REVIEW

Mediterranean Diet, Cognitive Function, and Dementia: A Systematic Review of the Evidence[1–3]

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ABSTRACT

A growing body of evidence suggests that adherence to the Mediterranean diet (MD) may protect against cognitive decline and dementia. Many epidemiologic studies and several randomized controlled trials (RCTs) have found positive effects of the MD on cognitive function, but findings remain inconsistent. The aim of this systematic review was to provide an update on the current knowledge of the effects of the MD on cognitive function, cognitive impairment, Alzheimer disease (AD), and all-type dementia. Five databases were searched—PubMed, Embase, CINAHL, CENTRAL, and PsycINFO (1806 to 25 May 2015)—with the use of prespecified criteria. Human studies that were published in English without any restriction on study type, population assessed, intervention period, follow-up time, or publication date, and that examined the association between adherence to the MD and cognitive function or dementia symptoms (as measured by cognitive function tests), were included. Only primary publication types were included. Thirty-two studies from 25 unique cohorts, including 5 RCTs and 27 observational studies, met the inclusion criteria. The majority of studies showed that the MD was associated with improved cognitive function, a decreased risk of cognitive impairment or decreased risk of dementia, or AD. Three studies found no correlation between the MD and AD, 3 further studies found no association between the MD and cognitive impairment, and 5 studies found no association between the MD and cognitive function. There was large heterogeneity, and studies differed with regard to quality. Based on the findings and the limitations in study design, we conclude that adherence to the MD is associated with better cognitive performance. However, it should be noted that the majority of findings come from epidemiologic studies that provide evidence for a correlation between the MD and cognition but not for a cause-and-effect relation. More controlled trials are required to establish a causational relation. *Adv Nutr* 2016;7:889–904.

Keywords: cognitive function, dietary patterns, Mediterranean diet, systematic review, dementia, Alzheimer disease, cognitive impairment

Introduction

With an aging population, the prevalence of dementia, characterized by progressive global deterioration of cognitive abilities in multiple domains—such as memory, learning, orientation, language, comprehension, and judgment—severe enough to interfere with daily life, is increasing (1). Although there are several types of dementia, the most common is Alzheimer disease (AD)[6], which accounts for >60% of cases (2). Based on current estimations, there are nearly 36 million people worldwide suffering with this condition, with evidence suggesting that >115 million people will be affected by 2050 (2). The burden of dementia, both of the disease itself and financially, is great on individuals, families, and public health services. Furthermore, the effectiveness of current pharmacologic treatments is inconsistent (3, 4). Despite the fact that the causes of dementia are multifactorial, there is a growing body of evidence showing that modifiable risk factors such as cardiometabolic disease and lifestyle play important roles; thus, nutrition poses an interesting avenue for investigation (5, 6). To this effect, reliable data to support the effectiveness of neuroprotective diets may serve to enhance preventive measures and critically change the way people at high risk of dementia are managed.

The interactions between nutrition and the aging brain are many and complex, but there are 3 main features that are likely to play a pivotal role (7): reduced blood flow (8), thought to be related to atherosclerosis and the formation

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[6] Abbreviations used: AD, Alzheimer disease; *CLU*, clusterin; CRP, C-reactive protein; CVD, cardiovascular disease; MCI, mild cognitive impairment; MD, Mediterranean diet; MedDietScore, Mediterranean diet score developed by Panagiotakos et al.; MedDiet+EVOO, Mediterranean diet enriched with extra-virgin olive oil; MedDiet+Nuts, Mediterranean diet enriched with nuts; MeDi score, Mediterranean diet score developed by Trichopolou et al.; MMSE, Mini-Mental State Examination; NFT, neurofibrillary tangle; *PICALM*, phosphatidylinositol-binding clathrin; PREDIMED, PREvención con Dieta MEDiterránea; RCT, randomized controlled trial; WHICAP, Washington/Hamilton Heights–Inwood Columbia Aging Project.
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of arterial plaques (8); mitochondrial dysfunction, resulting from accumulation of reactive oxygen species in the brain; and inflammation, which generally is considered to be a natural process of aging (9). A distinct feature of AD is the accumulation of β-amyloids and the formation of neurofibrillary tangles (NFTs) composed of highly phosphorylated forms of the microtubule-associated protein tau (7). NFTs disrupt the transfer of key neurotransmitters, nutrients, and growth factors through microtubules. At the same time, β-amyloids increase reactive oxygen species production, which exacerbates tau tangle formation possibly as a compensatory mechanism to oxidative stress (7).

The Mediterranean diet (MD) is characterized by high consumption of unrefined cereals, fruit, vegetables, legumes, and olive oil, moderate consumption of dairy products and alcohol, and low meat consumption (10). Among other benefits, adhering to the MD has been linked to a lower risk of various chronic conditions (11, 12), and its protective properties are thought to be a combination of the high intake of MUFAs and polyphenols from olive oil; PUFAs from fish; and antioxidants from fruit, vegetables, and wine (13).

To date, several studies have shown that individual nutrients characteristic of the MD, as well as the MD as a dietary pattern, reduce oxidative stress biomarkers and positively affect cognition. Intake of unsaturated FAs (both MUFAs and PUFAs) has been associated with improved cognitive performance and a decreased risk of age-related cognitive decline in long-term observational studies (14). Similarly, the intake of micronutrients such as vitamins C, E, and B-12; folate (15, 16); flavonoids (17); and carotenes (16) has been associated with a decreased risk of cognitive decline and AD in human observational studies.

Nevertheless, studies of single nutrients are difficult to apply in practice; thus, consideration of their synergistic effects in dietary patterns is more important (18). To this effect, there is some evidence that adhering to the MD might reduce oxidative stress (19) and inflammation (20), both of which are associated with an increased risk of cognitive decline (21, 22). In addition, an emerging body of evidence, mainly from prospective studies, suggests that the MD slows down age-related cognitive decline and the progression of dementia.

Nevertheless, to date, although several reviews have examined the evidence of the effects of the MD on cognitive function (23, 24), to our knowledge, only a few have used a systematic approach. The most recent systematic review specifically addressing this topic, published in 2013, included only 12 papers. It concluded that adherence to the MD is associated with slower cognitive decline and a lower risk of developing AD, and that more studies examining this association were needed (25). In addition, a meta-analysis, also published in 2013, assessed the effects of the MD on stroke, cognitive impairment, and depression and included a total of 22 studies, of which 8 were on cognitive impairment (26). It was shown that high and moderate adherence to the MD was associated with a reduced risk of cognitive impairment. To the best of our knowledge, since the publication of further studies, no review has synthesized findings from all types of studies examining the MD and cognitive function. Thus, the present systematic review aimed to provide a comprehensive update on the current knowledge of the topic by collating the evidence from all human studies of any design conducted on the MD and cognitive function and/or dementia.

Methods

This review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (27), with prespecification of all methods. A literature search was carried out by one reviewer (SDP) under supervision (EP) for studies that assessed the effect of adhering to the MD (exposure; as opposed to a low MD adherence or other diets, or no dietary change) on cognition. The following electronic databases were searched: PubMed (MEDLINE), CINAHL, CENTRAL (no restriction on publication time), PsycINFO (via Ovid) (1806 to 20 May 2015) and EMBASE (via Ovid) (1974 to 25 May 2015). The following search terms were used: cognition, dementia, Alzheimer's disease, attention, psychometrics, concentration, mild cognitive impairment, memory, spatial memory, long-term memory, short-term memory, and learning. Additional hand-searching of reference lists of relevant systematic reviews was carried out. An example of a full search strategy for PubMed (MEDLINE) can be found in the **Supplemental Methods**. The outcomes assessed included the following: measures of cognitive function or cognitive decline, prevalence of cognitive impairment or incident dementia, and progression of cognitive function, cognitive decline, cognitive impairment, or incident dementia (all-cause dementia or AD). Cognitive function or decline and dementia onset or progression were evaluated through cognitive function tests [e.g., the Mini-Mental State Examination (MMSE)] or other validated assessment methods. Several inclusion and exclusion criteria were specified. Inclusion criteria were human studies published in the English language, including randomized controlled trials (RCTs), prospective and retrospective observational studies that examined the effects of adherence to the MD or MD intervention on a defined score of cognitive function or decline, diagnosis of cognitive impairment, or diagnosis of dementia as outcomes. No restrictions were in place on study sample size or participants' age, sex, or health status. Studies examining individuals with or without signs of cognitive impairment at baseline and those in which cognitive function or dementia were not the only assessed outcome were included. Studies also were included if the MD was not the only type of diet examined. Exclusion criteria were systematic reviews, meta-analyses, narrative reviews, abstracts, conference reports, letters, commentaries, and opinions. Studies with insufficient information to evaluate the effect of the MD on cognitive function, nonhuman studies, studies examining diets not representative of an MD, studies in languages other than English, and studies examining only individual components of an MD also were excluded. Studies examining the effects of diet only on physiologic variables such as blood biomarkers or MRI scans were also excluded from this review. The primary outcome was the effect of MD adherence on cognitive performance. Eligibility assessment of the identified studies was done independently by both reviewers. If eligibility was disputed, this was discussed between the 2 reviewers and a consensus was reached. Data extraction was carried out by one reviewer (SDP) and checked independently by the second reviewer (EP). The following data were extracted from each study: study type, number of participants, participants' characteristics, dietary assessment methods, MD definitions and scores used, cognitive outcomes measured, cognitive assessment methods, cognitive domains measured, findings or outcomes, and study strengths and limitations.

Quality assessment was based on a previously used chart (25), which was adapted to add an item bank for evaluating the risk of bias and precision of observational studies (28). Quality assessment was taken into consideration in the synthesis of results.

Results

Study selection. The combined search result gave a total of 586 papers (**Figure 1**). After an initial review of titles and abstracts, 483 papers were excluded, leaving 103 papers, of

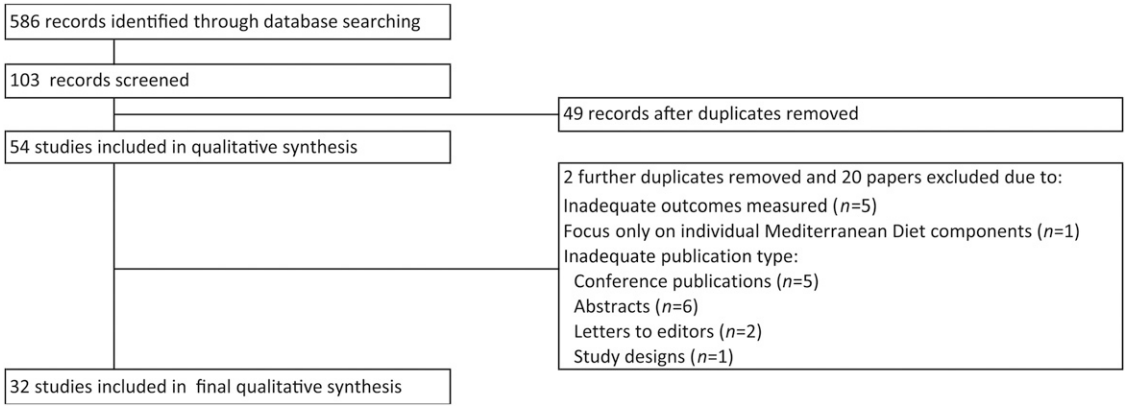

FIGURE 1 Flowchart of the study selection process.

which 49 were duplicates. Of these, 2 further duplicates were removed and 20 publications excluded for the reasons explained in Figure 1. Thus, a total of 32 papers met the inclusion criteria. Excluded tables and reasons for exclusion are shown in **Supplemental Table 1**.

Study characteristics. Key study characteristics are included in **Table 1**. Five RCTs and 27 observational studies met the inclusion criteria. Nineteen studies had female-dominant samples in which studies included only women, 1 study included only men, and 1 study did not report sex. Most of the studies ($n = 26$) included participants aged >60 y, whereas the sample size ranged from 25 (in RCTs) to over 17,000 participants (in cohort studies).

A description of the tools used to assess MD adherence or recommendations provided (for RCTs) can be found in **Supplemental Table 2**. In brief, time of adherence to the MD varied between RCTs, this being 10 d in one study (59), 12 wk in another study (60), and 6.5 y in the 3 publications of the PREDIMED (PREvención con DIeta MEDiterránea) study (56–58). Adherence to the MD was assessed in most studies with the use of either a score developed by Panagiotakos et al. (MedDietScore; 61) or a score developed by Trichopolou et al. (MeDi score; 31), whereas 7 studies modified the MeDi score to better suit the populations they were studying, and 1 study used a novel "Mediterranean-style diet" score.

Assessment of dietary intake. Dietary intake was assessed in the majority of studies with the use of semiquantitative FFQs that had from 61 to 215 food items. One study assessed dietary intake with a 24-h recall and a food-composition table that contained ~900 food and drink items (38). Another study used a 7-d food record and a validated precoded menu book (40), and a Health Habits and History Questionnaire including 128 food and drink items was used in one study (54) (Supplemental Table 2).

Cognitive assessment. The timing and tools used to assess cognitive function, as well as the specific domain assessed, are shown in **Supplemental Table 3**. In brief, the outcomes assessed varied in that 9 studies included risk of AD as outcome, 9 studies measured cognitive impairment, and 23 studies measured cognitive function and decline. Of these, 1 study measured all 3 outcomes (31), 2 studies measured both cognitive impairment and AD (47, 54), 2 studies measured cognitive function and cognitive impairment (33, 57), and 3 studies measured cognitive function and AD (37, 45, 53).

All studies used previously validated cognitive function tests but these varied. Nine studies assessed cognitive status based on only one test. The majority of studies used the MMSE to evaluate cognitive function, and many used the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association, now known as the Alzheimer's Association, and the Diagnostic and Statistical Manual of Mental Disorders IV for the diagnosis of cognitive impairment and dementia.

Study outcomes. The cognitive function assessment outcomes are shown in **Table 2**. In brief, of the 9 studies that measured the association between adherence to the MD and dementia, 6 studies found a protective effect and 3 studies did not find a statistically significant association. Furthermore, of the 10 studies measuring the association between the MD and mild cognitive impairment (MCI), 7 studies found the MD to be protective, whereas 3 studies did not find a significant association. In addition, 24 studies examined the association between the MD and cognitive function, and 5 studies, including 1 RCT (56), found no significant association. These findings are discussed in more detail below.

MD adherence and AD. In 2 of 5 longitudinal studies measuring MD adherence and AD, each additional MeDi score was associated with a 9% (HR: 0.91; 95% CI: 0.83, 0.98) (46) and a 13% (HR: 0.87; 95% CI: 0.78, 0.97) (53) lower risk of AD in individuals who were cognitively healthy at baseline. In a longitudinal analysis of 2 separate cohorts from the Washington Heights-Inwood Columbia Aging Project, the highest tertile of the MeDi combined with physical activity was associated with a 40% (HR: 0.60; 95% CI: 0.42, 0.87) (34) and a 48% (HR: 0.52; 95% CI: 0.30, 0.91) (45) reduced risk of developing AD, respectively, compared with the lowest tertile.

TABLE 1 Description of included studies[1]

Source	Study design	Sample size, *n*	Mean age, y	Female, %	Participant source	Country of origin	Participant cognitive status at baseline
Chan et al., 2013 (29)	Cross-sectional	3670	72	48	Cohort from Hong Kong	China	Mixed cognitive health status
Crichton et al., 2013 (30)	Cross-sectional	1183	40–65*	64	South Australian electoral rolls	Australia	Mixed cognitive health status
Gardener et al., 2012 (31)	Cross-sectional	652	72	58	AIBL Study of Ageing	Australia	Mixed healthy controls and participants with MCI and AD
Katsiardanis et al., 2013 (32)	Cross-sectional	557	65	57	Residents of Valestino	Greece	Mixed cognitive health status
Ye et al., 2013 (33)	Cross-sectional	1269	57	Not reported	Boston Puerto Rican Health Study	United States	Mixed cognitive health status
Scarmeas et al., 2006 (34)	Cross-sectional, case-control	1984	76	68	WHICAP project	United States	Subjects with AD and nondemented subjects
Cherbuin and Anstey, 2012 (35)	Longitudinal	1528	64	51	PATH study	Australia	Cognitively healthy
Corley et al., 2013 (36)	Longitudinal	882	70	50	Lothian Birth Cohort 1936 study	Scotland	Mixed cognitive health status
Feart et al., 2009 (37)	Longitudinal	1410	76	63	Three-City study	France	Elderly without diagnosis of dementia
Kesse-Guyot et al., 2013 (38)	Longitudinal	3083	52	46	SU.VI.MAX	France	Cognitively healthy participants
Koyama et al., 2015 (39)	Longitudinal	2326	75	51	Health ABC study	United States	No cognitive assessment at baseline
Olsson et al., 2015 (40)	Longitudinal	564	70	0	Uppsala longitudinal study	Sweden	Cognitively healthy participants
Psaltopoulou et al., 2008 (41)	Longitudinal	732	60	65	EPIC–Greece study	Greece	No cognitive assessment at baseline
Samieri et al., 2013 (42)	Longitudinal	10,670	59	100	Nurses' Health Study	United States	Cognitively healthy participants
Samieri et al., 2013 (43)	Longitudinal	6174	66	100	Women's Health Study	United States	Cognitively healthy participants
Samieri et al., 2013 (44)	Longitudinal	16,058	74	100	Nurses' Health Study	United States	Cognitively healthy participants
Scarmeas et al., 2009 (45)	Longitudinal	282	77	68	WHICAP project	United States	Subjects with AD and nondemented subjects
Scarmeas et al., 2009 (46)	Longitudinal	1875	77	68	WHICAP project	United States	Participants with MCI and cognitively healthy subjects
Scarmeas et al., 2006 (47)	Longitudinal	2258	77	69	WHICAP project	United States	Cognitively healthy participants
Tangney et al., 2014 (48)	Longitudinal	826	82	74	MAP project	United States	No cognitive assessment at baseline
Titova et al., 2013 (49)	Longitudinal	194	70	48	PIVUS study	Sweden	Mixed cognitive health status
Tsivgoulis, 2013 (50)	Longitudinal	17,478	64	57	REGARDS	United States	Cognitively healthy participants
Vercambre et al., 2012 (51)	Longitudinal	2504	>65*	100	Women's Antioxidant Cardiovascular Study	United States	Cognitively healthy participants
Wengreen et al., 2013 (52)	Longitudinal	3831	65	57	CCMS	United States	Cognitively healthy participants
Gu et al., 2010 (53)	Longitudinal/ cross-sectional	1219	77	67	WHICAP project	United States	Cognitively healthy participants
Roberts et al., 2010 (54)	Longitudinal/ cross-sectional	1233	70–89*	49	Rochester Epidemiology Project	United States	No cognitive assessment at baseline
Tangney et al., 2011 (55)	Longitudinal/ cross-sectional	3790	75	62	CHAP project	United States	No cognitive assessment at baseline
Martínez-Lapiscina et al., 2013 (56)	RCT	522	75	55	PREDIMED RCT	Spain	No cognitive assessment at baseline
Martínez-Lapiscina et al., 2013 (57)	RCT	285	67	55	PREDIMED RCT	Spain	No cognitive assessment at baseline
Martínez-Lapiscina et al., 2014 (58)	RCT	522	67	44	PREDIMED RCT	Spain	No cognitive assessment at baseline

(Continued)

TABLE 1 (*Continued*)

Source	Study design	Sample size, *n*	Mean age, y	Female, %	Participant source	Country of origin	Participant cognitive status at baseline
McMillan et al., 2011 (59)	RCT	25	21	27	Australian residents	Australia	No information on cognitive status at baseline
Wardle et al., 2000 (60)	RCT	176	53	52	London and Southeast England residents	England	No cognitive assessment at baseline

[1] *Mean age not provided. AD, Alzheimer disease; AIBL, Australian Imaging, Biomarkers, and Lifestyle; CCMS, Cache County Memory Study; CHAP, Chicago Health and Aging Project; EPIC, European Prospective Investigation into Cancer and Nutrition; Health ABC, Health, Aging, and Body Composition; MAP, Memory and Aging Project; MCI, mild cognitive impairment; PATH, Personality and Total Health Through Life; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors; PREDIMED, PREvención con Dieta MEDiterránea; RCT, randomized controlled trial; REGARDS, Reasons for Geographic and Racial Differences in Stroke; SU.VI.MAX, Supplementation with Vitamins and Mineral Antioxidants; WHICAP, Washington/Hamilton Heights–Inwood Columbia Aging Project.

It was also shown that each additional unit of the MeDi score was associated with a borderline significant 11% (HR: 0.89; 95% CI: 0.78, 1.02) reduced risk of conversion from MCI to AD (45). Of the included studies, only one used a case-control approach showing that **e**ach additional unit of the MeDi score was associated with a 24% decreased risk of AD (OR: 0.76; 95% CI: 0.66, 0.86). When compared with the reference, the highest tertile of MD adherence had a 69% (OR: 0.31; 95% CI: 0.16, 0.58) reduced risk of AD (47). In 1 of 3 cross-sectional studies measuring cognitive function (31), participants in the highest (compared with the lowest) MeDi score had a 19% (OR: 0.81; 95% CI: 0.71, 0.92) reduced risk of AD in the fully adjusted model.

MD adherence and cognitive impairment. In 1 of 3 longitudinal studies that measured cognitive impairment (45), every unit increase of the MeDi score was related to an 8% (HR: 0.92; 95% CI: 0.85, 0.99) reduction in risk of MCI and a borderline significant 28% lower risk of MCI (HR: 0.72, 95% CI: 0.52, 1.00) in the highest compared with the lowest tertile. Furthermore, another longitudinal study by Tsivgoulis et al. (50) showed that higher adherence to the MD was associated with a borderline significant 13% (OR: 0.87; 95% CI: 0.76, 1.00) reduction in risk of incident cognitive impairment. In 1 of 4 cross-sectional studies that measured cognitive impairment (31), there was a borderline 13% (OR: 0.87; 95% CI: 0.75, 1.00) reduction in risk of MCI in the highest (compared with the lowest) tertile of MD adherence. In another cross-sectional study by Ye et al. (33), the highest quintile of the MeDi score had a 49% (OR: 0.51; 95% CI: 0.33, 0.79) lower risk of cognitive impairment compared with the lowest quintile, and each additional unit of the MeDi score was associated with a 13% (OR: 0.87; 95% CI: 0.80, 0.94) lower risk. Similarly, in a cross-sectional study by Katsiardanis (32), each additional MedDietScore quintile was associated with a 12% reduction in risk of cognitive impairment (OR: 0.88; 95% CI: 0.80, 0.98) in men, but not in women.

Only 1 of 5 RCTs (57) examined the association between the MD and cognitive impairment, and found that 6.5 y of adherence to the MD enriched with extra-virgin olive oil (MedDiet+EVOO) resulted in a 66% (OR: 0.34; 95% CI: 0.12, 0.97) reduced risk of MCI compared with adherence to a low fat diet. Participants assigned to the MD enriched with nuts (MedDiet+Nuts) did not differ from controls (57). Because this publication is based on a subsample of the PREDIMED study, which originally was designed to assess the MD for the primary prevention of cardiovascular events, the study sample might not be sufficient, thus leading to estimates with wide CIs. With regard to the lack of effect of the MedDiet+Nuts, further research is necessary.

MD adherence and cognitive function and decline. All 18 longitudinal studies measured cognitive function and decline, and, overall, showed that higher adherence to the MD was associated with better global cognition and verbal ability. Low adherence was associated with poorer performance on the backward digit span test, phenomic fluency test (38), clock-drawing test (58), Telephone Interview for Cognitive Status test (44), MMSE (33, 37, 55, 56, 58), Symbol Digit Modalities Test, and East Boston Test (55). Low adherence also was associated with worse global cognition, verbal memory (36, 44), and immediate and delayed recall (48); and less limitation on mental health (42). One of the 18 longitudinal studies showed that the MD was marginally protective against cognitive decline and one found a small improvement in the composite cognitive function score (46, 53). The MD also was related to better global cognitive function (55) and a slower rate of global cognitive decline (48). Three cross-sectional studies measured cognitive function and decline, and it was shown that each Mediterranean diet score unit increase corresponded to a higher composite *z* score [$\beta = 0.013$; $P = 0.05$; the composite cognitive *z* score summarizes combined performance in memory, language, processing speed, and visuospatial ability (31, 42, 48)].

Lastly, 4 of 5 RCTs showed that the intervention with the MD was associated with significantly reduced confusion (60), better performance on the MMSE and clock-drawing test (56, 58), and better reaction time on the Corsi Block Test (59).

Sources of bias. The studies eligible for inclusion in this review were very heterogeneous; thus, possible sources of bias are discussed below. The quality and bias risk assessment is shown in **Supplemental Table 4**. All but one study (59) described participant characteristics clearly. The majority of participants were women, and only 3 studies included

TABLE 2 Cognitive function, cognitive impairment, and dementia assessment outcomes[1]

Source	Cognitive function	Cognitive impairment	Dementia	Confounders adjusted for
Chan et al., 2013 (29)	NA	No significant association between MeDi Score dietary pattern and cognitive impairment in men or women (P-trend $>$ 0.05). Highest tertile of the MD adherence: Men, OR: 0.89 (95% CI: 0.57, 1.42); Women, OR: 1.02 (95% CI: 0.76, 1.43) vs. lowest tertile.	NA	Age, BMI, PASE, energy intake, education level, Hong Kong ladder, community ladder, smoking status, alcohol use, number of activities of daily living, GDS, and GDS category.
Crichton et al., 2013 (30)	No significant associations between absolute MeDi Score and any of the self-appraised cognitive function or psychological well-being tests.	NA	NA	Age, sex, education, BMI, exercise, smoking, and total energy intake.
Gardener et al., 2012 (31)	Significant correlation between baseline MeDi score and change in MMSE score in HC (r = 0.098; P = 0.014). No significant correlation between MeDi score and the other neuropsychological tests in HC. Correlations: LM II (P = 0.779); D-KEFS (P = 0.294); CVLT II Long Delay (P = 0.472).	Significant association between high adherence to MD and reduced risk of MCI (OR: 0.866; 95% CI: 0.75, 1.00; $P < 0.05$). Significant 13–19% reduction in odds of being in the MCI category for each additional unit on the MeDi score.	Significant association between high adherence* to MD and reduced risk of AD (OR: 0.806; 95% CI: 0.71, 0.92; $P < 0.01$). Significant 19–26% reduction in risk of being in the AD category with each additional unit of the MeDi score vs. the reference HC category.	Age at assessment; sex; country of birth; education; apoE4 allele status; current smoking status; caloric intake; BMI; and history of stroke, diabetes, hypertension, angina and heart attack.
Katsiardanis et al., 2013 (32)	NA	Significant association between MD adherence and risk of MCI in men (OR: 0.88; 95% CI: 0.80, 0.98; P = 0.02) and women (OR: 1.11; 95% CI: 1.00, 1.22; P = 0.04).	NA	Age, education, social activity, smoking, depression symptomatology (with the use of the GDS), MedDietScore (range: 0–55), and metabolic syndrome.
Ye et al., 2013 (33)	Each MeDi score point was associated with a 0.14 point higher MMSE (P = 0.012). After adjustment for all confounders MD adherence was not significantly associated with executive function, memory, or attention.	Significantly reduced risk of cognitive impairment in those in the highest vs. lowest quintile of MeDi score (OR: 0.51; 95% CI: 0.33, 0.79). Significant negative association between each point of MeDi score and risk of cognitive impairment (OR: 0.87; 95% CI: 0.80, 0.94; P-trend < 0.001).	NA	Age, sex, educational attainment, household income below threshold, acculturation score, smoking status, physical activity score, supplement use, taking $>$5 types of medications within the previous 12 mo, BMI, hypertension, diabetes, total cholesterol, HDL cholesterol, and TGs.
Scarmeas et al., 2006 (34)	NA	NA	Significant reduction in prevalence of AD per unit increase in the MeDi score (OR: 0.76; 95% CI: 0.66, 0.86; $P < 0.001$) and for highest vs. lowest tertile of the MeDi score (OR: 0.31: 95% CI: 0.16, 0.58; $P < 0.001$).	Age, sex, education, ethnicity, cohort, caloric intake, apoE4, BMI, smoking, and comorbidity.
Cherbuin and Anstey, 2012 (35)	NA	No significant association between each unit increase in the MeDi score and CDR (OR: 1.18; 95% CI: 0.88, 1.57) or MCI (OR: 1.41; 95% CI: 0.95, 2.10) or any MCD (OR: 1.20; (95% CI: 0.98, 1.47).	NA	Age, sex, education, apoE4 genotype, BMI, physical activity, stroke, diabetes, hypertension, and total caloric intake.

(Continued)

TABLE 2 (*Continued*)

Source	Cognitive function	Cognitive impairment	Dementia	Confounders adjusted for
Corley et al., 2013 (36)	No significant association between the MD and IQ, processing speed, or memory in multivariate model. Significant positive correlation between "Mediterranean-style" pattern and verbal ability (NART, mean ± SD: 37.1 ± 7.5 vs. 33.0 ± 7.3, $P = 0.024$; WTAR, 43.4 ± 6.1 vs. 39.9 ± 6.5, $P = 0.001$), upper vs. lower tertile.	NA	NA	Sex, age at testing in later life, occupational social class, and IQ at age 11 y from the MHT.
Féart el al., 2009 (37)	Each unit increase in the MeDi score corresponds to 0.006 (95% CI: 0.0003, 0.01; $P = 0.04$) less cognitive decline per year on the MMSE.	NA	No significant association between MeDi score and dementia (HR: 1.12; 95% CI: 0.60, 2.10; $P = 0.72$ for highest vs. lowest on MeDi score tertile).	Age, sex, education, marital status, caloric intake, apoE4, physical exercise, 5 medications/d, depression score, BMI, diabetes, hypertension, tobacco use, hypercholesterolemia, and stroke.
Kesse-Guyot et al., 2013 (38)	No significance for most associations in the fully adjusted model, except for association between low MSDPS and poor phonemic fluency performance [−1.00 (95% CI: −1.85, −0.15); *P*-trend = 0.048], lowest vs. highest tertile.	NA	NA	Age, sex, education, follow-up time between baseline and cognitive evaluation, supplementation group during the trial phase, number of 24-h dietary records, energy intake, BMI, occupational status, tobacco use status, physical activity, memory difficulties at baseline, depressive symptoms concomitant with the cognitive function assessment, history of diabetes, hypertension, and cardiovascular disease.
Koyama et al., 2015 (39)	In the fully adjusted model, lower MedDietScores were associated with a significantly slower rate of cognitive decline on the 3MS score (mean: 0.22 points/y; 95% CI: 0.05, 0.39 points/y; $P = 0.01$) vs. those with high MedDietScores (only in black participants).	NA	NA	Age, sex, education, BMI, current smoking, physical activity, depression, diabetes, total energy intake, and socioeconomic status.
Olsson et al., 2015 (40)	NA	NA	No significant association between the mMDS and all-type cognitive impairment (OR: 0.82; 95% CI: 0.65, 1.05; *P*-trend = 0.41). No significant association between the mMDS and risk of AD (HR: 0.99; 95% CI: 0.44, 2.26) or all-type dementia (HR: 0.85; 95% CI: 0.44, 1.62) in highest vs. lowest tertile.	Energy intake as a continuous variable, educational level, physical activity, smoking, single household, and apoE genotype (absence of any E4 allele vs. presence of ≥1 E4 allele).
Psaltopoulou et al., 2008 (41)	Significant association for each unit increase in the MeDi score and 0.05 (95% CI: 0.09, 0.19; $P = 0.49$) higher cognitive function on the MMSE at follow-up.	NA	NA	Age, sex, education, marital status, caloric intake, height, physical activity, alcohol intake, smoking, depression, BMI, diabetes, and hypertension.

(Continued)

TABLE 2 (*Continued*)

Source	Cognitive function	Cognitive impairment	Dementia	Confounders adjusted for
Samieri et al., 2013 (42)	Significant association between 5th quintile of MeDi score and "no limitation of mental health"; prevalence ratio: 1.12 (95% CI: 1.04, 1.20); $P < 0.001$.	NA	NA	Age; education; marriage status; median income; median house value; family history of diabetes, cancer, and MI; physical activity; energy intake; smoking; multivitamin use; aspirin use; BMI; history of high blood pressure; and history of hypercholesterolemia.
Samieri et al., 2013 (43)	No significant association for alternate MeDi score and trajectories of repeated cognitive scores in the multivariate model (*P*-trend across quintiles = 0.26 and 0.40 for global cognition and verbal memory, respectively), nor with overall global cognition and verbal memory at older ages, assessed by averaging the 3 cognitive measures (*P*-trend = 0.63 and 0.44, respectively).	NA	NA	Age at the start of cognitive testing, race, higher education, annual household income, energy intake, Women's Health Study treatment assignment (aspirin and/or vitamin E), regular vigorous exercise, BMI, current smoking, history of T2DM, self-reported history of hypertension, use of antihypertensive medications or elevated systolic blood pressure, self-reported history of elevated cholesterol, use of lipid-lowering medications or elevated blood cholesterol, postmenopausal hormone use, or self-reported history of depression.
Samieri et al., 2013 (44)	Long-term MD exposure was estimated by averaging all repeated measures of diet (>13 y, on average). During examination of cognitive status in older age, each higher quintile of long-term MeDi score was linearly associated with better mean *z* scores [differences in mean *z* scores between highest and lowest quintiles of MD: 0.06 (95% CI: 0.01, 0.11); 0.05 (95% CI: 0.01, 0.08); and 0.06 (95% CI: 0.03, 0.10) standard units; *P*-trend = 0.004, 0.002, and <0.001 for TICS, global cognition, and verbal memory, respectively].	NA	NA	Age, education, long-term physical activity and energy intake, BMI, smoking, multivitamin use, and history of depression, diabetes, hypertension, hypercholesterolemia, or MI.
Scarmeas et al., 2009 (45)	NA	NA	Significant association between MeDi score and risk of AD (HR: 0.60, 95% CI: 0.42, 0.87; $P = 0.007$) for highest vs. lowest tertile on MeDi score.	Age, sex, education, ethnicity, cohort, caloric intake, apoE4, BMI, smoking, comorbidity, depression, leisure activities, and CDR score.
Scarmeas et al., 2009 (46)	NA	Significant decrease in MCI risk with each MeDi score increase (HR: 0.92; 95% CI: 0.85, 0.99; $P = 0.04$). Significant decrease in MCI risk for highest vs. lowest tertile of MeDi score (HR: 0.72; 95% CI: 0.52, 1.00; $P = 0.05$).	No significant association between MCI conversion to AD per unit increase in 0- to 9-point MeDi score (HR: 0.89, 95% CI: 0.78, 1.02; $P = 0.09$). Significant association between MCI to AD conversion (HR: 0.52; 95% CI: 0.30, 0.91; $P = 0.02$) for highest vs. lowest tertile on MeDi score.	Age, sex, education, ethnicity, cohort, caloric intake, apoE4, BMI, and time between first dietary assessment and baseline diagnosis.

(Continued)

TABLE 2 (*Continued*)

Source	Cognitive function	Cognitive impairment	Dementia	Confounders adjusted for
Scarmeas et al., 2006 (47)	Significant association between each unit increase in the MeDi score and 0.003 (95% CI: 0, 0.006; $P = 0.05$) less cognitive decline per year on the composite cognitive *z* score.	NA	Significant association between MeDi score and reduced risk of AD (HR: 0.91; 95% CI: 0.83, 0.98; $P = 0.015$ per unit increase in MeDi score); (HR: 0.60; 95% CI: 0.42, 0.87; *P*-trend = 0.007 for highest vs. lowest tertile).	Age, sex, education, ethnicity, cohort, caloric intake, apoE4, BMI, smoking, and comorbidity.
Tangney et al., 2014 (48)	Significant association for each unit increase in MedDietScore and a slower rate of global cognitive decline by 0.002 standardized units ($P = 0.01$) in mixed models adjusted for covariates. Only the upper tertile of MedDietScore was associated with rates of global cognitive change.	NA	NA	Energy, age, sex, education, and cognitive activities.
Titova et al., 2013 (49)	No significant association between MeDi score and the 7MS score; β value = 0.11; $P = 0.13$.	NA	NA	Sex, energy intake, education, self-reported physical activity, serum concentration of LDL cholesterol, BMI, systolic blood pressure, and HOMA-IR.
Tsivgoulis et al., 2013 (50)	NA	Significant reduction in likelihood of ICI with increased MeDi score (OR 0.87; 95% CI: 0.76, 1.00) with the use of a median split for MeDi score (0–4 vs. 5–9).	NA	Demographics, environment, vascular risk factors, antihypertensive medications, depressive symptoms, self-reported health status, incident stroke, and diabetes.
Vercambre et al., 2012 (51)	No significant associations across any MDS categories and any cognitive function tests. All *P* values > 0.05	NA	NA	Age, education, energy from diet, marital status, and physical activity.
Wengreen et al., 2013 (52)	Significant association between highest quintile of MD adherence and 0.94 higher score on the 3MS vs. those in the lowest quintile ($P = 0.001$). Differences consistent over 11 y.	NA	NA	Age; sex; education; BMI; frequency of moderate physical activity; multivitamin and mineral supplement use; history of drinking and smoking; and history of diabetes, heart attack, and stroke.
Gu et al., 2010 (53)	Better adherence to the MeDi score was marginally associated with significantly better cognitive performance at baseline: after adjusting for age, gender, race, and education, β = 0.013 ($p = 0.05$) for each unit increase of MeDi score.	NA	Longitudinal analysis: significant association between MeDi score and reduction in risk of AD (HR: 0.87; 95% CI: 0.78, 0.97; $P = 0.01$ per unit increase of MeDi score; HR: 0.68; 95% CI: 0.42, 1.08; *P*-trend = 0.1 for highest vs. lowest tertile of the MeDi score).	Age, sex, education, race, caloric intake, apoE4, BMI, smoking, comorbidity, insulin, and adiponectin.
Roberts et al., 2010 (54)	NA	Longitudinal analysis: no significant reduction in MCI risk with increased MeDi score (HR: 0.75, 95% CI: 0.46, 1.21; $P = 0.24$ for highest vs. lowest MeDi score tertile). Cross-sectional analysis: no significant reduction in prevalence of MCI (OR: 0.80; 95% CI: 0.52, 1.25; $P = 0.33$) in highest vs. lowest MeDi score tertile).	No significant association between MeDi score and risk of dementia, HR: 0.75 (95% CI: 0.46, 1.21; $P = 0.24$) for highest vs. lowest tertile on MeDi score.	Age, sex, education, caloric intake, apoE4, stroke, CHD, and depressive symptoms.

(Continued)

TABLE 2 (*Continued*)

Source	Cognitive function	Cognitive impairment	Dementia	Confounders adjusted for
Tangney et al., 2011 (55)	Significant association between each unit increase in the MedDietScore and 0.007 (95% CI: 0.003, 0.011; $P < 0.001$) increase on the global cognitive *z* score.	NA	NA	Age, sex, education, race, total energy intake, participation in cognitive activities, and interaction between time and dietary quality score.
Martínez-Lapiscina et al., 2013 (56)	Significant association between MedDiet+EVOO and higher mean MMSE (by 0.62; 95% CI: 0.18, 1.05; $P = 0.005$) and CDT (by 0.51; 95% CI: 0.20, 0.82; $P = 0.001$) vs. controls. Significant association between and MedDiet+Nuts and higher MMSE scores (by 0.57; 95% CI: 0.11, 1.03; $P = 0.015$) and CDT scores (by 0.33; 95% CI: 0.003, 0.67; $P = 0.048$) vs. controls.	NA	NA	Sex, age, education, family history of cognitive impairment or dementia, apoE4 genotype, hypertension, dyslipidemia, diabetes, smoking status, alcohol intake, BMI, physical activity, and total energy intake.
Martínez-Lapiscina et al., 2013 (57)	Significant association between MedDiet+EVOO group and better post-trial cognitive performance in all cognitive tests vs. the control group. These crude differences were not statistically significant after correcting for multiple comparisons (all *P* values > 0.05).	Significantly reduced MCI risk in participants allocated to the MedDiet+EVOO vs. the control group (OR: 0.34; 95% CI: 0.12, 0.97).	NA	Sex, age, education, apoE genotype, family history of cognitive impairment or dementia, smoking, physical activity, BMI, hypertension, dyslipidemia, diabetes, alcohol, and total energy intake.
Martínez-Lapiscina et al., 2014 (58)	Significant association between MD interventions and MMSE scores in non-apoE4 carriers (0.56; 95% CI: 0.15, 0.97; $P = 0.007$) and apoE4 carriers (1.61; 95% CI: 0.10, 3.13; $P = 0.037$). Significant association between MD interventions and CDT scores in non-apoE4 carriers (0.55; 95% CI: 0.25, 0.85; $P < 0.001$) and apoE4 carriers (0.33; 95% CI: −0.6, 1.27; $P = 0.477$).	NA	NA	Sex, age, education, family history of cognitive impairment or dementia, hypertension, dyslipidemia, diabetes, smoking status, alcohol intake, BMI, physical activity, and total energy intake.
McMillan et al., 2011 (59)	Significant improvement in cognitive function speed in the "Diet Change" group vs. the "No Change" group ($P = 0.002$) in a post hoc comparison.	NA	NA	Not reported.
Wardle et al., 2000 (60)	Those consuming the MD had a 1.5 (95% CI: 0.7, 2.3) reduction in confusion vs. a 0.5 (95% CI: −0.4, 1.3) reduction in the control group at 12 wk after baseline.	NA	NA	Weight loss only.

[1] *Definition of high adherence is not clear. AD, Alzheimer disease; CDR, clinical dementia rating; CDT, clock-drawing test; CHD, coronary heart disease; CVLT, California Verbal Learning Test; D-KEFS, Delis–Kaplan Executive Function System; GDS, Geriatric Depression Scale; HC, healthy controls; ICI, incident cognitive impairment; IQ, intelligence quotient; LM II, Logical Memory II; MCD, mild cognitive disorder; MCI, mild cognitive impairment; MD, Mediterranean diet; MDS, Mediterranean diet score; MedDietScore, Mediterranean diet score developed by Panagiotakos et al. (61); MedDiet+EVOO, Mediterranean Diet enriched with extra-virgin olive oil; MedDiet+Nuts, Mediterranean Diet enriched with nuts; MeDi score, Mediterranean diet score developed by Trichopolou et al. (13); MHT, Moray House Test; MI, myocardial infarction; mMDS, modified Mediterranean Diet Score; MMSE, Mini-Mental State Examination; MSDPS, Mediterranean-style dietary pattern score; NA, not applicable; NART, National Adult Reading Test; PASE, Physical Activity Scale for the Elderly, TICS, Telephone Interview for Cognitive Status; T2DM, type 2 diabetes mellitus; WTAR, Wechsler Test of Adult Reading; 3MS, Modified Mini-Mental State Examination; 7MS, 7-min screen.

mixed-sex samples (29, 32, 60). In addition, some studies used related cohorts: 5 recruited participants from the Washington/Hamilton Heights–Inwood Columbia Aging Project (WHICAP) 1992 and WHICAP 1999 studies (34, 45–47, 53) and 2 recruited participants from the Nurses' Health Study (42, 44). Moreover, 3 RCTs examined participants of the PREDIMED trial (56–58).

With regard to dietary assessment, the majority of studies used FFQs, with only 8 studies making use of professional interviewers or trained dietitians; thus, the majority of data obtained relied on self-reporting. Furthermore, 7 studies modified the MeDi score to better suit the populations they were studying. For example, in studies by Olsson et al. (40) and Titova et al. (49), nuts and seeds were not accounted for because of their very low consumption in Sweden, and legumes were put in the same category as fruit and vegetables. Because of variation in alcohol consumption, the term "moderate alcohol consumption" was defined differently across studies. Moreover, 2 studies did not include alcohol in the MD scores (36, 52) and, in one study, alcohol was scored in the same category as sweets (30). Among the 5 RCTs, the study by Wardle et al. (60) did not give any recommendations on legumes, nuts, seeds, or dairy products, whereas 2 studies did not include alcohol in the recommendation (59, 60).

Furthermore, in relation to the RCTs, there was variation in the control groups. These groups either continued their usual diet or were allocated to a low-fat or cholesterol-lowering diet. Potential sources of bias might also be present with regard to assessment of adherence to the MD, with 10 studies not assessing this throughout follow-up and 2 being unclear on how adherence was assessed (Supplemental Table 4). Blinding to dietary intervention also varied. In the included RCTs, 4 used a single-blind design, with the researchers assessing the outcomes being blinded to group assignment (56–59), and 1 was unclear about the blinding method (30). Assessment of cognition was carried out with the use of previously validated cognitive function tests in all studies, but there was variation. A cognitive examination was not performed at baseline in 5 studies, and 9 studies assessed cognitive status on the basis of only one test (Supplemental Table 3). Another potential source of bias was the fact that the fully adjusted models differed across studies. One study adjusted only for weight loss (60), and one did not report adjusting for any factors (59), whereas 3 studies with mixed-sex samples did not adjust for sex (29, 32, 60).

Loss to follow-up was another potential source of bias, with 6 of the included studies losing >30% of the original participants and none of them reporting performing a power analysis to account for this loss. Two studies were unclear about numbers of participants lost, and only 11 studies reported performing a power analysis to account for loss of participants (Supplemental Table 4).

With regard to outcomes, all studies clearly presented outcomes relevant to this review except for one, in which the effect of the MD on odds of AD, cognitive impairment, or cognitive function was not clear (31).

Discussion

Overall, 32 papers examined the effect of the MD on cognitive function, cognitive impairment, and dementia. Despite inconsistencies between findings, the majority of studies showed that the MD may contribute to better cognitive performance and may be protective against cognitive impairment and dementia, although further large RCTs are needed either to confirm or to dispute these findings.

Individual MD components. It is unclear whether the MD exerts its effects as a whole or through the action of its individual components, but findings suggest that some factors may be more important than others. For example, in the PREDIMED-NAVARRA study, the MedDiet+EVOO had a stronger positive effect on cognitive function and was the only dietary pattern that slowed the onset of MCI compared with the MedDiet+Nuts or a low-fat control diet. Moreover, the MedDiet+EVOO group performed better in visual and verbal memory domains (56, 57). In addition, since this systematic review was conducted, the PREDIMED-Barcelona study has been published, and again it was shown that a MedDiet+EVOO group scored better on some cognitive function tests (Rey Auditory Verbal Learning Test and Color Trail Test) than did controls, although no differences were observed for other cognitive tests, such as the MMSE, Animals Semantic Fluency Digit Span subtest from the Wechsler Adult Intelligence Scale, or the Verbal Paired Associates from the Wechsler Memory Scale (62). In 2 other studies included in this systematic review, a higher MUFA-to–saturated fat ratio was associated with better global cognition and verbal memory (43), and was protective against cognitive impairment (35). The impact of alcohol consumption was also inconsistent, with the WHICAP study finding that alcohol was independently associated with a lower risk of AD (46), and the Personality and Total Health Through Life study finding that increased alcohol consumption was related to an increased risk of MCI (35). On the other hand, whole grains (43, 52), nuts, and legumes (52) were associated independently with better cognitive performance, and legumes, nuts, and seeds were protective against cognitive impairment (32).

In contrast, some foods have been associated with a higher risk of cognitive decline. There was suggestive evidence that a higher consumption of milk and dairy was associated with a lower MMSE score, but this was found only in men and not in women (32). Furthermore, Titova et al. (49) showed that meat consumption was associated with a worse cognitive performance. In the study by Cherbuin and Anstey (35), consumption of fish and vegetables was associated with a greater risk of cognitive impairment. Nevertheless, because there were small dietary intake differences between low- and high-MD–adherence groups and neither followed a consistent pattern, these findings should be interpreted with caution.

Possible mechanisms. A typical aging brain displays signs of cell atrophy, which most likely are related to 3 main mechanisms, as explained in the Introduction, i.e., decline in

blood flow and supply, mitochondrial dysfunction (caused by oxidative stress), and increased inflammation. The brain of a patient with AD ages similarly, but there are small differences, such as the presence of NFTs and β-amyloid plaques (7). There are several possible mechanisms that might act on these factors and explain the positive effects of the MD on cognitive function.

The first is by decreasing vascular risk factors and thus improving blood flow to the brain. There is strong evidence to show that adherence to the MD reduces vascular risk factors such as LDL cholesterol and increases favorable HDL cholesterol (12). The largest to date RCT on the MD, the PREDIMED study showed that greater adherence to the MD caused a 30% reduction in RR of a major cardiovascular event (63). Cardiovascular disease (CVD) also is strongly correlated with cognitive dysfunction (64). However, Scarmeas et al. (65) showed that adjusting for vascular disease risk factors virtually kept the protective effect of the MD on AD unchanged, suggesting that these factors only play a small role in this association.

Second, the MD may exert protective effects on cognition through its effect on oxidative stress. The MD is known for being a rich source of antioxidants such as vitamin E, vitamin C, folate, and polyphenols (61). Mouse studies have shown that antioxidant supplementation, such as with vitamin E, lowers lipid oxidation products, increases intrinsic antioxidant activity, and improves mitochondrial function and cognitive performance (66). Epidemiologic studies suggest that vitamin E is protective against cognitive disorders (67), but a large human trial that assessed the effect of vitamin E on progression from MCI to AD found no difference compared with placebo (68). The findings of RCTs that used supplementation with vitamin C, vitamin B-12, and folate also were inconsistent (69, 70), suggesting that some of the benefits of nutrients might be due to synergistic effects or mediated by nutrient–nutrient interactions (70). In addition, it is possible that any potential benefits of supplementation are evident only in those who are deficient or have a low intake of a nutrient, such as in the case of folate (71).

Third, the effect of the MD on cognitive function may be mediated through lowering inflammation in the brain. The MD was shown to lower inflammatory biomarkers such as C-reactive protein (CRP) in neuritic plaques and NFTs in the brains and serum of AD patients (47). As found by Gu et al. (53), participants with the highest MD adherence had significantly lower high-sensitivity CRP concentration. However, the lower risk of AD in the same group was not mediated by high-sensitivity CRP concentration, still leaving questions for further research.

The MD also has been associated with lower risk of so-called cardiodiabesity or cardiometabolic syndrome (72). All these conditions have been associated independently with increased risk of dementia (73–76). Therefore, it is possible also that the MD indirectly improves cognitive function by lowering the risk of well-established risk factors. Moreover, certain components of the MD, such as legumes and whole-grain foods, may have indirect effects on cognition through their lower glycemic indexes, leading to reductions in blood glucose oscillations compared with those of a typical Western diet (77). As discussed in a previous systematic review, the effect of a long-term low–glycemic index diet on cognitive function in adults needs to be explored further (78).

In addition, given the evidence, it is clear that there may be some factors that play a modulatory role in the association of the MD and cognitive function. It was shown that the absolute risk of AD decreased even further when high adherence to the MD was combined with high physical activity (34). Potential gene–nutrient interactions also have been observed, such as in Martínez-Lapiscina et al. (58), in which a significant positive association between MD adherence and the MMSE score was found in carriers of the T minor allele on the clusterin (*CLU*) gene rs11136000 and phosphatidylinositol-binding clathrin (*PICALM*) assembly protein gene rs3851179 polymorphisms (genotypes associated with a higher risk of AD), and not in those without. Furthermore, in the same analysis, cognitive performance was better for non-apoE4 and for apoE4 carriers randomly assigned to the MedDiet than for those consuming the control diet, whereas clock-drawing test performance was not affected by apoE4–diet interactions. As is known, the E4 allele of apoE increases the risk of development of AD 10–12 times when in the homozygous state (79). These findings give grounds for further research on this issue. Moreover, in a study in a biracial population, adherence to the MD was associated with better cognitive function in black participants, but not in white participants (39), which may suggest a possible modulatory role of ethnicity. This effect could be mediated through a higher predisposition of black individuals to CVD. Differences in socioeconomic and educational status, which also have been linked with diet and cognition, respectively, might also be involved (39).

Strengths and limitations. The studies included in this review were very heterogeneous, and the overall quality of the studies was average. In addition to the sources of bias considered above, the weaknesses of included studies are discussed here.

Nine studies included participants <65 y of age. This could be important, considering that the prevalence of dementia increases exponentially with age from ~1% in those aged 65–69 y to 30% in individuals ≥90 y of age (23). Therefore, including younger participants could make cognitive decline harder to detect and require more years of follow-up. There was also a big overlap between samples of different studies, which may introduce a source of selection bias.

Moreover, FFQs may be associated with misreporting by the participants or problems with the level of detail captured by the questionnaire. Even participants without dementia but who are of an older age might find it difficult to complete a dietary assessment because of memory issues, difficulty in comprehending portion sizes and estimating frequencies, or a lower educational level. Furthermore, FFQs may poorly distinguish some key macronutrients such as fat types, which

could be critical, because MUFAs and PUFAs are major components of the MD. In addition, participants with AD or other dementia would not be able to complete a dietary assessment method themselves and thus are reliant on their caregivers to do so. This could lead to the introduction of another source of error, which again might vary between studies and dietary assessment methods.

Another potential limitation is related to the MD score used. In most studies, the MedDietScore and MeDi score were used to estimate MD adherence. A limitation of the MeDi score is that it uses thresholds based on cohort- and sex-specific medians for the intake of each MD component, possibly leading to bias and making the scores incomparable to samples from other populations. In contrast, the MedDietScore addresses this issue by calculating the frequency of consumption of certain foods. However, a limitation of all MD scores is that the same value could mean high and low consumption of different foods, giving little insight into which ones play a role in cognitive improvement and which ones do not (23). Moreover, 7 studies modified the MeDi score, which consequently diverts from what constitutes a traditional MD (10). Nevertheless, the modification of the MD allows studies to be performed on populations other than just those from the Mediterranean region. In addition, although in the traditional MD a modest amount of alcohol is consumed with meals, some RCTs did not include alcohol in their recommendation, probably because of ethical concerns. Another potential source of bias is the fact that dietary adherence was not assessed in many studies over the follow-up period (Supplemental Table 4). Thus, it is possible that participants changed their usual dietary patterns to healthier ones for the duration of the follow-up, thereby leading to expectancy bias. Furthermore, the use of a retrospective design might introduce another source of bias. Given that many participants showed signs of memory impairment, retrospective studies could give a distorted account of foods eaten by these individuals. It also should be noted that the nature of the interventions in nutrition studies (i.e., food), precludes the use of a double-blind design, potentially introducing further bias.

Moreover, the use of different cognitive function tests makes the findings difficult to compare. The majority of studies used the MMSE, which is a good method of monitoring the progression of dementia and is relatively better than other tests, such as the Six-Item Screener or the Modified Mini-Mental State Examination. Nevertheless, there are issues with the use of the MMSE, because it is not sensitive to cognitive changes in a healthy population (80) and its outcome previously has been shown to be dependent on educational status (81).

In addition, adjustment for confounders also varied, because the fully adjusted models differed significantly across studies. Many did not adjust for important confounders, such as diabetes, hypertension, or serum cholesterol concentrations. Moreover, all but 6 observational studies used an a priori approach, which assumes what comprises a healthy diet on the basis of current knowledge (82). In contrast, the most usual approach is a posteriori, which deducts conclusions from empirical evidence obtained in the study, without prior assumptions. Because of the above possible sources of bias, this approach might result in misreporting of the diet–disease relations.

This review poses some methodologic weaknesses. First, other than the excluded publication types mentioned in the protocol, there was no predefined study type or setting included or excluded from this review, giving rise to methodologic heterogeneity across studies and making their results difficult to compare. Along with this, there was no specification with regard to study settings, leading to study variation with respect to duration, samples sizes, and participant characteristics. This review only included studies in the English language, but given the nature of the topic, this could have excluded important findings published in the languages of the Mediterranean basin, e.g., those in Greek, Spanish, and Italian. This review also did not prespecify the types of MDs to be included, and this might have diverted from the impact of a traditional MD on cognitive function.

Some limitations with the way of assessing study quality also should be noted. Assessment was based on a previously published chart (25) adapted with the addition of items for the evaluation of the risk of bias and precision (28) and of selection bias (83). However, because of the different study designs included in this review, the quality assessment items were not applicable to the same extent to each study (83). It might have been preferable to use one single validated quality assessment scale, instead of adapting a previous one, although this might have been problematic because of the variation in study design. Alternatively, a different quality assessment scale could have been used to assess each type of study design. Finally, the review is limited because of the abovementioned large heterogeneity between the studies, which precluded conducting a meta-analysis.

This review poses several strengths in its methodology, which helps compensate for the limitations listed above. The principal strength is that it is the first systematic review to include such a large number of studies on the effects of the MD on cognitive function. This minimizes the impact of individual weaknesses on the final conclusion. In addition, this systematic review examined the effects of the MD as a whole, instead of its individual components, making the findings more applicable in practice. The protocol and the inclusion and exclusion criteria were prespecified before the database searches, limiting the possibility of a selection bias (Supplemental Methods).

Conclusion

Taking into account the study findings, but also the limitations and heterogeneity in study design, we conclude that adherence to the MD may contribute to better cognitive performance. Nevertheless, because the majority of studies are observational, a causational link cannot be assumed.

Based on the overall evidence, it is recommended that more RCTs and large epidemiologic studies with a posteriori approaches be conducted in order to provide empirical evidence for the role of the MD in cognitive function and

understand the significance of individual components, as well as their synergistic effects when put together. Samples should be large and include various ethnicities. Studying participants >65 y of age could make changes in cognitive performance easier to detect, giving stronger outcomes. Moreover, factors such as sex, presence or history of relevant comorbidities such as diabetes and CVD, and use of dietary supplementation should be considered and adjusted for. The effects of the MD on brain volume and function also should be examined with the use of physiologic tests and neuroimaging, such as with those used by Scarmeas et al. (84). This could give better insight into which neurologic systems are affected by diet. Mental screening tests are good at detecting the presence of dementia but not its origin. Cognitive assessment scales vary largely with regard to sensitivity, specificity, and cutoffs, and currently there is no gold standard for detecting cognitive function and impairment (85). Standardization of cognitive assessment methods could improve comparison of results from different studies and allow for meta-analyses to be performed.

Finally, we agree with the conclusion of Psaltopoulou et al. (41) that, based on current evidence, adoption of the MD as part of preventive measures to reduce the risk of cognitive decline and dementia is recommended in both clinical practice and public health settings.

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