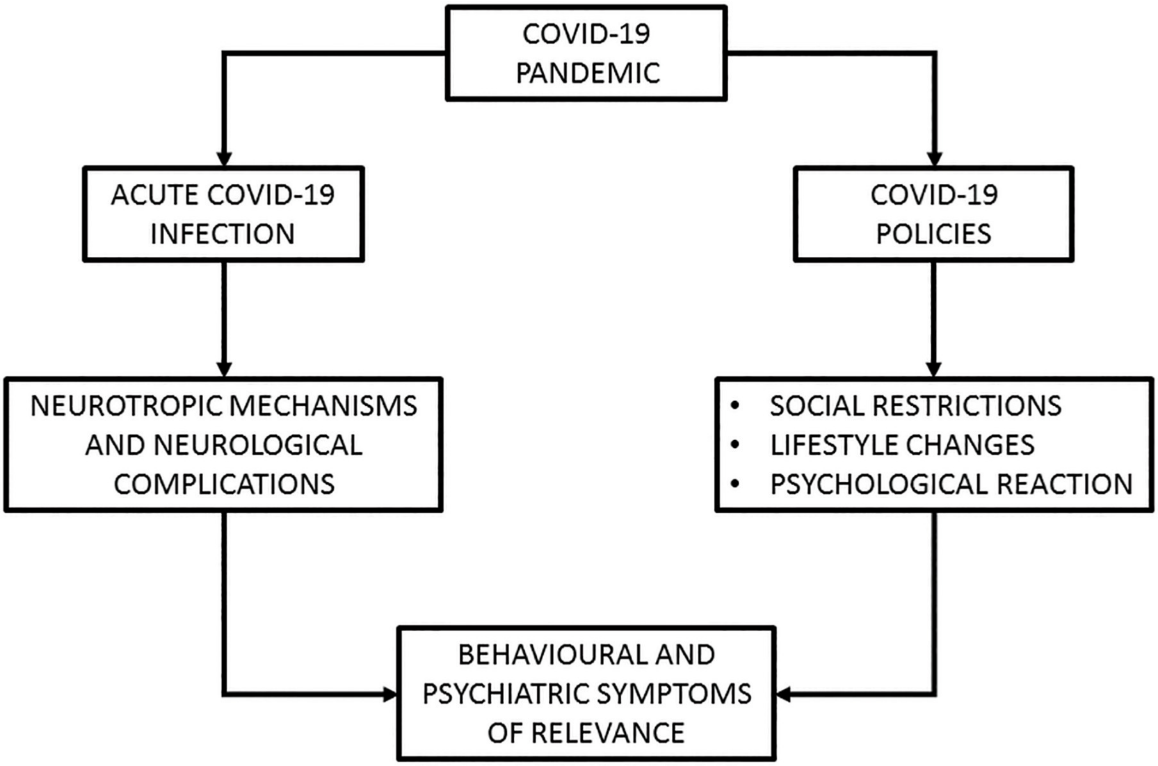

FIGURE 1 | Schematic representation of the theoretical framework whereby the COVID-19 pandemic would be associated to the onset/worsening of behavioural and psychiatric symptoms.

economics, standards of hygiene or the impact of COVID-19 on insurance companies). A third assessor (AV) helped resolving any disagreement on publications to be included. Additional papers with novel data relevant to this review that were not detected by the literature search but identified through other sources (i.e., references and key journals) were also screened and manually added.

RESULTS

The literature search across the two databases resulted in 344 entries. Of these, 127 were repetitions and were thus discarded. The remaining 217 manuscripts were screened to separate those including original data (i.e., observational studies, case series, single-case descriptions) from those not including original data. This led to 120 manuscripts being retained for further consideration, 7 of which were immediately discarded for not being published in English. It was at this point that each abstract (or, in the case of manuscripts such as letters and commentaries, the entire manuscript) was consulted by the two independent assessors. During the shortlisting process (illustrated in **Figure 2**), 14 manuscripts described studies carried out on adolescents or young-middle aged adults, and in other 13 manuscripts the age range included younger and older adults without a specific sub-sample of older adults only. Fourteen additional manuscripts were discarded because focussed on the study of medical personnel. Of the 72 remaining manuscripts, 10 focussed on disease mechanisms, 20 addressed clinical aspects of no interest for the current review while another 4 dealt with tangential aspects of the pandemic. Finally, 26 of the remaining manuscripts were discarded because their experimental hypothesis was about social or socio-psychological aspects of no direct relevance for this review. The remaining 12 manuscripts were included in the process of review. Three additional manuscripts of pertinence were found and manually added to this pool of publications, for a total of 15 manuscripts. These are reported in **Table 1** together with their main methodological aspects and outcome.

Individuals With Acute COVID-19 Infection

Eight papers focussed on the neuropsychiatric manifestations of COVID-19 infection, 2 carried out in older adults without dementia (13, 14) and 6 in older adults living with dementia, mostly due to AD aetiology (15–20). Study designs included: one single case (13), three case series (16, 19, 20), two single-centre retrospective analyses of hospital admissions (17, 18) and two multi-centre investigations, one retrospective analysis of COVID-19 cases (15) and one surveillance clinical repository purposely created (14).

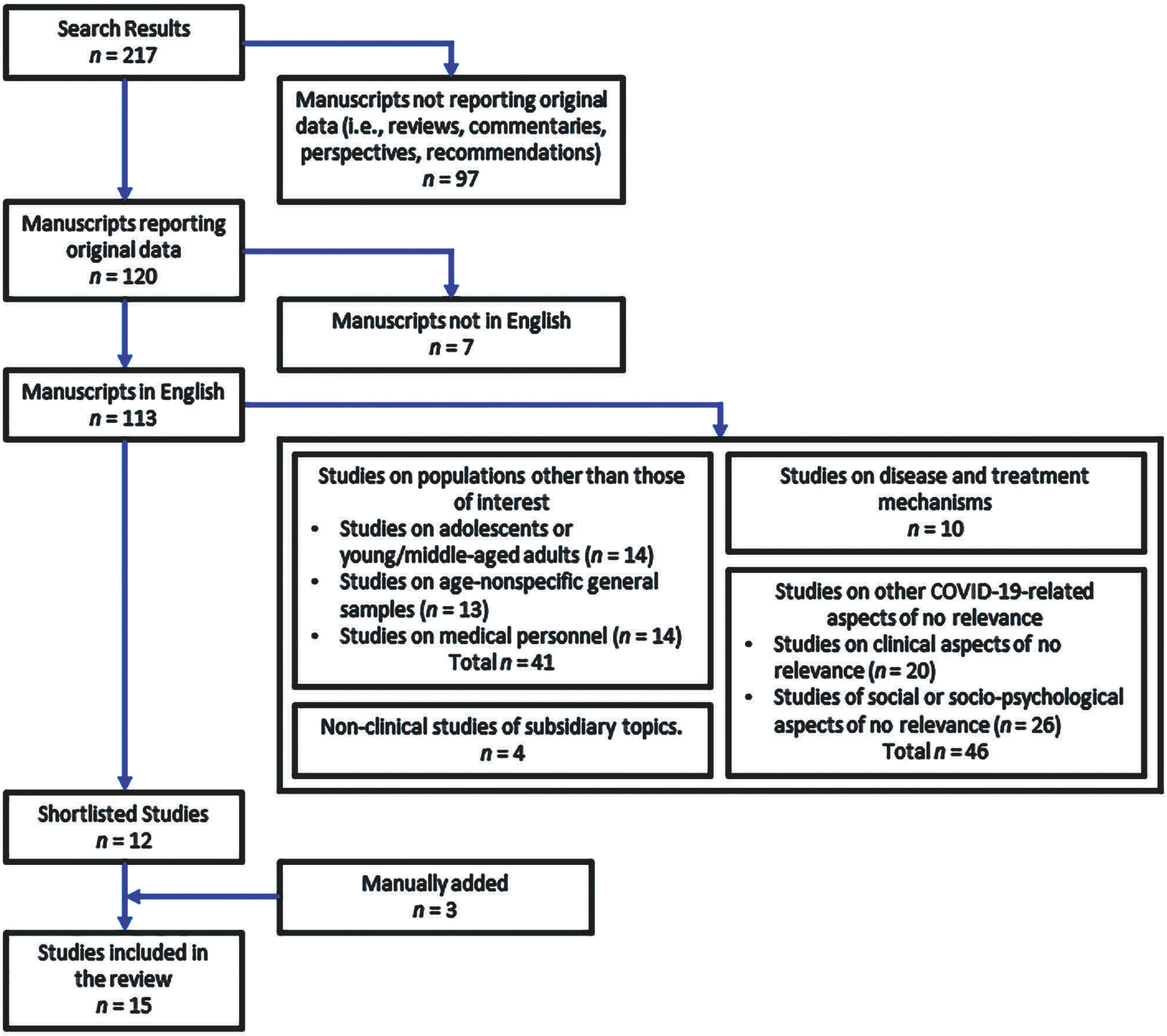

FIGURE 2 | Manuscript selection procedures adopted in this study.

Studies on Older Adults Without Dementia

Alkeridy et al. (13) described the single case of a 73-year-old man without dementia who resulted positive to testing for COVID-19. The authors observed that this patient presented exclusively with delirium at onset, in the absence of the most common symptoms observed in people infected with COVID-19 (i.e., high fever, dry cough and tiredness), as reported by the outline published by the World Health Organisation (https://www.who.int/health-topics/coronavirus#tab=tab_3). A multi-centre study including 125 patients (most of whom aged 60 or above) with COVID-19 and a complete clinical assessment, found that, at onset, 31.2% presented with, among other symptoms, altered mental status, i.e., acute alteration in personality, behaviour, cognition, or consciousness (14). As many as 59% of these patients met criteria for psychiatric diagnoses, with the great majority being new cases of psychoses, neurocognitive disorders, and affective disorders. In both studies, assessment of neuropsychiatric symptoms was based on a clinician's judgment, and no use of standardised tools was reported.

Studies Including Older Adults With Dementia

Three papers described case series reporting a total of 8 patients with dementia due to different underlying conditions: two unspecified and one with dementia with Lewy Bodies (16); 3 cases of AD (19, 20); one case of frontotemporal lobar degeneration and one of vascular dementia (20), respectively. All patients were aged 70 or above, 5 were women and 3 men. In all cases, the neuropsychiatric manifestations of COVID-19 were clinician-reported. At hospitalisation, all patients presented with

TABLE 1 | Characteristics and summary of the results of the studies included.

Article	COVID-19 effects	Population diagnosis	Methodology	Sample size	Age (years)	Neuropsychiatric symptoms	Assessment tools	Results
INDIVIDUALS WITH ACUTE COVID-19 INFECTION—STUDIES ON OLDER ADULTS WITHOUT DEMENTIA								
Alkeridy et al. (13)	Effects of infection	Older adults without dementia	Case description	1	73-year-old man	Delirium	Clinical judgment	The patient presented with delirium as onset symptom of COVID-19 infection.
Varatharaj et al. (14)	Effects of infection	Adults without dementia	Multi-centre clinical repository	153 (only 125 with complete assessments)	61–70 (*n* = 23), 71–80 (*n* = 31), 81–90 (*n* = 23), ≥ 91 (*n* = 5)	Altered mental status	Clinical judgment	Altered mental status was observed in 31.2% of the patients with complete assessments: 41% of these had encephalopathy/encephalitis, while 59% met the criteria for different psychiatric diagnoses (91.3% of which were new). The most common disorders were: psychoses, neurocognitive disorders, and affective disorders.
INDIVIDUALS WITH ACUTE COVID-19 INFECTION—STUDIES INCLUDING OLDER ADULTS WITH DEMENTIA								
Annweiler et al. (15)	Effects of infection	Older adults with and without MND above 70 years of age	Multi-centre retrospective description of last 10 patients per institution	353 (no MND = 219, MND = 134)	84.7 (±7.0)*	Delirium and altered consciousness	Clinical judgment	Older adults with compared to those without MND were more likely to present with delirium, both hypoactive (27.6 vs. 11.4%) and overactive (14.9 vs. 5.5%), and altered consciousness (17.2 vs. 6.4%). Rates of delirium and loss of consciousness were similar between individuals aged 70–80 and over 80.
Beach et al. (16)	Effects of infection	MND (unspecified cause) and DLB	Case series description	3 (an additional case with COVID-19 infection and schizophrenia also included)	70-year-old man, 76-year-old man, and 87-year-old woman	Delirium	Clinical judgment	Two cases of MND, one with behavioural and psychotic problems and one with depression with psychotic features, and one case of DLB presented with delirium and agitation during hospitalisation.
Bianchetti et al. (17)	Effects of infection	Dementia (unspecified cause)	Retrospective analysis of regional acute hospital admissions	627 (no dementia = 545, dementia = 82)	82.6 (± 5.3), IQR 80–86 (dementia)	Behavioural symptoms and delirium	Clinical judgement	At onset: most common symptom in people with dementia was delirium (67%), especially hypoactive (50%); behavioural symptoms were present in 11% of patients
Lovell et al. (18)	Effects of infection	Older adults with and without dementia (unspecified cause)	Retrospective analysis of case series	101 (dementia = 31)	82 (72–89)†	Agitation, drowsiness, and delirium	Clinical judgment	At time of referral to palliative care unit, dementia was the third most common comorbidity (30.7%). Overall, 42.5% of patients presented with agitation, 35.6% with drowsiness, and 23.8% with delirium.
Sinvani et al. (19)	Effects of infection	Advanced dementia due to AD	Case series description	1 (other two severe cases of older adults with COVID-19 infection were also included)	76-year-old woman	Behavioural symptoms	Clinical judgment	After a few days of hospitalisation, the patient showed agitation and violent behavioural changes that, however, resolved with personalised care.
Ward et al. (20)	Effects of infection	AD, FTD, VD	Case series description	4 (2 AD; 1 FTD, 1 VD)	83.3 (± 10.2)*, 3 women, and 1 man	Altered mental status	Clinical judgment	All cases presented at onset with delirium and agitation. Delirium was particularly severe in 2 cases and associated with loss of appetite and disorientation.

(Continued)

TABLE 1 | Continued

Article	COVID-19 effects	Population diagnosis	Methodology	Sample size	Age (years)	Neuropsychiatric symptoms	Assessment tools	Results
INDIVIDUALS WITHOUT COVID-19 INFECTION IN CONDITIONS OF INCREASED SOCIAL ISOLATION—STUDIES ON OLDER ADULTS WITHOUT DEMENTIA								
Emerson et al. (21)	Effects due to social isolation	Older adults without dementia above 60 years of age	Online survey	833	60–70 (*n* = 523), 71+ (*n* = 310)	Overall mental health and stress	Web-based survey, self-reported assessment	No differences in self-rated mental health were found between older adults aged 60–70 and 70+. However, the younger group reported having experienced higher levels of stress than the older group after social isolation enforcement.
Shrira et al. (22)	Effects due to social isolation	Older adults without dementia	Online questionnaire completed by older adults	277	69.58 (± 6.72)*, range 60–92	Anxiety, depression, and peritraumatic distress	Web-based GAD-7, PHQ-9, and PDI	Loneliness due to social isolation was positively associated with levels of anxiety, depression and peritraumatic distress, especially among individuals feeling older than their age.
INDIVIDUALS WITHOUT COVID-19 INFECTION IN CONDITIONS OF INCREASED SOCIAL ISOLATION—STUDIES INCLUDING OLDER ADULTS WITH DEMENTIA								
Boutoleau-Bretonnière et al. (23)	Effects due to social isolation	Dementia due to probable AD	Telephonic questionnaires administered to a caregiver	38	71.89 (± 8.24)*	NPS	NPI-Q	Caregiver-reported worsening of NPS in 26.3% of patients. Duration of confinement correlated with NPI-Q score and caregivers' distress in patients who showed worsening of NPS.
Canevelli et al. (24)	Effects due to social isolation	Dementia, MCI, SCD (unspecified cause)	Telephonic survey administered to patients or caregivers	139 (dementia = 96, MCI/SCD = 43)	80.5 (76–85)‡ (dementia); 73 (65.5–77.5)‡ (MCI/SCD)	NPS	Patient- and caregiver-reported changes	Overall, NPS improved in only a few patients (2.1% of demented and 7% of MCI/SCD), while NPS worsened in the majority of patients (57.3 and 48.8%, respectively), especially agitation, apathy, depression and irritability.
Fahed et al. (25)	Effects due to social isolation	Dementia due to AD	Case series description	1 (a second case of a patient with narcissistic personality disorder was also included)	83-year-old man	Behavioural symptoms	Clinical judgment	The patient was admitted to an inpatient psychiatric unit during COVID-19 pandemic because of severe agitation. During hospital stay he experienced mood lability, agitation and violent behaviours. All symptoms worsened after he was room isolated because suspected to have COVID-19. All interventions had little or no effect.
Lara et al. (26)	Effects due to social isolation	Dementia due to mild AD and amnestic MCI	Telephonic questionnaires administered to a caregiver	40 (AD = 20, MCI = 20)	77.4 (± 5.25)*	NPS	NPI	General worsening of NPI scores was observed after 5 weeks of confinement in agitation, apathy and aberrant motor behaviour symptoms particularly. Changes were similar between patient groups. Apathy and anxiety worsened especially in the MCI group; while apathy, agitation, and aberrant motor behaviours worsened mainly in the AD group.
Padala et al. (27)	Effects due to social isolation	Dementia due to AD	Case description	1	81-year-old man	NPS	NPI	After restrictions were enforced for relatives' visits to people in nursing homes, this patient with AD showed increased depression, anxiety, apathy, irritability, difficulty sleeping, and general restlessness. Symptoms improved after video calls with relative were arranged.

**mean (± Standard deviation).*

†median (Range).

‡mean (Interquartile range).

AD, Alzheimer's Disease; DLB, Dementia with Lewy Bodies; FTD, Frontotemporal Dementia; GAD-7, 7-item Generalized Anxiety Disorder scale; IQR, Interquartile range; MCI, Mild Cognitive Impairment; MND, Major Neurocognitive disorder; NPI, Neuropsychiatric Inventory; NPI-Q, Neuropsychiatric Inventory Questionnaire; NPS, Neuropsychiatric Symptoms; PDI, 13-item Peritraumatic Distress Inventory; PHQ-9, 9-item Patient Health Questionnaire; SCD, Subjective Cognitive Decline; VD, Vascular Dementia.

agitation and 7 out of 8 with delirium. In 2 cases of severe delirium, disorientation and loss of appetite were also reported (20). At least in one case, behavioural disturbance subsided with personalised care (19).

Retrospective investigations of large cohorts of hospitalised patients found that the most common symptoms in those with dementia were delirium, especially in its hypoactive variant, and altered consciousness (15, 17). Similarly, Lovell et al. (18) found that, among the more severe cases of COVID-19 infection admitted to palliative care units, about 30% were people with dementia and many presented with a range of neuropsychiatric symptoms, such as agitation, and delirium.

Individuals Without COVID-19 Infection in Conditions of Increased Social Isolation

Seven studies focussed on investigating the impact that social isolation due to COVID-19-related restrictions had on neuropsychiatric symptoms of older adults with (23–27) and without dementia (21, 22). Only one single case (27) and one case series (25) were described, while all the other studies used surveys/questionnaires implemented either via online (21, 22) or telephonic (23, 24, 26) administration. The majority of these studies included standardised tools to assess the presence and severity of neuropsychiatric symptoms, mostly the Neuropsychiatric Inventory (NPI) (23, 26, 27).

Studies on Older Adults Without Dementia

In a large online survey including 833 healthy older adults (aged $\geq$ 60) socially isolating during the COVID-19 pandemic, Emerson et al. (21) found no differences in self-rated mental health between older adults aged 60–70 and those aged above 70. However, the younger group reported higher levels of stress than the older group. Shrira et al. (22) observed a significant positive association between loneliness due to social isolation and levels of anxiety, depression, and peri-traumatic distress in older adults. This association was particularly strong for those individuals who felt older than their actual demographic age.

Studies Including Older Adults With Dementia

Emergence and worsening of neuropsychiatric symptoms were described in two patients with dementia due to AD after enforcement of social isolation measures. An 83-year-old man was hospitalised due to severe agitation that worsened after he was isolated to his room because suspected to have COVID-19, with little or no relief gained from either pharmacological or non-pharmacological interventions (25). An 81-year-old man, resident in a nursing home, experienced increasing depression, anxiety, apathy, irritability, difficulty sleeping, and general restlessness after his relative's visits had been suspended. All symptoms improved after video calls with his daughter were arranged (27).

In a telephone survey, caregivers of people with cognitive impairment reported mainly worsening of patients' neuropsychiatric symptoms, both when the underlying clinical diagnosis was subjective/mild cognitive impairment (48.8%) and dementia (57.3%), while only a small proportion noticed amelioration of symptoms (24). Greater impacts were especially observed for agitation, apathy, depression, and irritability. Similarly, negative changes in neuropsychiatric symptoms resulting in high NPI scores were reported by two studies: one found symptoms worsening in patients with more compromised cognitive status prior to social isolation and a direct correlation between length of social isolation and both severity of symptoms and caregivers' distress (23); and Lara et al. (26) observed that comparable changes, especially in apathy, occurred in both patients with mild cognitive impairment, and dementia due to AD.

DISCUSSION

The COVID-19 pandemic has taken the world by storm, inducing an unforeseen course of events that has had a significant impact on our lives. Aside from the medical emergency constituted by the actual viral infection, the diffusion of the virus throughout the world has snowballed into a series of substantial changes to the way we are now compelled to conceive a wide number of aspects of life such as healthcare, employment, financial resources, social interactions, welfare and even simple routine tasks that prior to this pandemic could be taken for granted. This has been a radical turn of events with which societies are coming to terms and, arguably, it will not be an easy task. For this reason, the advent of the pandemic has the potential to act as a major trigger for the onset or exacerbation of certain detrimental psychological traits that in turn may lead to behavioural/psychiatric symptoms of clinical concern. In this context, older people (i.e., older than 60) and people with dementia are among the segments of the population most susceptible to the detrimental effects of COVID-19. On one hand they are clinically vulnerable to the viral infection, on the other hand they are at risk of suffering from the negative consequences of reduced social interactions (**Figure 1**).

To shed light on this issue, in this review we searched the scientific literature in the attempt of putting together research findings and case descriptions on the topic published over the first half of 2020, focussing on behavioural and psychiatric symptoms, but giving equal emphasis to both "mechanistic" and "reactive" avenues of interference with normal psychological well-being in people undergoing normal or neurodegenerative processes of ageing.

Neuropsychiatric Symptoms in People Who Have Contracted COVID-19

Societies regularly see annual waves of viral infections during the colder part of the year [e.g., Vestergaard et al. (28)]. While yearly influenza presents itself as a serious yet, in a sense, "canonical" respiratory family of viruses, it has been long established that influenza-associated hospital admissions might present with mental disturbances of psychotic nature (29). Delirium, in particular, is often seen in clinical settings in concomitance with acute hospitalisation and infection. Likewise, a non-negligible amount of clinical evidence has been collected during the current emergency that suggests that COVID-19 may also affect the central nervous system to a significant extent. The evidence we have reviewed in the current manuscript is limited to a small number of studies that converge towards delirium being the most common behavioural symptom recorded at the peak of the infection, and even at onset, in the absence of any other symptoms (13), especially in patients with dementia (17). A substantial proportion of infected patients also experienced mental health problems sufficiently severe to meet criteria for a variety of new psychiatric diagnoses, as well as neurocognitive syndromes, these latter potentially unveiling ongoing latent neurodegenerative processes (14). Particularly affected were people with dementia, who presented often with agitation (16, 18–20) and altered consciousness (15, 18). It is important to remark that these findings were collected in clinical environments that, during the acute phase of the crisis, hosted exclusively severe cases in need of hospitalisation. As a consequence, it still remains undetermined whether milder infections may mechanistically lead to the presence of these or other psychiatric symptoms. Transient agitation in the acute care setting may occur even in an individual who does not have a diagnosis of cognitive impairment or psychiatric disorders, and might be due to a concatenation of neurological and biochemical factors, including an underlying infection, hypoxia, and medication side effects (30). Delirium, instead, is a state of confusion in which a sudden decline in attentional levels and cognitive resources is observed, and is typically seen in hospitalised patients. The occurrence of delirium is determined by a number of predisposing variables (the baseline vulnerability of the individual) as well as precipitating factors introduced during the hospital stay (31). It is well-known that the COVID-19 patients at highest risk of complications are those who show particular frailty (e.g., those who have co-occurring medical conditions). Likewise, major precipitating factors for delirium are "more than three medications added" and "use of bladder catheter" (31), that are a normal occurrence in the hospitalisation of the most severe cases. In summary, it is unfortunate that the frailest who require admission to an intensive care unit are also the more predisposed to developing delirium, and that the routines associated with hospitalisation provide a further hit that might exacerbate their profile. Meanwhile, the current acute neurological and biochemical changes increase the risk of agitation.

Aside from the manifestations recorded in the acute setting, it is possible that behavioural and psychiatric complications might also appear in the long run, in a chronic form (32). Although there still appears to be a paucity of neuropathological research (33), a study carried out on the brains of 18 adults between the ages of 53 and 75 fallen victim to the virus revealed neither CT-informed macrostructural abnormalities, nor microstructural damage ascribable to the virus, but only mild hypoxia-related modifications with, importantly, limited evidence of viral presence in the brain (34). Incoherently with these findings, however, structural magnetic resonance imaging of 30 *in vivo* severe acute cases revealed multifocal subcortical FLAIR and diffusion-weighted signal changes, compatible with oedema, particularly in the mediotemporal lobe, with an aetiological role played by haemorrhagic lesions as well (35). Similarly, a young adult hospitalised because of COVID-19-induced meningitis was described to have hyperintense FLAIR signal in the right hippocampus (36). While these scant pieces of evidence are extremely important to lay the foundations for hypotheses in support of the mechanistic causes of psychiatric and behavioural symptoms in COVID-19, it is too soon to establish a definite theoretical framework and define mechanistic models at the basis of chronic neurological and psychiatric symptoms. Although any mechanistic hypothesis would be, at this stage, speculative, it is of central importance to shed light on the map of regional brain damage caused by the virus, because the topography of network dysfunction may account for the onset of chronic behavioural symptoms. A number of studies has shown that the presence of psychiatric symptoms in patients with AD is associated with alterations of brain circuitry (37–39). If COVID-19 infection damages the neural tissue, it might result into an impoverishment of the neural pathways that support normal psychological functioning and could lead to the onset of cognitive and/or psychiatric dysfunction. Future studies investigating the long-term consequences of COVID-19 on brain function and psychiatric well-being will have the opportunity to address this specific theoretical issue. Moreover, a number of adults who have experienced a particularly severe acute disease might go on developing post-traumatic stress disorder symptoms (1) that would increase the burden on the "reactive" symptomatological profile. In summary, while the presence of delirium and agitation during the acute phase of the infection may be due to a more general neuroinflammatory response, more specific neural mechanisms might underlie the future presence of chronic psychiatric symptoms.

Neuropsychiatric Symptoms in People in Social Isolation Due to COVID-19 Pandemic

The studies here reviewed also highlight how healthy older adults forced to isolate socially reported high levels of stress (21), anxiety and depression that seem to be particularly associated with loneliness (22). Similarly, worsening or emergence of new neuropsychiatric symptoms was found in a substantial proportion (about 25–60%) of patients with cognitive decline as a result of social isolation (23, 24), although changes in symptom severity were found to be similar between patients with mild cognitive impairment and dementia (26). However, behavioural disturbances observed in some patients either hospitalised (25) or resident in nursing homes (27) appeared to be particularly severe and challenging to manage.

Most of these studies included assessment of neuropsychiatric symptoms by means of standardised tools (e.g., the NPI) compared to those carried out on people affected by COVID-19 that relied on clinical judgment. This is likely to be due to the fact that studies on socially-isolating older adults were conducted remotely, by recruiting people with no COVID-19 infection mostly living at home. Hence, these samples did not necessarily require clinical assessment of acute symptoms. In general, simple and exploratory designs were used, mainly in the form of online/telephone surveys, but control groups and pre-lockdown baseline data were not included, thus preventing definite conclusions on the strength of the recorded changes. Nonetheless, these publications suggest, overall, that conditions of social isolation led to exacerbation or manifestation of a variety of neuropsychiatric symptoms in cognitively healthy older adults (especially stress, mood and anxiety) and those with dementia (mainly agitation and apathy). These reports also provide interesting clues on which social factors might affect both trajectories of cognitive and mental health decline, which appear to be tightly interlinked. Indeed, the presence of neuropsychiatric symptoms is associated with more severe progression of cognitive decline in older adults with (40) and without cognitive impairments (41). Moreover, one of the studies in this review found that patients with AD whose caregivers reported to have experienced worsening of neuropsychiatric symptoms presented with significantly lower global cognitive status before social isolation enforcement (23).

However, a series of variables which can potentially mitigate decline in cognitive and neuropsychiatric symptoms in older adults were not taken into consideration by any of these studies. For instance, the number of people living in the household or the width of the social network in contact with them, e.g., neighbours or online/telephone contacts with friend and relatives. It has long been established that older adults participating in larger social networks appear to show lower rates of dementia (42). Indeed, social network size was found to be positively associated with maintenance of cognitive performance within the normal range over a longer period of time, thus postponing dementia onset independently of APOE status (43). Biomarkers associated with dysfunctional neural processes and AD have also been found to be modulated by patients' social context. Higher levels of serum brain-derived neurotrophic factor (involved, among other functions, in synaptogenesis) have been suggested to play a mediating role between emotional support gained through social engagement and risk of dementia (44). Moreover, patients with AD and larger social networks appeared to retain better cognitive performance even in the presence of high levels of AD pathology, i.e., load of brain amyloid plaques, assessed *post-mortem* (45).

Although the governmental instructions provided to older adults objectively steer towards increased isolation, the extent to which this translates into a psychological sense of loneliness may vary. In fact, the association between social isolation and mental health decline may be particularly mediated by subjective perceptions: Shankar et al. (46) observed that both loneliness and social isolation are significantly associated with cognitive decline over 4 years among older adults and several studies have suggested that the number of close relationships, poor social engagement/isolation and loneliness may significantly increase the likelihood of developing dementia (11, 12, 47). Similarly, older adults who experience both social isolation and loneliness have been found to report poorer health quality, with worse depressive symptoms and a higher number of comorbidities (8, 48–50). In fact, one study included in this review found that the relationship between loneliness and mental health was stronger in those who reported to feel older than their actual age (22).

These findings lead to the suggestion that higher social engagement and support experienced both before and during lockdown due to the COVID-19 pandemic might have had a protective/mitigating role by contributing to cognitive (51) and affective reserve (52). During the past few months we have witnessed a widespread mobilisation of people volunteering to offer support to the more vulnerable individuals in our societies and contributing to reduce social isolation (53). It is probably due to such fast society-wide changes that many older adults also felt to be part of a common effort to limit the spreading of COVID-19 and, as a consequence, experienced less loneliness despite an initial increase in the first phase of lockdown (54). However, it cannot be ruled out that protracted social isolation and/or loneliness might have also affected a range of biological processes (linked to neural dysfunction) that could have contributed to the manifestation of neuropsychiatric symptoms in older adults (55).

This review has highlighted and summarised preliminary findings available at time of writing on the effects that the current COVID-19 pandemic has on mental health of older adults. All the studies included were published in the past few months in a rapid response to the demand to obtain much needed insights on this dramatic situation. Negative effects of both viral infection and social isolation have been reported in older adults with and without dementia. These must be taken into account in order to overcome the challenges related to the delivery of effective care strategies for people with dementia in the last phases and after the end of this pandemic. Future studies in larger cohorts, with more robust designs and theory-grounded will be needed to gain more knowledge about the short-term and long-term biological and psycho-social effects of the COVID-19 pandemic on mental health of specific vulnerable populations of older adults, e.g., people with non-AD dementias that may present with more severe behavioural problems (56, 57), and to ascertain the biological and psycho-social mechanisms that may explain these findings, as well as the possible risk/protective factors.

AUTHOR'S NOTE

This is a summary of independent research carried out at the NIHR Sheffield Biomedical Research Centre (Translational Neuroscience).

AUTHOR CONTRIBUTIONS

AV conceived this study. RM and MD designed this study, carried out the literature search, selected the papers for inclusion, summarised the literature findings, and wrote this manuscript. AV reviewed and finalised this manuscript. All authors approved the final version of this manuscript.

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Psychosocial Impact of COVID-19 Nursing Home Restrictions on Visitors of Residents With Cognitive Impairment: A Cross-Sectional Study as Part of the Engaging Remotely in Care (ERiC) Project

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Background: COVID-19 has disproportionately affected older people. Visiting restrictions introduced since the start of the pandemic in residential care facilities (RCFs) may impact negatively on visitors including close family, friends, and guardians. We examined the effects of COVID-19 visiting restrictions on measures of perceived loneliness, well-being, and carer quality of life (QoL) amongst visitors of residents with and without cognitive impairment (CI) in Irish RCFs.

Methods: We created a cross-sectional online survey. Loneliness was measured with the UCLA brief loneliness scale, psychological well-being with the WHO-5 Well-being Index and carer QoL with the Adult Carer QoL Questionnaire (support for caring subscale). Satisfaction with care ("increased/same" and "decreased") was measured. A history of CI was reported by respondents. Sampling was by convenience with the link circulated through university mail lists and targeted social media accounts for 2 weeks in June 2020.

Results: In all, 225 responses were included of which 202 noted whether residents had reported CI. Most of the 202 identified themselves as immediate family (91%) and as female (82%). The majority (67%) were aged between 45 and 64 years. Most (80%) reported that their resident had CI. Approximately one-third indicated reduced satisfaction (27%) or that restrictions had impaired communication with nursing home staff (38%). Median loneliness scores were 4/9, well-being scores 60/100 and carer QoL scores 10/15. Visitors of those with CI reported significantly lower well-being ($p = 0.006$) but no difference in loneliness ($p = 0.114$) or QoL ($p = 0.305$). Reported CI ($p = 0.04$) remained an independent predictors of lower WHO-5 scores, after adjusting for age, sex, RCF location, and dementia stage (advanced), satisfaction with care (reduced), and perception of staff support measured on the Adult Carer QoL Questionnaire.

Conclusion: This survey suggests that many RCF visitors experienced low psychosocial and emotional well-being during the COVID-19 lockdown. Visitors of residents with CI report significantly poorer well-being as measured by the WHO-5 than those without. Additional research is required to understand the importance of disrupted caregiving roles resulting from visiting restrictions on well-being, particularly on visitors of residents with CI and how RCFs and their staff can support visitors to mitigate these.

Keywords: COVID-19, cognitive impairment (CI), nursing homes (source: MeSH), psychological well-being, Loneliness (source: MeSH, NLM)

BACKGROUND

Coronavirus disease 2019 (COVID-19) has disproportionately affected older adults (1), including residents in nursing homes (2). To date, over 40% of total confirmed COVID-19 deaths have occurred in Residential Care Facilities (RCF) (3). Residents are at increased risk of COVID-19 infection and experience more complications (3). To curb transmission, guidance on strict public health measures have been issued in many countries including restrictions on visiting nursing homes (4, 5).

COVID-19 has also had a negative impact on people with dementia (6) including those in RCF (7). International experts and societies such as Alzheimer's Disease International recommend health authorities provide integrated, interdisciplinary, and collaborative support to people with dementia and their caregivers (8). This may reduce the risk of compromised care and reductions in quality of life (QoL) during this challenging time (8). The psychological effects of COVID-19 broadly and specifically on vulnerable groups such as people with dementia and their caregivers are poorly studied. The need for such research is pressing and supported by mental health advocates including the UK Academy of Medical Sciences (9).

Visits from family and friends are central to the care of residents, buffering against loneliness, anxiety, and depression by providing continuity, advocacy, and emotional support. Visitors (family members and friends) also assist with personal care (10, 11). Visiting can provide residents with a sense of meaning, worthiness, and connectedness (12). The absence of strong social supports is therefore harmful to both the physical and psychological well-being of residents, and can lead to excess mortality risk (13). This is particularly the case for residents with dementia (14). When visitation is restricted or stopped, these interactions are lost. This also negatively affects visitors (family members and friends), disrupting bonds, coping mechanisms, and even their identities (15, 16). Families recognize their role as essential to quality care (17). Indeed, during this pandemic family caregivers have been recognized as the "invisible workforce" that has provided essential care and alleviated strain on health and social care systems (18).

Visiting restrictions may impact most negatively on those who continue to provide personal care to relatives after they institutionalized. Caregivers report difficulty coping with separation after placement (19). Spouses, those providing physical care and those who visit residents daily report the highest levels of anxiety and depression with almost half of visitors at risk of depression (20). These psychological symptoms are often as high as levels experienced prior to admission. Reduced control, personal and cultural expectations and greater worry over perceived decline of the resident may contribute to these findings (20). Few studies have examined the effects of visiting restrictions on caregivers and other visitors of residents. The importance of visiting rituals, particularly on those with cognitive impairment (CI) including dementia is also poorly understood (21). We hypothesized that visitors of residents with CI experience a disproportionally worse impact of visiting restrictions during the COVID-19 lockdown. Give these points, we conducted an online survey to quickly gather information to begin to postulate on the effects of COVID-19 visiting restrictions on measures of perceived loneliness, well-being and caregiver quality of life (QoL) amongst visitors of residents, comparing those with and without cognitive impairment in Ireland.

MATERIALS AND METHODS

Data Collection and Participants

This study is part of Engaging Remotely in Care (ERiC) project (https://www.ucc.ie/en/nursingmidwifery/research/theericprojectengagingremotelyincare/) with the goal of understanding better the impact of public health measures during COVID-19 on families, guardians, and close friends of individuals in RCFs. We developed a novel cross-sectional online survey using Google Docs. Data were collected using convenience sampling. The link to the survey was circulated through university mailing lists via the schools of nursing in colleges across Ireland. Social media accounts of local and regional newspapers were also targeted. Data were collected for 2 weeks up until the 30th of June 2020. Visitors (family members, friends, and legal guardians) of residents currently residing in RCFs in Ireland were eligible to complete the survey. All responses were anonymous and could not be linked back to specific patients. The online instrument was piloted by the research team and amended based on feedback. Informed (online) consent was required prior to respondents completing the questionnaire. Information on the nature of the survey, its purpose and the potential benefits and risks of participation were provided. The survey was entitled "*Impact of public health restrictions on families, guardians, and close friends of residents in Residential Care Facilities.*" Ethical approval was provided in advance after review by the Social Research Ethics Committee (SREC) of University College Cork (UCC).

Measures

Characteristics

A broad range of demographics were obtained from respondents. These included their own age (categorized into: 18–44, 45–54, 55–64, and 65+ years of age), sex, relationship to the resident (close family, friend, or guardian), their own employment status and living arrangements (alone or with others). The clinical status of the resident was also recorded including their approximate length of time in the RCF, location of the RCF unit (geographically by county or city, which were categorized by province, and by urban or rural setting). Respondents were asked whether the resident had CI and if known, whether this represented established dementia and if so, its stage (mild-moderate or severe). Whether the resident was receiving end-of-life care was also asked. The extent of the visitors' caregiving role was assessed by asking about their frequency of visits and the usual purpose of visits (activity based, direct provision of care). Specific questions related to COVID-19 were asked. As well as the perceived impact on communication with RCF staff during the COVID-19 pandemic, visitors satisfaction with care was measured on a Likert scale (from 1 "increased," 2 "the same," to 3 "decreased," dichotomized as "increased/same" or "decreased") during this time. Resident COVID-19 status (if known) was requested. Subjective reporting of whether they noted changes in the mood, activity of daily living (ADL) function or cognition while participating in phone or other interactions during visiting restrictions were sought. Whether they felt the resident was coping well with these restrictions was also asked.

Scales

Specific scales to assess the psychological status of visitors during the COVID-19 visiting restrictions were completed as part of the survey in order to infer their psychological impact. Subjective psychological well-being was scored with the World Health Organization Five Well-being Index (WHO-5) (22). Its structure mirrors the Major Depression Inventory measuring ICD 10 symptoms of depression (22). The raw score is calculated by totaling the responses of five Likert-scale questions exploring the frequency of recent (two-weeks) depressive symptoms (from zero "all of the time" to 5 "none of the time"). Scores range from 0 to 25. Zero represents the worst possible score and hence possible depression and 25 the best possible psychological well-being. A percentage score can be obtained, ranging from 0 to 100%, by multiplying the raw score by four. Loneliness was measured with the University of California, Los Angeles (UCLA) brief loneliness scale (2004 version) (23). This is a 20-item scale measuring the frequency with which an individual feels disconnected from others. Here, we used the first three items (each question was asked as "Thinking of your life as it is now....." with responses rated on a three point Likert scale as "hardly ever," "some of the time," and "often"). These were combined to calculate a "loneliness score" from 3 to 9 for each respondent. The lowest possible combined score on this modified version of the scale was 3 (indicating less frequent loneliness) and the highest was 9 (indicating more frequent loneliness). Carer QoL was measured with the Adult Carer QoL (AC-QoL) Questionnaire (24). It is a valid and reliable scale to assess caregivers' perceived challenges and resources (25). Although it has eight subscales, this study only applied one subscale (*Support for Caring*). This subscale measures the extent of support adult carers perceive that they receive, in this case in relation to staff at the RCF, encompassing emotional, practical, and professional support. The subscale includes five questions, each a four-point Likert scale (recording responses from "never" to "always"), giving a possible range of scores from 0 to 15. Higher scores indicate greater QoL; scores of 0–5 indicate a low reported QoL life, and may suggest problems or difficulties.

Statistical Analysis

Data were analyzed using SPSS V25.0 (Chicago, Illinois, USA) and R version 3.5.0 (2018-04-23)—"Joy in Playing" (26). Numerical data were assessed for normality using the Shapiro Wilk test, Kolmogorov–Smirnov test, and Q–Q plots and all were found to be non-normally distributed. Median and interquartile ranges were therefore reported and compared using the Mann–Whitney *U*-test. Three or more independent samples were compared with the Kruskal–Wallis test. Most data were categorical and frequency distributions (proportions) were compared with Chi-square tests. Linear regression was used to examine the strength of relationship between variables. In order to appreciate if multicollinearity influenced the results of the regression analysis, variance inflation factors (VIFs) were calculated. VIF measure how much the variance of the estimated regression coefficients are inflated compared to when the predictors are not linearly related (27). A generic threshold of $\geq$10 was applied to assess multi-collinearity (28), scores less than this indicating low risk of multicollinearity.

RESULTS

Respondent and Reported Resident Characteristics

In all, 230 responses were received. Of these, 225 were valid and were included in this analysis (i.e., duplicates were removed). Most respondents (91%) identified themselves as immediate family ("*Family who supports the person living in residential care such as spouse, son, daughter, in-law, etc.*"), the remainder as friends or legally appointed representatives. The majority were female (82%). Only 13% were aged $\geq$65 years; the majority (68%) were aged between 45 and 64 years. Eleven were aged between 75 and 84 years and only one respondent was aged $\geq$85. Most missing data were found for the "diagnostic condition list," with only 202 responses recorded for "any history of CI." A summary of responses from these are presented in **Table 1**. Most (80%, 162/202), identified that their resident had CI with 45% self-reporting this to be severe dementia. In all, 10% stated that the resident was receiving end-of-life care. Most nursing homes were in rural or suburban locations rather than urban; most were in the east and south of the country, where the two largest cities are located, Dublin and Cork, respectively. Half of these respondents indicated that prior to restrictions that they "always" or "usually" engaged in activities with residents when visiting and one-fifth that they "always" or "usually" engaged

TABLE 1 | Summary of survey responses including a comparison between respondents of residents with and without cognitive impairment.

Variable	**All respondents* ($n = 202$)**	**Residents living with known cognitive impairment ($n = 162$)**	**Residents without known cognitive impairment ($n = 40$)**	**Significance testing (p-value)**
Demographics (reported by respondents)				
Age				
18–44 years	39 (19%)	33 (20%)	6 (15%)	0.598
45–54 years	76 (38%)	63 (39%)	13 (33%)	
55–64 years	59 (29%)	45 (28%)	14 (35%)	
65+ years	28 (14%)	21 (13%)	7 (18%)	
Sex (% female)	165 (82%)	135 (83%)	30 (75%)	0.222
Relationship to resident (% close family)	184 (91%)	146 (90%)	38 (95%)	0.332
Employed	136 (67%)	112 (69%)	24 (60%)	0.270
Living arrangement (% living alone)	38 (19%)	31 (19%)	7 (18%)	0.813
Resident characteristics (reported by respondents)				
Institutionalized for at least a year (%)	141 (70%)	115 (71%)	26 (65%)	0.460
Resident with severe dementia (%)	73 (36%)	73 (45%)	0 (0%)	N/A
Resident receiving end-of-life care	19 (10%)	14 (9%)	5 (13%)	0.469
Location of nursing home				
Northwest (Connacht/Ulster)	29 (14%)	23 (14%)	6 (15%)	0.908
East (Leinster)	87 (43%)	71 (44%)	16 (40%)	
South (Munster)	86 (43%)	68 (42%)	18 (45%)	
Urban vs. Rural (% urban)	78 (39%)	60 (37%)	18 (45%)	0.354
Contact time (usual frequency of visits)				
At least twice a week	122 (60%)	102 (63%)	20 (50%)	0.010
Weekly to fortnightly	69 (34%)	55 (34%)	14 (35%)	
Several time a year or less	11 (5%)	5 (3%)	6 (15%)	
Visitor role				
Provide care (% who always/usually do)	45 (22%)	40 (25%)	5 (13%)	0.097
Do activities with resident (% who always/usually do)	101 (50%)	83 (51%)	18 (45%)	0.480
Impact of COVID-19 on visitor and resident (perceived/reported by respondents)				
Resident positive for COVID-19 (% positive)	18 (9%)	14 (9%)	4 (10%)	0.751
Impact of visit restrictions (visitor)				
Significant impact on communication	77 (38%)	59 (36%)	18 (45%)	0.317
Decreased satisfaction with care	55 (27%)	46 (28%)	9 (23%)	0.554
Impact of visit restrictions (resident)				
Resident coping well				
Yes	64 (32%)	48 (30%)	16 (40%)	0.315
Don't know	39 (19%)	34 (21%)	5 (13%)	
No	99 (49%)	80 (49%)	19 (48%)	
Change in mood (% Yes)	109 (54%)	83 (51%)	26 (65%)	0.055
Change in functioning (% Yes)	86 (43%)	69 (43%)	17 (43%)	0.122
Change in memory (% Yes)	104 (51%)	87 (54%)	17 (43%)	0.002

**This analysis only included those who responded to whether their resident was known or not known to be living cognitive impairment; Note 225 valid answers were received but 23 were missing data for cognitive impairment. N/A, Not applicable.*

in personal care with the resident. A higher proportion of those reporting that their resident has CI responded that they visited more frequently ($p = 0.01$) and that they "always" or "usually" engaged in personal care (25%) compared to those not reporting CI (13%), although this did not reach statistical significance ($p = 0.097$).

Perceived Impact of COVID-19

The next section of the survey assessed the perceived impact of the COVID-19 pandemic on respondents and the resident as perceived by respondents. This analysis focuses on the 202 responses where the presence or absence of CI was indicated. Eighteen of those with a response to the question on CI (9%)

answered that their resident had been diagnosed with COVID-19. In all, 38% indicated that visiting restrictions had a significant negative impact on communication with RCF staff and 27% reported decreased satisfaction with care. Visitors who reported lower satisfaction with care had statistically significantly lower self-reported well-being, a median WHO-5 Well-being Index score percentage score of 44 vs. 60%, ($p = 0.01$). Similarly, those reporting lower levels of satisfaction with the support offered by RCF staff (based on the item from the Adult Carer QoL Questionnaire) had significantly lower WHO-5 scores ($p = 0.002$).

Most and almost half of respondents (49%) reported that their resident was not coping well with restrictions. One in five did not know and one-third reported that there were coping. Half reported that their resident displayed a negative change (reduction) in mood, ADL function and memory during the pandemic. Comparing residents with and without reported CI, those living with CI were noted by visitors to have statistically significantly greater reductions in memory during the period of restrictions, 54 vs. 43% ($p = 0.002$). Examining the scales to infer the psychological impact of restrictions on respondents showed that median (interquartile) UCLA brief loneliness scale scores were 4/9 (± 3), WHO-5 well-being scores were 56/100 (± 36), and AC-QoL scores were 9/15 (± 6), see **Table 2**. In all, 72/162 (44%) reported WHO-5 scores below 50%.

On the AC-QoL, $\sim$one-fifth (17%) of respondents scored 0–5/15, indicating that support they received from RCF staff during this period was perceived to be poor. This suggests low self-reported QoL. Visitors of those with CI reported statistically significantly lower well-being scores over the past two weeks (56 vs. 76%, respectively, $p = 0.006$) but no difference in loneliness scores ($p = 0.114$) or carer QoL scores ($p = 0.305$). Linear regression modeling, showed that reported CI ($p = 0.04$) was an independent predictors of WHO-5 scores, after adjusting for age, sex, dementia stage (proportion with reported advanced dementia), perceived professional support provided by RCF staff (item taken from the Adult Carer QoL Questionnaire) and satisfaction with care (proportion reporting decreased satisfaction), see **Table 3**. Examining only those visitors reporting reduced satisfaction with care ($n = 55$), found no difference in WHO-5 scores after adjusting for age, sex, CI, and the presence/absence of perceived support from RCF staff. All VIFs for individual variables included in the regression models were marked lower than 10, indicating a low risk of collinearity.

TABLE 2 | Outcome measures for survey respondents assessing the psychological status of visiting restrictions during COVID-19 pandemic 2020.

Outcome measure	All residents* ($n = 202$)	Residents with cognitive impairment ($n = 162$)	Residents without cognitive impairment ($n = 40$)	*p*-value
WHO-5 Well-being Index score				
Raw score (Median and IQR)	15 (10–19)	14 (9–19)	19 (11.5–20)	0.006
WHO-5 Well-being index score				
Percentage score (Median and IQR)	60 (40–76)	56 (36–76)	76 (46–80)	
UCLA brief loneliness scale (modified version) (Median and IQR)	4 (3–6)	5 (3–6)	3.5 (3–6)	0.114
AC-QoL Questionnaire (support for caring subscale) (Median and IQR)	10 (7–13)	10 (7–12)	10 (6.5–14)	0.306
Family perception of care scale (Median and IQR)				
Total score	23 (18–28)	23.5 (19–29)	22 (15–27.5)	0.183
Resident care subscale	15 (11–18)	15 (12–19)	14 (8.5–17)	0.138
Communication subscale	8 (11–6)	8 (6–11)	7.5 (6–10.5)	0.558

**Two-hundred and twenty-five answered survey but 23 are missing data for cognitive impairment.*

AC-QoL, Adult Carer Quality of Life Questionnaire; WHO, World Health Organization; N/A, Not applicable.

DISCUSSION

This study, a national survey of family, friends, and guardians of residents in RCF in Ireland, conducted during the COVID-19 pandemic, found that a large proportion of respondents reported recent low well-being as well as feeling lonely and isolated. Almost a fifth reported that support for their role as caregivers from staff in RCFs was poor and that they had a low self-reported QoL as a result. Approximately one-third of respondents remarked that they were dissatisfied with care and that restrictions had impacted on the care of residents. Those reporting that their satisfaction with care received by their resident and with the support provided by RCF staff to them (taking the "happiness with professional support" item from Adult Carer QoL Questionnaire) were reduced during the lockdown were statistically significantly more likely to report lower well-being. Most perceived that residents were not coping well during this period. This may have impacted on their own feelings and perceptions of well-being, explaining the relatively low median WHO-5 well-being index scores and large proportion (44%) scoring <50%. This is not unexpected given that pandemics are associated with a range of negative psychological effects (29).

This study compared the responses of visitors reporting that their resident was living with CI with those that did not. Whether the cognitive status of residents may have influenced self-reporting of a range of psychological measures of mood (depression), loneliness, and QoL was examined. The results for scores on the WHO-5 here suggest that respondents of residents with CI have statistically significantly poorer well-being scores and were more likely to be depressed. Linear regression

TABLE 3 | Linear regression model showing the association between variables and WHO Well-being Index scores (range 0–100).

Variable	Estimate	Standard Error (S)	$p = X$
Age (category)	0.22	2.26	0.92
Sex (female)	−8.77	4.91	0.08
Location of RCF (urban)	0.05	0.28	0.86
Staff support (Item from Adult Carer QoL Questionnaire; % satisfied "Some of the time" or "Never")	−5.11	5.18	0.33
Satisfaction with care (% reduced)	−7.92	5.30	0.14
Cognitive Impairment (impaired)	11.46	5.46	0.04*
Dementia stage (advanced)	−0.006	4.73	0.99

N = 202; Adjusted r square = 0.08.
QoL, Quality of Life; RCF, Residential Care Facility.
**Statistically significant (0.038).*

showed that this remained significant after adjusting for potential confounders including the stage of dementia. The WHO-5, a short questionnaire consisting of five simple and non-invasive questions examining subjective well-being of the respondents, is a validated and accurate screening tool for depression. It is widely-used as an outcome measure in clinical trials across a broad range of scientific fields (22). Differences between those with and without CI may reflect different tensions and concerns specific to those visitors and the loss of their caring role during visiting restrictions. That families of those with dementia play a particularly active role in visiting residents with dementia supports this (30).

Of particular concern is that the majority of respondents who were in contact with residents during this period noted a decline in the mood, ADLs, and cognition (memory). This was significantly different (higher proportion) for those with CI with over half of these responding in the affirmative. This would be expected given the importance contact with family and friends has for residents with CI, particularly their role in supporting activities including cognitively stimulating activities (31) and in maintaining resident QoL (32). It is probable that the restriction of visits for a prolonged period is directly attributable to this decline, albeit this is a reported and unsubstantiated deterioration that may reflect respondents own concerns with the residents care.

Strengths, Limitations, and Next Steps

This study has a number of strengths and limitations affecting the interpretation of the results. Convenience sampling was used, potentially limiting the representativeness of the final sample obtained. Responses were predominantly from the provinces of Munster and Leinster (the two largest population centers), particularly from Cork in Munster where UCC is based. Few responses were from the West and North of the country. This indicates possible selection bias (under-coverage). It is likely that only the most motivated and computer literate respondents completed this online survey, introducing voluntary response and non-response bias. Other approaches to gathering data and more representative sampling should therefore be considered a priority. Most respondents (67%) were in the 45–64 year old age group (often children of residents), further reducing the generalizability of the findings. However, this represents the key age cohort for caregivers in Ireland with most aged between 45 and 64 years (33). A large majority of respondents to this survey were female, again potentially reducing the generalizability of the study, although this mirrors the demographic make-up of Irish carers (33), and higher numbers of female visitors to RCFs are reported in many studies, e.g., the Netherlands (34). Further, proportions were not significantly different between those with and without known CI. Most (91%) identified themselves as close family who usually support the resident. Given that these have an important role in supporting the care of people in RCF and are themselves more prone to anxiety and depression related to the institutionalization of their family member (20), the psychological impact of COVID-19 restrictions may be reflective of the true impact on families who usually support residents. The small sample size is a weakness of the study, representing only ∼1% of residents in RCF in Ireland; there are ∼22,500 residents aged over 65 years in nursing home care (35). This also limits the representativeness and generalizability of findings. However, sample size, as well as the design, should be informed by the purpose of a mental health survey (36). In this case, it was to quickly gather information to generate ideas, suggesting that rapid, low-cost convenience sampling may be acceptable (36). The need is engendered by the paucity of data on the psychological impact of the COVID-19 pandemic on visitors to RCFs. Larger samples may not necessarily overcome these biases, hence having a reasonably representative samples of visitors as is inferred by the demographics of this sample, is important. Nevertheless, the authors emphasize that associations found in this research may not reflect the true impact of COVID-19 on the target sample and causality cannot be inferred.

It is unclear how many residents are represented by the survey as different family members of the same resident could in theory have responded to the survey. While this could not be determined, it was possible to identify if the same individual attempted the survey a second time. All responses from the same IP address were removed. Another limitation is that there were some randomly distributed missing data. This can lead to bias and reduced precision when analyzing patient-reported outcomes (37). Surveys are prone to having missing data although in this case, the number of missing values was low. To address this, as most data were categorical, rather than imputing data, missing values were automatically removed (38). Further, the design of the survey minimized missing data by making key questions mandatory in order to progress to the end of the questionnaire.

As all responses were anonymous, the accuracy of responses could not be verified. It was therefore not possible to confirm whether information on diagnoses reported (e.g., the presence of dementia and its stage) were accurate and correctly classified. Such responses are prone to reporting bias and error. Nevertheless, the proportion of residents with reported CI in this study at 80%, is similar to the suggested true prevalence of dementia in nursing homes in Ireland, which although frequently under-diagnosed may be as high as 90% (39). Similarly, no data were available about the nursing homes included in the study. A follow-on study of both residents and of staff in the nursing homes and their view of the impact of lockdown restrictions on RCFs is planned as part of the ERIC project. The design of the study also limits the interpretation of the results. Specifically, as the study was cross-sectional, it was not possible to ascertain the baseline scores of the scales used to measure the psychological impact of visiting restrictions during the COVID-19 pandemic. As no measures were obtained prior to the lockdown, it is also impossible to determine whether these changed as a result of the lockdown. All responses reflected the well-being, QoL, and loneliness in a moment in time (recent weeks), though it was not possible to ascertain if the scores truly reflect the impact of COVID-19. While it is possible that having a relative in residential care with CI, heightened the negative psychological impacts of COVID-19, the cross-sectional nature of this survey means that causation cannot be inferred. This said, visitors of those with CI, are known to experience lower well-being at baseline and during periods of crisis including at the end-of-life (40). Similarly, CI and its severity are known to increase carer stress and burden (41). Further, this survey was conducted almost 4 months into the ongoing pandemic and asked specifically about COVID-19 and their experiences as well as the perceived experiences of their relative/friend during this period.

Finally, two out of three of the scales used to assess the psychological status of visitors during the COVID-19 RCF visiting restrictions were truncated, i.e., these were mostly sub-scales or sub-sections of the original scales with reduced reliability. This also reduces the generalizability and comparability of the findings. The decision to use these modified or subscale versions was made to minimize the length and complexity of the questionnaire, particularly given the broad target sample (ranging from younger caregivers/relatives to older spouses). This was largely successful given that the vast majority of questionnaires were completed fully with a relative paucity of missing data. Further, there is a need to combine existing scales as none have been specially designed and tested against the backdrop of a pandemic of this nature. Nevertheless, these are widely-used scales and their subscales are often used as stand-alone assessments of psychological well-being in studies. The WHO-5 for example, is validated as a screening tool with high sensitivity for both major and minor depression. It is shorter than the GDS-15 and is superior to the GDS-4 (42). Reducing the number of items was also important to attempt to limit the possibility of multicollinearity. As collinearity among covariates is an almost inevitable problem when analyzing survey data, VIFs were calculated taking a generic cut-off of $\geq$10 to assess this (28). VIFs are robust and account for complex design features (27). In these analyses, VIFs calculated for variables in the regression models indicated a low probability of collinearity.

Although visiting restrictions to RCFs in Ireland have begun to ease over recent weeks, the requirement to socially distance, wear face covering and limit visits to RCFs (both in duration and frequency) is likely to continue as the pandemic keeps up pace. This reinforces the need to develop solutions to overcome these restrictions (36) and improve communication and remote contact between visitors, residents and staff in RCF (43). These findings, limited in size and to a single country, should be examined in other settings and countries. Hence, research is now required to understand whether reduced well-being among respondents of residents reported to be living with CI is due to disrupted caregiving roles resulting from the restrictions imposed during this pandemic. The loss of this role and its associated meaning could account for such changes (15, 16).

Future research should likewise examine not only the impact of COVID-19 restrictions in RCFs on visitors but also on residents themselves, particularly given the pivotal role these visitors and their visits play in providing support for activities and the personal care of residents. Studying measures to mitigate the psychological impact is also required. To date, little research has been conducted into this with anecdotal evidence suggesting that social isolation during the pandemic is having seriously harmful consequences on residents including increased anxiety, depression, loneliness, and worsening dementia (44, 45). Given the pressing need to understand the prevalence of the psychological impact of COVID-19 on both residents and families, future surveys should therefore use rigorous methods that sample from the whole population (36). Qualitative studies would help shed light on the impacts.

CONCLUSIONS

In summary, this pragmatic hypothesis-generating study is the first to our knowledge to examine how visiting restrictions to RCFs during COVID-19 may have impacted on the psychological status of a variety of visitors but predominantly close family. The results indicate that many nursing home visitors are experiencing low psychological and emotional well-being during this pandemic. Well-being was significantly lower for those reporting that the resident they are connected with has CI. It may be that visitors and carers of those with CI in RCFs are experiencing lower well-being than those without known CI but limitations in the study design limit our ability to confirm this. We suggest that this may be related to visiting restrictions themselves, although further research is also required to evaluate this and the role staff working in RCFs can have in supporting visitors to mitigate reduced well-being during this pandemic. If confirmed there will be a need to identify measures to address their impact over a prolonged period, given the current lack of adequate treatments or a vaccine. The impact on residents and staff must also be investigated.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This study was reviewed by the Social Research Ethics Committee of University College Cork. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RO'C: design, statistical analysis, writing, and revising manuscript. MM, CD, CB, CK, and SF: concept, design, and data collection. MO'D: data management and statistical analysis. IH: concept, design, concept, and supervision. NC: concept, design, data collection, writing, and revising manuscript.

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Psychosocial Effects of Corona Measures on Patients With Dementia, Mild Cognitive Impairment and Subjective Cognitive Decline

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Background: The recent COVID-19 pandemic is not only a major healthcare problem in itself, but also poses enormous social challenges. Though nursing homes increasingly receive attention, the majority of people with cognitive decline and dementia live at home. We aimed to explore the psychosocial effects of corona measures in memory clinic (pre-)dementia patients and their caregivers.

Methods: Between April 28th and July 13th 2020, $n = 389$ patients of Alzheimer center Amsterdam [$n = 121$ symptomatic (age $= 69 \pm 6$, 33%F, MMSE $= 23 \pm 5$), $n = 268$ cognitively normal (age $= 66 \pm 8$, 40% F, MMSE $= 29 \pm 1$)] completed a survey on psychosocial effects of the corona measures. Questions related to social isolation, worries for faster cognitive decline, behavioral problems and discontinuation of care. In addition, $n = 147$ caregivers of symptomatic patients completed a similar survey with additional questions on caregiver burden.

Results: Social isolation was experienced by $n = 42$ (35%) symptomatic and $n = 67$ (25%) cognitively normal patients and two third of patients [$n = 129$ (66%); $n = 58$ (75%) symptomatic, $n = 71$ (61%) cognitively normal] reported that care was discontinued. Worries for faster cognitive decline were existed in symptomatic patients [$n = 44$ (44%)] and caregivers [$n = 73$ (53%)], but were also reported by a subgroup of cognitively normal patients [$n = 27$ (14%)]. Both patients [$n = 56$ (46%) symptomatic, $n = 102$ (38%) cognitively normal] and caregivers [$n = 72$ (48%)] reported an increase in psychological symptoms. More than three quarter of caregivers [$n = 111$(76%)] reported an increase in patients' behavioral problems. A higher caregiver burden was experienced by $n = 69$ (56%) of caregivers and $n = 43$ (29%) of them reported that a need for more support. Discontinuation of care (OR = 3.3 [1.3–7.9]), psychological (OR = 4.0 [1.6–9.9]) and behavioral problems (OR = 3.0 [1.0–9.0]) strongly related to experiencing a higher caregiver burden. Lastly, social isolation (OR = 3.2 [1.2–8.1]) and psychological symptoms (OR = 8.1 [2.8–23.7]) were red flags for worries for faster cognitive decline.

Conclusion: Not only symptomatic patients, but also cognitively normal patients express worries for faster cognitive decline and psychological symptoms. Moreover, we identified patients who are at risk of adverse outcomes of the corona measures, i.e., discontinued care, social isolation, psychological and behavioral problems. This underlines the need for health care professionals to provide ways to warrant the continuation of care and support (informal) networks surrounding patients and caregivers to mitigate the higher risk of negative psychosocial effects.

Keywords: COVID-19, dementia, MCI, SCD, psychosocial effects, behavioral problems, discontinuation of care

BACKGROUND

The recent COVID-19 pandemic is not only a major healthcare problem in itself, but also poses enormous societal challenges (1). People living with cognitive impairment and dementia may be doubly affected by this pandemic (2). On the one end, this population is more vulnerable for severe symptoms of the infection (3, 4). On the other hand, the issued measures (i.e., social distancing, lockdown) to combat spread of COVID-19 have great impact on the lives of these patients. There has been increasing interest for the devastating situation of dementia patients living in nursing homes (5–7), but the majority of patients with cognitive decline and dementia live at home and make use of a combination of formal and informal care. Formal care, like community care services, district nurse or day care institutions, was largely shut down, which further increased the burden on informal care, i.e., the caregiver. Moreover, the informal support network of children, neighbors, and volunteers became largely ineffective as a result of the measures. In addition, there is a large contingent of memory clinic patients who experience cognitive decline, but perform normal on cognitive testing, i.e., subjective cognitive decline (8). Also in these pre-dementia phases where patients are still cognitively normal but worried, the consequences of the corona crisis may cause an unbalance in mental health.

In times of uncertainty, staying socially connected is important. Due to social distancing and/or lockdown, many people sought for social connections online, which may be more difficult for memory clinic patients and their caregivers. As a result, feelings of loneliness, anxiety and uncertainty may have increased during the corona crisis. Furthermore, finding structure during the day is particularly difficult for individuals with cognitive impairment and the lack of daycare or other activities may result in faster cognitive decline, not only in the de stage of dementia, but also in pre-dementia stages. In turn, this may negatively affect the caregiver and deteriorate mental well-being in both the patient and caregiver.

In the current study, we aimed to evaluate the psychosocial effects of corona measures in terms of discontinued care, behavioral and psychological effects in patients with pre-dementia and their caregivers living at home. In addition, we set out to identify red flags for patients likely to be most severely affected by the corona measures.

METHODS

Patients

Between April 28th 2020 and July 13th 2020, we invited cognitively normal and symptomatic patients to complete a self-designed corona survey from the Amsterdam Dementia Cohort (9, 10). Patients were actively enrolled in one of the following three ongoing substudies of the Amsterdam Dementia Cohort: (1) SCIENCe project (11)–all with a diagnosis of subjective cognitive decline (SCD), i.e., cognitively normal. Participants with SCD attended our memory clinic for their cognitive complaints, but performed normal on cognitive testing. (2) Patients included in the DEvELOP study—all with a diagnosis of dementia with Lewy bodies (DLB), i.e., symptomatic patients; and (3) symptomatic patients included in the follow-up study of ABIDE-PET (12, 13). ABIDE-PET was a study that included patients from an unselected memory clinic cohort, and therefore contains patients with dementia, mild cognitive impairment and SCD. We invited $n = 916$ patients of whom $n = 389$ patients completed the corona survey; $n = 268$ cognitively normal and $n = 121$ symptomatic patients.

In addition, we invited caregivers of patients in (2) DEvELOP and (3) ABIDE-PET to complete a similar survey, with additional questions on caregiver burden. As in cognitively normal patients cognitive decline is not objectified and these patients function normally in daily life, they often have no informal caregiver. Therefore, partners of cognitively normal patients were not invited to fill in the caregiver survey. In total $n = 147$ caregivers [$n = 92$ (63%) patient-caregiver dyads, $n = 55$ (47%) caregiver only] participated.

Survey on Psychosocial Effects of Corona Measures

We developed the survey in collaboration with Alzheimer Nederland and via a bottom-up approach with expert opinions from neurologists (FB, PS) and a dementia nurse (FG). The survey consisted of questions on COVID-19 infection, discontinuation of care, social isolation and psychosocial effects. Discontinuation of care included questions on housekeeping, home aid, day care, community care services and visits to the general practitioner (GP) or hospital. Regarding psychosocial effects, the questionnaire included questions on apathy, change in sleeping behavior, loneliness, anxiety, uncertainty, depression, and worries for a possible COVID-19 infection or faster cognitive decline. The caregiver survey included questions on caregiver burden, whether the patient exhibited more behavioral problems, repetitive behavior and aggression, and questions on psychosocial effects experienced by the caregiver. The complete patient and caregiver surveys can be found in the supplemental data in **Supplementary Material**. Questions on discontinuation of day care and community care services were omitted in the survey that was distributed among cognitively normal patients.

Prior Cognition and Neuropsychiatric Symptoms

Demographic data of the patients were retrieved from the Amsterdam Dementia Cohort, and included age, sex, living situation, and marital status. We also retrieved the last reported mini-mental state examination (MMSE) and behavioral and psychological symptoms of dementia as reported on the neuropsychiatric inventory (NPI) (14) and geriatric depression scale (GDS) (15).

Statistical Analysis

We compared responders and non-responders on patient characteristics (age, sex, MMSE and diagnosis) using non-parametric tests where applicable. Descriptive statistics were used to report on the frequencies of discontinuation of care, social isolation, and psychosocial effects reported by patients and caregivers. For the analyses, answers were dichotomized into present if participants agreed or completely agreed with a statement, and absent if disagreed or completely disagreed. We used univariate logistic regression analysis to identify red flags for the presence of higher caregiver burden and worries for cognitive decline. Candidate determinants were patient characteristics (age, sex, MMSE), process measures (presence of social isolation, discontinued care) and patient or caregiver related measures [presence of psychological symptoms, neuropsychiatric problems (patients only)]. Additionally, we adjusted the analyses (ORs) for dementia subtype. All analyses were carried out in STATA SE14.

RESULTS

In total $n = 916$ patients were invited, of which $n = 389$ (42%) responded and $n = 527$ (58%) did not. Responders and non-responders did not differ in age or proportion of females. Responders had a higher last MMSE score (27 ± 4) compared to non-responders (24 ± 6, $p < 0.001$). Responders differed from non-responders with regard to diagnosis ($p < 0.001$), as responders were more often cognitively normal and less often dementia patients (**Supplementary Table 1**).

Patient and caregiver characteristics of the responders are summarized in **Table 1**. The mean age of symptomatic patients was 69 ± 6, $n = 40$ (33%) were female and almost all [$n = 97$ (91%)] lived with a partner. Cognitively normal patients were slightly younger (66 ± 8,) $n = 107$ (40%) were female and the majority lived with a partner [$n = 189$ (76%)]. Caregivers had a mean age of 67 ± 8, $n = 85$ (69%) was female.

Seventeen (5%) patients and $n = 4$ (3%) caregivers reported that they were probably infected with COVID-19. In four of them the infection was confirmed by the GP or Municipal Health Service.

TABLE 1 | Patient and caregiver characteristics.

		Patients				**Caregivers**
		All	**Cognitively normal**	**Symptomatic**		
		***N* = 389**	***N* = 268**	***N* = 121**		***N* = 147**
Age	389	67 ± 8	66 ± 8	69 ± 6	125	67 ± 8
Sex, F (%)	389	147 (38%)	107 (40%)	40 (33%)	124	85 (69%)
Diagnosis of patient	389				147	
SCD		268 (69%)	268 (100%)	*NA*		*NA*
MCI		35 (9%)	*NA*	35 (29%)		24 (16%)
Dementia		86 (22%)		86 (71%)		123 (84%)
AD		43 (50%)	*NA*	43 (50%)		59 (48%)
DLB		34 (40%)	*NA*	34 (40%)		44 (36%)
Dementia other		9 (10%)	*NA*	9 (10%)		20 (16%)
Last MMSE	384	27 ± 4	29 ± 1	23 ± 5		
Last NPI	284	10 ± 12	9 ± 11	11 ± 12		
Last GDS	162	3.6 ± 3	4.3 ± 3	3.2 ± 3		
Living situation of patient	355				131	
Alone		69 (19%)	59 (24%)	10 (9%)		13 (10%)
With partner/family		286 (81%)	189 (76%)	97 (91%)		118 (90%)
Relation to patient					125	
Partner		*NA*	*NA*	*NA*		115 (92%)
Daughter/son		*NA*	*NA*	*NA*		5 (4%)
Other		*NA*	*NA*	*NA*		5 (4%)
Patient-caregiver dyads		*NA*	*NA*	*NA*	147	92 (63%)

AD, Alzheimer's Disease; DLB, Dementia with Lewy bodies; GDS, Geriatric Depression Scale; MCI, Mild Cognitive Impairment; MMSE, mini-mental state examination; NPI, neuropsychiatric inventory; SCD, Subjective Cognitive Decline. n = 22 caregivers did not report on own demographic data. Time between completion of corona survey and last MMSE and was 1.00 ± 0.7 years, last NPI was 2.3 ± 0.9 and last GDS was 2.2 ± 1.1.

Social Isolation and Cognitive Decline

Social isolation was experienced by $n = 42$ (35%) symptomatic and $n = 67$ (25%) cognitively normal patients. This pertained to not seeing their friends [symptomatic: $n = 22$ (52%), cognitively normal: $n = 40$ (60%)] and family [symptomatic [$n = 24$ (57%), cognitively normal: $n = 31$ (46%)] during the COVID-19 pandemic (**Supplementary Figure 1**). $n = 7$ (17%)] of symptomatic patients and $n = 7$ (10%) of cognitively normal patients did not go outside at all.

Half of the caregivers [$n = 73$ (53%)] was worried for faster cognitive decline in the patient. These worries were also reported by symptomatic patients themselves [$n = 44$ (44%)] and were mentioned by a subgroup of cognitively normal patients [$n = 27$ (14%)]. More than half of caregivers reported a higher caregiver burden [$n = 69$ (56%)].

Psychological Effects

Figure 1 presents the self-reported increase in loneliness, anxiety, uncertainty and depression by symptomatic patients and caregivers. Almost half of participants reported an increase of one or more psychological symptoms [*n* = 56 (46%) symptomatic, *n* = 102 (38%) cognitively normal and *n* = 72 (48%) caregivers].

Behavioral Symptoms

We asked the caregivers whether they saw an increase in behavioral symptoms (apathy, changes in sleeping behavior, repetitive behavior and aggression) in the patient. An increase in patients' behavioral problems was reported by *n* = 111 (75%) of caregivers. Specifically, caregivers reported an increase in apathy [*n* = 72 (54%)], a change in sleeping behavior [*n* = 64 (48%)], increased repetitive behavior in *n* = 43 (34%) and patient aggression in *n* = 37 (30%).

When we asked patients directly about an increase in apathy and change in sleeping behavior, they reported increased apathy in *n* = 42 (40%) symptomatic and *n* = 47 (22%) cognitively normal patients. Change in sleeping behavior was reported by *n* = 40 (37%) symptomatic and *n* = 52 (25%) cognitively normal patients.

Discontinuation of Care

N = 43 (36%) symptomatic and *n* = 151 (56%) cognitively normal patients did not receive any care before the COVID-19 pandemic. Of the remaining *n* = 195 (*n* = 117 cognitively normal and *n* = 78 symptomatic), *n* = 129 (66%) [*n* = 58 (75%) symptomatic, *n* = 71 (61%) cognitively normal] reported discontinuation of care (**Figure 2**).

Only symptomatic patients were asked on discontinuation of community care services or day care. Of those symptomatic patients, *n* = 28 (36%) reported that they were not able to go to day care and *n* = 25 (32%) reported that community care services had halted. *N* = 17 (60%) patients were offered an alternative for day care, which mostly meant contact via telephone. Of the cognitively normal patients that reported regular care from the GP, a quarter stopped visiting the GP [*n* = 33 (28%)]. Roughly one out of five [*n* = 21 (18%)] symptomatic and a small minority [14 (5%)] of cognitively normal patients indicated that they needed more support than they were currently receiving. A quarter of caregivers [*n* = 43 (29%)] reported that they needed more support.

Red Flags

Logistic regression models were used to identify red flags for higher caregiver burden and worries for cognitive decline. Discontinued care (OR = 3.3 [1.3–7.9]), reporting one or more psychological symptoms by the caregiver (OR = 4.0 [1.6–9.9]) and behavioral problems at the patient level (OR = 3.0 [1.0–9.0]) were strongly related to a higher caregiver burden. Social isolation (OR = 3.2 [1.2–8.1]) and reporting one or more psychological symptoms by the patient (OR = 8.1 [2.8–23.7]) were determinants for worries for faster cognitive decline. Other determinants were not significant. Behavioral problems lost significance in relation to higher caregiver burden after adjustment for dementia subtype (OR = 2.3 [0.7–7.2]). Adjusting the analyses for dementia subtype did not change other results (**Supplementary Table 2**).

DISCUSSION

The current study showed that during the corona crisis social isolation, increased psychological symptoms, and discontinuation of care were frequently reported in pre-dementia patients and/or their caregivers living at home. Both patients and caregivers expressed worries for faster cognitive decline. Social isolation and psychological symptoms were red flags for these worries. Moreover, discontinuation of care, and psychological symptoms were strong predictors for experiencing a higher caregiver burden.

Social isolation due to the corona measures was experienced by one third of symptomatic patients, and by a quarter of cognitively normal memory clinic patients. Social interactions are important for patients with cognitive complaints, as is engaging in daily recreational activities, e.g., exercise (16, 17). During the corona crisis, many people sought for social connections online, but this is more difficult for patients with cognitive complaints. We even found that some patients did not go outside at all. This may worsen a patients' cognitive, mental and/or physical condition and this was indeed reported by patients (18–20). Of note, many patients were not able to go to the GP or hospital either at their own initiative or due to the closing of out-patient clinics. This may have gone at the expense of an increased risk of poor clinical outcome, also in the cognitive domain and even in cognitively normal patients, where the loss structure and social cohesion may be the final push toward onset of overt symptoms. The experience of social isolation was clearly a red flags for expedited cognitive decline and illustrates that is essential to prevent this feeling by pro-active policy aiming for social cohesion and patient empowerment, both on a government level and in the neighborhood.

The serious nature of the COVID-19 pandemic and the COVID-19 disease risk itself may also have impacted patients. As a result, the COVID-19 pandemic may have caused feelings of uncertainty and anxiety, especially in vulnerable elderly. This necessitates the availability of very easily understandable information on COVID-19. As patients with pre-dementia already lived with much uncertainty on the progression of their cognitive complaints, this may have made them more vulnerable for psychological symptoms during the COVID-19 pandemic. Due to corona (measures), half of the symptomatic patients and caregivers reported an increase in psychological symptoms, including feelings of loneliness, anxiety, depression and uncertainty. This is reason for concern as psychological and neuropsychiatric symptoms are known to be strongly related to cognitive decline, caregiver burden and quality of life (21–24). Also in cognitively normal patients, one third reported an increase in psychological symptoms. A recent review reported on the psychological impact of quarantine (25), and showed that psychological distress, amongst others depression, anxiety and insomnia, varied between 12 and 34% of people that were

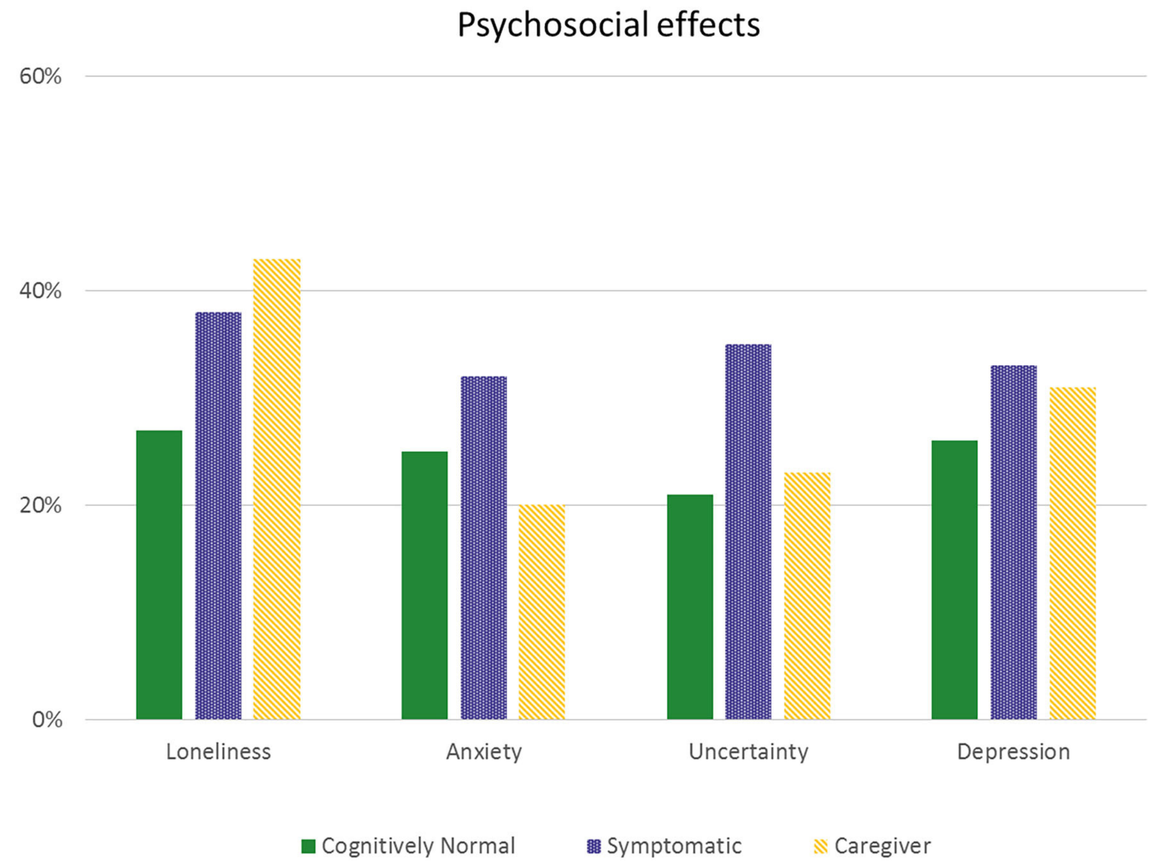

FIGURE 1 | Self-reported psychosocial effects. Self-reported increase in feelings of loneliness, anxiety, uncertainty and depression in patients and caregivers.

quarantined for several weeks (26, 27). However, these results came from the SARS epidemic in 2003, during which people were not able to go outside at all (27). In comparison, quarantine for the participants in the current study was not that stringent, as people in the Netherlands were advised to stay home, but were allowed to go outside for a walk or some grocery shopping. Nonetheless, we show that, despite these less stringent measures, psychological symptoms in pre-dementia patients and caregivers were much more frequent.

An increase in behavioral problems was reported by the three quarter of caregivers. Mostly, patients exhibited an increase in apathy or sleeping behavior, but also an increase in agitation and repetitive behavior. This may be an important moderator in the effect of discontinued care on higher caregiver burden. These behavioral problems may be even more problematic, as a recent review showed that patients who exhibit aggression, wandering or disinhibition are even at higher risk of catching and spreading COVID-19 (16), triggering a vicious circle as research now shows that catching COVID-19 has adverse impacts upon the brain and cognition.

More than half of caregivers reported a higher caregiver burden. This could even be under reported, as a recent report by the Dutch patient organization "Alzheimer Nederland" on a similar survey among caregivers, showed a higher caregiver burden in 80% of respondents (28). This difference could be due to differences in population, as the patients in our study were in general in a relatively mild disease stages. Red flags for overburdened caregivers were discontinuation of care, and the occurrence of psychological symptoms such as loneliness or anxiety either expressed by the patient or themselves. National and international efforts arise to set up conceptual frameworks that guide the management of key areas related to dementia care. In general, these frameworks point out that community-based health care professionals (HCP) together with a patients' social network play a pivotal role. Together they should identify families in need, support caregivers in dealing with problematic psychological and/or behavioral changes and help patients to engage in an active lifestyle at home. Our study shows that continuation of care is essential, and if physical visits are not possible, than alternatives, such as by phone or online should be actively pursued. Recently, in response to COVID-19 literature becomes available on how to redesign health care and telehealth has been advocated. The advantages of remote care for pre-dementia patients and their care partners may outweigh the difficulties of setting up this new way of working; outpatients do not have to visit the hospital, reduces need for traveling, minimizes complications and better fits a patients' daily routine (29, 30).

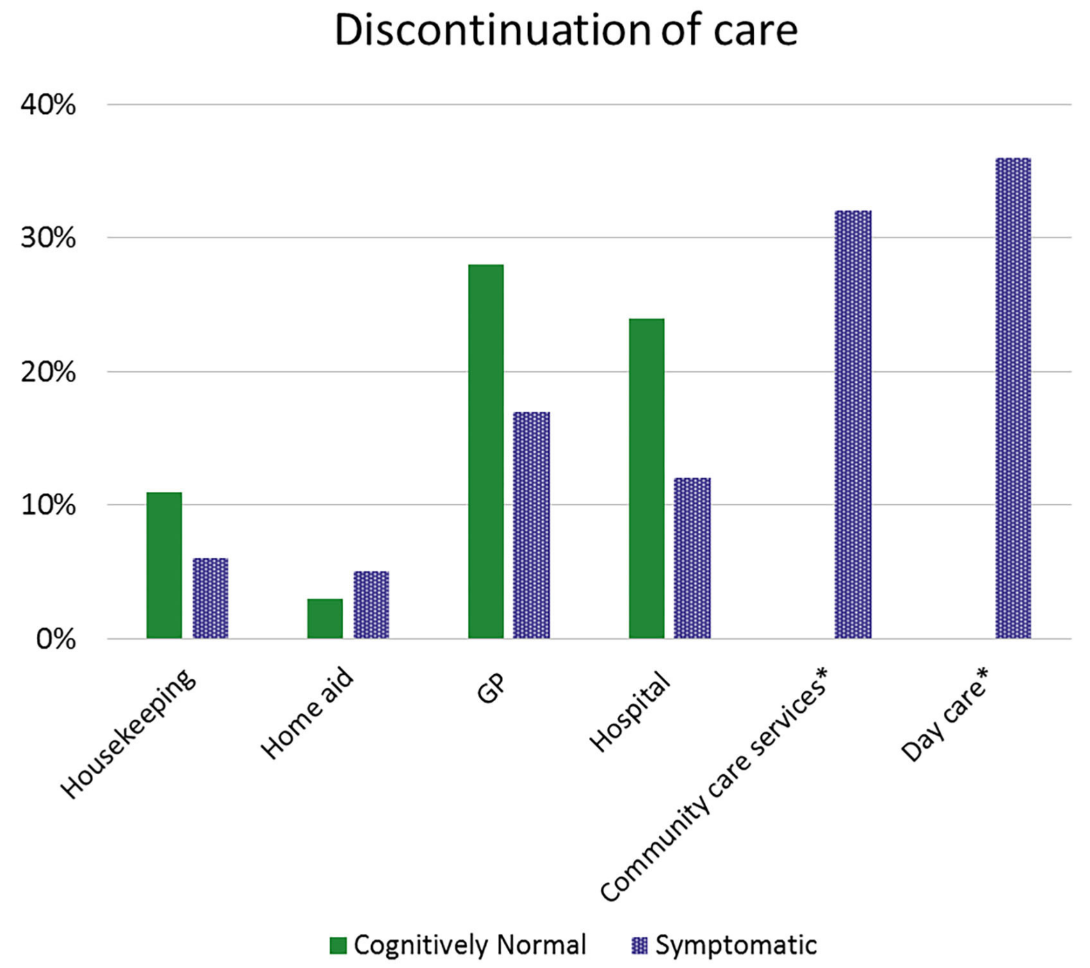

FIGURE 2 | Discontinuation of care. *Discontinuation of community care services and day care were only reported by symptomatic patients. GP, General Practitioner.

The association of psychological symptoms with higher caregiver burden and increased worries for cognitive decline shows that not only patients, but also their caregivers should be actively monitored, supported and empowered. In order to facilitate early recognition, governmental bodies should help to increase society's awareness of the challenges that vulnerable patients and their caregivers face due to corona and corona measures (31). Efforts should be made to help patients and caregivers to develop and maintain a daily routine during active lockdown measures, as the predictability of such a routine can decrease anxiety (29). Moreover, activities in and around the house can help to keep active and purposeful (20, 29). The current study adds to this by showing that there should not only be attention for symptomatic patients, but also for cognitively normal patients as they express significant worries for faster cognitive decline and often experience psychological symptoms as well.

Among the strengths of our study is the large sample of symptomatic and cognitively normal patients with different types of dementia, MCI and SCD. In addition, we had a large sample of caregivers that completed the survey. We were flexible to rise to the occasion as we had an online survey system in place in the midst of the corona crisis. As a result, we have a good overview of the effects of the corona measures on the whole spectrum of cognitive decline and dementia. While most attention has been paid to the institutionalized dementia patients, we show the vulnerability of those living at home.

Among the limitations is a potential selection bias. The included patients in the current study were able to complete a survey online, perhaps with help of a caregiver. By using an online survey we may not have reached everyone, as the survey may have been less accessible for people with severe cognitive complaints, suboptimal health literacy or diverse populations. Nonetheless, with this online nature of the survey we did befitted from the general atmosphere of the corona-times. Moreover, all patients participated in specific studies, which perhaps illustrates that they are socially active, and relatively less vulnerable. In response to the acuteness of the COVID-19 pandemic, we did not use a validated survey. Instead we developed a survey in collaboration with Alzheimer Nederland and via a bottom-up approach with expert opinions from neurologists, social scientists and dementia nurse. The survey, as any by definition, is subjective in nature and therefore we not only asked whether participants experience a certain item (for example social isolation), but also included follow-up questions to assess how this was experienced as this might differ from person to person. In addition, we did not invite partners of cognitively normal patients. In this way, we may have missed cases where cognitively normal patients did not notice that they became symptomatic, while in fact the partner did experience a sudden drop in cognitive functioning. In their patient consultations, our neurologists heard a few of such accounts. This further illustrates the relevance of awareness of the negative consequences of the corona measures particularly in pre-dementia stages.

According to simulation models, a second wave of a COVID-19 outbreak is likely to happen and new or prolonged measures to combat the spread will be issued (32). Preparing for a second wave, we show that memory clinic patients and their caregivers are a vulnerable group to look after, who experience negative impact in terms of psychological and behavioral symptoms, express worries for faster cognitive decline and experience a higher caregiver burden. This shows the need for health care providers and professionals to set up ways to warrant the continuation of care and to counsel patients and caregivers at higher risk of negative psychosocial effects.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article can be made available by the authors upon reasonable request. Requests to access the datasets should be directed to Ingrid S. van Maurik, i.vanmaurik@amsterdamumc.nl.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Review Committee of the VU University Medical Center. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

IM, SB, FG, FB, PS, and WF designed the study and corona survey. EB, MB, EL, AM, KB, and ML collected the data. IM conducted the data analysis and had full access to all data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. IM and WF interpreted the data and drafted the article. All authors revised the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.585686/full#supplementary-material

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Caring for Persons Living With Dementia During the COVID-19 Pandemic: Advocacy Perspectives From India

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The Coronavirus disease 2019 (COVID-19) pandemic has presented an unprecedented threat to global public and psychosocial health. Certain vulnerable populations, especially the older adults, are at disproportionate risks both to the physiological and social effects of the outbreak. A special section among them who face unique challenges during this pandemic, are those living with neurocognitive disorders, like dementia. Limited research in the field shows ApoE4 allele to confer an increased risk for COVID-19 severity, while the behavioral problems associated with dementia reduces compliance to precautionary measures, thereby exposing them to the virus and increasing caregiver strain. Reduced healthcare access, limited resources and fear of the infection act as major barriers to dementia care during such a crisis. Besides, there are the additional burden of stigma, abuse, ageism and financial impoverishment. Institutionalization, loneliness and lack of stimulation can potentially accelerate the cognitive decline and worsen the behavioral and psychological problems. India has been one of the worst hit countries by COVID-19 and shares a significant dementia load. As the country is aging fast along with the world, this commentary reviews the risks of people living with dementia during the pandemic and discusses certain advocacies for their care.

Keywords: COVID-19, coronavirus, dementia, neurocognitive, caregivers, advocacy, India

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COVID-19: THE PROBLEM STATEMENT

The world has endured 8 months of COVID-19 –initially reported as an outbreak at Wuhan, China in December, 2019 (1). The World Health Organization (WHO) recognized the infection as a pandemic on 11 March, 2020 (2). The first case of COVID-19 infection in India was reported on 30 January, 2020, the provisions of the Epidemic Diseases Act, 1897 were invoked on 11 March, 2020 and a national disaster announced on 14 March, 2020 (3, 4). During the pandemic, as noted by the WHO, though people of all age groups are at risk of contracting COVID-19 infection, older adults (aged 65 years and above) face a significantly higher risk of developing severe illness if they contract the disease due to the physiological changes that come with aging and other potential underlying health conditions (5). These include, but are not limited to heart disease, lung disease, diabetes mellitus, obesity, liver disease, and immunocompromised states. There is not, as of the present, any clear evidence of the interaction between the dementias and COVID-19 in older adults. However, there appears to be emerging evidence that homozygosity for the *ApoE* e4 genotype increases the risk of infection and of severe COVID-19 disease from the UK Biobank (6).

Among hospitalized older adults with the COVID-19 infection (indicative of moderate to severe disease), dementias appear to be a common comorbidity and are associated with increased risk of mortality (7). The increased all-cause mortality of patients in nursing homes (among whom older adults living with dementia are over-represented) amidst the COVID-19 pandemic, reported from the United States of America (USA), United Kingdom (UK) and South Korea may also be indicative of the increased risk associated with dementia (8–10). In addition, the care as usual of older adults living with dementia is affected in several ways due to the disruption of health services and diversion of resources to contain the pandemic. This has led to barriers in the pathway to care, potentially increased time to diagnosis and management, a shortage of essential medicines and interruption of rehabilitative services. The social network has also been impacted by the physical distancing directives. The United Nations (UN) and WHO have not explicitly addressed the risk to the health of persons living with dementia. The Center for Disease Control and Prevention (CDC) has provided comprehensive guidance for the caregivers of persons living with dementia in the community as well as for the tiered management of inmates of nursing homes by health care professionals (11). In India, the Government of India and the National Institute of Mental Health and Neuro Sciences (NIMHANS), Bengaluru have issued an advisory on caring for older adults and noted in the mental health guidelines that pre-existing cognitive impairment poses unique challenges during the pandemic (12). However, there is a deficit of official information and formal guidance about how to care for persons living with dementia both from the WHO and in the Indian context. Guidance for health care professionals, persons living with dementia and their caregivers are also available from several professional bodies, advocacy and not-for-profit organizations including the International Psychogeriatric Association, Dementia Alliance International, STRiDE dementia and Dementia Australia (13, 14). Advocacy groups for Alzheimer's dementia (the most commonly identified cause of dementia) such as Alzheimer's Association(AA), Alzheimer's disease International (ADI), Alzheimer Europe and Alzheimer's Society, UK provide similar information (15). However, there is a dearth of specific and tailored guidance for other neurodegenerative disorders, with Alzheimer's disease dominating the discourse. In the Indian context, non-governmental organizations (NGOs) such as Dementia Care Notes and the White Swan Foundation provide recommendations for caregivers of persons living with dementia, though guidelines for persons living with dementia themselves are sparse—indicating a perceived lack of autonomy and agency in those living with dementia (16, 17). Further, professional bodies are yet to release detailed guidance for health care professionals involved in the care of persons living with dementia. Older adults living with dementia, their caregivers and health care professionals involved in their management in the Indian context face specific concerns during the COVID-19 pandemic that merit discussion and targeted interventions (18). The authors therefore provide below a review of these concerns, highlighting their potential challenges and advocating recommendations for care.

CONCERNS

Information, Understanding, and Comprehension

Persons living with dementia bear cognitive deficits with regard to their working memory, encoding, information processing, comprehension, recall, language, reasoning, planning, and judgement. These deficits worsen with the severity of dementia and the relative degree of deficits vary with the nature of the dementia (19, 20). The nature of these deficits may impair persons living with dementia from understanding the nature of the COVID-19 pandemic and the guidelines placed in response to it, much less the need to comply with it. Persons living with dementia in the community will find it harder to comply by shelter in place, social distancing, usage of masks and gloves or sanitation. The difficulty in comprehension of information may worsen with the large volume of information pouring in each day related to the pandemic and the frequent changes in guidelines. Particular phenomena, such as confusional arousal, fluctuation in orientation, glycaemic disturbances, electrolyte disturbances, sun downing, visual and auditory impairment might worsen comprehension deficits. While much has been made of a possible worsening of anxiety, agitation, restlessness, aggression and other positive problematic behavioral symptoms—all persons with dementia are not alike and may react to the barrage of information about the pandemic in differing ways. Behavioral and psychological symptoms associated with dementia (BPSD) may make it difficult for older adults to comply with precautionary and therapeutic measures, though withdrawal may manifest as often as agitation. A concern unique to persons living with dementia in India is the multiplicity of languages, ethnicity and culture within a single country (17). Much of the information available is directed toward an English speaking urban audience—with only limited penetration into vernacular languages and rural or underprivileged populations. There is also limited fact-checking and verification of the authenticity of translated information, with scope for interpretation in differing ways—which can worsen ambiguity and anxiety.

Morbidity and Mortality Due to COVID-19 Infection

Emerging data from the UK Biobank Cohort reveals that persons living with dementia are over-represented among older adults with symptomatic or severe SARS-CoV-2 infection, in those requiring hospitalization, mechanical ventilatory support and those who have succumbed to the infection (6). Older adults with dementia are often frail, with impaired mobility, respiratory reflexes and regulation, immunocompromised, and likely to have multi-morbidity and poly-pharmacy—all of which are adverse prognostic factors for any infection.

Based on data from the Chinese Centre for Disease Control and Prevention, the age-adjusted fatality rate in 60–69 years is 3.6% which rises to 18% above 80 years (21). Further, age is also an independent risk-factor for non-pulmonary involvement and septicaemia, that can add to the morbidity. An age-wise comparative study by Liu et al. (22), reported three times increased mortality risk in people above 55 years who are affected by the outbreak. Ioannidis et al. (23) in their cross-sectional survey of 14 countries showed that people lesser than 65 years of age have 10-fold lesser risk of morbidity and mortality in India. The authors also highlighted the lack of systematic age-specific data in the developing countries. Further, more than 60% of the dementia cases are from low and middle-income countries (LMIC). This makes the "dual" burden of "age" and "cognitive impairment" all the more relevant in a populated and diverse LMIC country like India.

Further, there is also emerging data from the UK Biobank cohort, again, that the *ApoE* e4 genotype, associated with both delirium and dementia, particularly a 14-fold high risk of Alzheimer's disease confers a higher risk of infection. It appears to increase risks of severe COVID-19 infection independent of pre-existing dementia, cardiovascular disease, and type-2 diabetes. The *ApoE* e4 gene is co-expressed with ACE2 receptor in the respiratory epithelium and in type II alveolar cells as well as neurons and glia, which may indicate a possible inflammatory pathogenesis (6). The *ApoE* e4 genotype is less frequent in the Indian population than in people of European ancestry, though there is increased frequency of occurrence in persons with Alzheimer's dementia and vascular dementia (24). Hypoxia associated with COVID-19 infection can induce delirium—a poor prognostic factor for the infection, pre-existing dementia and overall all-cause mortality. India is facing a potential shortage of ventilators and intensive care as cases are on the rise—a shortage that will hit persons living with dementia harder (25). There has been an increase in mortality in nursing homes from USA, UK and East Asian—both due to the rapid spread of COVID-19 infection within a closed population and sudden, unexplained mortality—which may be partly indicative of the increased biological vulnerability of persons living with dementia (9). This is of relevance to and concerning in India, where there is a paucity of data from nursing homes. Palliative care in dementia can be considered to be a second priority at times of pandemic crisis.

Potential Worsening of Dementia With COVID-19 Infection

A possible increase in new onset ischemic stroke, intra-cranial hemorrhage and worsening of pre-existing cerebrovascular disease, including vascular dementia due to the inflammatory cascade triggered by the cytokine storm during NeuroCovid Stage II and III has been postulated by neurologists (26, 27). It has also been postulated that the inflammatory cascade may worsen other neuro-inflammatory and degenerative disorders such as Parkinson's disease and multiple sclerosis. This hypothesis is partly based upon the epidemic of encephalitis lethargica after the 1918 influenza pandemic. Similar observations of histological and motor symptoms of Parkinson's disease have been noted after H1N1 epidemic and outbreaks of West Nile Virus, Japanese Encephalitis B, Coxsackie Virus and HIV (28).

Cytokine imbalance is one of the many factors involved. Delirium has been reported as one of the commonest neuropsychiatric manifestation of COVID-19, pre-existing cognitive deficits being one of the important and obvious risks. Urinary retention, medical comorbidities, polypharmacy, cytochrome interactions, insomnia, tissue hypoxia, desaturation and use of hydroxychloroquine have been proposed as the risk factors for confusional states and worsening cognitive status in COVID-19 infections (29). In both animal and human models, the possible neural spread of SARS-CoV-2 has been linked to Angiotensin Converting Enzyme (ACE)-2 binding in respiratory and olfactory epithelium, invasion of the pyriform cortex and dissemination in hypothalamus, thalamus, parahippocampal cortex, basal ganglia, and amygdala (30). These brain regions are also implicated in neuro-degenerative disorders like dementia and a bi-directional relationship can thus be hypothesized. In an ecological study by Azarpazhooh et al. (31), healthy life-expectancy and dementia disability adjusted life years (DALY) were significantly related to the COVID-19 caseloads and mortality. Studies have also shown significant impact of COVID-19 related lifestyle changes, social isolation, loneliness and quarantine measures on the behavioral and psychological symptoms of dementia (BPSD), especially sleep disturbances, anxiety, depression, agitation and wandering (32, 33)

Loneliness and Social Isolation

Under-stimulation as a result of reduced social interaction may accentuate cognitive decline in those vulnerable. Lockdowns all over the world and in India limit opportunities for physical and cognitively stimulating activities. There is also a restriction on visits by friends and family in the community, in acute care and in long term care homes, including nursing homes. Social isolation and loneliness are likely to exacerbate cognitive deficits in persons living with dementia (34, 35). Services for older adults in the community and in hospitals are often segregated, which while allowing specialist care and reducing the waiting period, can worsen under-stimulation. Digitization has been postulated as an alternative to interaction and stimulation. However, India, where functional digital illiteracy is estimated to be above 90% is likely to have poor penetration of digital services in persons living with dementia—unless aided by a formal or informal caregiver (36). Poverty, lower education levels, unemployment and rural living make underprivileged populations less likely to have digital penetrance. Further, there are lesser digital services available in the vernacular language and which are respectful of diversity in culture, religion and ethnicity with aging (gero-diversity) (37).

Delay and Barriers in Pathways to Care for Dementia

The cessation of non-essential health care services, including dementia care and rehabilitation, and the diversion of health care resources toward pandemic control is a potential source of delay in and barrier to diagnosis, treatment and care of persons living with dementia in India. Older adults are encouraged to stay at home, and delay non-emergency consultations—with an increase in time to care for new onset dementias and barrier in the continuity of care of patients already on treatment (25). Structural procedures such as travel restrictions also limit the ability of patients with dementia to travel to hospitals—a factor of importance in India, where most of dementia care is available only in tertiary care facilities and in large urban areas (16). A delay of a few weeks to months may prove to be critical for persons living with dementia—especially young onset and rapidly progressive dementias, where a critical window of opportunity is lost (25). Another potential barrier to care is economic. In India, where 80% of care is delivered by the private sector, and dementia medicines and cognitive re-training do not come under subsidized state care—the care of a person living with dementia has always been an expensive affair for the average Indian household—costing between 3,000 and 15,000 Indian National Rupee (INR) a month at a conservative estimate (38). The only potential benefits available for senior citizens are old age pensions and disability benefits of 1,000–1,200 INR a month—with poor and inconsistent coverage which is inadequate to offset the costs of caring for a person with dementia. These financial constraints and loss of income to household represented by the pandemic and lockdown may further place critical care for dementia—including essential medicines out of the pocket of families (38).

Caregiver Burnout and Strain

Most of dementia care in India is delivered in the community and by informal caregivers- usually family and most commonly women (38). Constraints placed on persons living with dementia may hasten cognitive decline and worsen BPSD, worsening burnout of caregivers. Further, work from home and school vacations mean that family members now spend more time with persons living with dementia in close contact. This has potential to be a rich and fulfilling interaction but may also be a source of strain for caregivers who find themselves performing a double shift—professional and personal (39). Caregivers of persons with dementia usually report turning to informal work, or work with more flexible times, though lower paid, in order to balance their caregiving responsibilities. In India, 97% of paid work is estimated to be in the informal sector. The International Labor Organization estimates that poverty is estimated to double as a results of the pandemic (40). The caregivers of persons with dementia are over-represented in this sector and are vulnerable to a loss of income. These economic constraints is likely to interact with the physical limitations during the pandemic to compound dementia care and caregivers. Spouses are the most common caregivers of persons living with dementia and have to deal with increased vulnerability to the infection (38). Another concern for persons living with dementia is the potential separation from their spouse during quarantine or hospitalization, a terrifying experience for the couple. Spousal caregivers may also have to address the issue of who will take over care of the person with dementia in the event of their demise (41). The restrictions on advance directives, do not resuscitate choices, interment services and funerals are also potential sources of distress for persons with dementia and their spouses.

Abuse and Fraud

Reports of elder abuse has increased 10-fold across the world and 4-fold in India—including the NIMHANS elder helpline (42, 43). Persons with dementia are particularly vulnerable to abuse due to higher dependency needs. Further, the most common source of abuse is the caregiver, leading to the postulation that elder abuse may be a marker of caregiver burden. A HelpAge study in 2018 estimated 25% of Indian older adults had undergone elder abuse at some point, though conclusive data on persons living with dementia was lacking. This vulnerability is likely to increase (44). The limited availability of reporting and social welfare services in India—as well as the interruption of these services due to the pandemic is another risk factor. Persons living with dementia are also vulnerable to fraud, especially digital fraud, which is on the rise across the world during the pandemic (45). Again, conclusive data from India is lacking, but this is a potential area of vulnerability that would benefit from monitoring.

Health Care Professionals Involved in the Care of Persons Living With Dementia

Health care professionals involved in the care of persons living with dementia are struggling to provide appropriate care while maintaining the safety and welfare of their patients. Often, this care is delivered in stressful and resource poor settings, with inadequate structural provisions and safety equipment (46). Further, several health care professionals specialized in dementia care have been diverted to other health services for pandemic control—particularly in the public sector and must also deliver infection control. Masks and personal protective equipment used during consultation impair easy recognition of healthcare providers by persons with dementia and limit paralinguistic and non-verbal cues—a barrier to effective communication with the person. This may be accentuated in case of auditory and visual impairment (47). Primary health care is an important alternative, however, limited training in dementia and incomplete coverage of the population prevents it from being an effective alternative to tertiary referral. The possibility for the potentially inappropriate use of medication in persons with dementia is higher during pandemic control, when the focus is symptom control rather than comprehensive management.

RECOMMENDATIONS

Based upon these concerns in the care of persons living with dementia in India, the authors highlight some potential ways to address these, which may be incorporated into pandemic control. The comprehensive care of persons living with dementia, including appropriate safety and psychosocial considerations are an important component of public health. Unfortunately, this population has been left out of pandemic preparedness policies leading ambiguity in the guidelines for their care. Psychological well-being comes with physical security and the precautionary measures against the outbreak need to be well-guided and supervised by the caregivers tailored to the cognitive needs of people living with dementia. Acceptable standards of care need to be maintained considering the special needs of this population during such crisis, and the approaches that can be attempted differently are highlighted in brief:

- Information delivered to persons living with dementia must be performed slowly, with frequent pauses, in short and simple sentences with use of audio-visual aids. Communication can be attempted when the person is at their cognitive best during the day. Patients may be encouraged to revisit the information at periodic intervals. Pre-recorded audio and video material as well as simple infographic visual charts can act as cues help reinforce information.

- Psychological preparedness among the caregivers of people living with dementia is of paramount importance for the continuity of care. During such a contagious pandemic, there is always a possibility that the caregiver might himself/herself get infected with the pandemic and is unable to provide the required support. Alternative sources of care including friends, relatives, volunteers need to be planned and prepared for in advance. Tele-consultations are always a feasible option, especially as the National Institute of Mental Health and Neurosciences along with the Indian Psychiatric Society (IPS) has recently released the telepsychiatry guidelines, the first of its kind in India (48). Such guidelines set a standard of care for the physicians for virtual service delivery, which can be harnessed effectively in dementia care.
- Information to persons living with dementia is better delivered in the vernacular language, with tailored socio-cultural contexts. Information must also be relevant to the context of the individual. Meri Yaadein in the United Kingdom has provided excellent resource material on how practicing Muslims of the South East Asian ethnicity living with dementia and observing Ramadan during the pandemic may be handled in a culturally and religiously sensitive manner. Similar Indian material on COVID-19 and its impact upon the ethos and diversity of Indian life may help persons with dementia and their caregivers navigate the pandemic.
- Information, Education and Communication (IEC) for persons with dementia may be halted if the person expresses anxiety or becomes agitated and appropriate reassurance provided in a calm and soothing manner. Media has an important role to play for this awareness, but at the same time people with cognitive deficits are more prone to misinformation. Hence the authenticity of the sources need verification and guidance. Relevant and tailored information is better than an "information overload."
- A lower index of suspicion and testing of infection for persons living with dementia, their caregivers and inmates of nursing homes may be beneficial effective care and reduce morbidity and mortality.
- Research in the Indian context would fill an existing lacuna in the field. It may go a long way toward examining the potential interactions between the COVID-19 infection and neurodegenerative disorders and may guide informed care. This is of particular relavence with over two third of persons with dementia living in LAMI countries like India with numbers that are projected to increase with time.
- Attempts should be made to decentralize dementia care and integrate it into community health care and the district mental health programme (DMHP) to address barriers and delay in care.
- An early resumption of dementia care with due precautions and integration with tele-medicine where possible may cut down delay in diagnosis and care.
- Subsidization of dementia care where feasible, with coverage of investigations, medicines and training in welfare schemes such as the National Mental Health Programme (NMHP), National Policy on Senior Citizens and Ayushman Bharath would make dementia care during the pandemic more affordable.
- Interaction with family, friends and the community in a safe manner, regular physical and mental exercise and adequate nutrition and fluid intake in persons living with dementia need to be encouraged. Social connectedness is vital and digital services can be used to the extent feasible. Meeting or interacting with their loved ones or even pets, albeit virtually, can help both cognitive issues and BPSD. Simple steps like music, group activities, prayers, spending more time with people living with dementia can increase the "contact time" and help in reducing the behavioral issues.
- Addressal of caregiver burden, psychosocial support in the community, provision of social security and remuneration of informal caregivers is recommended. Some states such as Kerala provide remuneration of around 600 rupees per month to female unpaid caregivers of persons with mental or physical illness—a model which may be of use with rising unemployment. Caregivers need to be counseled about their own "respite" time to prevent burnout. The National mental health counseling helplines need to be availed and integrated with the elder service helplines.
- Helplines, legal aid and social services to protect vulnerable persons from abuse and fraud and provide remedial aid is recommended. This can be combined with the education of caregivers and the community. These measures would help address abuse and fraud targeting persons living with dementia—who currently have inadequate safeguards under India law. Early detection of abuse, legal hassle free reporting and appropriate mental health care of the abuse victims are essential. Training for home-based management of behavioral symptoms can help prevent unwarranted abuse.
- Advance directives may be discussed with persons living with dementia and their caregivers, particularly spouses to ensure their wishes are honored in management of the infection and of dementia.
- Health care professionals can be encouraged to provide dedicated care to persons living with dementia, where feasible and with appropriate precautions. Voice modulation and non-verbal communication may be required to traverse the barrier provided by masks and face-shields. A single point contact of care with a familiar health care professional may reassure the person living with dementia considerably. Family physicians thereby play an important role here. Addressal of stress and burnout in health care professionals, including peer and supervisory support may also make care more effective. The primary care health workers may benefit from added expertise in dementia care, and tele-training can be enabled during the current times for integration of various levels of health care.
- Most importantly, it's a collective responsibility at all levels of stakeholders to identify the needs of people with cognitive impairment, their caregivers and establish planned strategies for their assistance, improvisations that can be used even

post-pandemic. Few non-governmental organizations like the Alzheimer's and Related Disorders Society of India (ARDSI), often partners with Governmental initiatives for community dementia care and support. ARDSI has been providing support and guidance via telephonic, video and social media platforms (49). The Psychiatric Social Work team along with the District Mental Health Programme (DMHP) officials can ensure home-visits and medication availability for compliance.

- The above-mentioned provisions of care are only possible taking into account the respect for autonomy and dignity in people living with dementia, fostering independence, hope and empathy. The "need to care" should not be mis-perceived as "coercion" and "covert abuse." Engaging them in conversations related to their health and safety as much possible is helpful.

CONCLUSION

India is aging fast. It is estimated that 20 percent of the population will be over 65 years of age by 2050 (50). A projected 5.3 million people are affected with dementia in India at present. The Global Strategy and Action Plan on Aging and Health was adopted by the World Health Assembly in 2016 to prepare for the Decade of Healthy Aging which began in 2020 and is expected to last till 2030 (51). In lines with the same, people affected with dementia also deserve a "humanitarian" and "right-based" approach to age and live a healthy life. Neurocognitive disorders (including the dementias) are a significant co-morbidity that increases in prevalence over the lifespan. In this review, we have attempted to discuss how the persons living with dementia face dual risks due to both age and cognitive decline, which are accentuated by the pandemic. Sensory deficits, behavioral problems, caregiver strain, associated abuse and neglect, lack of recognition of autonomy, limited opportunities for advocacy and administrative apathy are important social problems that add to recognized biological risks. Ageism is a form of stigma in itself which may further compound pandemic related stigma in those affected. Bearing in mind this problem statement, the authors suggest a comprehensive care model with an integrated bio-psycho-social approach to address the needs of the persons with dementia and their caregivers in the Indian context. Health and social services can improve from continued training and increased sensitivity to the concerns of persons living with dementia. Further, India is still in the initial stages of the pandemic. Greater psychosocial morbidity is expected in the months to come. Systematic research into the experiences of persons living with dementia can help tailor effective healthcare. Caregivers and health professionals are important allies to persons living with dementia and can contribute to advocacy and care. As an ending note, the authors would like to state that pandemic control in India can be best achieved when persons living with dementia are made part of and advocates for, rather than mere recipients of care.

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

Both the authors were involved in conceptualization, literature review, and drafting the manuscript. The final version was read and approved by both the authors.

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Impact of COVID-19-Related Lockdown on Psychosocial, Cognitive, and Functional Well-Being in Adults With Down Syndrome

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People with Down Syndrome (DS) have a high prevalence of physical and psychiatric comorbidities and experience early-onset dementia. With the outbreak of CoVID-19 pandemic, strict social isolation measures have been necessary to prevent the spreading of the disease. Effects of this lockdown period on behavior, mood and cognition in people with DS have not been assessed so far. In the present clinical study, we investigated the impact of CoVID-19-related lockdown on psychosocial, cognitive and functional well-being in a sample population of 46 adults with DS. The interRAI Intellectual Disability standardized assessment instrument, which includes measures of social withdrawal, functional impairment, aggressive behavior and depressive symptoms, was used to perform a three time-point evaluation (two pre-lockdown and one post-lockdown) in 37 subjects of the study sample, and a two time point evaluation (one pre- and one post-lockdown) in 9 subjects. Two mixed linear regression models – one before and one after the lockdown – have been fitted for each scale in order to investigate the change in the time-dependent variation of the scores. In the pre-lockdown period, significant worsening over time (i.e., per year) was found for the Depression Rating Scale score ($\beta = 0.55$; 95% CI 0.34; 0.76). In the post-lockdown period, a significant worsening in social withdrawal ($\beta = 3.05$, 95% CI 0.39; 5.70), instrumental activities of daily living ($\beta = 1.13$, 95% CI 0.08; 2.18) and depression rating ($\beta = 1.65$, 95% CI 0.33; 2.97) scales scores was observed, as was a significant improvement in aggressive behavior ($\beta = -1.40$, 95% CI -2.69; -0.10). Despite the undoubtful importance of the lockdown in order to reduce the spreading of the CoVID-19 pandemic, the related social isolation measures suggest an exacerbation of depressive symptoms and a worsening in functional status in a sample of adults with DS. At the opposite, aggressive behavior was reduced after the lockdown period. This finding could be related to the increase of negative and depressive symptoms in the study population. Studies with longer follow-up period are needed to assess persistence of these effects.

Keywords: COVID-19, lockdown, down syndrome, functioning, well-being

INTRODUCTION

Down Syndrome (DS) is the most common genetic cause of developmental disability and cognitive impairment, with an incidence of about 1/800 live births (1). DS is also referred to as a "segmental" progeroid syndrome, with selected organ systems experiencing early aging and persons with this condition might present patterns of co-morbidities commonly observed in the older population (2). Moreover, people with DS start experiencing progressive cognitive impairment early in life, with a prevalence of dementia as high as 68–80% at the age of 65 years (3). The clinical picture of individuals with DS is often complicated by the presence of functional deficits, behavioral symptoms and nutritional and social problems, all of which have increased prevalence with age (4, 5). Sociality and social interactions are important for individuals with DS, who identify family involvement and affection as main supporting pillars in life (6). Interestingly, individuals with DS tend to have higher global scores for social adaptive skills compared to adults with other intellectual disabilities (ID) (7).

Despite the relatively high prevalence of DS in the general population, few data are available about the impact of Coronavirus disease-19 (COVID-19) among those with DS (8, 9). Concerns about the COVID-19 epidemic in this population are related to the presence of a dysfunctional immune system, possible exacerbations of psychiatric conditions and worsening of functional and cognitive impairment (10). With the pandemic outbreak, several countries including Italy implemented strict social isolation measures referred to as *lockdown*, to contain the contagion (11). The Italian government issued a provision to guarantee care to persons with disabilities during the lockdown period. In spite of that, a large part of the social assistance structures dedicated to people with DS and their caregivers had to drastically reduce their activities, depriving people with DS and their families/caregivers of effective support. This reduction of social, recreational and work activities during the lockdown may have impaired the physical and psychological resilience of the general population (12) and similarly may have triggered or exacerbated behavioral and mood changes or have worsened the global and cognitive functioning of adults with DS. However, no data are available yet on the effects of the lockdown in this vulnerable population. Therefore, the aim of the present study was to describe the impact of COVID-19-related lockdown on psychosocial, cognitive and functional well-being in a sample population of adults with Down syndrome.

METHODS

This clinical study included adults with DS, aged 18 years or older, followed at the outpatient clinic of the Geriatric Department of the Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore Rome, Italy since 2015 to date. Participants were referred to the clinic by DS associations and family physician and received a comprehensive medical assessment that included a multidimensional evaluation with the interRAI Intellectual Disability (InterRAI-ID) instrument (13–15).

The present study enrolled subjects with the following characteristics: adults with confirmed genetic diagnosis of DS, without severe intellectual disability (QI < 20) and either two InterRAI-ID evaluations from 2015 since the beginning of lockdown in Italy (11th of March 2020) or one InterRAI-ID evaluation within 6-months before the lockdown. Among these eligible participants, telephone-based interRAI-ID follow-up was performed after the lockdown (since 15th April 2020 to 31st May 2020) to all the persons/caregivers willing to participate.

The study was approved by the Ethical Committee of the Università Cattolica del Sacro Cuore. Informed consent was obtained from all participants. The surrogate legal representative was asked to get the information and give consent in those cases where individuals were unable to make the decision for themselves.

Psychosocial, Cognitive, and Functional Assessment With the InterRAI-ID Instrument

Psychosocial, cognitive and functional well-being were evaluated through the interRAI-ID instrument, which contains over 350 data elements including socio-demographic variables, clinical items about physical and cognitive status, functioning, behaviors, and signs, symptoms, syndromes and treatments being provided (15). Items are compiled by a trained assessor based on history and basic signs and symptoms (e.g., face expressions, disruptive behaviors, pain frequency and intensity) collected directly from the individual being assessed, by an informant selected among the closest relatives (parents or siblings) or long-standing caregiver; a number of questions are asked directly to the individual concerning his or her preferences, outlook and well-being. Clusters of items are set up in algorithms and scales to deliver clinically relevant triggers to inform subsequent clinical evaluation. Such scales have proven internally consistent and valid among adults with ID (15). Cognitive status is evaluated through the Cognitive Performance Scale (CPS) (16) ranging from 0 (no cognitive impairment) to 6 (severe cognitive impairment). Functional status is evaluated through the 7-point Activities of Daily Living Hierarchy (ADLH), used to identify persons requiring assistance in ADLs (17), and through the 7-point Instrumental Activities of Daily Living Hierarchy (IADLH), used to identify those requiring assistance with IADLs (18). The two scales ranges from 0 (independent) to 6 (totally dependent). Depressive symptoms are assessed through the

Depression Rating Scale (DRS), ranging from 0 to 14 with score ≥3 being indicative of depression DRS has been cross-validated with other scales such as the Hamilton Depression Scale (19). Aggressive behavior is assessed through the Aggressive Behavior scale (ABS), ranging from 0 to 12. A score from 1 to 4 defines mild/moderate aggressive behavior and scores ≥5 define severe aggressive behavior (20). The presence of negative symptoms, such as withdrawal from activities of interest, lack of motivation, reduction in social interaction or anhedonia, is evaluated through the Social Withdrawal Scale (SOCWD). Scores range from 0 to 12 with higher scores indicating higher levels of anhedonia (21). The presence of communication problems is evaluated through the Communication Scale (COMM), with score from 2 to 5 defining mild/moderate communication problems and scores from 6 to 8 defining severe communication problems (22). The PAIN scale scores pain in a 4-point scale, ranging from 0 (no pain) to 3 (severe daily pain) based on recollection by the person or the caregiver and is highly predictive of pain as measured by the Visual Analog Scale (23). ADLH and IADLH are coded according to the actual situation at the time of assessment while time frequencies of the items in the other scales are classified as present every day in the past 3 days, present in the past three days but not daily, present at least once in the last 30 days, not present (or present more than 30 days before the assessment).

Analytical Approach

Sample characteristics were reported as mean and standard deviation (SD) or count and percentage (%). To compare the changes in the abovementioned scales before and after the lockdown, the follow-up time was centered around an index date, the day when the lockdown was established in Italy (11th March 2020). A value for each of the scales at the index date was predicted for each individual: assuming a linear change, for those with two available observations before the index date, we performed intra-subject linear regressions, considering time as predictor. Predicted values were rounded to the nearest integer. Since in the imputation procedure the variables were treated as continuous, the predicted values could fall outside the real range of variation. In this case, the predicted values have been approximated to the largest or smallest value belonging to the range, depending on the situation. For those individuals with only one observation preceding the lockdown, the predicted values at the index date were set as equal to the values observed previously (which were observed no more than 6 months before the lockdown). With the aim to evaluate the changes in participant's condition during the lockdown, a sign test for matched data was performed for all the considered scales. The test compares the distribution of the estimated values at the beginning of the lockdown with the distribution of the values observed afterwards. The null hypothesis was that the median of the estimated values at time 0 was equal to the median of the values detected during the lockdown period. Two mixed linear regression models – one before and one after the index date – have been fitted for each scale in order to investigate the change in the time-dependent variation of the variables. All models were adjusted by age and sex and a random effect was introduced at the intercept. A $p < 0.05$ was considered as statistically significant. Stata (StataCorp) 16.0 was used in all analyses.

TABLE 1 | Sample characteristics before the lockdown.

	Mean/count (SD/%)
	***n* = 46**
Sex (female)	23 (50%)
Age (years)	40.6 (13.3)
Residential status	
Living at home	37 (80.4%)
Other (Institution, group home, etc.)	9 (19.6%)
Persons with legal guardian	18 (39.1%)
Living arrangement	
With parents or guardians	30 (65.2%)
With siblings	7 (15.2%)
With non-relatives	9 (19.6%)
Alcohol use (1 drink in last 14 days)	5 (10.9%)
BMI (Kg/m^2)	26.0 (4.6)
Medical conditions	
Language disorders	5 (10.9%)
Cognitive decline	8 (17.4%)
Depression	5 (10.9%)
Autistic spectrum disorders	1 (2.2%)
Congenital cardiopathy	12 (26.1%)
Obesity	10 (21.7%)
Blood Cells abnormalities	7 (15.2%)
Visual impairment	40 (87%)
Hypoacusis	13 (28.3%)
Thyroid diseases	23 (50.0%)
Obstructive sleep apneas	7 (15.2%)
Osteoporosis	11 (23.9%)
Psoriasis	7 (15.2%)
Musculo-skeletal disorders	9 (19.6%)
N. of drugs	2.3 (2.0)
N. of psychotropic drugs	0.5 (0.9)
Informal care (hours in last 3 days)	43.0 (30.5)

RESULTS

Since 2015, a total of 221 adult individuals with DS were evaluated with the InterRAI-ID assessment in our clinic. We present data about 46 eligible individuals that agreed to participate to the telephone-based interRAI-ID follow-up after the lockdown. Nine of them had received an evaluation within 6 months before the lockdown and 37 had received two from 2015 until the lockdown. The characteristics of the study population before the lockdown are shown in **Table 1**. Mean age was 40.6 ± 13.3 years, 23 subjects were female (50%). Overall, 18 individuals (39.1%) were under the protection of a legal guardian and 9 (19.6%) were living with non-relative persons. On average they had received 43.0 ± 30.5 of informal care from family members, friends or neighbors in the 3 days before the evaluation. The most frequent medical conditions were visual impairment (87%), thyroid diseases (50%), hypoacusis (23.8%) and congenital cardiopathies (26.1%). Neuropsychiatric conditions were also prevalent: dementia was present in 8 persons (17.4%), 5 presented depression (10.9%), and 5 had language disorders (10.9%). One subject had autistic spectrum disorders. The mean number of regularly used drugs was 2.3 ± 2.0 and the mean number of psychotropic drugs was 0.5 ± 0.9.

Table 2 shows the mean scores of the investigated scales and the results of the sign test for the evaluation of changes in physical and mental health scales before and after the lockdown. The number of subjects that have worsened, improved or remained constant was significantly different for the IADLH scale ($p = 0.003$), for the ABS ($p = 0.046$), for the DRS ($p = 0.032$) and for the SOCWD scale (0.011).

Figure 1 and **Table 3** shows the rate of change (β coefficient and 95% C.I.) over time of physical and mental health scales before and after the lockdown. Regarding the pre-lockdown period, a significant worsening over time (i.e., per year) was only found for the DRS score ($\beta = 0.55$; 95% CI 0.34; 0.76). Regarding the post-lockdown period, significant worsening in scores over time was found for the SOCWD scale ($\beta = 3.05$, 95% CI 0.39; 5.70), IADLH scale ($\beta = 1.13$, 95% CI 0.08; 2.18), and DRS ($\beta = 1.65$, 95% CI 0.33; 2.97), while a significant improvement was found for ABS ($\beta = -1.40$, 95% CI -2.69; -0.10). ADLH scale, CPS, COMM scale and PAIN scale did not show significant changes over time both during the pre-lockdown and in the post-lockdown period ($p > 0.05$ for all).

DISCUSSION

The present study shows that social isolation measures related to COVID-19 lockdown reverberated on the functional and psychosocial well-being of adults with DS. To our knowledge, this

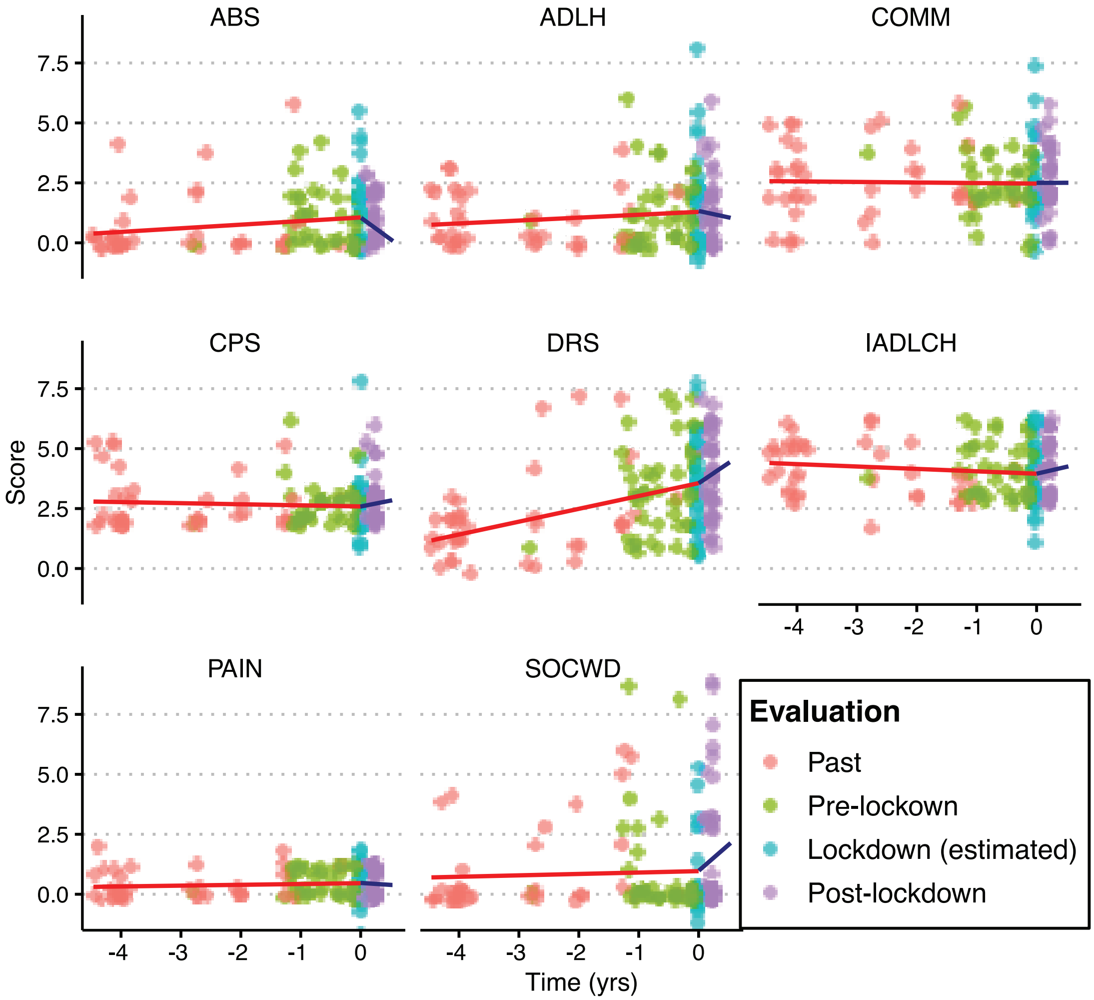

FIGURE 1 | Rate of change over time of physical and mental health scales before and after the lockdown. Points represent the scores obtained by each individual in the different evaluation events. Fit line in the pre-lockdown phase in red color; fit line in the post-lockdown phase in blue color. The fit parameters are specified in **Table 3**.

TABLE 2 | Mean scores of the scales before and after the lockdown and sign test for the evaluation of changes in participants condition during the lockdown.

	Mean score of tests[a]		Sign test for changes[b]			
	Before lockdown	After lockdown	Worsening	Improvement	No changes	*p*-value
ADLH	1.3 (1.5)	1.4 (1.3)	10	5	31	0.151
IADLH	3.9 (1.3)	4.2 (1.2)	11	1	34	**0.003**
ABS[c]	1.1 (1.4)	0.8 (1.0)	3	10	32	**0.046**
CPS	2.6 (0.8)	2.8 (1.0)	4	0	42	0.063
COMM	2.5 (1.4)	2.5 (1.3)	5	7	34	0.387
DRS	3.5 (2.0)	3.9 (1.7)	17	7	22	**0.032**
PAIN	0.5 (0.6)	0.4 (0.5)	0	3	43	0.125
SOCWD	0.8 (2.1)	1.6 (2.6)	13	3	30	**0.011**

[a] *Measures before lockdown refers to the values imputed at the beginning of the lockdown, while conditions after lockdown refers to the values observed afterwards.*

[b] *The test compares the estimated values at the start of the lockdown with those observed afterwards. For each scale, the number of subjects that have worsened, improved or remained constant is reported.*

[c] *There was no information regarding the value of the ABS variable after the lockdown for one of the study subjects. Therefore, that individual was not taken into consideration in the analysis of the ABS variable.*

Bold values highlight parameters with statistically significant change.

SOCWD, Social withdrawal scale; ADLH, ADL hierarchy scale; IADLH, IADL hierarchy scale; COMM, Communication Scale; ABS, Aggressive Behavior scale; DRS, Depression Rating scale; CPS, Cognitive performance scale.

TABLE 3 | Rate of change (β and 95% C.I.) over time of physical and mental health scales before and after the lockdown.

Functional scales	Pre-lockdown change per year			Post-lockdown change per year		
	β	95% C.I.	*p*-value	*β*	95% C.I.	*p*-value
SOCWD	0.04	−0.21; 0.30	0.742	**3.05**	**0.39; 5.70**	0.024
ADLH	0.09	−0.05; 0.25	0.208	0.23	−0.78; 1.24	0.651
IADLH	−0.10	−0.23; 0.02	0.112	**1.13**	**0.08; 2.18**	0.034
COMM	−0.03	−0.20; 0.14	0.759	−0.29	−1.23; 0.64	0.537
ABS	0.13	−0.03; 0.29	0.117	**−1.40**	**−2.69; −0.10**	0.034
DRS	**0.55**	**0.34; 0.76**	<0.001	**1.65**	**0.33; 2.97**	0.014
CPS	−0.03	−0.16; 0.09	0.595	0.55	−0.22; 1.31	0.164
PAIN	0.04	−0.03; 0.10	0.290	−0.26	−0.57; 0.05	0.106

C.I., confidence interval.

Bold values highlight parameters with statistically significant change.

For all measures positive changes mean worsening and negative changes improvement in scale.

is the first study describing the functional and psychosocial effects of the lockdown during the COVID-19 pandemic in people with DS.

Lockdown should be considered a potentially traumatic life-stressor event (24). Findings of our study should be discussed taking into account the adaptive behavior skills of individuals with DS. Throughout the lifespan, individuals with DS tend to demonstrate an adaptive behavior profile that involves relative strengths in receptive communication skills, domestic and community daily living skills and coping and interpersonal relationship socialization skills. Relative difficulties were reported in expressive and written communication (25). However, lower daily living coping skills and overall low adaptive behavior skills have been described for adults with DS when compared to age-matched general population individuals (26). Similar findings were found for elderly as compared to adult population {Cheng, 2014 #110}. In addition, in our sample, prevalence of visual and hearing impairment was high and sensorial deprivation can worsen adaptive behavior in adult individuals (27). But, it seems that vision problems do not decrease adaptive behavior skills in individuals with DS (28).

As expected from a lockdown-compliant population, our study sample showed a significant increase in social withdrawal scores (SOCWD) in the post-lockdown period. However, since the scale includes also dimensions other than social interactions indicators, the increase in SOCWD scores can also reflect an increase in anhedonia and lack of motivation. Notably, a high percentage of PTSD symptomatology, including anhedonia and sleep disturbances, was found also in a study including a sample of the general population in Italy (29). It is plausible that individuals with DS– frequently affected by neuropsychiatric conditions and dementia – may have been particularly prone to present such exacerbations.

We detected an increased depression burden during the post-lockdown period. Depressive symptoms are common among DS adults (30) and according to the pre-lockdown observation they appear to proceed faster than other measures. Yet, the time-dependent change in the DRS scores during the post-lockdown period was up to three time higher than pre-lockdown period, suggesting that stressor events (i.e., lockdown) could severely impact mood in individuals with DS (30). On the contrary, aggressive behavior scores (ABS) showed a significant decrease during post-lockdown period. A possible explanation of the decreased aggressive behavior observed in our study is that persons with DS are more likely to aggression toward peers or people who are not family members (31). Hence, social isolation could have reduced such external stimulation, resulting in a less demanding environment. On the other hand, it is known that catatonia and regression are frequent among young adults with DS facing stressful events (32), and internalized symptoms of depression emerge while externalized symptoms of aggressiveness decrease as they age (31). Indeed, social isolation in individuals with DS might have exacerbated or triggered negative symptoms (i.e., withdrawal, anhedonia, depression), while it could have mitigated aggressive behaviors.

From a functional point of view, there was a significant increase in IADL scores in the post-lockdown period, suggesting a decrease in independence in activities such as paying for things, shopping, and taking public transportation. On the one hand, this might be a consequence of the lockdown itself (compulsory stay-at-home policies, mandating closure of non-essential businesses), on the other hand it might have been the consequence of the disruption to their routines resulting in difficulties to understanding and adapting to the new requirements (such as wearing the face mask and respecting the contingent row at the supermarket), as has been described in the general elderly population (33). Conversely, the post-lockdown period did not show significant changes in ADL scores. This finding suggests that basic self-care activities such as dressing, washing and eating are less likely to be impaired by such stressor event.

The management of lockdown presents a perfect storm for mental distress for older people (34) and potentially even more for individuals with DS. Indeed, at any age individuals with ID present with significantly higher rates of mental health conditions when compared to the general population (35), and it is essential to thoroughly investigate their experience to devise effective ways of protecting them (10).

Limitations

The present study has some important limitations. The study sample is small and with pre-lockdown evaluations spread out over a large timeframe. Furthermore, subjects in study were enrolled from an outpatient clinic, and could therefore be characterized by more complex health needs compared to the general DS population. As a consequence, the sample can't be considered to be representative of the population with DS and the results should be interpreted in the light of the small sample size and the possible selection bias. Finally, although InterRAI-ID is validated both for in person and on the phone administration, the different routes of administration pre- and post-lockdown could have introduced further bias.

CONCLUSION

Despite the undoubtful importance of the lockdown in order to reduce the spreading of the COVID-19 pandemic, the related social isolation measures seemed to exacerbate depressive symptoms and some functional impairment in a population of adults with DS. Instead, aggressive behavior was less incident and could be related to the increase of negative and depressive symptoms. In light of such evidence, it will be important to assess in future studies the possible presence of long-term effects on the health of individuals with DS and how the disruptions of their routine affected not only other individuals with ID but also their caregivers. Doing this could lead to more awareness and to a novel insights in possible assistance and treatment strategies.

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 Ethical Committee of Università Cattolica del Sacro Cuore. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GO and RB designed and supervised the study. AP, EV, and AC assessed the participants and managed the dataset. DV and CD conceived and carried out the data analysis. EV and AC drafted the manuscript and coordinated the writing. GO, DV, AU, RB, LM, LF, and JH critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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The Influence of the COVID-19 Outbreak on the Lifestyle of Older Patients With Dementia or Mild Cognitive Impairment Who Live Alone

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Background: Under the COVID-19 outbreak, the Japanese government has strongly encouraged individuals to stay at home. The aim of the current study was to clarify the effects of the COVID-19 outbreak on the lifestyle of older adults with dementia or mild cognitive impairment (MCI) who live alone.

Methods: Seventy-four patients with dementia or MCI aged ≥65 years, who regularly visited the dementia clinic of the Department of Psychiatry, Osaka University Hospital, were recruited in this study. The patients were divided into two groups according to their living situation: living alone group ($n = 12$) and living together group ($n = 62$). Additionally, the spouses of patients aged ≥65 years were assigned to the healthy control group ($n = 37$). Subjects' lifestyle changes were evaluated between April 8 and 28, 2020.

Results: No subjects with acquaintances or relatives were infected with COVID-19 within the study period. The proportion of subjects who reduced going out in the living alone group, living together group and healthy control group was 18.2, 52.5, and 78.4%, respectively. The proportion of subjects who went out less frequently was significantly lower in both the living alone ($p < 0.01$) and living together ($p < 0.05$) groups than in the healthy control group.

Conclusion: Most patients with dementia or MCI who live alone did not limit their outings or activities during the COVID-19 outbreak. Regular monitoring for potential COVID-19 infection in people living alone with dementia is vital for their safety and well-being.

Keywords: COVID-19, dementia, mild cognitive impairment, living alone, stay at home

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INTRODUCTION

In Japan, an emergency declaration was issued, mainly in metropolitan areas, on April 7, 2020, because of the rapid increase in the number of patients affected by COVID-19. Under the declaration, the Japanese government urged the closure of non-essential businesses, schools and recreational facilities and strongly encouraged individuals to "stay at home," except when doing essential activities.

Older adults and individuals with serious underlying medical conditions are thought to be at higher risk of severe illness from COVID-19 (1). With the rapid aging of the Japanese society and the increasing proportion of nuclear families in Japan, the number of older people living alone with dementia is increasing (2). Dementia affects various brain functions and is associated with impaired judgment and decision-making (3); thus, individuals with dementia may not take appropriate safety and preventive measures against COVID-19 because of inadequate understanding of the risks, which could result in problems regarding safety, particularly among those who live alone. A previous study reported that perception of fewer social resources and worse cognitive performance are risk factors for harm in people with dementia who are living alone (4). Other studies have suggested that people with dementia who live alone are at higher risk of adverse outcomes, such as malnutrition and weight loss, than those living with others (5, 6). These findings suggest that patients living alone with dementia may require special care during the COVID-19 outbreak.

In this study, we aimed to answer the following questions: Are people with dementia changing their lifestyle amidst the COVID-19 outbreak? Are they feeling stressed about their current situation? Do they have physical symptoms, such as sleep disorders or loss of appetite? Are these changes more pronounced in patients with dementia who live alone?

MATERIALS AND METHODS

Subjects

This study was a prospective hospital-based cohort study. Subjects were recruited from those who regularly visited the dementia clinic of the Department of Psychiatry, Osaka University Hospital. All patients were examined comprehensively by psychiatrists (MHa, YS, TS, HK, KY, MI) and neurologists (EM) with sufficient experience in assessing patients with dementia. All patients underwent routine laboratory tests; standard neuropsychological and neurobehavioral examinations, including the Mini-Mental State Examination (MMSE) (7) and Clinical Dementia Rating (CDR) (8); and brain magnetic resonance imaging at the first visit. The diagnosis of each type of dementia and mild cognitive impairment (MCI) was established according to international consensus criteria. Specifically, the diagnoses of Alzheimer's disease (AD), dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), and MCI were based on the NIA-AA criteria for probable AD (9), the revised consensus criteria for probable DLB in 2017 (10), the consensus diagnostic criteria for behavioral variant FTD (11) and the consensus clinical diagnostic criteria in an international workshop for semantic dementia (12), and the criteria for MCI of Petersen's criteria (13), respectively. Consecutive patients with dementia or MCI who had a telephone visit or an outpatient visit to our dementia clinic between April 8 and 28, 2020 were included in this study. We set a short-term survey period of 3 weeks from the day after the emergency declaration to identify the short-term influence of the COVID-19 outbreak on the lifestyle of patients with dementia. The exclusion criteria were as follows: (1) patients aged <65 years, (2) patients with severe dementia (CDR 3), (3) patients who did not undergo MMSE within the last year, (4) patients in a nursing home, (5) patients without a reliable informant, and (6) patients who were unable to provide informed consent.

Patients with dementia or MCI were divided into two groups according to living situation: living alone group and living together group. Those who live with their families were assigned to the living together group. Additionally, the spouses of the patients aged ≥65 years were used as the healthy control group. If there was a cohabitant other than the couple, the spouse was excluded from the healthy control group.

All procedures followed the Clinical Study Guidelines of the Ethics Committee of Osaka University, Osaka, Japan, and were approved by the internal review board. After a complete description of all procedures in the study, informed consent was obtained from the patients and/or their caregivers in compliance with the research standards for human research and in accordance with the Declaration of Helsinki.

TABLE 1 | Lifestyle changes questionnaire.

Please tell us about the patient's current state compared with that in December
1.Is there any change in how the patient spend his or her days?
2.Is the patient going out less frequently?
3.Is the patient spending more time at home?
4.Is the patient engaging in less activity or exercise?
5.Is the patient taking more naps?
6.Did the COVID-19 outbreak increase the patient's mental stress?
7. Has the patient lost his or her appetite?
8.Is the patient's appetite increasing?
9.Does the patient have difficulty sleeping?
10.Has the patient had constipation?/Is the constipation worse?

When asking the healthy control group, we replaced "the patient" with "you" in each question.

Procedures

We evaluated the physical and mental conditions and lifestyle changes of the subjects during the COVID-19 outbreak using an original questionnaire (**Table 1**). In this study, we created a new questionnaire that could be easily and quickly conducted, even by telephone, although its validity and reliability have not been verified. Caregivers and/or patients were asked questions by the medical staff, including neuropsychologists (MS, YY, and NH), occupational therapists (MHo and YN), and a geriatric nurse (AN), at the time of the consultation, either by in-person interview or by telephone during the survey period. The current health status compared with that in December was assessed. Moreover, the respondents were instructed to answer "yes," "no," or "don't know" to each question. The "don't know" responses were not considered in the analyses. To compare the rates of subjects who answered "yes" to each question among the living alone, living together, and healthy control groups, we used the χ^2-test with Fisher's exact probability test and performed residual analysis using the Bonferroni z-test for each comparison when the overall group difference was significant. The statistical threshold was set at $p < 0.05$. All analyses were performed using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Twelve patients who live alone, 62 patients who live together with their families, and 37 caregivers participated in this study. **Table 2** shows the demographics of the subjects. We used the MMSE and CDR scores that were obtained within the year. A significant difference in sex and age among the three groups was found. The proportion of men was significantly lower in the living alone group than in the living together group ($p < 0.05$) and the healthy control groups ($p < 0.01$). Patients in the living alone group were significantly older than those in the living together group ($p < 0.01$) and the healthy control group ($p < 0.01$). No significant differences in the MMSE scores ($p = 0.955$) and the proportion of patients using care services ($p = 0.352$) between the living alone and living together groups were observed.

Table 3 shows the positive response rate for each question in the three groups. Significant group differences were observed for the positive response rates for "change in how to spend the day" ($p < 0.01$), "decrease in going out" ($p < 0.001$), "increase in staying at home" ($p < 0.001$), and "increase in mental stress" ($p < 0.001$). Z-tests showed that the positive response rate for "change in how to spend the day" was significantly higher in the healthy control group than in the living alone group ($p < 0.01$). The positive response rate for "decrease in going out" was significantly higher in the healthy control group than in the living alone ($p < 0.01$) and living together ($p < 0.05$) groups. The positive response rate for "increase in staying at home" was significantly higher in the living together ($p < 0.01$) and the healthy control ($p < 0.001$) groups than in the living alone group. The positive response rate for "increase in mental stress" was significantly higher in the healthy control group than in the living alone ($p < 0.01$) and living together ($p < 0.001$) groups. The subjects and their family or relatives were not infected with COVID-19 as confirmed by PCR test within the study period.

DISCUSSION

The major finding of this study is that most patients with dementia or MCI who live alone did not limit their outings or activities during the COVID-19 outbreak, whereas more than half of the patients who live together with their families reduced their frequency of going out. This finding may be attributed to the need of the patients living alone to go out for shopping; thus, they had to go out more often than those living together with their families. However, nearly 80% of healthy older adults who were caregivers of patients with dementia in this study reduced their frequency of going out, despite the need to go out for essential items. Hence, the reason why patients with dementia who live alone did not restrict their outings may be mainly attributed to poor recognition of the risk of COVID-19 infection, which could be associated with cognitive decline, rather than the need to go out. Additionally, patients who live alone had no caregivers nearby to encourage them to stay at home, which may also have an effect on their behavior. A previous study reported that worse cognitive performance is a risk factor for harm among people with dementia who are living alone (4). Therefore, regular monitoring for potential COVID-19 infection among people with cognitive impairment who are living alone appears to be vital for their safety and well-being.

During this COVID-19 pandemic, "stay at home" has been used as a public health slogan by the Japanese government. Consequently, numerous residents are experiencing social isolation, which could result in physical and psychological health issues, particularly among patients with dementia and their caregivers. More than 70% of the caregivers reported a reduced frequency of going out, and nearly 60% felt psychological stress. Conversely, patients with dementia or MCI reported significantly less psychological stress than caregivers, regardless of living conditions. Additionally, the results revealed that few patients with dementia had mental and physical changes such as insomnia or changes in appetite. Patients with dementia, particularly those living alone, exhibited little change in their lifestyle, which may have influenced the current results. Another possibility is that significant effects, such as mental stress, may have not yet emerged in patients with dementia during the survey, which was conducted shortly after the emergency declaration was made. Moreover, the mental stress of the patients may have been underestimated because the information in this study was mainly obtained from caregivers. However, our results suggest the urgent need for support for caregivers of people with dementia, as recommended by international dementia experts and Alzheimer's Disease International (14).

The demographic characteristics of the subjects who live alone were different from those of individuals who live with their families. Differences in the background characteristics, such as dementia type, sex, and age, between the groups may have influenced the results. The living alone group included three patients with FTD (25%), while the proportion of patients with FTD in the living together group was 12.9%. Patients with FTD tend to show distinctive unusual behaviors, such as disinhibition, loss of social awareness, and stereotyped behavior (11), which could make it difficult for them to adapt the drastic changes in lifestyle caused by the COVID-19 outbreak (15). The higher proportion of patients with FTD in the living alone group may have resulted in the higher frequency of going out. Regarding sex, the number of males was significantly lower in the living alone group than that in the living together group, which is consistent with previous reports (5, 16). Men, especially those who belong to the older generations in Japan, are less likely to be involved in housekeeping activities, such as shopping and cooking (17). Thus, the higher proportion of men in the living together group, who did not usually go shopping, may have contributed to the lower frequency of going out. Moreover, patients in the living alone group were significantly older than those in the living together and healthy control groups. Although the role of age in the ability of people with dementia to adapt to environmental changes remains unclear, age difference among the three groups in this study possibly influenced the results.

TABLE 2 | Subjects' demographics.

	Living alone group ($n = 12$)	Living together group ($n = 62$)	Healthy control group ($n = 37$)	*p*-value	*Post-hoc* test
Male/Female	1/11	26/36	22/15	0.007[a]	Living together, Control > Living alone
Age (years)	80.9 ± 7.9	75.4 ± 6.3	74.8 ± 5.7	0.012[b]	Living alone > Living together, Control
MMSE score	20.3 ± 4.8	20.4 ± 7.0	n.a.	0.955[c]	n.a.
CDR (0.5/1/2)	7/4/1	29/27/6	n.a.	0.622[d]	n.a.
Use of nursing care service	7 (58%)	26 (42%)	n.a.	0.352[a]	n.a.
Disease					
AD	6 (50%)	25 (40.3%)	n.a.	0.543[a]	n.a.
DLB	0	7 (11.3%)	n.a.	0.590[a]	n.a.
FTD	3 (25%)	8 (12.9%)	n.a.	0.371[a]	n.a.
MCI	3 (25%)	14 (22.6%)	n.a.	1.00[a]	n.a.
Others	0	8 (12.9%)	n.a.	0.339[a]	n.a.

Values are n or mean ± SD.
MMSE, Mini-mental State Examination; CDR, Clinical Dementia Rating; AD, Alzheimer's Disease; DLB, Dementia with Lewy bodies; FTD, frontotemporal dementia; MCI, mild cognitive impairment; n.a., not applicable.
[a]Fisher's exact probability test, [b]One-way analysis of variance, [c]t-test, [d]Mann-Whitney U-test.

TABLE 3 | Positive response rate for each question in the three groups.

	Living alone group ($n = 12$) (%)	Living together group ($n = 62$) (%)	Healthy control group ($n = 37$) (%)	*p*-value	*Z*-test with Bonferroni correction
1. Change in how to spend the day	16.7	50.8	70.3	0.004	Living alone < Control
2. Decrease in going out	18.2	52.5	78.4	0.001	Living alone, Living together < Control
3. Increase in staying at home	9.1	56.5	77.8	<0.001	Living alone < Living together, Control
4. Decrease in activity or exercise	16.7	54.9	47.2	0.053	n.a.
5. Increase in nap	25	22.6	11.1	0.326	n.a.
6. Increase in mental stress	9.1	18.6	58.3	<0.001	Living alone, Living together < Control
7. Loss of appetite	0	1.7	11.1	0.078	n.a.
8. Increase in appetite	0	15	2.8	0.068	n.a.
9. Sleeping disorder	33.3	17.9	40.7	0.061	n.a.
10. Constipation	9.1	13.0	10.8	0.972	n.a.

Analysis by χ^2-test with Fisher's exact probability test and Bonferroni z-test.
n.a., not applicable.

Several methodological issues limit the interpretation of our results. First, the number of patients living alone was small ($n = 12$) because we set a short-term survey period of 3 weeks. Thus, the severity of cognitive dysfunction, which could affect the lifestyle of patients with dementia, was not considered in our study. Second, we used an original questionnaire in this study, which has not been validated for reliability or validity. Third, we did not investigate the support of family and friends, which could affect the lifestyle of patients living alone. Nonetheless, no significant difference in the frequency of use of nursing care services between the living alone group and the living together group was found. Further investigations are needed to address this issue.

In conclusion, most of the patients with dementia or MCI who live alone in this study did not limit their outings or activities during the COVID-19 outbreak. Regular monitoring for potential COVID-19 infection among these patients is vital for their safety and well-being.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because Research data are not shared. Requests to access the datasets should be directed to Mamoru Hashimoto, mhashimoto@psy.med.osaka-u.ac.jp.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Osaka University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MHa contributed to the study concept, review of the literature, and writing of the manuscript. MS was involved in supervising the analysis and writing of the manuscript. MHo and AN contributed to the study design, data acquisition, data collection, and review of the manuscript. YY, NH, YN, YS, TS, HK, and KY were involved in the collection of data and review of the manuscript. EM was responsible for the critical review of the manuscript and the study design. MI contributed to the study concept, review of data, and review of the manuscript. All authors contributed to the article and approved the submitted version.

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COVID-19 Concerns Among Old Age Psychiatric In- and Out-Patients and the Employees Caring for Them, a Preliminary Study

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A questionnaire was administered to 14 patients admitted at the Department of Old Age Psychiatric 24-h unit at Oslo University Hospital with questions about experiences and fears regarding COVID-19. A similar adjusted questionnaire was administered to 19 outpatients. The purpose was to investigate if the patients had fears, anxieties, and quality of life issues related to COVID-19 that could affect their treatment. A quest back questionnaire with similar questions about patient care and work conditions was sent to the personnel working with these patients, and 46 of 81 responded. Most patients welcomed the strict measures that were applied, including a visitation ban for inpatients and a reduction in consultations for the outpatients. Most patients reported that they were not very scared of getting COVID-19, nor did many believe that they would die if they were infected. A minority of patients reported being very worried. The patients also differed on other issues related to the COVID-19 situation. A minority were negative to the interventions, rules, and regulations, and/or considered the risk of infection to be elevated at the clinic, and/or that the quality of their daily life was negatively impacted. Employees more often than patients were concerned about the COVID-19 influence on their health. They were also concerned about being at work amid the crisis. About half of their comments were related to the fear of inadvertently infecting patients with COVID-19. Also, a majority complained about aspects related to the implemented COVID-19 guidelines. This study is explorative in nature, mainly due to its small sample size, which makes it difficult to draw conclusions from the results. However, the results imply a need for addressing the COVID-19 concerns of both patients and employees, to prevent potential negative effects on treatment and overall life quality. Future research should investigate the self-reported effects of the pandemic situation on a larger sample size of elderly psychiatric patients.

Keywords: COVID-19, inpatients, outpatients, employees, fear, psychiatry, hospitalization

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INTRODUCTION

The novel coronavirus disease (COVID-19) was first detected in Wuhan, China in December 2019. Within 2 months it was declared a Public Health Emergency of international concern by the World Health Organization (1) and by mid-June 2020 the disease has caused over 400,000 deaths globally (2). In Norway, the first case was registered at the end of February, and in the following month, extensive measures described as the toughest and most invasive since World War II were initiated by the Norwegian Government to prevent the virus from spreading, aiming to reduce the scope of social contact between people from different households (3).

Since the pandemic outbreak, concerns have been raised about the psychological consequences of the pandemic situation and the measures undertaken to some vulnerable groups of people (4), including the elderly population, and particularly older persons with health problems, including psychiatric disorders. High age has been established a core risk factor for severe disease (5), and many of the common somatic diseases among the elderly place them in a risk group of severe disease if they were to be infected. This risk was increasingly reported in media, with examples from care homes in other countries with terrible outcomes. Thus, most elderly were fully aware of the risk and did their best to abide by the strict new rules and regulations on shielding and social distancing (6). However, particularly inpatients could fully control their environment. Thus, fear for epidemic and pandemic outbreaks were possible triggers of elevated psychological stress and anxiety in the general population of elderly (7) and possibly to a higher extent for groups with anxiety, depression, and mental health illness in general. Concerns have been raised about the psychiatric disease as a factor for elevated risk of infection, elevated barriers in assessing health services, and additional worsening of psychiatric symptoms (8, 9). Thus, older persons with mental health issues are possible victims of the cumulative/additive risk when additionally, being defined as a high-risk group of developing severe disease or death.

Furthermore, elderly persons who live alone or at an inpatient clinic risk being victims of the negative consequences of measures aiming for social distancing. This also applies to inpatients who are not allowed to receive visitors, one of the measures to prevent the disease to enter the clinic. A recent review of the psychological impact of quarantine has concluded that quarantine can lead to altered levels of stress and symptoms of depression (10). As a response to the pandemic, the Norwegian government advised the elderly to self-isolate and closed down day centers and voluntary projects aiming to help the elderly. These are possible causes of increased loneliness in this group (4, 11), leading to an elevated risk of anxiety and depression (12, 13). Collectively, these measures are concerns that may affect elderly persons with psychiatric disorders in multiple ways, obliging health professionals to be aware of possible consequences for symptoms and needs for treatment. Also, fear of being exposed to COVID-19 may affect the treatment of patients negatively if they become preoccupied with the fear of disease.

This study aimed to investigate how in- and outpatients in an old age psychiatry unit, and the personnel caring for them, are affected by the COVID-19 outbreak, regarding fear of being infected, perceived consequences of the pandemic situation and measures undertaken on symptom severity and treatment. The goal was to use this information to develop and implement appropriate interventions within each group regarding fear, conformity to interventions, rules and regulations, risk evaluation, and the quality of daily life.

METHODS

Questionnaire

We compiled a questionnaire with 13 statements regarding fear of being infected with COVID-19 (Q1, Q2, Q5), consequences of interventions, rules and regulations (Q3, Q7, Q10, Q11), risk evaluation (Q4, Q9, Q12), and consequences for daily life due to COVID-19 (Q6, Q8, Q13). The statements are listed in **Table 1**. The participants responded to each statement on a scale from 0 (agree) to 10 (disagree). The questionnaire was administered to inpatients and outpatients, and the personnel (employees) filled out a quest-back (14) form sent by e-mail to all employees with patient interaction. Some of the statements were slightly different for each group to be relevant to their situation. Six statements were identical for all groups. The data were collected from March to June. Similar restrictions were valid for the entire duration of testing.

A quest back option was ruled out for the patients, since they are of an age where the majority is not comfortable with using a computer, and since it was important to verify that they understood the questions correctly.

Participants

The clinic provides inpatient and outpatient treatment for persons over the age of 65 with psychiatric symptoms. The current patient sample is typical. The patients received appropriate medication and treatment according to their condition, such as physiotherapy, psychotherapy, occupational therapy, environmental therapy, conversational therapy, and group therapy.

Inclusion Criteria

The employees responsible for the patient's diagnosis and treatment made sure the recruited patients were fit to answer the questions. Patients with severe symptoms of depression, anxiety, or cognitive impairment were excluded, as were patients with ongoing psychosis or mania that could have influenced their ability to understand and answer the questions. The inclusion criteria for employees invited to participate, was that they interacted with the patients on a daily basis.

Inpatients

The inpatients are elderly, over the age of 65 with psychiatric disorders who require 24-h care. They were referred for assessment and treatment, and hospitalization periods vary from days to weeks. Most patients are referred from their primary care

TABLE 1 | Statements in the questionnaires (Q1–Q13).

Fear of infection with COVID-19	
Q1	I'm afraid of being infected with COVID-19[a,b,c]
Q2	I'm scared to die if I get infected with COVID-19[a,b,c]
Q5	I feel that fear of getting COVID-19 makes me sicker[a,b]/is heavy on me[c]
Consequences of interventions, rules, and regulations	
Q3	I feel that the measures at the clinic[a,b]/workplace[c] to prevent COVID-19 infection are too strict
Q7	I think the introduction of the visit ban[a]/measures to reduce infection due to COVID-19[b,c] was/were correct
Q10	I was given sufficient information about the COVID-19 situation at hospitalization[a]/at the department[b]/at my workplace[c]
Q11	I think the clinic[a,b]/workplace[c] guidelines to avoid infection were difficult to relate to
Risk evaluation	
Q4	I think the risk of infection is greater by being at the clinic[a,b]/at work[c] than being at home
Q9	I have concerns about being hospitalized[a]/meeting at the clinic[b]/being at work[c] due to the COVID-19 situation
Q12	I have taken other precautions myself to reduce the chances of getting infected[a,b,c] (yes/no[a,b])
Consequences of COVID-19	
Q6	I think my treatment at the clinic[a,b]/my working conditions[c] has gotten worse because of COVID-19
Q8	I think the COVID-19 situation has affected my health[a,b,c]
Q13	I think the COVID-19 situation has adversely affected my improvement process[a,b]/health situation[c] (yes/no[a,b])

[a] *Inpatients.*
[b] *Outpatients = 17.*
[c] *Employees.*

doctor, and all participants were voluntary admitted. When not at the hospital, most live at home. Some live alone and some with partners. All of them filled out the questionnaire while being hospitalized. The additional measures imposed on them included strict sanitation rules, restricted or canceled group activities and walks, and importantly, a ban on all visitations.

Outpatients

The outpatients are elderly, over the age of 65 with psychiatric disorders. They filled out the questionnaire as part of their visit to the outpatient clinic. They were referred from their primary care doctor or receive follow up treatment. Note that only home-dwelling patients participated, since the patients living in nursing homes were quarantined and not able to participate. The additional measures imposed on them included strict sanitation rules, canceled consultations, and partly telephone consultations/video (Confrere) consultations. Those who asked were mostly allowed to come to the outpatient clinic for their consultations.

Employees

The employees working with inpatients were in the process of moving from the countryside into the city to be collocated with the outpatient clinic. This led to increased stress and uncertainty for the employees, which in turn causes an increased burden on them in addition to the concerns caused by the COVID-19 outbreak. All personnel working with the patients were invited to participate in the anonymous quest back poll, and about two-thirds responded. The personnel include nurses, physiotherapists, occupational therapists, psychiatrists, psychologists, and other health personnel.

Comments

All patients could comment on their answers, and the comments are referred to when appropriate. The employees were only able to give a general comment at the end of the quest-back form.

Ethics

The study was evaluated by the data protection office at Oslo University Hospital, and the conditions for the study were revised and explained. The study was labeled as a quality enhancement study.

The inpatients and outpatients were asked to fill out the form as honestly as possible, and were told by the experimenter that their responses would be anonymous and not to be shared with other personnel. Their responses were typed into an Excel sheet by an experimenter. A key code was created, and the key code was recorded on the sheet and in the Excel sheet. A separate paper that contains a link between the patients and the key codes are kept locked. The coded response sheets are kept locked in a separate location.

The employees filled out the quest-back form on their computer, and their responses are completely anonymous. There is no stored information linking each respondent to his/her responses.

Analysis

Demographic characteristics and diagnostics of the inpatients and outpatients were presented as frequencies. Due to small group sizes, percentages were not presented. There was no demographic information about the employees registered, due to the complete anonymity of the survey. The main aim was to explore the within-group patterns, which were described by means and standard deviations (SDs) and medians and first and third quartiles. In addition, Spearman's correlation coefficients were calculated among statements covering the same topics. The overlapping statements (Q1, Q2, Q4, Q8, Q11, and Q12) were compared between the groups by Independent-Samples Median test or χ^2-test, as appropriate. The descriptive statistics are shown in **Table 2**. In the case of significant overall differences, the pairwise comparisons were carried out with Bonferroni correction applied for each statement. The comments of the inpatients and outpatients were described. The statistical analyses were performed in SPSS v 26.

RESULTS

The results are presented in **Figure 1**, see **Table 3** for demographics and diagnostics.

Fear of Infection With COVID-19

Statements Q1, Q2, and Q5 explore whether the participants were afraid to become ill with COVID-19, if they were scared of death if they caught the disease, and if they thought that any fears about catching the disease would have a negative effect on their treatment, or for the employees, if it would cause a burden on them.

Most of the inpatients answered that they were not afraid of being infected (median 8.5), and if they were to be infected, most inpatients answered that they were not afraid to die from it (median 9.5) and that the fear of getting COVID-19 did not make them sicker (median 8). The correlation between statements Q2 and Q5 was very strong, while other correlations were weak. The outpatients were moderately afraid of being infected or die from COVID-19 (median 5, correlation 0.6). They also indicated that the fear of getting COVID-19 did not make them sicker (median 8). The employees were moderately afraid of being infected (median 6), but not afraid of dying if they catch the disease (median 8). They also meant that the fear does not impose much load on them (median 5.5). The answers of the employees correlated positively but only moderately. There were overall differences between the groups regarding statement Q2 ($p = 0.008$), with the outpatients significantly more afraid to die than employees ($p = 0.010$), with no differences between other groups.

Notably, the minority of inpatients were very concerned, but the majority of the comments to statement Q1 shows that many are unconcerned "do not think I will be infected," "don't know anyone with the disease," "don't want to think about it" (7/11 comments), while a minority is quite afraid "due to my age," "I am old," "I think all must be afraid" (4/11 comments). The outpatients gave similar comments: not scared "I don't care since I have cancer," "I take precautions," or scared "since I have an underlying condition," "it's a terrible death." Comments to statement Q2 show a mixture where some "are not afraid of death," "think I will make it through," while others are very afraid due to underlying conditions. Comments to statement Q5 are overwhelmingly from those who are unconcerned (6/7 comments from the inpatients and 1/2 of the comments from the outpatients).

TABLE 2 | Descriptive statistics for questions within groups.

	Outpatients (*N* = 19)	**Inpatients (*N* = 14)**	**Employees (*N* = 46)**	**χ^2 (df)[6]**	***p*-value[7]**
Fear of infection with COVID-19					
Q1					
Mean (SD)	4.7 (3.9)	5.9 (4.6)	5.9 (2.8)		
Median (Q_1, Q_3)	5 (0, 8)	8.5 (0, 10)	6 (3.8, 8)	0.93 (2)	0.628
Q2					
Mean (SD)	4.5 (3.2)	6.6 (4.5)	7.1 (3.2)		
Median (Q_1, Q_3)	5 (2, 7)	9.5 (0, 10)	8 (5, 10)	9.72 (2)[8]	**0.008**
Q5					
Mean (SD)	6.7 (3.6)	6.9 (3.4)	5.9 (2.9)		
Median (Q_1, Q_3)	8 (5, 10)	8 (4.8, 10)	5.5 (4, 9)		
Consequences of interventions, rules and regulations					
Q3					
Mean (SD)	7.1 (3.6)	8.7 (3.1)	8.4 (2.6)		
Median (Q_1, Q_3)	9 (5, 10)	10 (9.8, 10)	10 (7, 10)		
Q7					
Mean (SD)	1.9 (3.0)[a]	1.6 (3.1)	1.9 (2.3)		
Median (Q_1, Q_3)	1 (0, 2.5)[a]	0 (0, 2.3)	1 (1, 1)		
Q10					
Mean (SD)	4.2 (4.2)[a]	2.1 (3.2)	2.5 (2.8)		
Median (Q_1, Q_3)	3 (0, 8.3)[a]	0.5 (0, 3.3)	1 (1, 2)		
Q11					
Mean (SD)	8.2 (3.0)[a]	8.6 (2.7)	8.5 (2.3)		
Median (Q_1, Q_3)	10 (8, 10)[a]	10 (7.5, 10)	9 (8, 10)		
Risk evaluation					
Q4					
Mean (SD)	6.6 (3.9)	6.4 (4.1)	4.8 (3.4)		
Median (Q_1, Q_3)	9 (3, 10)	8 (3, 10)	4 (1, 8)	3.30 (2)	0.192
Q9					
Mean (SD)	9.1 (2.0)[a]	7.7 (3.7)[c]	7.4 (3.3)		
Median (Q_1, Q_3)	10 (8.8, 10)[a]	10 (5, 10)[c]	9 (5, 10)		
Q12					
Yes, *n*	15[b]	6	23[d]	7.34 (2)[i]	**0.025**
Consequences of COVID-19					
Q6					
Mean (SD)	7.4 (3.3)	9 (2.2)	5.0 (3.0)		
Median (Q_1, Q_3)	9 (5, 10)	10 (8.8, 10)	4 (3, 8)		
Q8					
Mean (SD)	5.8 (3.3)[a]	7.0 (3.7)	7.3 (2.9)		
Median (Q_1, Q_3)	5 (3, 9.3)[a]	9 (3.5, 10)	8 (5, 10)	2.70 (2)	0.259
Q13					
Yes, *n*	6[a]	1[c]	6[e]		

[a] N = 18.

[b] N = 17.

[c] N = 13.

[d] N = 39.

[e] N = 36.

[f] Statistics for Independent-Samples Median test. (χ^b) with degrees of freedom (df).

[g] p-Value for Independent-Samples Median test.

[h] $\chi^b(1) = 8.53$ ($p = 0.010$) for pairwise comparison of outpatients vs. employees, $\chi^b(1) = 5.13$ ($p = 0.071$) for pairwise comparison of outpatients vs. inpatients, and $\chi^b(1) = 0.37$ ($p = 1.00$) for pairwise comparison of inpatients vs. employees.

[i] $\chi^b(1) = 4.65$ ($p = 0.093$) for pairwise comparison of outpatients vs. employees, $\chi^b(1) = 7.24$ ($p = 0.021$) for pairwise comparison of outpatients vs. inpatients, and $\chi^b(1) = 1.08$ ($p = 0.999$) for pairwise comparison of inpatients vs. employees.

The bold value indicates significant ($p < 0.05$).

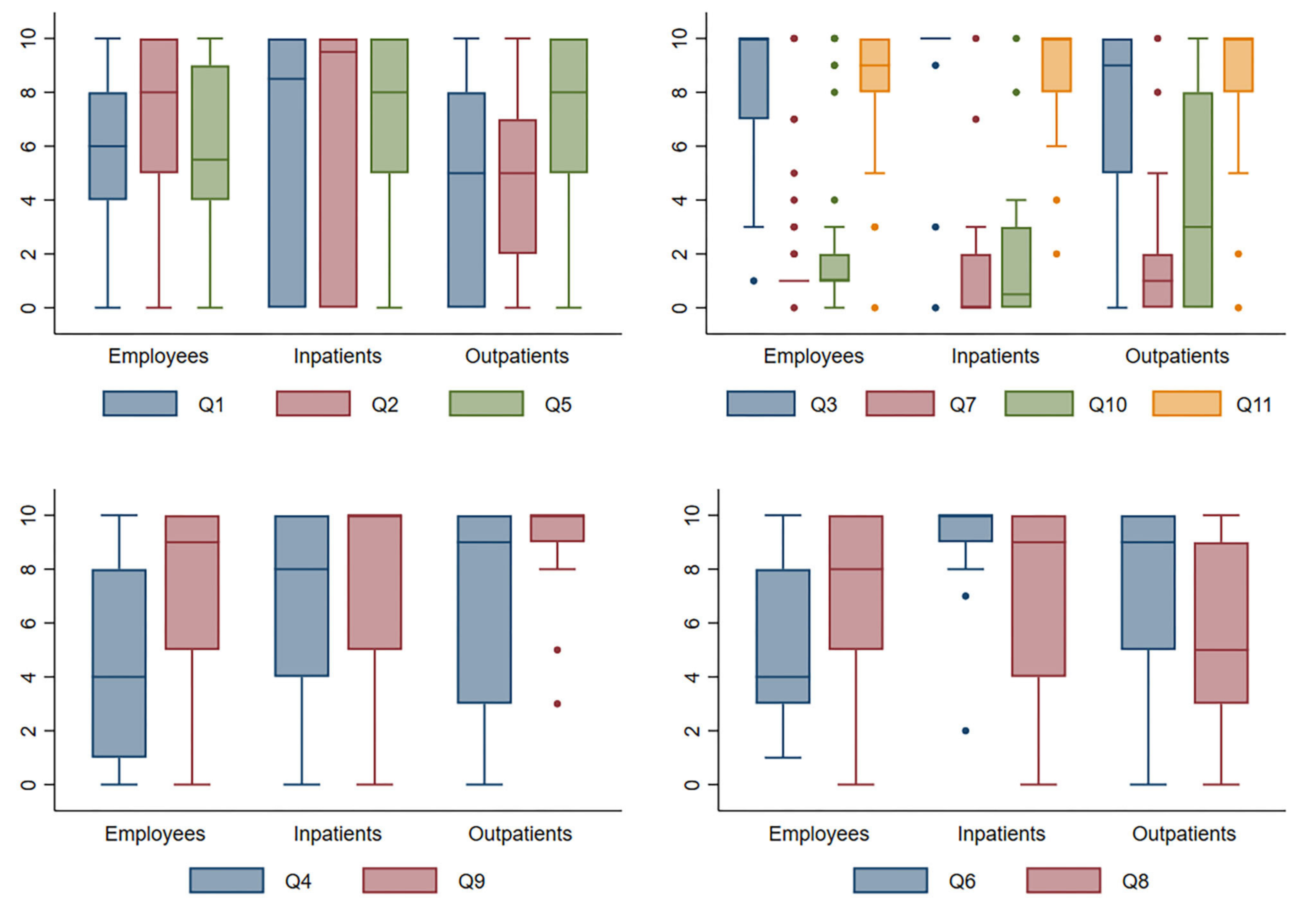

FIGURE 1 | The boxes present median and first and third quartiles. The lines at the bottom/top vertical bars present adjacent values defined as the most extreme values within 1.5 × IQR, where IQR is interquartile range, of the nearer quartile. The dots present outliers. Q1–Q11 corresponds to the statements in the questionnaires.

Consequences of Interventions, Rules, and Regulations

Statement Q3, Q7, Q10, and Q11 explore different aspects on how the interventions, rules, and regulations have been received and how easy they have been to relate to, and the perceived consequences of the measures taken.

Responses to statement Q7 show agreement among all participants that it was correct to implement strict measures to curb the spreading of COVID-19 to patients and personnel. The employees and the inpatients agreed that they have gotten enough information about the situation (statement Q10, median 1 and 0.5, respectively), while outpatients were slightly less satisfied with the information given to them (median 3). A large majority of the inpatients, outpatients and employees thought the measures had been appropriately strict (statement Q3), and it had not been difficult to relate to them (statement Q11). Among outpatients, the statements Q3 and Q7, and statements Q7 and Q11 correlated negatively moderately, while statements Q3 and Q11 correlated positively moderately. Moderate positive correlation was found between statements Q7 and Q10 among inpatients and negative moderate correlation between statements Q3 and Q7 among employees.

The inpatients' comments to statement Q3 showed overwhelming understanding for the measures taken at the hospital for inpatients (12/12 comments), and also from most outpatients (5/8 comments). A minority (3/8) outpatient complained about "teleconsultations," "no group sessions," and "postponement of meetings." Most inpatients (6/7) commented to statement Q7 that the visitation ban was warranted, while one commented that "visitors should be able to come if they are not sick." The outpatients had more general statements, but most comments were positive "feel taken care of," "protect the elderly," "thankful that precautions have been implemented." Comments from the inpatients to statement Q10 show positivity to the information they got, while the two comments from the outpatients both complained about lack of information about COVID-19. All comments to statement Q11 are positive "straightforward," "clear rules," "boring but OK."

TABLE 3 | Demographic characteristics, and diagnostics.

	Outpatients (19)	Inpatients (14)
Sex		
Women	13	8
Men	6	6
Age group		
50–59 years	0	2
60–69 years	6	5
70–79 years	7	3
80–90 years	6	4
Education level		
<10 years	2	5
10–15 years	10	6
16–20 years	4	3
Ed. level not entered	3	
Diagnosis (first and secondary)		
Depression	15	12
Anxiety	1	6
Bipolar	0	2
Psychosis	0	2
Cognitive deficit/dementia	2	1
Diag. not entered	3	1

Risk Evaluation

Statements Q4, Q9, and Q12 assess how the patients and employees evaluate the risks involved in being at the hospital or outpatient clinic, and whether they have taken any additional precautions to stay safe.

Statement Q4 showed that most inpatients and outpatients think they are safe (median 8 and 9, respectively). Note that the outpatients did not meet at the outpatient clinic as frequently as they normally would do, but partly participated in the online session via telephone or videoconference. Employees think they are not as safe as the patients (median 4). Neither the patients nor the employees think the risk is higher at clinic/work than at home (statement Q9). Among the outpatients and inpatients, statements Q4 and Q9 correlated positively, but only moderately. Most outpatients have taken other precautions to avoid being infected (statement Q12), with the exception of approximately half the inpatients and employees. There were also overall differences between the groups regarding statement Q12 ($p = 0.025$), but the pairwise comparison showed only significant difference between inpatients and outpatients ($p = 0.021$).

Comments to statement Q4 show a mixed picture where all inpatient and outpatient comments on hygiene are positive, and the minority commented concern about meeting more people. Comments to statement Q9 show the same pattern of comments, most feel "safe" and "trust," but a minority are concerned about "Increased risk of infection." Comments to statement Q12 list the precautions they have done, including "washing hands," "isolation," "avoid visiting stores," "gloves," "mask," "avoid public transport," "follow government advises."

Consequences for Daily Life Due to COVID-19

Statements Q6, Q8, and Q19 probed how the participants believed that their daily life has been affected by the COVID-19 outbreak.

The majority of inpatients and outpatients did not think their treatment (statement Q6) were affected by COVID-19 (median 10 and 9, respectively), while the employees complained about their working conditions (median 4). The improvement process (statement Q13) seems to be moderately or little affected by the COVID-19 restrictions among both outpatients and inpatients. While the inpatients did not claim that the COVID-19 affected their health (statement Q8, median 9), the outpatients' did think that their health was more affected due to the COVID-19 situation (median 5). The employees did not think the COVID-19 had affected their health in a large degree (statement Q8, median 8), and only a minority think the restrictions affected their health situation (statement Q13). While the statements did not correlate among the employees, statement Q8 and Q13 among in- and outpatients, and statement Q6 and Q13 among inpatients were negatively moderately correlated. In addition, statements Q6 and Q8 were positively moderately correlated among inpatients.

Even though a majority of inpatients and outpatients thought that the COVID-19 situation had not adversely affected their healing process, only those who responded oppositely commented. The comments are all related to aggravation of health problems or fears. Comments to statement Q8 from inpatients are overwhelming that the situation has not affected their health, one commented that "there are less activity and more worries." Comments from the outpatients are all from those who think the situation has affected their health, they complain about "negativity," "isolation," "lack of physiotherapy," and "insecurity."

General Comments to the Questionnaire From the Employees

Only 15 participants gave general comments to the statements. Five commented that they were concerned that they involuntarily may infect the patients since they may have the disease without showing symptoms, four uttered criticism to how the crisis has been handled, two complained about general stress, two mentioned additional stressors (moving process), and one uttered fear of getting the disease.

DISCUSSION

The patients were in general satisfied with the COVID-19 specific measures, even though some of the measures were quite invasive. They perceive that the measures were in their best interests. Even though most patients coped fine with the initial COVID-19 situation, a minority were afraid of the prospect and consequences of getting the disease, or were negative to the interventions, rules, and regulations, or considered that the risk of infection was elevated at the clinic, or that their quality daily life had been reduced. These are particularly important issues that need to be addressed in the interaction with the patients.

The COVID-19 pandemic can place elders in a situation where social isolation is difficult to avoid, especially those whose main source of social contact is outside of their homes (4). The elderly patients living at home must make active choices and, for example, restrain from meeting grandchildren, receive less help and care, not traveling collectively, etc. At the same time, several facilities were closed down (senior center, fitness center, restaurants, events). Some adjust fine, but as the responses to the statements show, patients, as well as the population at large, are individuals. Psychiatric patients can be particularly vulnerable to the negative effects of the COVID-19 pandemic and lockdown, such as isolation. Research have shown that they experience a larger increase in psychiatric symptoms like anxiety, depression, stress and insomnia during the pandemic compared to healthy controls (15), as well as symptoms of COVID-19-related stress (16, 17). These concerns also apply to elderly patients with cognitive decline, as the shut-down of societal functions can deprive them of needed social support and practical resources from their surroundings or community (18). Still, according to the results in this preliminary study, most of the included patients did well. They were not particularly afraid of the virus, and they understood and accepted the measures introduced by their section. However, one cannot ignore that a minority of patients reported a lot of fear and worry, and those who thought the pandemic situation had a negative impact on their daily lives and their improvement process. Due to the limited sample size and the current methodology, we could not predict who these patients are. Also, we did not measure how important each topic was for the patients, but from the comments, we often see stronger opinions from those who disagree with the majority. Thus, it becomes necessary to include thoughts and experiences about COVID-19 in the individual treatment of all patients, and conduct individual interviews to identify the patients who are negatively affected. From there, measures can be introduced to help these patients individually in the best possible way.

An unforeseen result is that most employees seem to be more frightened and worried than most patients. Although many employees have not responded, it nevertheless shows that the employees feel uncertain about their responsibility to the patient and how the regulations should be interpreted. Several employees felt that their working day was negatively affected by the pandemic situation. Other research also suggest that patients are not the only ones affected by the COVID-19 pandemic. A study done in China found that medical health workers risk mental health problems like anxiety, obsessive-compulsive symptoms, depression, insomnia, and somatization (19). The researchers suspected that the medical health workers experienced psychosocial stress due to a high workload and an unsafe work environment where many lack knowledge about the virus and how to prevent infection. Uncertainty and risk were indeed part of the employees' experiences with the pandemic situation, reported in our study. They had to familiarize themselves with the many new guidelines and regulations and experienced uncertainty about the responsibility for avoiding the spread of infection and caring for a group of patients at risk. This suggests the importance of good dialogue about this in the workplace.

The study has several weaknesses. The sample size is limited and the results cannot be generalized outside one psychiatric clinic in Norway. The questionnaires had not been verified as research tools. Even though similar restrictions were in place for the entire duration of testing, some respondents responded early in the COVID-19 pandemic (March–April) when there was intense media focus and many were surely overwhelmed by the fierce measures and severity of the situation, while others responded in May after there has been a more positive focus in the Norwegian media.

Regardless of its limitations, the results of this study imply the COVID-19 pandemic impact individuals quite differently, both among elderly psychiatric patients and the employees working with them. Further research should therefore strive to gain more knowledge in this area, preferably by using a larger sample size. It is useful to clarify exactly what characterizes the elderly patients with the highest risk of adverse effects from the COVID-19 pandemic, and whether clinical or demographic information can help us identify the patients (and employees) in need of extra care and attention during the pandemic situation.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical approval was not provided for this study on human participants because this study is considered a quality enhancement study outside the mandate of the regional ethics committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MK initiated the study, wrote the manuscript, and compiled the figures. EG developed the questionnaires and organized the quest-back form for the employees. EK contributed in writing the introduction and performs the literature search, gathered data from the outpatient clinic, and gathered consent forms from the outpatients, in addition she gave critical input on the interpretation of results and the discussion. TK administered the questionnaire and consent form for all inpatients, and made sure they understood the statement, she gathered and interpreted the comments from the inpatients. KG analyzed the data in SPSS, compiled **Table 3**, and contributed to the discussion. JB performed the group analysis in SPSS, compiled **Table 1**, and wrote the analysis and the results section of the manuscript. BM gave critical input from the initial planning until the final draft and contributed to the discussion and revised the document. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.576935/full#supplementary-material

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Social Frailty in the COVID-19 Pandemic Era

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Special attention and efforts to protect from or reduce health-related outcomes of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus triggering coronavirus disease 2019 (COVID-19), should be applied in susceptible populations, including frail older people. In particular, the early death cases occurred primarily in older people with a frailty status, possibly due to a weaker immune system fostering faster progression of the viral infection. Frailty is an age-related multidimensional clinical condition defined as a non-specific state of vulnerability, identifying older people at increased risk of falls, institutionalization, hospitalization, disability, dementia, and death. Among frailty phenotypes, social frailty has been least studied. It considers the role of socioeconomic context as a vulnerability status later in life. COVID-19 does not affect all populations equally, and social inequalities contribute to drive the spread of infections. It was known that the perception of social isolation, e.g., loneliness, affects mental and physical health, but the implicated molecular mechanisms, also related to the immune system, and its associated cognitive and health-related sequelae, are poorly understood. The increasing psychological distress derived by prolonged exposure to stress due to the lockdown scenario, and the reduced sources of support, contributed to making heavy demands on personal resources, i.e., self-efficacy and interpersonal variables. So, perceived loneliness may be a factor associated with psychological distress and an outcome in itself. In the COVID-19 pandemic era, a correct assessment of social frailty may be essential in terms of the prevention of late-life neuropsychiatric disorders.

Keywords: SARS-CoV-2, coronavirus, social dysfunction, loneliness, immune system, biomarkers, Late-Life Depression (LLD), Multimorbidity (MM)

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INTRODUCTION

Data coming from epidemiological studies suggest an association between aging and the risk of developing life-threatening health problems and mortality related to the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus implicated in coronavirus disease 2019 (COVID-19) (1). The hierarchical relationship and interlaced time courses of molecular, phenotypic, and functional aging domains have not yet been established in humans. Although justified and necessary, the COVID-19 lockdown will inevitably compromise mental health of susceptible age strata groups, especially frail older people. To understand the implications of a specific phenotype of the frailty construct named social frailty on mental health in the COVID-19 pandemic era, we need a good understanding of the time and metrics of aging, especially those indicating the continuum ranging from biological to phenotypic and functional aging (2).

The community healthcare professionals consider relevant the assessment of subtle biological, phenotypic and functional changes of mental health later in life, since the duration of the pandemic-related period of isolation remains uncertain. Neuropsychiatric consequences of brain damage or disease—i.e., mental disorders—can derive either from direct effects of infection on the central nervous system (CNS) or indirectly via the immune response or otherwise from medical therapy (3). Neurotropic and neuroinvasive effects of coronaviruses have been described in humans.

The present perspective article aims to explore the risk of social isolation and loneliness sequelae in older frail adults subjected to isolation measures during the ongoing COVID-19 pandemic, for both preventative and transmission-restricting purposes.

Social participation is an indicator of successful aging and important determinant of health-related outcomes, including mortality (4). According to a deficit accumulation approach to frailty phenotypes, social vulnerability can be measured as an index of social problems, or "deficits," such that the more social deficits one has, the more vulnerability to adverse outcomes one has. It is important to note that mental health in the geriatric population requires to be integrate in the wider context of the health status of socially frail individuals, also in view of the possibility of a weaker immune system permitting faster progression of viral infection. Fulfillment of basic social needs is necessary to function adequately and experience social well-being, just as basic physical needs fulfillment is required to experience physical well-being. Social frailty could be considered as a lack of resources to fulfill one's basic social needs (5). A correct assessment of social frailty is needed to prevent late-life neuropsychiatric disorders precipitated by the COVID-19 pandemic.

SARS-CoV-2 AND RELATIONSHIPS WITH THE CENTRAL NERVOUS SYSTEM

The epidemiological criteria about COVID-19 spread, from China to 229 countries, soared out of control to reach a pandemic. Globally, at the end of June 2020, there were 9,277,214 confirmed cases of COVID-19 (6), encompassing a wide clinical spectrum extending from asymptomatic infection, mild upper respiratory tract illness, to severe viral pneumonia with respiratory failure. SARS-CoV-2 enters human host cells by means of a receptor little expressed in the brain, the angiotensin converting enzyme 2 receptor. Additionally, SARS-CoV-2 can pass to the brain by means of the cribriform plate nearby to the olfactory bulb, enabling the virus to reach and affect the CNS, contributing to neurological tissue damage and to COVID-19-related morbidity and mortality. In particular, the reported hyposmia suggests, as shown for SARS-CoV-2, a nasal infection pathway allowing a possible direct access to the CNS (3).

Findings from the study by Helms and colleagues suggested that the most common neurological features in the COVID-19 patients were non-focal: confusion, agitation, dysexecutive syndrome, and diffusely boosted reflexes (7). Preliminary data suggested that delirium, confusion, agitation, and altered consciousness, as well as symptoms of depression, anxiety, and insomnia were also common in patients with COVID-19 (8). The etiology of the neuropsychiatric consequences of COVID-19 infection is likely multifactorial, including direct effects of viral infection inside the brain, a procoagulant state inducing cerebrovascular disease, a physiological impairment in terms of hypoxia deriving from respiratory failure, the activation of the immunological cascade, and the indirect effects of medical interventions, social isolation, the psychological impact deriving from a novel, severe, potentially fatal illness, concerns about infecting other people, and social stigma.

The immune response in SARS-CoV-2 infection has a major importance and may induce a hyperinflammatory state similar to the hemophagocytic lymphohisticytosis, featuring a transitory condition of increased C-reactive protein, ferritin, and interleukin-6 levels. Some of the psychiatric multimorbidity aspects might be explained by the well-described interplay between inflammation and depression (9, 10).

SOCIAL INEQUALITIES AND MENTAL HEALTH IN OLDER AGE

Regardless of COVID-19 pandemic, social inequalities are reported in mental disorders: income inequality, low levels of expected social support and educational attainment affect social participation, contributing to social exclusion especially in older age (11). The positive mental effects of abundant, stable social interactions from a person with a wide social network, can alleviate stress deriving from negative life events, resulting in speed recovery from illness, and preserving psychological health (12).

Everyday social environments rife with challenges represent an exposure to chronic stress whose proxy could be considered the socioeconomic status (SES) gradient. In the context of the current COVID-19 pandemic, there is a risk of increasing inequities in healthcare among vulnerable populations over the age of 65 and/or with multimorbidity, as potentially at-risk individuals (13). Furthermore, financial stress, transportation problems, and housing issues, as well as increased exposure to crime gained from a lower adolescent SES, may effectively compromise the benefits of a calm and mature personality on the stress response pathways, increasing the risk of dementia (14) (**Figure 1**).

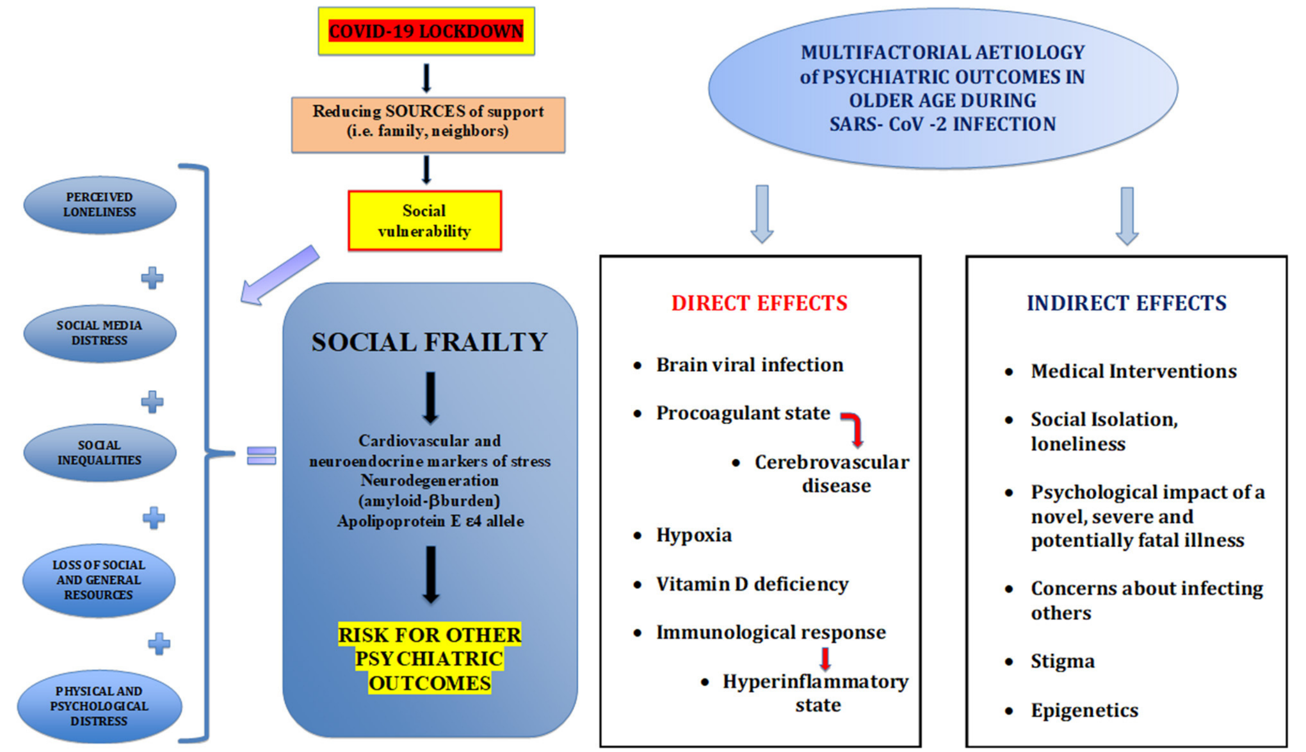


FIGURE 1 | Relationship between coronavirus disease 2019 (COVID-19) lockdown and social resources and direct and indirect effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus causing COVID-19, on psychiatric outcomes in older age.

LONELINESS, SOCIAL ISOLATION, AND LATE-LIFE NEUROPSYCHIATRIC DISORDERS DURING THE COVID-19 PANDEMIC: MECHANISMS OF ACTION

Several variables may explain why the current COVID-19 pandemic causes neuropsychiatric consequences especially in older age. The wider social impact of the pandemic and the legislative response, imposing physical distancing measures and quarantine, are among these reasons (15). The psychobiological etiological factors underlying anxiety and mood disorders arising at this social-environmental level should be better understood, as well as those at the genetic, molecular, or neural-circuitry level. An increasing body of research is focusing on the late-life depression–dementia interplay to probe the possible interaction between depression and aging mechanisms, including the influence of social determinants on epigenetic mechanisms (16).

Loneliness or emotional isolation is a subjective, undesirable experience, resulting from a cognitive mismatch between the quantity and quality of existing relationships and relationship standards. Loneliness has been viewed as a marker of psychosocial stress, resulting from depression, bereavement, and other social disconnection experiences. The downstream effects of loneliness on neural networks and systemic health is mediated by stress-related and inflammatory processes. In other words, great loneliness is linked to elevated cardiovascular and neuroendocrine markers of stress, impaired sleep, and proinflammatory physiological effects, that can cause neurodegeneration in the hippocampus and in other brain regions deputed to emotional regulation and cognition (17). Moreover, the amount of loneliness was associated to a greater brain amyloid-β (Aβ) protein burden after adjustment for demographic and clinical confounders, inversely Aβ-positive participants have a risk of 7.5 times higher to suffer from loneliness. These associations were stronger in apolipoprotein E ε4 allele carriers (18) (**Figure 1**).

Furthermore, physical activity and other healthy lifestyles worldwide were also affected by social distancing and quarantine restrictions (19). Home-isolation also tends to affect vitamin D levels by reducing the number of hours spent outdoors. There is evidence that vitamin D deficiency is linked to impaired immune function, potentially causing autoimmunity and increased risk of infections (20). Decreased levels of vitamin D might also determine a rise in mental health disorders (21).

It is interesting to note that, according to recent findings, psychosocial interventions (cognitive behavior therapy and multiple or combined interventions) are linked to an enhanced immune system function (proinflammatory cytokines or markers) and may therefore be useful for improving immune-related health (22, 23). It may be very important to study the mechanisms of psychosocial interventions and the link to beneficial effects on the immune system and health, particularly as related to COVID-19 infection (24). Epigenomics studies investigated molecular mechanisms by which loneliness exacerbates a wide range of neurodegenerative, psychiatric, and somatic diseases: Alzheimer's disease, psychiatric illness, immune dysfunction, and cancer gene sets seem to constitute essential targets for future investigations. The expression of pleiotropic genes at the time of death was found to be significantly enriched as a function of loneliness, experienced by a large sample of autopsied participants almost 5 years prior to death (25) (**Figure 1**).

PSYCHOSOCIAL DETERMINANTS AND COVID-19 MORTALITY

Older age is associated with greater mortality due to COVID-19. However, the vulnerability to physical comorbidities is not granted by physiological factors only, but also by psychosocial factors. Regardless of COVID-19 pandemic, it is known that different aspects of social relations are measured by social isolation and loneliness and both are slightly associated with different health outcomes and also mortality (social isolation to a greater degree than loneliness) (26). Currently, with the spread of COVID-19, social connectedness not necessarily is associated to higher mortality rate among older Italian adults (27). Inversely, variables associated with social isolation are found to be risk factors for an increased proportion of mortality in Italian patients aged 80 years and over. The conclusion could be that social relationships during a crisis impacting the frailest populations are a protective factor against increased mortality rates (27). Considering the lack of data on the acute effects of the illness, in terms of applicability to COVID-19, inferences must be drawn with care. Furthermore, no data on the post-illness phase have yet been described, although the higher COVID-19 mortality might be correlated with poorer psychiatric outcomes at a later date (8).

However, it should be made clear that physical frailty and social vulnerability (social frailty) are both entities clearly distinct, and that each contributes independently to mortality (28).

SOCIAL FRAILTY

Frailty is a dynamic process and an intermediate state of aging, detrimental for health, involving a progressive reduction in physical, psychological and/or social functions. This condition has implication for public health linked to its multiple clinical and social consequences, as well as its dynamic nature also in terms of prevention (29). Physical frailty components such as a slower gait, exhibit significant reciprocal relationships with cognition, and may thus be a transitional step in the progression to late-life cognitive decline in some older adults. But the vulnerability of older adults does not appear to be completely explained by the biological perspective (physical or deficit accumulations approaches to frailty) (30). Different frailty phenotypes have been associated with a variety of socioeconomic, behavioral, and other clinical characteristics, including lower education, lower income, female gender, unmarried status, obesity, underweight, multimorbidity, and premorbid disabilities (31).

The biopsychosocial model of frailty may add important advantages in terms of both assessment and intervention targets. Influenced by a range of variables, it has been defined as a dynamic state affecting an individual who experiences injuries in one or more human function fields (physical, psychological, social), that increases the risk of adverse outcomes (32). Although different theories on social needs exist, social frailty can be defined as the continuum of progressive loss of social and general resources, activities, or abilities serving during the course of life to fulfill one or more basic social needs. The framework of social frailty takes into account the various types of social and general resources (or constraints), social behaviors and activities, and self-management abilities, utilized for accomplishing (or affecting) social needs (5). For example, the fulfillment of the need to love and to be loved, the need to feel that one is doing the "right" thing according to relevant others and oneself, and to be part of a group with shared values. Furthermore, the need to distinguish oneself from others by means of specific talents or assets.

Acute illness is less well-tolerated by frail patients, but the degree of disease severity and the degree of frailty are each important (33), particularly in the COVID-19 pandemic era. Most importantly, the type and severity of the presenting illness are important variables independently associated with the clinical outcome and ability to fully recover. There are other mediating factors: female sex (34), smoking (35), and social vulnerability (36) that also influence the risk related to frailty status. A recent study conducted in Japanese older adults evidenced an association between social frailty with both cognitive and physical functions (37). Further studies are needed to confirm the hypothesized association between social frailty and cognitive and physical function. Moreover, compared to physical frailty and cognitive impairment, social frailty is more strongly associated with the occurrence of depressive symptoms among community-dwelling older adults after 4 years of follow-up (38). In other words, a greater incidence of neuropsychiatric disorders, directly proportional to the social frailty status, may be expected as late consequences of the COVID-19 pandemic.

SOCIAL FRAILTY ASSESSMENT TOOLS

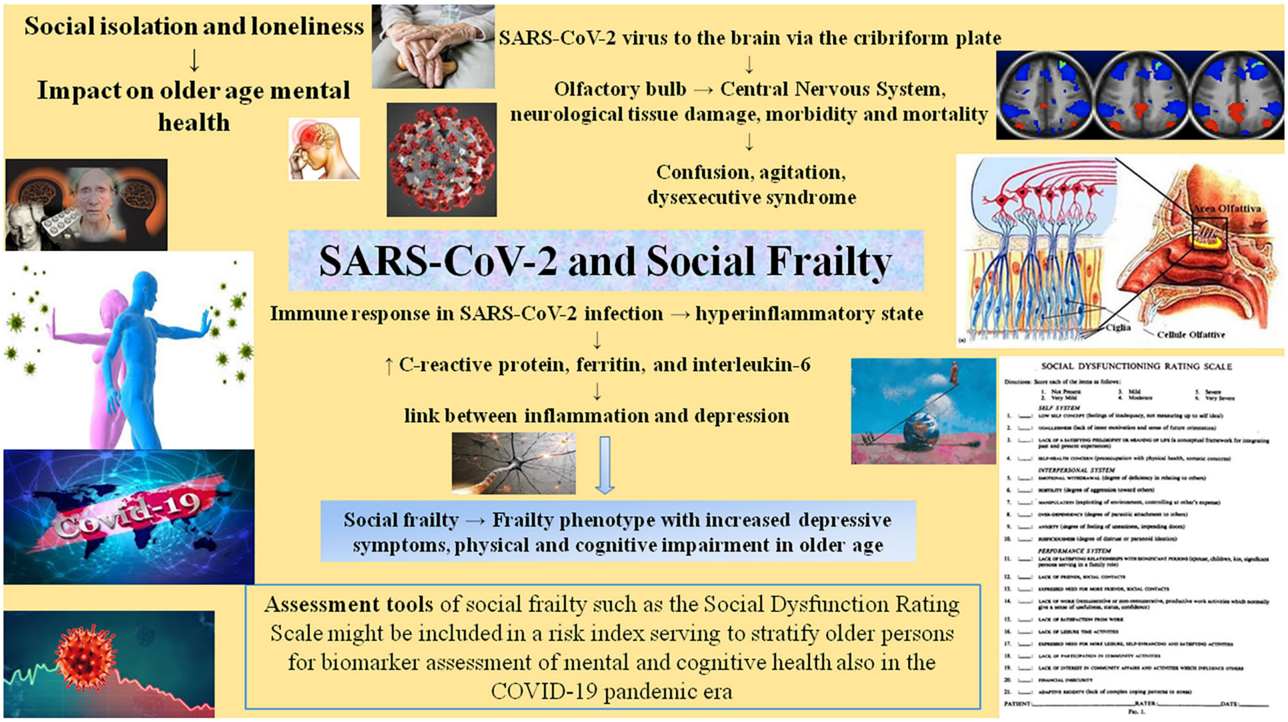
Deficit accumulation model of frailty can be understood to occur at many levels, from the (sub-)cellular level to tissues, organisms/complex systems and societies. Deficits can also accumulate at the tissue level and at the level of complex systems, i.e., in individual people or animals, which are effectively complex systems. Of particular relevance to the present discussion, deficits can also accumulate at levels higher than individuals, e.g., at the social level, pertaining to social environments and circumstances, and these are the clinical epiphenomena that we need to measure. More complex tools to evaluate social frailty basis beyond symptom scales/health checklists are needed (genetics, laboratory-based biomarkers, neuroimaging, etc), because social frailty could be considered a complex clinical phenotype.

Mental healthcare clinicians face substantial time challenges, including limited time available for evaluation for therapy, which does not yet include standardized assessments of social isolation and loneliness. The question is: what are we measuring to make interventions? Loneliness, social isolation, social relationships or all three? Social frailty is usually evaluated by single questions or items deriving from functional and depressive symptom scales or health checklists. But each of these instruments measures only partial aspects deriving from structural or functional aspects of social relationships, and is based on subjective responses (39).

Social frailty has been operazionalized with single questions or items from functional and depressive symptom scales or health checklists (40). A shared opinion is that there is heterogeneity in the definition of social frailty in different studies, and there is a request of homogeneity and simplification in the instruments of this assessment. Social contact, participation, depression, and loneliness characterize different scales of assessment of different social frailty models (41–44). Also, well-known instruments for assessing frailty in community-dwelling older people such as the Tilburg Frailty Indicator (45), aim to assess physical, psychological, and social frailty and their health-related outcomes (4). The Social Vulnerability Index, as a method of quantification of social vulnerability, predicted long-term mortality in different population-based settings and could have a role in this context of COVID-19 pandemic (46).

Recently, the Social Dysfunction Rating Scale (SDRS) was validated with a proposed cut-off for detecting social frailty in older age, for the purposes of considering possible interventions to maintain healthy aging (47). SDRS items are a mixture of subjective and objective evaluations considering both the rater's opinion and the subject's own self-evaluation. The scale includes important elements of functioning such as personal satisfaction and self-fulfillment and takes into account social role performance only peripherally (48). For example, among the items evaluating self-system, questions about self-concept, goallessness, meaning in life, self-health concerns are asked to the subjects; the investigation of interpersonal system implies to ask about emotional withdrawal, hostility, anxiety etc. Finally, questions about performances system consist in investigating lack of satisfying relationships with significant persons, express need for social contact or friends, lack of satisfaction from work, expressed need for more leisure activities, financial insecurities, etc.

The SDRS could be a valid instrument to capture size (isolation) and quality (loneliness, neuroticism) of social adjustment in older age. The perception of social dysfunction was not associated with material deprivation, and this adds another stratum of complexity in the assessment of health status in older age. Factorial analysis of SDRS's twenty-one items was performed (47) and five factors were identified for the 21-item SDRS, according to their loads in the analysis: social isolation; loneliness; feelings of contribution/uselessness; lack of leisure activities; anxiety for the health. Furthermore, SDRS was correlated to cognitive (apathy, Mini-Mental State Examination, and Frontal Assessment Battery) and psychiatric outcomes.



SOCIAL DYSFUNCTIONING RATING SCALE

Directions: Score each of the items as follows:

1. Not Present
2. Very Mild
3. Mild
4. Moderate
5. Severe
6. Very Severe

SELF SYSTEM

1. ____: LOW SELF CONCEPT (feelings of inadequacy, not measuring up to self ideal)
2. ____: GOALLESSNESS (lack of inner motivation and sense of future orientation)
3. ____: LACK OF A SATISFYING PHILOSOPHY OR MEANING OF LIFE (a conceptual framework for integrating past and present experiences)
4. ____: SELF-HEALTH CONCERN (preoccupation with physical health, somatic concerns)

INTERPERSONAL SYSTEM

5. ____: EMOTIONAL WITHDRAWAL (degree of deficiency in relating to others)
6. ____: HOSTILITY (degree of aggression toward others)
7. ____: MANIPULATION (exploiting of environment, controlling at other's expense)
8. ____: OVER-DEPENDENCY (degree of parasitic attachment to others)
9. ____: ANXIETY (degree of feeling of uneasiness, impending doom)
10. ____: SUSPICIOUSNESS (degree of distrust or paranoid ideation)

PERFORMANCE SYSTEM

11. ____: LACK OF SATISFYING RELATIONSHIPS WITH SIGNIFICANT PERSONS (spouse, children, kin, significant persons serving in a family role)
12. ____: LACK OF FRIENDS, SOCIAL CONTACTS
13. ____: EXPRESSED NEED FOR MORE FRIENDS, SOCIAL CONTACTS
14. ____: LACK OF WORK (remunerative or non-remunerative, productive work activities which normally give a sense of usefulness, status, confidence)
15. ____: LACK OF SATISFACTION FROM WORK
16. ____: LACK OF LEISURE TIME ACTIVITIES
17. ____: EXPRESSED NEED FOR MORE LEISURE, SELF-ENHANCING AND SATISFYING ACTIVITIES
18. ____: LACK OF PARTICIPATION IN COMMUNITY ACTIVITIES
19. ____: LACK OF INTEREST IN COMMUNITY AFFAIRS AND ACTIVITIES WHICH INFLUENCE OTHERS
20. ____: FINANCIAL INSECURITY
21. ____: ADAPTIVE RIGIDITY (lack of complex coping patterns to stress)

PATIENT:____________ RATER:____________ DATE:________

FIG. 1.

FIGURE 2 | The influence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on mental health in older age can impinge on social frailty, a particular frailty phenotype that has not yet been assigned a full, universally recognized definition. The mechanisms by which social isolation and loneliness affect mental health are now under study, also in terms of how best to assess them.

These concepts and findings may help us to develop low cost methods for screening older persons for mental health outcomes, and selecting participants for prevention interventions (48). In the present perspective article, we underline the importance of early detection and interventions on dysfunctional aspects of social functions. Social functioning and the SDRS might be included in a risk index helping to stratify older persons for biomarker assessment of mental and cognitive health (i.e., late-life depression or dementia) also in the COVID-19 pandemic era (49, 50) (**Figure 2**).

DISCUSSION

Loneliness could be tackled with various interventions (51), broadly divided into two categories, that is, social interventions and technological interventions. Social interventions applied to reduce loneliness include befriending, residential and school-based camps, reminiscence therapy, animal interventions, gardening, physical activity and technology (52). However, in older people, loneliness can create serious problems that could not be alleviated with the social support only (53). Therefore, particular in older age, other types of interventions are required such as technological interventions (i.e., digital applications, online social networks and social robots) to enhance emotional support and social interaction (54).

The media, such as television and radio, have become ever more important during the period of social isolation due to COVID-19 lockdown. However, in this climate, the level of distress and anxiety can height, because of news coverage. Internet, electronic communication and, first and foremost, social media, had offered an extraordinary increase in connectivity between people and societies, playing a principal role in forcing the spread of bad news and in deepening the impact of the worldwide major problems on mental health, considered an outcome. Thanks to the help of video calls, older people stay connected during the current crisis. In this way, they widen their social circle and increase the frequency of contact with existing contacts. However, based on a recent review, evidence of the efficacy of video call interventions in reducing older adults' loneliness, is currently very uncertain (55), as was the evidence of their effectiveness as a means of evaluating outcomes of symptoms of depression (55). More rigorous methods and larger samples of participants are required in terms of future standpoint for this area of research.

The future perspective of old age psychiatry in COVID-19 pandemic is to cope with the framework of negative moods, stress and socially mediated traumatic experiences and adverse developments deriving from social epidemiology (56). Social determinants may positively modulate the effects of epigenetic factors on neuropsychiatric disorders in older age also *via* the modulation of immune system. In the future, social incentive exposure—which relies on patient social and physical activation—could be a potential mechanism of treatment for different psychiatric disorders, including late-life depression (57). Moreover, social isolation and loneliness is a potentially modifiable risk factor for later psychiatric multimorbidity that may offer an opportunity to enhance psychiatric care in new ways by addressing the underlying causes, and building coalitions to increase engagement and support by others outside the healthcare system (50).

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

ML: conceptualization. ML and FP: manuscript writing and supervision. MLM and ID: drawn the figures. RS, AD, ER, GG, and MM AB: contributed to the bibliographic search, review, and editing.

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REVIEW
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Selecting Remote Measurement Technologies to Optimize Assessment of Function in Early Alzheimer's Disease: A Case Study

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Despite the importance of function in early Alzheimer's disease (AD), current measures are outdated and insensitive. Moreover, COVID-19 has heighted the need for remote assessment in older people, who are at higher risk of being infection and are particularly advised to use social distancing measures, yet the importance of diagnosis and treatment of dementia remains unchanged. The emergence of remote measurement technologies (RMTs) allows for more precise and objective measures of function. However, RMT selection is a critical challenge. Therefore, this case study outlines the processes through which we identified relevant functional domains, engaged with stakeholder groups to understand participants' perspectives and worked with technical experts to select relevant RMTs to examine function. After an extensive literature review to select functional domains relevant to AD biomarkers, quality of life, rate of disease progression and loss of independence, functional domains were ranked and grouped by the empirical evidence for each. For all functional domains, we amalgamated feedback from a patient advisory board. The results were prioritized into: highly relevant, relevant, neutral, and less relevant. This prioritized list of functional domains was then passed onto a group of experts in the use of RMTs in clinical and epidemiological studies to complete the selection process, which consisted of: (i) *identifying* relevant functional domains and RMTs; (ii) *synthesizing* proposals into final RMT selection, and (iii) *verifying* the quality of these decisions. Highly relevant functional domains were, "difficulties at work," "spatial navigation and memory," and "planning skills and memory required for task completion." All functional domains were successfully allocated commercially available RMTs that make remote measurement of function feasible. This case study provides a set of prioritized functional domains sensitive to the early stages of AD and a set of RMTs capable of targeting them. RMTs have huge potential to transform the way we assess function in AD—monitoring for change and stability continuously within the home environment, rather than during infrequent clinic visits. Our decomposition of RMT and functional domain selection into *identify, synthesize*, and *verify* activities, provides a pragmatic structure with potential to be adapted for use in future RMT selection processes.

Keywords: Alzheimer's disease, dementia—Alzheimer disease, function, mild cognitive impairment—MCI, remote measurement technologies, telemedicine, activities of daily living

INTRODUCTION

The study of Alzheimer's disease (AD) symptomatology typically focuses on the progressive deterioration of cognitive functions, neglecting real-world translation of functional impairment. The Food and Drug Administration (FDA) guidelines defines the emergence of mild but detectable functional impairment as signifying the transition from stage 2 to stage 3 of early AD, with a diagnosis of overt dementia (stage 4) being made as the functional impairment apparent during stage 3 worsens (1). Moreover, the recent emphasis on disease modification in clinical trials has concentrated focus on the early stages of AD (2). Functional improvement is also a typical primary endpoint in AD clinical trials (3). In addition to its clinical and research relevance, function is more resilient to demographic and cultural confounding factors than cognition (4). Individual and population differences, such as ethnic minority groups, scale translation, and societal and cultural relevance can impact the efficacy and relevance of typical "pen and paper" tests of function, so it is imperative that sensitive and relevant measures are available to examine the most environmentally appropriate means of assessing function.

A commonly used scale to measure function is the "Alzheimer's Disease Cooperative Study-Activity of Daily Living" (ADCS-ADL) (5), which can predict progression to dementia (6). Other functional scales include, "The Progressive Deterioration Scale," "AD Functional Assessment Change Scale," "Neuropsychological Test Battery" (NTB), and "Interview for Deterioration in Daily Living Activities in Dementia." More recent scales include, "The Everyday Cognition Scale" (ECog), measures daily manifestations of cognitive impairments in memory, planning, organization, language, divided attention, and visuospatial skills and is sensitive to mild cognitive impairment (MCI) subtypes (7), and the "Amsterdam Instrumental Activities of Daily Living Questionnaire," can differentiate those likely to convert to dementia from MCI and subjective cognitive decline (SCD) (8). However, such scales are reliant on self or informant reporting rather than objective assessment, neglecting more complex areas, such as social functioning, despite social functioning, loneliness, and social isolation's contribution to dementia risk and morbidity (9–11).

The relationship between cognition, including executive processes, and function is crucial in AD research, especially at the prodromal stage. ADLs involve varying degrees of cognitive and executive load, depending on whether the ADL is basic, instrumental or advanced. In its original conception, MCI was defined by a decline in cognition but not in daily function, however, the consensus criteria for amnestic MCI has since been revised to encompass a minimal impairment in advanced ADLs (12), although subsequent studies (13, 14) and metanalysis report instrumental ADLs are also impaired at the MCI stage (15, 16). Executive function (17, 18) and memory (19, 20), rather than demographic factors, have been found to accurately predict ADLs and ADLs also map onto neuroimaging features, such as subcortical white-matter hyperintensities in aging populations without dementia (21, 22). Functional status measured by ADLs also has prognostic purposes, as those with MCI and mild functional impairments at baseline are more likely to convert to overt dementia (13, 23).

REMOTE MEASUREMENT TECHNOLOGIES

The COVID-19 pandemic has heighted the need for remote assessment in older people, as they are at higher risk and are advised to minimize risk of infection by using social distancing measures, yet the importance of diagnosis and treatment of dementia remains unchanged. Advances in digital health, including electronic health records, portal technologies, and wireless communications, are likely to have a central role in future dementia assessment and care. Remote Measurement Technologies (RMTs), refers to, "any mobile technology that enables monitoring of a person's health status through a remote interface, with the data then either transmitted to a health care provider for review or to be used as a means of education for the user themselves" (24). RMTs may include a variety of sensors that detect changes in health status, offering a unique opportunity to accurately and continuously track and measure changes. RMTs can objectively, actively and passively collect numerous data points during everyday routines that include a variety of basic, instrumental and advanced ADLs. These datapoints can index symptom severity and progression, stability and regression, impact on daily life and response to treatment. Deploying RMTs to remotely capture signals related to function also offers the possibility of engaging people who would not normally want to participate in research and empowers patients by giving them an active and informed role in their own healthcare.

RMTs are gaining popularity in dementia research in measuring cognition (25) but for widespread implementation, it is critical that we use RMTs to measure relevant and sensitive variables that accurately, reliably, and objectively measure cognition and function. Due to COVID-19, older adults are recommended to use social distancing but such measures have the side-effect of reducing physical and social activity, as well as increasing loneliness and social isolation, all of which are associated with more rapid cognitive and functional decline (26). RMTs can collect valuable data on health status during such restrictions and provide an opportunity to shift how care and assessment is undertaken in dementia by deeply enriching information on disability, particularly function, where large datasets can be collected passively over several days, whilst patients go about their everyday routines, rather than relying on subjective anecdotal reporting, with its inherent biases.

RMTs are technically complex and, for most studies, it will be necessary to select technologies off-the-shelf, rather than engineer bespoke solutions. But, selecting RMTs from the marketplace is still a challenge. There is a broad spectrum of options, from those targeted at personal fitness and behavior change, through to research-grade data logging devices. Each represents a different attempt to balance compromises across data quality, technical reliability, and participant acceptability. Moreover, many manufacturers revise the hardware and software of their offerings annually, meaning published validation data, where it exists, rapidly becomes out of sync with what the marketplace can supply. Checklists, such as the Clinical Trials Transformation Initiative technology selection tool (27), listing important factors, can be used to ensure devices are evaluated thoroughly. These might motivate deep technical investigations such as, the review of developer application program interface (API) documentation, or empirical evaluation of current real-world sensor performance.

PATIENT AND PUBLIC INVOLVEMENT

Whether designing health services, digital health technologies, or clinical research studies, it is widely accepted that participants' be part of the process. This could be through pilot studies, group-based stakeholder workshops, or participant representation on project steering committees. For RMTs, which inherently have some manifestation within participants' everyday lives, the need to understand participants' perspectives is especially important. In the Innovative Medicines Initiative 2 (IMI)-funded, "Remote Assessment of Disease and Relapse—Central Nervous System" (RADAR-CNS, https://www.radar-cns.org/), it is hypothesized that Human-centered Design (HCD) methods might be usefully adapted to the challenge of *selecting* RMTs, and a novel three-stage iterative process based on HCD principles has been proposed (28).

"Remote Assessment of Disease and Relapse-Alzheimer's disease" (RADAR-AD, https://www.radar-ad.org/) is a European Horizon 2020-funded multi-stakeholder public-private consortium exploring the potential of RMTs to improve the assessment of function in early AD. RADAR-AD is closely working with people affected by AD (coordinated by the patient organization, Alzheimer Europe) and regulators, selecting and, if needed, modifying the most relevant available devices and apps to sensitively measure early and clinically meaningful functional decline in early AD. The mapping of prioritized functional domains to RMTs has the potential to radically improve our ability to understand the very earliest stages of AD progression and predict deleterious outcomes, such as loss of independence or conversion to dementia, compared to current clinical assessments. Therefore, the main objective of this paper is to outline the processes through which the RADAR-AD consortium has;

I. Identified relevant functional domains
II. Engaged with stakeholder groups to understand participants' perspectives
III. Worked with technical experts to select and evaluate relevant devices.

We systemically describe the procedures and rationale for the three separate but interrelated workstreams and how their outputs are amalgamated to provide the methodological and design framework for RADAR-AD.

METHODS

Functional Domains Clinical Literature Review

We carried out an extensive literature review to select functions relevant to AD biomarkers, quality of life (QoL), rate of disease progression and loss of independence. We based the literature review on "The US Cognition Working Group of the Critical Path Institute's Personal Report Outcome (PRO) Consortium's" report to the Food and Drug Administration (FDA), which focused on advanced ADLs and interpersonal functioning. PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) literature until March 2019 was searched using the keywords, "Alzheimer's disease," "early Alzheimer's disease," "activity of daily living," "activities of daily living," "basic activities of daily living," "instrumental activities of daily living," "advanced activities of daily living," "interpersonal functioning," "social functioning," "functional impairment," "functional status," "mild cognitive impairment," "MCI," "prodromal Alzheimer's disease," "preclinical Alzheimer's disease," "presymptomatic Alzheimer's disease," and "quality of life." Studies are tabulated to guide the prioritization of these preliminary functional domains (**Table 1**).

The search was then specified to sequentially include each of the individual ADLs and interpersonal functions from The US Cognition Working Group of the Critical Path Institute's PRO consortium report. Other studies were identified by reviewing relevant bibliographies in original papers. Clinical studies were included if the study participants had a confirmed diagnosis of AD (e.g., cerebrospinal fluid biomarkers) and used standardized instruments of evaluation. Functional domains where ranked and grouped by the empirical evidence for each to;

i) Predict MCI-to-AD dementia conversion
ii) Relevance to early AD
iii) Being predictive of decline in people with dementia.

RADAR-AD Patient Advisory Board Consultation

The results of the literature review were then handed over for discussion with the RADAR-AD Patient Advisory Board (RADAR-AD PAB). We particularly requested feedback on the relevance of the functional domain to the experience of having

TABLE 1 | The functional domain selection process resulted in the identification of the following functional domains, sorted by relevance.

Functional domain	Tier	Predicts MCI->AD conversion	Impaired in early AD	Predictive of decline	Reported by PAB
1. Difficulties at work	1	x	x	x	x
2. Spatial navigation and memory	1	x	x	x	x
3. Planning skills and memory required for task-completion	1	x	x	x	x
4. Managing finances	2	x		x	x
5. Self-care	2		x	x	x
6. Self-management, e.g., running errands and shopping	2	x		x	x
7. Acquiring new skills	2		x	x	x
8. Sleep quality and circadian rhythms	2		x	x	x
9. Use of technology/devices	2		x	x	x
10. Dysnomia, word finding difficulties	3		x	x	
11. Gait	3		x	x	
12. Difficulties driving	3		x	x	
13. Interpersonal interaction	3		x		x
14. Motivation, signs of apathy or withdrawal	4				x

Tier 1, highly relevant; Tier 2, relevant; Tier 3, neutral; Tier 4, less relevant.

AD or caring for someone with AD. The RADAR-AD PAB was established at the beginning of the project by Alzheimer Europe, in collaboration with the project partners. The composition of the RADAR-AD PAB, its approach and work in the context of RADAR-AD has been described elsewhere (https://www.radar-ad.org/patient-engagement/patient-advisory-board). Many of the members are from an existing working group of people with dementia and had been involved in Public Involvement (PI) activities in the past. The RADAR-AD PAB provides advice and influences relevant decisions in the conduct of the project. The topic of functioning was addressed in the first meeting of the RADAR-AD PAB, in Luxembourg in March 2019. The session lasted 2 h and was facilitated by two members of Alzheimer Europe with experience in PI. Before the meeting, members of the RADAR-PAB received accessible information about the project, functioning, dementia and the issues that RADAR-AD wanted to address.

The first part of the consultation addressed the understandings of people affected by AD of the term "functioning" and how these could differ from or complement the way this is typically portrayed. A semi-structured discussion approach was used. For the prioritization exercise, members were presented with the functional domains identified in the literature review and asked for their views. The task consisted of sorting the identified domains into three different piles (labeled as "very important," "fairly important," and "not important"), based on their experience and according to the perceived importance of each of the different domains in the early stages of dementia. In addition, as the functional domains linked to social activities have been less frequently considered in the existing literature, members were specifically asked to consider any missing elements. The results from this search criteria were prioritized into tiers:

- Tier 1—Highly relevant
- Tier 2—Relevant
- Tier 3—Neutral
- Tier 4—Less relevant.

Functional domains that met all three established criteria (predicts MCI-to-AD conversion, relevance to early AD, being predictive of decline in people with dementia) and were reported as relevant by the RADAR-AD PAB were grouped into tier 1, functional domains that met two of the criteria and were reported as relevant by the RADAR-AD PAB were grouped into tier 2, functional domains that met one of the criteria and were reported as relevant by the RADAR-AD PAB were grouped into tier 3 and functional domains that met 1 of the criteria were grouped into tier 4. Interpersonal domains are less studied than ADL's in AD, resulting in these domains meeting fewer criteria than the basic ADL, instrumental ADL and advanced ADL functional domains during the indexing of this list.

Remote Measurement Technology Selection for Functional Domain Measurement

Our RMT selection work consisted of three kinds of activity, which we refer to as:

i. *Identify*
ii. *Synthesize*
iii. *Verify*.

In the first, we sought to develop a broad understanding of the landscape for selection, taking the functional domains and PAB perspectives, and augmenting with a review of relevant technologies. In the second, we created candidate RMT selections, each with detailed reasonings, and brought the best aspects of each together into a single proposal. In the last, we went into depth to ensure that every aspect of our rationale for selection was well-founded. These were overlapping activities, rather than strict sequential phases.

Identify Activity

Work on selecting RMTs was conducted by a group of academic and industrial experts within the technology work package of RADAR-AD. It began, independently from the work on functional domains selection above, by reviewing the available apps, wearables, and fixed home sensor technologies, and generating ideas of potential uses for these as measures of daily function. A targeted, focused literature review was conducted to identify a wide range of internet of things (IoT) wearable sensors and devices in elderly care (29). Most of those solutions used either custom-made sensors that are not available to procure or commercially available wearables that are equally as effective. Toward identifying a range of commercial solutions, prior RMT reviews, such as IMI ROADMAP (30) and the choices of IMI RADAR-CNS played a role, but equally as influential were the experiences of the team members themselves in deploying such devices in previous clinical studies. Progressing from a long-list of devices to a short-list was straightforward and based on clear-cut criteria, such as measurement capability, battery life, water resistance (people with dementia may forget to remove devices when showering or bathing) and cost. Throughout this *identify* activity, collaborative working with the clinical experts involved in functional domain prioritization provided incremental updates and ensured that devices were not prematurely removed from the selection process.

Synthesize Activity

Moving from a shortlist of RMTs, each with good qualities, to a final selection of devices, was considerably harder. Our technical experts were each asked to propose a specific selection of RMTs, with a description of the clinical protocol for their proposed use, and a rationale for how these devices mapped to the functional domains. Given the challenging and heterogenous nature of our domains of interest, it was no surprise to find that these proposals had very significant differences. Presenting and explaining these detailed proposals to the rest of the group provided a way to:

i. Verify that they were technically feasible and correct
ii. Flush out novel solutions to the measurement challenge
iii. Unpack differing assumptions about what was clinically significant
iv. Compare our estimates of how acceptable each proposal would be to participants.

The strongest aspects of the best proposals were then combined to create a proposed final selection, and this was then iteratively refined until it could be agreed by the expert group. It was this “bringing together” which led us to refer to this part of our selection process as *synthesis*.

Verify Activity

There was a continual need to *verify* the information we were using to make decisions. Early in the process, we sought to verify technical claims made about various devices through in-depth examination of application programming interface (API) documentation, and evaluation of device outputs at the laboratory bench. A core feature of wearables and apps are measuring the number of steps a user takes based on their internal accelerometer sensor and then translating this to clinically valuable metrics such as physical activity levels, calories burned, sleep duration, depth, and interruptions. Therefore, we performed lab trials and assessed the accuracy of multiple wearables and apps in measuring “steps” as a core metric. As work progressed, we frequently needed to verify our understandings of what was clinically significant. Interactions with the clinical teams were therefore pivotal to the eventual choice of devices. During the process, we often used our prior experience to estimate the participant acceptability of our proposals. Periodically, we were able to engage with participants to verify their views. This was done initially through group-based evaluation with the RADAR-AD PAB and then later in dedicated workshop-based piloting. Participants in the workshop were presented with various device alternatives and rated them in terms of comfort, functionality, battery life, and price. They also addressed intrusiveness and privacy issues.

RESULTS

Functional Domains

The full list of functional domains from the literature review is detailed in **Supplementary Material 1** and functional domain feedback from RADAR-AD’s PAB is detailed in **Supplementary Material 2**.

Table 1 prioritizes these results in order of significance of predicting MCI-to-AD conversion, relevance to early AD, being predictive of decline in people with dementia and being ranked as important by the RADAR-AD PAB. Based on our criteria of each functional domain’s relevance, highly relevant functional domains are; “difficulties at work,” “spatial navigation and memory,” and “planning skills and memory required for task completion.” Relevant functional domains are, “managing finances,” “self-care,” “self-management,” “acquiring new skills,” “sleep quality and circadian rhythms,” and “use of technology/devices.” Neutral functional domains are, “dysnomia,” “word finding difficulties,” “gait,” “difficulties driving,” and “interpersonal interaction.” Functional domains of less relevance are, “motivation and signs of apathy or withdrawal.”

Remote Measurement Technology Selection

Table 2 allocates *verified* RMTs to the prioritized list of functional domains. While most of devices refer to specific brands and models that fulfill the particular requirements needed (functionality, data types, access to data etc.), the Smart Home sensor category requirements can be fulfilled by a broad range of products [e.g., the FIBARO (https://www.fibaro.com/en/), Plugwise (https://www.plugwise.com/nl_NL/), or other Z-Wave-compliant product families (https://www.z-wave.com/)]. While wearables and Smart Home devices can unobtrusively monitor participants at home, other devices require a certain protocol or exhibit technological peculiarities that mandate use in a lab setting only. This includes the Banking App, which simulates automated teller machine (ATM) use on a tablet—proved to be an effective marker (31) and the GAIT measurement protocol.

TABLE 2 | The device selection process identified remote measurement technologies that could capture digital signals from functional domains comparable to established measures of function.

Functional domain	Existing measures	Potential digital measures	Selected technologies
1. Difficulties at work	Amsterdam IADL	Brief daily app-based self-report or carer reports Sociometric wearable badges	Digitized Amsterdam iADL
2. Spatial navigation and memory	CDR Amsterdam IADL MMSE ECog ADCS-ADL FAQ	Gamification of navigational tasks GPS movement trajectories or deviation from navigation tools	Altoida Medical Device (https://altoida.com/) GPS (passive) RADAR-base app (passive)
3. Planning skills and memory required for task-completion	ADCS-ADL MMSE Amsterdam IADL ECog UPSA CDR	Phone app measures performance on gamified/virtual reality tests	Mezurio Altoida Medical Device Digitized Amsterdam iADL
4. Managing finances	ADCS-ADL UPSA ECog Amsterdam IADL SFS	Speed of resolving calculation exercises Speed of fulfilling "procedure" (i.e., filling out transfer form, authorizing transaction, etc.) Active tasks simulating banking activities	Banking app (31) Digitized Amsterdam iADL
5. Self-care	Amsterdam IADL UPSA ADCS-ADL CDR SFS	Carer uses smartphone app to report patients' self-care Smart sockets monitor domestic device use, e.g., kettle In-home movement sensors Smart tags monitor movement of key domestic artifacts e.g., fridge door Wearable cameras	Digitized Amsterdam iADL Oxford Metrics Group Autographer (passive) Smart Home Sensors for Presence, Appliance Usage, Open Door/Window (passive)
6. Self-management, e.g., running errands and shopping	ECog UPSA ECog NPI CDR Amsterdam IADL ADCS-ADL SFS	Phone app collects details of meals GPS data, deviations and accuracy of daily routine Gamified/virtual reality performance assessments	Digitized Amsterdam iADL Mezurio Smart Home Sensors for Presence, Appliance Usage, Open Door/Window (passive)
7. Acquiring new skills	CDR	Learning new gamified/virtual reality tests on a smartphone	Mezurio
8. Sleep quality and circadian rhythms	NPI Sleep Quality Index, Epworth Sleepiness scale	Mobile phone sleep tracker Wearable accelerometer or fitness tracker Wearable EEG headbands Bed-mounted or under-mattress sensors	Mezurio Fitbit Charge 3 (passive) Axivity AX3 (passive) DREEM Headband (https://dreem.com/en, passive)
9. Use of technology/devices	Amsterdam IADL MMSE ECog SFS	Frequency/duration and sophistication of smartphone use	Digitized Amsterdam iADL RADAR-base app (passive) Mezurio Altoida Medical Device
10. Dysnomia, word finding difficulties	MMSE	Active or passive analysis of speech and voice Keyboard dynamics	Mezurio
11. Gait	ADCS-ADL ECog	Dedicated gait sensors Smartphone-based walking test Fitness trackers	GaitUp Physilog Sensor (https://gaitup.com/physilog-sensor/) Fitbit Charge 3 (passive) Axivity AX3 (passive)
12. Difficulties driving	CDR Amsterdam IADL ECog	Smartphone GPS and accelerometer monitoring Driving diagnostic OBD2 data logger	Digitized Amsterdam iADL CANedge driving data logger (passive)
13. Interpersonal interaction		Wearable cameras Localized logging of nearby smartphone presence	Oxford Metrics Group Autographer (passive) RADAR-base app (passive)
14. Motivation, signs of apathy or withdrawal	SFS WHOdas 2.0 CDR MMSE NPI	App monitoring communication from/with phone Time spent in different locations Level of physical activity Social media use	Mezurio Oxford Metrics Group Autographer (passive) RADAR-base app (passive)

ADCS-ADL, Alzheimer's Disease Cooperative Study/Activities of Daily Living scale; CDR, Clinical Dementia Rating; ECog, Everyday Cognition; FAQ, Functional Activities Questionnaire; MMSE, Mini Mental State Examination; NPI, Neuropsychiatric Inventory; SFS, Social Functioning Scale; UPSA, University of California San Diego Performance-Based Skills Assessment; WHOdas 2.0, World Health Organization Disability Assessment Schedule.

DISCUSSION

This case study outlines the processes through which we identified relevant functional domains, engaged with stakeholder groups to understand participants' perspectives and worked with technical experts to select and evaluate relevant RMTs to measure function in early AD. Through a literature review and Delphi-type exercise, we identified and prioritized functional domains specific and sensitive to the early stages of AD progression and most predictive of deleterious outcomes, such as loss of independence or conversion to dementia that can be prioritized and targeted for RMT measurement. The input provided by members of the RADAR-AD PAB confirmed the great relevance of function for people affected by AD. Much of their discussions focused on the challenges that cognitive decline may pose to people who are working, as well as other complex tasks, which are part of daily life, such as finishing tasks or activities and managing the household or personal finances. Social activities and social life can also be greatly impacted and are areas that are particularly meaningful to people with dementia and carers. In addition, as functional domains are increasingly affected, measurement may become challenging, as the frequency of the activity may appear stable, but the quality and nature of functioning may have significantly deteriorated.

There is undoubtedly huge value in both the prioritized domains of function sensitive to the early stages of AD and in the selection of devices to measure them remotely. However, our selection of RMTs must be considered in relation to the specific requirements of the RADAR-AD project but they can be applied to any clinical studies that wish to employ RMTs. For example, the duration of our clinical study was important in deciding whether a device would be tolerable to participants, we selected devices that would fit within our budgetary constraints and, because RMTs exist within a fast-moving marketplace, any selection made today would need to be reviewed again by future projects.

The ongoing need for RMT selection makes reflecting on the process we followed especially relevant. We described our selection process as consisting of three inter-related activities. The *identify* activity, in which suitable devices were longlisted and then shortlisted, was relatively straightforward and drew on the team's existing experiences and technical skills. The structure of our project divided RMT selection from the identification of functional domains, but in retrospect it is clear that at least conceptually, these also fit well with the *identify* activity. Initially, the group made differing assumptions about how a device might be used or how options would be set-up based on our prior experience and in some cases, this led to discussion at cross-purposes. The antidote to this complexity was to ground each candidate selection of RMTs within a detailed proposal which outlined, not just a selection of complementary devices, but the exact clinical protocol for how each would be used, and the precise details of how it would be configured.

Despite being founded in such a comprehensive set of understandings, the *synthesize* activity was challenging:

i. A complete selection would involve multiple devices and since each device often had multiple sensors, there was often more than one way to achieve a similar aim
ii. Because devices were subject to similar engineering constraints (of battery life or sensor hardware), there was often no ideal solution to meet our clinical or participant experience requirements
iii. Some devices contained detailed configuration options, for example, to trade-off measurement frequency with battery life
iv. A single device could be deployed within a number of different clinical data collection protocols (worn for a long or short period, during daytime only, or at night too, etc.) each with a different impact on participant acceptability and the clinical value of the data.

The synthesize activity involved not just bringing complementary devices together into candidate selection proposals, but in further bringing the best of these proposals together into a final selection. It had many of the characteristics of a problem-solving task. Like many RMT selection projects, we had to make trade-offs between desirable criteria, like breadth of sensors, user experience, battery life, and data quality. For example, we wanted a wrist-worn device with raw high frequency accelerometer data, with over 24 h of battery life, a heartrate monitor, which would be acceptable to participants, and provide them with some feedback. While not immediately obvious, in the end the best solution was to have two wrist worn devices, a research-grade device logging raw accelerometer data, Axivity AX3 (https://axivity.com/product/ax3), and a fitness activity tracker, Fitbit Charge 3 (https://www.fitbit.com/us/products/trackers/charge3), logging heartrate measurements. This introduced the additional burden of wearing two devices, but after consultation with participants, this was considered a much better option than a single device that offers both kinds of functionality at the cost of bulkier casing and a much shorter battery life. Polling the RADAR-AD PAB on the issue validated this choice in the framework of our *verify* activities.

While the *identify* activity delivered a broad view, our *verify* activity was a deep and focused attempt to ensure every aspect of our selection rationale was rigorously challenged. This was by far the most interdisciplinary aspect of RMT selection. Our very first *verify* activities were technical in nature. For example, one expert group member proposed heart rate variability (HRV) as a measure which could be supplied from a specific wrist-worn device. When this was checked against technical documentation, it became clear that, while HRV is used by the device within several proprietary algorithms (and as such, was legitimately mentioned within marketing materials) the HRV measure was not made available to third parties through its standard APIs. Our choice of wrist-worn wearable pivoted around this issue for some time. Alternative device selections that would allow HRV were proposed but would introduce compromises in user experience. The matter was ultimately resolved when we sought to verify the scientific value of HRV to our project, and as a result of discussions with the clinical team, we resolved not to measure it. This was typical of an issue that required debate to flow swiftly back-and-forth across disciplinary divides.

Although initially technical in nature, as we began to propose concrete selections of candidate RMTs, our *verify* activities were soon also highly concerned with participants' perspectives. Initially, we relied heavily on our combined expertise in RMT. For example, we often talked about our expectations of participant burden or experience, based on our prior experiences. We reasoned that because the Axivity AX3 wearable device had been acceptable to participants of UK BioBank (32), that it would also be acceptable to the participants of RADAR-AD. This kind of experience-based assumption was incredibly useful and helped us to proceed rapidly. However, as we neared final selection it became increasingly critical that we rigorously verify every component of the rationale that we had established to support our selection choices: Just because a device had been acceptable to one participant group (with a shorter wear duration and a younger demographic), did that mean it would also be acceptable to ours? Acceptability was consequently verified through presentation to the RADAR-AD PAB and evaluation in a participant workshop.

RADAR-AD has benefited from the work of RADAR-CNS, including their HCD inspired framework, which adapted elements from *de novo* design methodologies to the challenge of RMT selection. It is surprising that we have not ended up with a selection process that more closely followed this framework. One simple explanation for this would be to recognize the substantial work that went into adapting our process to match the specific *a priori* structure of our project. Making the most effective use of the expertise available, from technologists, clinicians, and participants alike, was our overriding priority and strength. We clearly were informed by principles from HCD (28) and of course by aspects of "design thinking" more broadly (33). But pragmatic adaptation of these techniques to fit our circumstances, maximize our strengths, address our weaknesses, and solve the problems we encountered, became more influential on the shape of our eventual process than an abstract model.

Inherent tension exists between techniques intended for *de novo* design and a process of selection. RMT selection is a critical part of the design of a clinical study where devices are used, and it is clearly appropriate to draw on design methodology. However, equally as clear, is that selection involves deciding whether a study should adopt the design decisions taken by others during the production of a candidate RMT; do *their* design decisions work in *our* context? Unlike *de novo* design, there is usually at least some evidence that a candidate off-the-shelf RMT did work in a related context. Within our selection process, it was frequently the case that such evidence was highly informative, and it would have been inefficient not to have used it, but as the final selection neared, we nevertheless needed to empirically verify whether those conclusions would truly hold within our own study. The *verify* activity is thusly named to acknowledge this perceived difference between *de novo* design and RMT selection, while emphasizing the need for rigorous evaluation.

CONCLUSION

This case study provides a set of prioritized functional domains that are sensitive to the early stages of AD progression and a set of RMTs capable of targeting them. RMTs have huge potential to transform the way we assess function in AD, monitoring for change and stability continuously within the actual home environment, rather than during infrequent clinic visits. Technologies change rapidly and the ability to select the best RMTs is therefore critical. It is obvious that successful RMT selection must give equal weight to technical, clinical, and participant perspectives and this case study illustrates what such interdisciplinary working looks like in practice. Optimal selection is challenging. It must be broad to ensure no option is missed; it must also be deep to ensure every detail is correct and finding solutions may require solving problems that span disciplines. Finally, we decomposed RMT selection into three activities: *identify, synthesize,* and *verify*, which have potential to be adapted for use inside the selection processes of other projects.

AUTHOR CONTRIBUTIONS

AO and CH conceived the structure and content of the paper. AO, CH, NM, TS, GL, DG, AD-P, and DA provided revisions of the paper. DA was the coordinator of RADAR-AD. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.582207/full#supplementary-material

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The Effects of COVID-19 Among the Elderly Population: A Case for Closing the Digital Divide

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The COVID-19 pandemic has had huge effects on the daily lives of most individuals in the first half of 2020. Widespread lockdown and preventative measures have isolated individuals, affected the world economy, and limited access to physical and mental healthcare. While these measures may be necessary to minimize the spread of the virus, the negative physical, psychological, and social effects are evident. In response, technology has been adapted to try and mitigate these effects, offering individuals digital alternatives to many of the day-to-day activities which can no longer be completed normally. However, the elderly population, which has been worst affected by both the virus, and the lockdown measures, has seen the least benefits from these digital solutions. The age based digital divide describes a longstanding inequality in the access to, and skills to make use of, new technology. While this problem is not new, during the COVID-19 pandemic it has created a large portion of the population suffering from the negative effects of the crisis, and unable to make use of many of the digital measures put in place to help. This paper aims to explore the increased negative effects the digital divide is having in the elderly population during the COVID-19 pandemic. It also aims to highlight the need for increased attention and resources to go toward improving digital literacy in the elderly, and the need to put in place measures to offer immediate solutions during the COVID-19 crisis, and solutions to close the digital divide for good in the long-term.

Keywords: COVID-19, pandemic, digital divide, digital literacy, elderly

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INTRODUCTION

As the COVID-19 crisis evolves, the widespread effects of both the virus and the preventative measures being taken to protect the population are becoming clearer. At the time of writing this paper, the total number of confirmed cases of the virus has surpassed 34 million, and the number of deaths is over 1 million, and increasing daily (1). The economic consequences of this crisis have been immense, and researchers have suggested that the effect on world economies is likely to be felt for years (2–5). However, the COVID-19 crisis has brought with it a whole selection of other problems, including those not directly related to the virus, but to the lockdown measures which have been put in place across the globe. While the lockdown may be necessary to contain the virus, its effects, ranging from physical to psychological have already been noted. Early studies have suggested that the psychological effects of this crisis and the prolonged lockdown includes increased stress, anxiety and depression (6–11). Researchers have also warned to brace for a possible spike in suicide rates in the months following the crisis (12). In many regions the pandemic has caused difficulty accessing healthcare resources for non-COVID related problems (13), resulting in higher risk of poor outcomes for those suffering from other diseases (14). The disruption of workplaces, exercise routines, and widely imposed social isolation are all likely to have a large effect on the well-being of the population going forward. While there will not be a group of the population untouched by this crisis, the elderly population is likely to face the worst effects. Initial reports have shown that ∼80% of the deaths due to COVID-19 occur in those over the age of 65 (15). Since the virus has largely affected the elderly, lockdown measures for older individuals have been stricter, and may need to be extended in some countries (16, 17). This means that the elderly will be most impacted by the side effects that follow in the coming months (18).

While the changes and restrictions in daily life are noticeable and immense in many cases, digital tools and resources have been highlighted as possible means of mitigating the worst of the negative consequences. Social isolation has well-documented negative effects on well-being in individuals of all ages, but the effect has been shown to be magnified in older adults (19, 20). Social isolation often results in loneliness, which is a factor significantly associated with depression in elderly adults (21). Loneliness, isolation, and depression have all been shown to predict worse disease outcomes in older populations (22). Furthermore, depression and other mental health issues are linked to higher mortality rates in general, in those over 65 years old (23). The use of technology to continue to stay in touch with family, friends and loved ones has become an important way to combat these negative effects associated with prolonged loneliness and isolation. Virtual socializing and online events have become commonplace and have gone a long way to keeping people from being completely isolated while in lockdown (24, 25). The ability to remain in contact with friends and family via online video chat tools may also offer individuals more socializing opportunities to avoid loneliness. Online education has also become the new normal in many places, as schools and universities turn to online classes to keep student education on track (26). Furthermore, as individuals have more flexible schedules, or more free time during the lockdown, there has been a significant increase in the number of people making use of personal learning and development tools like language learning apps (27). Healthcare has also turned to digital solutions, and making both mental and physical healthcare available online has become more common and has been fairly successful in helping mitigate the negative effects of reduced healthcare access (28–34).

While technology may have gone a long way to mitigate negative effects of the crisis in the general population, the situation is more complicated in the elderly population. Access to, and ability to proficiently use technology is much lower in older populations than in younger adults (35, 36). This uneven distribution of technological access and skill is known as the digital divide, or the gray digital divide, and researchers have suggested it has continued to increase as the rate of technological innovation speeds up (37). This results in a paradoxical situation, in which the population most affected by the lockdown is also the population least helped by the digital tools aiming to mitigate the negative effects. This paper aims to highlight the negative effects of COVID-19 in the elderly population and explore how uneven access and proficiency in technology is contributing to increased negative outcomes within this population. This paper will end by making practical suggestions for how this digital divide can, and should, be addressed going forward.

THE EFFECTS OF COVID-19 ON THE ELDERLY POPULATION

Although it is currently unclear what the full extent of the effects of this pandemic will be, its negative impact on psychological well-being has become very evident. Early studies have already reported an increase in anxiety, and depression in the general population, especially those facing extended lockdowns (38, 39). These effects are magnified in the elderly population due largely to stricter lockdowns, higher threat of illness, and loss of social support (40). Prior studies have also reported that even outside of crisis times, the elderly population have relatively high rates of depressive symptoms (41, 42), which is troubling in the face of evidence that those suffering from pre-existing mental health conditions have been most affected by the negative psychological consequences of lockdowns (7). While increased mental health problems in the general population may already be a cause for concern, these concerns go beyond psychological well-being in the elderly. Studies have shown that depression in the elderly is linked the subsequent cognitive decline, and risk of Alzheimer's Disease (43, 44). This means that while many societies now face the immediate threat of increasing mental health concerns, the long-term effects could be devastating, as depression and stress result in the older generation facing hastened cognitive decline, and increased rates of Alzheimer's Disease. This problem will likely be even further worsened by the physical limitations put on the movement of individuals outside their homes, resulting in less exercise opportunities for many individuals. Several studies have shown that exercise, even in light to moderate doses and intensities, can have a significant positive effect on cognitive function in the elderly, especially in those with cognitive impairments, or neuropsychiatric disorders (45–49). Looking at this prior research, loss of socialization, increased mental strain and general mental health problems, and decreased exercise, could have substantial negative effects on the elderly population. Although the lockdowns may be temporary, these effects are likely to be long lasting, and could pose significant risks to the quality of life of the elderly population in the coming years.

However, the changes many countries have seen come into place since the start of the COVID-19 pandemic extend far beyond loss of socialization, and increased depression. Lockdowns have resulted in a significant shift in the functioning of day-to-day life: the world has gone digital. As hospitals have filled with COVID-19 patients, access to regular healthcare for non-COVID related disorders has been interrupted (50). Those who do not seek care for non-COVID related disorders may be at higher risk of illness and fatality during this period (51). This risk is likely to disproportionately affect the elderly, who have higher rates of health problems than younger populations and are more likely to be encouraged to avoid areas where they could contract the disease. In response to this problem, there has been a significant shift in healthcare into the digital world. Telehealth, or the act of providing healthcare digitally, and remotely, has become commonplace in many countries (28, 30, 32, 34). However, this shift has had fewer positive effects in the elderly than other populations. A recent study showed that about 40% of elderly individuals were unprepared to use telehealth resources, predominantly due to lack of skills to effectively make use of the technology (52). This has been further shown during the pandemic, as the group with the highest adoption of telemedicine use has been those aged 20–44, despite the fact that the elderly population generally have the highest yearly number of doctor and hospital visits (53, 54). Although there have been some recent efforts to create virtual geriatric clinics to support the elderly during the pandemic, research has shown these have had varying success, and have been met with a variety of problems related to difficulties with technology use (55). Therefore, despite being the group most in need of telehealth solutions, the elderly community has benefited from their implementation the least.

This shift into the digital realm extends beyond just the healthcare sector. Online access to COVID-19 related news, education, grocery delivery services, group socialization, and many more services have become commonplace. The world has adapted to try and make up for the loss of access to everyday resources, and in many areas, and for many people, this has been fairly effective (56–59). However, one group likely to benefit the least from these digital alternatives are the elderly population, who have significantly lower rates of internet usage and acceptance than other age groups (60, 61). This results in a worrying paradox: the population most negatively affected by the COVID-19 pandemic, are also the least likely to be able to access the resources put in place to mitigate the effects. This paradox can largely be attributed to the poor digital literacy skills found amongst the elderly population compared to younger groups, most commonly described as the digital divide.

THE DIGITAL DIVIDE

The digital divide is a term originally used to describe the gap in access to new technology which exists between different groups of people (62). Early research on this topic mostly focused on the differences in technological accessibility within poorer communities or countries (63–65) or the growing gender based digital divide (66–68). However, as technology has advanced and become more engrained in our daily lives, the case of the digital divide has become more complex. An article by (62) developed a model which suggested four different levels of technological access which the digital divide has an effect on. These levels included (1) Motivational Access, (2) Material Access, (3) Skills Access, (4) Usage Access. This makes an important distinction between a digital divide which exists on the basis of uneven material access to technology, a digital divide based on uneven motivation to use technology, and a digital divide based on uneven distribution of technological skills and ability to make use of technology.

In Western countries today, access to the internet, and use of technology in general is extremely high. In European countries more than 82.5% of the population uses the internet, and 86.5% of households have internet access (69). However, these numbers fail to capture a specific aspect of the digital divide: that which exists in the elderly population in Western countries. Statistics examining the use of, and access to, the internet collect less data from older participants, due to practical limitations, and often apply an upper age limit to their sample (35). This results in data which represents access and use of technology in the general adult population but fails to capture the significant gap in access among the elderly. Studies which examined the difference in technology access and use in the elderly have found that age significantly predicts not only lower access to technology, but also within technology users, less frequent and varied usage (35, 36). This results in a troubling conclusion: not only does the elderly population in Western countries have less access to technology than younger adults, but even those with access have less digital skills, and make more limited use of the technology they do have. This conclusion mirrors results from studies on digital literacy which have found that the elderly often have lower levels of skilled, competent use of technology in their daily lives (70, 71).

There are therefore several reasons for the existence of the so-called gray divide in elderly populations. Although fundamental access to technology may be a problem among some groups, especially those in poorer communities, rates of access to internet is generally quite high, especially in Western countries, and studies have shown that cost or ability to access technology only play a small role in the reason for lack of usage in older individuals (35). Instead, research suggests that the main determinants of this divide are low motivational access, and a general skills deficit (35). A recent study showed that elderly individuals who reported disliking technology mainly attributed this to the belief that it was inconvenient, or that the costs outweighed the benefits (72) The task of closing the digital divide therefore becomes an issue of not only improving elderly access to technology, and offering skills training so they can develop digital skills, but also implementing programs to increase the elderly population's motivation to use technology, and better understand the benefits it can offer. In the case of a lack of motivational access, community-based interventions may be especially beneficial, as they would allow for widespread targeting of the elderly, with the aim of encouraging transfer of motivation within the community as more individuals adopted technology usage.

The problem of the digital divide among the elderly is not new and has been a point of increasing scrutiny as technology has become a larger part of day-to-day life. However, while some studies and programs have attempted to explore possible solutions, little headway has been made on a large scale (73–75). Many studies on the topic of technology usage in the elderly focus on the design of technology and software which the elderly are more easily able to use, which has resulted in a variety of hardware and software design suggestions to tailor technology to the needs of elderly users (76–78). This research has shown that the elderly are more likely to own outdated technology than their younger counterparts, and can benefit from the design of simple user interfaces, and cost-friendly technology alternatives (79, 80). While this is a very important step which will lay the basis for how technology can be used by the elderly, focusing on community wide programs to improve digital access, motivation, and skills should be the next focus. The COVID-19 pandemic has had a huge impact on the global community, and the long-term side-effects are likely to be felt for years to come. This pandemic has also shifted the way individuals are using technology and has highlighted the importance of closing the digital divide amongst the elderly, to try and minimize the negative effects this crisis will have on an already highly affected portion of the population.

MITIGATING THE EFFECTS OF THE DIGITAL DIVIDE

While the digital divide in the elderly population is certainly not a new problem, the COVID-19 pandemic has made it clear that some immediate action needs to be taken to address it. In the short-term, there is a need to ensure that digital solutions to lockdown problems are also accessible to older populations. As of 2015, about 8.5% of the world population was aged 65 or older, and this number is growing every year (81). This is not a small group of people, and during the COVID-19 pandemic it is essential that society remains aware of the challenges they are facing and takes measures to mitigate them. Encouraging the use of digital solutions in elderly groups is necessary, and governments and care homes should take measures to ensure the elderly population is aware of the resources available online during this pandemic. Raising awareness of the resources which can be accessed and making them available to less technologically savvy older individuals could have large benefits. Online socializing events catering to older individuals would allow for social contact, without any risks of COVID-19 infection. The introduction of online exercise programs geared toward homebound older individuals could offer simple workout routines to reduce the physical risks of decreased exercise. While short-term measures are unlikely to reach all older individuals, especially those with minimal material access to technology, they could help maximize the usefulness of digital tools in older individuals without current knowledge of their availability.

While the short-term goals of tackling the digital divide should focus on minimizing the harmful effects of the COVID-19 pandemic, the long-term goals should focus on taking meaningful steps to close the digital divide between older and younger populations. Governments should be taking steps to put in place programs which increase access to technology and offer older individuals the opportunity to learn how to use them. Care homes and community centers should also take the opportunity to implement digital literacy programs for older individuals. These measures will need to take into account the differences in reasons for the digital divide which exist across various socio-economic and gender groups. Older individuals in poorer communities may face a larger problem from a lack of material access to technology, and in those communities an initial focus supporting the purchase and upkeep of technological resources for elderly groups may be required. However, in wealthier communities, the problem is more likely to rest on a lack of motivation to use technology and a lack of digital skills. Therefore, initiatives targeting those communities will more likely need to start with programs aimed at increasing motivation for technology use, and digital skills training. Differences in education level and literacy levels in the general community should also be taken into account to ensure that the correct programs can be implemented to target the underlying reasons for the digital divide.

Prior studies have shown that digital literacy programs for older individuals can be very effective and have long-term effects on their digital skills (74, 82). Furthermore, they have shown that programs and applications developed specifically for the elderly can result in a significant improvement in confidence and interest in using technology (83). Most of these programs involved digital skills training, which in turn resulted in increased self-efficacy and motivation to continue using technology. Research on the development and implementation of digital literacy training programs for the elderly is not lacking, merely the motivation to implement these programs on a large scale. Studies show that perceived ease of use, and perceived usefulness are both important aspects predicting use of technology among older populations (84). Both of these factors are can be targeted by information campaigns and community-based programs to help the elderly understand how technology can help them in their day-to-day lives. Increasing affordable access to technology, motivating usage, and improving overall digital skills must all form part of a complete campaign to decrease the uneven usage of technology. Given the current display of the harmful effects of the digital divide, and the fact that reliance on the internet, and technology in general, is likely to increase in the coming years, it is overdue, but more necessary than ever to take action and start to make changes that will contribute to the closing of the digital divide.

CONCLUSION

As the COVID-19 pandemic has progressed, the unforeseen side-effects have started to make themselves known. As lockdowns across the world change the day-to-day life of billions of people, the world has had to adapt to the changes. The shift to a focus on digital tools has been successful in minimizing many of the problems faced during the pandemic, and many individuals have continued to socialize, study, work and access healthcare via digital tools. However, the elderly population, who have historically faced a large inequality in access to, and ability to make use of technology, has not seen the same benefits as many other younger groups. The elderly population has been hit with some of the worst effects of the pandemic, with harsher lockdown measures, and increased risks of mental and physical health problems, and the digital divide has seen that the effects of these measures have not been minimized. There is a definite need for action, both in the short and long-term to minimize the negative effects the digital divide has during this pandemic, and to act to close the divide in the long term. Action by governments to increase access to technology and implement digital literacy programs in elderly populations is absolutely necessary, especially going forward into an increasingly digital future. While actions now many not be able to completely shield the elderly from the negative effects of the pandemic, they could minimize them, and ensure that going forward this issue is given the attention and resources it needs to finally close the age based digital divide.

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.

AUTHOR CONTRIBUTIONS

GM wrote, reviewed, and revised the manuscript.

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Psychological Distress After Covid-19 Recovery: Reciprocal Effects With Temperament and Emotional Dysregulation. An Exploratory Study of Patients Over 60 Years of Age Assessed in a Post-acute Care Service

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To study the long-term psychological effects of Covid-19 disease, we recruited 61 patients older than 60 years of age and administered the Kessler questionnaire K10 to assess psychological distress and classify them according to mental health risk groups. Patients' affective temperaments were assessed with the 39-item form of the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego (TEMPS-A-39) and emotional dysregulation with the Difficulties in Emotion Regulation Scale (DERS). Patients were divided in two samples according to their scores on the K10, i.e., a high likelihood of psychological distress group ($N = 18$) and a low likelihood of psychological distress group ($N = 43$). The two groups differed on their gender composition, in that more women ($N = 11$) were in the former and more men in the latter ($N = 29$) ($\chi^2 = 4.28$; $p = 0.039$). The high likelihood of psychological distress group scored higher on the Cyclothymic (3.39 ± 3.45 vs. 0.93 ± 1.08, $p < 0.001$) and the Depressive (2.28 ± 2.82 vs. 0.65 ± 1.09, $p = 0.01$) affective temperaments of the TEMPS and on the lack of Impulse control (12.67 ± 4.04 vs. 9.63 ± 3.14, $p = 0.003$) and lack of Clarity (15.00 ± 5.56 vs. 9.85 ± 4.67, $p = 0.004$) scales of the DERS. Our results show that having had Covid-19 may be related with high likelihood for psychological distress in advanced-age people and this may in turn be associated with impaired emotional regulation and higher scores on depressive and cyclothymic temperaments.

Keywords: COVID-19, nasopharyngeal swab, nasal swab, emotional dysregulation, affective temperaments, psychological distress, aging

INTRODUCTION

The Covid-19 outbreak and the subsequent lockdown have caused significant distress in the general population in many countries and resulted in various psychological problems in the caregivers (1), healthcare workers (2), and the patients themselves (3–5). Lockdown-related loneliness and isolation may play a part in this distress (6). Personal factors may affect the subsequent development of psychological problems, with people being classified according to their constitution and coping abilities into high-, medium-, and low-risk for the development of psychological symptoms, mainly anxiety, and depression (6). Depressive, anxiety, and sleep symptoms develop in patients with Covid-19 while in the hospital (4), but anxiety may persist after recovery (7).

The response to the Covid-19 pandemic could prove to be analogous to the response to natural disasters or other similar catastrophic events impinging upon a population (8), and may cause permanent distress in the affected population (9). Psychological/psychiatric consequences of disasters may persist as long as 12 years in one out of six members of the affected population (10). The psychological response to the Covid-19 pandemic has been promptly reported; in hardly-hit populations, it is similar to post-traumatic stress disorder (PTSD) symptomatology in the population (11). Similarly, patients who actually developed Covid-19 and survived, are likely to develop PTSD symptomatology (12). Patients with Covid-19 reported many PTSD and depressive symptoms (13). A meta-analysis reported depressed mood, insomnia, anxiety, irritability, memory impairment, fatigue, and traumatic memories as the most frequent complaints in the post-illness stage (14).

While physical symptoms may survive by 3 months the acute Covid-19 phase (15), there is currently a dearth of reports on the long-term psychological response of patients who recovered from Covid-19. Since individual factors determine individual patients' likelihood to develop psychological symptoms (6) and since these affect how each patient deals with life, they may affect coping abilities, and styles and the response to disease. Temperament refers to early-appearing individual differences in emotional reactivity; it is stable across the lifespan and has strong biological underpinnings. It consists of five subtypes, i.e., depressive (dysthymic), cyclothymic, hyperthymic, irritable, and anxious, and is important in determining individual responses to environmental challenge (16). Affective temperament could influence emotion-regulation mechanisms, with particular evidence for the cyclothymic temperament, which has been associated to emotional dysregulation (17). Emotion dysregulation is defined by difficulties in several areas, including the ability to understand and accept emotional experiences, modulate their intensity or duration, and manage emotional reactions in order to meet situational demands and avoid maladaptive behaviors, such as impulsive acts. Emotional dysregulation has been shown to moderate psychological distress (18, 19). Given the intercorrelations between these three constructs, we aimed to assess them through appropriate self-rated instruments in a population of patients who had recovered from Covid-19 and tested negative on two consecutive nasal and/or nasopharyngeal swabs. Our intention was to obtain data that could constitute positive or negative predictors of future psychiatric disorder.

MATERIALS AND METHODS

Patient Sample

Consecutive patients aged >60 years who had contracted Covid-19 infection and recovered were included in this study. Eligible patients were sought from those referring to the multidisciplinary post-acute care service where multiple specialists participate and that has been established at the Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore of Rome (Rome, Italy). (20). Assessment was comprehensive and included medical and psychiatric history, physical examination, and psychiatric status. Clinical characteristics, including clinical and drug treatment history, and other clinical measures, were inserted in a database. All patients were hospitalized at the Fondazione Policlinico Universitario Agostino Gemelli IRCCS and were referred to our post-acute service (Gemelli Against COVID-19 Post-Acute Care Service). Patients, after their discharge had to test negative on two consecutive nasal and/or nasopharyngeal swabs and be afebrile. Patients ($N = 61$) were invited to complete the self-rating questionnaires; they all volunteered. Those unable to provide informed consent or were not sufficiently fluent in Italian to complete the questionnaires were excluded ($N = 2$).

Psychometric Tools

To assess our sample, we used the following:

Difficulties in Emotional Regulation Scale (DERS)

To assess deficits in emotion regulation we used the Difficulties in Emotion Regulation Scale (DERS) (21), a 36-item self-report measure assessing typical levels of emotion dysregulation. Participants are required to rate each item on a 5-point Likert-type scale (1=almost never; 2=sometimes; 3=about half the time; 4=most of the time; and 5=almost always). Items 1, 2, 6, 7, 8, 10, 17, 20, 22, 24, and 34 are scored reverse. The validated Italian version was used (22, 23). The items are distributed on six dimensions: (1) Non-acceptance of emotional responses (NONACCEPT), items 11, 12, 21, 23, 25, and 29; (2) Difficulty engaging in Goal-directed behavior (GOALS), items 13, 18, 20, 26, and 33; (3) Impulse control difficulties (IMPULSE), items 3, 14, 19, 24, 27, and 32; (4) Lack of emotional awareness (AWARENESS), items 2, 6, 8, 10, 17, and 34 (all reverse); (5) Limited access to emotion regulation strategies (STRATEGIES): 15, 16, 22, 28, 30, 31, 35, and 36; and (6) Lack of emotional clarity (CLARITY): 1, 4, 5, 7, and 9. The total score is the sum of all items. Higher scores indicate greater difficulties with regulating emotions. The scale has shown convergent validity with other established measures of emotion dysregulation and fair test-retest reliability, internal consistency, and adequate predictive validity of several behavioral outcomes associated with emotion dysregulation (24, 25). It has no predefined cutoff; each cutoff is tailored to the investigated condition.

TEMPS-A-39

We used the validated Italian translation of the shorter, 39-item form of the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego (TEMPS-A-39) (26). This self-rated questionnaire investigates the prevalence of one of the above-mentioned five affective temperaments in an individual; responses in the short version are not as in the full, 110-item version as true or false (27), but rather Yes or No. This instrument has 39 statements with the first 12 referring to the cyclothymic temperament (C), items 13–19 to the depressive (dysthymic) temperament (D), items 20–28 to irritable temperament (I), 29–36 to hyperthymic (H), and 37–39 to the anxious temperament (A). The score on each temperament is the sum of the Yes responses. The tool has obtained evidence of diachronic stability in its various translations (test-retest coefficient range $\rho = 0.594$–0.84) and good internal consistency ($\alpha = 0.682$–0.893) (28, 29). The 39-item version has consistently shown a five-factor solution as the best fit (30).

K10

We used the K10 [Kessler 10 Psychological Distress Scale; (31)] to assess psychological distress in our post-COVID-19 population. K10, a 10-item questionnaire, provides a global measure of distress experienced in the last 4 weeks. We used the validated Italian translation (32). Each item is scored 1–5 on a Likert scale, where (1) is "None of the time," (2) "A little of the time," (3) "Some of the time," (4) "Most of the time," and (5) "All of the time;" items 3 and 6 are skipped and rated 1 if the preceding items were scored "None of the time." Low scores indicate low levels of psychological distress whereas high scores indicate high levels of psychological distress. Consistently with previous validation studies (33, 34), we adopted the cut-off score of >19 to detect the likelihood of presence of psychological distress. The 20 cutoff combined good sensitivity (0.66) and excellent specificity (0.92) in Andrews and Slade (33).

Study Design

This was a cross-sectional study. After their second consecutive negative nasal or nasopharyngeal swab, patients were invited to complete the three self-rated questionnaires. The testing occurred at the waiting room of the Geriatrics Service of the Columbus post-Covid-Hospital. Specifically-trained psychiatrists were available for psychometric tool application and helped out patients to efficiently complete the questionnaires.

After completing assessments, patients underwent thorough interviews to determine whether they should continue on being seen at the Psychiatric outpatient clinic of the Department of Psychiatry at the the Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore of Rome (Rome, Italy). Special emphasis was placed on their perceived sense of distress and loneliness. Further treatment was agreed upon with treating clinicians according to patient preference.

Ethics

Each patient was provided with detailed information regarding the purpose and design of the study and was asked to provide written informed consent to participate. We endorsed in this study the Principles of Human Rights, as adopted by the World Medical Association at the 18th WMA General Assembly, Helsinki, Finland, June 1964 and subsequently amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013. The study protocol was approved by the Ethics Committee of the Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore of Rome (Rome, Italy). Written informed consent has been obtained from all participants.

Statistical Analysis

First, we subdivided our sample into two groups according to K10 cutoffs in: (1) subjects without likelihood of psychological distress (total K10 score, <20); (2) subjects with likelihood of psychological distress (total K10 score at least 20). We compared the two groups on socio-demographic and clinical characteristics on the basis of the chi-squared test (χ^2) for nominal variables and one-way analysis of variance (ANOVA1way).

For the aims of this study, we focused on the distribution patterns of temperament and emotion dysregulation subscales in patents with and without psychological distress. Therefore, we conducted a series of one-way analyses of covariance (ANCOVA), to compare means among groups, setting temperament and emotion dysregulation subscales as dependent variables. Age, Sex, Living alone, Length of hospitalization, Admission to ICU, Use of Immunomodulating therapies, and Post-hospitalization interval until the assessment were inserted as covariates to control the statistical model for these variables. We used the statistical routines of SPSS Statistics 24.0 for Windows (IBMCo., Armonk, NewYork, United States, 2016).

Results

In our sample ($n = 61$), 18 subjects (29.51%) reported psychological distress. Sociodemographic and clinical characteristics are summarized in **Table 1**. The only significant difference was that there were more women than men in the group with likelihood of psychological distress ($N = 11$, 61.11% women vs. $N = 7$, 38.89% men) and less women than men in the group without likelihood of psychological distress ($N = 14$, 32.56% women vs. $N = 29$, 67.44% men) ($\chi^2 = 4.28$; $p = 0.039$). The two groups did not differ in other sociodemographic characteristics as for, living alone, lifetime history of psychiatric disorders, and COVID-19 related clinical characteristic (Length of hospitalization, Admission to Intensive care unit, Use of Immunomodulating therapies, and Post-hospitalization interval until the assessment).

A series of ANCOVAs showed that the group with psychological distress reported significantly higher scores on the cyclothymic ($p < 0.001$) and depressive temperaments ($p = 0.01$) than the one without psychological distress (**Table 2**). The high likelihood for psychological distress group also reported more impulsivity ($p = 0.003$) and lack of emotional clarity ($p = 0.004$) than individuals without likelihood of psychological distress (**Table 2**).

TABLE 1 | Sociodemographic and clinical characteristics.

Characteristics	No psychological distress (K10<20)	Psychological distress (K10≥20)	χ^2 or F	df	*p*
Overall sample, *n* (%)	43 (70.49)	18 (29.51)			
Females, *n* (%)	14 (32.56)	11 (61.11)	4.28	1	**0.039***
Age (Y), mean ± SD	67.98 ± 6.52	65.61 ± 6.25	1.71	1	0.196
Educational level (Y), mean ± SD	14.40 ± 4.60	11.64 ± 4.80	3.51	1	0.067
Occupational status, *n* (%)			5.31	2	0.070
Employed	15 (34.9)	7 (38.9)			
Unemployed	0 (0.0)	2 (11.1)			
Retired	28 (65.1)	9 (50.0)			
Marital status, *n* (%)			2.74	1	0.098
Married/living with partner	31 (72.1)	9 (50.0)			
Unmarried, living alone	12 (27.9)	9 (50.0)			
Ling alone, *n* (%)	8 (18.6)	3 (16.7)	0.03	1	0.85
Lifetime history of psychiatric disorders, *n* (%)	9 (20.9)	8 (44.4)	3.49	1	0.062
Length of hospitalization (Days), mean ± SD	15.36 (9.67)	19.50 (12.35)	1.92		0.71
Admission to ICU, *n* (%)	5 (11.6)	4 (22.2)	1.13	1	0.28
Use of Immunomodulating therapies, *n* (%)	15 (37.5)	8 (57.1)	1.63	1	0.20
Post-hospitalization interval (Days), mean ± SD	40.69 (18.87)	40.55 (18.67)	0.001	1	0.97

**$p < 0.05$; Significant results in bold characters. df, degrees of freedom; F, value of variance of the group means; M, mean; p, statistical significance; SD, standard deviation; Y, years; χ^2, chi-squared test, ICU, intensive care unit.*

TABLE 2 | Psychometric characteristics.

Characteristics	No psychological distress [N = 43]	Psychological distress [N = 18]	χ^2 or F	df	*p*
Temperament evaluation of Memphis, Pisa, Paris and San Diego autoquestionnaire (TEMPS-A)					
TEMPS-A cyclothymic, $\bar{x}$ ± SD	0.93 ± 1.08	3.39 ± 3.45	15.29	1	**<0.001*****
TEMPS-A depressive, $\bar{x}$ ± SD	0.65 ± 1.09	2.28 ± 2.82	6.83	1	**0.01***
TEMPS-A irritable, $\bar{x}$ ± SD	0.61 ± 1.02	1.17 ± 1.34	2.74	1	0.10
TEMPS-A hyperthymic, $\bar{x}$ ± SD	4.54 ± 1.96	4.61 ± 2.79	0.21	1	0.64
TEMPS-A anxious, $\bar{x}$ ± SD	0.93 ± 0.90	1.22 ± 0.88	0.003	1	0.94
Difficulties in emotion regulation scale (DERS)					
DERS Non-acceptance, $\bar{x}$ ± SD	11.27 ± 5.08	12.78 ± 5.33	0.76	1	0.38
DERS Goals, $\bar{x}$ ± SD	11.05 ± 4.25	12.28 ± 3.95	0.12	1	0.72
DERS Impulse, $\bar{x}$ ± SD	9.63 ± 3.14	12.67 ± 4.04	9.79	1	**0.003****
DERS Awareness, $\bar{x}$ ± SD	16.15 ± 5.41	16.28 ± 6.56	0.00	1	0.98
DERS Strategies, $\bar{x}$ ± SD	13.73 ± 4.49	15.61 ± 5.36	0.90	1	0.34
DERS Clarity, $\bar{x}$ ± SD	9.85 ± 4.67	15.00 ± 5.56	9.23	1	**0.004****

**$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. Significant results in bold characters. Abbreviations: DERS, Difficulties in Emotion Regulation Scale; df, degrees of freedom; F, value of variance of the group means; p, statistical significance; SD, standard deviation; TEMPS-A, Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire; $\bar{x}$, mean; χ^2, chi-squared test. Model controlled for Age, Sex, Living alone, Length of hospitalization, Admission to ICU, Use of Immunomodulating therapies, and Post-hospitalization interval.*

Discussion

In this study we found people who fully recovered from Covid-19 and who display at least two consecutive negative nasal/nasopharyngeal swabs to show considerably more psychological distress, as measured through the K10, than the Italian and worldwide general population (32, 35). We also found Post-Covid-19 women to be more vulnerable to psychological distress than their male counterparts. Patients who recovered from Covid-19 and who reported psychological distress presented with more occurrences of cyclothymic and depressive affective temperaments and scored higher on the DERS scale dimensions of lack of impulse control and lack of clarity.

In our study we found 29.51% of our sample to have high psychological distress. This prevalence is high for an advanced-age population (35). A previous study found only 1% of elderly Canadians to score above 15 on the K10, with an optimum cutoff for mild depressive symptoms to be in the 20–23 range after receiver operator characteristics (ROC) analysis (36). The fact that women are more vulnerable to psychological distress is in line with what is found in literature for both Covid-19 and other patient populations. Women generally report higher degrees of psychological distress (37, 38). This holds true also for the Covid-19 threat in the general population (39–41).

Our study showed cyclothymic and depressive temperaments to constitute predictors of psychological distress in patients who recovered from Covid-19. Depressive temperament is characterized by pessimism, high self-criticism, and affective dependency, whereas cyclothymic temperament is marked by sudden shifts in mood, energy, behavior, and thinking. Our results match those of a recent study investigating the psychological distress perceived by the Italian general population during the early phase of the COVID-19 pandemic (41). This study found cyclothymic, depressive, and anxious temperaments, along with adult attachment styles, to be specific risk factors for psychological distress. In particular, they found the insecure-anxious attachment dimension "Need for approval" of the Attachment Style Questionnaire (ASQ) to constitute a risk factor, while the ASQ "Confidence" and "Discomfort with closeness" dimensions of the secure and avoidant attachment styles to be protective from psychological distress. They hypothesized that cyclothymic/depressive individuals would be more likely to perceive the COVID-19 outbreak and the related social isolation as distressful and to experience increased negative affect in response to the pandemic (41). Our results suggest that this can be extended to patients who recovered from Covid-19. Data match those of another study conducted before Covid-19, which showed that students with high distress scored higher on the cyclothymic, depressive, irritable, and anxious TEMPS temperaments, compared to those with low psychological distress (19); in this study the authors assessed psychological distress trough the 12-item General Health Questionnaire (GHQ-12), in contrast to us, who used the K10. However, the two instruments have shown similar psychometric properties, internal consistency, and convergent validity (42), although the K10 performed slightly better than the GHQ-12 in one study (43) and identified more cases in another (44).

Our study highlights that emotional dysregulation could mediate the development of psychological distress in patients who recovered from Covid-19. Accordingly, deficits in affect regulation have also been observed in healthy individuals at risk for psychopathology and could influence the development of psychiatric symptoms in the context of stressful events (45). Nevertheless, the specific relationship between psychological distress and emotional dysregulation has been little investigated in literature. Psychological distress was shown to correlate with all DERS dimensions, save for Awareness, in a sample of university students of medium proportions (46) and with the Strategies, Impulse, and Clarity subscales in a small sample of patients with alcohol use disorder (47). Nevertheless, these data are not fully comparable with ours, since despite using the DERS, both these studies differed in the instrument used to assess psychological distress and none used the K10.

Our findings indicate that, among DERS dimensions, the lack of impulse control and clarity, along with with depressive and cyclothymic temperaments were associated with post Covid-19–related psychological distress. Interestingly, the lack of impulse control has been linked with the instability of cyclothymia (48). This is probably caused by reduced impulse control when mood is high and heightened reactions to experiences that are perceived as pleasurable. The lack of clarity about the nature of one's own emotions could also be linked with the tendency toward shifts in mood and energy. Furthermore, the cognitive uncertainty characterizing depressive traits could also include difficulties in recognizing emotional responses. In agreement with this, a specific correlation was found between the depressive and cyclothymic TEMPS temperament and DERS Impulse and Clarity scores (49).

In our advanced-age patients with past Covid-19 infection, who successfully recovered and were asymptomatic, we found no effect of loneliness on psychological distress, as measured through their marital/partnership status. This is not consistent with the finding that living alone was an independent predictor of psychological distress in an aged sample of healthy individuals (50). This result could be potentially explained by the effect of Covid-19–related forced isolation, which might overcome the effect of loneliness on psychological distress.

Taken together our data suggest that the past Covid-19 experience has enduring effects that affect psychological well-being and psychological distress; in turn, this exposes the individual to the likelihood of mental disease, especially anxiety and depressive disorders (31, 34, 36). An assessment of post-disaster disorders, like posttraumatic stress disorder, is mandatory. In fact, this disorder shares many clinical features with the above disorders, and patients with it are likely to score high on the K10 (51). The prompt response of mental health services to these new requirements could avoid the development of full-blown psychiatric disorders and ease public burden. Services could provide programs similar to those enforced or proposed for other PTSD-stricken populations (52, 53).

Limitations

This study has several limitations. First, its cross-sectional design prevents us from drawing conclusions on the causal relationships of the post-Covid-19 state and temperament, psychological distress, and difficulties in emotional regulation. Second, the small sample size may have limited the power of the study; hence, these findings should be intended as exploratory. The small convenience sample was due to the very specific population we wanted to assess (Consecutive patients aged >60 years who had contracted Covid-19 infection and recovered). Future studies with larger sample size are needed to confirm our initial speculations. Third, we specifically aimed to investigate whether Covid-19 has a long-term impact on psychological health in elderly people, and obtained evidence that it increases the likelihood of belonging to a high psychological distress group. These observations should be replicated in post-Covid-19 patients of other age ranges as well. Fourth, we included only patients who were hospitalized at the Fondazione Policlinico Universitario Agostino Gemelli IRCCS in Rome, Italy, and who were referred to the multi-specialized Gemelli Against COVID-19 Post-Acute Care. There are very few hospitals in Italy offering this type of service, preventing us from currently generalizing our results to other populations. Finally, the lack of information on previous history of personal distress is another limitation of our study. This is a potential shortcoming because past adverse events are specific risk factors for psychiatric symptoms (54, 55) and may increase vulnerability to the stressful effect of COVID-19 outbreak. Despite limitations, this is one of the few studies presenting data on patients recovered from the Covid-19 illness, assessing in person patients and finding a specific link between psychological distress and personality characteristics.

Conclusions

In this study we tested psychological constructs like psychological distress, difficulty with regulating emotions, and affective temperament dimensions in people who recovered from Covid-19 after their nasal or nasopharyngeal swabs were negative at least twice. We found the high likelihood for psychological distress group to score higher on the depressive (dysthymic) and cyclothymic affective temperaments and on the Impulsivity and (lack of) Clarity scales of the Difficulties in Emotion Regulation Scale. This population is worth investigating with other measures as well, using greater samples and longitudinal designs.

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 Ethics Committee of the Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore of Rome. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DJ, GDK, GG, MMol, MMod, SM, BT, AC, FL, and GS wrote the paper. All authors read and approved the final draft.

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Delirium: Clinical Presentation and Outcomes in Older COVID-19 Patients

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The aim of the study is to describe the clinical characteristics and outcomes of a series of older patients consecutively admitted into a non-ICU ward due to SARS-CoV-2 infection (14, males 11), developing delirium. Hypokinetic delirium with lethargy and confusion was observed in 43% of cases (6/14 patients). A total of eight patients exhibited hyperkinetic delirium and 50% of these patients (4/8) died. The overall mortality rate was 71% (10/14 patients). Among the four survivors we observed two different clinical patterns: two patients exhibited dementia and no ARDS (acute respiratory distress syndrome), while the remaining two patients exhibited ARDS and no dementia. The observed different clinical patterns of delirium (hypokinetic delirium; hyperkinetic delirium with or without dementia; hyperkinetic delirium with or without ARDS) identified patients with different prognosis: we believe these observations may have an impact on the management of older subjects with delirium due to COVID-19.

Keywords: COVID 19, delirium, elderly, frailty, mortality

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INTRODUCTION

Although the most frequent and life-threatening complications of coronavirus disease 19 (COVID-19) are respiratory, there are increasing reports of neurological and psychiatric involvement (1).

It is known that delirium can be the symptom of the presentation of many diseases, particularly in frail and older patients, and is recognized as an independent risk factor for mortality (2). The overall prevalence of delirium in the hospital setting is about 14–24%; its prevalence is higher, about 30%, in emergency, surgical, or medical wards (3, 4). To date, the clinical presentation of delirium in older patients with COVID-19 infection have rarely been described; in fact, although some studies focus on epidemiological data and outcome, few studies analyze the clinical aspects of delirium in COVID-19 (5–8). The aim of this study is to describe clinical characteristics and outcomes of a series of elderly patients presenting delirium as the main symptom of COVID-19.

MATERIALS AND METHODS

The study was carried out in the COVID ward in an Acute Care Hospital located in Brescia, one of the hardest hit cities by SARS-CoV-2 infection in northern Italy (9). We collected the characteristics of 14 older patients (age range 70–90, mean age 78.2; 11 males) consecutively admitted developing prevalent or incident delirium (respectively 10 and 4 cases). All the patients were admitted with a diagnosis of COVID-19, confirmed by a real-time reverse-transcriptase-polymerase chain reaction (rRT-PCR); three patients came from nursing homes, the remainder from home.

Medical information collected were age, sex, PaO_2/FiO_2, chest x-ray or CT, comorbidities [ischemic heart disease, chronic obstructive pulmonary disease (COPD), hypertension, diabetes, malignancies, neurodegenerative diseases], blood tests [hemoglobin, platelets count, neutrophils, lymphocytes, C-reactive protein (CRP), urea, and creatinine], and oxygen therapy (i.e., from nasal cannula to high flow cannula oxygen therapy to non-invasive ventilation). To assess the severity of COVID-19 pneumonia the SIAARTI criteria were followed, i.e., *mild ARDS* (acute respiratory distress syndrome): PaO_2/FiO ratio 201–300; *moderate ARDS*: 101–200, and *severe ARDS*: ≤ 100 (10). The diagnosis of dementia was made on the basis of the data collected from clinical records, while the severity of dementia was assessed by CDR (11) and functional status by the Barthel Index (12). CDR was estimated based on information collected from family members and the records of patients. Delirium was detected through 4At (assessment test for delirium and cognitive impairment) (13).

Clinical criteria were used to characterize delirium subtypes: hypoactive or hyperactive. The presence of a disturbance of consciousness was retrospectively defined by altered arousal.

RESULTS

Hyperactive delirium with aggression and agitation was observed in eight patients, while the remaining six patients exhibited hypoactive delirium with lethargy and confusion.

Moreover, dementia was diagnosed in six out of 14 patients; among these, four developed hypokinetic delirium, while the remaining two developed hyperkinetic delirium. Patients without dementia were younger, with a mean age of 74.1 years (see **Table 1**).

The drugs used to treat patients with hyperkinetic delirium were: lorazepam (2 cases), diazepam (1 cases), quetiapine (3 cases), and haloperidol (3 cases). Two patients with hypokinetic prevalent delirium were treated before hospitalization with brotizolam (1 case) and trazodone (1 case).

Two of the patients were hospitalized for stage III pneumonia (PaO_2/FiO_2 ratio >300), eight patients were hospitalized for stage IV pneumonia-mild ARDS ($200<PaO_2/FiO_2 \ <3008$), and four patients were hospitalized with stage IV pneumonia-moderate ARDS ($100<PaO_2/FiO_2<200$).

Upon admission, the patients presented the following symptoms: fever (7 cases), dyspnea (12 cases), cough (4 cases), fall and syncope (one case).

Almost all the patients (12/14) had a respiratory rate greater than 19.

The overall mortality rate was 71% (10/14 patients). All 6 of the patients exhibiting hypokinetic delirium and the 50% of patients (4/8) with hyperkinetic delirium died. Patients with hypokinetic delirium exhibited dementia and mild ARDS in four cases and no dementia and moderate ARDS in two cases.

Among the four survivors we observed two different clinical patterns: two patients exhibited dementia and no ARDS, while the remaining two patients exhibited ARDS and no dementia.

All patients living in a nursing home developed hypokinetic delirium and died.

A chest CT scan was taken for 11 of the patients: in two cases the lung involvement was less than 25%, in two cases it was from 50 to 75%, and in seven cases it was greater than 75%. The two cases with lower lung involvement survived; one patient with intermediate (50–75%) and one with greater involvement (>75%) also survived.

Each patient showed a high number of comorbidities: nine patients were affected by cardiovascular diseases (mainly coronary heart disease, atrial fibrillation, and heart failure), 12 by hypertension, and eight by diabetes. In particular, only four patients had no more than two comorbid conditions. In detail: survivors with hyperkinetic delirium had two or three comorbidities; deceased patients with hyperkinetic delirium had three or more comorbidities; deceased patients with hypokinetic delirium had two comorbidities in two cases and three or more in four cases.

DISCUSSION

With increasing frequency, delirium is reported as a symptom of the presentation of COVID-19 in older patients, although clinical aspects are rarely characterized (14). In a French series of elderly patients with COVID-19, delirium was present in 26.7% of patients, in two thirds of the cases in the hypokinetic form (15). In a series of hospitalized older patients with COVID-19 in the UK, delirium was observed in 25.2% of the sample (16). In older patients with dementia, delirium was a clinical manifestation of COVID-19 in 67% of cases, in 75% of these cases in the hypokinetic form (17). Mortality rates in these case series related to COVID-19 disease are still inconclusive and so comparison with other literature is uncertain.

In our patients with delirium, mortality was higher (71%) than previously reported for cases of hospitalized older people with delirium (ranging from 9 to 25%) (4). All subjects who developed hypokinetic delirium died. According to the literature, this form of delirium is associated with worse outcomes, particularly among patients affected by dementia (18). Multimorbidity is a condition associated with higher mortality, especially among patients who developed hypokinetic delirium: thus, hypokinetic delirium needs to be considered a marker of poor prognosis even in previously fit patients (3).

The onset of delirium is due to a complex interaction between the baseline vulnerability of the patient or predisposing factors and noxious insults or precipitating factors; recent observations lead us to believe that frailty and immunosenescence constitute factors that explain the excess mortality in elderly subjects with COVID-19 (19).

In our study, hyperkinetic delirium in cognitively unimpaired patients with mild ARDS had a better prognostic value than hypokinetic delirium in those with the same lung impairment.

TABLE 1 | Characteristics and outcomes of 14 older patients with confirmed diagnosis of COVID-19 and delirium.

Age range	From	CDR/Type of dementia	BoA	Comorbidities	Symptoms and signs	CT scan	PaO_2/FiO_2	Delirium	Drugs	Outcomes
90–94	NH	2 AD+VD	10	AF Lung cancer Previous venous thrombosis	Dyspnea RR 24	NA	245	Drowsiness (on admission)	–	Died (day 10)
80–84	NH	3 AD+VD	10	CHD Hypertension T2DM CKD Previous stroke Epilepsy	Fever Cough Dyspnea RR 36	NA	269	Drowsiness (on admission)	Trazodone (previous)	Died (day 12)
80–84	NH	4 AD	0	Hypertension UTI	Fever Dyspnea RR 36	NA	255	Drowsiness (on admission)	–	Died (day 5)
90–94	Home	3 AD+VD	0	HF CHD AF Previous stroke Gastritis	Fever Dyspnea Confused state RR 20	75%	261	Drowsiness (on admission)	Brotizolam (previous)	Died (day 2)
75–79	Home	0	100	T2DM Obesity	Fever Dyspnea Syncope RR 26	50–75%	148	Drowsiness (on admission)	None	Died (day 3)
75–79	Home	0	100	AF Hypertension T2DM	Cough Dyspnea RR 28	75%	136	Drowsiness (on admission)	None	Died (day 1)
70–74	Home	0	100	CHD Hypertension T2DM	Fever Dyspnea RR 20	75%	220	Agitation (day 2)	Quetiapine Lorazepam Haloperidol	Died (day 3)
70–74	Home	0	100	HF AF Hypertension T2DM	Fever Cough Dyspnea RR 17	75%	254	Agitation (day 2)	None	Died (day 5)
75–79	Home	0	100	Hypertension T2DM Peripheral artery disease	Cough Dyspnea RR 28	75%	260	Agitation (on admission)	Diazepam	Died (day 2)
70–74	Home	0	55	AF Hypertension T2DM Previous stroke Depression	Fever RR 16	75%	252	Agitation (on admission)	–	Died (day 10)
75–79	Home	2 AD+VD	40	AF Hypertension	Dyspnea RR 28	<25%	330	Agitation (day 2)	Haloperidol Quetiapine	Discharged (day 23)
85–89	Home	2 AD+VD	20	CHD Hypertension Gastritis	Confused state Falls RR 16	<25%	320	Agitation (on admission)	Citalopram, Haloperidol	Discharged (day 3)
70–74	Home	0	45	Hypertension T2DM	Fever Cough Dyspnea RR 22	75%	126	Agitation (on admission)	Quetiapine	Discharged (day 4)
75–79	Home	0	60	Hypertension PD Previous stroke	Dyspnea RR 20	50–75%	179	Agitation (day 2)	Lorazepam	Discharged (day 13)

NA, not available; AD, Alzheimer's disease; VD, vascular dementia; CDR, Clinical Dementia Rating Scale; BoA, Barthel Index score on admission; HF, heart failure; CHD, coronary heart disease; AF, atrial fibrillation; T2DM, type 2 diabetes mellitus; CKD, chronic kidney disease; PD, Parkinson disease; RR, respiratory rate; CT scan, visual quantitative evaluation of the acute lung inflammatory lesions involving each lobe.

Hyperkinetic delirium in patients with dementia was observed in non-ARDS pneumonia ($PaO_2/FiO_2 > 300$). Patients with hyperkinetic delirium who died had a higher noxious insult (i.e., $200 < PaO_2/FiO_2 < 300$) or dementia, and high level of comorbidities.

The high mortality rate of subjects developing delirium as an onset symptom of COVID-19, particularly in its hypokinetic form, could suggest brain involvement rather than the worsening effect of a pre-existing condition of frailty. Taking cognizance of the emergency due to the outbreak of COVID-19 and the consequent necessity of brief and easy-to-use tools and the involvement of non-expert doctors and nurses in COVID wards, to diagnose delirium we decided to use the 4AT test, a reliable tool designed for delirium detection in clinical practice (13).

Based on our observations, we hypothesize that delirium subtypes may be markers of biological severity of precipitating disease in COVID-19 patients. Specifically, patients suffering from a higher involvement of brain function and thus manifesting hypokinetic delirium, have a worse prognosis, while those who develop hyperkinetic delirium with a lower degree of dysregulation induced by the disease have a better chance of survival. Data on the ARDS stage confirm this interpretation since deceased patients with hypokinetic delirium and dementia were the most biologically compromised (with the most severe form of ARDS).

These different clinical patterns (hypokinetic delirium; hyperkinetic delirium with or without dementia; hyperkinetic delirium with or without ARDS) identify patients with different prognosis. Although the data were collected in a relatively limited number of cases, these observations may have an impact on the management of older subjects with delirium due to COVID-19.

In conclusion, our study indicates that delirium, particularly in the hypokinetic form, is related to a high risk of mortality in patients with COVID-19, especially in the presence of dementia. Therefore, a systematic recognition of this syndrome in COVID-19 patients is crucial for establishing a reliable prognosis.

DATA AVAILABILITY STATEMENT

All datasets presented in this study are included in the article/Supplementary Material.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico di Brescia. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

RR, FM, and GC contribute to evaluation of cases, data management and discussion. AB, LB, and MT reviewed and discussed the manuscript. AB and RR wrote the first draft. All authors carefully reviewed, discussed and contributed to various draft of the manuscript. All authors approved the final manuscript.

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HYPOTHESIS AND THEORY
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How Does SARS-CoV-2 Affect the Central Nervous System? A Working Hypothesis

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Interstitial pneumonia was the first manifestation to be recognized as caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); however, in just a few weeks, it became clear that the coronavirus disease-2019 (COVID-19) overrun tissues and more body organs than just the lungs, so much so that it could be considered a systemic pathology. Several studies reported the involvement of the conjunctiva, the gut, the heart and its pace, and vascular injuries such as thromboembolic complications and Kawasaki disease in children and toddlers were also described. More recently, it was reported that in a sample of 214 SARS-CoV-2 positive patients, 36.4% complained of neurological symptoms ranging from non-specific manifestations (dizziness, headache, and seizures), to more specific symptoms such hyposmia or hypogeusia, and stroke. Older individuals, especially males with comorbidities, appear to be at the highest risk of developing such severe complications related to the Central Nervous System (CNS) involvement. Neuropsychiatric manifestations in COVID-19 appear to develop in patients with and without pre-existing neurological disorders. Growing evidence suggests that SARS-CoV-2 binds to the human Angiotensin-Converting Enzyme 2 (ACE2) for the attachment and entrance inside host cells. By describing ACE2 and the whole Renin Angiotensin Aldosterone System (RAAS) we may better understand whether specific cell types may be affected by SARS-CoV-2 and whether their functioning can be disrupted in case of an infection. Since clear evidences of neurological interest have already been shown, by clarifying the topographical distribution and density of ACE2, we will be able to speculate how SARS-CoV-2 may affect the CNS and what is the pathogenetic mechanism by which it contributes to the specific clinical manifestations of the disease. Based on such evidences, we finally hypothesize the process of SARS-CoV-2 invasion of the CNS and provide a possible explanation for the onset or the exacerbation of some common neuropsychiatric disorders in the elderly including cognitive impairment and Alzheimer disease.

Keywords: COVID-19, SARS-CoV, RAAS, ACE2, Ang(1-7)/Mas, brain aging, neurodegenerative and psychiatric disorders abstract, Alzheimer disease

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BACKGROUND

A novel respiratory illness was identified in Wuhan, the capital and the most populous city in the province of Hubei, in Central China in December 2019 (1–3). After an initial outbreak of infection at Huanan seafood market, possibly due to close animal-human contact, a new disease, now called coronavirus disease-19 (COVID-19) very quickly disseminated within China (4, 5). The novel coronavirus, called severe acute respiratory syndrome coronavirus 2 (and abbreviated SARS-CoV-2), is a positive-sense single-stranded RNA coronavirus coming from a bat coronavirus which spilled over to infecting humans after contaminating an intermediate host, maybe a pangolin (6, 7), which shares the genetic characteristics of the severe acute respiratory syndrome coronavirus (SARS-CoV) family with the 79% of RNA overlapping (as both SARS-CoV, the virus from which the 2002-2003 outbreak originated, and SARS-CoV-2 are classified among the beta-coronavirus phylogeny). This virus was firstly identified in patients and was hypothesized to be the etiopathological agent of the respiratory illness (1, 5). However, compared to SARS-CoV, SARS-CoV-2 appears to have significantly higher transmission capabilities which may be due to gain-of-function in binding to host cells. In the following months the infection was rapidly also detected in many countries outside China and just a month after the first identification of the virus, the World Health Organization (WHO) announced SARS-CoV-2 to be a "public health emergency of international concern," and secondly a pandemic. By June 23rd, 2020, the pandemic had affected more than 200 countries, with 8,993,659 cases having been confirmed as COVID-19, including 469,587 deaths (8).

Growing evidence suggests that both SARS-CoV and SARS-CoV-2 appear to use the human angiotensin-convertase enzyme 2 (ACE2[1]) in order to infect host cells. With the aim to infect a host, the virus binds a molecule expressed by the cells of the latter (receptor) through its own protein that has the ability to bind it (ligand). The presence of the receptor allows the tissues that express it to become potential targets of the infection. Protein S is the main ligand that the SARS-CoV-2 virus uses to hook the ACE2 receptors expressed by the host cells and to infect their tissues. Protein S is divided into 2 subunits separated by a cleavage site ("furinic site"): the S1 subunit and the S2 subunit. The receptor expressed by host cells for SARS-CoV-2 S protein and SARS-CoV family viruses is the ACE2 protein. During the process of infection of the host cell, the S1 subunit binds to ACE2 and triggers a series of events that determine the process by which the S2 subunit determines the fusion between the viral capsid and the plasma membrane of the host cell. For this purpose, the action of the host protease transmembrane protease, serine 2 (TMPRSS2) that cuts the protein S in the 2 subunits at the level of the furinic site is necessary. This splitting process is essential to increase pathogenicity and improve the effectiveness of the merger process (13–15).

Since the beginning of the COVID-19 spread the most common clinical presentation of SARS-CoV-2 infection was characterized by mild to medium fever, dry cough, respiratory distress or dyspnea, with ground-glass pneumonia features on computed tomography (CT) scan (2, 16). Most recently, clinical reports were published demonstrating that SARS-CoV-2 affects the conjunctiva, the gastrointestinal tract, the heart and its pace, and may cause vascular injuries such as thromboembolic complications and Kawasaki disease in children and toddlers (17–19). A rapidly increasing number of evidences have also described neurological and psychiatric symptoms and complications, such as acute stroke (20, 21), hyposmia (22), Guillain–Barrè syndrome (23), and encephalitis (24). Emerging evidence suggests that the 36.4% of COVID-19 patients exhibit neurological symptoms including both central and peripheral signs (25). The first ones include consciousness-impairment, vomiting, headache, dizziness, and nausea, whilst the second ones are comprised of three types of hypoesthesia (hypoplasia, hypogeusia, and hyposmia), suggesting CNS-invading capabilities of the virus where it may affect the functioning of specific nuclei or neural circuits (25).

Among the neurological manifestations just described, those presenting early and those presenting later in the course of the COVID-19 pathology can be identified. Indeed agitation, confusion, and corticospinal tract signs affect above all patients hospitalized in intensive care units, COVID-19 can cause cerebrovascular ischemia and stroke also in young patients, Guillain-Barré syndrome (23), Miller-Fisher syndrome (26), and Kawasaki-like multi-system inflammatory syndromes now being recognized in children and teenagers by changing of coagulation and, in particular, to inflammation-induced disseminated intravascular coagulation (DIC) (20, 21). According to Heneka et al., it is possible to argue that four possible physiopathogenetic mechanisms through which SARS-CoV-2 affects the CNS can now be identified during the acute phase of COVID-19: (1) direct viral encephalitis, (2) systemic inflammation, (3) peripheral organ dysfunction (liver, kidney, lung), and (4) cerebrovascular changes. In the long term perspective, one or more of these mechanisms together may contribute to raise the risk for developing long-term neurological complications in COVID-19 survivor patients, either by worsening a pre-existing neurological disorder, or by onset of a new neurological pathology (19). This assumption is confirmed by the observation that about one third of COVID-19 patients discharged have cognitive and/or motor impairment (27). Connections between SARS-CoV-2 related infections and CNS pathologies are not to be unexpected, as the previously mentioned observations on COVID-19 appear to be in agreement with previous reports from Saudi Arabia in which significant neurological manifestations were found to be associated with Middle East Respiratory Syndrome (MERS-CoV) infection (28). Recent guidelines, however, do not include neuropsychiatric symptoms as typical COVID-19 symptomatology; for example, the WHO guidelines only report

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[1] ACE2 was first identified in 2000, as a homologous of a previously known protein, angiotensin-converting enzyme (ACE) (9, 10). Morphologically, it is a type I transmembrane protein which is comprised of 805 amino acids, a carboxy-terminal catalytic domain and alpha amino-terminal domain. In the catalytic domain an active site, called the zinc metalloprotein domain, matches 41.8% of the previously known ACE protein (10–12). Its corresponding gene is found in the short arm of the X chromosome (Xp22.2) (10). The ACE2 protein is found in many organs, specifically in the lungs, the kidneys, the testes, the intestine, the heart and, of particular interest for the aim of this paper, the brain (13).

headache and altered mental status as neurological criteria for probable COVID-19 cases (29).

Older aged patients, especially males, and patients with medical comorbidities and frailty, appear to be at the highest risk of developing more severe clinical pictures, including neurological symptoms and a higher rate of systemic complications. Data from the National Survey of Residential Care Facilities in the United States showed that seven out of 10 individuals in assisted living had some cognitive impairment, ranging from mild (29%) to severe cognitive impairment (19%) (30). Not surprisingly, recent findings from Azarpazhooh et al. suggest a significant correlation between dementia, disability-adjusted life years (DALYs), and COVID-19 cases (31) with a rate of dementia in hospitalized cases ranging from 6.8% (32) to 13.1% (33). Moreover, dementia is a strong predictor of COVID-19 mortality (31) and raises the issue of how to safeguard and how to implement self-quarantine measures in these patients.

Given these evidences, the aims of the present speculative article are manifold: firstly, we will describe the pathophysiological mechanism through which SARS-CoV-2 infection causes COVID-19 in humans, and secondly, we will focus on literature data suggesting the mechanism through which SARS-CoV-2 hijacks the CNS. Lastly, our final main purpose, and the real innovative hypothesized theory, will be to describe the neuropathogenicity of SARS-CoV-2 with the aim to explain neurocognitive and psychiatric symptoms, which are based on pathophysiological data and scientific evidences adding our speculative pathogenetic theory to the four mechanisms proposed by Heneka et al. as described above. In more detail, we aimed to examine the role of consequences of ACE2 binding by SARS-CoV-2 in the CNS through the collection of evidence in preclinical and clinical studies outlining the subsequent increase and/or reduction of the main components of Renin Angiotensin Aldosterone System (RAAS) at the CNS level. Based on this evidence, we hypothesize a possible pathogenetic mechanism through which the brain and its functions can be clinically altered during SARS-CoV-2 infection.

FROM SARS-COV-2 TO COVID-19: PATHOPHYSIOLOGICAL MECHANISM

The virus appears to be able to use two anatomical routes in order to reach, colonize and infect the CNS: (a) a body fluid pathway (such as liquor, lymph, or blood) and (b) a neural pathway. The main person-to-person routes of transmission for COVID-19 are close contact transmission and inhalation of respiratory droplets. Additionally, contact with the eye conjunctiva of SARS-CoV-2 containing droplets may allow, once the trigeminal nerve (V) is infected, for the virus to infect the brain by retrograde traveling. This route may result in impaired vision like hypoplasia. Additionally, SARS-CoV-2 can affect the sensory neurons which reach the taste buds of the tongue, from there it can infect the CNS through retrograde transport by reaching the nucleus of the solitary tract (VII, IX, and X) or the trigeminal nerve (V). This route may give a reason for hypogeusia. As the virus-containing respiratory droplets reach the mucous membrane that covers the nose, SARS-CoV-2 is also capable of entering the brain from the olfactory nerve (I), this may explain the clinical identification of hyposmia/anosmia in COVID-19 patients (34). In addition, in terms of body fluid invasion, the nasal mucosa provides a favorable environment for virus attack due to significant presence of blood and lymphatics capillary, which facilitate the entrance in the bloodstream after interaction with expressed ACE2 on endothelial cells. Finally, another modality of infection is the expression of ACE2 on epithelial cells that line the respiratory system, which enables respiratory viruses to cross into the bloodstream. The virus does not only use vascular pathways to spread into the CNS, neural pathways such as the vagus nerve branch (X) which innervates the respiratory system are used by the virus, causing clinical symptomatology such as dyspnea, dry cough, and worsening of acute respiratory distress syndrome (ARDS). Likewise, inadequate hand hygiene allows the virus to hijack the gastrointestinal tract and then to gain entry to the CNS through the blood vessels, lymphoid pathways, and the vagus nerve. Additionally, once the virus has entered the circulation it is also capable of invading the brain via the compromised blood-brain barrier (BBB), spreading to the liquor through leakage into the intracerebral lymphatic circulation of the CNS. Similarly, a damaged blood liquor barrier allows viruses in circulation to invade the fourth ventricle (34).

As upon described, recent studies confirmed that SARS-CoV-2 tethers to the ACE2 through their spike (S) protein (35, 36). Through the binding of the surface unit of the S protein (S1) to ACE2, viral attachment to target cells is facilitated. Additionally, once the receptor is bound, the virus has to access the cell cytosol in order to start its own replication, which is fulfilled by cellular serine protease TMPRSS2 through acid-dependent proteolytic cleavage of the S protein, a process similar to the priming of the S protein in SARS-CoV-2. After the binding between the S protein and ACE2, the S protein is then cut at both S1 and S2 sites level. This allows the exposure of the S2 site which allows the fusion of the viral and cell membranes. The step of cutting of the S protein through dibasic arginine sites by the protease TMPRSS2 that is expressed by the host cell to cleave the S protein in the S1 and S2 units is critical in order to allow both S2-induced membrane fusion and viral endocytosis with ACE2 in the host tissue (35, 36). A clathrin-dependent mechanism allows SARS-CoV-2 to be internalized, it then penetrates early endosomes. Once the spike protein of the virus comes in contact with ACE2 and binds it, the whole molecule or the transmembrane region of ACE2 enters the cell along with the virus by endocytosis. Subsequently, membrane fusion ensues and RNAs of the virus are released. The disintegrin and metalloprotease 17 (ADAM17) cuts the extracellular juxta-membrane region of ACE2. This phase is called "shedding." In conclusion, the internalization and subsequent shedding of ACE2 diminishes the concentration of ACE2 itself on the surface of host cell (13).

As suggested by Wrapp et al. (37), the higher virulence of SARS-CoV-2 might be due to the higher affinity of the S1 protein for the ACE2 protein compared with that of SARS-CoV. The result of SARS-CoV-2-induced ACE2 internalization is the loss of expression of ACE2 at cell surface level, which would compromise the capability of the cell to metabolize Ang II, a key step for the cell to produce Ang-(1-7), which is one of the most important cardio-vascular mediators of the peripheral action of Renin Angiotensin Aldosterone System (RAAS). Therefore, the rise in the ratio of Ang II:Ang-(1-7) which follows ACE2 endocytosis may drive the damage to the tissue which is at first induced by SARS-CoV-2 infection. Thus, a diminished ACE2 expression at the cell surface level may contribute to chronic loss of affected tissues functions and, in our hypothesis, to generate brain-functioning impairment due to the neurotrophic properties of SARS-CoV-2 (13). Based on the collected evidence and these assumptions, we hypothesize that the reduced concentration of ACE2 and the consequent rise in the ratio of Ang II:Ang-(1-7) may be a causal factor in the genesis of the pathological involvement of the CNS and may participate in the genesis of neuropsychiatric symptoms and neurological clinical manifestations from COVID-19. Based on this evidence, we hypothesize a possible pathogenetic mechanism through which the brain and its functions can be clinically altered during SARS-CoV-2 infection, with a specific focus on impairment of cognitive function during and after COVID-19 and especially on the potential SARS-CoV-2-induced neurodegeneration.

THE RENIN ANGIOTENSIN ALDOSTERONE SYSTEM (RAAS)

Overview

Renin was the first component of the RAAS once it was discovered that extracts from rabbit kidney affected blood pressure (36, 38). Then it was found that the constriction of the renal artery led to high blood pressure, which drove to the discovery of angiotensin (Ang) (39, 40). Once Ang was purified, two forms were isolated and described: Ang I and Ang II. Thus, the existence of an enzyme capable of converting Ang into Ang I and Ang II was hypothesized. This enzyme, named ACE, was subsequently isolated and characterized by Skeggs et al. (41). An arm of the RAAS system which counterbalances the continuous production of Ang II was then described and characterized. Two independent research groups (42, 43) have thus isolated ACE2, which works to generate proteins with cardioprotective action. The human ACE2 (hACE2) is a zinc metallopeptidase comprised of 805 amino acids which shares 42% of the sequence of ACE in the metalloprotease catalytic regions, and it is able to cleave the decapeptide Ang I to Ang-(1-9) and to cleave the octapeptide Ang II to Angiotensin-(1-7) [Ang-(1-7)] (17). Ang-(1-7) seems to be the most relevant cardioprotective protein from ACE2 action. As Ang-(1-7) interacts with the Mas receptor (MasR), the Ang-(1-7)/MasR axis comprises the second arm of the RAAS axis (13), and it appears to have cardioprotective properties (44). Recently, some studies discovered the ACE2 protease domain to be the main receptor entailed in the onset of severe acute respiratory syndrome-coronavirus (45) and, more recently, as a receptor involved in the infection from SARS-CoV-2 (15, 46).

Cascade

The synthesis of renin by the juxtaglomerular cells (JG), which are located near the afferent (and sometimes also the efferent) arteriole of the glomerulus of the kidney, is the first step in the RAAS cascade. A precursor of renin in the form of a pre-pro-hormone is synthetized and it is then cleaved at its N-terminal of 43 amino acids, forming renin as an active compound. Renin is then stored in granules which are released into the renal and systemic circulation by an exocytic step involving coupling of stimulus-secretion (**Figure 1**). There are four interdependent factors which cause the secretion of the active form of renin: (1) alterations in the delivery of sodium chloride (NaCl) to the cells of the macula densa, which are located in the distal tubule and to the JG cells, together they constitute the "JG apparatus"; (2) changes of pressure in the perfusion of the kidney which are recognized by the baroreceptor mechanism in the afferent arteriole; (3) direct effect of Ang II on JG cells (negative feedback); (4) orthosympathetic stimulation through beta-1 adrenergic receptors (43). Renin, through the proteolytic removal of the N-terminus portion of angiotensinogen, is capable of regulating the first, rate-limiting step of the process in order to form Ang I, a biologically inert decapeptide.

The liver is the primary organ in which circulating angiotensinogen is synthetized, however mRNA expression of angiotensinogen has been identified in many other organs such as brain, kidney, vascular, placenta, adipose tissue, ovary, and adrenal gland. ACE then cleaves the C-terminal dipeptide of Ang I producing Ang II, a protein which, unlike Ang I, is biologically active and is capable of producing vasoconstrictor effects. ACE works also to metabolize many different peptides to their inactive forms, such as kallidin and bradykinin. Therefore, ACE effects may potentially decrease vasodilation and increase vasoconstriction (47, 48). Even though Ang II is the most known active product of the RAAS, studies suggest that different metabolites of both Ang I and Ang II may be capable of biological effects, especially in tissues. The sequential cleavage by aminopeptidases of amino acids from the N-terminal of Ang I and Ang II produces Ang III, a heptapeptide which is discovered in the CNS where it maintains tonic blood pressure and which play a role in hypertension and Ang IV, which derives from the subsequent enzymatic cleavage of Ang III (49). Ang II is converted by the action of carboxy- peptidases ACE2, that has a significant structural homology to ACE, to Ang-(1-7), an heptapeptide with biological activity. ACE2 has a role in the production of Ang-(1-9), another biologically active peptide from the cleavage of the C-terminal of Ang I.

Angiotensin Receptors

Five subtypes of receptors mediating the effects of the RAAS biologically active peptides have been described as follows (49, 50):

- The type 1 receptor (AT1R), found typically in the form of a G protein-coupled receptor, which mediates the most well-known actions of Ang II, and among other functions it is involved in oxidative stress, inflammatory responses, and in the process of cell proliferation.
- The type 2 receptor (AT2R) is abundant during fetal life in the brain, kidney, and other sites, and its levels decrease markedly in the postnatal period.

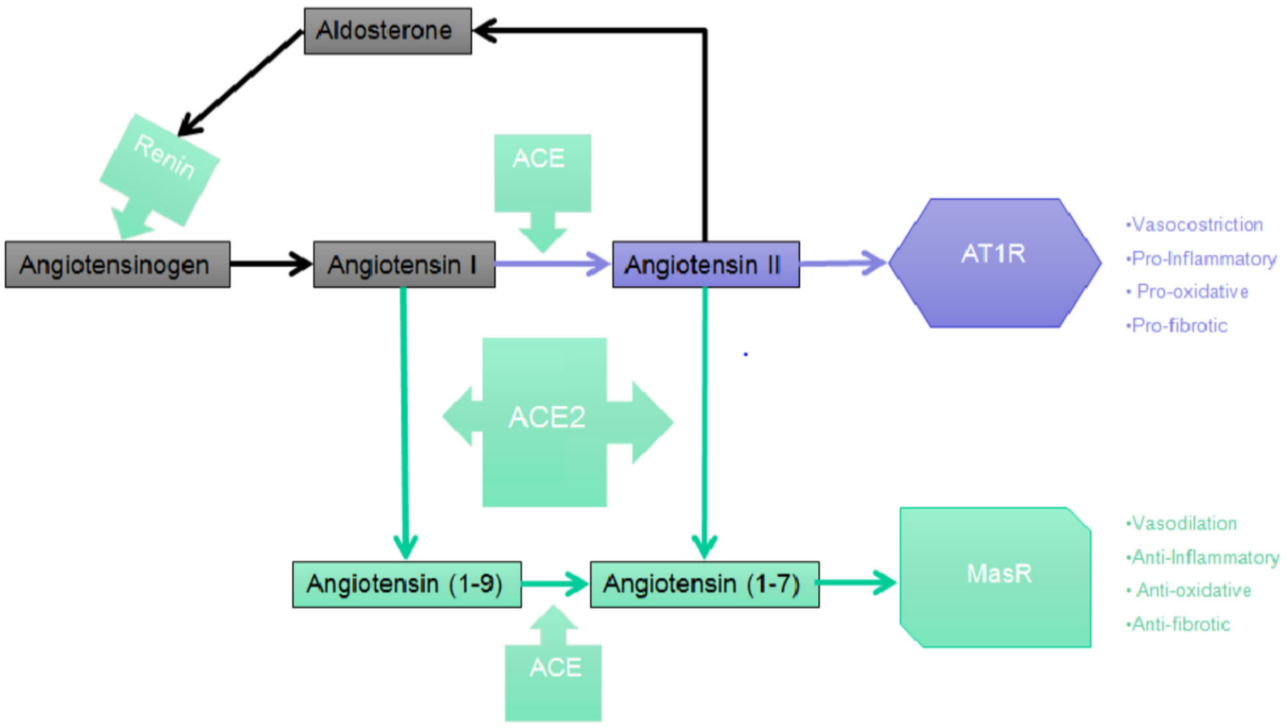

FIGURE 1 | The RAAS cascade. Simplified picture of the Central RAAS pathway depicting the main steps leading to the synthesis of Angiotensin (1-7) which, in turn, binds and activates with the highest affinity the MasR.

- The type 3 receptor (AT3R) has unknown biological functions.
- The type 4 receptor (AT4R) plays a role in the mediation of Ang II, Ang III, and Ang IV in the release of plasminogen activator inhibitor 1.
- MasR is involved in vasodilatation, natriuresis, antiproliferation, heart protection, and brain function modulation. Such effects are due to the C terminal truncated peptide Ang (1-7) and not to the binding of Ang II.

RAAS and CNS

Two different RAAS pathways have been described in the brain: the peripheral pathway, and the central pathway. The peripheral pathway allows for the peripheral access of RAAS components and involves both the forebrain and the circumventricular organs which surround the third and fourth ventricles, and it is constituted of fenestrated capillaries (51). Because of the BBB, which prevents peripheral RAAS constituents from entering most regions of the CNS, it is essential that there is synthesis of cerebral RAAS components in the brain. The central RAAS pathway is the main producer of locally synthesized angiotensin and links the medulla and the hypothalamus (51, 52). Additionally, other brain regions synthetize RAAS components as well. Both central and peripheral RAAS pathways contribute to the central control of cardiovascular homeostasis. In the CNS also, AT1R plays a role in vasoconstriction and is present on endothelial cells; on the contrary the AT2R plays a role in vasodilation (35, 51).

Ang II, Ang IV, Ang-(1-7), and Alamandine, that is produced from Ang-(1-7) via decarboxylase and from Angiotensin A via ACE2, are the main neuroactive forms of RAAS components. Ang-(1-7) binds to MasR with the strongest affinity, however it is also capable of binding AT2Rs and Mas-related-G protein coupled receptors (MrgDs). Alamandine attaches to MrgDs with the highest affinity. Ang II binds both AT1Rs and AT2Rs. Ang IV binds AT1Rs and AT4Rs. Receptors can be located on the plasma membrane of neuron, microglial cells and astrocytes, or intracellularly. The locations of intracellular receptors include neurosecretory vesicles, mitochondria and the nucleus. As previously described, ACE metabolizes Ang I into Ang II, and even though Ang II is capable of binding to both AT1R and AT2R, the upregulation of ACE increases AT1R activation specifically. AT1Rs are G-protein coupled receptors (GPCRs) which are located on basal ganglia, astrocytes, neurons, the hippocampus, microglia of the cortex and oligodendrocytes (53). The upregulation of ACE expression and the increase in the activation of AT1R signaling is a well-known process which regulates cell death, vasoconstriction (46, 47) and inflammation (15, 44). Conversely, AT2R, MasR, MrgD, and ACE2 possess vasodilation properties and are known for their positive effect on cognitive performance (50), promote the survival of cells (51), possess antioxidant effect (54), and promote anti-inflammatory processes (55). The MrgD, AT2R, and MasR pathways are interlinked, and reciprocally affect each other. MasRs and MrgDs ligands production is facilitated by ACE2. The activation of

AT2R enhances ACE2 expression (36). A decrease in MasRs and ACE2 mRNA, protein and activity was found in knocked-out animal models (56). All these processes taken together appear to suggest a reciprocal interplay between enzymes and receptors in order to keep a balance in the maintenance of a well-functioning and healthy brain in terms of plasticity and resilience.

ACE2, ANG-(1-7), AND CENTRAL NERVOUS SYSTEM: EVIDENCES FROM ANIMAL MODELS

The allocation of ACE2 in the CNS was under discussion since 2002 when suggestions of ACE2 mRNA were pointed out in the post-mortem human brain using quantitative real time polymerase chain reaction (RT-PCR) (57). Subsequently, with the aid of immunohistochemistry, ACE2 protein availability was found primarily at the level of endothelial and arterial smooth muscle of the vessel cells (16). Other evidence has outlined that ACE2 was found to be prevailing at the level of the glial cells (58). Additionally, Doobay et al. have outlined the presence of the mRNA and the ACE2 protein in the mouse brain, preponderantly in neurons (58). The evidence that SARS-CoV was found in infected patients brains, nearly always in neurons, substantiates the localization of ACE2 to the CNS (58, 59). Thanks to molecular biology techniques it has been found that ACE2 is ubiquitously spread throughout the brain, both in the nuclei that preside over the central modulation of cardiovascular functions (cardio-respiratory nuclei of the brainstem) and in brain areas responsible for other functions such as the motor cortex and the raphe (58).

While the role of ACE2 in the physiology and pathophysiology of the CNS is becoming better known, there is also an important body of knowledge supporting the fact that Ang-(1-7) plays a role in the brain. This peptide is mainly present in central brain areas linked to the control of blood pressure, such as the brainstem and the hypothalamus, and could play a synergic or opposite role on Ang II effects (60–63), as well as playing a role in neuromodulator action of cardiac baroreflex mechanisms and driving to a heightened responsiveness of this system (64), Ang-(1-7) has been outlined to roll out an relevant role in the negative modulation of norepinephrine release and to lead depressor responses in animal models, to enhance bradykinin levels, to boost the hypotensive upshots of bradykinin and to increase vasopressin and nitric oxide release (65–70). These effects are mediated by MasRs (65, 71), electively expressed in the CNS.

In spite of the fact that several data address that central ACE2 plays a predominant role in the conversion of Ang II into Ang-(1-7) in the brain, Elased et al. suggested that ACE2 activity in the CNS is more relevant than ACE activity under normal conditions compared to pathological conditions. This is completely inconsistent with previous findings proving that the physiological prominence of central Ang-(1-7) is uncovered in pathological circumstances and that its role is constrained in physiological conditions (72). On the other hand, it has been shown that the role in the CNS of ACE/Ang-(1-7)/MasR axis is not only limited to the control on cardiovascular function, but, in particular, thanks to the study of its inhibition, it has been highlighted that the ACE/Ang II/AT1R axis is involved in numerous other processes such as the regulation of the synthesis and release of neurotransmitters such as norepinephrine (NE), dopamine (DA), and y-aminobutyric acid (GABA) (72). For the sake of argument, in animal models Ang-(1-7) has proven to be capable to reduce the release of K+-induced NE in the hypothalamus, which in turn through a downregulation of the activity of tyrosine hydroxylase (TH) leads to a net reduction of the synthesis of NE. The fact that this inhibitory activity on NE release is experimentally blocked both by using a MasR antagonist such as A-779 and an AT2R antagonist such as PD123319, demonstrates the sharing of AT2R signaling in mediating this effect. Likewise, studies on aortic coarcted hypertensive rat models, show the ability of Ang-(1-7) to act inversely to Ang II on the release of hypothalamic NE, blocking its enhancing effects, and further showing the involvement of both receptor systems (MasR and AT2R). The administration of Ang-(1-7) to the rats in the striatum induces an increase in the release of both DA and GABA. The A-779, the MasR antagonist, is capable of inhibiting the increased release of GABA, but not of the DA; in order to obtain that result the co-administration of another antagonist is mandatory, EC33, which is an inhibitor of the enzyme that converts Ang-(1-7) in its metabolite Ang-(3-7). This evidence suggests that Ang-(1-7), through MasR, mediates the release of GABA, while the transformation in one of its active metabolites is fundamental to induce the release of DA (73).

Central Cardiovascular Regulation

Evidence from animal models of hyper- or hypo-expression of ACE2 lead to the following findings.

The hyper-expression of ACE2 in the CNS is linked to a protective phenotype for the most common cardiovascular diseases (hypertension, chronic heart failure, cardiac hypertrophy). In fact, it entails a depletion of Ang II in the brain and consequently an enhancement in the amount of nitric oxide (NO), which would counterbalance and negatively modulate the peripheral cardiovascular effects of the Ang II mediated, instead, by the cutback of nitric oxide synthase (NOS) and sympathetic activity (74). Moreover, ACE2 hyper-expression in the brain mitigates the occurrence of deoxycorticosterone acetate (DOCA)-salt hypertension. Consistently, the low expression of ACE2 through experiments in transgenic animal model (mice) demonstrated a risen oxidative stress and autonomic response disruptions as opposed to controls. Starting from this evidence, Xia et al. hypothesized that the mechanism underlying the antihypertensive and autonomic disruption effect mixed up a switch in the balance between the central Ang II-AT1R and the Ang-(1-7)/MasR signaling in favor of the latter (75).

Stroke and Brain Injury

Overexpression of ACE2 has been shown to mediate the circumscription of post-ischemic brain tissue damage in animal models (76–80) and, in particular, was combined with a lessening in the volume of the area of infarcted brain tissue under the same conditions (81, 82). The administration of the MasR antagonist, A779, was able to reverse these beneficial effects, suggesting once again how the pathophysiological mechanism underlying the extension of cerebrovascular damage following ischemia is recognized in the altered equilibrium between Ang II and Ang-(1-7) one of the main causal factors (76–80).

Cognition and Memory

Recent evidence showed that Ang-(1-7) and its receptor MasR may be pivotal for memory handling in the hippocampus brain area (83). Congruently, *in vivo* studies with animal models of ACE2 hypo-expression demonstrated a worsening in memory and cognitive functions (84), and an intensified synthesis of reactive oxygen species and a simultaneous reduction in the production of the brain neurotrophic factor (BDNF). These changes reversed after the administration of AT1R and Ang-(1-7) antagonists, suggesting the important role played by the biochemical signal mediated by MasR in the positive modulation of these brain functions (83).

Stress Response and Anxiety

Compared to controls, transgenic mice upregulating ACE2 exhibit behavior compatible with reduced anxiety levels (85). On the other hand, the MasR antagonist A779 reverts this behavior, suggesting that the Ang-(1-7)/MasR axis is involved in the modulation of anxiety levels and related behaviors. In a more recent study, using the same experimental model, Wang et al. reported a reduction in plasma corticosterone and proopiomelanocortin levels, assuming that ACE2 at the hypothalamic level by suppressing the synthesis of corticotropin releasing hormone (CRH) mediates the response to stress at the level of the hypothalamic-pituitary-adrenal (HPA) axis (86–89).

Serotonin and Neurogenesis

A reduced synthesis of serotonin has been observed in genetically modified animal models for hypo-expressing ACE2 (90). Intriguingly, this reduction was correlated with the reduced intestinal absorption and consequently reduced plasma levels of its tryptophan amino acid precursor (91, 92). In fact, ACE2 has a non-catalytic role in the transport of amino acids (AA) in the intestine, and this notion has led to the hypothesis that the effects of ACE2 can be mediated, at least in part, by its actions on the gastrointestinal tract and/or on the intestinal microbiota. Among the multiple functions performed by serotonin in the literature, emphasis has recently been placed on neurogenesis. Indeed, Klempin et al. demonstrated that cell proliferation prompted by exercise in the dentate gyrus is abolished in ACE2-deficient mice. However, further studies will be needed to characterize the effective mediation of Ang II and Ang-(1-7), to confirm those pieces of evidence which are currently still contradictory (90, 93).

ACE2, NEUROLOGICAL FUNCTIONING AND DISEASE: CLINICAL EVIDENCES FROM PRECLINICAL STUDIES AND FOCUS ON BRAIN AGING AND ALZHEIMER'S DISEASE

The RAAS hyper-activation has been identified in several neuropsychiatric disorders, including Alzheimer's Disease (AD) and Mood Disorders (56). Since the lowest common denominators in all these pathologies are neurodegeneration, insulin resistance and the inflammation cascade, great attention has been paid in the literature to the possible relationships between the dysregulation between the two functional axes of the RAAS and the underlying neuropathological processes, since Ang II, as previously mentioned, is a pleiotropic factor locally metabolized in the brain (94).

Two critical studies show that Ang-(1-7)/MasR axis is chiefly involved in normal learning and memory processes. Among others, Hellner et al. outlined that Ang-(1-7)/MasR signaling augments long term potentiation in the CA1 region of the hippocampus, a key region for learning processes and implicit configuration memory (95). Correspondingly, Lazaroni et al. likewise demonstrated in an experimental animal model hindering MasR in the CA1 region of the hippocampus, object recognition memory was hampered (83).

Evidences accumulated over the years show the contribution of the RAAS components in the modulation of cognitive functions and an imbalance between the two functional axes of RAAS in both AD and mild cognitive impairment (96, 97). It's well-known that plasma renin and aldosterone levels decrease with advancing age (98, 99) although the underlying mechanisms are not fully understood and might include the age-related reduction in the number and in the functioning of nephrons and a reduced response capacity of RAAS to stimuli. First, the decrease in the number of nephrons induces a compensatory hyperfiltration by the remaining nephrons which determines an increase in the quantity of sodium chloride at the level of the macula densa with a reduction in the shaping and outflow of the renin and consequently in the synthesis of Ang II and aldosterone and therefore in plasmatic levels (99). Several studies on animal models of the aging process have shown that the decrease in plasma rates of Ang II is not parallel to that of renin. Few studies have been performed to evaluate Ang II levels in the elderly. For example, Duggan et al. showed a non-significant reduction in plasma levels of Ang II in a small sample of the elderly that did not include the so-called "older old" subjects (100). Second, in aged animals the release of renin in response to acute volume depletion or to sodium restriction is reduced compared to that of an adult animal. The tubular response to aldosterone administration is also impaired, as well as the response of plasma aldosterone to potassium infusion.

RAAS elements such as Ang II, Ang IV, and Ang-(1-7), and their receptors AT2R, AT4R, and MasR which positively affect cognition are abundant under physiological condition in many cell types such as neurons, astrocytes and microglial cells. Conversely, under pathological conditions such as post-stroke cognitive impairment (PSCI), vascular cognitive impairment (VCI), Parkinson's disease (PD), AD, or in the physiological aging process, the Ang II/AT1R axis prevails and cognitive functioning worsens (101).

In vitro studies show that the administration of Ang II blocks the K-dependent release of Acetylcholine in the temporal cortex (102), alters synaptic transmission in neurons of the lateral geniculate nucleus (103), and has shown, in *in vivo* studies, to suppress the induction of long term potentiation (LTP) in the lateral nucleus of the rodent amygdala (104). The cholinergic system at the central level is notoriously directly involved in cognitive, arousal and attention processes (105), LTP is considered to be a neuronal model of learning. The induction effect on it is probably mediated by the action of AT1R as it is reversible upon administration of the specific AT1R antagonist Losartan, while this does not occur after administration of the specific AT2R antagonist (PD123319) (104). *In vitro* studies show that Ang II influences as well-long term depression (LTD) in the lateral amygdala by means of a mechanism involving L-type calcium channels and AT1R, suggesting a role for the plasticity changes in the lateral nucleus and a possible cellular mechanism essential for the beneficial effects of ACE inhibiting drugs on the cognitive improvement in AD (96, 106).

In vivo studies on animal models have only partially confirmed the above suggested *in vitro* (107). Through behavioral analysis in different tasks after administration of losartan, PD123319, or both, it has been found that both receptors, AT1R and AT2R, are involved in memory enhancement processes, albeit with different power and intensity, showing a preferential involvement of AT2R in the enhancement of acquisition and recall of avoidance behavior (108). Other studies, on the other hand, using learning tasks have diminished the role of endogenous Ang II by suggesting that in CA1 it does not modulate memory consolidation through AT1R and AT2R (109, 110). Using a different experimental paradigm, Akhavan et al. shows that Ang II display an important role in brokerage of the effect of exercise on learning and memory, although the basic biochemical mechanisms remain largely unknown (111).

In summary, a growing body of scientific evidence pointed out that the upregulation of ACE2 and an increased proportion of Ang-(1-7)/Ang II, parallel to the positive tailoring of Ang II signaling through AT2R and Ang-(1-7) through MasR, determine an improvement in cognitive function and is involved in the treatment of dementia, above all AD (**Figure 2**). More specifically, the cognitive outcomes of Ang II deficiency and/or abundance (**Figure 3**) have been studied above all in preclinical model studies. Even though the BBB is impervious to all RAAS components, it was hypothesized that the local brain RAAS may possess pharmacological and physiological properties in the CNS (112). Inconsistent findings about the contribution of Ang II in memory and learning process *in vivo* studies were reviewed by Gard (113). Learning and memory in rodents were found to be enhanced by Ang II (114), however other studies found evidence of Ang II harming cognitive function (115). Experimental evidence reports that one possible reason is that the short-term effect of Ang II would consist in improving cognitive functions; on the other hand, Ang II in the long term could contribute to the functional exhaustion of neurons and consequent cognitive deterioration. That may be because of the induction of cerebrovascular remodeling by Ang II, which, by driving oxidative stress and vascular inflammation, produces an impairment in cerebral blood flow regulation (CBF) (116, 117). Additionally, endothelial capacity in brain vessels was affected by central expression of Ang II in genetically modified animal model of Ang II-dependent hypertension (118, 119). Moreover, Ang II was capable of inducing astrocyte senescence, a process involved, via superoxide production, in age-related neurodegenerative disease (120). Conversely, perindopril, which acts as a centrally active ACE inhibitor, was found to counter cognitive dysfunction in a mice model of AD and in chronic central hypoperfusion rats (121). These results suggest that permanent Ang II stimulation negatively affects cognitive function through the stimulation of the AT1R via degradation of neurons such as an increase in cellular senescence, CNS inflammation and oxidative stress, and through a decrease in the liquor in the brain. Cognitive impairment then follows neuronal degeneration, as induced by the many stimuli of Ang II. In terms of the clinical relevance of the RAAS cascade modulation and neurodegenerative disease, we will focus on the epidemiologically most impacting dementia: AD.

Two main pathophysiological mechanisms have been proposed to explain neurodegeneration as a pathogenetic mechanism involved in AD: (i) the hypothesis based on amyloid cascade s and (ii) the hypothesis based on cholinergic neurotransmission. According to the former hypothesis, neurodegenerative aberrations that bring to clinically relevant AD are induced by Aβ (1–42) (122). More specifically, the cleavage of the amyloid precursor protein (APP) produces a peptide, Amyloid β (Aβ), which is a 39–42 amino acid peptide (123) ACE appears to affect Aβ metabolism, thus suggesting a link between RAAS and AD (124). ACE contributes to degradation of β-amyloid in the brain, that is responsible for AD and ACE2 mediated release of Ang-(1-7) peptide in nerve tissue has potential neuroprotective actions. Taking together these findings outline that the smaller ratio of ACE/ACE2 score may contribute to the onset or the speeding process of pathophysiology of AD.

With regard to the cholinergic hypothesis, a depletion of neurons characterizes AD, in particular of those neurons which express nicotinic acetylcholine receptors (nAChR) (125, 126). Moreover, even though few studies investigated the link between Ang II and α7nAChR, Marrero et al. found that Ang II appears to activate the tyrosine phosphatase Src homology region 2 domain-containing phosphatase-1 (SHP-1), resulting in the block of neuroprotection against Aβ(1–42) mediated by nicotine (127, 128). Additionally, they found Ang II to be capable of inhibiting in PC12 cells, via SHP-1 activation induced by AT2R, the α7nAChR-induced activation of the JAK2-PI-3 K cascade (128, 129).

In vivo model evidences of the involvement of RAAS in the neurodegenerative disorders mainly come from genetic studies and cerebrospinal fluid (CSF) levels of the metabolites of the RAAS cascade. Significant single nucleotide polymorphisms (SNPs) in ACE gene also showed association with AD risk. The

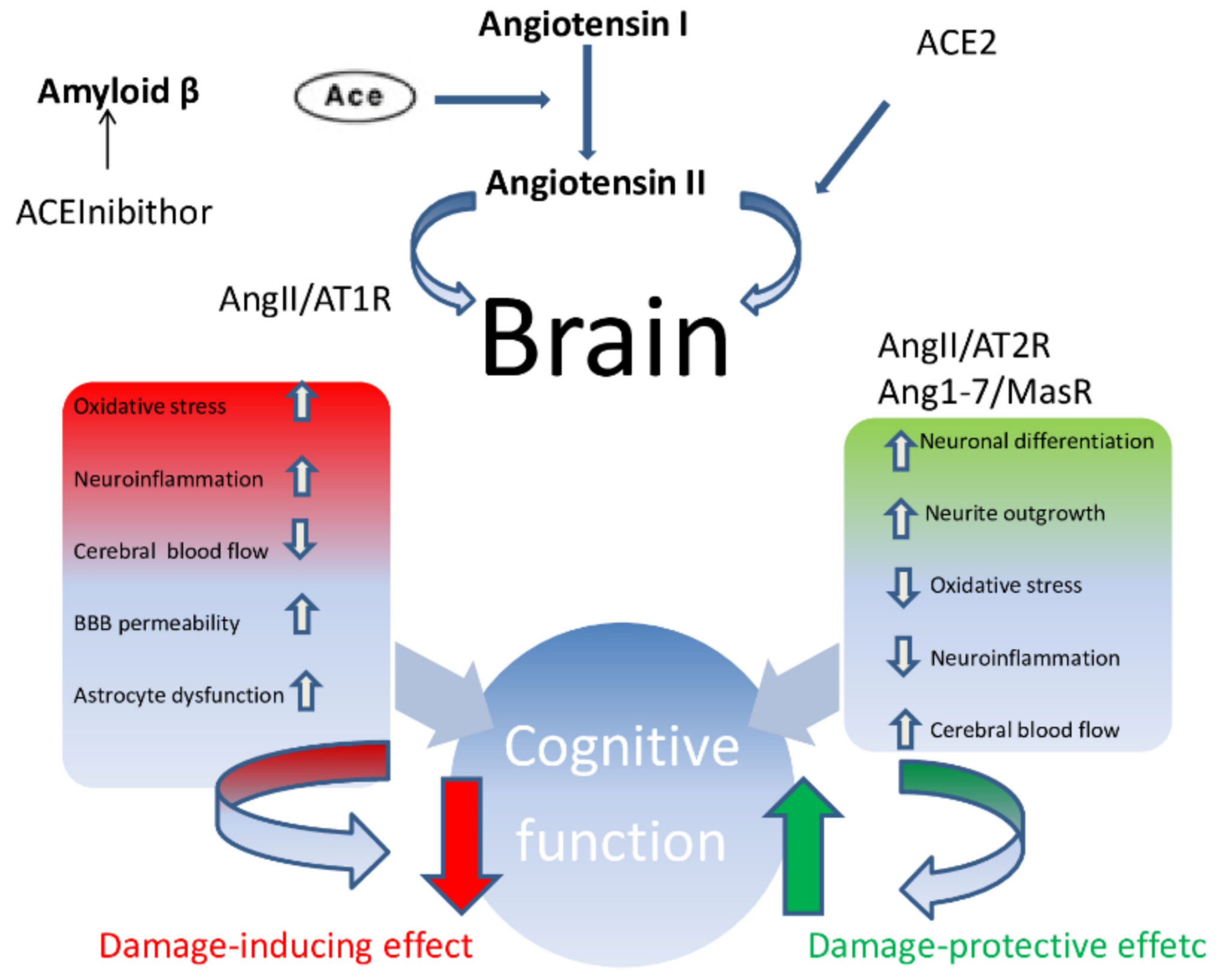

FIGURE 2 | Ace/AngII/AT1R axis–Ace/Ang (1-7)/MasR axis imbalance. In condition such as AD, vascular cognitive impairment and post-stroke cognitive impairment, the Ace/AngII/AT1R axis predominates magnifying and accelerating the development of cognitive impairment.

ACE gene insertion/deletion (I/D or indel) polymorphism has long been linked to AD. Fekih-Mrissa et al. have outlined that there was a significantly increased risk of AD in carriers of the D/D genotype (51.67% in patients vs. 31.67% in controls; $p = 0.008$, OR = 2.32). The D allele was also more frequently found in patients compared with controls (71.67 vs. 56.25%; $p = 0.003$, OR = 2.0). Moreover, as assessed by Mini-Mental State Examination, patients suffering from severe dementia were found predominantly in the D/D carriers group and, conversely, the D/D genotype and D allele were more frequently found in AD patients with severe dementia (130).

From a biochemical point of view, in 1986 Zubenko et al. showed that mean levels of the hydrolase ACE in CSF samples from a group of patients with dementia of the Alzheimer's type, were decreased (131). More recently, Kauwe et al. have conducted a genome-wide association study of CSF levels of 59 AD-related analytes. All analytes were measured using the Rules Based Medicine Human Discovery MAP Panel, which includes analytes relevant to several disease-related processes. They identified genetic associations with CSF levels of five proteins involved in amyloid processing and pro-inflammatory signaling. Among these proteins there was ACE, and SNPs associated with ACE protein levels are located within the coding regions of the corresponding structural gene. The genetic associations reported were new and suggested mechanisms for genetic control of CSF and plasma levels of these disease-related proteins. Significant SNPs in ACE showed association with AD risk in this study as well (132).

Taking together all these findings, it is possible to argue that the RAAS cascade is involved in neurodegenerative process. More specifically the constant activation by Ang II is capable of damaging neurons through AT1R stimulation via multiple cascades. Conversely, AT2R stimulation appears to protect

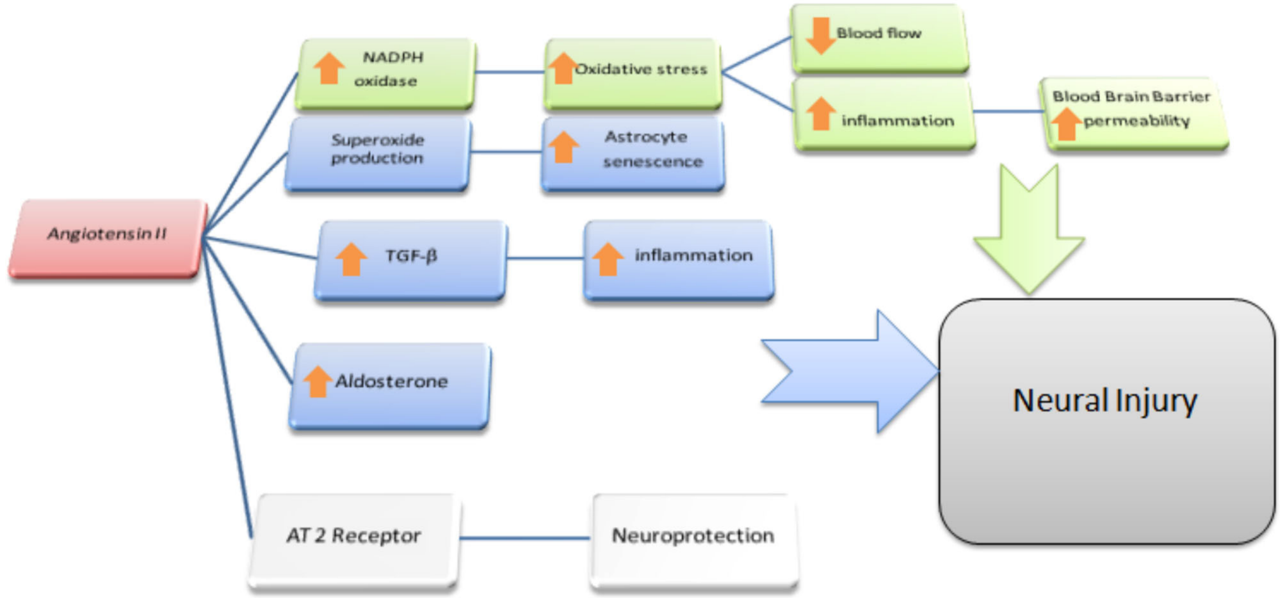

FIGURE 3 | Ang II and the Brain. Possible effects of Ang II on Non-neural cells: In green is outlined the cascade responsible for the reduction of blood flow and enhanced permeability of the BBB at the microvessels level; we depict in blu the reported effects of Ang II acting as a paracrine mediator in CNS: mainly in astrocytes where, via TGF-β upregulation and local aldosterone production, it exerts pro-inflammatory effects resulting in indirect neural damage. Moreover, via superoxide production, Ang II accelerates senescence and dysfunction of astrocytes itself. Both these processes are supposed to be cofactor in leading to cognitive dysfunction resulting in higher susceptibility to dementia.

against cognitive impairment, neural damage and the senescence process.

RAAS AND PSYCHIATRIC DISTURBANCES

Stress Related Disturbances

RAAS has been considered a stress response system similar to the HPA axis in which Ang II is considered an important stress hormone (133) that binds AT1R and AT2R located on stress-sensitive brain areas, including the HPA axis, amygdala, hippocampus and prefrontal cortex (134).

Similarly to the HPA system and its effects on cortisol, the RAAS cascade in humans has been considered a stress response system and higher levels of functioning are observed both following acute stress-related tasks and following stress chronically induced (133). Ang II is nowadays considered one of the most important stress hormones of the RAAS cascade, through the link with its AT1R and AT2R receptors in specific CNS regions such as the amygdala, the hippocampus, the prefrontal cortex and modulates the HPA axis, in particular through the link with paraventricular AT1R (133, 134). In fact, ACE inhibitors proved effective in regulating and desensitizing the HPA's response to stress (135). It is mandatory to mention that the effects mediated by AT2R in general counterbalance the action of Ang II on AT1R receptors, whose inhibition represents the main biological pathway of stress resistance and resilience (135).

Despite several clinical studies, there is still little evidence aimed at investigating the role of RAAS as an intervention target for the modulation of anxiety and stress response. In this regard, a 2012 observational study in patients suffering from post-traumatic stress disorder (PTSD), in which both the use of the AT1R antagonists and ACE inhibitors were associated with a protective profile regarding anxiety and fewer symptoms of the anxious spectrum in the patients examined (136). Unlike the RAAS cascade, ACE2/Ang-(1-7)/MasR axis has accumulated an increasing number of scientific evidences that qualify it as a protective factor in various neuropsychiatric pathologies, including psychosis, major depressive disorder (MDD), AD, PD, and stress disorders (79, 83, 88, 137). The protective effects on the central nervous tissue are mediated by anti-inflammatory and antithrombotic actions, as well as by the reduction of oxidative stress and apoptosis mediated by the latter (76, 138).

The central administration of Ang-(1-7) reduces the autonomic response to stress, reducing the high levels of stress-related hormones in the CNS, including Ang II itself, serotonin, DA and NE in the critical cerebral regions for this reply. MasR-KO mice in experiments showed increased durability of LTP and higher anxiety-like symptoms (87). The injection of Ang-(1-7), on the other hand, enhanced LTP through its action on NO and cyclooxygenase-2 in the lateral amygdala (139). Another study on the anxiolytic effects of Ang-(1-7) identified in the amygdala a correlation between the anxiolytic effects and the reduction of oxidative stress markers, and contextually the increase in the activity of glutathione peroxidase (140).

Consistent results were observed in transgenic mice overexpressing ACE2 and the GABAergic transmission: these mice tend to present an increased GABAergic tone specifically in the basolateral amygdala. High degree of ACE2 amount corresponds to high levels of Ang-(1-7) production which would induce an increased release of GABA locally, responsible for the anxiolytic effects observed (85). Another study found that in transgenic animal model (mice) with down-regulated synthesis of glial angiotensinogen, lower levels of serotonin synthesis and release in frontal and parietal cortex as well as in the hippocampus, which in turn could account for the depressive behavior shown by the experimental animals. Interestingly, this behavior is reversed both by the treatment with the serotonin selective reuptake inhibitor (SSRI) antidepressant fluoxetine, and by Ang-(1-7) injection (141).

Affective Disorders

There is not enough experimental evidence to evaluate the potential contribution of the components of the RAAS cascade as a biomarker or as a target of treatment strategy for affective disorders. However, studies have shown that drug free and/or naïve patients with a first episode of MDD have significantly higher circulating plasma levels of RAAS cascade components than healthy controls. Among the various components of the RAAS cascade, attention was paid to circulating levels of Aldosterone as a promising biomarker of affective disorders: in a study, low aldosterone levels related both to a greater clinical severity of depression and to an increase in suicidal behaviors (142).

Psychosis

In consideration of the aforementioned RAAS action on the modulation of the release and synthesis of DA (143), the potential role of ACE in the pathophysiology of schizophrenia and pathologies of the psychotic spectrum has been investigated. The results of the clinical studies carried out so far show contradictory results. In a recent study compared to healthy controls, patients with schizophrenic spectrum disorder show higher levels of circulating ACE (144–146). In contrast to these results, Wahlbeck et al. reported lower ACE activity than in controls examining the liquor of patients affected by schizophrenia (both in pharmacologically treated and in drug-free patients) (147). They also observed an inverse correlation between the enzyme activity of ACE and the CSF levels of DA and NE (148). In part, these conflicting results are attributable to methodological limits in the selection of the sample, since the population was not homogeneous regarding illness duration and drug co-treatment. Further studies that consider a greater stratification of the sample could shed light on the possible role of RAAS in disorders of the schizophrenic spectrum.

OUR GENERATING HYPOTHESIS

Considering the experimental data exposed and the scientific evidence mentioned so far, the mechanism of the cascade of the RAAS axis is characterized by the dynamic balance of two arms with a mutually counter-regulatory function. The first arm is that composed of the ACE/Ang II/AT1R with proinflammatory activity and the second arm is composed of ACE2/Ang-(1-7)/MasR with anti-inflammatory properties (149). In this context, the binding and subsequent modulation of the expression of ACE2 by SARS-CoV-2 would therefore not only be the way through which the virus generates the infection but also one of the main pathophysiological mechanisms of COVID-19. The disease would develop at least in part as a consequence of the imbalance of this dynamic balance in favor of the hyperactivity of the ACE/Ang II/AT1R branch due to the reduction in the expression and activity of the ACE2 enzyme. In fact, ACE2, following the interaction with the SARS-CoV-2 protein S, would undergo a process of endocytosis mediated by membrane enzymes with consequent reduction of the transformation of Ang II causing Ang-(1-7) hyperstimulation of AT1R and a higher prevalence of proinflammatory activity with a subsequent storm of cytokines leading to tissue damage. Data consistent with this deduction come from *in vivo* studies with animal models (mice) of lung injury. In fact, in these models a reduced expression of ACE2 and an increase in Ang II levels has been observed after administration of S [318–510] -Fc, an analog of the portion of the Spike protein of the SARS-CoV virus family that binds the ACE2 (150). Similar conclusions have been reported in hyperoxic damage studies in animal models (mice). Hyperoxia significantly reduced the expression of pulmonary ACE2 and enzymatic activity, leading to an increase in Ang II and a reduction in Ang-(1-7) levels. In these experimental models, the administration of Diminazene Aceturate (DIZE), an ACE2 agonist, restored the levels of Ang-(1-7). On the other hand, the administration of the ACE2 inhibitor, MLN-4760 further worsened the reduction in Ang-(1-7) levels in line with the even more marked increase in Ang II (151). The tissues involved include all those that express ACE2 and in which it has been shown to have functionally relevant enzymatic activity such as the pulmonary epithelium, the renal and cardiovascular system and the CNS. With regard to CNS, we postulate that hyperactivation of the ACE/Ang II/AT1R axis may contribute to the onset of neuropsychiatric symptoms and on the cognitive sphere in two chronologically distinct steps: (1) in the course of infection by SARS-CoV-2 they would be a direct consequence of the increased stimulation of the AT1R receptor and of the hyperproduction of the Ang-(1-7) fragment and of the consequent reduced stimulation of the MasR; (2) in the medium-long term the effects on the CNS would be the consequence of two events: (a) neurotoxicity mediated by the ACE/Ang II/AT1R axis in the absence of the full neuroprotective effect of the ACE2/Ang-(1-7)/MasR axis; (b) from neurovascular damage mediated by cytokine storm syndrome, associated mainly with severe forms of COVID-19, which leads to an excessive immune response that damages blood vessels caused by an increase in proinflammatory cytokines such as IL-1, IL-6, and TNF-α (152).

Regarding the virus neurotropism and neurovirulence, SARS-CoV-2 can colonize and infect the CNS through two main pathogenetic modalities: (1) through a retrograde neurogenic pathway and (2) through fluids (hematogenous, lymphatic, and CSF pathway). In the first modality it colonizes the nerve endings of the eyes, of the nasal cavity, of the oropharynx and of the respiratory tract interacting with the ACE2 receptor expressed on the surface of the nerve endings themselves. Then, after the enzyme endocytosis process, it goes through a calmodulin-dependent retrograde calcium-transport pathway toward the brain nuclei. In the second modality SARS-CoV-2 penetrates the CNS due to damage of the BBB mediated by the cytokine storm and the virus reaches the CNS mainly via hematogenous and lymphatic route. This transition would also generate at the CNS level a reduced expression of ACE2 and a consequent functional imbalance between the ACE/Ang II/AT1R axis (hyperactivated) and the ACE2/Ang-(1-7)/MasR axis (hypo-activated). In support of the pathophysiological importance of this functional imbalance there is also epidemiological evidence that the mortality rate of elderly COVID-19 patients with high blood pressure, diabetes and cardiovascular pathologies that already have an ACE/Ang II/AT1R axis hyperactivation and a down-regulation of the ACE2/Ang-(1-7)/MasR axis, is higher than other patients with SARS-CoV-2 related infection (153). Furthermore, the male sex would be at greater risk in all age groups (154). Consistent with this epidemiological evidence, Xudong et al. showed a significant reduction in ACE2 expression in animal models during the aging process which was greater in rat males than in rat females (155).

We postulate that the clinical consequences on the CNS are also to be causally related to the decrease in the concentration of ACE2 and the consequent increase in the Ang II/Ang-(1-7) ratio with an imbalance between ACE/Ang II/AT1R axis and the ACE2/Ang-(1-7)/MasR axis. Specifically, this functional alteration of the RAAS cascade would account for both the neuropsychiatric comorbidities described in the short term and medium-long term cognitive impairment. Compared to the latter, the oxidative damage and neurotoxicity associated with hyperactivity of the Ang II on the AT1R receptors can lead to the onset of long-term cognitive damage.

In the first few months of COVID-19 spread, a controversial topic was the use of angiotensin receptor blocking drugs (ARB) and ACE inhibitors (ACEI) in patients with COVID-19. Given that previous studies reported a higher mortality rate in aged COVID-19 patients with comorbidities such as hypertension, and given that these patients are likely to be treated with ACEI or ARB, the concern was whether the use of ACEI and ARB could aggravate the related SARS-CoV-2 morbidity and mortality. Data from *in vivo* studies, on animal models of cardiovascular diseases, ACEIs, more than ARBs, have demonstrated the ability to determine the increase in ACE2 mRNA levels, thus being able to increase the expression of receptors used by SARS-CoV-2, thus facilitating the entry of the virus into the host. However, the change in protein levels is not always consistent with mRNA levels and sometimes also goes in the opposite direction. To date, it is still uncertain whether ACEIs and ARBs increase the protein expression of ACE2. According to Bian et al. (156), there is currently no clear, consistent and conclusive evidence indicating that ACEI and/or ARB increase the risk of SARS-CoV-2 infection, as well as injury to target organs. Consistently, so far it is not necessary to recommend discontinuation of ACEI/ARB for patients treated with hypertension. ARBs and ACEIs have also been shown to play a significant role in preserving cognitive functions. Indeed Ho et al. found that patients with hypertension had worse basal memory and executive function performance, as well as a faster decline in 3-year follow-up memory than patients with normal blood pressure values unless they were treated with ARBs (157). The study showed more preserved memory functions than patients treated with antihypertensive drugs belonging to other classes (157). Patients treated with ARB showed better performance times in memory functions than patients treated with other antihypertensive drugs (158, 159), and better learning memory performance over time compared to all other groups, including those with no high blood pressure and patients treated with antihypertensive drugs (157). These data suggest that ARB treatment is linked to higher memory retention level than other antihypertensive drugs, especially those that go through BBB.

Consistent with our hypothesis that COVID-19 patients are at a greater risk of developing or worsening cognitive decline, and considering the evidence that ARBs and ACEIs could be protective therapeutic tools against cognitive decline, at the time of writing there is no evidence to support the transition to other antihypertensive drugs but rather, treatment with antihypertensive drugs aimed at modulating the RAAS cascade could actually be a protective factor regarding the onset or worsening of cognitive impairment symptoms and signs.

In order to test our working hypothesis, our goal is to first complete an observational study to monitor cognitive functions in patients with COVID-19 who are accessible to neurocognitive testing. Then we aim to prospectively observe patients recovered from SARS-CoV-2 infection to follow the possible decline in cognitive functioning by relating it to the levels of activity of the RAAS cascade. Alongside this monitoring, our goal is to follow the evolutionary framework of neuroimaging to understand if there is a correlation between the decline of cognitive functions, instrumental signs of neurodegeneration and altered activity of the balance of the two arms of the RAAS cascade: ACE/Ang II/AT1R with proinflammatory activity and ACE2/Ang-(1-7)/MasR with anti-inflammatory properties. These data will then be cross-referenced with ACEI or ARB treatment to answer a still open question about the advisability of treatment with these antihypertensive drugs during SARS-CoV-2 infection also from a neuropsychiatric point of view.

CONCLUSION

The SARS-CoV-2 pandemic represents an unprecedented challenge to healthcare systems around the world. At the onset of the pandemic, efforts by healthcare professionals and researchers focused on the urgency of treating patients who developed respiratory failure and needed assisted ventilation. However, it soon emerged that COVID-19 is a systemic pathology through the severe innate immune response and sustained rise of systemic cytokine levels (160). In fact, the innate immune response represents a predictor of mortality and severity of SARS-CoV-2 infection mediated through the production of cytokines and related inflammatory mediators found to be elevated such as interleukin-1β, interleukin-2, interleukin-2 receptor, interleukin-4, interleukin-10, interleukin-18, interferon-γ, C-reactive protein, granulocyte colony-stimulating factor, interferon-γ, CXCL10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor-α and parallel reduction of T cell mediated response and reduction of lymphocyte count. Among the various organs involved in COVID-19 pathology is the CNS (160). This assumption is confirmed by numerous pieces of experimental evidence which have now definitively shown that SARS-CoV-2 has significant neurovirulence involving, as well as serious clinical pictures of interstitial pneumonia and consequent severe acute respiratory syndromes, neurological symptoms. The first evidence of this was the study of Mao et al. gathered in three designated special care centers for COVID-19 (Main District, West Branch, and Tumor Center) of the Union Hospital of Huazhong University of Science and Technology in Wuhan, China. Out of 214 hospitalized COVID-19 patients, more than a third had neurological symptoms (159). Patients with more severe forms of SARS-CoV-2 infection were more likely to develop neurological symptoms. In fact, according to Li, 89% of COVID-19 patients who need respiratory assistance in the Intensive Care Unit report neurological manifestations, the most common of which are headache, nausea, and vomiting (45).

In addition, a case of SARS-CoV-2 viral encephalitis was reported in Beijing's Ditan hospital on March 4, 2020 (161). This clinical case, together with the data that collected the SARS-CoV-2 RNA in the cerebrospinal fluid, would confirm the neurotropism and neuroinfectious potential of SARS-CoV-2. More recently, in a study by Varatharaj et al. in the United Kingdom, complications from SARS-CoV-2 were reported in a group of 125 patients with neurological involvement: of the 62% who presented with a cerebrovascular event, a rate of 74% had an ischemic stroke, 12% an intracerebral hemorrhage and 1% a CNS vasculitis. Twenty-three percent of COVID-19 patients had unspecified encephalopathy and 18% had encephalitis (127). The remaining 59% of COVID-19 patients had symptoms characterizing an altered mental state and met the diagnostic criteria for psychiatric diagnosis after evaluation by the consultant psychiatrist. Ninety-two percent of these diagnoses were of new onset. Specifically, 43% of patients had new-onset psychosis, 26% had a neurocognitive syndrome (similar to dementia) and finally, 17% had an affective disorder (127).

The neurological manifestations described seem to be currently supported by the following mechanisms, as previously described in agreement with Heneka et al. (19): (1) direct viral encephalitis, (2) systemic inflammation, (3) peripheral organ dysfunction (liver, kidney, lung), and (4) cerebrovascular changes. In most cases, however, neurological manifestations of COVID-19 may arise from a combination of the above.

We propose a fourth possible mechanism, linked to the pathogenesis of SARS-CoV-2 infection or to the binding of the virus to ACE2, consequent to the downregulation of this receptor and to the alteration of the dynamic balance between the two arms of the RAAS: (1) ACE/Ang II/AT1R with proinflammatory activity and (2) ACE2/Ang-(1-7)/MasR with anti-inflammatory properties. In this speculative article we have generated a hypothesis that we reserve the right to verify in clinical practice in the following months on patients with acute SARS-CoV-2 infection and in the follow-up in COVID-19 survivors.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

DD, FP, and AA contributed to the conception and design of this paper. FP wrote the first draft of the manuscript. MS and LC collaborated in the editing of the manuscript. LC elaborated the figures. All authors contributed to manuscript revision, read, and approved the submitted version.

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STUDY PROTOCOL
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A Survey for Examining the Effects of COVID-19 and Infection Control Measures in Older Persons With Mild Cognitive Impairment and Dementia and Their Caregivers

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Background: During the first wave of the COVID-19 pandemic, many non-urgent outpatient services in Italy were closed due to the Government-enforced lockdown period. So far, little is known about what effect the pandemic, quarantine measures, and reductions in medical services had on people with cognitive impairment and their caregivers.

Objectives: To develop two versions (i.e., patients and informants/caregivers) of a survey designed to assess the impact of the COVID-19 pandemic during the first Italian lockdown period (11 March –4 May 2020) on Memory Clinic outpatients with Mild Cognitive Impairment (MCI) or dementia, and their caregivers.

Design: Psychiatrists, neuropsychologists, and epidemiologists developed two versions: one for patients with Mild Cognitive Impairment and other cognitive disorders, the other for their relatives and/or caregivers. Each version of the survey includes five sections: (a) socio-demographic information and access to technology devices; (b) individual COVID-19 protection methods; (c) knowledge about COVID-19; (d) the effect of COVID-19 on daily life; and (e) the effect of COVID-19 on emotional state.

Conclusion: Until an effective vaccine is developed it is likely that future waves of COVID-19 will result in shielding of vulnerable older adults. We believe that this instrument will be useful as a tool to collect information and help clinicians to promptly respond to changes in patients' cognitive, psychiatric, and somatic health needs, and to help for future planning in possible subsequent quarantine periods.

Keywords: COVID-19, SARS-CoV-2 coronavirus, neurocognitive disorders, mild cognitive impairment, MCI, dementia, caregivers, neuropsychiatric symptoms

INTRODUCTION

Since the first confirmed case of SARS-CoV-2 infection was reported in Wuhan China in December 2019 (1), the worldwide pandemic has already caused thousands of deaths in several countries, including Italy, which was one of the first European countries to be seriously affected (2, 3).

On 11 March 2020, the Italian Government implemented a series of measures to contain the spread of the virus including unprecedented levels and scales of quarantine, physical distancing, and community lockdowns with people staying at home, leaving only for essential services or activities (e.g., travel to work for essential workers, grocery shopping, urgent medical care etc.). In addition, many non-urgent outpatient services were closed and appointments canceled or postponed in order to reduce the risk of infection in patients and healthcare personnel and to ease burden on the national healthcare service (4). Many countries have employed similar lockdown and social distancing measures (5). Although this focus on procedures to urgently slow SARS-CoV-2 infection rates and minimize the number of infected individuals is of utmost importance, it also has relevant implications for the short—and long -term health and well-being of patients with non-communicable diseases (6), including neurological and psychiatric conditions. It is possible that patients with pre-existing clinical conditions may experience a worsening of their symptoms or an increase in disease progression in relation to some of the infection containment measures (e.g., due to lack of exercise, social isolation, etc.).

Patients with Mild and Major Neurocognitive Disorders [e.g., Mild Cognitive Impairment (MCI), Alzheimer Disease (AD)] are particularly vulnerable in the ongoing pandemic due to the high prevalence of chronic diseases and disabilities. These individuals have experienced a change in access to both formal and informal care during the pandemic. Additionally, the objective evidence of cognitive impairment (i.e., memory, executive function), may cause difficulties in following safeguarding procedures (such as wearing masks, social distancing, and hygiene) or in understanding the public health information issued to them, thus generating anxiety and emotional distress for both themselves and their caregivers. In patients with Neurocognitive Disorders an association between neuropsychiatric symptoms and lack of cognitive stimulation (7–9) and social isolation (10–12) have been shown. During periods of confinement, informal caregivers and family members may also experience management, economic, and personal difficulties (13, 14).

Since the beginning of the pandemic, the scientific community has made great efforts to investigate and document the possible effects of government containment measures on the population but evidence is sparse. Most studies focused on describing the effects of the pandemic on the general young and adult population, showing worsening in mood, anxiety, and manifestations similar to Post-traumatic Stress Disorder (15–21). Conflicting data also emerged from studies exploring the effect of confinement on quality of life and mental health in patients' with Neurocognitive Disorders. While one research group (22) reported that only a small percentage of people with AD experienced worsening of cognitive and neuropsychiatric aspects, others observed significative worsening of neuropsychiatric symptoms (i.e., agitation, apathy, and aberrant motor activity) without a decrease in quality of life in either patients and caregivers (23). These conflicting results may be due to methodological differences and to the fact that, in some cases, the authors remotely administered interviews that were not specifically developed for the ongoing pandemic. Consequently, instruments that specifically allow an overall and comparable assessment of the impact of the pandemic on patients affected by Neurocognitive Disorders and their caregivers are urgently needed.

Here we describe two versions of a survey to assess the impact of the COVID-19 pandemic during the first Italian lockdown period (11 March—4 May 2020) on Memory Clinic outpatients and their caregivers. Due to the risk of infection to staff and patients, the survey was developed to be administered remotely (e.g., by phone call) to ensure that characteristics of patients could be accurately documented during the lockdown period, without the need for face-to-face contact. We show our study protocol and the structure of the survey, to allow other research groups to use it or adapted it according to cultural characteristics.

The primary aim of the study was to develop a survey evaluating: (i) patients' knowledge of COVID-19 and recommended hygiene procedures, (ii) barriers that these patients face during lockdowns in terms of infection control, such as lack of masks and disinfectant gel, and physical health, such as access to outdoor space for exercise, (iii) effects of lockdown procedures on access to medical care, prescription drugs, and informal care, (iv) mood and other behaviors of patients and caregivers during periods of lockdown, including depressive symptoms, anxiety, and problems sleeping, (v) effects of confinement on patients, and how this affects caregivers, and vice versa, and (vi) factors (lifestyle, living situation etc.) that correlate with mood in both caregivers and patients.

METHODS AND ANALYSES

Development of the Survey

The "Effect of the COVID-19 Lockdown on Persons with Neurocognitive Disorders and their Caregivers Survey" was developed to comprehensively assess the impact of the COVID-19 lockdown on outpatients with MCI, dementia, and their caregivers. The survey has two versions: (i) patients and (ii) informants/caregivers. The latter was formulated to collect information about the informant/caregivers themselves as well as the older person that they were taking care of. The survey was developed by a group of experts specialized in Neurocognitive Disorders, including Geriatric Psychiatrists, Neuropsychologists, and Epidemiologists. They established crucial research questions of interest during the pandemic (e.g., What is the level of knowledge about COVID-19, protection methods and infection control measures etc.? What was the impact of the lockdown on the medical appointments and medication availability? Did the pandemic have an effect on daily activities? Did patients and caregivers express symptoms of anxiety, stress, depressed mood and other symptoms during lockdown? etc.).

It consists of five sections: (a) general information, including socio-demographic information and access to technology devices; (b) individual protection methods; (c) knowledge about COVID-19; (d) the effect of COVID-19 on daily life and (e) the effect of COVID-19 on emotional state. It includes novel questions devised to assess the new pandemic, as well as questions adapted from existing scales (24, 25). The survey was designed using language that was familiar to lay persons (e.g., using terms such as "coronavirus" etc.).

The "General Information" section in the patient version of the survey provides socio-demographic information about older adults, with a focus on their accommodation type, with whom they lived during the quarantine and collects information on tobacco and alcohol consumption (from questions 1 to 8). We included specific questions related to the environment of the individuals, including whether they had access to outdoor space, and what type of technology they had access to for communicating with family and friends. These questions were designed to identify whether any environmental factors were related to emotional state.

"Individual protection methods" (questions 9–11), assesses type of individual protection methods (e.g., if they have a surgical mask, if was difficult to obtain one, how often they wash their hands, and for how long). These questions were designed to assess whether there are any practical limitations that may lead to problems following Government guidelines (e.g., lack of face mask availability or cognitive difficulties in understanding regulations).

The third section, "Knowledge about COVID-19" (questions 12–16) investigates how well the patients kept themselves informed about COVID-19 and Government regulations through media.

The section "The effect of COVID-19 on daily life" (questions 17–31) is the core of the survey. It ranges from questions about concerns of COVID-19 (fear of infection and type of symptoms experienced in case of illness), how individuals changes their daily routines due to confinement, physical activities, help in basic and instrumental activities of daily living, changes in drug intake (e.g., due to forgetfulness), medical visits missed, difficulties in purchasing medication, type and frequency of communication with relatives and friends.

The last section "The effect of COVID-19 on emotional state" consist of 23 questions in both patients and caregivers; the informant version includes questions about distress-burnout.

The caregivers' version investigates similar aspects, with a focus both on the caregiver and patient; in this case the caregiver expresses their opinion on how the patient has coped with confinement and quarantine measures.

The survey was edited both in Italian and English. Both versions were translated and back-translated by native speakers. The complete survey is provided in **Appendices 1–4**.

Design of the Ongoing Study

We conducted an observational study using the two versions of the survey. To determine the sufficient sample size, a power analysis was conducted using G*Power with an alpha of 0.05, a power of 0.95, an effect size of 0.35 and a predictor number of 10. Based on the aforementioned assumptions, the desired total sample size was 80. Considering that comparable studies for dementia cohorts with a sample size > 100 showed efficacy in describing neuropsychiatric phenomena, we contacted 150 patients and 150 caregivers (26–28).

Patients and their caregivers were identified using a large, established research database from the outpatient Memory Clinic at Santa Lucia Foundation IRCSS, which has been used for previous studies (29–31). All patients referred to our clinic underwent extensive neurological, neuropsychiatric, and cognitive testing and diagnosis was made according to international diagnostic criteria (32). Patients who participated in previous research studies and who gave their permission to be contacted for future studies, were phoned by the research team (neuropsychologists) to ask if they would like to participate in the new survey. Those consenting to participate in the study were asked if they agree for their caregiver to be contacted. Caregiver has been defined as a family member, friend, or other, who undertakes unpaid care in and assistance in activities of daily living (child, spouse, etc.) (33). Data collected during the first Italian lockdown period will be used in future works.

ETHICS AND PROCEDURES

The Santa Lucia Foundation ethical review board approved the study protocol (code number CE/PROG.827). Prior to the administration of the survey, we fully informed participants about the study design, purposes and type of involvement required, specifying that they could withdraw from participation at any time. They had the opportunity to ask questions and they received a copy of the informed consent by post. In order to minimize unnecessary face-to-face contact and to adhere to Government restrictions, the survey was administered remotely (i.e., by phone call) by a trained psychologist or physician. The time of administration was ∼25 min.

DISCUSSION

The aim of this paper was to describe a comprehensive survey that was developed to assess specific aspects of the COVID-19 pandemic and infection control measures in patients with Neurocognitive Disorders and their caregivers. We aimed at providing a comprehensive instrument that can assess multiple consequences of the pandemic. Before the pandemic, there were no scales that could accurately assess the novel characteristics that individuals now face in relation to lockdown measures, such as whether patients have access to outdoor space for exercise and whether there are any changes in the amount of informal and formal care received. Importantly, our survey aimed at assessing how these factors may affect the mood and other neuropsychiatric behaviors of both patients and caregivers. Furthermore, the survey includes a specific section on caregiver distress and provides information on their point of view of how the patient is coping. Another novel aspect is the investigation of practical aspects that may have great importance in these patients, such as the effect of the lockdown access to medical appointments and treatments. Government regulations, restrictive measures, and other aspects of the pandemic are continually changing, making it challenging to develop a survey that will be fully relevant in the long term. For example, as new outbreaks occur, it is likely that some restrictive measures differ from the first wave of the pandemic. However, we believe that the present survey will be a useful tool to collect information about possible changes in patients' status and help clinicians to promptly respond to changes in patient's health.

The COVID-19 pandemic makes it important to design specific instruments to assess consequences which have never been experienced before. In addition, to assessing changes in patients' cognitive and mental health symptoms, our survey also provides important assessment of the secondary consequences of infection control measures, such as reduced access to medical services or difficulties getting prescriptions, and practical limitations that were faced by many people during the pandemic, such as access to reliable information on COVID-19 and lack of available infection protective equipment, such as masks and gloves. Responses to these questions could be relevant in the near future, when additional peaks or further waves of COVID-19 are highly possible. Policy makers may need to consider such limitations when planning subsequent lockdowns. The survey can also be used in the event of another lockdown period, to assess changes in patient and caregivers' status in comparison to the first wave of COVID-19.

Some limitations of the survey should be discussed. The pandemic is a completely novel event, and Italy was one of the first countries to be badly affected. It was important to act promptly because the restrictive measures on research and clinical activities by government regulations made it impossible to create a focus group on site with patient and caregiver advocates. Thus, the survey was not developed in conjunction with either patients or caregivers. However, a consensus meeting with a group of psychiatrists, neuropsychologists, and epidemiologists with extensive expertise on the target group was conducted. Another aspect to be considered is the lack of validated COVID-19 pandemic scales during the lockdown. Further, the COVID-19 pandemic is a rapidly evolving situation and it was challenging to develop a survey in the early stages of the pandemic, capturing all aspects that might affect patients with neurocognitive disorders in the first and subsequent potential COVID-19 outbreaks. There has been an unprecedented increase of scientific publications on the topic of COVID-19 (34–37), and evidence is emerging daily. For example, several publications have now indicated that there might be a form of post-traumatic stress disorder directly related to the virus and the lockdown scenarios (17, 20), yet our survey did not directly assess this issue. Our survey was designed to get a picture of the situation faced by memory clinic outpatients during the first wave of the pandemic, when only telephone assessment was possible, which limited the possibility to diagnose precisely complex mental disorders. However, focusing mainly on dimensional phenomenology, as we did, may capture fundamental aspect of status psychopathology.

DISSEMINATION

In future stages, we will describe the results collected using the survey in our Memory Clinic patients, who are already involved in other research projects (8, 29, 30, 38). We aim to compare the results of our survey with other assessments both in Italy and other countries. The two specific versions of the survey will allow to assess how patient characteristics affected caregiver status during the quarantine period and will hopefully highlight issues that need to be addressed in future outbreaks. Further, the rich pre-pandemic dataset from our memory clinic will allow to assess changes in mood and other neuropsychiatric characteristics during the quarantine period comparing to pre-pandemic status. Other secondary objectives that will be clarified include: how caregiver burden during the lockdown correlates to specific factors (e.g., increased patient stress) and how stress levels differed between caregivers living with and those separately from patients.

Until an effective vaccine is developed it is likely that future waves of COVID-19 will mostly affect vulnerable older adults, and we are confident that our survey will help to provide information to better protect them and their caregivers.

AUTHOR CONTRIBUTIONS

GS, NB, and KP conceived the study protocol and the structure and content of the paper. DP, NB, and KP wrote the paper. NB, VC, and GS provided revisions of the paper. 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/fpsyt.2020.599851/full#supplementary-material

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A Polish and German Population Study of Quality of Life, Well-Being, and Life Satisfaction in Older Adults During the COVID-19 Pandemic

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Introduction: Psychological studies undertaken during the COVID-19 pandemic rarely include people in their 60s or older. In our study, we studied the predictors of quality of life, well-being, and life satisfaction (including risky behavior, trait anxiety, feeling of threat, sleep quality, and optimism) during the pandemic in older people from Germany and Poland and compared them to three different age groups.

Methods: A total of 494 adults in four groups—60+ ($N = 60$), 50–60 ($N = 139$), 36–49 ($N = 155$), <35 ($N = 140$)—completed validated self-report questionnaires assessing: socio-demographic data, quality of life, trait anxiety, risk tolerance, Coronavirus threat, optimism regarding the pandemic, difficulty relaxing, life satisfaction, well-being, and sleep quality during the pandemic period.

Results: Older people rated their quality of life higher than did young (mean difference=0.74, SE=0.19, $p < 0.01$) and middle-aged (mean difference=0.79, SE=0.18, $p < 0.01$) participants, rated their life satisfaction higher than young (mean difference=1.23, $SE = 0.31$, $p < 0.01$) and middle-aged (mean difference=0.92, $SE = 0.30$, $p < 0.05$) participants, and rated their well-being higher than young (mean difference=1.40, $SE = 0.31$, $p < 0.01$) and middle-aged (mean difference=0.91, $SE = 0.31$, $p < 0.05$) participants. They also experienced lower levels of trait anxiety and Coronavirus threat (mean difference=-9.19, $SE = 1.90$, $p < 0.01$) than the younger age groups. They experienced greater risk tolerance (mean difference=1.38, SE=0.33, $p < 0.01$), sleep quality (F =1 .25; $eta^2 = 0.01$), and optimism ($F = 1.96$; $eta^2 = 0.01$), and had less difficulty relaxing during the pandemic ($F = 3.75$; $eta^2 = 0.02$) than middle-aged respondents.

Conclusions: Quality of life, life satisfaction, and well-being during the pandemic is affected by age, trait anxiety, and Coronavirus threat. Older people rated their quality of life, life satisfaction, and well-being during pandemic higher than young people, and experienced lower levels of trait anxiety and Coronavirus threat than the younger age groups. They experienced greater risk tolerance, sleep quality, and optimism, and had less difficulty relaxing than middle-aged respondents.

Keywords: anxiety, risk tolerance, quality of life, life satisfaction, well-being, sleep quality, orderly, Pandemic (COVID-19)

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INTRODUCTION

The first case of COVID-19 was reported in Wuhan City, China on the 9th January, 2020 (1), and currently over 8 million cases have been reported in 216 countries (2). The risk of death and serious complications associated with COVID-19 increases with age. Data from most countries indicates that the rise in mortality rates in people suffering from pre-existing medical conditions (severe chronic diseases, e.g., heart disease) was an additional factor burdening the elderly population (3, 4). At the same time, the co-occurrence of other chronic diseases may mask the COVID-19 infection (5).

To define "elderly," we used the cut-off age of 60 years, as suggested by the WHO (6). Data from the Oxford COVID-19 Evidence Service (from the 25th March 2020) indicates a risk of mortality of 3.6% for people in their 60s, which increases to 8.0 and 14.8% for people in their 70s and 80s, respectively (7). To date, about 80% of COVID-19-related deaths have been of people aged over 60. According to data from the United States, from 10 to 27% people aged over 85 are at risk of death (8, 9).

Apart from the psychological burden associated with the risk of getting infected with a potentially serious and often deadly disease, health authorities in many countries have introduced numerous restrictions that could themselves have had a detrimental effect on the psychological functioning of elderly people (10). The isolation regulations introduced in many countries, including Poland and Germany, limited the availability of many services important for the everyday functioning of elderly people, including medical facilities (which is particularly relevant for elderly individuals with chronic conditions, including mental illnesses). This could have had an adverse effect on their everyday emotional functioning (i.e., cause panic and anxiety) and their cognitive functioning (11).

The restricted contact with other people may have created a sense of danger of loss of social support, which is particularly important for elderly people. Social isolation, especially perceived social isolation (subjective and not necessarily accompanied by a real absence of social life), among older adults heightens their risk of cardiovascular, autoimmune, neurocognitive, and mental health problems (12, 13). Perceived social isolation has a stronger link with mental disorders, especially depressive symptoms (14–17) and neurodegeneration (13, 18).

Fear of COVID-19 has been shown to lead to various anxiety disorders (concerns, panic attacks, insomnia, fear of death, fear of the unknown, PTSD) and depressive states, sustained by the incessant flow of news regarding the virus, the number of infections, mortality rates, and insufficient control, and treatment measures (13). Psychological distress and anxiety [which is a common response to any stressful situation; (19)] impacts sleep quality (20, 21). Reduced sleep quality negatively affects life satisfaction, health status, as well as the social and emotional domains (21–23). Difficulties accessing medical services or specific psychiatric treatment have led to mental relapses and uncontrollable behaviors [hyperactivity, agitation, and self-harm; (24)]. Some researchers report that uncertainty about the possibility of becoming ill and dying and about the health of family and friends has heightened dysphoric mental states (25, 26). On the other hand, social distancing measures slow down the spread of the virus and prevent older people being exposed to the disease (8).

Another consequence of the pandemic was the emergence of widespread reliance on remote technologies; this could be a particular challenge for the elderly. However, because older adults are the least likely to use internet and mobile technologies, they may now experience a greater sense of isolation (11). It has been found that the lockdown and fears about the virus have led to stress in older adults (27). Because older adults are at risk of COVID-19, they are under enormous stress in addition to their existing vulnerabilities. Although the effects of social isolation are different to the effects of loneliness, efforts to reduce social isolation could lead to a lower mortality rate (26, 28).

Until now, the scarce research on the functioning of elderly people during the pandemic has focused on depression, stress, and distress, rather than the positive aspects of quality of life, life satisfaction, and well-being. Furthermore, it has concentrated mainly on those who contracted COVID, e.g., after respiratory rehabilitation (29) or on elderly individuals who are expected to become ill (30). Thus, we decided to include both the positive and negative aspects of the functioning of elderly people during the pandemic, independently of their concerns about falling ill and their health condition at the time of the study.

We understand life satisfaction as an individual's evaluation of their life as a whole, while quality of life refers to the level of general well-being (31–33). Both can be represented on a continuum, but, in the opinion of some researchers [see (34, 35)], life satisfaction is more subjective and can be affected by how a person feels on a given day, whereas quality of life can be measured and fluctuates less. But an individual's own assessment of their quality of life could also be subjective and affected by mood or circumstances (i.e., the current pandemic) and thus similarly variable. Positive well-being has been conceptualized by Ryff et al. (36) and others (37, 38) as subjective (hedonic) well-being, which emphasizes happiness and pleasure, and psychological (eudaimonic) well-being, which focuses on the fulfillment of human potential.

In our study, we focused on identifying the predictors of quality of life, well-being, sleep, and life satisfaction during the pandemic in older people from Central Europe (Germany and Poland), including factors such as risk behavior, trait anxiety, feeling of threat, sleep quality, and optimism, comparing them to three different age groups. This is the first study whose goal was to investigate the psychological functioning of older people during the COVID-19 pandemic and the first study to assess psychological outcomes of the COVID-19 pandemic in older people in Poland and Germany.

METHODS

Participants and Procedure

The sample comprised 494 adults (72% female, 24% males, 4% missing data) with a mean age of 42.97 years (range 16–82, *SD* = 9.77). Inclusion criteria were: age>18 years and consenting to participate in the study. Exclusion criteria included: age<18

TABLE 1 | Socio-demographic characteristics of the study sample.

Demographic variable	Female (n = 353)		Male (n = 120)		Total (n = 494)*	
	N	%	*N*	%	*n*	%
Age						
<35	101	28.6	33	27.5	140	28.3
36–49	123	34.8	23	19.2	155	311.4
50–60	95	26.9	35	29.2	139	28.1
60+	34	9.6	29	24.2	60	12.1
Nationality						
German	284	80.5	93	77.5	377	80.6
Polish	69	19.5	27	22.5	96	19.4
Education level						
Secondary education	147	41.6	52	43.3	208	42.1
University education	206	58.4	68	56.7	286	57.9
Marital status						
Single	83	23.5	29	24.2	115	23.3
Married or partnership	208	58.9	69	57.5	295	59.7
Divorced or separated	32	9.1	7	5.8	39	7.9
Widow/widower	1	0.3	–	–	1	0.2
Missing data	29	8.2	15	12.5	44	8.9

**21 participants did not answer the question about gender, therefore the total sample is not equal to the sum of men and women.*

years, not consenting to participate in the study, or no access to the Internet in order to fill-out the study. **Table 1** shows the socio-demographic characteristics of the sample. A large majority of the sample were German citizens (80.6%) and the remaining participants were from Poland. Participants were mainly in relationships (58.9%) or single (23.5%).

Most participants were not quarantined either before or during the study (n = 378, 76.5%); 83 people quarantined voluntarily and 33 were quarantined in accordance with official procedures. The number of quarantined participants varied across the surveyed age groups (29% for the youngest group, 17% for the middle-aged group, 22% for pre-retirement age, and 28% for older people).

Research Procedure

The study is a part of broader research project named Health Cube—Survey—Corona Virus COVID19 "Psychological coping, possibilities of crisis intervention and aftercare in companies and institutions for adults, parents and children." The study was conducted during the pandemic (specifically the period of restrictions between the 27th March and the end of April 2020) in Poland and Germany. The researchers contacted participants by email. The participants completed the surveys online via the link provided. Using Google Forms, a link to a self-report questionnaire was sent by e-mail or made public on other online platforms (e.g., Facebook, Instagram, Messenger, WhatsApp). Participants could contact the researchers via email or other online platforms at any time. The research project was reviewed and approved by the Ethical Committee (decision no. 30/2020) at the Institute of Psychology at the University of Gdansk, Poland. The following research tools were used:

1. A socio-demographic survey created for this study.
2. Quality of life was measured using the mean of an 11-item semantic differential scale (also known as a polarity, polarity profile, or impression differential; 36) consisting of the following items: nervous—free of complaints, confusing—clear, distracted—structured, frightening—fearless, aggressive—peaceful, insecure—self-confident, meaningless—meaningful, helpless—self-controlled, mistrusting—trusting, dependent—autonomous, contradicting—coherent. The short version of the scale was chosen because it measures some features of the long form of the questionnaire more economically. The original version of the semantic differential was developed by Osgood et al. (39) and is used to assess personality attitudes (40). The test respondents are given terms to differentiate between using bipolar scales (39). The given terms should be classified spontaneously rather than rationally and objectively (41). The reliability of the scale in the current study was assessed using Cronbach's alpha, which equaled 0.91.
3. Trait anxiety was measured with the Trait Anxiety Scale (42)—a self-report questionnaire consisting of 10 items (we used the sum of the responses as a measure of the variable). Trait anxiety is the "intraindividually relatively stable, but interindividually varying tendency to perceive situations as threatening and to react to them with an increased state of anxiety, whereby fearful individuals generally react more violently to threatening situations than non-fearful ones" (Krohne, p. 8). The reliability of the scale was assessed using Cronbach's alpha, which equalled 0.84.
4. Risk tolerance was assessed with the single-item Risk Tolerance scale (43): "How do you see yourself – how willing are you in general to take risks?." Respondents answered on a scale of 1–10 (1-not at all, 10-very much).
5. *The a*uthors' own five single-item measures concerning anxiety related to Coronavirus. Participants were asked to assess the strength of their fears about COVID-19 in relation to: *Coronavirus threat*— "Do you experience the situation regarding the Coronavirus as a threat?" (1-not at all, 10-very much); *Optimism regarding the pandemic*— "Are you optimistic regarding a solution?" (1-very pessimistic, 10-very optimistic); *Difficulty relaxing during the pandemic period*—("To what extent have you been able to completely relax in calm moments?" (1-without any problems, 10-with great difficulty); *Life satisfaction during the pandemic period*- "How satisfied are you with your life?" (1-not at all, 10-very much); *Wellbeing during the pandemic period*— "How would you describe your state of well-being?" (1-not very good, 10-very good).
6. In addition, the measurement of Coronavirus anxiety levels was supplemented with a single item concerning *Sleep quality*

during the pandemic period. Study participants reported their concerns on a five-point Likert scale (1-very bad, 2-bad, 3-medium, 4-good, and 5-very good).

7. Based on known, valid, and reliable measuring instruments, we have modified and developed a single-item scale for measuring general life satisfaction (43, 44).

These single-item scales are economical, valid, and reliable measuring instruments that can reasonably be used for group comparisons in the context of social science surveys if a measurement with more extensive scales is not possible (45). The reliability of these single-item scales was estimated using the test-retest method. In a quota sample with a repeated measurement interval of 6 weeks on average, the stability of the scales was rtt=0.67 (medium stability), which is sufficient for group examinations (45). All measures were in German, so they were translated into Polish and then back-translated. The original items were translated into Polish by two translators independently—a German teacher and a psychologist. Next, the translators settled upon the best Polish version, which was then back-translated (into German) by a Native Speaker who had not seen the original version. A bilingual translator assessed the agreement of the back translation with the original.

Statistical Analysis

Firstly, we classified respondents into four distinct age groups: young, middle-aged, pre-retirement, and older people. We used theoretical and, statistical criteria to generate these groups in order to give proper meaning to the findings of our study. Respondents in the group of young people were between 16 and 35 years old ($M = 28.57$, $SD = 4.81$); the middle-aged group consisted of people from 36 to 49 years old ($M = 41.83$, $SD = 3.86$); the pre-retirement group ranged from 50 to 60 years old ($M = 55.17$, $SD = 2.80$); and the older group ranged from 61 to 82 years old ($M = 65.70$, $SD = 5.20$).

Then we assessed the means, standard deviations, and intercorrelations (Pearson's r or Spearman's rho depending on the variable's scale) for the study variables on the entire sample. Age differences were assessed by ANOVA by calculating effect sizes. Internal consistency was assessed by calculating Cronbach's alpha coefficients for multi-item scales.

Finally, in order to test the hypothesis regarding the predictors of well-being, sleep, and life quality during the pandemic, we conducted a series of multiple regression analyses using only the sample of older people. Before running the regression analysis, we checked the predictors' multicollinearity using the variance inflation factor (VIF). We used SPSS 26 for all calculations.

RESULTS

Descriptive Statistics

Table 2 provides descriptive statistics and correlations of variables examined in the study. It is worth noting that trait anxiety was positively correlated with Coronavirus threat and difficulty relaxing during the pandemic period, while it was negatively correlated with risk tolerance and, all variables regarding quality of life during the pandemic period. The opposite was found for risk tolerance: there was a negative correlation with Coronavirus threat and difficulty relaxing during the pandemic period, and a positive correlation with all variables regarding quality of life.

Hypothesis Testing

To investigate the differences between older people and people from other age groups with respect to the variables examined in the study, we conducted an analysis of variance (ANOVA) with the Bonferroni multiple comparisons test. The results show a significant difference among people in different age groups with respect to anxiety as a trait, risk tolerance, difficulty relaxing, life satisfaction, well-being, and quality of life during the pandemic period. The means and standard deviation scores supported with the Bonferroni multiple comparisons test indicated that older people scored less than young people on anxiety (mean difference=-9.19, $SE = 1.90$, $p < 0.01$) and greater than young people on risk tolerance (mean difference = 1.38, $SE = 0.33$, $p < 0.01$). Older people scored less than middle-aged respondents (mean difference=-1.07, $SE = 0.38$, $p < 0.05$) on difficulty relaxing during the pandemic period, and more than young (mean difference=1.23, $SE = 0.31$, $p < 0.01$) and middle-aged (mean difference=0.92, $SE = 0.30$, $p < 0.05$) respondents on life satisfaction during the pandemic period; they scored more than young (mean difference=1.40, $SE = 0.31$, $p < 0.01$) and middle-aged (mean difference=0.91, $SE = 0.31$, $p < 0.05$) respondents on well-being during the pandemic period, as well as more than young (mean difference=0.74, $SE = 0.19$, $p < 0.01$) and middle-aged (mean difference=0.79, $SE = 0.18$, $p < 0.01$) participants on quality of life during the pandemic period. Descriptive statistics for the sample and ANOVA results are presented in **Table 3**.

In order to test predictions regarding the effects of risk tolerance, trait anxiety, difficulty relaxing, and optimism (controlling for age, sex, education level, and being quarantined) on dependent variables, four separate multiple regression analyses were run. The variance inflation factors estimated for predictors included in the models did not show the multicollinearity problems (VIF ranged from 1.04 to 1.84). For estimating regression coefficients and standard errors, we applied the bootstrap procedure with 1,000 samples. A summary of the results of these analyses is presented in **Table 4**.

The results of the four multiple regression analyses showed a significant and negative effect of trait anxiety on three of the tested variables: life satisfaction ($B = -0.08$, $SE = 0.02$, $\beta = -0.47$, $p < 0.01$), well-being ($B = -0.06$, $SE = 0.02$, $\beta = -0.39$, $p < 0.01$), and quality of life ($B = -0.04$, $SE = 0.01$, $\beta = -0.36$, $p < 0.01$) during the pandemic period (specifically, during the restriction period from the 27th March until the end of April), indicating that life satisfaction, well-being, and quality of life during the pandemic period were lower for older people with high anxiety. Additionally, we found that difficulty relaxing during the pandemic period was a significant, negatively correlated predictor of life satisfaction ($B = -0.25$, $SE = 0.10$, $\beta = -0.31$, $p < 0.05$) and wellbeing ($B = -0.23$, $SE = 0.10$, $\beta = -0.34$, $p < 0.05$).

TABLE 2 | Descriptive statistics and intercorrelation matrix for the variables examined in the study.

Variable	*M*	*SD*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
1. Trait anxiety	34.09	12.65	(0.84)								
2. Risk tolerance (trait)	5.63	2.17	−0.42**	–							
3. Coronavirus threat	5.44	2.61	0.29**	−0.21**	–						
4. Difficulty relaxing	3.98	2.52	0.45**	−0.22**	0.34**	–					
5. Optimism	6.58	2.31	−0.40**	0.28**	−0.40**	−0.35**	–				
6. Life satisfaction	7.19	2.02	−0.53**	0.28**	−0.26**	−0.44**	0.37**	–			
7. Sleep quality	3.56	1.01	−0.47**	0.14**	−0.14**	−0.45**	0.26**	0.26**	–		
8. Wellbeing	7.31	2.05	−0.57**	0.25**	−0.10*	−0.22**	0.26**	0.37**	0.28**	–	
9. Quality of life	4.52	1.23	−0.52**	0.24**	−0.39**	−0.52**	0.46**	0.53**	0.30**	0.36**	(0.91)

*N = 494, alphas on diagonal (for multi-item measures). *p < 0.05; **p < 0.01.*

TABLE 3 | Age differences among variables examined in the study.

Variable	Young	Middle-aged	Pre-retirement	Older	*F*	*eta²*
	M (SD)	M (SD)	M (SD)	M (SD)		
Trait anxiety	38.34 (12.62)	35.00 (13.12)	30.88 (11.81)	29.15 (9.61)	12.20**	0.07
Risk tolerance (trait)	4.94 (2.10)	5.63 (2.10)	6.01 (2.17)	6.32 (2.12)	8.45**	0.05
Coronavirus threat	5.11 (2.47)	5.63 (2.56)	5.62 (2.82)	5.32 (2.59)	1.29	0.01
Difficulty relaxing	3.95 (2.57)	4.49 (2.72)	3.70 (2.32)	3.42 (2.14)	3.73*	0.02
Optimism	6.49 (2.40)	6.29 (2.37)	6.91 (2.15)	6.78 (2.23)	1.96	0.01
Life satisfaction	6.74 (2.25)	6.94 (1.87)	7.63 (1.93)	7.86 (1.72)	7.68**	0.05
Sleep quality	3.45 (1.06)	3.53 (1.09)	3.65 (0.90)	3.67 (0.93)	1.25	0.01
Wellbeing	6.69 (2.20)	7.17 (2.05)	7.75 (1.94)	8.08 (1.44)	9.86**	0.06
Quality of life	4.37 (1.08)	4.32 (1.21)	4.65 (1.38)	5.11 (1.06)	7.31**	0.04

N = 494, df = 3.
**p < 0.05; **p < 0.01.*
*The differences remain significant even after excluding quarantined individuals (see **Supplementary Table 1**).*

DISCUSSION

Quality of life research in the 60+ age group during the pandemic suggests contradictory results. In our research, older people rated their quality of life, well-being, life satisfaction, and quality of sleep better than all three of the younger comparison groups. Vietnamese studies (30) show that during the COVID-19 pandemic, older people had lower quality of life than the younger age groups. Numerous studies, such as Huong et al. (46), have indicated associations between lower quality of life and older age (≥80 years), and lower education levels. In our opinion, the higher assessment of quality of life, well-being, and life satisfaction in the elderly people who took part in our study might be associated with both their education (most of them reported University education, i.e., 61.7%—which is more than in the total sample) and the financial stability (most of them with the right to retirement) of the elderly people in Poland and Germany during the pandemic. In contrast to younger individuals, people receiving retirement pensions were not facing the threat of job loss. This is supported by the existing literature, which indicates that higher levels of quality of life among people aged 60 years and older depend on factors broadly ranging from socioeconomic status to overall health and the ability to maintain an active and independent lifestyle (47, 48). Here, it is worth stressing that research indicates that older people perceive "successful aging" as positive when associated with the absence of illness and the experience of positive reinforcements in the areas of activity, income, social life, and the relationship with one's family (49). Creative and social activities that sustain belonging to a social group support the positive aging process (50). The higher assessment of quality of life, well-being, and life satisfaction in the studied sample of elderly people is also associated with lower anxiety.

The result indicating a lower level of perceived anxiety and Coronavirus threat in older people is interesting because this group is exposed to the greatest risk of developing COVID-19. Asian studies show that, during the COVID-19 pandemic, 37.1% of elderly people experienced depression and anxiety. Moreover, Qiu et al. (51) have recently indicated that the emotional reaction of older people aged (over 60 years old) is more pronounced. The study found gender differences in this emotional response, with women experiencing more anxiety and depression than men. However, in our study, gender was not a significant predictor of quality of life, well-being, or life satisfaction.

The results of our research indicate lower anxiety levels and Coronavirus threat levels in older people, which can depend on

TABLE 4 | Summary of results of multiple regression analyses.

Predictor	Life satisfaction during the pandemic period		Well-being during the pandemic period		Quality of life during the pandemic period		Sleep quality during the pandemic period	
	B [95% C.I.]	**SE**	**B [95% C.I.]**	**SE**	**B [95% C.I.]**	**SE**	**B [95% C.I.]**	**SE**
Age	−0.04 [−0.12;0.06]	0.05	0.04 [−0.06;0.10]	0.04	−0.04 [−0.09;0.02]	0.03	−.01 [−0.05;0.04]	0.02
Sex	0.13 [−0.63;0.96]	0.41	0.28 [−0.49;0.90]	0.35	−0.10 [−0.61;0.41]	0.25	0.03 [−0.49;0.73]	0.26
Education level	−0.38 [−1.15;0.43]	0.40	−0.92** [−1.45; −0.33]	0.28	−0.31 [−0.77;0.16]	0.24	0.07 [−0.45;0.73]	0.30
Quarantine	0.81 [−0.05; 1.57]	0.42	−0.31 [−0.96;0.36]	0.36	−0.36 [−1.01;0.27]	0.34	0.07 [−0.58;0.66]	0.31
Risk tolerance	0.03 [−0.12;0.25]	0.10	0.08 [−0.08;0.23]	0.08	0.04 [−0.10;0.15]	0.07	0.13 [−0.02;0.28]	0.08
Trait Anxiety	−0.08** [−0.12; −0.03]	0.02	−0.06** [−0.09; −0.03]	0.02	−0.04** [−0.06; −0.02]	0.01	−0.02 [−0.05;0.01]	0.01
Coronavirus threat	0.07 [−0.13;0.24]	0.09	0.13 [−0.01;0.26]	0.07	−0.04 [−0.15;0.07]	0.05	0.00 [−0.15;0.14]	0.07
Difficulty relaxing during the pandemic period	−0.25* [−0.46; −0.03]	0.11	−0.23* [−0.45; −0.07]	0.10	−0.08 [−0.15;0.06]	0.06	0.05 [−0.11;0.22]	0.08
Optimism regarding the pandemic	0.10 [−0.12;0.30]	0.11	0.12 [−0.03;0.28]	0.08	0.11 [.01;0.26]	0.06	−0.05 [−0.22;0.12]	0.09
Adjusted R^2	**0.39**		**0.44**		**0.47**		**−0.04**	

*The bold value indicates, B - unstandardized regression coefficient; C.I. - confidence interval; SE - standard error. N = 60, *p < 0.05, **p < 0.01, bootstrap results are based on 1,000 bootstrap samples.*

many variables. One explanation may be their limited access to news (beyond radio and TV) that could increase their awareness of COVID-19 and thus affect their level of anxiety. In addition, some studies indicate that despite the existence of COVID-19 measures and, in spite of the lockdown, some older people self-isolated less than others (52) because they needed to look after their grandchildren (while the nurseries, kindergartens, and schools were closed), which may have had a positive effect on their mood.

Relatively speaking, during a pandemic, older people may have the least to lose compared to younger people, who are afraid of losing their social status and jobs as well as not being able to provide for their families, as they generally have a well-established professional position and/or receive a pension. Throughout their lives, older people have experienced various crises. Some individuals from both countries are World War II survivors, but all older respondents grew up in the shadow of WWII, because their parents or grandparents experienced it; the same applies to Martial Law (13th December 1981–22nd July 1983) in Poland, and the erection (13th August 1961) and the fall of the Berlin Wall (9th November, 1998) in Germany. These experiences could have taught them to remain more detached from the news, but may have also given them the sense that—in the words of one of the participants—"one can live through anything." These experiences might have affected their perception of the COVID-19 pandemic. In addition, older people often compare themselves mainly with people from their own age group, who are often in a worse position (47).

A factor that seems to have a positive impact on life satisfaction is sleep. Recognized as an important element of human life, it strongly affects our emotional states. In addition, short sleep duration and poor sleep quality have a significant impact on lower life satisfaction levels (22, 53). Results indicating better quality of sleep (which is closely related to lower anxiety) in older participants may also explain higher life satisfaction. The results indicate a significant dissimilarity between people in different age groups with respect to trait anxiety, risk tolerance, difficulty relaxing, life satisfaction, well-being, and quality of life during the pandemic period.

In our research, older people had greater risk tolerance than young people. This result contradicts the findings of research indicating that risk appetite and the tendency toward risky behavior decrease with age (54, 55). However, it is worth noting that people differ systematically in their risky behavior, and risk avoidance, and willingness to take risks (56). This personality trait plays an important role in the COVID-19 crisis, because it influences steps taken to protect one's own health and the extent to which people put themselves in danger, for example, by disregarding rules (e.g., not wearing a face mask, ignoring social distancing rules). Empirical findings support the assumption that self-reported willingness to take risks is a personality trait that changes over time and depends on the situation and context (56).

Relationships between willingness to take risks and satisfaction with life (54, 57) and self-efficacy (58, 59) are also reported. People who describe themselves as highly willing to take risks often tend to behave in a risky manner (56). The life experience and personal development of older people may indicate that, for them, taking risks during the pandemic, and thus increasing self-efficacy, is necessary. Older people had less difficulty relaxing during the pandemic than middle-aged people. This is probably related to the previously described economic and professional stability and the greater occurrence of risky behavior.

In comparison to the three youngest groups of participants, older people felt greater optimism regarding the pandemic. Only the group of participants aged 50–60 was more optimistic than the oldest group, which may be associated with a more realistic approach to life than that of young people. Ferguson and Goodwin (60) found that optimism is a predictor of both subjective and mental well-being, while the perception of control (in our research, risk behavior) mediates the relationship between optimism and psychological well-being. Dispositional optimism has been defined as the generalized expectation that a person will obtain good outcomes in life (61). It is construed as a stable personality characteristic. The positive effects of optimism have been demonstrated across diverse, stressful situations (53, 62). The positive effects of optimism could be mediated through positive coping strategies, for example, optimists use more problem-focused strategies—information seeking and positive reframing (62). Many researchers indicate that younger adults are more optimistic than older adults about their own future in 15 years. In contrast, in Durbin et al. (63), both age groups were similarly optimistic about their future at age 85 and expected it to be more positive than others' futures at this age.

This result indicates that the elderly people were more optimistic during the COVID pandemic, which could be explained by the lower number of potential stressors—for instance those associated with potential job loss, which was common among young individuals (64). This could have translated into lower anxiety, which is associated with higher optimism (62).

Strengths

The main strength of this study was that the research was carried out in a strictly defined time frame, during the pandemic period (specifically the restrictions between the 27th March and the end of April 2020) in Central Europe in two countries (Poland and Germany), on a fairly large population with varied age, sex, and socioeconomic status. The study concerned risk factors negatively affecting quality of life, life satisfaction, and well-being, as well as protective factors, improving the assessment of the respondents' psychological state during the pandemic.

Another strength of this study is the use of simple, short, and easy-to-comprehend scales measuring various constructs, which means high efficiency at low cost. Overall, the single-item scales are economical, valid, and reliable measuring instruments that can reasonably be used for group comparisons in the context of social science surveys, if measurement with more extensive scales is not possible (45). The inclusion of various age groups and showing the determinants of quality of life, well-being, sleep, and life satisfaction of elderly people compared with other age groups are also strengths of this study.

Limitations

The limitations of this study include the fact that quality of life, life satisfaction, and well-being were restricted to a few selected factors. The sample of elderly people is not representative because it is more likely for older individuals to not be familiar with new technologies. The presented research deals with people who are able to use such technologies, and therefore also have more ways to stay in touch with others, are more informed etc. This could have influenced the results. People who do not use digital media (computer/mobile with online access) could not participate in the study. The elderly people who took part in this study were more likely to report higher education. Because older individuals are usually less likely to use digital media, we expected that this sample will be smaller than the sample of young individuals, and thus we could not ensure that the sample is representative in terms of education and profession. Another limitation of this study is the low number of participants aged more than 60 years (<20% of the overall sample, but we are comparing the elderly population with different age groups, so this could be a strong point of the research, too), as well as the low percentage of Polish participants. We were unable to include in this study all the variables which could affect quality of life, well-being, sleep, and life satisfaction in older adults during the COVID-19 pandemic, e.g., socioeconomic status.

CONCLUSION

The findings show that quality of life, life satisfaction, and well-being during the pandemic are affected by the respondent's age, trait anxiety, and Coronavirus threat. Older people rated their quality of life, life satisfaction, and well-being during the pandemic higher than young people and experienced lower levels of trait anxiety and Coronavirus threat compared to younger age groups. They experienced greater risk tolerance, sleep quality, and optimism regarding the pandemic and had less difficulty relaxing during the pandemic than middle-aged respondents.

In summary, it is worth noting that despite the better psychological functioning of older adults in comparison to young adults during the pandemic, it is necessary to implement various forms of help to improve the psychological resources encouraging quality of life in older people, including stress reduction methods which focus on the body, such as breathing meditation and Autogenic Training (65–68), as well as methods based on cognitive behavioral therapy (69).

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 Ethical Committee (decision no. 30/2020) at the Institute of Psychology at the University of Gdansk, Poland. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

IB-B: conceptualization, project administration, methodology, formal analysis, writing, and original draft preparation. MB: conceptualization, methodology, formal analysis, writing, original draft preparation, and supervision. PJ and LB: conceptualization, methodology, formal analysis, and writing. JK: conceptualization, investigation, and project administration. MS: conceptualization, methodology, formal analysis, writing, and supervision. 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/fpsyt.2020.585813/full#supplementary-material

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Mental Health Status of Psychogeriatric Patients During the 2019 New Coronavirus Disease (COVID-19) Pandemic and Effects on Caregiver Burden

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Introduction: There is a growing awareness about the noxious effects of the 2019 Coronavirus Disease (COVID-19) pandemic on the mental health of the elderly. However, there is limited information from clinically driven research. The objectives of the present study were to examine the magnitude of psychiatric symptoms and to determine their association with caregiver distress, in a cross-section of community-dwelling older adults and a subsample of aging adults with Down syndrome (DS) attending a psychogeriatric service in São Paulo, Brazil.

Method: Telephone-based interviews and electronically filled self-assessment questionnaires were used to collect information from patients and caregivers, addressing their impressions and concerns about the pandemic and related effects on the patient's emotional state and behavior. Clinical information was obtained from hospital charts, medical records, and psychometric tests administered through telephone interviews [Hospital Anxiety and Depression Scale (HADS) and Neuropsychiatric Inventory Questionnaire (NPI-Q)].

Results: We included 100 consecutive participants, comprising 71 older adults with psychogeriatric/neurocognitive disorders and 29 aging adults with DS. Higher HADS and NPI-Q scores were significantly associated with caregiver distress ($p < 0.05$) in both groups. Correlation analyses indicated strong, positive associations between caregiver burden and scores in HADS anxiety (HADS-A) and HADS depression (HADS-D) scales in the subsamples of euploid and DS subjects. Higher NPI-Q scores in the former group were also correlated with caregiver distress, with stronger associations for neuropsychiatric symptoms. Similar findings were observed among DS subjects. ANOVA tests indicated significant associations between NPI-Q scores and caregiver distress among dementia patients, as well as with HADS scores. Similar results were found after multiple linear regressions; as such, among the elderly subsample, higher scores in HADS-A ($p = 0.002$) and HADS-D ($p = 0.001$) predict a significant impact on

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caregiver burden ($p < 0.00001$, R^2 0.46); taking into consideration caregiver burden as a dependent variable and NPI-Q total score as an independent variable, we obtained significant strong prediction values for either DS ($p < 0.00001$, R^2 0.95) or elderly adults ($p < 0.00001$, R^2 0.88).

Conclusion: During the COVID-19 pandemic, patients with neurocognitive disorders present with clinically relevant neuropsychiatric symptoms, with significant impact on caregiver distress. Apathy, aberrant motor behavior, sleep disorders, and psychoses were the main psychopathological domains, which had determined caregiver burden worsening.

Keywords: coronavirus disease 2019 (COVID-19), pandemic, psychogeriatrics, Down syndrome, mental health, caregiver distress, caregiver burden

INTRODUCTION

The 2019 new coronavirus disease (COVID-19) was declared a "Public Health Emergency of International Concern" (PHIC) on January 30, 2020, and the World Health Organization (WHO) declared the "COVID-19 pandemic" on March 11, 2020 (1). In Brazil, the first case of COVID-19 was reported in São Paulo, on February 26, 2020, by the Brazilian Ministry of Health. To date, cases in Brazil surpass 1.3 million with more than 58,000 confirmed deaths (2). Social and economic issues, combined with a heterogeneous (often fragile) and overloaded healthcare system, have been major concerns over the past 4 months. The potentially catastrophic impact of the pandemic, combined with limitations derived from the disease containment measures, imposed significant mental health challenges to the population. Widespread concerns often arise in the pandemic crises, such as the persistent determination for self-protection, changes in daily routine, abrupt interruption of activities outside the home, and use of masks that make it difficult to recognize people's faces. In addition, problems of social interactions and emotionally charged reactions tend to erupt with the increase in the number of people living together in the same space. Together, these events may predispose to the exacerbation of psychiatric symptoms in vulnerable patients.

Recent studies have demonstrated that the elderly represent one of the most vulnerable populations to present with behavioral and mental disorders as a consequence of the COVID-19 pandemic (3), along with other at-risk subgroups such as the homeless (4), immigrant workers (5), pregnant women (6), and people with preexisting mental illnesses (7, 8). Although social isolation and interpersonal distancing have been adopted worldwide as measures to stall the dissemination of the viral infection, these measures also may exert a negative impact on the mental health of the population, particularly among the elderly. In addition to representing a sudden and significant change in their daily routine, social isolation may trigger feelings of abandonment and loneliness, therefore increasing the risk of depression (9). Older adults who live alone and are nonetheless still autonomous may become dependent on the help from relatives and neighbors for the provision of basic supplies, with subsequent impact on their mental health. In contrast, an increase in caregiver emotional burden is expected as a consequence of social isolation and other restrictions imposed by the pandemic on the mental health of less autonomous persons.

The COVID-19 pandemic has also been associated with an increase in the incidence of mental disorders (10), possibly occurring at a higher rate in severe forms of the disease (11). Psychological distress and psychiatric manifestations range from mild symptoms, such as feelings of frustration, distress, fear, and anger, to moderate and severe symptoms of anxiety, depression, sleep disorders, and worsening of preexisting psychiatric disorders (12, 13). In addition, the media overexposure of ambiguous and incomplete information regarding the pandemic, including untruthful and alarmist data, tends to generate feelings of uncertainty and to aggravate behavioral and mental disorders (11).

Studies with community-dwelling older persons reported rates of depression and anxiety symptoms up to 37.1% (12, 14), again occurring especially in those severely affected by the COVID-19 (11). Psychic suffering related to fear of dying from COVID-19 (4), as well as worsening of preexisting psychiatric disorders as consequence of the restrictions imposed by the pandemic, impacts directly on vulnerable populations (15, 16). A population-based study using self-reported questionnaires showed that of 52,730 respondents, 35% reported the presence of pandemic-related psychic distress, especially occurring in adults aged between 18 and 35 and in the elderly (17). However, it is relevant to determine the distinct characteristics between mental disorders presented in clinical and community settings, between rural and urban populations.

People with Down syndrome (DS) are considered to be at an even higher risk of contamination by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The risk of contamination occurs due to the dysregulation of the autoimmune system caused by trisomy 21 since childhood and the presence of preexisting clinical comorbidities, such as diabetes, obesity, respiratory diseases, and heart disease. Despite the scarcity of scientific evidence of the impact of COVID-19 on DS, recent literature on this topic points to the existence of exacerbated immune dysfunction, increasing the rates of inflammatory cytokines and chemokines in people with DS compared to individuals with normal karyotype, therefore requiring additional monitoring and specialized care (18) during the pandemic. Genetic changes that occur on chromosome 21 in people with DS are also significant risk factors for cognitive decline and early-onset Alzheimer's disease (AD) (19). As the life expectancy of individuals with DS goes on increasing because of improved health care, education level, and social support, the risk of progressing to dementia, mainly due to AD, may also reach higher proportions (20). Therefore, we have decided to better understand if these people exhibit special behavioral features suggesting a distinct psychopathological pattern, possibly concomitant with cognitive decline, or perhaps if they reveal sufficient resilience to protect themselves with respect to mental health in the context of the COVID-19 pandemic. These changes resulting from premature aging expose them to an even greater vulnerability in the face of natural disasters and global crises such as the COVID-19 pandemic (21).

There is little doubt about the need for an appropriate provision of care for certain population subgroups at increased risk of experiencing psychological and psychiatric distress related to the pandemic. On the human resources end, teams of mental health professionals are being allocated to deal with the specific needs that emerge in certain subgroups. Training programs for community-based healthcare professionals and development of online assessment using different types of media have been largely recommended. Online surveys have been used in various settings to assess the effects of the pandemic on mental health; educational materials and self-help content, available free of charge on institutional websites and other communication environments, were developed with a focus on mental health. Finally, the provision of remote assistance and guidance (telemedicine) increased the reach of these emergency strategies (22).

A small number of investigations, most of them cross-sectional, about the impact of COVID-19 on mental health faced an unexpected limitation. In a prospective and longitudinal study, Wang et al. (23) applied a questionnaire through an online survey platform to 1,738 people from the general population in China, aged 12–59 years. The questionnaire was completed twice, with a 4-week interval between both assessments. The first evaluation detected moderate-to-severe stress in 8.1% of people, depression in 16.5%, and anxiety in 28.8%, interestingly with no significant changes compared to the second assessment despite pandemic sharply increasing in this period. Several protective factors contributed to mental health stability, including high level of confidence in doctors, perceived survival likelihood and low risk of contracting COVID-19, satisfaction with health information, and personal precautionary measures.

The present study is part of an ongoing clinical effort to provide medical care and psychological support to elderly outpatients at a university-based, tertiary hospital in São Paulo, Brazil (HCFMUSP), during the COVID-19 pandemic fight. This cohort comprises older adults with preexisting psychiatric and neurocognitive disorders (mostly AD) and a subsample of aging adults with DS. The search strategy used in this study was based on telephone interviews and online survey questionnaires, intended to characterize the emerging needs of our patients in view of the restrictions precluding regular hospital consultations. Our specific goals were (a) to determine the presence and severity of psychopathological symptoms in a community-dwelling group of older adults with neuropsychiatric conditions, for example, neurocognitive disorder, mood disorder, anxiety, psychotic symptoms, apathy, and sleep disorders, as well as behavioral disturbances of adult patients with DS; and (b) to determine the association between the aforementioned symptoms on caregiver burden, particularly in the presence of severe psychological and behavioral disturbances.

METHODS

Study Group

The present study was designed with the general purpose of understanding pandemic-related mental changes in an at-risk population consisting of elderly patients with preexisting neuropsychiatric disorders and aging adults with DS. We decided to enroll these two groups in this COVID-19 study because (i) these two patient groups are indeed available in our psychogeriatric service and (ii) we understand that any clinical insights about the DS subgroup would be relevant, albeit distinct from euploid elders. The groups analyzed in this cross-sectional and exploratory study comprised a consecutive sample of patients routinely followed up by our Psychogeriatrics Team at the Instituto de Psiquiatria HCFMUSP, Brazil. Eligible subjects came from a relatively large community cohort, originally estimated at 500 individuals participating in this investigation of pandemic-related psychiatric disorders. Therefore, the results described in this article represent an interim analysis of a subsample of participants enrolled to date. At this moment, patients with dementia were considered as a single group, with no distinction between diagnostic types. All diagnoses disclosed in this study were based on DSM-V criteria, which were captured from the medical records.

Ethics

This study was carried out in accordance with the Institute of Psychiatry HCFMUSP guidelines on clinical research practices, as well as the Helsinki Declaration. Prior to admission in the study, the patient provided written informed consent if he/her was cognitively preserved, or this agreement was authorized by his/her legal representative. It was also reviewed and approved by the Research Ethics Committee (Comitê de Ética em Pesquisa—CEP) of HCFMUSP under approval number 4.190.468.

Assessment

We assembled via videoconferences a group of geriatric psychiatrists to build a questionnaire aiming to screen for (and monitor) the occurrence of psychiatric symptoms and changes in mental state of elderly patients with preexisting neuropsychiatric conditions during the first months of the Brazilian COVID-19 pandemic. This assessment instrument was designed to cover a wide range of mental health issues, including behavioral disturbances and emotional difficulties related to social isolation and daily routine acceptance; in addition, we assessed the caregivers' burden in light of the potential worsening of patients' neuropsychiatric symptoms. The full version of the study questionnaire is available to the readers as a **Supplementary Material**. We established that the informant had to be a close relative to the patient or a professional caregiver who maintained daily contact with him/her; therefore, enrollment was conditioned on the availability of an able informant.

Informant's Questionnaire

The assessment of changes in mental health status as a consequence of incident symptoms or relapse/worsening of preexisting conditions was captured by (i) specific questions dedicated to this aspect in the Informant's Questionnaire (online assessment) and (ii) by the perception of change in neuropsychiatric symptoms according to the clinician's judgment, captured by telephone interviews with the informants. In the first case, we used multiple-choice questions to address whether the informant had observed any recent changes in mental state or behavior that might be related to the COVID-19 crisis or if there had been any observable changes (from worsening to improvement) in the mental health state of the patient in the previous month. After these two introductory questions, we presented four additional multiple-choice questions to objectively address changes in sleep pattern, appetite, eating behavior, and weight. These questions were followed by a sequence of six check-box questions where the participant would be asked to indicate perceived changes in one or more symptoms, according to psychopathological domains (mood/affective, psychotic, behavioral/psychomotor, and cognitive). After each of these questions, the participant was able to express in writing his/her comments details about the aforementioned symptoms. As the majority of individuals in the study group had neurocognitive disorders, a set of questions was dedicated to estimate the informant's perception of changes in global cognition, functionality, and behavior.

Clinician's Questionnaire

Another questionnaire was prepared to assess distinct clinical aspects related to the patient's mental state in the context of the pandemic, for example, worsening of mood-related and behavioral symptoms, particularly if requiring the adjustment of the prescription of psychotropic drugs and medicines prescribed for the treatment of general medical conditions. We also assessed the difficulties faced by the family members or caregivers to manage behavioral disturbances presented by the patients during social isolation. A qualified member of our psychogeriatric team recovered data from the hospital charts, addressing the patients' medical records to complete this part of the questionnaire. Further, the Hospital Anxiety and Depression Scale (HADS) and Neuropsychiatric Inventory Questionnaire (NPI-Q) scale were administered by telephone interviews with the informants.

The HADS

The HADS (24) is an instrument widely used in different populations to detect the overall state and severity of anxiety and depression symptoms (25). The scale consists of two integrated subscales containing 14 mixed questions (seven for anxiety, HADS-A, and seven for depression, HADS-D). The items are focused on psychological manifestations in the last 2 weeks, excluding somatic signs and symptoms or avoiding dependence on physical diseases, such as fatigue, pain, headache, or dizziness (24, 26). Thus, this tool has been criticized for its overreliance on psychological domains as being the core symptoms of depression or anxiety (26). However, relevant clinical domains, for example, sleep disturbances, appetite disorders, and strange or delusional thoughts not inserted in the HADS, are apprehended through the NPI-Q, mentioned below.

The HADS was validated in a cohort of Brazilian people with a cutoff point of 8/9 for anxiety or depression (27) with specificity values of 93.7 and 72.6% for anxiety and 84.6 and 90.3% for depression, respectively (27). The scale has good internal consistency and case-finding properties (28).

The NPI-Q

The NPI-Q (29) has been administered to capture psychological and behavioral symptoms in patients with neurocognitive disorder and DS over the past month. This scale assesses 12 psychopathological domains commonly exhibited by patients with cognitive deterioration, focusing on severity, but not on the frequency of symptoms. The informant rates each psychopathological item according to the severity of the patient's symptoms as well as to himself suffering from emotional distress. Instructions are provided to guide the respondent to complete the questionnaire and anchor points for ratings. Thus, each item requires an answer like "yes" or "no." Subsequently, the severity of this item is classified as "mild" (1), "moderate" (2), or "severe" (3). The total NPI-Q severity ranges from 0 to 36. In addition, the NPI-Q assesses the primary caregiver distress related to each patient's response. The caregiver's distress varies from "not emotionally stressful" (0) to "extremely stressful" (5), with a total score extending from 0 to 60.

The NPI-Q has good test–retest reliability and convergent validity (30). The Brazilian version of the NPI-Q depicted a reliability of 0.97 for the severity subscale and 0.92 for the distress subscale, with moderate internal consistency for the severity subscale and strong consistency for the distress subscale (31). Therefore, the structural properties of the NPI-Q allow a comprehensive measurement of neuropsychiatric symptoms of patients with dementia in clinical practice or research settings (31).

Statistical Analysis

Descriptive statistics were calculated for sociodemographic characteristics, access to private or public health assistance, level of worry about the pandemic, concern-related variables, knowledge and level of compliance to precautionary measures, impact on preexisting mental disorders, complaints of fear and loneliness, presence of a caregiver or family member at home, and physical and psychological symptoms reported. Group comparisons of demographic variables used ANOVAs for continuous measures and Fisher's exact test. Spearman correlations were used to calculate the associations between sociodemographic characteristics, physical symptoms, symptoms of anxiety and depression, and caregiver burden. We used multiple linear regressions as NPI-Q subitems as the dependent variable and gender, HADS-A and HADS-D scores, and age as

TABLE 1 | Socio-demographic characteristics of both cohorts, elderly adults and DS patients.

Socio-demographic features	Elderly $n = 71$ (SD)	DS $n = 29$ (SD)
Age (years)	76.8 (8.7)	43.3 (13.4)
Gender M/F	22/ 49	14/ 15
Education (years)	12.8 (7.4)	13.4 (12.0)*
Marital status		
Married	53.0%	-
Separated/Widowed	38.8%	-
Single	8.2%	100%
Health assistance		
Public health system only	20.4%	73.7%
Private health insurance	79.6%	26.3%
Occupation		
Retired	75.5%	5.0%
Working	12.2%	10.0%
Unemployed	-	5.0%
Never worked	12.2%	80.0%

*DS, down syndrome; mean values for age and education; SD, standard deviation. *Down syndrome patients' years of education refer to special schooling.*

TABLE 2 | Clinical characteristics of both sub-samples, elderly adults and DS patients, as observed previously to the pandemic outbreak.

Clinical features previous to the pandemic	Elderly ($n = 71$)	DS ($n = 29$)
Presence of NCD	90.1% (64)	34.4% (10)
Severity of NCD		
MCI	40,6% (26)	30.0% (3)
Mild/Moderate dementia	35.9% (23)	60.0% (6)
Severe dementia	25.0% (16)	10.0% (1)
Depression	50.7% (36)	3.4% (1)
Bipolar affective disorder	2.8% (2)	0% (0)
Presence of CVD	78.9% (56)	55.2% (16)

DS, down syndrome; NCD, neurocognitive disorder; MCI, mild cognitive impairment; CVD, cardiovascular disease.

the independent variables. The same was made for the caregiver burden as the dependent variable and age, gender, HADS-A and HADS-D scores, and all NPI-Q total scores and subitems as the independent variables. All analyses were performed for each group separately (DS subjects and elderly adults). The significance level considered was $p < 0.05$, and all statistical analyses were performed using Stata version 15.0 for Mac.

RESULTS

Our sample consisted of 71 elderly adults and 29 DS patients. As displayed in **Table 1**, euploid subjects were considerably older than trisomic (DS) subjects and predominantly married; most of them had access to private health insurance assistance and were, for the most part, retired from previous occupations. As for the DS cohort, participants were evenly distributed between genders; they were all single, mostly dependent on the public health system; and the vast majority had never worked before, fully relying on family support.

Preexisting neuropsychiatric conditions were identified and are described in **Table 2**. The main diagnoses consisted of mild neurocognitive disorder [i.e., mild cognitive impairment (MCI) with either amnestic or multiple domain characteristics], major neurocognitive disorder (i.e., AD, vascular dementia, mixed dementia, frontotemporal dementia, and semantic dementia), and affective disorder (i.e., bipolar disorder and depression with or without related apathy syndrome).

Throughout the COVID-19 pandemic outbreak, we were able to recognize emerging or aggravating neuropsychiatric features such as mood symptoms, sleep problems, and psychotic disturbances. The most prevalent self-referred psychiatric symptoms in the elderly group were anxiety (65%), feeling of insecurity (44%), discouragement (38%), and irritability (35%) (**Figure 1**). Mood symptoms with depressive and anxious traits were measured by means of the HADS, yielding a maximum of 21 points for each subscale (HADS-A and HADS-D) and a total of 42 points for total HADS score (HADS-T). Mean scores for elderly adults and DS patients were, respectively, 7.6 (SD: 5.1) and 3.9 (SD: 3.5) for HADS-A; 8.9 (SD: 5.3) and 4.8 (SD: 5.1) for HADS-D; and 16.5 (SD: 8.4) and 8.8 (SD: 7.9) for HAD-T. **Figures 2–4** display scatter plots that illustrate how higher scores in the HADS-T and its subscales correlate with increased caregiver burden as well as with the severity of the neurocognitive diagnosis. Patients with dementia, therefore, present with worse HADS scores and higher caregiver impact.

With respect to specific and inherent aspects of the COVID-19 pandemic that might have contributed to the emergence or aggravation of mental health disturbances, elderly participants indicated the "impossibility of leaving the house" as the one responsible for greater impact (56%). It was closely followed by "social isolation" (43%); "apprehension toward the possibility of a relative getting sick" (43%); "alarmist information on the exposure risks" (37%); and "apprehension oneself might be infected" (37%) (**Figure 5**).

According to caregivers' reports, changes in cognitive status were observed in 34 elders, suggesting cognitive decline. Among the most prevalent new or evolutive symptoms, "worsened disorientation and confusion" accounted for the higher prevalence, occurring in 59% of patients, followed by "ceased performing usual tasks or activities" (50%), "higher dependence" (47%), "worsened disorganization" (44%), and being "more repetitive" (38%), which were also frequently reported (**Figure 6**).

ANOVA tests indicated statistically significant differences in mean HADS and NPI-Q scores and subscores when comparing the subsamples of elderly subjects with and without dementia (HADS-A, $p = 0.001$; HADS-D, $p = 0.002$; HADS-T, $p = 0.01$; NPI-Q-psychosis, $p < 0.0001$; NPI-Q-apathy, $p = 0.004$; NPI-Q-aggressiveness, $p < 0.0001$; NPI-Q-movement disorders, $p < 0.0001$; NPI-Q-sleep, $p < 0.0001$).

Spearman's correlation tests demonstrated statistically significant correlations between psychometric test scores (HADS and NPI-Q) and caregiver burden. In the subsamples of euploid

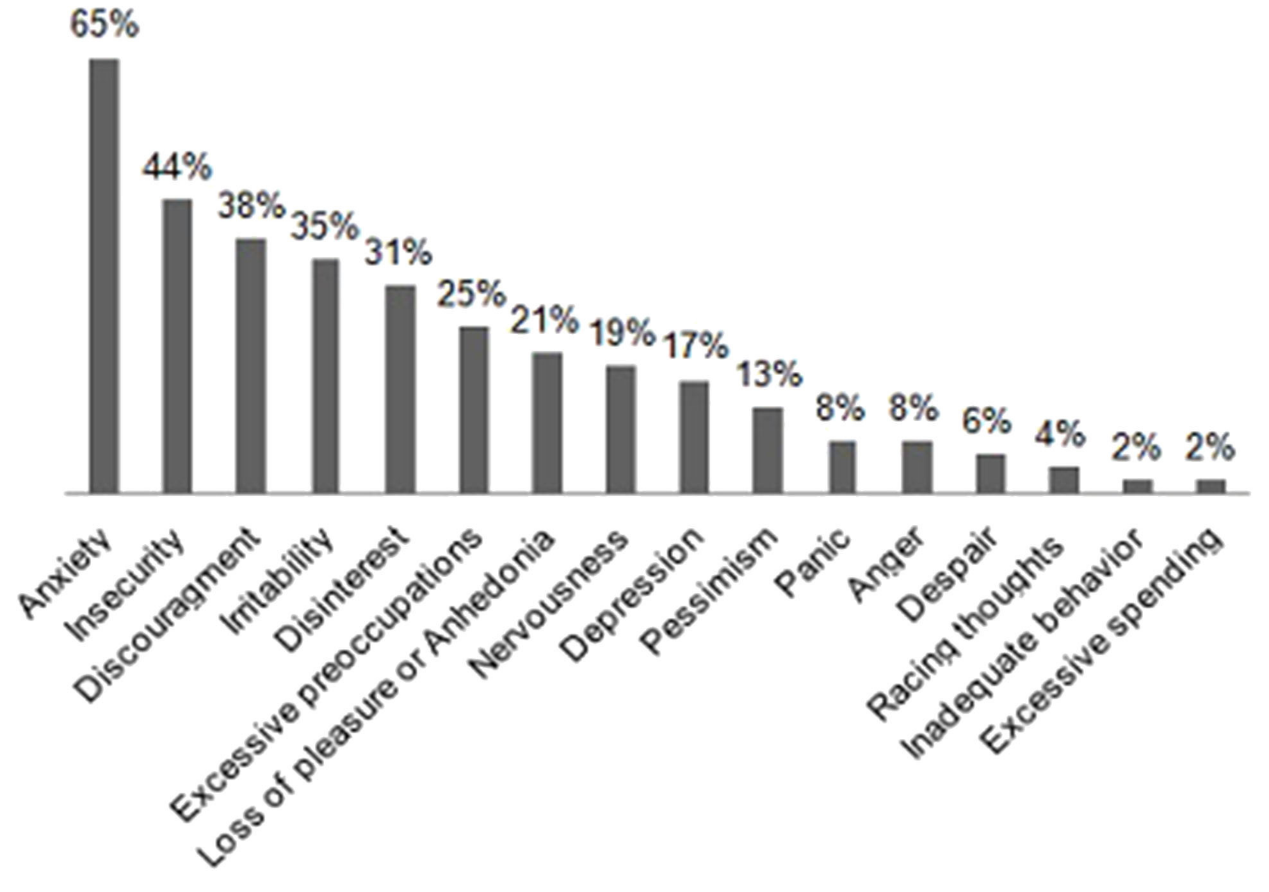

FIGURE 1 | Prevalences of psychiatric manifestations occurring during the COVID-19 crisisas observed in the elderly group ($n = 48$).

elders, these correlations were strong (HADS-T, 0.87; HADS-A, 0.78; and HADS-D, 0.80) and statistically significant ($p < 0.05$), whereas in the subsample of DS, these correlations were moderate to strong (HADS-T, 0.66; HADS-A, 0.52; and HADS-D, 0.55, $p < 0.05$ for all tests). Similar correlations were observed between the NPI-Q subscores (psychosis, aggressiveness, depression, apathy, irritability, aberrant movement disorder, and sleep disturbances) and the degree of caregiver burden. Among euploid elders, strong correlations were found for apathy (0.81), aberrant movement disorders (0.78), sleep disturbances (0.71), and psychosis (0.69); moderate correlations were found for irritability (0.66), depression (0.63), and aggressiveness (0.59). Among DS participants, correlations were strong for aberrant movement disorders (0.69), sleep disturbances (0.65), and irritability (0.67); and moderate correlations were found for aggressiveness (0.62), depression (0.52), and psychosis (0.57).

Multiple linear regressions demonstrated significant associations between NPI-Q scores and HADS-A and HADS-D scores in both groups. **Tables 3**, **4** display the results of this complete regression analysis for each subsample (DS and elderly adults). Also, among the elderly subsample, higher scores in HADS-A ($p = 0.002$) and HADS-D ($p = 0.001$) predict a significant impact on caregiver burden ($p < 0.00001$, R^2 0.46). Likewise, the regressions between caregiver burden as the dependent variable and NPI-Q total score as the independent variable showed significant strong prediction values for either DS ($p < 0.00001$, R^2 0.95) or elderly adults ($p < 0.00001$, R^2 0.88). **Table 5** displays the complete regression analysis among caregiver burden and each NPI-Q domain for both subsamples.

Pharmacological interventions to deal with emerging neuropsychiatric symptoms were required only in a minority of the cases, that is, 28.2% ($n = 20$) of euploid elders and 3.4% ($n = 1$) of DS subjects; whenever required, these procedures were largely due to sleep complaints (FET 0.016, $p = 0.038$).

As for adaptability, the elderly subjects were more prone to cope well with and willingly follow governmental recommendations when their neurocognitive diagnoses were less severe (0.52) and when their level of insight toward the pandemic was higher (0.52). Also, with reference to insight, elders with a better comprehension of the pandemic situation demonstrated higher levels of reactivity (0.63), meaning they coped better and reacted more favorably in compliance with official recommendations. Inverse significant correlations were found between the severity of caregiver impact and

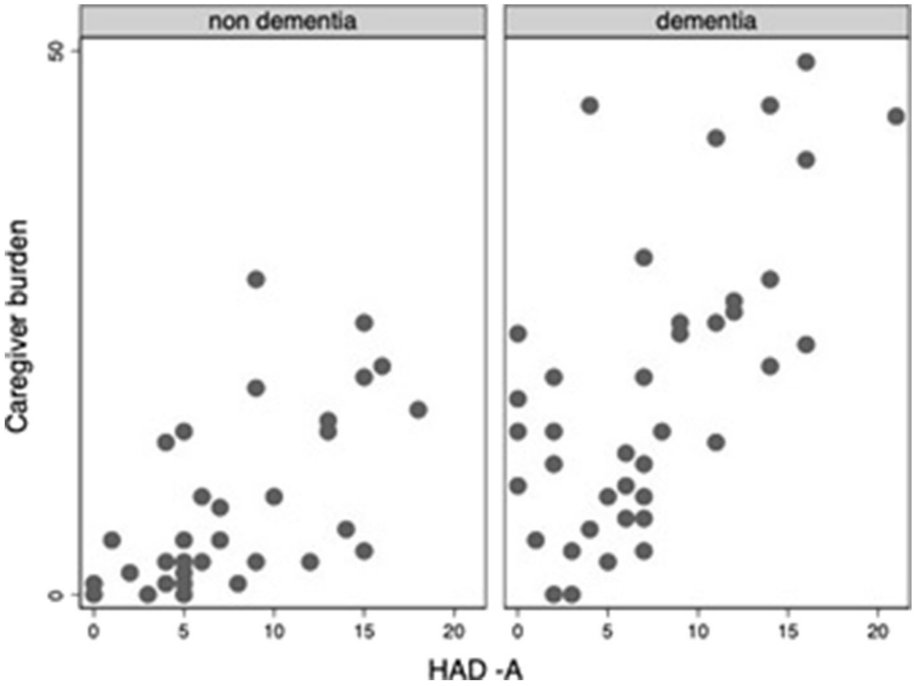

FIGURE 2 | Scatter plot of Caregiver burden and HAD-A scorcs among elderly adults (with and without dementia).

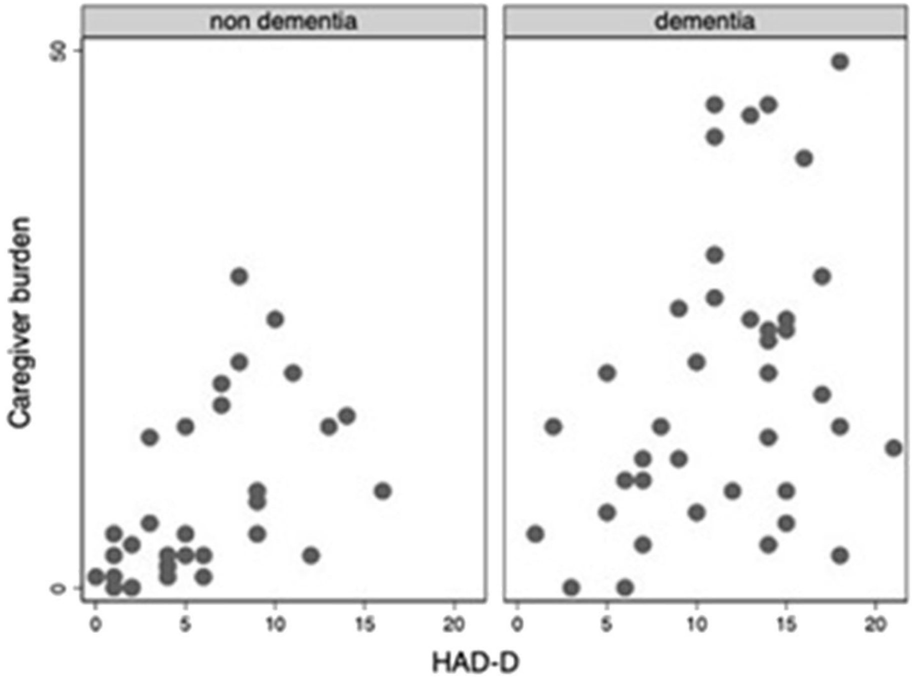

FIGURE 3 | Scatter plot of Caregiver burden and HAD-D scorcs among elderly adults (with and without dementia).

DS patients' level of insight on the pandemic (−0.50), the patient's concern about his/her own health (−0.52), and level of reactivity toward respecting hygiene measures (−0.61). Higher insight was strongly correlated with reactivity (0.92), suggesting these patients were more prone to be alert and follow sanitary recommendations.

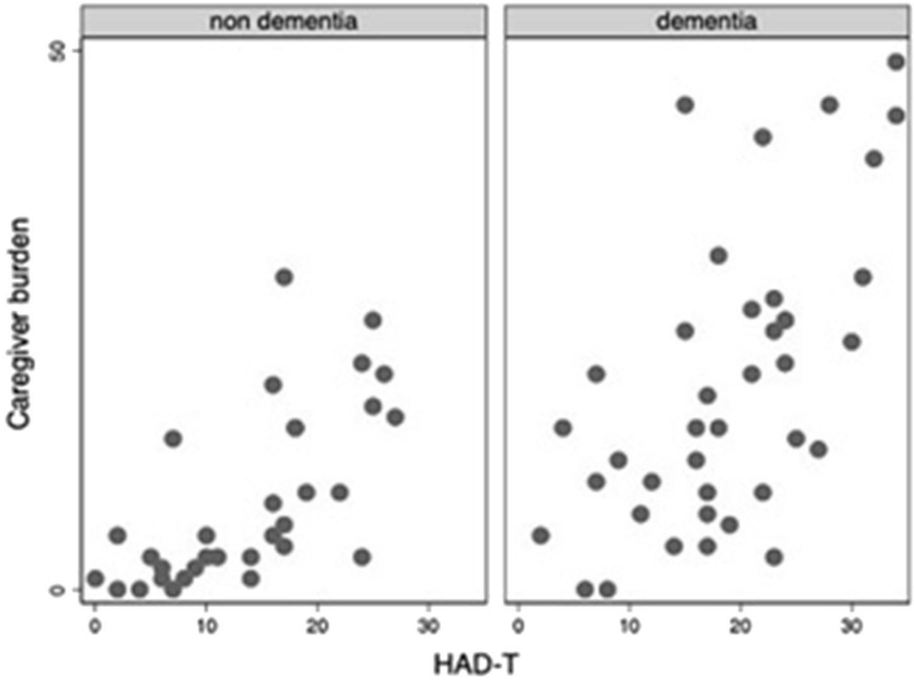

FIGURE 4 | Scatter plot of Caregiver burden and HAD-T scorcs among elderly adults (with and without dementia).

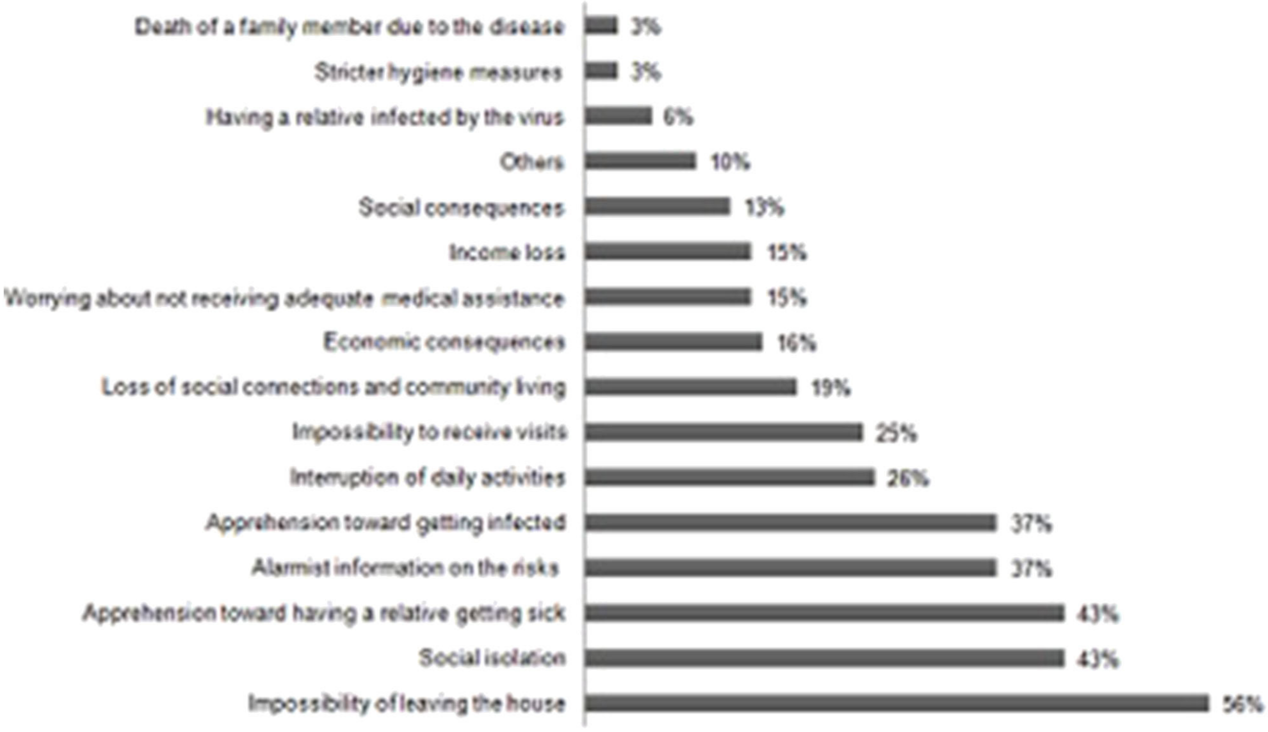

FIGURE 5 | Specific aspects of the COVID-19 pndemic that interfere with mental health ($n = 68$).

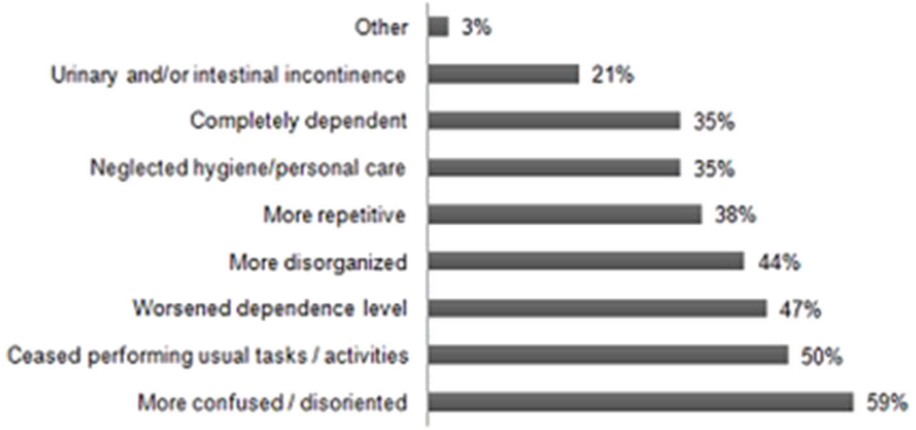

FIGURE 6 | Changes in cognitive-functional performance of elderly patients occuring during the COVID-19 pandemic (n = 34).

DISCUSSION

The present study was designed to monitor the mental state of the clients of a psychogeriatric clinic in São Paulo, Brazil, during the COVID-19 pandemic, using remote assessment methods. Our *a priori* hypothesis was that the restrictive measures related to the pandemic crisis could lead to a worsening of neuropsychiatric and behavioral symptoms, particularly in vulnerable subgroups. We found that mood-related symptoms were the most frequent complaints, reported by 65% of respondents. Based on data provided by the NPI-Q, among old patients, apathy, aberrant motor behaviors, sleep disorders, and psychotic symptoms compose a psychopathological constellation of symptoms commonly causing relevant caregiver emotional distress and creating considerable challenges for daily caring in quarantine. Regarding the impact on mental health, these manifestations were followed by others, such as irritability and concern with adaptability to new psychosocial demands. Therefore, symptoms of anxiety and depression, respectively depicted by HADS-A and HADS-D, significantly correlated with caregiver routine burden. Interestingly, correlations between psychopathological manifestations and caregiver distress were higher in the dementia group according to ANOVA tests, meaningfully for HADS-A, for HADS-D, and for several NPI-Q domains, such as psychosis, apathy, aggressiveness, aberrant movement disorders, and sleep.

In this study, apathy was a crucial source of impact on caregiver distress in the COVID-19 outbreak. It is a pervasive symptom affecting mostly patients with cognitive decline and includes a reduction in goal-directed activities concerned with behavior, cognition, emotions, and social interaction (32). Given the data described in the present work, apathy was a common neuropsychiatric symptom among patients with dementia, surely as a preexisting manifestation at the beginning of the pandemic. Our findings are in agreement with results reported by Lara and colleagues (33), who documented apathy as one of the most common psychopathological domains among patients with MCI or AD during the COVID-19 outbreak. Even though apathy can be separated from major depression because of distinct psychopathological features and different neurobiological ways, a substantial proportion of individuals may share clinical symptoms from both conditions (32).

Agitation was another psychopathological domain affected among old patients in the current study. This phenomenon was observed across all cognitive stages of dementia and encompasses erratic or repetitive behaviors, wandering, chaotic attitudes, and threats of verbal or physical aggression, causing critical impact on the well-being of patients and caregivers. Frequently, agitation is closely related to psychotic symptoms like delusions and hallucinations and seems to be predictive of a more severe course of cognitive impairment (34). Agitation and psychotic symptoms may coexist, and such co-occurrence subsequently aggravates behavioral disturbances and dangerous consequences for both the patient and caregiver (35).

Sleep complaints are characterized by trouble in initiating sleep, nighttime behavior disturbances, and daily somnolence. These symptoms were relevant complaints in old patients from our sample, also generating emotional charged reactions in caregivers. Concerning this issue, Casagrande et al. (36) conducted an investigation in a large Italian population by a web-based cross-sectional survey, broadcasted through different platforms and mainstream social media during the pandemic. They reported poor sleep quality, besides other clinical symptoms such as higher levels of generalized anxiety and greater psychological distress related to the COVID-19 outbreak. In particular, they emphasized a consistent connection between sleep disorders and behavioral disturbances, emotional dysregulation, anxiety, and depressive symptoms. Sleep fragmentation and loss of efficiency were common. In addition, not only did patients have sleep problems in the pandemic, insomnia is also a major concern for the medical staff due to the constant threat of contamination, being present in more than one-third of the clinical care team (37). Although there is insufficient evidence of direct causality between insomnia and viral contamination, it has been documented that shorter sleep duration, confirmed by wrist actigraphy measurement, increases

TABLE 3 | Multiple linear regressions: NPI-Q domains × age, gender, HAD-A score and HAD-D score of the DS subsample.

NPI-Q Domains	*F*	*P*-value	R^2	pAge	pGender	pHAD-A	pHAD-D
Psychosis	11.71	**0.0002**	0.7698	0.328	0.391	0.343	**0.007**
Aggressiveness	1.93	0.1617	0.3551	0.844	0.757	0.876	0.079
Depression	7.69	**0.0017**	0.6873	0.334	0.452	0.513	**0.004**
Apathy	6.17	**0.0045**	0.6379	0.584	0.831	0.113	0.059
Irritability	4.21	**0.0192**	0.5460	0.316	0.544	0.724	**0.008**
AMD	4.73	**0.0126**	0.5748	0.556	**0.024**	0.056	0.588
Sleep dist.	1.9	0.1662	0.3520	0.700	0.122	0.090	0.711
Apetite dist.	1.59	0.2323	0.3120	0.285	0.314	0.129	0.379

DS, down syndrome; AMD, aberrant movement disorders; dist., Disturbances.
The bold values refer to those with statistical significance.

TABLE 4 | Multiple linear regressions: NPI-Q domains × age, gender, HAD-A scores and HAD-D scores of the elderly adults subsample.

NPI-Q domains	*F*	*P*-value	R^2	pAge	pGender	pHAD-A	pHAD-D
Psychosis	3.78	**0.0104**	0.2696	0.070	0.552	0.175	**0.033**
Aggressiveness	4.42	**0.0046**	0.3012	**0.047**	0.812	**0.004**	0.230
Depression	2.17	0.0892	0.1748	0.754	0.515	0.326	**0.038**
Apathy	6.61	**0.0003**	0.3919	0.576	0.739	0.194	**>0.0001**
Irritability	8.13	**0.0001**	0.4423	0.396	0.814	**>0.0001**	0.097
AMD	4.54	**0.0040**	0.3068	0.111	**0.043**	0.089	**0.043**
Sleep dist.	1.69	0.1697	0.1419	0.957	0.308	0.376	0.061
Apetite dist.	0.44	0.7782	0.0413	0.238	0.902	0.970	0.492

AMD, aberrant movement disorders; dist., disturbances.
The bold values refer to those with statistical significance.

TABLE 5 | Multiple linear regressions: caregiver burden × NPI-Q domains scores of both groups.

DS	Caregiver burden	Elderly adults	Caregiver burden
F	540.42	*F*	32.93
***P*-value**	**<0.00001**	*P*-value	**<0.00001**
R^2	0.99	R^2	0.92
pPsychosis	**0.003**	pPsychosis	**0.000**
pAgressiveness	**0.000**	pAgressiveness	0.115
pDepression	**0.004**	pDepression	0.095
pApathy	**0.012**	pApathy	0.100
pIrritability	0.161	pIrritability	0.052
pAMD	0.335	pAMD	**0.002**
pSleep dist.	**0.000**	pSleep dist.	**0.036**
pAppetite dist.	0.307	pAppetite dist.	0.205

DS, down syndrome; AMD, aberrant movement disorders; dist., disturbances.
The bold values refer to those with statistical significance.

the reduction in the natural immune response and predicts risks for infectious illnesses (38).

Psychotic symptoms frequently emerge mainly in the later stages in neurodegenerative diseases and have been associated with agitation episodes and more rapid global deterioration, causing serious and dangerous repercussion in both patients and caregivers (34). Outcomes from our investigations confirmed that delusions and hallucinations of old patients actually generate relevant emotional distress for caregivers in the current COVID-19 outbreak.

The elderly group also revealed important insecurity feelings and was affected by discouragement. Some aspects strictly related to the COVID-19 pandemic might have aggravated the mental state of old patients from our sample. These aspects are "impossibility of leaving the house," "social isolation," "apprehension toward the possibility of a relative getting sick," "alarmist information on the exposure risks," and "apprehension that oneself might be infected." This composite picture does not appear to be a fortuitous event. Caregiver stress often has been related to emotionally charged responses characterized by exhaustion, anxiety, and irritability in the COVID-19 outbreak, and this phenomenon may induce the caregiver to misinterpret the patient symptoms, especially when behavioral disturbances are assessed by instruments configured with objective measurements (34, 35). Thus, assessment of psychopathological manifestations of a patient or informant deserves caution in this pandemic, especially through distance communication techniques, in the absence of face-to-face interaction.

According to scientific literature and reports from several countries, there is evidence that COVID-19 illness is progressively associated with underlying mental and neurological disorders, for example, anxiety, depression, sleep disturbances, delirium, dizziness, seizures, stroke, and hyposmia (39, 40). These findings bring on great concern since more than 20% of people over 60 years are affected by such preexisting illnesses (40).

As documented, after discharge patients struck by COVID-19 continued to present mental changes, including depression, anxiety, and post-traumatic stress, with high frequency and clinical relevance (41, 42). Even when the frequency does not appear to be high, the symptoms cause a significant impact on the patient's mental state. According to a large sample of 40,469 individuals with COVID-19, captured by real-time electronic records data from healthcare settings, 22.5% had any neuropsychiatric manifestations (43). In addition, they suffered from anxiety (4.6%), mood disorders (3.8%), sleep changes (3.4%), and suicidal ideation (0.2%).

Although the issue of news broadcasting by the media was not the focus of our work, it is an issue to be considered from the point of view of mental health. The excessive time spent on news exposure, the discrepancy between the amount and quality of information, conflicting messages, and some overdone coverage may induce mental changes in vulnerable populations. Li et al. (44) examined the prevalence of anxiety and depression symptoms associated with the time spent per day on news about the COVID-19 pandemic. The total prevalence was 20.4%, and rates ranged from 17.8% among individuals spending <5 min/day on news to 27.9% among those spending more than 1 h/day. Three psychosocial stressors—concern about infection; concern with income, work, and study; and disturbances caused by home quarantine—were significantly associated with the occurrence of anxiety and depression.

In unfavorable circumstances determined by the pandemic, the most fragile people may undergo sudden changes in their daily routine, with significant repercussions in psychological and behavioral status. Acute episodes of anxiety, panic attacks, irrational fears, paranoid convictions and strange behaviors, or silent resignation are common reactions converging to the fight-or-flight phenomenon (45). Elderly patients suffering from dementia or other neuropsychiatric conditions, as well as those with DS, in fact are strong candidates to display similar disorders. The mental state worsens with the increased risk related to death of family members, social isolation, difficulties in health care, and also with the profound and certainly long-term economic crisis arising. Together, these variables have been converging to an increased sense of uncertainty and helplessness among vulnerable people (45).

Caregiver burden and severity of neurocognitive diagnosis in people with DS, especially those with dementia, require better management of care during the pandemic. We know that people with dementia require different management in situations of stress (46). Despite the absence of scientific data on how the caregiver of the person with DS manifests psychological symptoms during the period of social isolation, it is known that these caregivers feel stressed and manifest psychological symptoms such as depression and anxiety (47) during the provision of care.

During the pandemic, caregivers of people with DS and dementia are likely to experience situations of increased stress due to the change in routine, requiring a change in the support model offered and better management of care provision in this situation outside the usual context (48). It is known that the effects of social isolation, in addition to the routine changes, the decrease in social life, and the withdrawal from activities carried out in institutions that provide support for people with DS and their families, can corroborate the increase in symptoms such as changes of humor reported by the caregivers who participated in this study (49).

The literature does not provide data on the adaptability of people with DS to the pandemic. However, even if the person with DS is not able to maintain a global comprehension of the impact of COVID-19 contamination on society, non-suspected cases of functional decline are still able to understand instructions and follow health recommendations (50) in a functional way in their daily lives.

Our findings are in agreement with a previous study carried out in Spain by Lara et al. (33). The authors investigated 20 individuals with MCI and 20 patients with mild AD older than 60 years who had undergone a first assessment during a month before the lockdown and were reassessed 5 weeks later. They used the NPI to detect behavioral and psychological symptoms and the EuroQol-5D scale to obtain quality-of-life characteristics, through phone interviews. The authors detected that the most affected domains, with respective scores, were apathy (5.75) and anxiety (5.30) for individuals with MCI and apathy (3.75), agitation (1.50), and aberrant motor behavior (2.00) for patients with AD. In addition, they observed a significant worsening of neuropsychiatric symptoms in both groups of MCI and AD during 5 weeks of lockdown mainly in agitation, apathy, and aberrant motor behavior. Moreover, caregivers also reported worsening with respect to their health, including mental status. As our patients were in social isolation, in general for some weeks, we compared our data with the second evaluation done by Lara and colleagues. Accordingly, caregivers investigated in our research also presented a worsening of emotional dysregulation.

Among inpatients, as expected, psychiatric symptoms must be severe, not only in those with a previous psychopathological history but also in those without chronic mental disorders. Parra and colleagues (51) conducted a single-center retrospective and observational study in Spain to describe new-onset psychotic episodes in people with COVID-19. The authors analyzed 10 patients over 18 years of age assessed by the emergency and liaison psychiatry departments at a selected hospital. Highly structured delusions of prejudice, persecutory, and referential beliefs, followed by spatial and temporal disorientation, inattention, agitation, and auditory and visual hallucinations, were the most frequent events. Pathological mechanisms, which could at least in part explain new-onset psychotic phenomena, comprise direct action of the virus into the central nervous system; also, indirect consequences of infection, for example, inflammatory reactions, metabolic disturbances, hypoxia, and prolonged immobilization, and iatrogenic outcomes from pharmacological treatments against the disease were related to the emergence of psychosis (51).

Due to the greater vulnerability associated with advanced age and medical comorbidities, elderly people, when affected, are at greater risk of serious COVID-19 outcomes. Moreover, the highly recommended social isolation, in turn, induces cognitive worsening and behavior deterioration, especially among those with dementia (52). In these circumstances, coping with worsening neuropsychiatric symptoms seems to be a valuable strategy. Resilience approaches including a structured daily routine based on cognitive stimulation, regular physical exercise, adequate diet, and sleep hygiene have been strongly recommended for maintaining mental health (53). In addition, easy access to psychiatric support for people with clinically relevant depressive or anxiety symptoms, post-traumatic stress disorder, or substance abuse should be incorporated into the comprehensive management in the COVID-19 pandemic (53).

Unsurprisingly, the COVID-19 outbreak has spread out the use of telemedicine as an assertive digital technology at the moment, and it tends to figure as an efficient long-term practice through video monitoring and other remote communication systems. Noteworthily, in the current circumstances is ongoing a new medical consultation strategy different from the traditional face-to-face interaction. Gathering technological communication resources to capture relevant data for faster decision making in clinical support emerges as a new post-pandemic challenge. Further research should be structured to assess neuropsychiatric conditions in the aging adult population, as well as to design selected and effective interventions in this situation.

Our investigation aligns with the aforementioned study pointing out that patients with cognitive decline are a particularly vulnerable population in the current scenario, who needs to be able to understand to make decisions about how to behave and what should be done. Cognitive decline, apathy, depression, and other psychopathological symptoms may interfere with the ability to understand, appreciate, or respond to most behavior safety recommendations. Furthermore, patients with AD often undergo stigmatization and resent the resource constraints due to the chronic nature of their disease and specific demands [54].

Currently, data on psychiatric disorders of patients with COVID-19 are still scarce. Several challenging issues must be highlighted. An essential proposal is to continue discussing the complex factors associated with mental suffering imposed by the persistent health crisis, to implement awareness on the risk of behavioral disturbances from existing psychiatric illnesses, and to promote resilient strategies to face this challenge (12).

Limitations

We acknowledge that the present set of data derives from an interim analysis of a preliminary sample of a larger study, and this must be viewed as a limitation. Nonetheless, it depicts the mental health status of psychogeriatric patients in the first 3 months of the Brazilian COVID-19 pandemic. Therefore, it is not certain whether the present findings and correlations will remain in the final sample that is intended to be three to four times larger. With this precaution in mind, one can speculate that the final overall picture may turn out to be even worse, as the pandemic progresses along with many direct and indirect challenges to mental health in these elderly patients.

This cross-sectional study based on a relatively small consecutive sample, without randomization, as well as the heterogeneity of diagnoses may have restricted additional comparisons and more extensive analyses. Moreover, assessments without a direct face-to-face interaction with the patient or caregiver, implicit in the distance communication techniques, may not capture the essential complexity of the psychopathological meaning. The absence of causality between the variables was another limitation determined by the methodological design, being feasible only to perform correlation analysis. The participants had different levels of education and financial income, which possibly interfered with the quality of data acquisition (e.g., utilization of technological resources that are required to fill the questionnaires). Taken together, these factors may have affected the interpretation of the results. However, the research represents only part of a large ongoing cohort study, and therefore, these methodological weaknesses should certainly be corrected.

Strengths

The present study was conceived as a quick response to the anticipation of clinical needs from our psychogeriatric patients during the Brazilian COVID-19 pandemic. Older adults with preexisting mental and neurocognitive disorders represent an at-risk population group, who were suddenly deprived from regular medical and rehabilitation care, given the restrictive measures that were imposed by sanitary authorities. We sought to understand their emerging symptoms and needs for care, and the present set of data enabled the implementation of proactive responses from our team using telemedicine resources.

Distinct from most studies addressing psychological/psychiatric symptoms arising in population groups exposed to the COVID-19 pandemic that were based exclusively on online questionnaires, our study included telephone interviews conducted by members of our multidisciplinary team (predominantly medical doctors), by which we were able to obtain psychometric data using validated scales (i.e., HADS and NPI-Q). In addition, given that all participants are outpatients in our psychogeriatric clinic, we could obtain reliable information from medical records in order to verify the clinical diagnoses and current prescriptions.

We also understand that the disposal of a subsample of aging adults with DS (along with a larger sample of older adults with normal karyotype) is another strength of the present study. There is a growing interest of AD researchers in DS cohorts, and most studies addressing dementia in DS do not merge these two samples. Therefore, we decided to enroll both samples in this COVID-19 study because these two patient groups are clients of our psychogeriatric service, and we understand that any insights about the effect of COVID-19 pandemic on the DS subgroup would be clinically relevant.

CONCLUSION

The COVID-19 pandemic triggered prompt responses and creative initiatives from the mental healthcare professionals in many countries. In the context of the pandemic, mental health became the focus of special attention with the development of interventions to assess populations at risk. Maintaining the focus on the clinical demands of COVID-19 patients, mental health also became a priority in the context of the pandemic, with interventions aimed at vulnerable groups in the general population.

The main target of this study was the comprehensive understanding of mental and behavioral changes of older adults with neuropsychiatric conditions and DS during the COVID-19 pandemic. Dementia patients presented with worse NPI scores and higher levels of caregiver burden. Neuropsychiatric symptoms such as anxiety, irritability, depression, apathy, aberrant movement disorders, and sleep disturbances were frequent and correlated with caregiver distress.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This study was reviewed and approved by the Research Ethics Committee (Comitê de Ética em Pesquisa – CEP) of HCFMUSP under approval number 4.190.468. The participants provided written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CP and JL: database. MP: introduction and task management. CC and LS: down's syndrome cohort. LV: statistical analysis. FS and OF: study design, development of study questionnaire, and final review of the manuscript. The LIM-27 Psychogeriatric Team cited at Acknowledgments in this paper were also actively involved in data collection and interim analyses/discussions related to the topic. All authors were involved at manuscript preparation and data collection.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.578672/full#supplementary-material

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frontiers in Psychiatry

ORIGINAL RESEARCH
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COVID-19 Pandemic and Psychiatric Symptoms: The Impact on Parkinson's Disease in the Elderly

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Background: The coronavirus disease 2019 (COVID-19) pandemic represents a condition of increased vulnerability and frailty for elderly patients with Parkinson's disease (PD). Social isolation may worsen the burden of the disease and specifically exacerbate psychiatric symptoms, often comorbid with PD. This study aimed at identifying risk/protective factors associated with subjective worsening of psychiatric symptomatology during the COVID-19 outbreak in a sample of individuals with PD aged 65 years or older.

Methods: Patients with PD routinely followed at the outpatient clinic of Gemelli University Hospital, Rome, were assessed for subjective worsening of psychiatric symptoms through a dedicated telephone survey, after Italy COVID-19 lockdown. Patients' medical records were reviewed to collect sociodemographic and clinical data, including lifetime psychiatric symptoms and pharmacological treatment.

Results: Overall, 134 individuals were assessed and 101 (75.4%) reported lifetime psychiatric symptoms. Among those, 23 (22.8%) presented with subjective worsening of psychiatric symptomatology during the COVID-19 outbreak. In this group, the most frequent symptom was depression (82.6%), followed by insomnia (52.2%). Subjective worsening of neurological symptoms (Wald = 24.03, df = 1, $p = 0.001$) and lifetime irritability (Wald = 6.35, df = 1, $p = 0.020$), together with younger age (Wald = 5.06, df = 1, $p = 0.038$) and female sex (Wald = 9.07 df = 1, $p = 0.007$), resulted as specific risk factors for ingravescence of psychiatric presentation. Lifetime pre-existing delusions, having received antipsychotics, and not having received mood stabilizer were also associated with subjective worsening of psychiatric symptomatology due to the COVID-19 pandemic.

Conclusions: Individuals with PD and lifetime history of psychiatric symptoms may be exposed to increased vulnerability to the stressful effect of COVID-19 outbreak. Interventions aimed at reducing irritability and mood instability might have an indirect effect on the health of patients with PD during the COVID-19 pandemic.

Keywords: COVID-19, Parkinson's disease, depression, psychosis, irritability, delusions, psychiatric symptom, mood stabilizers

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INTRODUCTION

In a very short time, our world has dramatically changed. The coronavirus disease 2019 (COVID-19) has disrupted normality across the globe, throwing all aspects of life into uncertainty. The situation is even more critical for patients affected by chronic neurological disorders, such as Parkinson's disease (PD). The more widespread challenge is the limited access to adequate care, as a consequence of self-isolation and social distancing that have been enforced on a global level. Elderly patients are particularly exposed to these conditions of increased vulnerability and frailty (1, 2). Based on data from large cohort studies (3) and systematic reviews of the literature (4), there is, to date, no evidence whether elderly individuals with PD are at increased risk for COVID-19, compared to individuals of similar age and with comparable comorbidities. Nevertheless, social isolation, especially if protracted, may worsen the burden of neurological disorders (5). According to this, our group recently demonstrated specific correlations between subjective worsening of neurological symptoms and consequences of social restrictions in a large sample of 2,167 outpatients with chronic neurologic diseases (6).

Psychiatric symptoms are common and disabling conditions in the clinical course of PD (7–9), and they are specifically highly prevalent in elderly patients with PD (10, 11). They include affective disorders, apathy and anhedonia, disorders of sleep and wakefulness, psychosis, and impulse control disorders (7, 12). Psychiatric features are typically multimorbid, characterized by great intra- and inter-individual variability in clinical presentation (8) and may be largely influenced by life stress events (13). The COVID-19 pandemic represents an important stressor associated with the exacerbation of psychiatric symptoms (14, 15). Recent data highlighted higher levels of psychological distress among the general population (16) and increased risk for recurrences and worsening in patients with neuropsychiatric disorders during the COVID-19 outbreak. Accordingly, preliminary reports over the last few weeks demonstrated higher levels of stress, depression, and anxiety in patients with PD compared to healthy controls (HC) (17, 18). They also confirmed impaired quality of life during social restriction (17).

However, studies in elderly people with PD specifically focused on the worsening of psychiatric symptoms due to COVID-19 pandemic are still lacking. Furthermore, insufficient data are available on lifetime risk/protective factors potentially associated with clinical exacerbation. This study aimed at filling these gaps by describing the prevalence of subjective worsening of psychiatric symptomatology during the COVID-19 outbreak, while identifying associated risk/protective factors, in a sample of individuals with PD aged 65 years or older.

METHODS

Patient Population

We assessed 134 individuals with PD who were regularly followed at the outpatient clinic of the Department of Neurology at Agostino Gemelli University Hospital Foundation IRCCS-Catholic University of the Sacred Heart in Rome. Patients were consecutively enrolled in the study if they had a scheduled visit during the lockdown. Individuals aged 65 years or older, Caucasian, and under stable psychopharmacological treatment for at least 6 months were included. Patients were excluded if they or their legal support administrators were unable to provide informed and valid consent at the time of the assessment. Patients not fluent in Italian, with severe and unstable medical conditions (i.e., not non-stabilized diabetes, oncologic disorders, clinically significant and unstable active gastrointestinal, renal, hepatic, endocrine, or cardiovascular disorder), dementia, or cognitive deterioration according to DSM-5 criteria, and Mini-Mental State Examination (MMSE) score <25 were also excluded from the study.

Data Collection

Sociodemographic and clinical data before the COVID-19 outbreak (i.e., age at onset of motor symptoms, neurological characteristics, lifetime psychiatric symptoms, and pharmacological treatment) were extracted from patients' medical records. Lifetime psychiatric symptoms were assessed through a semi-structured interview described below. Neurological characteristics were evaluated through the motor examination section of the Unified Parkinson's Disease Rating Scale (UPDRS) disease severity (UPDRS-III) (19) and the disease stage according to Hoehn and Yahr (H & Y) stage (20).

Information related to the impact of COVID-19 on psychiatric symptoms was collected through a telephone survey. The survey started on April 1, 2020, and ended on April 15, 2020. A semi-structured interview was adopted to evaluate the impact of social restrictions on psychiatric burden. The semi-structured interview, carried out by a senior psychologist, was based on current evidence on psychiatric disorders in PD (7), on DSM-5 criteria, and on clinical evaluation (not on simple yes/no answers to structured questions). The wording of the questions could be changed to improve/check understanding, and the final evaluation was also based on information from the caregiver (if available) and from any medical documentation. Specifically, the survey assessed the presence (classified as "yes" or "no") of depression, apathy/anhedonia, sleep disturbances (insomnia), rapid eye movement (REM) sleep behavior disorders (RBD), irritability, impulse control disorders (ICDs), delusions, and hallucinations. Furthermore, participants were also asked to report subjective worsening of psychiatric symptoms and neurological symptoms. If they reported a worsening of their clinical presentation, they were referred to a multidisciplinary team, composed by neurologists and psychiatrists experienced in the field of movement disorders, to adjust pharmacological treatment. All data collected about past and current psychiatric symptoms were entered in preprinted medical records.

The Survey was reviewed and approved by the Ethics Committee of the Agostino Gemelli University Hospital Foundation IRCCS-Catholic University of the Sacred Heart Ethics Committee, Rome. Because of the biological risks related to the pandemic, participants could not timely provide written informed consent. Therefore, during the phone call, verbal consent for study participation and use of anonymized data was obtained (immediate consent) according to information filed with the Ethics Committee. Participants were informed that written consent would be obtained at the first visit in the hospital (deferred consent).

Statistical Methods

For the aim of the study, in the analyses, we considered patients with lifetime history of psychiatric symptoms. We compared individuals who reported subjective worsening of psychiatric symptomatology during the COVID-19 outbreak with those reporting symptom stability on demographic characteristics, neurological characteristics (age at onset of motor symptoms, UPDRS-III score, H & Y stage, and worsening of neurological symptoms during the COVID-19 outbreak), lifetime type of psychiatric symptoms, and pharmacological treatment. Analyses used standard univariate/bivariate comparisons of continuous measures (ANOVA) and categorical measures (contingency table/χ^2) to assess significant differences between groups. The level of significance for the analyses was set at $p < 0.05$. In addition, we used a multivariate logistic regression model to identify lifetime risk and protective factors that significantly differentiated patients who reported (or did not report) worsened psychiatric presentation (considered as the dependent variable). All factors that resulted significant in the univariate analyses were included in the model and considered as independent variables. We examined possible multicollinearity between factors of interest using the variance inflation factor (VIF) indicator obtained from a linear regression analysis.

All the statistical analyses were carried out using the "Statistical Package for Social Science (SPSS)" program, version 25.0 (IBM Co., Armonk, NY).

RESULTS

In the total sample ($n = 134$), 101 (75.4%) patients reported lifetime psychiatric symptoms. Among those, 23 (22.8%) reported subjective worsening of psychiatric symptomatology during the COVID-19 outbreak. The most frequent symptom among patients reporting worsened symptoms was depression (82.6%), followed by insomnia (52.2%) (**Table 1** and **Figure 1**). In terms of demographic features, the two groups differed in sex ($\chi^2 = 8.87$, df = 1, $p = 0.003$) and age ($F = 9.38$, df = 1, $p = 0.003$) (**Table 2**). Specifically, most participants reporting symptom exacerbation were women ($n = 16$, 69.6%) and younger (mean age = 69.78 years, sd = 4.38) than those reporting symptom stability (female: $n = 27$, 34.6%; mean age = 73.94 years, sd = 6.08) (**Table 2**).

Subjective worsening of neurological symptoms along with lifetime pre-existing irritability and delusions, having received antipsychotics, and not having received mood stabilizer were associated with subjective worsening of psychiatric symptomatology during the COVID-19 outbreak (**Table 2**). Multivariate logistic regression specified that reporting neurological symptoms worsening during the pandemic (Wald = 24.03, df = 1, $p = 0.001$) and lifetime irritability (Wald = 6.35, df = 1, $p = 0.020$), together with younger age (Wald = 5.06, df = 1, $p = 0.038$) and female sex (Wald = 9.07 df = 1, $p = 0.007$), were associated with an increasing likelihood of exhibiting worsening of psychiatric symptoms during the COVID-19 pandemic. The logistic regression model was statistically significant ($\chi^2 = 65.8$, $p < 0.001$) and correctly classified 73.0% of cases. There was no significance of multicollinearity, as indicated by the fact that VIF of all variables of interest was <2.

TABLE 1 | Current psychiatric symptomatology in patients reporting symptoms worsening or stability during the COVID-19 outbreak.

Current psychiatric symptoms	Patients reporting symptoms worsening during the COVID-19 outbreak (n = 23) *N* (%)	Patients reporting symptoms stability during the COVID-19 outbreak (n = 78) *N* (%)
Depression	19 (82.6)	35 (44.9)
Apathy/anhedonia	6 (26.1)	9 (11.5)
Insomnia	12 (52.2)	27 (34.6)
RBD	5 (21.7)	4 (5.1)
Irritability	7 (30.4)	1 (1.3)
ICD	4 (17.4)	1 (1.3)
Delusions	5 (21.7)	0 (0)
Hallucinations	8 (34.8)	3 (3.8)

RBD, rapid eye movement (REM) sleep behavior disorders; ICD, impulse control disorders.

DISCUSSION

The COVID-19 pandemic has forced national health systems to rapidly set priorities in medical care, and this led to dramatic consequences for many patients with chronic conditions, including those with PD (3). The increased vulnerability of the elderly and those with comorbidities, along with the increased prevalence of PD with age, raises concerns about the potentially negative impact of the COVID-19 outbreak on people living with movement disorders (5). Psychiatric symptoms, in particular, could be greatly influenced by the social isolation imposed by the COVID-19 pandemic (14).

In our sample, up to 22.8% of patients with PD experienced worsening of their psychiatric clinical condition during the COVID-19 outbreak. The COVID-19 pandemic is profoundly modifying individuals' routines. Such drastic changes require a flexible adaptation to novel circumstances, a cognitive process partly related to/dependent on normal dopaminergic functioning (21, 22). A growing body of evidence suggests that many patients with PD may experience both cognitive and motor inflexibility, as a result of nigrostriatal dopamine depletion that is involved in the pathophysiological substrate of the disorder (23, 24). This might have a two-sided explanation. On the one hand, it has been hypothesized that dopamine-dependent adaptation subserves flexible coping mechanisms to environmental stressors (23, 25). On the other hand, increased psychological stress can temporarily worsen various motor symptoms, including

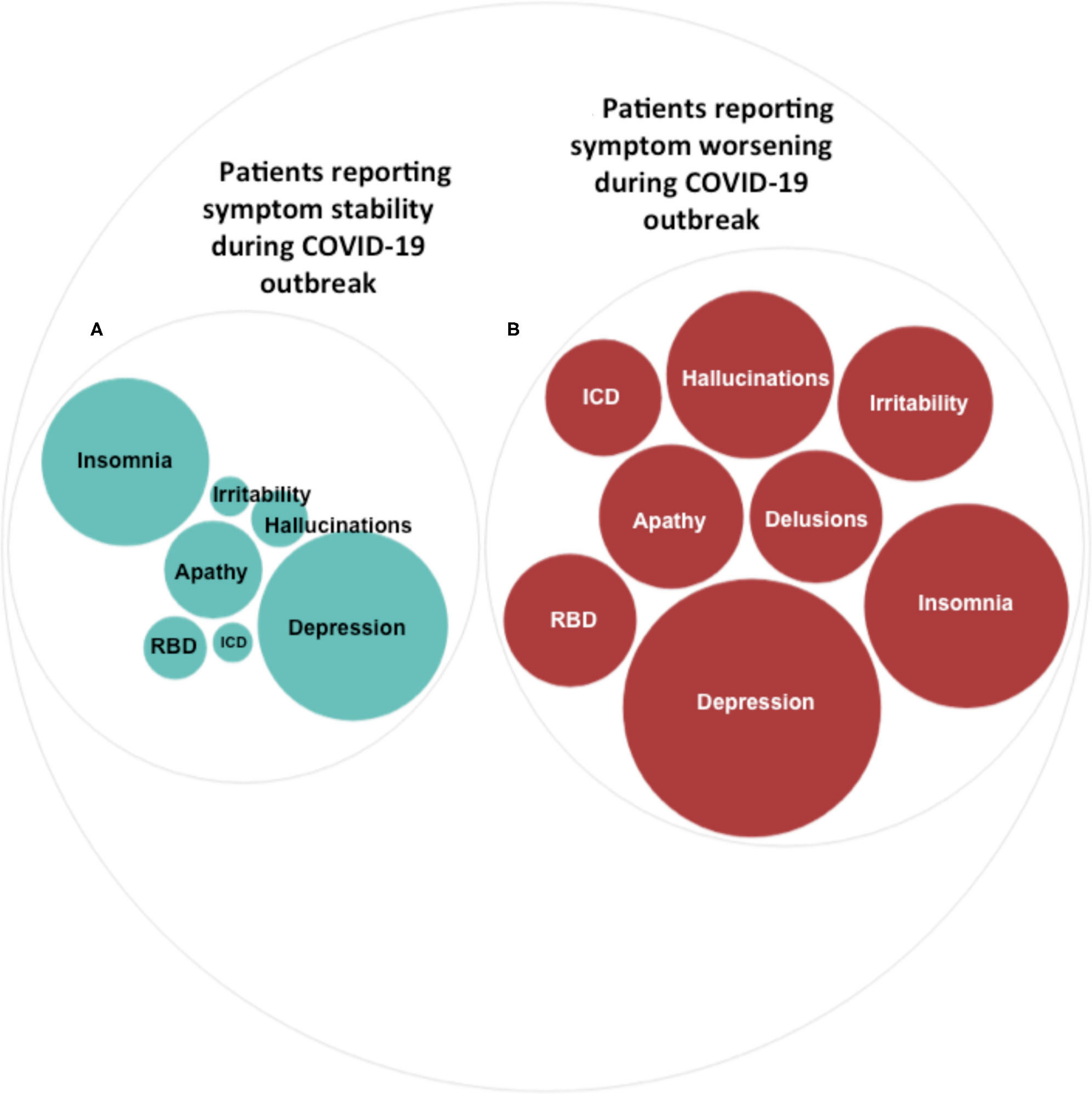

FIGURE 1 | Psychiatric symptoms during the COVID-19 outbreak. Prevalence of different types of psychiatric symptoms in patients reporting symptom stability **(A)** and in patients reporting symptom worsening **(B)** during the COVID-19 outbreak. The size of the circles indicates the percentages (%) of individuals in each group reporting specific psychiatric symptoms. Percentages are detailed in **Table 1**.

tremor, freezing of gait, or dyskinesias, and reduce the efficacy of dopaminergic medication (26, 27).

Consistently with available evidence (28), a relevant percentage of individuals with PD experienced subjective worsening of neurological symptomatology as a result of the COVID-19 outbreak. Besides, worsening of motor symptoms was the most sensitive clinical risk factor for ingravescence of psychiatric symptoms in patients with PD during the COVID-19 pandemic. Different reasons explaining the negative effect of lockdown on PD motor symptoms have been suggested, including increasing levels of stress that could worsen motor symptoms as well as the discontinuation of physiotherapy and/or reduction in physical activity (6). The relationship between psychiatric symptoms and PD follows a vicious cycle, with the presence of psychiatric disorder increasing the risk of PD, and vice versa. For instance, there is evidence that patients with PD

TABLE 2 | Lifetime features associated with symptoms worsening or stability during the COVID-19 outbreak.

	Patients reporting symptoms worsening during the COVID-19 outbreak ($n = 23$) *N* (%)	Patients reporting symptoms stability during the COVID-19 outbreak ($n = 78$) N (%)	χ^2	df	*p*
Age: mean ± (SD)	69.78 (4.38)	73.94 (6.08)	9.38	1	0.003*
Sex: *n* (%)	16 (69.6)	27 (34.6)	8.87	1	0.003*
Neurological characteristics					
Age at onset of motor symptoms: mean ± (SD)	58.56 (8.62)	62.75 (9.84)	3.37	1	0.069
UPDRS-III: mean ± (SD)	30.82 (13.22)	26.54 (11.83)	2.19	1	0.14
H & Y stage: mean ± (SD)	3.13 (0.99)	2.81 (0.94)	1.96	1	0.16
Subjective worsening of neurological symptoms during the COVID-19 outbreak: *n* (%)	18 (84.6)	12 (21.7)	33.60	1	<0.001*
Lifetime type of psychiatric symptoms					
Depression: *n* (%)	17 (73.9)	44 (56.4)	2.27	1	0.13
Apathy/anhedonia: *n* (%)	6 (26.1)	29 (37.2)	0.96	1	0.32
Insomnia: *n* (%)	13 (56.5)	54 (69.2)	1.28	1	0.25
RBD: *n* (%)	9 (39.1)	28 (35.9)	0.08	1	0.77
Irritability: *n* (%)	12 (52.2)	13 (16.7)	12.02	1	0.001*
ICD: *n* (%)	6 (26.1)	14 (17.9)	0.74	1	0.38
Delusions: *n* (%)	4 (17.4)	3 (3.8)	5.05	1	0.02*
Hallucinations: *n* (%)	3 (13.0)	15 (19.2)	0.46	1	0.49
Pharmacological treatment					
L-DOPA: *n* (%)	23 (100)	73 (93)	1.55	1	0.21
IMAO: *n* (%)	16 (69.6)	49 (62.8)	0.35	1	0.55
ICOMT: *n* (%)	7 (30.4)	13 (16.7)	2.12	1	0.14
Dopamine agonists: *n* (%)	11 (47.8)	33 (42.3)	0.22	1	0.63
Antidepressants: *n* (%)	8 (34.8)	27 (34.6)	0	1	0.98
Mood stabilizers: *n* (%)	1 (4.3%)	20 (25.6)	4.89	1	0.02*
Antipsychotics: *n* (%)	11 (47.8)	17 (21.8)	6.00	1	0.01*

*χ^2, Chi-square tests; df, Degrees of freedom; *significant p; UPDRS-III, the Unified Parkinson's Disease Rating Scale disease severity part III; H & Y stage, Hoehn and Yahr stage; RBD, rapid eye movement (REM) sleep behavior disorders; ICD, impulse control disorders; L-DOPA, levodopa; IMAO, monoamine oxidase inhibitors; ICOMT, catechol-O-methyltransferase-inhibitors.*

who experience on–off motor fluctuations are also more likely to encounter fluctuations in mood and energy levels. Mood swings are not entirely linked to dopaminergic dosing or PD neurodegeneration but are also observed in patients with a pre-existing psychiatric history or concurrent use of psychiatric medication, suggesting these may in fact be part of a larger symptom constellation (29).

The most frequent symptom in the group of patients presenting with worsening of psychiatric conditions was depression, which has been reported by up to 82.6% of individuals (**Table 1** and **Figure 1**). Depression has been shown to be the most common psychiatric symptom in patients with PD and has been indicated as a specific risk factor for developing the disease (30). One of the largest sample studies to date, using data from a matched cohort of 23,180 participants (4,634 patients with depression and 18,544 control patients), reported that patients with depression were 3.24 times more likely to develop PD compared with the control patients (31). Depression in PD is likely to result from a complex interaction of environmental and neurobiological factors. Neuroimaging analyses suggest that patients with PD reporting depression specifically exhibited widespread disruptions in both function and structure (32). Abnormalities have been primarily reported in subcortical nuclei and prefrontal–temporal–limbic circuits (33–35). Interestingly, the same brain networks have been highlighted as specific targets of stress-induced mood symptomatology (36–38).

Our results also found pre-existing lifetime irritability as a significant clinical risk factor for psychiatric symptom worsening in patients with PD during the COVID-19 pandemic. This is in line with previous observations specifically linking mood instability with irritability (39). Irritability, although often ignored by clinicians, is part of a strong principal factor of major depression (40), and it is associated with greater outcome severity and lower quality of life (40). Lifetime presence of delusions was also associated with symptom worsening during the COVID-19 outbreak. These results could indirectly suggest a more severe and susceptible phenotype in this group of patients. Psychosis in PD is associated with reduced quality of life and worse prognosis and is an independent predictor of increased mortality (41). According to this, although the biological etiology of psychosis in PD has not yet been clearly understood, previous studies hypothesized that psychotic symptoms formation might be linked with hypersensitivity of mesocorticolimbic dopaminergic receptors, cholinergic denervation, serotonergic/dopaminergic imbalance, and neurodegeneration of widespread limbic, paralimbic, and neocortical gray matter (42, 43).

In our study, individuals who developed psychiatric clinical deterioration were significantly more likely to be women and younger as compared to patients who did not present worsening of psychiatric symptoms. Gender is an important biological determinant of vulnerability to psychosocial stress, in addition to genetic, socio-cultural, hormonal, and developmental factors (16). Our results indicate that males are, to a certain degree, less likely to develop psychological symptoms in the face of a stressful event. This is in line with a recent review on mental health consequences of the COVID-19 pandemic, which reports higher risk of psychiatric symptoms and/or low psychological well-being in females compared to males (44). The same study indicated that findings on age as a risk factor for COVID-19-related psychological distress were inconsistent (44). In our study, we found that older age (in the age group of >65 years old) might be a protective factor against psychiatric clinical exacerbation in PD during the COVID-19 pandemic. We may speculate that this could be associated with the observed reduced behavioral reservoir of old individuals, which include psychiatric behaviors (45).

Psychiatric symptom worsening was also associated with a higher lifetime use of antipsychotics and a lower lifetime use of mood stabilizers. The higher rate of antipsychotics indicate worse disease clinical course, particularly with regard to delusions and hallucinations, and suggest higher instability of psychiatric symptoms in this group of patients (46). On the other hand, the higher rate of mood stabilizers may be linked to a potential protective effect of mood stabilization. In our sample, in particular, the use of mood stabilizers could have mitigated mood instability related to irritability through specific biological mechanisms. According to this, there is evidence that the benefits of mood stabilizers extend beyond affective stabilization (47–49) and include neuroprotection against several neuropsychiatric condition (48, 50, 51). Besides, mood stabilizers may prevent individuals with PD from experiencing abrupt shifts in mood, energy, behavior, and thinking when facing stressful events, which, in turn, may promote resilience (52).

Before presenting our conclusions, we must acknowledge some issues that might limit the generalizability of our results. First, the study has a cross-sectional design and lacks longitudinal follow-up of patients reporting symptoms worsening during the pandemic after the adjustment of their pharmacological treatment. Furthermore, the mental health impact of the COVID-19 outbreak on patients with PD could change during time. Therefore, long-term psychological implications of this population warrant further investigation. Second, the lack of standardized questionnaires for psychiatric symptoms is another limitation of our study. However, all patients underwent a detailed anamnesis, which included the evaluation of psychiatric clinical aspects. Third, the survey design required telephone contact rather than face-to-face assessment; as a consequence, the interview may be influenced by uncontrolled and recall bias.

In conclusion, our study highlighted that patients with PD are at increased risk of experiencing the negative sequelae of the pandemic in terms of both increased stress and limited access to standard neurological care, which can, in turn, adversely affect their psychiatric features. Depression in particular resulted as the most prevalent psychiatric symptom reported by patients presenting with clinical worsening. Our findings suggest that interventions aimed at reducing irritability and mood instability, such as the use of mood stabilizers, might have an indirect effect on the health and well-being of patients with PD during the COVID-19 pandemic.

CLINICAL VIGNETTE

We describe the case history of a 56 year-old patient, male, affected by PD, who developed an impressive psychosis during the lockdown period. Disease onset was in 2008 at the age of 44 with akinesia on his left leg and clumsiness in the same side. Except for motor symptoms of disease, he also showed a prodromal hyposmia. No other relevant diseases were reported. A DAT scan confirmed diagnosis in 2009. He started with rasagiline 1 mg qd and ropinirole, tapered up to 20 mg qd during the following years, with a marked improvement of his motor symptoms. Further on, trihexyphenidyl and amantadine were added to his therapy. Since 2011, he has showed mild impulsive compulsive behaviors, i.e., increased libido and compulsive hobbism. In 2017, he reported his first psychotic episode, characterized by persecutory delusions and auditory hallucinations. Ropinirole was tapered off and substituted by levodopa, while antipsychotic therapy with quetiapine up to 125 mg was started, with a gradual improvement of his psychiatric symptoms. In 2019, he stopped quetiapine and started psychotherapy and a physiotherapy program. He also reported motor fluctuations with mild wearing-off of levodopa therapy.

During 2019, the patient asked to change work position. Then, on February 2020, he started working with a new team and initially reported concentration and learning difficulties. On March 9, at the beginning of the Italian lockdown, the patient found himself at home alone in social isolation, without contacts with his working team. On May 2020, he started to show the first signs of a severe psychosis, characterized by psychomotor agitation, auditory hallucinations, and persecutory delusions. The persecutor was identified as a colleague who had had a past love story with his wife. Along with those symptoms, the patient reported instability of mood with irritability and insomnia. At psychiatric assessment, the patient scored 37 on the Young Mania Rating Scale (YMRS) (53). The patient showed no insight into his condition. At neurological examination, he showed mild hypomimia and hypophonia, slight and occasional rest tremor on his left hand, slight rigidity affecting the left extremities, slowing gait with reduced left arm swing, global bradykinesia with reduced amplitude, and slightly slow hand movements. The motor examination section of the Unified

Parkinson's Disease Rating Scale (UPDRS) had a total score of 14. On May 25, rasagiline was stopped, and levodopa and amantadine were reduced. Simultaneously, he was started again with quetiapine 25 mg at bedtime, without amelioration. Then, a multidisciplinary team, composed of neurologists and psychiatrists experienced in the field of movement disorders, started to manage the patient's care with a daily clinical follow-up. On June 16, the clinical team stopped quetiapine and prescribed clozapine 12.5 mg at bedtime, and then increased to 25 mg, which induced after only 3 days a marked and impressive improvement of psychotic symptoms (YMRS = 9), which was stable over the next month.

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 Ethics Committee of the Agostino Gemelli University Hospital Foundation IRCCS-Catholic University of the Sacred Heart Ethics Committee, Rome. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

DJ, MP, PC, and AB designed the study and wrote the protocol. DJ, MP, LM, CP, FB, II, AS, MD, GS, PC, and AB managed the literature searches and analyses. DJ, MP, and LM performed the statistical analysis and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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Effects of COVID-19 Infection Control Measures on Appointment Cancelation in an Italian Outpatient Memory Clinic

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Background: In the first wave of the COVID-19 pandemic in 2020, many countries made changes to the routine management of patients with non-communicable diseases, including neurocognitive disorders. Therefore, many "so-called" non-urgent elective procedures and outpatient appointments have been canceled or postponed, possibly impacting negatively on health and well-being of patients in the short- and long-term.

Aim: Here, we aimed at describing numbers and types of outpatient appointments canceled as a result of government's restrictive measures in our memory clinic.

Methods: The scheduled appointments at the memory clinic of the Santa Lucia Foundation IRCCS, Rome, Italy, are recorded in a comprehensive dataset under strict administrative control. Here, we compared appointments (first-time and follow-up) that were canceled from January to April 2020 with those of the corresponding months in 2019.

Results: We observed a substantial decrease in appointments during 2020. The majority of scheduled appointments were follow-up, and about a quarter were first-time appointments. We estimated that 66.7% and 77.4% of patients missed out respectively their first and follow-up appointments in our memory clinic due to government's restrictive measures in March–April 2020.

Conclusions: A large number of patients with neurocognitive disorders missed crucial appointments due to government's restrictive measures, and many experienced a delay in initial diagnosis and initiation of treatment. This has relevant impact on their treatment and consequently has (is still having and potentially will have) an increase on the healthcare service burden of clinics. Furthermore, as a second wave of COVID-19 affects Europe, and with winter approaching, it is a compelling priority to ensure easy and rapid access to appropriate assessment, care and treatment in the event of a new outbreak and potential subsequent lockdowns, with particular attention to the development of specific healthcare technologies customized to older persons with cognitive impairment.

Keywords: COVID-19, SARS-CoV-2 coronavirus, neurocognitive disorders, non-communicable disease, NCD

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INTRODUCTION

Since the first case of Severe Acute Respiratory Syndrome—Coronavirus-2 (SARS-Cov-2) was reported and confirmed in Wuhan in December 2019 (1) there have been a series of governments' restrictive measures worldwide to reduce the spread of the pandemic. In Italy, according to article 13 of the law decree number 14 of the march 9th 2020 of the President of the Italian Republic, each region had the possibility to suspend all non-urgent healthcare services. Consequently, elective procedures and appointments were canceled throughout the national territory.

Many countries have employed similar restrictive measures (2–4) and have made changes to the routine management of patients with non-communicable diseases [e.g., canceling "so-called" non-urgent appointments, which have important implications for the identification and treatment, and therefore for the progression of these chronic conditions (5)]. Although the focus on procedures to urgently slow SARS-CoV-2 infection rates and minimize the number of infected individuals has extreme importance, it has short- and long-term negative consequences on health and well-being of patients with non-communicable diseases, including neurocognitive disorders (NCD) (6–10).

In particular, this may affect not only the diagnosis of new-onset mild and major NCD but also have a potential negative effect on neuropsychiatric symptoms, medication adherence, and disease progression (11). In fact, many surveys have been structured to measure these aspects, specifically in patients during the appointment suspension and for future quarantines (12, 13). Until the pandemic is under regulation control, we will be unable to establish the extent that the postponement of routine clinical care has on persons with mild and major NCD.

In Italy, different types of health and socio-health services are available for people with NCD. According to the Observatory of Dementias from the Italian National Institute of Health there are 591 memory clinic in the whole country (data from the 2015 census) and more than three million people are directly involved in the formal and informal care of individuals with Alzheimer's disease nationwide (14). It is, therefore, of utmost importance to assess the impact of the pandemic-related changes to routine clinical management of persons with NCD.

In the present study we focused on patients with NCD whose neuropsychiatric care changed due to the first COVID-19 outbreak. Specifically, we aimed at comparing the appointments that were performed during the lockdown period (January to April 2020) to the same period of the previous year. In addition, based on the requests' reason, we classified the appointments into "first-time" and "follow-up" to determine how many people would experience a delay in receiving a new diagnosis, because of first-time appointment missed, and to estimate how many routine clinical follow-up care has been disrupted.

MATERIALS AND METHODS

The memory clinic of the Santa Lucia Foundation IRCCS is an outpatient clinic where patients with mild and major NCD are referred. Typically, after a first-time appointment, which includes psychiatric, neurological and neuropsychological assessment, patients attend follow-up appointments in which they are generally diagnosed using blood sampling, neuroimaging and other procedures and, if appropriate, prescribed therapy that is confirmed or gradually adjusted. Each appointment is recorded in a comprehensive dataset under strict administrative control.

In the present study, we verified the number of patients with scheduled appointments at the memory clinic at the Santa Lucia Foundation IRCCS from January to April 2020. We then recorded the number of appointments that were canceled

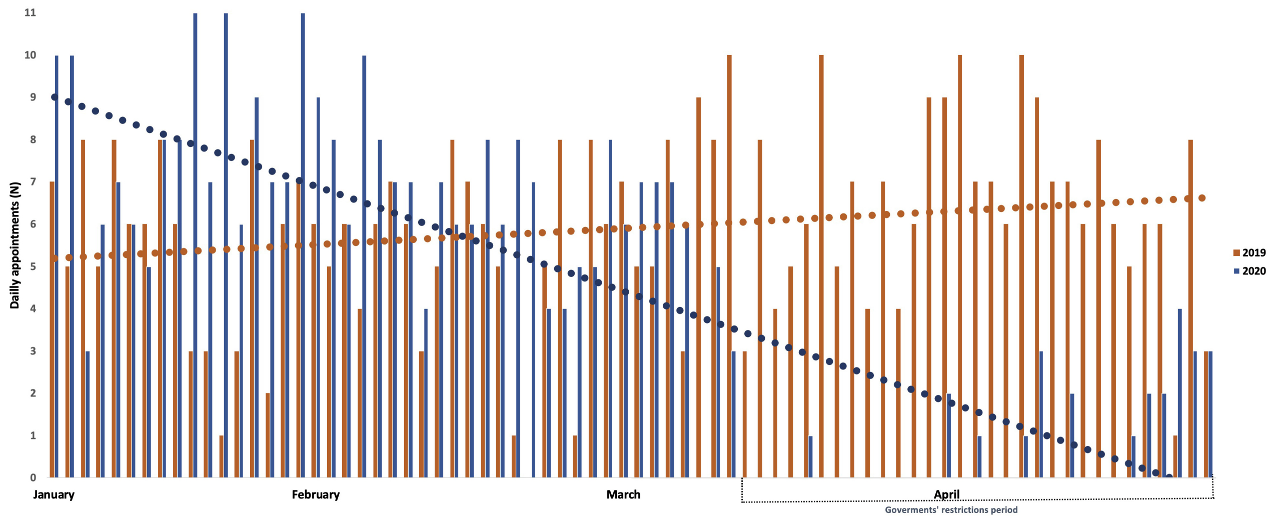

FIGURE 1 | Number of daily appointments conducted during January–April 2019 and 2020.

TABLE 1 | Number of appointments scheduled and conducted during 2019 and 2020.

	Total	Follow-up		First-time	
	n	*n*	*(%)*	*n*	*(%)*
Scheduled appointments					
2019					
January	120	78	65.0	42	35.0
February	149	99	66.4	50	33.6
March	171	127	74.3	44	25.7
April	159	121	76.1	38	23.9
2020					
January	190	125	65.8	65	34.2
February	185	125	67.6	60	32.4
March	150	108	72.0	42	28.0
April	174	160	92.0	14	8.0
Conducted appointments					
2019					
January	92	58	63.0	34	37.0
February	102	62	60.8	40	39.2
March	133	105	78.9	28	21.1
April	121	88	72.7	29	24.0
2020					
January	137	92	67.2	45	32.8
February	134	91	67.9	43	32.1
March	42	32	76.2	10	23.8
April	31	25	80.6	6	19.4

due to the government-enforced reduction of non-urgent healthcare services in Italy during the lockdown and compared these numbers with the appointments in the corresponding months of the previous year (January-April 2019). Records were independently checked by two neuropsychologists to determine whether the examination was (i) a follow-up appointment in patients already attending the memory clinic, (ii) a first-time appointment, and (iii) the reasons for requesting a first appointment.

STATISTICAL ANALYSIS

We compared the number of daily appointments conducted in the same period in 2019 and 2020 (January—April) using a z-test ($\alpha = 0.05$) to determine statistically significant differences between proportions.

RESULTS

Figure 1 shows the number of daily appointments conducted in the same months of 2019 and 2020 (January to April). We quantified a considerable decrease in appointments specifically during March-April 2020 and the vast majority of scheduled appointments were follow-up (**Table 1**). In such period, a total of 251 scheduled appointments were canceled (follow-up $N = 211$; first-time $N = 40$). **Figure 2** reports the proportion of canceled appointments (first-time and follow-up) in 2019 compared to 2020. Specifically, March and April show an increase in canceled appointments in 2020 compared to the previous year with 70.4% and 84.4% of follow-up appointments respectively, while only 17.3% and 27.3% were canceled in the same periods in 2019. Further, 76.2% (March) and 57.1% (April) of first-time appointments were canceled in 2020 respect to the 36.4% and 23.7% in the same months in 2019. In general, 72% of patients missed out their appointments during the lockdown period (i.e. 66.7% first-time and 77.4% of follow-up). There was a significant difference in the proportion of canceled follow-up ($p < 0.001$) and first-time ($p = 0.001$) appointments respectively in March and April 2020 compared to the same periods in 2019. As shown in **Table 2** (Reasons for scheduling a first-time appointment at the memory clinic), most patients (85.2%) were referred to our clinic for the first-time for a new diagnostic evaluation, while the remaining were either patients enrolled in clinical trials or those who already had a dementia diagnosis but require the adjustment or initiation of pharmacological treatment. Almost half of the first-time appointments were for people with cognitive disturbance that requires evaluation.

DISCUSSION

The COVID-19 outbreak dramatically hit Italy at the end of January 2020 and the government's restrictive measures included in the decree number 14 resulted in the cancelation of the majority of appointments in memory clinics. Our data highlight that many patients with pre-existing NCD missed potentially important follow-up appointments, and that a substantial number of first-time visit NCD had a delay in diagnoses. Considering the high prevalence of behavioral disorders in patients with NCD (e.g., depression, apathy, psychomotor, and psychotic syndromes), that 60% of NCD patients reported a rapid increase during quarantine (12) and that they are associated with acceleration of cognitive decline (15), such a delay in diagnosis and treatment may have serious consequences on patient outcomes. Moreover, these estimates suggest that the reduction in services will result in a large influx of first-time appointments (previously scheduled ones plus new first-time appointments) with a consequent lengthening of waiting lists and increased burden on already stretched healthcare services.

It is possibly premature to estimate the long-term effects that patients will experience as a result of missing their routine appointments. We, however, are confident that a number of patients will experience a worsening of symptoms due to lack of pharmacological control or support from psychologists and psychiatrists (16, 17). Moreover, the social restrictions and increased isolation may lead to increased negative effects on memory disorders and neuropsychiatric symptoms of older people with NCD (18, 19). In fact, recent data on this topic reported an increase of behavioral symptoms in elderly with dementia (8–10). It is also possible that there may be an increased need for assessment of new patients in geriatric psychiatry settings as a result of the negative consequence of quarantine and social distancing measures. In fact, psychological symptoms

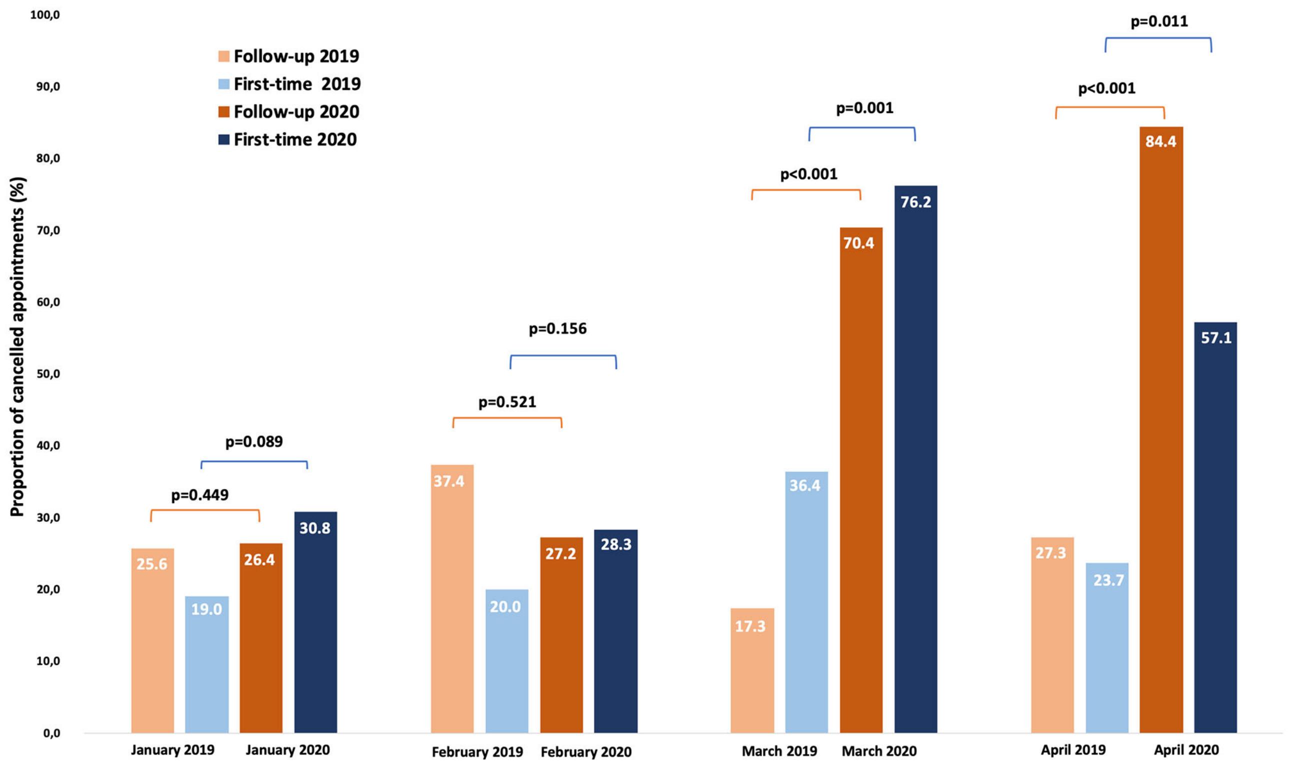

FIGURE 2 | Proportion of canceled appointments in 2019 compared to 2020.

TABLE 2 | Reasons for scheduling a first-time appointment at the memory clinic.

Reason	*n*	%
Diagnostic exam: Referrals for cognitive disturbances (memory, language, attention, orientation)	82	48.2
Diagnostic exam: Screening for cognitive functioning due to a familial case of a memory disorder	33	19.4
Diagnostic exam: Patient referrals for examination by another regional physician	30	17.6
Persons with an existing dementia diagnosis requiring evaluation/adjustment of pharmacological treatment	21	12.4
Patients enrolled in a clinical trial requiring the adjustment of pharmacological treatment or initiation of standard therapy	4	2.4

due to stressor events can contribute to cognitive decline (20) and social isolation, reduced social network, and loneliness can lead to generalized anxiety and major depression disorders in older individuals (21–23). Further, during lockdown it is likely that many older persons reduced their physical activity levels (5), which may impair symptoms; for example, cardiorespiratory fitness is also associated with cognitive functioning in older persons (24). This scenario may exacerbate psychological distress in caregivers, condition which may further worsen patients' behavioral symptoms, acting in a vicious loop of mutual increase of psychiatric burden (9).

NCD is a major public health concern and timely diagnosis is important for improving the course of illness and initiating appropriate therapeutics and care planning. Our study provides some absolute numbers in terms of how many patients who needed a first-time neuropsychiatric diagnostic evaluation in our clinic missed out on personalized care during the COVID-19 pandemic. In particular, a total of 72% of patients that scheduled an appointment during March and April 2020 missed it, with approximately a quarter of these being new patients, most of whom were referred for diagnostic evaluation. Diagnoses are made as a result of a process which usually takes time, in which the patient undergoes a series of procedures in order to gradually identify underlying pathologies. This means that, as a parallel effect, there will be a delay in diagnosing new cases of NCD, which may affect treatment and progression of the disorders as well as access to health and social care services (25).

In the current public health emergency, Italy was generally unprepared for digital healthcare approaches for managing patients, although some other countries had better training and facilities to keep in touch with patients remotely (26–28). Across the EU Member States there are still two fifths (40%) of older people (aged 65–74 years) who have never used a computer and this number is higher than two thirds in Italy (29). The low percentage of older people who are able to use technology (e.g., personal computer, internet, and other devices) is a barrier in terms of digitalization of medicine in Italy. However, the other obstacle is that only a small percentage of Italian medical services are equipped and trained to use healthcare technologies. So even if technology use increases in older persons, the healthcare system may not be able to provide digital medical support in a large number of cases (30).

Several pilot projects have focused on the usability of different types of technologies for older people with mild and major NCD in test laboratories or at home (e.g., PETAL and ReMember-Me projects, within Active & Assisted Living Programme - Horizon 2020); what emerged is a benefit for both patients and their caregivers, especially in terms of quality of life, occupational performance, and human dignity (31–33). In general, the use of Information and Communications Technology (ICT) by people with NCD is well-tolerated if devices are specifically designed to be easy to use for the target users and if they receive adequate training in order to learn how to use the technology and avoid issues due to their cognitive problems (34). Thus, one priority area for preparing Italy for potential future outbreaks of COVID-19 is to design and develop telemedicine solutions for individuals with cognitive impairment [i.e., remote memory clinics (35)], and to prepare adequate training for both healthcare professionals and patients.

Some limitations of the study should be discussed. The data only provide information about one memory clinic. It would be interesting to compare present data with those of others memory clinics in Italy or Europe. However, all Italian outpatient clinics adhered to the same government guidelines during the pandemic, which suggests that our results may be generalizable to those of the others. However, there may be differences in other countries depending on their infection-control strategy, especially in less developed countries. Therefore, our findings may not be fully applicable to low- or middle-income countries. Research in the short-term should focus on what effect the appointment cancelations had on patients in terms of their disease progression, cognitive functioning, and behavioral symptoms. Currently, healthcare professionals in the Italian National Health System are urgently trying to ease the backlog of patients by rescheduling canceled appointments. These efforts are still ongoing and continued infection-control limitations mean that many patients still have not returned for a clinical examination. Further, it will be interesting to compare disease and symptom progression in patients from countries that employed different policies to cope with the pandemic. Future research also needs to urgently develop and assess digital and telehealth alternatives with the aim to avoid the adverse consequence of a new period of social lockdown. In particular, it is important to find long-term alternatives to face-to-face outpatient services, potentially ICT and telehealth solutions that can support both patients and caregivers remotely (36–42). These solutions need to be user-friendly for people with cognitive and sensory impairment, for example including intuitive interface, clear and understandable symbols, big fonts, fewer commands and with colors that could help patients to remember different functions (43, 44). In general, telemedicine can reduce the risk for the development of negative outcomes in mental health precipitated by the reduction of social contact and less access to health services, improving dementia symptoms management like psychological and behavioral symptoms (45).

CONCLUSION

As expected, the data from our memory clinic in Rome showed that a large number of patients with NCD missed potentially important follow-up appointments during the pandemic, and many will experience a delay in initial diagnosis and beginning of treatment. Since COVID-19 continues to make its presence felt in healthcare all over the world, it is a compelling priority to ensure an easy and rapid access to appropriate assessment, care, and treatment in the event of a new outbreak and potential lockdown. Hence, a great challenge now is to convert this global emergency into a source of change that will see an implementation of telemedicine use by the healthcare system, alongside to traditional face-to-face medicine, developing specific technologies customized to older persons with cognitive impairment.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

GS and KP conceived the structure and content of the paper. DEP, NB, and KP wrote the paper. NB and VC provided revisions of the paper. All authors contributed to the article and approved the submitted version.

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Psychological, Social and Health-Related Challenges in Spanish Older Adults During the Lockdown of the COVID-19 First Wave

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Background: The global pandemic of COVID-19 has required a population lockdown. Spain has one of the oldest/most aging populations in the world and was one of the most affected countries. We aim to describe the psychological and social implications as well as health-related behaviors as a result of the lockdown in community-dwelling older adults.

Materials and Methods: Observational cross-sectional study. A total of 528 participants of over 60 years of age were recruited using snowball sampling technique during the lockdown of the COVID-19 first wave using an anonymous self-administered questionnaire composed of descriptive questions and validated scales for resilience (Brief Resilient Coping Scale) and emotions (Scale of Positive And Negative Experience).

Results: Most participants (76.9%) live with other people and have an open space at home (64%). Only 33.7% continued doing activities to promote healthy aging, 65.7% did less physical activity and 25.6% increased their intellectual activity. Most of them (83%) used electronic communication with family and friends to a greater extent, and left the house to run basic errands. Greater scores on resilience showed significant negative correlations with age and negative feelings, and positive correlations with the size of the social network and positive feelings. Lacking an open space at home was associated with more negative feelings.

Discussion: Older people are a vulnerable group severely affected by this pandemic crisis at multiple levels, requiring specific interventions to minimize the effects of changes in lifestyle that may be harmful. Detecting needs is essential to improve care and support from community health and social services, both nowadays and in future similar situations.

Keywords: coronaviral infections, social support, resilience, disaster vulnerability, emotions

INTRODUCTION

In January 2020, the World Health Organization (WHO) declared the outbreak of a new Coronavirus disease (COVID-19), to be a public health emergency of international concern. In March, the WHO characterized this disease as a pandemic (1). This led to a situation of global lockdown, where Spain was one of the countries to enforce stricter measures and restrictions. Despite the disease affecting people of all ages, data show that age is a risk factor in terms of complications and associated mortality (2). In this scenario, older people would be an especially vulnerable group to lockdown measures (3). This situation has been particularly important in the case of Spain, which has one of the oldest populations in Europe and is ranked third in the world of countries with the highest life expectancy (4). Several aspects play an important part in personal management of this stressful situation in older adults. These include fear of infection, management of preventive measures, loneliness, support from family and friends, leisure, exercise, and general lifestyle. In this context, the WHO has advised families to provide practical and emotional support by helping seniors to take preventive measures (for example, hand washing), guaranteeing access to their current medications, teaching them simple daily physical exercises to do at home, keeping everyday routines and schedules or helping to create new ones in a new environment, keeping in regular contact with their loved ones (for example, by phone, email, social networks or videoconference) as well as preserving regular sleep routines and healthy foods (1).

This strict and prolonged lockdown situation posed a challenge for the mental health and personal well-being for health and wellness -emotional, cognitive and physical- (5–8). Added to the direct effects of lockdown, the fear of becoming infected with COVID-19 through personal contact must be taken into account. In Spanish citizens confined to their homes, this fear was focused on those tasks that involved leaving home, such as going out to buy food or to the pharmacy. This fear of becoming infected, in interaction with the lockdown scenario, might increase feelings of social isolation and psychological distress, including depressive symptoms and avoidant behaviors (8, 9). To minimize the impact of this situation, personal and social resources become essential. Social support provided through telephone or telematics also become important in lessening the impact. Negative self-perceptions of aging may be related to negative outcomes for older adults and play an important role in the context of lockdown (8, 10). In addition, personal resources such as good management of emotions and resilience will be key to minimize the psychological consequences of this lockdown (11, 12). It is worth noting the importance of resilience, understood as a self-regulating mechanism of protection against the emergence of possible difficult consequences at certain times in life (13, 14), which plays a key role in healthy aging (15). Apart from the potential increases in stress levels and depressive symptoms due to perceived health risk and uncertainty about the future, concerns regarding the effect of the COVID-19 crises in old adults include the curtailing of physical activity and the increases in sedentary behaviors, nutritional changes due to limited shopping and fear of going out, as well as limited access to health services (16).

In addition to the personal and mental health resources of confined people, especially older adults, an important aspect to take into account in the situation of strict lockdown is the housing conditions. Although most people spend the bulk of their lives indoors, buildings are rarely intentionally designed or operated with the goal of promoting mental health (17). Previous works have shown that visual contact with nature has a reliable effect in physiological relaxation (18, 19), but the strict confinements due to the COVID-19 crisis have clearly shown the need to direct outdoor exposure and its potential implication for psychological, social and physical health (20). Amerio et al. (21) studied the relation between mental health and housing conditions, including housing dimension, presence or absence of liveable open space and quality of views, in 8,177 students from a university institute in Milan, Northern Italy, after 3 weeks of strict lockdown. Compared to students with absent to moderate depressive symptoms, students with moderate–severe and severe depressive symptoms lived in smaller apartments, with unusable balconies and poor-quality views from their apartments.

Our objective was to describe the psychological and social implications and health-related behaviors involved in the lockdown due to the COVID-19 pandemic in Galician adults over 60 years old. In order to obtain a more in-depth analysis of the data, groups of participants have been compared, grouping them according to whether they left home and experienced fear when doing so, and according to if they had access to any open space (garden, terrace, balcony) at home. We hypothesize a relation between experiencing fear or discomfort when leaving home, or not leaving home during the lockdown and demographic and social variables related to the risk of COVID-19 and the impact of confinement on the active aging process of the participants. Complementarily, we consider that these demographic and social variables can be predictors of whether old adults leave their home experiencing fear or discomfort, or if they do not leave home during the lockdown.

Regarding the role of psychological variables such as resilient coping and the presence of positive and negative feelings, the current evidence shows that psychological resources were related to the emotional response of the Spanish old adults during the strict lockdown of the COVID-19 first wave (8, 12). We hypothesize a relation between experiencing fear or discomfort when leaving home, or not leaving home during the lockdown and both the psychological resources (resilience) and the psychological response of old adults. Likewise, we speculated if these psychological variables could be predictors of whether old adults leave their home experiencing fear or discomfort, or they do not leave home during the lockdown.

Finally, according to the current evidence about the effect of the exposure to outdoors and its potential implication for psychological and social health, we hypothesize a relation between accesses to any open space (garden, terrace, balcony) at home during the strict lockdown of the COVID-19 first wave and demographic, social and psychological variables.

MATERIALS AND METHODS

Study Design and Data Collection

Observational, cross-sectional study. Non-probability sampling was used using snowball sampling technique. Sample recruitment was initiated through the most representative regional organizations in the promotion of active aging (Galician Association of Permanent Adult Training -ATEGAL-, Program Spaces +60 of Afundación, Red Cross), as well as through the specific university program for older people from our institution. Likewise, participants from the organizations promoting active aging and the university were asked to distribute the questionnaire among their contacts aged 60 and over.

Instrument

A self-administered questionnaire was distributed electronically (Forms, Microsoft Office 365 available by our university). *Ad-hoc* questions collected information on sociodemographic, psychological, and social data during the COVID-19 lockdown. To evaluate social networks, the specific question: "Approximately, how many close friends or close family do you have? (people with whom you are at ease and can talk about everything you can think of)" from the Spanish version of the Medical Outcomes Study (MOS) questionnaire for social support was used (22, 23). To obtain information regarding resilience, the Spanish version of the Brief Resilient Coping Scale (BRCS) was used (24). It is a 4-item questionnaire to assess optimism, perseverance, creativity and positive growth using a 6-point Likert scale, with higher scores showing greater resilience. To obtain the data on the presence of positive and negative emotions, a part of the Spanish validated version of the Scale of positive and negative experience (SPANE) was used (25). Specifically, two general items (Positive, Negative) and six specific items (Happy, Sad, Afraid, Joyful, Angry, Contented) were chosen. For each one, a number from 1 (Very Rarely) to 5 (Very Often) was selected. Scores were calculated for positive feelings (summation of the positive, happy, joyful, and contented scores) and for negative feelings (summation of the negative, sad, afraid and angry scores).

Participants

The sample consisted of adults living in the community. Exclusion criteria were (a) being under 60 years old, (b) be living outside Galicia (North-West region of Spain, Europe) during the lockdown declared in March 2020 by the Spanish government due to the COVID-19 pandemic (verified by requiring the postcode), and (c) not providing online informed consent. The study was undertaken between the 20th and 27th April 2020, before the announcement of relief measures which would allow the population to leave home for some hours. A total of 599 participants were recruited, of which 16 were excluded due to being younger than the required age and 55 for not meeting the geographic criteria.

Ethical Considerations

The study protocol was approved by the Ethics Committee of the University of Santiago de Compostela (reference 040520). Participation was voluntary and all data were processed anonymously according to the current national and European regulations on data protection and patient rights. Participants provided online informed consent.

Data Analysis

A descriptive analysis was performed by calculating frequencies and percentages for the categorical variables, and means, standard deviations, and association between variables through bivariate correlations for the continuous variables. Specific analyses were performed based on whether participants left the house during lockdown and whether such outings caused discomfort, both questions collapsing into a variable through which three groups were obtained: (a) participants who left and did not feel discomfort, (b) participants who left and felt discomfort, and (c) participants who did not leave the house. Specific analyses were also carried out based on whether the older adults studied had an open space in their home or not. Participants were compared according to both independent variables, through χ^2 for the categorical dependent variables, and through ANOVAs (and *post-hoc* comparisons with the Bonferroni test) and *t*-test for the quantitative variables.

A hierarchical multinomial logistic regression was complementarily used to identify risk and protective factors of leaving home during the confinement and experiencing fear or not when doing so. Following Losada-Baltar et al. (8), age-related sociodemographic variables connected to risks associated with COVID-19 and how the confinement is experienced (chronological age in years, gender, education level, living alone or not) were included in the first step, followed by personal circumstances during the lock-down associated with such experience and with its impact on the active aging process (participation in activities, physical activity, intellectual activities, diet changes, frequency of calls—video calls made and received), and, finally, psychosocial resources (resilient copying, positive feelings, negative feelings, social network). As has been explained, the available evidence supports that the psychosocial resources and the emotional state play a role in the response of the Spanish old adults during the strict lockdown of the COVID-19 first wave (8, 12).

RESULTS

Description of the Participants' Lockdown Situation

The analyzed sample consisted of 528 participants over 60 years old (64.6% women) as shown in **Table 1**. 76.9% lived with other people at home and 64% had an open space at home (a space belonging to the house, where a person may be outdoors but still at home, for example a garden, terrace or balcony). The vast majority (76.5%) belonged to active aging organizations before lockdown, but only 33.7% continued to carry out active aging activities during this period. Most participants (65.7%) performed less physical activity than before the lockdown, whereas 25.6% of the sample reported an increased intellectual activity. Most participants did not modify their diet during the lockdown and just 15.7% reported eating healthier. Since the

TABLE 1 | Sociodemographic, descriptive, psychological, social, and behavioral characteristics of the total sample ($n = 528$) during the COVID-19 lockdown.

Question	Answer	
How old are you? (years)	69.25 (6.75)	
	N	**% of the total sample**
Gender		
Male	187	35.4
Female	341	64.6
What is your educational level?		
Primary	71	13.4
Secondary	77	14.6
Professional training	65	12.3
University studies	315	59.7
Do you live alone?		
Yes	122	23.1
No	406	76.9
Do you have any open spaces (garden, terrace, balcony) at home?		
Yes	338	64
No	190	36
Have you participated in any cultural, recreational or rehabilitation activity for old adults?		
Before lockdown and currently	178	33.7
Before lockdown, but not currently	195	36.9
Neither before lockdown nor currently	155	29.4
During the lockdown, have you done more physical activity than before?		
More	47	8.9
Same	134	25.4
Less	347	65.7
During the lockdown, have you had more intellectual activity than before?		
More	135	25.6
Same	313	59.3
Less	80	15.2
During the lockdown, have you changed your diet?		
Healthier	83	15.7
Same	405	76.7
Less healthy	40	7.6
Have you left home since the beginning of the lockdown?		
Yes	364	68.9
No	164	31.1
Have you felt any kind of discomfort or fear when leaving home?		
Yes	132	25
No	232	43.9

(Continued)

TABLE 1 | Continued

Question	Answer	
	N	**% of the total sample**
Have you left home wearing a mask?		
Yes	257	48.7
No	107	20.3
Have you left home wearing gloves?		
Yes	259	49.1
No	105	19.9
Has anyone taught you how to use the mask and gloves correctly?		
Yes	230	43.6
No	134	25.4
During the lockdown, have you made more phone calls or video calls to family or friends than before?		
Yes	438	83
No	90	17
During the lockdown, have you received more phone calls or video calls from family or friends than before?		
Yes	439	83.1
No	89	16.9
Do you think you will feel any kind of discomfort when you leave home after the lockdown is over?		
Yes	182	34.5
Indifferent	48	9.1
No	298	56.4
Has this situation given you a more pessimistic view of your immediate future?		
Yes	239	45.3
Indifferent	62	11.7
No	227	43
Do you think your physical health will get worse?		
Yes	88	16.7
Indifferent	90	17.0
No	350	66.3
Do you think your family life will get worse?		
Yes	80	15.2
Indifferent	56	10.6
No	392	74.2
Do you think your social relationships will get worse?		
Yes	168	31.8
Indifferent	42	8
No	318	60.2

(Continued)

TABLE 1 | Continued

Question	Answer	
	N	% of the total sample
Do you think the pandemic will have any beneficial effect?		
Yes	101	19.1
Indifferent	70	13.3
No	357	67.6

Question/Scale	Mean (SD)
About how many close friends or close family do you have? (People with whom you feel comfortable and can talk about everything you can think of)	13.59 (12.60)
Resilient coping (BRCS) score	10.18 (2.76)
Positive feelings (SPANE-P) score	9.96 (4.65)
Negative feelings (SPANE-N) score	6.83 (2.70)

Results are shown as mean, and standard deviation (SD, in brackets), or frequency and percentage. BRCS, Brief Resilient Coping Scale; SPANE-P, Scale of Positive and Negative Experience—Positive feelings; SPANE-N, Scale of Positive and Negative Experience—Negative feelings.

lockdown began, 68.9% left their home to run an errand, mainly to go shopping for food or to the pharmacy and mostly wearing mask and gloves (**Table 1**). Two hundred and thirty people who left their houses (43.6% of the total sample), received information or instructions on the proper use of these protections.

The average size of the social network of the participants was 13.59 ± 12.60 people, and 83% made and received more calls from friends or family than before lockdown. Regarding the future, 34.5% think that they will feel some kind of discomfort when leaving home, that their physical health will not worsen (66.3%), nor their family life (74.2%), although this percentage is lower for social relations (60.2%). A large majority believes that this situation will not have a positive effect (67.6%).

BRCS showed significant correlation, in negative direction, with age [$r_{(526)} = -0.15$, $p = 0.001$] and SPANE-N [$r_{(526)} = -0.37$, $p = 0.001$], and positive, with SPANE-P [$r_{(526)} = 0.34$, $p = 0.001$] and with the size of the social network [$r_{(526)} = -0.14$, $p = 0.001$]. SPANE-P also correlated significantly, negatively, with SPANE-N [$r_{(526)} = -0.21$, $p = 0.001$], and positively with the size of the social network [$r_{(526)} = 0.17$, $p = 0.001$].

Differences Between Participants Who Left Home and Experienced Fear, and Those Who Did Not

Regarding the differences depending on whether the participant had left the house during lockdown, and the impact of these outings (**Table 2**), significant differences were found for age, gender, educational level, living alone, changes in intellectual activity and diet due to lockdown, use of gloves, pessimistic vision of the future, worsening of physical health and social relationships, and the presence of measured positive and negative feelings, although effect sizes are moderate only for educational level.

Regarding the results of the hierarchical logistic regression for explaining differences in these groups, a good fit of the model was obtained at step 1 when only the sociodemographic variables were included (Chi-square test = 93.99; $p < 0.01$), but a better fit when the personal circumstances during the confinement (Chi-square test = 122.60; $p < 0.01$) and both the personal circumstances and the psychosocial resources (Chi-square test =145.44; $p < 0.01$) were also included. The variables that significantly contributed to the difference between leaving home without feeling discomfort and leaving home with discomfort in the final model were: gender, changes in diet, positive feelings and negative feelings (**Table 3**). The variables that significantly contributed to the difference between leaving home without feeling discomfort and not leaving home were: age, gender, educative level and not living alone (**Table 4**).

Differences According to Availability of Open Spaces at Home

Regarding the differences depending on whether the participant has an open space at home, when comparing those who had an open space with those who did not, no significant differences were found but a tendency toward significant differences was observed in the SPANE-N (with open space: mean = 6.66, S.D. = 2.53; without open space: mean = 7.12, S.D. = 2.96; $t_{2,\,525} = -1.86$, $p = 0.064$).

DISCUSSION

The sample of Galician older adults studied during the lockdown decreed by the Spanish government due to the COVID-19 pandemic is mainly female, with an average age of 69 years and a high educational level. A third of participants have stopped participating in recreational or occupational activities during the lockdown, doing less physical activity. For over 2 months, strict "stay-at-home" or lockdown policies were maintained for all citizens, and houses became the only place where the population could sleep, eat, work, or do exercise. In this scenario, the closure of parks and exercise facilities might have been relevant factors related to the observed decrease of physical activity. Participants mostly increased the use of electronic communication to contact family or friends during the lockdown and considered that they have an important social network that could help them in case of need, stressing the potential positive consequences of the lockdown (26). This result is in line with previous findings showing very good levels of social support in Spanish older adults (27). According to the complex interrelation between social and health factors (28), social and family relations must be considered in tracking psychological changes after the lockdown. As regards the differences between people who left their homes during lockdown, felt fearful or not when doing so, and those who did not leave, most of the effect sizes are small. However, we consider the theoretical interest of these results according to the potential impact of a preventive restrictive quarantine in

TABLE 2 | Sociodemographic, descriptive, psychological, social, and behavioral differences depending on whether the participant has left home during lockdown or not.

Question	**Leaving home without discomfort (Group 1, *n* = 232)**		**Leaving home in discomfort (Group 2, *n* = 132)**		**Not leaving home (Group 3, *n* = 164)**		**Test**[a]	***p***	**Effect size**[b]
How old are you? (years)	68.56 (5.90)		67.48 (4.91)		71.66 (8.33)		17.24	0.001	0.06
	N	%	*N*	%	*N*	%			
Gender									
Male	105	45.3	42	31.8	40	24.4	12.29	0.001	0.19
Female	127	54.7	90	68.2	124	75.6			
What is your educational level?									
Primary	16	6.9	9	6.8	46	28	47.71	0.001	0.21
Secondary	39	16.8	22	16.7	16	9.8			
Professional training	25	10.8	17	12.9	23	14			
University studies	152	65.5	84	63.6	79	48.2			
Do you live alone?									
Yes	68	29.3	31	23.5	23	14	12.65	0.002	0.15
No	164	70.7	101	76.5	141	86			
Do you have any open space (garden, terrace, balcony) at home?									
Yes	144	62.1	83	62.9	111	67.7	1.41	0.493	0.05
No	88	37.9	49	37.1	53	32.3			
Did you participate in any cultural, recreational or rehabilitation activity for old adults?									
Before lockdown, but not currently	64	27.6	40	30.3	51	31.1	1.71	0.789	0.04
Before lockdown and currently	83	35.8	51	38.6	61	37.2			
Neither before lockdown nor currently	85	36.65	41	23.0	52	31.7			
During the lockdown, have you done more physical activity than before?									
More	157	67.7	94	71.2	96	58.5	6.84	0.145	0.08
Same	56	24.1	30	22.7	48	29.3			
Less	19	8.2	8	6.1	20	12.2			
During the lockdown, have you had more intellectual activity than before?									
More	26	11.2	27	20.5	27	16.5	11.85	0.018	0.11
Same	133	57.3	75	56.8	105	64.0			
Less	73	31.5	30	22.7	32	19.5			
Have you changed your diet?									
Healthier	13	5.6	17	12.9	10	6.1	10.71	0.030	0.10
No changes	189	81.5	90	68.2	126	76.8			
Less healthy	30	12.9	25	18.9	28	17.1			
Have you left the house wearing a mask?									
Yes	157	67.7	100	75.8		2.65	0.104	0.09	
No	75	32.3	32	24.2					
Have you left the house wearing gloves?									
Yes	151	65.15	108	81.8		11.48	0.001	0.18	
No	81	34.9	24	18.2					

(Continued)

TABLE 2 | Continued

Question	**Leaving home without discomfort (Group 1, *n* = 232)**		**Leaving home in discomfort (Group 2, *n* = 132)**		**Not leaving home (Group 3, *n* = 164)**		**Test**[a]	***p***	**Effect size**[b]
Has anyone taught you how to use the mask and gloves correctly?									
Yes	146	62.9	84	63.6		0.02	0.893	0.01	
No	86	37.1	48	36.4					
During the lockdown, have you made more phone calls or video calls?									
Yes	194	83.6	108	81.8	136	82.9	0.193	0.908	0.02
No	38	16.4	24	18.2	28	17.1			
During lockdown, have you received more calls/video?									
Yes	191	82.3	110	83.3	138	84.1	0.23	0.891	0.02
No	41	17.7	22	16.7	26	15.9			
Approximately, how many close friends or close family do you have?	13.82 (12.69)	14.03 (13.42)	12.90 (11.84)	0.37	0.692	0.00			
Has this situation given you a more pessimistic view of your immediate future?									
Yes	81	34.9	85	64.4	73	44.5	29.60	0.001	0.17
Indifferent	33	14.2	10	7.6	19	11.6			
No	118	50.9	37	28	71	43.9			
Do you think your physical health will get worse?									
Yes	27	11.6	26	19.7	35	21.3	19.55	0.001	0.14
Indifferent	32	13.8	34	25.8	24	14.6			
No	173	74.6	72	54.5	105	64			
Do you think your family life will get worse?									
Yes	27	11.6	30	22.7	23	14	9.03	0.060	0.09
Indifferent	23	9.9	15	11.4	18	11			
No	182	78.4	87	65.9	123	75			
Do you think your social relationships will get worse?									
Yes	56	24.1	53	40.2	59	36	13.97	0.007	0.12
Indifferent	19	8.2	13	9.8	10	6.1			
No	157	67.7	66	50	95	57.9			
Do you think the pandemic will have any beneficial effect?									
Yes	43	18.5	28	21.2	30	18.3	3.91	0.418	0.06
Indifferent	38	16.4	14	10.6	18	11			
No	151	65.1	90	68.2	116	70.7			
Resilient coping (BRCS)	10.34 (2.62)	9.91 (3.07)	10.17 (2.68)	1.03	0.357	0.00			
Positive feelings (SPANE-P)	10.40 (4.69)	8.74 (4.17)	10.31 (4.83)	6.12	0.002	0.02			
Negative feelings (SPANE-N)	6.35 (2.23)	7.58 (3.11)	6.89 (2.81)	8.98	0.001	0.03			

Results are shown as mean, and standard deviation (in brackets), or frequency and percentage. BRCS, Brief Resilient Coping Scale; SPANE-P, Scale of Positive and Negative Experience—Positive feelings; SPANE-N, Scale of Positive and Negative Experience—Negative feelings.

[a] *F(2, 525), and χ^2 (2, 528).*

[b] *η_p^2 with F, Cramer's V with χ^2.*

TABLE 3 | Hierarchical logistic regression models comparing the results of those participants leaving home with discomfort with those participants leaving home without discomfort (reference group).

	B	S.E.	Wald χ^2	*p*	OR	95% CI
Model 1						
Age	−0.03	0.02	1.80	0.24	0.97	0.94–1.01
Gender						
Male	−0.62	0.24	6.89	< 0.01	0.54	0.33–0.85
Female	0					
Education level						
Primary	0.04	0.45	0.01	0.94	1.04	0.43–2.52
Secondary	−0.12	0.31	0.15	0.70	0.89	0.49–1.62
Professional training	0.22	0.35	0.40	0.53	1.24	0.63–2.46
University studies	0					
Live alone						
Yes	−0.37	0.26	2.01	0.16	0.70	0.42–1.15
No	0					
Model 2						
Age	−0.02	0.02	0.80	0.37	0.98	0.94–1.02
Gender						
Male	−0.71	0.25	7.83	< 0.01	0.49	0.30–0.81
Female	0					
Education level						
Primary	−0.05	0.50	0.01	0.91	0.95	0.37–2.42
Secondary	−0.01	0.32	0.00	0.98	0.99	0.53–1.86
Professional training	0.13	0.36	0.13	0.72	1.14	0.56–2.31
University studies	0					
Live alone						
Yes	−0.41	0.27	2.35	0.13	0.66	0.39–1.12
No	0					
Activities for old adults						
Before lockdown and currently	0.37	0.31	1.44	0.23	1.44	0.79–2.63
Before lockdown, but not currently	0.13	0.28	0.23	0.63	1.14	0.66–1.97
Neither before nor currently	0					
Physical activity during lockdown						
More	0.44	0.46	0.89	0.34	1.55	0.62–3.84
Same	0.34	0.50	0.46	0.50	1.40	0.53–3.74
Less	0					
Intellectual activity during lockdown						
More	0.91	0.38	5.80	0.02	2.48	1.18–5.17
Same	0.39	0.28	1.99	0.16	1.48	0.86–2.54
Less	0					
Diet changes						
Healthier	0.15	0.49	0.10	0.75	1.17	0.45–3.03
Same	−0.78	0.32	5.85	< 0.05	0.46	0.24–0.86
Less healthy	0					
Have you made more phone calls?						
Yes	−0.13	0.38	0.12	0.73	0.88	0.41–1.85
No	0					
Have you received more phone calls?						
Yes	0.06	0.38	0.03	0.870	1.06	0.51–2.23
No	0					

(Continued)

TABLE 3 | Continued

	B	S.E.	Wald χ^2	p	OR	95% CI
Model 3						
Age	−0.02	0.02	0.67	0.41	0.98	0.94–1.03
Gender						
Male	−0.74	0.26	8.16	< 0.01	0.48	0.29–0.79
Female	0					
Education level						
Primary	−0.29	0.50	0.32	0.57	0.75	0.28–2.02
Secondary	−0.05	0.33	0.02	0.88	0.95	0.50–1.82
Professional training	0.16	0.37	0.20	0.65	1.18	0.57–2.43
University studies	0					
Live alone						
Yes	−0.35	0.28	1.57	0.21	0.71	0.41–1.22
No	0					
Activities for old adults						
Before lockdown and currently	0.40	0.31	1.64	0.20	1.50	0.81–2.80
Before lockdown, but not currently	0.12	0.28	0.18	0.67	1.13	0.64–1.97
Neither before nor currently	0					
Physical activity during lockdown						
More	0.40	0.48	0.71	0.40	1.49	0.59–3.81
Same	0.39	0.51	0.58	0.44	1.48	0.54–4.03
Less	0					
Intellectual activity during lockdown						
More	0.72	0.39	3.40	0.65	2.05	0.96–4.40
Same	0.36	0.28	1.66	0.20	1.44	0.83–2.50
Less	0					
Diet						
Healthier	−0.16	0.52	0.10	0.76	0.85	2.37
Same	−0.83	0.33	6.23	< 0.05	0.44	0.84
Less healthy	0					
Have you made more phone calls?						
Yes	−0.32	0.40	0.62	0.43	0.73	0.33–1.60
No	0					
Have you received more phone calls?						
Yes	0.20	0.40	0.25	0.61	1.22	0.56–2.65
No	0					
Approximately, how many close friends or close family do you have?	0.01	0.01	0.87	0.35	1.01	0.99–1.03
Resilient coping (BRCS) score	0.05	0.05	0.88	0.35	1.04	0.95–1.16
Positive feelings (SPANE-P) score	−0.08	0.03	7.97	< 0.01	0.92	0.87–0.98
Negative feelings (SPANE-N) score	0.14	0.05	8.78	< 0.01	1.15	1.05–1.26

Model 1 includes sociodemographic variables, Model 2 includes sociodemographic variables and personal circumstances during the lockdown, and Model 3 adds psychosocial resources.

the social and emotional lives of community-dwelling older adults, and also considering the hierarchical logistic regression supporting these findings.

Our results suggest two broad profiles of older adults experiencing problems resuming daily life after this strongly restrictive quarantine. The logistic regression model shows that leaving home with discomfort was more likely in women who had changed their diet and who experienced fewer positive feelings and more negative feelings. This group might have an increased risk of developing psychopathologies and therefore need more care and attention at the psychosocial level. On the other hand, those who did not leave the house are older, mainly female, with

TABLE 4 | Hierarchical logistic regression models comparing the results of those participants not leaving home with those participants leaving home without discomfort (reference group).

	B	S.E.	Wald χ^2	*p*-values	OR	95% CI
Model 1						
Age	0.05	0.02	8.80	< 0.01	1.05	1.02–1.09
Gender						
Male	−1.05	0.25	18.23	< 0.01	0.35	0.21–0.57
Female	0					
Education level						
Primary	1.25	0.35	12.77	< 0.01	3.51	2.76–6.99
Secondary	−0.27	0.34	0.61	0.44	0.77	0.39–1.50
Professional training	0.61	0.33	3.32	0.07	1.84	0.96–3.56
University studies	0					
Live alone						
Yes	−1.21	0.29	17.07	< 0.01	0.30	0.17–0.53
No	0					
Model 2						
Age	0.06	0.02	10.49	< 0.01	1.06	1.02–1.10
Gender						
Male	−1.10	0.26	18.02	< 0.01	0.33	0.20–0.55
Female	0					
Education level						
Primary	1.30	0.38	11.76	< 0.01	3.67	1.75–7.73
Secondary	−0.15	0.35	0.17	0.68	0.86	0.43–1.73
Professional training	0.51	0.35	2.15	0.14	1.66	0.84–3.28
University studies	0					
Live alone						
Yes	−1.27	0.30	17.61	< 0.001	0.28	0.15–0.51
No	0					
Activities for old adults						
Before lockdown and currently	0.16	0.30	0.29	0.59	1.18	0.65–2.13
Before lockdown, but not currently	0.02	0.28	0.00	0.95	1.02	0.59–1.75
Neither before nor currently	0					
Physical activity during lockdown						
More	−0.67	0.38	3.07	0.08	0.51	0.24–1.08
Same	−0.52	0.41	1.54	0.22	0.59	0.26–1.34
Less	0					
Intellectual activity during lockdown						
More	0.58	0.40	2.14	0.14	1.79	0.82–3.91
Same	0.40	0.28	2.10	0.15	1.49	0.87–2.57
Less	0					
Diet changes						
Healthier	−0.02	0.55	0.00	0.98	0.98	0.34–2.87
Same	−0.63	0.33	3.62	0.06	0.53	0.28–1.02
Less healthy	0					
Have you made more phone calls?						
Yes	0.32	0.39	0.69	0.41	1.38	0.64–2.98
No	0					
Have you received more phone calls?						
Yes	−0.09	0.38	0.06	0.81	0.91	0.44–1.92
No	0					
Model 3						
Age	0.06	0.02	10.54	< 0.01	1.06	1.02–1.10

(Continued)

TABLE 4 | Continued

	B	S.E.	Wald χ^2	*p*-values	OR	95% CI
Gender						
Male	−1.09	0.26	17.51	< 0.001	0.34	0.20–0.56
Female	0					
Education level						
Primary	1.30	0.39	11.34	0.00	3.68	1.72–7.86
Secondary	−0.11	0.36	0.09	0.77	0.90	0.45–1.81
Professional training	0.51	0.35	2.12	0.15	1.65	0.84–3.27
University studies	0					
Live alone						
Yes	−1.25	0.30	17.00	< 0.001	0.29	0.16–0.52
No	0					
Activities for old adults						
Before lockdown and currently	0.20	0.31	0.41	0.52	1.22	0.67–2.21
Before lockdown, but not currently	0.03	0.28	0.01	0.92	1.03	0.60–1.77
Neither before nor currently	0					
Physical activity during lockdown						
More	−0.67	0.39	3.01	0.08	0.51	0.24–1.09
Same	−0.52	0.42	1.52	0.21	0.60	0.26–1.36
Less	0					
Intellectual activity during lockdown						
More	0.63	0.40	2.41	0.12	1.87	0.85–4.12
Same	0.42	0.28	2.22	0.14	1.51	0.88–2.61
Less	0					
Diet						
Healthier	0.03	0.56	0.00	0.96	1.03	0.34–3.11
Same	−0.60	0.34	3.19	0.07	0.55	0.29-1.06
Less healthy	0					
Have you made more phone calls?						
Yes	0.27	0.40	0.47	0.50	1.31	0.60–2.86
No	0					
Have you received more phone calls						
Yes	−0.07	0.38	0.03	0.86	0.94	0.44–1.98
No	0					
Approximately, how many close friends or close family do you have?	0.00	0.00	0.08	0.78	1.00	0.98–1.01
Resilient coping (BRCS) score	0.05	0.05	0.81	0.37	1.05	0.95–1.15
Positive feelings (SPANE-P) score	0.00	0.03	0.00	0.98	1.00	0.95–1.05
Negative feelings (SPANE-N) score	0.05	0.05	1.19	0.27	2.06	0.96–1.16

Model 1 includes sociodemographic variables, Model 2 includes sociodemographic variables and personal circumstances during the lockdown, and Model 3 adds psychosocial resources.

a lower educational level and fewer live alone. Although it has not been measured, it seems reasonable to assume that they present increased limitations of personal autonomy and greater fragility. On a psychological level, this group scored similar to those who left the home and did not feel discomfort and better than those who left the home and presented discomfort. Regarding this profile of old-old women with primary education and not living alone, detecting their health needs is essential to improve care from community health services both now and in similar future situations.

Regarding the role of psychological variables, the lower presence of positive feelings and the higher presence of negative feelings were significant predictors of experiencing fear or discomfort when leaving home. Findings in general population have shown that having a positive affect might help individuals to adopt information-processing strategies during the COVID-19 outbreak that would improve their life satisfaction (29). Regarding resilient coping, BRCS scores were similar to previous studies with Spanish older adults without being in an emergency situation (30). Nevertheless, in our study resilience is not a significative predictor variable, in contrast with results by López et al. (12). More research is needed to clarify to what extent factors like resilience and personal attitudes, including those toward perception of the aging process, play a role in addressing challenges in this pandemic. Likewise, recent studies have investigated the relevance of pre-existing mental health comorbidities in coping with this exceptional situation. Psychiatric patients have shown higher levels of anxiety, depression, insomnia and more health concerns than healthy subjects (31), as well as more frequency of COVID-related stress (32).

In relation to the availability of open spaces at home, Stephens et al. have studied in the last decades the influence of housing conditions on the affective and functional state of older people (33). Studies have shown that housing conditions are even more predictive than the degree of dependency in predicting abandonment of the home and institutionalization (34). In line with Amerio et al. (21), our results point to a greater presence of negative feelings during quarantine in participants who do not have open spaces at home. It has been pointed out that housing design strategies should focus on larger living spaces and visible and accessible green areas (20, 21). These recommendations would be of higher importance in potentially frail older adults. It could be useful, for example, to previously identify vulnerable people lacking open spaces at home to consider rehousing or to give them priority and specific schedules for short outings in case of a new lockdown. An interdisciplinary effort is needed, especially in COVID-19 times, to study the effect of housing conditions on older adults' mental health and to promote healthy living spaces, including professionals from gerontology, mental health, epidemiology, environmental health and urban planning.

The study has several limitations arising from the very early stage of the pandemic when the data were collected, which include the sampling procedure, the exploratory nature of the data collected, and the use of parts of validated scales. The recruitment was carried out looking for a sample as representative as possible through contact with the most representative regional entities in the promotion of active aging. In view of the very urgent nature of data collection, a snowball technique was used as a complementary sampling procedure, as done previously in this exceptional context (9, 12). The resulting sample is greatly female and university-educated, with most participants belonging to active aging organizations and therefore with access to different activities. The wider presence of women is associated with their longer life expectancy as well as greater participation in activities for older adults, and is present in other studies with Spanish population [i.e., Juncos Rabadán et al. (35)]. However, the presence of a higher percentage of older adults with university studies, which could be due to the acquisition of data through an online questionnaire, as well as their belonging to active aging organizations in a specific region of Spain, limit the generalization of the results presented to broader profiles of older adults and other communities. Regarding the cross-sectional nature of the study, available data show how health-related behaviors improved across the lockdown showing how well the Spanish population adapted (36). Longitudinal investigations are needed to determine the emotional impact of the strict quarantine measures adopted by the Spanish government, and its differential impact in community-dwelling old adults. Finally, according to the exploratory nature of the study, we present a high number of group comparisons, which greatly increase the Type I error probability.

In conclusion, early evidence on the effects of lockdown on older adults during the months of March and April 2020 seems to indicate that it is necessary to promote actions to encourage their activity and psychological well-being. Their freedom of movement has been restricted, thus affecting their pattern of active aging (37, 38). In a possible relapse of this situation, certain characteristics such as those described (living alone, presence of psychological distress, type of housing, etc.) cannot easily be directly modified but should be carefully analyzed, since the older population would receive a great deal of support from social and health services. Whereas, other age groups have been encouraged to shift both education and work online to improve health-related behaviors during a possible second wave of the pandemic (36), in community-dwelling old adults the current data points to an importance of psycho-social support. If a strict lockdown is again needed, consideration must be given to improve housing conditions.

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 Ethics Committee of the University of Santiago de Compostela (reference 040520). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RR-G and DF: design of the work, acquisition, analysis and interpretation of the data, drafting the work. A-EM-S: design of the work, acquisition and interpretation of the data, revising it critically for important intellectual content. MG-C: conception and design of the work, acquisition and interpretation of the data, drafting the work. All authors contributed to the article and approved the submitted version.

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Changes in Motor, Cognitive, and Behavioral Symptoms in Parkinson's Disease and Mild Cognitive Impairment During the COVID-19 Lockdown

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Objective: The effects of the COVID-19 lockdown on subjects with prodromal phases of dementia are unknown. The aim of this study was to evaluate the motor, cognitive, and behavioral changes during the COVID-19 lockdown in Italy in patients with Parkinson's disease (PD) with and without mild cognitive impairment (PD-MCI and PD-NC) and in patients with MCI not associated with PD (MCInoPD).

Methods: A total of 34 patients with PD-NC, 31 PD-MCI, and 31 MCInoPD and their caregivers were interviewed 10 weeks after the COVID-19 lockdown in Italy, and changes in cognitive, behavioral, and motor symptoms were examined. Modified standardized scales, including the Neuropsychiatric Inventory (NPI) and the Movement Disorder Society, Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts I and II, were administered. Multivariate logistic regression was used to evaluate associated covariates by comparing PD-NC vs. PD-MCI and MCInoPD vs. PD-MCI.

Results: All groups showed a worsening of cognitive (39.6%), pre-existing (37.5%), and new (26%) behavioral symptoms, and motor symptoms (35.4%) during the COVID-19 lockdown, resulting in an increased caregiver burden in 26% of cases. After multivariate analysis, PD-MCI was significantly and positively associated with the IADL lost during quarantine (OR 3.9, CI 1.61–9.58), when compared to PD-NC. In the analysis of MCInoPD vs. PD-MCI, the latter showed a statistically significant worsening of motor symptoms than MCInoPD (OR 7.4, CI 1.09–45.44). Regarding NPI items, nighttime behaviors statistically differed in MCInoPD vs. PD-MCI (16.1% vs. 48.4%, $p = 0.007$). MDS-UPDRS parts I and II revealed that PD-MCI showed a significantly higher frequency of cognitive impairment ($p = 0.034$), fatigue ($p = 0.036$), and speech ($p = 0.013$) than PD-NC. On the contrary, PD-MCI showed significantly higher frequencies in several MDS-UPDRS items compared to MCInoPD, particularly regarding pain ($p = 0.001$), turning in bed ($p = 0.006$), getting out of bed ($p = 0.001$), and walking and balance ($p = 0.003$).

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Conclusion: The COVID-19 quarantine is associated with the worsening of cognitive, behavioral, and motor symptoms in subjects with PD and MCI, particularly in PD-MCI. There is a need to implement specific strategies to contain the effects of quarantine in patients with PD and cognitive impairment and their caregivers.

Keywords: COVID-19, quarantine, Parkinson's disease, cognitive impairment, behavioral symptoms, motor impairment, caregiver burden

INTRODUCTION

In late December 2019 an acute, severe respiratory syndrome due to coronavirus 2 (SARS-CoV-2) was reported in Wuhan, China. The illness spread rapidly worldwide, leading to the global pandemic of coronavirus disease 2019 (COVID-19). Between December 31, 2019 and July 27, 2020, there were 16,249,165 cases of COVID-19 worldwide, and 649,208 deaths have been reported. Specifically, in Europe there were 2,806,595 cases of COVID-19, with 246,118 cases in Italy resulting in 35,107 deaths[1]. In response to the growing COVID-19 pandemic in Italy, the Italian prime minister imposed a national quarantine on March 9, 2020, and a national task force of the Italian National Institute of Health was established (1). The lockdown ended on May 18, 2020, leaving far-reaching economic and social consequences. Most frequent COVID-19 clinical manifestations include cough, fever, fatigue, myalgia, gastrointestinal symptoms, and anosmia (2). The disease has also been associated with neurological abnormalities, described in up to 35% of cases (3). Reported neurological manifestations are, in decreasing order of frequency, taste/olfactory disorders (35.6%), myalgia (18.5%), headache (10.7%), stroke (8.1%), dizziness (7.9%), impaired consciousness (7.8%), and seizure (1.5%) (4).

Neurodegenerative disorders, including Alzheimer's disease (AD) and Parkinson's disease (PD), are very prevalent diseases in the elderly, constituting some of the greatest future medical challenges, due to aging populations. These subjects are frail individuals with specific cognitive, motor, and behavioral symptoms with inherent problems of adaptation to changes and environmental stressors (5, 6). Furthermore, neurodegenerative diseases have been associated with an increased burden for the caregiver, leading to behavioral disturbances, particularly depression (7).

The clinical presentation of COVID-19 in dementia is rather atypical. Its onset is often characterized by delirium, particularly of the hypoactive form, and worsening disability (8). Furthermore, a pre-existing diagnosis of dementia is an independent risk factor for COVID-19 hospitalization and related mortality in the UK Biobank Community Cohort (9). The effect of COVID-19 quarantine on subjects with dementia and its preclinical phase (i.e., Mild Cognitive Impairment (MCI) (10) has been poorly investigated. In a French report conducted in 38 AD patients, approximately 25% showed new symptoms or a worsening of pre-existing neuropsychiatric symptoms (NPS) during the lockdown period (11). Others reported that the most affected NPS symptoms during confinement in MCI and AD were apathy, anxiety, agitation, and wandering (12).

The authors of the present study know of no PD studies specifically evaluating the effect of COVID-19 on patients with PD and cognitive impairment. It was reported in recent research that COVID-19 significantly worsened motor and non-motor symptoms in PD, although cognitive functioning was marginally involved. However, these authors did not include subjects with PD with mild cognitive impairment (PD-MCI), nor did they perform a baseline neuropsychological evaluation (13).

Overall, there is a paucity of knowledge relating to the cognitive, motor, and behavioral symptoms in patients with PD during the COVID-19 quarantine, particularly in those with PD-MCI. Furthermore, few data have been described for MCI, the intermediate state between normal aging and AD. Therefore, there is a need for research to assess the impact of the COVID-19 lockdown on the natural course of the preclinical phases of dementia, which are associated with AD and PD. To answer this question, the aim of the present study was to evaluate cognitive, behavioral, and motor changes in patients with PD and MCI during the COVID-19 lockdown in Italy. The specific research aims of the study were 2-fold: to evaluate the impact of cognitive impairment during the COVID-19 lockdown in subjects with PD, for this purpose, collected data were compared in PD patients with and without MCI; and to evaluate the impact of motor impairment in subjects with MCI, collected data from PD-MCI patients vs. MCI not associated with PD (MCInoPD) were compared.

MATERIALS AND METHODS

Study Population

A cross-sectional study was carried out that included 96 patients: 34 with PD with normal cognition (PD-NC), 31 affected by PD-MCI, and 31 with MCInoPD. Patients who underwent a comprehensive motor, clinical, and cognitive assessment (i.e., baseline assessment) in the 2 months preceding the COVID-19 lockdown in Italy (from March 9, 2020 to May 18, 2020) (14, 15) were enrolled. Subjects attended the "Parkinson's disease and Movement Disorders Center" and the "Memory Center" of the Neurologic Unit of the "Policlinico Vittorio Emanuele" in Catania and the Memory and Parkinson's Disease Center of the "Policlinico Paolo Giaccone" in Palermo, all of which belong to the PArkinson's disease Cognitive impairment Study [PACOS] and to the PREclinical Cognitive Impairment Study in the Elderly [PRECISE].

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[1] Available online at: https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases (accessed July 27, 2020).

The PACOS Baseline Assessment

The PACOS study is a prospective cohort study, aimed at evaluating frequency, clinical features, and biomarkers associated with MCI in a large hospital-based sample of PD patients, whose details have been previously described (16, 17). All patients underwent a standard neurological examination performed by neurologists experienced in movement disorders, including the Unified Parkinson Disease Rating Scale—Motor Evaluation (UPDRS-ME) (18) and the Hoehn and Yahr scale (19). The overall burden of dopaminergic drugs was evaluated with the Levodopa Equivalent Daily Dosage (LED) (20, 21). Patients were classified according to cognitive performance as PD-NC or PD-MCI. Functional independence was assessed with the Basic and the Instrumental Activities of Daily Living (BADL and IADL, respectively) (22, 23), and scored as the number of items lost for each scale. Inclusion criteria for this study were a diagnosis of PD according to the Brain Bank criteria (24); a diagnosis of PD-MCI according to MDS level II criteria (25); and mild-moderate PD (e.g., Hoehn and Yahr Stage I–III). The exclusion criteria were the presence of significant depression, excluded using the Hamilton Depression Rating Scale, considering cut-off scores as suggested by the MDS (26) and a diagnosis of dementia in PD (PDD), according to the MDS task force criteria for PDD (27).

The PRECISE Baseline Assessment

The PRECISE is a prospective, cohort study aimed at evaluating clinical, cognitive, behavioral, and biomarkers associated with Subjective Cognitive Decline and MCI in a large hospital-based sample of the elderly, which began recently and is still ongoing. Inclusion criteria were a diagnosis of MCInoPD according to modified Petersen's criteria (28) as follows: (1) self and/or informant report of cognitive complaint; and (2) objective cognitive impairment (all subjects underwent a neuropsychological assessment including the Mini Mental State Examination (MMSE) (29) as a test of global cognition). Subsequently, a complete neuropsychological battery including two tests for each cognitive domain (e.g., episodic memory, selective and divided attention, executive functioning, language, and visuospatial functioning) was administered. Details regarding administration procedures and Italian normative data for score adjustment, based on age and education, as well as normality cut-off scores ($\geq$95% of the lower tolerance limit of the normal population distribution), were available for each test battery (30, 31); (3) preserved independence in functional abilities [e.g., preserved number of BADL (22) and with no or minimal impairment regarding IADL lost (23)]; and (4) cognitive deterioration, representing a decline from a previously higher ability level [global Clinical Dementia Rating scale score of 0.5 (32)]. Current depressive symptoms were assessed by the 15-item version of the Geriatric Depression Scale at the recommended cut-off score of 5 (33). Exclusion criteria were (1) a diagnosis of dementia according to the DSM-IV-TR criteria (34) and (2) vascular cognitive impairment, according to clinical history of stroke and a routine 1.5T MRI scan (Signa HDxt; GE Medical System, Milwaukee, WI, USA) to exclude relevant vascular lesions, which would affect cognition, as described previously (35).

All participants provided written fully informed consent prior to entering the studies, which were approved by the local Ethics Committee (PACOS approval number 3/2018; PRECISE approval number 01/2019) and were in accordance with the Declaration of Helsinki.

Caregivers' and Patients' Interview Related to the COVID-19 Lockdown Period

Telephone interviews were carried out with the patients and their caregivers immediately after the end of the COVID-19 lockdown in Italy (May 20–30, 2020). All participants provided initially oral and then written informed consent prior to entering the COVID extension study (Ethics Committee approval number 5/2020).

Due to the different assessment modalities (face-to-face examination at baseline vs. telephone interview after quarantine), the telephone interview included data obtained from caregivers using a semi-structured questionnaire as well as modified, standardized scales, which were administered to the caregivers and the patients, as follows:

- *Caregiver questionnaire*: An *ad hoc* questionnaire was administered, including specific dichotomic questions (e.g., presence vs. absence) regarding patients' modifications in cognitive, behavioral, and motor symptoms during the quarantine. Specifically, caregivers were asked about cognitive changes through questions assessing the new onset/worsening of memory deficits, temporospatial disorientation, word-finding difficulty, confusion, and topographical disorientation. Behavioral symptoms were assessed using the entry question for each Neuropsychiatric Inventory (NPI) domain (36) by evaluating the worsening of pre-existing and the new onset of neuropsychiatric symptoms (NPS) occurring during the lockdown period. Referring to new onset/worsening of motor symptoms, questions related to motor slowing, tremor, difficulty in getting out of the bed, and rising from a chair were administered. At the end of this section, the caregiver was asked to indicate whether the disease had worsened during quarantine and whether its burden had increased during the lockdown.
- *Standardized scales*: Included the evaluation of cognitive, behavioral, and motor modifications with respect to the commencement of the lockdown period. Changes in global cognition were evaluated with the Italian telephone version of the MMSE (Itel-MMSE) (37). Behavioral modifications were carried out with the NPI, a fully structured caregiver interview, which measures 12 behavioral symptoms (36). For the purpose of the present research, only the presence–absence of each symptom was collected by evaluating the worsening of pre-existing and the new onset of NPS. Non-motor and motor changes were evaluated with the MDS-UPDRS Parts I and II, which scored non-motor and motor aspects of daily living experiences, respectively. For the present research, original questions were slightly modified, using a dichotomous variable with 0 = symptom absent or stable and 1 = symptom worsened and/or of new onset. Lastly, the number of IADL lost after quarantine was evaluated (25).

Statistical Analysis

The data were analyzed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). Data cleaning was performed prior to data analysis by considering range and consistency checks. Quantitative variables were described using mean and standard deviation, while qualitative variables were expressed as number and percentage. The demographic and clinical variables among groups were evaluated with one-way analysis of variance (ANOVA) with *post hoc* Scheffe's test for multiple comparisons and chi-square analysis followed by Fisher's exact test, as required. For all analyses the significance level was set at 0.05.

In order to evaluate variables associated with PD-MCI (outcome variable), an unconditional logistic regression analysis was performed for each study variable. Two different analyses were performed: (1) to test the impact of cognitive impairment during the COVID-19 lockdown period in subjects with PD, PD-NC was compared to PD-MCI; and (2) to evaluate the impact of motor impairment in subjects with MCInoPD, the latter was compared to PD-MCI. Regarding logistic regression analysis, the odds ratios (OR) with 95% confidence intervals (CI) were calculated. Parameters associated with the outcome at the univariate analysis with p-value ≤ 0.05 were included in the final multivariate analysis, which was further adjusted for age, gender, and education, considered a priori confounders.

RESULTS

Baseline Characteristics of PD-NC, PD-MCI, and MCInoPD

A total of 96 patients, 34 with PD-NC, 31 affected by PD-MCI, and 31 with MCInoPD, were enrolled in the present study. With regard to demographic characteristics, the groups did not differ by age (p = 0.238), gender (p = 0.242), and education (p = 0.724) (see **Table 1**). ANOVA revealed a significant disease-duration effect between groups ($p < 0.0001$), and after Scheffe's *post hoc* analysis, PD-MCI showed a significantly longer disease duration than MCInoPD ($p < 0.0001$).

Concerning overall cognition and disability, ANOVA showed significant differences in MMSE score ($p < 0.0001$), the number of BADL ($p < 0.0001$), and IADL ($p < 0.0001$) lost within groups. A *post hoc* analysis revealed that PD-MCI had a significant lower MMSE performance ($p < 0.0001$) and a higher number of IADL lost ($p < 0.0001$) than PD-NC, while, as expected, the latter group showed a significantly better performance in BADL than both PD-MCI and MCInoPD ($p < 0.0001$ for both comparisons).

With respect to motor parameters, there was no significant difference in LED and the Hoehn and Yahr score between PD-NC and PD-MCI ($p = 0.704$ and $p = 0.192$, respectively). Lastly, with regard to caregivers' features, no significant differences in ANOVA were observed relating to age ($p = 0.800$), gender ($p = 0.845$), and education ($p = 0.604$) between groups.

Influence of COVID-19 Quarantine on Cognitive, Behavioral, and Motor Symptoms in PD-NC, PD-MCI, and MCInoPD

ANOVA revealed significant differences concerning global cognition after quarantine in the Itel-MMSE score within groups (p = 0.008), although there were no significant differences regarding MMSE scores in pair comparisons. In addition, the number of IADL lost after quarantine significantly differed in ANOVA between groups ($p \leq 0.0001$), with PD-MCI showing the highest number of IADL lost, compared with PD-NC ($p \leq 0.0001$), and MCInoPD ($p = 0.047$) (see **Table 2**).

Based on caregivers' reports, no significant differences between groups in ANOVA were observed in worsening of cognition ($p = 0.544$), worsening of pre-existent NPS ($p = 0.718$), and disease acceleration (p = 0.325). On the contrary, ANOVA revealed a significant difference in the new onset of NPS within groups ($p = 0.038$), with PD-MCI showing a significantly higher new onset of NPS than PD-NC (p = 0.014) in pair comparison. In addition, ANOVA revealed significant differences between groups in the worsening of motor symptoms ($p \leq 0.0001$) and increased caregiver burden (p = 0.040). Specifically, the latter differences proved to be significant at pair comparison for PD-MCI vs. MCInoPD, with the former group showing a significantly higher burden than the latter regarding worsening of motor symptoms ($p \leq 0.0001$) and increased caregiver burden (p = 0.015). Of interest, a significant difference in pair comparison concerning worsening of motor symptoms ($p \leq 0.0001$) and increased caregiver burden ($p = 0.026$) was also observed when comparing PD vs. MCInoPD (data not shown).

Univariate and Multivariate Analysis of Cognitive, Behavioral, and Motor Changes After COVID-19 Quarantine in PD-NC vs. PD-MCI and MCInoPD vs. PD-MCI

PD-NC vs. PD-MCI

First, PD-NC and PD-MCI were compared using logistic regression analysis to evaluate the effect of quarantine on global cognition, disability, and behavioral and motor changes between groups. As expected, the Itel-MMSE after quarantine was significantly higher in subjects with PD-NC than with PD-MCI (OR 0.8, CI 0.66–0.99). Furthermore, the number of IADL lost after quarantine was positively associated with PD-MCI (OR 3.6, CI 1.53–8.41). After multivariate analysis and considering age, gender, and education as a priori confounders, the IADL lost after quarantine (OR 3.9, CI 1.61–9.58) and the Itel-MMSE (OR 0.7, CI 0.55–0.97) were still statistically significant. On the contrary, with respect to variables collected through caregiver reports after quarantine (e.g., changes in NPS, motor and cognitive status, disease acceleration, and caregiver burden), all these comparisons were not significant at univariate analysis between PD-NC and PD-MCI.

MCInoPD vs. PD-MCI

As regards the comparison between MCInoPD and PD-MCI, univariate analysis showed that the number of IADL lost

TABLE 1 | Baseline characteristics of PD-NC, PD-MCI, and MCInoPD.

	Total (*n* = 96)	**PD-NC (*n* = 34)**	**PD-MCI (*n* = 31)**	**MCInoPD (*n* = 31)**	***p*-value**	***post hoc p*-value PD-NC vs. PD-MCI**	***post hoc p*-value PD-MCI vs. MCInoPD**
Patients							
Age, years	67.3 ± 11.2	65.4 ± 9.6	66.7 ± 14.7	70.0 ± 8.3	0.238	0.664	0.281
Gender male (*n*, %)	58 (60.4)	23 (67.6)	20 (64.5)	15 (48.4)	0.242	0.790	0.200
Education, years	9.9 ± 4.2	10.1 ± 4.2	10.2 ± 4.1	9.4 ± 4.2	0.724	0.944	0.469
Disease duration, years	4.6 ± 3.6	6.2 ± 3.8	6.5 ± 2.8	1.7 ± 1.1	<0.0001	0.769	<0.0001
MMSE	26.4 ± 2.7	27.9 ± 1.8	26.1 ± 2.0	25.0 ± 3.2	<0.0001	<0.0001	0.099
LED (mg/day)	–	537.3 ± 407.5	502.3 ± 319.0	–		0.704	–
Hoehn and Yahr	–	2.2 ± 0.5	2.4 ± 0.5	–		0.192	–
Number of BADL lost	0.3 ± 0.6	0.06 ± 0.2	0.8 ± 0.9	0.1 ± 0.3	<0.0001	<0.0001	<0.0001
Number of IADL lost	0.7 ± 1.2	0.1 ± 0.4	1.3 ± 1.4	0.7 ± 1.1	<0.0001	<0.0001	0.065
Caregivers							
Age, years	61.4 ± 12.6	61.0 ± 12.1	62.6 ± 12.5	60.5 ± 13.5	0.800	0.613	0.535
Gender male (*n*, %)	28 (29.2)	11 (32.4)	9 (29)	8 (25.8)	0.845	0.772	0.776
Education, years	10.2 ± 4.0	10.5 ± 3.8	9.6 ± 4.1	10.5 ± 4.2	0.604	0.363	0.411

Data are expressed as mean ± standard deviation and number and percentage. PD-NC, Parkinson's disease with normal cognition; PD-MCI, Parkinson's disease with mild cognitive impairment; MCInoPD, mild cognitive impairment not associated with Parkinson's disease; MMSE, Mini Mental State Examination; LED, Levodopa Equivalent Daily Dosage; BADL, Basic Activities of Daily Living; IADL, Instrumental Activities of Daily Living.

TABLE 2 | Influence of COVID-19 quarantine on cognitive, behavioral, and motor symptoms in PD-NC, PD-MCI, and MCInoPD.

	PD-NC (*n* = 34)	**PD-MCI (*n* = 31)**	**MCInoPD (*n* = 31)**	***p*-value**	***post hoc p*-value PD-NC vs. PD-MCI**	***post hoc p*-value PD-MCI vs. MCInoPD**
Itel-MMSE after quarantine	24.3 ± 2.8	22.9 ± 2.4	22.1 ± 3.3	0.008	0.149	0.532
Number of IADL lost after quarantine	0.1 ± 0.5	1.6 ± 1.8	0.8 ± 1.2	<0.0001	<0.0001	0.047
Worsening of cognition*	10 (30.3)	14 (45.2)	13 (41.9)	0.544	0.289	0.798
Worsening of pre-existent NPS*	11 (32.4)	13 (41.9)	12 (38.7)	0.718	0.424	0.796
New onset of NPS*	5 (14.7)	13 (41.9)	7 (22.6)	0.038	0.014	0.103
Worsening of motor symptoms*	18 (52.9)	14 (45.2)	2 (6.4)	<0.0001	0.531	<0.0001
Disease acceleration*	8 (23.5)	3 (9.7)	5 (16.3)	0.325	0.137	0.449
Increased caregiver burden*	11 (32.3)	11 (35.5)	3 (9.7)	0.040	0.790	0.015

*Data are expressed as mean ± standard deviation and number and percentage. PD-NC, Parkinson's disease with normal cognition; PD-MCI, Parkinson's disease with mild cognitive impairment; MCInoPD, mild cognitive impairment not associated with Parkinson's disease; Itel-MMSE, Italian telephone Mini Mental State Examination; IADL, Instrumental Activities of Daily Living; NPS, neuropsychiatric symptoms. *data obtained from caregiver interview.*

after quarantine was positively associated with PD-MCI (OR 1.4, CI 1.0–2.03), while no significant difference between groups in the Itel-MMSE was observed. However, the association between PD-MCI and number of IADL lost after quarantine was not confirmed after multivariate analysis (see **Table 3**). Regarding caregivers' report, univariate analysis showed that worsening of motor symptoms (OR 11.9, CI 2.41–59.03) and increased caregiver burden (OR 5.1, CI 1.27–20.81) were positively associated with PD-MCI. However, after multivariate analysis, only the association between worsening of motor symptoms and PD-MCI was confirmed (OR 7.4, CI 1.09–45.44).

Of interest, a diagnosis of PD was also positively associated with worsening of motor symptoms (OR 16.3, CI 3.35–79.46) and increased caregiver burden (OR 5.1, CI 1.27–20.81) at univariate analysis in comparison with MCInoPD subjects. This result was confirmed after multivariate analysis (worsening of motor symptoms: OR 20.4, CI 3.66–113.98; increased caregiver burden: OR 4.9, CI 1.06–22.83) (data not shown).

NPI and MDS-UPDRS Changes in PD-NC, PD-MCI, and MCInoPD During Quarantine

First, changes during the lockdown period of NPS in NPI were evaluated (see **Supplementary Tables 1a, 2a**; **Figure 1**). Except

TABLE 3 | Univariate and multivariate analysis of cognitive, behavioral, and motor changes after Covid-19 quarantine in PD-NC vs. PD-MCI and MCInoPD vs. PD-MCI.

	PD-NC vs. PD-MCI						MCInoPD vs. PD-MCI					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age, years#	1.0	0.97–1.10	0.660	1.0	0.92–1.07	0.921	1.0	0.93–1.02	0.296	1.0	0.91–1.07	0.743
Gender, male#	0.9	0.31–2.43	0.790	1.9	0.43–8.18	0.399	1.9	0.70–5.37	0.202	1.7	0.47–6.28	0.413
Education, years#	1.0	0.89–1.13	0.943	1.1	0.94–1.39	0.193	1.0	0.92–1.18	0.463	1.0	0.88–1.20	0.704
Itel-MMSE after quarantine	0.8	0.66–0.99	0.041	0.7	0.55–0.97	0.031	1.1	0.93–1.32	0.270			
IADL lost after quarantine	3.6	1.53–8.41	0.003	3.9	1.61–9.58	0.003	1.4	1.0–2.03	0.048	1.1	0.64–1.76	0.702
Worsening of cognition*	1.7	0.62–4.72	0.291				1.1	0.42–3.11	0.798			
Worsening of pre-existent NPS*	1.5	0.54–4.15	0.425				1.1	0.41–3.16	0.796			
New onset of NPS*	4.2	1.28–13.73	0.18				2.5	0.82–7.47	0.107			
Worsening of motor symptoms*	0.7	0.28–1.94	0.531				11.9	2.41–59.03	0.002	7.4	1.09–45.44	0.040
Disease acceleration*	0.3	0.08–1.45	0.148				0.6	0.12–2.57	0.453			
Increased caregiver burden*	1.2	0.41–3.21	0.790				5.1	1.27–20.81	0.022	2.1	0.36–12.52	0.408

*PD-NC, Parkinson's disease with normal cognition; PD-MCI, Parkinson's Disease with mild cognitive impairment; MCInoPD, mild cognitive impairment not associated with Parkinson's disease; OR, odds ratio; CI, confidence interval; Itel-MMSE, Italian telephone Mini Mental State Examination; IADL, Instrumental Activities of Daily Living; NPS, neuropsychiatric symptoms. #Considered a priori confounders; *data obtained from caregiver interview.*

for appetite/eating disturbances, subjects with PD-MCI showed higher frequencies in all the NPI symptoms, when compared to PD-NC. However, a significant, borderline trend was found only for depression ($p = 0.067$), euphoria ($p = 0.063$), and aberrant motor behavior ($p = 0.067$). Similarly, PD-MCI showed higher frequencies of NPS in all NPI domains when compared to MCInoPD. Significant results were found for nighttime behaviors ($p = 0.007$), with borderline significant results for depression ($p = 0.066$) and aberrant motor behavior ($p = 0.086$).

Changes during the quarantine period in MDS-UPDRS Parts I and II were also evaluated (see **Supplementary Tables 1b, 2b**; **Figure 2**). Concerning MDS-UPDRS Part I in PD-NC vs. PD-MCI, the latter showed significant higher frequencies in cognitive impairment ($p = 0.034$) and fatigue ($p = 0.036$) than the former, with borderline significant differences for depressed mood ($p = 0.067$) and sleep problems ($p = 0.063$). With respect to MDS-UPDRS Part II, patients with PD-MCI showed significant higher frequencies than PD-NC in speech ($p = 0.013$). Subsequently, MDS-UPDRS items were compared in MCInoPD vs. PD-MCI. As regards MDS-UPDRS Part I, PD-MCI showed significant higher frequencies for sleep problems ($p = 0.025$), pain and other sensations ($p = 0.001$), urinary problems ($p = 0.039$), constipation problems ($p = 0.039$) and fatigue ($p = 0.016$), with borderline significant differences for depressed mood ($p = 0.066$), daytime sleepiness ($p = 0.082$), and light-headedness on standing ($p = 0.076$). Regarding MDS-UPDRS Part II, PD-MCI showed significant higher frequencies in speech ($p = 0.020$), saliva and drooling ($p = 0.039$), turning in bed ($p = 0.006$), tremor ($p = 0.012$), getting out of bed ($p = 0.001$), and walking and balance ($p = 0.003$), with borderline significance values for dressing ($p = 0.086$) and hygiene ($p = 0.086$).

DISCUSSION

The present research evaluated the impact of 10 weeks of lockdown in PD patients with and without MCI and in subjects with MCI not associated with PD during the COVID-19 epidemic in Italy. COVID-19 quarantine led to a worsening of cognitive, behavioral, and motor symptoms in subjects with PD and MCI. According to the caregivers' reports, social distancing and isolation due to lockdown led to a relevant worsening of cognition in nearly 40% of patients, worsening of NPS in 37.5%, new onset of NPS in 26%, and worsening of motor functioning in approximately 35% of patients. Consequently, the caregiver's burden during lockdown increased in over 25% of cases.

Concerning the baseline characteristics of the study groups, subjects with PD-MCI showed a significant longer disease duration than MCInoPD. Regarding global cognition, the latter group performed worse at baseline MMSE than both PD-NC and PD-MCI, but this result was significant only when comparing MCInoPD vs. PD-NC. Similarly, a significant difference within groups was found for BADL and IADL, with PD-MCI showing the highest number of activities lost, when compared to PD-NC and MCInoPD. With reference to the caregivers' characteristics, no differences were found within groups. An examination of the parameters collected after the COVID-19 quarantine revealed a

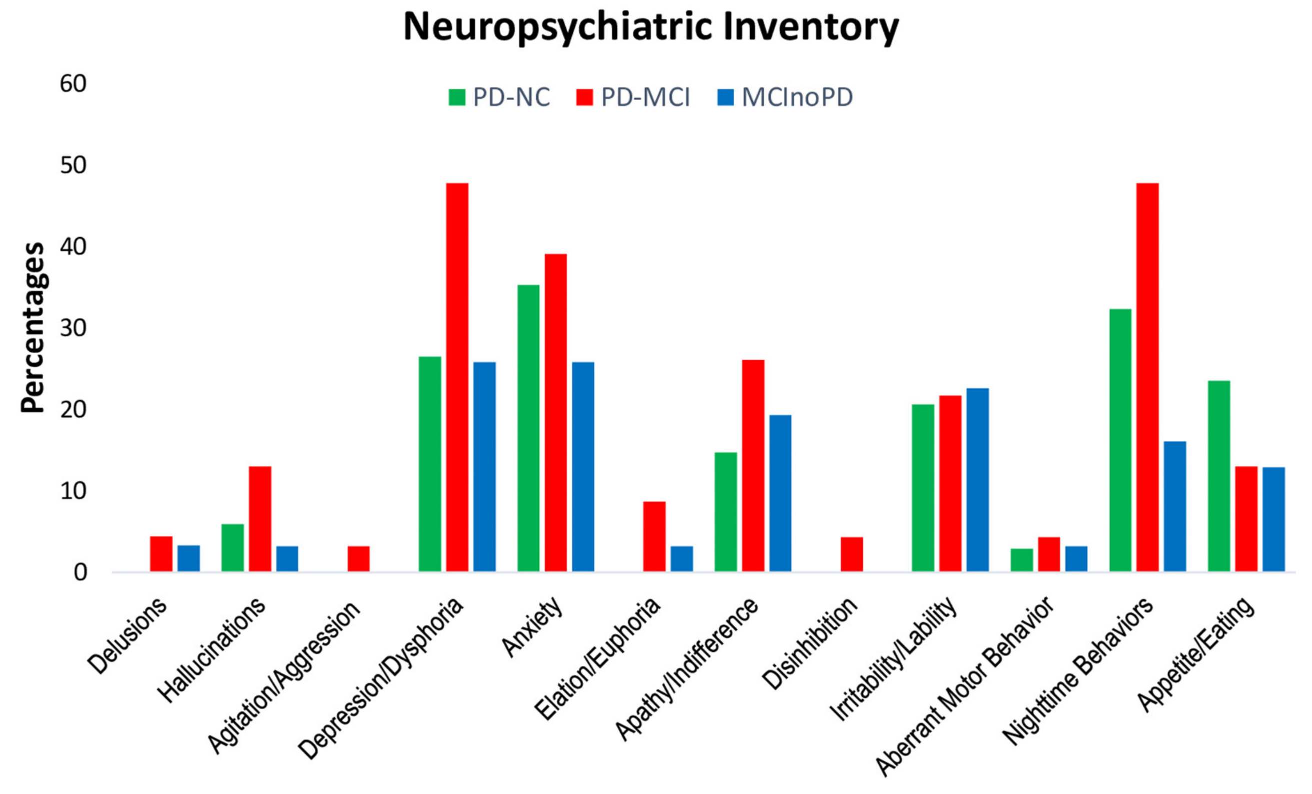

FIGURE 1 | Changes in NPI in PD-NC, PD-MCI and MCInoPD. NPI, Neuropsychiatric Inventory; PD-NC, Parkinson's disease with Normal Cognition; PD-MCI, Parkinson's disease with Mild Cognitive Impairment; MCInoPD, Mild Cognitive Impairment not associated with Parkinson's Disease.

significant difference regarding the Itel-MMSE within groups, although groups did not differ at pair comparison. Contrarily, PD-MCI lost a significantly higher number of IADL during the lockdown period comparing PD-NC and MCInoPD. An examination of variables collected via caregivers' reports revealed a significant difference for new onset NPS, and this occurred with a higher frequency in PD-MCI vs. PD-NC. Furthermore, worsening of motor symptoms and increased caregiver burden significantly increased during the lockdown period in both PD groups, compared to MCInoPD.

First, the effect of cognitive impairment in PD during the COVID-19 lockdown period was examined by comparing PD-NC vs. PD-MCI patients. A multivariate logistic regression analysis demonstrated that the number of IADL lost during the quarantine period was significantly and positively associated with PD-MCI. Furthermore, and as expected, PD-NC patients showed significant higher Itel-MMSE scores than PD-MCI. The two PD groups did not significantly differ in the worsening of their cognitive, behavioral, and motor symptoms, disease acceleration, and increased caregiver burden. Concerning NPI and MDS-UPDRS Parts I and II performance after the lockdown period, the effect of quarantine in subjects with PD was mainly associated with cognitive impairment. Indeed, PD-NC vs. PD-MCI did not differ with respect to motor symptoms, while the latter showed significantly higher frequencies of cognitive impairment and speech disturbances than the former. The authors of the present study know of only one study that examined the effect of COVID-19 on patients with PD, comparing motor and non-motor symptoms in subjects with and without the infection (13). Those authors found that clinical symptoms significantly worsened in the COVID-19 group, although cognitive functioning was marginally involved. However, the authors of that study did not specifically evaluate subjects with PD-MCI and, moreover, they did not assess the effects of COVID quarantine in patients with PD.

Subsequently, the effect of motor impairment in MCI during the COVID-19 lockdown was assessed comparing MCInoPD vs. PD-MCI patients. Multivariate logistic regression analysis demonstrated that PD-MCI was significantly and positively associated with the worsening of motor symptoms, with a subsequent increased caregiver burden compared to MCInoPD, and this result was also confirmed when comparing PD-NC vs. MCInoPD. The latter result suggests that social isolation and a reduction in cognitive stimulation and physical activity during the COVID-19 lockdown period differentially impact subjects with neurodegenerative diseases. Specifically, PD patients seem to be more susceptible than MCInoPD, regardless of the presence/absence of a concomitant cognitive impairment. Concerning NPI and MDS-UPDRS performance

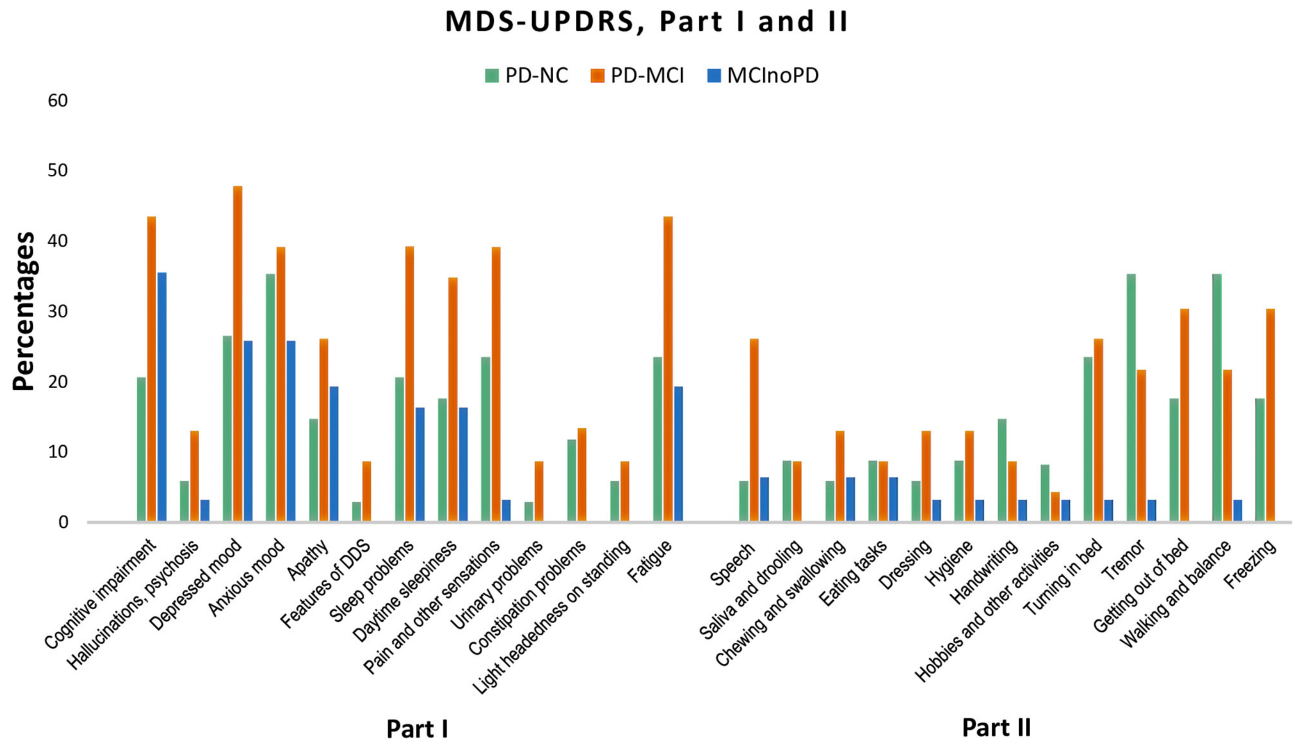

FIGURE 2 | Changes in MDS-UPDRS Part I and Part II in PD-NC, PD-MCI and MCInoPD. MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; PD-NC, Parkinson's disease with Normal Cognition; PD-MCI, Parkinson's Disease with Mild Cognitive Impairment; MCInoPD, Mild Cognitive Impairment not associated with Parkinson's Disease. DDS, Dopamine Dysregulation Syndrome.

after confinement, the present data suggest that PD-MCI showed a higher frequency of motor (e.g., turning in bed, tremor, getting out of bed, and walking/balance) and non-motor symptoms (sleep problems and nighttime behaviors, pain, urinary and constipation problems, and fatigue) than MCInoPD. The authors of the present study are aware of only one study to date that describes the effect of the COVID-19 quarantine period on subjects with MCI (12). In this Spanish report, the authors found that the most affected NPS symptoms during confinement in 20 MCI subjects were apathy and anxiety. These data confirm the results of the present study, which showed that MCInoPD patients overall had a significant worsening in NPS during COVID-19 confinement. However, in the Lara et al. study (12), the authors did not include subjects with PD, thus a comparison of this study with data from the present research is not entirely feasible.

Overall, the results of the present research suggest that the COVID-19 quarantine in subjects with MCI has a greater impact on PD-specific symptoms, rather than cognitive. This is probably due to the obligatory increase in sedentary lifestyle due to the COVID-19 confinement in the elderly with motor impairment, such as those with PD, leading to a greater deterioration in cognitive and behavioral functioning compared to those subjects without motor impairment. Indeed, it is well-known that physical inactivity is a risk factor for cognitive impairment and depression, also exacerbating various non-motor symptoms, including insomnia and constipation (38). This issue was tested recently by a double-blind randomized controlled trial, which found that a multidomain intervention (including regular exercise) could improve or maintain cognitive functioning in at-risk elderly individuals from the general population (39).

In the present research, a comprehensive assessment aimed at evaluating the effects of quarantine in Italian patients with PD and MCI was conducted. Caregivers and patients completed an *ad hoc,* semi-structured questionnaire, in addition to standardized scales to evaluate the effect of social distancing and isolation during the lockdown. To the best of our knowledge, this is the first study that has investigated the effects of quarantine in patients with PD-MCI, comparing the latter to those with MCInoPD.

Nevertheless, some limitations of the present study should be pointed out. First, the relatively small sample size of the groups might increase the likelihood of spurious associations and a lack of significance (e.g., the results approached significance for many NPI and MDS-UPDRS items). Second, although analyses were adjusted for potential confounders, residual confounding (e.g., medical comorbidity, the use of psychotropic drugs) cannot be excluded. Third, MCInoPD was diagnosed according to clinical criteria (28), with some inevitable uncertainty about diagnostic accuracy. MCI is a condition with multiple sources of heterogeneity, including clinical presentation, etiology, and prognosis (10). However, a comprehensive clinical protocol for MCInoPD was used and diagnoses were supported by brain imaging. Fourth, due to the cross-sectional design of the study, it is unclear whether the observed clinical worsening represents a transient or a persistent phenomenon. For this reason, a follow-up evaluation of patients has already been envisaged. Finally, caregiver rating bias was also reported in subjects with MCInoPD, and it may well be associated with the caregiver burden (40). Accordingly, data based on caregiver ratings should be interpreted with caution due to the increased caregiver burden described in the present research.

In conclusion, results of the present research show that the COVID-19 related-quarantine has exacerbated cognitive, behavioral, and motor symptoms in subjects with PD, particularly in PD-MCI. The Italian National Health Care System needs to plan specific health strategies to guarantee appropriate care in subjects with cognitive impairment and their caregivers. To this end, telemedicine and digital technology devices would be of particular assistance in remote monitoring and care of subjects with cognitive impairment during confinement due to the COVID-19 pandemic.

DATA AVAILABILITY STATEMENT

Anonymized raw data are available by the authors if required.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee Palermo 1: approval number: 5/2020. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RB designed and conceptualized the study, collected and interpreted the data, and drafted the manuscript for intellectual content. AL designed and conceptualized the study, collected the data, ran the analyses and interpreted the data, and revised the manuscript for intellectual content. AN designed and conceptualized the study, interpreted the data, and revised the manuscript for intellectual content. MC, CEC, CD'A, LD, GL, and TL collected the data and revised the manuscript for intellectual content. MZ interpreted the data and revised the manuscript for intellectual content. RM designed and conceptualized the study, collected the data, ran the analyses and interpreted the data, and drafted and revised the manuscript for intellectual content. All authors approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.590134/full#supplementary-material

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ORIGINAL RESEARCH
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Risk Factors Underlying COVID-19 Lockdown-Induced Mental Distress

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Recent reports suggest that the COVID-19 lockdown resulted in changes in mental health, however, potential age-related changes and risk factors remain unknown. We measured COVID-19 lockdown-induced stress levels and the severity of depressive symptoms prior to and during the COVID-19 lockdown in different age groups and then searched for potential risk factors in a well-characterized general population-based sample. A total of 715 participants were tested for mental distress and related risk factors at two time-points, baseline testing prior to COVID-19 and follow-up testing during COVID-19, using a battery of validated psychological tests including the Perceived Stress Scale and the Patient Health Questionnaire. Longitudinal measurements revealed that the prevalence of moderate to high stress and the severity of depressive symptoms increased 1.4- and 5.5-fold, respectively, during the COVID-19 lockdown. This surge in mental distress was more severe in women, but was present in all age groups with the older age group exhibiting, cross-sectionally, the lowest levels of mental distress prior to and during the lockdown. Illness perception, personality characteristics such as a feeling of loneliness, and several lifestyle components were found to be associated with a significant increase in mental distress. The observed changes in mental health and the identified potential risk factors underlying these changes provide critical data justifying timely and public emergency-tailored preventive, diagnostic, and therapeutic mental health interventions, which should be integrated into future public health policies globally.

Keywords: COVID-19, stress levels, depressive symptoms, risk factors, feeling of loneliness

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INTRODUCTION

The novel coronavirus disease 2019 (COVID-19) outbreak in Wuhan, China, evolved rapidly into a pandemic with businesses, governments, and international organizations taking unprecedented action to limit the threat to global health. At an individual level, the COVID-19 pandemic presented several challenges ranging from fear of infection by a poorly understood illness with unclear prognosis to the limited possibilities of diagnostics and a shortage of personal protection equipment (1). At a societal level, actions to curb the spread of COVID-19 led to the implementation of unfamiliar public health measures such as social isolation and distancing, remote education and work, and a ban on travel (2). Several of these measures have already been reported to influence mental health in the general population in previous outbreaks (3–5). For example, up to 33% of surveyed participants reported increased worries during the swine flu outbreak in the UK (6), 48% of the general population exhibited depressive symptoms during the Ebola outbreak in Sierra Leone (7), and 57% of subjects reported increased irritability during the severe acute respiratory syndrome (SARS) outbreak in Hong Kong (8). Although these outbreaks were geographically limited compared with COVID-19, findings from these outbreaks are consistent with the earliest studies evaluating the impact of the COVID-19 lockdown on mental health. These studies largely estimated the frequency of the diverse components of mental distress cross-sectionally either in specific populations such as healthcare professionals (9–11) or in convenience samples from regions of the world that were at the forefront of the COVID-19 pandemic, such as China (12, 13) and Italy (14). More recently, longitudinal studies examining the impact of COVID-19 on mental health have started to emerge (**Table 1**, **Supplementary Figure 1**). These studies most commonly assessed general mental distress at the time (26–30) or addressed specific symptoms of mental distress by comparing COVID-19 with pre-COVID-19 data obtained largely from national survey-based probability samples (17, 19–21, 31). Collectively, these studies showed significantly increased mental distress in response to COVID-19. Relatively few studies to date, however, addressed age-related changes and investigated risk factors associated with COVID-19-induced mental distress (32, 33). As a result, the mechanisms underlying the development of mental distress in response to COVID-19 remain poorly understood. To address this gap, we took advantage of a well-characterized general population-based sample representing randomly selected 1% of the population of the city of Brno, Czech Republic, randomly selected, to critically measure changes in mental health during the COVID-19-induced lockdown in order to probe for age-related changes and potential risk factors.

MATERIALS AND METHODS

Study Design and Sample

A summary of the Kardiovize study baseline examination protocol and characteristics of the general population-based sample have been published previously (34). In brief, the Kardiovize study is a prospective longitudinal epidemiological cohort that investigates health-related topics in Central Europe carried out on a representative randomly selected 1% population sample of the residents of the city of Brno, Czech Republic. Between March 16 and May 17, 2020, the Czech Republic implemented a strict public lockdown in response to the COVID-19 pandemic, which included national quarantine with the closure of schools, shops (except for daily essentials), restaurants, and borders, social distancing, and the obligatory use of personal protection equipment. At the beginning of the COVID-19 outbreak in Europe, the COVID-19 add-on study protocol, including a custom designed e-questionnaire, was promptly prepared. Its purpose was to measure changes in mental health during the COVID-19 lockdown and to identify potential risk factors underlying these changes. The original COVID-19 add-on study was conducted from April 24 to May 27, 2020.

TABLE 1 | Review of current longitudinal studies on the impact of COVID-19 on mental health.

Authors	Country	Sample size (N)	Source of pre-COVID-19 data	Source of COVID-19 data	Main impact of COVID-19 on mental health
Shanahan et al. (15), Psychol Med	Switzerland	768	Zurich project on the social development	Online survey	Increase in mental distress
Brailovskaia et al. (16), Int J Clin Heal Psychol	Germany	436	Bochum optimism and mental health project	Online survey	Stress affects COVID-19 response
McGinty et al. (17), JAMA	USA	35,000	NORC's AmeriSpeak panel	Online survey	Increase of mental distress
Van der Velden et al. (18), J Affect Disord	Netherland	3,983	Dutch longitudinal population-based LISS panel	Online survey	No change in mental distress
Pierce et al. (19), The Lancet Psychiatry	UK	17,452	UK household longitudinal study	Online survey	Increase of mental distress
Niedzwiedz et al. (20), medRxiv	UK	9,748	UK household longitudinal survey	Online survey	Increase of mental distress
Chandola et al. (21), medRxiv	UK	17,452	UK household longitudinal survey	Online survey	Higher incidence of common mental disorder
Daly et al. (22), Psychol Med	UK	12,074	UK household longitudinal survey	Online survey	Increase of mental health problems
Kwong et al. (23), medRxiv	UK	10659	Avon longitudinal study of parents and children and generation Scotland: Scottish family health study	Online survey	Increased anxiety
Kim et al. (24), medRxiv	South Africa	221	Developmental pathways for health research unit epidemiological surveillance study	Phone survey	Predicted greater depressive symptoms
Biddle et al. (25)	Australia	1,745	ANUpoll	Online survey	Increase of mental distress

Selection Procedure

The inclusion criteria for the COVID-19 add-on study were all participants of the Kardiovize study with available baseline data on stress and depressive symptoms (**Supplementary Figure 2**). Those diagnosed with a COVID-19 infection (two cases) were excluded. A total of 1,823 Kardiovize study participants were invited electronically to join the COVID-19 add-on study. An e-questionnaire was completed by 715 participants in roughly 4 weeks through an online survey module using a validated RedCap software tool (35). The e-questionnaire consisted of several items (see section Measures and Instruments), including the Perceived Stress Scale (36) (PSS) and the Patient Health Questionnaire (37) (PHQ), which were also assessed during the baseline measurements of the original Kardiovize study in previous years.

Measures and Instruments

The e-questionnaire measured general demographics (sex, age, education, and marital status), including questions on how the COVID-19 lockdown affected participant's lifestyle, their experience with the COVID-19 lockdown, as well as their current medical status (**Supplementary Material**). Several psychological questionnaires evaluating stress, depressive symptoms, illness perception, and loneliness were also included. In brief, the presence and severity of stress was assessed using PSS with a scale ranging from 0 to 40. Stress levels were categorized as low (score of 0–13), medium (score of 14–26), or high (score of 27–40). The presence and severity of depressive symptoms was assessed using the identical two items from the PHQ-9 (prior to COVID-19) and the PHQ-4 (38) (during COVID-19) with a scale range of 0–6. Depressive symptoms were considered present if the sum of the score of the two PHQ items were $\geq$3 (38). The perception of COVID-19 was assessed using the Brief-Illness Perception Questionnaire (B-IPQ) (39), which evaluates cognitive, and emotional illness perception using a 10-point Likert scale with a total score ranging from 8 to 80. Observed scores were categorized into terciles (weak, moderate, strong). Item-level analysis was used to assess the perception of COVID-19 measured by the B-IPQ. The feeling of loneliness was assessed using the UCLA 3-item Loneliness Scale (3LS) (40) with a score range of 3–9. The presence of a feeling of loneliness was defined as a UCLA 3LS score $\geq$6. Resilience was assessed using the Connor-Davidson Resilience Scale (41) with a score range of 0–8. The presence of resilience was defined as low (score of 0–5), medium (score of 6–7), or high (score of 8). Resilient coping was assessed using the Brief Resilient Coping Scale (42) with a score range of 4–20. Resilient coping was defined as low (score of 4–13), medium (score of 14–16), or high (score of 17–20).

Compliance with COVID-19 lockdown measures was examined using a series of 4-point Likert scales: 1 (always), 2 (sometimes), 3 (seldom), and 4 (never). Spending quarantine alone or with others was measured using a multiple choice item that was transformed to a binary variable (alone/with others) (**Supplementary Materials**). Changes in nutrition, sleep length, and frequency of exercise were measured using self-reported ordinal items with levels "improved," "without change" (referred to as "stable"), and "worsened." The effect of COVID-19 lockdown measures on finances was examined using a 4-point ordinal item (with levels 1 "not at all," 2 "just a little bit," 3 "pretty much," and 4 "extremely") which were transformed into a 3-category variable with levels "none" (former level 1), "moderate" (former levels 2-3), and "extreme" (former level 4). Finally, the presence of selected diseases was measured using binary items.

Data Analysis

Descriptive statistics were conducted for the socio-demographic variables and behavioral parameters. To test for age-related changes in mental health in response to the COVID-19 lockdown, participants were examined in three separate age groups, namely young (24–40 yr), middle-aged (41–55 yr), and older (56–68 yr) age groups. Age groups (based on age during the COVID-19 add-on study) were selected as a balance between an even distribution of respondents and adulthood developmental characteristics. Missing values were identified in baseline stress ($N = 13$) and depressive symptom ($N = 19$) data, representing 1.8 and 2.7% of the sample, respectively. No missing value imputation was performed, only cases with a complete pair of values were used in statistical analysis. The missing data were considered completely at random with no overlapping cases and no observable pattern in their distribution in relation to sex, age, or education. There were no significant differences in the mean scores of stress levels and the severity of depressive symptoms between participants with and without baseline missing values. A one sample chi-square test was used to assess the characteristics of the research sample. A Fisher's exact test was used to examine differences in compliance with COVID-19 lockdown measures. Normality of the data assessed using a Shapiro-Wilk test disclosed a violation of the normality rules. As a result, a McNemar's test was used to assess differences in prevalence of nominal stress levels and the presence of depressive symptoms. Changes of stress and depressive symptoms were calculated as a median of difference between repeated measures (during COVID-19 score minus prior to COVID-19 score). We used a non-parametric Wilcoxon signed-rank test for repeated measure differences between prior to COVID-19 and during COVID-19 lockdown levels of stress and depressive symptoms. Between-group differences (based on sex, age, etc.) in cross-sectional levels and longitudinal median differences of stress and depressive symptoms were examined using a Mann–Whitney *U*-test and a Kruskal–Wallis test with a Dunn-Bonferroni *post-hoc* test to correct for multiple comparisons. The respective effect size indicators were calculated and transformed to Pearson's r for a uniform evaluation of effect sizes. Significance was evaluated at an $\alpha = 0.05$, all confidence intervals were set at the 95% level, and all testing was 2-sided. All observed values are presented as median and interquartile range [IQR] unless otherwise indicated. Data were analyzed using SPSS v.21 and the figures were generated in R v.3.6.3 (https://www.r-project.org/) with the ggplot2 (v.1.0.12) and pheatmap (v.2.3.3.0) packages.

Ethical Consideration

The research protocol of the COVID-19 add-on study was approved by the Kardiovize study Internal Review Board as

TABLE 2 | Demographic characteristics of the COVID-19 general population-based sample.

	***N* (%)**	***P***
N	715	
Age (mean ±SD)	46.12 ± 10.94	
Sex		
Men	336 (47%)	0.11
Women	379 (53%)	
Age groups		
24–40 yrs	265 (37.1%)	<0.001
41–55 yrs	267 (37.3%)	
56–68 yrs	183 (25.6%)	
Education		
Without GCSE[a]	92 (12.9%)	<0.001
With GCSE[a]	274 (38.4%)	
University[b]	347 (48.7%)	
Family members		
1	100 (14.0%)	<0.001
2	256 (35.9%)	
3	145 (20.3%)	
4+	213 (29.8%)	

[a] *GCSE, General Certificate of Secondary Education.*

[b] *University education includes higher vocational school, bachelor, master, and doctoral degrees.*

well as by the St. Anne's University Hospital ethics committee. Written informed consent was obtained from all participants of the COVID-19 add-on study.

RESULTS

Demographics of the COVID-19 Population-Based Sample

The COVID-19 population-based sample consisted of 715 participants, among whom 379 (53%) were women and 336 (47%) were men, with a mean age of 46.12 (range, 24–68; SD, 10.94) (**Table 2**). The distribution of participants in the age groups was acceptably even. Participants were largely well-educated considering many of them completed university studies (347, 48.7%), followed by those with General Certificate of Secondary Education (GCSE) (274, 38.4%). Couples and small families represented approximately half of the population sample.

Compliance With COVID-19 Lockdown Measures

We first investigated how well the participants of the COVID-19 add-on study complied with the national lockdown measures imposed by the Czech government. To this end, we asked participants of the COVID-19 add-on study whether they always, sometimes, seldom, or never observed individual national lockdown measures. We found that 77.6, 75.7, and 51.6% of the participants "always" observed wearing a mask, increased hand hygiene, and respected the maximum of two people staying together in public places, respectively (**Supplementary Table 1**). Restriction of leaving home only when necessary (going to work, essential grocery, and medicine shopping), respecting 2 m social distancing, and reducing physical contact were "always" observed in 25.9, 33.6, and 30.8% and "sometimes" observed in 48, 57.5, and 55.9% of the participants, respectively. Women were statistically significantly more compliant in regard to all national lockdown measures compared to men. The older age group was statistically significantly more compliant in wearing a mask, in respecting 2 m social distancing, and in reducing physical contact compared with young and middle-aged adults. In regard to increased hand hygiene, respecting the maximum of two people staying together in public places, restricting leaving home only when necessary, and reducing physical contact, however, the older age group behaved similarly to the other age groups.

Stress Levels During the COVID-19 Lockdown

We first measured stress that participants may have incurred during the COVID-19 lockdown. The prevalence of moderate to high stress amounted to 253 (35.4%, CI=32.5–39.7) and 359 participants (51.1%, CI=47.4–54.9) prior to and during the COVID-19 lockdown, respectively. The number of participants reporting moderate to high stress thus increased 1.4 times during the COVID-19 lockdown ($P < 0.001$) (**Figure 1A**). Accordingly, the PSS mean score also increased significantly in response to the COVID-19 lockdown ($P < 0.001$) (**Figure 1B**). This significant increase in stress during the COVID-19 lockdown was observed in both sexes (both $P < 0.001$), however, the observed surge in stress levels was significantly higher in women than in men ($P = 0.01$) (**Figure 1C**). Intriguingly, despite the fact that all age groups witnessed a significant and comparable increase in stress levels in response to the COVID-19 lockdown ($P < 0.001$), the older age group exhibited significantly lower stress levels prior to ($P < 0.001$) and during COVID-19 ($P < 0.001$) compared with the younger age groups (**Figure 1D**).

Depressive Symptoms During COVID-19 Lockdown

We next examined depressive symptoms prior to and during the COVID-19 lockdown. The prevalence of depressive symptoms amounted to 49 (7%, CI=5.3–9.2) and 269 cases (38.6%, CI=35.0–42.4) prior to and during the COVID-19 lockdown, respectively (**Figure 2A**). The number of participants reporting depressive symptoms thus increased 5.5 times during the COVID-19 lockdown compared with the pre-COVID-19 period ($P < 0.001$). Similarly, the severity of depressive symptoms also increased significantly during the COVID-19 lockdown ($P < 0.001$) (**Figure 2B**). This rise in depressive symptoms was present in both sexes (both $P < 0.001$), however, the observed increase in the severity of depressive symptoms was significantly higher in women than in men ($P = 0.002$) (**Figure 2C**). All age groups showed a significant and comparable increase in the severity of depressive symptoms in response to COVID-19 (all $P < 0.001$) with the older age group exhibiting a significantly lower severity of depressive symptoms prior to ($P = 0.004$), but not during the COVID-19 lockdown ($P = 0.062$) (**Figure 2D**).

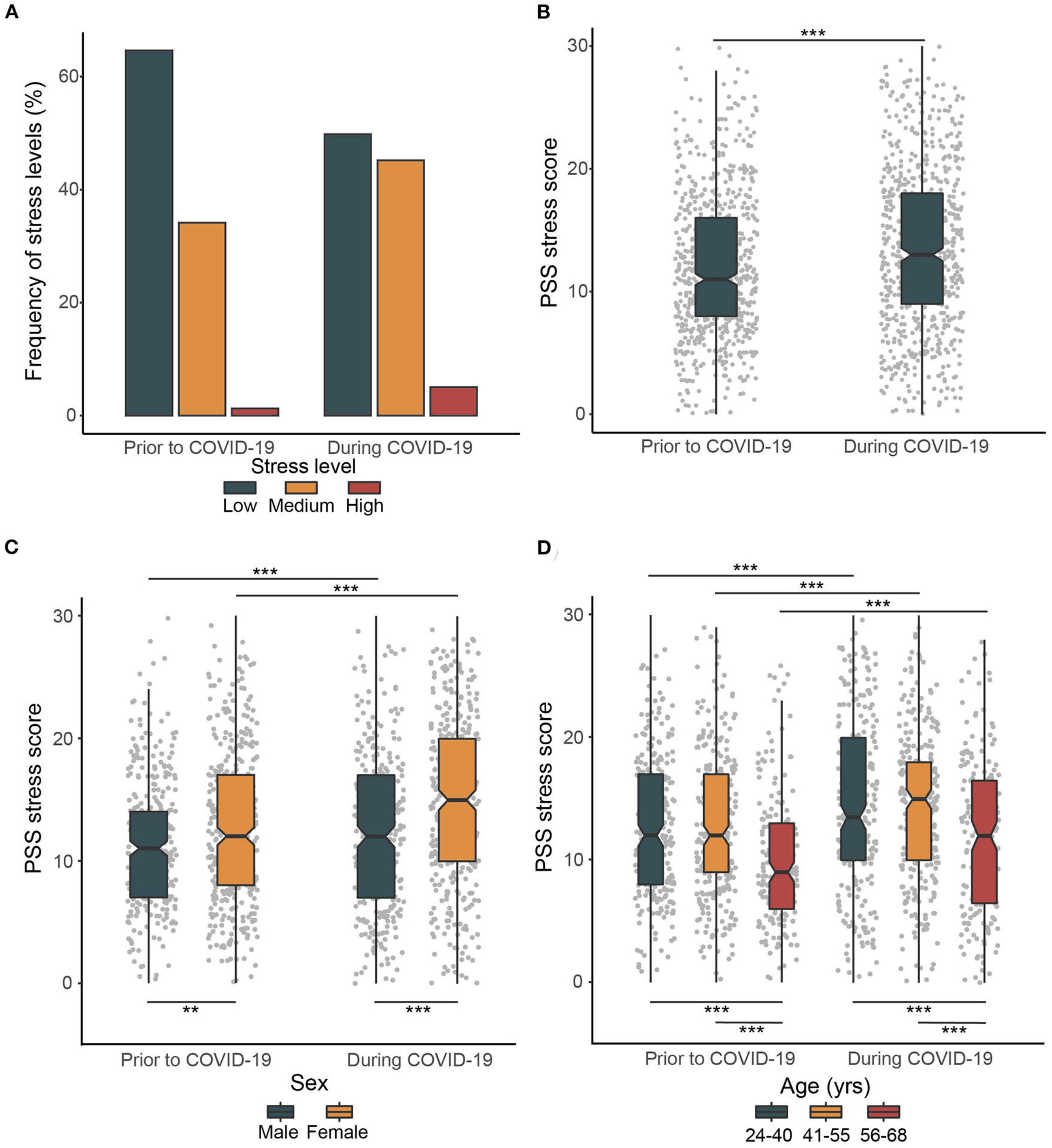

FIGURE 1 | Prevalence of stress level prior to and during COVID-19 lockdown. **(A)** Frequency of stress levels prior to and during COVID-19 lockdown. **(B)** Changes in PSS stress score prior to and during COVID-19. **(C)** Sex differences in changes in stress levels prior to and during COVID-19. **(D)** Age group differences in changes in stress levels prior to and during COVID-19. The box plots with whiskers represent the median and the first and the third quartiles are extended by 1.5 times the interquartile range. Upper horizontal bars indicate significant differences in stress levels prior to and during COVID-19, lower horizontal bars indicate significant cross-sectional differences in stress levels between individual groups (**$P < 0.01$, ***$P < 0.001$).

Risk Factors Associated With Increased Stress Levels and Depressive Symptoms

In order to identify potential risk factors associated with the observed significant increase in stress levels and the severity of depressive symptoms in response to the COVID-19 lockdown, we investigated several aspects of illness perception, personality characteristics, lifestyle, and medical conditions. We first asked whether the perception of COVID-19 contributed to stress levels and depressive symptoms. The B-IPQ results showed that those who perceived COVID-19 as most threatening exhibited significantly higher stress levels and severity of depressive symptoms ($P < 0.001$) (**Figure 3**). Stress levels and severity of depressive symptoms were mostly affected by the general worry about COVID-19, the effect of COVID-19 on their emotional processing, the impact of COVID-19 on life, and the timeline of the COVID-19 risk (**Supplementary Table 2**). Moreover, the severity of depressive symptoms was to some degree also affected by the difficulties in understanding COVID-19 symptoms and mistrust in COVID-19 treatment options.

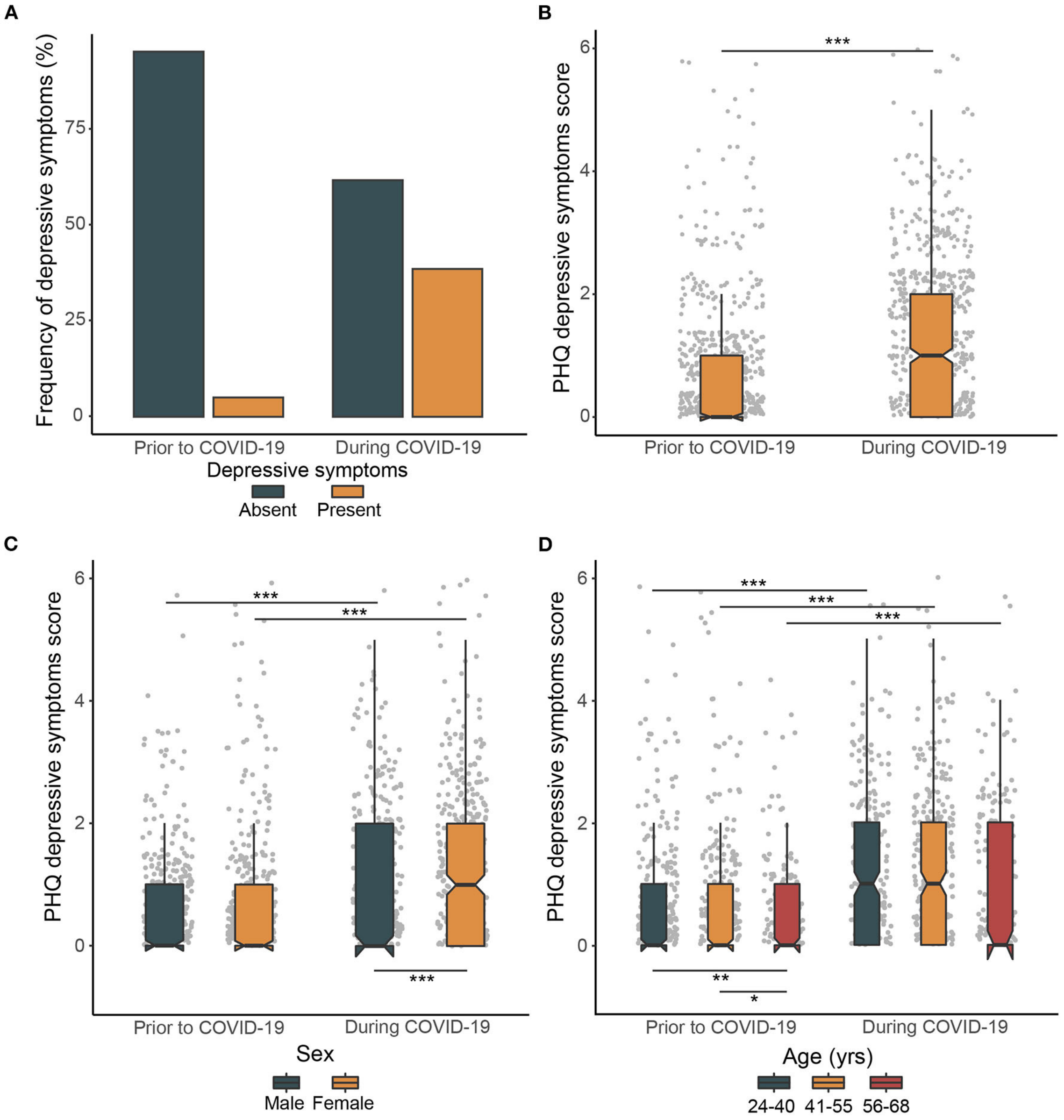

FIGURE 2 | Prevalence of severity of depressive symptoms prior to and during COVID-19 lockdown. **(A)** Frequency of depressive symptoms prior to and during COVID-19 lockdown. **(B)** Changes in the PHQ depressive symptoms score prior to and during COVID-19. **(C)** Sex differences in changes in the severity of depressive symptoms prior to and during COVID-19. **(D)** Age group differences in changes in the severity of depressive symptoms prior to and during COVID-19. The box plots with whiskers represent the median and the first and the third quartiles are extended by 1.5 times the interquartile range. Upper horizontal bars indicate significant differences in severity of depressive symptoms prior to and during COVID-19, lower horizontal bars indicate significant cross-sectional differences in severity of depressive symptoms between individual groups (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$).

We next explored different personality characteristics in relation to changes in stress and depressive symptoms during the COVID-19 lockdown (**Figure 3**). The UCLA 3LS results revealed that a feeling of loneliness was associated with a significant increase in stress levels and severity of depressive symptoms in response to lockdown ($P < 0.001$). The lack of resilience measured using the Connor-Davidson Resilience scale also resulted in a significant increase in stress levels ($P < 0.001$) and severity of depressive symptoms ($P = 0.007$) during the COVID-19 lockdown. Non-adaptive coping strategies examined using the Brief Resilient Coping scale on the other hand, only produced a significant increase in stress levels ($P = 0.001$).

Social isolation and distancing represented a major change in lifestyle during the COVID-19 lockdown. As a result, we investigated the association between different lifestyle components and changes in stress and depressive symptoms during COVID-19 (**Figure 3**). We found that those who reported spending quarantine at home alone or with others both exhibited

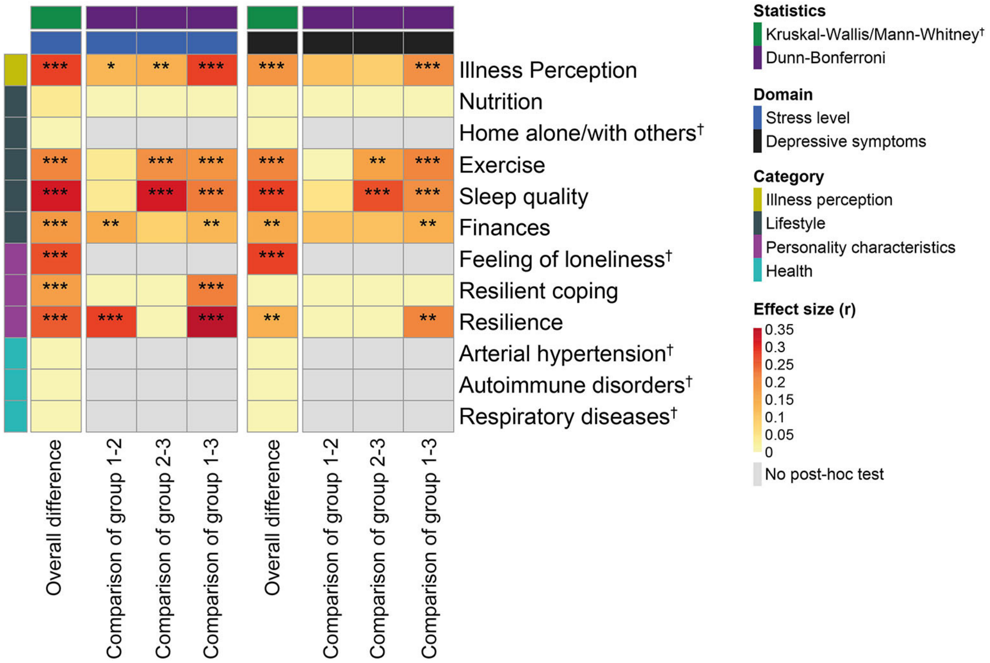

FIGURE 3 | Association between stress levels, severity of depressive symptoms, and potential underlying risk factors during the COVID-19 lockdown. Heatmap showing Pearson's r effect sizes with levels of significance based on a Kruskal–Wallis/Dunn–Bonferroni test (with adjustment for multiple comparisons) and whenever appropriate a Mann–Whitney *U*-test (**P* < 0.05, ***P* < 0.01, ****P* < 0.001). Group comparisons refer to *post hoc* tests where for illness perception, finances, resilient coping and resilience groups 1, 2, and 3 correspond to minor, moderate, and significant response, respectively, while for nutrition, exercise, and sleep quality groups 1, 2, and 3 correspond to improved, unchanged, and worsened response, respectively.

significantly increased stress levels and depressive symptoms (all $P < 0.001$). This indicated that social isolation did not play a role in changes to stress levels ($P = 0.77$) and depressive symptoms ($P = 0.33$) during the lockdown. Similarly, changes in nutrition during the COVID-19 lockdown were also not associated with increased stress and depressive symptoms ($P =$ 0.25 and 0.37). In contrast, those who exercised less and reported poor sleep all demonstrated a significant increase in stress levels and depressive symptoms (all $P < 0.001$). Last, but not least, all those who reported that COVID-19 influenced their financial situation reported significantly increased stress levels and severity of depressive symptoms (all $P < 0.001$).

Considering the pathophysiology of COVID-19, which exploits ACE receptors to access respiratory cells and promotes a significant immune response, we last evaluated whether participants afflicted by arterial hypertension, respiratory diseases, or autoimmune disorders showed changes in stress levels and depressive symptoms in response to the COVID-19 lockdown (**Figure 3**). We found that none of the participants afflicted by arterial hypertension, respiratory diseases, or autoimmune disorders exhibited significant changes in stress levels ($P = 0.26$, 0.77, 0.87) and depressive symptoms ($P = 0.87$, 0.84, 0.18).

DISCUSSION

The main goal of this *ad hoc* study precipitated by the COVID-19 pandemic was to explore potential risk factors underlying mental distress in response to the COVID-19 lockdown. To this end, we first measured changes in stress levels and depressive symptoms longitudinally in a well-characterized population-based sample. We next searched for age-related changes and potential risk factors linked to the measured changes in stress levels and depressive symptoms during the COVID-19 lockdown.

Considering we planned to investigate changes in mental distress in response to the COVID-19 lockdown, we first asked whether participants of the COVID-19 add-on study complied with the government-imposed COVID-19 lockdown measures. We found that a large majority of the COVID-19 add-on study participants complied with the government-imposed lockdown measures comparable to COVID-19 lockdown compliance rates reported by others (43–45). However, we also learned that the COVID-19 add-on study participants demonstrated better compliance with some measures such as wearing a mask than with other measures such as the restriction of leaving home only when necessary. Our data also showed that women and the older age group demonstrated better compliance with government-imposed lockdown measures than men and younger adults.

Knowing that the COVID-19 add-on study participants complied satisfactorily with the government-imposed lockdown measures, we next measured the impact of COVID-19 lockdown on stress levels and the severity of depressive symptoms. Our measurements showed that COVID-19 lockdown resulted in a significant 1.4- and 5.5-fold increase in stress levels and depressive symptoms, respectively. The observed increase in stress levels and severity of depressive symptoms is consistent with reported cross-sectional (26, 46, 47) and longitudinal (15, 17, 19) general population studies. In agreement with previous reports (48, 49), we found a more pronounced impact of the COVID-19 lockdown on the mental health of women.

All age groups exhibited a significant and comparable increase in mental distress in response to the COVID-19 lockdown, with the older age group showing generally lower levels of mental distress. These longitudinal findings extend our current understanding of the interaction between age and COVID-19 (50–52) by showing that all age groups exhibited the same susceptibility to COVID-19-induced mental distress. Cross-sectional analysis of these findings indicated a benefit of the generally lower mental distress in the older group despite the same susceptibility to COVID-19-induced mental distress compared to other age groups. This may be due to the association of greater worries about studies, job security, and financial stability with the younger age group, and the richer life experiences and reduced life expectations in the older group (53–55).

Longitudinal measurement of the increase in stress and depressive symptoms in response to the COVID-19 lockdown enabled us to search for potential risk factors linked to the observed changes in mental health. We identified illness perception, several personality characteristics, and lifestyle components, but not pre-existing medical conditions, as potential risk factors. In brief, those who perceived COVID-19 as emotionally threatening exhibited the highest significant increase in stress levels and severity of depressive symptoms. Similarly, a feeling of loneliness was identified as the most significant risk factor translating into a major surge in stress levels and severity of depressive symptoms in response to the COVID-19 lockdown. This finding is in agreement with recent reports (21, 56) and further corroborates the intimate link between the feeling of loneliness and mental distress (57–60). On a different note, we also identified the positive effect of resilience and resilient coping on COVID-19 lockdown-induced mental distress (32, 61). This finding in particular, may be well-suited for interventions designed to decrease and better control mental distress in response to public health emergencies. In contrast to other changes in lifestyle, such as exercising and sleep, our study found no association between mental distress and spending the government-imposed quarantine alone or with others. This is inconsistent with recent cross-sectional studies (62–64), but could also be the consequence of suboptimal compliance with observing the restriction of leaving home only when necessary. In summary, although further research is needed to demonstrate causality, we here identified several potential risk factors associated directly with the surge in mental distress in response to the COVID-19 lockdown.

There are several major strengths of our study. First, we measured stress and depression longitudinally in a well-characterized population sample, which contrasts with convenience or probabilistic sampling using national surveys. Second, we thoroughly investigated the role of age in the observed surge in mental distress in response to the COVID-19 lockdown. And third, we critically investigated potential risk factors based on the longitudinally measured increase in stress levels and severity of depressive symptoms in response to the COVID-19 lockdown using an extensive battery of measurement instruments.

Our study has also its limitations. First, the population sample is rather small compared to some recently reported studies (17, 19, 65). Second, only 40% of the participants of the Kardiovize study accepted the electronic invitation to participate in the COVID-19 add-on study. Although one may envision many reasons for the observed low enrolment rate, it could well be that those exhibiting the highest mental distress in response to COVID-19 were actually those who most commonly declined participation in the COVID-19 add-on study. In this case, our measurements are an underestimation of the actual impact of COVID-19 on mental health. And third, the Kardiovize and COVID-19 add-on study participants in general mostly represented the urban population with a higher education compared with the rural population.

In conclusion, this study provides repeated measure-based evidence of an increase in stress levels and the severity of depressive symptoms in a sample of the general population during the COVID-19 lockdown. Importantly, older participants showed the same degree of susceptibility to the COVID-19-induced mental distress as the younger group, but benefited from generally lower mental distress. Finally, our study identified illness perception, a feeling of loneliness, resilience and resilient coping, and several lifestyle changes as potential risk factors underlying the observed surge in mental distress in response to the COVID-19 lockdown. Observed mental distress and many of the identified risk factors can be prevented, diagnosed, and treated, although such interventions need to be tailored to the public health emergency setting. More intense and better organized approaches to mental distress and the underlying risk factors in the general population need to be integrated into global public health policies to protect mental health during future pandemics.

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. Anne's University Hospital ethics committee and Kardiovize study Internal Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GS and JN had full access to all the data in the study, take responsibility for the integrity of the data, the accuracy of the data analysis, and wrote the draft of the manuscript. GS conceived the idea of this study. JN made the statistical analysis. All authors contributed to the critical revision of the manuscript for important intellectual content.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.603014/full#supplementary-material

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A Preliminary Investigation of the Views of People With Parkinson's (With and Without Psychosis) and Caregivers on Participating in Clinical Trials During the Covid-19 Pandemic: An Online Survey

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Background: The coronavirus pandemic is having a profound impact on non-COVID-19 related research, including the delivery of clinical trials for patients with Parkinson's disease.

Objectives: A preliminary investigation to explore the views of Parkinson's disease (PD) patients, with and without experience of psychosis symptoms, and carers on the resumption of clinical research and adaptations to trials in light of COVID-19.

Methods: An anonymous self-administered online survey was completed by 30 PD patients and six family members/carers via the Parkinson's UK Research Support Network to explore current perceptions on taking part in PD research and how a planned clinical trial for psychosis in PD may be adapted so participants feel safe.

Results: Ninety-one percent of respondents were enthusiastic about the continuation of non-COVID-19 related research as long as certain safety measures were in place. Ninety-four percent stated that they would be happy to complete assessments virtually. However, they noted that care should be taken to ensure that this does not exclude participants, particularly those with more advanced PD who may require assistance using portable electronic devices. Regular and supportive communication from the research team was also seen as important for maintaining the psychological well-being of participants while taking part in the trial.

Conclusions: In the era of COVID-19 pandemic, standard approaches will have to be modified and rapid adoption of virtual assessments will be critical for the continuation of clinical research. It is important that alongside the traditional methods, new tools are developed, and older ones validated for virtual assessments, to allow safe and comprehensive assessments vital for ongoing research in people with Parkinson's.

Keywords: hallucinations and delusions, patient and public involvement (PPI), COVID-19, clinical trial, psychosis, survey, Parkinson's disease

INTRODUCTION

The current coronavirus disease 2019 (COVID-19) pandemic is having a huge impact on healthcare systems and broader society across the world. Patients with chronic conditions are being significantly affected by loss of social contact, constraints on movement and disruption to access to both urgent and routine healthcare, with many outpatient appointments being canceled or postponed (1, 2). While implementation of telemedicine has increased dramatically (3), allowing for the continuation of ongoing care and remote monitoring (2, 4, 5) all of these factors raise some serious concerns for the health and well-being of patients with Parkinson's disease (PD) (6).

Although research has played an important part in our response to COVID-19, the outbreak has also had an impact on the conduct and delivery of non-COVID-19 related research. Most other research has been paused or significantly reduced, including many clinical trials for PD (7, 8). While this is understandable due to concern for the safety of trial participants and research staff, it is vital that trials resume in order to meet the unmet clinical needs for people with PD (9).

Parkinson's disease psychosis (PDP) refers to the range of hallucinations and delusions that occur in PD (10). Their prevalence increases with illness duration, with most patients eventually developing such symptoms (11). Although there are a number of clinical options available for treating PDP, they are either not very effective or require specialized monitoring of side effects (12). It is vitally important that promising interventions continue to be tested in the form of a clinical trial. In light of the current pandemic, changes to the traditional methods used for delivering research are therefore required so that research can resume as soon as it is safe to do so (13).

In considering these changes, it is vital that researchers work with patients and the public to understand their views on research participation during pandemic times and to ensure that trial adaptations are practical for future study participants. Patient and public involvement (PPI) is defined as research being carried out "with" or "by" members of the public rather than "to," "about," or "for" them (14). It is an essential activity in all stages of the research process and ensures the acceptability and relevance of research (15). This study reports the results of an online survey that was developed together with a group of PPI advisors to explore PD patients' views on taking part in research during the current pandemic and how a planned clinical trial for people with PDP may be best adapted so that participants feel safe. To ensure that the results of the survey were reflective of the participants who would be taking part in the planned clinical trial, we were specifically interested in recruiting people with experience of psychosis symptoms. However, as the results of this survey would be of interest to a much wider audience (e.g., those conducting research with patients with other neuropsychiatric disorders or older adults more generally), the survey was open to anyone with PD.

METHODS

Views were gathered using an online survey, which included a mixture of closed- and open-ended questions, the full details of which are provided in the **Supplementary Material**. The survey was co-created with three patient advisors (whose involvement was facilitated by Parkinson's UK) to ensure that the questions being asked in the survey were relevant to and informed by the perspective of people with PD. The patient advisors provided input on the questions, response options and format of the initial draft of the survey. The survey consisted of 19 questions: six questions gathering details about survey respondents, seven questions related to general perceptions about taking part in research at the current time, followed by five more specific questions about adaptations to the planned clinical trial investigating psychosis in PD. It should be noted that for some of the questions, multiple responses could be selected (see questions with "Tick all that apply" statement in **Supplementary Material**). The final question was a free text option asking what physical or psychological support would help people with PD take part in research at this time.

An invitation to participate was distributed by Parkinson's UK to their Research Support Network—an online network that brings together people driven to help find a cure and better treatments for PD (16). The survey was open to (inclusion criteria) anyone affected by Parkinson's- including partners, carers and family members of those with the condition, and people who had experience of hallucinations and/or delusions were especially encouraged to participate to ensure that any changes being made to the planned clinical trial were inclusive and accessible to future participants. The questionnaire was in English and sent out via email, so excluded those who were not-fluent in English or who did not have access to computers or have an email address. Caregivers or family members were able to complete the survey on behalf of a person affected by PD (e.g., the person with PD was unable to complete the survey themselves). People expressed their interest to Parkinson's UK and were then sent a link to the survey, along with a plain English summary of the trial. The survey was administered using SmartSurvey, an online survey software and questionnaire tool. As any adaptations to the planned clinical trial were required to be processed within a timely manner, the survey was open to responses from 26 June to 6 July 2020.

Survey responses were fully anonymized and no identifiable information was collected. The survey was conducted as a PPI activity therefore no ethical approval was required. Informed consent was obtained from all participants.

Simple statistical summaries were generated for the closed form responses to each survey item. Since responses to the open-ended questions were fairly succinct, no formal qualitative analysis or prespecified framework were imposed on the open response data. To aid interpretation of the quantitative results, free-text responses were grouped into categories and classified as being positive, negative or neutral in tone (for example, whether respondents were generally positive, had reservations or were reluctant about the continuation of research in their comments).

RESULTS

Thirty people with PD (83%) and six carers, partners or family members (17%) completed the survey. Fourteen (47%) of the respondents with PD had experience of psychosis symptoms: five had experience of hallucinations, two of delusions, and seven of both symptoms of psychosis. All six carers lived with someone who had experience of psychosis symptoms: three each with experience of hallucinations alone and both hallucinations and delusions. **Table 1** details characteristics of the survey respondents and **Table 2** the main results of the closed form responses.

General Feelings on Taking Part in Research

When asked what their feelings were about taking part in research at present, or in the near future, given the current COVID-19 pandemic, the majority of respondents (69%) were positive about the continuation of non-COVID-19 related research as long as it was safe to do so. This was supported by numerous comments about the importance of research:

> *"It is important to carry on with research as life goes on research is still necessary to help with finding a cure. Without this there will not be any answers. Whatever we come up against we all have to deal with."*
> "*I am keen to take part in any trials regarding PD. There is no cure, that doesn't mean we shouldn't be looking for one.*"
> "*I think research is very important and if it can be carried out in a safe way I'm happy to participate."*
> *"I am quite happy to take part in research if it may help my wife and the many others suffering from Parkinson's."*

Some respondents (22%) were positive but had reservations or requirements for participation to feel safe:

> *"I have no objection to taking part in clinical research, providing my participation takes place within the safe rules governing COVID-19."*
> "*I have to take sensible precautions."*
> "*I would like to be tested to see if I have had COVID-19 before taking part."*

TABLE 1 | Details of survey respondents: PD participants, and carers/partners/family members on behalf of PD participants.

		PD participants, $n = 30$ (%)	Carers, $n = 6$ (%)
Time since PD diagnosis	Within the last year	1 (3)	0 (0)
	1–5 years	12 (40)	1 (17)
	5–10 years	8 (27)	2 (33)
	10–15 years	3 (10)	2 (33)
	More than 15 years	6 (20)	1 (17)
Experience of psychotic symptoms*	Experience of hallucinations and delusions	7 (24)	3 (50)
	Experience of hallucinations	5 (17)	3 (50)
	Experience of delusions	2 (7)	0 (0)
	No experience of hallucinations or delusions	15 (52)	0 (0)
Living arrangements	Living with partner	25 (83)	5 (83)
	Living with family/friends	1 (3)	0 (0)
	Living on their own	4 (13)	0 (0)
	Other (live in carer)	0 (0)	1 (17)
Previous participation in research	No previous participation	12 (40)	3 (50)
	Participation in online research	17 (57)	2 (33)
	Participation in a clinical trial	3 (10)	1 (17)
	Other	1 (3)	0 (0)

**Missing data from one participant with PD.*
PD, Parkinson's Disease.

TABLE 2 | Survey responses to closed form questions from PD participants with and without experience of psychosis symptoms and from carers, family members or partners.

Survey questions	**Response options**	**PD participant with psychosis symptoms, $n = 14$* (%)**	**PD participant without psychosis symptoms, $N = 15$* (%)**	**Carers, family members or partners, $n = 6$ (%)**
Preference for study visit location	More comfortable taking part in research from home	4 (29)	4 (27)	5 (83)
	More comfortable taking part in research that involved a visit to a clinical setting	2 (14)	1 (7)	0 (0)
	Comfortable either way	8 (57)	10 (67)	1 (17)
	Not comfortable either way	0 (0)	0 (0)	0 (0)
What might help a home visit from a researcher feel safe	PPE for the researcher	9 (64)	11 (73)	4 (67)
	PPE for participant	8 (57)	8 (53)	1 (17)
	The researcher traveling by car (not using public transport)	8 (57)	9 (60)	4 (67)
	The researcher having regular tests for COVID-19	8 (57)	9 (60)	5 (83)
Maximum length of time for home visit	1 h	1 (7)	7 (47)	3 (50)
	2 h	11 (79)	5 (33)	3 (50)
	3 h	1 (7)	1 (7)	0 (0)
	4 h	0 (0)	0 (0)	0 (0)
	5 h	1 (7)	2 (13)	0 (0)
What might help a study visit in a clinical setting feel safe	PPE for the researcher	10 (71)	10 (67)	4 (67)
	Participants being required to wear a mask	9 (64)	10 (67)	3 (50)
	Participants being required to use their own personal transport or being offered a taxi	12 (86)	9 (60)	4 (67)
	Thorough cleaning of assessment rooms in between participants	9 (64)	8 (53)	3 (50)
Maximum length of time for visit to clinical setting	1 h	0 (0)	5 (33)	3 (50)
	2 h	12 (86)	6 (40)	3 (50)
	3 h	0 (0)	1 (7)	0 (0)
	4 h	1 (7)	0 (0)	0 (0)
	5 h	1 (7)	3 (20)	0 (0)
Willingness to complete study assessments virtually	Yes	13 (93)	15 (100)	5 (83)
	No	1 (7)	0 (0)	1 (17)
Willingness to take a finger-prick blood test at home	Yes	14 (100)	14 (93)	6 (100)
	Not sure	0 (0)	1 (7)	0 (0)
Willingness to take a pregnancy test at home	Yes	2 (14)	2 (13)	1 (17)
	No	2 (6)	0 (0)	0 (0)
	Not applicable	10 (71)	13 (87)	5 (83)
Willingness to track of study drug compliance at home	Yes	14 (100)	14 (93)	5 (83)
	Not sure	0 (0)	1 (7)	1 (17)

**Missing data from one participant with PD who did not respond to the question asking whether they had experience of hallucinations and/or delusions.*
PPE, Personal protective equipment.

It was also clear from some of the comments that participants were particularly reluctant to attend hospital visits, preferring research activities to be conducted virtually:

> *"I feel comfortable with taking part in PD related research activities but would prefer not to have to visit hospitals and clinics."*

> *"I am happy to do on-line research but will not attend either a hospital or a face to face meeting of any type."*

Only a couple of respondents (6%), both of whom had experience of psychosis symptoms, expressed reluctance to participate in research at the present time.

Preferred Location and Length of Time for Visits

When asked whether respondents would feel more comfortable taking part in research if they did not have to visit a clinical setting, over 50% said they would feel comfortable either way, 39% said they would feel more comfortable taking part in research from home, 8% said they would feel more comfortable taking part in research that involved a clinical setting and no respondents selected "I would not feel comfortable either way." Carers were more inclined (83%) toward study visits taking place at their home compared to PD participants (27%). These respondents were often caring for people with complex needs and did not think it appropriate to visit other settings.

In response to the question asking how they would feel about a researcher visiting their home to conduct study visits, 69% of respondents expressed that they would be agreeable to a researcher conducting a home visit, and a further 22% stated that they would be willing as long as appropriate safety measures were taken. This was backed up by open-text comments throughout the survey:

> *"I am happy to do that. As long as all precautionary measures are put in place on both sides."*
> "*As long as exemplary COVID-19 precautions are taken—not a problem for me."*

To help make a home visit from a researcher feel safe, many respondents selected that they would like to see all the multiple-choice options that we provided in the survey being applied: (1) personal protective equipment (PPE) for the researcher (67%), (2) the researcher having regular tests for COVID-19 (64%), (3) the researcher traveling by car (not using public transport) (61%), and (4) PPE for the participant (47%). Further suggestions included meetings to be held outdoors (for example, in participant's gardens) and maintaining a safe distance between the participant and researcher.

Similarly, when asked what would help to make a study visit at a local hospital feel safe, most respondents selected all of the multiple-choice options that we provided in the survey: (1) participants being required to use their own personal transport or being offered a taxi (72%), (2) researchers wearing personal protective equipment (67%), (3) participants being required to wear a mask (61%), and (4) thorough cleaning of assessment rooms in between participants (58%). In addition, most respondents were willing for both home (67%) and hospital (75%) visits to last 2 hours or more.

Only 17% of carers and 44% of PD participants with experience of delusions felt that participants should be required to wear PPE in their own homes, compared to 60% of PD participants without symptoms of delusions (no experience of psychosis or symptoms of hallucinations only). PD participants with experience of delusions were also more likely to require researchers (89%) and participants (100%) to use personal transport when traveling to study visits compared to participants without these symptoms (45 and 60% respectively).

Virtual Assessments

A breakdown of the types of assessment that respondents would be amenable to completing virtually as part of the planned clinical trial is provided in **Table 3**. Only two respondents, both of whom had experience of psychosis, said they would not feel comfortable carrying out study assessments virtually.

Telephone calls was the preferred method for remote follow-up compared to video call or online surveys. Reasons for this varied in the open text comments but were mainly driven by issues with connectivity and feelings of discomfort toward the use of internet-based technology:

> *"On the whole I don't like video calls as I feel self-conscious, but I would be prepared to overcome this."*
> *"I am not comfortable using my computer, so I prefer to fill in a real form than a virtual one."*

When asked what would make virtual assessments easier to complete, respondents noted that questionnaires should be easy to understand and come with clear guidance and instructions. Support from a family member or carer and flexibility in the way that assessments could be completed (i.e., ability to complete in several sittings), were also seen as important in the comments:

> *"My mother would need assistance of a carer to complete any assessment and responses would be by 3rd party from the carers."*

Almost all respondents were willing to take a finger-prick home blood test (as a remote alternative to venepuncture) (97%) as long as they had clear instructions and, if required, the support of a carer. Respondents were also willing to monitor compliance with study drugs (i.e., pill counts (94%)) at home. Suggestions for what would make this easier to complete included the use of an online diary and pill dispensers.

Additional Support

The final question in the survey asked what other physical or psychological support would help people with PD take part in a research study at this time. Supportive and regular contact from research teams, preferably with a designated contact for the length of the study, was frequently suggested by respondents. For those with psychosis symptoms, importance was also given in the comments to the emotional support required when answering difficult questions relating to their symptoms:

> *"Dealing with distress caused by recalling upsetting episodes of hallucinations."*

Other recommendations included maintained engagement with the progress of the trial and the requirement for peer or carer support to assist with participation in the trial, particularly when considering remote assessments that require use of technology.

TABLE 3 | Study assessments that respondents would be willing to complete virtually or whether they would prefer face to face.

	Telephone, *N* = 36 (%)	Video call, *n* = 36 (%)	Online survey, *n* = 36 (%)	Prefer face to face, *n* = 36 (%)
Consent	32 (89)	24 (67)	24 (67)	3 (8)
Medical history and current medications	30 (83)	23 (64)	24 (67)	5 (14)
Sociodemographic information	31 (86)	22 (61)	25 (69)	3 (8)
Adverse events	27 (75)	22 (61)	21 (58)	7 (19)
Motor symptoms of PD	28 (78)	24 (67)	24 (67)	4 (11)
Non-motor symptoms of PD	27 (75)	23 (64)	26 (72)	5 (14)
Quality of life	29 (81)	21 (58)	24 (67)	6 (17)

PD, Parkinson's Disease.

DISCUSSION

Following the Guidance for Reporting Involvement of Patients and Public, 2 (GRIPP2; see **Supplementary Material**), this paper highlights the importance of PPI in ensuring that any changes that are made to the way that we deliver research for people with PD in a world with COVID-19 are acceptable to those who will be participating (17).

Our survey findings suggest that despite the current pandemic, PD patients and their carers see the importance of research and remain enthusiastic about participation. Although a small proportion of respondents in this survey was anxious about taking part in research in the short term, most respondents were comfortable for researchers to conduct face to face study assessments, as long as adequate safety precautions were in place.

Much of the open-ended data provided by the respondents emphasized the importance of taking a flexible approach to research. Following the COVID-19 pandemic, there has been rapid growth and development in the area of telemedicine and digital healthcare, which can be easily adapted for use in PD research for the evaluation of both motor and non-motor symptoms (2). While virtual follow-up may not be possible for all types of assessment [for example, physical examinations (18)], it may help reduce the length of time required for in-person visits, thereby potentially reducing the likelihood of infection acquired during the study visit (3, 19). Whilst almost all respondents reported that they would feel comfortable carrying out some of the study assessments and questionnaires virtually, care would be needed to ensure that we do not exclude participants, particularly those without the skills or support to use portable electronic devices (20). Researchers should therefore be prepared to provide additional information and one-to-one support to ensure that participants feel comfortable. Providing options in the way that participants can interact with researchers during visits and throughout the study was identified as being of the utmost importance so that participants felt supported. Virtual assessments in the clinical trial may therefore be used as part of a flexible package of follow-up methods, alongside traditional telephone and face to face approaches (21).

Although the sample size of our survey was small, this is likely attributable to our short period of data collection and request for people who had experience of psychosis. Nevertheless, this was important to ensure that some of the views were reflective of the sample who will be taking part in the planned clinical trial for psychosis in PD. Psychosis typically occurs in the later stages of PD, with risk factors including older age, increased duration and severity of PD, and significant psychiatric or medical comorbidity (11, 22). While there is currently no evidence to suggest that those with PD are at increased risk of contracting coronavirus (9, 23), advanced PD patients [for whom the prevalence of PDP ranges from 20 to 70% (11)] may be more susceptible and at greater risk for respiratory complications after a COVID-19 infection (24). Despite this, attitudes toward the continuation of research in the current climate were equally positive among participants both with, and without, experience of psychosis. Analysis between the two groups showed that those with experience of PDP (particularly carers and family members) were more inclined toward face to face visits taking place in a home setting, and open responses emphasized the requirement for ongoing physical and psychological support from carers and the research team, however, the sample size is too small to draw conclusions about such patterns.

All carers, partners and family members who participated in the survey lived with someone who had experience of psychosis symptoms. It is therefore not surprising that carers preferred study visits to take place in an environment in which the participant is familiar. Although our numbers were too small to demonstrate differences between the groups with any certainty, it does seem that carers and participants with experience of delusions were also less likely to suggest that participants wear PPE during a home visit. While the benefits of PPE are clear, we must be aware of the potentially disorientating impact that wearing PPE may have on patients, particularly those suffering from symptoms of psychosis. It is therefore important that researchers provide participants with additional information on what to expect during study participation, including clear information about any COVID safety measures that are in place, prior to the study visit. Not only will this provide reassurance, but it may also help reduce any anxiety and enable a more informed decision about research participation.

In the early stages of PD, hallucinations typically occur with insight initially preserved, whereas in the later disease stages, patients might not recognize the hallucinations as unreal anymore due to the onset of false beliefs (delusions) (10, 12). Given this progression, one might anticipate respondents with experience of delusions to have impaired insight compared to those with no experience of psychosis symptoms or experience of hallucinations only. Interestingly however, this did not appear to be the case among respondents of this survey. The only difference in responses between PD participants with and without symptoms of delusions was the requirement for researchers and participants to use their own personal transport or taxis when traveling to study visits, perhaps showing an increased awareness of the risks associated with COVID-19 among this more advanced PD population group. However, such an interpretation is tentative because of the small size of the sub-groups.

Limitations

Only 11% of participants had previous experience of a clinical trial, so may not be familiar with the types of procedures and assessments that this would typically involve. However, the fact that these participants still expressed their interest in taking part in future trials and research is noteworthy. It is also worth mentioning that self-report of psychotic symptoms would depend on respondent's insight and willingness to share such information, hence could have been under-reported. The results of this survey should also be considered in the context of a group with a specific interest in PD research. Despite this, it was clear from the responses that members of the Research Support Network used their knowledge of other people with PD as well as their own experiences, and their views were invaluable in informing how best to adapt the clinical trial. PPI members will continue to inform and improve participation in this research through their involvement with the trial's Patient Advisory Group and Trial Steering Committee.

Although our sample size was small, this survey was conducted with a fairly unique population, and highlights for the first time the views of PD patients and caregivers on taking part in research during the COVID-19 pandemic. The sample size was also deemed appropriate because of the exploratory nature of this research and the focus on identifying initial attitudes about the topic. While this study focused on patients with PD, many of the broader insights and recommendations will also be applicable to those involved in the design and delivery of clinical research with patients with other neuropsychiatric disorders as well an older adult population more generally.

Future Research

Although the sample size was deemed appropriate due to the exploratory nature of this research, a larger sample may have identified additional viewpoints or provided more nuanced explanations for PD patients and caregivers attitudes toward the continuation of research during pandemic times. It would therefore be useful to conduct a broader survey on the topic of adapting research in light of COVID-19, helping ensure that adaptations made to clinical studies are informed by the needs of people affected by Parkinson's. Future research would benefit from collecting data on current neurological, psychiatric and cognitive status, treatment and caregiver burden to determine whether these symptoms would influence responses. Researchers might also consider asking questions about all the types of devices participants have access to in their home and/or their technical literacy. It would be useful for upcoming clinical trials in PD to add a qualitative component to their study to capture the views and opinions of participants who are taking part in research on any ethical challenges or other barriers encountered, especially during the period of the pandemic.

CONCLUSION

Non-COVID-19 related research remains of critical importance and must not be neglected. Although patients with PD remain enthusiastic about participation in research, a flexible approach to the way that we redesign and deliver our studies in a world where travel and face to face contact are restricted is required. New tools should be developed and existing tools should be validated for virtual use as a matter of urgency to ensure research can continue to be delivered during the COVID-19 pandemic.

DATA AVAILABILITY STATEMENT

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

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 patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LV, SB, KM, NR, and AA: conceptualization. KM, AA, NR, LG, MS, GG, LV, and SB: survey design. AA and KM: analysis and interpretation of data. KM, LV, AA, NR, GG, and MS: writing—original draft. KM, AA, NR, MS, GG, LV, DA, KC, SB, DF, and CB: writing—revising and providing the final approval of work. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.602480/full#supplementary-material

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Prevalence and Risk Factors of Anxiety, Depression, and Sleep Problems Among Caregivers of People Living With Neurocognitive Disorders During the COVID-19 Pandemic

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Objectives: To estimate the prevalence of anxiety, depression, and sleep problems among caregivers of persons living with neurocognitive disorders (PLWND) during the COVID-19 pandemic in China and investigate whether the COVID-19-related experiences were associated with the presence of anxiety, depression, and sleep problems.

Methods: From March 1 to 31, 2020, 160 caregivers of PLWND participated in an online cross-sectional survey on the prevalence of anxiety, depression, and sleep problems. The 7-item Generalized Anxiety Disorder Scale (GAD-7) was administered to measure anxiety symptoms, and the 2-item Patient Health Questionnaire (PHQ-2) was used to assess depressive symptoms. Questions on sleep duration and sleep quality enquired about sleep problems. Six items were used to explore the COVID-19-related experiences, including community-level infection contact and the level of exposure to media information. We computed the prevalence rate of anxiety, depressive symptoms, and sleep problems. Univariate and multivariate logistic regression analyses were performed to investigate factors associated with these mental health problems.

Results: The prevalence rate of anxiety, depression, and sleep problems were 46.9%, 36.3%, and 9.4%. Approximately 55 participants (34.4%) presented with two or more mental health problems. Women had a higher risk of developing anxiety symptoms (OR, 5.284; 95% CI, 2.068–13.503; $p = 0.001$). Having a mental disorder (OR, 5.104; 95% CI, 1.522–17.114; $p = 0.008$) was associated with an increased risk of depressive symptoms. Caregivers who preferred to access positive information (OR, 0.215; 95% CI, 0.058–0.793; $p = 0.021$) was associated with decreased risk of sleep problems.

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Conclusion: Anxiety and depressive symptoms were common among caregivers of older adults with dementia or mild cognitive impairment during the COVID-19 pandemic. Being female was an independent risk factor for experiencing anxiety symptoms. Preexisting mental disorders increased the risk of depressive symptoms among caregivers, while caregivers who prefer to access positive media information decreased sleep problems.

Keywords: COVID-19, anxiety, depression, caregiver, neurocognitive disorders

INTRODUCTION

Family caregivers of persons living with neurocognitive disorders (PLWND), including dementia or mild cognitive impairment (MCI), often describe the experience as "enduring stress and frustration" (1). More than 80% of PLWND reported stressful experiences, including physical strains, psychological responses, and social isolation (2, 3). Previous studies observed that mental health problems such as anxiety, depression, and sleep problems were prominent among caregivers, especially those taking care of people with challenging behaviors (4).

During the COVID-19 pandemic, PLWNDs may become stressed when exposed to a replacement of caregivers, e.g., the children, instead of the domestic helper (5). Older adults living with dementia were vulnerable during the COVID-19 outbreak because they had limited access to accurate information, difficulty in remembering safeguard procedures, forgetting the warnings, and lacking sufficient self-quarantine measures. The COVID-19 pandemic may expose PLWND to a higher risk of infection and increased caregivers' concerns (6). The double hit of COVID-19 pandemics and the mental burden of caring for PLWND brought about significant problems (7).

The caregivers of PLWND tended to experience mental stress and feel isolated and helpless (8). Previous studies have shown that caregivers suffer from anxiety, fatigue, sleep disorders, and other mental health problems when in close contact with patients with emerging infectious diseases such as SARS (9), MERS-CoV infection (10, 11), Ebola (12), and H1N1 infection (13). During the COVID-19 outbreak, PLWNDs were likely to develop challenging behaviors, leading to a more significant caregiver burden in both physical and psychological aspects (7). For example, caregivers not only had higher workloads of caring for the PLWNDs but also worried about the PLWNDs' physical conditions in case of virus infection. However, the existing studies scarcely estimated the prevalence of anxiety, depressive symptoms, and sleep problems among caregivers of PLWND in China.

Besides, the associated factors related to these mental health problems were not studied well during the COVID-19 pandemic. The social-distancing measures implemented during the challenging time may impose additional pressure on the caregivers. Previous studies found that caregivers' support groups may benefit caregivers in reducing their stress (14). During the pandemic, the face-to-face caregiver support service was suspended and later transited to virtual meetings. In case of any suspected or confirmed cases of COVID-19 in the community, strict lockdown regulation would be implemented locally. The social network and connectedness among caregivers and service providers may be compromised. Also, when lived in such an isolated environment, family members may worry about the unknown conditions of severe emergencies and the protective equipment's short supply (7, 15). Whether the COVID-19 related experience affected the mental health status of caregivers remained unclear.

Previous studies have also shown that sensationalized media reports disseminated unauthorized information might even cause public panic (16–18). During the COVID-19, TV news, internet websites, and social media such as WeChat and WeBlog became mainstream information exchange and communication. Information related to COVID-19 flooded in daily life. Gao et al. found that a high prevalence of mental health problems was associated with frequent social media exposure during the COVID-19 outbreak (19). One explanation was that misinformation might drive fear, anxiety, and worries during unprecedented times. However, the impact of media exposure on the mental health status of the caregivers of PLWND was not studied. Additionally, whether the type of messages and the channels of communications were associated with the prevalence of mental health problems has yet to be elucidated.

Therefore, we hypothesized that mental health problems, particularly anxiety, depression, and sleep problems, were common among caregivers of PLWND. The high prevalence of these symptoms was also associated with the community-level COVID-19 contact and the level, nature, and channels of media exposure. To test these hypotheses, we conducted a cross-sectional survey during the COVID-19 outbreak. The study primarily aimed to estimate the prevalence of anxiety symptoms, depressive symptoms, sleep problems, and the coexistence of these three problems during the COVID-19 pandemic in China. Secondly, it aimed to explore whether the COVID-19-related experiences were associated with the risk of these mental health problems.

METHODS

From March 1 to 31, 2020, the cross-sectional survey was conducted among older adults' family caregivers through an anonymous online questionnaire through the Questionnaire Star platform. The URL link was distributed through the geriatric mental health service network by members of the Chinese Society of Geriatric Psychiatry. The online survey was first disseminated to older adults' caregivers and encouraged them to pass it on to other caregivers. To improve the response rate, the questions about mental health status were set as required items. The respondents would receive a reminder if some questions were missed during the survey. For the present study analysis, we identified the family caregivers who took care of persons with dementia or mild cognitive impairment as the study participants.

Study Participants

As illustrated in **Figure 1**, 160 caregivers of PLWND participated in the study. The inclusion criteria for caregivers of PLWND included family members who (1) took care of PLWND at home and (2) spent at least 6 h per week with care recipients. All caregivers must have essential listening, speaking, reading, and writing abilities and could use a smartphone or computer to ensure their completion of the self-reported questionnaire and online surveys.

The ethics committee of Peking University Sixth Hospital approved the study protocol. All subjects provided their consent by answering the screening question, "Are you willing to participate in the survey?" The survey was anonymous. No personal information could be identified in the questionnaire.

Screening of Mental Health Problems

The 7-item Generalized Anxiety Disorder Scale (GAD-7) was used to screen for anxiety symptoms. The cutoff score for anxiety was $\geq$5. The two-item Patient Health Questionnaire (PHQ-2) inquiring of loss of interest and the low mood was used to screen for depressive symptoms. The cutoff score for depression was $\geq$2 (20). Two questions were used to screen for sleep problems: "How long on average did you sleep per day in the past month?" and "How has your sleep quality changed in the past month?" Sleep problems were defined as follows: (1) a daily average duration of sleep $<$ 4 h or $>$ 8 h, and (2) more reduced sleep quality than before.

Evaluation of the COVID-19-Related Experiences

Six questions were used to evaluate the COVID-19-related experiences, including two items on the community-level infection contact and four questions on the level of exposure to media information (see **Appendix** in the Supplementary Document).

The questions examining the community-level infection contact were: "Did you have close contact with any individual with confirmed or suspected COVID-19?" and "Was there anyone confirmed or suspected with COVID-19 in your community and neighborhood?." A response of "yes" to either question indicated a positive experience of community-level infection contact.

Four questions were used to measure the level of exposure to media information: the time spent browsing information per day ($<$1, 1–3, 3–6, or $>$6 h); the individual's preference to access the nature of media information (primarily positive, half positive/half negative or mostly negative), and the "positive" information means bring support and hope, the "negative" information means fear and panic; the number of channels used to obtain information (including TV news, the internet, social media platforms such as WeChat and WeBlog, the newspaper, relatives and friends, community workers, or others); and the reliability of the information obtained (information from TV, newspaper and community workers was classified as highly reliable; information from other channels was classified as potentially reliable).

Medical History

Two questions identified the medical history of physical and mental conditions: "Have you ever been diagnosed with any of the following physical diseases, including hypertension, diabetes, heart disease, chronic bronchitis, stroke, Parkinson's disease, chronic renal insufficiency, chronic pain, or others?" and "Have you ever been diagnosed with any of the following mental disorders, including depressive disorders, anxiety disorders, obsessive-compulsive disorders, schizophrenia, dementia, mild cognitive impairment, or others?"

Statistical Analysis

Data analysis was performed using SPSS statistical software version 26.0. The significance level was set at $p < 0.05$.

The prevalence of depressive symptoms, anxiety symptoms, and sleep problems was calculated using the cutoff mentioned above scores and reported as the percentages of cases in different populations. Participants were classified as a normal comparison, having any single mental health problem, or having multiple mental health problems. χ^2 tests were used to compare the subjects' demographic characteristics, including age, sex, education level, marital status, place of residence, medical history, degree of community-level infection contact, and level of exposure to pandemic information between subgroups. We also performed Chi-Square tests to compare the demographic characteristics, COVID-19 related experiences, and mental health status between caregivers of people with dementia and MCI.

To explore the potential associated factors with anxiety, depressive symptoms, and sleep problem, we performed multiple logistic regression analyses and calculated odds ratios (ORs) and 95% CIs. The covariates included sex, history of preexisting mental disorders, degree of community-level infection contact, and level of exposure to pandemic information. As there was no significant difference in age, educational level, history of physical conditions, marital status, place of residence, we did not include these variables as covariates in the logistic regression analysis.

RESULTS

As presented in **Table 1**, approximately three-quarters of caregivers were women, and most participants were younger than 60 years old, married, and residing in cities. About 37.5% of the caregivers had physical conditions, and 8.8% had preexisting mental disorders.

Of all study participants, 75 (46.9%) presented with significant anxiety symptoms, 58 (36.3%) had depression symptoms, and 15 (9.4%) reported sleep problems. As shown in **Tables 1**, **2**, anxiety symptoms were more frequent among women than men

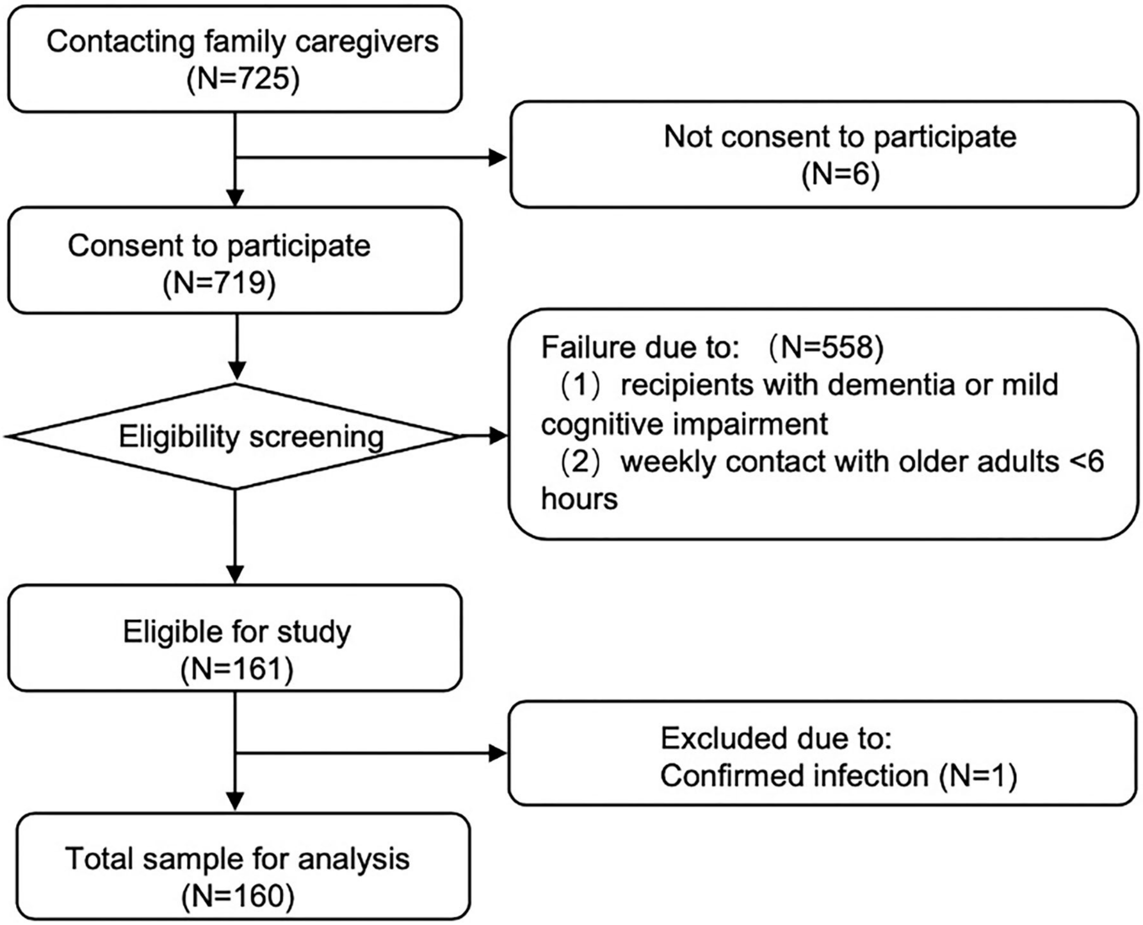

FIGURE 1 | Flow chart of subject recruitment and participation in the online survey.

(54.4 vs. 20.0%, $\chi^2 = 12.994$, $p < 0.001$), among caregivers with physical conditions than those who were healthy (58.3 vs. 40.0%, $\chi^2 = 5.061$, $p = 0.024$), and among caregivers with preexisting mental disorders than those without (78.6 vs. 43.8%, $\chi^2 = 6.190$, $p = 0.013$). Depression symptoms were more common among caregivers with preexisting mental conditions than healthy (71.4 vs. 32.9%, $\chi^2 = 8.216$, $p = 0.004$). Caregivers who were preferred to access positive information than obtain half positive/half negative or primarily pessimistic information had a lower prevalence of sleep disturbance (3.7 vs. 15.2%, $\chi^2 = 6.210$, $p = 0.013$). There were no significant differences in demographic characteristics, COVID-19-related experiences (see **Supplementary Table 1**), the prevalence of anxiety, depressive symptoms, and sleep problems (see **Supplementary Table 2**) between people's caregivers with dementia and MCI.

Multivariate regression analysis showed that female sex (OR = 5.284, 95% CI = 2.068–13.503, $p = 0.001$) was associated with an increased risk of experiencing anxiety symptoms. Preexisting mental disorders (OR = 5.104, 95% CI = 1.522–17.114, $p = 0.008$) were associated with an increased risk of depression symptoms. Preferring access to positive messages (OR = 0.215, 95% CI = 0.058–0.793, $p = 0.021$) may reduce sleep problems (**Table 2**).

Among all participants, 55 (34.4%) had two or more mental health problems, of which ∼80% of the subjects had anxiety symptoms and depressive symptoms simultaneously. As shown in **Table 3**, having two or more types of symptoms was more prevalent among caregivers who had preexisting mental disorders than those without (71.4 vs. 30.8%, $\chi^2 = 11.123$, $p = 0.004$). However, the effect of preexisting mental conditions on multimorbidity was not significant in the multivariate analysis.

DISCUSSION

Our study found that approximately half of the caregivers of old adults with neurocognitive disorders had anxiety symptoms, and two-fifths of caregivers had depression symptoms during the COVID-19. The study also identified that females had a higher risk of anxiety symptoms; those having preexisting mental disorders were more likely to develop depression symptoms, while enhanced access to positive media information decreased the risk of sleep problems.

TABLE 1 | Comparisons of demographic characteristics and COVID-19-related experiences among mental health status subgroups.

Variable	All home caregivers (N = 160)	Anxiety		p-value	Depression		p-value	Sleep problems		p-value
		No (N = 85)	Yes (N = 75)		No (N = 102)	Yes (N = 58)		No (N = 145)	Yes (N = 15)	
Age										
<60 years	112 (70.0%)	59 (52.7%)	53 (47.3%)	0.863	69 (61.6%)	43 (38.4%)	0.389	102 (91.1%)	10 (8.9%)	0.767
≥60 years	48 (30.0%)	26 (54.2%)	22 (45.8%)		33 (68.8%)	15 (31.3%)		43 (89.6%)	5 (10.4%)	
Gender										
Men	35 (21.9%)	28 (80.0%)	7 (20.0%)	<0.001	25 (71.4%)	10 (28.6%)	0.285	30 (85.7%)	5 (14.3%)	0.259
Women	125 (78.1%)	57 (45.6%)	68 (54.4%)		77 (61.6%)	48 (38.4%)		115 (92.0%)	10 (8.0%)	
Schooling educational level										
≤9 years	34 (21.3%)	16 (47.1%)	18 (52.9%)	0.424	22 (64.7%)	12 (35.3%)	0.896	32 (94.1%)	2 (5.9%)	0.431
>9 years	126 (78.8%)	69 (54.8%)	57 (45.2%)		80 (63.5%)	46 (36.5%)		113 (89.7%)	13 (10.3%)	
Marital status										
Married	137 (85.6%)	73 (53.3%)	64 (46.7%)	0.921	88 (64.2%)	49 (35.8%)	0.756	123 (89.8%)	14 (10.2%)	0.371
Single/divorced/widowed	23 (14.4%)	12 (52.2%)	11 (47.8%)		14 (60.9%)	9 (39.1%)		22 (95.7%)	1 (4.3%)	
Residence										
Urban	144 (90.0%)	74 (51.4%)	70 (48.6%)	0.187	92 (63.9%)	52 (36.1%)	0.913	130 (90.3%)	14 (9.7%)	0.651
Suburban/rural	16 (10.0%)	11 (68.8%)	5 (31.3%)		10 (62.5%)	6 (37.5%)		15 (93.8%)	1 (6.3%)	
Physical conditions										
Yes	60 (37.5%)	25 (41.7%)	35 (58.3%)	0.024	37 (61.7%)	23 (38.3%)	0.671	53 (88.3%)	7 (11.7%)	0.441
No	100 (62.5%)	60 (60.0%)	40 (40.0%)		65 (65.0%)	35 (35.0%)		92 (92.0%)	8 (8.0%)	
Preexisting mental disorders										
Yes	14 (8.8%)	3 (21.4%)	11 (78.6%)	0.013	4 (28.6%)	10 (71.4%)	0.004	11 (78.6%)	4 (21.4%)	0.105
No	146 (91.3%)	82 (56.2%)	64 (43.8%)		98 (67.1%)	48 (32.9%)		134 (91.8%)	12 (8.2%)	
Community-level infection contact										
Yes	33 (20.6%)	15 (45.5%)	18 (54.5%)	0.322	18 (54.5%)	15 (45.5%)	0.217	30 (90.9%)	3 (9.1%)	0.950
No	127 (79.4%)	70 (55.1%)	57 (44.9%)		84 (66.1%)	43 (33.9%)		115 (90.6%)	12 (9.4%)	
Time spent browsing information										
<1 h	35 (21.9%)	19 (54.3%)	16 (45.7%)	0.721	20 (57.1%)	15 (42.9%)	0.789	30 (85.7%)	5 (14.3%)	0.156
1-3 h	87 (54.4%)	43 (49.4%)	44 (50.6%)		56 (64.4%)	31 (35.6%)		79 (90.8%)	8 (9.2%)	
3-6 h	28 (17.5%)	17 (60.7%)	11 (39.3%)		19 (67.9%)	9 (32.1%)		28 (100%)	0 (0%)	
>6 h	10 (6.2%)	6 (60.0%)	4 (40.0%)		7 (70.0%)	3 (30.0%)		8 (80.0%)	2 (20.0%)	
Preference for the nature of information										
Primarily positive	81 (50.6%)	47 (58.0%)	34 (42.0%)	0.209	54 (66.7%)	27 (33.3%)	0.437	78 (96.3%)	3 (3.7%)	0.013
Half positive/half negative or primarily negative	79 (49.4%)	38 (48.1%)	41 (51.9%)		48 (60.8%)	31 (39.2%)		67 (84.8%)	12 (15.2%)	
Number of channels used to obtain information		2.82 ± 1.255	3.05 ± 1.283	0.836	2.86 ± 1.227	3.05 ± 1.343	0.372	2.90 ± 1.284	3.27 ± 1.100	0.470
Reliability of the information obtained		2.04 ± 0.933	2.12 ± 0.982	0.951	2.06 ± 0.930	2.10 ± 1.003	0.650	2.07 ± 0.967	2.20 ± 0.841	0.275

Our study found that anxiety and depressive symptoms were common among caregivers of PLWND. The estimates were higher than those reported during routine care before the COVID-19 outbreak (21). As we have observed, during this COVID-19 pandemic, family members who took care of persons with dementia were exposed to physical and psychological stress, which may contribute to a more significant caregiver burden (5). A study previously found that family caregivers reported substantial emotional and social burdens even within the 1st year of receiving a diagnosis of Alzheimer's disease. The caregiver burden increased with the concerns of behavioral problems (22). During the COVID-19 outbreak, older adults with dementia relied on their caregivers to manage household chores due to the restriction of mass transportation and outdoor activities. Thus, the physical and time burden was increased. In addition to being concerned about the risky situation of the contagious disease, the caregivers may become exhausted with a feeling of suffering and burnout (23).

TABLE 2 | Univariate and multivariate analysis of factors associated with anxiety, depression, and sleep problems.

Variables	Univariate analysis						Multivariate analysis					
	GAD-7		PHQ-2		Sleep problem		GAD-7		PHQ-2		Sleep problem	
	χ^2	*p*-value	χ^2	*p*-value	χ^2	*P*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age	0.030	0.863	0.742	0.389	0.088	0.767						
Gender	12.994	<0.001	1.143	0.285	1.272	0.259	5.284 (2.068–13.503)	0.001				
Schooling education level	0.638	0.424	0.017	0.896	0.620	0.431						
Marital status	0.010	0.921	0.096	0.756	0.799	0.371						
Place of residence	1.743	0.187	0.012	0.913	0.204	0.651						
Physical conditions	5.061	0.024	0.180	0.671	0.593	0.441	2.011 (0.960–4.216)	0.064				
Preexisting mental disorders	6.190	0.013	8.216	0.004	2.624	0.105	3.099 (0.732–13.217)	0.125	5.104 (1.522–17.114)	0.008		
Community-level infection-contacting experience	0.982	0.322	1.524	0.217	0.004	0.950						
Time spent on reading media messages	1.335	0.721	1.049	0.789	5.222	0.156						
Preference to the media messages	1.582	0.209	0.604	0.437	6.210	0.013					0.215 (0.058–0.793)	0.021
Number of channels to obtain relevant information	0.043	0.836	0.803	0.372	0.525	0.470						
Reliability of obtained information	0.004	0.951	0.206	0.650	1.200	0.275						

The caregiver gender was frequently reported to be associated with caregivers' mental health problems. Our study observed that female caregivers had a higher risk of anxiety symptoms. The finding was consistent with previous studies (24). Globally, almost 80% of the caregivers are women as they could be the wife, daughter, or daughter-in-law of the person with dementia (25). Caring for dementia predicted a higher level of burden. Gender might influence the individual's kinship roles and personal perceptions of caregiving burden. Previous studies have found that female caregivers tended to report more mental health problems than male caregivers (26, 27). The help-seeking behaviors of the caregivers might account for such a tendency. Almberg et al. found gender differences in coping with the caregiving burden: men expressed a need for social support; women showed a positive attitude toward the relationships with other family members and thus exhibited more mental health problems. Men might have more access to external resources for help, which alleviated the stress and burden (26).

Our survey showed that caregivers who had preexisting mental disorders were at a higher risk of depression symptoms during the COVID-19. Patients with severe mental illness may be the most vulnerable populations when facing disaster (28). Those caregivers who have severe mental illnesses may have difficulty taking time off from the care recipient and may lack sufficient insurance to cover testing and treatment (29). The caregivers with preexisting mental health problems in our study also had a high tendency to present several symptoms. The mental health problems of the caregivers were overlooked, especially during the social distancing period. Caregivers who had poor psychological health, high depressive symptoms, and elevated anxiety symptoms experienced a more significant burden from their caregiving (4). The greater burden may lead to job dissatisfaction and possibly further impair work performance and aggravate more burnout experiences. Such problems were prominent during the outbreak of COVID-19 (29). These findings highlight that timely and continuously mental health care needs to be developed urgently. However, further studies are warranted to explore which preexisting mental disorders were more specific to trigger depressive symptoms during the COVID-19 pandemic and other emergencies.

Interestingly, our study revealed that caregivers who preferred to obtain favorable media information decreased the risk of sleep problems. During the COVID-19, one of the most stressful situations was the contagion's unpredictability and uncertainty. These, along with misinformation, might raise concerns in public. An overabundance of misinformation on social media imposed a significant risk to public mental health during the pandemic crisis (19, 30). Preference for positive media information would allow an individual to consider the potential risk and challenges critically. Timely access and utilization of accurate information may benefit the mental well-being of caregivers.

LIMITATIONS

The research findings need to be interpreted with caution, as there are several limitations. First, the subject selection bias was innegligible in the online survey. Only those willing to discuss psychology-related topics were counted, while those who refused were not investigated thoroughly. Second, during the

TABLE 3 | Comparisons of demographic characteristics and COVID-19-related experiences among those with mental health multimorbidity, those with single morbidity, and normal controls.

Variable	Normal controls ($N = 73$)	Single morbidity ($N = 32$)	Multimorbidity ($N = 55$)	χ^2	*p*-value
Age					
<60 years	50 (44.6%)	22 (19.6%)	40 (35.7%)	0.298	0.862
≥60 years	23 (47.9%)	10 (20.8%)	15 (31.3%)		
Gender					
Women	52 (41.6%)	25 (20.0%)	48 (38.4%)	4.722	0.094
Men	21 (60.0%)	7 (20.0%)	7 (20.0%)		
Schooling educational level					
≤9 years	13 (38.2%)	10 (29.4%)	11 (32.4%)	2.480	0.289
>9 years	60 (47.6%)	22 (17.5%)	44 (34.9%)		
Marital status					
Married	62 (45.3%)	28 (20.4%)	47 (34.3%)	0.121	0.941
Single/divorced/widowed	11 (47.8%)	4 (17.4%)	8 (34.8%)		
Residence					
Urban	65 (45.1%)	28 (19.4%)	51 (35.4%)	0.751	0.687
Suburban/rural	8 (50.0%)	4 (25.0%)	4 (25.0%)		
Physical conditions					
Yes	21 (35.0%)	15 (25.0%)	24 (40.0%)	4.459	0.108
No	52 (52.0%)	17 (17.0%)	31 (31.0%)		
Preexisting mental disorders					
Yes	1 (7.1%)	3 (21.4%)	10 (71.4%)	11.123	0.004
No	72 (49.3%)	29 (19.9%)	45 (30.8%)		
Community-level infection contact					
Yes	13 (39.4%)	5 (15.2%)	15 (45.5%)	2.327	0.312
No	60 (47.2%)	27 (21.3%)	40 (31.5%)		
Time spent browsing information					
<1 h	14 (40.0%)	7 (20.0%)	14 (40.0%)	4.842	0.564
1–3 h	39 (44.8%)	17 (19.5%)	31 (35.6%)		
3–6 h	16 (57.1%)	4 (14.3%)	8 (28.6%)		
>6 h	4 (40.0%)	4 (40.0%)	2 (20.0%)		
Preference for the nature of information					
Primarily positive	42 (51.9%)	15 (18.5%)	24 (29.6%)	2.649	0.266
Half positive/half negative or primarily negative	31 (39.2%)	17 (21.5%)	31 (39.2%)		
Number of channels used to obtain information	2.79 ± 1.269	3.09 ± 1.201	3.02 ± 1.312	0.634	0.674
Reliability of the information obtained	2.03 ± 0.951	2.19 ± 0.914	2.07 ± 0.993	0.569	0.802

study period, it was not feasible to reach individual caregivers due to social distancing regulations. The online survey may not be universally accessible by all relevant stakeholders of caregivers. For example, spouse caregivers might not participate because they might have limited access to mobile technology. Therefore, it would be more informative to conduct face-to-face or telephone-based interviews with spouse caregivers in future studies. Last, it remained controversial whether the inclusion of caregivers of individuals with MCI would lower the estimates of the prevalence of mental stress. One might argue that old adults with MCI by definition preserve autonomy in everyday life, implying that their caregivers' role could be quite different from that in dementia. In fact, during the COVID-19 outbreak, memory problems in MCI affected family caregivers more often than usual. For example, repeated asking questions interfered with the caregivers who worked at home during the pandemic. In our study, there was no difference in the mental health status between subgroups of dementia and MCI. However, the distribution of the two subgroups was uneven and prevented from the subgroup analysis. Therefore, we advise that the caregivers' roles and psychological responses in a different cognitive impairment stage need further investigations.

CONCLUSION

Anxiety and depression were prevalent among caregivers of neurocognitive disorders during the COVID-19 epidemic, especially among females and those with preexisting mental conditions. The findings highlight that, during unprecedented times, continuous mental health care is warranted for caregivers of persons living with neurocognitive disorders. However, the mental health status of caregivers should be monitored during the post-epidemic era.

DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during the current study are not publicly available because we are preparing an additional manuscript. However, they are available upon reasonable request to the corresponding author, HW (huali_wang@bjmu.edu.cn).

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Peking University Sixth Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

QL and HZ contributed to the study design, data collection, analysis, interpretation, and drafted the manuscript. MZ, TL, and WM contributed to the study design, data collection, analysis, and interpretation. CA, YC, SL, and WK contributed to the data collection, research, and interpretation. XY and HW conceived the study, contributed to data interpretation, and critical revision of the manuscript. HW had primary responsibility for the final content. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.590343/full#supplementary-material

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"The Graying Minority": Lived Experiences and Psychosocial Challenges of Older Transgender Adults During the COVID-19 Pandemic in India, A Qualitative Exploration

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Background: The Coronavirus disease 2019 (COVID-19) has emerged as a global health threat. Certain factors like age, an immunocompromised state, and social impoverishment, etc. can add to health vulnerabilities during this pandemic. One such group is older transgender adults, who often bear a combination of these risks. As the world is aging fast, their numbers have also been increasing. With this in mind, this study explores the lived experiences and psychosocial challenges of older transgender adults during the COVID-19 pandemic in India.

Methods: A qualitative approach was used. Ten individuals with "transgender" identity above the age of 60 were recruited with consent through purposive sampling. In-depth interviews were conducted on the telephone using a pre-designed interview schedule. They were recorded, translated, and transcribed verbatim. Hasse's adaptation of Colaizzi's phenomenological method was used for analysis. Independent coding and respondent validation were used to ensure the rigor of data.

Results: The super-arching categories (with themes) were marginalization ("second" priority, stigma, social disconnection), the dual burden of "age" and "gender" (ageism, othering, and psychosexual difficulties), and multi-faceted survival threats (physical, emotional, financial) during the pandemic. Social rituals, spirituality, hope, and acceptance of "gender dissonance" emerged as the main coping factors, whereas their unmet needs were social inclusion, awareness related to COVID-19, mental health care, and audience to their distress.

Conclusion: The elderly gender minorities are at increased emotional and social risks during the ongoing pandemic, and their voices are mostly unheard. The need for policy implementation and community awareness about their social welfare is vital to improving their health and well-being.

Keywords: COVID-19, coronavirus, pandemic, older adults, transgender, gender minorities, lived experiences, qualitative

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INTRODUCTION

The last 8 months have seen the emergence of a new global health threat, the Coronavirus disease 2019 (COVID-19). After being declared a pandemic by the World Health Organization (WHO), it has affected more than 37 million, with nearly a million people succumbing to the infection (1). After a four-phased lockdown, India has faced a surge of cases and is presently among the countries with the highest case burden (1). Every section of the population has been facing unique challenges during the outbreak but certain minorities are at increased risk in terms of the direct effects of the virus, its psychosocial offshoots, and the lockdown and distancing measures that are used to attempt to contain it. Age and immunocompromised states have been documented to be the two most important factors in deciding the morbidity and fatality rate of COVID-19 (2). The elderly have a unique bio-psychosocial vulnerability. It includes increased pulmonary involvement due to the virus, risk of psychological disorders like depression, anxiety, sleep disturbances, and social factors like loss of autonomy, loneliness, and isolation (3). Certain minority sections have a combination of many such risk factors, one of them being the older transgender population (as a part of the Lesbian, Gay, Bisexual, Transgender, and Queer–LGBTQ community). They share the combined risks of all the issues mentioned above and are primarily neglected in disaster preparedness and management planning. Besides, victimization from the traditional social stereotyping, "third gender" based discrimination, and associated factors like poverty and administrative apathy, they also have increased dependency and segregation based on age. As a part of the Movement Advancement Project, a recent brief by the Centre for American Progress discussed that there are 2.7 and 1.1 million people of the LGBTQ community above the age of 50 and 65 years, respectively. Within this, 20 percent of them are "people of color," which further worsens health disparities during COVID-19 (4). Data also showed that older transgender adults suffer from mistreatment at long-term facilities and that they have double the risk of poverty and social impoverishment (5). Many transgender individuals also remain on gender-affirming (hormonal or surgical) treatments that have been shown to improve their quality of life, especially in older adults (6), and access to and the availability of such treatments might be a challenge during disaster situations, leading to unforeseen physical and emotional consequences.

The World Professional Association for Transgender Health (WPATH), in association with the Sappho Good Practice Guide, India, has laid down consensus guidelines for diagnosis, hormone therapy, recommendations for sex reaffirmation surgeries, and subsequent follow-ups. The guidelines stress multi-disciplinary efforts, appropriate knowledge regarding the procedures, and adequate psychological support, both pre and post-treatments (7). However, prevalent misconceptions and misinformation in India have led to unscrupulous "conversion therapies" that are unfortunately recommended to "cure" transgender and homosexual individuals. Mostly practiced by faith-healers, preachers, shamans, and quacks, these "curative treatments" commonly involve unsupervised steroids and sex reassignment surgeries (SRS) without consent and the understanding of the individuals involved, which can be psychologically devastating. Although there is no specific Indian law prohibiting "conversion therapy," it has been proposed that it violates the Right to Privacy (Article 21 of the Indian Constitution) and has been widely regarded as "illegal and unethical" by the Indian Psychiatric Society (IPS) (8). A positive step in this regard has been the Transgender Person (Protection of Rights) Act, 2019, based on "equitable access to health" for this special population. Under this Act, the government provisions for accommodation and education for transgender persons and there is a mandate that at least one Government hospital in every state needs to provide SRS free of cost, with informed consent and counseling. The exact rules are expected to be further clarified and implemented soon, but whether it improves the "rights" of transgender individuals remains to be seen (9).

In India, transgender people are traditionally known as "*Hijras*." They are often equated with *"Kinnars"* (mythological singers and dancers), as represented in the Kamasutra (ancient Hindu text of sexuality) and even in the epics like Mahabharata (in characters such as *Brihanalla* and *Shikhandi*) (10). For generations throughout history, they have undergone poverty, rejection, neglect, and separation from their own families due to their "identity." Some even undergo rituals (Nirvaan) to remove their genitalia (11). Over time, their communities have become well-organized, claiming their rights. Irrespective of the widespread advocacy in popular media and literature, they have been subject to socio-economic neglect for decades and legal ambiguity about their sexual identity (12). Even though the Supreme Court in 2014 recognized the Hijras as the "third gender" and subsequently in 2018, decriminalized Section 377, which stated consensual sexual activity between adults of same-sex as a crime, the social acceptance of these legislations is far from reality, and the discrimination against these gender minorities continues (13). Literature related to their "own stories" is scarce, especially in the aged population.

METHODS

Study Design and Participants

The study followed a qualitative method, using a social constructivist paradigm. In contrast to the positivist paradigm, this paradigm permits the researcher to be open-minded and flexible in exploration, rather than intervening or analyzing based on pre-fixed notions. Furthermore, we chose the phenomenological approach as we wanted to understand the specific "experiences and challenges" of a particular population in the context of an ongoing crisis. Such paradigms have been used in previous studies for studying phenomena like experiences of motherhood, pain, and post-traumatic stress among women, war veterans, and disaster-survivors, respectively (14). Telephonic interviews were conducted with 10 elderly people (aged above 60 years) from the LGBTQ community, who identified their gender identity as "transgender." We considered the age of "60" as a cut-off for the elderly in this population based on the United Nations/WHO age recommendations (15). However, a range of people aged between 50 and 65 years has been taken in earlier studies on older LGBTQ adults. As access to this sector of the population is difficult, we used purposive sampling. The index participant was known to one of the researchers, who eventually introduced them to interested others. We tried to obtain detailed descriptions of their experiences and the challenges they have faced during the COVID-19 pandemic and the associated lockdowns. A phenomenological approach was used for analysis.

The Working Definition of "Transgender"

Though transgender or "trans" is commonly used as an umbrella term, for this study, we considered "transgender" as any person for whom their gender identity or expression is different from the sex assigned at birth (or that written in their birth certificate) (16).

We obtained appropriate ethical approval from the Institute board. The participants were initially contacted via telephone, informed about the objectives of the study, and we sought informed consent verbally. Interestingly, all 10 participants welcomed the study initiative and were willing to participate without hesitation. A General Health Questionnaire (GHQ)-12 and Hindi Mental Status Examination (HMSE) were used as screeners for any psychiatric and cognitive disorders. The cut-offs were 3 and 19, respectively (17, 18). We obtained thematic saturation with seven participants. However, we interviewed three more for super-saturation of the data. To ensure confidentiality, we assigned respective numbers (instead of names) to maintain anonymity in transcripts. All transcripts were audio-recorded with consent and then transcribed verbatim. Only the researchers had access to data, which was password protected. The study followed the Standards for Reporting Qualitative Research guidelines (19).

Procedures

The initial semi-structured interview schedule was designed based on a literature review, which was later modified based on the first two interviews. In that sense, they can be considered to be a pilot for this study. We recorded the socio-demographic details in a separate datasheet. The questions involved in the schedule were open-ended, facilitating rich data regarding their difficulties during the COVID-19 pandemic, their psychosocial needs, access to health care, perceived stigma and discrimination, and the effects of lockdown measures. The salient questions of the interview schedule are summarized in **Appendix**.

Probing questions like "*can you tell me more about it,*" "*how did that happen,*" "*please elaborate on the context,*" etc. were used to receive rich data on their lived experiences. The analysis was done simultaneously with data collection by both the researchers independently to add to the rigor.

Data Analysis

We used Haase's adaptation of Colaizzi's method for analysis (20, 21). It adopted a phenomenological model, which involves the exploration of the subjective experience under investigation. This approach was chosen as we wanted to know the "lived experiences" of the transgender population. The concept of "intersubjectivity" was used in the analysis to understand the circumstances of "social suffering" from the viewpoint of these individuals. Colaizzi's method essentially involves the following sequential steps:

- Familiarization (running through the transcript several times for a better understanding).
- Identification of significant statements and restating them in "general" terms.
- Formulating meanings relevant to the phenomenon of interest.
- Clustering "identified meanings" into categories, themes, and sub-themes.
- Rigorous discussion among researchers to develop an exhaustive description of the clustered themes.
- Developing a conceptual structure of the studied phenomenon.
- Respondent validation from the participants (seeking verification of the developed structure).

As mentioned, the verbatim transcripts were translated into English (with cross-translation to check for validity). The transcripts and memos were read several times through thematic coding until significant recurrent phrases emerged, and they were re-described in general terms to formulate contextual meanings and then organized and structured by discussion among the researchers. We clustered the super-arched topics into relevant categories and themes, along with verbatim data supporting each of them.

Ensuring Scientific Rigor

Trustworthiness and credibility are used to establish rigor in qualitative studies, which are different from the concepts of reliability and validity that underpin quantitative research (22). The researchers independently analyzed data using Colaizzi's methods, as mentioned above, categorizing the themes based on the contextual factors affecting the participants, which were then discussed among the research team to reach a consensus on the structural organization of the results. After the first round of analysis, the researchers went back to the participants, five of whom were interviewed again as part of the process of "respondent validation." Based on their inputs, the hierarchy of the data was modified and supplemented by this additional information. A data trail was maintained so that the steps of qualitative analysis could be traced back to the original interviews.

RESULTS

The sample consisted of 10 elderly people from the transgender community. Four participants identified as "third gender," while two preferred "male" gender, one preferred female, and one did not want to disclose gender and orientation. Six participants resided with their families or friends, and four lived alone. Among the latter, one resided at an old-age care home and another in temporary shelters, frequently living on the streets. They belonged to various states of Karnataka, a mix of lower and middle socioeconomic status. Throughout the pandemic, eight of them resided in the same place, whereas two had changed residence. One of these two included the homeless individual who kept changing temporary shelters for support. Only two participants received an old-age pension, as they had previously been employed in Government sector jobs. Six others were not aware of the senior citizen benefits of the country. Two were unemployed, whereas others did menial jobs for a living, apart from the homeless person, who at times begged at street signals. Four of them did not have a valid VOTER or AADHAR card (proof of identity in India). The mean age of the participants was 66.4 years. The mean GHQ-12 and HMSE scores were 1.7 and 25.2, respectively. The mean duration of the interviews was 45.20 min. We conducted the interviews in April and May 2020 when India underwent a four-phased lockdown to curtail the COVID-19 outbreak. The socio-demographic parameters for each of the elderly participants are mentioned in **Table 1.**

The experiences of participants during the pandemic were broadly categorized into feelings of marginalization (perceived stigma, discrimination, social exclusion, loss of dignity, and reduced access to health-care), vulnerability due to the "dual burden" of age and gender (prejudice of ageism, impaired sexual well-being, feelings of "othering"), as well as multiple physiological, psychosocial, and economic survival threats. Social rituals and festivities within their community, acceptance of their "gender dissonance," and spirituality provided them hope and helped them cope with the adversities. Knowledge-attitude-practice (KAP) gap regarding the outbreak was a major concern among them, while the predominant "unmet needs" were social inclusion, emotional well-being, social benefits, and receiving an "outlet or audience" for their suffering.

The resultant super-arching categories and themes, along with the respective sub-themes, are summarized in **Table 2.** They are supported by the key verbal excerpts of the participants, which are mentioned in the table and contextualized in subsequent discussion.

DISCUSSION

Dual Burden of "Age" and "Gender": Marginalization

Biological disasters like COVID-19 often hit the most vulnerable in the worst ways. Advanced age and belonging to a gender minority group are both crucial susceptibilities during the pandemic. They contribute to the "minority stress" of marginalized populations like the homeless, migrants, socially impoverished, and especially the Black, Asian, and minority ethnic (BAME) communities, as already postulated during the ongoing outbreak. These include social insecurity, unemployment, experiences of racism, prejudice and xenophobia, lack of social welfare benefits, precarious work, increased risk of infection due to lack of precautionary measures and overcrowding, and most importantly, lack of knowledge and awareness related to the pandemic and its related issues (23, 24).

The study participants revealed a sense of increased "ageism" during the ongoing outbreak, which has also been raised as a potential concern in public health guidance measures for the "elderly" during COVID-19.

> "Throughout our lives, we have been 'observed' differently, now it's even more as we are old. We even get called names when we ask for help." **(P6, on discussing information-seeking about the pandemic)**

Such age-related prejudice and attitudes that consider the "elderly" as a "justified loss" for the sake of younger lives were also documented during the Severe Acute Respiratory Syndrome (SARS) and Ebola outbreaks (25, 26). Age itself becomes an essential factor for the "third gender" as many of the societal and sexually acceptable roles of transgender people tend to get to be affected by age.

In the Indian context, transgender people or *Hijras* take to baby showering ceremonies *(Badhaai)*, which are an essential source of income, and during the pandemic have become scarce. Furthermore, the "sexual vitality" and "auspiciousness" of the Hijras, for which one welcomes them in ceremonies decreases with age, and hence older transgender adults often run out of income (27). Seven participants also looked at such social rituals as their source of coping and connectedness with society.

> "We look forward to Badhaais and Varanas (rituals)! This is something we have been doing since we are young. Other people welcome us during these times. It has become our true festival! This disease has taken it away from us!" **(P4, on how she feels excluded from the society during the pandemic)**

> "In spite of all the 'hate' for us, society requires us for these ceremonies. Now, with the fear of infection, they don't even allow us near people's houses. Our livelihood and connections both are at risk!" **(P6, while describing the cessation of rituals during the ongoing crisis)**

Most participants mentioned being the "second priority" for health and legal services, including access to medications, medical protective equipment, and testing.

> "For [the] last three months, I have been so used to hearing: 'people like you should come later, any way you are old, what's the need… just go and stay with your people…' It hurts you know, it feels we are 'aliens' in this world. This adds to my uncertainty…" **(P8, on help-seeking during COVID-19)**

Indian society has been marked with discriminative social reactions toward transgender people, who are often the subject of ridicule and fun. Conforming to social acceptance, many of them reluctantly assume the "social roles" of sexually seductive behavior with the opposite sex, begging, or petty crimes. Talwar (28) in *The Third Sex and Human Rights* discusses the deprivation of human rights, poverty, and violence inflicted upon this community in India. Besides financial constraints and unemployment, many individuals from the Hijra community are forced to pursue a living through extortion, begging, exhibitionism, and sex work (an activity often socially stereotyped as associated with transgender individuals). The violence directed against transgender people has been widespread

TABLE 1 | The socio-demographics of participants.

Participant	Age	Age at transition	Socio-economic status	Sexual orientation	Living arrangement	Education	Job	Old-age pension
P1	64	18	Low	Bisexual	With son	Not formally educated	Unemployed	No
P2	60	22	Low	Gay	Alone	Class 10	Works in a shop	No
P3	67	Doesn't recall	Middle	Lesbian	Living with a partner	Graduate	Retired	Yes
P4	63	20	Low	Lesbian	With daughter	Class 4	Domestic help	No
P5	70	Doesn't recall	Middle	Queer	In old-age home	Class 6	Unemployed	No
P6	75	Doesn't recall	Low	Gay	With friends	Not formally educated	Vegetable vendor	No
P7	60	28	Middle	Bisexual	With partner	Class 12	Private company	No
P8	69	23	Low	Lesbian	Temporary shelters	Not formally educated	Begging	No
P9	65	Doesn't recall	Middle	Bisexual	Joint family	Graduate	Retired	Yes
P10	71	30	Low	Didn't disclose	Alone	Class 8	Manual labor	No

and often brutal, and is documented as taking place in their places of residence, prisons, police stations, and other public spaces (29). Boggs et al. (30), in their focus group discussions of 73 older LGBTQ participants, mentioned the intersection of "ageism" and "cisgenderism" as an under-recognized barrier to health, social and legal access. Trans PULSE, an Ontario-wide research study, showed a lack of sensitivity to health care and discrimination in health care access among the transgender population (31). This is more pronounced in a pandemic crisis, as amidst the vulnerability, these participants are also the victims of "othering" that classically forms the "we vs. they" dichotomy. "Othering" is a term used to denote expressions of prejudice based on a "group identity," in this case the "third gender." Social stereotypes help to maintaining and perpetuate this group-based inequality and marginalization, thus depriving a certain "group" of their rights and social privileges (32).

> "See, here she has come again…I have heard this all my life! Now it has increased, and the moment I go to any shop, people start behaving weird and push away. It's as if... I am the source of infection." **(P2, when asked about social reactions during the pandemic)**

> "They were supplying free masks and soaps. I couldn't stand in the queue due to the constant ridicule and mockery that I saw in people. At times I feel… getting the infection is better than facing such insult at this age!" **(P9, discussing the precautionary measures)**

The resultant "minority" stress has been explained in terms of the Health, Stigma, and Discrimination model (33), where facilitators like disasters, societal apathy, and prejudice toward age-related and sexual minorities can eventually led to detrimental psychosocial outcomes during crises (23).

Six participants reported self-stigma, a common finding in the LGBTQ community when they feel guilt about their "sexuality" and social notions that are against them, meaning they are further segregated from the mainstream and adopt their "community customs and rituals" (34). Social attribution theories posit that a constant negative stereotype against a certain individual or group can lead to self-doubt, decreased self-esteem and self-stigma, when that individual or group starts internalizing those "faulty beliefs" and attributes them to their social status (35). This causes further social exclusion and decreased help-seeking, especially during crises, which worsens othering.

> "I have always been seen as 'seductive' in personal and professional circles; I have no idea why! Now I have come to believe that probably my gender is responsible for this… age changes a lot in you… and there are certain 'blames' you cannot take any more at this age." **(P10, on how she was blamed for being "provocative" in public)**

> *"I feel that I am different… I have always felt that way… people passing sexual comments and ridiculing me… that's how we, Hijras live…even in this situation, we need to go out for living…but get threatened by people and police telling we are on 'business'! I get tired of my 'appearance' at times and wish it was different."* **(P4, when asked about livelihood challenges)**

In the above excerpts, participants mentioned social stereotypes against their communities and how they have internalized these misrepresentations over time. While P10 started "believing" the blame attributed to her gender, P4 wished she could change her appearance for the "sake of society." Other transgender individuals in our study also mentioned "reduced self-esteem" and developing a "hatred toward themselves" after constantly battling social injustice and prejudice. The self-stigma generated in an already marginalized community can be further detrimental to their ability to cope during the crisis.

Loneliness, social disconnectedness, and depression were reported by 8 out of 10 participants. Major factors that have influenced these feelings include restricted travel, physical distancing, and difficulties in using and accessing technology

TABLE 2 | Categories, themes, and verbal excerpts of the analysis.

Super-arching category	Subordinate themes	Verbal excerpts from participants
Marginalization	"Second priority" in health care	*"Be it medicine shops or checkups at clinics, the moment they saw me they told me to wait or come later."* (P2)
	Stigma & discrimination (including self-stigma)	*"I have faced this throughout life. Now people look at me in a way as if I am responsible for the virus."* *"Masks help not only against the virus Saheb but also to protect my identity."*
	Social disconnection from peers	*"Amidst all these fears of infection, I wish we could meet and spent some time singing as we used to. But can't travel during the lockdown."*
	Perceived loss of dignity	*"People around have never really liked me. But now they ridicule me…"* *"Who likes to be treated as an object. I am simply dictated terms by the police on the road and my old-age home manager."*
Dual burden of "Age and Gender"	Prominence of ageism	*"I hear things like… you people won't change even when you are old! Why Saheb, what have we done!"* *"My family and neighbors don't want to come near me as I am old and probably have got more of the infection…"*
	Deprived psychosexual needs	*"Intimacy with my partner is a major comfort. But he goes for work. So, we don't feel comfortable making love…"*
	"Cornered" in their communities	*"I am mostly not able to join the group due to age. Now even when they discuss any health-related matters among themselves, I am left out."*
Multi-faceted "Survival threats"	Physiological	*"When they distributed masks, they did not give me. I already stay in an overcrowded room with three others."* *"I wanted to get tested, but they told me to get HIV testing!"*
	Psychological	*"I feel really lonely and sad. My partner is far away. And people don't talk to me over here."*
	Financial	*"I had a small job in a shop. That has been closed due to lockdown. No one wants to offer me any financial help. I don't want to resort to begging like others."* *"The Baadhaai (baby-showering) ceremonies are our main source of bread. We are not being allowed anywhere."*
Coping	Social rituals and pride celebrations	*"I know about this place where all of us gather and celebrate. Someone told me it is this time of the year. I wish it could have happened."* *"I am looking forward to the online Pride festivals. It will give me a lot of support in this lockdown."*
	Acceptance of the discomfort of belonging to the "third gender"	*"What the pandemic taught me was that the virus doesn't discriminate. I finally will at peace with my identity."*
	Spirituality	*"My prayers and faith in God kept me moving all these days, even when I had to beg for a living. Never knew it will be so helpful now!"*
	Hope	*"I have seen worst times, Saheb. I am hopeful this, too, shall pass!"* *"I believe in tomorrow. The rest of my days, I want to live with that belief. It helps in this uncertainty."*
Unmet needs	Knowledge, attitude, practice (KAP) related to COVID-19	*"I only know that old people are dying. Do I need to get tested? Some medicine is being recommended. Should I take it?"* *"Someone was explaining something in the local language in a meeting about COVID. They didn't let me in!"*
	Social inclusion	*"I stay alone. Every day with a fear that I will get the infection and die without treatment. I wish I could share this with others."*
	Mental health care	*"Every time I have gone to the doctor, people like you when they grow old, these things happen. Nobody asks or understands why I get sad and anxious!"*
	The audience for their "voices"	*"I don't know after how many days, someone asked this Budda (old man), about his difficulties!"* *"You really want to know how we feel, or it is just for your research?"*

(in 5 participants). Even though digital connectivity and telemedicine have repeatedly been used during the pandemic, they can be real challenges in lower and middle-income (LAMI) countries like India, where technology still fails to reach the masses, especially in the rural areas and minorities. Furthermore, age, with its sensory and cognitive limitations and frailty, can impair the appropriate use of video-connections with loved ones, which can lead to further loneliness and social segregation. Berger (36), in his classic text "Gay and Gray," describes cases of homosexual and transgender men whose narratives reveal loneliness, existential crisis, and "age" as an acceptance of the age-old discrimination that they face. The "discomfort with their gender" that some participants experienced during most of their lives due to their "transgender" identity seemed more acceptable during the pandemic, as they navigated these adversities. Some attributed these problems to age, others to wisdom, while others felt that "suffering" due to COVID-19 has made them more resilient.

> "All throughout I wished I was like the 'others'! My gender kept bothering me like a curse from birth. Living through so much of difficult times, it mattered little… Everyone was suffering and dying the same way. I don't know when, but I had stopped wanting to be 'different'!" **(P2, while discussing discomfort with the third gender)**

> *"Sometimes I feel this was needed… I witnessed the death of my friends, colleagues… there is so much suffering all around… I somehow feel stronger, more ready to face the world…"* **(P10, on the effect of the outbreak on coping)**

> *"Age brings in experiences, wisdom, acceptance, and much more… all my life I have faced hardships, even in daily existence… it's tougher times now, deaths, medicines, hospitalizations all around… with my age anyway I have nothing to lose… so I try to make maximum out of my life now, irrespective of everything… I tell others the same…"* **(P5, when asked about suggestions for others in the old-age home)**

Psychotherapy for the elderly often uses such lived experiences, building upon notions of resilience and post-traumatic growth after disasters/crises, based on existential and humanistic approaches (37). Earlier studies have mentioned age and experience as enabling factors for community inclusion (38). However, our participants felt "othered" in their community, which forms a significant part of the societal stigma that is potentially harmful to coping and mental health.

> "They say people who are living on the streets are being targeted for having the infection. I have the additional issue of being a Hijra. They were almost forcibly admitting me to the hospital… even without testing…" **(P1, when asked about the challenges they face)**

There is also a common myth that the elderly do not have sexual needs, and these ideas were challenged by P4 and P7, who mentioned that they "cannot even experience intimacy to soothe us during difficult times as they (their partners) go out for work, and the risk of infection" is present. The pandemic's effect on psychosexual health and deprivation of "social touch" remains largely unspoken but is critically detrimental to well-being. As COVID-19 is a highly contagious infection, this has led to doubts relating to sexual transmission and a definitive fear of intimacy. Sexual relationships and sexual well-being can be affected, irrespective of age or gender specifications (39).

> "Our relationship and closeness have literally formed my core strength in the worst of times. He goes out, so we sleep in separate rooms… the infection has created an emotional wall between us…" **(P3, on relationships during COVID-19)**

> *"Intimacy with my partner is a major comfort. But he goes for work. So, we don't feel comfortable making love… It makes me weak and vulnerable!"* **(P7, on how the crisis has affected coping)**

It is important to note here that resilience and strength emerging from their relationships and intimacy served as "viable supports" during the pandemic crisis. This is in contrast to models of psychological resilience being conceptualized as "personal internal attributes" based on Western mainstream psychology schools (40). The authors further emphasized the "social functioning" that can be vital for coping and in developing problem-solving approaches during the crisis. In large-scale social threats like the COVID-19 pandemic, the need for social enmeshment and emotional bonding with their partners fostered love, care, and support, which were reflected in our participants.

Disasters in the Transgender Elderly as "Survival Threats"

Overall, the above factors together generated physiological, emotional, and financial pressures for participants. Losing priority and stigma kept them at a "backfoot" for health care, their voices unheard, and the uncertainty of the COVID-19 situation was amplified due to the double fear of "aging" and "being deprived." Many of the participants reported mentioning that "old people are dying fast," which they encountered in the media, with detailed information about morbidities that added to their fear. Besides, it is essential to understand that frequent comorbidity of Human Immunodeficiency Virus (HIV), diabetes, and other chronic medical conditions, compounded by neglect, often leads to persistent immunocompromised states in transgender people. These, along with age, can form the two most crucial risk factors for morbidity and fatality in COVID-19 (41). Associated mental illness and substance abuse often worsen the situation. Seven of our participants mentioned that their suffering lacked the audience, though the community was superficially concerned. It made them feel "invisible to society," resonating with "how they have always felt." Empathy and compassion were not sensed by the people around them, and even financial support was difficult to access. In the absence of employment and social benefits (such as a pension) for most of them, this made the situation even more dire.

> "My neighbors would not want to interact with me. I was old, staying alone, and even basic needs were difficult… people knew that, but I hardly even got anyone asking how I am doing…"
> **(P2, while discussing the unmet needs)**

> "'Take care' is the maximum assurance that I have received! Nobody bothered about how I needed to care for myself staying on the streets…Even begging didn't help."
> **(P8, on social indifference to suffering)**

There has been a traditional association between the LGBTQ group and disasters. McKinnon et al. (42) mentioned how the voices of this community were largely under-represented by mainstream media during the Brisbane floods or the Christchurch earthquake of 2011. There was mention of similar marginalization during the Queensland floods (43). The same authors have also written about the "Queer domicide" wherein homelessness was a significant offshoot of natural disasters in gender minorities as the administrative policies that respond to these crises remained neutral or respond to the needs of the perceived status quo (44). The *Higashinihon Dai-Shinsai* (The Great Japan Disaster) of 2011, which began with a tsunami and earthquake, led to a lack of shelters, mass stigma, bullying, violence, and social exclusion for the Japanese LGBTQ community, effects that have been vastly under-represented in the literature (45). Systematic research and policies related to the plight of the LGBTQ population in India during disasters also lack standardization. The present study recommends that LGBT rights are incorporated into and allowed for in disaster ethics and disaster preparedness planning. The literature on this subject also documents that many older transgender adults do not have fixed jobs and are dependent on their families, homes, and communities, which decreases their autonomy and increases their risk of abuse. The homeless individual who took part in this study faces overcrowding, lack of quarantine facilities, and proper shelters, an experience shared by thousands of migrants all across India during the lockdown. Their age, gender, and the social crisis are a "triple blow" to their present condition.

> "People usually help seniors, don't they! Am I any different because of my gender? Can't I expect the same help from others who are much younger than me…"
> **(P5, on being an "invisible sufferer" during the pandemic)**

> "There was no respect for age or humanity… how can I expect help!"
> **(P7, while talking about distress)**

While these were their vulnerabilities, we will now discuss how transgender individuals have navigated the crisis and the barriers they face.

Coping, Resilience, and Barriers to Care

Five participants in this study were aware of the Pride movement and ongoing Pride month. Two knew that there was some celebration scheduled for their community at this point of the year, and three were unaware. Pride celebrations emerged after the Stone Wall riots in 1969, and mark the ongoing protest and expression of the social integrity of the LGBTQ community (46). Around 220 pride festivals have been canceled across the world due to the COVID-19 situation, and even though some organizations held events online, there was limited impact and access (47). In India, elderly participation in the Pride Movement has always been scarce (48), which creates a situation of "seclusion within seclusion." The participants looked forward to a regular get-together of their community as a way of coping during the ongoing crisis. While most did not identify the festival with a "name," they were aware of celebrations being canceled due to the pandemic situation. Even local festivities within their community were compromised, which affected their social support. This is a notable reflection of emotional expression in the Indian socio-cultural context. While discussing "gender, depression and emotion," Davar (49) examines Indian folk stories and contrasts the "collective" emotional expressions of Indians rather than the usual homogenized view of singularity. This collectivism was more prominent in the marginalized sector of the population that we studied.

> "I know about this place where all of us gather and celebrate. Someone told me it is this time of the year. I wish it could have happened."
> **(P3, while discussing Pride celebrations during a pandemic)**

> "I don't know too much about it and what they call [it]. But in our community, we have small celebrations, cooking, singing, and all… nobody dared to do all these… it will lead to more trouble in society, as such we are always blamed…"
> **(P8, when asked about festivities in the community)**

Spirituality and hope emerged as essential themes in seven and five participants, respectively. Ross et al. (38), while studying a group of transgender individuals, mentions that "personal development" and optimism are essential factors in building resilience, even though the study subjects were not older adults. Spirituality and hope for the future play an essential role in coping in our study subjects, forming a part of their "self-identity."

> "I used to go to Hanumanji's temple whenever possible, irrespective of all odds. It really helped. There was so much peace there…"
> **(P3, while talking about religious practices)**

> "God or not, there is a force I believe in and worship. Can't explain! But that gives me hope…"
> **(P10, when asked about spirituality and coping)**

The need to identify oneself with society for perceived self-worth, irrespective of disabilities, formed an essential aspect of the community health care needs of the elderly in a systematic review done by Holm and Severinsson (50). A low level of spirituality has been associated with a poor ability to cope emotionally and higher rates of depression in Indian older adults (51).

All the participants agreed that they lacked awareness about the necessary measures and ongoing situation about the pandemic. Only two followed social media updates, and apart from the numbers projected in the newspapers, they had questions about safety and testing for COVID-19. Three were increasingly dependent on their families while four others worked in shops as manual laborers and domestic help and lost working days during the lockdown. Salary cuts and unemployment have been widespread during the COVID-19 pandemic. Data from the PSB Research group in the United States showed that 30 percent of the LGBTQ community had their working hours reduced and salary decreased, compared to 22 percent of the general population (52). This creates a sense of mistrust and anger at the administration for the participants. Media reports mention increased socio-economic deprivation for the Indian LGBTQ community during the lockdown, a rise in abuse at the hands of their own families, and social harassment, which adds to the pre-existing burden caused by the pandemic (53).

All of the study participants agreed that they felt like an "outcast" even when they repeatedly heard people saying "we are in this together." Eight of them reported lacking an audience for their problems, which was why they welcomed the interview.

> "Thanks to your research that you are asking… I felt good sharing these issues with someone, very few bother… already old, now more of a burden to the society!" **(P4, toward the end of the interview)**
>
> "Media arrives and raises thousands of questions when needed. Nothing changes! Maybe nothing will, but at least you asked…" **(P3, while reflecting on the present study)**

Social integrity and support are essential components in creating resilience during widespread disasters. These needs were not met in most participants. To summarize, the "dual burden of ageism and third gender" along with marginalizing factors decreased their access to health care and created physically unsafe and emotionally insecure environments, which along with "dependence" and "poor awareness" increased their physical and psychosocial vulnerabilities to the COVID-19 situation.

Our study had a small sample size and is subject to the usual limitations of qualitative research, such as subjective interpretation and reduced generalizability**.** The ongoing pandemic crisis could also have exaggerated participant responses to questions related to their suffering. However, in a marginalized sector of the population, each voice matters, and our study benefits from a rigorous methodology, analysis, and reflecting and providing a platform for these usually "unheard and invisible" voices. As requested by the participants, the researchers present these "narratives" as representations and accounts of social suffering, rather than mere data.

CONCLUSION

India is aging fast, as are the increasing number of gender minorities. Guidance on the care of the elderly by the WHO as well as the Ministry of Health and Family Welfare (MoHFw) in India are comprehensive, but unfortunately fail to mention the already neglected experiences of the transgender community (54, 55). Wang et al. (41) have recently appealed to the Government and private sector to consider the holistic care of transgender groups, advocating community-based screening for their needs, online consultations, and a reshaping of policies that accommodates their health-care needs and enhances access. Associated with this are HIV management and harm-reduction techniques for substance abuse in this population during the pandemic. *Aging with Pride: The National Health, Aging and Sexuality/Gender* (NHAS) study has proposed the "Health Equity Promotion" model for older transgender adults, based on a bio-psychosocial understanding of their unique vulnerabilities (56). The Coronavirus Preparedness and Response Supplemental Appropriations Act and The Coronavirus Aid, Relief, and Economic Security (CARES) Act passed by the U.S. Congress during the pandemic are inclusive of LGBTQ communities (57). Such models could be adopted by the Indian Government, especially with the numbers of this population increasing. Our study sample was small, but the rich data from the participants, the thematic saturation, and the holistic representation from various backgrounds strengthened the study. These results indicate that the needs of gender minorities are still largely unmet, especially in older adults. However, these findings need to be interpreted in the Indian socio-cultural context. The Indian Pandemic Act of 1897, needs to be overhauled to consider the needs of both seniors and the transgender population, which could help preparedness for similar crises in the future. Banerjee and Nair (23) have discussed the different "vulnerability areas" of transgender individuals during the COVID-19 crisis and suggested interventions to mitigate physiological risks, social discrimination, sexual stigma, substance abuse, and to preserve psychological well-being, economic stability, sexual health, and gender-based equality. The authors highlight the unique needs of the elderly LGBTQ population and foreground the need to prevent ageism, stigma, and appropriate social rehabilitation measures. The under-representation of older adults in India's LGBTQ movements has been a growing concern in recent years, particularly in terms of their civil rights and socio-economic security. Care homes are often not suited to their needs and can turn into potential sites of abuse. Transgender individuals are not immune to the frailty, cognitive, and sensory deficits of aging and will need similar care. This sensitivity needs to be emphasized at all levels, by active collaboration between physicians, human rights activists, the media, and government administration (58). As the pandemic is still in its early period, the coming months will be crucial for undertaking more systematic research into lived experiences and risks due to COVID-19, apart from focusing on testing and symptom-based management. Similarly, our collective responsibility is to be aware of the unmet needs of this community in terms of social inclusion, care, and support rather than discrimination. Only then can their health emerge as a priority and not an option.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by JSS Academy of Higher Education & Research, JSS University, Mysuru, Karnataka, India. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DB was involved in data curation, analysis, and drafting of the manuscript. TSSR was responsible for designing the study, data collection, reviewing, and editing the manuscript. Both authors conceived the study, read and agreed on the final version of the paper.

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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.

APPENDIX

The Key Questions of the Semi-structured Interview Schedule

- What difference did you face between the pre-pandemic and the COVID-19 times?
- How do you think the pandemic has affected your mental well-being?
- How do you think your age affected your perceptions related to the current crisis?
- What challenges did you face due to the pandemic situation?
- What type of support have you received?
- What do you think could have been done to make your experiences better during this time?
- What were the difficulties in seeking psychological care during the pandemic?
- What were your unmet needs?
- How do you think the COVID-19 situation might affect your future?
- What message would you like to provide for the elderly from the same community?

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Perceptions, Experiences, and Challenges of Physicians Involved in Dementia Care During the COVID-19 Lockdown in India: A Qualitative Study

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Introduction: With 5.3 million people living with dementia in India and the pandemic wreaking havoc, dementia care has faced unique challenges during the outbreak, with reduced healthcare access, travel restriction, long-term lockdown and fear of hospitalization. We explored the experiences and barriers faced by the physicians involved in dementia care during the lockdown period.

Methods: A qualitative approach was used with purposive sampling. After an initial pilot, 148 physicians were included in the study. They were virtually interviewed in-depth based on a pre-designed semi-structured questionnaire, in areas related to tele-consultations, attributes related to dementia care, challenges faced and way forward. Interviews were recorded, transcribed and thematically analyzed using Nvivo-10 software. Triangulation, peer debriefing and respondent validation were used to ensure rigor.

Results: The overarching categories that emerged were "Tele-medicine as the future of dementia care in India," "people living with dementia being uniquely susceptible to the pandemic with a triple burden of: *age, ageism and lack of autonomy*" and "markedly reduced healthcare access in this population with significant mental health burden of caregivers." The experiences of the physicians were categorized into their challenges during the lockdown period and perceptions related to specific facets of dementia care during the crisis. The general physicians expressed special "unmet needs" of dementia-specific training and specialist collaboration. Most of the participants perceived ambiguity related to the newly released telepsychiatry guidelines.

Conclusion: Resource constraints and pandemic burden are currently high. This study looks at the "voices" of those actively providing dementia care during the ongoing crisis and to the best of our knowledge, is the first one from India to do so. Concurring with their experiences, PwD and their families are exposed to multiple vulnerabilities during COVID-19, need tailored care, especially at the primary healthcare level which includes general physicians. These relevant "voices" are discussed in light of the new tele-psychiatry guidelines and further optimization of dementia care in an aging India.

Keywords: dementia care, COVID-19, lockdown, healthcare workers, experiences, India

INTRODUCTION

Older adults have been one of the most vulnerable populations during the Coronavirus 2019 (COVID-19) pandemic. Besides being exposed to the physiological risks of infection and increased fatality, it is further compounded by frailty, medical comorbidities, polypharmacy and pre-existing pulmonary complications (1). Furthermore, they are also prone to the persistent psychosocial offshoots of the pandemic including grief, isolation, loneliness, depression, anxiety and sleep disturbances (2). Among the elderly, people living with dementia (PwD) have been especially affected during the pandemic and consequent lockdown, with a multitude of factors contributing to the same. Lack of cognitive stimulation, mobility restriction, isolation, worsening of behavioral and psychological symptoms of dementia (BPSD), enhanced confusional states, increased chances of delirium, reduced adherence to precautionary measures, increased risks of abuse and institutionalization are some of the many factors contributing to the worsening of their overall health and cognitive status, and thus the consequent frailty (3, 4). The world is aging fast and it is projected that 1 in 5 people from the low and middle-income countries (LMIC) are going to be above 60 years of age. With an increase in older adults, there would be a proportionate increase in dementia prevalence, with a 5–7% projected rise in India and China. The absolute number of PwD is estimated to double by 2030, and treble by 2050, especially in the sub-continent (5). With a present 5.3 million dementia cases in the country, huge mental health gap (mhGAP), inadequate penetration of telepsychiatry and prolonged lockdown and economic downfall due to COVID-19, India has been facing unique challenges with dementia care. Marginalization, human rights deprivation, reduced healthcare access, increased symptoms of BPSD, social segregation and abuse have been reported sporadically among PwD in India during the last 6 months (6, 7). Systematic research in this area is still lacking. With a paradigm shift of mental healthcare delivery to virtual platforms, it is vital to understand the experiences and challenges faced by the nation's physicians while providing dementia care.

In general, physicians and other healthcare workers have faced unique plight during the pandemic. Studies have shown increase in stress, burnout, absenteeism, and stigma especially among the frontline workers (8, 9). Increased rates of depression, anxiety, sleep disturbances and post-traumatic stress have been reported among the physicians in a recent systematic review, especially in the developing countries with limited resources and increased COVID-19 burden (10). India is one of the low and middle-income countries (LMIC) that has one physician per 1,456 people as compared to the 1:1,000 ratio recommended by the World Health Organization (WHO) (11). It is also one of the countries with highest pandemic case load and due to the heterogeneity of the population, physicians in all specialties have faced significant challenges in delivery of adequate healthcare services during these crisis times. Even though differences have existed between the Indian Medical Association (IMA) and the Indian Government related to the COVID-19 policies for physicians, the administration has attempted several constructive steps in this regard (12). Healthcare resource building, ensuring medical safety for the physicians, staffing guidelines and timely payments, training in tele-consultations and round-the-clock psychological support are some of these measures. The Ministry of Health and Family Welfare (MoHFw), Government of India has mentioned about training guides for all level of healthcare workers, salary insurance, specific protocols for management of COVID-19 cases, testing and rational use of Personal Protective Equipment (PPE) in its officially released "measures" to ensure safety of healthcare workers (13). Nevertheless, systematic assessment of their daily challenges, taking into account their perspectives while policymaking and evaluating their psychosocial distress are sub-optimal that affect the implementation of the above-mentioned measures. The rise in violence, stigma, discrimination and dissatisfaction among the medical fraternity and prevalent misinformation in the media resonate the same (12). Gauging the situation, the WHO has collaborated with the Indian Government in training health workers and paramilitary forces in pandemic-specific measures using training of trainers (ToT) approach. The covered areas are epidemiology of COVID-19, bio-medical waste management, triage, mock drills, management of cases and peer-support for emotional well-being (14). While dealing with neurocognitive disorders itself is a challenging task during the pandemic, physicians in geriatric care face this "dual burden" of personal career-related adversities as well as the difficulties in caring for PwD during the pandemic-crisis. With this in the background, this study attempted to explore the "voices" of health care workers (HCW) at multiple sites in India with relation to consultations and care for PwD and their families.

METHODS

The study adopted a qualitative design with a constructivist approach and was approved by the JSSAHER Institutional Ethics Committee (JSSAHER University, Mysore) in March 2020. A "constructivist" paradigm as opposed to a positivist approach enables the researcher to stay "hypothesis-free" and conduct the work with the possibility of "multiple truths." This is especially important in studying public perceptions as they cannot be statistically scaled or quantified and hence an *a-priori* hypothesis will be redundant in this case. It also helps in building an empathetic and collaborative relationship with the study participants, which is vital in qualitative methodology (15). A semi-structured interview guide was designed comprising of open-ended questions based on detailed discussion among the researchers, their clinical experiences related to the ongoing challenges of dementia care and existing literature on the challenges of HCW. It was piloted on eight participants initially and subsequently refined. Using professional connections and the directory available from the Indian Psychiatric Society (IPS), the physicians were contacted through email. Both snowballing and purposive sampling were used. The initial email asked if the particular physician was involved in consulting PwD during the lockdown period and were providing virtual consultations as well. These two conditions were necessary for inclusion in the study. Also, the mail explained the objectives and purpose of their study and sought their electronic informed consent. All participants provided explicit consent for participation in the study. The researchers ensured that the participation is well-distributed among the specialties (psychiatrists, neurologists, general physicians) who are involved in dementia care, the area and set-up of practice, age, gender and years of experience. This was again obtained through purposive and representative sampling. Physicians involved in long-term dementia care facilities were excluded as the patient profile, consultation patterns and physician engagement would have a totally different profile in that case and could potentially dilute the overall study results.

Though initially aimed at a multi-site Indian study, this particular paper looks at participants from various states of Southern India. The study was conducted between April–June 2020 when India was undergoing complete lockdown due to COVID-19. The actual interview was held virtually over Zoom/Google Meet over 1–3 sessions after obtaining consent. The first author, who was trained and certified in qualitative research methodology, conducted the interviews in Hindi and English. Each session lasted for an average of 102 ± 10.5 min. The semi-structured interview guide was used with open-ended probes, prompts and regular memo writing which would be later used for analysis (**Box 1**). The questions were aimed to explore their experiences, perceptions, and challenges related to dementia care consultations, with special emphasis on virtual service delivery. The interviews were recorded with consent and the responses transcribed and translated verbatim with back-translation with a researcher with bi-linguistic proficiency.

BOX 1 | Semi-structured interview guide used for the study.

- How has dementia care been different from you during the COVID-19 related lockdown?
- How do you feel about tele-consultation for people living with dementia and their caregivers?
- Please describe the facilitators and barriers related to virtual consultations for dementia care.
- How were the challenges in dementia consultations different from the pre-COVID times?
- What were the concerns expressed by people with dementia and their caregivers during your consultations? How did you manage them during the lockdown times?
- How has clinical and psychosocial concerns in dementia changed during the ongoing crisis?
- How has your role as a physician involved in dementia care changed due to the pandemic situations?
- What have your personal challenges been? *(not included in the study)*
- Considering the uncertainties of the pandemic, how do you foresee dementia care in the post-pandemic aftermath: please describe.

For the general physicians

- What were the challenges in "primary dementia care" that you have faced and what were your perceived "unmet needs"?
- How has primary dementia care been different during COVID-19 times?
- How do you think your consultations for people living with dementia were different from specialist consultations?

Analysis

Charmaz's applied thematic analysis was used for the study (16). Data from the participants was generated through the above-mentioned semi-structured interview guide. Each interview was read word-by-word and coded (initial codes followed by clustering of codes to form "focused codes" and finally the mutual relationship between codes called axial coding). The coding was done by two independent researchers (first and fourth authors), who are trained in qualitative research. This was accompanied by a process of memo analysis and constant comparison back-and-forth with the coded data and the original transcripts for the rigor. The responses were analyzed in context and framework and the final hierarchy of themes and categories were reached only after rigorous discussion and brainstorming by all the researchers. Considering the voluminous amount of qualitative data, NVivo 10 software was used to organize and aid the analysis. However, each dataset was still manually coded for "immersion in data" and context which are important factors in such analysis. Nvivo 10 necessarily helps in storage, codification, organization and categorization of the qualitative data. It also facilitates the analysis, but the steps and process of coding and constant comparison have to be manual and can only be assisted by the software. Thematic saturation was achieved with 138 participants, however, 10 more were interviewed for super-saturation. After the initial invitation, 45 physicians hadn't responded and 23 did not consent for the study. Among the latter, majority mentioned lack of time while some others did not provide a reason for unwillingness to participate. Rigor was enhanced by triangulation in analysis, peer debriefing and respondent validation (where the initial results after the first round of analysis were presented to 50% of the sample and their inputs were sought about whether the results represented their "voices") (17). The entire process of analysis was completed in about 2 months.

RESULTS

The terms physicians, general physicians (GPs) and HCW have been used interchangeably. The socio-demographics of the participants and their responses toward the interview are presented in **Table 1**. The mean age of the participants was 39.2 ± 5.3 years and the mean years of experience was 10.2 ± 2.4. The main categories and themes are summarized in **Table 2**. The results are divided mainly into the challenges faced related to dementia-case consultations during the lockdown, their experiences about various attributes of dementia care during that period, specific perceptions related to virtual (tele/video) service delivery and finally the specific themes that emerged related to the GPs. The authors agree that the GPs form a heterogeneous population and are bound to have different requirements and challenges with regards to dementia care, irrespective of the pandemic. However, considering the scarcity of specialist services in a developing country like India, GPs form the backbone of health care attending to most first consultations of neuropsychiatric disorders. Hence, the authors included them in the study which wanted to explore the experiences of any physicians dealing with PwD. Nevertheless, the detailed results

TABLE 1 | Socio-demographics of the study participants ($n = 148$).

Attribute	Types	No. (%)
States	Karnataka	68 (45.9)
	Tamil Nadu	31 (20.9)
	Andhra Pradesh	20 (13.5)
	Kerala	29 (19.5)
Specialty	Psychiatrists	66 (41.9)
	Neurologists	32 (21.6)
	General Physicians	50 (33.7)
Age (years)	25–35	49 (33.1)
	35–45	56 (37.8)
	45–55	25 (16.9)
	>55	18 (12.2)
Gender	Male	80 (54.0)
	Female	68 (46.0)
Area of practice	Urban	72 (48.6)
	Semi-urban	30 (20.3)
	Rural	46 (31.1)
Set-up of practice	Government	53 (35.8)
	Private (solo)	75 (50.7)
	Private (organization)	20 (13.5)
Experience (years)	0–5	23 (15.5)
	5–10	52 (35.1)
	>10 years	73 (49.3)
Modes of consultation during the lockdown	Only telephonic	7 (4.7)
	Only video	21 (14.1)
	Both telephonic and video	80 (54.1)
	Virtual and in-person	40 (27.0)
Opinion about the study interview	Useful	115 (77.7)
	Not useful	10 (6.7)
	Neutral	15 (10.1)
	Preferred not to say	8 (5.4)

related to the experiences of the GPs, their challenges and unmet needs will be presented in a separate paper. The overarching themes across all three specialties and irrespective of any other attributes included the recognition of PwD to have a "dual" vulnerability during the COVID-19 related crisis, concerns about their reduced access to care and perceived utility of "tele-medicine" as a promising platform for dementia care even in the post-pandemic aftermath. Most of the participant physicians shared their own "stress" as well during the lockdown crisis (though that was not a part of the study), welcomed the interview and felt that sharing their experiences especially related to dementia care was cathartic for them as well.

The verbatim excerpts supporting the generated themes are presented below (**Table 2**). Due to space constraints, only the pertinent ones are included in the manuscript. The detailed responses from the study are available from the authors on request.

DISCUSSION

Tele-Medicine for Dementia Care: Pros and Caveats

Telemedicine aims at providing health care at distance to vouchsafe the interest of advancing the health of individuals and their communities (18). In a socio-culturally diverse and populated nation like India, virtual consultations can go a long way in reducing stigma, travel costs and enhancing healthcare access. This is in sync with the increased internet coverage in rural areas over the last decade and tripled smartphone usage during the pandemic (19). As highlighted in this study, physicians found themselves at a critical crossroads with tele-dementia care during the lockdown. This assumes a renewed importance for maintenance treatment in PwD, monitoring, management of BPSD and caregiver education, especially with the increased risk of complications and infection following hospitalization during the pandemic. Soares et al. (20) while discussing telecare for BPSD during COVID-19, describe it as a "viable tool" for monitoring clinical stability, however, cautions about cost, resistance to change, age of the patient, and technical challenges. Implementing remote memory clinics has also been recommended to help screening, digital cognitive training, pragmatic benefits of which can outlast the pandemic (21). HCP in this study rather admitted technical ease in consultations but were worried about the virtual assessments. The PwD may be technologically challenged, not comfortable with screen usage, compromised cognition may be further deteriorated due to the above. Vision and hearing impairment may compound the above leading to errors in assessment and compliance with instructions. Challenges in the cognitive assessment in general in the Indian population get more challenging virtually due to the multitude of cultural practices and vernacular languages, which predilect faulty assessment due to the dearth of language-sensitive assessment scales (22). Further, BPSD made cross-sectional assessments and monitoring for symptomatic severity problematic according to the physicians, leading to inadequate titration of psychotropic dosages.

Along similar lines, the assessment of physical health status was mentioned by many as a hurdle, especially in non-AD and those with medical co-morbidities. This increased the frequency of adverse effects due to psychotropic use in patients with dementia. The problem of patient's autonomy was a major "highlight" based on the current rights-based model and person-centered approach. According to our study, physicians were concerned about tele-care vicariously promoting proxy consultations, which mostly the patient's voices staying "unheard." This can have a significant impact on dementia care during an already existing biopsychosocial crisis.

The newly released telemedicine and telepsychiatry guidelines 2020 (23), though helpful standards are still a long way from translating into actual clinical practice. The lack of awareness thereof and legal implications consequent to violation of the same is a harsh reality, as reflected by the "perceptions" in our study. Most anti-dementia drugs and anti-psychotics come in the "list B" of these guidelines and can only be given on follow-ups, which leads to difficulty in decision-making during the first consults (23). In the guidelines, a tele follow-up consultation is defined as *"patient consulting with the same psychiatrist within 6 months of his/her previous in-person consultation"* and the present consultation is for the continuation of care of the same clinical condition. Pragmatically, this is not always possible due to the

TABLE 2 | Categories and themes from the analysis (*n* = 148).

Categories	Themes (% response)	Verbal excerpts of participants
Challenges	• Virtual cognitive assessment in PwD (91%) • Worsening of behavioral and cognitive problems (90%) • Fear and stigma about in-person care (62%) • Availability of medications (43%) • Lack of patient advocacy: the establishment of therapeutic rapport (95%)	• *"It was indeed very difficult to apply scales over phone/video. The connection kept breaking and the patient could hardly comprehend what is being asked for"* • *"Most patients felt "locked inside" their rooms in absence of any stimulation and their agitation increased as well as memory disturbances"* • *"In most districts memantine and psychotropics were not available. Even though unmanageable at home, the family was scared of getting her admitted"* • *"I rarely spoke to the patient. Most virtual consults were on a proxy. It made engaging the patient all the more difficult"*
Experiences of dementia care during lockdown period	• Overuse of psychotropics to control BPSD (72%) • Reduction of autonomy and self-report (88%) • Perceived abuse from the patients (overt and covert) (69%) • Loneliness and isolation: contributing to behavioral worsening (96%) • Lack of basic amenities and Caregiver burnout/stress (85%)	• *"I found myself in a helpless situation. It was difficult to explain behavioral management to the family. I had to hike up the dose of risperidone multiple times"* • *"She complained of being locked in her room for the fear of getting infected and infecting others. Almost always she was tearful.."* • *"Most of my dementia patients are having increased depression, anxiety and sleep disturbances due to the prolonged loneliness and having no one to interact with"* • *"The husband was more concerned about the helper. The paid caregiver was off during the lockdown and he was even afraid to go to the market for daily necessities"*
Perceptions related to the online consultation	• Ambiguity related to the Telemedicine guidelines and legal implications (67%) • Ease of online consultation by the patients and reduced need for hospital visits (52%) • Enhanced access to healthcare for the patient population (69%) • Better maintenance treatment (47%) • Better cross-referral and discussion of other medical conditions (42%) • Ease of delivering basic psychoeducation involving multiple caregivers (62%) • Use of AI for cognitive stimulation (27%)	• *"We know about the guidelines being released. But its being hardly followed. I am not really aware of the legal responsibilities"* • *"Patients keep requesting for physical examination. It's so essential in neuropsychiatry. How will I prescribe without being sure…"* • *"It was easier to discuss with the cardiologist virtually, sometimes on the same platform. The need for physical referrals often delays it"* • *"For those who are doing well, they were quite satisfied with the tele-consultations"* • *"I didn't expect my rural clients to be so comfortable with video consults. They were quite tech-savvy, it surprised me. This is going to be the new norm"* • *"Demonstrating Lumosity/Brainwave/Cogmap was much easier. It was hands-on and certain families could implement it"*
Specific perceptions of the general physicians	• Challenges in assessment and screening of dementia (84%) • Overuse of medications (67%) • Lack of perceived satisfaction with the care delivery (52%) • Better expert referrals and discussion (42%) • Better learning: the need for virtual training (80%)	• *"Dementia has always been a challenge to us, especially early identification and conveying the diagnosis. The COVID times have made it even more difficult"* • *"Virtual consults are easy, but I often don't feel we are doing enough for the clients apart from prescribing the same meds"* • *"It is easier to virtually reach out for the district psychiatrist regularly. It helps a lot in understanding the cases. I hope it stays that way"* • *"Tele-medicine needs to specifically focus on training us in dementia care"*
**Overarching themes	• PwD considered as "especially vulnerable population": Triple burden of *"age, ageism and autonomy"* (95%) • Decreased access to care (91%) • The perceived benefit of telemedicine as a "way of future" for dementia care (90%)	• *"I keep hearing about "vulnerable" populations during the pandemic. Well, these individuals share the burden of age, stigma and memory issues."* • *"People living with dementia are in an impoverished state. They are most deprived of care among all the other psychiatric illnesses"* • *"At least others can express their need, they are sadly not able to "convey" that and are often neglected in this crisis, lonely and isolated…"* • *"It might have its limitations, but the way forward with limited manpower is telemedicine. It's the way to go, especially in developing countries."* • *"Dementia care has a huge potential to be digitalized. Policies, guidelines and training need to be tailored accordingly"*

individual preferences of the patients and professional availability of the physicians. Hence, prescribing medications for dementia patients over telephonic follow-ups was an "ambiguous" area for most psychiatrists. More than half of the neurologists and two-thirds of general physicians in our sample were not aware of the newly released guidelines. One of the possible reasons could have been that the guidelines were released during the time of the present study and were not yet popularized when the interviews were being conducted. Besides, there was also confusion about the applicability of the "same condition for continuation of care" as the initial visit necessary for telephonic follow-up. For example, many patients with dementia opted for review consultations to deal with the associated medical comorbidities or familial issues, which were not directly linked to the cognitive disorder *per se*, for which they had initially consulted. Another important concern raised by our participants was related to the consent of the patients and advanced directives. These tend to emerge as vital issues in dementia care, especially in areas of palliative care, end-of-life management and physician-assisted suicide (24). Though the Telepsychiatry guidelines explicitly discuss about documenting patient's consent, comfort to speak about his/her issues in the presence of family members and following the advanced directives as laid down by the patient: more than 90% of all our participants were not clear about the exact provisions to be followed. However, neither these guidelines nor the Indian Mental Healthcare Act (MHCA), 2017 specifically address the end-of-life concerns and related medico-legal issues in dementia care. The need for multiple online consultations for prescription along with the unavailability of medications during the lockdown in rural pockets, delayed the initiation of treatment. Though some doctors mentioned the use of AI for home-based cognitive exercises, they were limited to the urban areas and were themselves trained in the same. Most of our participants mentioned resistance to the use of "digital interventions" by the caregivers apart from basic consultation. The advocacy of online or digitally-assisted cognitive training and rehabilitation for dementia patients was 67, 31, and 15% in the psychiatrists, neurologists and general physicians in our study, respectively.

In a yin-yang world, the advantages of telemedicine are also many which were resonated in our study. In India, respite centers for PwD are their own homes with primary caregivers usually being family members. Thus, with the advent of tele-medicine the synchronous sensitization and education of the patient along with multiple caregivers including paid attenders, has not only becoming easier but also economical. The community approach of facilitating availability, affordability, accessibility, acceptability, continuity is further enshrined on tele-consultations (25). Tirthalli et al. (26) have rightly pointed out the difficulty in in-person consultations with face-masks, as a mental status examination is much more about "non-verbal cues" rather than clinical interviewing. This need for "unmasking of mind" becomes all the important in dementia care, where the expressive and comprehensive deficits tend to be further compromised "behind the mask." Hence, the scope of tele-consultations. Multiple caregivers could be involved in the "behavioral assessment and analysis" in our study, which helps the treatment of BPSD. This is in line with our participants looking up to telemedicine as the "future of integrated dementia care" that involves easy cross-specialty referral. With a rapidly aging sub-continent with increased dementia-burden and limited, localized specialized resources, tele-care has been viewed by the physicians as a "dual-edged" path.

Dementia Care During the Ongoing Pandemic

The ongoing pandemic has a bidirectional effect on dementia. The chances of cognitive impairment including delirium are higher in patients with COVID-19 who are already having dementia (3). Besides, the lack of understanding, comprehension, following social distancing protocols and hand hygiene predisposes PwD to the outbreak. The social isolation and loneliness perceived by our HCW can potentially worsen both the cognitive symptoms and BPSD (27). Added to that, was the "perceived abuse and prejudice" that was reported by the care-providers and they felt the "virtual medium" as a barrier for appropriate psychosocial interventions in this regard. Abuse and ageism related to dementia have been reported to be on the rise in developing countries, which can further impair the quality of life in PwD (1, 7). During the lockdown restrictions, the loss of autonomy and "coercive care" were also reported by our participants which was often relayed by the caregivers themselves. Similar "helplessness and benevolent restrictive" measures were reported by the caregivers in another qualitative study from India during the COVID-19 situation (28). These can hamper the dyadic relationship between PwD and their caregivers, consequently increasing the vicious cycle of elder abuse (29). Especially, in the Indian context where family members have the onus of caregiving and dementia is considered to be a part of normal aging. The above "red flags" were mentioned as reasons for a delay in diagnosis and help-seeking during the lockdown, with the need to use an inadvertent dose of psychotropics for "immediate relief" of both patients and caregivers, however increasing the risk of adverse effects and potentially against the "first-line" non-pharmacological management guidelines for BPSD (30). "The start low go slow" approach was reported as "better said than done" by our physicians, as medicines with sedative properties were self-titrated by the caregivers. The necessary need for the caregivers to identify signs of deterioration, adverse effects, medical complications were also hampered by the time and bandwidth-limited digital consultations during the lockdown. Due to the rising COVID caseload in India and predominant deaths in the older age-group (31), even patients needing hospitalizations were requested to be managed online, which was a major perceived challenge by the HCW. Significant caregiver burden emerged, mostly due to BPSD, uncertainty, socio-economic issues, and lack of paid caregivers, which have also been reported in studies from other developing countries (32). They could be better dealt with tele-consultations, as per the physicians involved in dementia care. Expectedly, caregiver interventions have the potential to improve the overall health of PwD as well.

Another important factor is the fear of COVID-19 that reduces healthcare access in older adults and their families, as well as builds up stigma for hospital visits. Both these factors can impair dementia care together with the imbalanced healthcare resource allocation in many countries. The physicians in our study reported difficulty in maintaining in-person appointments with significantly reduced compliance even when the out-patient services were running. Similar findings have been reported from Italy by Spalletta et al. (33) where 66.7 and 77.4% of patients had missed out on their first and follow-up visits, respectively, during the first wave of the pandemic, mainly due to the administrative restrictive measures imposed to curb the viral spread. The authors highlighted enhanced access of healthcare by PwD and their caregivers as a "compelling priority" to prevent burden of the gradually re-opening healthcare clinics. Van Jaarsveld (34) mentions about the "digital divide" that has impacted the elderly population and their healthcare system the most and focuses on digital literacy as an important facilitating tool for optimal utilization of tele-medicine services. The same was resonated by most of our physicians supporting digital-training of all stakeholders involved in dementia care (patients, caregivers, healthcare workers, and administrators) and highlighting the importance of digital health-education to improve public awareness. Service delivery and resource allocation for dementia care were also concerns raised by the participants. Decreased community support, primary healthcare facilities and social networking were reported among Spanish older adults in a recent study (35). Triage during pandemic care, especially critical care beds and ventilators, tend to be vital, more so in settings with limited resources. This assumes paramount importance in older adults, who are more susceptible to both mortality and morbidity due to COVID-19. A cross-sectional online survey done in Canadian physicians reported "presence of dementia" and likelihood of survival as two important factors in deciding healthcare resource allocation during the pandemic (36). The participants of the study were unsure about the required social support to organize and implement the necessary resource allocation. This has been replicated in Indian studies as well where the physicians have felt underprepared to make appropriate health-triage decisions especially in older adults, and perceived lack of emotional support (37). In our study, the general physicians reported this concern much more, especially those working in primary and sub-urban healthcare settings with limited resources. In many cases, patients affected with COVID-19 with comorbid dementia were considered to be the "last priority" due to therapeutic nihilism. This would affect both the course of dementia as well as the infection, impairing the overall quality of life. The neurologists in our study preferred psychiatric referrals for psychosocial interventions and focused more on pharmacotherapy for the control of BPSD.

The "Triple Burden" During COVID-19: Age, Ageism, and Autonomy

There is a complex and dynamic interaction between an individual with dementia who has high dependency needs, living with various psychosocial adversities including the risk of abuse that is further complicated by the challenges posed by COVID-19 pandemic. This tetrad of "age, ageism, autonomy and COVID-19" expressed in our study seems to act synergistically in increasing the burden of PwD. Aging inherently poses several challenges and the risk of severe illness from COVID-19 increases with age. Eighty percent of the COVID-19 deaths in developed countries and 50% of the COIVD-19 deaths in India have been adults more than 60 years of age (38). COVID-19 has posed special needs of social distancing and self-isolation. In this highly dependable population requiring a physical form of care, this could lead to neglect, prejudice of ageism and also physical abuse which might go unnoticed by the physician over tele-consultations or go unreported. This is concerning with an already rising rate of elder abuse in India during the lockdown (39).

While the need for dependency and care is acknowledged, our participants felt it essential to balance it by preserving the autonomy of the PwD. While autonomy is an ethical construct that demands the highest advocacy, studies have reported that autonomy restriction can further increase the behavioral problems related to dementia (40). Some of the important factors leading to abuse according to our study could be poor knowledge about managing BPSD among the caregivers, caregiver burden, restriction of autonomy, and limitations of virtual consultations. Various studies have reported the successful use of patient-tailored, home-based psycho-educational interventions delivered *via* user-friendly online platforms to handle behavioral disturbances in PwD and reduce mood as well as anxiety symptoms among their caregivers which have resulted in an improved quality of life of the dyad (41).

Barriers for the General Physicians in India

India has 0.75 psychiatrists per 100,000 population compared to six psychiatrists per 100,000 population in high-income countries (42). Also, there is only one neurologist catering to a population of one million in India. Dementia care is majorly dealt with by primary care set-ups in communities (43). Studies have reported that primary care physicians face challenges in diagnosis, and a majority of the PwD go unrecognized (43). The existing treatment gap for dementia in India is estimated to be around 90% with scarce specialist resources (44). Previous studies have identified barriers such as lack of support for patients, caregivers, and physicians, time and financial constraints, stigma, diagnostic uncertainty, and concerns around disclosure of the illness in the diagnosis and management of PwD among the primary care physicians (45). Another study among primary care physicians identified challenges such as lack of confidence in neurocognitive evaluation, implementation of screening, interpretation of standard diagnostic procedures, and prognostication. Unique needs such as managing medical comorbidities, polypharmacy, behavioral and psychological symptoms further complicate the care of the PwD (46). This study highlights several of these challenges similarly faced by physicians as the previous studies that have been conducted worldwide and additionally identifies certain COVID-19 related unique concerns. While on one hand, some of the challenges faced by the primary care physicians have further accentuated during COVID-19, several areas are identified which appear to hold a promise. The physicians in this study have identified telemedicine as a potential tool to assist management of PwD including facilitation of cross-referral. They have however expressed dissatisfaction due to the perceived lack of training in terms of holistic management of a PwD and need to use "more sedative medications" to manage BPSD during COVID-19.

The recently released telepsychiatry guidelines also mention about the collaborative consultation between any healthcare workers and the psychiatrist, especially in community and custodial settings (23). These include primary care physicians, nurses and other allied healthcare professionals. It provides for such cross-consultations in custodial, correctional, community areas, and rehabilitation centers as well as during home-visits, medical camps, and primary healthcare establishments. While such provisions were welcome for dementia-care and psychiatric training by the general physicians, the challenges conveyed by our participants were excessive workload, lack of digital resources and good connections in primary healthcare centers, poor collaboration with the specialists and time-constraints. More than half of the general physicians in our sample reported time being a crucial component in the dementia-care as the "need for quick improvement in behavioral symptoms" and "waiting for specialist referral" often led to losing the patient to follow-up. This often lead to self-perceived "threat to their competence," reduced confidence for dementia care and increased use of psychotropics in our participants. They revealed the need for "better guidance" and cross-collaboration with psychiatrists and neurologists to manage patients with dementia and their families, but most were unaware of the newly released guidelines that could facilitate the same. Given the dearth of trained health professionals who manage dementia, alternative options of capacity building, task shifting, training, and the use of digital mental health intervention are highly recommended. The recently launched ECHO project by the National Institute of Mental Health and Neurosciences (NIMHANS) in Dementia Care is one such promising step (47). Further exploration of the "unmet needs" of general physicians involved in primary dementia care will help address policies and programs. Adequate tele-training of primary HCW, cross-collaboration and specialist guidance might be more pragmatic in the "digital future of dementia care" as mentioned by the physicians in our study.

The present study being qualitative has its inherent limitations, one of which is limited generalizability. However, qualitative studies in general are not intended have widely generalizable findings, as the perceptions of individuals are contextual from a constructivist vantage point of research, where even a "single voice" matters. Also, our sample size is relatively larger for a qualitative study and we have tried our best to have a representative sample from various regions, area of practice, and age-groups through purposive sampling. The physicians were however only from South India, and cannot be considered to be a pan-Indian sample. The other possible limitation is the researchers' bias while coding the data, themselves being physicians and facing similar challenges. We tried to deal with this by "constant comparison" of the analyzed results with the verbatim excerpts from the participants. Also, at each level of coding, there was rigorous discussion among the researchers with independent coding by two researchers. Lastly, the study was conducted during the period of COVID-19 related lockdown and the associated psychosocial challenges could have colored the opinion of the physicians; however, that was one of the objectives of the study. Besides, we haven't categorized the results based on age, years of experience and speciality but we also didn't find any major differences in the perceptions/experiences based on these attributes. There were certain nuanced variations in the themes among the groups which are highlighted in the discussion. To summarize, even with these pragmatic limitations, the study was rigorous in design and analysis with the results being grounded in the "voices" of the participants.

CONCLUSION

The pandemic has been an unprecedented crisis for vulnerable populations. The Indian Ministry of Health and Family Welfare (MoHFw) in its "Health Advisory for Elderly Population during COVID-19" has stressed the special needs of older people with cognitive impairment, their healthcare access and preservation of rights and autonomy (48). The newly released telemedicine guidelines will serve as an effective anchor for implementing virtual "dementia care," provided the physicians are well-versed with it. Most of the 5.3 million PwD are in the semi-urban and rural areas of India, and tele-health even with its pragmatic "caveats" can reduce travel costs, enhance access to care, decrease infection risks during a pandemic and improve specialist consultations. This study looks at the "voices" of those actively providing this healthcare and to the best of our knowledge, is the first one from India to do so. Concurring with their experiences, PwD and their families are exposed to multiple vulnerabilities during COVID-19, need tailored care, especially at the primary healthcare level which includes general physicians. Addressing the unmet needs of the physicians involved in dementia care during this time, improvisation of virtual cognitive assessments and cognitive rehabilitation, and further research into the systematization of digital platforms for such purposes can shape practice and policies even in the post-pandemic aftermath and during such futuristic crises. The newly released telepsychiatry guidelines have the potential to form an effective anchor for the same, and subsequent research into dementia care in India needs to explore the understanding, implementation and feedback related to the same.

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by JSS Academy of Higher Education and Research.

The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DB, PV, and BV were involved in data collection, curation, organization, and drafted the manuscript. DB and TR were independently involved in analysis, and also responsible for editing and supervising. All authors have read and approved the final version of the manuscript, and involved in the study conceptualization, intellectual content, and design.

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Changes in Lifestyle, Behaviors, and Risk Factors for Cognitive Impairment in Older Persons During the First Wave of the Coronavirus Disease 2019 Pandemic in Finland: Results From the FINGER Study

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Aims: This study aimed to describe how the first phase of the coronavirus disease 2019 (COVID-19) pandemic affected older persons from the general Finnish population who are at risk of developing or have cognitive impairment, specifically, to describe whether participants experienced a change in risk factors that are relevant for the prevention of cognitive decline including diet, physical activity, access to medical care, socially and cognitively stimulating activities, and emotional health and well-being.

Method: A postal survey was sent in June 2020 to 859 participants from the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), an ongoing longitudinal study. The survey was developed to assess the effect of the COVID-19 pandemic and related infection-control measures on daily life, specifically commitment to distancing measures, access to health care and social services, daily activities, and changes in cognitive and social activities.

Results: By September 2020, 613 (71%) participants responded (mean age = 77.7 years, 32% lived alone, and 80% had at least one chronic condition). Three quarters adopted some distancing practices during the first months of the pandemic. Older participants were more likely to practice total isolation than younger ones (29 vs. 19%; $p = 0.003$). Non-acute health-care visits were canceled for 5% of the participants who needed appointments, but cancellations in dental health care (43%), home aid (30%), and rehabilitative services (53%) were more common. Pandemic-related changes were reported in social engagements, for example, less contact with friends (55%) and family (31%), or less frequent attendance in cultural events (38%) or associations

(25%), although remote contact with others increased for 40%. Feelings of loneliness increased for 21%, particularly those who were older ($p = 0.023$) or living alone ($p < 0.001$). Physical activity reduced for 34%, but dietary habits remained stable or improved. Pandemic-related changes in lifestyle and activities were more evident among those living alone.

Conclusions: Finnish older persons generally reported less negative changes in lifestyles and behaviors during the pandemic than expected. Older people and those living alone seemed more susceptible to negative changes. It is important to compare how coping strategies may compare with other European countries to identify factors that may help older individuals to maintain healthy lifestyles during future waves of COVID-19.

Keywords: COVID-19, SARS-CoV-2 (CoVID-19), quarantine, non-communicable diseases, lifestyle, prevention, cognitive impairment, aging

INTRODUCTION

Multidomain lifestyle interventions targeted at community-dwelling older persons, such as the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) study (1), have shown that multiple aspects of health (e.g., diet, exercise, cognitive training, and metabolic/vascular risk monitoring) are important for reducing the risk of cognitive decline. Recent guidelines from the World Health Organization (WHO)[1] for reducing the risk of cognitive decline and dementia emphasize the need to control vascular and metabolic risk factors and lifestyle-related factors. Many of these risk factors are common to other noncommunicable diseases (NCDs) (2), and indeed, the FINGER study reported that multidomain interventions can also help to prevent or delay other negative health outcomes, including decline in physical functioning and multimorbidity over 2 years of follow-up (3, 4). In light of the restrictions enforced in many counties during the coronavirus disease 2019 (COVID-19) pandemic to control the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, we must consider if these initiatives have a short- and/or long-term effects on risk factors for NCDs and cognitive impairment, especially in older individuals. It has been hypothesized that changes in diet, levels of physical activity, cognitive and social stimulation, and access to routine NCD management may occur in some individuals during the pandemic and that this may affect their long-term health (5), potentially altering their risk of developing NCDs in the future. Surveys conducted during the first wave of the pandemic have reported reduced physical activity, dietary changes, and disruptions to NCD care, among others, in various countries (6–12). However, as each country applied varying strategies to contain the spread of the COVID-19 virus, information is needed concerning how these initiatives have affected persons living in different countries.

As of 23 October 2020, there were 14,474 confirmed cases of COVID-19 in Finland[2], with the first reported cases occurring on 29 January 2020 and a peak of COVID-19-related deaths occurring in mid-April[3]. On 16 March 2020, the Emergency Powers Act was implemented, with decisions to suspend contact teaching; limitations to public gatherings; closure of public services such as museums, libraries, and sports facilities; ban of visitors to care institutions and hospitals; instructions to work remotely; reduction of non-acute health and social services; and further travel restrictions. A strong but not compulsory guideline for persons over 70 years of age was given in that they must refrain from contact with other persons to the extent possible (quarantine-like conditions). Some restrictions were gradually lifted during May and June 2020, including opening of, first, outdoor, and, then, indoor recreational facilities. On 23 June, the age-based strong recommendation to avoid personal contact was lifted.

Research into the effects of the COVID-19 pandemic and associated infection-control measures is ongoing in many countries. Ongoing population-based longitudinal studies can provide important insight into how the pandemic has affected the general population: first, because they provide quick access to already established research participants and, second, because they provide pre-pandemic data on individuals' health and functioning to allow for accurate measures of change. The FINGER study (1, 13), described later, was a 2-year multidomain intervention aimed at delaying cognitive decline in community-dwelling persons aged 60–77 who were at risk of developing cognitive impairment or dementia. The study was initiated in 2009, and until now, participants have undergone a comprehensive follow-up evaluation to assess cognitive and health status at 2, 5, and 7 years of follow-up. A 10-year follow-up was planned in 2020 but was halted as a result of the COVID-19

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[1] Available online at: https://www.who.int/mental_health/neurology/dementia/guidelines_risk_reduction/en/ (accessed October 23, 2020).

[2] Available online at: THL/National Infectious Disease Register. https://experience.arcgis.com/experience/92e9bb33fac744c9a084381fc35aa3c7 (accessed 23/10/2020).

[3] Available online at: https://sampo.thl.fi/pivot/prod/en/epirapo/covid19case/fact_epirapo_covid19case (accessed January 27, 2020).

pandemic. Within the context of the WORLDWIDE-FINGERS-SARS-COV-2 INITIATIVE of multidomain prevention trials (14), which is an initiative to test and adapt the FINGER intervention model in over 25 countries worldwide, we developed a postal survey to assess how COVID-19 and associated infection-control measures (such as quarantines and lockdowns) would affect participants in terms of changes in lifestyle, risk factors, social stimulation, and access to medical care. Preliminary data from the Finnish FINGER COVID-19 survey are now available.

The aim of the current study is to describe how the first phase of the COVID-19 pandemic affected older persons from the general Finnish population who are at risk of developing dementia. Previous studies suggest that, particularly, social isolation during the pandemic has negative impact on both physical and mental health (15). Specific objectives are to describe whether participants experienced a change in risk factors that are relevant for the prevention of cognitive decline, dementia, and other NCDs, including diet, physical activity, access to medical care (and, thus, opportunities for controlling vascular and metabolic risk factors), socially and cognitively stimulating activities, and emotional health and well-being.

METHODS

Setting and Study Population

FINGER is a multidomain lifestyle intervention trial covering six areas in Finland (ClinicalTrials.gov NCT01041989). The study comprises a population-based sample recruited from previous national surveys. Participants were aged 60–77 years in the beginning of the study and had an elevated risk of developing dementia based on CAIDE dementia risk score (13, 16). They underwent screening with a short neuropsychological examination with the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) test battery (17) and medical examination by a study physician. Participants with a CAIDE dementia risk score of 6 or higher were invited to the trial, if they were free of dementia and conditions affecting safe engagement in the intervention and had cognitive performance at average level or slightly below than expected for age. They were randomized 1:1 to multidomain lifestyle intervention or regular health advice. All participants in the multidomain intervention group received intervention in four domains: dietary counseling, exercise training, cognitive training, and management of cardiovascular and metabolic factors (13).

The original intervention period lasted for 2 years for each participant (during 2009–2013), and post-intervention follow-up examinations have been conducted at 5 and 7 years (3 and 5 years after the intervention). A 10-year follow-up was planned to start in 2020, but when the COVID-19 outbreak emerged, face-to-face examinations were postponed. A specific survey with questions relating to the COVID-19 pandemic was developed (see details later), and participants were mailed with a questionnaire in June 2020, immediately following the strict restrictions initiated in Finland due to the first wave of COVID-19 (**Figure 1**).

A total of 859 participants from the original FINGER population ($n = 1,259$, 69%) were eligible for invitation to answer the questionnaire after those who had died ($n = 182$) or previously withdrawn from the study ($n = 218$) were excluded.

The survey is an amendment to the current FINGER protocol and was approved by the coordinating ethics committee of the hospital district for the Helsinki and Uusimaa region.

COVID-19 Questionnaire

The questionnaire included questions about health, health-care use, lifestyles and daily living, quality of life, mood, and personality in relation to the COVID-19 outbreak. The survey is harmonized with the questionnaire devised within the WORLDWIDE-FINGERS-SARS-COV-2 INITIATIVE for later pooled analyses, and partly with the Finnish population-based survey[4] conducted on all adult ages, run by the Finnish Institute for Health and Welfare, to enable the comparison of different age groups later.

In the current paper, we focus on describing the effect of the COVID-19 pandemic and related infection-control measures on daily life among older adults, specifically their commitment to distancing measures, access to health care and social services, daily living, and any relevant changes in cognitive and social activities. The survey provided information on the following characteristics:

1) Sociodemographic Characteristics

Age, education, and marital status were collected at FINGER baseline, and marital status again in the COVID-19 questionnaire. Age at the time of compiling the COVID-19 questionnaire was calculated based on dates in the questionnaires (or 1 July 2020 for comparing respondents with non-respondents). Marital status was dichotomized into those living with someone (married or cohabitation) vs. living alone (single, divorced, or widow). Information on housing was also collected. For age-group comparisons, age was grouped based on median value, that is, below or above 77.7 years.

2) Distancing Measures During the COVID-19 Pandemic

Participants were asked if they considered that they had followed a self-chosen isolation/quarantine (staying at home and nobody visiting); quarantine enforced by authorities; total social distancing (no shopping or running errands indoors, but possibly going out, e.g., for a walk); and partial social distancing (e.g., running essential errands or meeting people outdoors while keeping distance). Participants were allowed to select as many options as they thought necessary and to specify amount of weeks they followed each type of isolation since the beginning of the pandemic. They were also asked if they continued to practice some type of isolation at the time of completing the questionnaire.

We combined self-chosen and authority-enforced isolation into one group for reporting, and we calculated total time spent in total isolation. Furthermore, a total amount of time spent with some type of distancing measures, less strict than total isolation, was calculated. If the same participant reported not having adopted any distancing measures but still chose some of

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[4] Available online at: https://thl.fi/en/web/thlfi-en/research-and-expertwork/projects-and-programmes/serological-population-study-of-the-coronavirus-epidemic (accessed October 30, 2020)

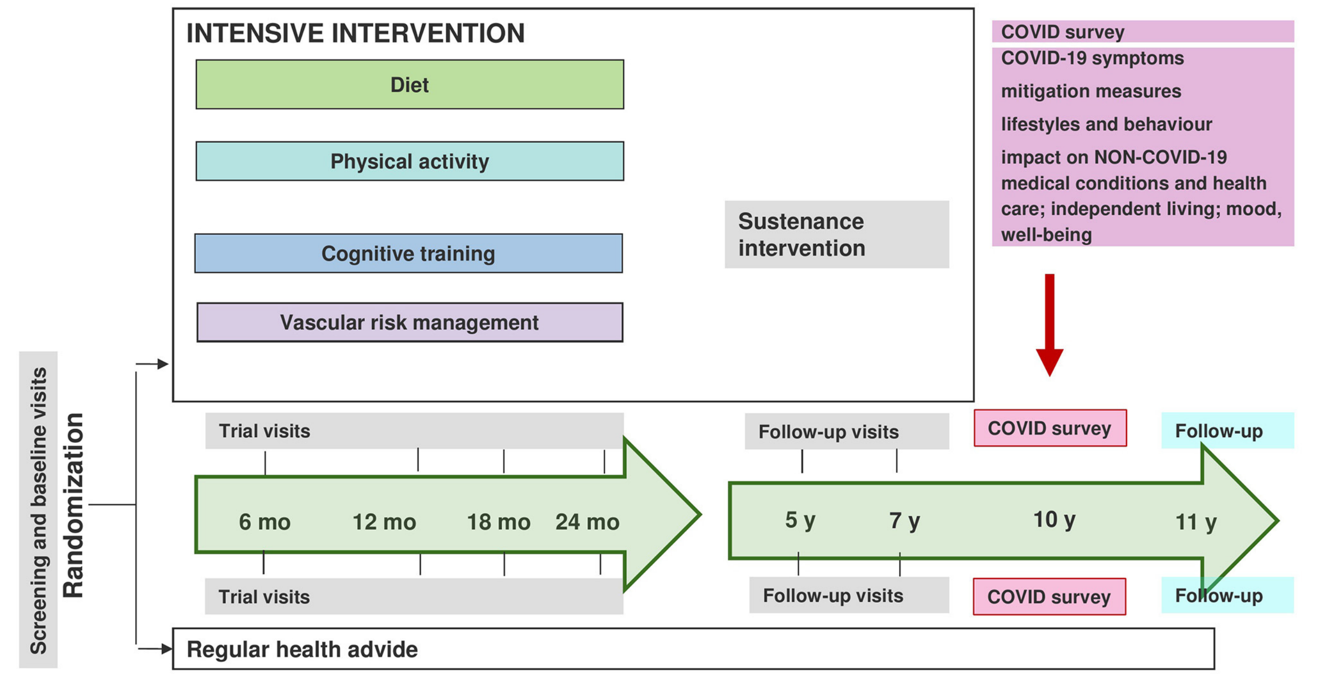

FIGURE 1 | Overview of the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) study setting.

the options related to them, he/she was considered as having adopted distancing. As many participants had missing values or zero for weeks of the chosen distancing type, they were included when reporting numbers of people who practiced each specific type of distancing, but their time estimate was not taken into account when calculating the average duration.

3) Non-Acute Health-Care Usage During the COVID-19 Pandemic

Participants were asked to report any chronic condition that they had been diagnosed with from a list, including asthma, chronic obstructive pulmonary disease, other lung disease, diabetes or elevated blood glucose, high cholesterol, hypertension, heart disease (angina pectoris, coronary artery disease, previous heart attack or angioplasty or bypass surgery), cardiac failure, cancer, cancer treatment, epilepsy, mental health condition (e.g., depression, anxiety, etc.), cognitive impairment or memory disorder, cerebral hemorrhage or other cerebrovascular disease, multiple sclerosis, rheumatoid arthritis, renal failure, organ transplant, condition, and/or drugs that weaken the immune system. For each chosen condition, they were asked if they had had issues in getting treatment for that condition during the COVID-19 outbreak. The options were canceling an appointment themselves, having an appointment canceled by health-care professionals, having remote medical examinations (phone call or video call), having face-to-face appointments as usual, or not needing any medical care.

Access to dental health care, mental health care, social services, supportive services (e.g., home care or home aid), or rehabilitation services (e.g., physiotherapy or daytime activities) during the COVID-19 outbreak were also asked. Supportive or rehabilitation services were asked for the participant or for a close person from the same household. Participants were asked to choose if they had canceled a visit themselves, had a visit canceled by the professional, had visits/help face to face as usual, or not needed any visits/help. An option for remote contact was not provided in this question.

4) Changes in Daily Life, Lifestyle, and Emotional Health During the COVID-19 Pandemic and Related Periods of Infection-Control Measures

Participants were asked to evaluate how the COVID-19 pandemic and related restrictions have affected their experienced daily life. We included questions about time spent with family, contact with friends and relatives, experience of loneliness, experience of closeness with other people, family conflict, fear or experience of domestic violence or violence by a close relative, hopefulness for the future, leisure time physical activity, smoking, alcohol use, sleep problems and nightmares, number of meals and snacks per day, appetite, vegetable consumption (raw and cooked vegetables and salad excluding potato), fruit and berry consumption, snacking (sweets, chocolate, soft drinks, chips, biscuits, etc., consumption), internet use (e.g., smartphone, computer, and tablet), using digital services for everyday routines (e.g., ordering food online and online banking), using digital services or contact by phone for social and health-care services (e.g., speaking with a doctor or nurse), and remote contact with relatives and friends (messaging and video or phone calls). For each item, we asked if it was similar before the pandemic, decreased or increased, or not applicable/relevant to the participant. For the current analyses, no change and "not applicable" were merged to focus on changes experienced during the pandemic. Items for which decrease was considered a positive change (i.e., loneliness, discordance in the family, fear of violence, sleeping problem, smoking, alcohol consumption, and unhealthy snacks) were recoded to ease interpretation of results, and change in all items is categorized as no change, worsening, or improvement.

5) Changes in Engagement in Social and Cognitive Activities as a Result of the COVID-19 Pandemic or Related Infection-Control Measures

Social and cognitive activities were evaluated with the same questions that we used previously in the FINGER trial (13) and included questions concerning average frequency of reading, doing crosswords, writing, games, listening or playing music, communal activities or participation in societies, studying, handicrafts, gardening, looking after children (other people's; either family or friends), and voluntary work. Frequency of engagement in those activities was measured on a 7-point Likert scale with alternatives from daily to never (daily; four to six times per week; two to three times per week; once a week; two to three times per month; a few times per year; and never). The same items and same scale were presented twice; first, the participants were advised to evaluate their life before the pandemic and then during the pandemic. For the current analyses, we defined change as transition in frequency categories between the two timepoints and categorized as any decrease, the same frequency, or any increase. Any increase in activities was considered positive, and changes in these activities are referred as no change, worsening, or improvement.

6) Changes on Self-Rated Health and Quality of Life

Participants were asked to evaluate if their quality of life, physical condition, functional status, memory, or overall health had changed during the COVID-19 pandemic. Options for each question included better, worse, or similar compared with pre-pandemic time or "I do not know." Similar and not being able to say were combined in these analyses. For memory, there were more options with "slightly" or "significantly" better and worse, which were merged to provide final options as no change, worse, or better.

Statistical Methods

We report descriptive data as mean and standard deviation for continuous variables and counts and proportions for factor variables. Comparisons were executed between respondents and non-respondents for main characteristics, and between age groups and marital status for the COVID-19 questionnaire data. Comparisons were done using t-test or χ^2-test, as appropriate. Analyses were executed with Stata/SE version 16.1.

RESULTS

The postal survey was sent out on 22 June 2020. Preliminary data are available for 613 participants (97% were living at home) who returned their questionnaires by post before 1 September 2020 (one empty questionnaire returned, total $n = 614$), after which a second questionnaire was mailed to non-respondents (collection ongoing). Participants from the original FINGER study who were included in the current sample were younger: their mean age was 68.2 (SD 4.7) at baseline and 78.1 (4.6) years in July 2020, compared with those not in the sample who were 69.9 (4.6) at baseline and 79.7 (4.5) in July 2020 ($p < 0.001$, respectively). The COVID-19 survey sample also had higher baseline education with 10.3 (3.5) years compared with 9.5 (3.4) among those not in the sample ($p = 0.001$). In the sample, those who responded were younger than those who did not (77.7 vs. 79.7 years in July 2020, $p < 0.001$) but did not differ in education (**Table 1**).

Response rate was slightly higher among those who were living with someone (73 vs. 66%, $p = 0.040$). The majority ($n = 577$, 97%) of persons were able to answer themselves, while 18 (3%) needed help in completing the questionnaire or it was completed by someone else.

Data related to practicing distancing measures are presented in **Table 2**. The majority of participants ($n = 458$; 75%) reported practicing some social distancing, and the average duration of any type (or all types in total) was 9.2 weeks. At the time of completing the questionnaire, 354 (66%) reported still practicing some restrictions, with partial social distancing as the most common type ($n = 255$, 48%). Older participants (above median 77 years) reported any type of distancing less often than younger persons (71 vs. 79%, $p = 0.025$) but more often total isolation (29 vs. 19%, $p = 0.003$). Partial isolation was less common among older participants (47 vs. 63%, $p < 0.001$). Persons who lived alone were more likely to not do any social distancing (30 vs. 22%, $p = 0.056$), but there were no differences in specific types of distancing.

The presence of chronic health conditions was reported by most participants ($n = 481$, 78%; number of diagnoses ranged from 1 to 7), with 54% of the study population reporting to have two or more chronic conditions (**Table 1**). Access to non-acute health care during the first phase of the COVID-19 pandemic is reported in **Table 3**. Approximately half the participants did not need care for their condition(s) during the first 4 months of the pandemic, and about one quarter had participated in a normal face-to-face visit. It was uncommon for health-care professionals to cancel appointments (~5% in the whole group with a condition and 10% among those who needed an examination). However, cancellation of other types of services was much more common; 109 (17% of the whole population, 45% of those who were due to have visit) reported some type of service being canceled by the professional, and 56 (9% in the whole sample; 23% among those in need) canceled the visits themselves. The most needed service that was more often canceled by the professionals was dental health care, but the proportion of canceled visits/help was almost equal in mental health care, social services, home aid, and rehabilitation (**Table 3**).

Self-evaluated experiences of changes to aspects of daily life, lifestyle, social and cognitive activities, and self-rated health are presented in **Figure 2**. The items in the questionnaire are ranked according to the difference in negative and positive changes; that is, the items with the most negative changes (without a substantial amount of positive changes) are presented first, and items with most often reported positive change are reported last within each category. Most of the daily life and lifestyle-related items did not change substantially, especially alcohol consumption, smoking, and fear of domestic violence. Appetite changed in

TABLE 1 | Characteristics of the sample based on participation.

	Respondents (*n* = 613)		Non-respondents (*n* = 246)[a]		
	Mean	**(SD)**	**Mean**	**(SD)**	***P*-value[b]**
Age at FINGER baseline (years)	67.9	(4.6)	69.6	(4.7)	<0.001
Education (years)	10.2	(3.5)	10.1	(3.4)	0.572
Age at the time of COVID-19 questionnaire (years)[c]	77.7	(4.5)	79.5	(4.7)	<0.001
	n	**%**	***n***	**%**	
Women	299	48.8%	107	43.5%	0.161
Original intervention group	297	48.5%	135	54.9%	0.089
Living with someone at baseline	474	77.6%	173	70.9%	0.040
Living at capital area	213	34.7%	91	37.0%	0.534
Living with someone at the time of COVID-19 questionnaire	408	67.6%	n/a		
Chronic conditions (self-report)					
0	123	20.4%	n/a		
1	153	25.3%			
2+	328	54.3%			

COVID-19, coronavirus disease 2019; FINGER, Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability.

[a] *Non-respondents as of September 2020; these data are preliminary, with the second data collection still ongoing from non-respondents.*

[b] *p-values from t-test for independent samples for continuous variables or χ^2-test for categorical variables.*

[c] *Age calculated at the time of sending the questionnaire.*

TABLE 2 | Distancing measures during the first wave of the 2020 COVID-19 pandemic.

	Participants reporting the type of distancing		Reporting duration	Average duration in weeks	
	n	**%**	***n***	**Mean**	**(SD)**
No distancing	153	(25.0)			
Any distancing[a]	458	(75.0)	324	9.2	(3.9)
Total isolation (self-initiated or authority-enforced)	146	(23.9)	122	7.1	(4.0)
Social distancing	149	(24.4)	133	8.3	(3.7)
Partial social distancing	334	(54.7)	260	8.2	(4.0)

COVID-19, coronavirus disease 2019.

[a] *Participants reporting total isolation, social distancing, or partial distancing, or any combination of them. Duration calculated as a total of all types reported.*

TABLE 3 | Need and cancellation of non-acute health-care visits and other services during the first wave of the 2020 COVID-19 pandemic.

	No need		Participant canceled		Professional canceled		Remote contact[a]		Normal appointment	
	n	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Among those with at least one chronic condition, *n* = 481[b]										
Health-care visits related to non-acute chronic conditions	261	54.3	14	2.9	23	4.8	36	7.5	131	27.2
Among all participants (proportions of cancellation types among those in need of a visit, *n* = 6-205)										
Dental health care	369	64.3	44	21.5	88	42.9	n/a		73	35.6
Mental health care	541	98.9	1	16.7	2	33.3	n/a		3	50
Social services	541	98.9	0	0	3	50	n/a		3	50
Home aid and services	530	96.4	4	20	6	30	n/a		10	50
Rehabilitative services and day services	496	90.3	12	22.6	28	52.8	n/a		13	24.5

COVID-19, coronavirus disease 2019.

[a] *This option was not provided for other types of care needed.*

[b] *Participants reported need and cancellation for each of the condition separately, and thus, the same participants may have reported several cancellation alternatives. Proportions are calculated using all participants who reported having conditions, not only among those who answered to the need and cancellation question, and thus do not sum up to 100%.*

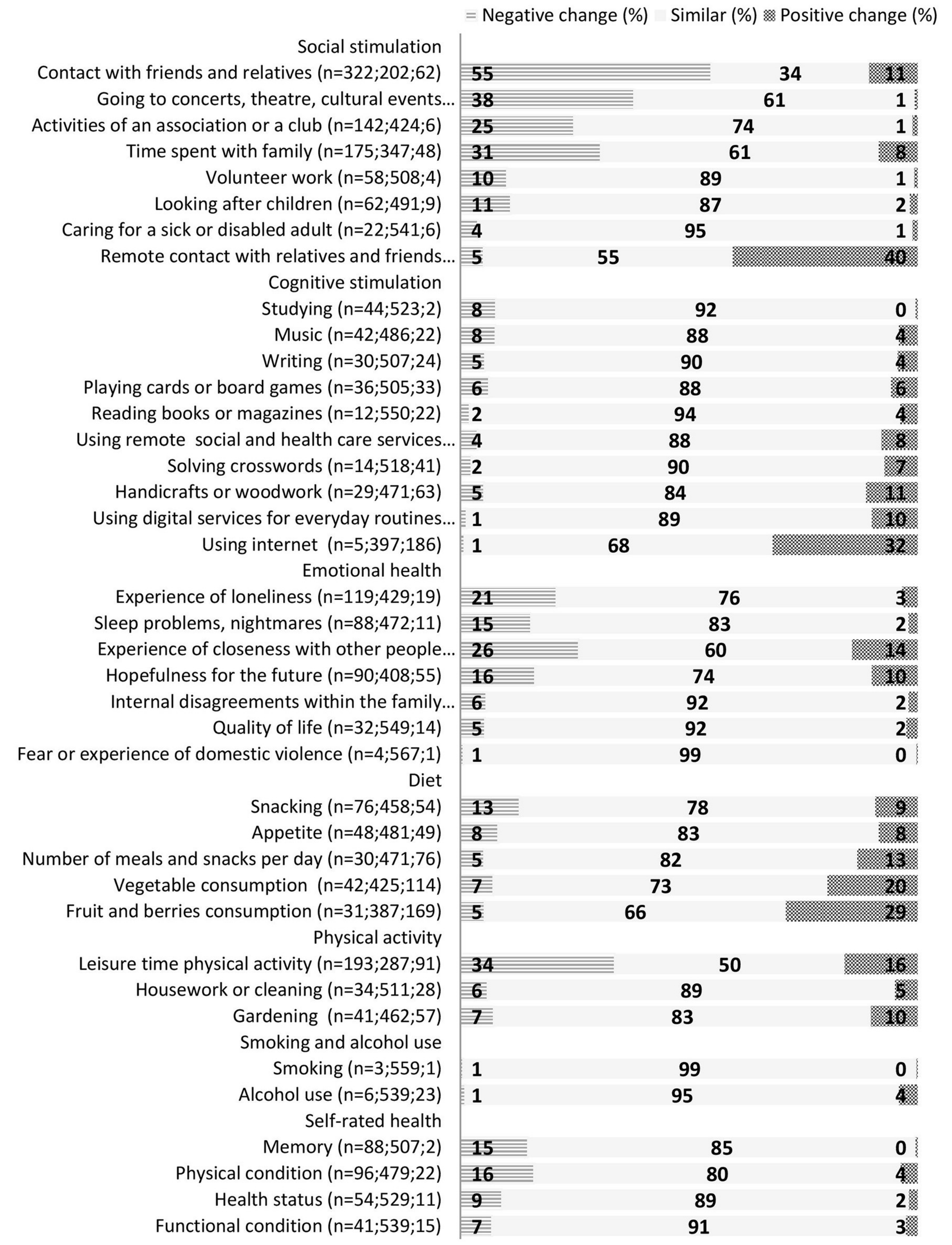

FIGURE 2 | Self-evaluated changes in cognitive and social activities, emotional health, and lifestyle during the first wave of the 2020 COVID-19 pandemic.

both directions equally. Remote contact with friends and using the internet in general was reported as having increased, both of which were considered as improvement. Time spent with family and contact with friends was reduced, as well as amount of physical activity. However, many participants reported doing more physical activity during the pandemic. Changes in diet were mostly positive, with increased consumption of both fruits and vegetables.

For changes in social and cognitive activities, participants mostly reported negative changes in attending cultural events such as concerts and theater, or meetings in clubs or societies. Voluntary work and looking after children also reduced during the pandemic. Few items in the hobby-type of activities had a positive change, but doing handicrafts was reported somewhat more often.

Self-rated health, physical functioning, memory, physical condition, and quality of life were relatively stable (**Figure 2**). There was a negative change in health, functioning, and quality of life in 9, 7, and 5% of respondents, respectively; and physical condition was evaluated as worsened for 16% and memory for 15% of the participants.

Older participants reported an increase in feelings of loneliness more often than younger participants (25 vs. 17%, $p = 0.023$), and a smaller proportion of older compared with younger participants reported that internet usage increased (24 vs. 39%, $p > 0.001$). Looking after children was more commonly reduced among the younger participants compared with older persons (15 vs. 7%, $p = 0.004$).

All items from **Figure 2** that are different between participants who lived alone or with someone are presented in **Figure 3**, ranked according to the difference between these group in negative and positive changes (the items with more favorable changes among those living alone are presented first, and the items with more negative changes among those living alone are last). Participants who lived alone reported a negative change in time spent with family more often ($p < 0.001$), but they reported decreased contact with friends less often ($p < 0.001$). Increased feelings of loneliness were more common ($p > 0.001$). They also reported more often a reduction in physical activity ($p = 0.\ 013$) and in vegetable intake ($p = 0.024$). Appetite was more often changed among those living alone, but changes were both positive and negative ($p = 0.025$). Those living alone more often reported a reduction in participating in clubs and societies ($p = 0.026$), and more increase in time spent reading ($p = 0.036$). They also reported a negative change in physical functioning more often than those who lived with others ($p = 0.014$) and more changes in self-rated health (both directions, proportion of similar as before $p = 0.045$).

DISCUSSION

Our survey reports lifestyle and health behaviors during the first wave of the COVID-19 pandemic (March–May 2020) in a sample of Finnish older adults who all were at risk of dementia, and some already had dementia. About three quarters of participants practiced social distancing measures, over an average of more than 9 weeks, with older participants more likely to practice total isolation than younger ones. Importantly, despite the relaxing of infection-control measures, about two thirds of participants were still practicing some social distancing measures when they sent their survey responses, mostly partial distancing. In terms of behaviors and factors that can affect cognitive decline, we found different patterns depending on the type of activity. Cognitively stimulating activities such as using the internet, doing handicrafts, and solving crosswords were largely unchanged or increased. However, attending concerts, theater, or other cultural events of participating in activities of clubs or associations decreased, as expected. In terms of diet, fruit and vegetable consumption mostly improved or remained unchanged. Leisure time physical activity was reduced for a third of the survey participants. Although most of the participants in the sample have one or more chronic health conditions; health care for chronic conditions was not hugely affected during the pandemic, with <10% missing planned health-care visits. Some behavior changes were more pronounced in older persons and those living alone, mostly the latter.

It is well-established that a combination of healthy lifestyle factors, including diet, physical exercise, opportunities for cognitive and social stimulation, and metabolic and vascular risk monitoring, is important for reducing risk of cognitive decline and disability (18, 19). The results of our study suggest that, mostly, these lifestyle factors did not change dramatically in our sample during the first wave of the COVID-19 pandemic. The most relevant change was a reduction in leisure time physical activity, as expected, because most sports and leisure facilities were closed. Another study in community-dwelling older adults in Japan also reported a decline in physical activity during the COVID-19 pandemic (6). However, it was a positive finding that many dietary aspects improved in our study population, including vegetable and fruit intake. In contrast, a study on Italian older persons with subjective cognitive deficits or mild cognitive impairment (MCI) found that they were more likely to engage in lifestyle changes that were potentially harmful to their future cognitive decline during compared with before the pandemic (20). Approximately half of this population underwent a dietary intervention as part of the FINGER trial and may, thus, have been more aware of the risks of unhealthy diets and possibly more likely to adopt healthier dietary changes during a period when they may have been worried about ill health as a result of being indoors. Furthermore, during lockdown, people were likely to spend more time at home and may have had more time for cooking.

As metabolic and vascular risk monitoring is an important element of multidomain interventions, we were interested to see whether participants experienced a reduction in access to health care. Only 10% of people who needed a medical appointment were unable to attend them because they had been canceled by the health-care professional. Interestingly, despite the Government action to cancel non-urgent health care, a quarter of our participants had a normal medical appointment during the first wave of the pandemic. This is in contrast with studies from other countries that report significant disruptions to non-acute, routine NCD care during the first wave of the pandemic (9, 10). However, the restrictions in Finland were gradually lifted in May–June, and there is a possibility that these appointments were postponed, although completed by the time of the questionnaire. A study from the Netherlands identified patients who are at risk of adverse outcomes of the corona measures, that is, discontinued care, social isolation, psychological, and behavioral problem (21).

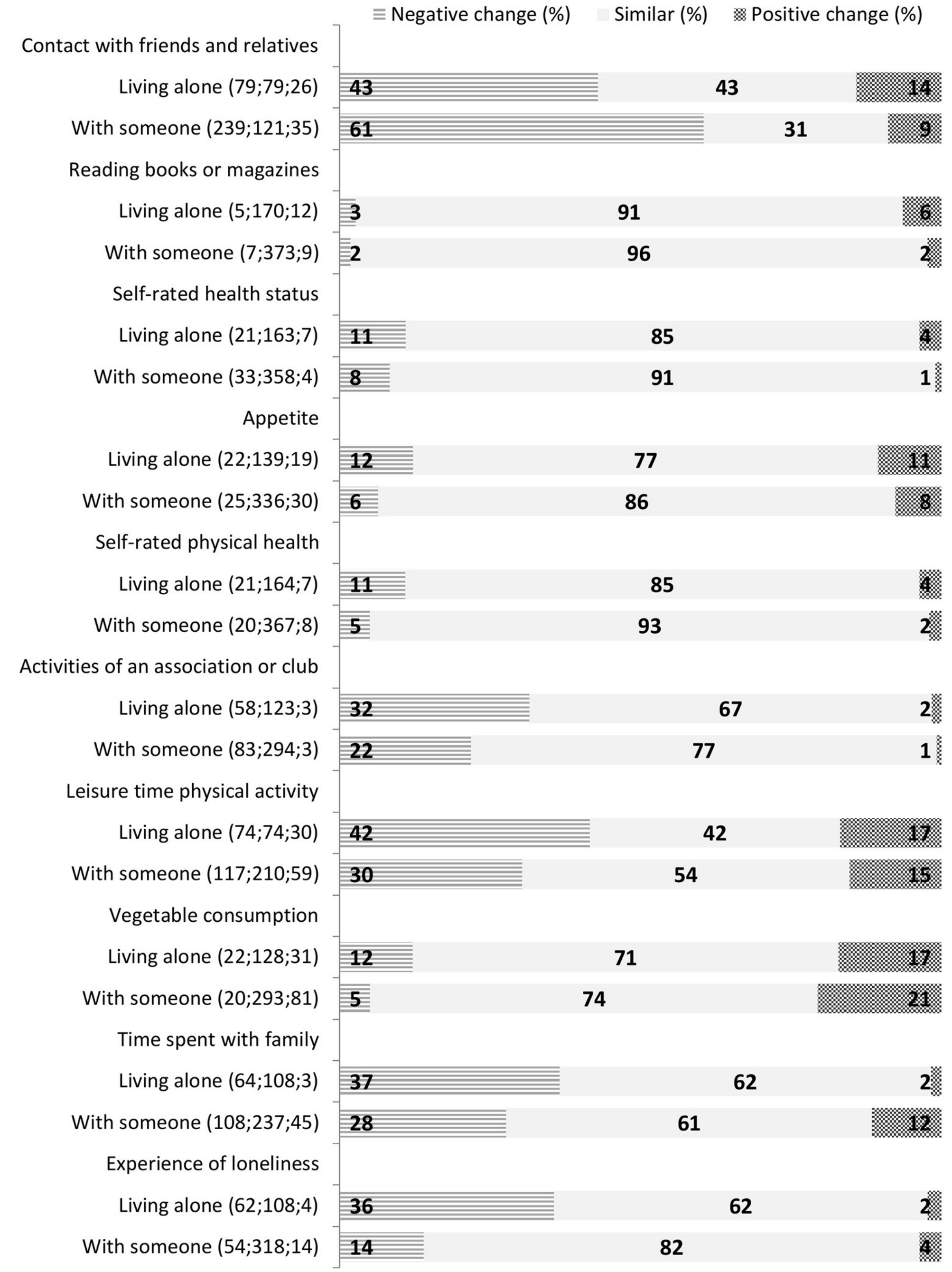

FIGURE 3 | Self-evaluated changes in cognitive and social activities, emotional health, and lifestyle that were significantly ($p < 0.05$) different between those living alone or with someone.

The survey revealed some important results on social distancing. Although the Finnish Government made strong recommendations for social distancing, they did not enforce any rules. About 75% of participants practiced social distancing measures over an average of more than 9 weeks, which suggests that this sample was quite compliant with Government recommendations. Importantly, despite a relaxing of infection-control measures occurring in the summer, about two thirds of participants were still practicing some social distancing measures when they sent their survey responses (most persons returned their surveys in June–July).

Living status affected change in lifestyles, with those living alone more likely to report a reduction in time spent with family, although less likely with friends. They still reported increased feelings of loneliness, reduction in physical activity and physical functioning, and less improvement in vegetable intake than those who lived with others. More people who lived alone reported not following any social distancing measures, compared with people who live with others. A Japanese study reported that most patients with dementia or MCI who lived alone did not limit their outings or activities during the COVID-19 outbreak, but they were less likely to go out than healthy people (22). Older participants reported an increase in feelings of loneliness more often than younger participants, but no other major differences in age were found except a less increase in internet usage. A study from Germany and Poland reported that older people rated their quality higher of life, life satisfaction, and well-being during pandemic higher than did younger people (23).

Self-rated health, physical functioning, physical condition, and quality of life were relatively stable, but some emotional factors changed, interestingly, in both directions. For example, while there was a negative change in hopefulness for the future in 16% of people, 10% had a positive change. Similarly, although a quarter of people experienced less closeness with others, 14% had a positive change. This reflects how individual experiences of the COVID-19 pandemic can vary greatly. It will be interesting to establish which factors affect an individual's emotional response. For example, the CHARIOT COVID-19 Rapid Response Study reported that women; younger participants; and those who were single, widowed or divorced reported more feelings of loneliness and poor sleep, while those living alone were more likely to indicate poorer changes in depression and/or anxiety symptoms (24). Differences in levels of cognitive impairment are likely to also cause differences. A multicenter Italian study on outpatients with dementia concluded that infection-control policies such as quarantine can induce a rapid increase of behavioral and psychological symptoms of dementia (BPSD) in more than half of the patients (25).

Compared with the first results of the changes reported in the Finnish general population[5,6], older adults in our study reported similar reduction in contacts with family and friends, with 62% having reduction in time spent with either family or friends. However, hopefulness was less often decreased in our population, and lifestyles such as in increases in snacking and any direction of changes in leisure time physical activity were less evident in this older population. It could be expected that everyday lives of older people, who are no longer working, are less affected by the pandemic than persons who are of working age and may tend to move outside their home more and engage more in activities with other people. However, restrictions in meeting family and friends may be more difficult to manage for older people, especially those living alone. It was evident in our results that while isolation is less adopted, consequences of restrictions may be more significant for those living alone.

The strengths of our study are that we conducted a survey in an already established research cohort, with a large sample, using a questionnaire designed within the World-Wide FINGERS Network (14), to allow future international comparisons. Response rate was high (71%), and the pre-pandemic data from previous waves of the FINGER project (since 2009) will allow for us to evaluate objective changes in health and lifestyle status in the future. However, the data are preliminary. Currently, we only have access to self-reported behavior change, whereas in the future, we will be able to compare with participants' previous comprehensive data from FINGER project. However, no other ethically acceptable alternatives than self-reports were available at the moment of the survey to avoid risk of infection of participants or staff via face-to-face interviews. The generalization of our results may be limited. First, there were some differences in respondents; those who sent back responses were younger and more likely to be living with someone. Second, the FINGER participants were originally selected due to their age and risk of developing cognitive impairment, and therefore, our results are only generalizable to this group of adults. There is also a potential selection bias because almost half the participants were part of the original FINGER intervention group, and therefore, they may be more aware of the importance of risk factor control and less likely to engage in negative health behaviors than other populations, even during the pandemic. Another potential limitation is that our survey was sent out to participants in June 2020, at the end of the first wave of the pandemic. Participants were asked to respond in terms of their behavior during the first wave of the pandemic, and therefore, their responses may have been less accurate because they had to recall their behaviors. Further, it is possible that behaviors may have changed over the period; some people may have been more active or engaged in more health behaviors in the beginning or vice versa. Therefore, we aimed to assess an overall change in behavior before and during the pandemic. Finally, we used simple statistical methods for comparing age groups and those living alone vs. not living alone, without adjusting for other covariates. These are preliminary descriptive data of the cohort, and we will later be able to combine these data with data collected from earlier FINGER follow-ups and also adjust for more covariates.

Results from our survey have relevant implications. Changes in health and lifestyle factors in older people may have important relevance for their long-term health and cognition by changing risk factors and, consequently, risk for future NCDs. Indeed, the findings of the FINGER intervention have highlighted the importance of multiple domains for preventing cognitive decline as well as other outcomes such as multimorbidity (4). Further, although we did not find many cancellations in routine NCD health-care appointments, it has been highlighted that changes in routine medical care, especially in older persons, will have a significant effect on risk factor management, potentially increasing risk of future NCDs and affecting mortality due

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[5] Available online at: https://thl.fi/en/web/thlfi-en/-/the-coronavirus-epidemic-has-reduced-social-interaction-and-the-use-of-services-impact-on-lifestyles-as-well (accessed 30/10/2020).

[6] Available online at: https://www.julkari.fi/handle/10024/139889 (accessed 30/10/2020).

to delays in diagnosis (26). Further, research into changes in lifestyle risk factors as a result of the pandemic are important, not only because these risk factors are relevant for NCDs but also because they can play a role in viral infections and viruses such as COVID-19. For example, a systematic review highlighted the importance of balanced nutrition for preventing and managing viral infections such as COVID-19, especially in older populations (27).

Europe is already undergoing a second wave, and new partial or total lockdown scenarios are already occurring in some countries and are likely in others. It is not possible to predict how long the COVID-19 pandemic will continue, and how often waves will reoccur. It is likely, therefore, that older individuals and those with NCDs, who are more likely to experience COVID-19 complications and related death (28, 29), will need to continue methods to shield themselves to avoid risk of SARS-CoV-2 infection in coming months or years. Therefore, it is imperative to understand how infection-control measures will affect lifestyle behaviors and NCD risk factors, and how to manage these in the short and long term. Future comparisons of country-specific policies and infection-control measures are therefore imperative to understand how people behave as a result of different measures. Indeed, it is interesting that the majority of participants in the current study practiced social distancing, despite no enforcement of recommendations by the Finnish Authorities. A recent Eurobarometer released in October 2020 suggested that Finnish people were one of the European nationalities that were more likely to report finding it easier to cope with confinement measures than other European countries[7]. Thus, cross-country comparisons focusing on specific factors that may influence differences in coping abilities may provide valuable insights.

Future Research/Unanswered Questions

The current paper reports preliminary data from the FINGER COVID-19 survey. In the future, we plan to assess responses from the COVID-19 survey in relation to participants' pre-pandemic status. Further, as we developed the survey in collaboration with the WORLDWIDE-FINGERS-SARS-COV-2 INITIATIVE, it will be possible in the near future to make cross-country comparisons of how the COVID-19 pandemic affect older persons at risk of cognitive impairment in different settings. The survey is aligned with the WHO "Neurology and COVID-19 Global Forum," which aims to enable harmonized approaches to clinical management, surveillance, and research on neurological disorders in the context of the COVID-19 pandemic. Future research should focus on individual characteristics that predict which people are most affected by lockdowns and infection-control policies, including differences according to age, sex, cognition, social support, living conditions, and access to outdoor space, among others. Further, an important avenue for future research is the possibility of developing and testing remote multidomain interventions (digital and telehealth) to replace face-to-face options during COVID-19 times.

CONCLUSIONS

In conclusion, our survey of older persons in Finland at risk of cognitive impairment showed that there were less negatives changes in lifestyles and behaviors in this population than expected. However, age and living status may affect changes in risk factors that can increase the risk of cognitive decline and other negative outcomes such as disability and mortality.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because Public deposition of the de-identified data set is not possible due to legal and ethical reasons, and complete de-identification is not possible as this investigation is part of an ongoing study. The study participants gave informed consent which includes data use only under confidentiality agreement. Further, the data contains large amount of sensitive information and public data deposition may pose privacy concerns. Those fulfilling the requirements for viewing confidential data as required by the Finnish law and the Finnish Institute for Health and Welfare are able to access the data after completion of material transfer agreement. Requests to access the datasets should be directed to kirjaamo@thl.fi.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa, Finland. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MK, TN, and AS devised the study objectives. MK, TN, AS, JL, FM, and KP designed the survey and interpreted the results. MK, TN, JL were responsible for data collection. JL and KP conducted the data analysis and results and wrote the article. MK, TN, AS, and FM critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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[7] Available online at: https://ec.europa.eu/commfrontoffice/publicopinion/index.cfm/survey/getsurveydetail/instruments/standard/surveyky/2262 (accessed October 30, 2020).

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Effectiveness of a Family Support Intervention on Caregiving Burden in Family of Elderly Patients With Cognitive Decline After the COVID-19 Lockdown

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Background: The coronavirus disease 2019 (COVID-19) pandemic had a great impact on patients with cognitive decline or dementia. The lockdown period may exacerbate behavioral disorders and worsen distress of caregivers. The aim of this study is to evaluate the effectiveness of a family support intervention on the negative effects that the COVID-19 lockdown may have on patients and related caregivers.

Methods: We recruited patients whose related caregivers had attended a family support course before the COVID-19 lockdown. The course was for family members of patients with cognitive decline or dementia and consisted in eight meetings during which the participants received information about the disease, the management of neuropsychiatric symptoms, and community resources and services available for patients with dementia. Data on cognitive decline, neuropsychiatric symptoms, and functional status had been collected before the course with the Mini-Mental State Examination (MMSE), the Neuropsychiatric Inventory (NPI), and the Instrumental (IADL) and Basic (BADL) Activities of Daily Living scales, respectively. The caregiving burden had been evaluated at the end of the course by means of the Zarit Burden Interview (ZBI). After the COVID-19 lockdown, a phone interview was made to compare neuropsychiatric symptoms, functional status, and caregiver's burden with the previous evaluation.

Results: There were no significant changes before and after the COVID-19 lockdown in the mean NPI score. The IADL, BADL, and ZBI scores were significantly lower after lockdown than before. The BADL scores were inversely associated with ZBI scores. Thus, despite a worsening of patients' functional status, the caregivers' burden decreased significantly probably due to the positive effect of the family support intervention.

Conclusions: Our study demonstrated that a complete family support intervention for caregivers of patients with cognitive decline or dementia can reduce the burden of care even in a particular negative period, such as the COVID-19 lockdown.

Keywords: dementia, Alzheimer's disease, caregiver, behavioral disorders, non-pharmacological treatment, neuropsychiatric symptoms, psychoeducational interventions, burden

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic had a great impact on the global population. Among them, older people are still paying the higher price in terms of mortality, probably because of underlying chronic illnesses, such as hypertension, diabetes, ischemic heart disease, chronic obstructive pulmonary disease, and hematological and oncological diseases, which represent the main dangerous factors of this infection (1). The high risk of mortality following COVID-19 infection in the elderly population is now well-known, whereas the impact that the lockdown restrictive measures have had on the general population and on frail elderly people in particular is not yet completely clear.

In fact, during the lockdown period, the whole Italian population was confined at home, the normal daily routine was completely disrupted, no longer allowing regular motor activity and social interactions that for many elderly people were of fundamental importance. In addition, many facilities for the elderly were no longer able to provide their services: the day centers in the residential facilities were closed, and community resources were temporarily interrupted.

It was observed that the COVID-19 lockdown-related restrictions had a great impact on patients with mild cognitive impairment (MCI) or dementia (2) with worsening of the behavioral and psychological symptoms of dementia, also called neuropsychiatric symptoms (3, 4). Neuropsychiatric symptoms are a group of heterogeneous symptoms that include psychosis, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, aberrant motor activity, night-time behavioral disturbances, and appetite and eating abnormalities (5). Neuropsychiatric symptoms occur at all stages of cognitive disorders including pre-clinical, MCI, or dementia (6) and are associated with more rapid cognitive decline and poor functional status (7). Neuropsychiatric symptoms are a frequent reason for institutionalization (8), have a high prevalence in residents of long-term care homes (9), are associated with increased mortality risk, and cause considerable suffering for individuals with dementia and their caregivers (10). Moreover, neuropsychiatric symptoms are the most stressful aspects strongly reducing the quality of life for both patients and caregivers (11), leading to medical interventions, changes in pharmacological therapy, and greater use of drugs potentially harmful for the elderly, such as neuroleptics and benzodiazepines (12, 13).

Two recent studies found worsening of neuropsychiatric symptoms in patients with MCI or Alzheimer's disease (AD) during the COVID-19 confinement (3, 4). Moreover, the duration of confinement was significantly correlated with the severity of symptoms as well as with the caregivers' distress (3). Another sub-study of a multicenter nation-wide survey based on a structured telephone interview delivered to family caregivers of patients with AD or other types of dementia found an increased prevalence of symptoms of anxiety, feeling of helplessness, anguish, concern for patient health, and familial conflicts reported by caregivers after COVID-19 quarantine (14).

Caregivers of persons with dementia commonly show high levels of psychological distress and burden related to the emotional involvement and to the comprehension and acceptance of a disease that currently does not have a specific cure (15); moreover, most of the caregivers are not prepared to deal with neuropsychiatric symptoms requiring guidance on where and how to get practical help and some advice. Several data in the literature support the efficacy of specific interventions in reducing neuropsychiatric symptoms in related caregiver's burden. A recent systematic review and meta-analysis found that psychoeducational programs focused on improving management and problem-solving in difficult situations lead to a significant reduction of the level of stress and burden of the caregivers (16). Moreover, some data suggest that individual psychoeducational interventions have the strongest effects (17), whereas more recent findings suggest better efficacy of group interventions (15).

It has been highlighted that the COVID-19 quarantine can determine neuropsychiatric symptoms increase in patients with dementia and higher burden of their caregivers (14, 18). A recent study found that 51.9% of patients with dementia had worsening of preexisting neuropsychiatric symptoms, 26% of patients had new neuropsychiatric symptoms onset, and 27.6% of patients requested drug modifications related to neuropsychiatric symptoms. Moreover, stress-related symptoms and increased burden were experienced by two-thirds of caregivers (14) during the quarantine.

Considering that specific psychoeducational interventions can reduce the stress of caregivers, the purpose of this study is to evaluate the effectiveness of a family support intervention on the caregivers' burden after the COVID-19 lockdown. In particular, we suppose that the family caregivers who received training on non-pharmacological dementia management strategies are able to address the neuropsychiatric symptoms during the COVID-19 lockdown and thus they have a low level of caregiving burden.

METHODS

Participants

We collected data from the Alzheimer's Regional Center of the ASST Rhodense, an outpatient memory clinic near Milan (Italy). We included only those patients whose related caregivers participated to the last edition of the course for family members of patients with AD that took place from September to December 2019. Inclusion criteria were: (1) patients with at least one cognitive evaluation within 3 months before the course, (2) caregivers who participated to the first two meetings and at least to the 50% of the course, (3) caregivers able to undergo testing procedures, and (4) caregivers must have, in the judgement of the clinician, frequent and sufficient contact with the patient to be able to provide accurate information regarding the patient's cognitive, behavioral, and functional status: a contact was considered "sufficient" when the caregiver was living with the patient or, in case the patient was living alone (i.e., for patients with MCI), when the caregiver had daily contact with the patient.

Of the 94 patients, 41 were excluded because the caregiver did not participate to at least four of eight meetings. Eight patients were excluded because the caregivers refused to fill out the burden caregiver questionnaire. We also excluded 4 subjects because the caregivers did not attend the first two meetings that were essential to learn important information about the disease and how to handle neuropsychiatric symptoms and problems related to dementia. Finally, we excluded 7 patients because the caregivers did not have sufficient contact with the patients. Thus, the final study population consisted of 34 patients and related caregivers. Each patient and caregiver had signed an informed consent for the use and processing of personal data before participating to the course for family members.

Family Support Intervention

We propose a family support intervention every year, for the family members of our patients to support them in acquiring and maintaining the difficult caregiver's role. Our family support intervention consists in a training course divided into eight meetings during which the participants receive information on different aspects of the disease, they are instructed on the management of behavioral and psychological symptoms associated with dementia, and they acquire knowledge about public care services and associations for family members in our area.

Each meeting is divided into a part of frontal lesson of about 80 minutes and a part of about 40 minutes in which there is a lot of time for questions and for sharing experiences. At each meeting, one or more speakers (specialists from the memory clinic, psychologists, lawyers, nurses, physiotherapists, representatives of the voluntary association, and general practitioners) take part. Moreover, a specialist from the memory clinic (clinician or psychologist) moderates the discussion and sharing part. The first two meetings are dedicated to the description of the cognitive disease, the different types of dementia, and the related behavioral disorders: the participants are informed on the definition and natural course of the disease, and they are advised on pharmacological therapies and progress in research, cognitive and motor stimulation, prevention, and lifestyles. The third and fourth meetings are focused on illustration, sharing, and training on non-pharmacological interventions of cognitive and behavioral disorders especially at the level of home care management by the caregivers. The fifth meeting is about legal issues related to AD or other forms of dementia, with particular attention to the role of the legal administrator. The topic of the sixth meeting is the severe phase of dementia and the end-of-life care for people with dementia: the principles of intervention and the role of the general practitioner in collaboration with the specialist are debated. In the seventh lesson, a psychologist discusses the theme of the family and AD, giving strategies for best living with people with dementia. Finally, in the last meeting, the local resources for people with dementia are described: Alzheimer's volunteers' groups, Alzheimer's association programs, social resources, and nursing homes. The main family course program is available as **Supplementary Material**.

At the end of each meeting, data were collected by means of questionnaires administered to family members in order to monitor risk situations and to evaluate the effectiveness of proposed intervention.

Patients and Family Members Evaluation

For each patient, the following categories of data were collected: demographic data, diagnosis, and level of cognitive decline. All patients must have a complete clinical and neuropsychological evaluation to confirm the diagnosis of cognitive decline and/or dementia. The National Institutes of Health and the Alzheimer's Association (NIA-AA) criteria were used for the diagnosis of MCI (19) and AD (20). Specific international criteria were adopted for other types of dementia (21).

For what concerns the level of cognitive decline, an evaluation in the outpatient memory clinic was performed no more than 3 months before the course for family members. The level of cognitive decline was assessed with the Mini-Mental State Examination (MMSE) (22), the neuropsychiatric symptoms were assessed with the Neuropsychiatric Inventory (NPI) (5), and the level of functioning was assessed with the Instrumental Activity of Daily Living (IADL) scale (23) and the Basic Activity of Daily Living (BADL) scale (24). At the end of the last meeting of the course for family members, the Zarit Burden Interview (ZBI) was administered. The ZBI is an interview for assessing the burden of the caregivers of people with dementia (25). It is a self-report scale that presents self-directed descriptions of management difficulties experienced in the care of a patient with dementia. The ZBI consists of 22 items rated on a 5-point Likert scale that ranges from 0 (never) to 4 (nearly always) with the sum of scores ranging between 0 and 88. Higher scores indicate greater burden.

In May 2020, after 8 weeks of the COVID-19 lockdown, a phone interview with a family member was made to investigate the family's fruition of community resources for dementia before lockdown and health resources during and after lockdown. We interviewed the family member representing the primary caregivers who attended the course (26). In particular, we investigated if patients took part to local community initiatives (i.e., community resources, day care centers, and cognitive training and cognitive rehabilitation groups) before lockdown, if they had COVID-19 infection, hospitalization, and delirium, or if they took advantage of other medical resources (i.e., call to general practitioner, memory clinic, and Alzheimer's associations) during and after the COVID-19 lockdown. During the phone call, the NPI, IADL, BADL and ZBI were also administered.

Statistical Analysis

The distribution of the analyzed variables was verified using the Shapiro–Wilk test: all continuous variables, except MMSE and age, had a non-normal distribution. Thus, the comparison between pre- and post-lockdown for socio-demographic data and clinical variables was performed using Wilcoxon signed-rank test.

To evaluate the association between caregiver burden during the lockdown and socio-demographic and functional variables, multiple regression analysis was performed. The standardized coefficients (beta) were calculated. ZBI delta score was entered as a dependent variable, whereas delta scores of total NPI, IADL, and BADL (post-lockdown score minus pre-lockdown score), age, sex, and years of education were entered as independent variables. The level of statistical significance was defined as $p < 0.05$.

RESULTS

In the final sample of 34 patients, 76.5% were female. Mean age ± standard deviation (SD) was 81.5 ± 5.2 years, and mean educational level ± SD was 6.3 ± 2.6 years. Concerning diagnosis, 25 patients (73.5%) had AD, 6 (17.6%) had mixed dementia (AD associated with cerebrovascular disease), 1 (2.9%) had Lewy-body dementia, and 2 (5.9%) were classified as MCI.

The 52.9% of patients were married, and 47.1% were widowed; 70.6% of patients were living with a caregiver, whereas 29.4% of them were living alone. The primary caregivers who attended the course were sons (64.7%), spouses (32.4%), and others (2.9%).

Before the COVID-19 lockdown, 5 patients (14.7%) made use of community resources, 3 patients (8.8%) regularly attended day care center, 1 patient (2.9%) was involved in a cognitive rehabilitation group, and 1 patient (2.9%) benefited from cognitive individual home stimulation.

During the COVID-19 lockdown, only 1 patient (2.9%) had delirium, and 3 patients (8.8%) resorted to clinical care (1 patient referred to a general practitioner, and 2 patients called the outpatient memory clinic). Only for 2 patients, it was necessary to add neuroleptic to the standard pharmacological therapy: no benzodiazepines nor other psychoactive drugs were added. None of the patients got COVID-19 infection nor was hospitalized.

Table 1 shows the pre- and post-COVID-19 lockdown values of clinical variables: our sample of patients had a mean MMSE total score of 16.9 (SD = 5.1, range 3–28). After the COVID-19 lockdown, there was a decrease of NPI total score and NPI caregiver stress score, but it was not statistically significant. Both IADL and BADL total scores were lower after lockdown, indicating a significant functional loss. After lockdown, the ZBI mean score was lower than before, which means a significant lower caregiving burden.

In order to evaluate the possible association between ZBI delta score (post-lockdown ZBI score–pre-lockdown ZBI score) and delta score of others clinical variables (post-lockdown score–pre-lockdown score), we performed multiple regression analyses: ZBI delta score was negatively associated with BADL delta score ($\beta = -0.603$, $t = -3.811$, $p = 0.001$), meaning that higher disability on basic activities of daily life was associated with higher caregiving burden (**Figure 1**).

TABLE 1 | Clinical variables pre- and post-COVID-19 lockdown.

Variable name	Pre-COVID-19 lockdown		Post-COVID-19 lockdown		p
	Mean	SD	Mean	SD	
MMSE	16.9	5.1	n.a.	n.a.	
NPI total	13.2	14.9	10.8	15.2	0.136
NPI caregiver stress	6.6	7.1	5.7	7.1	0.284
IADL	3.12	2.3	2.4	2.0	0.005**
BADL	5.1	1.3	4.7	1.7	0.013*
ZBI	31.6	13.9	25.3	12.9	0.000***

SD, standard deviation; MMSE, Mini-Mental State Examination; n.a., not available; NPI, Neuropsychiatric Inventory; IADL, Instrumental Activity of Daily Living; BADL, Basic Activity of Daily Living; ZBI, Zarit Burden Interview. $^{*} = p < 0.05$; $^{**} = p < 0.01$; $^{***} = p < 0.001$.

DISCUSSION

To our knowledge, this is the first study that analyzes the effectiveness of a structured family support intervention on the possible negative effects that the COVID-19 lockdown could have as determined on elderly people with cognitive decline or dementia. We found that, after lockdown, patients whose family members attended the course did not have a worsening of neuropsychiatric symptoms; moreover, the relative caregivers showed less caregiving burden despite a worsening of patients' disability, and finally, there was an extremely low request of medical interventions.

The COVID-19 pandemic had a significant impact on all social and economic sectors worldwide (27); moreover, the general population had to bear the increasing burden of the epidemic with important consequences in terms of psychological impact (28). The elderly with impaired cognition or dementia suffered more the consequences of the COVID-19 lockdown: they could have difficulties in understanding restriction measures, their routine was altered, and social interaction was almost reset; moreover, cognitive stimulation programs were interrupted leading to important alterations in these patients (4), such as the onset or the worsening of neuropsychiatric symptoms. Neuropsychiatric symptoms are described in institutionalized elderly people without dementia (29), in stroke patients (30), in Parkinson's disease (31) and in AD patients, and in other dementia patients (32). They accelerate the progression of disease and institutionalization, and they predict poorer quality of life, increased disability of patients, and great distress for patients and caregivers (33). Lara et al. (4) found worsening of some neuropsychiatric symptoms (agitation, apathy, and aberrant motor activity) after 5 weeks of lockdown in a sample of MCI and AD Spanish population; moreover, many patients and caregivers reported that their health condition had worsened after confinement (4). In another study by Boutoleau-Bretonniere and colleagues, caregivers of 38 patients with AD have been contacted. They were confined to their homes for nearly 2 months, and they were asked to report whether patients experienced any change in neuropsychiatric symptoms during, compared with before, the confinement and rate its severity and impact on themselves using the Neuropsychiatric Inventory—Questionnaire (3). The authors found neuropsychiatric symptom changes during lockdown only in 10 AD patients. For these patients, the neuropsychiatric changes were significantly correlated with symptoms severity and caregivers' distress (3). The lack of neuropsychiatric assessment before the confinement limits the results of the study.

In our study, we did not find a worsening of neuropsychiatric symptoms despite the negative impact that the COVID-19 lockdown could have had on patients with cognitive decline or dementia. We think that this result is to be mentioned and it

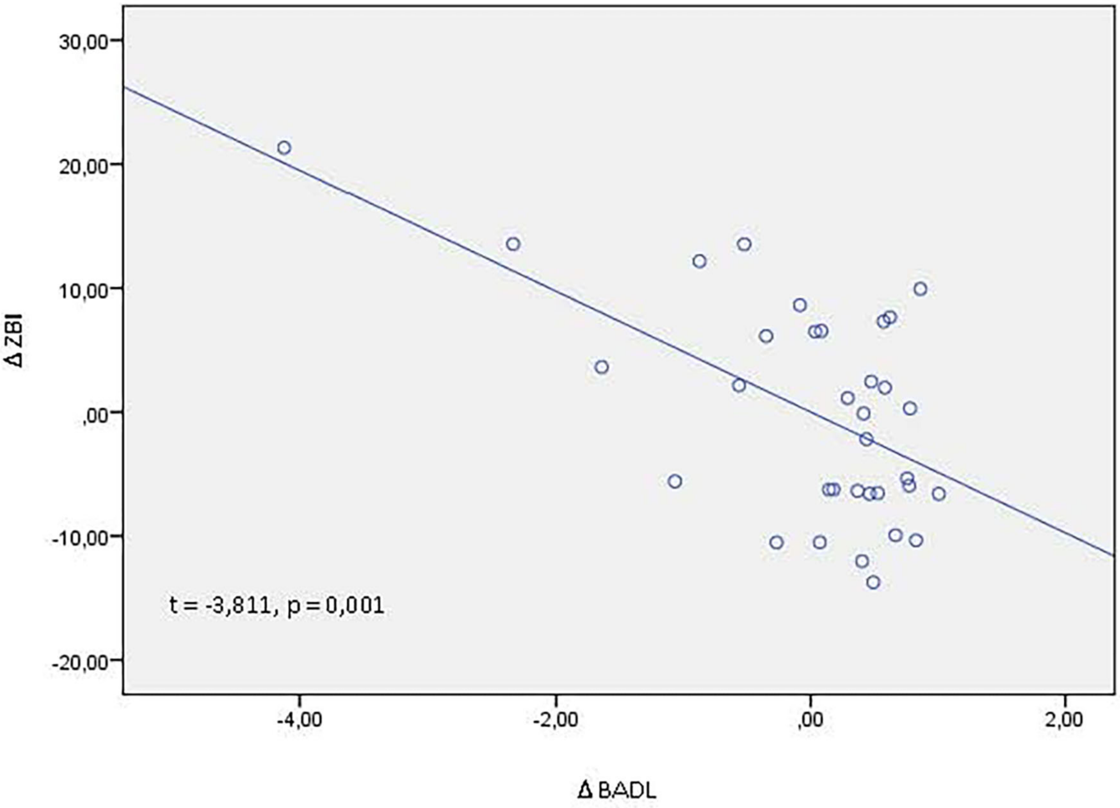

FIGURE 1 | Partial regression plot between Δ ZBI (post-lockdown ZBI score – pre-lockdown ZBI score) and Δ BADL (post-lockdown BADL score – pre-lockdown BADL score). ZBI, zarit burden interview; BADL, basic activities of daily living; *t*, *t* test statistic; *p*, statistical significance.

is likely to be related to the management of neuropsychiatric symptoms learned during the course for family members. Several studies support the efficacy of non-pharmacological treatment, such as sensory stimulation interventions, cognitive/emotion-oriented interventions, behavior management techniques, and other therapies, on neuropsychiatric symptoms in patients with dementia (34). Studies also show that caregiver support, education, training, and skill development finalized to effectively problem solve and communicate can be beneficial (35). In our study, only a quarter of patients attended specific programs that can be considered as non-pharmacological treatment (i.e., day care centers, cognitive rehabilitation groups, and individual cognitive stimulation); thus, we believe that specific information on the disease and the management of behavioral disorders given to family caregivers during the course was powerful in reducing the possible negative effects that the COVID-19 lockdown could have on patients' behaviors. Moreover, the obtained results could be partly attributable also to the full pathway of care proposed in the memory clinic and of which the course belonged to. After the diagnostic process, the patient and the family members have an interview with both geriatrician and specialist nurse: the physician communicates the diagnosis and shares therapeutic, prognostic, and assistance aspects, and the nurse defines the care strategies, such as non-pharmacological home management of cognitive and behavioral disorders, and gives helpful information on lifestyle and community resources for patients with dementia. During the interview, special emphasis is placed on the importance of attending the course of training and support of family members in order to optimize the management of the disease and improve living with the patient. Finally, to motivate family caregivers to attend the course, it is described as a decisive therapeutic intervention that must be associated with pharmacological therapy. The effectiveness of the family support intervention could be also evident on the low use of medical resources. Recent data from telehealth home support during the COVID-19 confinement for community-dwelling older adults with MCI or mild dementia found that 39% of respondents had contacted health and social services (36), whereas in our sample, only 8.8% of patients have needed a contact.

Another interesting result is that caregiving burden was higher before than after lockdown. This could be due to several reasons: first, it could be a direct effect of the knowledges learned during the course. There are a lot of data in the literature demonstrating that psychoeducational interventions have a strong effect on caregiver's burden: most of the interventions are based on educational programs focused on increasing caregivers' knowledge of the disease and developing specific skills to deal with challenges in caregiving (16), such as in our course. At the first caregiving burden evaluation, performed at the end of the course for family members, the caregivers acquired information that they will have implemented in the months after. Indeed, during the course, we pay great attention to promote caregiver resilience and positive growth, we make participants aware on what community resources are available, we show some simple relaxation techniques that can help relieve stress, we highlight the benefit of physical activity in reducing stress and improving overall well-being, we give information to better understand and cope with the behaviors and personality changes that often accompany AD and other types of dementia, we give contacts for phone and online support, and we give financial and legal information that can be useful for future care and decisions. Second, this result could be related also to the not worsening of neuropsychiatric symptoms that we found and described previously. Research studies have consistently found neuropsychiatric symptoms to be most disturbing to family caregivers (37). In addition, long-term longitudinal studies showed that neuropsychiatric symptoms early during dementia (38), as well as their subsequent worsening (39), were most predictive of increases in burden scores over time. Neuropsychiatric symptoms are distressing for family caregivers because they are unpredictable, disruptive, difficult to manage, potentially embarrassing or abusive, and sleep depriving (37). We did not find a worsening of neuropsychiatric symptoms from the evaluation made before the family course and that after lockdown, and this may have influenced the caregiving burden. Third, the caregiving burden reduction could be the result of lockdown itself. This is the eventuality if the interviewed caregiver was isolated from the patient during the lockdown period and so the caregiver did not have to undergo the behavioral symptoms related to dementia. However, we must note that more than 70% of patients were living with the interviewed caregiver. Moreover, the lockdown may have caused an attention switch to more stressful situations than caregiving itself or the caregiver gets used to the caregiver environment.

Finally, we want to discuss the results on the functional status of our sample of patients: from the first evaluation, made before the family course, and the second one, it has been 8–10 months. During this time, we can suppose a progressive worsening of dementia severity that includes a progressive loss of independence in IADL and BADL, as we found in our data. Interestingly, caregiving burden was associated only to BADL, with higher burden associated with higher loss of BADL, and this data was evident on the results of regression analysis. BADLs consist of self-care tasks that include bathing, grooming, dressing, toilet hygiene, functional mobility, and self-feeding. The impairment of these basic activities increases the personal involvement of the caregiver in terms of the number of daily care hours, leading to higher caregiving burden (40). In a large survey of caregivers in five European countries, BADL impairment emerged as the most problematic area, followed by behavior problems, cognitive impairment, and communication problems (41). Another study showed that functional dependency was more strongly correlated with the number of care hours than neuropsychiatric symptoms and was the only factor independently associated with missing hours at work for those who were employed (42). Based on these data, we can suppose that support actions aimed at lightening the ADL-related workload can also improve caregiving burden.

Before conclusions, some limitations of this study should be acknowledged. First, the sample of the study is not very large; moreover, most variables did not have a normal distribution. Thus, to overcome possible statistical bias, we performed non-parametric statistical analysis. Second, the first evaluation was made by personal interview, whereas the second one was made by phone, and this could be a risk of bias. Third, we cannot collect data on the cognitive status of patients after lockdown due to pandemic restriction. Fourth, the lockdown itself may have determined a low use of medical resources. Finally, a control group of patients whose caregivers did not attend family course is missing.

The strengths of our study include a longitudinal evaluation with the same tests performed close to a family support intervention and after a dramatic event, such as pandemic lockdown.

CONCLUSIONS AND IMPLICATIONS

In conclusion, our study demonstrated that a complete family support intervention with the aim to teach, train, and aid caregivers of patients with MCI, AD, and other types of dementia can reduce the caregivers' burden even in a particular negative period, such as the COVID-19 lockdown.

The implementation of non-pharmacological strategies in the treatment of patients with dementia can reduce the use of potentially harmful drugs and improve the quality of life of patients and caregivers.

DATA AVAILABILITY STATEMENT

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

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 patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LC and EM had the initial idea. EM and CC collected the data. LC and FA analyzed the data. LC wrote the first draft. All authors carefully reviewed, discussed and contributed to various draft of the manuscript. All authors approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.590104/full#supplementary-material

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Stressful Life Events and Resilience During the COVID-19 Lockdown Measures in Italy: Association With Mental Health Outcomes and Age

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Background: The COVID-19 pandemic, due to its disproportionated higher morbidity and mortality rates in the older age, has been considered to be a "geropandemic." Several studies, however, have found that older age is associated with lower psychological distress in relation to the COVID-19 outbreak and related lockdown measures.

Aim: To explore the role of Resilience as a mediator between stressful COVID-19 related life events and depressive and, anxiety symptoms and perceived stress, and to ascertain the role of age as a moderator of the mediator's effect.

Methods: An on-line survey was spread through social networks during the first lockdown in Italy. Depressive and anxiety symptoms and perceived stress were measured using the Italian version of the Patient Health Questionnaire-9 (PHQ-9), the Generalized Anxiety Disorder Questionnaire-7 (GAD-7) and the Perceived Stress Scale (PSS). Resilience was measured using the Italian version of the Resilience Scale for Adults (RSA). Stressful COVID-19 related life events were explored using a checklist of events derived from the International Adjustment Disorder Questionnaire (IADQ). After a preliminary panel of linear regressions, mediation was tested using Structural Equation Modeling and inspecting the bootstrapped indirect effects. Afterwards, age was introduced as a mediator of the indirect effect in a moderated mediation analysis.

Results: Twenty one thousand three hundred and thirty four subjects completed the questionnaire, 17,178 (80.52%) were female, 748 (3.5%) were >60 years old. In the whole sample, the presence of any stressful event was associated with depressive and anxiety symptoms and perceived stress. Resilience mediated the effects of stressful COVID-19-related events on depressive and anxiety symptoms and perceived stress. The moderated mediation analysis revealed that age moderated the mediation effect of Resilience between the presence of a stressful event and the selected outcomes.

Conclusion: Taken together, our results show that age moderates the mediating effect of Resilience in the relationship between COVID-19-related stressful events and depressive and anxiety symptoms and perceived stress. Older adults' Resilience was less influenced by stressful events, and this could be one of the reasons accounting for the better mental health outcomes observed in the older age.

Keywords: old age, resilience, COVID-19, mental health, stress

INTRODUCTION

The COVID-19 pandemic, due to its disproportionated higher morbidity and mortality rates in the older age, has been considered to be a "geropandemic" (1). Several studies, however, have found that older age is associated with lower psychological distress in relation to the COVID-19 outbreak and lockdown measures. Younger individuals, especially women, report higher levels of depressive, anxious and stress-related symptoms compared to older age (2–4). The evidence that older age is associated with better psychological outcomes is in apparent contrast with the increased physical vulnerability of the elderly to the COVID-19. Despite morbidity and mortality is highly correlated with age (5), a recent study found that older adults show slightly less COVID-19-related worries compared to younger participants (2). On the other hand, several studies have highlighted issues such as isolation and loneliness.

Resilience could be one of the putative psychological factors that could account for a better adaptation to the COVID-19 pandemic in the elderly. In the geriatric literature, resilience is associated with successful aging (6), lower mortality, lower depressive symptoms, increased quality of life and better lifestyle behaviors.

Resilience is considered a protective mechanism operating in the face of negative stressors (7), and it is constantly associated with better psychological well-being and lower mental illness. It has been suggested that older adults may express higher levels of resilience compared to the younger ones (8), in particular regarding emotion regulation and problem-solving dimensions. In contrast, younger individuals show slightly higher social support, in the context of reduced overall resilience levels. According to a recent systematic review, resilience in older adults could be operationalized as a 4-dimension construct, that includes intrapersonal, interpersonal, spiritual and experiential protective factors (9). It is noteworthy that these factors are differentially associated with age or environmental circumstances, being interpersonal factors the most volatile over time and spiritual and experiential factors being associated with older age.

Age differences in resilience levels could be associated with the difference in mental health outcomes across the general population. It has been reported that during the lockdown, resilience levels were lower than normative data in younger adults aged 18–35 years (10), and this was suggested as one key factor affecting the general population's mental health and pessimism about the future of the pandemic.

Few studies have addressed the relation between resilience, mental health and age at the time of the COVID-19 pandemic. In a recent study on a US sample, higher resilience was associated with lower depressive and anxiety symptoms in the general population (2). In his study, the mitigating effect of high resilience with lower anxiety was stronger in older age. Such finding was associated with lower COVID-19-related worries in the older age. In another study on a Turkish sample, older age was associated with both higher resilience and lower depression rates (11).

The exact pathways by which resilience interacts with age in affecting mental health remains unclear. The present study aims to address the role of resilience in older adults with respect to mental health outcomes during the COVID-19 pandemic. Our hypothesis is that the role of Resilience in mitigating the impact of COVID-related stressful life events may be different at different ages. To test this hypothesis, it was firstly tested whether resilience would mediate the relationship between COVID-19-related stressful events and depressive and anxiety symptoms and perceived stress (mediation). Secondly, we tested whether the indirect effect of stressful events on depressive and anxiety symptoms and perceived stress via resilience would be moderated by age. Such model is referred to as Moderated Mediation, i.e., a model in which a mediator has a different effect at different levels of a moderating variable (12).

METHODS

Study Design

This study is a cross-sectional web-based observational study, and it is a part of a long-term monitoring program of mental health outcomes in the general population and health care workers. On-line consent was obtained from the participants. At 3 weeks after the beginning of the lockdown, an anonymous survey was conducted among a self-selected sample from the Italian population. Every person living in Italy $\geq$ 18 years old was eligible. Approval for this study was obtained from IRB at the University of L'Aquila. This study adheres to the Declaration of Helsinki.

Sampling Strategy and On-Line Questionnaire Dissemination

For the purpose of this study, the questionnaire was spread using sponsored adverts on Facebook®, as well as using a snowball spreading technique starting from the researchers' acquaintances. Because of the particular dissemination technique, it was not possible to have precise data on response rate, however using the Facebook Ads app, it was possible to estimate that the number of link clicks was about 100.000, while the ad reached nearly 1 million people.

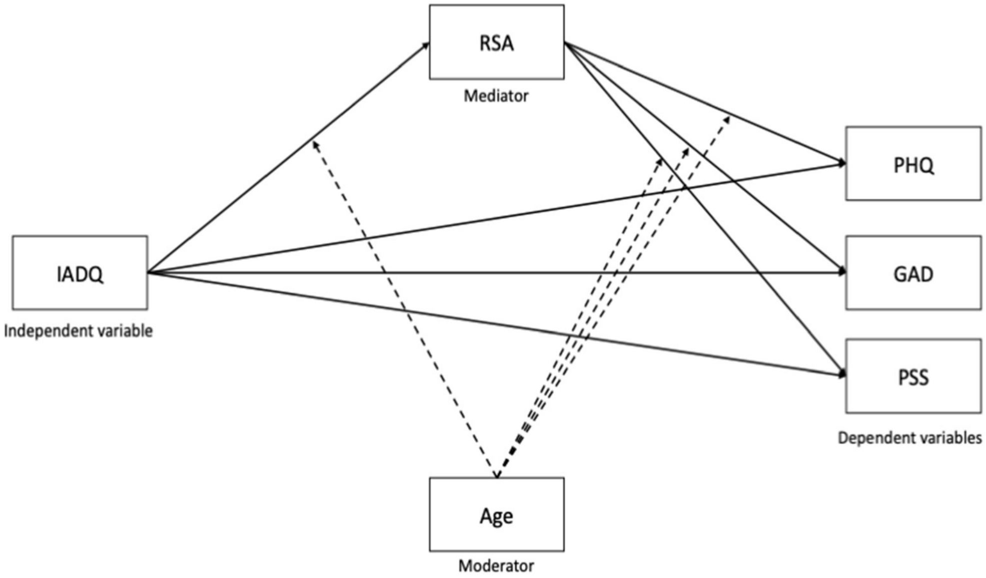

FIGURE 1 | Proposed moderated mediation model. PHQ, Patient Health Questionnaire; GAD, Generalized Anxiety Questionnaire; PSS, Perceived Stress Questionnaire; RSA, Resilience Scale for Adults; IADQ, International Adjustment Disorder Questionnaire – stressful events checklist.

TABLE 1 | Sample characteristics.

	Total sample	**<60 yr**	**≥60 yr**	**Statistics (χ^2 or Mann-Whitney as appropriate)**
	Mean (SD)/*N* (%)	**Mean (SD)/*N* (%)**	**Mean (SD)/*N* (%)**	
Age	38.95 (12.77)	38.07 (12.09)	63.12 (4.62)	
Gender				$\chi^2_{(1)} = 05.66; p = 0.017$
Male	4,155 (19.48%)	3,984 (19.35%)	171 (22.86%)	
Female	17,178 (80.52%)	16,601 (80.65%)	577 (77.14%)	
History of psychiatric disorders	6,067 (28.51%)	5,860 (28.54%)	207 (27.71%)	$\chi^2_{(1)} = 0241; p = 0.623$
N° of Stressful events	0.81 (1.14)	0.83 (1.14)	0.35 (0.77)	$z = 12.32; p < 0.001$
PHQ	10.67 (6.39)	10.78 (6.38)	7.79 7.79)	$z = 12.84; p < 0.001$
GAD	9.03 (5.95)	9.13 (5.95)	6.26 (5.36)	$z = 13.24; p < 0.001$
PSS	24.60 (8.40)	24.76 (8.37)	20.38 (8.06)	$z = 13.85; p < 0.001$
RSA	36.96 (11.84)	37.04 (11.81)	34.68 (12.32)	$z = 5.40; p < 0.001$

PHQ, Patient Health Questionnaire; GAD, Generalized Anxiety Questionnaire; PSS, Perceived Stress Questionnaire; RSA, Resilience Scale for Adults.

Outcome Measures

The Italian version of the 9-item Patient Health Questionnaire (PHQ-9) was used to assess depressive symptoms. PHQ-9 comprises nine depressive symptoms, rated on a 4-point Likert scale, range 0–27. The total score has been taken into consideration as a continuous variable. PHQ-9 is a widely used instrument in epidemiological research as a depression screener. In our sample, internal consistency was $a = 0.87$.

The Italian version of the 7-item Generalized anxiety disorder questionnaire (GAD-7) was used to assess anxiety symptoms. GAD-7 includes seven symptoms, rated on a 4-point Likert scale, range 0–21 (13). The total score has been taken into consideration as a continuous variable. GAD-7 is a widely used instrument in epidemiological research as anxiety screener. In our sample, internal consistency was $a = 0.91$.

The Italian version of the 10-item Perceived Stress Scale (PSS) was used to assess perceived stress. PSS includes ten items rated on a 0–4 Likert scale. In our sample, internal consistency was $a = 0.87$.

Independent Variables, Covariates, and Confounders

Age was used both as a continuous and binary variable, with a cut-off of 60 years old as a separation between older and younger adults.

TABLE 2 | Association between age and depression, anxiety and stress.

	Unadjusted		Adjusted§	
	b (95% CI)	***p***	**b (95% CI)**	***p***
Age → PHQ Total	−0.11 (−0.12, −0.10)	<0.001	−0.12 (−0.12, −0.11)	<0.001
Age → GAD Total	−0.098 (−0.10, −0.09)	<0.001	−0.10 (−0.11, −0.10)	<0.001
Age → PSS Total	−0.16 (−0.17, −0.16)	<0.001	−0.17 (−0.18, −0.16)	<0.001

§adjusted for gender, region and education level. PHQ, Patient Health Questionnaire; GAD, Generalized Anxiety Questionnaire; PSS, Perceived Stress Questionnaire.

Stressful events were assessed using the International Adjustment Disorder Questionnaire (IADQ) checklist of stressful events (14). The IADQ checklist explores eight different stressful events, namely economic, job and study difficulties, problems related to housing, relational problems, own's and a loved one's health problems, caregiving problems. In the original version, each item has a yes/no response. We modified the response as follows: "*no/yes/yes, due to COVID-19 pandemic or lockdown*" in order to capture COVID-19 related stressful events. For this study, a binary variable was created with 0 = "no stressful events due to COVID-19" and 1 = "one or more stressful events due to COVID-19."

Resilience was assessed using the 11-items Resilience Scale for Adults (RSA). The RSA-11 was obtained from the original 33 item version (15). Participants answer on a 7-point semantic differential scale in which each item has a positive and a negative attribute at each end of the scale continuum. For this study, the RSA-11 total score was taken into account, with higher scores indicating lower levels of Resilience.

The following potential confounders were selected: Gender; Geographical Area (Northern Italy: Aosta Valley, Piedmont, Lombardy, Liguria, Trentino-Alto Adige, Veneto, Friuli-Venezia Giulia, Emilia-Romagna; Center Italy: Tuscany, Umbria, Marche, Lazio; Southern Italy: Abruzzo, Molise, Puglia, Campania, Calabria, Basilicata, Sicily and Sardinia); Education level (lower education, undergraduate, graduate, post-graduate degree).

Statistical Analysis

All statistical analyses were conducted using STATA® 16 (StataCorp).

Firstly, the following associations were tested using a panel of linear or logistic regressions, as appropriate for the dependent variable:

1) association between age and PHQ-9, GAD-7 and PSS
2) association between RSA and stressful events and PHQ-9, GAD-7 and PSS
3) association between RSA and stressful events and age.

Secondly, a mediation model was fitted on PHQ-9, GAD-7 and PSS, with stressful events as independent variable and RSA as mediator. Mediation was tested by bootstrapping the indirect effect at 5,000 replications. The significance of the bootstrapped indirect effects was ascertained inspecting the normal-based and bias-corrected confidence intervals.

TABLE 3 | Association between risk and protective factors and depression, anxiety and stress.

	Unadjusted		Adjusted§	
	b (95% CI)	***p***	**b (95% CI)**	***p***
Any IADQ → PHQ Total	0.44 (0.41, 0.46)	<0.001	0.42 (0.39, 0.44)	<0.001
Any IADQ → GAD Total	0.42 (0.39, 0.44)	<0.001	0.40 (0.37, 0.42)	<0.001
Any IADQ → PSS Total	0.46 (0.43, 0.48)	<0.001	0.43 (0.41, 0.46)	<0.001
RSA → PHQ Total	0.58 (0.57, 0.59)	<0.001	0.57 (0.56, 0.58)	<0.001
RSA → GAD Total	0.52 (0.50, 0.53)	<0.001	0.51 (0.50, 0.52)	<0.001
RSA → PSS Total	0.54 (0.53, 0.55)	<0.001	0.54 (0.52, 0.55)	<0.001

PHQ, Patient Health Questionnaire; GAD, Generalized Anxiety Questionnaire; PSS, Perceived Stress Questionnaire; RSA, Resilience Scale for Adults; IADQ, International Adjustment Disorder Questionnaire – stressful events checklist. RSA, PHQ, GAD, and PSS are standardized values. §adjusted for gender, region and education level.

TABLE 4 | Association between risk and protective factors and age.

	Unadjusted		Adjusted§	
	b (95% CI)	***p***	**b (95% CI)**	***p***
*Age → Any IADQ	−0.44 (−0.47, −0.41)	<0.001	−0.46 (−0.49, −0.43)	<0.001
Age → RSA	−0.14 (−0.16, −0.13)	<0.001	−0.15 (−0.16, −0.13)	<0.001
*Old Age → Any IADQ	−1.00 (−1.17, −0.83)	<0.001	−1.00 (−1.17, −0.82)	<0.001
Old Age → RSA	−0.20 (−0.27, −0.12)	<0.001	−0.21 (−0.29, −0.14)	<0.001

**logit function, dependent variable is binary. §adjusted for gender, region and education level. RSA, Resilience Scale for Adults; IADQ, International Adjustment Disorder Questionnaire – stressful events checklist.*

Finally, conditional indirect effects of COVID-19 stressful events on PHQ-9, GAD-7 and PSS via RSA, entering age as a moderator were tested. This model is referred to as "Moderated Mediation" and it is largely founded on Model 59 by Hayes (12). In **Figure 1** we show the proposed model for the moderated mediation. The significance of the bootstrapped conditional indirect effects was ascertained inspecting the normal-based and bias-corrected confidence intervals.

RESULTS

Sample Characteristics

Sample characteristics are reported in **Table 1**. Twenty-one thousand three hundred thirty-four subjects participated in the study. Of these, 17,178 (80.52%) were female. Mean age was 38.95 (SD = 12.77); 748 (3.51%) subjects were 60 or older.

Associations Between Selected Variables

Tables 2–4 report the linear associations between age, resilience, COVID-19 related stressful events and psychopathology. In our sample, age was inversely associated with PHQ-9, GAD-7 and PSS (**Table 2**). This association held after adjusting for the selected confounders. The presence of any stressful event was associated with PHQ-9, GAD-7 and PSS (**Table 3**). Better resilience resources (i.e., a lower score on the RSA-11)

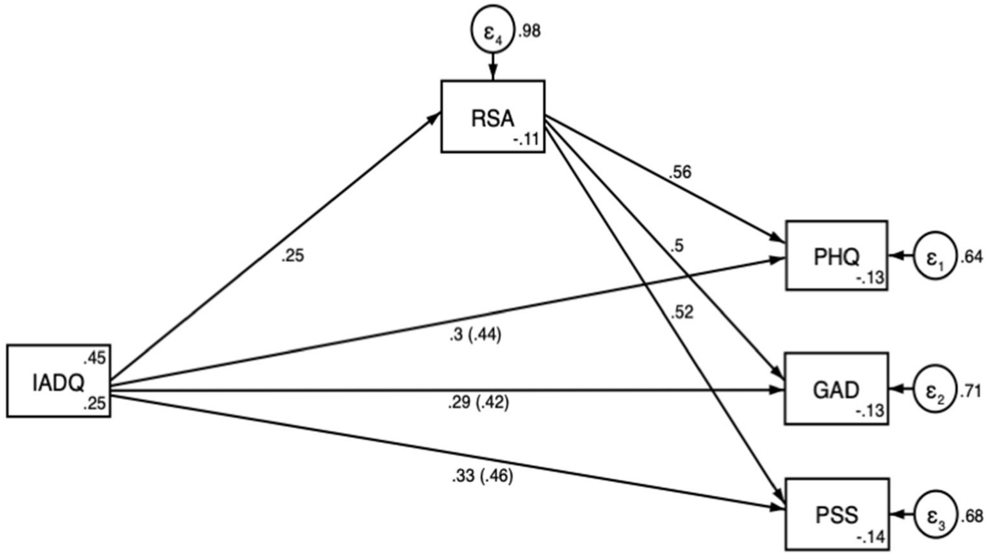

FIGURE 2 | Mediation analysis path diagram with direct effects and, in parenthesis, total effects. PHQ, Patient Health Questionnaire; GAD, Generalized Anxiety Questionnaire; PSS, Perceived Stress Questionnaire; RSA, Resilience Scale for Adults; IADQ, International Adjustment Disorder Questionnaire – stressful events checklist.

was inversely associated with PHQ-9, GAD-7 and PSS. These associations held after adjusting for the selected confounders.

Finally, age was associated with lower odds of endorsing any COVID-19-related stressful event and with better resilience (**Table 4**). These associations held after adjusting for the selected confounders.

Mediation Analysis

Mediation analysis (**Figure 2** and **Table 5**) showed that the impact of COVID-related stressful events on PHQ-9, GAD-7 and PSS was very similar. RSA partially mediated the impact of stressful events on the selected outcomes, as confirmed by inspection of the Bootstrapped confidence intervals of the indirect effect through RSA.

Moderated Mediation Analysis

Table 6 reports the bootstrapped indirect effects with normal-based and bias-corrected confidence intervals of the moderated mediation model. The confidence intervals of the interaction term Age × RSA, which represents the conditional indirect effect, show that Age moderated the mediation effect of resilience on PHQ-9, GAD-7 and PSS.

DISCUSSION

We presented a cross-sectional study aimed to evaluate how resilience differs in an age-dependent manner, representing a key feature in older adults with respect to mental health outcomes during the COVID-19 pandemic.

Results showed that age is negatively associated with PHQ-9, GAD-7 and PSS scores. This was significant even controlling for confounding factors such as gender, region and education level. In particular, having an older age (i.e., over 60-year-old) is two-fold more negatively associated with these variables. These findings highlight that older adults report lower levels of depressive symptoms, anxiety and stress compared to a younger population. People aged 60 and over usually have a higher mortality rate and are at higher risk of developing significant complications, causing them to follow more stringent measures than the others. For these reasons an inversed trend would have been expected. Although these results might be considered as counterintuitive, a number of authors have emphasized how younger people tend to report higher levels of depressive and anxiety symptoms than older ages during pandemics (16–19). This may be explained by multiple reasons, as people aged below 60 are less likely to be retired, therefore being more preoccupied about their occupational programs and economic incomes since they might lose their job (20, 21). Furthermore, it is a matter of fact that younger people are keener on spending a consistent amount of time on social networks or other news apps (22). As a result, an information overload, also defined as "infodemic," where fake news, racist opinions, magic potions and conspiracy theories are easily disclosed, may account for their higher scores (23). Lastly, older adults are more likely to have faced a number of major life events than their counterparts, having, therefore, a bigger wealth of experience that would allow them to face adversities more easily. In other words, older adults may better rely on their resilience when dealing with such situations. However, it is important to notice that mental health outcomes in this study were addressed using screeners that are more focused on the affective and cognitive components of anxiety and depression, rather than somatic complaints or loneliness, which are common features of psychological distress in the elderly.

TABLE 5 | Path analysis results.

	Coef	Confidence intervals
Direct effects		
RSA → PHQ	0.56 (0.55, 0.57)	(0.55, 0.57)
IADQ → PHQ	0.30 (0.27, 0.32)	(0.27, 0.32)
RSA → GAD	0.50 (0.49, 0.51)	(0.49, 0.51)
IADQ → GAD	0.29 (0.27, 0.31)	(0.27, 0.31)
RSA → PSS	0.52 (0.51, 0.53)	(0.51, 0.53)
IADQ → PSS	0.33 (0.30, 0.35)	(0.30, 0.35)
IADQ → RSA	0.25 (0.22, 0.28)	(0.22, 0.28)
Total effects		
RSA → PHQ	0.56 (0.55, 0.57)	(0.55, 0.57)
IADQ → PHQ	0.42 (0.41, 0.46)	(0.41, 0.46)
RSA → GAD	0.50 (0.49, 0.51)	(0.49, 0.51)
IADQ → GAD	0.42 (0.39, 0.44)	(0.39, 0.44)
RSA → PSS	0.52 (0.51, 0.53)	(0.51, 0.53)
IADQ → PSS	0.46 (0.43, 0.48)	(0.43, 0.48)
IADQ → RSA	0.25 (0.22, 0.28)	(0.22, 0.28)
Bootstrapped indirect effects		
IADQ → (RSA) → PHQ	0.14	0.12, 0.15 (*N*)
		0.12, 0.16 (BC)
IADQ → (RSA) → GAD	0.12	0.11, 0.14 (*N*)
		0.11, 0.14 (BC)
IADQ → (RSA) → PSS	0.13	0.11, 0.14 (*N*)
		0.11, 0.14 (BC)

(N), Normal-based (95% Conf. Interval); (BC), Bias-corrected confidence interval; PHQ, Patient Health Questionnaire; GAD, Generalized Anxiety Questionnaire; PSS, Perceived Stress Questionnaire; RSA, Resilience Scale for Adults; IADQ, International Adjustment Disorder Questionnaire – stressful events checklist.

TABLE 6 | Conditional Indirect effects of the moderated mediation model.

Bootstrapped indirect effects	Coef	Confidence intervals
IADQ → (RSA) → PHQ	0.13	0.08, 0.17 (*N*)
		0.06, 0.17 (BC)
IADQ → (RSA) → GAD	0.10	0.07, 0.14 (*N*)
		0.05, 0.13 (BC)
IADQ → (RSA) → PSS	0.10	0.06, 0.13 (*N*)
		0.08, 0.14 (BC)

PHQ, Patient Health Questionnaire; GAD, Generalized Anxiety Questionnaire; PSS, Perceived Stress Questionnaire; RSA, Resilience Scale for Adults; IADQ, International Adjustment Disorder Questionnaire – stressful events checklist.

According to the latest researches, COVID-19 pandemic has caused a significant increase in the prevalence of anxiety, stress and depressive symptoms (3, 4, 24). Indeed, it is not surprising that our findings showed a positive association between stressful events and depressive symptoms, anxiety and perceived stress. Notably, even controlling for potentially confounding factors like education levels, results were still significant. Indeed, according to previous studies, people with higher levels of education are more likely to develop depression and anxiety as they might be more aware of their own state of health (25).

In line with our hypothesis and consistent with previous literature, RSA scores are linearly associated with PHQ-9, GAD-7 and PSS. This means that higher levels of resilience act through a "buffering effect" on such variables, therefore mitigating COVID-19 related stressors (2).

Supporting the hypothesis that older adults have better abilities to manage calamities and to get by during difficult times, regression analyses showed that age is inversely associated with any of IADQ items and RSA scores. Results are even higher when old age is set as the independent variable, meaning that people aged 60 and over perform remarkably better at successfully overcome stressful life events such as COVID-19 pandemic. These findings are in line with previous research, as a number of authors have recognized how older people generally have high levels of resilience during difficult times, despite their own state of health, socioeconomic status and past personal experiences (26).

Our simple mediation analysis highlighted the role of COVID-19-related stressful events on resilience, reporting a positive association with RSA scores. These findings show that bigger stressful events are capable of affecting one's ability to cope with adversities. Moreover, other than having a direct effect on PHQ, GAD-7 and PSS scores, IADQ acts indirectly on these three variables. Indeed, when setting RSA as a mediating variable, regression coefficients still show a positive association with PHQ, GAD-7 and PSS scores. In other words, COVID-19-related traumatic events (e.g., losing loved ones, lockdown stringent measures, poor economic incomes) may impact directly on enhancing depressive symptoms, anxiety and perceived stress, or indirectly, lowering one's buffering effect of resilience.

The present mediating effect of RSA is different depending on the age of the subjects. In older people, resilience influences the psychopathological outcome more strongly compared to younger adults, meaning that their buffering effect is higher on depressive and anxiety symptoms and stress than their counterparts. Nevertheless, stressful events might impact differently on people aged 60 or over, with their resilience turning out to be more fragile compared to people aged under 60.

Our findings gather a strong relevance, as even if older people have stronger aptitudes to cope with difficult situations, they might experience what has been defined as a "double-burden," having their buffering abilities compromised by the disease itself (27). Indeed, in addition to their physical vulnerability, in terms of infection risk, morbidity and mortality, they might acquire a mental vulnerability, which would then lead to alarming scenarios with worse clinical outcomes.

The present work suffers from a number of important limitations – notably related to the on-line sampling technique and due to its cross-sectional fashion. Firstly, social network-based recruitment carries a significant selection bias, as people are self-selected, without inclusion criteria, and measures are self-reported. Moreover, on-line sampling may introduce a selection bias excluding subjects with poor informatic literacy or even cognitive deficits. As a matter of fact, internet use is associated with a number of factors that promote successful aging, including cognitive functioning and higher socioeconomic status (28). Secondly, although follow-up data will be collected across time, the cross-sectional design of this study does not leave enough room for causal inferences. For these reasons, caution must be taken into account when generalizing results to the population. Thirdly, limitations concern the inability to address cognitive deficits using an on-line survey. Indeed, it is worth noticing how a number of relevant factors may negatively influence the psychological distress in older adults, including physical comorbidities, functional and cognitive impairments as well as loneliness and neglect. The counterpart of resilience is in fact frailty, defined as a condition of both physical and mental dysregulation that leads to a higher vulnerability and therefore worse health outcomes (29). However, data on physical comorbidities and dependency, that could definitely influence the selected outcomes in the elderly, were not collected.

Key strengths of our research are represented by its large sample size and its distinctive timing in collecting data, which was gathered when lockdown measures were implemented in Italy.

In conclusion, we found that older age is associated with higher levels of resilience. This would allow them to face weighty adversities such as COVID-19 pandemic more powerfully than the others. However, stressful life events may act stronger on them, compromising their buffering coping abilities, with higher rates of depression, anxiety and stress. As COVID-19 pandemic might have brought us in a new era of communication and technological progress, it will be important to develop more home-based agendas that would improve older people well-being and therefore enhance their resilience.

CONCLUSION

This study addressed the age-dependent effect of resilience in mediating the impact of COVID-19 stressful events on depressive and anxiety symptoms and perceived stress. Our findings suggest that resilience plays a central role in protecting older adults from psychological distress and should therefore be taken into account in general health policies as well as treatment strategies.

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 L'Aquila. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RR, VS, FP, and GL: conceptualization. RR: methodology, formal analysis, and data curation. RR and TJ: writing–original draft. RR, VS, TJ, FP, and GL: writing– review and editing. All authors contributed to the article and approved the submitted version.

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Toward Optimal Management of Behavioral and Psychological Symptoms of Dementia: Insights From a COVID-19 Pandemic Experience

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The first wave of SARS-CoV-2 has deeply affected long term care facilities in the province of Quebec. In response, governmental officials took protective measures, such as suspending visits and activities and even requiring residents to self-isolate to their room. Consequently, residents with major cognitive impairments were cut from their routine as well as from significant social interactions, support, and stimulation essential to their well-being. This isolation negatively affected many residents. For some of them, the loss of bearings resulted in newly or deteriorated behavioral and psychological symptoms of dementia (BPSD). These residents were then more at risk of contracting the virus or contaminating others. To face this challenge, hotels in the Greater Montreal area were transformed into temporary care facilities. As members of a multidisciplinary team specialized in the management of BPSD, we were asked to support the redeployed staff who had little experience in this domain. In this paper, we present the innovative tools implemented in this uncommon work setting. We also discuss factors identified as facilitating the care and treatment of people with BPSD. This experience leads us to propose avenues toward better BPSD management.

Keywords: COVID-19, dementia, major neurocognitive disorder, behavioral and psychologic symptoms of dementia, neuropsychiatric symptoms, non-pharmacological intervention, long-term care, caregiver

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INTRODUCTION

Behavioral and psychological symptoms of dementia (BPSD) are highly prevalent in patients with neurocognitive disorder (NCD), affecting more than 80% of patients in the course of their disease (1). BPSD includes a variety of heterogeneous symptoms, arising from interactions between dementia severity, environmental factors, unmet needs, somatic diseases, as well as personality and life experiences of the patient. According to a meta-analysis, the most frequent BPSD would be apathy (prevalence of 49%), followed by depression (42%), aggression (40%), anxiety (39%), sleep disorder (39%), irritability (36%), appetite disorder (34%), aberrant motor behavior (32%), delusion (31%), disinhibition (17%), and hallucination (16%) (2).

Other studies consider neuropsychiatric syndromes instead of single symptoms. According to one of them, neuropsychiatric symptoms could be classified into five distinct sub-syndromes: apathetic (as unique syndrome), affective (anxiety and depression), psychomotor (agitation, irritability, and aberrant motor behavior), psychotic (delusions and hallucinations), and manic (disinhibition and euphoria) (3).

It is important to address BPSD as it is associated with distress in nursing staff, special treatment needs as well as behavioral, medical and care complications (e.g., psychiatric consults, neurotropic drugs, physical/verbal aggressions, falls) (4).

Knowing the low efficacy of antipsychotic drugs concerning BPSD, and their deleterious side effects, there is now a consensus in the literature that non-pharmacological approaches should be the first choice of treatment when dealing with NCD related symptoms (5). These strategies encompass a large range of individually tailored interventions aimed at improving symptoms in patients and reducing caregiver stress by adapting routines, environment, or interaction with carers. However, implementing these approaches in real-world settings remains challenging for numerous reasons: poor access to expertise (6), unfamiliarity with non-pharmacological treatment among physicians, a well-established culture of psychotropic prescription to face "aggressive" behaviors (7, 8) and staff's lack of time and training (9).

Moreover, the COVID-19 pandemic brought its share of challenges regarding BPSD management. Since older adults were identified as a particularly vulnerable population group, Quebec authorities decreed restrictive measures for their protection. These measures were particularly drastic in long-term care facilities, where most residents suffer from major NCD. Residents were confined to their nursing homes and even to their room. Visits were banned and social activities were suspended, depriving residents of their usual interactions, stimulation, and routines. These protective measures forced residents to live in an impoverished and stressful environment, in which their basic psychosocial needs were not fulfilled. Studies have demonstrated the dramatic impact of quarantine on the clinical symptoms of patients with NCD. Some authors reported not only a worsening of cognitive function, but also an aggravation of behavioral symptoms in 51.9% of the patients, such as irritability, apathy, and agitation, or the onset of new behavioral symptoms for 25.9% of them, namely irritability, sleep disturbance, and agitation, with therapy adjustments required. Quarantine was also associated with an increase of caregiver's burden, mainly anxiety, depression, irritability, and distress (10).

Facilities for older adults in Quebec were particularly affected by the pandemic. The situation became critical in many of them. Medical care demands were high because of COVID infection among residents and many residences were understaffed because of the virus spreading among staff members. These conditions made residents' management difficult and propitious to adverse events. Also, contamination risks were hard to handle as many residents were not able to cope with the sanitary rules because of their cognitive state and limited adaptative mechanisms. Moreover, due to the disruptive impact of COVID-19 on the healthcare system, BPSD could not be addressed as needed. As seen in other countries (11), services dedicated to patients with NCD and BPSD were diminished, canceled or restricted to emergencies, decreasing the overall quality of care for these patients as well as impeding support and recommendations normally given to care facilities.

Since home care facilities were overwhelmed by the situation, some residents presenting BPSD were temporarily relocated to hotels of the Greater Montreal area. These were transformed into dedicated non-conventional sites, with the hope of limiting the risk of virus propagation.

In one of these hotels, members of our mobile team, composed of neuropsychologists and occupational therapists specialized in the management of BPSD, were dispatched to support the frontline health workers. Between April 8th and June 29th, 2020, one hundred and sixty-five residents were transferred to the hotel. To be admitted, the premise was that residents were not able to respect sanitary rules because of cognitive impairments. Only few exceptions included patients admitted based on the risk of contaminating another older adult living in the same space (e.g., spouse). Residents came from eastern Montreal, a multicultural district with lower economic conditions. They came from either retirement homes or intermediate care units. Except for the aforementioned particular cases, all residents presented major NCD with mild to moderate BPSD (wandering, depressive symptoms, repetitive questioning, following carers closely, refusal of collaboration for ADL). We estimate that over 90% of the residents required at least one intervention during their stay, while approximately half of them needed a more sustained implication of our team.

A few days after opening, many obstacles as to the care and security of people presenting NCD with neuropsychiatric symptoms were observed. Indeed, staff members deployed to hotels, such as nurses, physicians, and patient attendants, often came from different medical backgrounds. Most of the orderlies volunteering following a governmental appeal had no previous experience in the healthcare system at all. Finally, the physical environment was unfit for older people coping with the loss of independence: furniture and bathrooms were not adapted, corridors were dark and deprived of windows, emergency exits were easily accessible, and room doors could be locked from the inside. These features had the potential to generate more BPSD.

Working in this unconventional setting meant adapting our usual intervention methods. At least one member of our team was on-site Monday to Friday, from 6 A.M. to 10 P.M. We favored regular discussions directly with the staff to gather information about problematic situations, instead of the usual questionnaires or observational charts. We adapted our schedule to be able to exchange with staff members of every shift. To promote knowledge about BPSD, different teaching methods were used: direct feedback and coaching, modeling, discussions in small groups, and informative posters disposed on walls featuring notions of BPSD and strategies (refusal management, diversion, adapted active listening, etc.). Furthermore, to promote a person-centered approach, we wrote an information sheet of relevant information for most patients, with the help of a family member when possible. It was hung near the bedroom door, with the patient's or family's consent. Finally, we leveraged the technological advantage granted by WIFI access—which is lacking in most nursing homes –in the management of BPSD.

These new working conditions revealed many facilitators allowing to implement a person-centered approach and non-pharmacological strategies to address BPSD. One of the major takeaways from our experience was the speed with which staff members were able to learn the basic foundation of BPSD management, even with no prior experience in healthcare. Indeed, within a few weeks, we observed that regular staff members became more independent and seemed better at generating strategies by themselves while facing new behavioral challenges. In our opinion, this efficiency translated into benefits for the patients, who's distress seemed more easily soothed, daily care appeared to be less stressful and they seemed more quickly reassured when needed.

FACILITATORS IN THE MANAGEMENT OF BPSD

Culture and Leadership

Realizing the challenges associated with BPSD, managers quickly required the full-time presence of our specialized team. Such inclusion among staff contrasted with our usual role of external consultants. The choice of the organization to integrate us emphasized the value of our presence from the beginning, it helped us to be perceived as allies and reinforced the importance of using our services when needed. Furthermore, they considered it essential to give employees access to the expertise required for the implementation of good practices. In different healthcare settings, leadership, and tangible support from the organization is known to be a key factor allowing to successfully apply a new skill (12, 13). It is also important to note that since we worked in a non-traditional site, this establishment had no organizational culture on which to build; no dominant mindset nor established protocol for the management of BPSD. Thus, staff members and managers seemed more willing to adapt to changes when necessary.

Full-Time Presence

Working on-site brought many benefits. Staff quickly became familiar with our role and the type of situations in which we could be useful. Indeed, a home-made questionnaire administered at the closing of the hotel revealed that our regular presence brought a feeling of reassurance and relief for the majority of employees (88.2% agreed or strongly agreed with this statement). It also granted us unusual flexibility in providing opportunities for multiple learning exposures facilitating knowledge translation (14). We adapted our work to staff needs and occurring problematics and we delivered teaching according to staff availability to ensure receptivity. Also, we could modify our schedule to reach staff members from all shifts, which was essential knowing that some BPSD appear at specific times of the day or with specific caregivers. Having access to local experts dedicated to support staff has been demonstrated to be beneficial for patients in acute care settings (15).

Evidently, the ease of communication between our team and staff members accelerated the pace at which a problematic situation could be solved. We could intervene as soon as required, avoiding filling long requests and delays in care support. We were able to collect, directly from employees involved, the information pertaining to the challenging behavior, its circumstances of appearance, the approach used, and the subsequent reactions. Consequently, we benefitted from more detailed information than if gathered from a postponed debriefing or a third party. Finally, elaboration and adjustments of the intervention plans were faster than usually possible, allowing to solve a problematic dynamic before it crystallized.

Teaching Methods

Our new work environment was conducive to the use of numerous teaching methods to promote knowledge and ensure skills acquisition as to care provided to older adults. Firstly, as we could witness the ongoing interactions between patients and staff, we could offer immediate feedback and coaching to support novice staff members to adjust their approach to reduce BPSD. Feedback was given during or immediately after the intervention, making it specific, and based on observations. Timely and concrete feedback is known to be a powerful tool to promote learning (16). Also, we could ourselves participate in care when necessary, which offered opportunities to demonstrate strategies and thus served as modeling experience. For instance, when observing a conversation between a patient asking for hairspray and an attendant refusing by providing lengthy explanations, we would gently slip into the conversation and reassure the patient saying we would take care of the situation. A comeback with the attendant was done to explain, as she observed, how her answer could be modified in order to adapt it to the patient's comprehension capabilities and avoid an escalade. Multimodal educational interventions such as modeling and mentorship are recognized to facilitate integration of new skills (14).

Innovative Tools

Patient attendants and orderlies were the ones providing care and interacting with patients on a daily basis. However, they had no access to personal information about them, such as their past, habits, personality, and usual reactions. In addition, most patients could not properly communicate their needs because of their cognitive impairments. It is often the case that personal information is kept confidential, yet it complicates the individualized approach recommended for BPSD management. To overcome this issue, we wrote an information sheet, for patients presenting neuropsychiatric symptoms. It comprised information to facilitate interactions and behavior management, namely the patient's main interests, prior occupation, meaningful souvenirs, strategies recommended, and so on. Special attention was paid to avoid prejudicial or confidential data. This sheet was also meant to be collaborative, not only to demonstrate we valued staff's observations, regardless of their role or title, but also to facilitate communication between staff members, a challenge often reported in the management of BPSD (17). Having access to these personal facts was judged to be "essential" or "very useful" by nearly 95% of the staff surveyed to be efficient in their interventions. Our clinical impression is that the impact was most positive for patients, who could benefit from personalized care, meaningful conversations, and activities corresponding to interests.

Another new tool we integrated at the hotel was the support of technology to our interventions. Thanks to donations, one or two electronic tablets were provided on each floor (of 14–22 patients). We soon realized these devices were powerful avenues in managing and preventing BPSD. Possibilities were almost infinite, ranging from ludic applications, internet sites for music and videos, to different kinds of social media and video calls to maintain a connection with loved ones. The choice of application could be adapted to the person's interests, needs and capacities, sometimes with trial and error. We noticed benefits on patients' mood, collaboration and level of agitation when using electronic devices, especially when used to support activities (e.g., choral) or ADL (e.g., meals taken in video calls with a family member to stimulate appetite).

Motivation

Unprecedented times has revealed a particular propensity to help in a proportion of the population. Orderlies who volunteered to work in a COVID-19 environment were generally touched by the situation of older adults depicted in the media and came with a motivation to serve and to contribute. Of course, the fact that their initial familiarity with cognitive impairments and BPSD was low could have boosted their curiosity and their inclination toward learning. Yet, their disposition evoked the concept of intrinsic motivation, which is known to allow greater receptivity, openness, and cognitive availability for new notions taught (18). Their attitude and eagerness to learn were remarkable. Furthermore, the fact that staff contributed to successful interventions may have increased motivation to integrate the proposed person-centered approach via basic reinforcement principles.

The Perceived Role of Patient Attendants and Orderlies

The novelty of the environment allowed us to introduce an optimal model of BPSD management. We emphasized from the beginning the legitimacy of non-pharmacological interventions and we underlined that engaging in those interventions was as important as taking care of other needs, such as ADL. We taught staff members that encouraging social interactions was a powerful tool to prevent BPSD. Orderlies quickly integrated patients' occupation as a central part of their role and valued their engagement into residents' well-being, even though it wasn't explicitly part of their task description when hired. Study report that patient attendants are not encouraged to communicate small but important observations that could help in the management of BPSD (17). This is in contrast with the philosophy of care we put forward at the hotel. From our clinical perspective, the adoption of this more holistic vision brought more satisfaction for caregivers and deeper connections with patients, which also benefited the patients.

Multidisciplinarity

We knew before the pandemic that disciplines such as ours are complementary in managing BPSD. Each profession has expertise specific to its field of interest, which is best suited for different situations. At the hotel, caseloads were naturally divided according to one's expertise, with transparent communication between professions (e.g., a neuropsychologist would lead cases where psychological symptoms were prominent, whereas an occupational therapist would be requested for cases of resistance during hygiene). The integration of psychosocial disciplines are essential parts of the equation in the success of BPSD management (19), and our experience persuaded us of the relevance of this type of expertise among staff members, who are used to a dominant medical model of care.

Staff Ratio

One of the major contrasts in our work conditions, as opposed to those of the standard health care system, was the higher ratio of staff member/patient (orderlies and attendants combined). Indeed, the ratio at the hotel was on average 1 for 3.3 patients, as opposed to 1 for 5–7 patients in regular clinical settings in Quebec. Although the COVID environment meant that tasks took more time to assure safety and lower the contamination risks, staff availability was nevertheless more considerable than usual. More staff was present to address patients' needs and to do so in an individualized manner. They had more time to concentrate on a single patient if needed. Support from peers was easier to find in case of a complex situation. Also, staff members were more receptive when feedback was provided regarding a specific situation. Finally, stability of the staff was an important stake. Qualitatively, we noticed that the regular staff came to know each patient's particularities, which was advantageous to patients who could benefit of a more personalized and constant approach.

DISCUSSION

Numerous challenges pertain to the implementation of non-pharmacological interventions for BPSD. However, our recent experience as clinicians, in an atypical work setting brought by the COVID-19 pandemic, demonstrated it was possible for novice staff members to quickly integrate a person-centered approach with older adults having major NCD. The present article sheds light on multiple factors identified as contributing to the ease with which the staff acquired a new skill set to face mild to moderate BPSD. These facilitators refer to the culture and leadership, full-time presence of experts, diverse teaching methods, innovative tools, motivation, positive perceived role of staff, multidisciplinarity, and good staff ratio. We feel our observations are valuable to share in order to guide the scientific community, organizations, and clinicians, as to the factors we need to document and promote to better judge BPSD interventions (see **Table 1** for facilitators and examples of their implications).

Until now, the facilitators allowing the implementation of non-pharmacological approaches have received little attention as compared to the approaches themselves. Although some interventions were shown to be efficient, a certain number of reviews report inconsistent results. The differences in the ways the interventions are defined, applied and measured, as well as the complexity to synthesize the studies, are suggested to explain these inconsistencies (8, 20–22). Yet, our experience had us question the importance given to a particular intervention, as opposed to the environment and conditions in which it is applied. Indeed, the facilitators identified above might account for a significant part of the variance when measuring the efficacy of an intervention.

TABLE 1 | Facilitators identified in the management of BPSD and concrete implications.

Facilitators	Implications
Culture and leadership	• Value the importance of using non-pharmacological strategies • Recognize the necessity to have access to experts
Full-time presence	• Have an expert working on site to ensure rapid contact • Have the expert dedicated to the task of supporting staff with BPSD management
Teaching methods	• Use knowledge translation science • Give timely and concrete feedback • Favor multimodal and multiple learning exposures
Innovative tools	• Be creative to favor access to relevant patient information and to improve communication among staff • Integrate technology into care
Motivation	• Develop motivation to facilitate learning of new skills • Facilitate successful interventions to increase motivation
Perceived role of patient attendants and orderlies	• Favor patient attendants and orderlies' contribution beyond activities of daily living • Involve them in the reflections and actions regarding BPSD management
Multidisciplinarity	• Integrate different disciplines to have a holistic perspective • Value psychosocial expertise
Staff ratio	• Acknowledge that a greater ratio allows more time to facilitate BPSD management

Studying the effect of multi-level interventions is possible, but methodologically very challenging. The environment of care comprises many variables which can affect outcome measures, and trying to split elements of interventions are not thought to lead to beneficial outcome (13, 23). In our setting, we also noticed that the facilitators identified operated synergistically. For example, the high staff-patient ratio, and the fact that our team was easily accessible, played an important role to further help other facilitators to push through. The high ratio gave staff enough time to think about the challenging situations, request help when needed, and thus integrated more rapidly the strategies taught. It provided staff with the psychological and cognitive disposition sufficient to engage in demanding tasks, which is known to motivate a behavior change toward better practice (24). Also, the fact that we were entirely dedicated to supporting staff in the management of BPSD gave us the opportunity to use recommended teaching methods (14). As it happens, having access to direct feedback is one of three key elements suggested to facilitate the application of a skill, together with organizational culture and leadership (12). Moreover, the success of the application of a fostered practice highly depends on tangible support from managers (12, 13). A positive commitment of the organization attributes value to their employees, bringing them to perceive their role as pivotal for the well-being of the patient. This value translates notably into proper access to patient information, allowing personalized interventions. This type of management support sets conditions for staff members to feel proud, it improves job satisfaction and favors a stable workforce (13).

Our experience reiterated that optimal care for older adults with major NCD can only be achieved by adopting a holistic vision of care. Indeed, disturbing behaviors are often triggered by unfulfilled needs, arising when care is task-driven, as opposed to person-centered. Furthermore, relying on a dominant medical model of care is susceptible to lead to the neglect of psychosocial needs (25, 26). In that context, integrating various psychosocial disciplines is essential in order to succeed in the management of BPSD (19).

LIMITATIONS

Due to the emergency situation of the pandemic, concepts presented in this paper are empirical and mostly rest on clinical observations. Indeed, data collection was hard to achieve for many reasons: patients were sent to the hotel with few information about their medical condition, our team was reoriented within < 24-h notice preventing all scientific preparation, and it was not possible to prioritize data collection over our clinical role.

The environment described in this paper is an unconventional context, not representative of what is known from usual settings. Thus, the specific characteristics of the facilitators exposed are not meant to be transferable to all clinical contexts and cannot serve as formal recommendations. Instead, the perspective presented in this paper is rather an attempt to shed light as to the multitude of variables influencing the management of BPSD and its success.

CONCLUSION

In conclusion, this paper highlights the vast number of variables implicated in the management of BPSD and the necessity to take them into account when measuring the efficacy of an intervention. To lean toward optimal care, future research would take advantage of looking beyond the interventions *per se*. Further analysis of the context in which the non-pharmacological intervention is applied could capture the complexity of BPSD and lead to greater clinical impact.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

KD: worked full-time as neuropsychologist at the COVID-19 hotel. Substantial contribution to the conception and design of the work; literature search and appraisal of the quality of included papers; first draft of most parts of the work; acquisition, analysis, and interpretation of data; critical revision for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work and ensure accuracy and integrity of all parts of the work. JB: worked full-time as occupational therapist at the COVID-19 hotel. Contribution to the conception and design of the work; first draft of some parts of the work; critical revision for intellectual content; final approval of the version to be published. CO: worked full-time as neuropsychologist at the COVID-19 hotel. Contribution to the conception and design of the work; literature search and appraisal of the quality of included papers; first draft of some parts of the work; critical revision for intellectual content; final approval of the version to be published. All authors contributed to the article and approved the submitted version.

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