Proceedings of the Nutrition Society (2012), **71**, 1–13 doi:10.1017/S0029665111003296
 First published online 9 November 2011

A meeting of the Nutrition Society hosted by the Irish Section jointly with the American Society for Nutrition was held at University College Cork, Republic of Ireland on 15–17 June 2011

70th Anniversary Conference on 'Vitamins in early development and healthy aging: impact on infectious and chronic disease'

Symposium 1: Vitamins and cognitive development and performance

Nutritional determinants of cognitive aging and dementia

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The objective of this review is to provide an overview of nutritional factors involved in cognitive aging and dementia with a focus on nutrients that are also important in neurocognitive development. Several dietary components were targeted, including antioxidant nutrients, dietary fats and B-vitamins. A critical review of the literature on each nutrient group is presented, beginning with laboratory and animal studies of the underlying biological mechanisms, followed by prospective epidemiological studies and randomised clinical trials. The evidence to date is fairly strong for protective associations of vitamin E from food sources, the *n*-3 fatty acid, DHA, found in fish, a high ratio of polyunsaturated to saturated fats, and vitamin B_{12} and folate. Attention to the level of nutrient intake is crucial for interpreting the literature and the inconsistencies across studies. Most of the epidemiological studies that observe associations have sufficient numbers of individuals who have both low and adequate nutrient status. Few of the randomised clinical trials are designed to target participants who have low baseline status before randomising to vitamin supplement treatments, and this may have resulted in negative findings. *Post-hoc* analyses by some of the trials reveal vitamin effects in individuals with low baseline intakes. The field of diet and dementia is a relatively young area of study. Much further work needs to be done to understand dietary determinants of cognitive aging and diseases. Further, these studies must be particularly focused on the levels of nutrient intake or status that confer optimum or suboptimal brain functioning.

Nutrition: Cognitive decline: Dementia: Antioxidant nutrients: Dietary fats

After more than a decade of research on nutrition and the aging brain, a number of promising nutritional factors have emerged that are also important to neurocognitive development. This review describes the evidence for these nutritional factors that show the most promise in the prevention of neurodegenerative disease. Among these are antioxidant nutrients, B-vitamins, dietary fat composition and *n*-3 fatty acids. Each of these factors has a body of literature to support underlying biological mechanisms for association as well as evidence of association from prospective epidemiological studies. The clinical trial evidence for vitamin supplements has been disappointing, but very few of these trials were designed to test whether supplementation is effective in persons who have low nutrient status for that particular dietary component. In general, potential recommendations to maintain a healthy brain reflect those that have been demonstrated to maintain a healthy heart: physical activity combined with a diet that has a high ratio of unsaturated to saturated fats, vegetables, fruits and fish. In this review, we first describe common neurodegenerative diseases of aging and some basic fundamentals in nutrient absorption and physiological function. These sections are followed by a review of the evidence for each dietary component.

Dementia

Dementia is a condition that is non-specific to any one disease and is characterised by a loss of major brain function in two or more areas of cognition, such as memory,

Abbreviations: AD, Alzheimer's disease; THF, tetrahydrofolate.

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thinking, language, judgment and behaviour[1]. Alzheimer's disease (AD) is the primary cause of dementia in persons aged 60 years and older, representing 60–80% of cases[2]. The second most common cause is vascular dementia or dementia due to the occurrence of multiple strokes[3]. Most degenerative dementia is caused by mixed pathologies characteristic of AD, cerebral infarctions and Lewy bodies[4]. Although most dementias are irreversible, the course of some forms can be stopped or reversed if found soon enough (e.g. dementia due to vitamin deficiencies, brain tumours, chronic alcohol abuse and medication use)[1].

Alzheimer's disease

AD is a common condition in older age. The overall prevalence among individuals aged 65 years and older has been estimated to be 10–13%[2,5] and the rate increases exponentially with older age: from 3% among 65–74-year-olds to 19% among 75–84-year-olds and nearly half (47%) of those aged 85 years and older[2]. Because the oldest age groups are also the fastest growing in the USA, the number of individuals with AD is expected to almost triple from six million in 2010 to sixteen million by the year 2050[6]. Thus, by mid-century approximately 25% of the USA population will be aged 65 years and older, and more than one-third will likely develop dementia[6].

The clinical diagnosis of AD requires impairment in memory and at least one other cognitive domain[7]. The disease is neuropathologically characterised by extracellular deposition of amyloid β into senile plaques, intraneuronal formation of neurofibrillary tangles composed of hyperphosphorylated τ protein, and loss of neurons and synapses in the neocortex, hippocampus and other subcortical areas of the brain[8]. The primary risk factors for late-onset AD include older age, the apoE-4 genotype, head injury, family history, low education and low participation in cognitively stimulating activities[9]. CVD conditions and risk factors are the primary focus of the current research in AD[9,10]. Among these factors are physical activity[11], diet[12], hypertension[13,14], obesity[15], hypercholesterolaemia[14], diabetes[16], heart disease[17], stroke[18], metabolic syndrome[19,20] and statin[21,22] and non-steroidal anti-inflammatory[23] medications. The strong ties between CVD and diet and between CVD and dementia support the idea that diet also plays a role in dementia at the very least through its effect on cardiovascular-related conditions. Genetic causes of AD are restricted to early-onset cases in persons less than 60 years of age and account for only 1% of all cases[24].

Cognitive decline

Central to all degenerative dementias is decline in cognitive abilities. Thus, an important and complementary area of study is individual change over time in neuropsychological test performance. These types of studies do not require clinical neurological evaluation by expert neurologists and thus are less costly than are studies of dementia diagnosis. Also, larger populations can be studied to examine risk factor associations with cognitive decline earlier in the disease process resulting in greater statistical power and less bias than studies using clinical diagnosis of dementia[25]. In this type of study design in which exposures of interest are related to within-person rates of cognitive decline, to the extent that potential confounding factors for individuals remain constant over the cognitive assessment periods, confounding bias is minimised[25]. The outcome (change in neuropsychological test performance) is not subjected to biases in clinician diagnosis arising from cultural, educational or other reasons. The greater the number of cognitive tests administered at each assessment period and the greater the number of cognitive assessments, the more accurate the measure of cognitive decline.

Cognitive decline is not disease specific. Therefore, a finding of association between a risk factor and cognitive decline does not necessarily mean that one should observe an association between the risk factor and any one of the dementia diseases in that population. However, one might be concerned to observe a risk factor association with a specific type of dementia in the study population but not with cognitive decline. This could be an indicator of a spurious disease association or perhaps early disease effects on the risk factor.

Nutrition and the blood–brain barrier

Nutrients, by definition, are molecules that are essential for human function. Most are not synthesised *in vivo* and thus must be consumed through diet. Some dietary components, like cholesterol, are synthesised by human subjects and therefore considered non-essential. The brain is an organ with high metabolic activity and also a high rate of nutrient turnover. Nourishment of the brain occurs through a myriad of nutrient-specific transport systems and physiological mechanisms that serve to replace the constant turnover of nutrients. To enter the brain, nutrients are transported either from blood through cerebral capillaries of the blood–brain barrier or through the choroid plexus of the blood–cerebral spinal fluid barrier by mechanisms of facilitated diffusion, active transport, binding receptors and endosomes, and ion channels, among others[26]. Some of these nutrient transport systems, such as for glucose, ascorbic acid and folate, have homoeostatic functions that serve to transport less into the brain when plasma levels are high and more into the brain when plasma levels are low[27,28].

Studies of nutrient deficiencies in animals and in human subjects help to understand the nutrients' roles in the brain. For example, vitamin E deficiency syndrome causes a number of neurological symptoms including ataxia, decreased vibration sensation, lack of reflexes, paralyses of eye muscles and decline in cognitive function[29–31].

Nutrient level and physiological function

A well-established principle of nutrition is that nutrient level has a non-linear, inverted U-shaped association with physiological function. Optimal function occurs over a fairly wide range of nutrient intake levels. However, both deficient levels and toxically high levels may result in

https://doi.org/10.1017/S0029665111003296 Published online by Cambridge University Press

marginal physiological function or even death. This basic nutritional principle plays an important role in interpreting results and inconsistencies among epidemiological studies and randomised clinical trials[32,33]. Study populations and clinical trial cohorts for which the range of nutrient level does not span levels associated with both marginal and optimal physiological function will not produce findings of association between the nutrient and the disease outcome.

Antioxidant nutrients

Underlying biologic mechanisms of antioxidant nutrients

The brain is a site of high metabolic activity and is especially prone to oxidative stress and damage to neural tissue[34–36]. A prevailing theory is that oxidative damage and neural inflammation are the underlying biological mechanisms of neurodegenerative disorders like AD and Parkinson's disease[37–40]. There are two types of antioxidants in the body: antioxidant enzymes that prevent the generation of toxic substances and antioxidant nutrients that neutralise free radicals and singlet molecules of O[41]. The antioxidant enzymes require the availability of selected nutrients, including Mn, Cu, Se and Zn[41]. Antioxidant nutrients include vitamin E (tocopherols), vitamin C, carotenoids and flavonoids. The antioxidant nutrients may play more important roles in the aging brain than in other organs of the body due to the fact that there are relatively fewer antioxidant enzymes for neuronal protection[42]. There is also evidence that vitamin E may play a role in the developing brain. For example, infants with cystic fibrosis who had prolonged deficiency levels of α-tocopherol (<300 μ/dl plasma) had statistically significantly lower scores ($P<0{\cdot}05$) on cognitive tests in childhood[31,43].

Epidemiological evidence from prospective studies for vitamin E in food

The prospective epidemiological studies of dietary vitamin E (i.e. from food sources) consistently show statistically significant inverse associations with incident dementia and AD, and with cognitive decline (Table 1). The one negative study was the Washington Heights-Inwood Columbia Ageing Project[44]. One possible explanation for the negative finding may be that the Washington Heights-Inwood Columbia Ageing Project study population had a narrow range of low intake levels (4–7 mg/d for the quartile medians). The top quartile median intake level of 7 mg/d was in the lowest tertile of intake of 10 mg/d in the Rotterdam study that reported positive findings for vitamin E[45].

Findings from studies of biochemical levels of vitamin E are less consistent than that for the self-reported diet studies (Table 1). A comparison of the ranges of biochemical vitamin E levels revealed that differences in the ranges could account for null findings in some studies. For example, population levels in the negative study by Ravaglia *et al.*[46] are likely too low to provide protective benefit; the highest tertile level of α-tocopherol of 6·5 μmol/mmol cholesterol was in the lowest tertile of that reported by Mangialasche *et al.*, a positive study[47]. Similarly, the entire biochemical range of vitamin E levels in the Nurses' Health Study[48], a null study, may be within the optimum range for cognitive function; the lowest tertile of α-tocopherol (median 24·85 μmol/l) fell within the highest tertile of the Persones Agèe QUID study (<25 μmol/l)[49]. In the Persones Agèe QUID study, which had a wide range of α-tocopherol levels, the risk of dementia was three times higher ($P = 0{\cdot}03$) in the lowest tertile (11–21 μmol/l) compared with the highest tertile (25–55 μmol/l) level[49]. Another explanation for the seemingly inconsistent findings may be that total tocopherol intake is more important for neuroprotection than the individual tocopherols alone. In the Kungsholmen study[47] plasma levels of total tocopherols, total tocotrienols and total vitamin E were each inversely associated with incident AD, but none of the individual tocopherols in isolation was associated. In fact, none of the biochemical studies found association with the individual tocopherols (Table 1).

Evidence for other antioxidant nutrients

At this stage in the research there is weak evidence to support protection against dementia by dietary intake of other antioxidant nutrients (e.g. vitamin C, β-carotene and flavonoids). Only the Cache County Study[50] found protective benefit with high dietary intakes of vitamin C and β-carotene against the development of dementia (Table 1). Investigators from the Rotterdam study initially reported statistically significant inverse associations after 6 years of follow-up for vitamin C, and for smokers only, for β-carotene and flavonoids[45]. However, these protective associations were not maintained after 9·6 years of follow-up; only the inverse association for vitamin E remained statistically significant[51] (Table 1).

Absence of evidence for antioxidant vitamin supplements

A number of prospective epidemiological studies[44,50,52–57] and four randomised clinical trials[58–61] examined the relation of vitamin E supplement use to AD or cognitive decline. With few exceptions[50] both types of studies found null associations of vitamin E supplement use with the cognitive outcomes. Dose level may play a role in the negative findings of studies that investigated α-tocopherol supplements. Vitamin supplement users and clinical trial participants tend to be healthy behaviour-seeking individuals and their diets likely already provide sufficient levels of nutrients for optimum functioning. In the Chicago Health and Ageing Project, vitamin E supplement use was inversely associated with cognitive decline but only among the participants who had low levels of intake from food[55]. In this study, vitamin E supplementation was not associated with further reductions in the rate of cognitive decline among participants who had high food-intake levels of vitamin E. *Post-hoc* analyses of the Women's Health Study randomised trial revealed a statistically significant effect of vitamin E supplementation on the rate of cognitive decline among women who had low dietary intake at the baseline (below the median of 6·1 mg/d)[60]. These investigators performed similar *post-hoc* analyses for the Women's Antioxidant and Cardiovascular Study but using a much higher cut-off (15 mg/d)

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Table 1. Prospective studies of dietary antioxidant nutrients and dementia outcomes*

Study	Population	Years follow-up	Outcome	Nutrient measure	Vitamin E	Vitamin C	β-Carotene	Other, carotene	Flavonoids
Devore *et al.*[51]	Rotterdam, *n* 5395, 55+ years	9·6 years	AD (*n* 365), Dem (*n* 465)	FFQ	↓	–	–		–
Mangialasche *et al.*[47]	Kungsholmen, *n* 232, 80+ years	3·6 years	AD (*n* 57)	Plasma					
				Total tocopherol	↓				
				Total tocotrienol	↓				
				Total vitamin E	↓				
				αT, δT, βT, γT	–				
Sundelof *et al.*[193]	Uppsala, *n* 616, 70 years; *n* 761, 77 years	12·3 years	AD (*n* 40; 47), Dem (*n* 86; 80)	Serum					
				αT	–				
				γT	–				
Ravaglia *et al.*[46]	Conselice IT, *n* 761	3·8 years	MCI (*n* 52), Dem (*n* 43)	Plasma					
				αT, δT, βT	–				
				γT	U				
Wengreen *et al.*[194]	Cache Co., *n* 3831, 65 years	7 years	3MS	FFQ	↓	↓	↓		
Kang & Grodstein[48]	NHS, *n* 858, 70+ years	10 years	Cog decline	Plasma					
				αT	–				
				γT	–				
Corrada *et al.*[178]	BLSA, *n* 579, >60 years	9·3 years	AD (*n* 57)	7 d diet diary	↓†	–		–	
Morris *et al.*[195]	CHAP, *n* 3718, 65+ years	6 years	Cog decline	FFQ					
				Total tocopherol	↓				
				αT, γT	↓				
				βT, δT	–				
	n 1041	4 years	AD (*n* 162)	Total tocopherol,	↓				
				δT, γT	–				
				βT, αT	↓				
Helmer *et al.*[49]	PAQUID, France, *n* 186, >65 years	9 years	Dem (*n* 46)	Plasma	↓	–			
Luchsinger *et al.*[44]	WHICAP, *n* 980, 65+ years	4 years	AD (*n* 242)	FFQ	–	–	–		
Morris *et al.*[54]	CHAP, *n* 815, 65+ years	2·3 years	AD (*n* 131)	FFQ	↓	–	–		
Morris *et al.*[55]	*n* 2889, 65+ years	3·2 years	Cog decline	FFQ	↓	–	–		
Engelhart *et al.*[45]	Rotterdam, *n* 5395, 55+ years	6 years	AD (*n* 146)	FFQ	↓	↓	–‡		–‡
Commenges *et al.*[196]	PAQUID, *n* 1367, 65+ years	3 years	AD (*n* 66)	FFQ					↓
Berr *et al.*[197]	EVA, France, *n* 1166, 60–70 years	4 years	MMSE decline	Plasma			–		
				Erythrocytes	–				

AD, Alzheimer's disease; BLSA, Baltimore Longitudinal Study of Aging; Dem, dementia; Cog, cognitive; CHAP, Chicago Health and Ageing Project; EVA, Etude du Vieillissement Arteriél; MCI, mild cognitive impairment; MMSE, mini-mental status examination; 3MS, three mini-mental staus examinations; NHS, Nurses' Health Study; PAQUID, Persones Agèe QUID; WHICAP, Washington Heights-Inwood Columbia Ageing Project.

*Upward arrows indicate statistically significant increased risk; downward arrows, statistically significant decreased risk; –, no association; blank, not examined.

†Marginally statistically significant ($P = 0{\cdot}07$) in low powered study.

‡Statistically significant interaction; inverse association in current smokers. No association overall.

than in the Women's Health Study and found no effect of vitamin E supplementation[58]. This raises the possibility that the level of nutrient insufficiency for cognitive function is closer to 6 mg/d than to 15 mg/d. Populations vary considerably in vitamin E intake levels. For example, nearly the entire New York Washington Heights-Inwood Columbia Ageing Project study cohort was below 6 mg/d[44], whereas less than 20 % of the Chicago Health and Ageing Project study cohort had intakes this low[54].

Although the epidemiological evidence for a protective relation of dietary β-carotene on dementia is weak, there is evidence from the randomised trials that higher levels consumed through vitamin supplementation over the long term may have protective benefits. In the Physicians' Health Study, β-carotene supplementation (50 mg every other day) for 18 years significantly reduced the rate of cognitive decline, but there was no effect of the β-carotene supplement after 1 year of supplementation[59]. Also, in *post-hoc* analyses of the Women's Antioxidant and Cardiovascular Health Study, women in the lowest quintile of total carotenoid intake at baseline (<3·09 mg/d) who were randomised to the β-carotene arm had statistically significantly slower rate of cognitive decline compared with the women in the placebo arm (*P* for interaction 0·02)[58].

Plausible explanations for inconsistent findings for food and supplements

There are a number of differences between dietary and supplement sources of nutrient intake that could account for the positive findings for dietary intake and negative findings for supplemental intake. One difference is that the vitamin E form used in the supplement studies was high-dose α-tocopherol, usually twenty-five to fifty times the levels consumed through diet. The vitamin E measured in the dietary studies was not a single form but a combination of four tocopherols (α-, β-, δ- and γ- tocopherols) and their sterioisomers (α-, β-, δ- and γ- tocotrienols). α-Tocopherol has its own transfer protein that preferentially incorporates α-tocopherol into the plasma over other tocopherol forms. Consumption of high doses of α-tocopherol (e.g. through high-dose vitamin supplements) may not be functionally optimal. Studies have shown that consumption of high-dose α-tocopherol decreases the absorption of γ-tocopherol, a potent anti-inflammatory[62] and that the highest level of antioxidant and anti-inflammatory action occurs with a combination of tocopherols[63]. These studies highlight an important feature of diet which was not replicated in the vitamin supplement trials. Foods provide multiple dietary constituents at complementary dose levels to enhance absorption and metabolism for optimum physiological effect.

Lipids and dementia

Lipids comprise a broad group of molecules that include fatty acids (four classes: saturated, *trans*, polyunsaturated and monounsaturated) and cholesterols (LDL-cholesterol, HDL-cholesterol and TAG)[64]. Their biological functions are concerned with energy storage, molecular signalling and as structural components of cell membranes[64]. Most lipids can be synthesised by human subjects endogenously. The exceptions are two essential PUFA, α-linoleic acid (found in vegetable oils) and α-linolenic acid (found in flax seed, walnut and soya oils, nuts, seeds, wholegrains and seafood)[64]. Dietary fat composition is one of the stronger predictors of blood lipid levels. A diet that is high in saturated and *trans* fats and low in polyunsaturated and monounsaturated fats results in a poor lipid profile of increased levels of LDL-cholesterol and TAG and decreased levels of HDL-cholesterol[65–67].

Biological mechanisms of lipids in dementia

Lipids represent the primary dry weight structure of the brain and the lipid, cholesterol, plays a central role in AD[68]. ApoE, a gene encoding cholesterol transport, is an established risk factor for AD in which the ApoE allele is associated with at least a doubling in risk[69,70]. Depletion of brain cholesterol reduces the generation of amyloid β[71]. In animal models, a high-fat, hypercholesterolaemic diet has been shown to result in multiple deleterious effects on the brain including: significant amyloid β burden[72–74], phosphorylated τ[75], impaired cognition[75–78], increased immunoreactivity[72,75] and microglia activation[79] and decreased brain membrane fluidity and brain-derived neurotrophic factor[77]. In contrast, animals fed diets enriched with corn oil (polyunsaturated fat) or olive oil (monounsaturated fat) had increased memory performance and activation of protein F_1[80].

Dietary fat composition and dementia

The epidemiological evidence for the association of dietary fat composition and dementia comes from several lines of evidence including dietary intake and biochemical levels of fatty acids, and blood lipid levels. The prospective epidemiological studies of dietary fat composition fairly consistently show increased risk of dementia and faster rate of cognitive decline with higher intakes of saturated fat[81–87], although there are some negative studies[88,89]. The limited number of prospective studies that investigated the association of *trans* fat intake found increased dementia risk[81,84,85]. Studies of polyunsaturated and monounsaturated fat intakes are very inconsistent with some finding inverse associations[81,83,84,90] and others no association[82,86–89] with dementia outcomes. One complicating factor in the interpretation of these studies is that intakes of 'healthy fats' (polyunsaturated and monounsaturated) are positively correlated with intakes of the unhealthy fats (saturated and *trans*). This can result in considerable negative confounding (i.e. confounding in the opposite direction of the true relation) that likely obscured real associations. Very few of these studies analysed the different dietary fats conjointly in the statistical analyses. Those that did control for intakes of other fats found inverse associations of polyunsaturated and monounsaturated fats with incident AD[84] and cognitive decline[81,85]. Even so, the evidence for associations of polyunsaturated and monounsaturated fats in and of themselves is weak for dementia outcomes. It could be that the

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composition of the diet towards a higher ratio of unsaturated to saturated fats is what is most important for protection against dementia; of four studies that examined this relation[81,82,84,85], three found inverse associations[81,84,85].

Examination of the prospective blood lipid studies reveal an interesting pattern from middle-to-late adulthood in which, overall, blood cholesterol levels decrease with older age but the highest rate of decrease occurs among those who had the highest cholesterol levels in mid-life[91,92]. Studies relating mid-life cholesterol to late-life dementia have shown that compared with non-demented individuals, those who become demented exhibit a greater decrease in blood cholesterol level with older age[92]. The same phenomenon has been demonstrated in longitudinal studies of blood pressure[13] and weight[15]. This may explain why most studies that examined blood cholesterol in mid-life have observed positive associations with the risk of dementia in late life[14,22,92–97], but findings of studies that examined cholesterol levels in late life are either null[20,98,99] or inconsistent with some showing positive associations with dementia risk[100,101] and others showing inverse associations[102,103]. One plausible explanation may be that the disease process of dementia accelerates the decreases with older age in levels of cholesterol, blood pressure and weight.

n-3 *Fatty acids and the brain*

The *n*-3 fatty acids are a class of polyunsaturated fat that includes three nutritionally important species: α-linolenic acid (18:3 *n*-3), EPA (20:5 *n*-3) and DHA (22:6 *n*-3). Mammals cannot synthesise α-linolenic acid and so it must be consumed through oils (e.g. soyabean, flaxseed, black currant and rapeseed) wheat germ, soyabeans, or nuts (e.g. walnuts). In human subjects, α-linolenic acid is elongated and desaturated to form EPA and DHA, but this conversion is not more than 0·5%[104]. Fish and seafood are a direct natural dietary source of DHA and EPA, although eggs and meats can also contain these *n*-3 fatty acids in animals with supplemented feed or who graze on certain grasses that contain α-linolenic acid.

DHA primary lipid in metabolically active brain regions

DHA is the primary *n*-3 fatty acid in the brain; other species of *n*-3 fatty acids are uncommonly found[105]. DHA is the predominant lipid in the most metabolically active areas of the brain including the cerebral cortex, synaptosomes and mitochondria[106,107]. In laboratory studies, animals fed diets enriched with *n*-3 PUFA had superior learning acquisition and memory performance[106,108–116] including in aged mice[109,117–119], better regulation of neuronal membrane excitability[120–125], increased levels of neurotransmitters and receptors[126–129], increased hippocampal nerve growth[130], greater fluidity of synaptic membranes[109] and reduced ischaemic damage to neurons[131].

Cardiovascular mechanisms of fish protection

Fish and *n*-3 fatty acids have favourable effects on the cardiovascular system including lower blood pressure, lower TAG and reduced cardiac death (one fish meal per week)[104]. In a meta-analysis of nine prospective studies of incident stroke there was a dose–response inverse association with increased fish consumption[132]. Thus, in addition to the earlier-described mechanisms of DHA on brain health, dietary fish consumption may be protective particularly of vascular dementia through their beneficial effects on these cardiovascular risk factors.

Epidemiological evidence for fish and n-3 *fatty acids and dementia*

In prospective studies, consumption of fish was associated with lower risk of incident dementia[133–138], stroke[139,140,141,142], and cognitive decline[86,143]. A number of studies investigated the relation of fish intake to risk of developing AD. In all cases, the estimated OR were in the protective direction and most were statistically significant at a low level of intake of just one fish meal per week[133–138,144]. The Rotterdam Study reported significant reduction in risk after 2·1 years of follow-up[135], but the association after 9 years was not statistically significant[144]. One plausible explanation for these discrepant findings may be misclassification error in the dietary exposure as diet was not reassessed to capture potential changes in fish consumption over the 9-year period. Two of the studies observed the inverse association with dementia only among persons who were apoE-4 negative[134,145], but this was not observed in other studies[135–138,144]. Of interest, the relation of fish consumption to AD risk in the Cardiovascular Health Study was specific to fatty fish and not to fried fish[134]. This raises the question of whether fish preparation might alter the neuroprotective benefit given that frying reduces the *n*-3 fatty acid levels and increases saturated fat intake. In the Women's Health Initiative Observational Study, women who consumed five or more servings per week of baked or broiled fish had a 30% reduction in the risk of incident heart failure, whereas women who consumed one or more weekly servings of fried fish had an increase in risk (hazard ratio 1·5, 95% CI 7·2, 1·8)[146].

A few randomised trials on the effects of DHA supplements on cognitive decline reported negative findings. A major flaw in the designs of these trials[147,148] is that they allowed fish consumption up to three fish meals per week among all trial participants. This is far above the level (one fish meal per week) that was observed to be inversely associated with dementia in the majority of epidemiological studies. As a result, the difference between treatment and placebo groups in intake levels at the level of benefit may have been minimised thus resulting in null findings of the supplement.

Several studies examined the relation between fish consumption and decline in cognitive test scores with two studies showing statistically significant reductions at just one fish meal per week[143,149], whereas the third study was null[148]. Neither of the two positive studies observed statistically significant inverse associations with dietary intake levels of the marine *n*-3 fatty acids[143,149]. However, of the six studies that measured biochemical levels of *n*-3 fatty acids, three observed statistically significant reductions in the rate of cognitive decline[83,86,150] and two others

https://doi.org/10.1017/S0029665111003296 Published online by Cambridge University Press

observed inverse associations with dementia[89,137]. The apparent inconsistency may be due to the fact that food frequency assessment of marine *n*-3 fatty acid intake is relatively imprecise. This is because most questionnaires employ at most three general questions on fish consumption and thus do not capture well the different levels of EPA and DHA contained in different types of fish. Correlations between dietary levels of the *n*-3 fatty acids and biochemical levels are typically about 0·35[151].

B-vitamins and the brain

Among the B-vitamins, the two that have received the greatest attention for brain health in the scientific literature are vitamin B_9 (folate) and vitamin B_{12} (cobalamin). These are co-factor nutrients that are known to affect neurocognitive development and neurodegeneration. The importance of adequate folate intake in the first trimester of pregnancy to prevent congenital neural tube defects is now well established[152]. This prompted the United States Department of Agriculture to mandate fortification of the grain supply in 1998 with folic acid at 140 µg per 100 g grain[153]. The prevalence of low-serum folate has since decreased from 16–22 % pre-fortification to 0·5–1·7 % post-fortification[154]. This required level of fortification was considered generally safe; however, controversy still exists regarding the safety for population subgroups like the elderly.

Vitamin B_{12} and folate: cofactors in metabolic pathways

Vitamin B_{12} and folate have essential and intertwined roles in human health as they are co-factors in the metabolism of DNA and erythrocytes synthesis and with methionine and S-adenosylmethionine synthesis. Both vitamin B_{12} and folate (5-methyl-tetrahydrofolate (THF)) are required for the remethylation of homocysteine to methionine, while simultaneously demethylating 5-methyl-THF to THF[155]. Thus, with vitamin B_{12} deficiency, there is an accumulation of homocysteine and 5-methyl-THF. Vitamin B_{12} deficiency syndrome is characterised by peripheral neuropathy, megaloblastic anaemia, fatigue, depression and cognitive impairment[156]. The neuropathy characteristic of vitamin B_{12} deficiency is probably the result of the block in this pathway because myelin basic protein is 'hypomethylated'. The typical haematological manifestations of vitamin B_{12} and folate deficiency (megaloblastic anaemia and granulocyte hypersegmentation) are thought to be the result of a reduction in DNA synthesis when 5,10-methylene-THF is lacking. Synthetic folic acid may correct this problem if the tissue contains an enzyme that can reduce folic acid to THF.

B-vitamins, cognitive decline and Alzheimer's disease

Epidemiologic studies and randomised clinical trials on the international scene for B-vitamins and cognition have produced seemingly inconsistent findings that may reflect the complex interrelation of vitamin B_{12} and folate in the metabolic pathways as well as differences among study populations in vitamin deficiencies, vitamin supplementation and food fortification. An important public health issue is whether or under what conditions, B-vitamin supplementation and food fortification are of benefit or harm to older persons. Vitamin B_{12} deficiency is common in older adults[157,158]. Folate deficiency, on the other hand, is now a rare occurrence in the USA since the folic acid fortification[154].

In recent years, there has been a lot of interest in vitamin B_{12} and folate as risk factors for dementia. This interest is largely based on their relations as co-factors in the metabolism of homocysteine. Homocysteine has been related to the risk of developing AD in some[159,160] but not all studies[161] and remains a topic of interest. The mechanism for association is not known, although homocysteine and folate deficiency have been shown to be neurotoxic in mouse models of AD[162,163].

Commonly, observational studies and randomised trials that examine nutrient effects on disease processes do not consider dose level when interpreting study results and trial design and, as noted earlier, this consideration is particularly important for folate because of folic acid fortification in some countries. Populations will also differ in vitamin B_{12} nutriture depending on the prevalence of atrophic gastritis and the use of medications that affect gastric acidity in addition to dietary and supplemental intake. Thus, some of the inconsistent findings across studies of B-vitamin effects on cognitive decline and dementia may be due to the range of nutrient status in the study population. Of ten cohort studies that examined the relations of these B-vitamins and cognitive decline, four reported protective associations with folate[164–167] and three reported protective associations with vitamin B_{12}[165,168–170] but many found no association with one or the other B-vitamin[165,170–174]. The Chicago Health and Ageing Project study found a deleterious effect of faster decline among persons with food and/or supplement intakes exceeding 400 µg/d[6]. This USA study took place primarily post-fortification. The deleterious findings with high levels of folic acid were also reported in a cross-sectional study of National Health and Nutrition Examination Survey data[175] in which persons with low vitamin B_{12} status and elevated serum folate concentrations were more likely to manifest impaired cognitive performance than those with normal serum folate concentrations.

A number of prospective studies that examined the relation between folate and dementia found inverse associations[176–180], although several studies did not[159,181,182]. In contrast, the studies that examined the association of vitamin B_{12} with AD were null[159,176–178,180–182]. There have been a number of randomised trials of the effects of supplementation with folic acid and vitamin B_{12} on cognitive decline. Most of the trials included a small number of subjects and supplemented over short periods of weeks or months, thus making it difficult to interpret the null results. Of several large randomised trials that tested B-vitamin supplementation for longer periods of time (i.e. 2–10 years)[183–186], only one[183] targeted individuals who had low folate status. In this trial, after 3 years of folic acid supplementation, the treated group had a statistically significant slower rate of cognitive decline compared with the placebo group[183].

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In another randomised trial of folic acid, vitamin B_{12} and vitamin B_6 supplementation in older persons with high homocysteine (VITACOG and ISRCTN 94410159), 2 years of treatment reduced decline in global cognition and in memory[184]. Treated subjects in this trial also had evidence of reduced brain atrophy compared with participants taking placebo[187]. Two other trials tested a combination therapy of folate, vitamin B_{12} and vitamin B_6 on cognitive decline and found no effect overall[185,186]. It is noteworthy that *post-hoc* analyses of one of these negative trials[186] found protective effects of the B-vitamin supplement among women who had low B-vitamin intake at baseline.

In summary, based on the current available evidence, insufficient levels of vitamin B_{12} and folate may be associated with faster cognitive decline. While there is some evidence to support that insufficient folate may also increase the risk of developing AD this is not the case for vitamin B_{12}. In addition, there is a possibility that exposure to high levels of folic acid in vitamin supplements or fortified food may be also associated with cognitive decline. In view of the folate fortification policy in some countries, this needs to be investigated further. Mandatory food fortification and vitamin supplementation have resulted in unprecedented numbers of persons with high circulating folic acid concentrations in the USA[158]. This substantially raises the potential for misdiagnosis of subtle vitamin B_{12} deficiency and increases prevalence of its neurologic syndrome. Masking of vitamin B_{12} deficiency can occur when there is correction of the macrocytic anaemia but not of the neurologic consequences. In case reports nearly five decades ago, folic acid treatment of vitamin B_{12}-deficient individuals was reported to aggravate neurological complications[156,188]. These older reports gain greater importance in light of the recent Chicago Health and Ageing Project and National Health and Nutrition Examination Survey studies[168,175]. The possible adverse outcomes cannot be ignored in the face of the prevalence of subtle vitamin B_{12} deficiency and the dramatic increase in folate intake that has occurred in the USA and other countries that have mandatory fortification.

Conclusion

The available evidence from laboratory, animal and epidemiological studies shows promise for protection against cognitive decline and dementia through a number of dietary components. The strongest, most consistent evidence is for dietary intakes of vitamin E, fish and *n*-3 fatty acids, high ratio of polyunsaturated to saturated fats, and the B-vitamins, particularly folate and vitamin B_{12}. These dietary components are prominent in the Mediterranean diet that is high in vegetables, fruits, fish, whole grains, legumes and monounsaturated oils, and low in meats and high-fat dairy. Several prospective studies reported protective associations of adherence to the Mediterranean diet with cognitive decline[189–191] and dementias[192]. The studies on vitamin E and B-vitamins suggest that it is low intake or low vitamin status that are deleterious for brain function and health. That is, persons with adequate vitamin status may not benefit further from vitamin supplemental intake. Few randomised clinical trials are designed to test these observed relations from the epidemiological studies. The trial participants are generally recruited without regard to nutrient intake or vitamin status, and all participants are allowed to take multivitamins (or consume fish in DHA supplement trials), thus further diluting a potential treatment effect. To most appropriately test the effect of nutrients on brain-related conditions, randomised clinical trials need to target individuals who have less than adequate nutrient status. The field of diet and neurodegenerative diseases is still very young. Much further research is needed to understand the roles of different dietary components in the aging brain and also their interactions among each other, with genetic risk factors and with various conditions.

Acknowledgements

The author declares no conflicts of interest.

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