Diet and Alzheimer's Disease

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Alzheimer's disease (AD) is increasing in prevalence. There are no known preventive or curative measures. There is evidence that oxidative stress, homocysteine-related vitamins, fats, and alcohol have a role in the pathogenesis of AD. Some epidemiologic studies suggest that higher dietary intake of antioxidants, vitamins B_6, B_{12}, and folate, unsaturated fatty acids, and fish are related to a lower risk of AD, but reports are inconsistent. Modest to moderate alcohol intake, particularly wine, may be related to a lower risk of AD. The Mediterranean diet may also be related to lower AD risk. However, randomized clinical trials of supplements of vitamins E, B_{12}, B_6, and folate have shown no cognitive benefit, and randomized trials for other nutrients or diets in AD are not available. The existing evidence does not support the recommendation of specific supplements, foods, or diets for the prevention of AD.

Introduction

The main objective of this article is to provide the reader with a brief review and important concepts of the epidemiologic study of the relation between diet and sporadic or late-onset Alzheimer's disease (AD). For this purpose, we provide a summary and update of a previous review [1] and summarize the evidence linking diet and AD from the Washington Heights-Inwood Columbia Aging Project (WHICAP) in New York City. This article is intended as a brief primer, not as a comprehensive review. Thus, we do not cover all available studies but present those that are representative of the field, particularly prospective epidemiologic studies and clinical trials.

AD Burden and Pathophysiology

AD is the main cause of sporadic dementia in the elderly [2]. There are no known curative or preventive measures for AD, but delaying the onset could decrease its prevalence and public health burden [3]. Thus, there have been extensive research efforts in identifying risk factors for AD, including diet. The risk of sporadic AD increases with age. It is also higher in persons with lower education. The only robust genetic risk factor for AD is the apolipoprotein E (APOE)-ε4 allele [4]. APOE-ε4 may also modify the relation between risk factors and AD and may modulate the response to diet [5]. Vascular risk factors and cerebrovascular disease are increasingly recognized as potential risk factors for AD [6]. The pathologic hallmarks of AD in the brain include deposits of extracellular amyloid beta (Aβ) protein in diffuse plaques and in plaques containing elements of degenerating neurons, termed neuritic plaques. Intracellular changes include deposits of abnormally hyperphosphorylated tau protein (a microtubule assembly protein) in the form of neurofibrillary tangles. The main culprit in AD is thought to be the deposition of Aβ in the brain [7], leading to loss of synapses and neuronal destruction. Thus, it is thought that dietary factors that affect AD risk are those that have an effect on the amyloid cascade. Another potentially important mechanism linking diet and AD is cardiovascular and cerebrovascular disease [1]. We briefly discuss how specific nutrients could be related to these two pathways. Figure 1 summarizes how diet may be related to AD. Following the existing literature, we have divided this review into micronutrients, macronutrients, and dietary patterns. Table 1 summarizes the evidence linking diet and AD in WHICAP.

Micronutrients

Antioxidants

Increased production and deposition of Aβ are early events in AD and increase oxidative stress [8]. It is not clear whether this is a primary or secondary event. Thus, it has been hypothesized that dietary antioxidants could prevent AD. The usual antioxidants studied include tocopherol (vitamin E), ascorbic acid (vitamin C), and carotenes. Dietary antioxidants may also decrease cerebrovascular disease, and this may be an indirect mechanism linking antioxidants to AD [9].

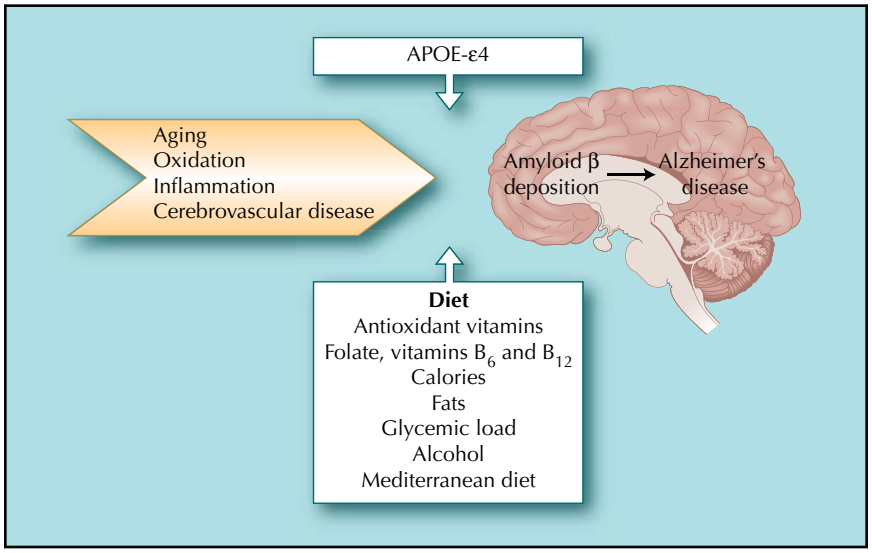

Figure 1. Potential pathways linking diet to Alzheimer's disease (AD). Aging and related processes, oxidation, inflammation, and cerebrovascular disease may cause the deposition of amyloid beta, thought to be the main step in the pathogenesis of AD. Dietary factors may modulate the risk of AD through their actions on these processes, although the exact mechanisms remain uncertain. Apolipoprotein E (APOE)-ε4, a genetic risk factor for sporadic AD, may modify the effects of diet.

Some studies have found that antioxidant supplements are related to a higher risk of AD. A study of over 3000 elderly Japanese-American men in Hawaii found that intake of supplements of vitamin C and E was related to a lower risk of vascular dementia but not AD [10]. A study among 4000 subjects aged 65 years and older found that a combination of vitamin C and E supplements, but not supplements of individual antioxidants, was associated with a lower risk of AD [11]. Conversely, other studies have found that antioxidants in foods, but not in supplements, are related to a lower risk of AD. A study in 6441 subjects 55 years and older in the Netherlands found that dietary intake of vitamins E and C, but not supplement intake, was associated with a lower risk of AD [12]. A study in Chicago in 815 individuals aged 65 years and older found that dietary vitamin E, but not supplements, was associated with a lower risk of AD [13]. A similar study in WHICAP in 980 individuals aged 65 years and older followed for 4 years did not find any association between dietary, supplement, or total intake of carotenes, vitamin E, or vitamin C and a lower risk of AD [14]. In summary, prospective epidemiologic studies of the relation between dietary and supplement intake of antioxidants and AD have shown inconsistent results.

There are few clinical trials studying this question. One trial randomized persons with AD to 2000 units of vitamin E and/or selegiline or placebo and found that intake of vitamin E was related to a longer time to institutionalization but was not related to cognitive outcomes [15]. A recent trial of vitamin E supplementation in persons with amnestic mild cognitive impairment (MCI), a transitional stage between normal cognition and AD [16], failed to show prevention of progression to AD [17••]. Whether antioxidant supplements should be recommended, and at what doses, seems a matter of individual judgment for the clinician and the patient. One of the arguments often made by clinicians is that antioxidants may not help, but they do not hurt either. There has been recent evidence that antioxidant supplements may not be safe. A recent meta-analysis of vitamin E supplementation in the prevention of heart disease found increased mortality risk in those taking the supplements [18]. Thus, the most conservative approach given current evidence is to not recommend antioxidant supplements for the prevention of AD.

Homocysteine and vitamins B_6, B_{12}, and folate

Homocysteine has surfaced as a potential risk factor for cardiovascular disease and dementia [19]. Homocysteine levels in blood are largely determined by dietary intake and levels of vitamins B_{12}, B_6, and folate [20], but homocysteine also increases with age and with diminishing renal function. Homocysteine is a precursor of methionine and cysteine. Folate and vitamin B_{12} are needed for the conversion of homocysteine to methionine, and vitamin B_6 is needed for the conversion of homocysteine to cysteine. Homocysteine can act in the brain and possibly in the AD pathway through vascular mechanisms or as a neurotoxin [21], but the mechanisms are not clear. Lower serum concentrations of folate, but not vitamins B_{12} and B_6, are correlated with atrophy of the cerebral cortex on autopsy, a surrogate marker of neurodegenerative disease [22]. Homocysteine levels over 14 μmol/L doubled the risk of AD in the Framingham study [19], but there was no relation between the blood levels of folate, vitamin B_6, and vitamin B_{12} to the risk of AD. A study from WHICAP found that the association between high homocysteine levels and AD was confounded by age [23], and there was no association between a level of homocysteine over 14 μmol/L (the usual limit of normal) and the risk of AD. Several more prospective studies have found associations between homocysteine and AD [24], but the WHICAP study is one of the few reporting no association. Thus, it is presumed that homocysteine is a potential mechanism for a relation of the intake of vitamins B_{12}, B_6, and folate with AD.

Table 1. Summary of studies relating diet to Alzheimer's disease in the Washington Heights-Inwood Columbia Aging Project in New York City

Study	Nutrient	Finding
Luchsinger et al. [14]	Antioxidants	Neither dietary, supplemental, or total intake of carotenes and vitamins C and E were associated with a decreased risk of AD
Luchsinger et al. [36]	Caloric and fat intake	Compared with those in the lowest quartile, individuals in the highest quartile of caloric intake (HR of 1.5; 95% CI, 1.0–2.2) had an increased risk of AD. Among individuals with the APOE-ε4 allele, the HR of AD for the highest quartile of calorie intake was 2.3 (95% CI, 1.1–4.7) and the HR of AD for the highest quartile of fat intake was 2.3 (95% CI, 1.1–4.9) compared with the lowest quartiles. The HR of AD for the highest quartiles of calorie and fat intake compared with the lowest quartiles among individuals without the APOE-ε4 allele were close to 1 and not statistically significant.
Luchsinger et al. [49]	Alcohol	After adjusting for age, gender, APOE-ε4 status, education, and other alcoholic beverages, only intake of up to 3 daily servings of wine was associated with a lower risk of AD (HR of 0.55; 95% CI, 0.34–0.89). Intakes of liquor, beer, or total alcohol were not associated with a lower risk of AD. Stratified analyses by the APOE-ε4 allele revealed that the association between wine consumption and lower risk of AD was confined to individuals without the APOE-ε4 allele.
Luchsinger et al. [29]	Folate, vitamins B_{12} and B_6	The highest quartile of total folate intake was related to a lower risk of AD (HR for the fourth quartile of 0.5; 95% CI, 0.3–0.9; *P* for trend = 0.02) after adjustment for age, gender, education, ethnic group, APOE-ε4, diabetes, hypertension, current smoking, heart disease, stroke, and vitamins B_6 and B_{12}. Vitamins B_6 and B_{12} were not related to the risk of AD.
Luchsinger et al. [42]	Glycemic load	There was no association between glycemic load and AD after adjustment for age, gender, education, ethnic group, and presence of diabetes. There was no evidence of modification by age, gender, APOE-ε4, and presence of diabetes. The only dietary variable associated with a higher risk of AD was total calories (HR of AD for a 1-log unit increase of 2.2; 95% CI, 1.4–3.5) after adjustment for age, gender, ethnic group, education, diabetes, and APOE-ε4.
Scarmeas et al. [55•]	Mediterranean diet	Higher adherence to the Mediterranean diet was associated with lower risk of AD (HR of 0.91; 95% CI, 0.83–0.98; *P* = 0.015). Compared with subjects in the lowest tertile, subjects in the middle tertile had a HR of 0.85 (95% CI, 0.63–1.16) and those at the highest tertile had a HR of 0.60 (95% CI, 0.42–0.87) for AD (*P* for trend = 0.007).

AD—Alzheimer's disease; APOE—apolipoprotein E; HR—hazard ratio.

Several studies have found that homocysteine-related vitamins are associated with a higher AD risk. One study in 370 persons without dementia at baseline aged 75 years and older found that during 3 years of follow-up, subjects with lower vitamin B_{12} or folate levels ($B_{12} \leq 150$ pmol/L and folate ≤ 10 nmol/L) had twice the risk of developing AD compared with individuals with higher levels [25]. Conversely, another study in 410 subjects aged 75 to 85 years with low B_{12} levels (< 150 pg/mL) followed for 5 years showed no increased risk [26]. One study in Chicago found no association between dietary folate, vitamin B_{12}, and vitamin B_6 and AD [27], and the same group unexpectedly found that higher folate intake was related to a higher risk of cognitive decline [28]. A study in WHICAP recently found that that folate, but not vitamins B_{12} and B_6, was related to a lower risk of AD, although there was no relation between homocysteine and AD in the same study. This association was stronger when the study was adjusted for vitamins B_{12} and B_6 [29]. Since 1998, cereal grain products in the United States have been fortified with folic acid. There is concern that although folic acid fortification may improve anemia in persons with B_{12} deficiency, it could exacerbate neuropsychiatric complications, either because of masking of B_{12} deficiency or other mechanisms [30]. A recent cross-sectional analysis of the National Health and Nutrition Examination Survey data showed that in

elderly people with low serum B_{12}, high folate levels were related to cognitive impairment and anemia [30].

In summary, there are inconsistent data relating homocysteine and related vitamins to the risk of AD. At least one study suggests that higher intake of folate could be detrimental, and there are concerns about the effects of high folate levels in the presence of B_{12} deficiency. A trial of the supplementation of folate, vitamin B_6, and vitamin B_{12} in the secondary prevention of stroke found no benefit [31]. A 2-year, double-blind, placebo-controlled, randomized clinical trial of homocysteine-lowering treatment with vitamin B_{12}, vitamin B_6, and folate supplements in 276 participants 65 years of age or older with plasma homocysteine concentrations of at least 13 μmol/L found a lower homocysteine level in the treatment group but no differences in cognition at 2 years [32••], putting into question the results of observational studies. A secondary analysis of this trial found evidence suggestive of harm in cognitive function. Thus, it seems that supplementation with vitamins B_{12}, B_6, and folate should be reserved for usual clinical indications and not for the prevention of AD.

Macronutrients

Total calories

Animal models have shown that dietary restriction extends the lifespan in rodents and increases the resistance of neurons to degeneration [33]. Thus, caloric restriction may decrease the risk of AD. We found in WHICAP that persons in the fourth quartile of caloric intake had a higher risk of AD, and this association seemed stronger in persons with the APOE-ε4 allele.

Dietary fats

Intake of nonhydrogenated unsaturated fats, lower intake of hydrogenated and saturated fats, and higher intake of omega-3 polyunsaturated fatty acids from fish or vegetable sources can lower the risk of cardiovascular disease [34], potentially reducing AD through vascular mechanisms. Higher intake of fats may also cause oxidation [35], which may directly affect amyloid deposition or its effects. Among 980 elderly subjects followed for 4 years in WHICAP, the risk of AD was higher in subjects in the highest quartile of total fat intake who had the APOE-ε4 allele [36]. Another study found that higher intakes of saturated and trans unsaturated fatty acids were associated with a higher risk of AD regardless of the APOE genotype [37]. This study also found that intake of fish and fish-related fats was related to a lower risk of AD [38]. However, fat intake of any type was not related to dementia or AD in a study of over 5000 persons aged 55 years or older [39].

In summary, there are few studies relating intake of different types of fats and the risk of AD, and the results have been inconsistent. There are no trial data and recommendations cannot be made based on these studies. However, a diet low in saturated and trans fatty acids and higher in monounsaturated, polyunsaturated, and fish-related fats is associated with a lower risk of cardiovascular disease, and it may be reasonable to extend their benefits to the prevention of AD.

Glycemic load

There has been increasing interest in the role of low-carbohydrate diets in the prevention of diabetes and other diseases [40]. The putative mechanism for the relation between glycemic index and disease is insulin resistance. Because high insulin levels and diabetes may be related to a higher risk of AD [41], it is plausible that diets with high glycemic load (the product of carbohydrate quantity and the insulin response capacity of specific carbohydrates) could be related to AD. To the best of our knowledge, there is only one study addressing the question in WHICAP. No relation was found between calorie-adjusted glycemic load and the risk of AD [42], but the relation between high caloric intake and AD persisted after adjustment for glycemic load.

Alcohol

Moderate alcohol intake is related to greater brain atrophy, but is also related to fewer silent brain infarcts, less white matter disease [43], and a lower risk of clinical stroke [44]. Wine may contain antioxidants not present in beer and liquor, such as flavonoids, which may have additional benefits to those of alcohol [45]. One nested case-control study in subjects aged 65 years and older showed that consumption of 1 to 6 drinks of alcohol weekly, regardless of type, was related to a lower risk of AD [46] compared with abstainers. Another study showed that consumption of up to 3 servings of alcohol per day was related to a lower risk of AD compared with those who never drank alcohol, also without differential associations by beverage type [47]. A nested case control study of individuals aged 65 years and older found that monthly or weekly intake of wine, but not other alcoholic beverages, was associated with a lower risk of AD [48]. Similarly, a study in WHICAP found in individuals aged 65 years and older that intake of up to 3 servings of wine per day, but not other alcoholic beverages, was associated with a lower risk of AD [49]. A study in individuals aged 65 years and over in which wine was almost exclusively the only alcoholic beverage reported that moderate wine consumption (3 or 4 glasses a day) was associated with a lower risk of AD and overall dementia, whereas mild consumption (1 or 2 glasses a day) was associated with a lower risk of AD but not dementia [50]. Another study also reported a lower risk of AD with consumption of wine but not other alcoholic beverages [51]. Most of these studies found data suggesting that heavy alcohol intake (four or more servings of alcohol daily) was related to a higher risk of dementia, but the results were not statistically significant given the small numbers of elderly people who reported heavy alcohol intake.

There are no available randomized trials of the effects of alcoholic beverages. It seems reasonable to advise those who drink to maintain moderation (less than 3 servings of wine a day). It also seems reasonable not to recommend alcohol intake to those who do not drink in light of the potential for abuse and addiction and other potential adverse events, such as falls in the elderly.

Dietary patterns and AD

One of the characteristics of the evidence reviewed thus far is that it is reductionistic. That is, it is hypothesized that individual nutrients contained in foods may have effects on AD, neglecting the possible importance of the additive or synergistic effects of other nutrients within and across particular foods that form part of a diet. Thus, there is growing interest in exploring whole types of foods (eg, tomatoes, fruits, and vegetables) and dietary patterns. One dietary pattern that has attracted increasing interest is the Mediterranean diet (MeDi). The MeDi is related to lower risk for cardiovascular disease [52], several forms of cancer [53], and overall mortality [54]. 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 in salad dressing and cooking) but low intake of saturated fatty acids; a moderately high intake of fish; a low-to-moderate intake of dairy products (mostly in the form of 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. Therefore, the MeDi seems to encapsulate many of the components reported as potentially beneficial for AD in previous sections. The MeDi has been shown to be associated with a lower risk of oxidation, inflammation, vascular, and metabolic disease. Thus, it is conceivable that the MeDi-related protection for AD could be occurring via several mechanistic pathways. We found in WHICAP among 2258 patients that higher adherence to the MeDi is related to a lower risk of AD [55•]. No single component of the MeDi was responsible for this association, suggesting that the additive or synergistic effects of foods in the MeDI, and not a particular nutrient, were responsible for this association. We also found that this association was not explained by vascular disease.

Limitations of the data relating diet to AD

One of the main limitations of studies of diet and disease is error in the measurement of nutrients [56]. If the measurement error is not related to the outcome, it will result in underestimation of true associations. If the measurement error is different according to the outcome status, it can lead to underestimation or overestimation of the associations. The development of AD may be the consequence of lifelong exposures, or at least, of exposures that begin in middle age or later adult life. Most studies examining the relation between diet and AD have been conducted in subjects over the age of 65 years. Individuals in this age group may be in an advanced stage in the latency period of AD. Thus, the capacity to change the course of disease with dietary interventions may be limited. Moreover, dietary patterns reported in studies may reflect the consequence of preclinical AD, which may include changes in the senses of smell and taste [57], resulting in changes in eating behavior.

Another potential limitation is the reductionistic approach to diet analysis. It is assumed that the nutrient having an effect in someone who eats a lot of carrots is carotenoids, neglecting all other nutrients and interactions found in carrots, and the other foods they are accompanied with. The whole may have greater effects than the parts, and in this sense the study of dietary patterns such as the MeDi is welcomed and necessary. Finally, it is important to point out that most of the data relating diet and AD in humans comes from epidemiologic studies with few clinical trials. There have been sobering examples of the lack of translation of apparent benefit in epidemiologic data to clinical trials, such as the case of hormone replacement therapy and dementia [58].

Conclusions

There is some evidence from observational studies suggesting that dietary antioxidants, homocysteine-related vitamins, lower caloric intake, lower fat intake, higher intake of polyunsaturated fatty acids and fish and fish-related fatty acids, mild to moderate alcohol and wine intake, and the Mediterranean diet are related to a lower risk of AD. However, the evidence is not consistent and the few instances in which clinical trials are available have not confirmed the results of epidemiologic studies. Thus, existing evidence does not support the recommendation of dietary supplements or particular diets or foods specifically for the prevention or treatment of AD.

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