

# Alzheimer disease: protective factors<sup>1,2</sup>

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**ABSTRACT** Approximately 6–8% of all persons aged >65 y have Alzheimer disease and the prevalence of the disease is increasing. Any intervention strategy aimed at decreasing risks or delaying the onset of the disease will therefore have a substantial effect on health care costs. Nutrition seems to be one of the factors that may play a protective role in Alzheimer disease. Many studies suggest that oxidative stress and the accumulation of free radicals are involved in the pathophysiology of the disease. Several studies have shown the existence of a correlation between cognitive skills and the serum concentrations of folate, vitamin B-12, vitamin B-6, and, more recently, homocysteine. However, nutritional factors have to be studied not alone but with the other factors related to Alzheimer disease: genetics, estrogen, anti-inflammatory drug use, and socioeconomic variables. The objective of this article was to review recent studies in this field. *Am J Clin Nutr* 2000;71(suppl):643S–9S.

**KEY WORDS** Alzheimer disease, nutrition, estrogen, homocysteine, nonsteroidal antiinflammatory drugs

## INTRODUCTION

The pathologic origin and etiology of Alzheimer disease have remained unknown since the dementia was originally described in 1907. Alzheimer disease is the cause of more than half of all cases of dementia in elderly subjects; the economic cost of Alzheimer disease is higher than that of heart disease and cancer together (1). Approximately 6–8% of all persons >65 y of age have Alzheimer disease (2) and the prevalence of the disease is increasing rapidly (3). Any intervention strategy aimed at decreasing risks or delaying the onset of the disease will therefore have a substantial effect on health care costs. The objective of this article was to review various studies carried out in this field.

## THE INFLAMMATORY HYPOTHESIS IN ALZHEIMER DISEASE

One hypothesis of the etiology of Alzheimer disease is based on autopsy studies that have shown some inflammatory reactions to be important contributors to neuronal loss (4). Proteins present include complement proteins, complement inhibitors, inflammatory cytokines, protease, and protease inhibitors. Several studies have shown microglia to be most closely associated with neuritic plaques, possibly indicating that they play a role in converting diffuse senile plaques into the neuritic form (5, 6). Recently,

Netland et al (7) found that activated microglia surrounded immunopositive amyloid  $\beta$ -protein deposits but that this response was significantly attenuated in animals receiving indomethacin treatment. On the basis of these observations, it was suggested that a sequence of events is initiated by an unknown stimulus that activates the complement cascade, which in turn leads to an inflammatory reaction and cell destruction. The factor or factors that trigger the complement cascade are unknown. Blocking this cascade could be a major therapeutic pathway (8). A current view is that long-term use of nonsteroidal antiinflammatory drugs (NSAIDs) may decrease the risk of Alzheimer disease.

This view derives from epidemiologic studies that found that there may be an inverse relation between the occurrence of Alzheimer disease and those rheumatoid diseases requiring long-term NSAID treatment, although the results remain contradictory (range of odds ratios: 0.16–1.19) (9–16). Part of this contradiction is likely to be due to differences in methods used in the various studies.

In a longitudinal study, McGeer et al (17) found an odds ratio of 0.14 for Alzheimer disease risk in 923 elderly persons with rheumatoid arthritis (0.41%) compared with the general population of elderly persons (2.7%). This association between rheumatoid arthritis and decreased Alzheimer disease prevalence, however, was not found by Beard et al (18), who reported a frequency of 4.4% in a patient population with rheumatoid arthritis. Such inconsistencies may be attributed to the fact that the study by Beard et al was a retrospective study (1950–1975), and during that period the most widely used drugs were salicylates. The more powerful NSAIDs were introduced much later.

Mylykangas-Luosujarvi and Isomaki (19) analyzed the official death statistics for the year 1989 in the Finnish population aged >55 y. Alzheimer disease occurred significantly less frequently in patients with rheumatoid arthritis than in the rest of the population (0.12% compared with 0.54%; odds ratio: 0.23; CI: 0.065, 0.826). A logical interpretative basis for this observed negative relation between Alzheimer disease and rheumatoid arthritis or osteoarthritis is the use of NSAIDs. An interesting study by Breitner et al (14) of 50 pairs of twins with Alzheimer disease, 52% of whom were monozygotes, showed that the prior use of NSAIDs, corticosteroids,

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**TABLE 1**

Epidemiologic surveys of the relation between estrogen replacement therapy and Alzheimer disease (AD)

Reference and type of study	Estrogen users		OR and CI
	AD	Control	
	%		
Case-control			
Heyman et al (36) ( <i>n</i> = 23 AD, 56 control)	15	7.5	2.38
Graves et al (37) ( <i>n</i> = 60 AD, 60 control)	18	16	1.15 (0.5, 2.64)
Brenner et al (38) ( <i>n</i> = 107 AD, 120 control) <sup>1</sup>	49	48	1.1 (0.6, 1.8)
Paganini-Hill and Henderson (39) ( <i>n</i> = 138 AD, 550 control)	37.5	46	0.69 (0.46, 1.03)
Henderson et al (34) ( <i>n</i> = 143 AD, 92 control)	7	18	0.33 (0.15, 0.75)
Lerner et al (35) ( <i>n</i> = 56 AD, 101 control) <sup>1</sup>	29	45	—
Paganini-Hill and Henderson (40) ( <i>n</i> = 248 AD, 1198 control)	39	48.5	0.65 (0.49, 0.88)
Prospective			
Morrison et al (41) ( <i>n</i> = 38 AD)	—	—	0.44 (0.20, 0.97) <sup>2</sup>
Tang et al (42) ( <i>n</i> = 167 AD, 957 control)	5	15	0.40 (0.22, 0.85) <sup>2</sup>

<sup>1</sup>Nested case-control study.<sup>2</sup>Relative risk.

or both delayed the onset of the disease by 3 y. Andersen et al (20), who monitored an elderly population >55 y of age for >3 y, reported a rate of only 1.4% for Alzheimer disease in the NSAID users (5/365) compared with 2.5% in the other subjects (147/5893). After correction for the duration of the course of the disease, Rich et al (21) showed that Alzheimer disease patients who took NSAIDs (32 patients) were less seriously affected than were those who did not (177 patients). Corrada et al (22) carried out a prospective study between 1958 and 1994 in 1417 elderly men and 648 elderly women; during that period, 110 subjects developed Alzheimer disease. The relative risk (RR) of developing Alzheimer disease was lower for NSAID users and was inversely related to the duration of drug use. Similar results were also reported by Stewart et al (23).

Therapeutic trials with NSAIDs are rare and usually involve a small number of patients (24, 25). However, indomethacin seemed significantly more effective than a placebo in stabilizing cognitive skills when it was tested in Alzheimer disease patients (24). These results are still uncertain and the type of drug that should be used has not yet been defined. Some authors (26) have even reported a decrease in cognitive skills in users of the NSAIDs naproxen and ibuprofen. New evidence that cyclooxygenase is involved in neurodegeneration along with the development of selective cyclooxygenase inhibitors has led to renewed interest in the therapeutic potential of NSAIDs in Alzheimer disease (27).

## ESTROGEN AND ALZHEIMER DISEASE

The beneficial effects of estrogen replacement therapy, particularly on the cardiovascular system and in preventing osteoporosis, have been widely shown. Prominent among factors that may contribute to dementia and specifically to dementia of the Alzheimer type, is cerebral vascular disease (28). In both Alzheimer disease and the vascular dementias, cerebral blood

flow is diminished in regions of the brain affected by the disease process (29). Estrogen is a potent factor that not only prevents vascular disease but also improves blood flow in diseased vessels, including blood flow in regions of the brain affected by Alzheimer disease (28). In women, a history of myocardial infarction increases the risk of developing Alzheimer disease (30). Also, patients with Alzheimer disease tend to be thinner than others (31), and this decrease in weight is directly linked to a drop in the blood estrogen concentration in women after menopause (32). Some investigators stress the association between a low body mass index and alteration of cognitive functions (31, 33). However, the decrease in weight may also be a direct effect of the disease, and remains to be resolved.

The data on the relation between estrogen replacement therapy and Alzheimer disease are summarized in **Table 1**. As can be seen, the data are controversial. Several studies have suggested that estrogen treatment is beneficial in Alzheimer disease whereas others found no effect. The case-control study of the diagnosis of Alzheimer disease, based on death certificates, supports the view that the dose and duration of estrogen replacement therapy are protective variables against Alzheimer disease by Paganini-Hill and Henderson (39, 40). In 1994, from 2529 women who died between 1981 and 1992, Paganini-Hill and Henderson (39) identified 138 women with Alzheimer disease mentioned on the death certificate. The risk of Alzheimer disease and related dementia was less in estrogen users than in nonusers (OR: 0.69; 95% CI: 0.46, 1.03). Three years later (40), they found 248 women with Alzheimer disease mentioned on the death certificate. The protective effect of estrogen appears to be even more significant in more recent data from this group (OR: 0.65; 95% CI: 0.49, 0.88). This negative association was not seen by others (36, 37). However, the population samples sizes in these studies were small and few women were receiving estrogen replacement therapy.

Other investigators have stressed the possible effect of estrogen on verbal memory. Dementia-free, potentially estrogen-deficient women maintained their performance on verbal memory tests when treated with estrogen, whereas those taking a placebo showed decreased performance (43–45). Kimura (46) compared the neurocognitive skills of 2 groups of women of similar age (>50 y of age) and similar education; one group ( $n = 21$ ) was receiving estrogen replacement therapy and the other ( $n = 33$ ) was not. On the basis of this comparison, it was suggested that estrogen plays a protective role against the decline of intellectual faculties. The results of another study in this area conducted by Barrett-Connor and Kritz-Silverstein (47) refuted this hypothesis. This latter study started between 1972 and 1974 and involved 800 women who were monitored up to 1988–1991 (mean age:  $76.9 \pm 6.7$  y). A battery of 12 neuropsychologic tests showed no significant difference in neurocognitive skills between those who were receiving estrogen replacement therapy and those who were not. Nevertheless, those who had received estrogen replacement therapy in the past had a Mini-Mental State Examination (MMSE) score that was significantly higher than that of those who had never been treated.

In confirmed Alzheimer disease, estrogen seems to stabilize cognitive skills. Henderson et al (34, 48) showed a significantly higher MMSE score in the hormone-treated group of patients than in a group of patients who were not treated with estrogen but were otherwise similar in age, educational level, and duration of symptoms. Various therapeutic trials have yielded similar results (49–54) (Table 2). Randomized trials in this field are rare. Caldwell (49) and Kantor et al (50) reported an improvement in neurocognitive skills in estrogen-treated patients in comparison with the placebo groups, but the number of women with Alzheimer disease was not determined. Also, Honjo et al (51) reported a significant improvement in results of psychometric tests during the third week of estrogen treatment in women suffering from Alzheimer disease in comparison with placebo-treated control patients. Last, a double-blind, randomized, placebo-controlled trial to assess the effect of tacrine (Parke-Davis Pharmaceutical, Ann Arbor, MI) in Alzheimer disease, suggested that this agent has a synergetic effect when combined with estrogen (55). This observation requires further confirmation, particularly because the women who were treated with both drugs were younger and had a higher educational level than the other group of women.

A major drawback of these therapeutic trials is that the improvement in cognitive skills is associated with an improvement in symptoms of depression, and there is no information as to which of these 2 is the direct result of the hormone's action. Neither do we know the mechanism that underlies these putative hormone-related effects within the brain. These effects include the alleviation of depression, an increase in neuron growth factors, an increase in blood flow in the brain, an interaction with the different neurotransmitters, as well as antioxidation (56–58). Recently, Yaffe et al (59) published a meta-analysis of 10 studies of postmenopausal estrogen use and risk of dementia using standard meta-analytic methods. Meta-analysis of the studies suggested a 29% decreased risk of developing dementia in estrogen users. If large-scale controlled studies were to confirm these data, the potential advantages of estrogen replacement therapy would be reinforced.

Several studies have shown a relation of low education to dementia, and specifically Alzheimer disease (60). In the Canadian Study of Health and Aging (13), those with less education were at higher risk of Alzheimer disease, with an OR of 4.00 (95% CI: 2.49, 6.43) for those with 0–6 y, in comparison with those with >10 y. Recently, Launer et al (61) found in a prospective study of 528 dementia patients that low education level increased the risk of Alzheimer disease (RR: 4.55; 95% CI: 1.64, 12.57) in women with <8 y of education.

#### NUTRITIONAL FACTORS AND ALZHEIMER DISEASE

Nutrition seems to be one of the factors that may play a protective role in Alzheimer disease. Many studies suggest that oxidative stress and the accumulation of free radicals is involved in the pathophysiology of the disease (62, 63). An excess of free radicals is responsible for excessive lipid peroxidation, which can accelerate neuron degeneration (62).

One model for the study of aging is based on energy-restriction studies in animal models, which have shown that energy restriction is associated with extension of life expectancy (64–66). The data from these studies also showed that energy restriction is associated with a decrease in all the degenerative pathologies linked to the aging process, particularly to a delay in the appearance of degenerative brain disease (67–69). The mechanism by which

**TABLE 2**  
Clinical trials assessing the therapeutic effect of estrogen on cognitive skills<sup>1</sup>

Reference and type of study	Estrogen type and dose	Duration	Number of subjects treated	Number of subjects untreated	Outcomes
<b>Randomized</b>					
Caldwell (49)	2 mg estradiol/wk, im	12 mo	13	15	Significant improvement of total Wechsler Scale score in estrogen group
Kantor et al (50)	0.625 mg conjugated estrogen/d	3 y	25	25	Improvement of cognitive test results in estrogen group
Honjo et al (51)	1.25 mg conjugated estrogen/d	3 wk	7	7	Improvement in 1 of 3 cognitive test results in estrogen group ( $P < 0.05$ )
<b>Open</b>					
Fillit et al (52)	2 mg estradiol/d	6 wk	7	—	Improvement in 2 of 5 cognitive scale scores ( $P = 0.03$ ) compared with baseline score
Honjo et al (53)	1.25 mg conjugated estrogen/d	6 wk	7	7	Improvement in 1 of 2 cognitive scale scores ( $P < 0.05$ )
Ohkura et al (54)	1.25 mg conjugated estrogen/d	6 wk	15	15	Significant improvement in 2 cognitive scale scores compared with baseline

<sup>1</sup>im, intramuscular.

**TABLE 3**  
Relation between vitamin status and cognitive skills in elderly patients

Reference	Study population	Methods	Results and conclusions
Goodwin et al (72)	260 subjects >60 y of age	Evaluation of energy intake, plasma vitamin assays, memorization and abstraction tests	Correlation between low vitamin C and vitamin B-12 concentrations and decreased performance in cognitive test; correlation between low riboflavin or folic acid concentrations and poor scores on the abstraction tests
Tucker et al (73)	28 subjects aged >60 y in apparently good health	Electroencephalogram recorded while neuropsychologic tests are performed, biochemical assays	Significant relation between the highest thiamine and riboflavin concentrations, satisfactory responses to the tests, and intensity of global $\alpha$ activity; correlation between the recordings and vitamin C, carotene and vitamin A, folate, zinc, and iron concentrations
Lauque et al (87)	91 subjects, mean age 73 y	Evaluation of neuropsychologic skills and attention, evaluation of nutrition	Correlation between satisfactory cognitive skills, assessed by using the Weis code and dietary intake of thiamine, vitamin C, and vitamin B-6
Riggs et al (74)	70 male subjects aged 54–81 y	Cognitive tests (eg, verbal fluency, Boston naming test, and spatial copying test), biochemical assays	Correlation between high concentrations of homocysteine and low folate and vitamin B-12 with decreased performance in the spatial copying test (dexterity); correlation between high vitamin B-6 concentrations and improved performance in the memorization tests
La Rue et al (75)	137 subjects aged 66–90 y (longitudinal study carried out over 6 y)	Cognitive tests (Wechsler memory scale, Rey-Osterrieth complex figure test, Shipley-Hartford abstraction test), evaluation of dietary intake, biochemical assays	Correlation between improved abstraction performance and plasma concentrations and high thiamine, riboflavin, niacin, and folate intakes; correlation between better visual performance and high plasma vitamin C concentrations. Significant relation between past nutritional status assessed via biochemical markers (vitamins A, E, B-6, and B-12) and cognitive performance
Perrig et al (88)	442 subjects aged >65 y	Cognitive tests (working memory, free recall, recognition, Wais-R vocabulary test), biochemical assays	Correlation between high concentrations of ascorbic acid or $\beta$ -carotene and better cognitive performance
Ortega et al (89)	260 subjects aged 65–90 y	Mini-Mental State Examination, Pfeiffer's Mental Status Questionnaire, biochemical assays, evaluation of dietary intake	Diet depleted in fatty acids, saturated fatty acids, and cholesterol, but rich in carbohydrates, fibers, vitamins (folates, vitamins C and E, and $\beta$ -carotene), and minerals (zinc and iron) seems necessary to improve the general health of the subjects and also to improve cognitive skills

these restricted-energy diets affect longevity remains undefined. Nevertheless, it seems that one main effect is to decrease oxidative stress and production of free radicals (70). The possibility that energy restriction is also beneficial to human beings has not yet been explored, although there is a great likelihood that it would be as effective as that seen in animal models (71).

Several studies have shown a correlation between cognitive skills and the serum concentration of certain B vitamins (72–75). These correlations, which are the subject of an accompanying article by Selhub et al (76), have often been seen in subjects with Alzheimer disease. Alzheimer disease subjects usually have low serum vitamin concentrations, particularly vitamin B-12 (77–83). Ikeda et al (79) showed lower vitamin B-12 concentrations in the cerebrospinal fluid, but not in plasma, of patients with Alzheimer disease than in patients with other types of dementia. The nature of the relation between Alzheimer disease and vitamin B-12 deficiency is not yet known. Vitamin B-12 deficiency, folate deficiency, or both may lead to reduced synthesis of methionine and *S*-adenosylmethionine, which in turn could restrict the availability of the methyl groups that are essential for the metabolism of myelin, neurotransmitters such as acetylcholine, and membrane phospholipids (77). This putative hypomethylation could disturb some aspects of brain metabolism, which may be responsible for the development of cognitive impairment (75).

In recent years, there have been reports that deficiencies of folate, vitamin B-12, or vitamin B-6 are associated with increased plasma homocysteine concentrations (74–83). An elevation of plasma homocysteine is linked to an increased risk of vascular, cardiac, and cerebral pathologies. Excess homocysteine could have a deleterious effect on the blood vessel walls. This effect could explain why elderly subjects with long-term vitamin deficiencies develop minor neurologic disorders caused by small cerebrovascular lesions (84). The cognitive impairment that occurs in elderly subjects may therefore be mediated by homocysteine-related cerebrovascular lesions (75). Joosten et al (83) showed that subjects with Alzheimer disease had significantly higher concentrations of homocysteine and methylmalonic acid (a marker of vitamin B-12 deficiency) than those observed in dementia-free patients. These results suggest that there is a relation between a high homocysteine concentration and dementia. Bell et al (85) showed that 17% of depressive patients had high homocysteine concentrations, a proportion that was significantly higher than that seen in control subjects. Hyperhomocysteinemia appears to be another biochemical factor, in addition to apolipoprotein (apo) E/4, which both increase the risk of vascular disease and Alzheimer disease (86). In view of all these facts, trials with vitamin B supplements are warranted.

Other micronutrients may play a protective role against Alzheimer disease through their antioxidant effect. These

include vitamins A, E, C, and  $\beta$ -carotene as well as minerals such as zinc (73, 75, 87–89). Studies relating micronutrient status and cognitive impairment are summarized in **Table 3**.

Goodwin et al (72) showed a close relation between a decrease in cognitive test results and subdeficiencies of various vitamins and minerals in 260 subjects >60 y of age. A follow-up study of the same population after 10 y (75) confirmed these original results. In our study on food intake in an elderly population that had aged successfully (87), we also found a correlation between deficiency of zinc, vitamin C, and vitamin E and a higher number of errors on the Wechsler and Mésulam subtests of the Wechsler memory test. We confirmed these results recently with lower vitamin C plasma concentrations in Alzheimer disease patients than in control subjects (90). Sano et al (91) published a study showing the effect of treatment with 2000 IU vitamin E compared with placebo or selegiline in elderly subjects with Alzheimer disease; vitamin E effectively prolonged the patients' survival. However, the observed effect of vitamin E was not on cognitive skills. Projects are currently under way to carry out studies in patients with Alzheimer disease at a less serious stage. The doses of vitamin E to be used are still a subject of debate. In a prospective 4-y epidemiologic study of 633 elderly persons, Morris et al (92) found a lower incidence of Alzheimer disease in users of high amounts of vitamin C and vitamin E supplements than in nonusers.


Other investigators have studied the protective effect of red wine against Alzheimer disease. Orgogozzo et al (93) carried out a prospective study of 3777 elderly subjects aged >65 y who were living at home in the southwestern region of France. Mean daily alcohol consumption was recorded on the initial questionnaire with the main objective of identifying new Alzheimer disease cases according to the accepted criteria at 2 follow-ups: 1 after 1 y and 1 after 3 y. The authors showed that the incidence of Alzheimer disease was lower in subjects who drank a moderate amount of wine, between 250 and 500 mL/d (3–4 glasses/d) than in nondrinkers. Further information, however, is scanty; the possibility that moderate wine consumption may be a preventive measure against Alzheimer disease needs further confirmation.

Last, the apo E4 allele is known to be a risk factor for Alzheimer disease. Subjects with an apo E4 allele run a higher risk of developing Alzheimer disease than do those who do not have this allele. The preliminary findings, which were restricted to familial forms of Alzheimer disease, have been generalized to sporadic forms with any age of onset (94–97). The risk is even greater in homozygotes (98). In contrast, the apo E2 allele appears to be a protective factor against Alzheimer disease (97, 99, 100). In the New Mexico Aging Process Study, we studied cognitive skills in those with and without the E4 allele. The study involved a cohort of subjects in good general health with no Alzheimer-type pathology (101). The persons who presented with at least one E4 allele had more cognitive impairment and the difference was significant on the MMSE as well as on the reminder tests and other neurocognitive tests. These data were recently confirmed by a longitudinal study by O'Hara et al (102). In this 5-y study, older adults with the apo E3/4 genotype showed a significantly greater decline in performance on delayed recall of verbal material than did those with the apo E3/3 genotype.

This raises the problem of prevention policy. One could put forward the hypothesis that the risk of Alzheimer disease is likely to be higher when several risk factors are combined, especially when they are combined with genetic susceptibility. Cor-

rection of various deficiencies in micronutrients might prove to be particularly useful to these people.

## CONCLUSION

The pathophysiology of Alzheimer disease is very complex and may include genetic, physiologic, as well as nutritional elements, some of which may be linked. This alleged linkage offers the basis for potential intervention for the prevention or the slowing down of those processes that lead to Alzheimer disease. However, it is important to recognize that such an intervention can only be effective if it starts when the process of neurologic deterioration is in its early stages. Our understanding, and hence our ability to identify these early stages, is far from complete and effort must therefore be placed in this area and on development of strategies for intervention. 

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