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Association between the mediterranean diet and cognitive health among healthy adults: A systematic review and meta-analysis

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Background: An increasing prevalence of cognitive disorders warrants comprehensive systematic reviews on the effect of diet on cognitive health. Studies have suggested that the Mediterranean (MeDi) diet has protective effects against metabolic diseases. However, comprehensive systematic reviews on the effect of the MeDi diet on the cognitive decline are limited. We investigated whether adherence to the MeDi diet could lower the risk of the cognitive disorder or improve cognitive function in older adults.

Methods: In this systematic review and meta-analysis, PubMed, Web of Science, PsycINFO, Scopus, and Cochrane databases were searched from inception to June 2021. Cohort studies and randomized controlled trials (RCTs) were included. The effect sizes were estimated as log risk ratios and standard mean differences (SMDs) with 95% confidence intervals (CIs). The Newcastle–Ottawa score and Cochrane Collaboration’s tool were used to assess the risk of bias in cohort studies and RCTs, respectively.

Results: Of the 1,687 screened studies, 31 cohort studies and five RCTs met the eligibility criteria for qualitative analysis; 26 cohort studies and two RCTs were included in the meta-analysis. In the cohort studies, high adherence to the MeDi diet was associated with lower risk of mild cognitive impairment (MCI) [risk ratio (RR) = 0.75 (0.66–0.86)], and Alzheimer’s disease (AD) [RR = 0.71 (0.56–0.89)]. In the RCTs, high adherence to the MeDi diet was associated with better episodic [SMD = 0.20 (0.09–0.30)] and working memories [SMD = 0.17 (0.01–0.32)] than lowest group.

Conclusion: Adherence to the MeDi diet may reduce the risk of MCI and AD. However, other associations with cognitive outcomes (global cognition, working memory, and episodic memory) remain open to interpretation. Overall, the MeDi diet is recommended to prevent or delay cognitive disorders

and improve cognitive function. Further, long-term RCTs are warranted to strengthen the evidence.

Systematic review registration: [<https://www.crd.york.ac.uk>], identifier [CRD42021276801].

KEYWORDS

cognitive function, mild cognitive impairment, dementia, Alzheimer's disease, Mediterranean diet (MD)

Introduction

Mild cognitive impairment (MCI) is defined as a cognitive decline greater than that expected for the age and education level of the individual while not interfering with activities of daily living (1). MCI is a stage in the progression from normal cognitive function to dementia (2). Globally, dementia is the seventh most common cause of death and the most common cause of illness in older adults. According to the WHO, there are currently more than 55 million confirmed cases of dementia worldwide, and the number of new cases is increasing at a rate of 10 million per year. In addition to this, the number of people with dementia is projected to grow to 78 million by 2030 and 139 million by 2050. This is owing to the increasing proportion of older people worldwide. The most commonly diagnosed form of dementia is Alzheimer's disease (AD), which accounts for approximately 60–70% of cases (3). According to the Alzheimer's Association, the number of deaths from AD increased by 145% from 2000 to 2019 (4). Moreover, during the coronavirus disease pandemic, deaths owing to AD and dementia have increased by 16% (5). AD is an irreversible degenerative brain disease (6), and currently, there is no cure for dementia (3). Therefore, determining whether cognitive impairment can be prevented or delayed by dietary modification is important.

The Mediterranean (MeDi) diet is a dietary pattern that has been followed by the Mediterranean Basin countries since the early 1960s (7) and is mainly based on abundant plant-based consumption with food that is minimally processed, seasonal, fresh, and locally grown. Fresh fruit is consumed every day, and olive oil is the main source of fat. Additionally, low-to-moderate amounts of fish and seafood, poultry, and dairy products are consumed daily. A regular but moderate amount of wine is also consumed, along with 0–4 eggs that are consumed per week. Sweets containing sugar or honey and red meat are sparingly consumed (8).

The association between the MeDi diet and increased longevity and reduced mortality and morbidity from certain cancers and other nutrition-related diseases has been widely studied (9–12). However, whether adherence to the MeDi

diet can prevent or delay the risk of cognitive disorders and improve cognitive function remains understudied. While some epidemiological studies did not show a relationship (13–15), others have shown positive associations between the MeDi diet and the prevention of cognitive disorders and improvement in cognitive function (16–19). Although several systematic reviews focusing on cognitive disorders or cognitive function have been published (20–25), there is no systematic review to quantitatively evaluate the association between cognitive disorders and cognitive function from both prospective studies and RCTs simultaneously. In addition, although previous reviews conducted meta-analyses, they did not conduct any further analysis to investigate the high heterogeneity source, which might lead to results bias. Therefore, we performed a systematic review and meta-analysis of both cohort studies and randomized controlled trials (RCTs) to comprehensively analyze the association between adherence to the MeDi diet and cognitive disorders (i.e., MCI, dementia, and AD) and cognitive functions (i.e., attention, episodic memory, executive function, global cognition, processing speed, and working memory). Furthermore, we conducted subgroup and meta-regression analyses to identify whether a wide range of characteristics contributed to the differences in the results of the cohort studies.

Methods

Literature search

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (26). A protocol was designed and registered in the PROSPERO database (PROSPERO 2021 CRD42021276801). We searched five electronic databases: PubMed, Web of Science, PsycINFO, Scopus, and Cochrane, for articles published before June 2021. The search terms used were “Mediterranean diet,” “mild cognitive impairment,” “dementia,” “Alzheimer's disease,” and “cognitive function,” and only English articles were included. Two authors independently screened the titles and abstracts of the research papers. After this, they read

the full texts to identify potentially eligible studies. The PICOS criteria are shown in [Table 1](#); see [Supplementary Table 1](#) for the detailed search methodology.

Selection criteria

Studies were selected and included based on the following inclusion criteria:

1. Studies that were published in English, with no restrictions on the study sample size or the participants' age, sex, or health status.
2. Studies that were RCTs or prospective observational studies and investigated the relationship between adherence to the MeDi diet and cognitive function (including attention, episodic memory, executive function, global cognition, processing speed, or working memory) or the risk of cognitive disorders (including MCI, dementia, or AD).
3. If two studies used the same cohort database, both were included.

The exclusion criteria were as follows:

1. Studies that did not adhere to the MeDi diet. For example, studies with adherence to a particular national dietary pattern or a healthy eating index.
2. Studies that included participants with cognitive disorders or abnormal cognitive functioning at baseline.
3. Case-control studies, cross-sectional studies, systematic reviews, narrative reviews, conference reports, or letters.

Data extraction

Two authors (JF and L-JT) independently extracted data using the same extraction method. In the case of a dispute, a third author (SS) helped reach a consensus. The data on the last name of the first author, publication year, the health status of participants, follow-up duration, baseline age, percentage of men, sample size, dietary assessment method, MeDi diet

assessment method, cognitive assessment methods, cognitive domains measured, and results were extracted from cohort studies. For the RCTs, data on the last name of the first author, publication year, country, population selection, follow-up duration, intervention group, placebo group, dietary assessment methods, and the MeDi diet assessment method, the baseline age and number of participants, outcome test methods, and results were extracted. Two reviewers independently assessed cognitive disorders and cognitive function of cohort studies and cognitive function of RCTs. Cognitive disorders included MCI, dementia, and AD, which were based on the battery of neuropsychological test or diagnosis criteria. Cognitive function included attention, episodic memory, executive function, global cognition, processing speed, and working memory, which were tested by the Mini-Mental State Examination (MMSE) or other common cognitive function tests [e.g., Telephone Interview for Cognitive Status (TICS), the Digit Span-Backward Test (DST)].

Quality assessment

Two independent reviewers evaluated the quality of the cohort studies and RCTs. The Newcastle–Ottawa score (NOS) was used to evaluate the quality of the prospective cohort studies (27). Scores of ≥ 7 were considered high-quality scores, and scores of ≤ 4 were considered low-quality scores. The Cochrane Collaboration tool was used to evaluate the risk of bias in RCTs (28). The deviation from risk assessment criteria for each factor was divided into three levels—“high,” “low,” and “unclear” risk of bias.

Statistical analyses

We performed a meta-analysis on three cognitive disorders and six cognitive domains. From the cohort studies, we extracted risk ratios (RRs) [hazard ratio (HRs) or odds ratio (ORs)] with 95% confidence intervals (CIs) for cognitive disorders (MCI, dementia, and AD) and effect sizes and standard errors for cognitive function (episodic memory, global cognition, and working memory). Owing to the asymmetry of the RRs, these values were log-transformed (base 10) (29). From RCTs, we extracted changed means and changed standard deviation (SD) for cognitive function (attention, episodic memory, executive function, global cognition, processing speed, and working memory). If the results of the original manuscript contained only the means or SD of the baseline and final groups, the changed mean was calculated by subtracting the final mean from the baseline mean. Changed SD was obtained using the following equation, where the correlation coefficient R was set at 0.5 (30).

$$SD_{change} = \sqrt{SD_{baseline}^2 + SD_{final}^2 - 2 \times R \times SD_{baseline} \times SD_{final}}$$

TABLE 1 PICOS criteria for inclusion of studies.

| Parameter | Description |
|--------------|--|
| Population | Cognitively normal adults |
| Intervention | Adherence to the MeDi diet |
| Comparison | Normal diet or low adherence to the MeDi diet |
| Outcomes | Mild cognitive impairment or dementia or Alzheimer's disease or cognitive function |
| Study design | Cohort studies or RCTs |

RCT, randomized controlled trial; MeDi diet, Mediterranean diet.

If the study reported 95% CI instead of SD, we used the following formula:

$$SD = \sqrt{N} \times \frac{95\%CI_{upper} - 95\%CI_{lower}}{2 \times t \text{ value}}$$

All statistical analyses were performed in STATA MP 17.0 and the Review Manager 5.4. A two-tailed *P* value of < 0.05 was considered statistically significant. The heterogeneity test in this review was examined using the Cochran's Q test and quantified using the *I*² statistic. For medium and low heterogeneity (*I*² of < 50%), fixed-effects models were used, while random-effects models were used for high heterogeneity (*I*² of ≥ 75%) (31, 32). Moreover, potential sources of heterogeneity were examined using meta-regression and subgroup analysis based on covariates such as study location: (1) Mediterranean region or (2) non-Mediterranean region; publication year: (1) after 2015 or (2) before 2015; duration of follow-up: (1) ≥ 5 years or (2) < 5 years; method of assessing dietary intake: (1) food frequency questionnaire (FFQ) or (2) others; and study quality: (1) scores = 9, (2) scores = 8, or (3) scores = 7 (30, 33, 34). Publication bias was assessed based on at least 10 studies and was quantitatively assessed using Egger's test, Begg's test, and funnel plots (35).

Results

Literature selection

A total of 1,687 studies in PubMed, Web of Science, PsycINFO, Scopus, and Cochrane databases were identified. Of these, 820 studies were excluded after searching the keywords and reviewing the studies by their titles to assess relevance and eligibility. The abstracts of 103 studies were reviewed, after which the full texts of 47 studies were assessed. After excluding irrelevant studies and including reviews and cross-sectional studies, 31 cohort studies and five RCTs were included in the qualitative assessment. Finally, 26 cohort studies and two RCTs that met the criteria were included in the meta-analysis (Figure 1).

Study characteristics

In total, 31 cohort studies and five RCTs were included in the review. Characteristics of prospective studies and RCTs are summarized in Tables 2 and 3, respectively. Nine cohort studies were conducted in the Mediterranean countries of France, Greece, Spain, and Italy (15, 36–43), while the other 22 studies were from China, the United States of America, Australia, Sweden, the United Kingdom, and Singapore (13, 14, 16–19, 44–60). Most studies (*n* = 25) were women dominant, with five studies including only women and three studies

including only men (19, 41, 47). The sample sizes varied from 200 to 27,842 participants. Additionally, follow-up median or mean durations ranged from 2.2 to 26 years, and baseline ages ranged from 45 to 92 years. The cut-off value selected by most of the studies was over 65 years (*n* = 13). The majority of studies used an FFQ to assess the MeDi diet (*n* = 26), and two of these studies used both an FFQ and a 24-h dietary recall to assess diets (15, 16). Among the studies using an FFQ, two used the Council of Victoria FFQ and Women's Health Initiative FFQ, while the others used the food groups' semi-quantitative FFQ (14, 45). Moreover, the MeDi diet was primarily scored on a 0–9 scoring range (*n* = 25), while 1 study used a 0–15 MeDi diet score, defined by Morris et al. (55, 61) and 5 studies used a 0–55 MeDi diet score, defined by Panagiotakos et al. (17, 36, 46, 56, 57). Cognitive function was assessed using a large number of tests to quantify the cognitive domains of global cognition, episodic memory, working memory, processing speed, executive function, and attention. The most common and widely used test was MMSE (*n* = 19), which included tests on attention, language, memory, visual-spatial skills, and orientation. Owing to individual differences in research, studies used different cognitive function tests, including the DST, TICS, Benton Visual Retention Test (BVRT).

Five RCTs were eligible for inclusion, all of which had a parallel design and included cognitively stable participants (62–66). Of the five RCTs, two were from Australia with follow-up times of only 0.5 years and an average participant age of over 70 years (62, 63). The other three RCTs were from Spain, with a follow-up duration range of 3–6.5 years and an average participant age of 67 years (65–67). The earliest and most recent trials were conducted in 2011 (65) and 2020 (62), respectively. Of the trials conducted in Spain, intervention groups were subdivided into the following two groups: those receiving a free allotment of extra virgin olive oil (EVOO) or unprocessed mixed nuts. To ensure the accuracy and rigor of the MeDi diet, participants received a collection of recipes or intensive education. As for the control group, participants were asked to maintain their current lifestyle or advised to adhere to a low-fat diet. In the five RCTs, there were 883 participants in the experimental groups and 396 participants in the control groups. Several methods were used to assess cognitive function, including the MMSE, Rey Auditory Verbal Learning Test, and Color Trail Test.

Quality assessment

Of the 31 cohort studies, 93.6% achieved high-quality NOS scores (*n* = 29), and only two studies had scores of 6 and were, thus, regarded as having a high risk of bias (Supplementary Table 2 shows the NOS grades of the

TABLE 2 Main characteristics of the included cohort studies.

| References | Country | Study characteristics and demographics | | | | | Mediterranean diet score | | Cognitive outcome measure | | Results |
|--------------------------|---------------|--|--------------|--------------|----------|-------------|-----------------------------|----------------------|-----------------------------------|---|--|
| | | Participant selection | Follow-up, y | Baseline age | Male (%) | Sample size | Diet method | MeDi score | Method | Cognitive domains | |
| Bhushan et al. (19) | United States | US male Health professionals | 26 | 40–75 | 100 | 27,842 | FFQ | 0–9 MeDi diet score | SCF score | Global cognition | The MeDi diet was strongly related to lower subjective cognitive function |
| Charisis et al. (36) | Greece | Non-demented individuals | 3 | 64 | 40.3 | 1,046 | FFQ | 0–55 MeDi diet score | NT | Memory, language, attention, executive function, visuospatial perception | The MeDi diet was associated with a reduced risk for dementia and cognitive decline |
| Cherbuin and Anstey (13) | Australia | Healthy participants | 4 | 60–64 | 48.2 | 1,528 | FFQ | 0–9 MeDi diet score | MMSE | Global cognition | The MeDi diet was not found to be protective against cognitive decline |
| Feart et al. (15) | France | Healthy participants without dementia | 4.1 | > 65 | 37.4 | 1,410 | FFQ and 24 h dietary recall | 0–9 MeDi diet score | MMSE, IST, BVRT, FCSRT | Global cognition, semantic verbal fluency, verbal production speed, immediate visual memory, verbal episodic memory | The MeDi diet was associated with lower MMSE cognitive decline |
| Galbete et al. (39) | Spain | Healthy Spanish | 8 | > 55 | 71.0 | 823 | FFQ | 0–9 MeDi diet score | TICS-m | Immediate memory, delayed recall, orientation, attention, calculation, language | High adherence to the MeDi diet might be associated with better cognitive function |
| Gallucci et al. (40) | Italy | Healthy participants | 7 | > 77 | 38.8 | 309 | FFQ | 0–9 MeDi diet score | MMSE | Global cognition | There was no significant association between the MeDi diet and cognitive function |
| Gardener et al. (45) | Australia | Healthy participants | 3 | > 60 | 39.8 | 527 | CCVFFQ | 0–9 MeDi diet score | Global cognitive score | Verbal memory, visual memory, executive function, language, attention, visuospatial function | The AusMeDi diet was associated with better performance in the executive function cognitive domain |
| Gu et al. (18) | United States | Healthy participants without dementia | 3.8 | > 65 | 33.4 | 1,219 | FFQ | 0–9 MeDi diet score | Composite cognitive Z-score | Memory, language, processing speed, visual-spatial ability | Better adherence to the MeDi diet was significantly associated with lower risk for AD |
| Haring et al. (14) | United States | Healthy participants without dementia | 9.11 | 65–79 | 0 | 6,425 | WHI-FFQ | 0–9 MeDi diet score | MMSE, CERAD, DSM-IV | Global cognition, verbal fluency, verbal learning and memory, constructive praxis, executive function | Adherence to the MeDi diet did not modify the risk for cognitive decline |
| Kesse-Guyot et al. (42) | France | Healthy participants | 13 | > 45 | 53.7 | 3,083 | 24 h dietary recall | 0–9 MeDi diet score | RI-48, VFT, DST, Delis-Kaplan TMT | Episodic memory, semantic memory, short-term and working memory, mental flexibility | There was no beneficial effect of the MeDi diet adherence on cognitive function |

(Continued)

TABLE 2 (Continued)

| References | Country | Study characteristics and demographics | | | | | Mediterranean diet score | | Cognitive outcome measure | | Results |
|--------------------------|---------------|--|--------------|--------------|----------|-------------|--------------------------|----------------------|--|---|---|
| | | Participant selection | Follow-up, y | Baseline age | Male (%) | Sample size | Diet method | MeDi score | Method | Cognitive domains | |
| Koyama et al. (46) | United States | Healthy participants | 7.9 | 70–79 | 48.7 | 2,326 | FFQ | 0–55 MeDi diet score | 3MS score | Orientation, registration, attention, recall, visuospatial ability | High adherence to the MeDi diet may reduce the rate of cognitive decline among black older adults, but not white older adults |
| Lutski et al. (41) | Israel | Cognitively normal participants | 4.8 | 45–74 | 100 | 200 | 4-day dietary record | 0–9 MeDi diet score | Computerized cognitive test | Memory, executive function, visual-spatial, attention | Poor vs high adherence was associated with a greater decline in overall cognitive performance |
| Morris et al. (17) | United States | Healthy old adults without AD | 4.5 | 58–98 | 24.0 | 923 | FFQ | 0–55 MeDi diet score | Alzheimer's incidence rate | Episodic memory, global cognition, processing speed, reasoning, semantic memory, working memory | The MeDi diet was associated with lower AD rates |
| Olsson et al. (47) | Sweden | Healthy participants | 12 | >70 | 100 | 1,038 | 7-day dietary record | 0–9 MeDi diet score | MMSE, NINCDS-ADRDA, DSM-IV | Global cognition | Adherence to the MeDi diet did not modify the risk for cognitive decline |
| Psaltopoulou et al. (43) | Greece | Healthy participants | 8 | >60 | 35.1 | 732 | FFQ | 0–9 MeDi diet score | MMSE, GDS score | Global cognition | PUFA and seed oil as two dietary variables which were alternatively substituted for MeDi diet Score may have adverse effects on performance on cognitive function |
| Qin et al. (48) | China | Healthy participants | 5.3 | >55 | 49.7 | 1,650 | 24 h dietary recall | 0–9 MeDi diet score | Cognitive screening test | Immediate memory, orientation | There was no association among adults aged < 65 years, among adults aged > 65 years, adherence to the MeDi diet had a slower rate of cognitive decline |
| Roberts et al. (49) | United States | Healthy participants | 2.2 | 70–89 | 53.0 | 1,233 | FFQ | 0–9 MeDi diet score | CDR, NT | Memory, executive function, language, visuospatial | Adherence to the MeDi diet did not modify the risk for cognitive decline |
| Samieri et al. (50) | United States | Healthy older women | 6 | >70 | 0 | 16,058 | FFQ | 0–9 MeDi diet score | TICS, EBMT, TICS-m, category fluency test, DST | Global cognition, verbal memory, working memory, attention | Long-term MeDi diet adherence was related to moderately better cognitive change |
| Samieri et al. (51) | United States | Healthy older women | 4 | >65 | 0 | 6,174 | FFQ | 0–9 MeDi diet score | TICS, EBMT, TICS-m, category fluency test, DST | Global cognition, verbal memory | No association of the MeDi diet with cognitive decline |

(Continued)

TABLE 2 (Continued)

| References | Country | Study characteristics and demographics | | | | | Mediterranean diet score | | Cognitive outcome measure | | Results |
|--------------------------|----------------|---|--------------|--------------|----------|-------------|--------------------------|----------------------|---------------------------------|---|--|
| | | Participant selection | Follow-up, y | Baseline age | Male (%) | Sample size | Diet method | MeDi score | Method | Cognitive domains | |
| Scarmeas et al. (52) | United States | Cognitively normal participants | 4.5 | >65 | 32.0 | 1,393 | FFQ | 0–9 MeDi diet score | Alzheimer's incidence rate, CDR | Memory, executive, language, visuospatial | Higher adherence to the MeDi diet was associated with a reduced risk of developing MCI |
| Scarmeas et al. (53) | United States | Cognitively normal participants | 4.3 | >65 | 31.0 | 1,880 | FFQ | 0–9 MeDi diet score | NAB | Memory, orientation, language, construction | Higher adherence to the MeDi diet was associated with a reduced risk of developing AD |
| Scarmeas et al. (54) | United States | Cognitively normal participants | 4 | >65 | 32.0 | 2,258 | FFQ | 0–9 MeDi diet score | NAB | Memory, orientation, language, construction | Higher adherence to the MeDi diet was associated with a reduced risk of developing AD |
| Shannon et al. (55) | United Kingdom | Healthy older individuals with CVD risk | 13 | 48–92 | 44.0 | 8,009 | FFQ | 0–15 MeDi diet score | SF-EMSE, HVLIT | Global cognition, verbal episodic memory, nonverbal episodic memory, attention, simple processing speed, complex processing speed, memory | High adherence to the MeDi diet was associated with good cognitive function and low risk of poor cognition in older adults: verbal episodic memory |
| Tanaka et al. (37) | Italy | Cognitively normal participants | 10.1 | >65 | 43.5 | 832 | FFQ | 0–9 MeDi diet score | MMSE | Global cognition | Adherence to the MeDi diet can have long-lasting protective effects on cognitive decline and may be an effective strategy to prevent or delay dementia |
| Tangney et al. (56) | United States | Healthy participants | 4.1 | >65 | 26.0 | 826 | FFQ | 0–55 MeDi diet score | 19 cognitive tests | Global cognition, episodic memory, executive function, processing speed, semantic memory, working memory | The MeDi diet pattern may reduce the rate of global cognitive decline with older age |
| Tangney et al. (57) | United States | Healthy participants | 7.6 | >65 | 38.3 | 3,790 | FFQ | 0–55 MeDi diet score | EBMT, MMSE, SDMT | Global cognition | The MeDi diet pattern may reduce the rate of cognitive decline with older age |
| Trichopoulou et al. (38) | Greece | Healthy participants | 6.6 | >65 | 35.9 | 401 | FFQ | 0–9 MeDi diet score | MMSE | Global cognition | Adherence to the traditional MeDi diet was highly likely to protect against cognitive decline |

(Continued)

TABLE 2 (Continued)

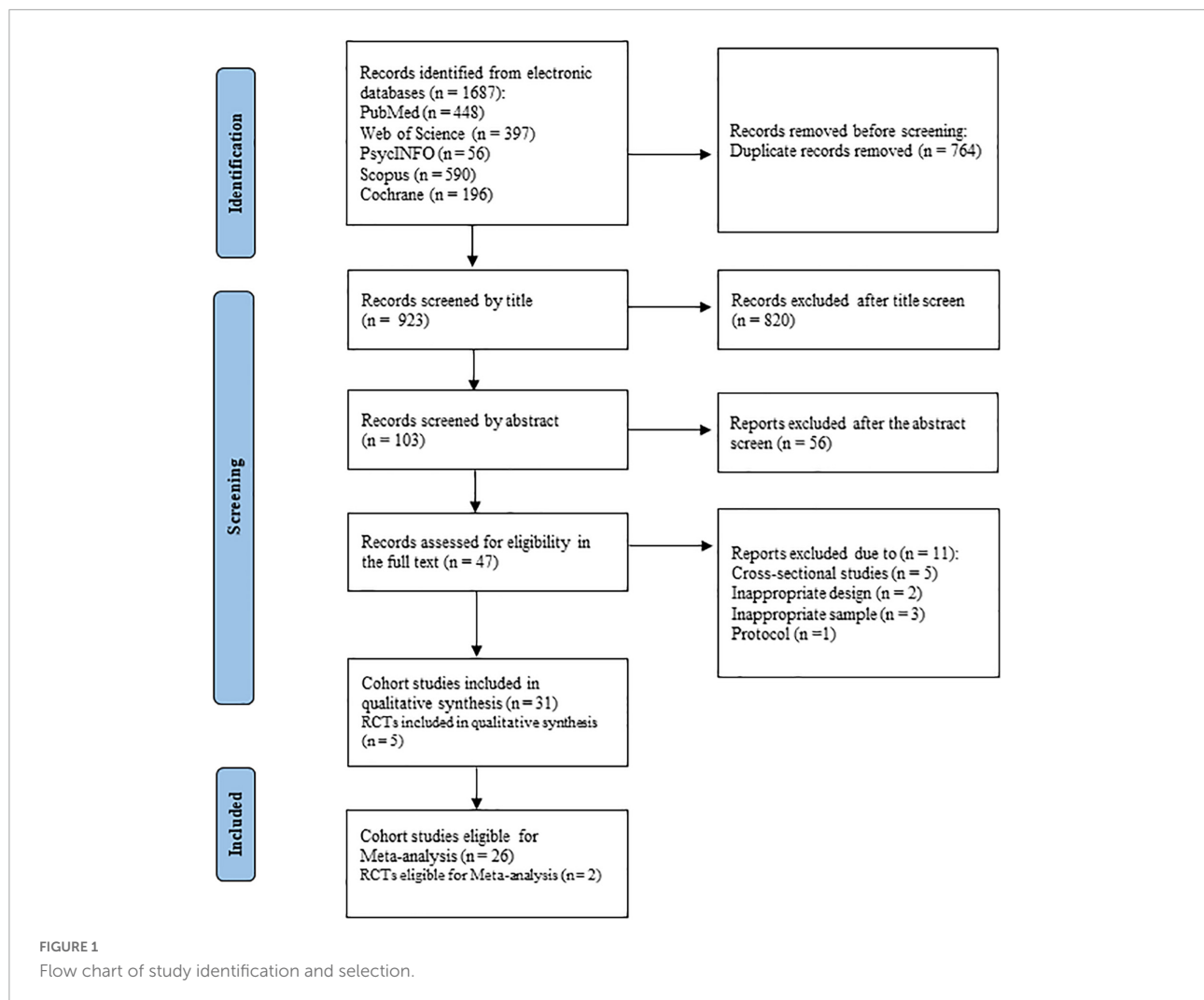
| References | Country | Study characteristics and demographics | | | | | Mediterranean diet score | | Cognitive outcome measure | | Results |
|------------------------|---------------|--|--------------|--------------|----------|-------------|-----------------------------|---------------------|---------------------------|---|--|
| | | Participant selection | Follow-up, y | Baseline age | Male (%) | Sample size | Diet method | MeDi score | Method | Cognitive domains | |
| Tsivgoulis et al. (58) | United States | Participants without MCI | 4 | 45–98 | 43.0 | 17,478 | FFQ | 0–9 MeDi diet score | SIS | Cognition | Adherence to the MeDi diet was associated with a lower likelihood of ICI in nondiabetic participants |
| Vercambre et al. (59) | United States | US female Health professionals | 5.4 | >65 | 0 | 2,504 | FFQ | 0–9 MeDi diet score | TICS, EBMT, TICS-m, EBMT | Global cognition, verbal memory, category fluency | No association of the MeDi diet with subsequent 5-year cognitive change |
| Wengreen et al. (60) | United States | Cognitively normal participants | 10.6 | >65 | 42.9 | 3,580 | FFQ | 0–9 MeDi diet score | 3MS score | Global cognition | Adherence to the MeDi diet was associated with cognitive function in older men and women |
| Wu et al. (16) | Singapore | Healthy participants | 19.7 | 45–74 | 40.8 | 16,948 | FFQ and 24 h dietary recall | 0–9 MeDi diet score | SM-MMSE | Global cognition | Adherence to the MeDi diet patterns in midlife is associated with a lower risk of cognitive impairment in later life in Chinese adults |

MeDi diet, Mediterranean diet; SCF, Subjective cognitive function; NT, neuropsychological test; MMSE, Mini-Mental State Examination; IST, Isaacs set test; BVRT, Benton visual retention test; FCSRT, Free and cued selective reminding test; TICS-m, Telephone interview of cognitive status-modified; CCVFFQ, Council of Victoria food frequency questionnaire; AusMeDi diet, Australia Mediterranean diet; WHI-FFQ, Women's health initiative food frequency questionnaire; CERAD, Consortium to establish a registry for Alzheimer's disease; DSM-IV, Diagnostic and statistical manual of mental disorders; RI-48, Rappel Indiqué (cued recall)-48 items; TMT, trail-making test; VFT, verbal fluency tasks; DST, Digit span-backward test; 3MS score, Modified Mini-Mental State Examination score; SES, Socioeconomic status; NINCDS-ADRDA, National institute of neurological and communication disorders and stroke-Alzheimer's disease; GDS score, Geriatric depression scale score; TICS, Telephone interview for cognitive status; EBMT, East Boston memory test; PUFA, Polyunsaturated acids; CDR, Clinical dementia rating; MCI, Mild cognitive impairment; AD, Alzheimer's disease; NAB, Neuropsychological Assessment Battery; SF-EMSE, Short form extended mental state exam; SDMT, symbol digit modalities test; HVLT, Hopkins verbal learning test; SIS, The six-items screener; ICI, Incident cognitive impairment; SM-MMSE, Singapore modified MMSE.

TABLE 3 Main characteristics of the included randomized controlled trials.

| References | Country | Population | Duration | Intervention | Placebo group | Dietary | MeDi score | Baseline age | Subjects (N) | Loss | Outcome method | Results |
|--------------------------------|-----------|--|-----------|--|--|---------|------------|--|---------------------------------|---------------------------------|---|--|
| Hardman et al. (62) | Australia | Healthy older adults | 0.5 years | The diet group received a collection of recipes in keeping with MeDi diet style, and with the assistance of dietary consultants from Health Care 2 | Maintenance of their current lifestyle | FFQ | 0–9 | EG: 77.68 ± 7.38 CG: 78.22 ± 5.81 | EG: 18 CG: 25 | EG: 28% CG: 7% | SUCCAB | The MeDi diet has the potential to improve aspects of cognition in aging population |
| Knight et al. (63) | Australia | Healthy older adults | 0.5 years | Participants were closely monitored on a fortnightly basis in an informed meeting that followed MeDi diet food pyramids | Participants were asked to simply maintain their customary lifestyle and dietary pattern | FFQ | 0–9 | EG: 72.1 ± 4.9 CG: 72.0 ± 5.0 | EG: 70 CG: 67 | EG: 19% CG: 17% | A comprehensive battery of 11 cognitive tests | There was no beneficial effect of the MeDi diet intervention on cognitive function among healthy older adults |
| Martinez-Lapiscina et al. (64) | Spain | Cognitively normal participants at high CVD risk | 6.5 years | Participants received intensive education and advice to increase adherence to MeDi diet. Participants received free allotments of either EVOO (1 L/week) or 30 g/day of raw, unprocessed mixed nuts (15 g walnuts, 7.5 g almonds and 7.5 g hazelnuts) | Participants received intensive education and advice to increase adherence to the low-fat diet and received advice to reduce all types of fat and non-food gifts as an incentive to improve compliance | FFQ | 0–14 | All: 67.38 ± 5.65 | EGE: 224 EGN: 166 CG: 132 | EGE: 36% EGN: 53% CG: 63% | MMSE, CDT | An intervention with the MeDi diet enhanced with either EVOO or nuts appears to improve cognition compared with a low-fat diet |
| Sanchez-Villegas et al. (65) | Spain | Cognitively normal participants at high CVD risk | 3 years | The groups assigned to MeDi diet were advised to use extra virgin olive oil for cooking. Each participant had a personal interview with a trained dietician and a group session conducted by the same dietician every 3 months during these 4 years | Participants were advised to reduce all types of fat and were given recommendations according to the American guidelines | FFQ | 0–14 | EGE: 68.1 ± 6.1 EGN: 67.4 ± 5.7 CG: 68.0 ± 6.1 | EGE: 91 EGN: 75 CG: 77 | / | ELISA kit | Adherence to the MeDi diet was associated to an improvement in plasma BDNF concentrations in individuals with depression and to prevent depression and cognitive decline |
| Valls-Pedret et al. (66) | Spain | Cognitively normal participants at high CVD risk | 4.1 years | Participants were educated on how to follow the MeDi diet and received supplemental foods at no cost. Participants received free allotments of either EVOO (1 L/week) or 30 g/day of raw, unprocessed mixed nuts (15 g walnuts, 7.5 g almonds and 7.5 g hazelnuts) | Participants were advised to reduce all dietary fat | FFQ | 0–14 | EGE: 67.9 ± 5.4 EGN: 66.7 ± 5.3 CG: 65.5 ± 5.8 | EGE: 127 EGN: 112 CG: 95 | EGE: 18% EGN: 24% CG: 34% | MMSE, RAVLT, substest of Wechsler memory scale, animal fluency test, Wechsler adult intelligence scale, CTT | The MeDi diet supplemented with olive oil or nuts was associated with improved cognitive function |

MeDi diet, Mediterranean diet; SUCCAB, Swinburne university computerized cognitive assessment battery; CDT, Clock drawing test; MMSE, Mini-Mental State Examination; EVOO, Extra virgin olive oil; EG, Experiment group; CG, Control group; EGE, Mediterranean diet plus Extra virgin olive oil; EGN, Mediterranean diet plus nuts; BDNF, Brain-derived neurotrophic factor; RAVLT, Rey Auditory Verbal Learning Test; CTT, Color trail test.



31 cohort studies). Regarding selection bias, all five RCTs mentioned random sequence generation, and four trials were conducted with allocation concealment (**Supplementary Figure 1** summarizes the risk of bias in the five RCTs). All five trials had a high risk of performance bias, without participant blinding, and three trials were blinded to outcome assessment. Four of these trials had a low risk of bias in incomplete outcome data, as it had been properly addressed. One trial, however, had a high risk of attrition bias. All five RCTs were free from reporting and other biases.

Meta-analysis

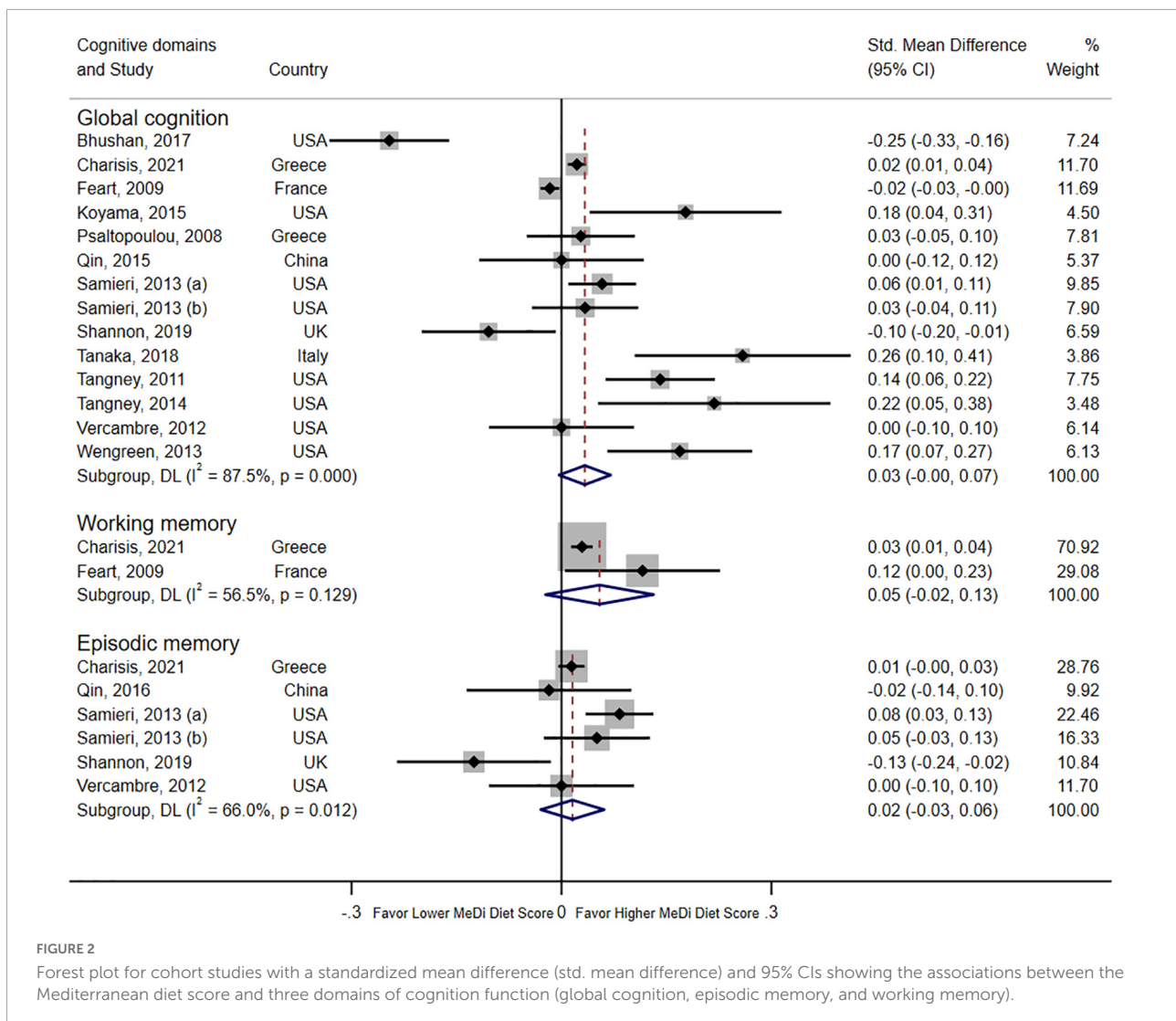
Effects on cognitive function in cohort studies

A forest plot revealed the relationship between adherence to the MeDi diet and three domains of cognitive function in 14 cohort studies (**Figure 2**). Pooled results did not show significant associations with global cognition when compared with the

lowest group (SMD = 0.03; 95% CI: 0.00–0.07; $I^2 = 87.5\%$, $P < 0.000$). No significant associations were found with episodic memory (SMD = 0.02; 95% CI: -0.03–0.06; $I^2 = 66.0\%$, $P = 0.012$) or working memory (SMD = 0.05; 95% CI: -0.02–0.13; $I^2 = 56.5\%$, $P = 0.129$).

Effects on cognitive disorders in cohort studies

The forest plot shown in **Figure 3** displays the relationship between adherence to the MeDi diet and three types of cognitive disorders in 17 cohort studies. Pooled results of high adherence to the MeDi diet showed a positive association with reduced risk of MCI (RR = 0.75; 95% CI: 0.66–0.86; $I^2 = 63.7\%$, $P = 0.002$). Moreover, pooled results indicated that high adherence to the MeDi diet was not associated with reduced risk of dementia (RR = 0.85; 95% CI: 0.59–1.23, $P = 0.399$; $I^2 = 61.3\%$, $P = 0.024$). The pooled analysis, however, indicated that the MeDi diet could reduce the risk of AD by 29% (RR = 0.71; 95% CI: 0.56–0.89; $I^2 = 52.3\%$, $P = 0.063$).



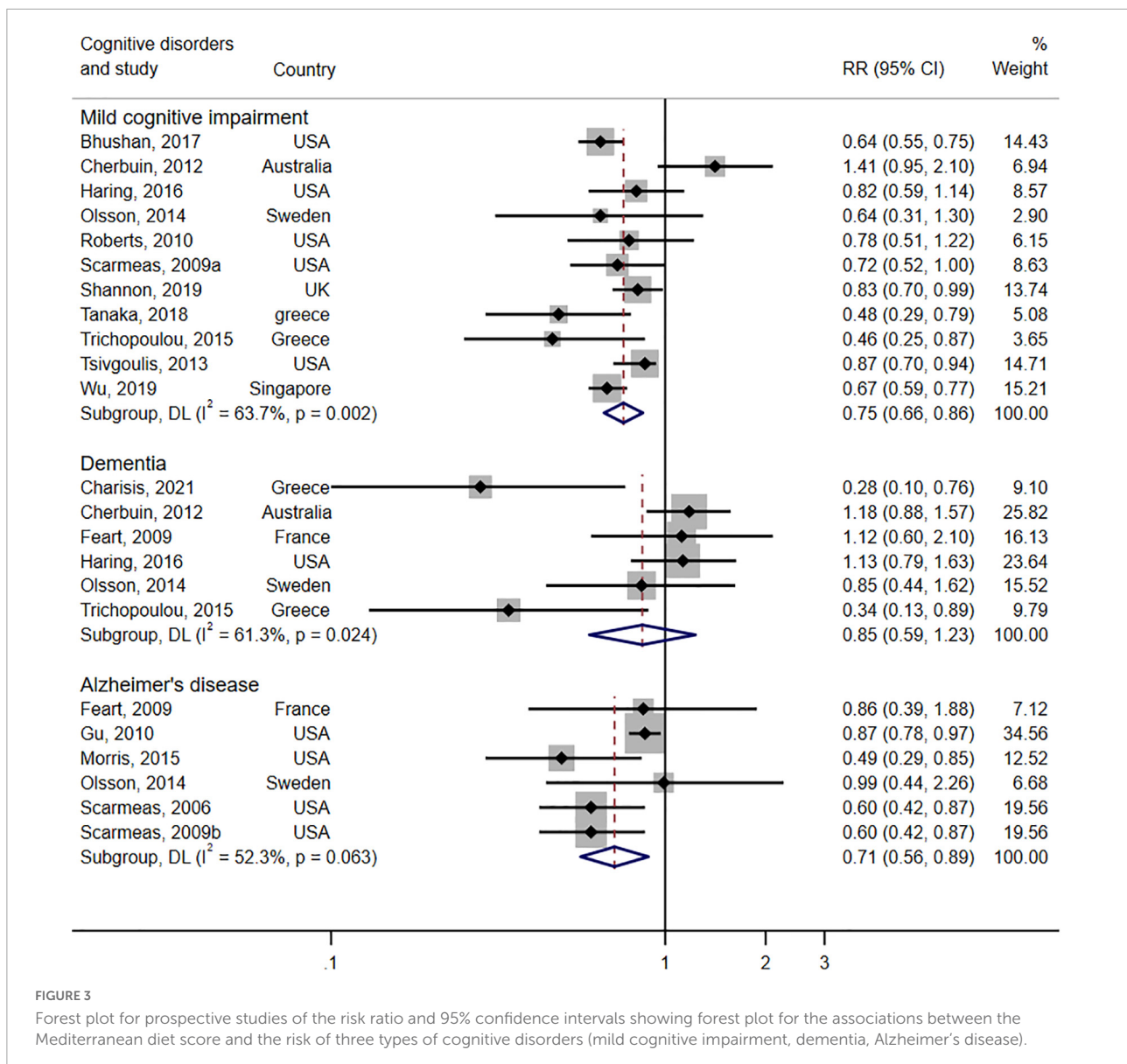
Effects on cognitive function in randomized control trials

Two RCTs examined the effects on cognitive function based on six types of cognitive domains (Figure 4). The pooled results indicated that the MeDi diet could strengthen working memory (SMD = 0.17; 95% CI: 0.01–0.32, $P = 0.033$; $I^2 = 11.8\%$, $P = 0.339$), episodic memory (SMD = 0.20; 95% CI: 0.09–0.30, $P < 0.000$; $I^2 = 19.0\%$, $P = 0.285$), and global cognition (SMD = 0.19; 95% CI: 0.00–0.39, $P = 0.046$; $I^2 = 0.0\%$, $P = 0.460$) as compared with the control group. On the contrary, the MeDi diet showed an adverse effect on attention (SMD = -0.41; 95% CI: -0.67–0.16, $P = 0.001$; $I^2 = 0.0\%$, $P = 0.417$) and was not associated with executive function and processing speed ($P = 0.374$, $P = 0.625$, respectively); both parameters showed no between-study heterogeneity ($I^2 = 9.4\%$, $I^2 = 0.0\%$, respectively).

Meta-regression and subgroup analysis

Subgroup and meta-regression analyses were performed in the cohort studies on the following covariates: study location, study published year, duration of follow-up, dietary intake assessment method, and study quality. However, owing to the limited number of studies (<10), the meta-regression was only conducted for global cognition and MCI risk (Supplementary Tables 3, 5).

Regarding the relationship between the MeDi diet and global cognition, no covariates were found to affect heterogeneity except for the dietary assessment method ($P < 0.000$; Supplementary Table 3). A subgroup analysis of different assessment methods showed that studies using methods other than an FFQ had a negative association with global cognition (SMD = -0.02, 95% CI: -0.03–0.00; $I^2 = 0.0\%$). Pooled results of meta regression analyses revealed that study



location, study published year, and duration of follow-up affect heterogeneity ($P < 0.05$) in terms of the MeDi diet and MCI risk, whereas the exposure assessment method and study quality do not affect heterogeneity ($P = 0.307$; $P = 0.059$; **Supplementary Table 5**). Subgroup analysis found no heterogeneity among Mediterranean region studies ($I^2 = 0.0\%$), while high adherence to the MeDi diet was associated with lower risk of MCI (RR = 0.57; 95% CI: 0.32–0.70).

The relationship between the MeDi diet and episodic memory or dementia was examined in the subgroup analysis (**Supplementary Tables 4, 6**). Pooled results revealed a positive association between high MeDi diet score and episodic memory in studies conducted before 2015 with low heterogeneity (SMD = 0.06; 95% CI: 0.02–0.10; $I^2 = 8.4\%$) and studies with follow up duration < 5 years without heterogeneity

(SMD = 0.02; 95% CI: 0.00–0.03; $I^2 = 0.0\%$; **Supplementary Table 4**). For dementia, study location, study published year, and exposure assessment method affected heterogeneity. For the Non-Mediterranean region, studies conducted before 2015 and exposure assessments conducted using other method, there was no heterogeneity (All $I^2 = 0.0\%$; **Supplementary Table 6**).

Publication bias

Owing to the limitations in evidence (requiring more than 10 studies), publication bias was only investigated for cohort studies that analyzed the associations between the MeDi diet and global cognition and MCI. No publication bias was found (**Supplementary Figure 2** shows the funnel plot), and both

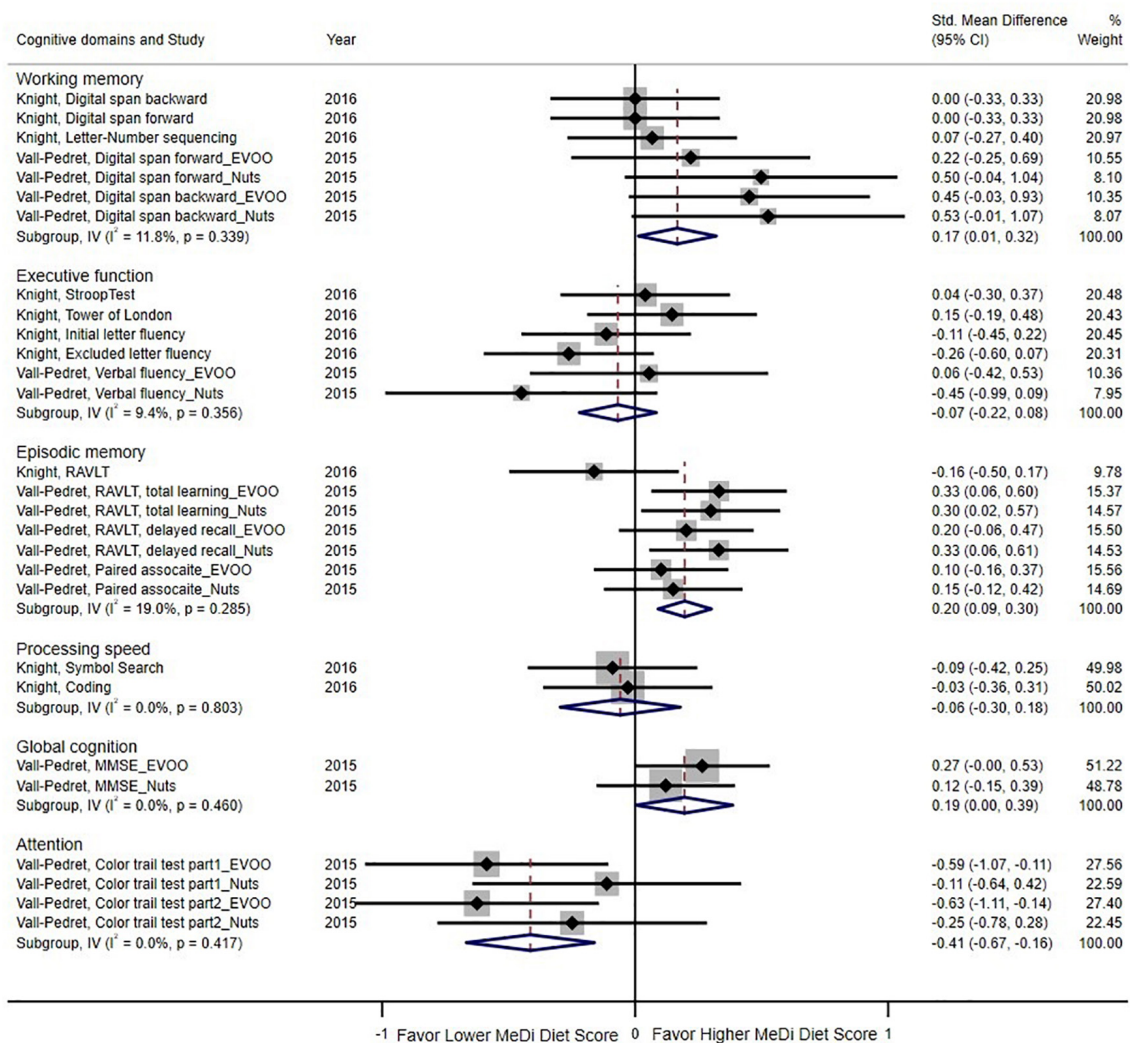


FIGURE 4

Forest plot for randomized controlled trials of standardized mean difference (std. mean difference) and 95% confidence intervals showing forest plot for the associations between the Mediterranean diet score and cognition function by cognitive domains (working memory, executive function, episodic memory, processing speed, global function, attention). MMSE, Mini-Mental State Examination; EVOO, Extra virgin olive oil; RAVLT, Rey Auditory Verbal Learning Test.

Egger's and Begg's tests showed no publication bias in the relationship between adherence to the MeDi diet and global cognition in the cohort studies (Egger's test: $P = 0.330$; Begg's test: $P = 0.443$). A funnel plot of the relationship between the MeDi diet score and MCI risk in cohort studies was designed (Supplementary Figure 3 shows the funnel plot), and no publication bias was found. Both Egger's and Begg's tests showed similar results (Egger's test: $P = 0.968$; Begg's test: $P = 0.876$).

Discussion

This systematic review and meta-analysis qualitatively analyzed 31 cohort studies and five RCTs and quantitatively

analyzed 26 cohort studies and two RCTs. Pooled results of the RCTs indicated that adherence to the MeDi diet could increase global cognition, episodic memory, and working memory but may reduce attention. The main findings from the prospective studies indicated that high adherence to the MeDi diet could reduce MCI and AD risks. However, no significant associations between adherence to the MeDi diet and cognitive function or dementia were found in the cohort studies.

Our results on cognitive function from the prospective studies are in partial agreement with those of previous studies. Loughrey et al. conducted the first systematic review that investigated the relationship between the MeDi diet and cognitive function (delayed recall, episodic memory, global memory, and working memory) among healthy older adults

(24). Their conclusions were similar to our findings, and the differences were mostly not significant, with a small effect size. However, there was high heterogeneity in the effect size. Several possible explanations were given for the contradiction. First, this could have been due to different MeDi diet scoring methods used in the studies. Similarly, when the same MeDi diet score was used, there were individual differences as it was not possible to ensure that every participant strictly adhered to the MeDi diet. Moreover, the current MeDi diet differs from the traditional MeDi diet owing to social, economic, geographical, cultural, and educational factors (68). In addition, differences in cooking methods may have had an impact on the bioavailability of nutrients which could indirectly affect cognitive function. The impact of cooking method varies. For example, gently fried can enhance glucose metabolism which may be linked to increased cognitive function, and it does not destroy dietary phenolic compounds as compared to frying (69). Studies have found that high-temperature cooking such as frying produces acrylamide, and dietary exposure to acrylamide is associated with cognitive function decline (70). Loughrey et al. inferred that the MeDi diet was beneficial in improving global cognition, which is contrary to our findings (24). This may be due to the use of the MMSE scale in the included studies, which may not be sensitive to cognitive changes in healthy populations, according to Gluhm et al. (71). Secondly, some of the populations included in the studies were relatively young (approximately 40 years). Therefore, the effects of the MeDi diet on cognitive changes may have been highly confounded by other factors.

In 2021, a meta-analysis indicated that the results on the relationship between the MeDi diet and cognitive disorders were similar to those in our study. In particular, high adherence to the MeDi diet was beneficial to lower the risk of MCI and AD (22). The Spanish team included 22 studies in the qualitative analysis and 11 studies in the meta-analysis and concluded that the MeDi diet could lower the risk of MCI (RR = 0.91, 95% CI: 0.85–0.97) and AD (RR = 0.89, 95% CI: 0.84–0.93) (22). Before this, Wu et al. and Singh et al. both reached similar conclusions (20, 21), indicating that higher adherence to the MeDi diet could reduce MCI incidence by 17 and 27%, respectively, and AD incidence by 40 and 36%, respectively. Many meta-analyses have demonstrated the effects of representative food groups or potentially beneficial nutrients in the MeDi diet on cognitive health. The MeDi diet typically includes daily consumption of vegetables, fruits, whole grains, and moderate consumption of fish and red wine, as well as partaking in exercise (8). Intake of foods, such as fruit, vegetables, fish, and cereals, as well as nutrients, including vitamins and omega 3, can reduce mild and even severe cognitive impairment (72–75). The MeDi diet may also reduce cognitive decline by reducing oxidative stress (76, 77). Furthermore, in 2004, Chrysohoou et al. conducted the Attica

study and found that adherence to the MeDi diet could lower C-reactive protein (CRP) and interleukin levels, thus protecting cognitive health (78, 79). Gu et al. showed similar results in 2010, indicating that high adherence to the MeDi diet could lower high-sensitivity CRP levels, thereby reducing the risk of AD by 34% (18). Additionally, there is some evidence that olive oil plays a key role in the MeDi diet and may be protective against AD risk, especially in ApoE4 carriers (70, 80). Therefore, it may be important to modulate pathways affected by genetic risk factors (i.e., ApoE 4), as ApoE is the most important susceptibility locus and a non-modifiable genetic risk factor for AD (64, 81). Many systematic reviews uncovered no association between high MeDi diet score and dementia (21, 23). A meta-analysis conducted by Wu et al. indicated that adherence to the MeDi diet was not related to dementia risk (RR = 1.07, 95% CI: 0.81–1.42) (21), which is consistent with our results. A possible explanation for this is that the effect of the MeDi diet on dementia may be in delaying the onset of dementia, which would take at least 5 years, if not 10+ years, to reveal (82).

Regarding the relationship between the MeDi diet and cognitive function in RCTs, the earliest meta-analysis of RCTs on this topic was presented by Loughrey et al. in 2017. They showed that high adherence to the MeDi diet could strengthen delayed recall, global cognition, and working memory, but no such association with attention was found (24). In 2018, Radd-Vagenas et al. also conducted a systematic review and meta-analysis of RCTs and reported the effects of the MeDi diet on seven cognitive domains (global cognition, attention, verbal and visual memory, working memory, processing speed, and executive function) (83). However, part of the results was inconsistent with our conclusion, as we found that high adherence to the MeDi diet had an adverse effect on attention. This discrepancy was likely owing to the limited evidence, as our review only analyzed the RCTs conducted by Vall-Pedret et al. and Knight et al. (63, 66). Therefore, future clinical studies are undoubtedly needed to obtain more convincing results. Secondly, since the Mediterranean diet is a dietary pattern rather than a single diet or diet group, it is possible that one of the diet groups considered as Mediterranean had a negative impact on cognitive function but was masked by the effects of other groups. For example, studies have shown that meat consumption is associated with poorer cognitive function (84). Animal models have revealed that these meat products contain a large amount of saturated fatty acids, trans fatty acids, conjugated linoleic acid, and other substances, which may adversely affect the central nervous system and impact cognitive function (85).

Of note, the pooled results of the included cohort studies and RCTs in our study were not the same, which may have been due to the insufficient number of included studies. Second, differences in the assessment of the MeDi diet also led to differences in the results. Third, the follow-up period

was extremely short, as the RCT conducted by Knight et al. lasted for only 6 months (63), while cognitive function needs time to develop detectable change. Lastly, there was a lack of standardized tests for cognitive health to measure changes in cognitive function.

The strength of this paper primarily lies in the following four factors: First, only cohort studies and RCTs were included in this review, and the results were discussed and analyzed separately. Second, this review strictly followed the PRISMA guidelines in the review process, and each step was carefully checked and examined. Third, a meta-regression analysis was conducted to determine the source of heterogeneity. Finally, when performing data extraction, we attempted to contact the authors to obtain accurate raw data. However, there were also limitations to our study. First, the MeDi diet assessment scores and cognitive function testing methods were different, which may have caused bias in the results. Additionally, differences in the dietary assessment methods may also limit comparability and increase error. Third, the follow-up duration of some cohort studies may have been too short to account for changes in cognitive function. Finally, we could not control for dietary differences due to regional variations. Although all studies adhered to the MeDi diet, it was thought that it would be easier and more effective for people from MeDi regions to follow the MeDi diet than for people in other regions.

In summary, this review provided significant evidence that adherence to the MeDi diet could lower the risk of MCI and AD, whereas adherence to the MeDi diet was not related to dementia and other specific cognitive function domains (global cognition, working memory, and episodic memory) in the cohort studies. Across the RCTs, high adherence to the MeDi diet was positively associated with global cognition, working memory, and episodic memory. However, a negative association between the MeDi diet and attention was found. Overall, the MeDi diet is recommended to prevent or delay cognitive disorders and improve cognitive function. These results reinforce further clinical trials on the association between the MeDi diet and cognitive health, with longer follow-up time, especially on attention. Besides that, studies focus on cooking methods, cooking frequency in the MeDi diet was suggested to conduct as well.

Data availability statement

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

Author contributions

JF and L-JT: literature review and data extraction, data synthesis and statistical analysis, manuscript drafting. SS and JL: manuscript critical revision. All authors approved the final version to be submitted.

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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.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fnut.2022.946361/full#supplementary-material>

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