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DASH and Mediterranean-type Dietary Patterns to Maintain Cognitive Health

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Abstract

There is growing consensus that as the US population ages, nearly a third will experience stroke, dementia or even both. Thus, interest in the role that diet may play in preserving cognitive abilities continues to grow especially in absence of truly effective treatments for dementia, of which Alzheimer's disease (AD) is the most common form. The purpose of this review is to examine whether two *a priori* dietary patterns influence the rate of cognitive decline or the onset of dementia. Evidence from neuropathology reports of those who have died with AD or with mild cognitive impairment (MCI) or without cognitive impairment suggests that often the pathological hallmarks of AD---amyloid deposition and presence of tangles are present along with vascular lesions. Hypertension and stroke are strongly associated with incident dementia. Thus, it is possible that lifestyle approaches designed to prevent or reduce cardiovascular risk factors, conditions or diseases may also provide added benefits for brain health.

Keywords

Mediterranean diet; DASH diet; diet patterns; dietary scores; accordance; adherence; cognitive decline; dementia; Alzheimer's disease; mild cognitive impairment; incident dementia

Introduction

The Dietary Approach to Stop Hypertension (DASH) diet is a recommended dietary plan for all Americans, especially those with hypertension (1). The DASH diet has been shown to be protective against hypertension, cardiovascular disease and diabetes (1, 2), conditions shown to increase cognitive decline, executive function and attention (3-5). Similarly, adherence to a Mediterranean-style diet (Medit) pattern is inversely associated with a wide range of chronic diseases--- in particular, stroke, cardiovascular disease, diabetes ---and all-cause mortality (6-8). Because vascular factors can contribute to cognitive impairment, it is logical to hypothesize that both of these dietary patterns may protect against cognitive decline and/or dementia. However, conflicting evidence exists regarding the neuroprotective

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benefits of a Medit pattern and rather limited evidence exists for that of the DASH pattern and cognitive changes. In this review we examine some of the possible reasons for these discrepancies. Are the inconsistent findings attributable to the manner in which the dietary patterns defined or how investigators define cognitive outcomes or the duration of or frequency of repeated cognitive measurements? Was there adequate control for or adjustment for possible confounders? These issues will be examined in this review of recent evidence for DASH and Medit dietary patterns and their putative role in slowing cognitive decline. Longitudinal studies, both cohorts and clinical trials, with repeated cognitive assessments over time will be emphasized. We must acknowledge the excellent systematic review on the Medit diet and cognitive function and dementia by Lourida and colleagues (9). Our review addresses both Medit as well as DASH dietary patterns and includes several more recent studies for the Medit pattern. We choose to focus on how the dietary pattern is operationalized, ie., the diet scores and whether such scores capture the intended dietary pattern.

How do we define the DASH and Medit dietary patterns?

The DASH diet is characterized by high consumption of fruits, vegetables, nuts/seeds/legumes, lean meats/fish/poultry, low- or non-fat dairy and low consumption of sweets, saturated fats, and sodium. The pattern has been extensively studied in both short-term feeding trials and free living trials in both hypertensive and normotensive populations; the consensus is that this plan is efficacious for all (1, 10, 11)

The Medit diet pattern was first popularized by Dr. Ancel Keys in his book (12); the dietary components include extra virgin olive oil, whole and minimally processed grains, legumes, vegetables, fruit, nuts, fish, and regular but modest intake of wine or alcohol (13). Both of these constituents afford a plethora of polyphenols in addition to the rich monounsaturated fatty acid content of olive oil. Thus, at least two features of the traditional Medit diet that differentiate this pattern from that of DASH are the almost exclusive use of olive oil and moderate consumption of wine with meals. The DASH diet plan can be modified to emphasize mono-unsaturated fats which *may* include olive oil (14) but there is no emphasis on regular alcohol or wine consumption. In fact, alcohol restriction was one key behavioral target employed by the PREMIER trial group (10). This was because excessive amounts (more than 210 g per week) of alcohol could elevate systolic blood pressure through several mechanisms including vasoconstriction (15), and also contribute to poor weight maintenance. On the other hand, in the DASH diet plan, all dairy products are low-fat or non-fat in effort to keep the proportion of energy from saturated fat less than or equal to 6%. The traditional Medit did not include such restrictions in large part because cheese and other dairy items were inherently lower in saturated fat composition in Mediterranean countries. Such food items have been traditionally produced locally from goats and sheep fed on indigenous greens and hence, their tissues reflect a different fatty acid composition particularly with respect to omega 3 content (16, 17). However, because of changes in agricultural practices in the Mediterranean region, a recent working group has also recommended a greater emphasis for all Medit patterns to include low fat dairy products (18).

Scores applied to FFQ response to evaluate accordance or adherence[1] to DASH and Medit dietary patterns

Several scoring paradigms have been used to capture the key food and/or dietary components that comprise the DASH and Medit patterns. When modifications are made to these scores, this can prevent cross-study comparisons, making it more difficult to summarize and to bring consensus and new direction to the field of nutritional epidemiology. The scoring paradigms selected are those which have been applied to cohorts in which repeated cognitive assessments have been made. Most often, a food frequency questionnaire (FFQ) is administered to the participant in which the frequency and usual portions of food items consumed in the past year (often 140 items or more) is collected. Based on these responses the accordance or adherence to a particular scoring system is assessed.

The first 2 columns in Table 1 describe the components of two commonly used DASH scores. The first is a scoring scheme originally created by Folsom and colleagues (19) and further modified by Epstein et al (20) with 10 equally weighted targets--- 7 food group components and 3 dietary components--- dietary sodium, the proportion of energy from total fat and the proportion of energy from saturated fat. A score of 1 was assigned if the target amount for the component was achieved, 0.5 for an intermediate target, and a score of 0 if the amount reported was less than the minimum target.

The Nurses' Health Study investigators (21) offered a different scoring paradigm with 8 food group items and a score with values ranging from 8 to 40. Food group intakes of FFQ respondents were classified into quintiles. Those of benefit for blood pressure lowering included five components (whole grains, fruits, vegetables, nuts with legumes, and low-fat dairy). Those with food intakes that were classified in quintile 1 were assigned 1 point and those in quintile 5, 5 points. For intakes of foods or nutrients that should be limited (red and processed meats, sodium, sweetened beverages), the scoring was the opposite; those with the highest quintile were assigned 1 point, while those with the lowest intakes were assigned a value of 5. In terms of sodium, the criterion for a positive score is more conservative than that for the modified Folsom score.

For the Medit diet, there are two principal scoring approaches that have been the basis for numerous publications. Further revisions have been applied by researchers, in particular, those evaluating accordance or adherence of population samples from non-Mediterranean countries. As shown in Table 1, by far the most popular is the dichotomous scoring system created and revised by Trichopoulou and coworkers (22) referred to as the “MeDi score”; other variations have also been used by other groups, such as the alternate MeDi (23). Scoring is binomial with nine components, because the sex-specific median consumption level for each of the nine components (and eight in the case of the alternate MeDi) is used as a cutoff. Persons whose intake of key foods (i.e., fruits) is at or greater than the median are

[1]Accordance should be used to evaluate how closely one's diet approximates the Mediterranean diet pyramid in populations that have not received formal education on this diet pattern, though many living in this region might argue this. In those received formal education of what is to eaten, the better term is ‘adherence’.

assigned a value of 1, and persons whose intake is below the median receive a 0. Note for this scoring paradigm, olive oil consumption is not assessed, but rather a ratio of two dietary components---monounsaturated fatty acids to saturated fatty acids. Component group-items such as red meats are inversely scored; persons with consumption below the median cutoff are assigned a value of 1. Alcohol is scored differently from the other components. Men receive a 1 if they consume the optimal range of 10 to 50 g of ethanol per day, and women receive a 1 if they consume the optimal range of 5 to 25 g of ethanol per day. Anywhere outside of that amount is given a zero (too high or too low). Scores range from 0 to 9, a score of 9 being the most accordant or adherent to the Mediterranean diet. Again, for all components other than alcohol/wine, it is the sex-specific distribution of that food item or diet fat ratio that determines whether a person is assigned a 1 or 0. In the alternate MeDi scoring system developed by Fung and coworkers (23) whole grains is the scored component instead of total grains, and potatoes are excluded from the vegetable totals.

For the second Medit score----the MedDiet score as developed by Panagiotakos and coworkers (24), there are 11 components--- of which one of the components is olive oil, another is potatoes. These authors state that the potato is not classically a part of the Mediterranean diet pyramid, but was selected because of it is a rich source of B vitamins, Vitamin C, potassium, magnesium and fiber and hence, cardioprotective. Each food component can be assigned a value from 1 to 5. A high score is desired; a score of 55 is considered most accordant to the Mediterranean diet. Assignment of a value is not dependent on the reported intake distribution; rather it is based on achieving the target number of food servings when a '5' is assigned. Higher frequencies of consumption yield the most points, except for red meat and meat products, poultry, and full-fat dairy components. For those foods not consistent with the Mediterranean pattern (i.e., red meat and meat products), the opposite scores were assigned (i.e., a score of 0 for participants consuming these items more than 10 times per week to a score of 5 for less than or equal to once per week). In this system as well, alcohol is scored differently from the other components. The most points are given for consuming alcohol in moderation, <300 mL per day but >0 mL per day. Some components are scored inversely. For example, a score 5 is given for lower consumption (≤ 1 serving per week) of red meats, and 0 is given for a high frequency of consumption (>10 servings per week) of red meats.

In the recent PREDIMED primary prevention trial of more than 7000 Spanish older high cardiovascular risk adults (25), a brief 14-item questionnaire was administered 4 times a year for more than 4 years to gauge adherence to two different Medit interventions (26). Like the MedDiet scoring system by Panagiotakos and coworkers (24), specific target amounts (or frequencies) of key foods were the basis for score assignment, but in this tool assigned values were either 1 or 0. Unlike the MeDi score however, the score assignment was not based on the population distribution (above or below the sex specific median).

Definitions of Alzheimer's Disease (AD), Mild Cognitive Impairment (MCI), and Cognitive Health

Alzheimer's disease (AD) is the most common form of dementia; by 2050, it is estimated that there will be 100 million cases (27). The impact of AD and other dementias will be costly in many ways—quality of life as well as the cost of the healthcare burden. Two distinguishing features of AD include extraneuronal senile amyloid containing plaques and intraneuronal neurofibrillary tangles. AD is a slow progressive neurodegeneration accompanied by impairment in cognition, behavior and daily function. Mild cognitive impairment is a condition characterized a mild memory or cognitive impairment, yet the person has no marked disability. This condition has a high rate of progression to AD (28). Hence, many researchers wish to identify incident MCI so that preventive strategies such as dietary modification or physical and cognitive activities may influence progression to AD.

Other diagnostic criteria have been proposed for age-related cognitive decline; in DSM-IV, this condition is defined as "an objectively identified decline in cognitive functioning consequent to the aging process that is within normal limits given the person's age", but surprisingly there are no specific criteria diagnostically (29).

Cognition is composed of several components or domains. The number of domains needed to adequately assess cognitive performance is not well defined among neuropsychologists and neuroepidemiologists. Which domains are selected is dependent on the aims of the study, but for studies of cognition among older persons these often include memory (episodic, working, and semantic), attention, language and visuospatial ability. However performance on these tests is influenced by many factors other than the functional aspect being measured. One of the best compromises to circumvent many of the limitations in performance tests is through the use of multiple tests for each domain, and the use of tests with demonstrated reliability. What is preferable is determine change in performance tests because cognitive change is typically the focus of interest when a disease process such as AD is being examined (30).

What is the evidence for the protective role of the DASH pattern and cognitive decline?

As shown in Table 2, there are 4 reports in which adherence or accordance to a DASH pattern and cognitive health have been measured. In the first, a clinical trial of four months' duration, DASH adherence to a modification of the Folsom score was evaluated using on responses to a four day food record (for macronutrient and energy intakes) and a one month food frequency questionnaire or FFQ (for food group intakes) administered at baseline and 4 months post randomization (31). There was no difference in DASH adherence between the two DASH groups and in both, there was an improvement in psychomotor speed with DASH adherence. In our analyses of cognitive change in more than 800 much older adults over a period of nearly 5 years (32), rates of change in global and all cognitive domains (including psychomotor speed, based on 4 different tests in Memory and Aging Project or MAP) were reduced in those with greater accordance to a DASH pattern. The DASH scoring approach was similar beween these reports. It is intriquing that in different age groups, with different protocols (in ENCORE, middle-aged participants were counseled on the DASH diet plan while MAP was an ongoing cohort of much older adults) and different study duration (4 months vs 4.7y), the DASH dietary plan was associated with beneficial cognitive changes. In both reports from the Cache County cohort, the alternate DASH scoring system (21) was applied to the FFQ responses. In the paper by Norton and coworkers (33), the DASH score was one of 6 behaviors assessed in relation to incident dementia or AD over a period of 6 or more years; dietary behaviors in conjunction with others decreased risk of incident dementia. In the study by Wengreen et al, (34), a significant reduction in rates of global cognitive decline was observed with higher DASH scores. The approach of Wengreen and coworkers was a little different because they summed scores across quintiles similar to an approach used by Kesse-Guyot et al using the MeDi scoring (35).

What is the evidence for the protective role of the Medit pattern and cognitive decline?

Exactly 17 different reports on the Medit pattern with the cognitive outcomes including decline, function and/or incident Alzheimer's disease, dementia or mild cognitive impairment or MCI and published since 2006 are identified in Table 2. Our emphasis was on longitudinally measured cognitive performance or incident dementias. The studies in table 2 reflect 14 different cohorts, four from Mediterranean countries, another two from Australia, and the remaining from the US. All but one constructed Medit scores based on FFQs with 62 to 156 items. In 13 reports, the MeDi scores were applied to 10 non-Mediterranean population samples. These include the WHICAP studies (36-39), the Cache County study (34), the French Three City cohort (40) and the REGARDS cohort (41). Higher MeDi scores were related to slower declines or lower incident cognitive impairment. In both Australian studies, MeDi scores were not related to cognitive decline; however, a slightly younger sample was studied and a different analytic approach were used (analysis of covariance), one that might be sensitive to dropouts, though very similar multivariable adjustments were employed. The alternate MeDi (aMeDi) scoring paradigm of Fung and coworkers (23) was used to assess Medit accordance in non-Mediterranean countries---specifically, among participants in the Women's Health Study (42) and the Nurses' Health Study (43); in neither were MeDi scores related to cognitive change. In both, telephone administered battery of cognitive tests were administered and repeated over time. In both only women were studied. In the Chicago Health and Aging Project (44), and in the Women's Antioxidant Cardiovascular Study or WACS (45), the MedDiet scores were computed for participants of these cohorts. These were both older cohorts, followed for similar lengths of time, and some of the same cognitive tests. However, the WACS cohort was exclusively female and largely white; the CHAP cohort was 60% black and 40% male. Only the Chicago investigators observed a marked reduction in cognitive decline with higher MedDiet accordance. It is uncertain whether any of these factors contributed to the discrepant findings.

In all but two studies described in Table 2 cognitive assessments were made prospectively, mild cognitive impairment was assessed in five studies, and incident Alzheimer's disease or dementia in five. Reduced risk of MCI or AD was observed in four of the five studies, but four were from the same cohort.

Finally, some of the investigators examined individual food group contributions to rates of cognitive change in their population. Wengreen and coworkers (34) observed that the whole grains (a component of the DASH score they adopted, though also a component of MedDiet scores) and legumes as well as nuts (both Medit score components) were associated with reductions in rates of the decline similar to those for the total DASH or total Medit scores. Like Wengreen and coworkers, our group reported that the nuts/seeds/legumes component was inversely associated with rate of cognitive declines, along with DASH score components for vegetables, fats, and saturated fat (32). In the Mayo Clinic Study, polyunsaturated plus monounsaturated fatty acids to saturated fatty acid ratio was associated with a reduced odds of MCI (46). Samieri and coworkers (42) also observed that this component was related to more favorable cognitive changes among older women.

Conclusion

In this review of two *a priori* dietary patterns, there was good agreement among the limited number of studies (all in the US) regarding the protective influence of a DASH adherent or accordant pattern on cognitive changes. The role of a Medit pattern is not consistent across the many cohorts. It is this author's opinion that use of a Medt score that specifies target amounts of key foods or nutrients would provide a better benchmark to compare the effectiveness of such dietary patterns across different cohorts especially those in non-Mediterranean countries. There is also a suggestion that perhaps sex and even age decile may modify these associations with Medit scores. Future studies especially those in which DASH and Medit patterns are the active treatment intervention may help to clarify whether such cognitive benefit is realized.

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Table 1

Components of the Dietary Approaches to Stop Hypertension (DASH) and Mediterranean (MEdit) Dietary Patterns

Food Group (serving/d)	DASH Diet Scores		Medit Diet Score	
	Folsom et al score as modified by ENCORE investigators(19, 20)	**Modified DASH Score (21): based on quintile distribution, 1 to 5 points for each**	**Trichopoulou, et al (22): dichotomous score: 9 components: 0 or 1 points**	**Panagiotakos, et al (24): ordinal scale, 11 components: 1 to 5 point scale**
Total grains	√		√	
Whole or Non-refined grains		√		√
Legumes	√ Combined with nuts & seeds	√ Combined with nuts	√	√ Combined with nuts & beans
Vegetables	√	√	√	√
Nuts	Combined with legumes & seeds	Combined with legumes	√ Combined with fruits	
Fruits	√	√	Combined with nuts	√
Fish	√ Inverse; combined with meats, poultry		√	√
Full-fat dairy	√*		√	√
Low-fat dairy		√		
All Meats	Inverse; combined with fish, poultry		√ Inverse	√ Inverse
Red and Processed meats		√ Inverse		
Poultry	Inverse; combined with fish, all meats		√ Inverse	√ Inverse
Olive Oil				√
Sweetened beverages	See "Sweets"	√		
Potatoes				√
Wine, alcohol			√ Value of 1 for men for 10-50g/d; for women, 5-25g/d above, assigned	√ 0 for > 700 mL/d or 0 ml/d; <300mL/d = 5, 300mL = 4; 400=3; etc.
Sodium	√ Inverse, 1 point for ≤ 2400 mg/d, 0.5 for 2400 to 3000 mg/d, and 0 for > 3000mg.d	√ Inverse, 5 point for less than 1041 mg, and 1 point for 2676 mg/d and higher		
Sweets	Inverse			
% energy from fat	√			

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Food Group (serving/d)	DASH Diet Scores		Medit Diet Score	
	Folsom et al score as modified by ENCORE investigators(19, 20)	**Modified DASH Score (21): based on quintile distribution, 1 to 5 points for each**	**Trichopoulou, et al (22): dichotomous score: 9 components: 0 or 1 points**	**Panagiotakos, et al (24): ordinal scale, 11 components: 1 to 5 point scale**
	Inverse, 1 point for ≤ 27; 0.5 for 28 to 29; 0 ≥30			
% energy from saturated fat	√ Inverse, 1 point for ≤ 6; 0.5 for 7 to 8; 0 ≥9			
Monousaturated Fats/Saturated Fat			√	

*√The DASH & PREMIER trials (47, 48) actually emphasized low fat dairy products, but neither Folsom and colleagues or Epstein and coworkers made this distinction; all dairy was included.

Table 2

Summary of studies of DASH or Medit dietary patterns on cognitive decline or Incident dementia or Alzheimer's disease*

Investigators	Dietary Pattern Defined as	Study Name and Design Type	Participant Description	Cognitive Outcomes Measured	Follow -up	Findings:
Smith PJ et al (2011) (31)	Based on FFQ: modification of **DASH** score by Folsom et al[1,2]	ENCORE RCT: DASH diet alone; DASH + weight management; usual care control	124 overweight hypertensive patients, mean age, 52.3 ± 9.5y; 35% male	*Psychomotor speed*: Ruff 2 and 7; Digit symbol substitution tests) *Executive-memory-learning (EFML):* Trail-making test B-A, Stroop Interference, Digit span, Verbal fluency (animal naming), verbal paired associates, controlled word association test	0 & 4 months	Compared to control subjects, DASH + weight: improvements in EFML (p=0.008) and psychomotor speed (p=0.023) DASH alone: improvements in psychomotor speed (p=0.036)
Norton MC et al (2012) (33)	Based on FFQ: **DASH** score[3]; healthy diet =above median DASH score	Cache County Memory Health and Aging	N= 2544; average age, 73.0 ±5.7y; ; 51% male, education: 13.7 ± 4.1y	4 triennial waves since 1995; incident dementia or Alzheimer's disease	6.3 ± 5.3y	Used 6 lifestyle behaviors of which diet was one; healthy behaviors plus religiosity decreased HR for dementia (0.58, p=0.005)
Tangney CC et al 2013 (32)	Based on a FFQ: **DASH** score by Folsom et al[1,2]	Memory and Aging Project cohort	N=818;average 81.5 ± 7.1y, 26% male; education 14.9 ± 3.0y, 94% white	2 or more cognitive assessments; each session 19 cognitive tests, 5 domains: episodic memory. semantic memory, working memory, visuospatial ability, and perceptual speed	4.7y	Per 1 unit change in DASH score, cognitive decline rate slower by 0.010 standardized units (SEE=0.004, p=0.006); significant declines in all cognitive domains
Wengreen H et al (2013) (34)	Based on FFQ: energy adjusted rank order **DASH** scores[3] and **MeDi** scores[4]	Cache County study on Memory, Health & Aging	N=3831; median age,74.3y, > 90% white; 40% male	Repeated modified MMSE a minimum of 4 times	11y	Persons in highest quintile of DASH scores had 0.97 MMSE points higher than did subjects in the lowest quintile; for MeDi scores, the difference between high and low quintile, 0.94 points. Both, p=0.001.
Scarmeas et al(2006) (49)	Based on FFQ: 0-9 point **MeDi** dichotomous score[4]	WHICAP- NY	N=2258; average age, 77.2y; 33% male; white,28%; black, 33%; Hispanic, 38%; 9.9 y (average) of education	Cognitive **decline,** repeat measures every 1.5y (Average Z score of 12 neuropsychological tests for memory, orientation, abstract reasoning, language, construction); incident Alzheimer's disease (NINCDS-ADRDA)	4y	Each unit increase in MeDi score corresponds to β=0.003 (95%CI (0.0 to 0.006);p=0.047 less **cognitive decline** per year on composite Z score Incident AD, HR=0.91 (0.83 -0.98) p=0.015
Psaltopoulou T et al (2008) (50)	Based on FFQ: 0-9 point **MeDi** dichotomous score[4]	EPIC cohort, Greece: ILDA	N=732 subjects, 60 y and older; 35.1% male	Cognitive **function**: MMSE and Geriatric Depression scale	8 y	Each unit increase in MeDi score corresponds to β= 0.05 (95%CI (-0.09 to 0.19);p=0.49, higher function on MMSE at followup
Scarmeas et al (2009) (37)	Based on FFQ: 0-9 point **MeDi** dichotomous score[4] Also examined physical activity[5]	WHICAP - NY	N=1880; average age, 77.2 ± 6.6y; 31% male; white,28%; black, 32%; Hispanic, 38%; 10.1 average y education	**incident** Alzheimer's disease(AD) (NINCDS-ADRDA)	5.4y	HR for incident AD=0.60 (0.42-87), p=0.008 for highest vs (1st) lowest tertile of MeDi; HR for incident AD=0.67 (0.47-95), p=0.03 for much physical activity
Scarmeas et al (2009) (38)	Based on FFQ: 0-9 point **MeDi** dichotomous score[4]	WHICAP- NY	N=1393; average age, 76.9y; 32% male	CDR, Disability & Functional Limitations Scale, Blessed Functional Activities scale & impairment in 1 or more domains for MCI-Alzheimer's disease **NINCDS-ADRDA**	4.5y	Trend HR for MCI=0.85 (0.72-1.0, p=0.05); Trend for MCI to AD conversion, HR=0.89 (0.78-1.02) p=0.09 per unit

Investigators	Dietary Pattern Defined as	Study Name and Design Type	Participant Description	Cognitive Outcomes Measured	Follow -up	Findings:
						increase in MeDi score; Trend for MCI to AD conversion increase in MeDi score; Trend for MCI to AD conversion increase in MeDi score; Trend for MCI to AD conversion increase in MeDi score; Trend for MCI to AD conversion st) lowest tertile
Feart C et al (2009) (40)	Based on FFQ: 0-9point **MeDi** dichotomous score[4]	Three City Cohort (3C) study, France	N=1410, average age, 75.9y	**Cognitive decline**: MMSE, Isaacs Set test, Benton Visual Retention test, Free and Cued Selective Reminding test **and incident dementia**	5y	Each unit increase in MeDi score corresponds to β=-0.006 (95%CI (-0.003 to -0.01);p=0.04 less **decline** on MMSE errors, but *not on other tests* nor for risk of incident dementia (HR= 1.12 95%CI: 0.6,2.1, p=0.72
Gu et al (2010) (51)	Based on FFQ: 0-9 point **MeDi** dichotomous score[4]	WHICAP II: cross-sectional & Longitudinal- NY	N=1219; average age, 76.7; 33.4% male; 31.3% white; 29.5% black; 37.5% Hispanic	Cognitive function (Average Z score of 15 neuropsychological tests for memory, processing speed, visuospatial ability, language), (DSM-IIIR) for all cause dementia; incident Alzheimer's disease	3.8y	HR=0.87 (0.78-0.97), p=0.01 per unit increase in MeDi; when hsCRP added, HR =0.66 (0.41-1.06), p=0.05; no mediation by inflammatory or metabolic markers
Roberts et al (2010) (46)	Based on FFQ: 0-9point **MeDi** dichotomous score[4]	Mayo Clinic Study of Aging: cross-sectional & Longitudinal- MN	N=1233; average age,79.6y; 50.8% male	Prevalent MCI; and MCI/Dementia risk (DSM-IV for all cause dementia)	2.2y	Incident Dementia (n=23); HR=0.75 (95%CI=0.46-1.21), p=0.24 for lowest tertile to highMeDi; the mono + polyunsaturated to saturated fatty acid ratio associated with reduced odds of MCI (OR= 0.52, 0.31-0.81, p=0.007)
Tangney et al (2011) (44)	Based on FFQ at baseline: 0-55 point **MedDiet** ordinal scale[6]	CHAP: cross-sectional & Longitudinal-Chicago,IL	N=3590; average age,75.4y; 60.2% black, 39.3% male	Cognitive function and cognitive decline based on repeated tests every 3 y (average Z score of 4 tests: MMSE, East Boston tests of immediate & delayed recall, Symbol Digit Modalities test)	7.6y	Each unit increase in MedDiet score corresponds to β=0.0014 (95%CI (0.0006 to 0.0022) **p<0.001 less declin**e per year on composite cognitive Z score
Cherbuin et al (2011) (52)	Based on FFQ: 0-9 point **MeDi** dichotomous score[4]	PATH Through Life study, Australia	N=1474; average age, 62.5y; 59.8% male	3 waves; Cognitive decline (same as above), MCI, CDR 0.5, any- MCD	8y	Each unit increase in MeDi score corresponds to β=0.01 (95%CI (-0.04 to 0.06);p=0.71 less **decline** per year on global cognitive Z score over 8 y
Cherbuin & Ashley (2012) (53)	Based on FFQ: 0-9 point **MeDi** dichotomous score[4]	PATH Through Life study, Australia	N=1528; average age, 62.5y; 59.8% male	2 waves; Cognitive **decline** (average Z-score of MMSE, California Verbal Learning test, Symbol Digit Modalities test, Purdue Pegboard test, MCI, CDR 0.5, any MCD	4y	Each unit increase in MeDi corresponds to β= 0.02 (95%CI (-0.02 to 0.06);p=0.37 less **decline** per year on global cognitive Z score over 4 y
Gardener S et al (2012) (54)	Based on Cancer Council of Victoria FFQ at baseline & scores 0-9 point **MeDi** dichotomous[4]	Australian Imaging, Biomarkers and Lifestyle study of Aging cohort	N=664; average age,72.7y; 42% male	Cognitive **function** assessed 18 months after FFQ (MMSE, Logical Memory II, California Verbal Learning test (long delay) and Delis-Kaplan verbal fluency (executive function)	----	Cross-sectional analyses; higher MeDi in healthy controls, lower scores in AD (p<0.001)

Investigators	Dietary Pattern Defined as	Study Name and Design Type	Participant Description	Cognitive Outcomes Measured	Follow -up	Findings:
Vercambre M-N et al (2012) (45)	Based on FFQ at a baseline (1995-6): 0-9 point **MeDi** dichotomous score[4] For long-term 0-55 point **MedDiet** ordinal scale[3]	Cohort follow-up of the RCT known as WACS, a secondary CV prevention trial of US female health professionals-	N=2054; average age, 72.5 y, all women, 94% white	Telephone cognitive tests (5) of *global function* (composite of z-scores of *verbal memory* (10-word list & East Boston memory (delayed and immediate for both), *category fluency* (CERAD) 3-4years later first cognitive assessment, then repeated 3 more times at 2 y intervals; 93% had at least 2	5.4y	No relation between MeDi scores and multivariable adjusted annual rates of change in global composite score or GCS (mean difference in GCS per additional MeDi score -0.001 (p=0.40 for trend), no significant differences in cognitive **decline** with MedDiet scores, p=0.58
Tsivgoulis G et al (2013) (41)	Based on FFQ: 0-9 point **MeD**i dichotomous score[4]	REGARDS 2003-2007 US cohort	N=17,478; average age, 64.4 ± 4.1y, 31% black, 43% male	Six-item screener (SIS) for cognitive function At baseline and annually, **incident cognitive impairment** (ICI): a decrease from SIS of 5-6 to ≤4.	4.5y	**ICI** associated with high adherence to MeDi in non-diabetic individuals (OR=0.81 (0.70-0.91), p=0.007, but not with diabetic individuals
Kesse-Guyot E et al (2013) (35)	Based on repeated 24 h recalls (1994-1996): 0-9 point **MeDi** dichotomous score[4] and MSDPS[7]	Cohort Follow-up of the RCT, SU.VI.MAX study	N=3083; average age, 65.4 ± 4.6y at time of cognitive eval, 54% male	Cognitive **function:** 13 y later administered in 2007-2009: Cued recall for *episodic memory*; verbal and phonetic fluency for *Lexical-semantic memory*, *working memory*-forward and backward digit span task; *mental fle xibility*, Delis-Kaplan trail-making test	13y	No association between MeDi or MSDPS and **cognitive function**, except for phonetic fluency score positive associations with MSDPS (p=0.05), and working memory positive association with MeDi (p=0.03)
Samieri C et al (2013) (43)	Based on FFQ in 1984, 1986, 190, 1994, 1998 using **alternate MeDi** (**aMeDi**) 0-9 points[8] For long-term **aMeDi**, averaged all before first cognitive assessment	Nurses Health Study cohort	N=14,337 for global score change, change in verbal memory; average age, 74.2 ± 2.3 y, all women	4 repeated cognitive tests over time or averaged; 1st is a telephone version of the MMSE, afterwards, these tests added: 10-word list & East Boston memory (delayed and immediate for both), backward digit span task, category fluency (CERAD)	6 y	Long-term accordance to aMeDi modestly associated with global cognitive **function** and verbal memory in later life but **not with cognitive change** after a 6 y period (p=0.84, p=0.70, respectively).
Samieri C et al (2013) (42)	Based on FFQ in 1998 using **aMeDi** 0-9 points[8]	Cognitive substudy of Women's Health study, a primary prevention 2 × 2 RCT of aspirin and vitamin E	N=6174, average age at first cognitive exam, 72.0 ±4.1y; 96% white; all women	Cognitive battery 5.6 y later by for first, a telephone assessment, then 2 more in person assessments, 2 y apart, *global cognitive function* or GCS (composite of z-scores of *verbal memory* (10-word list & East Boston memory (delayed and immediate for both), *language and executive function*, category fluency (CERAD)	4 y	No association between aMeDi with cognitive measures (p for score quintiles medians × time interaction, 0.26 for GCS, 0.40 for verbal memory; among components, higher monounsaturated-saturated ratios associated with more favorable cognitive trajectories, p=0.03.
Martinez-Lapiscina EH et al (2013) (55)	14-item score: 2 Medit groups: one given extra virgin olive oil (EVOO), 2nd mixed nuts (+Nuts) vs low-fat control	PREDIMED-NAVARRA Randomized Clinical trial: 2 Medit intervention vs lowfat	N=522 patients, age 74.6y at end, 44.6% male	2ndary outcomes: only one cognitive assessment at end of trial, none at baseline; MMSE, and Clock Drawing Test or CDT Also incident dementia, depression & MCI;	6.5y	Cognitive function: higher MMSE and CDT scores in EVOO vs control, p=0.005, p=0.001, respectively; also higher for +Nuts, p=0.015, p=0.048. After 6.5 y of trial, 18 & 19 cases of MCI in 2 Medit groups, 23 in low-fat group

*DASH=Dietary Approaches to Stop Hypertension; Medit= Mediterranean diet; FFQ=food frequency questionnaire; ENCORE=Exercise and Nutrition Interventions for Cardiovascular Health; RCT=Randomized Clinical trial; HR= hazard ratio; MMSE=Mini Mental State Examination; EPIC=European Prospective investigation into Cancer and Nutrition; ILDA=Greek words for elders and diet;, WHICAP=Washington Heights-Inwood Columbia Aging Project; NINCDS-ADRDA= National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; MCI=mild cognitive impairment; MCD =Mild cognitive disorder, CDR=Clinical Dementia Rating; PATH= Personality And Total Health through life study; CHAP= Chicago Health and Aging Project; WACS=Women's Antioxidant Cardiovascular Study; REGARDS=Reasons for Geographic and Racial Differences; MSDPS=Mediterranean Style Dietary Pattern Score; SU.VI.MAX = Supplementation with Vitamins and Mineral Antioxidants; WHI= Women's Health Initiative; CERAD=Consortium to Establish a Registry for Alzheimer's Disease; DSM-IIIR=Diagnostic and Statistical Manual of Mental Disorders

[1] DASH score reported by Folsom and colleagues (19)

[2] DASH score further modified by Epstein et al (20)

[3] DASH score reported by Fung et al (21)

[4] Based on the MeDi score by Trichopoulou et al (22)

[5] Based on the Godin leisure time exercise questionnaire (56)

[6] Based on 0-55 MedDiet ordinal score of Panagiotakos and coworkers (24)

[7] Based on the Mediterranean Style Dietary Pattern Score by Rumawas et al (57)

[8] Based on the alternate MeDi based on that of Trichopoulou et al (22), but modified by Fung et al (23)