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Nutrition and neurodegeneration: epidemiological evidence and challenges for future research

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The prevention of dementias, such as Alzheimer's disease (AD), is a growing public health concern, due to a lack of effective curative treatment options and a rising global prevalence. Various potential risk or preventive factors have been suggested by epidemiological research, including modifiable lifestyle factors such as diet. Current epidemiological data are in favour of a protective role of certain micronutrients (B vitamins related to homocysteine metabolism, the anti-oxidant vitamins C and E, flavonoids, polyunsatured omega-3 fatty acids, vitamin D) and macronutrients (fish) in the prevention of cognitive decline and dementia/AD. Some factors have been targeted by interventions tested in randomized controlled trials (RCTs), but many of the results are conflicting with observational evidence. Epidemiological analysis of the relations between nutrient consumption and cognitive decline is complex and it is highly unlikely that a single component plays a major role. In addition, since multiple factors across the life course influence brain function in late life, multidomain interventions might be more promising in the prevention of cognitive decline and dementia/AD. Designing such trials remains very challenging for researchers. The main objective of this paper is to review the epidemiologic data linking potential protective factors to cognitive decline or dementia/AD, focusing particularly on the roles of adiposity, caloric restriction, micro (group B vitamins related to homocysteine metabolism, the anti-oxidant vitamins C and E, flavonoids, polyunsatured omega-3 fatty acids, vitamin D) and macronutrients (fish). Limitations of the current data, divergence with results of interventional prevention studies and challenges for future research are discussed.

The ageing of the population which affects all developed countries leads to an increase in age-related diseases, headed by the dementias and by Alzheimer's disease (AD) in particular. At the present time, AD accounts for 70% of prevalent dementias. Its incidence is increasing markedly and according to current predictions the numbers of persons affected will double every 20 years [1]. In their recently published study, Brookmeyer *et al.* [1] estimated at 26.6 million the number of Alzheimer's patients worldwide in 2006 (ranging between 11.4 to 59.4 million according to the geographical area considered). Their forecast for the future indicates that this number could be multiplied by four by 2050 and reach 106.8 million (variation of 47.2 to 221.2 million), affecting one in 85 persons. The onset of AD is generally insidious. It appears increasingly evident that the underlying pathophysiological mechanisms are active long before the appearance of the clinical symptoms of the disease. In the absence of curative treatments, prevention appears to open up interesting perspectives. Projections of epidemiological data show us that while the prevalence of AD is 5% after 65 years and 25% after 85 years, delaying the onset of the clinical phase of the disease by just 1 year reduces its prevalence by 25%, and a 5 year delay in onset would decrease the prevalence in the population by 50% after 5 years of application of preventive measures [2]. 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. Current

epidemiological data are in favour of a protective role of certain micronutrients (group B vitamins related to homocysteine metabolism, the anti-oxidant vitamins C and E, flavonoids, polyunsatured omega-3 fatty acids, vitamin D) and macronutrients (fish) in the prevention of cognitive decline and dementia/AD [3]. There is also increasing evidence for the role of total adiposity, usually measured clinically by body mass index (BMI), and central adiposity in AD [4]. In addition, it is now well established that caloric restriction could be used to promote successful brain ageing [5]. Increasing attention is being paid, not to the characteristics of the subjects in the years preceding diagnosis, but in a more global manner to the subject's entire life and in particular to the mid-life period towards the age of 50 years [6, 7]. Clarification of the relation between nutrition 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. The aim of this paper is to review the epidemiological data linking potential nutritional factors to risk of cognitive decline and dementia/AD, focusing particularly on the roles of adiposity, caloric restriction, micro (group B vitamins related to homocysteine metabolism, the anti-oxidant vitamins C and E, flavonoids, polyunsatured omega-3 fatty acids, vitamin D) and macronutrients (fish). Results from recent meta-analyses, reviews, longitudinal studies and randomized controlled trials (RCTs) assessing the prevention of both cognitive decline and dementia/AD are included. Limitation of the current data, divergence with results of interventional prevention studies and challenges for future research are discussed.

Summary of findings from prospective studies and RCTs

BMI, cognitive decline and risk of dementia/AD

There is increasing evidence for the role of total adiposity and central adiposity in AD [8–18]. Data remain however conflicting. A recent review [4] including analyses of salient studies published in 2007 and 2008 concluded that (i) central adiposity in middle age predicts dementia in old age, (ii) the relation between high adiposity and dementia is attenuated with older age, (iii) waist circumference in old age (a measure of central adiposity) may be a better predictor of dementia than BMI and (iv) lower BMI predicts dementia in elderly people and weight loss may precede dementia diagnosis by decades, which may explain seemingly paradoxical findings [19–24]. In a recent paper studying the potential relationship between healthy lifestyle in mid-life and risk of dementia in 3468 Japanese-American men followed in the Honolulu Asia Aging study within 25 years, authors found after examining each factor individually that BMI in mid-life was most strongly associated with greater risk of overall dementia in later-life (OR = 1.87, 95% CI = 1.26, 2.77; BMI >25.0 *vs.* <22.6 kg m^{-2}) [25].

In addition, post-mortem examinations in 298 individuals, who were followed in the Honolulu-Asia Aging study, found that low BMI was associated with a higher degree of AD pathology [26]. Moreover, obesity in individuals with high levels of adiposity in mid-life is associated with neuronal and/or myelin abnormalities, primarily in the frontal lobe and so might have an effect on accelerated ageing [18].

In total, prevention and manipulation of adiposity in mid-life may provide a means to prevent cognitive decline and dementia/AD.

Caloric restriction, cognitive decline and risk of dementia/AD

Accumulation of experimental evidence suggests that caloric restriction may offer protection against age-related neuronal loss and neurodegenerative disorders. Hypotheses linking caloric restriction to cognitive ability include increase in insulin sensitivity, anti-inflammatory mechanisms (les 2), reduction of neural oxidative stress, promotion of synaptic plasticity, induction of various stress and neurotrophic/neuroprotective factors [5, 27]. Data from RCTs in adults are however limited. To our knowledge, there are only two RCTs in humans which examined the effect of caloric restriction alone or in combination with physical exercise on cognitive function. In the GALERIE study (Comprehensive Assessment of long term Effects of reducing Intake of Energy) [28], 48 participants were randomized to one of four groups: control (weight maintenance) (mean age 37 $\pm$ 7 years), caloric restriction (25% restriction) (mean age 39 $\pm$ 5 years), caloric restriction plus structured exercise (12.5% restriction plus 12.5% increased energy expenditure via exercise) (mean age 36 $\pm$ 6 years) or low calorie diet (890 kcal day^{-1} diet until 15% weight loss, followed by weight maintenance) (mean age 38 $\pm$ 8 years). Cognitive tests (verbal memory, visual memory, attention/concentration) were conducted at baseline and months 3 and 6. No consistent pattern of verbal memory, visual retention/memory, or attention/concentration deficits emerged during the trial. Daily energy deficit was not significantly associated with change in cognitive test performance. These conclusions must be interpreted in the context of study limitations (small sample size and limited statistical power). More recently, in the ENCORE study (Exercise and Nutrition Interventions for Cardiovascular Health) [29], 124 participants, mean age of 52 $\pm$ 9 years, with elevated blood pressure (BP) (systolic BP 130 to 159 mm Hg or diastolic BP 85 to 99 mm Hg) who were sedentary and overweight or obese (BMI 25 to 40 kg m^{-2}) were randomized to the Dietary Approaches to Stop Hypertension (DASH) diet alone, DASH combined with a behavioural weight management programme including exercise and caloric restriction or a usual diet control group. Participants completed a battery of neurocognitive

tests of executive function-memory learning and psychomotor speed at baseline and 4 months after the intervention. Participants on the DASH diet combined with a behavioural weight management programme exhibited greater improvements in executive function-memory learning ($P = 0.008$) and psychomotor speed ($P = 0.023$) compared with the usual diet control. Neurocognitive improvements appeared to be mediated by increased aerobic fitness and weight loss.

In total, because the long term effects (over 1 year) of caloric restriction in older people are not yet known, precautions should be taken before engaging in such a caloric restriction regimen. In order to design new RCTs in the future and propose specific recommendations, additional studies are needed to determine if the effects of caloric restriction are long lasting or only active during the restriction period, as well as the length the caloric restriction must be continued to see benefits in adults. Moreover, it seems that 'multidomain' interventions will be proposed in the future combining caloric restriction with other lifestyle components, such as physical exercise. Finally, the clarification of the mechanisms through which caloric restriction may beneficially influence AD neuropathology will help in the development of lifestyle therapeutic strategies in AD and possibly other neurodegenerative disorders.

Nutrients, cognitive decline and risk of dementia/AD

Anti-oxidants Experimental, clinical, neuropathological and epidemiological investigations have implicated oxidative stress as a possible factor in the pathogenesis of cognitive decline and dementia. Multiple lines of evidence indicate that oxidative stress not only strongly participates in an early stage of AD prior to cytopathology, but plays an important role in inducing and activating multiple cell signalling pathways that contribute to the lesion formations of toxic substances and then promote the development of AD.

Exogenous anti-oxidants (such as vitamin E and C, carotenoids, flavonoids) decrease free radical mediated damage caused by toxic chain reactions in neuronal cells and reduce the toxicity of beta-amyloid in *in vitro* studies of brains of patients with AD [30]. The use of anti-oxidants for prevention of dementia has been evaluated in several observational studies with varying results [31–37]. Two large prospective studies reported that higher dietary intake of anti-oxidants was associated with a lower risk of AD [31, 32]. Nevertheless, these studies had significant limitations such as the use of a food frequency questionnaire to estimate nutrient intake in patients with potential cognitive impairment. Then, neither study found an association between anti-oxidant supplements and AD risk but only with anti-oxidant intake from food.

Several RCTs with vitamin E and cognitive decline have been published in older adults with normal cognition, but none has found an association between supplementation and decreased risk of cognitive decline over follow-up times [38–40]. A long term supplementation in β-carotene (50 mg every other day for 18 years) showed a beneficial effect compared with the placebo group [41].

Some studies examined the relationship between combinations of anti-oxidants on cognitive performance. A recent RCT on an anti-oxidants complex supplementation (including 34 elements) has shown an increased cognitive performance during the 4 months of follow-up compared with the placebo group [42]. In the SU.VI.MAX study (Supplementation in Vitamins and Mineral Anti-oxidants) [43], 4447 French participants aged 45–60 years were randomized to receive daily vitamin C (120 mg), β-carotene (6 mg), vitamin E (30 mg), selenium (100 µg) and zinc (20 mg) in combination or as a placebo. Six years after the end of the trial, subjects receiving active anti-oxidant supplementation had better episodic memory scores (mean difference 0.61, 95% CI 0.02, 1.20).

In addition, the neuroprotective effects of natural anti-oxidants, such as *Ginkgo biloba*, have been suggested. Results from the Ginkgo Evaluation of Memory (GEM) randomized controlled trial [44] provided, however, evidence that treatment with *Ginkgo biloba* does not slow the rate of cognitive decline in older adults. Through examination of the effect modification by baseline cognitive status (mild cognitive impairment *vs.* normal cognition), the authors concluded that *Ginkgo biloba* affected neither cognitive changes associated with dementia prodrome nor cognitive changes associated with normal ageing [44, 45]. An earlier article from the GEM study [46] reported that *Ginkgo biloba* was not effective in reducing the overall incidence rate of dementia or AD. A lower risk of progression of cognitive decline was found in a small RCT involving 118 older adults with no cognitive impairment (84 years and over) [47]. However, treatment was also associated with an increased incidence of strokes in the treatment group [47]. Results of the French GuidAge trial conducted in 2854 older adults (70 years and over) reporting memory complaints and treated during 5 years, showed that long term use of standardized *Ginkgo biloba* extract (5 years) did not reduce the risk of progression to AD compared with placebo [48]. Finally, in a Cochrane review including 45 RCTs (36 small RCTs of duration less than 3 months plus nine RCTs of 6 months duration), authors concluded that *Ginkgo biloba* appears to be safe in use with no excess side effects compared with placebo but they did not find evidence that *Ginkgo biloba* has predictable and clinically significant benefit for people with cognitive impairment or dementia [49]. The authors underlined the unsatisfactory methods used in these trials. A major limitation of this review could be the combined evaluation of cognitive decline and dementia [50]. A statistically significant advantage of *Ginkgo biloba* compared with placebo in improving cognition for demented patients was recently described in the meta-analysis of Weinmann *et al*. [50] (nine trials, 12 to 52 weeks duration, 2372 patients).

In total, the results on anti-oxidant nutrients and cognitive decline or dementia may suggest the importance of having a balanced combination of several anti-oxidant nutrients in order to exert a significant preventive effect on cognitive decline and dementia. We must, however, use these data cautiously for future recommendations. There is a growing concern regarding the risk of mortality associated with anti-oxidant supplementation. A recent meta-analysis [51], studying the effect of anti-oxidant supplements on mortality in randomized primary and secondary prevention trials, showed that treatment with β-carotene, vitamin A, or vitamin E might increase mortality. According to the authors, the potential impact of vitamin C and selenium on mortality needs further study. There is also presently no clear evidence that *Ginkgo biloba* promotes successful cognitive ageing.

Vitamin B It has now been proved that vitamin B6, vitamin B12 and folate deficiency, as co-factors in the methylation of homocysteine are associated with increased homocysteine concentrations. Supraphysiological concentrations of homocysteine or deficits in folate and vitamin B12 should promote amyloid and tau protein accumulation and neuronal death, and also have a direct effect on cognitive decline. The potential mechanisms whereby homocysteine might mediate cognitive decline and dementia include: neurotoxicity induced by activation of N-methl-D-aspartate receptors, promotion of apoptosis, vascular injury from promotion of atherogenesis and proliferation of smooth muscle cells, platelet activation and increased burden of ischaemic strokes and white matter lesions [52]. While there is some evidence that elevated serum homocysteine and/or low serum concentrations of folate, vitamin B6 and vitamin B12 may be associated with impaired cognition and risk of dementia, there are no convincing data that vitamin supplementation prevents dementia [53–56].

A possible benefit from folate therapy was suggested in a longitudinal (non-randomized) study of 965 older individuals, in whom a lower incidence of AD was noted among those in the highest quartile of total folate intake after adjustments [57]. Neither vitamin B6 nor B12 intake was associated with the risk of AD.

Several RCTs tested the effects of supplementation with one or more supplementations with folate, vitamin B12 or vitamin B6 in older healthy adults [58–62]. Only two trials have shown a positive effect on cognition. In the FACIT trial, 818 participants with elevated serum homocysteine aged 50 to 70 years were randomized to receive daily folate supplementation (800 mg day^{-1}) or placebo. The results showed that folate supplementation for 3 years was associated with improved performance on memory, sensorimotor speed and information processing speed compared with placebo [59]. More recently, a RCT [62] tested the effect of daily oral supplementation of folate (400 μg day^{-1}) and vitamin B12 (100 μg day^{-1}) in 900 adults aged 60–74 years. Results showed that supplementation improved the Telephone Interview for Cognitive Status-Modified (TICS-M) total ($P = 0.032$, effect size d = 0.17), the TICS-M immediate ($P = 0.046$, d = 0.15) and TICS-M delayed recall ($P = 0.013$, effect size d = 0.18) scores at 24 months in comparison with placebo. No significant changes were evident in orientation, attention, semantic memory, processing speed or informant reports. We are currently waiting the results of the OPEN study [63] conducted in 200 older people with vitamin B12 deficiency, aged 75 years or over, who were randomly allocated to receive either a daily oral tablet containing vitamin B12 or a matching placebo tablet. Primary outcomes assessed at 12 months were electrophysiological indices of peripheral and central neurosensory responses required for mobility and sensory function. Cognitive performance (including tests of memory, executive function and psychomotor speed) are part of secondary outcomes.

Supplementation with B vitamins was tested in patients with mild to moderate AD in two RCTs [64, 65]. Only one has reported a positive impact of supplementation (folate 5 mg day^{-1} and vitamin B12 1 mg day^{-1} for 24 months) on cognitive decline among patients with elevated plasma homocysteine (>13 μmol l^{-1}) compared with placebo [65]. Moreover, the cognitive decline and the accelerated rate of brain atrophy could be slowed by treatment with B vitamins (folate 0.8 mg day^{-1}, vitamin B12 0.5 mg day^{-1} and vitamin B6 20 mg day^{-1} for 24 months) in people with mild cognitive impairment (MCI) in particular in those with elevated homocysteine [66, 67] (the VITACOG study).

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. Confounding bias is particularly likely for folate intake as it is associated with many dietary (e.g. anti-oxidant 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.

Vitamin D Epidemiologic investigations have revealed a beneficial role of vitamin D in muscle function, cardiovascular health, diabetes and cancer prevention. Low levels of serum 25-hydroxyvitamin D are also associated with increased odds of prevalent cognitive dysfunction, AD and all cause dementia in a number of studies, raising the possibility that vitamin D plays a role in the aetiology of cognitive dysfunction and dementia. Vitamin D

contributes to neuroprotection by modulating the production of nerve growth, neurotrophin, glial cell derived neurotrophic factor, nitric oxide synthase and choline acetyl transferase [68], and neuroprotective mechanisms including vasoprotection and amyloid phagocytosis and clearance [69, 70]. However, the majority of human studies reporting associations between vitamin D and cognition or dementia have been cross-sectional or case-control designs. Two recent large prospective studies established a temporal relationship with cognitive decline. First, Slinin *et al*. [71] found little evidence of independent associations between lower 25-hydroxyvitamin D concentration and baseline global and executive cognitive function or incident cognitive decline in a cohort of 1604 men enrolled in the Osteoporotic Fractures in Men Study and followed them for an average of 4.6 years. Second, low concentrations of vitamin D were associated with cognitive decline over a 6 year observation period in a population of 858 adults enrolled in the InCHIANTI study [72]. Moreover, it was recently demonstrated that baseline serum vitamin D deficiency predicted the onset of non-Alzheimer dementias within 7 years among older women from the EPIDOS cohort [73]. To our knowledge, no large RCT specifically designed to explore the impact of vitamin D supplementation in the prevention of cognitive decline has been published.

In patients with AD, the AD-IDEA trial [74] is currently in recruitment. This RCT tested the hypothesis that the combination of memantine and vitamin D may provide enhanced protection against several degenerative processes linked to AD. All patients received memantine 20 mg daily and one of the two treatment options, vitamin D or placebo. The primary outcome was the change in Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog).

In total, prospective studies and RCTs are needed to confirm that vitamin D deficiency is causally related to cognitive decline and to open up important new possibilities for treatment and prevention.

Fatty acids Fatty acids have been suggested to play a role in modulating the risk of cognitive impairment and dementia based on observational studies. Polyunsaturated fats (PUFA) comprise two major classes, the n-6 class (e.g. linoleic acid and arachidonic acid) and the n-3 class [e.g. α-linolenic acid, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)]. Several mechanisms have been postulated for the possible protective role of n-3 PUFA in dementia. DHA is a key component of membrane phospholipids in the brain and adequate n-3 PUFA status may help maintain integrity and neuronal function. The oxidative products of PUFA act as key cellular mediators of inflammation, allergy and immunity, oxidative stress, bronchial constriction, vascular response and thrombosis and may thereby influence risk especially for vascular dementia. DHA may be directly involved in enhancing neuronal health in the ageing brain through a range of potential mechanisms. DHA may modify the expression of genes that regulate a variety of biological functions potentially important for cognitive health, including neurogenesis and neuronal function [75]. Fatty fish is the primary dietary source of longer chain n-3 fatty acids, EPA and DHA. In observational studies, high dietary intake of saturated and trans-unsaturated (hydrogenated) fats may increase the risk of cognitive decline and AD [76, 77], but evidence is conflicting [78]. The potential effects of dietary intake of fish and omega-3 fatty acids on the risk of dementia or cognitive decline have been studied as well. The findings have been mixed, but most studies have shown a benefit for higher fish consumption [79–82] or on the accumulation of white matter abnormalities measured on brain MRI [83]. Some studies have investigated the effects of specific omega-3 fatty acids, especially DHA and found dietary DHA in the highest tertile measured at baseline was associated with lower rates of incident dementia over follow-up [84, 85].

Four RCTs have been published on the effects of specific omega-3 fatty acids in normal healthy adults on cognitive performance [86–89]. Only one of them [87] has found positive results by investigating the effect of a daily oral DHA supplementation (900 mg day^{-1}) for 24 weeks in 485 adults aged 55 years and older on cognitive functions. Intention-to-treat analysis showed significantly fewer Paired Associate Learning (PAL) six pattern errors with DHA *vs.* placebo at 24 weeks (difference score, -1.63 ± 0.76, 95% CI -3.1, -0.14, $P = 0.03$). DHA supplementation was also associated with improved immediate and delayed verbal recognition memory (VRM) scores ($P < 0.02$), but not working memory or executive function tests.

In patients with AD or MCI, none RCT have supported a therapeutic role for omega-3 fatty acid supplementation [90, 91]. Freund-Levi *et al* [91] have reported a positive effect of n-3 fatty acid supplementation on cognitive functions but in a small group of patients with very mild AD (MMSE >27 points).

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 PUFAs could have a preventive effect against dementia through their anti-thrombotic and anti-inflammatory properties in addition to their specific effect on neural functions.

Combinations of nutrients The hypothesis that combinations of certain nutrients could provide clinically relevant benefits to patients with AD formed the basis of the development of the medical food 'Souvenaid', which is a multinutrient drink designed to improve synapse formation [92]. The efficacy, tolerability and safety of

'Souvenaid' was tested in a proof of concept clinical trial conducted in 225 drug-naïve AD patients (mean MMSE score of 23.9, mean age of 73.7 years). Patients were randomized to active product 'Souvenaid' or a control drink, taken once daily for 12 weeks. The active product 'Souvenaid' contains a specific formulation of nutrients registered as Fortasyn Connect (EPA 300 mg/daily dose, DHA 1200 mg/daily dose, Vitamin E 40 mg/daily dose, Vitamin C 80 mg/daily dose, vitamin B12 3 μg/daily dose, vitamin B6 1 mg/daily dose and Folate 400 μg/daily dose) plus other vitamins, minerals, trace elements and macronutrients. Primary outcome measures were the delayed verbal recall task of the Wechsler Memory Scale-revised (WMS-r) and the 13-item modified ADAS-cog at week 12. Results showed a significant improvement in the WMS-r delayed verbal recall in the active group compared with control ($P = 0.026$) but not in modified ADAS-cog. In the subgroup of patients with very mild AD (120 patients with baseline MMSE between 24 and 26), results showed a greater improvement in the WMS-r delayed verbal recall in the active group compared with control ($P = 0.011$) and in the WMS-r immediate verbal recall ($P = 0.157$) [92]. Secondary analysis was made in this cohort [93] where the study population was divided into two subgroups: patients with 'low' baseline ADAS-cog scores (<25.0) and patients with 'high' baseline ADAS-cog scores (≥25.0). Repeated measures models for each patient were used to determine the relationship between ADAS-cog score and intervention up to 24 weeks. A significant treatment effect ($P = 0.046$) was shown in patients with 'high' baseline ADAS-cog, but not in patients with 'low' baseline ADAS-cog. Overall, intake adherence was significantly correlated with ADAS-cog improvement in the active product group (correlation coefficient = –0.260; $P = 0.019$), but not in the control group.

In addition, the effects of B vitamins and omega-3 fatty acid supplementation on cognition in a high risk population were tested in an ancillary study of the SU.FOL.OM3 (Supplementation with FOLate, vitamins B6 and B12 and/or omega-3 fatty acids) secondary prevention trial conducted in France between 2003 and 2009 [94]. The present sample included 1748 men and women aged 45–80 years with a history of myocardial infarction, unstable angina or ischaemic stroke. Participants were assigned in a 2 × 2 factorial design to one of the following four groups: folate (0, 56 mg), vitamin B6 (3 mg) and vitamin B12 (0, 2 mg); EPA and DHA (600 mg) in a 2:1 ratio; vitamins B and omega-3 fatty acids; or placebo. No significant main effects on cognitive function (evaluated by the French version of the modified Telephone interview for Cognitive Status) after 4 years of supplementation were found. However, authors found some evidence of disease history- and age-specific effects. In the subgroup with prior stroke, for example, participants assigned to receive B vitamins plus omega-3 fatty acids were significantly less likely to have a decreased score on the temporal orientation task than those assigned to receive placebo.

Methodological statements

In his paper, Daffner [95] discussed advantages and limitations of epidemiologic/cohort studies, animal/basic sciences studies, human proof of concept studies, and human intervention studies, the four major lines of evidence available to examine whether a proposed factor my have an impact on the promotion of successful cognitive ageing. According to this author, the advantages of epidemiological/cohort studies include their large number of subjects and their acquisition of information about many factors. Particularly valuable to the study of successful cognitive ageing is the ability of epidemiological studies to follow subjects over years to decades. A major limitation to this line of investigation is that findings can only establish the presence of an association between a designated factor and a clinical outcome, which is not proof of causality. Uncertainty remains about the potential influence of unidentified factors and whether an intervention directed at a particular factor would necessarily change the outcome in clinically significant ways. That can be explain why results found in prospective cohort studies have not been confirmed by RCTs.

Many methodological explanations for divergent observational and experimental results for dementia prevention were also identified in the review proposed by Coley *et al*. [96]. The most common methodological limits concern precision to measure some exposures (self or proxy report rather than objective measures leading to misclassification), measurement of exposure variations over time (and not only at one time point), timing of intervention (some interventions may have differential effects according to the time of exposure), confounding factors taken into account (many studies did not consider, for example, the importance of adjusting for the presence of ApoE4). The action of n-3 PUFA on the ageing brain might therefore differ according to ApoE polymorphism and several epidemiological studies suggest a protective effect of long-chain n-3 PUFA on cognitive decline only in those who do not carry the allele 4 but with inconsistent results [97]), mode of collection of nutritional data used, forms and doses of the vitamins used in randomized controlled studies (Table 1), duration of follow-up, duration of intervention, insufficient statistical power, variation of outcome definition, and consideration of attrition rate.

Finally, risk factors can change over time, with different life periods having their own sets of exposures to different risk factors. The influence of different aspects of diet is likely to vary over the course of life. It is important to identify the critical periods during which an individual is a greatest risk of damage if exposed to a specific nutrient deficiency.

Table 1

Nutrition and prevention of cognitive decline or dementia/Alzheimer's disease: data from randomized controlled trials conducted in cognitively normal elderly subjects

Caloric restriction				
Martin *et al*. 2007 [28]	Outcomes: Cognitive tests (verbal memory, visual memory, attention/concentration)	Intervention: Caloric restriction alone or with physical exercise Follow-up: 6 months	Participants: n = 48; four groups: control (weight maintenance) (mean age 37 ± 7 years), caloric restriction (25% restriction) (mean age 39 ± 5 years), caloric restriction plus structured exercise (12.5% restriction plus 12.5% increased energy expenditure via exercise) (mean age 36 ± 6 years), or low-calorie diet (890 kcal day^{-1} diet until 15% weight loss, followed by weight maintenance) (mean age 38 ± 8 years).	Daily energy deficit was not significantly associated with change in cognitive test performance.
Smith *et al*. 2010 [29]*	Outcomes: Neurocognitive tests of executive function-memory-learning and psychomotor speed	Intervention: Caloric restriction with physical exercise Follow-up: 4 months	Participants: n = 124, mean age of 52 ± 9 years, with elevated blood pressure, sedentary and overweight or obese (BMI 25 to 40 kg m^{-1}); three groups: Dietary Approaches to Stop Hypertension (DASH), diet alone, DASH combined with a behavioural weight management programme including exercise and caloric restriction, or usual diet control group	Participants on the DASH diet combined with a behavioural weight management programme exhibited greater improvements in executive function-memory-learning (P = 0.008) and psychomotor speed (P = 0.023) compared with the usual diet control.
Anti-oxidants				
Yaffe *et al*. 2004 [38]	Outcomes: AREDS (Age-Related Eye Disease Study) cognitive battery included six validated cognitive tests with eight components: The Modified MMSE, Animal Category, Letter Fluency, Logical Memory part I and II, Wechsler Memory Scale Revised, Immediate Recall, Word List Mean; Buschke Selective Reminding Test and Digits Backwards.	Intervention: Anti-oxidants or zinc and copper or both Follow-up: Median of 6.9 years	Participants: n = 2 166, mean age of 75 ± 5 years, four groups: daily oral tablets containing anti-oxidants (vitamin C, 500 mg; vitamin E, 400 IU; beta carotene, 15 mg), zinc and copper (zinc, 80 mg; cupric oxide, 2 mg), anti-oxidants plus zinc and copper or placebo	Compared with placebo, anti-oxidants with or without zinc and copper did not have a significant effect on cognitive performance
Kang *et al*. 2006 [39]	Outcomes: Three cognitive assessments of general cognition, verbal memory and category fluency administered by telephone at 2 year intervals. The primary outcome was a global composite score averaging performance on all tests	Intervention: Vitamin E Follow-up: 2 years	Participants: n = 39 876 women, 65 years or older, two groups: 600 IU of vitamin E on alternate days or placebo	No differences in global score between the vitamin E and placebo groups at the first assessment (5.6 years after randomization) or at the last assessment (9.6 years of treatment)
Grodstein *et al*. 2007 [41]*	Outcomes: General cognition, verbal memory and category fluency. The primary end point was a global score averaging all tests	Intervention: Beta carotene Follow-up: 18 years	Participants: n = 5 956 men, older than 65 years, two groups: beta carotene (50 mg, alternate days) or placebo	No impact of short term (1 year) β-carotene supplementation on cognitive performance The mean global score was significantly higher in the beta carotene group than in the placebo group in long term supplementation (18 years) (mean difference in z scores, 0.047 standard units; P = 0.03) On verbal memory, men receiving long term beta carotene supplementation also performed significantly better than the placebo group (mean difference in z scores, 0.063; P = 0.007)

Table 1
Continued

Kang *et al*. 2009 [40]	Outcomes: Five cognitive tests assessed by telephone. The primary outcome was a global composite score averaging all scores	Intervention: Vitamin E, vitamin C, beta carotene Follow-up: 5.4 years	Participants: *n* = 2 824 women, 65 years or older, with CVD or ≥three coronary risk factors, three groups: vitamin E (402 mg every other day), beta carotene (50 mg every other day), and vitamin C (500 mg daily)	Vitamin E supplementation and beta carotene supplementation were not associated with slower rates of cognitive change Although vitamin C supplementation was associated with better performance at the last assessment (mean difference, 0.13; 95% confidence interval, 0.06 to 0.20; *P* = 0.0005), it was not associated with cognitive change over time
Summers *et al*. 2010 [42]*	Outcomes: Memory testing with a 50 part paired association test and a 20-word immediate recall test	Intervention: Complex anti-oxidant blend (including 34 elements) Follow-up: 4 months	Participants: *n* = 86, aged of 50 to 75 years, two groups: active treatment or placebo	Memory testing with a 50 part paired association test and a 20 word immediate recall test were significantly improved, *P* = 0.015 and *P* = 0.005 respectively
Kesse-Guyot *et al*. 2011 [43]*	Outcomes: four neuropsychological tests (six tasks)	Intervention: Complex anti-oxidant blend Follow-up: 6 years	Participants: *n* = 4 447, aged 45–60 years, two groups: daily vitamin C (120 mg), β-carotene (6 mg), vitamin E (30 mg), selenium (100 μg), and zinc (20 mg) in combination or placebo	Subjects receiving active anti-oxidant supplementation had better episodic memory scores (mean difference: 0.61; 95% CI 0.02, 1.20)
Gingko biloba				
DeKosky *et al*. 2008 Snitz *et al*. 2009 [44, 46]	Outcomes: Rates of change over time in the Modified MMSE, in the ADAS-Cog, and in neuropsychological domains of memory, attention, visual-spatial construction, language, and executive functions	Intervention: *Ginkgo biloba* Follow-up: Median follow-up of 6.1 year	Participants: *n* = 3 069 older adults aged 75 years or older (approximately 15% with MCI at baseline), two groups: *Ginkgo biloba* extract 120 mg twice daily or placebo	After a median of 6 years of follow-up, treatment did not reduce the risk of all-causes of dementia in the cohort (HR = 1.12, 95% CI 0.94, 1.33) or in the subset of patients with MCI at baseline (HR = 1.13, CI 0.85, 1.50)
Dodge *et al*. 2008 [47]*	Outcomes: Risk of progression from CDR = 0 to CDR = 0.5 and decline in episodic memory	Intervention: *Ginkgo biloba* Follow-up: 42 months	Participants: *n* = 118 older adults aged of 84 years or over	Treatment group had a lower risk of progression of cognitive decline (HR = 0.33, *P* = 0.02) but also an increased incidence of strokes (*P* = 0.01)
Vellas *et al*. 2012 [48]	Outcomes: conversion to probable AD	Intervention: *Ginkgo biloba* Follow-up: 5 years	Participants: *n* = 2 854 adults aged 70 years or older who spontaneously reported memory complaints, two groups: twice per day dose of 120 mg standardised *Ginkgo biloba* extract (EGb761) or matched placebo.	By 5 years, 61 participants in the Ginkgo group had been diagnosed with probable Alzheimer's disease (1.2 cases per 100 person-years) compared with 73 participants in the placebo group [1.4 cases per 100 person-years; hazard ratio (HR) 0.84, 95% CI 0.60, 1.18; *P* = 0.306], but the risk was not proportional
Vitamins B				
McMahon *et al*. 2006 [58]	Outcomes: plasma homocysteine concentration and tests of cognition	Intervention: Folate and vitamin B6 and B12 Follow-up: 2 years	Participants: *n* = 276, 65 years or older, with plasma homocysteine concentrations of at least 13 μmol l^{-1}, two groups: daily supplement containing folate (1 000 μg) and vitamins B12 (500 μg) and B6 (10 mg) or placebo	On average, the plasma homocysteine concentration was 4.36 μmol l^{-1} lower in the vitamin group than in the placebo group (*P* < 0.001) There were no significant differences between the vitamin and placebo groups in the scores on tests of cognition
Durga *et al*. 2007 [59]	Outcomes: Change in performance for memory, sensorimotor speed, complex speed, information processing speed and word fluency	Intervention: Folate Follow-up: 3 years	Participants: *n* = 818, with elevated serum homocysteine, aged 50 to 70 years, two groups: daily folate supplementation (800 mg day^{-1}) or placebo	Folate supplementation for 3 years was associated with improved performance on memory, sensorimotor speed and information processing speed compared with placebo

Table 1

Continued

Kang *et al*. 2008 [61]	Outcomes: Telephone cognitive function testing was administered up to four times over 5.4 years with five tests of general cognition, verbal memory, and category fluency. Repeated-measures analyses were conducted, and the primary outcome was a global composite score averaging all test results	Intervention: Folate and vitamin B6 and B12 Follow-up: 5.4 years	Participants: *n* = 2 009 women, aged 65 years or older, with CVD or ≥three coronary risk factors, two groups: combination of B vitamins (2.5 mg folate day^{-1}, 50 mg vitamin B6 day^{-1}, and 1 mg vitamin B12 day^{-1}) or placebo	Mean cognitive change from baseline did not differ between the B vitamin and placebo groups (difference in change in global score: 0.03; 95% CI –0.03, 0.08; *P* = 0.30)
Ford *et al*. 2010 [60]	Outcomes: The primary outcome of interest was the change in the ADAS-cog. A secondary aim of the study was to determine if supplementation with vitamins decreased the risk of cognitive impairment and dementia	Intervention: Folate and vitamin B6 and B12 Follow-up: 8 years	Participants: *n* = 299 hypertensive men, 75 years and older, two groups: folate (2 mg), vitamin B6 (25 mg), and B12 (500 μg) daily supplementation or placebo over 2 years	There was no difference in the ADAS-cog change from baseline to 24 months between the placebo and vitamins group There was a non-significant decrease in the risk of cognitive impairment and dementia over 8 years of follow-up
Walker *et al*. 2012 [62]*	Outcomes: Main outcome measures examined change in cognitive functioning by using the Telephone Interview for Cognitive Status-Modified (TICS-M), the Brief Test of Adult Cognition by Telephone (processing speed) and the Informant Questionnaire on Cognitive Decline in the Elderly	Intervention: Folate and vitamin B12 Follow-up: 2 years	Participants: *n* = 900, aged 60–74 years, two groups: daily oral supplementation of folate (400 μg day^{-1}) and vitamin B12 (100 μg day^{-1}) or placebo	Supplementation improved the TICS-M total (*P* = 0.032; effect size d = 0.17), the TICS-M immediate (*P* = 0.046; d = 0.15), and TICS-M delayed recall (*P* = 0.013; effect size d = 0.18) scores at 24 months in comparison with placebo No significant changes were evident in orientation, attention, semantic memory, processing speed, or informant reports
Omega-3 and fish				
Van de Rest *et al*. 2008 [86]	Outcomes: Extensive neuropsychological test battery that included the cognitive domains of attention, sensorimotor speed, memory, and executive function	Intervention: EPA + DHA Follow-up: 26 weeks	Participants: *n* = 302, aged 65 years or older, three groups: 1 800 mg day^{-1} EPA-DHA, 400 mg day^{-1} EPA-DHA, or placebo	At 26 weeks, there were no significant differential changes in any of the cognitive domains for either low dose or high dose fish oil supplementation compared with placebo
Yurko-Mauro *et al*. 2010 [87]*	Outcomes: The primary outcome was the CANTAB Paired Associate Learning (PAL) which is a visuospatial learning and episodic memory test	Intervention: DHA Follow-up: 24 weeks	Participants: *n* = 485, aged ≥55 years, two groups: 900 mg day^{-1} of DHA or placebo	Intention-to-treat analysis demonstrated significantly fewer PAL six pattern errors with DHA *vs.* placebo at 24 weeks (difference score, –1.63 ± 0.76, 95% CI –3.1, 0.14, *P* = 0.03) DHA supplementation was associated with improved immediate and delayed Verbal Recognition Memory scores (*P* < 0.02), but not working memory or executive function tests (secondary outcomes)
Dangour *et al*. 2010 [88]	Outcomes: battery of cognitive tests, including the primary outcome, the California Verbal Learning Test (CVLT)	Intervention: EPA + DHA Follow-up: 24 months	Participants: *n* = 867, aged 70–79 years, 2 groups: daily 200 mg EPA plus 500 mg DHA or placebo	No change in cognitive function scores over 24 months Intention-to-treat analysis showed no significant differences between trial arms at 24 months in the CVLT or any secondary cognitive outcome
Geleijnse *et al*. 2011 [89]	Outcomes: MMSE	Intervention: EPA + DHA or ALA or EPA + DHA + ALA Follow-up: 40 months	Participants: *n* = 2 911 coronary patients aged 60 to 80 years, four groups: margarines that provided 400 mg day^{-1} of EPA-DHA, 2 g day^{-1} of ALA, both EPA-DHA and ALA, or placebo	Changes in MMSE score did not differ significantly between EPA-DHA and placebo (–0.65 *vs.* –0.69 points, *P* = 0.44) or between ALA and placebo (–0.60 *vs.* –0.74 points, *P* = 0.12) The risk of cognitive decline was 1.03 (95% CI 0.84, 1.26, *P* = 0.80) for EPA-DHA (*vs.* placebo) and 0.90 (0.74, 1.10, *P* = 0.31) for ALA (*vs.* placebo)

Table 1
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Combination of nutrients				
Andreeva *et al*. 2011 [94]	Outcomes: French version of the modified Telephone interview for Cognitive Status	Intervention: Vitamins B9, B6, B12 and omega-3 Follow-up: 4 years	Participants: *n* = 1 748, aged 45–80 years, with a history of myocardial infarction, unstable angina or ischemic stroke, four groups: folate (0, 56 mg), vitamin B6 (3 mg) and vitamin B12 (0, 02 mg); EPA and DHA (600 mg) in a 2 : 1 ratio; vitamins B and omega-3 fatty acids; placebo	No significant main effects on cognitive function after 4 years of supplementation
Physical activity				
Lautenschlager *et al*. 2008 [122]*	Outcomes: ADAS-cog score	Intervention: Physical activity Follow-up: 18 months	Participants: *n* = 138 with reported memory problems but no criteria for dementia, two groups: 24 week home-based programme of physical activity or education and usual care	In an intent-to-treat analysis, participants in the intervention group improved 0.26 points (95% CI –0.89, 0.54) and those in the usual care group deteriorated 1.04 points (95% CI 0.32, 1.82) on the ADAS-Cog at the end of the intervention The absolute difference of the outcome measure between the intervention and control groups was –1.3 points (95% CI –2.38, –0.22) at the end of the intervention At 18 months, participants in the intervention group improved 0.73 points (95% CI –1.27, 0.03) on the ADAS-Cog, and those in the usual care group improved 0.04 points (95% CI –0.46, 0.88). Word list delayed recall and CDR sum of boxes improved modestly as well, whereas word list total immediate recall, digit symbol coding, verbal fluency, Beck depression score, and Medical Outcomes 36-Item Short-Form physical and mental component summaries did not change significantly

*Results are positive only for these studies. AD, Alzheimer's disease; ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; ALA, alpha-linolenic acid; BMI, body mass index; CDR, Clinical Dementia Rating; CVD, cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MMSE, Mini Mental State Examination; MRI, magnetic resonance imaging.

Perspective for the future: using optimal interventions (e.g. multidomain approach)

At the present time, it is still difficult to propose specific recommendations for the prevention of AD. Epidemiological analysis of the relations between nutrient consumption and cognitive decline is complex and it is highly unlikely that a single component plays a major role. We need to pursue studies which will improve our knowledge of the biochemical mechanisms underlying the pathophysiological processes and identify potential therapeutic agents, and which in a public health perspective will examine food groups and dietary patterns. There is converging evidence that composite dietary patterns, such as the Mediterranean diet, are related to lower risk for cardiovascular disease, several forms of cancer and overall mortality. Recent papers showed that higher adherence to a diet approaching the Mediterranean diet is associated with reduced risk of cognitive decline and dementia/AD [98–103]. Several mechanisms have been proposed underlying the suggested protective role of Mediterranean diet against age-related changes in cognitive function, predementia syndromes and dementia: vascular variables and non-vascular biological mechanisms such as metabolic, oxidative and inflammatory processes [104]. This underlines the need to consider interactions between micro- and macronutrients for future research. Detailed study of social, economic and cultural transformations of the end of the life cycle, from cessation of professional activity until

the end of life, and the consequences of these transformations on food habits, from obtaining supply to actual food intake, is 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 [3].

Accumulating evidence, mainly from longitudinal observational studies, suggests that higher levels of physical activity may help maintain cognitive function during ageing. A systematic review published in 2004 analyzed the results of 15 longitudinal observational studies that addressed the impact of lifestyle with cognition or dementia [6]. Most studies examining the relationship between physical activities including physical leisure activities and both dementia and AD were positive. Several studies continue to support these findings [103, 105–115]. One study found that in 69 older adults, higher levels of physical exercise over the previous decade were associated with reduced beta-amyloid uptake on positron emission tomography [116].

Several RCTs on the association between physical activity and cognitive decline in patients with dementia or MCI were published recently [117–121]. In one trial, 31 patients with dementia (mean age 81.8 $\pm$ 5.3 years) were randomized in two groups: the intervention group received a 5 week physical activity programme involving three 1 h sessions per week and the control group had no physical activity. After 15 weeks, subjects from the intervention group improved their Rapid Evaluation of Cognitive Functions test overall score ($P < 0.01$), while those in the control group decreased it [118]. In another RCT in 33 patients with amnestic MCI aged 55 to 85 years, the intervention group received a programme of aerobic physical activity (treadmill, stationary bike or elliptical, 45–60 min day^{-1}, four times a week[1] for 6 months). The results showed an improvement of executive functions at 6 months among women in the intervention group [119]. A more recent trial examined the effects of mind body physical exercise (Tai Chi) on cognitive function in 389 patients with a Clinical Dementia Rating (CDR) of 0.5 or amnestic-MCI. Patients were randomized into two groups: the intervention group received Tai Chi sessions or stretching and toning exercise at least three times a week and 30 min per day. At 5 months, both groups showed an improvement in global cognitive function, delayed recall and subjective cognitive complaints ($P < 0.05$), improvements in visual spans and CDR sum of boxes scores were observed in the intervention group ($P < 0.001$). Logistic regression analysis controlled for baseline group differences in education and cognitive function suggested that the intervention group was associated with stable CDR (OR = 0.14, 95%CI 0.03, 0.71, $P = 0.02$) [121].

To our knowledge, there is only one trial on the association between physical activity and risk of dementia which included subjects with cognitive complaint but without criteria of dementia. In this study, 170 adults aged 49 years or over were randomized to receive a programme of physical activity at home (at least 150 min of moderate activity a week) or to an education/usual care. After 24 weeks, patients in the intervention group improved their cognitive performances compared with patients in the placebo group. After 18 months, results were similar [122].

It is important to know whether physical activity and diet confer independent associations because individuals who exercise often belong to a higher educational-socioeconomic strata, are more health conscious, and in general tend to follow healthier eating habits. The magnitude of such potential associations with AD in individuals engaging in such activities is also of great interest from a public health point of view. In their study, Scarmeas *et al*. [103] investigated the combined association of diet and physical activity with AD risk. Analyses were based on data collected in two cohorts comprising 1880 community-dwelling elderly without dementia living in New York. A total of 282 incident AD cases occurred during a mean of 5.4 (3.3) years of follow-up. When considered simultaneously, both Mediterranean-type diet adherence and physical activity were associated with lower AD risk. Compared with individuals neither adhering to the diet nor participating in physical activity, those both adhering to the diet and participating in physical activity had a lower risk of AD. The investigation of which particular dimensions of lifestyle are associated with disease risk is important. This work supports the idea that intervention focused only on a single factor in late life is not likely to be effective. Since multiple factors across the life course influence brain function in late life, multidomain interventions might be more promising in the prevention of cognitive decline. Some specific challenges need to be underlined in designing trials involving multidomain interventions, firstly, surrounding the specific selection of subjects [95]. We can imagine that subjects who accept to modify multiple lifestyle domains are likely to have a higher level of education and better overall health, meaning that it may be difficult to demonstrate an effect of the intervention. Observance in multidomain trials is difficult to assess if the intervention combines on different lifestyle factors. If the intervention is based around lifestyle recommendations, it will be difficult to evaluate precisely actual behavioural modifications. In these interventions, it is impossible to maintain double-blind conditions, and difficult to define an adequate control group, especially for physical exercise interventions. It is also difficult to identify the independent effects of each factor, because they may act through common mechanisms (e.g. via cardiovascular mechanisms), and there may be between-group contamination.

Multi-intervention preventive vascular trials have already been conducted. For example, in The Nurses' Health Study [123], a multi-intervention, heart disease trial, participants were asked to adopt many little lifestyle changes rather than make a single dramatic one. They were asked to keep their BMI below 27 kg m^{-2}, restrict alcohol to

one half serving per day, eat more than the median for grains, fruit and vegetables, and to exercise moderately. All those who complied had a relative risk for heart disease risk of 0.2. Another good example of a multi-intervention trial is the Dietary Approaches to Stop Hypertension (DASH) trial [124], which combined medication with dietary regulation, including reduced sodium, emphasis on fruit and vegetables, and potassium intake. This trial concluded that these interventions can control blood pressure quite well.

We need now to develop similar trials for cognitive decline. The frail elderly persons, who seem to be more likely to develop cognitive decline, appears to be a first target. In addition, we need to use biomarkers in this new generation of preventive trials to improve diagnostic accuracy, especially early in the course of AD and to help us to stratify AD cases, as well as identifying and monitoring the biochemical effects of the interventions. A recent proposal to include pathologically linked biomarkers of AD in the clinical diagnostic criteria has the potential to reduce the frequency of a false positive diagnosis and increase the validity of a clinical diagnosis of AD, especially at its earliest symptomatic stage [125]. Potential biomarkers include atrophy on MRI, changes in brain function as assessed by fMRI, EEG or FDG PET which measures brain metabolism, amyloid PET (directly assess brain amyloid) as well as blood and CSF markers of tau and Aβ amyloid and other proteins and metabolites (indirectly estimate levels of brain amyloid plaques). Biomarkers measuring brain Aβ amyloid deposits will be used to identify subjects with a greater risk for cognitive decline and conversion to dementia, and to facilitate clinical design by targeting the 'at risk' population, and decreasing sample size and study duration.

To conclude, we report two recent RCTs designed with the aim of testing the effectiveness of mutli domain intervention on the cognitive and functional decline (the MAPT and DO-HEALTH trials).

The MAPT trial is a multicentre study to assess benefits of multidomain intervention and omega-3 on prevention of cognitive decline in frail elderly people followed during 3 years. It is a randomized, placebo controlled study, using a four group design including three treatment groups (omega-3 alone, multidomain intervention alone, omega-3 plus multi-domain intervention) and a placebo group (Principal Investigator: Professor Vellas) [126]. The inclusion period began in May 2008 and was completed in February 2011. Participants were enrolled from various sources, including advertisement in the local media, conference, general practitioners and memory clinics in 13 French cities. A total of 1680 fulfilled the eligibility criteria and were entered into the study. The study is coordinated from the hospital reference centre in Toulouse. The MAPT study treatment period will end in February 2014. The protocol is registered on a public-access clinical trial database (http://www.clinicaltrials.gov).

The recruitment goal for the MAPT trial is to enrol a sample of frail elderly people, aged 70 years and over, living independently with good functional and cognitive status. Definition of frailty is to date not consensual but we practically used three clinical components to identify frail persons based on epidemiological evidence: spontaneous memory complaint expressed to the general practitioner, limitation in one instrumental activity of daily living (ability to use the telephone, shop, prepare meals, do housekeeping, do one's laundry, use transportation, follow a medication schedule and manage money) (IADL) and slow walking speed.

The multidomain intervention consists of collective training sessions and a yearly personalized preventive consultation which aims to detect dementia risk factors (sensory disturbances, difficulty in walking, nutritional disturbances, vascular risk factors) and to set up management in collaboration with the general practitioner. Training sessions are conducted in small groups (6–8 participants) settings in twelve 120 min sessions over the first 2 months (two sessions a week for the first month and one session a week the second month). Each training session during these 'intensive period' includes 60 min for the cognitive training, 45 min for the physical training and 15 min for nutritional advice. After the second month, sessions are planned monthly throughout the 3 year intervention period to reinforce the key messages of the programme and increase compliance. Participants are asked to use a diary to record their cognitive and physical activities each month. Booster training will be delivered in each multidomain group 1 and 2 years after their initial training sessions.

We performed neuroimaging examinations (PET-scan and MRI) in sub-groups of participants: (i) to explore the effects of interventions on cerebral atrophy (total brain volume and hippocampal volume) (MRI-MAPT ancillary study): MRI is performed within the 2 months following the inclusion visit (or the 6 month follow-up visit) and at 36 months. Currently, 504 subjects have undergone baseline MRI, (ii) to explore the effects of multidomain intervention on cerebral metabolism (FDG-PET ancillary study): FDG-PET scans are performed at baseline, 6 months and 1 year in a sub-group of 68 participants followed in Toulouse centre and (iii) to evaluate brain amyloid deposits (Florbetapir-PET ancillary study). Florbetapir-PET imaging is proposed within the 2 years of follow-up. Currently, 187 participants have been enrolled.

The DO-HEALTH trial is a multinational study to assess benefits of vitamin D3, omega-3 and home exercise on prevention of chronic diseases in the elderly. The DO-HEALTH study (VitaminD3-Omega3-Home Exercise-Healthy Ageing and Longevity Trial) will be Europe's largest healthy ageing study (Principal investigator: Professor Bischoff-Ferrari). It expects to provide solid evidence for the efficacy and safety of three simple preventive interventions: vitamin D, omega-3 fatty acids and a simple home

exercise programme. DO-HEALTH hopes to provide definitive evidence that the three interventions, alone or combined, are able to reduce the number of fractures, the functional and cognitive decline, the risk of hypertension and the risk of infections in the elderly population.

Conclusions

Nearly all of the data linking nutrition to cognitive decline or dementia/AD comes from observational studies and results are sometimes conflicting because of methodologic issues. It seems necessary 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. RCTs of dietary interventions have yielded mixed findings and need to be conducted that they focus on specific groups of subjects (middle-aged and elderly populations; subjects with vitamin deficiencies or normal and high levels). Such research identifying the role of specifics nutrients, foods or dietary behaviors, is an indispensable step before we can propose specific recommendations in the future.

In the absence of curative treatment, even if it is difficult to change lifestyle habits, lifestyle factors (diet, social engagement, cognitive stimulation, physical exercise) seem the most reasonable candidates for prevention trials at the current time, in particular due to their safety. Due to the difficulties in conducting a multidomain intervention, RCTs may not represent the gold standard in this field, and large public health interventions at the population level may be required. However, such interventions would have to be feasible, cost-effective and easily transferable in order to have a real public health impact.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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