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Nutrition and risk of dementia: overview and methodological issues

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Abstract

After little more than two decades of research on nutrition and dementia, there is strong evidence for preventive effects of vitamin E, B vitamins, and n-3 fatty acids, and deleterious effects of saturated fat, on dementia. Among specific foods with evidence of neuroprotection are green leafy vegetables and other vegetables, berries, and seafood. A number of studies have examined dietary patterns, particularly the Mediterranean and DASH (Dietary Approaches to Stop Hypertension) diets; neither of these diets is tailored to the specific foods and nutrients that have been identified as neuroprotective. A new diet, called MIND (Mediterranean–DASH Intervention for Neurodegenerative Delay), incorporates many elements of the Mediterranean and DASH diets but with modifications that reflect the best evidence for brain neuroprotection. The evidence in support of the relation of various nutrients and the Mediterranean diet to dementia has been inconsistent. The seeming inconsistencies may be explained by inattention to nutrient/food intake levels in the interpretation of study findings and trial design. This includes a shifting metric among studies for scoring adherence to the Mediterranean diet. Future studies should pay particular attention to levels of intake in the design and analyses of nutritional studies.

Keywords

diet patterns; dementia; Alzheimer’s disease; cognitive decline

Introduction

More than two decades of research on nutritional risk factors for dementia has yielded promising but not yet definitive findings of the foods and nutrients to include or avoid in one’s diet to prevent dementia. Here, I briefly summarize the scientific evidence to date on the relations of nutrients, foods, and diet patterns to dementia, followed by important methodological issues that impede the advancement of the science in this area.

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Conflicts of interest

The author declares no conflicts of interest.

Nutrients and the brain

Epidemiological and animal studies have provided a firm basis on which to consider the neuroprotective effects of individual nutrients, such as vitamin E, B vitamins, and the n-3 fatty acid docosahexaenoic acid (22:6).[1] These effects are also supported by the literature on the relation of food to the risk of dementia, with positive associations observed for vegetables (especially green leafy vegetables, which are good sources of folate, vitamin E, and carotenoids), seafood (a source of n-3 fatty acids), and berries (a source of polyphenols).[1] More limited data are available on the neuroprotective benefits of monounsaturated fat, carotenoids, polyphenols, and vitamin D. Diets high in saturated and trans fats have been shown to increase cognitive decline and the risk of developing dementia,[2] and deleterious effects have been suggested for excessive intakes of iron,[3] copper (in conjunction with high saturated-fat diets),[4] and synthetic folate or folic acid, among individuals with low vitamin B12 status.[5–7]

Nutrients and other dietary components are required for normal physiological functioning of the brain and are essential for neuronal protection against cell injury and oxidative stress.[8] The brain is an organ with high metabolic activity and a high rate of nutrient turnover, and nourishment of the brain occurs through a myriad of nutrient-specific transport systems and physiologic mechanisms that serve to replace the constant turnover of nutrients.[9] Many dietary components cannot be synthesized in humans de novo and so must be consumed through external sources. The blood–brain barrier allows passage of nutrients through various passive and selective transport systems.[9]

Diet-pattern studies on dementia

Dietary patterns in relation to disease has been a focus of the field of dementia in recent years. This useful approach takes into account the fact that foods and nutrients are biologically interactive and act in concert rather than as solitary physiological agents. Also, public health recommendations can be communicated in a more meaningful way by describing food groups to include or avoid in one’s diet rather the nutrient composition of individual foods, which are less well-known by the lay public. However, studies of dietary patterns have shown inconsistent results and further study is required to establish a diet that is specific to dementia prevention. Faster decline in cognitive abilities has been observed with diet patterns that are consistent with a Westernized diet,[10,11] but the findings for prudent diet patterns are inconsistent.[10,11] No associations have been observed for cognitive decline with higher scores on the Healthy Eating Index that is based on the U.S. Department of Agriculture (USDA) dietary guidelines[12] or for incident dementia with higher scores on the World Health Organization (WHO)-recommended diet[13] or a low-carbohydrate diet pattern.[13]

Most of the epidemiological studies of dietary patterns have investigated the Mediterranean diet, and only four [12,14–16] of the 10 informative studies on this diet [12,14,16–22] have found clear protective effects against cognitive decline or dementia: the Washington Heights–Inwood Columbia Aging Project (WHICAP),[14] the Chicago Health and Aging Project (CHAP),[12] the Memory and Aging Project (MAP),[23] and Reasons for Geographic and Racial Differences in Stroke (REGARDS).[16] Several of the studies that did not observe

dietary effects on cognitive decline did find associations with overall cognitive level.[17,19,21] However, these results should not be interpreted as supportive evidence for dietary protection against cognitive decline, because overall cognitive level in these statistical models largely represents level of attained cognitive ability or peak intelligence rather than changes in ability associated with neurodegeneration. The factors that play into individuals' neurocognitive development to peak intelligence may or may not be the same as those that cause neurodegeneration.

Significant support for the effects of the Mediterranean diet on the aging brain come from a sub-study of PREDIMED (Prevención con Dieta Mediterránea), a randomized diet-intervention trial conducted in Spain. The trial sub-study analyzed cognitive function as a secondary outcome and found that, compared with subjects on a low-fat control diet, those on the intervention diets (Mediterranean diet plus extra-virgin olive oil and the Mediterranean diet plus nuts) had higher scores on the Mini Mental State Examination (MMSE) and the Clock-Drawing Test (CDT) after 6.5 years.[24]

Another dietary pattern that has been examined in relation to cognitive decline is Dietary Approaches to Stop Hypertension (DASH), a diet that has been shown by randomized clinical trials in the U.S. to protect against many cardiovascular risk factors of dementia. Some of the protective effects of DASH include lower blood pressure[25] and blood low-density lipoprotein (LDL) cholesterol levels,[26–29] weight reduction,[30,31] reduced oxidative stress and inflammation,[28,32–34] improved insulin sensitivity,[29,35] and reduced incidence of diabetes.[36] One prospective epidemiological study that related the DASH diet score to cognitive decline observed an inverse association with higher DASH scores,[37] whereas in another study, higher DASH scores were associated with overall cognitive performance but not with cognitive decline.[21] In a small trial conducted in 137 overweight, sedentary, and hypertensive individuals, those randomized to the DASH diet intervention had better scores on tests of psychomotor speed after 4 months of treatment, compared with the participants randomized to the usual-diet control group.[38]

These trials provide promising evidence that adherence to an overall diet pattern can delay the progression to dementia. The DASH[39,40] and Mediterranean[41] diets have many similar components, such as emphasis on natural plant-based foods and limited consumption of red meat, but there are differences: the Mediterranean diet is a cultural diet that uniquely emphasizes daily intakes of olive oil (monounsaturated fat), fish, and potatoes, and moderate wine consumption, whereas DASH uniquely emphasizes dairy consumption and restricted intakes of sodium, commercial sweets, and saturated fat.

MIND diet pattern focused on brain health

Although both the cultural-based Mediterranean diet and the blood pressure–lowering DASH diet have demonstrated protective effects on cardiovascular conditions that can adversely affect the brain, neither diet is specific for the levels and types of foods shown to protect the brain against neurodegeneration. To address this gap in the literature, investigators at Rush University created a new diet, called the Mediterranean–DASH Intervention for Neurodegenerative Delay (MIND). MIND is a hybrid of the DASH and Mediterranean diets but with modifications that reflect the most compelling scientific

evidence on foods and nutrients that protect the brain.[15,23] The three diets have the same basic components, such as emphasis on natural plant-based foods and limited animal and high saturated-fat foods. However, the MIND diet uniquely specifies green leafy vegetables and berries as well as servings of food components that reflect the nutrition–dementia study findings. Among the different types of vegetables, the green leafy variety has been identified as having the strongest protective effects against cognitive decline.[42–44] In the Rush Memory and Aging Project, the rate of decline among those who consumed 1–2 servings per day was the equivalent of being 11 years younger in age compared with those who rarely or never consumed green leafy vegetables.[44] Green leafy vegetables are rich sources of lutein, folate, vitamin E, beta carotene, and polyphenols, nutrients that have been related to brain health. Prospective epidemiological studies of dementia do not observe a protective benefit from the consumption of fruits in general.[42,43,45,46] Dietary intakes of berries, however, have been demonstrated to improve memory and brain neuroprotection in multiple animal studies[47] and to slow cognitive decline in the Nurses' Health Study.[48] However, certain food components and servings of the DASH and Mediterranean diets are not included in the MIND diet because there is a lack of evidence for their importance for brain health, including high consumption of fruits (3–4 servings in both the DASH and Mediterranean),[41,49] dairy (DASH),[49] and potatoes and high fish consumption (2 servings/day and 6 meals/week, respectively, in the Mediterranean diet[41]). The MIND diet recommends one or more fish meals per week on the basis of prospective study evidence that this frequency is sufficient to lower dementia risk and that there is no additional benefit evident from higher servings per week.[50–52] The MIND diet does include many other food components of the DASH or Mediterranean diets, including extra-virgin olive oil, nuts, whole grains, and low-fat sources of protein, such as legumes and poultry.

The relative ability to predict cognitive decline and Alzheimer's disease (AD) risk on the basis of adherence to these diets was examined in the Rush Memory and Aging Project, a study of 960 Chicago community residents, aged 58–98 years, who were followed, on average, for 4.7 years. A MIND diet score was developed to quantify how closely participants' usual diets were in accordance with the 10 brain-healthy food groups (green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, seafood, poultry, olive oil, and wine) and with the five unhealthy food groups (red meats, butter and stick margarine, cheese, pastries and sweets, and fried/fast food). The participants who scored highest (top tertile) on the 15-component MIND diet score had a slower rate of cognitive decline that was approximately equivalent to being 7.5 years younger in age.[15] The MIND diet score was more predictive of cognitive decline than either of the Mediterranean[41] or DASH scores;[38] the standardized β coefficients of the estimated diet effects were 4.39 for MIND, 2.46 for the Mediterranean, and 2.60 for DASH.[15]

In the same study population, the Rush investigators examined the relations of these three dietary scores to incident AD in separate proportional hazards models adjusted for age, sex, education, APOE-ε4, participation in cognitively stimulating activities, physical activity, and total energy intake.[23] Compared with the rate of AD for participants in the lowest tertile of MIND scores, significantly lower rates of AD were observed for those in the second (hazard ratio (HR) = 0.65, 95% CI 0.44, 0.98) and highest tertiles (HR = 0.47, 95% CI 0.26, 0.76) of MIND diet scores.[23] In similar adjusted models, only the third tertiles of the DASH (HR =

0.61, 95% CI 0.38, 0.97) and Mediterranean (HR = 0.46, 95% CI 0.26, 0.79) diets were associated with lower AD rates.[23] These data suggest that even loosely adhering to the MIND diet may help to delay the occurrence of AD.

It is important that the findings of protective relations of the MIND diet score and cognitive decline are replicated in other cohort studies to confirm these associations. To establish a causal relation between diet and prevention of dementia, a diet intervention trial is required. Modifications to the MIND diet score would be expected as new foods and nutrients are identified from scientific advances in the field of nutrition and brain neurodegeneration, a field that is currently underdeveloped.

Methodological issues in the field of nutrition and dementia

Nutrient level

Consideration of the level of benefit from individual nutrients and/or foods is essential to the interpretation of findings across studies and the advancement of the science on nutrition and dementia. It is also important for designing clinical trials and for translating science into public health recommendations. Individual studies should present their data so that the estimates of effect are readily apparent across the range of nutrient exposure. Quintiles or other quantiles of nutrient exposure are an excellent format to convey the point and range of nutrient level at which there is an observed effect on a dementia outcome. Quintile analyses are also beneficial for investigating the relations of nutrients to disease outcomes that typically are not linear. A basic principle of nutrition is that there is a wide intermediate range of nutrient level that affords optimum physiological functioning; nutrient levels above or below this range may result in marginal functioning or even death.[53] To advance the science, it is important to determine what this optimum level of benefit is for each nutrient and food studied. It may be that the positive findings observed in one study are across a range of nutrient levels or food intake that is not well represented in another study that did not observe an association. In this case, the null study should not be interpreted as evidence that the nutrient is not related to the disease.

Dietary pattern scores

Related to the abovementioned methodological issue of nutrient/food intake level is an unfortunate practice among studies reporting on the Mediterranean diet, particularly with respect to the use of the MeDi score. The original MedDi score was developed in a Greek population in which the diets represented a range of adherence levels to the traditional Greek diet.[54,55] The Greek study participants were scored with a 1 or 0 for each of nine food components on the basis of whether they fell above or below the median intake of that Greek population. In the majority of studies that have investigated the effects of a Mediterranean diet pattern on dementia outcomes, this same scoring system for the MedDi was used, including the use of within-population median servings, even though the studies were with non-Mediterranean populations, primarily in the United States. For example, the median number of vegetable servings per day was four in the original Greek population and one had to consume four or more vegetable servings to receive a score of 1 for that food component,[54] in contrast with medians of less than 1, 1, or 2 daily servings of vegetables in

the various Westernized populations studied. This practice—of using the within-population median intake levels for scoring—resulted in a floating metric of intake across studies. The findings on the effect of the Mediterranean diet on dementia are inconsistent across studies and primarily null (Table 1), but because of the use of highly variable within-population medians to score adherence to dietary components, the results are not interpretable or comparable. Among the few studies that used the number of traditional Greek servings as the scoring metric, protective associations were observed for cognitive decline[12,15,37,56,57] and incident AD[23] with higher Mediterranean diet score.

Use of absolute levels of intake of foods and food categories has several advantages over relative cut-offs based on within-population levels of intake. First, findings across studies are more interpretable when they have a common metric. Second, important information about the optimum level of brain benefit for different dietary components becomes known when the data are analyzed and presented in terms of servings per day across different studies in different populations. And third, the scientific findings on optimum nutrition for brain health can be more easily translated to the general public when framed in terms of servings per day. One advantage of the MIND diet score is that the scoring for each dietary component is based on absolute as opposed to relative levels of intake. For many of the dietary components (e.g., seafood, vegetables), the intake levels required for optimum scores were based on direct scientific evidence for brain health. For other dietary components (e.g., whole grains, poultry), direct evidence for brain health is lacking and optimum scores are based on the cardiovascular disease literature.

Future research directions

The public health importance of diet for dementia prevention cannot be overstated. Effective diet intervention has the potential for population-wide effects with respect to delaying dementia onset, and there is very high public demand for dietary guidance for prevention of cognitive decline and AD. However, the state of the science is not at a point where sound dietary recommendations can be made. The best way moving forward to understanding how nutrition affects the brain and neurodegenerative diseases is through a comprehensive iterative approach using laboratory and animal models, epidemiological studies, and randomized trials, and at all levels: nutrients, biomarkers, food groups, and overall diets. Each type of study design and nutritional measurement provides a unique and important perspective, as well as its own limitations; thus, no single approach is sufficient alone to advance the science. Animal and laboratory studies provide information on the biological mechanisms linking nutrients to cell function and neurodegenerative disease but are limited by highly controlled laboratory conditions and by physiological systems that may not be applicable to the human condition. Epidemiological studies allow for cost-effective and comprehensive assessment of nutritional relations to brain health and disease at different dose and duration levels and as modified by other dietary components and behaviors, genotypes, or other personal characteristics, and by various health conditions and disease states. However, these observational studies are also susceptible to bias in measurements as well as to confounding by other disease factors that co-occur with dietary practices and nutrient status. There is much lower risk of these types of biases in the randomized trial design, but trials are so specific to patient type and to nutrient dose, composition, and

duration, that they are prone to low generalizability, or worse—to totally missing the relevant constituent parts of the relation. In particular, none of the U.S. vitamin supplement trials to date have considered participants' nutrient status in the trial design, and they have had null results for cognitive and other outcomes. However, participants of prevention trials are likely to already practice healthy lifestyle behaviors, and therefore, it is unlikely that many participants will have low nutrient status. Also, the vast majority of the trials allow multivitamin use during the intervention period. Thus, on the basis of the findings of epidemiological studies, in which the observed estimates of effect occur between low nutrient levels versus moderate to high levels obtained through food sources, these trials will most surely result in null findings. In order to advance the science on nutrition and dementia, future trials need to consider nutrient level in the trial inclusion criteria.

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Table 1

Prospective studies relating the Mediterranean diet to cognitive change and incident dementia

Study	*n*	Outcome	Result[b]	Score metric
MAP (Morris *et al.*[15,23])	960	Alzheimer's disease	↓	Greek
		global cognition	↓	
Greek (Trichopoulou *et al.*[57])	401	MMSE	↓	Greek
Swedes (Olsson *et al.*[13])	1138	dementia	–	within population
MAP (Tangney *et al.*[37])	960	global cognition	↓	Greek
HealthABC (Koyama *et al.*[56])	2326	3MS	↓	Greek
REGARDS (Tsivgoulis *et al.*[16])	17,478	SIS	↓	within population
WHS (Samieri *et al.*[19])	6174	global cognition	–	within population
Cache Co (Wengreen *et al.*[21])	3831	3MS	–	within population
WACS (Vercambre *et al.*[20])	2504	global cognition	–	within population
NHS (Samieri *et al.*[17])	16,058	global cognition	–	within population
CHAP (Tangney *et al.*[12])	3,790	global cognition	↓	Greek
Mayo Clinic (Roberts *et al.*[18])	1233	MCI	–	within population
3 Cities (Feart *et al.*[22])	1410	MMSE/3 tests[a]	±	within population
		dementia	–	
WHICAP (Scarmeas *et al.*[58])	1884	Alzheimer's disease	↓	within population

[a]The three tests are the Isaacs Set Test, Benton Visual Retention Test, and Free and Cued Selective Reminding Test.

[b]↓ = reduced cognitive decline or reduced incidence of dementia; – = no association.

Abbreviations: MAP, Memory and Aging Project; REGARDS, Reasons for Geographic and Racial Differences in Stroke; WHS, Women's Health Study; Cache Co, Cache County Study on Memory, Health, and Aging; WACS, Women's Antioxidant Cardiovascular Study; NHS, Nurses' Health Study; CHAP, Chicago Health and Aging Project; WHICAP, Washington Heights–Inwood Columbia Aging Project; MMSE, Mini Mental Status Examination; 3MS, Modified Mini Mental State Examination; SIS, Six-Item Screener; MCI, incident mild cognitive impairment.