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REVIEW ARTICLE

The Impact of Nutrition on Cognition in the Elderly

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Abstract The possibility that nutritional manipulation may protect against cognitive decline and dementia is an inviting prospect. However data supporting a beneficial effect of a particular dietary pattern is limited. Although studies have demonstrated a health benefit to dietary plans that are high in fiber, whole grains, natural sugar and fish while maintaining lower intake in meat dairy and poultry, the ability to identify the most salient factors of these diets have been unsuccessful. Several aspects of diet have been studied in detail and provided support for potential mechanisms for improving cognition. Clinical trials have explored these mechanisms through supplementation studies with minimal benefits being observed. Continuing work to hone the mechanisms and refine our knowledge of dietary benefits is described.

Keywords Alzheimer's Disease · Dementia Cognitive Impairment · Nutrition

Introduction

Alzheimer Disease and cognitive impairment increases with age and estimates are that nearly half of the population over the age of 85 have the diagnosis or have some evidence of cognitive loss. Considering the late age of onset it is reasonable to consider that environmental factors are at least as likely to contribute to the disease as genetic ones. Diet and ultimately nutrition are major environmental factors that may play a role in this late-onset disease. However it is difficult to study these factors because they are at least in part the result of circumstances of yet other environmental factors including climate, natural resources, culture and lifestyle. These variables may also have a direct impact on cognition and neurodegeneration. Nevertheless we have many analytic techniques that allow us to examine dietary factors with good precision. This review begins by examining quantitative and qualitative features of studies on diet to identify associations with dementia and cognitive loss. Research on the role of specific dietary elements, to the extent that they are measured via food and supplement intake inventories, is also reviewed with an emphasis on lipids and fats, alcohol and commonly occurring vitamins and minerals. Many assumptions about mechanisms are made based on findings from single studies and laboratory models are often invoked to support the mechanism. While this approach may strengthen the evidence for a proposed mechanism there is little support to insure that the model truly captures the dietary finding. Thus, here we will focus on the breadth of the evidence or lack of it, for dietary influence on cognition. While mechanisms may be mentioned, particularly when they are relevant to dietary and supplement intake, a comprehensively and critical review of this topic is beyond the scope of this article.

Special issue dedicated to John P. Blass.

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Dietary Intake Studies

Several observational studies have reported a positive association between cognitive function and total food intake [1, 2]. These cross-sectional studies suggest that among non-demented community dwelling elders' higher intake of most ''healthy'' food categories are associated with better cognition and the results have been observed in both European and Asian samples. These same studies identified some food categories with the opposite association (higher intake resulting in lower cognitive scores). In particular, refined sugars, high cholesterol and trans fats (e.g. eggs and certain oils) appear to be associated with poorer cognitive performance. Important demographic confounders of these associations such as age (higher age is associated with lower cognitive scores), gender (men may be more sensitive to cholesterol's effects on cognition) and socioeconomic status (more affluent and healthy lifestyle, better nutrition and cognition) as well as methodological confounds such as the arbitrary nature of food category, pattern and ratio of food types, and control for caloric intake make it difficult to evaluate these reports.

Attempts to standardize the definition of food categories, patterns of food intake and quality of food groups as well as the quantity are addressed by studies of the ''Mediterranean Diet'', which has been described as high in vegetables, legumes, fruits and nuts, cereal and fish, low intake of meat, poultry, and dairy products, and moderate intake of alcohol [3]. Scarmeas et al. evaluated the diet of over 2,000 non-demented community dwelling elders aged 65 and older living in a multi-ethnic community of Northern Manhattan. Detailed dietary information was collected with a validated questionnaire and the information was used to calculate the MeDi Score, which estimates adherence to a Mediterranean diet [4]. Over a 4-year follow-up period those with higher MeDi scores (i.e. greater adherence to a Mediterranean diet) had lower risk of dementia. In addition the risk of cognitive decline was also reduced with greater adherence. Of interest, those with greatest adherence were more likely to be non-smokers and of Hispanic ethnicity, though the beneficial effect of the diet was continued to be observed even after adjustment for these factors.

Several studies have examined specific elements of the Mediterranean diet, such as fish consumption. Morris et al. [5] followed 815 elderly individuals and found reduced risk of AD in those who ate 1 or more fish-meals per week. The same authors followed 3,718 individuals in the Chicago Health and Aging Project and reported that those who ate one or more fish-meals per week had a 10–13% reduced rate of decline [6]. Other studies have found similar results showing reduced risk of impaired cognitive function with greater fish consumption [7] and a negative correlation between fish consumption and cognitive decline and impairment in elderly men [8]. Proposed mechanisms for these effects often focus on fish oils, omega-3 fatty acids as a neuroprotective agent and this explored more below. However studies of this specific mechanism in the laboratory typically do not model other aspects of a high fish diet such as lowered intake of saturated fats in other forms of protein such as meat.

Dietary Fat Intake and Type of Fat intake

Several studies have investigated the association between dietary fat intake and dementia and cognitive decline, including studies of fat from fish and fish oils. The results from these studies have been mixed. Findings from one study suggested that high intake of saturated and trans-unsaturated fat are associated with increased risk of cognitive decline [9]. In the same study, it was also observed that higher intake of monounsaturated fat and a high ratio of polyunsaturated to saturated fat intake was associated with reduced cognitive decline. Similarly, Solfrizzi et al. [10, 11] reported results from the Italian Longitudinal Study on Aging indicating a significant positive correlation between monounsaturated and polyunsaturated fatty acid intake and scores on cognitive testing in non-demented elderly. Studying the same population, however, for incidence of Mild Cognitive Impairment (MCI), no association was found, after adjustments, between dietary fatty acid intake and incidence of MCI [12]. Whalley et al. recently reported the results from a study of 350 non-demented elderly, in which he examined the effect of fatty acids commonly found in fish oil, on cognition. The ratio of fatty acids (erythrocyte n-3 fatty acids to docosahexaenoic acid (DHA)) rather than the levels of individual types was most predictive of cognitive performance [13]. Not all studies were able to observe this association. Manzato et al. [14] used phospholipid fatty acid composition to determine the amount and types of fats present in the diet of an elderly sample. They report no correlation between type of fatty acid intake and measures of cognition. This finding, however, could also be attributed to a metabolic deficiency and not dietary intake. In the Rotterdam study of 5,395 subjects with normal cognition, followed for 6 years neither *high* intake of total, saturated, trans fat nor *low* intake of monounsaturated fatty acids, polyunsaturated fatty acids, n-6 polyunsat-

urated fatty acid, and n-3 polyunsaturated fatty acid had any association with the risk of dementia [15].

Alternative Protein Sources: Soy

Sixty seven percent of the world's consumption of protein comes from soy and 30% of the world's consumption of oil and fats are derived from soy [16]. These numbers provide rationale for dietary studies of soy intake. However there are few studies, which have reported an association between dietary intake of soy and cognitive outcomes or dementia. The nature of the evidence to support this association is often the perception of lower rates of dementia in populations with higher soy intake. However this perception is difficult to support since there are few studies of formal assessment of cognitive function and dementia in relationship to diet. One study of Japanese men in Hawaii found tofu consumption, a common soy food product, was associated with an increased risk of dementia [17]. This prospective epidemiologic study may indicate a degree of acculturation in immigrant populations and may not be readily generalizable. This result is in contrast to studies of soya in small trials, which demonstrate an association with better memory performance at least among young adults over short term exposure [18] and among postmenopausal women [19] Of note these latter studies reflect supplementation to western diets for very short intervals.

Much has been made of the fact that soy isoflavones are compounds similar to estrogen and they have been investigated for supplementation use in post-menopausal women. The similarity to estrogen is difficult to interpret since estrogenic effects on cognition, particularly in late life are not evident. Nevertheless the topic is fairly widely studied and some but not all studies have reported cognitive benefits from soy isoflavone supplementation. In one 6-month study of 78 post-menopausal women, results suggest improvement in cognitive function with supplementation, as almost one third of cognitive tests were significantly higher in the supplemented group [20]. In another trial of isoflavones, 56 post-menopausal women were randomized to placebo or isoflavone treatment. The treatment group improved significantly and did significantly better than the placebo group on measures of verbal memory and there was a trend of improvement on other cognitive measures with the treatment group [21]. In an additional soy supplementation trial, the cognitive testing revealed an improvement in frontal lobe function only in the treatment group [22]. Not all clinical trials of soy isoflavones have reported benefits, however. One such study of 202 healthy post-menopausal women reported no cognitive benefits from supplementation after 12 months of treatment [23]. There appear to be significant differences between observational studies and clinical trials of soy protein.

In total the beneficial effects of soy protein are less than clear. It is possible that cognitive benefits may come from its replacement of other protein sources with high trans fat or saturated fat content. However a consistent association between high soy diet and positive cognitive function is not supported by the breadth of available data.

Much has been made of the possibility that dietary isoflavones may be the critical ingredient in soy and possibly other foods. Flavonoids demonstrate effective anti-oxidant behavior in cellular models and have been associated with neuroprotection. Pharmaceutical agents have been developed and tested to determine if this mechanisms has a cognitive benefit inhuman studies (for a review see: Stein and Sano [24]. However, it is unclear that that dietary manipulation of this specific mechanism will have a clinical benefit.

Alcohol Intake

Moderate consumption of alcohol, and in particular red wine, a component of the Mediterranean diet, has been reported to have an impact on the risk of cognitive decline and dementia in observational studies of the elderly [25–28]. In a nested case control design of 1709 participants in the Copenhagen City Heart Study, after adjustment for confounding variables, an association was found between weekly and monthly wine intake and lower risk of dementia, but the association with total alcohol and other types of alcohol was not significant [28]. In another study of 11,102 women aged 70 years or older, with longitudinal data in the Nurses Health Study, moderate drinking (defined as drinking up to 14.9 g/day) was associated with better scores on a cognitive screen (i.e. TICS) than non-drinking. Moderate drinking was also associated with less cognitive decline on follow-up. The risk of cognitive decline among drinkers was reduced by about 15% (RR 0.85; 95% CI, 0.74–0.98) compared to non-drinkers. While each type of alcohol (beer wine and other spirits) had a significant effect on baseline scores, the type did not effect decline [25]. A longitudinal study of 2,273 subjects from the PAQUID study in Gironde and Dordogne, France also found cognitive benefits to alcohol use [27]. After an average follow-up

of 3 years, a significant inverse relationship was found between moderate (3–4 glasses/day) wine-drinking and incidence of dementia and Alzheimer's. After adjustments for demographic variables and baseline MMSE, for incident dementia the OR was 0.17, $P < 0.01$ and for incident Alzheimer Disease the OR was 0.25–0.28, $P < 0.03$. One limitation of these studies is the lack of consistency in the type of alcohol. The trend, however, appears to reveal some benefit with wine intake. Another limitation is a selection bias against individuals with higher intake that may lead to comorbidity, yielding selective elimination from the follow-up sample.

The polyphenol, resveratrol, which is found in the skin of red grapes (*Vitis vinifera*) may be the ingredient responsible for the ''red wine'' effect. In vitro, resveratrol has been found to have a protective effect against β-amyloid-induced oxidative stress suggesting a neuroprotective potential [29, 30].

Clinical trials of resveratrol are very limited. However, a small randomized clinical trial using resveratrol in combination with glucose and malate in patients with mild to moderate AD found significant benefit on the ADAS-cog and Mini Mental State Examination compared to a placebo control [31]. Of note, the doses of resveratrol far exceed those that might be achieved by the levels healthy drinking observed in the observational studies. While the clinical trial results are promising and worthy of confirmatory work, it is unclear that they actually model the benefit observed with red wine or other alcohol intake.

Fruits and Vegetables

Fruits and vegetables reflect distinct food groups in the Mediterranean diet and in the ADA food pyramid [32]. The benefits of these food groups are often thought to be through the anti-oxidant properties that foods in this class provide. Oxidative stress has been implicated in aging and Alzheimer's Disease and age related cognitive decline. Anti-oxidants can be found naturally in foods like fruits and vegetables or can be taken as supplements, like vitamins E and C. It is noteworthy that dietary doses are far below supplement doses and it is unclear if the action is the same at different dose levels. The benefits, however, at any dose level remain unclear. A study of 13,388 women found that total fruit intake was not associated with cognitive function, but total vegetable intake was significantly associated with reduced cognitive decline [33]. Others have recently reported on fruit and vegetable drink and the risk of dementia. Among a cohort of 1,589 elderly Asians living in the US (mean age at enrollment of 71.8 years with 54.4% women) followed for 6.3 years (SD: 2.6 years), there was a lower rate of Alzheimer Disease among those who reported frequent juice drinking (≥3/week) with a hazard ratio of 0.24 (95% CI, 0.09–0.61) and 0.84 (95% CI, 0.31–2.29) for those drinking juices 1 to 2 times per week (P for trend <0.01) compared to those who drank juice less than once per week. The juice effect has been attributed to polyphenol intake however juice drinkers tended to have lower intake of fat (either saturated or unsaturated fatty acids) and higher dietary intake of vitamin C, but not vitamin E or β-carotene [34]. These findings illustrate the idea that it may be the dietary pattern and a wide range of lifestyle issues that are responsible for observed benefit.

In observational studies, anti-oxidants Vitamin E and Vitamin C in the diet have been associated with at reduced risk of dementia [35–37]. Morris et al. specifically examined intake of vitamin E from foods in a large study of community dwelling elderly. The results from this study showed that dietary intake of vitamin E was associated with reduced risk of AD (RR 0.74; 95% CI, 0.62–0.88) and slower rate of cognitive change [37]. In a study of supplementation by elderly women, it was reported that long-term use of Vitamin E with Vitamin C was significantly associated with better performance on cognitive testing ($P = 0.03$) than those who had never used either supplement, while the finding with either supplement alone was not conclusive [38]. Not all studies have identified beneficial effects of dietary vitamins For example the study which identified a benefit from polyphenols in juices (described above) did not find a benefit for dietary anti-oxidant vitamin intake (i.e. Vitamin E, C or β-carotene).

When these anti-oxidant supplements were tested in clinical trials, the results were varied. Several primary prevention studies did not find any protective benefit for incidence of AD [39–43]. In one recent study of Vitamin E supplementation in a large sample size of patients with Mild Cognitive Impairment showed no significant difference between supplemented group and placebo group in the rate of progression to AD [39]. Two other studies of Vitamin E supplementation in patients with AD showed no improvement in cognitive testing with treatment [44].

Recently anti-oxidant intake from vitamin E supplementation has been associated with increased mortality [45] and cardiac morbidity [46]. These meta-analyses and large-scale clinical trials have primarily found these negative effects with doses greater than 400 IU, a dose, which far exceeds dietary levels. Thus

while the benefit is unclear, the dose limiting effect of dietary vitamins may have a built in protection.

In addition to anti-oxidant mechanisms, anti-inflammatory mechanisms have been invoked as contributing to the benefit of these food groups. Studies have demonstrated that dietary levels of fruit intake and of vitamin C are inversely related to levels of C reactive protein, an inflammatory marker [47], and vegetable intake is inversely associated with tissue plasminogen activator, a marker of endothelial dysfunction. However the support for the anti-inflammatory mechanisms having a benefit on cognition appears to be weakening with the breadth of failed clinical trials with an array of anti-inflammatory agents [48].

Other Dietary Vitamins: (B12, B6, B1, B2, Niacin (B3) and Folate (B9))

Several vitamins that are obtained through diet have been studied. B vitamins can be found in leafy green vegetables, liver, turkey, tuna, fortified cereals, nuts, and some fruits. Several studies have reported an association between B vitamin levels in blood and cognitive decline and dementia [49–63]. In some studies that examine the specific B-vitamins from serum and blood count in subjects (no record of method as dietary or supplementation), folate (B9), which can be found in leafy green vegetables, has been found to have an inverse association with cognitive decline and dementia [49–51, 53–51, 56–51, 60, 61, 63]. It is important to recognize that while serum levels can be effected by diet they can also be affected by other factors, including environmental, metabolic and genetic.

One study found the opposite effect for folate using dietary inventories, with high intake associated with greater cognitive decline. These results were reported from a bi-racial community cohort dwelling in the US (N = 3,718). Those with the highest intake of folate (742 μg/day) had a faster rate of cognitive decline. Reports from this same community (Chicago Health and Aging Project) examined other B-vitamins. In another analysis, 1,041 subjects were examined for incidence of Alzheimer's and dietary intake of B-vitamins folate, B12 and B6 as gauged by the Harvard food frequency questionnaire. After adjustments for confounding variables, there was no association between dietary intake of B12, B6 or folate and incidence of AD [64].

A clinical trial of B-vitamin supplementation in 211 healthy women ages ranging from 20 to 92 noted significant improvement only on a few measures of memory. Further results from this study revealed little benefit from B-vitamin supplementation on cognition [65]. Other trials have examined multivitamins and vitamin complexes, although none have reported more than minimal beneficial effect. These studies are difficult to summarize and interpret because there is no standard vitamin formulation and because the cognitive outcomes vary widely [66–68].

More on Mechanisms

Dietary benefits in protecting against cognitive decline and dementia are difficult to observe. At best the findings are weak and inconsistent. When there is observational evidence it has been difficult to replicate in experimental designs in human subjects. One problem is that experimental design takes the form of manipulation of a single component or proposed mechanism of action, when in fact dietary intake may best be understood by synergy of actions. For example dietary effects on cardiovascular risk factors may have an impact on cognitive function although the evidence that risks such as diabetes, hypercholesterolemia and hypertension, is also modest [69]. The dietary data provides an opportunity to identify factors worthy of further study and presents the challenge for future designs that can tease out the relevant combination of factors (see Table 1).

Conclusion

Awareness of the role of nutrition in health is long-standing with recent interest focusing on the impact of diet on cognition. While many components of food have been studied in isolation the benefit achieved via food intake may depend not only on the individual component but on the milieu in which it is taken. This may include the ratio of one food type to another, the coexistence of vitamins in food groups eaten together or abstention from one food eaten with another. Dietary components including vitamins and specific macronutrients may act synergistically. Further early life dietary patterns may also have an impact. The features which may maximize cognitive benefit form dietary intake are difficult to study as they require long observation periods and sufficient numbers to over come the bias of other factors which may interfere with observing a beneficial effect. The limited results to date provide the most hope for studies to understand the synergy of effects from diets high in grains, fruit and vegetables. Since most recommendations indicate that these food categories should make up the largest portion of the diet, it will be important to understand the factors that maximize cognition. Considerations include the fact that these

Table 1 Summary of studies and trials on diet, nutrition and cognition in aging populations

Title/Author/year	Investigated factor (if any)	Sample size/population	Results/Comments
Relationships between dietary intake and cognitive function level in Korean elderly people [1]	Diet, foods consumed	449 men and women healthy, normal, Korean community dwelling elderly over 60 y/o	In women, lower intakes of total amount of foods, cereals, vegetables, fruits, milk, spices, and also, energy, protein, fat, carbohydrate, Ca, P, Fe, Vitamin A, thiamin, riboflavin, and niacin were associated with worse cognitive performance compared to normal subjects ($P < 0.05$). In men, significantly lower intakes of fruits, fiber, and Vitamin C were associated with worse cognitive performance compared to normal subjects ($P < 0.05$). This study is weakened by the lack of control for caloric restriction and ratio of foods' intake.
Influence of nutrition on cognitive function in a group of elderly, independently living people [2]	Types of food consumed	168 healthy, normal, community dwelling elderly 65–90 y/o MMSE <24	Trend of ''adequate'' MMSE (<28) associated with greater intakes of total food, fish, alcohol, and lower intakes of 'various' food—chocolate, cakes and sweets. Adequate MMSE significantly associated with less consumption of lipids and saturated fats ($P < 0.05$) and intake of thiamine, folate and Vitamin C ($P < 0.05$). Limits of this study include the lack of caloric measurement and analysis as well as a lack of specificity of foods (e.g. ''various foods'' group).
Med Diet & Fat			
Mediterranean diet and risk for Alzheimer's Disease [4]	Mediterranean diet. The MeDi is characterized by high intake of vegetables, legumes, fruits, and cereals; high intake of unsaturated fatty acids (mostly in the form of olive oil), but low intake of saturated fatty acids; a moderately high intake of fish; a low-to-moderate intake of dairy products (mostly cheese or yogurt); a low intake of meat and poultry; and a regular but moderate amount of ethanol, primarily in the form of wine and generally during meals.	2,258 healthy, normal community dwelling elderly individuals mean age 77.2 ± 6.6 WHICAP project	Higher adherence to the MeDi significantly associated with lower risk of AD Hazard ratio—0.91 $P = 0.015$ Well-designed and controlled study.
Consumption of Fish and n-3 Fatty Acids and Risk of Incident AD [5]	Fish consumption and n-3 fatty acids	815 healthy, normal community dwelling, elderly 65–94 y/o	Total intake of fatty acids was inversely assoc. w/ AD (P for trend = 0.01), persons who consumed at least 1 fish meal per week had a 60% less chance of AD than persons who never or rarely consumed fish. Prospective study, mean follow-up 3.9 years
Dietary intake of fatty acids and fish in relation to cognitive performance at middle age [7]	Fish and fatty acids	1,613 community dwelling subjects from 45–70 y/o 1,450 normal cognition 163 cognitively impaired	Reduced risk of impaired cognitive function with fatty fish intake ($P < 0.05$) and omega-3 PUFA intake ($P < 0.05$) Cross-sectional study

Table 1 continued

Title/Author/year	Investigated factor (if any)	Sample size/population	Results/Comments
Dietary Fats and the Risk of Incident AD [9]	Fat intake	815 healthy, normal community dwelling elderly (at baseline) 65 y/o+	After adjustments for demographics and APOE, intake of ω-6 polyunsaturated fats inversely associated with AD (P for trend < 0.05). After adjustments animal and trans fats, intake of vegetable fat linearly associated with AD (P = 0.002). Prospective study, mean follow-up 3.9 years
Fish Consumption and Cognitive Decline in a Large Community Study [6]	Fish and Omega-3 Fatty acid intake	3,718 persons	Rate of cognitive decline reduced (10–13% per year) for those who ate 1 or more fish meal/ week compared to those who ate less fish-meals.
High monounsaturated fatty acids intake protects against age-related cognitive decline [10]	Fatty Acids	278 healthy normal community dwelling, elderly 65 y/o+	Significant positive correlation between monounsaturated fatty acid intake and 2 cognitive tests; MMSE and Digit Cancellation test.
Dietary fatty acids intakes and rate of mild cognitive impairment: The Italian Longitudinal Study on Aging [12]	Dietary Fatty Acids	278 community dwelling elderly subjects 65–84 y/ o	No association between dietary fat and incidence of MCI. *Non-significant* trend towards protective effect of polyunsaturated fats
Dietary intake of unsaturated fatty acids and age-related cognitive decline: a 8.5 year follow-up of the Italian Longitudinal Study on Aging [11]	MUFA and PUFA	278 community dwelling elderly 65–84 y/o	High intake of MUFA and PUFA significantly associated with a better cognitive performance (P < 0.05) after adjustments for demographics, BMI and estimated change in cognitive function due to energy intake. Prospective study, followed over 8.5 years.
Cognitive aging, childhood intelligence, and the use of food supplements: possible involvement of n-3 fatty acids [13]	Food intake, including fat	350 community dwelling elderly, ~64 y/o	Significantly greater scores on the Block design subtest for users of fish oil and vitamins.
Cognitive functions are not affected by dietary fatty acids in elderly subjects in the Pro. V.A. study population [14]	Fatty acid intake	Veterans over the age of 65	No assoc. between MMSE and plasma phospholipids acid composition. This study is limited in that dietary intake was not assessed.
Diet and risk of dementia: Does fat matter?: The Rotterdam Study [15]	Fat	5,395 non demented subjects surveyed	High intake of total, saturated, trans fat, and cholesterol and low intake of MUFA, PUFA, n-6 PUFA, and n-3 PUFA were not associated with increased risk of dementia
Alcohol/Wine			
Effects of Moderate Alcohol consumption on cognitive function in women [25]	Alcohol	11,102 elderly women of varying health from the Nurses Health Study Mean age = 74	Moderate drinkers had a significant association with less-decline, no effect observed of the type of alcohol (relative risk 0.85, 95% CI, 0.7–0.93). Well-controlled study.
The effects of wine and tobacco consumption on cognitive performance in the elderly: a longitudinal study of relative risk [26]	Wine and alcohol	225 healthy, normal, community dwelling elderly	No protective effect from AD from wine when the OR is adjusted to include residence (community or institution) in this longitudinal study.

Table 1 continued

Title/Author/year	Investigated factor (if any)	Sample size/population	Results/Comments
Amount and type of alcohol and risk of dementia [28]	Alcohol	1,709 community dwelling elderly, 65 + 83 dementia patients 1,626 healthy controls	Monthly and weekly intake of wine associated with a lower risk of dementia (adjusted RR = 0.43 (0.23–0.82) and 0.33 (0.13–0.86) respectively) while monthly intake of beer was significantly associated with dementia (adjusted RR = 2.28 (1.13–4.60). Well-controlled study.
Wine consumption and dementia in the elderly: a prospective community study in the Bordeaux area [27]	Wine	2,273 healthy, normal community dwelling elderly, 65 y/o+	Inverse relationship between moderate wine drinking and incident dementia (adjusted OR: 0.55, $P < 0.05$)
Fruits and Vegetables (Vitamins)			
Fruit and vegetable consumption and cognitive decline in aging women [33]	Fruit and vegetable intake	13,388 community dwelling elderly women, mean age: 74.2 Nurse's Health Study	Fruit intake not associated with cognition or cognitive decline, cruciferous (mustard family—cabbage, broccoli, cauliflower, mustard greens, etc.) vegetable intake was significantly associated with better global cognitive score (0.04 units, $P < 0.001$)
Dietary intake of anti-oxidants and risk of Alzheimer's Disease [35]	Anti-oxidant intake from questionnaire on consumption	5,395 subjects healthy, normal community dwelling elderly 55 y/o+	High intake of Vitamins C and E associated with lower risk of AD (RR = 0.82, CI, 0.69–8–0.99)). Longitudinal study, mean follow up 6 years. Well-controlled study.
Fruit and Vegetable Juices and Alzheimer's Disease: the Kame Project [34]	Fruit and vegetable juice consumption	1,836 community dwelling, healthy normal Japanese American elderly over 65 y/o	After adjustment for potential confounders, the hazard ratio for probable Alzheimer's disease was 0.24 (95% CI, 0.09–0.61) comparing subjects who drank juices at least 3 times per week with those who drank less often than once per week with a hazard ratio of 0.84 (95% CI, 0.31–2.29) for those drinking juices 1 to 2 times per week (P for trend < 0.01). This study is weakened by the lack of control for type of fruit and vegetable juice.
Dietary intake of antioxidant nutrients and the risk of incident Alzheimer's disease in a biracial community study [36]	Vitamin E, C, and other anti-oxidant nutrients	81,565+, free of AD at baseline	*Without* the APOE 4 allele, Vitamin E from food adjusted RR = 0.36
High dose antioxidant supplements and cognitive function in community dwelling elderly women [38]	Supplementation	14,968 community dwelling women, ≥70 y/o Nurse's Health Study cohort	Global cog test score of Vitamin E with Vitamin C long-term supplement users was significantly better in than women who never used ($P = 0.03$), and trend for higher scores with increasing duration ($P = 0.04$)
Relation of the tocopherol form to incident Alzheimer's disease and cognitive change [37]	Food intake and Vit E supplement intake	6,158 Chicago Health and Aging Project, ≥65, disease free at BL	After adjustments (including type of fat), higher intake of Vit E (RR 0.74) from food and alpha tocopherol (RR 0.56) associated with reduced risk of AD

Table 1 continued

Title/Author/year	Investigated factor (if any)	Sample size/population	Results/Comments
Vitamin E and Donepezil for the treatment of mild cognitive impairment [39]	Vitamin E and Donepezil 2,000 IU Vit E 10 mg Donepezil	769 MCI subjects, 212 developed PAD or Possible AD Placebo: 259 Donepezil: 253 Vit E: 257	No sig. differences in progression to AD with Vit E group
Donepezil, rivastigmine, and Vitamin E in Alzheimer's Disease: a combined P300 event-related potentials/neuropsychologic evaluation over 6 months [40]	Donepezil Vitamin E Rivastigmine	54 completers (all PAD): 20 Donepezil group 18 Vit E group 16 Rivastigmine group	No improvements on cog. testing with Vit E group, small benefit with AChEI: Decreased P300 latencies with Rivastigmine and Donepezil. Increased P300 latencies with Vitamin E. Well-controlled study.
Donepezil versus Vitamin E in Alzheimer's Disease: Part 2: mild versus moderate-severe Alzheimer's Disease [41]	Vitamin E and Donepezil1000 IU of Vitamin E for 15 days followed by 2,000 IU and 5 mg of Donepezil for 15 days followed by 10 mg for 5 months, 15 days	30 mild AD pts. 30 moderate AD pts.	P300 Latencies increased for Vitamin E treated patients of both dementia levels, no effect on cognitive testing with Vitamin E treated patients of both dementia levels
Safety and Efficacy of Idebenone versus Tacrine in Patients with Alzheimer's Disease: Results of a Randomized, Double-Blind, Parallel Group multi-center study [43]	Idebenone Tacrine	203 pts. with PAD: 99 received Tacrine104 received Idebenone	Statistically significant difference in improvement on Efficacy Index score, no relevant difference between cognitive test scores.
B-Vitamins			
Dietary folate and B12 intake and cognitive decline among community dwelling older persons [64]	Folate, B12, from food questionnaire	3,718 community dwelling elderly 65 y/o+	Faster rate of cog decline assoc. w/ high folate intake, high B12 associated with slower decline, only among the oldest participants. Longitudinal study, follow-up at 3 and 6 years.
Associations between dietary intake of folate and Vitamin B12 and B6 and self reported cognitive function and psychological well-being in Australian men and women in midlife [54]	Self report cog and memory status and self report food questionnaire	1,183 community dwelling men and women of middle age	B12 and B6 associated with memory function in men and folate and B6 associated with better memory function in women
Short-term folate, Vitamin B12 or Vitamin B6 supplementation slightly affects memory performance but not mood in women of various ages [65]	750 μg folate, 15 μg B12 75, mg B6 OR placebo	211 community dwelling, healthy young, middle-aged, and older women 56, 20–30 y/o 80, 45–55 y/o 75, 65–92 y/o	In the older age group, out of several cognitive tests, the only significant finding was better scores on a delayed word recognition task between the folate supplement group and the placebo group.
Soy			
Psychological assessment of the effects of treatment with phytoestrogens on post-menopausal women: a randomized, double blind placebo controlled study [20]	Soy isoflavones 60 mg/day	78 healthy, post-menopausal women, average age 49.5 ± 4.1	Digit Symbol pairs correctly recalled treatment grp sig better ($P = 0.04$) Digit span backward treatment group sig better (0.05) Memory was not evaluated.

Table 1 continued

Title/Author/year	Investigated factor (if any)	Sample size/population	Results/Comments
Cognitive improvement after 6 weeks of soy supplements in post-menopausal women is limited to frontal lobe function [22]	60 mg Novasoy or placebo for 6 weeks	50 post-menopausal women (51–66)	Treatment grp sig better on "simple rule reversal" ($P < 0.05$) and "complex rule reversal" ($P < 0.03$) and "planning ability" ($P < 0.05$) No effects of soy on long-term memory, category generation, or sustained attention.
Effect of soy protein containing isoflavones on cognitive function, bone mineral density, and plasma lipids in post-menopausal women: a randomized controlled trial [23]	25.6 g of soy protein, containing 99 mg of isoflavones	202 healthy post-menopausal women, 60–75 y/o	After 1 year, no significant differences between groups on tests of cognitive domains including memory, executive function, naming, verbal fluency, and attention.
Isoflavones and cognitive function in older women: the Soy and Post-menopausal Health in Aging study [21]	110 mg isoflavones/day or placebo	56 healthy, normal community dwelling women 55–74 y/o	Treatment group did significantly better on category fluency (after age and edu adjustments $P = 0.05$), no significant differences on measures of memory or executive function (Trails A and B)

food groups are low in caloric density, perhaps replacing higher caloric density foods. They may provide a wide range of anti-oxidant benefits that are not yet understood. Mechanisms of neural repair and protection via anti-inflammatory mechanism and cell signaling modifications have been cited as potential mediators for a benefit on cognition and should be studied further However, unlike supplementation or pharmacological agents, dietary intake has built in controls which may limit the side effects that can be observed with other interventions. Randomized controlled trials of the most hopeful aspects of nutrition are needed to provide convincing evidence of dietary benefit on cognition. Limited results so far indicate that the pattern of intake, such as that seen in the Mediterranean diet, with a focus on high intake of vegetables legumes, low intake of meat and dairy and moderate intake of alcohol, may be worth future research pursuits.

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