Diet and Prevention of Cognitive Decline and Dementia

The potential effect of nutrition has become a topic of increasing scientific and public interest. In particular, there are arguments that nutrients such as vitamins, trace minerals, lipids, can affect the risk of cognitive decline and dementia, especially in frail elderly people at risk of deficiencies. In this article, Dr. Gillette-Guyonnet and Dr. Vellas review data from prospective studies and randomized clinical trials relating diet to the risk of cognitive decline and dementia.

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The number of elderly subjects who will suffer from cognitive impairment and dementia will continue to increase in the near future as a consequence of the 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 elderly people at risk for deficiencies. This article reviews data from prospective studies and randomized clinical trials (RCTs) relating diet to the risk of cognitive decline and dementia, especially Alzheimer's disease (AD). It focuses 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 recent scientific literature.

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Macronutrients and Cognitive Decline and Dementia

Observational studies have suggested that among macronutrients, fatty acids play a role in modulating the risk of cognitive impairment and dementia. 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. Fatty acids can be categorized briefly into saturated fatty acids (SFA) and unsaturated fatty acids (UFA). Polyunsaturated fats (PUFA) comprise of 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.,* linolenic acid [18:3n-3], eicosapentaenoic acid [EPA 20:5n-3] and docosahexaenoic acid [DHA 22:6n-3]). 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-inflammatory

(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.[1]

The prospective studies of dietary fat and cognitive decline or dementia are sometimes conflicting however. Certain associations are frequently found (see Table 1).[2-16] High intakes of saturated and trans-unsaturated (hydrogenated) fats were generally positively associated with increased risk of AD, whereas high intakes of PUFA and monounsaturated fats (MUFA) were protective against cognitive decline in the elderly in prospective studies.

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.[12] 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.[3] 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 Chicago Health and Aging Project (CHAP) cohort between saturated and trans fats and copper intake[4] in accordance with a recent animal model,[17] in which neurodegenerative changes caused by a hypercholesterolemic diet were exacerbated by consumption of trace amounts of copper in drinking water. Moreover, fish consumption (n-3 PUFA) has been associated with lower risk of AD in longitudinal cohort studies.[2,7,11,14-15,18]

To date, three RCTs on the role of n-3 fatty acids in elderly people are in progress and examine:

1) the effects 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;[19]
2) the effects of 900 mg/day of DHA for 24 weeks on improved cognitive functioning among elderly people (age ≥ 55 years) with a subjective memory complaint;[20] 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 to 79 years (Older People And n-3 Long chain polyunsaturated fatty acids (OPAL) study).[21]

To our knowledge, a single randomized 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.[22] 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). Additional analysis performed in order to determine the potential effects of dietary omega-3 supplementation on psychiatric and behavioural symptoms, and daily function, were also negative.[23] Some differences however emerged according to the ApoE genotype.

Observational studies have suggested that among macronutrients, fatty acids play a role in modulating the risk of cognitive impairment and dementia.

Micronutrients and Age-related Cognitive Decline and Dementia

Homocysteine-related vitamins (B vitamins). Much attention has been given to B vitamins (especially, folate, vitamins B12 and B6) as preventive factors against cognitive decline and dementia.[24-30] 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 homocysteine (Hcy), and the importance of deficiencies in these nutrients to increased Hcy concentration.[31-34] Supraphysiologic levels of Hcy

Table 1

Nutrition and Prevention of Cognitive Decline: Data from Prospective Studies on Fatty Acids and Fish

Authors	Population	Results
Schaefer et al, 2006[2]	899 subjects initially free of dementia; median age: 76 years (The Framingham Heart Study)	higher plasma PC DHA levels associated with a RR of 0.53 of developing all-cause dementia (95% CI: 0.29, 0.97)
Laitinen et al, 2006[3]	1,449 subjects; age 65-80 years	among the ApoE4 carriers, moderate intake of PUFA at midlife decreased the risk of dementia (OR = 0.40, 95% CI: 0.17-0.94), whereas saturated fat intake was associated with an increased risk (OR=2.45, 95% CI: 1.10-5.47)
Morris et al, 2006[4]	3,718 community residents initially free of AD, age ≥ 65 years (The CHAP study)	among persons whose diets were high in saturated and trans fats, higher copper intake was associated with a faster rate of cognitive decline
Solfrizzi et al, 2006[5]	599 nondemented elderly subjects; age 65 – 84 years (The ISLA study)	no significant association was found between PUFA intake and the rate of MCI after controlling for the possible confounders
Solfrizzi et al, 2006[6]	599 nondemented elderly subjects; age 65 – 84 years (The ISLA study)	high MUFA and PUFA energy intake and total energy intake were significantly associated with better cognitive performance
Morris et al, 2005[7]	3,718 residents initially free of AD; age ≥ 65 years (The CHAP study)	compared with persons who consumed fish less than weekly, the rate of cognitive decline was 10% slower (-0.090 SU/year) among persons who consumed 1 fish meal per week and 13% slower (-0.088 SU/year) among those who consumed 2 or more fish meals per week
Morris et al, 2004[8]	2,560 residents initially free of AD; age ≥ 65 years (The CHAP study)	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
Heude et al, 2003[9]	246 healthy elderly; age: 63-74 years (The EVA study)	higher proportions of n-6 PUFA were associated with greater risk of cognitive decline (OR=1.59; 95% CI=1.04, 2.44); a higher proportion of n-3 PUFA was conversely associated with a lower risk (OR=0.59; 95% CI=0.38, 0.93)
Morris et al, 2003[10]	815 residents initially free of AD; age ≥ 65 years (The CHAP study)	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)
Morris et al, 2003[11]	815 residents initially free of AD; age ≥ 65 years (The CHAP study)	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)
Luchsinger et al, 2002[12]	980 elderly individuals free of dementia; age ≥ 65 years (The WHICAP study)	among individuals with ApoE4, the HR of AD for the highest quartiles of calorie and fat intake were 2.27 (95% CI=1.11, 4.68; *p* for tend=.07) and 2.31 (95% CI=1.09, 4.89; *p* for trend=.02) compared with the lowest quartiles
Engelhart et al, 2002[13]	5,295 subjects with normal cognition; age ≥ 55 years (The Rotterdam study)	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
Barberger-Gateau et al, 2002[14]	1,416 participants; age ≥ 68 years (the Paquid study)	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 protective effect of fish and seafood was partly explained by higher education of regular consumers
Kalmijn et al, 1997[15]	476 men; age 69-89 years (the Zutphen Elderly study)	high-fish consumption tended to be inversely associated with cognitive decline (0R=0.45, 95% CI=0.17, 1.16); no association was found between n-3 PUFA and cognitive impairment

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 methylaction and/or redox potentials thus promoting calcium influx, amyloid and tau protein accumulation, apoptosis and neuronal death.[35-40]

Most prospective studies suggest a protective role of B vitamins, especially vitamins B9 and B12, on cognitive decline and dementia (see Table 2).[41-52] One study found an unexpected detrimental effect with faster decline among persons who had high folate intakes (> 400 µg/day).[44] 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 µg/day. The existing epidemiologic 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.[25-42] 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.

Four small clinical trials tested the effects of supplementation with one or more of folic acid, vitamin B12 and vitamin B6 among healthy individuals[53] or cognitively impaired and demented older individuals.[54-56] They found no effect on cognition. One possible explanation is that these studies may have been underpowered to detect small effects.[57-58] In a more recent trial conducted by Eussen et al,[59] 195 older persons, free-living or in care-facility homes, were randomized to receive 1000 g of vitamin B12, or 1000 g of vitamin B12 plus 400 g of folic acid, or placebo for 24 weeks. There was no positive benefit on cognition, assessed by an extensive neuropsychologic 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 also 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 g) plus vitamins B12 (500 g) 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.[60] 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 total Hcy concentrations decreased by 26% in subjects on folic acid vs. placebo.[61]

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Antioxidant nutrients. Experimental, clinical, neuropathologic and epidemiologic investigations have implicated oxidative stress, involving the accumulation of free radicals with resultant oxidative damage, as a possible factor in the

Table 2

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

Authors	Population	Results
Luchsinger et al, 2007[41]	965 elderly individuals free of dementia; age ≥65 years (The WHICAP study)	- the highest quartile of total folate intake was related to a lower risk of AD (HR = 0.5; 95% CI = 0.3, 0.9; $p = 0.02$ for trend)
Morris et al, 2006[42]	1,041 residents initially free of AD; age ≥65 years (The CHAP study)	- no association was found between folate or vit B12 intakes and the risk of AD
Kado et al, 2005[43]	499 high-functioning community-dwellers; age 70-79 years (The MacArthur Studies of Successful Aging)	- 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; $p = 0.04$).
Morris et al, 2005[44]	3,718 residents initially free of AD; age ≥65 years (The CHAP study)	- 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.
Corrada et al, 2005[45]	579 nondemented elderly volunteers; age 49-93 years (The Baltimore Longitudinal Study of Aging)	- 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
Mooijaart et al, 2005[46]	599 subjects; 85 years of age (The Leiden 85-Plus Study)	- there were no significant associations of serum concentrations of homocysteine, vit B12 or folic acid with rate of cognitive decline
Tucker et al, 2005[47]	321 aging men; age 50-85 years (The Veterans Affairs Normative Aging Study)	- 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.
Ravaglia et al, 2005[48]	816 subjects initially free of dementia ; mean age 74 years (The Conselice Study of Brain Aging)	- in the subjects with hyperhomocysteinemia (tHcy >15 µg/day), 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; $p = 0.005$) and AD (1.98; 95% CI: 1.15, 3.40; $p = 0.014$)
Luchsinger et al, 2004[49]	909 elderly subjects ; age 77.2 ± 6.3 years (The WHICAP study)	- adjusted HR of AD for the highest quartile of Hcy was 1.4 (95% CI : 0.8, 2.4; p for trend = 0.31)
Teunissen et al, 2003[50]	144 subjects; age 30-80 years	- no correlation was observed between serum Hcy, vit B12 and folic acid concentrations, and performance at any of the time-points
Seshadri et al, 2002[51]	1,092 subjects without dementia; mean age: 76 years (The Framingham study)	- the risk of AD nearly doubled with plasma tHcy level greater than 14 µg/day.
Wang et al, 2001[52]	370 nondemented persons; age ≥75 years (The Kungsholmen Projet)	- 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) - 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

Note : AD: Alzheimer's disease; CI: confidence interval; Hcy: homocysteine; HR: hazard ratio; RR: relative risk; tHcy: total homocysteine; vit: vitamin.

pathogenesis of cognitive decline and dementia. Select antioxidants, including vitamins E, C, carotenes, 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.[62-63] Finally, it has been suggested that vitamins E and C, carotenoids, and flavonoids may lose their effectiveness as antioxidants or even act as pro-oxidants *in vitro* under certain circumstances. 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.[64] 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.[65]

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 (see Table 3).[66-80] The results are nevertheless in favour of a possible role of the vitamin E more than of the vitamin C, but also of carotenoids[66-67] and selenium.[73,80-81] The observational studies of vitamins A, E, C and minerals (zinc, selenium) supplements are much more contradictory and have important bias of indication and selection of the participants. One possible 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,[69] 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.

There have been two published RCTs 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.[82] 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.[83] 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.[84] Recently, the results of the MAVIS (Mineral And Vitamin Intervention Study) trial provided no evidence for a beneficial effect of daily multivitamin and multimineral supplements for 12 months on memory and executive functioning in 910 community-living people over 65 years.[85] The possibility of beneficial effects in older people (aged 75 years and over) and those at greater risk of nutritional deficiency deserved however further

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Table 3

Nutrition and Prevention of Cognitive Decline: Data from Prospective Studies on Antioxidant Nutrients

Authors	Population	Results
Akbaraly et al, 2007[66]	1,389 subjects; age 60-71 years (The EVA study)	probability of cognitive decline increased with the decrease of plasma Se change over time
Hu et al, 2006[67]	455 elderly; age 65 years (the MacArthur Studies of Successful Aging)	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
Maxwell et al, 2005[68]	894 subjects with no evidence of dementia, age ≥65 years (The CHSA study)	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[69]	1,041 persons clinically evaluated for analysis of AD and 3,718 persons for analysis of cognitive change; age ≥ 65 years (The CHAP study)	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
Zandi et al, 2004[70]	3,227 elderly county residents ; age ≥65 years (The Cache County Study)	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)
Laurin et al, 2004[71]	2,459 Japanese-American men; age 71-93 years (The Honolulu-Asia Aging Study)	no association was found between intakes of beta-carotene, flavonoids, vit E, vit C and the risk of dementia or its subtypes
Luchsinger et al, 2003[72]	980 elderly subjects initially free of dementia; age ≥65 years (The WHICAP study)	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
Gray et al, 2003[73]	2,082 elderly subjects initially free of dementia; age ≥65 years (The Epidemiologic Studies of the Elderly)	current antioxidant users had a 29% lower risk of experiencing cognitive decline (adjusted RR=0.71; 95% CI=0.49, 1.01)
Grodstein et al, 2003[74]	14,968 women; age 70-79 years (The Nurses' Health Study)	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
Morris et al, 2002[75]	815 residents free of AD at baseline; age ≥65 years (The CHAP study)	among persons ApoE negative, 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= 0.05)
Engelhart et al, 2002[76]	5,395 participants initially free of dementia; age ≥55 years (The Rotterdam study)	high intake of vit C and vit E was associated with lower risk of AD (rate ratios [RRs] per 1-SD increase in intake were 0.82, 95% CI=0.68-0.99 and 0.82, 95% CI = 0.68-1.00, respectively)
Morris et al, 2002[77]	2,889 community residents; age ≥65 years (The CHAP study)	there was a 36% reduction in the rate of decline among persons in the highest quintile of total vit E intake (-4.3 x 10 –2 SU/year) compared with those in the lowest quintile (-6.7 x 10 –2 SU/year)
Masaki et al, 2000[78]	3,385 men; age 71-93 years (The Honolulu-Asia Aging study)	intake of supplements of both vitamins related to low risk of VaD (OR=0.12; 95% CI=0.02, 0.88) but not to risk of AD
Commenges et al, 2000[79]	1,367 French participants; age 65 years (The Paquid study)	the age-adjusted RR of dementia was 0.55 for the two highest tertiles of flavonoids intakes compared to the lowest (95% CI = 0.34, 0.90; p = 0.02)
Berr et al, 2000[80]	1,166 high cognitive functioning subjects; age 60-70 (The EVA study)	subjects with low levels of Se have an increased risk of cognitive decline (OR=1.58; 95% CI = 1.08-2.31)

Note: AD: Alzheimer's disease; CI; confidence interval; HR: hazard ratio; OR: odds ratio; RR: relative risk; Se: selenium; SU: standardized units; vit: vitamin; Zn: zinc

attention. 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).

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,[86] 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 epidemiologic and RCT studies are consequently needed to determine the optimal trial design. 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. Also, many vitamin supplement trials have not considered participants' baseline vitamin levels in establishing eligibility criteria or in post-trial analyses.

Future Research Directions

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.[87-88] 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.[89] This finding underlines the need to consider interactions between micro- and macronutrients for future research. The first prospective studies focused on the relation between food groups and cognitive decline or dementia are summarized in Table 4.[90-94]

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 RCTs 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.

Table 4

Nutrition and Prevention of Cognitive Decline: Data from Prospective Studies on Food Groups and Dietary Patterns

Authors	Population	Results
LWengreen et al, 2006[90]	3,632 elderly (The Cache County Study on Memory, Health and Aging)	- 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
Raffaitin et al, 2006[91]	8,085 initially non-demented subjects; age ≥65 years (The 3C study)	- 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; $p = 0.01$) - similar patterns were found with the risk of AD
Morris et al, 2006[92]	3,718 participants; age ≥65 years (The CHAP study)	- 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 ($p = 0.02$)
Dai et al, 2006[93]	1,836 Japanese Americans free of dementia; age ≥65 years (The Kame project)	- 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 <0.01); this inverse association was more pronounced among ApoE4 carriers
Scarmeas et al, 2006[94]	2,258 community-based nondemented individuals; mean age 77.2 ± 6.6 years (The WHICAP study)	- high adherence to the MeDi was associated with lower risk for AD (HR: 0.91; 95% CI: 0.83, 0.98; $p = 0.0015$)

Note: AD: Alzheimer's disease; CI: confidence interval; HR: hazard ratio; MeDi = Mediterranean diet ; OR: odds ratio; RR: relative risk; SU: standardized units

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