

Mediterranean Diet and Cognitive Outcomes

Epidemiological Evidence Suggestive, Randomized Trials Needed

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Coronary heart disease, a leading cause of death and disability worldwide, is largely preventable. Unhealthy lifestyles, particularly bad dietary habits, contribute nearly 80% of population-attributable risk.¹ Unfortunately, the same cannot be said about Alzheimer disease (AD) and related types of dementia—devastating diseases with incidence rates that are increasing exponentially due to increasing longevity.² In spite of much epidemiological, clinical, and experimental research, there are still no effective strategies to prevent AD, delay its onset, or, least of all, cure the disease. As in many age-related conditions, oxidative stress leading to chronic inflammation plays a major role in age-related neurodegeneration, attendant cognitive decline, and progression to dementia.³ Oxidative stress is counteracted by antioxidants, which are integral components of vegetable foods. For this reason, antioxidants and improved nutrition have long been considered potential strategies to delay cognitive decline and prevent progression to AD.⁴⁻⁶ As has been comprehensively reviewed,⁵ epidemiological data suggest a protective role on cognitive decline and dementia of n-3 fatty acids, B-vitamins, and antioxidant nutrients such as vitamins E and C, carotenoids, and flavonoids, a subtype of polyphenols. However, clinical trials of supplementation with these nutrients in either healthy or cognitively impaired older persons have generally failed to uncover a clear benefit.⁷

Where the “single nutrient” approach has failed, perhaps the “whole diet” might help. The current paradigm in nutritional epidemiology is to analyze diet patterns instead of isolated foods or nutrients because patterns can capture the cumulative effects of the overall diet.^{8,9} This approach has proven valuable in observational studies of age-related cognitive decline and AD.¹⁰ Among dietary patterns, the Mediterranean diet (MeDiet) might be the healthiest. A recent meta-analysis of 18 prospective cohort studies showed that conformity to the MeDiet confers consistent protection against cardiovascular diseases, neurodegenerative disorders, cancer, and overall mortality.¹¹ In randomized clinical trials, Mediterranean-style diets have provided beneficial effects on cardiometabolic markers such as body weight, blood pressure, lipids, insulin resistance, and inflammation.¹²

The MeDiet is identified as the traditional dietary pattern found in Crete, Greece, Italy, and Spain in the early 1960s. The diet is characterized by high intake of cereals, vegetables, fruits, nuts, and olive oil; moderate intake of fish and alcohol (mostly wine); and low intake of dairy products, red meat and meat products, and sweets.¹³ The MeDiet fits the concept of a healthful eating pattern with overall nutrient adequacy.¹⁴ Given that the MeDiet is plant-based and antioxidant-rich, there are fair grounds to believe that long-term adherence might protect against cognitive decline and AD.¹⁰ Indeed, although not without inconsistencies, there is accumulating evidence for the effectiveness of the MeDiet in

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slowing cognitive decline and reducing AD risk.¹⁵ Two papers in this issue of *Epidemiology* make significant contributions to the topic while feeding the controversy.^{16,17}

Lourida et al¹⁶ perform a systematic review of published studies reporting on exposure to the MeDiet and cognitive outcomes. They find 12 scientifically sound papers—11 observational studies and a small, short-term clinical trial. Seven studies were conducted in the United States, three in Australia, and two in Mediterranean countries (France and Greece). Most studies included cognitively healthy men and women sampled from community dwelling older adults starting at age 60 years. The studies built MeDiet scores based on information collected at baseline in food frequency questionnaires, performed cognitive evaluations prospectively, had follow-up for at least 2 years, and duly adjusted data for known confounders including sex, education, apolipoprotein E genotype, and vascular risk factors. The study outcomes fell into three broad categories: cognitive function (8 studies), mild cognitive impairment (4 studies), and dementia, usually AD (7 studies). No study specifically assessed vascular dementia. Although there were contradictory findings and marked heterogeneity among studies, results in general suggest that increasing conformity with the MeDiet has no effect on mild cognitive impairment, but slows cognitive decline and reduces the risk of developing AD. The benefit on AD, however, stems exclusively from five studies reporting on two related cohorts from the Washington Heights-Inwood Columbia Aging Project.

Separate analyses for certain food groups in two of the studies included in the review found that high vegetable intake and high ratios of dietary monounsaturated fatty acid (MUFA) to saturated fatty acid were associated with a lower risk of mild cognitive impairment, whereas moderate wine consumption was associated with reduced rates of cognitive decline. This analysis provides a moderately optimistic message on the MeDiet as a useful tool against cognitive decline and dementia but acknowledges the many limitations of the studies: dietary intake assessed only once before cognitive testing (not accounting for long-term dietary intake), variation in MeDiet scores, diversity of neuropsychological instruments used (some limited to the Mini-Mental State Examination), and the unavoidable possibility of residual confounding in observational studies, which does not allow causal inference. For instance, there is the general perception that people with high MeDiet scores have healthier lifestyles than those with lesser adherence, and this can confuse the results even after multiple adjustments in risk analyses. Last but not least, the comparability of MeDiets across different countries reveals substantial differences in consumption of two key foods with strong antioxidant properties: virgin olive oil is used abundantly and wine consumed regularly in Mediterranean countries, but not in the United States.

The paper by Samieri et al¹⁷ reports on a substudy of the US Women's Health Study examining the association

of adherence to the MeDiet with cognitive function and its changes over 4 years in a large sample of elderly women. The results show no association of the overall MeDiet with cognitive scores or their temporal changes. Authors also tested the association of increasing intake of individual components of the MeDiet on cognitive performance. Interestingly, increasing intake of whole grains and fatty fish and an increasing ratio of monounsaturated to saturated fatty acids were independently associated with better averaged cognition at older ages after mutual adjustment for the other food components. However, women in the younger age group (below the median of 71 years) in the top quintile of the monounsaturated to saturated fatty acid ratio paradoxically had worse initial global cognition, a finding for which the authors do not find an explanation. The fatty acid ratio was small and only increased marginally across quintiles of intake (range, 0.9–1.3), indicating almost similar sources of saturated and MUFAs in the diet, which might have confused the results. The reported use of olive oil—a staple in the MeDiet—was marginal as usual in non-Mediterranean countries. The overall negative results of this large and well-done observational study contribute to the controversy on the effects of the MeDiet on age-related cognitive deterioration.

Attesting to the increasing interest in possible effects of the MeDiet on cognitive function, three new observational studies^{18–20} have been published since submission of the systematic review.¹⁶ Among 2,504 women at high cardiovascular risk aged ≥ 65 years who participated in the US Women's Antioxidant Cardiovascular Study, adherence to the MeDiet was unrelated to cognitive change after follow-up for 5.4 years.¹⁸ A substudy from the Nurses' Health Study, also conducted in the United States, investigated 16,058 women aged ≥ 70 years and found that long-term adherence to the MeDiet was not associated with cognitive decline after 6 years, although diet was related to both average global cognitive function and verbal memory.¹⁹ In a study from France, Kesse-Guyot et al²⁰ showed that midlife adherence to the MeDiet in 3,083 subjects was not associated with global cognitive performance assessed 13 years later. A major limitation of this study is that cognitive testing was not performed at baseline, thus precluding assessment of changes over time. These studies generally suggest no association of the MeDiet with cognitive performance, but other recent publications do support a beneficial effect. For instance, Valls-Pedret et al²¹ cross-sectionally assessed 447 Spanish subjects at high cardiovascular risk with a battery of neuropsychological tests and found that higher consumption of some polyphenol-rich foods characteristic of the MeDiet (namely wine, virgin olive oil, and walnuts) were independently related to better cognitive outcomes. In that study, urinary polyphenol excretion (a biomarker of intake) was also linearly associated with better scores in immediate verbal memory.

Two recent magnetic resonance imaging investigations from the North Manhattan Study, which follows a multiethnic cohort for stroke incidence and risk factors, suggest a strong beneficial impact of the MedDiet on both subclinical brain infarcts²² and white matter hyperintensities,²³ a marker of small vessel disease. These results are important because they put the focus on an alternate mechanism through which the MeDiet may promote brain health, namely protection against cerebrovascular disease. It is increasingly recognized that AD and microvascular brain damage often overlap in the neuropathology of cognitive impairment in later life.²⁴ Given that higher adherence to the MeDiet is associated with a reduced burden of cardiometabolic risk factors,¹⁴ MeDiet is likely to prevent vascular disease of the brain as well. At least two large prospective studies, one from the U.S.²⁵ and another from Greece²⁶, have suggested that the MeDiet prevents stroke.²⁵ The Three-City study from France also showed that use of olive oil, a key component of the MeDiet, was associated with a reduced risk of stroke.²⁷

There is only one possible conclusion after reviewing the epidemiological literature on the MeDiet and age-related cognitive deterioration, AD, and stroke: we are in dire need of randomized clinical trials! Although not primarily focused on neurodegenerative disorders, one such study, the PREvención con DIeta MEDiterránea (PREDIMED) trial, has been published recently.²⁸ The PREDIMED study is a primary prevention nutrition intervention trial conducted in 7,447 older subjects at high cardiovascular risk living in Spain. MeDiets supplemented with extra-virgin olive oil or nuts implemented for nearly 5 years reduced the incidence of cardiovascular diseases by 30%, compared with a low-fat, control diet. Risk of stroke was reduced by 34% by the MeDiet with olive oil and by 49% by the MeDiet with nuts.²⁷ The effect of MeDiets on incidence of neurodegenerative disease (a secondary outcome of the PREDIMED trial) should be known in the near future. Also, a subgroup of cognitively healthy PREDIMED participants has been prospectively investigated with a battery of neuropsychological tests; results should be available soon. Data from PREDIMED might eventually confirm or dispel the notion that the MeDiet provides optimal food for the brain. In the meantime, there is sufficient evidence to recommend the MeDiet to anybody who wishes to age in good health while enjoying their food.

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