Alzheimer disease: protective factors[1,2]

Fati Nourhashémi, Sophie Gillette-Guyonnet, Sandrine Andrieu, Anne Ghisolfi, Pierre Jean Ousset, Hélène Grandjean, Alain Grand, Jacques Pous, Bruno Vellas, and Jean-Louis Albarède

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, antiinflammatory 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 β-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.

Myllykangas-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,

[1] From the Department of Internal Medicine and Clinical Gerontology, University Hospital, Toulouse, France, and INSERM CJF 94-06, Toulouse, France.

[2] Address reprint requests to B Vellas, Centre de Geriatrie, CHU Purpan Casselardit, 31300 Toulouse, France. E-mail: vellas.b@chu-toulouse.fr.

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

[1] Nested case-control study.
[2] 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 of 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 in 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 ± 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[1]

Reference and type of study	Estrogen type and dose	Duration	Number of subjects treated	Number of subjects untreated	Outcomes
Randomized					
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 ($P < 0.05$)
Open					
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

[1] 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 α 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 Wais 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 β-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 β-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 accompaning 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 β-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 Wais 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. Correction 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.

REFERENCES

1. Schneider EP. The aging of America: impact on health care costs. JAMA 1990;263:2335–40.
2. Small GW, Rabins PV, Barry PP, et al. Diagnosis and treatment of Alzheimer disease and related disorders. Consensus statement of the American Association for Geriatric Psychiatry, the Alzheimer's Association and the American Geriatrics Society. JAMA 1997;278:1363–71.
3. Jorm AF, Korten AE, Henderson AS. The prevalence of dementia: a quantitative integration of the literature. Acta Psychiatr Scand 1987;76:465–79.
4. McGeer PL, McGeer EG. Glial cell reactions in neurodegenerative diseases: pathophysiology and therapeutic interventions. Alzheimer Dis Assoc Disord 1998;12(suppl):S1–6.
5. MacKenzie IRA, Munoz DG. Nonsteroidal anti-inflammatory drug use and Alzheimer pathology in aging. Neurology 1998;50:986–90.
6. Uchihara T, Akiyama H, Kondo H, Ikeda K. Activated microglial cells are colocalized with perivascular deposits of amyloid-beta protein in Alzheimer's disease brain. Stroke 1997;28:1948–50.
7. Netland EE, Newton JL, Majocha RE, Tate BA. Indomethacin reverses the microglial response to amyloid beta-protein. Neurobiol Aging 1998;19:201–4.
8. McGeer PL, Rogers J. Anti-inflammatory agents as a therapeutic approach to Alzheimer's disease. Neurology 1992;42:447–9.
9. Heyman A, Wilkinson WE, Stafford JA, Helms MJ, Sigmon AH, Weinberg T. Alzheimer's disease: a study of epidemiological aspects. Ann Neurol 1984;15:335–41.
10. French LR, Schuman LM, Mortimer JA, Hutton JT, Boatman RA, Christians B. A case-control study of dementia of the Alzheimer type. Am J Epidemiol 1985;121:414–21.
11. Broe GA, Henderson AS, Creasey H, et al. A case-control study of Alzheimer's disease in Australia. Neurology 1990;40:1698–707.
12. Li G, Shen YC, Chen CH, Zhau YW, Silverman JM. A case control study of Alzheimer's disease in China. Neurology 1992;42:1481–2.
13. Anonymous. The Canadian Study of Health and Aging: risk factors for Alzheimer's disease in Canada. Neurology 1994;44:2073–80.
14. Breitner JCS, Gau BA, Welsh KA, et al. Inverse association of anti-inflammatory treatments and Alzheimer's disease: initial results of co-twin control study. Neurology 1994;44:227–32.
15. Graves AB, White E, Koepsell TD, et al. A case-control study of Alzheimer's disease. Ann Neurol 1990;28:766–74.
16. Jenkinson ML, Bliss MR, Brain AT, Scott DL. Rheumatoid arthritis and senile dementia of the Alzheimer's type. Br J Rheumatol 1989;28:86–8.
17. McGeer PL, McGeer E, Rogers J, Sibley J. Anti-inflammatory drugs and Alzheimer disease. Lancet 1990;335:1037 (letter).
18. Beard CM, Kokman E, Kurland LT. Rheumatoid arthritis and susceptibility to Alzheimer's disease. Lancet 1991;337:1426 (letter).

19. Myllykangas-Luosujarvi R, Isomaki H. Alzheimer's disease and rheumatoid arthritis. Br J Rheumatol 1994;33:501–2.
20. Andersen K, Launer LJ, Ott A, Hoes AW, Breteler MMB, Hofman A. Do nonsteroidal anti-inflammatory drugs decrease the risk for Alzheimer's disease? The Rotterdam Study. Neurology 1995;45:1441–5.
21. Rich JB, Rasmusson DX, Folstein MF, Carson KA, Kawas C, Brandt J. Nonsteroidal anti-inflammatory drugs in Alzheimer's disease. Neurology 1995;45:51–5.
22. Corrada M, Stewart W, Kawas C. Nonsteroidal anti-inflammatory drugs and the risk of Alzheimer's disease. Neurology 1996;46:A433 (abstr).
23. Stewart WF, Kawas C, Corrada M, Metter EJ. Risk of Alzheimer's disease and duration of NSAID use. Neurology 1997;48:626–32.
24. Rogers J, Kirby LC, Hempelman SR, et al. Clinical trial of indomethacin in Alzheimer's disease. Neurology 1993;43:1609–11.
25. Bruce-Jones PNE, Crome P, Kalra L. Indomethacin and cognitive function in healthy elderly volunteers. Br J Clin Pharmacol 1994;38:45–51.
26. Goodwin JS, Regan M. Cognitive dysfunction associated with naproxen and ibuprofen in the elderly. Arthritis Rheum 1982;25:1013–5.
27. Pasinetti GM. Cyclooxygenase and inflammation in Alzheimer's disease: experimental approaches and clinical interventions. J Neurosci Res 1998;54:1–6.
28. Birge SJ. The role of estrogen in the treatment of Alzheimer's disease. Neurology 1997;48(suppl):S36–41.
29. Eberling JL, Jagust WJ, Reed BR, Baker MG. Reduced temporal lobe blood flow in Alzheimer's disease. Neurobiol Aging 1992;13:483–91.
30. Aronson MK, Ooi WL, Morgenstern H, et al. Women, myocardial infarction, and dementia in the very old. Neurology 1990;40:1102–6.
31. Berlinger WG, Potter JF. Low body mass index in demented outpatients. J Am Geriatr Soc 1991;39:973–8.
32. Meldrum DR, Davidson BJ, Tataryn IV, Judd HL. Changes in circulating steroids with aging in post menopausal women. Obstet Gynecol 1981;57:624–8.
33. Buckwalter JG, Schneider LS, Wilshire TW, Dunn ME, Henderson VW. Body-weight, estrogen and cognitive functioning in Alzheimer's disease: an analysis of the Tacrine study-group data. Arch Gerontol Geriatr 1997;24:261–7.
34. Henderson VW, Paganini-Hill A, Emanuel CK, Dunn ME, Buckwalter JG. Estrogen replacement therapy in older women. Comparisons between Alzheimer's disease cases and nondemented control subjects. Arch Neurol 1994;51:896–9.
35. Lerner A, Cole R, Debanne S, et al. Immunological and endocrine conditions in an Alzheimer's disease case-control study. Neuroepidemiology 1995;14:307 (abstr).
36. Heyman A, Wilkinson WE, Stafford JA, Helms MJ, Sigmon AH, Weinberg T. Alzheimer's disease: a study of epidemiological aspects. Ann Neurol 1984;15:335–41.
37. Graves AB, White E, Koepsell TD, et al. A case-control study of Alzheimer's disease. Ann Neurol 1990;28:766–74.
38. Brenner DE, Kukull WA, Stergachis A, et al. Postmenopausal estrogen replacement therapy and the risk of Alzheimer's disease: a population-based case-control study. Am J Epidemiol 1994;140:262–7.
39. Paganini-Hill A, Henderson VW. Estrogen deficiency and risk of Alzheimer's disease in women. Am J Epidemiol 1994;140:256–61.
40. Paganini-Hill A, Henderson VW. Estrogen replacement therapy and risk of Alzheimer disease. Arch Intern Med 1996;156:2213–7.
41. Morrison A, Resnick S, Corrada M, Zonderman A, Kawas C. A prospective study of estrogen replacement therapy and risk of developing Alzheimer's disease in the Baltimore longitudinal study of aging. Neurology 1996;46(suppl):A435–6.
42. Tang MX, Jacobs D, Stern Y, et al. Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. Lancet 1996;348:429–32.
43. Kampen DL, Sherwin BB. Estrogen use and verbal memory in healthy postmenopausal women. Obstet Gynecol 1994;83:979–83.
44. Phillips SM, Sherwin BB. Effects of estrogen on memory function in surgically menopausal women. Psychoneuroendocrinology 1992;17:485–95.
45. Sherwin BB, Tulandi T. "Add-back" estrogen reverses cognitive deficits induced by gonadotrophin-releasing hormone agonist in women with leiomyomata uteri. J Clin Endocrinol Metab 1996;81:2545–9.
46. Kimura D. Estrogen replacement therapy may protect against intellectual decline in postmenopausal women. Horm Behav 1995;29:312–21.
47. Barrett-Connor E, Kritz-Silverstein D. Estrogen replacement therapy and cognitive function in older women. JAMA 1993;269:2637–41.
48. Henderson VW, Watt L, Buckwalter JG. Cognitive skills associated with estrogen replacement in women with Alzheimer disease. Psychoneuroendocrinology 1996;21:421–30.
49. Caldwell BM. An evaluation of psychological effects of sex hormone administration in aged women. J Gerontol 1954;9:168–74.
50. Kantor HI, Michael CM, Shore H. Estrogen for older women, a three year study. Am J Obstet Gynecol 1973;116:115–8.
51. Honjo H, Tanaka K, Kashiwagi T, et al. Senile dementia—Alzheimer's disease type and estrogen. Horm Metab Res 1995;27:204–7.
52. Fillit H, Weinreb H, Cholst I, et al. Observations in a preliminary open trial of estradiol therapy for senile dementia-Alzheimer's type. Psychoneuroendocrinology 1986;11:337–45.
53. Honjo H, Ogino Y, Naitoh K, et al. In vivo effects by estrone sulfate on the central nervous system-senile dementia (Alzheimer's type). J Steroid Biochem 1989;34:521–5.
54. Ohkura T, Isse K, Akazawa K, Hamamoto M, Yaoi Y, Hagino N. Evaluation of estrogen treatment in female patients with dementia of the Alzheimer type. Endocr J 1994;41:361–71.
55. Schneider LS, Farlow MR, Henderson VW, Pogoda JM. Effects of estrogen replacement therapy on response to tacrine in patients with Alzheimers disease. Neurology 1996;46:1580–4.
56. Wickelgren I. Estrogen stakes claim to cognition. Science 1997; 276:675–8.
57. André G. Estrogènes et maladie d'Alzheimer: les mécanismes d'action. (Estrogen and Alzheimer disease: the mechanisms of action.) Reprod Hum Horm 1996;9:145–50 (in French).
58. Goodman Y, Bruce AJ, Cheng B, Mattson MP. Estrogens attenuate and corticosterone exacerbates excitotoxicity, oxidative injury, and amyloid B peptide toxicity in hippocampal neurons. J Neurochem 1996; 66:1836–44.
59. Yaffe K, Sawaya G, Lieburg I, Grady D. Estrogen therapy in postmenopausal women. Effect on cognitive function and dementia. JAMA 1998;279:688–95.
60. Ott A, Breteler MMB, van Harskamp F, et al. Prevalence of Alzheimer's disease and vascular dementia: association with education. The Rotterdam study. BMJ 1995;310:970–3.
61. Launer LJ, Andersen K, Dewey ME, et al. Rates and risk factors for dementia and Alzheimer's disease. Results from EURODEM pooled analyses. Neurology 1999;52:78–84.
62. Jaendel C, Nicolas MB, Dubois F, Nabet-Belleville F, Penin F, Cuny G. Lipid peroxidation and free radical scavengers in Alzheimer's disease. Gerontology 1989;35:275–82.
63. Frey WH, Najarian MM, Kumar KS. Endogenous Alzheimer's brain factor and oxidised glutathione inhibit antagonist binding to the muscarinic receptor. Brain Res 1996;714:87–94.
64. Masoro EJ. Dietary restriction and aging. J Am Geriatr Soc 1993; 41:994–9.
65. Nolen G. Effects of various restricted dietary regimens on the growth, health, and longevity of albino rats. J Nutr 1972;102:1477–94.
66. Masoro EJ. Food restriction in rodents: an evaluation of its role in the study of aging. J Gerontol Biol Sci 1988;43:B59–64.
67. Moore WA, Davey VA, Weindruch R, Walford R, Ivy GO. The effect of caloric restriction on lipofuscin accumulation in mouse brain with age. Gerontology 1995;41:173–85.
68. Weed JL, Lane MA, Roth GS, Speer DL, Ingram DK. Activity measures in rhesus monkeys on long-term calorie restriction. Physiol Behav 1997;62:97–103.
69. Ingram DK, Cutler RG, Weindruch R. Dietary restriction and aging: the initiation of a primate study. J Gerontol 1990;45:B148–63.

70. Yu BP, Yang R. Critical of the free radical theory of aging. Ann N Y Acad Sci 1996;786:1–11.
71. Velthuis-te Wierik EJ, van den Berg H, Schaafsma G, Hendricks HF, Brouwer A. Energy restriction, a useful intervention to retard human ageing? Results of a feasibility study. Eur J Clin Nutr 1994;48:138–48.
72. Goodwin JS, Goodwin JM, Garry PJ. Association between nutritional status and cognitive functioning in a healthy elderly population. JAMA 1983;249:2917–21.
73. Tucker DM, Penland JG, Sandstead HH, Milne DB, Heck DG, Klevay LM. Nutrition status and brain function in aging. Am J Clin Nutr 1990;52:93–102.
74. Riggs KM, Spiro A III, Tucker K, Rush D. Relations of vitamin B-12, vitamin B-6, folate, and homocysteine to cognitive performance in the Normative Aging Study. Am J Clin Nutr 1996;63:306–14.
75. La Rue A, Koehler KM, Wayne SJ, Chiulli SJ, Haaland KY, Garry PJ. Nutritional status and cognitive functioning in a normally aging sample: a 6-y reassessment. Am J Clin Nutr 1997;65:20–9.
76. Selhub J, Bagley LC, Miller J, Rosenberg IH. B vitamins, homocysteine, and neurocognitive function in the elderly. Am J Clin Nutr 2000;71(suppl):614S–20S.
77. McCaddon A, Kelly CL. Familial Alzheimer's disease and vitamin B12 deficiency. Age Ageing 1994;23:334–7.
78. Hector M, Burton JR. What are the psychiatric manifestations of vitamin B12 deficiency ? J Am Geriatr Soc 1988;36:1105–12.
79. Ikeda T, Furukawa Y, Mashimoto S, Takahashi K, Yamada M. Vitamin B12 levels in serum and cerebrospinal fluid of people with Alzheimer's disease. Acta Psychiatr Scand 1990;82:327–9.
80. Levitt AJ, Karlinsky H. Folate, vitamin B12 and cognitive impairment in patients with Alzheimer's disease. Acta Psychiatr Scand 1992;86:301–5.
81. Kristensen MO, Gulmann NC, Christensen JEJ, Ostergaard K, Rasmussen K. Serum cobalamin and methylmalonic acid in Alzheimer dementia. Acta Neurol Scand 1993;87:475–81.
82. Basun H, Fratiglioni L, Winblad B. Cobalamin levels are not reduced in Alzheimer's disease: results from a population based study. J Am Geriatr Soc 1994;42:132–6.
83. Joosten E, Lesaffre E, Riezler R, et al. Is metabolic evidence for vitamin B-12 and folate deficiency more frequent in elderly patients with Alzheimer's disease? J Gerontol A Biol Sci Med Sci 1997;52:M76–9.
84. Boushey CJ, Beresford SAA, Omenn GS, Motulsky AG. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. JAMA 1995;274:1049–57.
85. Bell IR, Edman JS, Selhub J, et al. Plasma homocysteine in vascular disease and in nonvascular dementia of depressed elderly people. Acta Psychiatr Scand 1992;86:386–90.
86. Diaz-Arrastia R. Hyperhomocysteinemia: a new risk factor for Alzheimer disease? Arch Neurol 1998;55:1–2.
87. Lauque S, Wegner A, Ousset PJ, et al. Etude comparative des apports alimentaires et des fonctions neuro-psychologiques explorées par le test de code de Wais. [Comparative study on nutritional intake and cognitive functions (WAIS code).] Age Nutr 1995;6:68–72 (in French).
88. Perrig WJ, Perrig P, Stèhelin B. The relation between antioxidants and memory performance in the old and very old. J Am Geriatr Soc 1997;45:718–24.
89. Ortega RM, Requejo AM, Andres P, et al. Dietary intake and cognitive function in a group of elderly people. Am J Clin Nutr 1997;66:803–9.
90. Riviere S, Birlouez-Aragon I, Nourhashemi F, Vellas B. Low plasma vitamin C in Alzheimer patients despite an adequate diet. Int J Geriatr Psychiatr 1998;13:749–54.
91. Sano M, Ernesto C, Thomas RG, et al. A controlled trial of selegiline, alpha tocopherol, or both as treatment for Alzheimer's disease. N Engl J Med 1997;336:1216–22.
92. Morris MC, Beckett LA, Scherr PA, et al. Vitamin E and vitamin C supplement use and risk of incident Alzheimer disease. Alzheimer Dis Assoc Disord 1998;12:121–6.
93. Orgogozzo JM, Dartigues JF, Lafont S, et al. Wine consumption and dementia in the elderly: a prospective community study in the Bordeaux area. Rev Neurol 1997;153:185–92.
94. Strittmatter WJ, Saunders AM, Schmechel D, et al. Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late onset familial Alzheimer disease. Proc Nat Acad Sci U S A 1993;90:1977–81.
95. Saunders AM, Strittmatter WJ, Schmechel D, et al. Association of apolipoprotein E allele E4 with late-onset familial and sporadic Alzheimer's disease. Neurology 1993;43:1467–72.
96. Chartier-Harlin MC, Parfitt M, Legrain S, et al. Apolipoprotein E, epsilon 4 allele as a major risk factor sporadic early and late-onset forms of Alzheimer's disease. Hum Mol Genet 1994;3:569–74.
97. Farrer LA, Cupples A, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. JAMA 1997;278:1349–56.
98. Poirier J. Apolipoprotein E in animal models of CNS injury and in Alzheimer's disease. Trends Neurosci 1997;17:525–30.
99. Corder EH, Saunders AM, Rish NJ, et al. Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. Nat Genet 1994;7:180–4.
100. Roses AD. Apolipoprotein E alleles as risk factors in Alzheimer disease. Annu Rev Med 1996;47:387–400.
101. La Rue A, Haaland KY. Neurological, psychological, cognitive function. In: Garry PJ, Owen GM, Eldridge TO, eds. The New-Mexico Aging Process Study 1980–1997. Albuquerque, NM: University of New Mexico Press, 1997:210–40.
102. O'Hara R, Yesavage J, Kraemer HC, et al. The APOE ϵ4 allele is associated with decline on delayed recall performance in community-dwelling older adults. J Am Geriatr Soc 1998;46:1493–8.