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The role of nutrition in Alzheimer's disease: epidemiological evidence

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Abstract

The prevalence of Alzheimer's disease (AD) increases exponentially with age but there is limited knowledge of the modifiable risk factors for AD. However, there is growing evidence for possible dietary risk factors in the development of AD and cognitive decline with age, such as antioxidant nutrients, fish, dietary fats, and B-vitamins. Numerous animal and laboratory studies have shown that antioxidant nutrients can protect the brain from oxidative and inflammatory damage, but there are limited data available from epidemiological studies. There is more substantial epidemiological evidence from a number of recent studies that demonstrate a protective role of omega-3 fatty acids, such as docosahexaenoic acid, in AD and cognitive decline. This review will focus on epidemiological evidence investigating the relationship between nutrition and AD, focusing particularly on the roles of dietary fats and antioxidants.

Keywords

Alzheimer's disease; cholesterol; dementia; docosahexaenoic acid; nutrition; omega-3 fatty acids; vitamin C; vitamin E

Introduction

It is estimated that 24 million people are affected by dementia worldwide, with 4.6 million new cases annually [1]. Because of the rapid increase in demographical aging in all world regions, global prevalence of dementia is predicted to double every 20 years to over 80 million people by 2040 [1]. Alzheimer's disease (AD) is the most common form of dementia and accounts for 50–60% of all cases [2].

There is limited knowledge of the modifiable risk factors for AD. The most well-established risk factor is older age but there is also good epidemiological evidence to suggest that low education and the APOE lipoprotein ε4 (APOE-ε4) genotype can increase the risk of developing AD [3]. There have been a number of studies suggesting that cardiovascular risk factors increase the risk of AD and dementia, including hypertension [3–5], hypercholesterolemia [5–7], heart disease [3,8], diabetes [3,9–11], alcohol consumption [12,13], smoking [3,14], physical activity [15,16], and obesity [17,18]. Data from several lines of evidence suggest that the relationship between diet and AD is similar to that

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Conflicts of interest
The author declares no conflicts of interest.

between diet and coronary heart disease. A growing body of evidence suggests that certain dietary components (e.g., antioxidant nutrients, fish, dietary fats, and B-vitamins) may play a protective role in the risk of age-related cognitive decline and AD.

The two classes of medication currently available for the treatment of patients with AD afford only modest symptomatic improvements and do not address the progressive neurodegeneration that underlies the illness [19]. Thus, the potential role of nutrition in the development of AD is of substantial interest as there is a strong unmet need for novel, effective, strategies that are preventative and therapeutic.

Chicago Health and Aging Project

The Chicago Health and Aging Project (CHAP) is an ongoing study of dietary and other risk factors of cognitive decline and incident AD amongst residents of a geographically defined community [20,21]. This study forms the basis for many of the results presented in this review.

The CHAP began in 1993 with a door-to-door census of three neighborhoods on the south side of Chicago, namely Morgan Park, Beverly, and Washington Heights. A total of 6158 residents aged ≥65 years participated (overall response rate was 78.9%) in the first phases of the project, although more than 3000 additional residents were added to the study as they became age-eligible. Data presented in this review come from the first project phase. The study population was 62% white, 38% black, and 0.4% of other races. Baseline in-home interviews that included cognitive testing were conducted from 1993 to 1997 and were repeated in two follow-up interviews. In addition, stratified random samples were selected for clinical evaluation of prevalent disease at baseline and of incident disease at each of the follow-up assessment periods. Each cycle of population interviews and clinical evaluations occurred at approximately 3-year intervals over a 6-year period. All study participants completed a self-administered food-frequency questionnaire (FFQ; [22]) at a median of 1.2 years from the baseline cognitive interview and from the date that disease-free status was determined in the clinical evaluation samples. A total of 4390 of the 6158 study participants had two or more cognitive assessments; of these participants, 213 individuals were eliminated who had an invalid FFQ and 460 who completed the FFQ > 2.5 years after baseline, which left 3718 participants for analysis of cognitive change. A total of 1141 participants (1041 with complete data for analysis) were clinically evaluated for incident AD. More detailed descriptions of the CHAP study design were published previously [20,21]. The Institutional Review Board of Rush University Medical Center approved the study and all participants gave written informed consent.

Role of dietary fats in AD

Metabolic studies have shown that diets with a high ratio of saturated fat to polyunsaturated or monounsaturated fats result in a poor plasma cholesterol profile, characterized by an increase in low-density lipoprotein and a decrease in high-density lipoprotein cholesterol [23]. Trans-unsaturated fats, obtained from partially hydrogenated vegetable oils are reported to be particularly hypercholesterolemic [24].

The association of dietary fat with plasma cholesterol levels is highly relevant as cholesterol may play a central role in AD. For example, cholesterol is involved in both the generation and deposition of amyloid beta (Aβ; [25]) and the most important genetic risk factor for AD is the APOE-ε4 allele, the protein product of which is the principal cholesterol transport in the brain. Experimental animal studies have demonstrated that diet-induced hypercholesterolemia increases Aβ deposition in the brain [26,27] and rats fed a diet rich in unsaturated fat exhibited superior learning and memory [28].

Some prospective studies have reported lower risk of AD and dementia amongst persons prescribed cholesterol-lowering statin drugs compared with those that were not prescribed these medications [29,30]. It remains to be determined whether this reduced risk of AD is a consequence of the cholesterol-lowering properties of these medications. However, there is evidence that elevated mid-life serum cholesterol levels are associated with increased risk of AD in old age. For instance, a study with 444 Finnish men found that an elevated blood cholesterol level (> 6.5 mmol/l) in midlife was associated with three times the risk of developing AD in late life [6].

Three prospective dietary studies conducted in Chicago [The CHAP study; 31], New York [32], and Rotterdam [33] examined the role of dietary fat intake in the development of AD in the general population. The CHAP study reported the strongest evidence of an association. Intake of saturated fat was associated with a doubling in the risk of AD amongst persons in the fifth quintile of intake compared with those in the first quintile. (Table 1; [31]) Trans-unsaturated fats was associated with two to three times the risk of developing AD beginning at the second quintile of intake. Persons in the highest quintile of n-6 polyunsaturated fat intake had 70% lower risk of AD compared with persons in the first quintile. Monounsaturated fat intake was not significantly associated with AD in these models that were adjusted for age, sex, race, education, and APOE-ε4. However, because intake of monounsaturated fat is highly correlated with both intakes of saturated and trans-fats, it is important to adjust for potential confounding by these variables when examining the relation of monounsaturated fat and AD risk. When the model was further adjusted for intakes of other types of fat (saturated, trans, n-6 polyunsaturated), there was evidence of 80% reduction in risk amongst persons in the fourth and fifth quintiles of monounsaturated fat intake.

The New York study found evidence of a greater 4-year risk of AD in individuals with higher intakes of total fat and saturated fat, but no evidence of an association with the intake of polyunsaturated fat [32]. The findings of the Rotterdam study revealed an increased risk of disease with higher intakes of total fat, saturated fat, and cholesterol after 2 years of follow-up [33], but none of the dietary fats was associated with AD after 6 years of follow-up [34]. In conclusion, further studies are clearly required to determine whether the composition of fat in the diet is causally related to risk of AD.

Omega-3 fatty acids

Long-chain omega-3 fatty acids, a type of polyunsaturated fat consumed almost exclusively from fish may hold promise for the prevention and treatment of AD. Docosahexaenoic acid (DHA, 22:6n-3) is the principal omega-3 polyunsaturated fatty acid constituent of neuronal membranes, present in approximately 30–40% of the phospholipids of the cerebral cortex gray matter and photoreceptor cells in the retina [35]. DHA is particularly abundant in the more metabolically active areas of the brain such as the cerebral cortex, synaptosomes, and mitochondria. Neurons lack the enzymes necessary for *de novo* synthesis of DHA and it is obtained either directly from the diet or synthesized endogenously from its precursors α-linolenic acid (18:3n-3) and eicosapentaenoic acid (EPA, 20:5n-3) [36].

The majority of the evidence for the neuroprotective effects of the omega-3 fatty acids stems from investigations of their importance as essential dietary components in early brain development. Indeed, DHA is essential for prenatal development of the brain and for maintenance of brain function and vision in adults [37]. In animal models, rodents that were fed diets enriched with omega-3 fatty acids exhibited enhanced learning and memory compared with rodents fed control diets [38–40]. Furthermore, animal studies have also demonstrated that dietary supplementation with omega-3 fatty acids results in enhanced regulation of neuronal membrane excitability [41], improved capacity for neuronal

transmission [42], and reduced oxidative damage [43]. Several epidemiological studies have shown protective relations of increased fish consumption and omega-3 fatty acids to AD [33,44–49].

Observations in the CHAP study have demonstrated that individuals who consumed less than one fish meal per week had a 12% greater rate of cognitive decline compared with individuals who consumed just one fish meal or more a week. Furthermore, consumption of one fish meal a week was associated with a 60% reduction in the risk of developing AD [47]. The relative risk of AD according to intake of the omega-3 fatty acids was also examined in the CHAP study (Table 2) [47]. Higher total intake of the omega-3 fatty acids was significantly associated with a lower risk for AD. DHA provided the strongest association, EPA was not associated and α-linolenic acid was associated with lower risk only amongst persons with the APOE-ε4 allele.

A number of groups have also investigated consumption of fish or omega-3 fatty acids in relation to risk of developing AD. The Rotterdam Study reported a 70% significant reduction in risk of AD after 2 years of follow-up with consumption of one fish meal per week, but a 6-year follow up of this study did not find an association between omega-3 fatty acids and the risk of AD [33,34]. In the Framingham Study, amongst 899 men and women who were free of dementia at baseline (median age of 76.0 years), those in the top quartile range of phosphatidylcholine DHA levels had a significant 47% reduction in the risk of developing all-cause dementia over a mean 9.1 years [50]. The Zutphen Study found that fish consumers had significantly ($P = 0.01$) less subsequent cognitive decline than did non-consumers [51]. The Etude du Vieillissement Arteriel study also found that a higher proportion of total omega-3 fatty acids in erythrocyte membranes were associated with a lower risk of cognitive decline whilst total omega-6 polyunsaturated fatty acids were associated with a greater risk of cognitive decline [52]. More recently, the Three-City cohort study conducted in Bordeaux, Dijon, and Montpellier examined a total of 8085 non-demented participants aged ≥65 over a 4-year period [49]. The findings revealed that weekly consumption of fish was associated with a reduced risk of AD (HR 0.65, 95% CI 0.43–0.99) and regular consumption of omega-3 rich oils was associated with a decreased risk for all causes of dementia (HR 0.46, 95% CI 0.19–1.11). Conversely, regular consumption of omega-6 rich oils, not compensated by consumption of omega-3 rich oils or fish, was associated with an increased risk of dementia (HR 2.12, 95% CI 1.30–3.46) amongst APOE-ε4 non-carriers.

Overall, the data for fish and omega-3 fatty acids consumption and risk of AD are consistent across studies; only a limited number of epidemiological studies have not found such an association [53]. Whilst these epidemiological studies show promise that dietary intake of fish and omega-3 fatty acids may protect against AD, confirmatory evidence from clinical trials is needed to attribute the findings to a causal association. Several trials are currently in progress to examine the effect of fish oil supplements on cognitive decline and the development of AD. One of these trials randomized 302 healthy participants aged 65 years and older to one of three groups: 1800 mg/day EPA + DHA, 400 mg/day EPA + DHA, and placebo. There was no overall treatment effect after 6 months of treatment; however, subgroup analyses found significant improvement in attention on both the low and high doses of omega-3 fatty acids [54].

Role of dietary antioxidants in AD

Numerous animal and laboratory studies have shown that AD involves oxidative and inflammatory processes, although it is not known whether these processes are a cause or consequence (or both) of the disease. Oxidative stress and the inflammatory process results

ultimately in a disruption of neuronal cell functioning and signaling, leading to neuronal cell death. Antioxidants such as vitamins E and C constitute the body's endogenous defense mechanisms to combat oxidative stress. Vitamin E is a potent chain-breaking antioxidant that resides within cell membranes whilst vitamin C circulates in the plasma and retains the additional function of restoring vitamin E.

Laboratory studies have shown that the antioxidants (vitamin E in particular) protect the brain from oxidative and inflammatory damage [55,56]. In animal models, rodents fed diets supplemented with antioxidants exhibited superior learning acquisition and memory retention compared with rodents on control diets. At death, the brains of the antioxidant-fed rodents exhibited less neuronal cell loss and less evidence of oxidative damage and inflammation [57,58].

Both the CHAP [59] and the Rotterdam study [60] found a lower risk of AD associated with a higher dietary intake of vitamin E. In contrast, another prospective study conducted in New York found no association [61]. However, the vitamin E intake in the New York study may have been too low to provide a neuroprotective benefit; the median of 7 IU/day for individuals in the upper tertile of intake was comparable to the lowest intake levels in the CHAP and Rotterdam studies.

Of the three epidemiological investigations, only the Rotterdam study revealed a reduced risk of AD associated with a high dietary intake of vitamin C. The CHAP study found that participants with the highest food intake of vitamin C were more likely to have a history of stroke or hypertension, thus it is possible that these persons may have increased their vitamin C consumption as a recent preventive measure, thus obscuring a potential protective association with AD.

Dietary supplements

A number of prospective studies [59–66] have examined vitamin E and vitamin C supplement use in relation to AD, and only one found evidence of a reduced risk of AD [66]. Traditionally, vitamin E supplements have contained only α-tocopherol, the most biologically active form of vitamin E; however, γ-tocopherol is the more abundant form in the US diet. Whilst α-tocopherol is the more potent antioxidant, γ-tocopherol also has anti-inflammatory properties [67]. Studies in humans indicate that the combined intake of the eight different forms of tocopherol reduces oxidative stress and inflammation to a greater degree than α-tocopherol alone [68].

The strongest evidence for antioxidant protection against AD rests with high dietary intake of vitamin E. The richest food sources of vitamin E include vegetable oils, margarine, nuts (especially almonds), and seeds (especially sunflower seeds). Moderate amounts of vitamin E are found in whole grains, egg yolk, and a limited number of vegetables (e.g., collard greens) and fruits (e.g., avocados, apples, melon).

Conclusions

Our understanding of dietary influences on AD is in its infancy; however, a growing number of epidemiological studies indicate that there is a strong relationship between nutrition and AD. Whilst saturated fats and high serum cholesterol is associated with an increased risk of AD, consumption of long-chain polyunsaturated omega-3 fatty acids (particularly DHA) and antioxidants such as vitamin E appear to lower risk. Persons should limit their intake of foods that are high in saturated and trans-unsaturated fats, such as red meats, butter, ice cream, and commercially baked products.

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Table 1

Adjusted relative risks[a] of incident AD by quintile of intake of specific types of dietary fats amongst 815 persons after 3.9 years of follow-up, CHAP, 1993–2000 [31]

	Type of fat			
Quintile	**Saturated**	**Trans**	**n-6 Polyunsaturated**	**Monounsaturated**
1	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
2	1.8 (0.7–4.3)	2.4 (1.1–5.3)	0.8 (0.4–1.6)	1.0 (0.4–2.3)
3	1.1 (0.5–2.8)	2.9 (1.2–7.2)	0.9 (0.4–1.6)	0.8 (0.3–2.2)
4	1.4 (0.5–3.6)	1.8 (0.8–4.2)	0.6 (0.2–1.6)	0.5 (0.2–1.2)
5	2.2 (1.1–4.7)	2.5 (1.0–6.2)	0.3 (0.1–0.8)	0.8 (0.4–1.8)

Multivariable relative risks are based on logistic regression models with terms from the age-adjusted model plus sex, race (black/white), education (years), *APOE* genotype (any ε4 allele versus none) and the interaction between race and *APOE* ε4. AD, Alzheimer's disease; CHAP, Chicago Health and Aging Project.

[a] *P*-value for linear trend is based on logistic regression models with the nutrient variable modeled as a continuous variable with persons in each quintile assigned the median value for that quintile.

Table 2

Multivariable relative risk of AD by quintile of intake of total omega-3 fatty acids, DHA and EPA amongst 815 persons after 3.9 years of follow-up, CHAP, 1993–2000 [47]

Quintile	Total omega-3 fatty acids	DHA	EPA
1	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
2	1.2 (0.5–3.0)	0.8 (0.3–2.1)	_[a]
3	0.6 (0.2–1.7)	0.4 (0.1–1.0)	1.1 (0.4–2.8)
4	0.7 (0.3–1.6)	0.2 (0.1–0.8)	0.5 (0.2–1.2)
5	0.4 (0.1–0.9)	0.3 (0.1–0.9)	0.9 (0.4–2.3)
P-value trend	0.01	0.02	0.40

The highest quintile of intake showed a 60% significant reduction in the relative risk of AD for total omega-3 fatty acid. There was a significant reduction with DHA beginning at the third quintile whilst EPA had no association with the risk of developing AD. Multivariable relative risks are based on logistic regression models with terms from the age-adjusted model plus sex, race (black/white), education (years), *APOE* genotype (any ε4 allele versus none), the interaction between race and *APOE* ε4 and period of observations (years). AD, Alzheimer's disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; CHAP, Chicago Health and Aging Project; *P*-value for linear trend is based on logistic regression models with the nutrient variable modeled as a continuous variable with persons in each quintile assigned the median value for that quintile.

[a]For this analysis, quintile two was combined with quintile one because the intake level was 0 g/day for 40% of the participants.