THEMED REVIEW

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The Role of Dietary and Lifestyle Factors in Maintaining Cognitive Health

Abstract: *Concern over loss of cognitive function, including descent into Alzheimer's disease or dementia, grips a growing percentage of men and women worldwide as the global population ages. Many studies, though not all, suggest that maintaining cognitive health, as well as slowing and even preventing cognitive decline, dementia, and Alzheimer's disease, can be achieved by consuming healthy diets over a long enough period of time. This appears to be the case even for those who initiated dietary changes later in life, as evidenced by an intervention study assessing consumption of a healthy diet among those who were >50 years of age. All such diets share the common traits of being rich in fruits, vegetables, whole grains, and fish or seafood, while also being low in red meat and sweets. A Mediterranean-style diet shares these characteristics and has been associated with an estimated 40% lower risk of cognitive impairment, including mild cognitive impairment, dementia, and Alzheimer's disease in prospective studies, in addition to being associated with both a 65% lower risk of mild cognitive impairment and improved cognitive performance in a notable randomized controlled trial.*

Keywords: cognition; cognitive health; cognitive function; mild cognitive impairment; dementia; Alzheimer's disease; diet; dietary patterns; Mediterranean diet

> The MD [Mediterranean-style diet] has been studied by many more investigators than any other healthy dietary pattern.

The role of diet in maintaining cognitive health is currently of considerable research interest. Dietary patterns are often studied, rather than focusing on isolated nutrients or specific foods, for several reasons. People consume complete diets, rather than foods in isolation, thus in order to make dietary recommendations easier to understand and follow, elucidating beneficial dietary patterns is of great benefit.[1] Also, when examining multiple components of a diet simultaneously, food and nutrient interactions can be revealed together for their harm or benefit.[2,3] Dietary patterns with varying definitions including a Mediterranean-style diet (MD),[4-23] the DASH (Dietary Approaches to Stop Hypertension) diet,[13,24] and the French national nutrition and health program[25] have been evaluated for their association with several measures of cognitive health.

Cognitive Health

Cognitive health can be studied in several different ways, for example, by assessing (*a*) the rate of cognitive decline,[16-18,20,26,27] (*b*) the maintenance of cognitive performance,* or (*c*) by studying the incidence of cognitive diseases such as dementia, mild cognitive impairment (MCI) or Alzheimer's disease (AD).[4-10] Dementia is characterized by a debilitating loss of memory, cognitive

*Refs 11-15, 19, 21, 24, 25, 28, 29.

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function, and the ability to live independently.[30,31] It currently affects approximately 47 million people worldwide, with prevalence expected to more than triple by 2050.[31] With the escalating cost of dementia reaching 1% of the world's gross domestic product in 2010, and as the prevalence of dementia increases over time concomitant with the rise in the aging population globally, the economic, societal, and personal burdens of disease become increasingly evident.[31]

Dementia is the umbrella under which MCI and AD fall.[30,31] MCI is considered the first step along the path away from normal cognitive aging.[32] Those with MCI fare worse on tests of cognitive health than those who are aging normally, but still perform better than those with AD.[32] AD is typified by neuronal damage and a loss of connectivity between neurons in the brain, leading to an impairment of proper brain function.[33] Among some diagnosed with AD, amyloid plaques (deposits of amyloid protein in the spaces between neurons in the brain) and tau tangles (tau protein deposited inside neurons of the brain that clump together forming neurofibrillary tangles causing the microtubule network within the neuron to collapse) develop.[33] Early-onset AD is typically seen among those with genetic predisposition and can occur among those in their late 30s to those in their 50s. Late-onset AD, which accounts for the majority of cases, may be multifactorial in its causes, with genetics, environment, and lifestyle all potentially playing a role.[33] Tests of memory and language can be used to assess cognitive status, for example, the Mini-Mental State Examination; alternatively, the *DSM-IV* criteria for dementia diagnosis can been used.[34,35] Because AD develops over a long period of time, lacking AD diagnosis may not mean that brain pathology indicative of AD does not exist. In postmortem brain examinations from the Rush Memory and Aging Project, more than half of the cohort exhibited neuropathology fulfilling the criteria for AD; however, not all of those who fulfilled the criteria were diagnosed with dementia (as defined by clinical exam and the Mini-Mental State Exam); in fact, 43.9% of those without dementia were found to have AD brain pathology.[36,37] And studies have shown that even among those who are largely asymptomatic, beta-amyloid accumulation, indicative of AD, leads to reduced brain cell connectivity and is a signal of preclinical AD.[33] Therefore, it is plausible that undetected disease progression may affect many lifestyle factors, which means that reverse causation may be an important limitation when conducting epidemiologic studies.

Dietary Patterns

Several healthy dietary patterns have been associated with improved cognitive function, and these dietary patterns have several components in common: a high consumption of fruits, vegetables, and whole grains along with a low consumption of red meat and sweets (Table 1). Interestingly, several dietary components that have been shown to be beneficial for cognitive health are a part of many of these dietary patterns. Antioxidants, polyphenols, long-chain omega-3 fatty acids, and polyunsaturated and monounsaturated fats have been shown to be beneficial, while saturated fats, omega-6 fatty acids, and refined carbohydrates and sugars have been shown to be detrimental.[15,21]

The MD[4-23] has been studied by many more investigators than any other healthy dietary pattern. The MD, the definition of which may vary between studies and populations, is typically defined as being higher in fruits, vegetables, legumes, nuts, fish and seafood while also being lower in dairy products and meat, particularly processed meats, and moderate alcohol (typically red wine) consumption[20] and has been associated with beneficial* or null† results in several cross-sectional studies, cohort studies, and randomized controlled trials (see Table 2).

Other dietary patterns that have been shown to be beneficial include the DASH diet,[13,24] and those that follow national dietary guidelines (such as those of the United States and France).[25,26] The main components of these dietary patterns are outlined in Table 1. The Dietary Approached to Stop Hypertension (DASH) diet is a low-fat diet, high in fruits and vegetables, whole grains, poultry, fish, and nuts, with little red meat, sugar sweetened beverages or desserts.[38] The most recently developed dietary pattern associated with cognitive health is the Mediterranean-Dietary Approaches to Stop Hypertension Diet Intervention for Neurodegenerative Delay (MIND) diet. Developed at Rush University, the MIND diet was studied in their Memory and Aging Project cohort. This diet, a combination of the MD and DASH diets, is characterized by brain healthy and unhealthy food groups as determined through literature review.[39] The brain healthy food groups include vegetables, particularly green leafy vegetables, berries, whole grains, nuts, beans, seafood, poultry, and wine, with olive oil used as the main cooking oil. The unhealthy food groups include red meat, cheese, butter and margarine (solid), sweets and pastries, and fast food (particularly fried foods).[39]

The French National Nutrition and Health Program was established to improve health and created dietary guidelines promoting a high consumption of fruits and vegetables, whole grains, fats from vegetable rather than animal sources, seafood and water, moderate dairy, bread, potatoes, cereals, legumes, poultry, eggs, and alcohol intake, and a low consumption of soda, sweets, and salt.[25] Healthy and traditional French dietary patterns were also studied in the same cohort. The healthy dietary pattern was high in fiber, calcium, beta-carotene, folic acid, vitamin E, vitamin C, and omega-3 and omega-6 long-chain polyunsaturated fats while also being low in alcohol and saturated fat, while the traditional pattern had similar components but was higher in total fat, including polyunsaturated and monounsaturated

*Refs 4-6, 8, 10, 11, 13, 16, 18-21, 23.
†Refs 7, 9, 12, 14, 15, 17, 22.

Table 1.

Components of Main Dietary Patterns Associated With Cognitive Health.

	Mediterranean Diet	DASH Diet	MIND Diet	Healthy Eating Index	French National Nutrition and Health Program
High consumption	Fruits	Fruits	Berries	Fruits	Fruits
	Vegetables	Vegetables	Vegetables (green leafy vegetables)	Vegetables	Vegetables
	Legumes	Whole grains	Whole grains	Whole grains	Whole grains
	Nuts	Poultry	Poultry	Low-fat dairy	Vegetable fats
	Fish	Fish	Seafood	Fish	Seafood
	Seafood	Nuts	Nuts	Lean meats	Water
			Beans		
			Wine		
			Olive oil		
Moderate consumption	Alcohol				Dairy
					Bread
					Potatoes
					Cereals
					Legumes
					Poultry
					Eggs
					Alcohol
Low consumption	Dairy products	Fats (low-fat diet)	Red meat		Soda
	Meat (processed meats)	Red meat	Fast food (fried foods)		Sweets
		Sugar sweetened beverages	Cheese		Salt
		Desserts	Butter		
			Margarine (solid)		
			Sweets		
			Pastries		

fat, alcohol, and protein, while being lower in carbohydrates and calcium.[28]

Other diets that have been studied include the Traditional Taiwanese diet, characterized by a high intakes of fruits, vegetables, and legumes, and a moderate consumption of meat, poultry, eggs, and fish, as well as a healthy dietary pattern in this same population, characterized by a higher consumption of fruits and vegetables, fish, and legumes, and a lower

Table 2.

Dietary Patterns and Cognitive Health: Overview of the Association Between Dietary Patterns and Cognitive Health by Study Design.

Study Design	Dietary Pattern	Outcomes	Associations Found
Cohort study	Mediterranean	Cognitive impairment	7 beneficial[4-6,8,10,16,18,23]
	Mediterranean	Dementia	7 beneficial[4-6,8,10,16,18,23]
	Mediterranean	Alzheimer's disease	10 null[4,5,7-10,17,22,23]
	Mediterranean	Cognitive performance	3 beneficial[12,13] 7 null[11,14,15]
Cohort study	DASH	Cognitive performance	4 beneficial[13,24] 1 null[24]
	DASH	Alzheimer's disease	1 null[23]
Cohort study	French National Nutrition and Health Program	Cognitive performance	1 beneficial[25] 1 null[25]
Cohort study	Healthy and traditional dietary patterns	Cognitive performance	2 beneficial[28] 1 null[28]
	Healthy and traditional dietary patterns	Cognitive decline	3 null[16,27]
Cohort study	Canadian Healthy Eating Index	Cognitive performance	1 null[29]
Cohort study	Recommended food score	Cognitive decline	1 beneficial[26]
Cohort study	MIND diet	Cognitive decline	1 beneficial[39]
	MIND diet	Alzheimer's disease	1 beneficial[23]
Randomized controlled trial	Mediterranean	Cognitive performance	3 beneficial[19,21]
	Mediterranean	Cognitive impairment	1 beneficial[20] 1 null[20]

consumption of meat and eggs.[27] Finally, diet quality, as quantified by a recommended food score based on foods included in the American Dietary Guidelines has also been studied in relation to cognitive health and is defined by a higher consumption of fruits, vegetables, whole grains, low-fat dairy, fish, and lean meats.[26]

A Posteriori Dietary Patterns

In addition to the dietary patterns mentioned above, all of which were established prior to running statistical analyses and are based on typical or traditional dietary patterns (eg, the Mediterranean diet) or recommended diets (eg, the DASH diet), dietary patterns can also been developed using statistical methods. The dietary or biomarker data particular to each cohort being studied is used to develop unique dietary patterns associated with disease outcomes. These are known as a posteriori dietary patterns.

A posteriori dietary pattern can be developed using techniques including reduced rank regression, factor analysis, or cluster analysis.[1,40]

Using reduced rank regression to explain the most variability in levels of omega-3 and omega-6 polyunsaturated fatty acids, saturated and monounsaturated fatty acids, and vitamins E, B, and folate, Gu et al identified a dietary pattern characterized by higher amounts of fruits, vegetables (cruciferous, dark, and green leafy), tomatoes, fish, and nuts and lower amounts of meat (red and organ), butter, and high-fat dairy products. High adherence to this patterns was associated with a 38% lower risk of AD.[41] Ozawa et al determined a dietary pattern explaining the most variation in levels of saturated, monounsaturated, and polyunsaturated fatty acids, vitamin C, calcium, potassium, and magnesium.

This pattern was higher in vegetables, soybeans (and soybean products), dairy products, and algae, and lower in rice, and associated with a 34% lower risk of developing dementia and vascular dementia.[42]

A majority of studies have used principal components analysis (PCA), or factor analysis, to determine dietary patterns associated with cognitive health, where correlated food groups are grouped together.[43] For example, using PCA, foods (factors) were identified by Tomata et al that explained the greatest between-person variation in 39 foods consumed by cohort participants that were then used to create a dietary pattern score for each participant. They found that a Japanese dietary pattern, high in vegetables (green and yellow), seaweed, miso soup, rice, pickles, fish, and green tea, and low in coffee, beef, and pork, was associated with a 20% lower risk of developing dementia.[1,44] PCA was also used by Akbaraly et al to determine 2 dietary patterns: a "whole food" pattern associated with lower cognitive deficit and a "processed food" pattern associated with greater cognitive deficit.[45] The "whole food" pattern was high in leafy and cruciferous vegetables, fruits, tomatoes, fish, salad dressing, and legumes, while the "processed food" pattern was high in desserts, sweets, fried and processed foods, margarine, refined grains, and high-fat dairy.[45] Similarly, factor analysis has been used to determine that eating a "Western" dietary pattern (high in red and processed meat, refined carbohydrates, sugar and alcohol, not including wine) led to hastened cognitive decline, while a "prudent" dietary pattern (high in vegetables, fruit, whole grains, fish, low-fat dairy, poultry, legumes, rice, pasta, and water with the use of oils for cooking and dressings) slowed cognitive decline, and those with a high adherence to a "Western" diet tempered the cognitive effects of such eating by nearly 50% when also following the "prudent" dietary pattern closely.[46] Pearson et al found that a diet high in green leafy vegetables, tomatoes, salad dressing, and alcohol (wine and liquor) was associated with better cognitive performance and a lower odds of incident cognitive impairment, while a Southern diet, high in fried foods, eggs, organ and processed meats, and sugar sweetened beverages was associated with poorer cognitive performance and an increased odds of incident cognitive impairment.[47] Consuming a diet high in vegetables and fruits (particularly tomatoes, dark green and leafy green vegetables, and cruciferous vegetables), as well as a diet high in coffee, nuts, and whole grains, both developed using factor analysis, has been shown to reduce the risk of cognitive impairment.[48] Factor analysis was also used by Qin et al to determine a "wheat-based diverse" dietary pattern, similar in some aspects to an adapted Mediterranean diet, high in fruits, nuts, fish, dairy, and grains, while also being low in saturated fats for cooking, that was associated with slowed cognitive decline in a Chinese cohort among adults 65 years of age and older.[18]

Cluster analysis, where cohort participants are grouped into homogenous clusters,[43] has been used to determine a healthy dietary pattern, associated with improved cognitive health, which was high in fruits, vegetables, cereals and bread, and dairy products, and among men this pattern was high in alcohol intake.[49] Similarly, in a Korean cohort, Kim et al used cluster analysis and revealed that a diet high in fruits (and fruit juices), multigrain rice, dairy products, and fish was associated with a lower risk of cognitive impairment when compared to a diet higher in white rice, noodles, and coffee (the latter was used as the reference group).[43]

Overall, these studies lend further support to the claim that consuming a diet rich in fruits and vegetables may help preserve cognitive health.

Studies of Cognitive Health and Dietary Patterns

Randomized Clinical Trials

The use of randomized controlled trials (RCTs) can provide some of the strongest evidence for causation in the diet-disease relationship. RCTs, by design, eliminate the confounding that can skew results in cohort studies (see Table 3).

RCTs of the MD have provided strong evidence that adhering to this diet can help maintain cognitive health. The Spanish PREDIMED RCT has shown that higher consumption of a MD, supplemented daily with either olive oil or nuts over 6.5 years, among those who are on average 74 years of age, can increase cognitive performance and decrease the risk of MCI by up to 65% when compared to a low-fat diet (mean difference in Mini-Mental State Exam score for MD + extra virgin olive oil [EVOO]: +0.62, 95% confidence interval [CI]: 0.18, 1.05, *P*-value = 0.005, MD + Nuts: +0.57, 95% CI: 0.11, 1.03, *P*-value = 0.015; incidence of MCI for MD + EVOO: odds ratio [OR] = 0.341, 95% CI: 0.120, 0.969, *P*-value = 0.044, MD + Nuts: OR = 0.563, 95% CI: 0.222, 1.427, *P*-value 0.226).[19]

Evidence for an association between the MIND diet and both cognitive decline and brain neurodegeneration will be examined in a recently funded phase III, 3-year, RCT in the United States. Among 600 individuals, 65 years of age and older, those without cognitive impairment will be studied. The participants are not currently eating healthy diets and all are overweight.[50]

Prospective Studies

Prospective studies have investigated several endpoints related to cognitive health, and while the aforementioned RCT has provided the strongest evidence for the importance of consuming a healthy diet for the maintenance of cognitive health, it is important to note that proper adjustment for the correct confounders can lead investigators using observational data to obtain results comparable to those found in RCTs.[51]

Table 3.

Dietary Patterns and Cognitive Health: A Review of the Literature.

Author and Year	Cohort	Study Size	Study Period (Mean Years)	Age at Baseline (Mean Years)	Exposure	Outcome	Effect Estimate
Scarmeas et al (2006)	WHICAP	2258	4	≥65	Mediterranean diet score (tertiles)	Incident Alzheimer's disease	Continuous HR = 0.91 (95% CI: 0.83, 0.98), *P*-value 0.015 T1 (low) = Ref T2 HR = 0.85 (95% CI: 0.63, 1.16) T3 HR = 0.60 (95% CI: 0.42, 0.87), *P*-value trend = 0.007
Scarmeas et al (2009)	WHICAP	1393	4.5	≥65	Mediterranean diet score (tertiles)	Incident mild cognitive impairment and Alzheimer's disease	Incident MCI: Continuous HR = 0.92 (95% CI: 0.85, 0.99), *P*-value 0.04 T1 (low) = Ref, *P*-value trend 0.05 T2 HR = 0.83 (95% CI: 0.62, 1.12), *P*-value 0.24 T3 HR = 0.72 (95% CI: 0.52, 1.00), *P*-value 0.05 Incident AD: Continuous HR = 0.89 (95% CI: 0.78, 1.02), *P*-value 0.09 T1 (low) = Ref, *P*-value trend 0.02 T2 HR = 0.55 (95% CI: 0.34, 0.90), *P*-value 0.01 T3 HR = 0.52 (95% CI: 0.30, 0.92), *P*-value 0.02
Scarmeas et al (2009)	WHICAP	1880	5.4	≥65	Mediterranean diet score (tertiles) and physical activity	Incident Alzheimer's disease	T1 (low) = Ref, *P*-value trend 0.008 T2 HR = 0.98 (95% CI: 0.72, 1.33), *P*-value 0.88 T3 HR = 0.60 (95% CI: 0.42, 0.87), *P*-value 0.007 Low diet score + low PA HR = Ref High diet score + low PA HR = 0.77 (95% CI: 0.53, 1.13), *P*-value 0.18 Low diet score + high PA HR = 0.81 (95% CI: 0.57, 1.16), *P*-value 0.26 High diet score + high PA HR = 0.65 (95% CI: 0.44, 0.96), *P*-value 0.03 *P*-value trend: 0.03

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Table 3. (continued)

Author and Year	Cohort	Study Size	Study Period (Mean Years)	Age at Baseline (Mean Years)	Exposure	Outcome	Effect Estimate
Feart et al (2009)	Three City	1410	5	75.9	Mediterranean diet score (tertiles)	Incident Alzheimer's disease	T1 (low) = Ref T2 HR = 0.99 (95% CI: 0.51, 1.94) T3 HR = 0.86 (95% CI: 0.39, 1.88), *P*-value trend: 0.72
Feart et al (2009)	Three City	1410	5	75.9	Mediterranean diet score (tertiles)	Incident dementia	T1 (low) = Ref T2 HR = 1.11 (95% CI: 0.63, 1.94) T3 HR = 1.12 (95% CI: 0.60, 2.10), *P*-value trend: 0.72
Gu et al (2010)	WHICAP	1219	4	≥65	Mediterranean diet score (tertiles)	Incident Alzheimer's disease	Continuous HR = 0.87 (95% CI: 0.78, 0.97), *P*-value 0.01 T1 (low) = Ref T2 HR = 0.56 (95% CI: 0.36, 0.86), *P*-value 0.01 T3 HR = 0.68 (95% CI: 0.42, 1.08), *P*-value 0.10 *P*-value trend: 0.06
Morris et al (2015)	Rush Memory and Aging Project	923	4.5	58-98 (mean ~81 years)	Mediterranean, MIND, and DASH diets	Incident Alzheimer's disease	Mediterranean diet: T1 (low) = Ref T2 HR = 0.81 (95% CI: 0.53, 1.21) T3 HR = 0.49 (95% CI: 0.29, 0.85), *P*-value trend: 0.01 MIND diet: T1 (low) = Ref T2 HR = 0.64 (95% CI: 0.42, 0.97) T3 HR = 0.48 (95% CI: 0.29, 0.79), *P*-value trend:0.003 DASH diet: T1 (low) = Ref T2 HR = 0.98 (0.64, 1.46) T3 HR = 0.60 (0.37, 0.96), *P*-value trend: 0.06
Roberts et al (2010)	Rochester Epi. Project	1141	2.2 (median)	70-89	Mediterranean diet score (tertiles)	Incident MCI or dementia	T1 (low) = Ref T2 HR = 0.79 (95% CI: 0.51, 1.21), *P*-value: 0.28 T3 HR = 0.75 (95% CI: 0.46, 1.21), *P*-value: 0.24

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Table 3. (continued)

Author and Year	Cohort	Study Size	Study Period (Mean Years)	Age at Baseline (Mean Years)	Exposure	Outcome	Effect Estimate
Tsivgoulis et al (2013)	REGARDS	17 478	4	64.4	Mediterranean diet score (dichotomous)	Incident cognitive impairment	Low adherence = Ref High OR = 0.87 (95% CI: 0.76, 1.00), *P*-value 0.0460 Nondiabetics: High OR = 0.81 (95% CI: 0.70, 0.94), *P*-value 0.0066 Diabetics: High OR = 1.27 (95% CI: 0.95, 1.71), *P*-value 0.1063
Samieri et al (2013)	NHS	16,058	13	74.3	Alternate Mediterranean diet (quintiles)	Cognitive status, global cognition, and verbal memory	Cognitive status (mean difference in score): Q1 = Ref, *P*-value trend: 0.004 Q2 = 0.02 (95% CI: −0.02, 0.07), Q3 = 0.03 (95% CI: −0.01, 0.08) Q4 = 0.06 (95% CI: 0.02, 0.11), Q5 = 0.06 (95% CI: 0.01, 0.11) Global cognitive function (mean difference in score): Q1 = Ref, *P*-value trend: 0.002 Q2 = 0.02 (95% CI: −0.01, 0.05), Q3 = 0.03 (95% CI: −0.00, 0.06) Q4 = 0.04 (95% CI: 0.01, 0.07), Q5 = 0.05 (95% CI: 0.01, 0.08) Verbal memory (mean difference in score): Q1 = Ref, *P*-value trend <0.001 Q2 = 0.01 (95% CI: −0.03, 0.04), Q3 = 0.03 (95% CI: −0.01, 0.06) Q4 = 0.04 (95% CI: 0.01, 0.08), Q5 = 0.06 (95% CI: 0.03, 0.10)

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Table 3. (continued)

Author and Year	Cohort	Study Size	Study Period (Mean Years)	Age at Baseline (Mean Years)	Exposure	Outcome	Effect Estimate
Samieri et al (2013)	WHS	6174	5.6	71.9	Alternate Mediterranean diet (quintiles)	Global cognition and verbal memory	Global cognitive function (mean difference in score): Q1 = Ref, *P*-value trend 0.63 Q2 = 0.03 (95% CI: −0.02, 0.08), Q3 = 0.02 (95% CI: −0.03, 0.06) Q4 = 0.02 (95% CI: −0.03, 0.07), Q5 = 0.02 (95% CI: −0.03, 0.06) Verbal memory (mean difference in score): Q1 = Ref, *P*-value trend 0.44 Q2 = 0.04 (95% CI: −0.02, 0.09), Q3 = 0.01 (95% CI: −0.04, 0.06) Q4 = 0.03 (95% CI: −0.02, 0.08), Q5 = 0.03 (95% CI: −0.02, 0.07)
Wengreen et al (2013)	Cache County Memory	3580	10.6	≥65	Mediterranean diet score (quintiles)	Cognitive performance (difference −10.6 years)	Q1 = Ref Q2 = 0.68 ±- 0.29, Q3 = 0.62 ± 0.29 Q4 = 0.83 ± 0.29, Q5 = 0.94 ± 0.29 *P*-value trend: 0.022, *P*-value Q5 vs Q1: 0.0014
Kesse et al (2013)	SU.VI.MAX	3083	13	52	Mediterranean diet and Mediterranean style dietary pattern score (tertiles)	Cognitive performance (mean difference over 13 years)	Mediterranean diet adherence: T1 = −0.18 (−1.09, 0.73) T2 = 0.58 (−0.21, 1.37) T3 (high) = Ref, *P*-value trend = 0.27 Mediterranean style dietary pattern adherence: T1 = −0.41 (−1.23, 0.40) T2 = −0.17 (−0.96, 0.63) T3 (high) = Ref, *P*-value trend 0.12

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Table 3. (continued)

Author and Year	Cohort	Study Size	Study Period (Mean Years)	Age at Baseline (Mean Years)	Exposure	Outcome	Effect Estimate
Psaltopoulou et al (2008)	EPIC-Greece	732	6.4-12.6	≥60	Mediterranean diet score	Cognitive function	Mean MMSE score: β (per unit change in MeDi score) = 0.05 (95% CI: –0.09, 0.19), *P*-value = 0.485
Cherubin et al (2012)	PATH Through Life	1528	4	60-64	Mediterranean diet score	Cognitive impairment or dementia	Mild cognitive impairment: OR = 1.41 (95% CI: 0.95, 2.10), *P*-value 0.087 Clinical dementia rating: OR = 1.18 (95% CI: 0.88, 1.57), *P*-value 0.266 Any mild cognitive disorder: OR = 1.20 (95% CI: 0.98, 1.47), *P*-value 0.079
Tangney et al (2013)	CHAP	3790	7.6	75.4	Mediterranean diet score	Cognitive decline	Global cognitive score: MedDiet score β = 0.0014, *P*-value 0.0004 MedDiet wine score β = 0.0014, *P*-value 0.0009
Vercambre et al (2012)	WACS	2504	5.4	≥65	Mediterranean diet score (tertiles)	Cognitive decline	Difference in annual rate of global cognitive decline: T1 (low) = Ref T2 = 0.01 (95% CI: –0.01, 0.02) T3 = 0.00 (95% CI: –0.02, 0.01), *P*-value trend: 0.88
Qin et al (2015)	CHNS	1650	5.3	≥55	Adapted Mediterranean diet score (tertiles)	Cognitive decline/ change	Difference in mean rate of change in cognitive function: T1 β = Ref T2 β = 0.018 (–0.019, 0.056) T3 β = 0.042 (0.001, 0.027)

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Table 3. (continued)

Author and Year	Cohort	Study Size	Study Period (Mean Years)	Age at Baseline (Mean Years)	Exposure	Outcome	Effect Estimate
Martínez-Lapiscina et al (2013)	PREDIMED (RCT)	522	6.5	74.6	Mediterranean diet + nuts or EVOO	Cognitive performance	Mean difference in MMSE score: Low fat = Ref MedDiet + EVOO: +0.62 (95% CI: 0.18, 1.05), *P*-value 0.005 MedDiet + Nuts: +0.57 (95% CI: 0.11, 1.03), *P*-value 0.015 Mean difference in CDT score: Low fat = Ref MedDiet + EVOO: +0.51 (95% CI: 0.20, 0.82), *P*-value 0.001 MedDiet + Nuts: +0.33 (95% CI: 0.003, 0.67), *P*-value 0.048
Valls-Pedret et al (2015)	PREDIMED (RCT)	447	4.1 (median)	66.9	Mediterranean diet + nuts or EVOO	Cognitive performance change	Change in cognitive composites score: Low-fat = –0.38 (–0.57, –0.18) MedDiet + EVOO OR = 0.05 (–0.11, 0.21), *P*-value 0.005 MedDiet + Nuts OR = –0.05 (–0.27, 0.18), *P*-value <0.05
Martínez-Lapiscina et al (2013)	PREDIMED (RCT)	285	6.5	74.1	Mediterranean diet + nuts or EVOO	Cognitive status (mild cognitive impairment)	Low-fat = Ref MedDiet + EVOO OR = 0.341 (95% CI: 0.120, 0.969), *P*-value 0.044 MedDiet + Nuts OR = 0.563 (95% CI: 0.222, 1.427), *P*-value 0.226

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Table 3. (continued)

Author and Year	Cohort	Study Size	Study Period (Mean Years)	Age at Baseline (Mean Years)	Exposure	Outcome	Effect Estimate
Kesse et al (2011)	SU.VI.MAX	2135	13	52.6 men; 51.6 women	French National Nutrition and Health Program (quartiles)	Cognitive performance	Verbal Memory: β = 0.41 (95% CI: 0.17, 0.64) *P*-value <.05 Q1 = 48.81 ± 0.82, Q2 = 49.59 ± 0.83 Q3 = 50.48 ± 0.83, Q4 = 50.43 ± 0.85, *P*-value trend = 0.003 Executive functioning: β = –0.09 (95% CI: –0.33, 0.14), *P*-value >.05 Q1 = 49.46 ± 0.84, Q2 = 49.66 ± 0.85 Q3 = 49.90 ± 0.85, Q4 = 49.04 ± 0.86, *P*-value trend = 0.60
Kesse et al (2012)	SU.VI.MAX	3054	13	52.1	Healthy and traditional dietary patterns (quartiles)	Cognitive performance (mean test score)	Global cognitive function: Q1 = 48.9 ± 0.7, Q2 = 49.4 ± 0.7 Q3 = 50.8 ± 0.7, Q4 = 50.1 ± 0.7, *P*-value trend: 0.001 Verbal memory: Q1 = 49.1 ± 0.7, Q2 = 49.5 ± 0.7 Q3 = 50.6 ± 0.7, Q4 = 50.3 ± 0.7, *P*-value trend: 0.01 Executive functioning: Q1 = 49.3 ± 0.7, Q2 = 49.6 ± 0.7 Q3 = 50.6 ± 0.7, Q4 = 49.8 ± 0.7, *P*-value trend 0.13
Shatenstein et al (2012)	NuAge	1488	3	74.1 men; 74.4 women	Canadian Healthy Eating Index	Cognitive performance	β = –0.0008 ± 0.00403, *P*-value = 0.852
Wengreen et al (2013)	Cache County Memory	3580	10.6	≥65	DASH diet score (quintiles)	Cognitive performance (difference over 10.6 years)	Q1 = Ref Q2 = 0.35 ± 0.29, Q3 = 0.68 ± 0.29 Q4 = 0.96 ± 0.29, Q5 = 0.97 ± 0.29, *P*-value trend: 0.0001, *P*-value Q5 vs Q1: 0.0009

(continued)

Table 3. (continued)

Author and Year	Cohort	Study Size	Study Period (Mean Years)	Age at Baseline (Mean Years)	Exposure	Outcome	Effect Estimate
Smith et al (2010)	ENCORE (RCT)	124	4 months	52.3	DASH diet score	Cognitive function	Psychomotor speed test: DASH *P*-value 0.36, DASH + WM *P*-value 0.023 Executive function-memory-learning tests: DASH: no significant *P*-values DASH + WM *P*-values: 0.026, 0.045, and 0.024
Wengreen et al (2013)	Cache County Memory	3580	~11	≥65	Recommended food score (quartiles)	Cognitive decline (decrease in score over 11 years)	Q1 = −5.15 ± 0.69 Least Varied Diet Q2 = −3.98 ± 1.0, Q3 = −4.91 ± 1.08 Q4 = −3.41 ± 0.79 Most Varied Diet *P*-value Q5 vs Q1: 0.013
Tangney et al (2013)	CHAP	3790	7.6	75.4	Healthy eating index score	Cognitive decline	Global cognitive score: β = 0.0002, *P*-value = 0.214
Tsai et al (2015)	TLSA	235 78	8	73	Traditional diet Healthy diet	Cognitive decline	Traditional diet: OR = 1.37 (0.85, 2.21), *P*-value 0.20 Healthy diet: OR = 1.13 (0.53, 2.41), *P*-value 0.75
Morris et al (2015)	Rush Memory and Aging Project	960	4.7	81.4	MIND diet	Cognitive decline	Global cognitive score: β = 0.0092, *P*-value <0.0001

Abbreviations: HR, hazard ratio; CI, confidence interval; MCI, mild cognitive impairment; PA, physical activity; OR, odds ratio; MMSE, Mini-Mental State Examination; RCT, randomized controlled trial.

We will begin by reviewing the associations found between diet and incident MCI, AD, and dementia. Scarmeas et al found, in an elderly cohort of participants ≥65 years of age, that over 4.5 years those people in the highest tertile of MD consumption had the lowest risk of MCI compared to those in the lowest tertile (hazard ratio [HR] = 0.72, 95% CI: 0.52, 1.00, *P*-value = 0.05).[5] And, among those who developed MCI the risk of progression to AD was 45% lower among those with moderate adherence (HR = 0.55, 95% CI: 0.34, 0.90, *P*-value = 0.01) and 48% lower among those with the highest adherence to the MD (HR = 0.52, 95% CI: 0.30, 0.92, *P*-value = 0.02).[5] In addition, Tsivgoulis et al found that over 4 years those who consumed a MD had lower odds of incident cognitive impairment (high OR = 0.87, 95% CI: 0.76, 1.00, *P*-value = 0.0460) among participants who were, on average, 64 years of age at baseline.[10] However, Roberts et al did not find a significant relationship between incidence of MCI and the MD (highest tertile vs lowest HR = 0.75, 95% CI: 0.46, 1.21, *P*-value = 0.24) in their shorter study of 2.2 years among relatively older participants 70-89 years of age.[9]

With the incidence of AD as the study endpoint, Morris et al recently found that those in the highest tertile of MD consumption had a significantly lower incidence of AD than those in the lowest tertile (HR = 0.46, 95% CI = 0.26, 0.79) over 4.5 years among participants between 58 and 98 years of age (average age was approximately 81 years).[23] They also found that those in the highest 2 tertiles of MIND diet consumption had a lower rate of AD than those in the lowest tertile (tertile 3 vs 1 HR = 0.47, 95% CI = 0.26, 0.75; tertile 2 vs 1 HR = 0.65, 95% CI = 0.44, 0.98).[23] Scarmeas et al found, in 3 separate studies where participants were ≥65 years of age, that those people in the highest tertile of MD consumption had a lower risk of AD compared to those in the lowest tertile (HR = 0.60, 95% CI: 0.42, 0.87, *P*-value trend = 0.008;[6] HR = 0.52, 95% CI: 0.30, 0.92, *P*-value 0.02;[5] HR = 0.60, 95% CI: 0.42, 0.87, *P*-value = 0.007[4]) over a period of up to 5.4 years. However, Gu et al found in the same cohort that there was no significant benefit to consuming such a diet over 4 years among those in the highest tertile compare to those in the lowest tertile of diet consumption (HR = 0.68, 95% CI: 0.42, 1.08, *P*-value = 0.10),[8] but that those in the second tertile with a moderate consumption of MD had a 44% lower risk of developing AD (HR = 0.56, 95% CI: 0.36, 0.86, *P*-value = 0.01); it may be that adjustment for intermediate inflammatory biomarkers (hsCRP, insulin and adiponectin) attenuated the relationship between AD and the MD in this analysis (the trend of increasing risk of AD along increasing tertiles of MD was significant when there was no adjustment for biomarkers, *P*-value = 0.04).[8] Feart et al similarly found null results among participants who were 75.9 years of age, on average, over 5 years when comparing those in the highest tertile of MD consumption to those in the lowest (HR = 0.86, 95% CI: 0.39, 1.88, *P*-value = 0.71).[7]

These data suggest that the MD may be beneficial in preventing the incidence of MCI and/or AD, and while some studies have found null results, there have not any been studies suggesting any harm in consuming a MD.

With incident dementia as the study endpoint, which encompasses many more specific diseases including AD, the relationship with the MD is less clear, with studies finding no significant benefit for those consuming the highest amounts of these foods when compared to those consuming the least over 5 years among those who were 75.9 years on average (HR = 1.12, 95% CI: 0.60, 2.10, *P*-value = 0.72),[7] and over 2.2 years among those 70 to 89 years of age (HR = 0.75, 95% CI: 0.46, 1.21, *P*-value = 0.24).[9] These were, however, studies of relatively short duration among participants who were relatively old, thus, significant results might not have been found as a longer period of cumulative MD consumption earlier in life may be required to alter dementia outcomes. However, a recent meta-analysis found, when considering dementia, AD, and MCI together in their analysis, that consumption of the MD was associated with a significantly decreased risk of these outcomes (HR = 0.69, 95% CI: 0.57, 0.84).[52]

Results on dietary patterns and the rate of cognitive decline, as a separate and distinct endpoint, have been mixed. When considering cognitive decline and increased dietary variety as a measure of diet health, those who consumed the most varied diet, as based on the recommended food score following the American Dietary Guidelines, had test scores that did not decrease as quickly as those with the least varied diet over 11 years (Q1 [lease varied diet] = −5.15 ± 0.69, Q4 [most varied diet] = −3.41 ± 0.79, *P*-value Q4 vs Q1 = 0.0013) among those who were ≥65 years of age.[26] While improved diet quality may be associated with slowed cognitive decline, this finding has not been replicated in other studies of healthy dietary patterns, aside from the MD. Tangney et al found that those with a higher adherence to a Healthy Eating Index, based on the American Dietary Guidelines, did not have a significantly slower rate of cognitive decline, among those 75.4 years of age on average, over a 7.6-year period (for each 1-point increase in the Health Eating Index score, with a score range from 0 to 55 and the cognitive score was higher by β = 0.0002, *P*-value = 0.214).[16] Similarly, Tsai et al found no association between cognitive decline and (*a*) a traditional Taiwanese diet (OR = 1.37, 95% CI = 0.85, 2.21, *P*-value 0.20) or (*b*) a healthy dietary pattern (OR = 1.13, 95% CI = 0.53, 2.41, *P*-value 0.75) over 8 years among those who were 73 years of age on average.[27]

Taking a closer look at cognitive decline and the MD, Tangney et al found, among participants who were an average of 75.4 years of age, that those with a higher adherence to the MD had a slower rate of cognitive decline over a 7.6-year period, where cognitive function was assessed every 3 years (for each 1-point increase in MD score, with a score range from 0 to 55, the cognitive score was higher by β = 0.0014, *P*-value = 0.0004).[16] Similarly, Qin et al found that those in the highest tertile of MD consumption had a slower rate of

cognitive decline over an average of 5.3 years when compared to those in the lowest tertile among participants who were ≥55 years of age (difference in mean standardized unit change per year β = 0.042, 95% CI: 0.001, 0.027).[18] These differences in cognitive score are modest and other studies have not found a significant association between the MD and a slowed rate of cognitive decline; however, it is notable that the null studies presented below were conducted over shorter periods of time that may not adequately capture the cumulative effect of the MD on cognitive health.

Vercambre et al found no significant difference in the annual rate of cognitive decline over 5 years among women ≥65 years of age when comparing those in the highest tertile of MD to those in the lowest (rate of change in global cognitive score = 0.00, 95% CI: −0.02, 0.01, *P*-value = 0.88).[17] Additionally, Cherubin et al found no association between the MD and cognitive change over 4 years among participants 60 to 64 years of age (MCI: OR = 1.41, 95% CI: 0.95, 2.10, *P*-value 0.087; Clinical dementia rating: OR = 1.18, 95% CI: 0.88, 1.57, *P*-value 0.266; Any mild cognitive disorder: OR = 1.20, 95% CI: 0.98, 1.47, *P*-value 0.079).[22] Thus, it appears that consumption of a MD may have only a moderate impact on preventing cognitive decline over the shorter periods of time used in these studies, but such limited effects should not be extrapolated to infer that there is little benefit to consuming a MD over one's lifetime as benefits have been shown in studies of longer duration.

Interestingly, Morris et al found over approximately 4.5 years that among participants who were 81.4 years of age, on average, that those with a higher adherence to the MIND diet experienced slowed cognitive decline (β = 0.0092; *P*-value <.0001), effectively meaning that they were the equivalent of 7.5 years younger than study participants with a low adherence to the MIND diet.[39]

Results were also mixed when cognitive performance was measured as an endpoint, where measures of cognitive function were studied (instead of the rate of cognitive decline) to determine if those consuming a healthy diet were better at maintaining their cognitive health. Study period duration may again have a bearing on the results, as can be seen in the analyses of 2 separate cohorts of women by Samieri et al. In the first study, conducted in the Nurses' Health Study over an average of 13 years among women who were on average 74.3 years of age, they found that those consuming the highest quintile of an Alternate MD which uniquely emphasizes the importance of increased monounsaturated fat consumption along with lower saturated fat consumption, in addition to giving importance to the staples of a typically defined MD that is rich in fruits, vegetables, whole grains, nuts, and fish[12] had higher scores for global cognitive function (mean difference in *Z*-score Q5 vs Q1 = 0.05, 95% CI: 0.01, 0.08, *P*-value trend along quintiles = 0.002), verbal memory (mean difference in *Z*-score Q5 vs Q1 = 0.06, 95% CI: 0.03, 0.10, *P*-value trend <.001), and cognitive status, as measured by the Telephone Interview of Cognitive Status, adapted from the Mini-Mental State Exam (mean difference in *Z*-score Q5 vs Q1 = 0.06, 95% CI: 0.01, 0.11, *P*-value trend = 0.004) when compared to those in the lowest quintile. In the second study, conducted in the Women's Health Initiative over 5.6 years among women who were an average of 71.9 years of age, they found no significant associations between the Alternate MD and cognitive function (global cognitive function mean difference in *Z*-score Q5 vs Q1 = 0.02, 95% CI: −0.03, 0.06, *P*-value trend along quintiles = 0.63, verbal memory mean difference in *Z*-score Q5 vs Q1 = 0.03, 95% CI: −0.02, 0.07, *P*-value trend = 0.44).[11] We see from these 2 studies that significant results were found when the study period was longer, perhaps meaning that cumulative diet over a longer period of time may be needed to effect cognitive health. This is further evidenced by a study from Wengreen et al who found that those in the highest quintile of MD consumption scored significantly higher on a test of cognitive function than those in the lowest quintile over an 11-year period among participants ≥65 years of age (difference in Modified Mini-Mental State Exam score, Q5 vs Q1 = 0.94 ± 0.29, *P*-value = 0.001).[13]

Two additional studies found no significant relationship between the MD and cognitive function, even though they were conducted over more than a decade. Kesse-Guyot et al investigated the association between a MD computed in a fashion similar to the above studies as well as a MD pattern including the same dietary components, but weighting the dietary pattern score by the quantities of foods eaten; for example, if 50% of the foods eaten by a participant are included in the MD score, their total diet score is weighted by 0.5. Over a 13-year study period they found no significant association between either MD and most tests of cognitive function, including a composite cognitive score among participants who were an average of 52 years of age. And Psaltopoulou also found no significant difference in cognitive function with increasing adherence to a MD over a 6- to 13-year period among those who were ≥60 years of age (β = 0.05, 95% CI: −0.09, 0.19, *P*-value = 0.485).[15] However, Kesse-Guyot et al did find that those consuming a MD had higher scores of short-term and working memory (difference in backward digit span score comparing low to high dietary adherence = −0.64, 95% CI: −1.60, 0.32, and medium to high = 0.03, 95% CI: −0.81, 0.86, *P*-value trend = 0.03) and those consuming the weighted MD had higher scores of lexical-semantic memory, where the test involves listing all known words beginning with the letter "p" in 2 minutes (difference in phonemic fluency score comparing low to high dietary adherence = −1.00, 95% CI: −1.85, −0.15, and medium to high = −0.61, 95% CI: −1.45, 0.22, *P*-value trend = 0.05).[14]

Higher consumption of the DASH diet has been associated with improved cognitive performance over an 11-year period among those who were ≥65 years of age (difference in Modified Mini-Mental State Exam score, Q5 vs Q1 =

0.97 ± 0.29, *P*-value = 0.0000).[13] Another study found that both the DASH diet alone or the DASH diet plus 30 minutes of aerobic exercise 3 times per week and weight loss counseling lead to improved cognitive test results after only 4 months of intervention among those who were an average of 52.3 years of age (Psychomotor speed test: DASH *P*-value = 0.036, DASH + exercise/counseling *P*-value = 0.023, Executive function-memory-learning tests: DASH + exercise/counseling *P*-value <.05).[24]

Higher adherence to the French National Nutrition and Health Program dietary pattern was associated with higher scores on tests of verbal memory (β = 0.41, 95% CI: 0.17, 0.64, *P*-value < 0.05, *P*-value trend across continuous quartiles = 0.003) but not with tests of executive function (β = −0.09, 95% CI: −0.33, 0.14, *P*-value > 0.05, *P*-value trend across continuous quartiles = 0.60) over 13 years among men and women who were on average 52 years of age.[25] Healthy and traditional French dietary patterns were also studied in the same cohort. They found that those with a higher adherence to a healthy diet had higher test scores of global cognitive function and verbal memory, but no significant difference in executive functioning (global cognitive function: Q1 [low dietary adherence] = 48.9 ± 0.7, Q4 [high dietary adherence] = 50.1 ± 0.7, *P*-value trend = 0.001; verbal memory: Q1 = 49.1 ± 0.7, Q4 = 50.3 ± 0.7, *P*-value trend = 0.01; executive functioning: Q1 = 49.3 ± 0.7, Q4 = 49.8 ± 0.7, *P*-value trend = 0.13) and there was no significant difference in test scores comparing those in the highest to lowest quartiles of adherence to the traditional French diet (global cognitive function: *P*-value trend = 0.68; verbal memory: *P*-value trend = 0.32; executive functioning: *P*-value trend = 0.60).[28] Similarly, the Canadian Eating Index, based on the Canadian dietary guidelines, has also been studied, but no significant association was found with cognitive performance over 3 years among those who were an average of 74 years of age (β = −0.00008 ± 0.000403, *P*-value = 0.852).[29]

Meta-Analyses

Meta-analysis can be a useful way to summarize the literature, when between-study heterogeneity is not pronounced and when methodology is otherwise consistent. The meta-analysis by Psaltopoulou included 8 studies of mixed design (including Scarmeas,[4,5] Roberts,[9] and Feart,[7] discussed above) and found that high adherence to a MD was associated with a lower risk of cognitive impairment, including MCI, dementia and AD, by 40% (RR = 0.60, 95% CI = 0.43, 0.83).[15] When they considered only longitudinal cohort studies, apart from cross-sectional or case-control studies, this relationship remained (RR = 0.72, 95% CI = 0.58, 0.88),[15] which lends greater support to their conclusion that consuming a MD may prevent cognitive impairment, as reverse causation is potentially minimized by the cohort study design when dietary exposures during the early stages of disease development are not included in the analysis. While this meta-analysis provides evidence of the benefits of consuming a MD, meta-analyses are often limited by the studies they can include—for example, diet needs to be similarly treated in order to make coherent comparisons. In this meta-analysis only studies where diet was treated as a categorical variable, where high or moderate adherence to a MD was compared to low adherence; this, by definition, excludes studies where diet was treated as a continuous variable and, as we have already noted, the findings of these studies were mixed. Furthermore, each study was performed in different populations (some older, some younger) and included different confounders, such as age, sex, or total calories, which might have led to either the attenuation or amplification of some results; the decision to include only certain studies on MD may have affected the overall results of the meta-analysis, leading to the significant protective effect found here. However, a more recent systematic review of prospective studies of the MD and cognition similarly concluded that such a diet was beneficial in regard to all measures of cognitive health.[53]

Overall, evidence from RCTs and cohort studies support the assertion that the consumption of a healthy dietary pattern can help in maintaining cognitive health. Although some studies found no significant results, only beneficial results were found otherwise. As such, consumption of these diets over time appears to be either beneficial or neutral (at worst) in maintaining cognitive health, particularly if certain MD staples are consumed over an extended period of time. For example, 2 studies found that consuming more whole grains, a main component of the MD that includes foods such as dark bread, oatmeal, and brown rice, tested higher on measures of cognitive health.[11,13]

Conclusion

Consumption of healthy dietary patterns, including a variety of fruits and vegetables, whole grains, and fish/seafood while also avoiding red and processed meats and sweets may go far in maintaining cognitive health. An intervention study and RCT have shown this to be the case even among those initiating such dietary changes in older age. Of a variety of healthy dietary patterns, the MD has been heavily studied and has been shown to be beneficial in maintaining cognitive health and in preventing cognitive decline, including MCI and AD. It also appears that consumption of a health dietary pattern over a long period of time, perhaps for more than approximately 5 years, may be required to obtain the full benefits of such diets on cognition.

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Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.

Informed Consent

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Trial Registration

Not applicable, because this article does not contain any clinical trials. AJLM

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