

# Mediterranean Diet, Cognitive Function, and Dementia

## A Systematic Review

Ilianna Lourida,<sup>a</sup> Maya Soni,<sup>b</sup> Joanna Thompson-Coon,<sup>a</sup> Nitin Purandare,<sup>a†</sup> Iain A. Lang,<sup>a,c</sup>  
Obioha C. Ukoumunne,<sup>a</sup> and David J. Llewellyn<sup>b</sup>

**Background:** Adherence to a Mediterranean diet has been associated with lower risk of various age-related diseases including dementia. Although narrative reviews have been published, no systematic review has synthesized studies on the association between Mediterranean diet adherence and cognitive function or dementia.

**Methods:** We conducted a systematic review of 11 electronic databases (including Medline) of published articles up to January 2012. Reference lists, selected journal contents, and relevant websites were also searched. Study selection, data extraction, and quality assessment were performed independently by two reviewers using predefined criteria. Studies were included if they examined the association between a Mediterranean diet adherence score and cognitive function or dementia.

**Results:** Twelve eligible papers (11 observational studies and one randomized controlled trial) were identified, describing seven unique cohorts. Despite methodological heterogeneity and limited statistical power in some studies, there was a reasonably consistent pattern of associations. Higher adherence to Mediterranean diet was associated with better cognitive function, lower rates of cognitive decline, and reduced risk of Alzheimer disease in nine out of 12 studies, whereas results for mild cognitive impairment were inconsistent.

**Conclusions:** Published studies suggest that greater adherence to Mediterranean diet is associated with slower cognitive decline and lower risk of developing Alzheimer disease. Further studies would be useful to clarify the association with mild cognitive impairment and vascular dementia. Long-term randomized controlled trials

promoting a Mediterranean diet may help establish whether improved adherence helps to prevent or delay the onset of Alzheimer disease and dementia. (*Epidemiology* 2013;24: 479–489)

Due to rapid population aging worldwide, health problems related to aging (including Alzheimer disease and dementia) are projected to add to the high clinical, social, and economic burden of caring for persons with dementia.<sup>1</sup> There is currently no cure for dementia, and available treatment strategies offer mainly symptomatic benefits. Thus, strategies to prevent or delay onset of dementia by changes in lifestyle factors, such as diet, are important.

The Mediterranean diet has been associated with reduced risk for a wide range of age-related conditions such as stroke, type 2 diabetes, cardiovascular disease, and all-cause mortality.<sup>2–5</sup> The traditional Mediterranean diet refers to a multinutrient dietary profile characterized by high intake of fruits, vegetables, cereals, and legumes; low consumption of saturated fats with olive oil as the main source of fat; moderate consumption of fish; low to moderate intake of dairy products (in the form of yogurt and cheese); low consumption of red meat and meat products; and moderate amount of alcohol (especially wine) usually consumed during meals.<sup>6</sup> Recently, a number of narrative reviews have presented evidence for an association between a Mediterranean-type diet and decreased risk of dementia. Findings from prospective studies suggest that greater adherence to Mediterranean diet may be associated with slower cognitive decline and reduced risk of Alzheimer disease.<sup>7–9</sup> In the light of these findings, it has been suggested that improving adherence to the Mediterranean diet may delay or prevent the onset of dementia.

To date, however, no systematic review has synthesized these findings. Our objective was to systematically review the literature to synthesize and evaluate available evidence on the association between adherence to Mediterranean diet and cognitive function or dementia.

## METHODS

### Identification of Studies

A systematic review was conducted following the general principles published by the UK National Health Service

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†Deceased. From the <sup>a</sup>Peninsula Collaboration for Leadership in Applied Health Research and Care, University of Exeter Medical School, Exeter, United Kingdom; <sup>b</sup>University of Exeter Medical School, Exeter, United Kingdom; and <sup>c</sup>Public Health Directorate, NHS Devon, Exeter, United Kingdom.

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**Editors' note:** Related articles appear on pages 490, 500, and 503.

Correspondence: David J. Llewellyn, University of Exeter Medical School, Salmon Pool Lane, Exeter, Devon, EX2 4SG, United Kingdom. E-mail: [David.Llewellyn@exeter.ac.uk](mailto:David.Llewellyn@exeter.ac.uk).

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Centre for Reviews and Dissemination.<sup>10</sup> We developed a pre-defined protocol following consultation with experts in the field (eAppendix, <http://links.lww.com/EDE/A676>).

We searched the following electronic databases for relevant studies from inception to January 2012: Medline, EMBASE, and PsycINFO (via Ovid); Science Citation Index Expanded, Social Sciences Citation Index, Arts and Humanities Citation Index, Conference Proceedings Citation Index (via the Web of Science interface); the Health Management Information Consortium, the Cumulative Index to Nursing and Allied Health Literature, and the Allied and Complementary Medicine Database (via the National Health Service evidence database); and the Cochrane Library of Systematic Reviews. The search strategies used text words and relevant indexing (MeSH terms) to capture studies investigating the association between adherence to a Mediterranean diet and cognitive function and dementia. Search terms “Mediterranean diet,” “cognition,” “dementia,” “Alzheimer,” “memory,” “mild cognitive impairment,” and “neuropsychological tests” were keywords. The search strategy is shown in the eAppendix (<http://links.lww.com/EDE/A676>).

Forward and backwards citation searching was used to identify any additional relevant studies. The Archives of Neurology (January 1990 to December 2011), the Journal of the American Medical Association (5 January 2000 to 11 January 2012), and the American Journal of Clinical Nutrition (January 1990 to December 2011) were hand-searched, having been identified as particularly important journals in the field.

We performed internet searches for the following websites: Alzheimer’s Society ([www.alzheimers.org.uk/](http://www.alzheimers.org.uk/)), Alzheimer’s Disease Research ([www.ahaf.org/alzheimers/](http://www.ahaf.org/alzheimers/)), Alzheimer’s Disease International ([www.alz.co.uk/](http://www.alz.co.uk/)), Alzheimer’s Research UK ([www.alzheimersresearchuk.org/](http://www.alzheimersresearchuk.org/)), and Alzheimer’s Association ([www.alz.org/](http://www.alz.org/)). The section of each website labeled “Research” or research-related tabs (eg, “research portfolio,” “researchers and professionals”) was screened in detail on 16 January 2012. The corresponding authors of all included studies were contacted to identify any additional studies.

## Study Selection

Studies were included if they examined the association of a defined score used to measure adherence to the Mediterranean diet and included cognitive function or dementia as outcomes. There was no restriction in study design or language of publication. Conference abstracts were included if there were sufficient details to allow appraisal of study quality. We excluded studies evaluating adherence to a recommended guideline, to a dietary pattern other than a Mediterranean diet, or to individual components and not Mediterranean diet as a whole. We also excluded letters and editorials that did not include original research findings. The titles and abstracts retrieved by the electronic searches were screened independently by two reviewers (I.L. and M.S.). The full text of

potentially relevant papers was retrieved and screened in the same way. Any discrepancies were resolved through discussion with a third reviewer (D.J.L.).

## Data Extraction and Quality Assessment

A customized data extraction form was developed, pilot tested on three included studies, and refined accordingly. Data on study and participant characteristics, exposure, method of cognitive assessment, and relevant outcomes were independently extracted by two reviewers (I.L. and M.S.). We contacted one author who provided numerical data and clarification for two studies (one published article and one conference abstract).<sup>11,12</sup> The quality of the design and reporting of included studies were independently assessed by two reviewers (I.L. and M.S.), using custom checklists for the appraisal of observational studies and randomized trials (eAppendix, <http://links.lww.com/EDE/A676>). These checklists were derived from existing widely used questionnaires<sup>13–15</sup> and included items addressing issues related to population, recruitment, assessment of exposure and outcome, confounding, and statistical analyses. Discrepancies were resolved by discussion with a third reviewer (J.T.-C.) where necessary.

## RESULTS

### Study Characteristics

The combination of searches yielded a total of 719 references. Duplicates were excluded ( $n = 195$ ). Title and abstract screening resulted in the exclusion of further 508 papers. Full texts of the remaining 16 papers were obtained for detailed review. Four papers were excluded following full text screening: a book chapter, a narrative review, and two studies that focused on specific components of the Mediterranean diet instead of the dietary pattern as a whole. This left 12 papers eligible for inclusion (Figure).

Table 1 describes the characteristics of the 12 papers (seven unique cohorts). All had been published from 2006 onwards. Two were conducted in Mediterranean countries (France and Greece),<sup>16,17</sup> three in Australia,<sup>11,12,18</sup> and the rest in the United States.<sup>19–25</sup> Eight had a longitudinal design, one was a single-blind randomized trial with follow-up after only 10 days, one was a nested case-control study, and three reported both cross-sectional and longitudinal findings. Five of the papers were based on participants of two related cohort studies recruited in 1992 and 1999 as part of the Washington Heights-Inwood Columbia Aging Project.<sup>20–23,25</sup> Most studies included both sexes with the proportion of women being slightly higher in all but one study. Several studies were based on samples of community-dwelling older adults 65 years old and above at baseline; one study focused on people aged 70–89 years<sup>24</sup> and two recruited participants aged 60 to 64 years;<sup>11,12</sup> the randomized trial included only young women (mean age = 21.1 years).<sup>18</sup> Sample size ranged from 25 to 3790 subjects, whereas mean follow-up ranged from 10 days to 8.0 years.

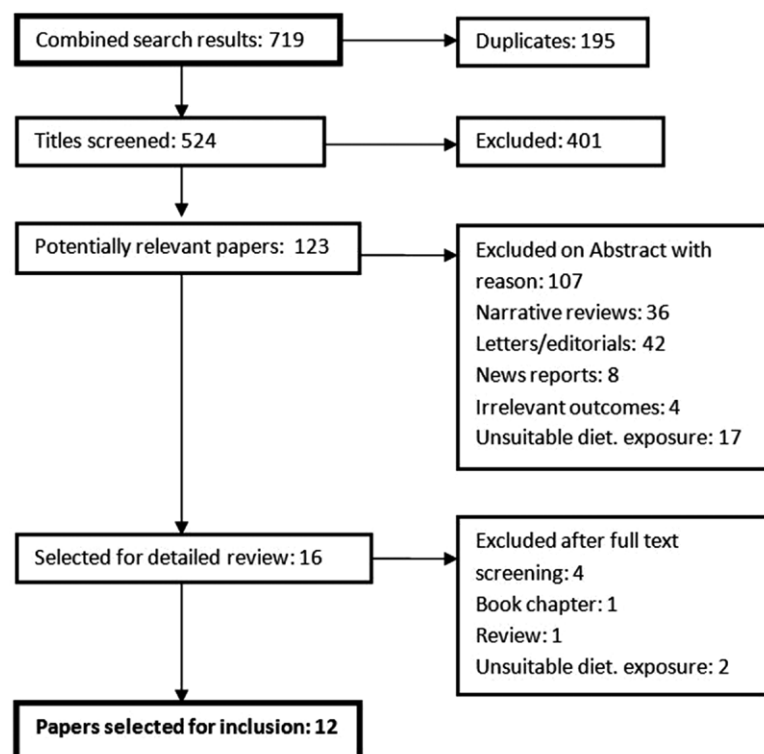


FIGURE. Flowchart of selection process of studies included in the review.

### Adherence to Mediterranean Diet

All studies used variations of a food frequency questionnaire to assess average dietary intake for the year preceding the study. The number of food questionnaire items ranged from 61 to 236 and provided details about foods, beverages, and consumption frequency, usual portion sizes, and cooking style. Most of the studies (10 papers) calculated caloric intake (kcal) converted into daily gram intakes for each of the seven food groups considered characteristic of the Mediterranean dietary pattern: fruits, vegetables, cereals, legumes, dairy, fish, and meat. The dietary profile also included calculation of fat intake (using the ratio of daily intake of monounsaturated fats to saturated fats) and classification of alcohol consumption. Sex-specific median cut points were used to assign a value of 0 or 1 to each of these nine dietary components. Adding the value assigned to each component generated a total Mediterranean Diet score, ranging from 0 to 9, where higher scores represented better adherence.

A similar approach using 5-point increments for daily or weekly consumption of 10 food groups and alcohol was adopted in the Chicago Health and Aging Project (CHAP) study for the calculation of the Mediterranean diet score on a scale from 0 to 45.<sup>19</sup> The randomized trial considered adherence to Mediterranean diet successful if 80% or more of the meals and snacks reported in a food diary completed by participants were in accordance with the Mediterranean dietary pattern. Adherence was quantified either as a continuous score (0–9 points or 0–45) or tertile-defined categories (low, middle, high), whereas some studies ( $n = 6$ ) reported analyses in both forms. Ten studies reported a mean score of adherence to Mediterranean diet.

However, direct numerical comparisons across studies are problematic as they used different dietary indexes to assess adherence. The mean level of adherence to Mediterranean diet was low to moderate across studies. This was true even for the populations from the two Mediterranean countries, where fewer than one-third of the participants had high adherence (scores 6–9) (eTable, <http://links.lww.com/EDE/A676>).

### Relevant Outcomes

Measures of cognitive functioning were identified in eight publications, mild cognitive impairment in four papers, and dementia in seven studies (five of which focused specifically on Alzheimer disease). No studies examined other key dementia subtypes (such as vascular dementia or Lewy body dementia).

All but one<sup>17</sup> of the studies performed cognitive assessments prospectively. The majority of studies utilized information from neuropsychological batteries that produced a composite cognitive score for each participant, whereas five administered the Mini-Mental State Examination test (MMSE) as part of their neuropsychological assessment.<sup>11,12,16,17,19</sup> Assessments also included memory (short- and long-term), language (comprehension, naming, fluency), executive function, visual-spatial skills, orientation, and abstract reasoning and construction (copying and matching). For one study, the MMSE was the sole measure of cognitive function.<sup>17</sup> Longitudinal studies examining mild cognitive impairment<sup>11,12,22,24</sup> and dementia risk<sup>16,20–24</sup> adopted a stepwise process to evaluate global cognitive function and detect mild cognitive impairment or dementia. The whole study population was screened,

**TABLE 1.** Characteristics of Included Studies

Study	Study Design	Study Name	Country	Sample Size	Mean Age <sup>a</sup>	Women %	Follow-up No. Years	Adjustment <sup>b</sup>	Outcomes
Feart et al <sup>16</sup>	Longitudinal	Three City (3C) study	France	1,410	75.9	62.6	5	Age, sex, education, marital status, caloric intake, ApoE ε4, physical exercise, ≥5 medications per day, depression score, BMI, diabetes, hypertension, tobacco use, hypercholesterolemia, stroke	Cognitive decline, Dementia risk
Psaltopoulou et al <sup>17</sup>	Longitudinal	ILIDA	Greece	732	≥60	64.9	8	Age, sex, education, marital status, caloric intake, height, physical activity, alcohol intake, smoking, depression, BMI, diabetes, hypertension	Cognitive decline
Cherbuin and Anstey <sup>11</sup>	Longitudinal	PATH Through Life Study	Australia	1,528	62.5	51.2	4	Age, sex, education, caloric intake, ApoE ε4, physical activity, BMI, stroke, diabetes, hypertension	Cognitive decline, MCI, CDR 0.5, any-MCD
Cherbuin et al <sup>12</sup>	Longitudinal	PATH Through Life Study	Australia	1,474	62.5	51.2	8	Age, sex, education, caloric intake, ApoE ε4, physical activity, BMI, stroke, diabetes, hypertension	Cognitive decline, MCI, CDR 0.5, any-MCD
Scarmeas et al <sup>20</sup>	Longitudinal	WHICAP	USA	2,258	77.2	68	4	Age, sex, education, ethnicity, cohort, caloric intake, ApoE ε4, BMI, smoking, comorbidity	Cognitive decline, AD risk
Scarmeas et al <sup>21</sup>	Longitudinal	WHICAP	USA	1,880	77.2	69	5.4	Age, sex, education, ethnicity, cohort, caloric intake, ApoE ε4, BMI, smoking, comorbidity, depression, leisure activities, CDR score	AD risk
Scarmeas et al <sup>22</sup>	Longitudinal	WHICAP	USA	1,393	76.9	68	4.5	Age, sex, education, ethnicity, cohort, caloric intake, ApoE ε4, BMI, time between 1st diet.ass. and baseline diagnosis	MCI risk, conversion to AD
Gu et al <sup>23</sup>	Cross-sectional/ Longitudinal	WHICAP II	USA	1,219	76.7	66.6	3.8	Age, sex, education, race, caloric intake, ApoE ε4, BMI, smoking, comorbidity	Cognitive function/ AD
Roberts et al <sup>24</sup>	Cross-sectional/ Longitudinal	Mayo Clinic Study of Aging	USA	1,233	79.6 <sup>c</sup>	49.2	2.2	Age, sex, education, caloric intake, ApoE ε4, stroke, CHD, depressive symptoms	Prevalent MCI / MCI risk, Dementia risk
Tangney et al <sup>19</sup>	Cross-sectional/ Longitudinal	CHAP	USA	3,790	75.4	61.7	7.6	Age, sex, education, race, total energy intake, participation in cognitive activities, interaction between time and dietary quality score	Cognitive function / cognitive decline
Scarmeas et al <sup>25</sup>	Cross-sectional	WHICAP	USA	1,984	76.3	68	(no follow-up)	Age, sex, education, ethnicity, cohort, caloric intake, ApoE ε4, BMI, smoking, comorbidity	Prevalent AD
McMillan et al <sup>18</sup>	Randomized controlled trial	(not given)	Australia	25	21.12	27	10-day	(not reported)	Cognitive function

AD, Alzheimer disease; ApoE ε4 indicates apolipoprotein E ε4 allele; BMI, body mass index; CDR, Clinical Dementia Rating scale; CHAP, Chicago Health and Aging Project; CHD, coronary heart disease; MCD, mild cognitive disorder; MCI, mild cognitive impairment; WHICAP, Washington Heights-Inwood Columbia Aging Project.

<sup>a</sup>Mean age at baseline unless otherwise stated.

<sup>b</sup>Adjustments refer to longitudinal analyses.

<sup>c</sup>Median.



with more detailed examination of participants suspected of having cognitive impairment or dementia.

### Quality Assessment

Overall the quality of included papers was moderate (Table 2). Follow-up time and sample size in some studies may have been insufficient to detect outcomes of interest,<sup>11,16,17,24</sup> with power calculations reported in only three studies.<sup>16,21,24</sup> Participants were representative of the populations from which they were drawn in nine studies (representing five unique cohorts), and their characteristics were described clearly in the majority of them. Ten studies did not use standardized median cut points for each food component, and the diet score was calculated in a study-specific manner. Reporting of variables related to diet adherence and statistical analyses was often inadequate. There was great variability in the instruments used for cognitive assessment, making studies difficult to compare. This was especially true for the diagnosis of mild cognitive impairment and global cognition scores.

### Adherence to Mediterranean Diet and Cognitive Function

Both studies with cross-sectional data showed evidence of a positive association between Mediterranean diet adherence and cognitive function.<sup>19,23</sup> Three of six studies<sup>11,12,16,17,19,20</sup> that examined prospectively the relationship of Mediterranean diet adherence with cognitive decline suggested that greater adherence was associated with reduced decline. Results from the studies conducted in Mediterranean countries were inconsistent.<sup>16,17</sup> The randomized trial<sup>18</sup> found that compared with the control group, participants assigned to follow the Mediterranean diet over 10 days improved on only one of the 14 tasks used to assess changes in cognitive function, the Corsi Block Task (spatial working memory). The treatment group also showed slower reaction times on the numeric working memory and word recognition task (Table 3).

### Adherence to Mediterranean Diet and Mild Cognitive Impairment

Four studies investigated the relationship between adherence to Mediterranean diet and mild cognitive impairment using both the continuous score and the tertile-defined categories of adherence (Table 4). Studies examining risk of mild cognitive impairment by unit increase on the Mediterranean Diet score (0–9) gave inconsistent results.<sup>11,12,22</sup> The two studies<sup>22,24</sup> that examined mild cognitive impairment risk across Mediterranean Diet tertiles found similar results with hazard ratios for the highest tertile compared with the lowest ranging from 0.72 (95% confidence interval [CI] = 0.52–1.00) to 0.75 (95% CI = 0.46–1.21).

### Adherence to Mediterranean Diet and Dementia

Two studies that examined incidence of all-cause dementia in relation to Mediterranean diet adherence had inconsistent results<sup>16,24</sup> (Table 5). All four prospective studies

of Alzheimer disease risk from the Columbia Aging Project (following older adults for various time intervals between 1992 through 2006) found a favorable association with the Mediterranean dietary pattern. Reduced risk of developing Alzheimer disease across studies ranged from 34% to 40% for nondemented persons in the highest tertile of adherence compared with the lowest (0–3).<sup>20–23</sup> Moreover, an 11% reduction in the risk of mild cognitive impairment converting to Alzheimer disease was observed for each unit increase in the Mediterranean diet score. This was especially true for persons with nonamnesic impairment.<sup>22</sup> Greater adherence to Mediterranean diet was also associated with lower risk for Alzheimer disease prevalence in the case-control study nested within the original cohort.<sup>25</sup>

## DISCUSSION

We identified 12 papers reporting an association between adherence to Mediterranean diet and cognitive function or dementia. Adherence to the Mediterranean diet may be associated with lower rates of cognitive decline. Our analysis also shows an emerging relationship between higher adherence and reduced risk for Alzheimer disease. The benefits of Mediterranean diet adherence were particularly evident in studies with mean baseline ages above 75 years, possibly because the higher risk of incident cognitive problems in this age group made it easier to detect differences in outcomes between those who consumed a Mediterranean diet and those who did not.

Evidence is accumulating for the effectiveness of the Mediterranean dietary pattern on the prevention of various age-related diseases, including dementia. Narrative reviews have suggested that stricter adherence to Mediterranean diet is associated with slower cognitive decline and reduced risk of Alzheimer disease. In a recent meta-analysis, a two-point increase in the Mediterranean diet adherence scale was associated with 13% reduction in the incidence of neurodegenerative diseases (risk ratio = 0.87 [95% CI = 0.81–0.94]).<sup>26</sup> The meta-analysis combined dementia with other degenerative diseases such as Parkinson's disease; our systematic review is the first to address the association between adherence to Mediterranean diet and dementia specifically and includes more recent studies.

There has been a focus on individual components of the Mediterranean diet, such as  $\omega$ -3 fatty acids<sup>27</sup> or olive oil as the main source of monounsaturated fats<sup>28</sup> and their neuroprotective properties. Indeed, separate analyses for certain food groups in two of the studies found that high vegetable intake and high lipids ratio (monounsaturated fat plus polyunsaturated fat in relation to saturated fat) were associated with a reduced risk for mild cognitive impairment,<sup>24</sup> whereas moderate wine consumption was associated with reduced rates of cognitive decline.<sup>19</sup> Although the advantages of Mediterranean diet are relevant for non-Mediterranean populations,<sup>29</sup> it is often argued that studies are not always comparable because there are substantial differences in dietary composition among

**TABLE 2. Quality Assessment of Included Studies**

Quality Indicator	Longitudinal Design						Longitudinal (+ Cross-Sectional Data)			Cross-sectional		Randomized Controlled Trial <sup>a</sup>
	Cherbuin and Anstey <sup>11</sup>	Cherbuin et al <sup>12</sup>	Cherbuin et al <sup>16</sup>	Psaltopoulou et al <sup>17</sup>	Tangney et al <sup>19</sup>	Scarmeas et al <sup>20</sup>	Scarmeas et al <sup>21</sup>	Scarmeas et al <sup>22</sup>	Gu et al <sup>23</sup>	Roberts et al <sup>24</sup>	Scarmeas et al <sup>25</sup>	McMillan et al <sup>18</sup>
Participants' key characteristics described clearly, and inclusion and exclusion criteria included	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Population of interest represented by sample	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Method(s) used to assess adherence to Mediterranean diet adequately described	Yes	Partial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial
Validity and reliability of diet measurement tool(s) and reference provided	Yes	Partial	Partial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Adherence stability during follow-up measured and described	No	No	Unclear	No	Yes	Yes	Unclear	Unclear	Unclear	No	N/A	N/A
Demonstration that outcome of interest was absent at baseline	Yes	Yes	Yes	N/A	N/A	Yes	Yes	No	Yes	Yes	N/A	N/A
Validity and reliability of cognitive measurement tool(s)—diagnostic criteria or definitions provided	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Potential confounders mentioned and controlled for in the analyses	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Specification of number of participants at each stage	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	N/A	Yes
Number of participants lost to follow-up less than 30% of sample	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	N/A	Yes
Key characteristics and reasons for participants lost to follow-up described	Yes	Yes	Partial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Yes
Loss to follow-up accounted for in the analysis	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	N/A	No
Estimates of effect with CIs and P values provided	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial
Justification for the number of participants and evidence that power calculations were considered/provided	Unclear	Unclear	Yes	N/A	N/A	Unclear	Yes	Unclear	Unclear	Yes	Unclear	No

N/A indicates not applicable.  
<sup>a</sup>Additional questions were used for quality assessment of the trial and can be found in the eAppendix (<http://links.lww.com/EDE/A676>).

**TABLE 3.** Results of Included Studies for the Association Between Adherence to Mediterranean Diet and Cognitive Decline or Cognitive Performance

Study	Cognitive Assessment <sup>a</sup>	Methods	Results
Longitudinal (cognitive decline)			
Feart et al <sup>16</sup>	Individual scores on: MMSE, Isaacs Set Test, Benton Visual Retention Test, Free and Cued Selective Reminding Test	Mixed effects models <sup>c,g</sup> 0-9-point MeDi score	Each unit increase in the MeDi score corresponds to 0.006 (95% CI = 0.0003–0.01; <i>P</i> = 0.04) less cognitive decline per year on the MMSE
Psaltopoulou et al <sup>17</sup>	MMSE	Linear regression <sup>b,h</sup> 0-9-point MeDi score	Each unit increase in the MeDi score at baseline corresponds to 0.05 (95% CI = –0.09 to 0.19; <i>P</i> = 0.49) higher cognitive function on MMSE at follow-up
Cherbuin and Anstey <sup>11</sup> (Wave 2)	Average Z score of: MMSE, California Verbal Learning Test, Symbol Digit Modalities Test, Purdue Pegboard test for investigation of cognitive change	Analysis of covariance <sup>b,i</sup> 0-9-point MeDi score	Each unit increase in the MeDi score corresponds to 0.02 (95% CI = –0.02 to 0.06; <i>P</i> = 0.37) less cognitive decline on the cognitive Z score over 4 years
Cherbuin et al <sup>12</sup> (Wave 3)	Average Z score of: MMSE, California Verbal Learning Test, Symbol Digit Modalities Test, Purdue Pegboard test for investigation of cognitive change	Analysis of covariance <sup>b,i</sup> 0-9-point MeDi score	Each unit increase in the MeDi score corresponds to 0.01 (95% CI = –0.04 to 0.06; <i>P</i> = 0.71) greater cognitive decline on the cognitive Z score over 8 years
Scarmeas et al <sup>20</sup>	Average Z score of: 12 neuropsychological tests to assess memory, orientation, abstract reasoning, language, construction	Marginal models using Generalised Estimating Equations <sup>d,j</sup> 0-9-point MeDi score	Each unit increase in the MeDi score corresponds to 0.003 (95% CI = 0–0.006; <i>P</i> = 0.05) less cognitive decline per year on the composite cognitive Z score
Tangney et al <sup>19</sup>	Average Z score of: MMSE, East Boston tests of immediate and delayed recall, Symbol Digit Modalities Test for global cognitive function measure	Mixed effects models <sup>b,g</sup> 0-45-point MedDiet score	Each unit increase in the MedDiet score corresponds to 0.0014 (95% CI = 0.0006–0.0022; <i>P</i> < 0.001) less cognitive decline per year on the global cognitive Z score
Cross-sectional (cognitive function)			
Gu et al <sup>23</sup>	Average Z score of: 15 neuropsychological tests to assess memory, language, processing speed, visual-spatial ability to summarize cognitive performance	Linear regression <sup>e,h</sup> 0-9-point MeDi score	Each unit increase in the MeDi score corresponds to 0.013 (95% CI = 0–0.026; <i>P</i> = 0.05) increase on the composite cognitive Z score
Tangney et al <sup>19</sup>	Average Z score of: MMSE, East Boston tests of immediate and delayed recall, Symbol Digit Modalities Test for global cognitive function measure	Linear regression <sup>f,h</sup> 0-45-point MedDiet score	Each unit increase in the MedDiet score corresponds to 0.007 (95% CI = 0.003–0.011; <i>P</i> < 0.001) increase on the global cognitive Z score at baseline
Randomized controlled trial			
McMillan et al <sup>18</sup>	Individual scores on: 21 items of the COMPASS battery with tasks to assess change in attention, working memory, long-term memory, executive function	Repeated measures analysis of variance <sup>k</sup> Food diary	The Mediterranean Diet group performed faster on the Corsi Block Task ( <i>P</i> < 0.001) but was slower on the Numeric Working Memory and Word Recognition tasks (both, <i>P</i> = 0.04) than the control group

COMPASS indicates the Computerised Mental Performance Assessment; MeDi/MedDiet score, Mediterranean Diet Score.

<sup>a</sup>Cognitive assessment performed at baseline and repeated at follow-up except in the study by Psaltopoulou et al.<sup>17</sup>

<sup>b</sup>Adjusted for variables as shown in relevant column in Table 1.

<sup>c</sup>Adjusted for variables as shown in relevant column in Table 1 plus their interaction with time.

<sup>d</sup>Adjusted for age, sex, education, ethnicity, cohort, baseline cognitive performance, and time.

<sup>e</sup>Adjusted for age, sex, education, and race.

<sup>f</sup>Adjusted for age, sex, race, education, participation in cognitive activities, and total energy intake.

<sup>g</sup>Mixed effects models used to quantify relationship between increase in Mediterranean diet score and rate of change in cognitive function, with outcome at baseline and follow-up used as the dependent variable, and Mediterranean diet score, time and interaction between Mediterranean diet score and time used as independent variables.

<sup>h</sup>Linear regression used to estimate change in outcome (cognitive Z score) for each unit increase in Mediterranean diet score, with composite cognitive Z score as the dependent variable and Mediterranean diet score as the independent variable.

<sup>i</sup>Analysis of covariance used to estimate change in outcome (cognitive Z score) for each unit increase in Mediterranean diet score, with outcome at follow-up used as the dependent variable, and Mediterranean diet score and outcome score at baseline used as independent variables.

<sup>j</sup>Marginal models using Generalised Estimating Equations used to quantify impact of increase in Mediterranean diet score on rate of change in cognitive function, with outcome at baseline and follow-up used as the dependent variable and Mediterranean diet score, time and interaction between Mediterranean diet score and time used as independent variables.

<sup>k</sup>Repeated measures analysis of variance to estimate the effect of diet change intervention on change from baseline to follow-up in cognitive performance with trial arms status, time and interaction between trial arm status and time as independent variables.

**TABLE 4.** Results of Included Studies for the Association Between Adherence to Mediterranean Diet and Mild Cognitive Impairment

Study	Cognitive Domains Assessed	Diagnostic Criteria	Results
Longitudinal			
Cherbuin and Anstey <sup>11</sup> (Wave 2)	Memory, language, executive function, recall of constructional praxis, agnosia	International Consensus Criteria, CDR scale for MCI, and DSM-IV for diagnosis of dementia	MCI (n = 10):OR = 1.41 (95% CI = 0.95–2.10; <i>P</i> = 0.09) per unit increase in 0–9–point MeDi score. CDR 0.5 (n = 19):OR = 1.18 (95% CI = 0.88–1.57; <i>P</i> = 0.27) per unit increase in 0–9–point MeDi score. Any-MCD (n = 37):OR = 1.2 (95% CI = 0.98–1.47; <i>P</i> = 0.08) per unit increase in 0–9–point MeDi score
Cherbuin et al <sup>12</sup> (Wave 3)	Memory, language, executive function, recall of constructional praxis, agnosia	International Consensus Criteria, CDR scale for MCI, and DSM-IV for diagnosis of dementia	MCI (n = 30):HR = 1.06 (95% CI = 0.85–1.34; <i>P</i> = 0.59) per unit increase in 0–9–point MeDi score. CDR 0.5 (n = 38):HR = 1.01 (95% CI = 0.82–1.23; <i>P</i> = 0.97) per unit increase in 0–9–point MeDi score. Any-MCD (n = 60):HR = 1.07 (95% CI = 0.92–2.56; <i>P</i> = 0.39) per unit increase in 0–9–point MeDi score
Roberts et al <sup>24</sup>	Memory, language, executive function, visuospatial skills	CDR scale, impairment in at least one cognitive domain for MCI, and DSM-IV for diagnosis of dementia	MCI risk (n = 93):HR = 0.75 (95% CI = 0.46–1.21; <i>P</i> = 0.24) for highest tertile compared with lowest on MeDi score
Scarmeas et al <sup>22</sup>	Memory, language, orientation, abstract reasoning, construction	CDR scale, Disability and Functional Limitations Scale, Blessed Functional Activities Scale and impairment in at least one cognitive domain for MCI, and DSM-III-R for diagnosis of dementia and NINCDS-ADRDA criteria for Alzheimer's disease	MCI risk (n = 275):HR = 0.92 (95% CI = 0.85–0.99; <i>P</i> = 0.04) per unit increase in 0–9–point MeDi score. HR = 0.72 (95% CI = 0.52–1.00; <i>P</i> = 0.05) for highest tertile compared with lowest on MeDi score
Cross-sectional			
Roberts et al <sup>24</sup>	Memory, language, executive function, visuospatial skills	CDR scale, impairment in one or more of the cognitive domains for MCI, and DSM-IV for diagnosis of dementia	Prevalent MCI:OR = 0.80 (95% CI = 0.52–1.25; <i>P</i> = 0.33) for highest tertile compared with lowest on MeDi score

Any-MCD indicates any-mild cognitive disorder; CDR, Clinical Dementia Rating scale; HR, hazard ratio; MCI, mild cognitive impairment; MeDi score, Mediterranean Diet score; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria; n, number of participants with outcome in parentheses; OR, odds ratio.

countries. A more detailed examination reveals this is especially true for fatty acids.<sup>11,17,20</sup> Although olive oil is the hallmark of Mediterranean diet, differences in the origin of monounsaturated fats or cooking style (eg, baked vs. fried) could partly explain these inconsistencies.<sup>11,30</sup> Studies comparing types of olive oil concluded that compared with refined oil, virgin olive oil (rich in phenolic content) has additional anti-inflammatory and antioxidant properties beneficial to cellular function and cardiovascular health.<sup>31</sup>

### Potential Underlying Mechanisms

The Mediterranean diet may exert its effects on cognitive health through multiple biologic mechanisms. Relationships with reduced risk of coronary heart disease, hypertension, diabetes,<sup>5,32,33</sup> dyslipidemia, and metabolic syndrome<sup>34</sup> have been observed, and these conditions have also been associated with mild cognitive impairment, dementia, or Alzheimer disease. Higher adherence may also facilitate metabolic control because it has been related to improved insulin sensitivity and glucose metabolism.<sup>35</sup> Furthermore, oxidative stress increases

with age and results in oxidative damage—a state often observed in the brain of patients with Alzheimer disease.<sup>36</sup> Typical components of the Mediterranean diet (namely fruits, vegetables, wine, and virgin olive oil) are rich in antioxidants such as vitamin C and E, carotenoids, and flavonoids.<sup>37–39</sup> Decreased oxidative stress found in people adhering to a Mediterranean-type diet could partially explain their lowered risk for dementia.<sup>40</sup> Neurons are protected against oxidative stress by neurotrophins (basic proteins) such as the brain-derived neurotrophic factor, and there is some evidence that Mediterranean diet may increase plasma brain-derived neurotrophic factor concentrations.<sup>41</sup> Neurotransmitter synthesis, synaptic plasticity, and cell metabolism are influenced by vitamin C and B complex vitamin intake.<sup>42</sup> Inflammatory processes have also been suggested for Alzheimer pathogenesis. Higher concentrations of C-reactive protein, a nonspecific marker of inflammation, have been associated with increased risk for cognitive decline, Alzheimer disease, and vascular dementia,<sup>43</sup> whereas better adherence to Mediterranean diet has been associated with lower levels of C-reactive protein.<sup>44</sup> The ATTICA study<sup>44</sup>



**TABLE 5.** Results of Included Studies for the Association Between Adherence to Mediterranean Diet and Dementia or Alzheimer Disease (AD)

Study	Cognitive Domains Assessed	Diagnostic Criteria	Results
Longitudinal			
Feart et al <sup>16</sup>	Visual and verbal memory, language, orientation	DSM-IV for all-cause dementia	Dementia (n = 99):HR = 1.12 (95% CI = 0.60–2.10; <i>P</i> = 0.72) for highest tertile compared with lowest on MeDi score
Roberts et al <sup>24</sup>	Memory, language, executive function, visuospatial skills	DSM-IV for all-cause dementia	Dementia (n = 23):HR = 0.75 (95% CI = 0.46–1.21; <i>P</i> = 0.24) for highest tertile compared with lowest on MeDi score
Gu et al <sup>23</sup>	Memory, language, orientation, abstract reasoning, construction	DSM-III-R for all-cause dementia and NINCDS-ADRDA for Alzheimer disease	AD (n = 118):HR = 0.87 (95% CI = 0.78–0.97; <i>P</i> = 0.01) per unit increase in 0–9–point MeDi score. HR = 0.66 (95% CI = 0.41–1.04; <i>P</i> for trend = 0.04) for highest tertile-based category compared with lowest on MeDi score
Scarmeas et al <sup>20</sup>	Memory, language, orientation, abstract reasoning, construction	DSM-III-R for all-cause dementia and NINCDS-ADRDA for Alzheimer disease	AD (n = 262):HR = 0.91 (95% CI = 0.83–0.98; <i>P</i> = 0.015) per unit increase in MeDi score. HR = 0.60 (95% CI = 0.42–0.87; <i>P</i> for trend = 0.007) for highest tertile compared with lowest on MeDi score
Scarmeas et al <sup>21</sup>	Memory, language, orientation, abstract reasoning, construction	DSM-III-R for all-cause dementia and NINCDS-ADRDA for Alzheimer disease	AD (n = 282):HR = 0.60 (95% CI = 0.42–0.87; <i>P</i> = 0.007) for highest tertile compared with lowest on MeDi score plus physical activity
Scarmeas et al <sup>22</sup>	Memory, language, orientation, abstract reasoning, construction	CDR scale, Disability and Functional Limitations Scale, Blessed Functional Activities Scale and impairment in at least one cognitive domain for MCI and DSM-III-R for all-cause dementia and NINCDS-ADRDA for Alzheimer disease	MCI conversion to AD (n = 106):HR = 0.89 (95% CI = 0.78–1.02; <i>P</i> = 0.09) per unit increase in 0–9–point MeDi score. HR = 0.52 (95% CI = 0.30–0.91; <i>P</i> = 0.02) for highest tertile compared with lowest on MeDi score
Cross-sectional			
Scarmeas et al <sup>25</sup>	Memory, language, orientation, abstract reasoning, construction	DSM-III-R for all-cause dementia and NINCDS-ADRDA for Alzheimer disease	Prevalent AD (n = 194):OR = 0.76 (95% CI = 0.66–0.86; <i>P</i> < 0.001) per unit increase in 0–9–point MeDi score. OR = 0.31 (95% CI = 0.16–0.58; <i>P</i> < 0.001) for highest tertile compared with lowest on MeDi score

CDR indicates Clinical Dementia Rating scale; HR, hazard ratio; MCI, mild cognitive impairment; MeDi score, Mediterranean Diet score; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria; OR, odds ratio.

also found that interleukin levels were reduced by 17%, and there were beneficial changes in other markers involved in inflammation and coagulation processes including homocysteine, white blood cell count, and fibrinogen.

## Methodological Considerations

Eleven out of the 12 papers were observational and cannot be used to confirm whether the association is causal. However, the cohort studies with long follow-up periods and large samples suggest an association between Mediterranean diet adherence and reduced risk of cognitive decline and Alzheimer disease.<sup>21,22</sup> Findings in relation to Alzheimer disease risk, however, are all based on analyses conducted within a single project (Columbia). The composition of the cohort was multiethnic with a high proportion of African-Americans and Caribbean Hispanics. Previous research has demonstrated increased Alzheimer disease and vascular dementia incidence rates in these ethnic groups (although these results remain controversial),<sup>45,46</sup> and further replication may clarify a potential association with ethnicity. Evidence

supported by well-designed, long-term randomized trials that can manipulate dietary intake according to specific dietary patterns and assess changes in cognitive function will strengthen findings and clarify trends identified in the systematic review. The one randomized trial in the review had several important limitations (limited dietary assessment method, only 10 days follow-up, recruitment through snowballing, limited to women, and small sample size), which may have biased the results and limited its external validity. Present study designs do not allow the determination of causal relationships, but at least suggest that higher adherence to the Mediterranean diet influences cognitive outcomes. The reverse could also be true: people may experience changes in appetite, food preferences, and eating habits both before diagnosis and as part of dementia itself.<sup>47,48</sup> To address this possibility, several studies excluded persons with dementia or Alzheimer disease from the dietary analyses and used multiple dietary assessments to investigate adherence stability over time.<sup>16,19–21</sup> Cognitive decline and Alzheimer disease processes may start several years—even decades—before the

onset of symptoms. Observing middle-aged adults with long-term adherence to Mediterranean diet could enable a more in-depth understanding of the relationship with cognition and dementia subtypes and perhaps indicate an optimum time window when dietary interventions would be most beneficial for changing the course of the disease.<sup>49</sup>

Comparing outcomes is challenging because a variety of tools was used to assess cognitive function in the various studies. There are also issues related to the measurement of adherence, such as the use of food frequency questionnaires with various number of items and the study-specific cutoffs for dietary intake and score calculation, that limit comparability and increase the risk of misclassification bias. The rather small proportion of persons with high adherence to Mediterranean diet, either measured on a continuous score or in tertile-defined categories, as well as the limited cases ( $\leq 100$ ) identified in some studies, may have limited statistical power to detect an association with incident mild cognitive impairment or dementia.

Regarding statistical analyses, various methods were applied to estimate changes in cognition, whereas each study used a different set of factors to adjust for potential confounders (see Tables 1 and 3). Only two papers report additional analyses in an attempt to reduce bias due to confounding (ie, propensity scores),<sup>21,24</sup> and residual confounding cannot be excluded. For example, depressive symptoms have been related to cognitive impairment and dementia, and adherence to the Mediterranean dietary pattern has been associated with reduced risk of depression (four studies adjusted for depression; see Table 1).<sup>50,51</sup> It is also possible that older people following a Mediterranean-type diet may generally lead a healthier lifestyle, which in turn protects them from dementia. Finally, missing-data details were underreported and were limited to comparisons of characteristics between those who were and were not lost to follow-up. Complete case analysis was generally used; only one out of 12 papers reported imputation of missing values in some covariates for the analyses of adjusted models.<sup>21</sup>

The current analysis has several advantages over previous reviews. It is the first systematic review to address the association between adherence to the Mediterranean dietary pattern and cognitive function and dementia. Second, this review was conducted using a predefined protocol and applying specific inclusion and exclusion criteria, without restrictions in study design or language of publication. We applied an extensive search strategy combining a variety of different methods to identify relevant papers and data extraction, and quality assessments were performed independently by two reviewers. Thus, we are confident that we have identified the currently available evidence. However, the substantial variability in methods of cognitive assessment and statistical analyses used meant the findings were not compatible for meta-analysis. Further studies adopting more coherent and uniform methodology and analyses would allow for better

quantification of the association of Mediterranean diet adherence with cognitive function and dementia.

Additional studies are also warranted to clarify the association with additional key dementia subtypes (notably vascular dementia and dementia with Lewy bodies) and to clarify the mechanisms by which adherence to a Mediterranean diet may protect against dementia. Long-term randomized controlled trials promoting adherence to a Mediterranean diet may help establish whether improved adherence helps to prevent or delay the onset of Alzheimer disease and dementia.

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