

IANA TASK FORCE ON NUTRITION AND COGNITIVE DECLINE WITH AGING

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Abstract: Cognitive impairment can be influenced by a number of factors. The potential effect of nutrition has become a topic of increasing scientific and public interest. In particular, there are arguments that nutrients (food and/or supplements) such as vitamins, trace minerals, lipids, can affect the risk of cognitive decline and dementia, especially in frail elderly people at risk of deficiencies. Our objective in this paper is to review data relating diet to risk of cognitive decline and dementia, especially Alzheimer's disease (AD). We chose to focus our statements on homocysteine-related vitamins (B-vitamins), antioxidant nutrients (vitamins E and C, carotenoids, flavonoids, enzymatic cofactors) and dietary lipids. Results of epidemiological studies may sometimes appear conflicting; however, certain associations are frequently found. High intake of saturated and trans-unsaturated (hydrogenated) fats were positively associated with increased risk of AD, whereas intake of polyunsaturated and monounsaturated fats were protective against cognitive decline in the elderly in prospective studies. Fish consumption has been associated with lower risk of AD in longitudinal cohort studies. Moreover, epidemiologic data suggest a protective role of the B-vitamins, especially vitamins B9 and B12, on cognitive decline and dementia. Finally, the results on antioxidant nutrients may suggest the importance of having a balanced combination of several antioxidant nutrients to exert a significant effect on the prevention of cognitive decline and dementia, while taking into account the potential adverse effects of these nutrients. There is no lack of attractive hypotheses to support research on the relationships between nutrition and cognitive decline. It is important to stress the need to develop further prospective studies of sufficiently long duration, including subjects whose diet is monitored at a sufficiently early stage or at least before disease or cognitive decline exist. Meta-analyses should be developed, and on the basis of their results the most appropriate interventional studies can be planned. These studies must control for the greatest number of known confounding factors and take into account the impact of the standard social determinants of food habits, such as the regional cultures, social status, and educational level.

Key words: Dementia, cognitive fonction, micronutrients, macronutrients, malnutrition, frailty.

The human life span is increasing and there is a need to maintain functional well-being in old age. Cognitive function is a major determinant of quality of life in older age. The number of elderly subjects who will suffer from cognitive impairment and dementia will further increase in the near future as a consequence of the progressive ageing of the population. The onset of dementia is insidious, and the underlying pathologies are believed to be active for many years before the cognitive loss becomes apparent. Strategies to prevent the onset of cognitive impairment and slow down its progression in older persons are therefore needed. Cognitive impairment can be influenced by a number of factors and the potential effect of nutrition has become a topic of increasing scientific and public interest. In particular, there are arguments suggesting that nutrients (food and/or supplements) such as vitamins, trace minerals or lipids can affect the risk of cognitive decline and dementia, especially in frail elderly people at risk of deficiencies.

Clarification of the relation between nutrients and cognition through epidemiological studies is important because consistent evidence of a prospective association would more strongly support the need for intervention trials testing the effectiveness of nutrient therapy in preventing cognitive decline and dementia. Our objective in this paper is to review data relating diet to risk of cognitive decline and dementia, especially Alzheimer's disease (AD). We chose to focus our statements on homocysteine-related vitamins (B vitamins), antioxidant nutrients (vitamins E and C, carotenoids, flavonoids, enzymatic cofactors) and dietary lipids, which are some of the more common nutrients addressed in the recent scientific literature. We consider in turn the age-related changes in nutrients involved in brain functioning and the epidemiological evidence on macro- and micronutrients in relation to age-related cognitive decline and dementia. We then go on to discuss methodological statements and future research directions.

Age-related changes in nutrients involved in brain functioning

We describe in this section age-associated changes in nutritional status which may affect brain functioning. As an indication, we show in Appendix 1 the Recommended Dietary Allowances (RDAs) for the elderly in the United States (US) and France.

Dietary habits, nutrient intakes and ageing processes are interrelated and are of particular importance among the elderly. Older people are often at nutritional risk not only because of alterations in taste and smell, or impaired digestion, absorption or utilisation of nutrients due to chronic disease or drug-nutrient interactions, but also as a result of various physical, socioeconomic and behavioural factors that may limit the quantity or quality of food ingested. In particular, ageing is accompanied by major stages which lead to changes in eating habits: retirement and cessation of outside activity, involving reorganisation of daily life (fewer meals taken outside the home, lower income, redistribution of domestic roles, fewer invitations and loss of friends and family leading to less varied meals); declining health and loss of independence requiring the provision of assistance because of difficulty with shopping and meal preparation (meal delivery, medical surveillance of diet); and sometimes admission to an institution. As appetite and the quantity of food consumed decline, the quality of dietary intake becomes increasingly important with advancing age. A high quality of diet was positively related to survival and to a delay in the deterioration in health status in a European population living at home at older ages (1-4). Moreover, studies provide evidence that low intakes of energy (<21 kcal/kg) and selected nutrients (vitamins D, E, C, folates, carotenoids) are independently associated with frailty, which is common in older adults and is considered as a state of high vulnerability for adverse health outcomes including disability, dependency, falls, need for long-term care and mortality (5-7).

At the present time, very few data are available on the dietary habits of the elderly. Feart et al (8) studied macronutrient consumption in a population of aged persons living in France to seek possible associations between the pattern of consumption and sociodemographic characteristics. A nutritional investigation (24-hour recall) was carried out in 1786 participants in the Three City (3C) study (666 men, 1120 women, mean age 77 years). Mean energy intake differed according to sex (2005 kcal/day for men vs. 1514 kcal/day for women; $p < 0.0001$), decreased significantly with age and increased with educational level and income. 73% of subjects had a total energy intake (TEI) of less than 30 kcal/kg/day. Protein consumption (a mean of 18% of TEI) differed according to sex and 44% of subjects consumed less than 1 g/kg/day of protein. Women consumed more carbohydrate (46% of TEI). Fat made up 30.5% of TEI in men and 31.5% in women, mostly in the form of saturated fatty acids (43% of total fat). Polyunsaturated fatty acids (PUFA) accounted for

15% of total fat. Consumption of omega-6 PUFA, as well as the omega-6/omega-3 ratio, were higher in subjects with low education than in those with a high educational level. The decrease of mean intake of energy and macronutrients with age was previously described in the Euronut-Seneca (Survey in Europe on Nutrition and the Elderly, a Concerted Action) study, conducted among people aged 70-75 years in 12 European countries (9, 10). These data are of particular interest as they allow us to identify sub-groups of elderly at risk of nutritional deficiencies who could benefit from specific nutritional programmes.

Epidemiological studies commonly demonstrate that elderly sectors of the population have higher rates of nutritional deficiency, in particular deficiencies of antioxidant nutrients (β -carotene, vitamins C and E, zinc, selenium) or B vitamin (11-19). Descriptive analysis of the vitamin data collected at baseline and 4 years later in the Euronut-Seneca cohort showed that there is considerable diversity in the vitamin status of the inhabitants of the European regions examined, with no definite geographical pattern emerging, suggesting that the vitamin data must be analysed together with other aspects of nutrition, anthropometry, life-style and health to allow meaningful interpretation of all data (12, 14). Markers used to estimate prevalence of nutrient deficiencies differ widely between studies. There is considerable inter-assay variability in vitamins, especially in folate and vitamin B12, making application of uniform cut-off values almost impossible. We can however draw an overall picture.

Prevalence of B-vitamin deficiencies

The metabolisms of folate and vitamin B12 are closely linked. These vitamins are two important co-factors involved in the common metabolic pathway and play a part in the methylation processes that are essential for brain function. Vitamin B12 deficiency is common with older age, occurring in more than 20% of persons 65 years and older (3, 20), as the result of increased prevalence of gastritis and other digestive conditions that interfere with absorption (21). Individuals with biologically significant vitamin B12 deficiency almost always have elevated plasma levels of total homocysteine (Hcy) and methylmalonic acid (22, 23). Consequently, measurement of blood levels of either of these metabolites can be used to confirm the diagnosis of vitamin B12 deficiency. Similarly, individuals with reduced folate status have elevated levels of Hcy. It has been reported that on average about 1 in 20 people aged 65-74 had low vitamin concentration levels (serum vitamin B12 <150 pmol/L) or had metabolically significant vitamin B12 deficiency (<200 pmol/L and Hcy >20 μ mol/L). About 1 in 10 people aged 75 years or older had low vitamin B12 levels or metabolically significant B12 deficiency. Similar estimates for each age group were found for prevalence of folate deficiency (serum folate <5 nmol/L) or metabolically significant folate deficiency (<7 nmol/L and Hcy >20 μ mol/L). Only about 10% of people with low vitamin B12 levels also

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had low folate levels (24, 25). Additionally, recent data based on a population of 579 nondemented elderly (Baltimore Longitudinal Study of Aging, ≥ 60 years) showed that dietary intake ranged from 204.8 to 341.6 $\mu\text{g/day}$ (median: 259.5) for folate, 1.4 to 2.2 mg/day (median: 1.8) for B6 and 3.1 to 6.4 $\mu\text{g/day}$ (median: 4.4) for vitamin B12. For folate, the median of total intake was below the dietary reference intake (DRI) whereas it was well above the DRI for total intake of B6 and B12. Only 13% of participants ($n=73$) reached DRI levels of folate with diet alone. However, diet alone was sufficient for most participants to reach the DRI for vitamin B12 (87%) and vitamin B6 (81%) (26).

As yet, data on plasma tHcy values in the elderly are insufficient. The normal range of plasma Hcy levels is 5-15 $\mu\text{mol/L}$. Hyperhomocysteinemia is defined as a plasma Hcy level $>15 \mu\text{mol/L}$ and is classified as moderate (15-30 $\mu\text{mol/L}$), intermediate (30-100 $\mu\text{mol/L}$) or severe ($>100 \mu\text{mol/L}$). The prevalence of hyperhomocysteinemia in the general population is between 5 to 10%. However, the rate may be as high as 30% in the population older than 65 years, according to the Framingham study (27).

Since the US fortification programme in 1998, folate deficiency (serum folate $<6.8 \text{ nmol/L}$) has been reported to occur in 0.5% of the general population compared to 16% before fortification (28); among persons aged 65 years and older who may be at higher risk for B12 deficiencies, there are higher percentages of both Whites and Blacks consuming more than 1000 $\mu\text{g/day}$ (the Tolerable Upper Intake level) since fortification (29). The prevalence of hyperhomocysteinemia may also have declined by approximately 50% in the US (27). In a recent study performed among 2196 participants in the Maracaibo Aging Study, aged over 55 years, plasma tHcy values ranged from 4.1 to 31.8 $\mu\text{mol/L}$ with a median of $11.5 \pm 4.7 \mu\text{mol/L}$. The values increased with age, were significantly higher in men than in women, and exhibited inverse correlations with folate and vitamin B12 (30). Data from the National Health and Nutrition Examination Survey showed a mean value of plasma tHcy of $9.27 \pm 0.08 \mu\text{mol/L}$ for men aged 51 to 70 years and $11.30 \pm 0.15 \mu\text{mol/L}$ for men older than 70 years; for women, mean values for these age groups were $7.88 \pm 0.10 \mu\text{mol/L}$ and $10.18 \pm 0.22 \mu\text{mol/L}$, respectively (31).

We underline the fact that the large difference in reference values for folates between different countries has led to the exclusion of an incredibly vast number of patients from the Alzhemed trial because of the application of American norms which are not appropriate for the European population.

Prevalence of antioxidant nutrient deficiencies

Age is an important determinant of serum values of antioxidants, especially for α -tocopherol, β -carotene and vitamin C (32, 33). A relationship between oxidative stress (TBAR-S, plasma thiol group, total glutathione) and age in a free-living healthy elderly population was also addressed in a recent work (34). Data for prevalence of selected antioxidant

nutrient deficiencies are available in only a few studies and are heterogeneous. A study performed among 420 individuals, aged 79 years or older (Iowa Rural Health Study), showed that the percentage of subjects with inadequate intakes of selected nutrients exceeded 60% for vitamin E and 25% for vitamin C or zinc (18). Prevalence of vitamin E deficiency (\bullet -tocopherol $< 11.6 \mu\text{mol/L}$) was estimated at 1.1% in the European Euronut-Seneca cohort at baseline and decreased with age (0.6% after a 4-year follow-up period) (14). Data collected among 981 healthy community-dwelling elderly subjects participating in the Zincage project showed that plasma zinc was lower in nonagenarians compared with younger subjects. The prevalence of zinc deficiency ($<10 \mu\text{mol/L}$) increased with age, with normal zinc levels ($>11 \mu\text{mol/L}$) observed in about 80% of adult subjects and in only 37% of nonagenarians (35). In the Zenith study, the percentage of subjects presenting a zinc deficiency was 4.8% in middle-aged subjects (55-70 years) and 5.6 in older subjects (70-87 years). The percentage of subjects whose intake was below 2/3 of the European RDA for people older than 55 years was 3.20% in middle-aged subjects and 3.55% in older subjects (36). In the Etude du Vieillissement Artériel (EVA) study, only a small number of individuals had baseline selenium concentration below the cut-off level of 0.75 $\mu\text{mol/L}$, which has been defined by a group of European experts as a value related to selenium subdeficiency (37, 38). Selenium concentrations were in the same range as those in most European populations (39) but lower than the suggested optimal plasma selenium concentration for glutathione peroxidase activity (1.25 $\mu\text{mol/L}$). Low plasma selenium concentrations were associated with higher mortality even after controlling for various potential confounding factors. These results are in agreement with the low percentages of selenium deficiencies reported as a possible explanation for longevity in the nonagenarian-centenarian study (40).

The epidemiological evidence on macro- and micronutrients in relation to age-related cognitive decline and dementia

Epidemiological data on diet and cognitive decline in humans suggest that certain macro- and micronutrients may have a preventive effect even if data are still conflicting: higher intake of vitamin C, vitamin E, flavonoids, unsaturated fatty acids, fish; higher levels of vitamin B12 and folate; and lower total fats have been linked to a lower risk for AD or slower cognitive decline. At the same time, other studies have found that the risk for AD or cognitive decline is not associated with intake of antioxidants such as vitamin C, vitamin E and carotenes, to fats or to levels of vitamin B12. Dietary pattern (e.g. Mediterranean diet) analysis in relation to cognitive decline and AD has also recently received growing attention.

Most of the evidence relating to the prevention of cognitive decline is derived from animal and observational studies, which may be cross-sectional, case-control or longitudinal. Several cross-sectional studies have indicated a relation between

particular nutrients and the presence of cognitive impairment and AD. However, while cross-sectional studies are useful for hypothesis generation, the findings cannot be interpreted as evidence for a protective effect of nutrients, largely because it is impossible to determine whether an observed relation is a cause or an effect of a disease process. Case-control studies share similar problems. Prospective cohort studies that assess nutrient exposure in a group initially unaffected by disease and follow the group over time for incident disease provide the correct temporal relation for a cause-effect interpretation of diet-disease associations (41). We consequently chose to summarize only prospective studies. We also report findings from randomised clinical trials (RCT) (Tables 1 to 3).

Macronutrients

Potential biological mechanisms

Among the macronutrients, fatty acids have been suggested to play a role in modulating the risk of cognitive impairment and dementia based on observational studies. The degree of saturation of fatty acids and the position of the first double bond in essential fatty acids are the most critical factors determining the effects of dietary fats on the risk of cognitive decline or dementia. The interaction of dietary lipids and apolipoprotein E (ApoE) isoforms may determine the risk and rate of sustained autoperoxidation within cellular membranes and the efficacy of membrane repair. Fatty acids can be categorized briefly into saturated fatty acids (SFA) and unsaturated fatty acids (UFA). SFA, such as stearic acid, are present in products such as meat, dairy products, cookies and pastries. Monounsaturated fatty acids (MUFA) are most frequently consumed in olive oil. Polyunsaturated fats comprise two major classes: the n-6 class (e.g. linoleic acid [18:2n-6] and arachidonic acid [20:4n-6]) and the n-3 class (e.g. α -linolenic acid [18:3n-3], eicosapentaenoic acid [EPA 20:5n-3] and docosahexaenoic acid [DHA 22:6n-3]). Polyunsaturated fatty acids (PUFA) are a primary component of neuronal membrane phospholipids and are essential for brain development and functioning. In addition to their role in the composition and fluidity of neuron membranes and their vascular properties, PUFA have a modulating effect on neuro-inflammation, pro-(n-6) vs. anti-inflammatory (n-3), which is involved in neurodegenerative pathology. Fatty fish is the primary dietary source of the longer chain n-3 fatty acids, EPA and DHA. The main sources of n-6 PUFA are vegetable oils (42).

Prospective studies of fatty acids in relation to cognitive decline and dementia

The studies of dietary fat and cognitive decline or dementia are inconsistent (Table 1). In the EVA study, higher levels of n-3 fatty acids in erythrocyte membranes were associated with reduced risk of cognitive decline over 3 years, whereas higher levels of n-6 fatty acids were associated with increased cognitive decline (43). A significant 47% reduction in the risk

of developing all-cause dementia was also observed for subjects in the upper quartile of baseline plasma phosphatidylcholine (PC) DHA in the Framingham study (44). A higher risk of AD was observed with increased intake of saturated fat in the Rotterdam study (45), but subsequent analysis after 6 years of follow-up found no association for any type of fat (46). It is possible that the shorter follow-up period (2.1 vs. 6 years) of the first study, and a consequently smaller number of incident cases of dementia, may explain discrepancies. In the Chicago Health and Aging Project (CHAP) analyses, persons with high intakes of either saturated or trans fats experienced 2 to 3 times the risk of incident AD (47) and a faster rate of cognitive decline (48). Similar results were recently found in the Italian Longitudinal Study on Aging (ILSA), where high MUFA and PUFA energy intakes were associated with a better cognitive performance among elderly people aged 65-84 years (49). These results must however be interpreted cautiously as n-3 and n-6 PUFA were not studied independently. To our knowledge, only one study has investigated the impact of dietary fatty acids on the rate of mild cognitive impairment (MCI), and no statistically significant association was found; high PUFA intake appeared to have however a borderline non-significant trend for a protective effect against the development of MCI (50).

In the Washington Heights-Inwood Columbia Aging Project (WHICAP) study, higher fat intake was associated with double the risk of incident AD but only among participants who had the ApoE4 genotype (51). A similar pattern was found in a Finnish study, in which high saturated fat intake in mid-life was associated with increased risk of late-life dementia and moderate intake of PUFA with a decreased risk, especially among ApoE4 carriers (52). These two studies underline the problem of complex interactions between nutritional intakes and genetic characteristics, especially for genes involved in lipid metabolism and transport. Finally, a strong statistical interaction was recently observed in the CHAP cohort between saturated and trans fats and copper intake (53) in accordance with a recent animal model (54), in which neurodegenerative changes caused by a hypercholesterolemic diet were exacerbated by consumption of trace amounts of copper in drinking water.

Several epidemiological studies reported findings of a lower risk of AD and cognitive decline among fish consumers. Five longitudinal studies have shown a significant relationship between regular fish consumption (at least weekly) and decreased risk of incident dementia (55-58) or cognitive decline (59). Barberger-Gateau et al (60) have recently examined the correlates of regular fish consumption in elderly community dwellers from the Three City study in order to identify potential confounders in the relationship between fish consumption and dementia. They found that socioeconomic status (education, income), intake of fruit, vegetables and alcohol, hypertension, past stroke, and depressive symptomatology were potential confounders in the relationship between fish consumption and

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dementia. All these factors have previously been found to be associated with risk of dementia, either in a protective or a detrimental way. According to the authors, these findings suggest that their potential confounding effect should be systematically considered when studying nutritional risk factors of dementia.

Potential benefits of n-3 PUFA supplementation: data from RCT

RCT are the only means to definitely exclude confounders from the true effect of fish components such as n-3 PUFA on dementia and cognitive decline, and to determine the optimal intake. To date, three clinical trials on n-3 fatty acids are in process in elderly people, and are testing: 1/ the effects on cognitive decline of n-3 PUFA (EPA and DHA) at high dose (1.8 g/day) and low dose (400 mg/day) compared with placebo for 26 weeks in 300 persons aged 65 years and older (61); 2/ the effects of 900 mg/day of DHA for 24 weeks on improved cognitive functioning among elderly people (age \geq 55 years) with a subjective memory complaint (62); and 3/ the effects of 0.5 g/day of DHA and 0.2 g/day of EPA for 24 months in healthy cognitively normal adults aged 70-79 years (Older People And n-3 Long chain polyunsaturated fatty acids (OPAL) study) (63).

To our knowledge, a single randomised clinical trial has been published examining the effect of n-3 fatty acid supplementation on cognitive functioning, assessed by MMSE and ADAS-cog, in patients with mild to moderate AD (64). It did not document any effect in patients with mild to moderate AD at 6 months. However, positive effects were observed in a small group of patients with very mild AD (MMSE $>$ 27 points).

In conclusion, high intakes of saturated and trans-unsaturated (hydrogenated) fats were positively associated with increased risk of AD, whereas high intakes of polyunsaturated and monounsaturated fats were protective against cognitive decline in the elderly in prospective studies. Fish consumption (n-3 PUFA) has been associated with lower risk of AD in longitudinal cohort studies. N-3 PUFA could have a preventive effect against dementia through their anti-thrombotic and anti-inflammatory properties in addition to their specific effect on neural functions.

Homocysteine-related vitamins (B vitamins)

Potential biological mechanisms

Much attention has been given to B vitamins (especially, folate, vitamins B12 and B6) as preventive factors against cognitive decline and dementia (27,41,65-69). The primary theoretical basis for this argument rests on the known relations of folate, vitamin B12 and vitamin B6 as co-factors in the methylation of Hcy, and the importance of deficiencies in these nutrients to increased Hcy concentration (22-23,70-71). Supraphysiological levels of Hcy are neurotoxic in cell culture

and in vivo mouse models, suggesting that Hcy toxicity may have a direct effect on cognitive decline. Numerous studies in recent years have investigated the role of Hcy as a cause of brain damage. Hcy itself, or folate and vitamin B12 deficiency, can cause disturbed methyl-action and/or redox potentials thus promoting calcium influx, amyloid and tau protein accumulation, apoptosis and neuronal death (72-77). The Hcy effect may also be mediated by activating the N-methyl-D-aspartate receptor subtype (78). Numerous neurotoxic effects of Hcy can be blocked by folate, glutamate receptor antagonists or various antioxidants (79-80). In addition to the Hcy theory, other potential biological mechanisms of B vitamins are proposed. The folate cycle, which synthesises methyl groups, is essential for many genomic and non-genomic methylation reactions via S-adenosylmethionine and, indirectly, for the synthesis of nucleotides and DNA (66).

Prospective studies of B vitamins and Hcy in relation to cognitive decline and dementia

Among prospective studies examining the relation between B vitamins and cognitive decline in the healthy elderly (81-85), only two studies found a prospective association with low folate levels (81,84). One study found an unexpected detrimental effect with faster decline among persons who had high folate intakes ($>$ 400 μ g/day) (82). The mechanisms by which high folate intake may increase cognitive decline are not clear. With widespread multivitamin use and folic acid fortification, it is likely that a significant percentage of the population is consuming more than the upper limit and well above the dietary reference intake of 400 μ g/day (Table 2).

Moreover, there are a limited number of prospective cohort studies on B vitamins and dementia, and the findings have not been consistent. Seven prospective studies examined levels of the B vitamins and Hcy in relation to incident dementia (26,86-91). Of four studies that used serum measures (88-91), one found a significantly greater risk of developing AD among persons who had low levels of either vitamin B12 (\leq 150 pmol/L) or folate ($<$ 10 nmol/L) (91) and another study also observed greater risk in subjects with low serum folate levels ($<$ 11.8 nmol/L) (88). In the Framingham study, there was no association with serum measures of the B vitamins, although Hcy concentration was positively associated with higher risk of incident AD. This study reported that baseline hyperhomocysteinemia (tHcy $>$ 14 μ mol/L) was associated with almost double the risk of dementia and AD over an 8-year follow-up period (90). Nevertheless, these data have yet to be replicated. In the WHICAP study, no association between baseline Hcy and subsequent risk of dementia or cognitive decline was found (89). Three other studies have examined dietary intake of B vitamins with incident AD; results were also inconsistent. High folate intake was associated with reduced risk of developing AD in the Baltimore Longitudinal Study of Aging (26), but there was no association with vitamin supplement and/or food intake of folate in the CHAP study

(87). The data from the Baltimore Longitudinal Study of Aging are consistent with those of Luchsinger et al (86), who showed that higher folate intake may decrease the risk of AD independent of other risk factors and levels of vitamins B6 and B12 among 965 persons 65 years older followed up for a mean period of 6 years. In both studies, no association was found with total intake of vitamins B12 or B6.

Potential benefits of B-vitamin supplementation: data from RCT

Four small clinical trials tested the effects of supplementation with one or more of folic acid, vitamin B12 and vitamin B6 among healthy individuals (92) or cognitively impaired and demented older individuals (93-95). They found no effect on cognition. One possible explanation is that these studies may have been underpowered to detect small effects. According to a recent Cochrane review (96), it was not possible to pool the data because the trials studied different populations, different doses of folic acid, and in a case of one trial, vitamin B12 was also given. Moreover, the study of Sommer (94) did not provide enough data for interpretation: enrolment involved an unspecified small number of patients with AD who received 10 mg of folic acid for an unspecified period, and measures of cognition and mood were not reported (96-97). In a more recent trial conducted by Eussen et al (98), 195 older persons, free-living or in care-facility homes, were randomised to receive 1000 µg of vitamin B12, or 1000 µg of vitamin B12 plus 400 µg of folic acid, or placebo for 24 weeks. There was no positive benefit on cognition, assessed by an extensive neuropsychological test battery, of either vitamin B12 or vitamin B12 plus folic acid, although the vitamin B12 deficiency was corrected. The small number of subjects and the short duration of intervention are probably the major limitations of this trial. Another trial conducted among 276 healthy older people (65 years and older) aimed to test the hypothesis that lowering the plasma Hcy concentration, with a daily supplement containing folate (1000 µg) plus vitamins B12 (500 µg) and B6 (10 mg), improves cognitive function. The plasma Hcy concentration was lower in the vitamin group than in the placebo group but no result was in favour of a beneficial effect of vitamin B supplementation on cognitive performance (99). Finally, the effect of 3-year folic acid supplementation (800 mg/day vs. placebo) on cognitive function was tested in 818 men and women aged 50 to 70 years. People recruited were most likely to benefit from folate supplementation, and have high plasma concentrations of Hcy (≥ 13 mmol/L) and normal serum vitamin B12 (≥ 200 pmol/L). This trial showed that folic acid significantly improved memory, sensorimotor speed and information processing speed. Biochemical measures of folate were significantly increased and plasma tHcy concentrations decreased by 26% in subjects on folic acid vs. placebo (100).

In conclusion, the existing epidemiological evidence for protective associations of the B vitamins is a first step but it is still limited. A major limitation of many of the prospective

studies of B vitamins that could account for the inconsistent findings is the lack of statistical control for dietary confounders (41,87). Confounding bias is particularly likely for folate intake as it is associated with many dietary (e.g. antioxidant nutrients, other B vitamins, dietary fats) and other healthy lifestyle variables that have been implicated as protective factors for AD and cognitive decline. More prospective studies are consequently needed that adequately control for dietary confounders including carotenoids, especially lutein, niacin, dietary fats, and indicators of vitamin B12 deficiency such as methylmalonic acid.

Antioxidant nutrients

Potential biological mechanisms

Experimental, clinical, neuropathological and epidemiological investigations have implicated oxidative stress, involving the accumulation of free radicals with resultant oxidative damage, as a possible factor in the pathogenesis of cognitive decline and dementia. Recent data suggested that lipid peroxidation is an early event in the brain in amnesic mild cognitive impairment (101). Select antioxidants, including vitamins E, C, carotenoids, polyphenols (flavonoids), and enzymatic cofactors of superoxide dismutase and glutathione peroxidase (zinc, selenium, manganese), may reduce neuronal damage and death from oxidative reactions by inhibiting the generation of reactive oxygen species (ROS), lipid peroxidation, apoptosis, protein oxidation, damage to cell membranes and/or DNA and beta-amyloid toxicity or deposition (102-103). Finally, it has been suggested that vitamins E and C, carotenoids, and flavonoids may lose their effectiveness as antioxidants or even act as prooxidants under certain circumstances in vitro, for example, at high concentration or high partial pressures of oxygen, in the presence of metal ions such as iron or copper, under mild oxidative conditions without coantioxidants, and at a high concentration of carotenoid itself (104). It has also been established that iron may generate ROS through the Fenton reaction. The dual role of iron as a necessary, but potentially toxic, element for normal neuronal function is currently discussed (105). The possibility that the production of ROS is a primary event of cognitive decline has led to research exploring how antioxidants in foods and supplements can affect cognitive decline and dementia (106).

Prospective studies of antioxidant nutrients in relation to cognitive decline and dementia

Data published in the EVA study have suggested that free oxygen radicals may be involved in cognitive impairment (107). In this study, the relationship between the enzymatic system, restricted to copper zinc superoxide dismutase (CuZn-SOD) and seleno-dependent glutathione peroxidase (GSH-Px), and decline in cognitive function was investigated among 980 subjects aged 62-72 years. Cognitive decline over a 4-year

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period was associated with lower activity of the protective GSH-Px and higher activity of the ambiguous CuZn-SOD. Variation in the CuZn-SOD/GSH-Px ratio suggested that the equilibrium between these two enzymes is related to cognitive decline.

The results of studies exploring the association between dietary intake or supplemental intake of antioxidants and cognitive decline or dementia have compelling similarities but also inconsistencies (Table 3). Six studies have examined the effect on cognitive decline or dementia of food intake of the antioxidant nutrients, with five (108-112) of the six (108-113) finding statistically significant inverse associations. No association was found between midlife intakes of β -carotene, flavonoids, and vitamins E and C, and the risk of late-life dementia or its most prevalent subtypes (114). Of five observational studies of vitamin supplements (115-119), four have reported an inverse association between the use of vitamin E and vitamin C supplements and the risk of AD (118) or cognitive decline (116-117,119). One explanation for the inconsistent findings for food and supplement sources of antioxidant nutrients is that high dose α -tocopherol may not be beneficial. Vitamin E supplements usually consist of α -tocopherol only, one of the 4 tocopherol forms (α , β , γ , δ). α -tocopherol is the most biologically active form of vitamin E and the most potent antioxidant. There is emerging evidence that high doses of α -tocopherol decrease the absorption of γ -tocopherol, which has powerful anti-inflammatory properties and is a major scavenger of reactive nitrogen species. It is possible that the beneficial effect of vitamin E is not due to α -tocopherol alone but to another tocopherol form or to a combination of tocopherol forms. In the CHAP study (112), α - and γ -tocopherols from food sources were each significantly associated with slower cognitive decline over 6 years and with lower risk of AD, but the combination of the two tocopherols had the strongest association.

One study has investigated the cross-sectional relation between cognitive performances and the different plasma carotenoids, xanthophylls (lutein, zeaxanthin, β -cryptoxanthin) and carotenes (lycopene, α -carotene, trans β -carotene and cis β -carotene), and found that low levels of specific plasma carotenoids (lycopene and zeaxanthin) were associated with poor cognitive functioning in a highly educated free-living elderly community (EVA study) (120). It was previously demonstrated in a prospective study that high levels of β -carotene may offer protection from cognitive decline in persons with greater genetic susceptibility as evidenced by the presence of the ApoE4 allele (121).

Only one study has investigated the relationship between longitudinal cognitive decline and baseline selenium level (122). In this study, the greatest declines in cognitive function were associated with the lowest plasma selenium concentrations at baseline. Limited data are available from selenium supplementation studies in the elderly. In the Duke Established Populations for Epidemiologic Studies of the

Elderly (EPESE), Gray et al (117) showed that subjects who currently used antioxidant supplements (vitamins C, E, A and selenium or zinc) had a lower risk of cognitive decline than nonusers. However, with multiantioxidant supplementation it is difficult to isolate the specific effect of selenium. In a recent study, Akbaraly et al (123) investigated the relationships between short-term (the first 2 years) and long-term selenium changes (9-year) with cognitive changes during the 9-year follow-up of the EVA study. They showed that decreases in selenium were associated with cognitive decline, after controlling for potential confounders. Among subjects who had a decrease in their plasma selenium levels, the greater the decrease, the higher the probability of cognitive decline. There was no association between short-term (2-year) selenium change and cognitive changes.

Finally, in the European Zincage project, a substantial cross-sectional relationship between plasma zinc status and all psychological dimensions studied (cognitive decline, depression, perceived stress) was found among 853 healthy elderly (≥ 60 years). The results were more evident when the zinc status indicated a deficiency of this trace element ($< 11 \mu\text{M}$) (124).

Potential benefits of supplementation with vitamin E or zinc: data from RCT

There have been two published RCT on vitamin E and AD. In the more recent trial, vitamin E (2000 IU/day) had no effect on progression to AD among persons with mild cognitive impairment (125). In an earlier trial, the same vitamin E dose was significantly related to a combined outcome of time to death, institutionalisation, loss of the ability to perform basic activities of daily living or severe dementia, among AD patients of moderate severity after adjustment (126). Results of the first primary prevention trial of vitamin E supplementation (600 IU/day for about 4 years) on cognitive decline have just been published. There were no significant differences with supplementation in change in performance over time for global cognitive score among generally healthy older women (127).

One RCT on zinc supplementation has been published and showed that 6-month supplementation at moderate doses in healthy French subjects aged 55-70 years had no effect in vitro copper-induced LDL oxidation (128).

Finally, one trial investigating the use of vitamin E and selenium for preventing AD is now being conducted among 10,700 men aged 62 years and older (PREADVISE study).

In conclusion, the results on antioxidant nutrients and cognitive decline or dementia may suggest the importance of having a balanced combination of several antioxidant nutrients in order to exert a significant preventive effect on cognitive decline and dementia. We must however use these data cautiously for future recommendations. A recent meta-analysis (129), studying the effect of antioxidant supplements on mortality in randomised primary and secondary prevention trials, showed that treatment with β -carotene, vitamin A, and

vitamin E may increase mortality. According to the authors, the potential impact of vitamin C and selenium on mortality needs further study. Extensive epidemiological and RCT studies are consequently needed to determine the optimal trial design.

Methodological statements and future research directions

Methodological statements

There are several potential explanations for the inconsistent findings. Firstly, the apparently conflicting results could be due in part to some methodological differences between prospective studies with regard to the following points :

- tools used for dietary assessment (semi-quantitative food frequency questionnaire, 24-h recall, 3-day dietary record)
- selection of participants: results could depend on the timing of measurement (middle-life or late-life) and on exposure. One possible explanation for differences in findings is that studies in younger people (e.g. ≥ 55 years and older vs. ≥ 65 years and older) could be exploring an earlier stage of the latency period of AD in which they could be more susceptible to diet.
- lack of statistical control for confounding factors (dietary factors, social factors, living arrangements) and drop-outs
- use of one-time cognitive assessment: in this case, studies cannot separate attained or lifetime cognitive ability from cognitive decline due to age or disease. Confounding bias is highly likely in these types of studies because cognitive ability is related to many factors such as education, socio-economic status, healthy lifestyle behaviours or depression.
- use of only one point of dietary assessment: many of the studies have measured dietary intake initially and assumed that baseline values are stable in individuals during the years of follow-up, whereas changes could occur over time.
- lack of adequate examination of possible non-linear associations between nutrients and cognitive outcomes.
- lack of consideration of individual interactive factors such as genetic factors (e.g. ApoE) or behavioural habits.

Secondly, our paper is focused on late adult life effects of several dietary components that could influence the risk of AD by protecting against tissue damage. Nevertheless, we cannot exclude the possibility that poor cognitive function itself may increase the risk of poor nutrition.

Thirdly, the seemingly contradictory results between the observational studies and the RCT could be explained by the fact that the doses used in clinical trials were much higher than the highest levels achieved by usual dietary intake which have been found to be associated with the lowest risk of cognitive decline in observational studies. Additionally, many vitamin supplement trials have not considered participants' baseline vitamin levels in establishing eligibility criteria or in post-trial analyses.

Finally, we must underline that the influence of different aspects of diet is likely to vary over the life course. It is

important to identify the critical periods during which an individual is at greatest risk of damage if exposed to a specific nutrient deficiency. For example, in early life, the amount of PUFA intake is important for the rapid brain growth that occurs in the third trimester and postnatal period. A deficit in PUFA during this period may influence future cognitive evolution and be associated with lower cognitive ability in mid-life and greater cognitive decline in later life.

Future research directions

Whereas it is useful to examine individual dietary components to increase our understanding of the biochemical mechanisms underlying disease processes and to identify potential therapeutic agents, it is also helpful, especially from a public health perspective, to understand associations at the level of food groups or dietary patterns. There is converging evidence that composite dietary patterns, such as the Mediterranean Diet (MeDi), are related to lower risk for cardiovascular disease, several forms of cancer and overall mortality (130,131). The MeDi includes many of the components reported as potentially beneficial for cognitive decline and dementia; it is characterized by high intake of vegetables, legumes, fruits and cereals; high intake of unsaturated fatty acids (mostly in the form of olive oil), but low intake of saturated fatty acids; a moderately high intake of fish, a low to moderate intake of dairy products; 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. A recent paper showed that higher adherence to a diet approaching the MeDi is associated with reduced risk for AD (132). This finding underlines the need to consider interactions between micro- and macronutrients for future research. Detailed study of the social, economic and cultural transformations of the end of the life cycle, from cessation of professional activity until the end of life, and of the consequences of these transformations on food habits, from obtaining supply to actual food intakes, are an area of research which could broaden the classic question of social determinants of cognitive decline by repositioning it within the dynamic material and social process of ageing (133-136).

We reported here the first prospective studies focused on the relation between food groups and cognitive decline or dementia (Table 4). In the CHAP study, Morris et al (137) investigated the association between rate of cognitive change and dietary consumption of fruits and vegetables, as they are rich sources of antioxidant nutrients and bioactive compounds (e.g. vitamin E, vitamin C, carotenoids, and flavonoids) and are also low in saturated fats. They showed that high vegetable (especially green leafy vegetables) but not fruit consumption may be associated with slower rate of cognitive decline with older age over a 6-year period. Similar results were previously observed in the Nurses' Health Study (138). Moreover, a recent study has found that consumption of fruit and vegetable juices was significantly associated with a reduced risk of AD, especially

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among ApoE4 carriers (139). The potential influence of the ApoE genotype was also found in new data from the Cache County Study on Memory, Health and Aging (140) and the 3C study (58). In both studies, higher intakes of fruits and vegetables and consumption of fish at least once a week were associated respectively with reduced risk of cognitive decline or dementia, in particular among ApoE4 non-carriers. The potential effect of ApoE needs to be confirmed in biological studies.

In conclusion, it is important to stress the need to develop further prospective studies of adequate duration, including subjects whose diet is monitored at a sufficiently early stage or at least before the onset of disease or cognitive decline. Meta-analyses should be developed, and on the basis of their results the most appropriate interventional studies can be planned. These studies must control for the greatest number of known confounding factors. More RCT need to be conducted that focus on specific types of patients (middle-aged and elderly populations) to determine vitamin supplementation effects in participants who have deficiencies of the vitamin, normal levels, and high levels. The field would also benefit greatly by the conduct of studies using longitudinal analyses of multiple tests of cognition and multiple assessment periods. There is no lack of attractive hypotheses to support research on the relationships between nutrition and cognitive decline. Such research, identifying the role of certain nutrients, certain foods or certain dietary behaviours, is an indispensable step before we can propose specific recommendations in the future. The impact of the standard social determinants and the cultural determinants of food habits, such as regional cultures, social status and educational level, will obviously need to be considered. It would be of great value to adapt communication strategies and nutritional advice to eating habits and to the stage of ageing.

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Appendix 1

Recommended Dietary Allowances (RDAs) for the elderly in the United States (US) and France for nutrients involved in brain functioning.

	French RDAs *	US RDAs **
<i>Minerals</i>		
Iron (mg/day)	10	M : 8 / W : 8
Zinc (mg/day)	15	M : 11 / W : 8
Copper (mg/day)	1.5	M : 0.9 / W : 0.9
Selenium (µg/day)	80	M : 55 / W : 55
<i>Lipid-soluble vitamins</i>		
Vit A (µg /day)	M : 700 / W : 600	M : 900 / W : 700
Vit D (µg/day)	10 - 15	M : 15 / W : 15
(IU/d)	400 - 600	
<i>Antioxidant vitamins</i>		
Vit E (mg/day)	20 - 50	M : 15 / W : 15
Vit C (mg/day)	100 -120	M : 90 / W : 75
<i>B vitamins</i>		
B6 (mg/day)	2.2	M : 1.3 / W : 1.1
B9 (µg/day)	400	M : 400 / W : 400
B12 (µg/day)	3	M : 2.4 / W : 2.4

Note: M: men; W: women; * values for people > 75 years; ** values for people > 70 years. RDAs are set to meet the needs of almost all (97 to 98 percent) individuals in a group. Source: <http://www.nap.edu> and Cynober, Nutr Clin Met 2001; 14: suppl 1, 1s-64s

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Table 1 Nutrition and prevention of cognitive decline: data from prospective studies and randomized clinical trials on fatty acids and fish

Authors	Study design
<p>Prospective studies</p> <ul style="list-style-type: none"> • <u>Schaefer et al., 2006 (44)</u> 	<ul style="list-style-type: none"> - exposure: plasma phosphatidylcholine (PC) DHA content - outcome: incident dementia - participants: 899 subjects initially free of dementia (median age: 76 years) (The Framingham Heart Study) - mean follow-up: 9.1 years <p>Adjustment for age, sex, education, ApoE4, plasma Hcy concentration</p> <ul style="list-style-type: none"> - results: 99 subjects developed dementia (including 71 cases of AD). Compared with subjects in the lower 3 quartiles, subjects in the upper quartile of baseline plasma PC DHA levels had a RR of 0.53 of developing all-cause dementia (95% CI: 0.29, 0.97) and 0.61 of developing AD (95% CI: 0.31, 1.18)
<ul style="list-style-type: none"> • <u>Laitinen et al., 2006 (52)</u> 	<ul style="list-style-type: none"> - exposure: fat intake from spreads and milk products in midlife - outcome: incident dementia - participants: 1449 subjects from random population based samples initially studied in midlife (1972, 1977, 1982 or 1987) and re-examined in 1998; age 65-80 years in 1998 - mean follow-up: 21 years <p>Adjustment for demographic variables, vascular risk factors and disorders, ApoE genotype, subtypes of fats</p> <ul style="list-style-type: none"> - results: moderate intake of PUFA at midlife decreased the risk of dementia (OR = 0.40, 95% CI: 0.17-0.94 for the 2nd quartile vs. 1st quartile), whereas saturated fat intake was associated with an increased risk (OR=2.45, 95% CI: 1.10-5.47 for the 2nd quartile). The associations were seen only among the ApoE4 carriers
<ul style="list-style-type: none"> • <u>Morris et al., 2006 (53)</u> 	<ul style="list-style-type: none"> - exposure: copper and fat intakes - outcome: cognitive decline measured by changes in a global cognitive score (MMSE, EBMT immediate and delayed recall, Symbol Digit Modalities Test) - participants: 3718 community residents, age ≥ 65 years (CHAP study) - mean follow-up: 5.5 years <p>Adjustment for sex, race, education, cognitive activities, physical activities, vascular risk factors and disorders, vit E in food, total vit C, niacin in food, total folate, PUFA, intakes of copper, zinc and iron, age, age squared, time of observation, interaction terms between time and each covariate</p> <ul style="list-style-type: none"> - results: among persons whose diets were high in saturated and trans fats, higher copper intake was associated with a faster rate of cognitive decline: the difference in rates for persons in the highest (median, 2.75 mg/day) vs. lowest (median, 0.88 mg/day) quintiles of total copper intake was -6.14 SU per year (p<0.001)
<ul style="list-style-type: none"> • <u>Solfrizzi et al., 2006 (50)</u> 	<ul style="list-style-type: none"> - exposure: dietary fatty acids - outcome: incident MCI - participants: 278, 186 and 95 nondemented elderly subjects evaluated in 1992-1993, 1995-1996 and 2000-2001 (ISLA study) - median follow-up: 2.6 years <p>Adjustment for age, sex, education, Charlson comorbidity index, total found energy intake</p> <ul style="list-style-type: none"> - results: 18 new events of MCI were diagnosed. High PUFA intake appeared to be a protective factor against the development of MCI (HR=0.65; 95% CI = 0.43, 0.98; p trend<0.04); however, after controlling for the possible confounders, no significant association was found. No significant association between other dietary fatty acids intakes and the rate of MCI was found
<ul style="list-style-type: none"> • <u>Solfrizzi et al., 2006 (49)</u> 	<ul style="list-style-type: none"> - exposure: MUFA and PUFA intakes - outcome: rate of change in cognitive function measured by the MMSE - participants: 278, 186 and 95 nondemented elderly subjects evaluated in 1992-1993, 1995-1996 and 2000-2001 (ISLA study); age 65-84 years - mean follow-up: 8.5 years <p>Adjustment for age, sex, education, Charlson comorbidity index, total energy intake, BMI, MMSE baseline score</p> <ul style="list-style-type: none"> - results: high MUFA and PUFA energy intake and total energy intake were significantly associated with better cognitive performance
<ul style="list-style-type: none"> • <u>Morris et al., 2005 (59)</u> 	<ul style="list-style-type: none"> - exposure: fish and n-3 fatty acids intakes - outcome: cognitive decline measured by changes in a global cognitive score (MMSE, EBMT immediate and delayed recall, Symbol Digit Modalities Test) - participants: 3718 residents initially free of AD; age ≥ 65 years (CHAP study) - mean follow-up: 6 years <p>Adjustment for age, sex, race, education, cognitive activity, physical activity, alcohol consumption, total energy intake</p> <ul style="list-style-type: none"> - results: compared with a decline rate in score of -0.100 SU/year among persons who consumed fish less than weekly, the rate was 10% slower (-0.090 SU/year) among persons who consumed 1 fish meal per week and 13% slower (-0.088 SU/year) among persons who consumed 2 or more fish meals per week

Table 1 (following)

Authors	Study design
• <u>Morris et al, 2004 (48)</u>	<ul style="list-style-type: none"> - exposure: fat intake - outcome: cognitive decline measured by changes in a global cognitive score (MMSE, EBMT immediate and delayed recall, Symbol Digit Modalities Test) - participants: 2560 participants with no history of heart attack, stroke or diabetes; age ≥ 65 years (CHAP study) - mean follow-up: 6 years <p>Adjustment for demographic and cardiovascular risk factors, intakes of antioxidant nutrients, other dietary fats</p> <ul style="list-style-type: none"> - results: higher intakes of saturated fat (p for trend=0.04) and trans-unsaturated fat (p for trend=0.07) were linearly associated with greater decline in cognitive score over 6 years; these associations became stronger when persons whose fat intake changed in recent years or whose baseline cognitive scores were in the lowest 15% were eliminated. Inverse associations with cognitive decline were observed in the restricted analysis for high intake of MUFA and a high ratio of PUFA to saturated fat intake. Intakes of total fat, vegetable and animal fats, and cholesterol were not associated with cognitive change.
• <u>Heude et al, 2003 (43)</u>	<ul style="list-style-type: none"> - exposure: erythrocyte membrane fatty acid composition - outcome: cognitive decline measured by MMSE - participants: 246 healthy elderly; age : 63-74 years (EVA study) - mean follow-up: 4 years <p>Adjustment for age, sex, education, initial MMSE score</p> <ul style="list-style-type: none"> - results: higher proportions of n-6 PUFA were associated with greater risk of cognitive decline (OR=1.59; 95% CI=1.04, 2.44) for 1-SD differences in fatty acid proportions. A higher proportion of n-3 PUFA was conversely associated with a lower risk of cognitive decline (OR=0.59; 95% CI=0.38, 0.93)
• <u>Morris et al, 2003 (47)</u>	<ul style="list-style-type: none"> - exposure: fat intake - outcome: incident AD - participants: 815 community residents unaffected by AD, age ≥ 65 years (CHAP study) - mean follow-up: 3.9 years <p>Adjustment for age, sex, race, education, ApoE4</p> <ul style="list-style-type: none"> - results: 131 persons developed AD. Intakes of saturated fat and trans-unsaturated fat were positively associated with risk of AD. Intakes of n-6 PUFA and MUFA were inversely associated with risk of AD. Persons in the upper fifth of saturated fat intake had 2.2 times the risk of incident AD compared with persons in the lowest fifth (95% CI = 1.1, 4.7); risk also increased with the second fifth of intake (RR=2.4; 95% CI = 1.1, 5.3). Linear inverse associations between AD and vegetable fat (p=0.002) were observed. Intakes of total and animal fats, and dietary cholesterol were not associated with AD.
• <u>Morris et al, 2003 (57)</u>	<ul style="list-style-type: none"> - exposure: intake of different types of n-3 fatty acids and fish consumption - outcome: incident AD - participants: 815 community residents unaffected by AD, age ≥ 65 years (CHAP study) - mean follow-up: 3.9 years <p>Adjustment for age, intakes of other dietary fats, vit E, cardiovascular risk factors</p> <ul style="list-style-type: none"> - results: 131 persons developed AD. Participants who consumed fish once per week or more had 60% less risk of AD compared with those who rarely or never ate fish (RR=0.4; 95% CI : 0.2, 0.9). Total intake of n-3 PUFA was associated with reduced risk of AD, as was intake of DHA. EPA was not associated with AD.
• <u>Luchsinger et al, 2002 (51)</u>	<ul style="list-style-type: none"> - exposure: daily intake of calories, carbohydrates, fats and protein - outcome: incident AD - participants: 980 elderly individuals free of dementia - mean follow-up: 4 years <p>Adjustment for age, sex, education, ethnic group</p> <ul style="list-style-type: none"> - results: 242 incident cases of AD (6 cases per 100 person-years). Among individuals with ApoE4, the HR of AD for the highest quartiles of calorie and fat intake were 2.27 (95% CI=1.1, 4.68; p for tend=07) and 2.31 (95% CI=1.09, 4.89; p for tend=02) respectively, compared with the lowest quartiles
• <u>Engelhart et al, 2002 (46)</u>	<ul style="list-style-type: none"> - exposure: fat intake - outcome: incident dementia - participants : 5295 subjects with normal cognition, age ≥ 55 years (Rotterdam study) - mean follow-up: 6 years <p>Adjustment for age, gender, education, total energy intake, vit E intake</p> <ul style="list-style-type: none"> - results: 197 subjects developed dementia (146 AD, 29 VaD). High intake of total, saturated, trans fat and cholesterol was not associated with increased risk of dementia or its subtypes. Similar result was found for low intake of MUFA, PUFA, n-6 PUFA and n-3 PUFA

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Table 1 (following)

Authors	Study design
• <u>Barberger-Gateau et al., 2002 (56)</u>	<ul style="list-style-type: none"> - exposure: fish consumption - outcome: incident dementia - participants: 1416 participants, age ≥ 68 years (Paquid study) - mean follow-up: 7 years <p>Adjustment for age, sex, education</p> <ul style="list-style-type: none"> - results: 170 participants developed dementia (including 135 AD). Participants who ate fish or seafood at least once a week had a significantly lower risk of being diagnosed as having dementia (age and sex adjusted HR=0.66, 95% CI= 0.47, 0.93); the HR for AD was equal to 0.69 with borderline significance (95% CI=0.47, 1.01). The age, sex and education adjusted HR for dementia was 0.73 (95% CI=0.52, 1.03), indicating that the protective effect of fish and seafood was partly explained by higher education of regular consumers.
• <u>Kalmijn et al., 1997 (55)</u>	<ul style="list-style-type: none"> - exposure: n-3 PUFA intake and fish consumption - outcome: cognitive decline defined as a drop of > 2 points of MMSE over a 3-year period - participants: 476 men; age 69-89 years (Zutphen Elderly study) - mean follow-up: 3 years <p>Adjustment for age, education, cigarette smoking, alcohol consumption, energy intake</p> <ul style="list-style-type: none"> - results: high fish consumption tended to be inversely associated with cognitive decline (OR=0.45, 95% CI=0.17, 1.16). No association was found between n-3 PUFA and cognitive impairment
• <u>Kalmijn et al., 1997 (45)</u>	<ul style="list-style-type: none"> - exposure: fat intake - outcome: incident dementia - participants: 5386 non-demented participants; age ≥ 55 years (Rotterdam study) - mean follow-up: 2.1 years <p>Adjustment for age, sex, education, energy intake</p> <ul style="list-style-type: none"> - results: high intakes of the following nutrients were associated with an increased risk of dementia: total fat (RR=2.4, 95% CI: 1.1, 5.2), saturated fat (RR=1.9, 95% CI=0.9, 4.0) and cholesterol (RR=1.7, 95% CI=0.9, 3.2). Dementia with a vascular component was strongly related to total fat and saturated fat. Fish consumption was inversely related to incident dementia (RR=0.4, 95% CI=0.2, 0.91) and AD (RR=0.3, 95% CI=0.1, 0.9)
Randomized clinical trial	
• <u>Freund-Levi et al., 2006 (64)</u>	<ul style="list-style-type: none"> - intervention: n-3 fatty acid supplementation - outcome: cognitive functions (MMSE and ADAS-cog) - participants: 204 patients with AD (mean age: 74 ± 9 years), treated with ChEIs, who had a MMSE score of 15 points or more were randomized to daily intake of 1.7 g DHA and 0.6 g EPA (n-3 acid-treated group) or placebo for 6 months, after which all received n-3 fatty acid supplementation for another 6 months - results: at 6 months, the decline in cognitive function did not differ between the groups. In a subgroup (n=32) with MCI (MMSE score > 27), a significant reduction in MMSE decline rate was observed in the n-3 fatty acid-treated group compared with the placebo group. A similar arrest in decline rate was observed between 6 and 12 months in the placebo subgroup when receiving n-3 fatty acid supplementation

Note: AD: Alzheimer's disease; CI: confidence interval; DHA: docosahexaenoic acid; Hcy: homocysteine; ChEIs: cholinesterase inhibitors; EBMT: East Boston Memory test; EPA: eicosapentaenoic acid; HR: hazard ratio; MMSE: Mini-Mental State Examination; MUFA: monounsaturated fatty acid; MCI: mild cognitive impairment; PUFA: polyunsaturated fatty; RR: relative risk; SU: standardized units; VaD: vascular dementia

Table 2

Nutrition and prevention of cognitive decline: data from prospective studies and randomized clinical trials on homocysteine-related B vitamins

Authors	Study design
Prospective studies	
• <u>Luchsinger et al., 2007 (86)</u>	<ul style="list-style-type: none"> - exposure: intake of folate and vitamins B6 and B12 - outcome: incident AD - participants: 965 persons 65 years or older without dementia at baseline (WHICAP study) - mean follow-up: 6.1 ± 3.3 years <p>Adjustment for age, sex, education, ethnic group, ApoE4, vitamins B6 and B12 levels, cardiovascular risk factors</p> <ul style="list-style-type: none"> - results: 192 persons developed incident AD. The highest quartile of total folate intake was related to a lower risk of AD (HR = 0.5; 95% CI =0.3, 0.9; p=0.2 for trend). Vit B12, and B6 levels were not related to the risk of AD.

Table 2 (following)

Authors	Study design
• <u>Morris et al., 2006 (87)</u>	<ul style="list-style-type: none"> - exposure: dietary intakes of folate, B12, B6 - outcome: incident AD - participants: 1041 residents initially free of AD, ≥ 65 years (CHAP study) - mean follow-up: 3.9 years <p>Adjustment for age, sex, race, education, cognitive activities, ApoE4, dietary intake of vitamin E, total niacin</p> <ul style="list-style-type: none"> - results: 162 persons developed incident AD. No association between quintiles of folate intake or of vit B12 intake was found with the risk of developing AD. Intake of vit B6 was not associated with incident AD after control for dietary intakes of vit E and total niacin
• <u>Kado et al., 2005 (81)</u>	<ul style="list-style-type: none"> - exposure: tHcy and related vitamin plasma concentrations - outcome: cognitive decline measured by changes in a total cognitive score (Boston Naming test, perception and reproduction of spatial associations, Delayed Recognition Span Test, Wechsler Adult Intelligence Scale-Revised, abstract concept formation) - participants: 499 high-functioning community-dwelling persons; age 70 to 79 years (MacArthur Studies of Successful Aging) - mean follow-up: 7 years <p>Adjustment for age, sex, education, baseline cognitive function, baseline physical function, smoking, homocysteine and vitamin levels</p> <ul style="list-style-type: none"> - results: subjects in the lowest quartile of folate had a 1.6-fold increased risk of 7-year cognitive decline (95% CI : 1.01, 2.31; p=0.04).
• <u>Morris et al., 2005 (82)</u>	<ul style="list-style-type: none"> - exposure: dietary intakes of folate and vit B12 - outcome: rates of age-related cognitive change assessed by changes in a global cognitive score (MMSE, EBMT immediate and delayed recall, Symbol Digit Modalities Test) - participants: 3718 residents initially free of AD, ≥ 65 years (CHAP study) - mean follow-up: 6 years <p>Adjustment for age, sex, education, race, vit E, vit C</p> <ul style="list-style-type: none"> - results: the rate of cognitive decline among persons in the top fifth of total folate intake (median, 742 µg/day) was more than twice that of those in the lowest fifth of intake (median, 186 µg/day). Similar patterns were found with high folate intake from food and with folate vit supplementation of more than 400 µg/day. High total B12 intake was associated with slower cognitive decline only among the oldest participants.
• <u>Corrada et al., 2005 (26)</u>	<ul style="list-style-type: none"> - exposure: total intake (diet plus supplements) of antioxidant vitamins (E, C, carotenoids) and B vitamins (folate, B12, B6) - outcome: incident AD - participants: 579 nondemented elderly volunteers, age 49 to 93 years (Baltimore Longitudinal Study of Aging) - mean follow-up: 9.3 years <p>Adjustment for age, gender, education, caloric intake</p> <ul style="list-style-type: none"> - results: 57 persons developed incident AD. Higher intake of folate (RR=0.1; 95% CI : 0.22, 0.76), vit E (RR=0.56; 95% CI : 0.30, 1.06) and vit B6 (RR=0.41; 95% CI : 0.20, 0.84) were associated individually with decreased risk of AD. When the 3 vitamins were analysed together, only total intake of folate at or above the DRI (RR=0.45; 95% CI : 0.21, 0.97) was associated with a significant decreased risk of AD. No association was found with total intake of vit B12, vit C or carotenoids
• <u>Mooijaart et al., 2005 (83)</u>	<ul style="list-style-type: none"> - exposure: serum concentrations of homocysteine, vit B12, or folic acid - outcome: cognitive decline assessed by changes in scores of a battery of cognitive tests (MMSE, Stroop test, a letter digit coding test, a word recall test) - participants: 599 subjects; 85 years of age (Leiden 85-Plus Study) - mean follow-up: 4 years <p>Adjustment for sex and education level</p> <ul style="list-style-type: none"> - results: there were no significant associations of serum concentrations of Hcy, vit B12 or folic acid with rate of cognitive decline (battery of cognitive tests : MMSE, Stroop test, a letter digit coding test, a word recall test)
• <u>Tucker et al., 2005 (84)</u>	<ul style="list-style-type: none"> - exposure: plasma tHcy, folate, vit B12, vit B6 and dietary B vit intakes - outcome: changes in cognitive measures (MMSE, verbal fluency and constructional praxis adapted from the revised Wechsler Adult Intelligence Scale and the CERAD batteries) - participants: 321 aging men, age 50 to 85 years (Veterans Affairs Normative Aging Study) - mean follow-up: 3 years <p>Adjustment for baseline cognitive measures, age, education, smoking, alcohol intake, BMI, diabetes, systolic blood pressure, time of second measure relative to folic acid fortification, time interval between the 2 cognitive measures, serum creatinine (for plasma) or total energy intake (for diet)</p> <ul style="list-style-type: none"> - results: decline in constructional praxis (spatial copying) was significantly associated with plasma tHcy, folate, vit B6, vit B12 and with the dietary intake of each vitamin. Dietary folate was also protective against a decline in verbal fluency. A high homocysteine concentration was associated with a decline in recall memory.
• <u>Ravaglia et al., 2005 (88)</u>	<ul style="list-style-type: none"> - exposure: high plasma tHcy concentrations - outcome: incident AD

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Table 2 (following)

Authors	Study design
• Luchsinger et al. 2004 (89)	<ul style="list-style-type: none"> - participants: 816 subjects initially free of dementia, mean age 74 years (Conselice Study of Brain Aging) - mean follow-up: 4 years <p>Adjustment for age, sex, education, ApoE genotype, vascular risk factors, serum concentrations of folate and vit B12</p> <ul style="list-style-type: none"> - results: 112 persons developed dementia (including 70 cases of AD). In the subjects with hyperhomocysteinemia (tHcy >15 μmol/l), HR was 2.08 (95% CI: 1.31, 3.30; p=0.002) for dementia and 2.11 (95% CI: 1.19, 3.76; p=0.011) for AD. Low folate concentrations (≤ 11.8 nmol/L) were independently associated with an increased risk of both dementia (1.87; 95% CI: 1.21, 2.89; p=0.0005) and AD (1.98; 95% CI: 1.15, 3.40; p=0.014). No significant relation was found with vit B12. - exposure: high tHcy levels - outcome: incident AD - participants: 909 elderly subjects, age 77.2 ± 6.3 years (WHICAP study) - mean follow-up: 1.5 years <p>Adjustment for age, sex, education, ApoE4</p> <ul style="list-style-type: none"> - results: 109 persons developed AD (incidence: 3206 person-years). Adjusted HR of AD for the highest quartile of tHcy was 1.4 (95% CI : 0.8, 2.4; p for trend=0.31). High tHcy levels were not related to a decline in memory scores over time. Age was a significant confounder in all the analyses - exposure: serum tHcy concentration - outcome: cognitive decline measured by changes in scores of a battery of cognitive tests (Letter-Digit coding test, Stroop test, Word Learning Test total and delayed recall) - participants: 144 subjects, age 30 to 80 years - mean follow-up: 6 years <p>Adjustment for age, sex, education</p> <ul style="list-style-type: none"> - results: no correlation was observed between serum tHcy, vit B12 and folic acid concentrations, and performance at any of the time-points
• Teunissen et al. 2003 (85)	<ul style="list-style-type: none"> - exposure: plasma tHcy level - outcome: incident dementia - participants: 1092 subjects without dementia; mean age: 76 years (Framingham study) - mean follow-up: 8 years <p>Adjustment for age, sex, education, ApoE genotype, plasma vitamin levels, vascular risk factors</p> <ul style="list-style-type: none"> - results: 111 persons developed dementia (including 83 cases of AD). The RR of dementia was 1.4 (95% CI: 1.1, 1.9) for each increase of 1 SD in the log-transformed tHcy value at baseline or 8 years earlier. The RR of AD was 1.8 (95% CI: 1.3, 2.5) per increase of 1 SD at baseline and 1.6 (95% CI: 1.2, 2.1) per increase of 1 SD eight years before baseline. The risk of AD nearly doubled with plasma tHcy level greater than 14 μmol/l - exposure: serum level of vitamin B12 and folate - outcome: incident AD - participants: 370 nondemented persons, age ≥ 75 years (Kungsholmen Project) - mean follow-up: 3 years <p>Adjustment for age, sex, education</p> <ul style="list-style-type: none"> - results: persons with low levels of B12 (≤ 150 pmol/l) or folate (≤ 10 nmol/l) had twice the risk of developing AD (RR=2.1, 95% CI: 1.2, 3.5) compared with people with normal levels of vit. Similar relative risk was found for subjects with both vitamins at low levels and for low levels of B12 or folate respectively defined as ≤ 250 pmol/l or ≤ 12 nmol/l
• Wang et al. 2001 (91)	<ul style="list-style-type: none"> - intervention: daily supplementation with folic acid - outcome: cognitive function (world learning test, concept shifting test, Stroop colour-word test, verbal fluency test, letter digit substitution test) - participants: 818 subjects (50-70 years) were randomly assigned to receive 800 μg daily oral folic acid or placebo for 3 years - results: the 3-year change in memory, information processing speed, and sensorimotor speed were significantly better in the folic acid group than in the placebo group <p>intervention: daily supplementation with high doses of oral vit B12 alone or in combination with folic acid</p> <ul style="list-style-type: none"> - outcome: cognitive function (MMSE, GDS, CDR) - participants: 195 free-living older persons and older persons living in care-facility homes, aged ≥ 70 years, with mild vit B12 deficiency randomly assigned to receive 1000 μg vit B12, 1000 μg vit B12 plus 400 μg folic acid or placebo for 24 weeks - results: neither supplementation with vit B12 alone nor that in combination with folic acid was accompanied by any improvement in cognitive function (Mild vit B12 deficiency: a serum vit B12 concentration between 100 and 200 pmol/L, a plasma MMA concentration ≥ 0.32 μmol/L, and a serum creatinine concentration < 120 μmol/L)
• Durga et al. 2007 (100)	<ul style="list-style-type: none"> - intervention: daily supplementation with high doses of oral vit B12 alone or in combination with folic acid - outcome: cognitive function (MMSE, GDS, CDR) - participants: 195 free-living older persons and older persons living in care-facility homes, aged ≥ 70 years, with mild vit B12 deficiency randomly assigned to receive 1000 μg vit B12, 1000 μg vit B12 plus 400 μg folic acid or placebo for 24 weeks - results: neither supplementation with vit B12 alone nor that in combination with folic acid was accompanied by any improvement in cognitive function (Mild vit B12 deficiency: a serum vit B12 concentration between 100 and 200 pmol/L, a plasma MMA concentration ≥ 0.32 μmol/L, and a serum creatinine concentration < 120 μmol/L)
• Eussen et al. 2006 (98)	<ul style="list-style-type: none"> - intervention: daily supplementation with high doses of oral vit B12 alone or in combination with folic acid - outcome: cognitive function (MMSE, GDS, CDR) - participants: 195 free-living older persons and older persons living in care-facility homes, aged ≥ 70 years, with mild vit B12 deficiency randomly assigned to receive 1000 μg vit B12, 1000 μg vit B12 plus 400 μg folic acid or placebo for 24 weeks - results: neither supplementation with vit B12 alone nor that in combination with folic acid was accompanied by any improvement in cognitive function (Mild vit B12 deficiency: a serum vit B12 concentration between 100 and 200 pmol/L, a plasma MMA concentration ≥ 0.32 μmol/L, and a serum creatinine concentration < 120 μmol/L)

Table 2 (following)

Authors	Study design
<ul style="list-style-type: none"> • McMahon et al. 2006 (99) 	<ul style="list-style-type: none"> - intervention: Hey-lowering treatment - outcome: cognitive function (MMSE, RAVLT, COWAT, Category Word Fluency Test, Trail Making Test, National Adult Reading Test) - participants : 276 healthy participants, ≥ 65 years with plasma homocysteine concentrations of at least 13 μmol/L, randomly assigned to receive a daily supplement containing folate (1000 μg), vitamin B12 (500 μg) and vitamin B6 (10 mg) for 2 years - results: plasma homocysteine concentration was 4.36 μmol/L lower in the vitamin group than in the placebo group during follow-up. There were no significant differences between the vitamin and placebo groups in cognition test scores
<ul style="list-style-type: none"> • Vital trial collaborative group 2003 (Clarke et al. 2003) (95) 	<ul style="list-style-type: none"> - intervention: aspirin and vitamin supplements - outcome: biochemical efficacy (blood for Hey, folate, Vit B); urine for markers of platelet activation and ROS and cognitive function (MMSE, ADAS-cog) - participants: 149 people at high risk of dementia were randomized to receive either low dose aspirin (81 mg) or placebo; and folic acid (2 mg) plus vit B12 (1 mg) or placebo; and vit E (500 mg) plus C (200 mg) or placebo for 12 weeks - results: B vitamins lowered plasma Hey concentration by 30%. No effect of treatment on cognitive function was detected
<ul style="list-style-type: none"> • Bryan et al. 2002 (92) 	<ul style="list-style-type: none"> - intervention: short-term folate, vit B12 or vit B6 supplementation - outcome: cognitive function and mood (Boxes test, Digit Symbol Coding-120s, symbol search, Digit Span Backward, Letter Number Sequencing, RAVLT, immediate recall, delayed recall, Digit Symbol Coding- symbol recall, activity recall, Stroop test, self-ordered pointing task, uses for common objects, TMT, verbal fluency test, Excluded Letter Fluency, Wechsler Adult Intelligence Scale-III Vocabulary, Spot the Word test) - participants: 211 healthy younger, middle-aged, and older women, who took either 750 μg folate, 15 μg vit B12, 75 mg vit B6 or placebo daily for 35 days - results: supplementation had a significant positive effect on some measures of memory performance only and no effect on mood. Dietary intake status was associated with speed of processing, recall and recognition, and verbal ability
<ul style="list-style-type: none"> • Fioravanti et al. 1997 (93) 	<ul style="list-style-type: none"> - intervention: folic acid supplementation - outcome: cognitive functions (Randt memory test, acquisition and recall, delayed recall, memory index, encoding factor, cognitive efficiency, attention efficiency) - participants: 30 patients with abnormal cognitive decline and folate level below 3 ng/ml randomly assigned to receive folic acid supplementation for 60 days or placebo - results: patients treated showed a significant improvement of both memory and attention efficiency when compared with a placebo group. The intensity of memory improvement was positively correlated with initial severity of folate deficiency. The severity of initial cognitive decline was unrelated to the degree of folate deficiency

Note : AD: Alzheimer's disease; BMI: body mass index; CDR: Clinical Dementia Rating; CI: confidence interval; COWAT: Controlled Oral Word Association Test; DRI: dietary reference intake; EBMT: East Boston Memory Test; GDS: Geriatric Depression Scale; Hey: homocysteine; HR: hazard ratio; MCI: mild cognitive impairment; MMSE: Mini Mental State examination; TMT: Trail Making Test; RAVLT: Rey Auditory Verbal Learning Test; RR: relative risk; ROS: reactive oxygen species; tHey: total homocysteine; vit: vitamin; VaD: vascular dementia

Table 3
Nutrition and prevention of cognitive decline: data from prospective studies and randomized clinical trials on antioxidant nutrients

Authors	Study design
<ul style="list-style-type: none"> • Akbaraly et al. 2007 (120) 	<ul style="list-style-type: none"> - exposure: serum selenium levels - outcome: cognitive decline measured by changes in MMSE, TMTB, DSS, FTT - participants: 1389 subjects, age 60-71 years (EVA study) - mean follow-up: 9 years - Adjustment for time, sex, education, baseline Se level, cardiovascular risk factors - results: decline in Se was associated with cognitive decline as measured by 4 neuropsychological tests. Probability of cognitive decline increased with the decrease of plasma Se change over time
<ul style="list-style-type: none"> • Hu et al. 2006 (121) 	<ul style="list-style-type: none"> - exposure: serum β-carotene and ApoE genotype - outcome: cognitive decline measured by changes in SPMSQ score - participants: 455 elderly, age ≥ 65 years (MacArthur Studies of Successful Aging) - mean follow-up: 7 years - Adjustment for age, sex, race, baseline SPMSQ score, education, income, smoking status, alcohol consumption, serum CRP and IL6 levels, total and HDL cholesterol level, BMI - results: the adjusted OR of high β-carotene level for cognitive decline was 0.11 (95% CI=0.02, 0.57) in participants with at least one ApoE4 allele and 0.89 (95% CI=0.54, 1.47) among those who were ApoE4 negative

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Table 3 (following)

Authors	Study design
• Maxwell et al. 2005 (119)	<ul style="list-style-type: none"> - exposure: supplemental use of antioxidant vitamins - outcome: subsequent risk of cognitive decline (decrease in 3MS score of 10 points or more) - participants: 894 subjects with no evidence of dementia (CSHA study), age \geq 65 years - mean follow-up: 5 years - Adjustment for age, sex, education, sitting diastolic blood pressure, baseline 3MS score, baseline institutional residence - results: subjects reporting a combined use of vitamin E and C supplements and/or multivitamin consumption at baseline were significantly less likely to experience significant cognitive decline (adjusted OR=0.51; 95% CI=0.29, 0.90)
• Morris et al. 2005 (112)	<ul style="list-style-type: none"> - exposure: food intakes of vit E, α-tocopherol equivalents, individual tocopherols - outcome: cognitive decline measured by changes in a global cognitive score (MMSE, EBMT immediate and delayed recall, Symbol Digit Modalities Test) and incident AD - participants: 1041 persons clinically evaluated for analysis of AD and 3718 persons for analysis of cognitive change ; age \geq 65 years (CHAP study) - mean follow-up: 6 years - Adjustment for age, sex, race, education, ApoE4 genotype, interaction between ApoE4 and race, time from the determination of disease-free status to the time of clinical evaluation of incident disease, frequency of participation in cognitive activities, intakes of saturated fat, trans unsaturated, DHA - results: 162 persons developed AD. Higher intakes of vit E (RR=0.74 per 5 mg/d increase; 95% CI=0.62, 0.88) and α-tocopherol equivalents (RR=0.56 per 5 mg/day increase; 95% CI=0.32, 0.98) were associated with a reduced incidence of AD. A slower rate of cognitive decline was associated with intakes of vit E, and α-γ-tocopherols equivalents
• Zandi et al. 2004 (118)	<ul style="list-style-type: none"> - exposure: supplemental use of antioxidant vitamins - outcome: incident AD - participants: 3227 elderly county residents, age \geq 65 years (Cache County Study) - mean follow-up: 3 years - Adjustment for age, sex, education, dummy-coded terms for the presence of 1 and 2 ApoE4 alleles, interactions between age and the dummy-coded ApoE4 terms, an indicator term for general health status - results: 104 persons developed AD. Use of vit E and C supplements in combination was associated with reduced AD incidence (adjusted HR=0.36; 95% CI=0.09, 0.99). No evidence of a protective effect with use of vit E or C supplements alone was found.
• Laurin et al. 2004 (114)	<ul style="list-style-type: none"> - exposure: midlife dietary intake of antioxidants - outcome: incident dementia - participants: 2459 Japanese-American men, age 71 to 93 years (Honolulu-Asia Aging Study) - mean follow-up: 6 years - Adjustment for age, education, physical activity, cardiovascular risk factors, supplemental vitamin intake, total energy intake, ApoE4 genotype - results: 235 persons developed dementia (102 AD cases, 44 VaD cases, 38 AD cases with contributing cerebrovascular disease). Intakes of β-carotene, flavonoids, vit E, vit C were not associated with the risk of dementia or its subtypes
• Luchsinger et al. 2003 (113)	<ul style="list-style-type: none"> - exposure: intake of antioxidant vitamins - outcome: incident AD - participants: 980 elderly subjects initially free of dementia, age \geq 65 years (WHICAP study) - mean follow-up: 4 years - Adjustment for age, education, sex, ApoE4 status, ethnicity, smoking - results: 242 subjects developed AD in 4023 person-years of follow-up (6 per 100 person-years). Intake of carotenes and vit C or vit E in supplemental or dietary (nonsupplemental) form or in both forms was not related to a decreased risk of AD
• Grav et al. 2003 (117)	<ul style="list-style-type: none"> - exposure: use of supplemental antioxidants (vit A, C, E plus Se or Zn) - outcome: cognitive decline defined as an increase of \geq 2 errors on the SPMSQ - participants: 2082 elderly subjects initially free of dementia, age \geq 65 years (Epidemiologic Studies of the Elderly) - mean follow-up: 7 years - Adjustment for age, sex, race, education, residence, income, BMI, smoking history, alcohol consumption, health status index - results: 34.5% experienced cognitive decline during follow-up. Current antioxidant users had a 29% lower risk of experiencing cognitive decline (adjusted RR=0.71; 95% CI=0.49, 1.01)
• Grodsstein et al. 2003 (116)	<ul style="list-style-type: none"> - exposure: use of supplements containing vit C and E - outcome: cognitive function measured by a global cognitive score (TICS, 10-Word list immediate, 10-Word list delayed, EBMT immediate and delayed recall, verbal fluency, digits backward) - participants: 14968 women, age 70 to 79 years (Nurses' Health Study)

Table 3 (following)

Authors	Study design
<ul style="list-style-type: none"> • Morris et al. 2002 (110) 	<ul style="list-style-type: none"> - mean follow-up: 15 years - Adjustment for age at interview, education, history of diabetes, hypertension and heart disease; multivitamin use, anti-depressant use, HRT, BMI, aspirin use, smoking, mental-health index, energy-fatigue index - results: 33% of women currently used both specific vit E and C supplements. Long-term current users of vit E with vit C supplements had better global scores than non-users. There was a trend for increasingly higher mean scores with increasing durations of use. These associations were strongest among women with low dietary intakes of α-tocopherol - exposure: intake of antioxidant nutrients, vit E, vit C, β-carotene - outcome: incident AD - participants: 815 residents free of AD at baseline, age \geq 65 years (CHAP study) - mean follow-up: 3.9 years - Adjustment for age, education, sex, race, ApoE4 genotype, length of follow-up - results: increasing vit E intake from foods was associated with decreased risk of developing AD: RR from lowest to highest quintiles of intake were 1.00, 0.71 (95% CI=0.24, 2.07), 0.62 (95% CI=0.26, 1.45), 0.71 (95% CI=0.27, 1.88) and 0.30 (95% CI=0.10, 0.92) (p for trend=.05). The protective effect of vit E was observed only among persons who were ApoE4 negative. Adjustment for other baseline dietary factors reduced the protective association. Intake of vit C, β-carotene, vit E from supplements was not significantly associated with risk of AD.
<p>Randomized clinical trial</p> <ul style="list-style-type: none"> • Feillet-Coudray et al. 2006 (128) • Kang et al. 2006 (127) 	<ul style="list-style-type: none"> - intervention: supplementation with Zn - outcome: in vitro copper-induced oxidation of LDL - participants: 95 healthy subjects (age 55-70 years, Zenith study) were randomly assigned to receive either a placebo or 15 or 30 mg Zn/day as two capsules in the morning for 6 months - results: Zn supplementation significantly increased serum Zn levels but did not significantly modify copper, iron or vit E status. Zn supplementation had no effect on in vitro LDL oxidation parameters - intervention: supplementation with vit E - outcome: a global composite score averaging performance on all tests (3 repeated assessments by telephone at 2-year intervals: TICS, a telephone adaptation of the MMSE, immediate and delayed recall of the East Boston Memory Test, delayed recall of the TICS 10-word list, category fluency) - participants: 6377 women 65 years or older participated in a sub-study of cognitive function of the Women's Health Study (WHS). WHS is a randomised, double-blind, placebo controlled trial of vit E supplementation (600 IU on alternate days) begun between 1992 and 1995. The sub-study was initiated 5.6 years after randomisation and was conducted for 4 years - results: there were no differences in global score between the vit E and placebo groups 5.6 years and 9.6 years after randomisation. Mean cognitive change over time was also similar in the vit E group compared with the placebo group for the global score. The RR of substantial decline in the global score in the vit E group compared with placebo was 0.92 (95% CI=0.77, 1.10)
<ul style="list-style-type: none"> • Petersen et al. 2005 (125) 	<ul style="list-style-type: none"> - intervention: supplementation with vit E or treatment with donepezil - outcome: clinically possible or probable AD - participants: 769 subjects with aMCI were randomly assigned to receive daily either vit E (2000 IU) or donepezil (10 mg) or placebo for 3 years - results: 212 subjects developed AD. There were no significant differences in the probability of progression to AD in the vit E compared to donepezil or placebo groups during the 3 years of treatment. No significant differences emerged among ApoE4 carriers between the vit E and placebo groups
<ul style="list-style-type: none"> • Sano et al. 1997 (126) 	<ul style="list-style-type: none"> - intervention: treatment with selegiline, α-tocopherol or both α-tocopherol and selegiline - outcome: time to death, institutionalization, loss of ability to perform basic activities of daily living, or severe dementia (defined as a CDR of 3) - participants: 341 patients with AD of moderate severity were randomly assigned to receive either the selective monoamine oxidase inhibitor selegiline (10 mg/day), or α-tocopherol (vit E, 2000 IU/day) or both selegiline and α-tocopherol or placebo for 2 years - results: as compared with the placebo group (440 days), there were significant delays in the time to primary outcome for the patients treated with selegiline (median time, 655 days; p=0.012), α-tocopherol (670 days, p=0.001) or combination therapy (585 days, p=0.049) after adjustment on baseline MMSE score

Note: AD: Alzheimer's disease; aMCI: amnesic subtype of Mild Cognitive Impairment; CDR: Clinical Dementia Rating; BMI: Body Mass Index; CI: confidence interval; DSS: Digit Symbol Substitution; EBMT: East Boston Memory Test; FTT: Finger Tapping Test; HR: hazard ratio; GDS: Geriatric Depression Scale; HRT: hormone replacement therapy; MeD: Mediterranean diet; MMSE: Mini Mental State Examination; 3MS: Modified Mini Mental State; MUFA: monounsaturated fatty acid; OR: odds ratio; PSS: Perceived Stress Scale; PUFA: polyunsaturated fatty; RR: relative risk; Se: selenium; SPMQ: Short Portable Mental Status Questionnaire; SU: standardized units; TMTB: Trail Making Test part B; TICS: Telephone Interview of Cognitive Status; VaD: vascular dementia; vit: vitamin; Zn: zinc

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Table 4
Nutrition and prevention of cognitive decline: data from prospective studies on food groups and dietary patterns

Authors	Study design
<p>Prospective studies</p> <p>• <u>Wengreen et al., 2006 (140)</u></p>	<p>- exposure: dietary consumption of fruit, vegetables and fish</p> <p>- outcome: cognitive decline (3MS 'Modified MMSE')</p> <p>- participants: 3632 elderly (Cache County Study on Memory, Health and Aging)</p> <p>- mean follow-up: 7 years</p> <p>Adjustment for age, gender, education</p> <p>- results: participants in the highest quintile of 'fruit and vegetables' intake had average scores 0.94 points higher than those in the lowest quintile (p=0.01). Participants consuming > 1 serving of fish per week had average 3MS scores 0.81 points that those not consuming fish (p=0.008). Participants with high intakes of both 'fruit and vegetables' and fish had average 3MS scores 1.50 higher than those of the low intakes especially among ApoE4 non-carriers</p>
<p>• <u>Raffaïtin et al., 2006 (58)</u></p>	<p>- exposure: dietary consumption of fruit, vegetables and fish</p> <p>- outcome: incident dementia</p> <p>- participants: 8085 initially non demented subjects, age ≥ 65 years (3C study)</p> <p>- mean follow-up: 4 years</p> <p>Adjustment for age, sex, race, education, centre, income, marital status</p> <p>- results: similar patterns were found with the risk of AD: 282 subjects developed dementia (including 183 AD). Daily consumption of fruits and vegetables were associated with a reduced risk of all causes dementia (RR=0.70, 95%CI: 0.52, 0.94; p=0.02). Fish consumption (at least once a week) was associated with a reduced risk of dementia only in ApoE4 non carriers (RR=0.60, 95% CI: 0.41-0.89; p=0.01)</p>
<p>• <u>Morris et al., 2006 (137)</u></p>	<p>- exposure: fruit and vegetable consumption</p> <p>- outcome: cognitive decline measured by changes in a global measure of multiple tests (East Boston Tests of immediate memory and delayed recall, Symbol Digit Modalities Test).</p> <p>- participants: 3718 participants, age ≥ 65 years (CHAP study)</p> <p>- mean follow-up: 6 years</p> <p>Adjustment for age, sex, race, education</p> <p>- results: compared with the rate of cognitive decline among persons in the lowest quintile of vegetable intake, the rate for persons in the fourth quintile was slower by 0.019 SU/year (p=0.01) and by 0.018 SU/year (p=0.02) in the fifth quintile (p=0.02). Fruit consumption was not associated with cognitive change</p>
<p>• <u>Dai et al., 2006 (139)</u></p>	<p>- exposure: fruit and vegetable juice consumption</p> <p>- outcome: incident AD</p> <p>- participants: 1836 Japanese Americans free of dementia, age ≥ 65 years (Kame project)</p> <p>- mean follow-up: 9 years</p> <p>Adjustment for age, dietary intake of vit C, vit E and β-carotene</p> <p>- results: the HR for AD was 0.24 (95% CI=0.09, 0.61) for subjects who drank juices at least 3 times per week versus those who drank juices less often than once per week (p for trend <.01). This inverse association was more pronounced among ApoE4 carriers. No association were found for dietary intake of vitamins E, C or β-carotene or tea consumption</p>
<p>• <u>Scarmeas et al., 2006 (132)</u></p>	<p>- exposure: MeDi</p> <p>- outcome: incident AD</p> <p>- participants: 2258 community-based nondemented individuals (WHICAP study); mean age, 77.2 ± 6.6 years</p> <p>- mean follow-up: 4 ± 3 years (range:0.2-13.9)</p> <p>Adjustment for cohort, age, sex, ethnicity, education, ApoE genotype, caloric intake, smoking, comorbidity index, BMI</p> <p>- results: 262 persons developed incident AD. High adherence to the MeDi was associated with lower risk for AD (HR: 0.91; 95% CI: 0.83, 0.98; p=0.0015). Compared with subjects in the lowest MeDi tertile, subjects in the middle MeDi tertile had a HR of 0.85 (95% CI: 0.63, 1.16) and those of the highest tertile had a HR of 0.60 (95% CI: 0.42, 0.87)(p for trend=0.007)</p>

Note: AD: Alzheimer's disease; BMI: Body Mass Index; CI: confidence interval; HR: hazard ratio; MeDi = Mediterranean diet; MMSE: Mini Mental State Examination; OR: odds ratio; RR: relative risk; SU: standardized units