REVIEW

The Impact of the Mediterranean Diet on the Cognitive Functioning of Healthy Older Adults: A Systematic Review and Meta-Analysis

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ABSTRACT

Evidence from epidemiologic studies suggests a relation between the Mediterranean diet (MeDi) and cognitive function, but results are inconsistent. Prior reviews have not provided pooled data from meta-analysis of longitudinal studies and randomized controlled trials (RCTs), or they included younger adult participants. This systematic review and meta-analysis examines the impact of the MeDi on the cognitive functioning of healthy older adults. Fifteen cohort studies with 41,492 participants and 2 RCTs with 309 and 162 participants in intervention and control groups, respectively, were included. The primary outcome of interest was cognitive function, divided into domains of memory and executive function. Meta-analysis of cohort studies revealed a significant association between MeDi and older adults' episodic memory (n = 25,369, r = 0.01, P = 0.03) and global cognition (n = 41,492, r = 0.05, $P \leq$ 0.001), but not working memory (n = 1487, r = 0.007, P = 0.93) or semantic memory (n = 1487, r = 0.08, P = 0.28). Meta-analysis of RCTs revealed that compared with controls, the MeDi improved delayed recall (n = 429, P = 0.01), working memory (n = 566, P = 0.03), and global cognition (n = 429, P = 0.047), but not episodic memory (n = 566, P = 0.15), immediate recall (n = 566, P = 0.17), paired associates (n = 429, P = 0.20), attention (n = 566, P = 0.69), processing speed (n = 566, P = 0.35), or verbal fluency (n = 566, P = 0.12). The strongest evidence suggests a beneficial effect of the MeDi on older adults' global cognition. This article discusses the influence of study design and components of the MeDi on cognitive function and considers possible mechanisms. *Adv Nutr* 2017;8:571–86.

Keywords: systematic review, meta-analysis, Mediterranean diet, cognitive functioning, healthy older adults

Introduction

As a result of longer lifespans, there has been a substantial increase in the prevalence of age-related cognitive decline (1), commonly observed as a steady decline in episodic memory and executive function (2). As decline approaches impairment, it is associated with a concomitant impairment in daily functioning (3) and an increased risk of incident dementia (4). Interventions focused on lifestyle factors such as a healthy diet could provide a cost-effective and practical approach to reducing or slowing age-related cognitive decline (5). The relative ease with which dietary interventions could be implemented may therefore have profound implications on public health policy (6).

The Mediterranean diet (MeDi), reflecting the food patterns of Greece and Southern Italy in the early 1960s (7), was first described in the Seven Countries Study by Keys et al. (8). Keys et al. reported that the MeDi was associated with a reduced risk of mortality from ischemic heart disease in particular, as well as cancers and other chronic diseases. Subsequent research provided supportive evidence linking the MeDi to a lower risk of mortality and improved health outcomes (9, 10). The MeDi is characterized by a high intake of vegetables, legumes, fruits, nuts, cereals, and olive oil but a low intake of saturated lipids and meat, moderate intake of fish, low to moderate intake of dairy products, and regular but moderate intake of alcohol (usually wine). This dietary pattern provides essential micronutrients, fibers, and other plant foods believed to promote good health (7).

Numerous epidemiological studies have investigated the relation between the MeDi and cognitive function. Systematic reviews of epidemiological studies suggest that the MeDi

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Abbreviations used: AD, Alzheimer disease; CMA, Comprehensive Meta-Analysis; MeDi, Mediterranean diet; RCT, randomized controlled trial; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

is associated with a reduced risk of mild cognitive impairment and dementia, including Alzheimer disease (AD) (9, 11–15), and a reduced decline in cognitive function, including episodic memory and executive function (13–17). However, findings regarding the impact of the MeDi on the cognitive health of older adults without cognitive impairment remain inconsistent across reviews, which may be attributable to a number of reasons. Previous reviews included data from younger and older adults (16), included older adults with cognitive impairment (14), considered dementia and AD outcomes alongside cognitive function (13, 15), included duplicate randomized controlled trial (RCT) data (16), or did not include RCT data (12, 17). Although 3 meta-analyses examined the relation between the MeDi and the risk of mild cognitive impairment (9, 11), cognitive impairment (18), and AD (11), there is currently no published meta-analysis to our knowledge that provides a quantitative measure of the association between the MeDi and specific cognitive functions of healthy older adults.

Our review updates the extant literature by examining the association between the MeDi and the cognitive performance of older adults without known cognitive impairment. Specifically, a systematic review and meta-analysis was conducted that included data from both RCTs and longitudinal cohort studies to investigate the relation between the MeDi and cognitive domains of memory (including recognition, immediate recall, delayed recall, face-name recall, paired associates, and semantic memory), executive function (including working memory, verbal fluency, reasoning, attention, and processing speed), and global cognitive function.

Methods

Search strategy

We searched the PubMed, Cochrane Library, EMBASE, and Scopus databases to identify RCTs and cohort studies written in English. Search terms "Mediterranean diet" and "cognition" were used (search strategy with results, **Supplemental Table 1**). We supplemented database searches with reference lists in review art, authors' own files, and Google Scholar. We screened titles and abstracts to exclude articles that did not meet inclusion criteria. Full texts of remaining studies were then screened for eligibility by 2 independent reviewers. Disagreements were resolved through discussions with our expert authors (study selection flowchart, **Figure 1**).

Selection criteria

We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Cohort studies and RCTs that investigated the effects of the MeDi on the cognitive function of community-dwelling older adults (aged ≥50 y) with no known cognitive impairment were included. We excluded studies if participants had a diagnosis of any cardiovascular disease or other serious medical, psychiatric, or neurological problems (**Supplemental Table 2**). RCTs required ≥10 participants/condition to be included in the review. Two independent reviewers assessed the risk of bias in individual studies; the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) instrument was used to assess risk of bias in cohort studies (**Supplemental Table 3**), whereas guidelines outlined in Section

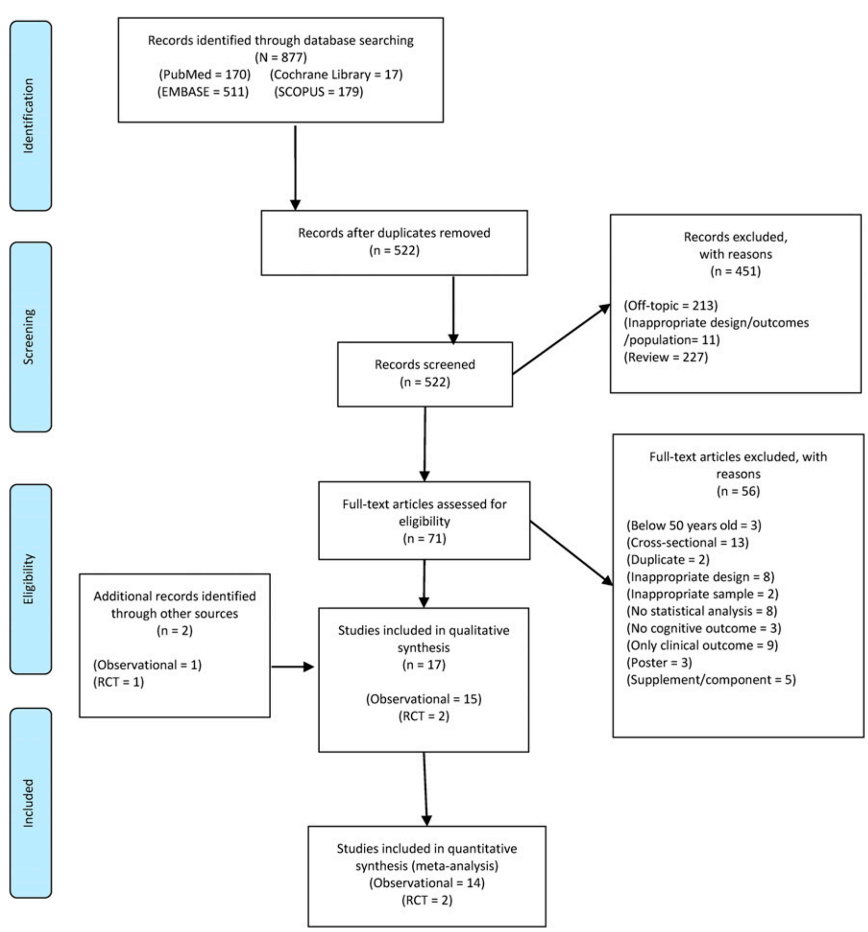

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. RCT, randomized controlled trial.

8 of the *Cochrane Handbook for Systematic Reviews of Interventions* were used to assess risk of bias in RCTs (**Supplemental Table 4**).

The primary outcome of interest was cognitive function, divided into the domains of memory and executive function. As in prior reviews (19, 20), subcategories were created within each domain, depending on measures used across studies. Memory subcategory tests included recognition, immediate recall, delayed recall, face-name recall, paired associates, and semantic memory. Executive function subcategory tests included working memory, verbal fluency, reasoning, attention, and processing speed. Composite measures of episodic memory (e.g., immediate and delayed recall) and executive function were also included. Global cognition was measured using composite measures of cognitive function.

Statistical analysis

Data extraction was conducted by 2 independent reviewers and cross-checked by a member of the expert panel. We used Comprehensive Meta-Analysis (CMA) software version 3.0 (Biostat) to conduct the analysis. For trials, the summary measure of treatment effect was the standardized mean difference, which is the absolute mean difference divided by the SD. The summary statistics required for each outcome were the number of participants in the intervention and control groups at baseline and posttest, the mean change from baseline, and the SD of the mean change. If change-from-baseline scores were not provided, they were calculated using baseline and posttest means and SDs. Change SDs were calculated assuming zero correlation between the measures at baseline and follow-up. Although this method may overestimate the SD of the change from baseline, it is a conservative approach, which is preferable in a meta-analysis (21). For cohort studies, Pearson's r correlation coefficient was chosen, with a positive result indicating that the MeDi was associated with reduced cognitive decline. All effect sizes were first converted to Fisher's Z and then to r. Where the predictor variable was continuous, unstandardized β values were standardized by dividing them by the SE where available. Where the SE was not available, the P value was used to estimate correlation. Standardized β values were converted to r by dividing them by the square root of the sample size. Where the predictor variable was categorical, β values were entered into CMA as either raw mean differences or as Cohen's d as appropriate and converted to Fisher's Z. ORs were converted to Fisher's Z in CMA and then to r. Subgroups in cohort studies (e.g., tertiles of MeDi scores) were combined.

Individual effect sizes were combined using the inverse variance random-effects method (22). This was used to allow the incorporation of heterogeneity among studies. Heterogeneity was examined using Q, and any P value $\leq$0–10 was considered statistically significant (23). Inconsistency was examined using I^2 and the following grades were applied: <25% (very low), 25 to <50% (low), 50 to <75% (moderate), and $\geq$75% (large) (23). Multiple-publication bias was avoided by using data from the most recently published study. Priority was given to outcomes that were adjusted for covariates and that removed cognitively impaired participants. For both meta-analyses of cognitive function, multiple tests of the same cognitive domain from the same study were collapsed into one effect size and subgroups were analyzed independently as separate effect sizes. Small-study effects (publication bias, etc.) were examined using funnel plots and the regression-intercept approach of Egger et al. (24), provided that there were $\geq$10 effect sizes (24, 25). To examine the effects of each result on the overall findings, outcomes were analyzed having deleted each study from the model once. Cumulative meta-analysis, ranked by year, was used to examine the accumulation of evidence over time (26). Sensitivity analyses were performed to investigate the robustness of the results with regard to *1*) study factors (country or region, study length, age of sample, sex ratio, education, and risk of bias), *2*) test factors (MeDi assessment, cognitive test used), and *3*) analysis factors (whether covariates included age, sex, education, race, vascular risk factors, physical activity, energy intake, and removal of participants with dementia from baseline or analysis). Categorical variables were examined using moderator analysis, provided that there were $\geq$3 outcomes/category; and continuous variables were examined using meta-regression, provided that there were $\geq$4 outcomes for analysis.

Results

Study characteristics

Fifteen cohort studies were eligible for inclusion (**Table 1**). One study examined the same cohort as a later study and was not included in quantitative analysis (41). The remaining studies had 41,492 participants, with study lengths ranging from 2 to 10.6 y (mean: 5.7 y). The MeDi was scored using the methods of Trichopoulou et al. (28) in 8 studies, Panagiotakos et al. (34) in 2 studies, and the Mediterranean–Dietary Approaches to Stop Hypertension Trial diet intervention for neurodegenerative delay (35) in 1 study and alternate methods in 2 studies.

Two RCTs were eligible for inclusion, with 309 participants in the MeDi intervention groups and 162 in the control groups (**Table 2**). Participants in the experimental group were typically advised on dietary changes. Supplementary foods or vouchers were given or residential kitchen staff members were advised on appropriate changes. Participants in control groups were either advised on diet or given vouchers. Compliance was assessed through biomarkers and questionnaires. Both studies reported good compliance. One study focused on participants at risk for cardiovascular disease but excluded those with cardiovascular disease and thus was deemed eligible for inclusion.

Cohort studies

Meta-analysis revealed a significant association between the MeDi and episodic memory ($P = 0.03$) and global cognition ($P < 0.001$), but not working memory ($P = 0.93$) or semantic memory ($P = 0.28$) (**Figure 2**, **Table 3**). There was statistically significant heterogeneity for all 4 outcomes included in the meta-analysis. Inconsistency was moderate for episodic memory and large for global cognition, semantic memory, and working memory. With each group deleted from the model once, results remained the same across all deletions for episodic memory and global cognition (**Supplemental Figure 1**). Cumulative meta-analysis, ranked by year, showed that episodic memory was not significantly associated with the MeDi for all years examined, but global cognition has been significantly associated with the MeDi since 2011 (**Table 4**, **Supplemental Figure 2**). Analysis on small study effects was conducted for global cognition only. Qualitative analysis using a funnel plot demonstrated moderate to no asymmetry (**Supplemental Figure 3**). Further quantitative analysis with Egger's test of the intercept found statistically significant and thus potential small study effects. No further analysis was conducted on semantic memory or working memory because there were only 2 outcomes.

Meta-regression was used to examine study length, STROBE risk of bias, age (mean and minimum), and sex (percentage of women) for episodic memory (**Supplemental Table 5**). None of the results were significant. Study length, STROBE risk of bias, age (mean and minimum), sex (percentage of women), and education (percentage of tertiary education) were examined for global cognition (**Supplemental Table 6**). Only the result for STROBE risk of bias was significant ($P = 0.01$). For global cognition, there were also sufficient

TABLE 1 Characteristics of included cohort studies[1]

Study, year (ref)	Study characteristics: Population	Study characteristics: Mean length, y	Study characteristics: *n*	Baseline demographics: Mean age, y	Baseline demographics: Sex, % women	STROBE	Food intake assessment/MeDi score	Covariates	Outcome of interest	Additional notes
Cherbuin and Anstey, 2012 (27)	PATH Through Life study: population-based sample of community-dwelling adults aged 60–64 y randomly selected from electoral roll in Australia	5	1491	62.5 ± 1.5	51.2	21	CSIROFFQ plus Australian food composition tables Trichopoulou et al. (28)	Age, sex, education, apoE ε4 status, BMI, physical activity, stroke, diabetes, hypertension, and energy intake	Global cognition[2]	Participants with MCI and dementia were removed from analysis. Among MeDi components, higher intake of fish was associated with less cognitive decline (*P* = 0.011) and a higher ratio of monounsaturated to saturated fats was associated with cognitive decline (*P* = 0.008)
Féart et al., 2009 (29)	Three-City Study: population-based sample of community-dwelling adults aged ≥65 y from Bordeaux	5	1410	75.9 ± 4.8	62.6	22	Validated FFQ plus 24-h dietary recall assessed by dietitian Trichopoulou et al. (28)	Age, sex, education, marital status, energy intake, physical activity, BMI, diabetes, hypercholesterolemia, hypertension, smoking status, stroke, depression, ≥5 medicines/d, apoE ε4 status, and their interaction with time	Global cognition[3], immediate recall (BVRT[2], FCSRT[3]), verbal fluency[2]	Participants with dementia were removed from analysis; when participants with dementia were included, FCSRT score was nonsignificant (*P* = 0.08) When MeDi was assessed as a categorical variable, the highest, but not middle, category was significantly associated with global cognition and FCSRT
Galbete et al., 2015 (30)	SUN project: sample of university graduates aged ≥65 y in Spain	2	823	61.9 ± 6	27.1	22	Validated FFQ sent by mail Trichopoulou et al. (28)	Age, sex, college education, follow-up time between baseline and cognitive evaluation, energy intake, physical activity, BMI, CVD, diabetes, hypercholesterolemia, hypertension, smoking status, and apoE ε4 status	Global cognition[3]	In multivariate analysis, participants with higher adherence to the MeDi had significantly better cognitive function compared to the moderate and lowest categories
Gallucci et al., 2013 (31)	TRELONG study: population-based sample aged 70–79 y selected from registry office and stratified for age and sex	7	309	79.1 ± 9.7	61.2	18	Assessed intake of cereals, fish, vegetables, and fruit MeDi status (yes/no) based on food intake	None	Global cognition[2]	The majority adhered to the MeDi (92%). Only univariate analysis was conducted with the MeDi variable, which found a nonsignificant association; the MeDi was not included in multivariate analysis

(Continued)

TABLE 1 (*Continued*)

Study, year (ref)	Study characteristics: Population	Study characteristics: Mean length, y	Study characteristics: *n*	Baseline demographics: Mean age, y	Baseline demographics: Sex, % women	STROBE	Food intake assessment/ MeDi score	Covariates	Outcome of interest	Additional notes
Gardener et al., 2015 (32)	AIBL study: cohort study of healthy controls aged ≥60 y in Australia	3	527	69.3 ± 6.4	60.2	19	CCVFFQ assessed food intake over past year Trichopoulou et al. (28)	Age, sex, years of education, country of birth (Australia vs. other), energy intake, angina, BMI, diabetes, heart attack, hypertension, smoking status, stroke, and apoE ε4 status	Attention[2], episodic memory (composite[2], RCFT[2]), executive function[3], global cognition[2], semantic memory[2], and working memory[2]	Those with MCI and AD were excluded from analysis; subgroup analysis found that MeDi was associated with better executive function in apoE ε4 allele carriers ($P < 0.01$) but not noncarriers
Koyama et al., 2015 (33)	HABC study: population sample of Medicare-eligible, community-dwelling adults aged 70–79 y in the United States	8	2326	74.6 ± 2.9	51.3	21	Block FFQ (Berkeley, CA) administered by trained examiners Panagiotakos et al. (34)	Age, sex, education, BMI, smoking status, physical activity, depression, diabetes, energy intake, and SES	Global cognition (black subgroup[3], white subgroup[2])	Those with dementia included in analysis; MeDi was significantly associated with global cognition among black but not white subgroups when assessed both as tertiles ($P = 0.01$) and per increase in points ($P = 0.02$)
Morris et al., 2015 (35)	Rush MAP: sample of residents >40 y of retirement communities and senior public housing units in the United States	4.7	960	81.4 ± 7.2	75	22	FFQ administered during clinical evaluations MIND score	Age, sex, education, cognitive activities, apoE ε4 status, smoking status, physical activity, energy intake, stroke, myocardial infarction, diabetes, hypertension, time, and time interactions with each covariate	Episodic memory[3], global cognition[3], processing speed[3], reasoning[3], semantic memory[3], working memory[3]	Participants with dementia were excluded The difference in decline rates for highest vs. lowest tertile of MeDi score was equivalent to being 7.5 y younger in age Excluding those with MCI at baseline increased the association by 9.5%; removing those whose MeDi score changed significantly also increased the association (30–78%) with all cognitive functions (except reasoning)
Qin et al., 2015 (36)	CHNS study: population-based sample of community-dwelling adults aged ≥55 y in China	5.3	1650	63.5 (NA)	50.3	22	Validated in-person 24-h dietary recalls over 3 consecutive days administered by trained interviewers	Age, sex, education, region, urbanization index, annual household income per capita, energy intake, physical activity, smoking status, BMI, hypertension, time, and time interactions with each covariate	Episodic memory[2], global cognition (composite[2], TICS-mod[2])	Participants aged ≥65 y in the highest, but not medium, tertile had a significantly slower rate of cognitive decline in all domains compared with lowest tertile; outcomes in this age group were also significant when MeDi was assessed as a continuous variable

(*Continued*)

TABLE 1 (*Continued*)

Study, year (ref)	Study characteristics			Baseline demographics		STROBE	Food intake assessment/ MeDi score	Covariates	Outcome of interest	Additional notes
	Population	Mean length, y	*n*	Mean age, y	Sex, % women					
							Trichopoulou et al. (28) adapted for China			No significant associations with cognitive function were found for adults aged <65 y or when age groups were combined No significant differences reported when excluding subjects with the lowest 10% baseline cognitive scores
Samieri et al., 2013 (37)	WHS: substudy of WHS participants aged ≥65 y from an RCT of low-dose aspirin and vitamin E supplements for primary prevention of CVD and cancer in women in the United States	5	6174	71.9 ± 4.1	100	21	Validated self-administered FFQ Trichopoulou et al. (28) adapted for the United States	Age, race, education, income, energy intake, physical activity, BMI, smoking, diabetes, hypertension, hypercholesterolemia, hormone use, depression, and treatment arm	Episodic memory[2], global cognition[2]	Results were nonsignificant for cognitive outcomes for all quintiles compared to the lowest quintile Among MeDi components, a higher ratio of monounsaturated to saturated fats was associated with more favorable episodic memory ($P = 0.05$) and global cognition ($P = 0.03$) Whole grain intake was associated with better global cognition ($P = 0.02$)
Samieri et al., 2013a (38)	NHS: substudy in participants from female registered nurses in the United States who were aged ≥70 y and free of stroke	6	16,058	74.3 ± 2.3	100	20	Self-administered FFQ Trichopoulou et al. (28) adapted for the United States	Age, education, physical activity, energy intake, BMI, smoking status, multivitamin use, depression, diabetes, hypertension, hypercholesterolemia, and myocardial infarction	Episodic memory[2], global cognition (composite[2], TICS[2])	MeDi was significantly associated with mean cognitive score across assessments ($P < 0.005$ all domains) but not rate of change in cognitive score Among MeDi components, vegetable intake was associated with less decline in global cognition (P-trend = 0.04), and a higher ratio of monounsaturated to saturated fats was associated with less decline in episodic memory and global cognition (P-trend = 0.001)

(*Continued*)

TABLE 1 (*Continued*)

Study, year (ref)	Study characteristics: Population	Study characteristics: Mean length, y	Study characteristics: *n*	Baseline demographics: Mean age, y	Baseline demographics: Sex, % women	STROBE	Food intake assessment/ MeDi score	Covariates	Outcome of interest	Additional notes
Scarmeas et al., 2006 (39)	WHICAP study: sample of 2 related cohorts who were Medicare beneficiaries aged ≥65 y stratified for ethnicity and age in the United States	4	2226	77.2 ± 6.6	67.7	21	Willet's SFFQ (Cambridge, MA) administered by trained interviewers Trichopoulou et al. (28) adapted for the United States	Cohort, age, sex, education, ethnicity, baseline cognitive performance, baseline MeDi, time, and MeDi × time interaction	Global cognition[3]	Sample included those with AD Greater per-unit adherence to the MeDi was associated with 0.3% of an SD less decline per year
Tangney et al., 2011 (40)	CHAP study: sample of community-dwelling adults aged ≥65 y in the United States	7.6	3790	75.4 ± 6.2	61.7	19	Modified Harvard FFQ (assessed intake over the past year) either self-administered or by interview Panagiotakos et al. (34)	Age, sex, race, education, participation in cognitive activities, energy intake, and MeDi × time interaction	Global cognition[3]	Results remained significant when those in the bottom 10% of baseline cognitive scores were excluded Results also remained significant when those with heart disease or stroke were excluded
Tangney et al., 2014 (41)	Rush MAP: sample of residents of >40-y retirement communities and senior public housing units in the United States	4.1	826	81.5 ± 7.1	74	22	MAP FFQ modified from CHAP study FFQ and self-administered Panagiotakos et al. (34)	Age, sex, education, energy intake, and cognitive activities	Global cognition[3], episodic memory[3], executive function[2], processing speed[2], semantic memory[2], working memory[2]	MeDi was assessed as a continuous variable When MeDi was examined in tertiles, the highest tertile was significantly associated with rates of change in global cognition and episodic, semantic, and working memory ($P = 0.003$) There was little change in results when those in the bottom 10% of baseline cognitive scores or possible dementia at baseline were excluded
Trichopoulou et al., 2015 (10)	EPIC study: subsample from European cohort study of adults aged ≥65 y based in Greece	6.6	401	74 (NA)	64.1	21	Validated FFQ administered by an interviewer Trichopoulou et al. (28)	Age, sex, years of education, BMI, physical activity, smoking status, diabetes, hypertension, cohabiting, and total energy intake	Global cognition[3]	MeDi was significantly associated with mildly (−4 to −1 points) and substantially (≤−5 points) lower MMSE score ($P = 0.012$ and 0.025, respectively) Among participants aged ≥75 y only, the association was significant with substantially ($P = 0.013$) but not mildly ($P = 0.059$) lower scores

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TABLE 1 (*Continued*)

Study, year (ref)	Study characteristics		Baseline demographics			STROBE	Food intake assessment/ MeDi score	Covariates	Outcome of interest	Additional notes
	Population	Mean length, y	*n*	Mean age, y	Sex, % women					
Wengreen et al., 2013 (42)	CCSMHA: population-based sample of community-dwelling adults aged ≥65 y in the United States	10.6	3580	74.1 ± 9.9	57.1	20	Self-administered; FFQ based on Harvard FFQ Adapted MeDi score	Age, sex, education, BMI, physical activity, multivitamin/mineral supplement use, alcohol and smoking status, diabetes, heart attack, and stroke	Global cognition[2]	Those with dementia were excluded from analysis Subjects in the highest 4 quintiles of MeDi had significantly higher scores compared to the lowest quintile (*P*-trend = 0.0022) at baseline; these differences were maintained and there was no significant difference between quintiles in rate of change

[1] AD, Alzheimer disease; AIBL, Australian Imaging, Biomarkers and Lifestyle; apoE ε4, apolipoprotein E genotype; BVRT, Benton Visual Retention Test; CCSMHA, Cache County Study on Memory, Health and Aging; CCVFFQ, Cancer Council of Victoria FFQ; CHAP, Chicago Health and Aging Project; CHNS, China Health and Nutrition Survey; CSIROFFQ, Commonwealth Scientific and Industrial Research Organization FFQ; CVD, cardiovascular disease; EPIC, European Prospective Investigation into Cancer and Nutrition; FCSRT, Free and Cued Selective Reminding Test; HABC, Health, Aging and Body Composition; MAP, Memory and Aging Project; MCI, mild cognitive impairment; MeDi, Mediterranean diet; MIND, Mediterranean–DASH (Dietary Approach to Systolic Hypertension) Diet Intervention for neurodegenerative delay; NA, not available; NHS, Nurses' Health Study; PATH, Personality & Total Health; RCFT, Rey Complex Figure Test; RCT, randomized controlled trial; ref, reference; SES, socioeconomic status; SFFQ, semi-quantitative food frequency questionnaire; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; SUN, Seguimiento Universidad de Navarra; TICS, Telephone Interview for Cognitive Status; TICS-mod, Telephone Interview for Cognitive Status–modified; TRELONG, Treviso Longeva; WHICAP, Washington Heights–Inwood Columbia Aging Project; WHS, Women's Health Study.

[2] No association with rate of change in cognitive function.

[3] Association with reduced rate of decline in cognitive function.

data to examine country per region of the study, whether dementia participants were removed from analysis, and whether the following covariates were controlled for: race/ethnicity, education (mean years and level), vascular factors, BMI, and smoking. No result was significant (**Supplemental Table 7**). There were insufficient data to examine variables for the remaining outcomes of interest or the method used to calculate MeDi score in moderator analysis. We examined the pooled result for any method with ≥2 global cognition outcomes. The pooled results for the methods of Trichopoulou et al. (28) and Panagiotakos et al. (34) were each significant, whereas the results for those using their own scoring method were not.

In individual studies, significant associations were reported between the MeDi and processing speed ($P \leq 0.001$) and reasoning ($P = 0.002$), but not attention ($P = 0.56$), verbal fluency ($P = 0.16$), episodic memory ($P = 0.24$), immediate recall ($P = 0.34$), or semantic memory ($P = 0.28$). Data were not available for the remaining outcomes of interest of recognition and face-name recall.

RCTs

Meta-analysis results revealed that compared with controls, the MeDi group had significantly improved performance on measures of delayed recall ($P = 0.01$), working memory ($P = 0.03$), and global cognition ($P = 0.047$). There were no significant differences between groups on measures of episodic memory ($P = 0.15$), immediate recall ($P = 0.17$), paired associates ($P = 0.2$), attention ($P = 0.69$), processing speed ($P = 0.35$), or verbal fluency ($P = 0.12$) (**Figure 3**, **Table 5**). Data were not available for the remaining outcomes of interest, including recognition, face-name recall, reasoning, or semantic memory.

There was statistically significant heterogeneity for attention and episodic memory. Inconsistency was moderate for attention and episodic memory, low for processing speed, and very low for the remaining domains assessed. With each group deleted from the model once, results remained the same across all deletions for all domains assessed (**Supplemental Figure 4**). Cumulative meta-analysis, ranked by year, showed that episodic memory was significant before 2016 from 2015 and working memory has been significant since 2015 (**Supplemental Figure 5**). Because of the small number of trials available, no analysis was conducted on small study effects. No further analysis on delayed recall, global cognition, and paired associates was conducted because there were only 2 outcomes. There were insufficient data to examine any moderators or covariates.

MeDi components

None of the trials examined the association between individual components of the MeDi with outcomes on cognitive measures. However, 1 trial (44) examined the impact of 2 variations of the diet in 2 clinical groups: one group was given the MeDi with extra-virgin olive oil, and the other was given the MeDi with mixed nuts. Significantly different results in

TABLE 2 Characteristics of included randomized controlled trials[1]

Study, year (ref)	Intervention	Methods	Participants: *n* EG	*n* CG	Age, y: mean ± SD EG	Age, y: mean ± SD CG	Sex, % women EG	Sex, % women CG	Outcome of interest	Additional notes
Knight et al., 2015 (43)	MeDi intervention versus habitual diet control Adelaide, Australia	Participants were advised on which group they had been allocated to and were monitored on a fortnightly basis by a dietitian to check that the diet was followed to standards. Food was provided to the EG and vouchers to the CG to promote compliance; compliance was checked through biomarkers and questionnaires Follow-up: 3 and 6 mo	70	67	>65: 72.1 ± 4.9	72.0 ± 5.0	47.1	59.7	Attention (Stroop[2], TOL[2]), episodic memory[2], immediate recall (BVRT[2], DSF[2]), processing speed (WAIS IV SS[2] and Coding[2]), verbal fluency (ELF[2], ILF[2]), working memory (DSB[2], LNS[2]), global cognition[2]	In multivariable-adjusted models, EGs did not perform significantly better than CG for executive functioning (P = 0.33), processing speed (P = 0.15), memory (P = 0.50), visual-spatial ability (P = 0.48), or global cognition (P = 0.19)
Valls-Pedret et al., 2015 (44)	3 conditions: MeDi plus EVOO (EG1), MeDi plus nuts (EG2), and low-fat diet advice (CG) Barcelona, Spain	EGs were given quarterly sessions on how to follow the MeDi; supplemental foods (EVOO and mixed nuts) were provided at no extra cost. CG participants were scheduled for yearly visits and given advice on low-fat diet for 3 y; the CG then received personalized advice and group sessions for remainder of trial and received small nonfood gifts; compliance was checked through biomarkers and questionnaires Follow-up: median 4.1 y	127 (EG1) and 112 (EG2)	95	55–80: 67.9 ± 5.4 (EG1) and 66.7 ± 5.3 (EG2)	65.5 ± 5.8	52.8 (EG1) and 48.2 (EG2)	51.6	Attention[3], delayed recall[2], episodic memory[4], global cognition[2], immediate recall[2], paired associates[2], processing speed[4], verbal fluency[2], working memory[2]	Significant improvement in memory composite for MeDi plus nuts vs. CG (P = 0.04); significant improvement in frontal (P = 0.003) and global cognition (P = 0.005) composites for MeDi plus EVOO vs. CG

[1] BVRT, Benton Visual Retention Test; CG, control group; DSB, Digit Span Backward; DSF, Digit Span Forward; EG, experimental group; ELF, excluded letter fluency; EVOO, extra-virgin olive oil; ILF, initial letter fluency; LNS, letter number sequencing; MeDi, Mediterranean diet; ref, reference; SS, symbol search; TOL, Tower of London; WAIS, Wechsler Adult Intelligence Scale.
[2] No improvement in function.
[3] Slower rate of decline.
[4] Improved function.

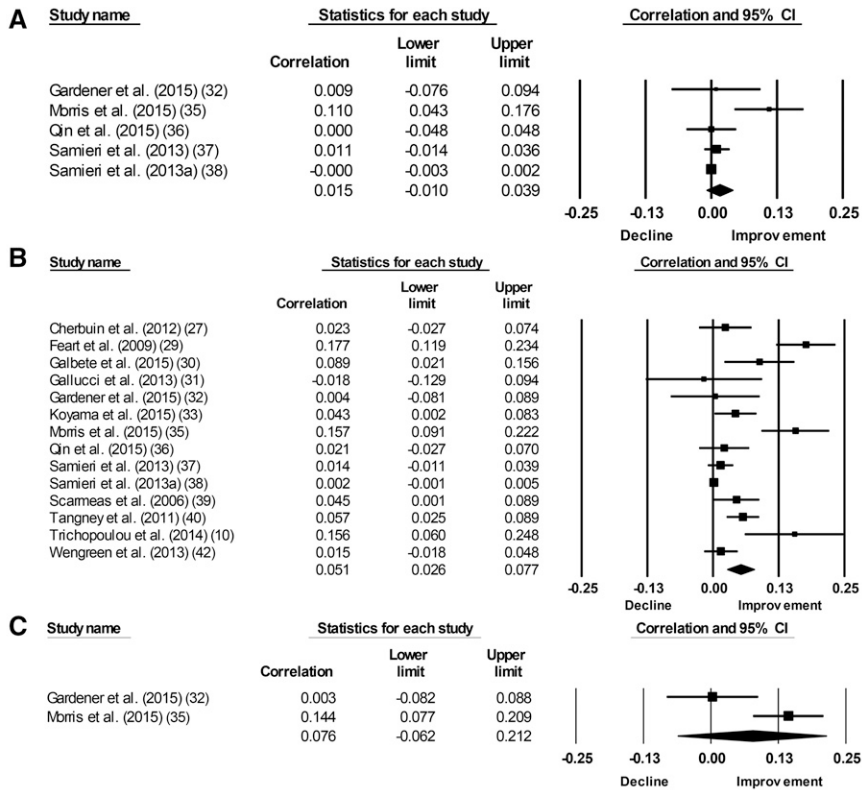

FIGURE 2 Forest plots for observational studies showing plots for episodic memory (A), global cognition (B), and semantic memory (C).

favor of the extra-virgin olive oil group were reported for the executive measure of attention ($P = 0.02$). Differences between groups were not significant for delayed recall ($P = 0.51$), episodic memory ($P = 0.87$), global cognition ($P = 0.46$), immediate recall ($P = 0.54$), paired associates ($P = 0.81$), processing speed ($P = 0.06$), verbal fluency ($P = 0.2$), and working memory ($P = 0.97$).

Among cohort studies, 3 articles examined the association of components of the MeDi with change in cognitive function (27, 37, 38). Samieri et al. (37, 38) reported a higher ratio of monounsaturated to saturated fats as being associated with less decline in episodic memory and global cognition ($P \leq 0.05$). Conversely, Cherbuin and Anstey (27) reported a higher ratio of monounsaturated to saturated fats as being significantly associated with greater decline in global cognition ($P = 0.008$). Other components significantly associated with reduced global cognitive decline included higher intake of fish ($P = 0.011$) (27), whole grains ($P = 0.02$) (37), and vegetables ($P = 0.04$) (38). No other component of the MeDi examined, including intake of alcohol, fruit, legumes, meat , or nuts, was associated with global cognition (27, 37, 38) or episodic memory (37, 38).

Discussion

This review examined the association in cohort studies and RCTs of the MeDi with the cognitive function of older adults without cognitive impairment. Although several meta-analytic reviews on the MeDi and cognition have been published, the current review differs in terms of the targeted population (healthy older adults) and the included outcomes (different domains of cognitive function). To our knowledge, this is the first meta-analysis to provide a detailed examination of the relation between the MeDi and

TABLE 3 Mediterranean diet and cognitive function: main cohort results[1]

Variable	Studies, *n*	Participants, *n*	*r*	95% CI	*Z*	*P*	*Q*	*Q* (*P*)	I^2, %
Attention	1	527	0.025	−0.06, 0.11	0.58	0.56	0	>0.99	0
Episodic memory	5	25,369	0.015	−0.01, 0.039	1.16	0.24	11.13	−0.03	64.05
Global cognition	13	41,492	0.051	0.026, 0.077	3.95	<0.001	91.7	<0.001	85.82
Immediate recall	1	1177	0.029	−0.03, 0.088	0.96	−0.34	0	>0.99	0
Processing speed	1	960	0.146	0.079, 0.212	4.24	<0.001	0	>0.99	0
Reasoning	1	960	0.107	0.039, 0.173	3.09	−0.002	0	>0.99	0
Semantic memory	2	1487	0.076	−0.062, 0.212	1.079	−0.28	6.51	−0.01	84.63
Verbal fluency	1	1177	0.043	−0.016, 0.102	1.42	−0.16	0	>0.99	0
Working memory	2	1487	0.007	−0.15, 0.164	0.09	−0.93	8.5	−0.004	88.24

[1] I^2, inconsistency; *Q*, heterogeneity; *Z*, *z* score.

TABLE 4 Mediterranean diet and cognitive function: results of further analysis for cohort studies[1]

Variable	Egger's test of the intercept				One study removed		Cumulative analysis
	β_0[2]	95% CI	df	*P*, 1-tailed	Study	Point difference, smallest to largest (%)	Significant since
Episodic memory	NA	NA	NA	NA	ND	0.028 (100)	NS
Global cognition	2.17	0.98, 3.37	12	0.001	ND	0.017 (29.8)	2011

[1] NA, not applicable; ND, no difference.

[2] Intercept (results remained statistically significant when each study was deleted from the model).

healthy older adults' recognition, immediate recall, delayed recall, face-name recall, paired associates, semantic memory, working memory, verbal fluency, reasoning, attention, processing speed, and global cognitive function. Among cohort studies, there were sufficient data to pool results for episodic memory, global cognition, semantic memory, and working memory. Greater adherence to the MeDi was associated with improved function on measures of global cognition only. However, results were not consistent across studies and there was significant heterogeneity. Single results for attention, immediate recall, and verbal fluency were not significant, but effect sizes for processing speed and reasoning reached significance. Sensitivity analyses were conducted examining moderators and covariates where possible; a significant association was found between greater effect size and higher STROBE score only. Among RCTs, the MeDi was associated with improved delayed recall, global cognition, and working memory, but not attention, episodic memory, immediate recall, paired associates, processing speed, or verbal fluency. Heterogeneity was nonsignificant for delayed recall, global cognition, and working memory with very low inconsistency. There were insufficient data for moderator or meta-regression analysis.

Cohort studies

Across cohort studies, pooled analysis resulted in a significant association between the MeDi and global cognition only, although analysis of individual studies showed an association between the MeDi and processing speed and reasoning. This finding is somewhat surprising, given the conclusions of previous systematic reviews in this area (13–16). This may, however, be explained by the inclusion of cross-sectional data in all other reviews apart from one (14). For example, one included study did not show an association between the MeDi and change in global cognition and episodic memory; but secondary analysis of the association of the MeDi with the mean score of global cognitive function across 4 time points resulted in a significant cross-sectional association ($P < 0.005$) (38). We only included cohort studies that reported cognitive change scores across time. Furthermore, there was considerable heterogeneity and inconsistency for all pooled outcomes, which we explored using sensitivity analysis but found no possible explanations apart from a greater effect size for global cognition in those studies with a lower risk of bias. Factors that may contribute to our findings are discussed in more detail below.

RCTs

We found only 2 RCTs examining the effect of the MeDi on the cognitive function of healthy older adults, thus making any conclusions tentative. To our knowledge, this is the first meta-analysis of RCTs using the MeDi as an intervention. Meta-analysis of 9 pooled outcomes from these RCTs showed significant improvement for the intervention groups compared with controls on measures of delayed recall, global cognition, and working memory. A previous systematic review reported that the MeDi was associated with improved outcomes on tests of global cognition and executive function (16). However, because of a lack of RCTs, these results were observed in single trials rather than in pooled analyses. It should be noted that results for delayed recall and global cognition, as well as 2 of the 3 results for working memory, came from 2 intervention groups in the same trial (44). This was the only study that reported significant between-group differences. This discrepancy may be attributable to differences in methodology or samples. This study reported a median follow-up of 4.1 y, whereas the second study was of shorter duration (6 mo) (43). It may take longer-term adherence to the MeDi to observe any changes in cognitive function similar to the impact of exercise (20). There was a large difference in minimum age (55 y compared with 65 y) between studies but mean age was closer (66.8 y compared with 72.1 y), which may have implications for the effectiveness of a dietary intervention, particularly if the mechanisms (e.g., vascular mechanisms) are age dependent. Previous reviews on cardiovascular and cardiometabolic factors and cognitive decline suggest an age-dependent association, particularly in midlife (40–59 y), with a weaker association among those age ≥75 y (45).

The results across both observational and RCT studies consistently indicate that the MeDi benefits global cognition. There were, however, differences between observational and RCT data in relation to the impact of the MeDi on specific cognitive domains. Results from cohort studies showed associations between the MeDi and processing speed and reasoning, whereas RCTs reported that the MeDi improved delayed recall, working memory, and executive function compared with controls. These divergent findings could simply be a result of the distinct study designs and follow-up periods. It should be noted, however, that executive functions include processing speed, working memory, and reasoning (46); although there were some specific differences, both study designs consistently report an association between the MeDi and some aspect of executive function. Relatedly, outcome measures used in included RCTs to measure "executive function" (43) were included as measures of "working memory" in cohort studies (40). Such variations in terms of reporting

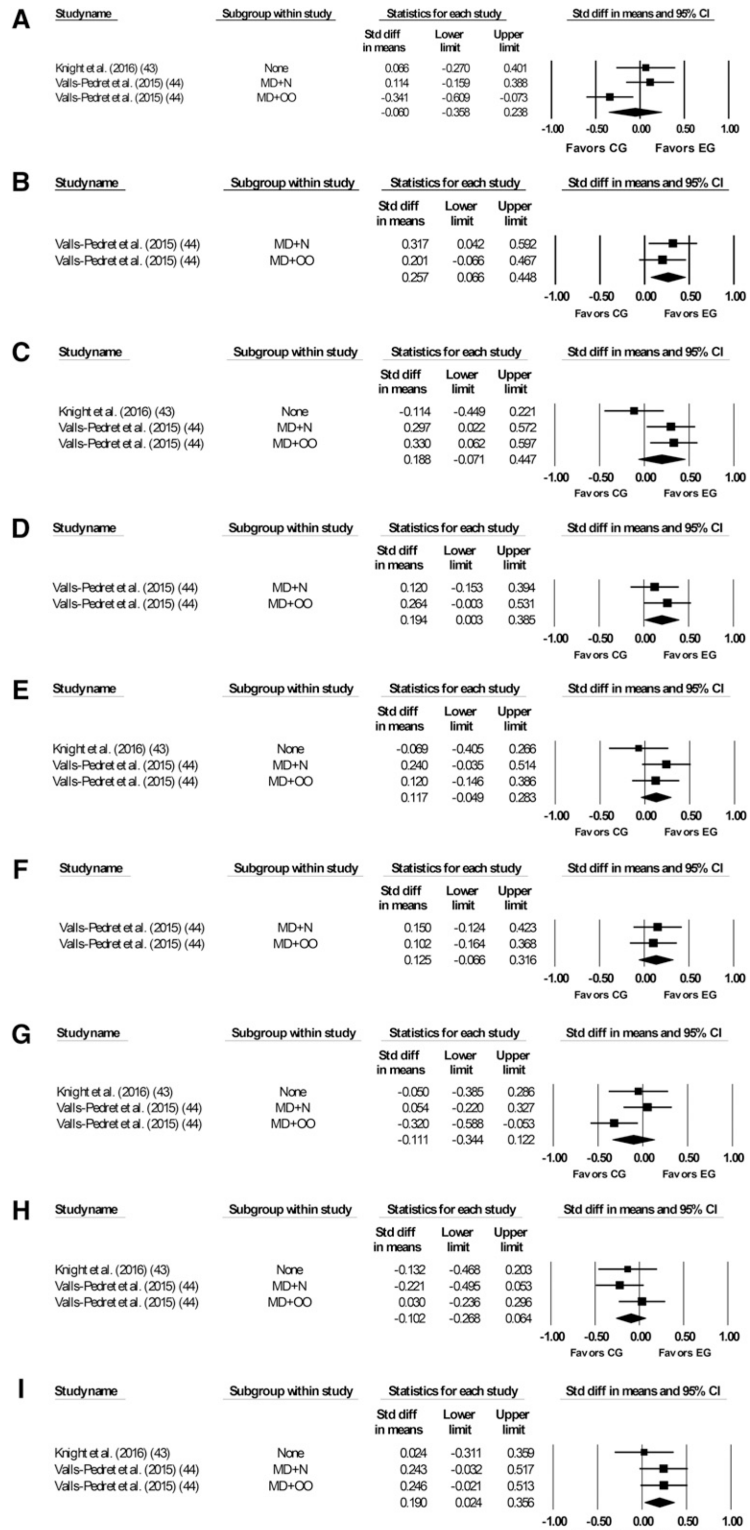

FIGURE 3 Forest plots for randomized controlled trials showing plots for attention (A), delayed recall (B), episodic memory (C), global cognition (D), immediate recall (E), paired associates (F), processing speed (G), verbal fluency (H), and working memory (I). CG, control group; EG, experimental group; MD, Mediterranean Diet; N, nuts; OO, olive oil.

cognitive tests and domains measured may result in incorrect assumptions of inconsistent results. All of the studies in this review included a measure of global cognition; however, only some measured either memory or executive function, and the specific ability area measured within each subdomain varied largely across studies. Undoubtedly, greater homogeneity across selected outcome measures would help to address this issue. Further RCTs using similar cognitive test batteries are needed to corroborate our findings and to further explore possible reasons for differences in outcomes. We outline several potential areas of interest for future trials below.

TABLE 5 Mediterranean diet and cognitive function: main randomized controlled trial results[1]

Variable	Study or subgroup, *n*	Participants[2], *n*	$\overline{X}$	95% CI	*Z*	*P*	*Q*	*Q (P)*	I^2, %
Attention	3	566	−0.06	−0.036, 0.24	−0.4	−0.69	6.3	−0.04	68.23
Delayed recall	2	429	0.26	0.07, 0.45	2.63	−0.01	0.35	−0.55	0.0
Episodic memory	3	566	0.19	−0.07, 0.45	1.42	−0.15	4.75	−0.09	57.85
Global cognition	2	429	0.19	0.003, 0.39	1.99	−0.047	0.54	−0.46	0.0
Immediate recall	3	566	0.12	−0.05, 0.28	1.39	−0.17	1.96	−0.38	0.0
Paired associates	2	429	0.13	−0.07, 0.32	1.29	−0.2	0.06	−0.81	0.0
Processing speed	3	566	−0.11	−0.34, 0.12	−0.93	−0.35	3.87	−0.15	48.28
Verbal fluency	3	566	−0.1	−0.27, 0.06	−1.2	−0.23	1.71	−0.43	0.0
Working memory	3	566	0.19	0.02, 0.36	2.24	−0.03	1.26	−0.53	0.0

[1] One subgroup was included for Knight et al. (43) and 2 subgroups were included for Valls-Pedret et al. (44). I^2, inconsistency; *Q*, heterogeneity; $\overline{X}$, standard difference in means; *Z*, *z* score.
[2] The total number of participants refers to the sum of participants for each included effect size.

MeDi components

Only a small number of cohort studies performed secondary analysis examining the association between components of the MeDi with cognitive function (27, 37, 38). Although all results for ratios of monounsaturated to saturated fats were significant, they were contradictory, possibly because of differences in geographic location. Interestingly, one of the included RCTs examined whether supplementation with extra-virgin olive oil would affect outcomes (44). Results showed that compared with controls, the MeDi plus olive oil group showed significantly greater improvements to memory and executive function. There was no significant difference for another intervention group in the same trial, which had the MeDi supplemented with mixed nuts. This is consistent with other studies that have examined the effects of olive oil and mono- and polyunsaturated fats on age-related cognitive changes in memory, executive function, and global cognition (47–49). Furthermore, in cohort studies, higher intake of fish and vegetables was also significantly associated with reduced cognitive decline. Other studies examining these individual components support this finding (50–53). No other components of the MeDi were reported to have a significant association with cognitive function. Specific MeDi components, rather than the overall pattern, may be beneficial for cognitive function. Thus, examining the association between dietary patterns and cognition, rather than individual components, may contribute to inconsistency in results and mask effects on brain health. However, these conclusions are limited, because no RCTs to date have examined the association of MeDi components with cognition.

Possible mechanisms

The MeDi provides a rich source of antioxidants, vitamins, and unsaturated FAs that may affect possible biological mechanisms of neurocognitive aging (54–56). These mechanisms might include better neurovascular health (57) or a reduction of oxidative stress, metabolic factors, or reduced chronic inflammation (56, 58).

There is epidemiological evidence of reduced levels of inflammatory and oxidative markers and a reduced risk of cardiodiabesity with greater conformity to the MeDi (59, 60). Support for a vascular mechanism comes from neuroimaging studies, including the North Manhattan Study, which reported a beneficial impact of the MeDi on white matter hyperintensities (61), and the Bordeaux Three-City Study of 146 participants, which reported an association between the MeDi and preserved white matter microstructure and structural connectivity, related to improved episodic memory, executive function, and global cognition (62). Further support favoring improved cognition through vascular mechanisms comes from a New York study, which reported that higher adherence of 707 elderly people to the MeDi was associated with reduced cerebrovascular disease burden (63), and from the PREDIMED study, which reported an association between the MeDi and stroke prevention (64).

Promotion of cerebrovascular health through a MeDi may facilitate more efficient clearance of amyloid β from the brain (65, 66). Interestingly, our moderator analysis found no significant differences in effect size for global cognition between those that controlled for vascular factors and those that did not among cohort studies. This is consistent with a neuroimaging study by Scarmeas et al. (58), who found no evidence for a vascular mediation between MeDi with AD outcome, an association that they reported as significant. Further support for nonvascular mechanisms of brain protection by the MeDi comes from ancillary analyses of the PREDIMED cohort, in which the MeDi was associated with a reduction in depression and increased levels of circulating brain-derived neurotrophic factor (44).

Neuroimaging research examining components of the MeDi reports that higher fish intake and lower meat intake were linked with higher total brain, gray matter, and white matter volume (67). In addition, low consumption of meat and meat products was linked to better global cognition and greater total brain volume (68). Conversely, a recent study examining the MeDi and structural brain changes in a Scottish cohort of 73- to 76-y-olds failed to replicate previously reported associations between meat and fish consumption and total brain or gray matter volume (69). Luciano et al. (69) considered the possibility that the discrepant findings might be explained by variations in the quantity and type of meat and fish consumed across studies. Most MeDi studies employ self-report FFQs, which often exclude descriptions of the distribution of meat consumption (65–67). FFQs are also largely subjective and are therefore at risk of differential reporting regarding actual dietary practices. The availability of different types of food in different regions may affect study results (70), and country-specific lifestyles might lead to misclassification regarding adherence to the MeDi (71). An examination of studies conducted in traditional Mediterranean countries would be beneficial, because elderly populations living in Mediterranean countries are more likely to adhere to a homogenous and strict MeDi (72, 73).

Limitations

A substantial problem in using the meta-analytic approach is the heterogeneity in methodology, population, and outcome measurement between studies. We attempted to minimize this by rigorous selection criteria, data preparation (e.g., allocation of tests to appropriate cognitive domains), and planned extensive sensitivity analyses. Typically, a limitation of meta-analysis of cognition in cohort studies is that causal effects cannot be inferred from correlations, but we also conducted a meta-analysis of RCTs to examine possible causal effects on cognition. However, the small number of RCTs retrieved from our search is a limitation. We only included published data, thus running the risk of overestimating intervention effects; however, one of the included trials was published despite no evidence for any intervention effect in any of the cognitive outcomes assessed.

Conclusions and recommendations

The analysis of pooled data from 15 cohort studies and 2 RCTs suggests that adherence to the MeDi might benefit global cognition for healthy older adults. Results also showed evidence of some benefit of the MeDi in domains of delayed recall, working memory, processing speed, and reasoning. Some clear limitations provided guidelines for future studies; future RCTs should consider including older adults from a broad age range, particularly middle-aged (>50 y) and older (>75 y) adults, to examine differences in the impact of the MeDi owing to any possible age-dependent associations. Our sensitivity analysis of cohort studies showed no effects for mean or minimum age on episodic memory or global cognition. However, the lowest mean age among our included cohort studies was 61.9 y, which may be too late to detect any age differences in rate of cognitive decline.

Future observational studies and trials should examine the influence of individual components of the MeDi with cognitive outcomes. Our review indicates that only some components, including olive oil, fish, and vegetables, have beneficial effects. Standardization of study protocol and outcome measurement would be beneficial. Because it may take a long-term intervention to observe changes or maintenance effects in cognition, future RCTs should consider an intervention term of ≥2 y. Studies examining the impact of the MeDi on biomarkers that reflect inflammation would give further insight into any potential mechanism underpinning the effects of the MeDi on cognition. This would guide future trials taking a multitherapeutic approach to enhance modification of these mechanisms (i.e., an intervention using the MeDi in conjunction with exercise) (74).

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