Nutrition 31 (2015) 261–275

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Review

Inadequate supply of vitamins and DHA in the elderly: Implications for brain aging and Alzheimer-type dementia

M. Hasan Mohajeri Ph.D. *, Barbara Troesch Ph.D., Peter Weber M.D., Ph.D.

DSM Nutritional Products Ltd., R&D Human Nutrition and Health, Basel, Switzerland

ARTICLE INFO

Article history:
Received 12 February 2014
Accepted 4 June 2014

Keywords:
Aging
Vitamin intake
Alzheimer
Diet
Drug therapy

ABSTRACT

Alzheimer's disease (AD) is the most prevalent, severe, and disabling cause of dementia worldwide. To date, AD therapy is primarily targeted toward palliative treatment of symptoms rather than prevention of disease progression. So far, no pharmacologic interventions have changed the onset or progression of AD and their use is accompanied by side effects. The major obstacle in managing AD and designing therapeutic strategies is the difficulty in retarding neuronal loss in the diseased brain once the pathologic events leading to neuronal death have started. Therefore, a promising alternative strategy is to maintain a healthy neuronal population in the aging brain for as long as possible. One factor evidently important for neuronal health and function is the optimal supply of nutrients necessary for maintaining normal functioning of the brain. Mechanistic studies, epidemiologic analyses, and randomized controlled intervention trials provide insight to the positive effects of docosahexaenoic acid (DHA) and micronutrients such as the vitamin B family, and vitamins E, C, and D, in helping neurons to cope with aging. These nutrients are inexpensive in use, have virtually no side effects when used at recommended doses, are essential for life, have established modes of action, and are broadly accepted by the general public. This review provides some evidence that the use of vitamins and DHA for the aging population in general, and for individuals at risk in particular, is a viable alternative approach to delaying brain aging and for protecting against the onset of AD pathology.

Introduction

In the 20th century, life expectancy increased by > 30 y, which, combined with declining fertility rates, led to a dramatic shift in demographic characteristics [1]. By the year 2040, more than one in four Europeans will be older than age 65 y and one in seven will be > 75 y of age [2]. Consequently, demand for health and long-term care, as well as expenses for pensions and social security, will increase significantly. More importantly, health expectancy is 8 to 11 y shorter than life expectancy, that is, the last decade of life is marked by disability and disease [1], to which the loss of cognitive functions and the increase in dementia is an important contributor. Dementia is not a disease with a given etiology, but it is rather a group of chronic symptoms that are common to different neurologic disorders. These symptoms can include disorientation and impaired memory, language and reasoning competencies. Moreover, demented individuals progressively lose the capability to care for themselves accompanied by a deterioration of nutritional status [3].

Here we combine intake data and physiological data for proper brain functioning, as well as results from epidemiology studies and randomized placebo-controlled trials to examine the importance of micronutrients and polyunsaturated fatty acids (PUFAs) during brain aging and for maintaining neuronal health and proper cognitive performance. An attempt is made to define the role of nutrition in the development and progression of Alzheimer's disease (AD), which appears to be of particular interest as there is so far no curative treatment established for these patients. We will primarily concentrate on late-onset, sporadic AD, as it is the most common form and is thought to have a weaker genetic component [4]. Therefore, a greater potential for the effects of environmental factors, such as nutrition, may be anticipated.

MHM and PW designed and contributed the concept to the manuscript. MHM and BT reviewed the literature. All authors contributed to writing the manuscript. The authors are employed by DSM Nutritional Products, but no conflicts of interest exist in relation to the studies described and the content of this paper.

* Corresponding author. Tel.: +41 61 815 8484; fax: +41 61 815 8840.
E-mail address: hasan.mohajeri@dsm.com (M. H. Mohajeri).

http://dx.doi.org/10.1016/j.nut.2014.06.016

Impact of aging on nutrient intake and utilization

Aging has been defined as the collection of changes that render human beings progressively more likely to die [5]. Indeed, one of its hallmarks in humans is an age-related increase in mortality rates shortly after maturity [5]. Although the aging process itself is distinct from disease, it increases the vulnerability to become infirm [6,7]. It is important to mention that brain aging is not a single process, but an accumulation of modifications, affecting different parts of the brain to varying degrees [8]. Aging and its linked pathologies also are accompanied by a multitude of social changes. Decreased income after retirement, lack of mobility and social contacts, as well as intake of multiple medications, chronic alcoholism, depressive mood, and loss of appetite often lead to a decrease in food intake [9]. Due to physical disabilities and confusion resulting from dementia, depression, or other psychological factors, older individuals tend to be less capable of preparing meals for themselves [9], resulting in decreased food intake [10]. Additionally, the mechanisms controlling food intake and the ability to compensate normal daily fluctuations in energy intake appear to decline with age [10,11]. Moreover, the correlation between stomach content and hunger declines, and meals become smaller and less frequent [12]. This reduced effectiveness to detect and react to hunger makes this population particularly vulnerable to malnutrition [10]. Furthermore, appetite is reduced by weakened taste and smell sensitivities, various pathological conditions or medications, and impaired chewing due to ill-fitting dentures [13]. Decreased secretion of saliva due to age, or the intake of certain drugs, also makes swallowing more difficult [14].

In addition to age-related issues with swallowing and food intake, the efficiency of the stomach often is impaired due to decreased secretion of gastric acid, pepsin, and mucus as well as a reduction in gastric emptying and blood supply, although this is rarely caused by older age alone [14]. Malabsorption may be the result of surgery or pathological conditions such as Crohn's, Whipple's, or celiac diseases; alcoholism; or certain infections [15,16]. Infections with *Heliobacter pylori*, which is widespread in older people, manifests with symptoms such as anorexia, problems swallowing, bleeding in the upper gastrointestinal tract, vomiting, weight loss, and anemia [14]. With age, the gut microbiota shifts toward an increase in enterobacteria at the cost of anaerobes and bifidobacteria, which increases the vulnerability to diarrheal diseases [17]. The susceptibility is further elevated by increased intake of antibiotics or other drugs and a decreased immune defense [18]. At the same time, constipation is widespread due to lack of exercise, dehydration, low intake of dietary fibers, and drug treatment [19]. Another common cause for constipation is irritable bowel syndrome, which also can cause anemia, weight loss, and rectal bleeding [14]. These changes have been associated with increased risk for malnutrition and inadequate supplies of micronutrients in the older population [20] (Fig.1).

Alzheimer's disease

AD, an age-related debilitating progressive neurologic disease, is the leading cause of senile dementia and the fourth leading cause of death in industrialized societies [21]. Currently, >35 million individuals are afflicted with AD worldwide, and these numbers are expected to quadruple by 2050 [22]. Although deaths from HIV, stroke, and heart disease decreased between 2000 and 2008 by 29%, 20% and 13%, respectively, there was a 66% increase in deaths related directly to AD during the same period (www.alz.org/). The number of AD patients is expected to reach 13.5 million by 2050 in the United States, resulting in >$1 trillion in patient care costs (www.alz.org). No disease-curing drug has been developed so far for treating AD, making it one of the most pressing public health problems in the world today [23]. Institutionalized care for demented individuals, especially AD patients, is a large challenge for health and social welfare systems. Existing AD options of medication, aiming to extend the half-life of the neurotransmitters acetylcholine, or modulate the *N*-methyl-D-aspartate receptor activity in the brain, can, at most, temporarily retard some of the cognitive decline associated with the disease, but they by no means, halt or reverse its progression [24–26].

AD is clinically diagnosed by progressive memory loss accompanied by another cognitive dysfunction, such as information-processing or language impairment. A final diagnosis, however, is only possible at biopsy, where the presence of intracellular neurofibrillary tangles, extra-cellular amyloid (Aβ) plaque depositions, and neuronal loss confirm the AD pathology [27,28]. The etiologic events leading to their generation are not entirely understood. Mutations in genes encoding amyloid precursor protein, presenilin 1 and 2 (APP, PS1, and PS2) are found in familial AD and lead to accelerated deposition of Aβ in animal models [28,29]. These findings strengthen the so-called amyloid cascade hypothesis as a dominant theory of AD pathophysiology, and they provide associations between the presence of toxic-soluble amyloid oligomers and AD. Animal data show indeed that overexpressing human Aβ peptide in brains of transgenic mice mimics some of the pathologies observed in AD, including the deposition of amyloid plaques. Such in vivo studies set the basis for designing therapeutic approaches in humans. These animal models, however, do not represent the full biochemical and cellular changes found in AD [30] and despite the preclinical evidence, attempts at ameliorating AD pathology by removing amyloid plaques from the patient's brain have been unsuccessful [29–32]. The problem for AD therapy in humans is that well before dementia manifests itself, protein aggregates trigger a number of cellular changes leading to irreversible neuronal injury and loss. Anti-amyloid interventions proved to be disappointing in the clinic, even worsening the pathology at times [33]. This clinical inefficiency of anti-amyloid therapies questions the validity of the amyloid cascade hypothesis to the extent that some investigators openly question whether this hypothesis should be tested further [34] and it also has been claimed that deposition of Aβ in the AD brain is a consequence rather than a cause of AD [35–38]. Several additional mechanisms were proposed as alternative or combinatory mechanisms to explain AD pathophysiology including hormonal influence [39], inflammatory pathways [40], metabolic dysfunction [41], dysregulation of metal ion homeostasis [42], oxidative stress [43,44] and tau phosphorylation [45–48]. Although all of these mechanisms are implicated in the disease, none of these theories completely explains AD pathology. Therefore, it is not surprising that therapeutic strategies relying on any specific mechanism have not resulted in any pharmaceutical breakthrough for AD treatment to date.

Nutritional status of the older population

Physiological changes linked to aging lead to decreased needs for energy intake in older adults compared with young adults with the same height, weight, and level of activity, whereas requirements for micronutrients remain high [49]. Moreover, high-energy, low-nutrient foods constitute approximately 25% of the total energy intake in people >50 y in the United States [50], making it difficult to meet their needs for micronutrients. In other segments of the older population, the situation might be even

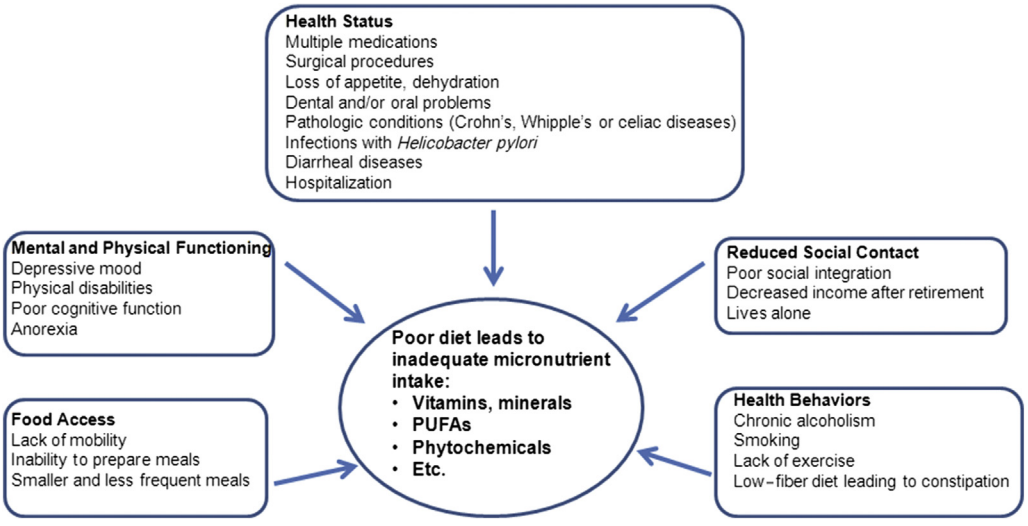

Fig. 1. Older adults are at risk for malnutrition. Various factors may cause poor coverage with essential nutrients and possible malnutrition in this age group. PUFA, polyunsaturated fatty acid.

more critical: Energy intake in ~50% to 75% residents of German nursing homes was found to be low [51]. The reduced energy recommendations and intakes highlight the importance of nutrient-dense foods for the older population [52]. Nutrient density refers to foods that have high levels of essential nutrients per food unit and are therefore deemed high-quality foods [53]. It was shown that nutrient density decreased as household budget available for food went down [54]. Given the often reduced budgets of the older population, this adds a further difficulty in achieving a balanced diet with sufficient micronutrients.

Various nutrients are crucial for proper brain functioning, especially in the elderly, and adequate intakes are essential given the age-related changes described. To get a better understanding of the adequacy of vitamin intake in older individuals in Western countries, we analyzed data collected in the frame of dietary surveys in the United States [55–57]. Data were selected for all adult participants with complete and reliable dietary records in the age range >70 y (n = 2545). The method of data collection and analysis was described elsewhere [58]. National Health and Nutrition Examination Survey (NHANES) data from 2003 to 2008 shows that intakes of vitamin A, C, D, E, K and folate are low in a significant proportion of the older population in the United States (Fig. 2A, B). In Germany, vitamin D and folate appear to be the most critical vitamins in people ages 65 to 80 y, followed by vitamins E and C [59] (Table 1), in both institutionalized and community-dwelling elderly. More than 50% of older residents in German nursing homes consumed the majority of vitamins at levels often well below recommendations [51]. The European Nutrition and Health Survey also reported that average intakes of vitamin D and folate for most countries are below the recommended levels, whereas around 50% of the countries have average intakes of vitamin E and C that are below recommendations [60]. Consequently, a significant proportion of older citizens can be expected to be at risk for multiple micronutrient deficiencies. Hospitalization, which is more likely in this age group, may add an additional risk for inadequate nutrition as it is reported that nutritional status is likely to worsen during a hospital stay (for a review see [61]). One reason given for the high prevalence of inadequate intakes even in affluent societies is lack of awareness of the problem not just in the general public, but also among health care professionals and decision makers [62]. Although the controlled environment of the hospital would allow for improved nutrition, this opportunity has so far been neglected, likely due to lack of awareness and differing priorities. Consequently, it has repeatedly been stipulated that nutrition takes a more prominent role in the training of physicians [63].

In the United States, the nutrient-poor diet is partially compensated by the use of dietary supplements. The 1999 to 2000 NHANES reported that >35% of people ages ≥60 take micronutrient supplements on a regular basis [64]. In Germany, this was not the case as only around 3% of tis age group were taking supplements [51]. A similar situation most likely exists with micronutrients supplied by fortification and enrichment, as it was found that fortification served as a significant source for vitamins and minerals in the United States [65], but not in Europe [66].

Vitamin B_{12} intake levels are reported to be mostly above the Recommended Dietary Allowance (Table 2, Fig. 2) for older individuals in the United States. However, given the level of atrophic gastritis found in this age group [67] and the recommendations of doses of ≥1000 μg/d for people with malabsorption [68], concerns about the sufficiency of intake or bioavailability remain. Data collected in NHANES 1999 to 2004 found that 5% to 25% of people ages ≥60 had low serum vitamin B_{12} levels, depending on the cutoff used [69]. In Germany, intakes are lower still; vitamin B_{12} deficiency is therefore likely to be even more common.

The increased needs of many micronutrients, such as calcium and vitamin D in this group are difficult to meet from diet alone [70]. The same applies to levels of vitamin E, an important antioxidant in the human body as concluded by the European Food Safety Authority (EFSA; efsa.europa.eu). Vitamin E deficiency has been implicated in various chronic degenerative diseases [11]. The risk for nutrient intakes below the Estimated Average Requirements is reduced four times in older persons who regularly used supplements one or more micronutrients [71]. In older men, the prevalence of vitamins A and E and folate intake below the recommendations decreased from 53% to 4%, from 93% to 14%, and from 75% to 7%, respectively, with the use of supplements [71].

Cognitively normal aged brains can exhibit characteristic markers of AD

A healthy brain is one of the organs with the highest metabolic activities, and it uses a large proportion of the total nutrient

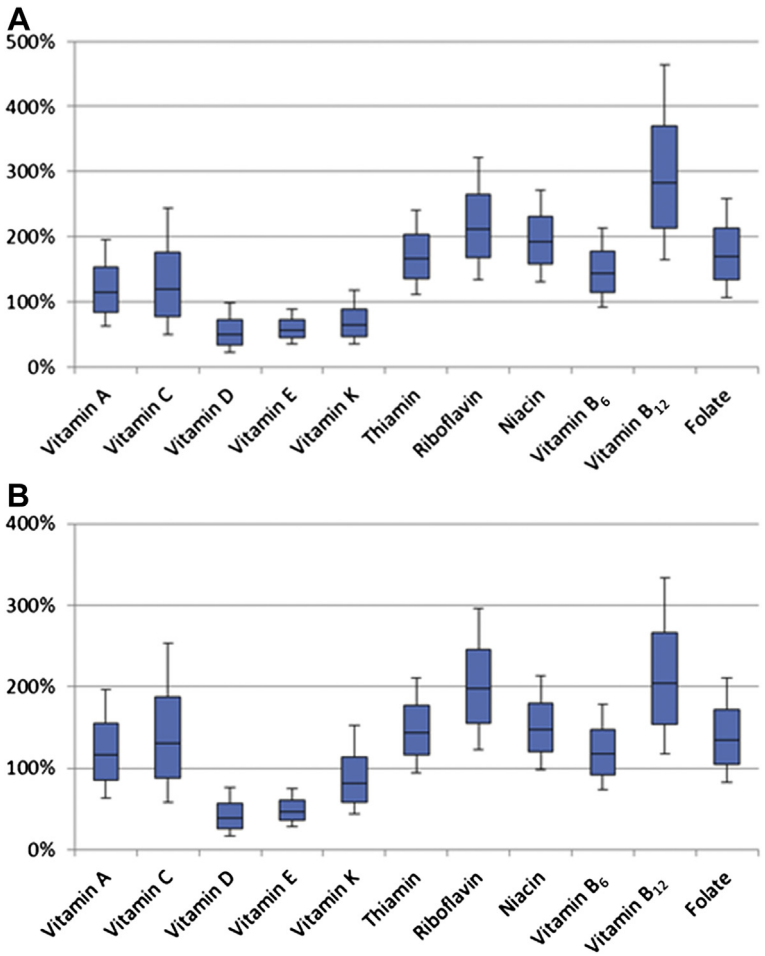

Fig. 2. Vitamin intake in the older U.S. population. Vitamin intake in older men (n = 1274) (A) and women (n = 1271) (B) in the United States relative to estimated average requirements for the age group of >70 y old [139,141,183,184]. The boxplots indicate 10th, 25th, 50th, 75th, and 90th percentiles.

and energy intake. Furthermore, the maintenance of properly functioning neural tissue is tightly regulated and depends on optimal intakes of vitamins, structural nutrients, and minerals. The brain is metabolically very active, depends on glucose for energy production, and consumes ~20% of the total blood glucose, although it only accounts for 2% to 3% of body weight in adult humans [72]. This high demand for energy makes the brain susceptible to any metabolic insufficiency caused by a shortage of essential nutrients [73].

Neurons are postmitotic, extremely specialized, and long-living cells. As a result, they have a limited capacity to cope with environmental stress and accumulating age-related events [74]. Additionally, because neurons in the brain do not regenerate, the accumulation of damage may exceed the capacity of repair mechanisms [75]. Also, the antioxidant machinery is less active in brain neurons compared with other organs [76]. Therefore, an aging brain has altered requirements of essential nutrients including vitamins, and this need is even more pronounced in dementia or depression [76]. In AD, markers of oxidative stress are elevated in the brain, indicating an increased level of oxidative stress and/or a decreased capacity to repair nucleic acid damage [77]. A shared factor in normal brain aging, age-related degenerative processes, common to a variety of neurodegenerative disorders, appears to be a decay of mitochondrial function [78]. One likely reason for this loss of function is the age-related accumulation of oxidative damage to mitochondrial proteins, causing structural deformation and defects in key enzyme function [79]. Defective mitochondria also lead to a shortage of the energy supply to neurons, which in turn, may start the pathogenic cascades leading to age-associated neuronal loss in AD [80,81].

Older individuals with an inadequate supply of micronutrients and antioxidants may be at a higher risk for alterations in brain functioning and loss of mental and emotional abilities. Additionally, some of the neuropathologic changes associated with AD (elevated amyloid burden) and cerebrovascular disease (white matter hyperintensities) are also observed in clinically normal older adults [78,79,82]. Both amyloid accumulation and white matter abnormalities among clinically normal older adults provide a possible link to AD and cerebral amyloid angiopathy [83].

Moreover, prospective longitudinal studies in cognitively normal older adults revealed that up to 45% of nondemented individuals would histopathologically meet the criteria for AD [84]. In particular, the pattern of regional distribution of pathologic changes in nondemented controls was shown to match that of AD patients. Thus, mounting evidence from pathologic studies supports the view that AD is a continuous spectrum between asymptomatic lesions in cognitively normal older adults and dementia, with mild cognitive impairment (MCI) as a transition phase. The existence of pathologic hallmarks in cognitively normal individuals suggests that they likely represent the earliest stages of neuropathology, too early in the course of the disease to be clinically manifest. These data support the notion

Table 1
Proportion of the population with vitamin intakes below recommended levels in the general population and in the institutionalized older population in Germany

	General [59] (65–80 y)		Institutionalized [51] (>65 y)		Recommendation [185]	
	Men (%)	Women (%)	Men (%)	Women (%)	Men	Women
n	1469	1562	148	606		
Vitamin A	13.2	8.9	47.3	40.3	1 mg RE/d	0.8 mg RE/d
Vitamin D	94.2	97.4	92.6	95.7	5 μg/d*	5 μg/d*
Vitamin E	46.7	47.4	82.4	85.8	12 mg TE/d	11 mg TE/d
Thiamin	20.2	40.4	57.4	82.5	1 mg/d	1 mg/d
Riboflavin	18.5	31.8	50.7	63	1.2 mg/d	1.2 mg/d
Niacin	0.6	2.1	13.8	28.7	13 mg/d	13 mg/d
Vitamin B_6	11.3	13.9	68.2	68.2	1.4 mg/d	1.2 mg/d
Folate	89.5	90.8	98.6	97	400 μg/d	400 μg/d
Vitamin B_{12}	9.8	26.3	48	48	3 μg/d	3 μg/d
Vitamin C	30.6	30.0	84.6	84.6	100 mg/d	100 mg/d

RE, retinol equivalent; TE, tocopherol equivalent
* The recommendations for vitamin D have since been increased to 20 μg/d [186].

that advanced aging is associated with multiple neuropathologic cascades impacting cognitive function [83,85]. Importantly, age-related decline of neuronal numbers in the brain is reported in susceptible young adults [86], showing that processes leading to neuronal loss and the impairment of brain functions may begin at much younger ages than generally assumed. Clinical research shows that episodic memory, the ability to recall events in time and place, declines with age, starting as early as 20 y (93). This finding is in agreement with animal experiments showing the age-related neuronal loss in the rat brain starts at the end of adolescence (94). Therefore, the search for validated biomarker profiles for early detection of beginning pathology in healthy populations is of upmost importance. Moreover, holistic intervention strategies, including sufficient access to micronutrients, may be required to mitigate early decline in memory and to improve mental well-being.

Classical pharmacologic anti-AD therapies

Enormous resources have been dedicated to developing pharmacologic therapeutics for AD, but they have done little to help patients to date [23]. Pharmacologic approaches for primary or secondary prevention of AD target neurotransmission, Aβ production, aggregation or clearance, tau proteins or neurotrophins, or they increase brain resistance to Aβ or modulate synaptic plasticity and nerve growth [23]. Moreover, hormone replacement therapy, nonsteroidal anti-inflammatory drugs, cholinesterase inhibitors, and immunization therapy were examined in randomized controlled trials (RCTs). All have either failed to causally affect the onset or progression of AD pathology or have been associated with safety concerns prompting the conclusion that a single target or pathogenic pathway for AD is unlikely to be identified owing to the complexity of the disease involving manifold interactions on several levels including genes, proteins, organelles, cells, organs, whole organism, and environment levels [26,87]. A comprehensive review of completed and ongoing clinical trials is given elsewhere and concluded that none of the AD treatments to date provide curative protection against AD pathogenesis, even if some short-term symptomatic relief is evident [88]. Moreover, the study postulated that focusing on several targets implicated in AD pathology exhibits the best chances of success [88].

Table 2
Recommended Intakes for Men and Women in the United States for the Age Group >70 y [139,141,183,184]

Vitamin	Unit/d	U.S. EAR	
		Men	Women
Vitamin A	μg RE	625	500
Vitamin D	μg	10	10
Vitamin E	mg TE	12	12
Thiamine	mg	1.0	0.9
Riboflavin	mg	1.1	0.9
Niacin	mg	12	12
Vitamin B_6	mg	1.4	1.3
Vitamin B_{12}	μg	2.0	2.0
Folic acid	μg	320	320
Vitamin C	mg	75	60
Vitamin K*	μg	120	90

EAR, Estimated Average Requirements; RE, retinol equivalent; TE, tocopherol equivalent
* Average nutrient requirement.

The effect of essential micronutrients on the metabolism of aging brain and cognitive health

Several mechanisms are identified by which micronutrients affect cognitive function [89,90]:

1. Some essential nutrients are implicated in the synthesis of neurotransmitters, amino acids, biogenic amines, and steroids. Specifically, the metabolism of dopamine and noradrenaline within the central nervous system (CNS) depends on vitamins B_2, B_6, B_{12}, nicotinamide, folate, and vitamin C [90].
2. Thiamine, thiamine triphosphate, vitamin E, and PUFAs are constituents of neuronal membranes, affecting membrane-dependent properties such as neurite outgrowth, action potential generation, and signal transduction.
3. Pyridoxine deficiency leads to changes in the receptor binding of a number of neurotransmitters, including glutamate and glycine.
4. Energy production in the brain is heavily dependent on several vitamins and minerals, such as vitamin B family members and vitamin C, as they are essential cofactors in glycolysis, the citric acid cycle, and the respiratory chain for producing adenosine triphosphate from glucose [73,90].

Another pathway linking micronutrients to cognitive function in the adult brain is the metabolism of homocysteine (Hcy) [91]. Hcy is an amino acid produced in the body from dietary methionine and is essential for normal cellular functions. However, high Hcy concentrations can undermine normal cellular functioning. Folate and vitamins B_6 and B_{12} are implicated in the metabolism of Hcy. Vitamin B_{12} plays an important role in the transformation of Hcy into the amino acid methionine. Vitamin

Table 3
Hcy levels in AD patients and controls

Study		AD patients		Healthy controls		*P*-value
		Serum levels	n	Serum levels	n	
Joosten et al. 1997 [187]	μmol/L	18.3 (8.2–41)*	52	12.3 (6.8–22.1)*	49	<0.01
Clarke et al. 1998 [188]	μmol/L	15.3 ± 8.4†,‡	164	13.2 ± 4.0	108	<0.05
Fekkes et al. 1998 [189]	μmol/L	19.4 ± 9.2	14	17.9 ± 3.5	17	NS
Leblhuber et al. 2000 [190]	μmol/L	17.8 ± 6.6	19	13.8 ± 4.2	19	<0.04
Postiglione et al. 2001 [191]	μmol/L	20.9 ± 15.0	74	11.8 ± 5.0	74	<0.001
Hogervorst et al. 2002 [192]	μmol/L	14.7 ± 4.9	137	12.8 ± 3.9	277	NS
McIlroy et al. 2002 [193]	μmol/L	14.7 (10.9–19.4)§	83	10.7 (8.1–13.3)§	71	<0.001
Mizrahi et al. 2003 [194]	μmol/L	12.3 ± 4.3	64	11.5 ± 3.7	64	NS
Religa et al. 2003 [195]	μmol/L	18.0 ± 9.9	99	14.4 ± 4.5	100	<0.0001
Gallucci et al. 2004 [196]	μmol/L	21.4 ± 10.6	137	15.5 ± 5.2	42	<0.01
Malaguarnera et al. 2004 [197]	μmol/L	22.3 ± 4.51	22	10.7 ± 3.00	24	<0.0001
Mizrahi et al. 2004 [198]	μmol/L	20.6 ± 8.7	75	16.4 ± 6.5	155	<0.001
Nilsson et al. 2004 [199]	μmol/L	17.9 ± 8.4	159	14.7 ± 4.1	51	<0.01
Quadri et al. 2004 [200]	μmol/L	16.8 ± 7.0	74	14.6 ± 6.1	55	NS
De Silva et al. 2005 [201]	μmol/L	13.3 ± 5.3	23	8.3 ± 2.3	21	<0.01
Da Silva et al. 2006 [202]	μmol/L	18.3 ± 7.6	42	15.3 ± 7.5	50	<0.05
Bottiglieri et al. 2001 [203]	μmol/L	12.4 ± 11.1	48	11.7 ± 6.2	22	<0.01
Nägga et al. 2003 [204]	μmol/L	16.5 ± 6.4	47	12.9 ± 4.2	101	<0.05
Köseoglu et al. 2007 [205]	μmol/L	14.2 ± 2.97	51	10.3 ± 1.28	40	<0.001
Storey et al. 2003 [206]	μmol/L	14.4 ± 2.7	50	10.6 ± 3.2	50	<0.0001
Folin et al. 2005 [207]	μmol/L	21.01 ± 7.80	79	15.78 ± 5.55	24	<0.05
Quadri et al. 2005 [208]	μmol/L	16.9 ± 7.3	111	14.4 ± 6.1	79	NS
Miller et al. 2002 [209]	μmol/L	10.6 ± 2.0	32	9.3 ± 2.2	22	NS

AD, Alzheimer's disease; Hcy, homocysteine; NS, not significant
* Geometric mean with 95% range.
† Mean with SD (all such values).
‡ Clinically diagnosed patients, for histologically confirmed cases (n = 76), mean Hcy increases to 16.3 ± 7.4, $P < 0.01$.
§ Geometric mean with interquartile range.

B_6 and folate are cofactors necessary for this reaction and, in their absence, Hcy accumulates [90,92]. Clinical research shows that plasma levels of Hcy are significantly higher in cases of cognitive impairment when compared with controls [93]. Likewise, the severity of cognitive impairment has been associated with increased concentrations of plasma Hcy [94]. Moreover, a significantly higher risk for AD was reported when both folate and B_{12} levels were low, and it has been suggested that high Hcy and low B vitamin levels predict cognitive decline in aging men [95]. Various prospective or case–control studies report Hcy levels in AD patients and controls, showing that they tend to be higher in AD (Table 3).

The systematic evaluation of association and/or causal tie between marginal vitamin deficiencies and cognitive function has gained broad acceptance in the past decades. The concept of marginal vitamin deficiencies (suboptimal vitamin status) was first proposed almost 3 decades ago [96] and in a study that introduced the triage theory [97]. According to the triage theory, borderline micronutrient deficiencies accelerate aging, cancer, and neural decay potentially causing impairment of brain function with age.

Here, we emphasize the importance of an adequate vitamin supply for mental health by summarizing some of the mental disorders caused directly by insufficient vitamin intake or use (Fig. 3). Thiamine deficiency causes beriberi and Wernicke-Korsakoff syndrome with symptoms varying from confusion and depression to psychosis, coma, and memory impairment [98]. Treatment consists of reversing the thiamine deficiency with supplemental thiamine. Deficiency of niacin in the diet causes the disease pellagra, which is characterized by diarrhea, dermatitis, and dementia. Common psychiatric symptoms of niacin deficiency include irritability, poor concentration, anxiety, fatigue, restlessness, apathy, and depression due to perturbed serotonin synthesis [99]. Vitamin B_6 deficiency can be detected by a characteristic abnormal electroencephalogram, nerve degeneration, and peripheral neuritis [100]. Neurologic symptoms of vitamin B_6 deficiency include confusion and neuropathy. A modest vitamin B_6 deficiency results in impaired tryptophan-niacin conversion affecting neurotransmitter balance within the CNS, and may lead to mood fluctuations in depressed individuals. Additionally, pyridoxal phosphate–dependent enzymes play a role in the biosynthesis of five important neurotransmitters: serotonin, dopamine, adrenaline, noradrenaline and γ-aminobutyric acid [100]. A vitamin B_6 deficiency alone is relatively uncommon and often occurs in association with other vitamins of the B complex, especially folate or vitamin B_{12} [101]. As already mentioned, insufficient supply of B vitamins, especially of thiamine, riboflavin, folate, and vitamin B_{12} are implicated in high Hcy levels and cognitive deficits, and new data suggest that B vitamins have a preventative role against AD pathology (see later). Vitamin B_6 deficiency also can result in impaired transsulfuration of methionine to cysteine [102] systemically affecting the antioxidant capacity and protein structure in the body and brain.

Vitamins C and E likely play roles as antioxidants in the brain. After the pituitary gland and leukocytes, the brain has higher vitamin C content than any other organ. Vitamin C is essential for the synthesis of the neurotransmitters dopamine and noradrenaline [101,102], and it modulates tyrosine metabolism [103,104]. Furthermore, ascorbate may also act as an antioxidant protecting neurons against oxidative stress [105], particularly because it also is needed for recycling vitamin E to its antioxidant form [106]. Vitamin E is important for proper neuronal functioning [107] and its deficiency leads primarily to neurologic dysfunction such as spinocerebellar ataxia and dysarthria [108]. As a potent antioxidant, a free radical scavenger, and a constituent of neuronal membranes, vitamin E prevents the oxidation of lipids and PUFAs [108]. It has an effect on gene expression [109–112] and is a modulator of enzymatic activities [113]. The only symptoms of vitamin E deficiency in humans, caused by mutations in the gene for α-tocopherol transfer protein, are

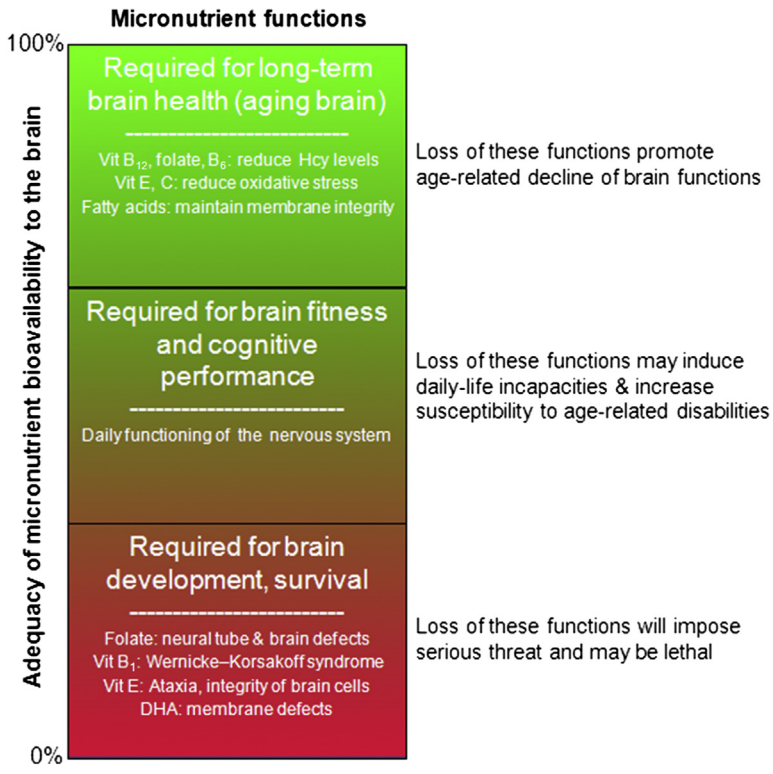

Fig. 3. Use of micronutrients depends on their extent of availability. Scarcity of micronutriessssnt supply enforces a prioritization of allocation to functions ensuring survival. When micronutrients are sufficiently supplied throughout life, they may help to maintain brain functions as individuals age, thus potentially preventing dementia. DHA, docosahexaenoic acid; Hcy, homocysteine.

neurologic complications that are similar to those of Friedreich's ataxia. Such symptoms can be treated completely by vitamin E supplementation therapy [114,115]. Additionally, low plasma levels of tocopherols and tocotrienols are associated with increased odds of MCI and AD [116,117].

Low vitamin D levels are associated with anxiety and a decline in mood, especially in the winter months [118]. Recent data show that supplementation of healthy individuals with vitamin D_3 for 5 d prevents mood decline [118]. Vitamin D receptors are expressed broadly in the brain [119], and several new studies hint to the importance of vitamin D for normal cognitive performance, especially in older populations [119–123].

Long-chain ω-3 PUFAs, such as DHA, are important building blocks for neuronal cell membranes and are instrumental in brain development, neurotransmission, modulation of ion channels, and neuroprotection [31,124]. Brain DHA levels decrease with age, especially among AD patients, indicating that a reduced DHA content may contribute to deterioration in memory and other cognitive functions [31,34]. Recent data favor a role for PUFA in slowing cognitive decline in older individuals when treated before clinical manifestation of dementia [31,34], but this work also suggested that the beneficial effects of PUFA supplementation may depend on stage of disease, other dietary mediators, and apolipoprotein (Apo) E status [125]. In general, accumulative data support the potential of DHA to support cognitive functions in older populations, before the onset of AD symptoms. However, the benefits of ω-3 supplementation become marginal and debatable in individuals already diagnosed with AD.

It is known that malnutrition causes oxidative stress and inflammation in aged brains, which in turn may damage neural tissues and compromise brain functions as people age [126]. Nutrition-dependent biological mechanisms associated with aging include accumulative oxidative stress [73], inflammatory stress [127], Hcy metabolism [91], and advanced glycation end products [128]. The intrinsic common feature of all these factors is that they respond and adapt to the diet. One consequence of inadequately supplying the brain with micronutrients is the activation of the above mechanisms, potentially leading to pathologic cues such as reduced cerebral blood supply, glucose tolerance, or brain atrophy, which change a healthy brain to an AD brain over several decades [129]. Thus, there is a wealth of observations and experimental knowledge that effective functioning of the brain depends on an adequate and constant nutrient supply and that nutrition and in particular micronutrients are key for cognitive performance and mental well-being.

Epidemiologic data on the role of micronutrients in cognitive health and AD

Epidemiologic studies show that multivitamins and minerals, consumed as fruits, vegetables, or dietary supplements are associated with lower risk for developing cognitive deficits [130–133]. Table 4 summarizes some of the studies that compared serum levels of micronutrients in AD patients with controls. Although the results are mixed, they provide evidence that some of these micronutrients play an important role in the etiology of AD. This is apparent from the fact that, in many cases, AD patients have significantly lower serum levels of micronutrients than those of their healthy peers. Serum levels are merely crude snapshots of an individual's nutritional status, and it is likely that nutritional adequacy throughout the lifecycle or during critical periods might be more relevant. Nonetheless, many studies show that higher micronutrient serum levels are

linked to lower risks for developing AD with advanced age. A meta-analysis of seven case–control studies tested the hypothesis that hypovitaminosis D could be associated with AD. The authors showed that higher dietary intake of vitamin D was associated with a lower risk for developing AD among older women [120, 134] and that AD cases have lower 25-hydroxy vitamin D concentrations than controls [120] (Table 4). Also, in a prospectively followed cohort of 498 older women initially not taking vitamin D supplements, the baseline dietary intake of vitamin D was associated with the risk for onset of AD within 7 y [122]. The highest consumption of dietary vitamin D was associated with a 4.35-fold decrease in the risk for developing AD [122].

Dietary data collected in a longitudinal study of 5092 individuals ages ≥65 y who were residents of Cache County, Utah, were retrospectively evaluated [135]. In this population, a dietary intake of B vitamins from food and supplements appeared to be unrelated to the incidence of dementia and AD. The authors suggested that further studies examining associations between dietary intakes of B vitamins, biomarkers of vitamin B status, and cognitive end points are warranted [135]. In contrast, in a study that followed 965 individuals ages ≥65 y without dementia at baseline for 6.1 y, high folate intake was shown to be linked to decreased risk for AD independent of other risk factors and levels of vitamins B_6 and B_{12} [136]. In another prospective study, 579 nondemented older volunteers from the Baltimore Longitudinal Study of Aging were followed for 9.3 y. Fifty-seven participants developed AD. Higher intake of folate and vitamins E and B_6 were associated individually with a decreased risk for AD after adjusting for age, sex, education, and calorie intake [137]. These results are consistent with data showing that symptoms of deficiencies in vitamin E and B vitamins are neurologic [138–141]. The Baltimore study further showed that participants who had intakes ≥400 μg of folates had a 55% reduction in risk for developing AD. Because intake of 400 μg folate could only be achieved by supplementation, these authors concluded that many people do not get the recommended amounts of folates in their diets [103]. These data are in agreement with another study showing that red blood cell folate, but not serum folate, was decreased in Australian AD patients compared with healthy controls [142]. Following an inverted U-shape curve, high folate levels in red blood cells were associated with worse long-term episodic memory, total episodic memory, and global cognition. A critical review of published literature provided solid evidence that high Hcy plasma levels are linked to a growing number of diseases including AD [93]. In a cohort of 1112 participants (768 controls, 133 MCI, and 211 AD), plasma Hcy levels were associated with cognitive deterioration [142]. Furthermore, poor vitamin B_{12} status was associated with neurologic problems and other health-related conditions, including poor cognition and AD [143].

An exhaustive review of literature showed that AD patients exhibit generally low vitamin C levels in their plasma and that maintaining healthy vitamin C levels can have a protective function against age-related cognitive decline and AD [144]. Plasma levels of vitamins E and C were both lower in patients with MCI and AD compared with controls [145] (Table 4). Other reports hint to a protective role of vitamin E against AD. For example, a Swedish-Italian study showed that, after a follow-up period of 6 y, high plasma levels of vitamin E at baseline were associated with a reduced risk for AD in advanced age. The neuroprotective effect of vitamin E in this study seemed to be related to the combination of different forms, rather than to α-tocopherol alone [88]. One meta-analysis demonstrated that increased vitamin E intake reduced AD risk in the older population [146]. The results of this meta-analysis suggested that vitamins E and C and β-carotene intakes can help lower the risk for AD, and among the three antioxidants, vitamin E exhibits the most significant protective effect [146]. Epidemiologic data show that cognitive scores were directly correlated with blood levels of α-tocopherol and lycopene [147] and that vitamin E intake, from foods or supplements, was associated with less cognitive decline with age [148]. Additionally, increasing vitamin E intake from foods was associated with decreased risk for developing AD after adjustment for age, education, sex, race, ApoE ε-4, and length of follow-up [149]. These data are supported by findings that telomeres, a marker of biological longevity, are longer in healthy women who had higher intakes of vitamins C and E from foods [150]. Along the same line of evidence, vitamin E was shown to increase life expectancy in men, depending on dietary vitamin C intake and smoking [151]. Further support of a positive role of vitamin E in brain function and maintenance is provided by the finding that cognitively normal centenarians exhibit normal levels of plasma vitamin E and A [152], possibly contributing to the protection of centenarians against oxidative stress and thereby to their extreme longevity.

Existing evidence links greater dietary intake of fish and (ω-3) PUFA to better early brain development and lowered risk for cognitive disorders in late life [124]. Cross-sectional and prospective cohort data have demonstrated that reduced dietary intake or low brain levels of DHA are associated with accelerated cognitive decline or the development of incipient dementia, including AD. In a community-dwelling cohort, levels of α-linolenic acid, eicosapentaenoic acid, and DHA were assessed in serum phospholipids of 280 volunteers between 35 and 54 y of age, free of major neuropsychiatric disorders, and not taking fish oil supplements [153,154]. Only the associations between DHA and nonverbal reasoning and working memory persisted after additional adjustment for participant education and vocabulary scores. Thus, among the three key PUFAs, only DHA was associated with major aspects of cognitive performance in healthy adults <55 y old. These findings suggest that DHA is related to brain health throughout the life span and may have implications for clinical trials of neuropsychiatric disorders [153,154].

Randomized controlled trials examining nutrients for AD prevention and treatment

Evidence provided by numerous studies pinpoints to a fundamental role of vitamins in cognitive performance in older adults: A systematic review and meta-analysis of RCT reporting the chronic effects (≥1 mo) of oral multivitamin supplementation on any valid cognitive outcome was performed in 2012 [155]. The authors concluded that multivitamins enhanced immediate free-recall memory in cognitively healthy adults [155]. In another study, 818 mentally healthy adults, ages 50 to 75 y, were randomized to receive a daily tablet containing 800 μg folic acid or placebo for 3 y: Participants taking folic acid performed better on memory tests than the placebo-treated group and as well as individuals who were 5 y younger. Additionally, folate-supplemented individuals exhibited scores of information processing that were similar to those who were 2 y younger [156]. These data were consistent with the Baltimore Longitudinal Study of Aging, showing that intake of folates and vitamins E and B_6 lowered risk for AD [137]. It has been demonstrated that supplementing AD patients with high doses of vitamins B_6 and B_{12} and folate lowers plasma Hcy concentration [157]. Most importantly, under conditions of healthy nutrition, Hcy levels could be reduced further by administration of high-dose supplements of folic acid and vitamins B_6 and B_{12} [158].

Table 4
Data on serum vitamin levels in AD patients and controls from Cross-sectional and case–control studies

Vitamin	Study		AD patients		Healthy controls		*P*-value
			Serum level	N	Serum level	n	
Folate	Joosten et al. 1997 [187]	μg/L	3.5 (1.3–9.7)*	52	3.8 (1.8–8.2)	49	NS
	Clarke et al. 1998 [188]	nmol/L	17.6 ± 10.7†,‡	164	22.9 ± 10.0	108	<0.01
	Leblhuber et al. 2000 [190]	ng/mL	4.4 ± 1.5	19	6.3 ± 4.1	19	NS
	Postiglione et al. 2001 [191]	ng/L	5.7 ± 2.1	74	8.5 ± 3.2	74	<0.001
	McIlroy et al. 2002 [193]	μg/L	4.5 (3.2–6.5)*	83	5.1 (3.8–7.6)	71	<0.01
	Religa et al. 2003 [195]	ng/mL	8.5 ± 3.4	99	7.6 ± 5.4	100	NS
	Gallucci et al. 2004 [196]	ng/mL	5.1 ± 2.7	137	6.2 ± 4.9	42	NS
	Malaguarnera et al. 2004 [197]	nmol/L	10.0 ± 2.72	22	13.9 ± 3.0	24	<0.001
	Mizrahi et al. 2004 [198]	nmol/L	4.3 ± 3.2	75	4.8 ± 2.6	155	NS
	Nilsson et al. 2004 [199]	nmol/L	297 ± 112	159	339 ± 151	51	NS
	Quadri et al. 2004 [200]	nmol/L	13.6 ± 5.6	74	16.9 ± 5.8	55	NS
	Quadri et al. 2005 [208]	nmol/L	13.1 ± 5.9	111	16.8 ± 5.5	79	NS
	De Silva et al. 2005 [201]	ng/mL	7.0 ± 3.7	23	8.7 ± 4.3	21	NS
	Bottiglieri et al. 2001 [203]	nmol/L	8.0 ± 3.4	48	12.1 ± 10.0	14§	NS
	Miller et al. 2002 [209]	ng/mL	461 ± 159	32	496 ± 212	22	NS
	Köseoglu et al. 2007 [205]	ng/mL	9.45 ± 1.94	51	12.4 ± 1.50	40	<0.001
	Renvall et al. 1989 [210]	ng/mL	428 ± 213	27	582 ± 230	10	<0.06
Vitamin B_{12}	Joosten et al. 1997 [187]	ng/L	284 (80–999)	52	284 (119–673)	49	NS
	Clarke et al. 1998 [188]	pmol/L	236 ± 112	164	253 ± 100	108	NS
	Leblhuber et al. 2000 [190]	pg/mL	352.4 ± 129.3	19	383.3 ± 188.2	19	NS
	Postiglione et al. 2001 [191]	pmol/L	491 ± 144	74	780 ± 211	74	<0.001
	McIlroy et al. 2002 [193]	ng/L	4.5 (3.2–6.6)	83	5.1 (3.8–7.6)	71	NS
	Religa et al. 2003 [195]	pg/mL	316.7 ± 139.5	99	413.5 ± 241.3	100	<0.05
	Gallucci et al. 2004 [196]	pg/mL	375.9 ± 228.4	137	479.7 ± 402.8	42	NS
	Malaguarnera et al. 2004 [197]	pmol/L	392.1 ± 65.32	22	438.6 ± 61.62	24	<0.05
	Mizrahi et al. 2004 [198]	pmol/L	322.9 ± 136.0	75	350.5 ± 175.3	155	NS
	Nilsson et al. 2004 [199]	pmol/L	254 ± 97	159	257 ± 129	51	NS
	Quadri et al. 2004 [200]	pmol/L	281 ± 111	74	278 ± 99	55	NS
	Quadri et al. 2005 [208]	pmol/L	272 ± 108	111	275 ± 96	79	NS
	De Silva et al. 2005 [201]	pg/mL	483 ± 134.5	23	494 ± 139	21	NS
	Bottiglieri et al. 2001 [203]	pmol/L	353 ± 20.5	48	481 ± 22.6	14§	<0.05
	Nägga et al. 2003 [204]	pmol/L	274 ± 80	47	307 ± 153	94	NS
	Köseoglu et al. 2007 [205]	pg/mL	280 ± 20.9	51	389.2 ± 28.58	40	<0.001
	Miller et al. 2002 [209]	pg/mL	533 ± 281	32	452 ± 202	22	NS
	Renvall et al. 1989 [210]	pg/mL	442 ± 37	21	542 ± 178	22	<0.05
Vitamin B_6	McIlroy et al. 2002 [193]	nmol/L	5.6 (4.0–8.5)	83	6.4 (4.7–10.4)	71	<0.05
	Malaguarnera et al. 2004 [197]	nmol/L	52.0 ± 10.78	22	57.5 ± 8.19	24	NS
	Miller et al. 2002 [209]	nmol/L	121 ± 254	32	64 ± 37	22	NS
Vitamin C	Rinaldi et al. 2003 [145]	μmol/L	25.9 ± 8.9	63	52.4 ± 16.5	56	<0.0001
Vitamin E	Rinaldi et al. 2003 [145]	μmol/L	37.7 ± 5.8	63	50.2 ± 10.2	56	<0.0001
	Bourdel-Marchasson et al. 2001 [211]	mg/L	15.1 ± 3.5	20	18.2 ± 3.6	23	<0.01
	Managialasche et al. 2012 [116]	μmol/mmol cholesterol	6.49 ± 1.54	168	7.80 ± 2.07	187	<0.0001
Vitamin A	Rinaldi et al. 2003 [145]	μmol/L	2.1 ± 0.4	63	2.6 ± 0.3	56	<0.001
	Bourdel-Marchasson et al. 2001 [211]	mg/L	0.54 ± 0.19	20	0.71 ± 0.24	23	<0.05
	Jiménez-Jiménez et al. 1999 [212]	μmol/L	1.60 ± 0.40	38	1.89 ± 0.53	42	<0.05
B-Carotene	Rinaldi et al. 2003 [145]	μmol/L	0.59 ± 0.28	63	0.57 ± 0.33	56	NS
	Jiménez-Jiménez et al. 1999 [212]	μmol/L	0.21 ± 0.14	38	0.32 ± 0.26	42	<0.05
Thiamine	Renvall et al. 1989 [210]	IU mL^{-1} h^{-1}	4.3 ± 1.6‖	15	3.9 ± 1.6‖	33	NS
	Renvall et al. 1989 [210]	IU min^{-1} g Hb^{-1}	1.5 ± 0.5¶	14	1.8 ± 0.4¶	28	NS
Vitamin D	Sato et al. 1998 [213]	ng/mL	7.1 ± 3.9	46	21.6 3.1	140	<0.0001
	Martyn et al. 1989 [214]	μg/L	11.5#	27	14.3#	34	<0.05
	Sato et al. 2005 [215]	ng/mL	9.2 ± 3.5	100	24.5 ± 6.0	100	<0.0001
	Evatt et al. 2008 [216]	ng/mL	34.8 ± 15.4	97	37.0 ± 14.5	99	NS
	Buell et al. 2010 [217]	ng/mL	16.9 ± 6.3	41	20.0 ± 8.2	211	<0.01
	Ferrier et al. 1990 [218]	nmol/L	32 ± 9	15	40 ± 25	15	NS
	Kipen et al. 1995 [219]	nmol/L	61 ± 33	20	90 ± 38	40	<0.05
Vitamin K_1	Sato et al. 2005 [215]	ng/mL	0.12 ± 0.11	100	0.24 ± 0.11	100	<0.0001
ω-3	Tully et al. 2003 [220]	g EPA/100 g fatty acid	0.98 ± 0.87	108	1.58 ± 0.62	45	<0.001
		g DHA/100 g fatty acid	0.56 ± 0.41	108	1.15 ± 0.88	45	<0.001

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; Hb, hemoglobin
* Geometric mean with interquartile range (all such values).
† Mean ± SD (all such values).
‡ Clinically diagnosed patients, for histologically confirmed cases (n = 76), mean serum folate decreases to 15.2 ± 9.5 ($P < 0.01$) and vitamin B_{12} to 215 ± 79 (<0.05).
§ Elderly patients with neurologic conditions other than dementia.
‖ Transketolase activity measured as μmol sedokeptolose-7-phosphate produced/mL blood/h.
¶ Transketolase activity measured as pentose-5-phosphate used/min/g Hb.
# Mean value.

The therapeutic effect of an 8-mo treatment with an antioxidant drink containing polyphenols and vitamins B and C for AD treatment was tested in an RCT enrolling 48 mild and moderate AD patients and 52 age-matched controls [159]. Daily consumption of the antioxidant and vitamin drink for a relatively short time led to a smaller increase in Hcy levels, compared with

the placebo group, not only in cognitively healthy individuals, but also in patients with moderate AD. These data are suggestive of the potency of such treatments to reduce AD risk in healthy individuals and in early stages of AD.

Because hippocampal atrophy is an established indicator for conversion from the normal aging process to developing MCI and dementia, one group [160] studied whether vitamin B supplementation, which lowers levels of total plasma Hcy, could slow the rate of brain atrophy in individuals with MCI. High-doses of folic acid and vitamins B_6 and B_{12} or placebo were given to participants with MCI ages $\geq$70 y for 24 mo and changes in the rate of atrophy of the whole brain were assessed by serial volumetric magnetic resonance imaging scans. The treatment response was related to baseline Hcy levels and a greater rate of atrophy was associated with lower final cognitive test scores. These results indicate that treatment with Hcy-lowering B vitamins slows brain atrophy and improves cognitive scores in older adults with MCI. Moreover, the mean total plasma Hcy was 30% lower in those treated with B vitamins relative to placebo. B vitamins also stabilized executive function relative to placebo during the treatment period as there were significant benefits of B vitamin treatment among participants with baseline Hcy above the median (11.3 mmol/L) in global cognition, episodic memory, and semantic memory [161].

These results were confirmed by another trial (N = 156) that demonstrated that B vitamin treatment reduced cerebral atrophy in gray matter (GM) regions specifically vulnerable to AD. In the placebo group, higher Hcy levels at baseline were associated with faster GM atrophy, which was largely prevented by B vitamin treatment [162]. A causal Bayesian network analysis indicated the following chain of events: B vitamins lower Hcy, which directly leads to a decrease in GM atrophy, thereby slowing cognitive decline. These results show that B vitamin supplementation can slow the atrophy of specific brain regions that are a key component of the AD process and that are associated with cognitive decline [162]. They also indicated that B vitamins slow cognitive and clinical decline in MCI patients, which is reflected by a reduced progression of age-related brain atrophy [161].

Plasma levels of antioxidant micronutrients, including vitamins E and C and β-carotene, are reduced in MCI and AD individuals when compared with age-matched controls. As oxidative damage appears early in the course of AD pathophysiology, increased intake of these micronutrients may reduce risk for AD [145]. A RCT showed that various tocopherol forms contribute to the vitamin E protective effects against AD [163]. These data suggest lower antioxidant defenses in various neurologic conditions (i.e., against lipid peroxidation). Most recently, a multicenter RCT treated 613 patients with mild to moderate AD with either 2000 IU/d of α-tocopherol (n = 152), 20 mg/d of memantine (n = 155), a combination of both (n = 154), or placebo (n = 152) [164]. The study showed that high-dose α-tocopherol supplementation in patients with mild to moderate AD (who were already receiving acetylcholinesterase inhibitors as a drug therapy) resulted in slower functional decline. The α-tocopherol–treated group exhibited a delay in clinical progression of 19% per year compared with placebo. These findings suggest benefit of (synthetic) α-tocopherol in mild to moderate AD by slowing functional decline and decreasing caregiver burden [164]. These are encouraging data for vitamin E because of the significant results obtained for the primary outcome and for the absence of severe adverse effects. These findings also confirmed those of an earlier RCT in individuals with moderate to severe AD. In that particular trial, AD progression, as determined by cognitive testing, was delayed in patients receiving 2000 IU/d of α-tocopherol both alone and in combination with selegiline (a selective monoamine oxidase inhibitor) [165].

Because PUFAs are enriched in the brain and are among the most oxygen-sensitive constituents of cells, it is conceivable that a reduction in the level of a potent antioxidant such as vitamin E has a strong effect on brain physiology and function.

Several clinical trials investigating the effects of (ω-3) PUFA supplementation in AD have been completed [166], and they provide evidence for the role of (ω-3) PUFAs, especially DHA, in improving brain health and cognitive function. A multicenter RCT was performed at 51 U.S. research sites and involved 402 patients with mild to moderate AD. Participants were randomly assigned to algal DHA at a dose of 2 g/d or to identical placebo supplementation for 18 mo. Cognitive scores and the rate of brain atrophy were not changed by the treatment in this cohort [167]. DHA, however, did increase cognitive performance in another RCT that tested mentally healthy individuals >55 y of age (n = 485) [168,169]. Supplementation of 900 mg/d algal DHA for 24 wk led to significantly fewer paired associative learning errors than placebo. Significant positive effects on verbal recognition memory and significant decreases in resting heart rate with DHA also were observed, indicating improved learning and episodic memory functions as well as cardiovascular benefits associated with normal aging [168]. The studies just cited confirmed previous data, obtained by smaller supplementation studies, comparing PUFA effects on cognitive and psychiatric symptoms in older people [170–173]. These RCTs provided evidence that PUFA supplementation consistently proved beneficial to improvement of cognitive abilities in individuals with MCI, whereas the effects on AD patients were not obvious [170,172]. In parallel, other RCTs showed that PUFA supplements improved depressive symptoms in individuals with MCI [173], whereas neuropsychiatric symptoms were not affected by a similar supplementation regimen in patients with AD [171]. It is also noteworthy that recent data showed that (ω-3) PUFA supplementation in MCI patients for 6 mo may attenuate telomere shortening occurring with age in erythrocytes [174].

Collectively, the data reveal a beneficial role for prophylactic DHA in preventing or ameliorating cognitive decline in healthy older adult populations, although its therapeutic effect for AD has not been demonstrated. Also, the benefits of DHA and lutein in unimpaired older women was explored in the context of a 4-mo RCT [175] revealing that verbal fluency scores improved significantly in the DHA, lutein, and combined treatment groups. Measures of mental processing speed, accuracy, and mood were not affected by supplementation [175]. Finally, the carotenoid β-carotene was tested to support cognitive function in adults. The Physicians' Health Study II showed that short β-carotene supplementation (50 mg, alternate days) had no effect on cognitive performance. In contrast, among 4052 participants with a mean treatment of 18 y, the global score and verbal memory were significantly higher in the treated group [176].

Discussion

Epidemiologic associations, mechanistic studies, and intervention trials in humans deliver mounting evidence for the importance of micronutrients in supporting cognitive performance. These mechanisms can be categorized into pathways modulating energy requirements of the brain, influencing cellular structure, integrity, and membrane properties, modifying receptor activity through changes in neurotransmitter release and signal transduction, and by altering Hcy metabolism.

AD is one of the most prevalent, severe, and disabling disorders that places a heavy burden on individuals and their families. Experiencing lack of curative effects of current pharmacologic therapies, it was suggested that the research must fundamentally rethink the way AD is treated, namely after the onset of clinical symptoms [24–26]. It is noted that the neuronal loss might be too advanced when the disease is clinically obvious and therefore a presymptomatic therapy is probably a promising way of preventing dementia. AD is best understood as a "dynamic and compensatory" disease that damages the brain depending mainly on the severity of the external aggression and on the structural reserve [76]. This model suggests that the clinical expression of the disease may vary widely over time, depending on individual vulnerability to the initial phases of the degenerative process, the severity of the AD pathologic process at the molecular and cellular levels, and the efficiency and evolution over time of compensatory brain mechanisms. Curative treatments are suggested by this model to be functional only if they are administrated long before the emergence of clinically overt symptoms, either to counterbalance the biological compromise that precedes the cognitive breakdown or to promote functional compensation [177]. Regardless of its exact molecular mechanisms, AD-type dementia may be viewed as a failure of these compensatory mechanisms in the course of progressive neurodegeneration. Researchers agree that AD decreases the number of synapses thereby impairing cognition leading ultimately to dementia [178]. Thus, they advocate strongly that treatment scenarios should not only concentrate on treating AD hallmarks, that is, decreasing amyloid or tau brain load, but also must preserve these natural compensatory mechanisms [76]. More importantly, it is suggested that Aβ deposition may be a consequence, rather than a causative factor, in disease pathogenesis [37,38,179], but this is still a matter of scientific debate.

Preclinical and clinical findings indicate that the benefits of micronutrients, including vitamins, on the aging brain exceed normalizing the vitamin deficiencies associated with aging conditions. As explained by triage theory [97] and substantiated by several intervention trials, high vitamin levels in the blood and tissue may slow cellular and chemical changes that may be responsible for the suboptimal functioning of the aged brain, ultimately resulting in neuronal loss and compromised cognition (Fig. 3). A balanced diet should cover the overall micronutrient requirements. Nonetheless, even in industrialized countries many segments of the population do not consume sufficient vitamins and minerals as they do not comply with dietary recommendations [50]. Moreover, needs may be elevated due to demanding life circumstances in which people with adequate intake may become insufficiently covered. Nutritional needs are known to be increased during periods of extensive physical exercise, growth, emotional and physiological stress, demanding cognitive tasks, the use of oral contraceptives, pregnancy and lactation, smoking, high alcohol consumption, prolonged therapy with antibiotics, older age, and restricted dietary intake due to disease or dieting for weight loss [89]. In such situations, people are particularly prone to develop vitamin deficiencies and require specific coverage with micronutrients including vitamins, minerals, and essential fatty acids.

It must be mentioned here that several factors may result in inconsistent findings in studies of micronutrient supplementation and cognitive performance in aged and AD individuals. A detailed assessments of the challenges in conducting human studies to investigate effects of (micro)nutrients was published recently [180]. An editorial article [181], however, seriously challenged the effectiveness of multivitamins to positively affect brain functions. As for the cognitive performance, it was cited that Grodstein et al. found no beneficial effects of multivitamins in their cohort of healthy male physicians [181]. These authors, however, provided the explanation that the doses consumed may be too low or the population may be too well nourished to benefit from multivitamin supplementation [182]. These data are remarkable because they hint to the difficulties of designing and interpreting RCTs using (micro)nutrients considering the fact that Grodstein et al. have already published in the same cohort of healthy physicians, the usefulness of β-carotene to improve cognitive performance [176]. Other explanations for inconsistent results may include the fact that as these supplements are nutritional products, they have modest effect sizes and cannot be expected to benefit all individuals equally because the effects may be modified by genetic background, lifestyle factors, and nutritional habits. Obviously, the outcome of supplementation studies also depend on the health status of the participants. Moreover, some work has been performed with poorly defined supplements, making it likely that the dose and bioavailability of such supplements were low or variable and thus unlikely to have clinical effects. Furthermore, statistically significant effects may be masked by various technical details, such as the types and routes of administration of the supplements or failure to systematically quantify and understand the pharmacokinetics and pharmacodynamics of a given supplement. Finally, the choice of appropriately sensitive, validated, and standardized test measures for measuring biomarkers and behavior, sufficient sample sizes for statistical power, and the duration of supplementation are all instrumental in establishing the effects of supplementation.

Some of the most promising data has been reported for B vitamins, vitamin E, and DHA supporting brain functions and improving memory for healthy older adults experiencing declines in cognitive function that occur naturally with age. Such decline is known to precede AD. Acknowledging these benefits, the EFSA approved health claims for these micronutrients such as "contributes to normal mental performance," "contributes to normal psychological functions," "contributes to normal homocysteine metabolism," and "contributes to the maintenance of normal brain function" to mention a few (efsa.europa.eu).

Conclusion

AD-type brain alterations increase with age in individuals without dementia. AD-like marker patterns are reported in cerebrospinal fluid of about one-third of cognitively unaffected older adults [4] or in their brains [78,79,82]. New therapeutics were put to the test in the last decade that target the production or accelerated removal of Aβ from AD brains with the hope to directly interfere with AD pathophysiology. Unfortunately, these therapeutic strategies delivered mixed results accompanied by lack of efficacy and severe side effects (53). In summary, continued and progressive cognitive decline in AD patients is inevitable with current therapies.

We summarized here the data showing that a large portion of the general population is inadequately supplied with various vitamins, even in industrialized countries. Notably, aged populations, especially those living in institutionalized settings, are at higher risk for receiving insufficient levels of essential micronutrients. Moreover, several vitamins and DHA are necessary for proper brain functioning, and their deficiencies negatively influence cognitive performance. Epidemiologic studies show that such insufficiencies are associated with age-related cognitive decline, the prodromal stage of AD, and to AD. Therefore, some experts argue that it is important to diagnose AD as early as

possible [166–168] to enable disease treatment before full-blown pathology affects the brain. Such efforts would open the possibility of prophylactic (nutritional) and drug therapies for AD [169].

In recent years we have witnessed many well-designed RCTs providing evidence that different dietary compounds could help to reduce risks for MCI and AD and to promote the maintenance of cognitive performance. Therefore, essential nutrients may have great potential in delaying the onset of AD if individuals have a lifelong optimal supply. The lack of an established therapy against AD, whose incidence is anticipated to increase further and rapidly in an aging society, and the established roles of a whole host of (micro)nutrients draw our attention toward optimizing the nutritional status of not only older adults but also the general population. Such efforts will sharpen our knowledge of preventive strategies and provide additional support to established therapeutic concepts as they become available.

Acknowledgments

The authors acknowledge N. Seifert for technical assistance and Dr. C. Butt for critically reading this manuscript.

References

[1] Lunenfeld B. An aging world–demographic characteristics and challenges. Gynecol Endocrinol 2008;24:1–3.
[2] Kinsella K, He W. An aging world: 2008 International population reports. Washington, DC: U.S. Department of Health and Human Services, National Institute of Health, National Institute of Aging; 2009.
[3] Sergi G, De Rui M, Coin A, Inelmen EM, Manzato E. Weight loss and Alzheimer's disease: temporal and aetiologic connections. Proc Nutr Soc 2013;72:160–5.
[4] Mattsson N, Rosen E, Hansson O, Andreasen N, Parnetti L, Jonsson M, et al. Age and diagnostic performance of Alzheimer disease CSF biomarkers. Neurology 2012;78:468–76.
[5] de Magalhães JP. http://www.senescence.info/aging_definition.html. 2013. Accessed November 1, 2013.
[6] Hayflick L. Biological aging is no longer an unsolved problem. Ann N Y Acad Sci 2007;1100:1–13.
[7] Carnes BA, Staats DO, Sonntag WE. Does senescence give rise to disease? Mech Ageing Dev 2008;129:693–9.
[8] Robert L, Labat-Robert J, Robert A. Genetic, epigenetic and post-translational mechanisms of aging. Biogerontol 2010;11:387–99.
[9] Johnson KA, Bernard MA, Funderburg K. Vitamin nutrition in older adults. Clin Geriatr Med 2002;18:773–99.
[10] De Castro JM, Stroebele N. Food intake in the real world: implications for nutrition and aging. Clin Geriatr Med 2002;18:685–97.
[11] Charlton KE. Eating well: ageing gracefully! Asia Pac J Clin Nutr 2002;11:S607–17.
[12] De Castro JM. Age-related changes in spontaneous food intake and hunger in humans. Appetite 1993;21:255–72.
[13] Russell RM, Rasmussen H. The impact of nutritional needs of older adults on recommended food intakes. Nutr Clin Care 1999;2:164–76.
[14] D'Souza AL. Ageing and the gut. Postgrad Med J 2007;83:44–53.
[15] Andrès E, Loukili NH, Noel E, Kaltenbach G, Abdelgheni MB, Perrin AE, et al. Vitamin B12 (cobalamin) deficiency in elderly patients. CMAJ 2004;171:251–9.
[16] Carmel R. Current concepts in Cobalamin deficiency. Annu Rev Med 2000;51:357–75.
[17] Hébuterne X. Gut changes attributed to ageing: effects on intestinal microflora. Curr Opin Clin Nutr Metab Care 2003;6:49–54.
[18] Farthing MJ. Diarrhoea: a significant worldwide problem. Int J Microb Agents 2000;14:65–9.
[19] Merkel IS, Locher J, Burgio K, Towers A, Wald A. Physiologic and psychological characteristics of an elderly population with chronic constipation. Am J Gastroenterol 1993;88:1854–9.
[20] Buffa R, Floris GU, Putzu PF, Marini E. Body composition variations in ageing. Coll Antropol 2011;35:259–65.
[21] Thies W, Bleiler L. Alzheimer's disease facts and figures. Alzheimers Dement 2011;7:208–44.
[22] Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. Alzheimer disease in the US population: prevalence estimates using the 2000 census. Arch Neurol 2003;60:1119–22.
[23] Lindsley CW. Alzheimer's disease: development of disease-modifying treatments is the challenge for our generation. ACS Chem Neurosci 2012;3:804–5.
[24] Vacca JP. Approaches toward new Alzheimer's treatments. ACS Med Chem Lett 2012;3:861.
[25] Mangialasche F, Solomon A, Winblad B, Mecocci P, Kivipelto M. Alzheimer's disease: clinical trials and drug development. Lancet Neurol 2010;9:702–16.
[26] Mohajeri MH. The underestimated potential of the immune system in prevention of Alzheimer's disease pathology. Bioessays 2007;29:927–32.
[27] Pimplikar SW, Nixon RA, Robakis NK, Shen J, Tsai LH. Amyloid-independent mechanisms in Alzheimer's disease pathogenesis. J Neurosci 2010;30:14946–54.
[28] Selkoe DJ. Resolving controversies on the path to Alzheimer's therapeutics. Nat Med 2011;17:1060–5.
[29] Ghosal K, Pimplikar SW. Aging and excitotoxic stress exacerbate neural circuit reorganization in amyloid precursor protein intracellular domain transgenic mice. Neurobiol Aging 2011;32:2320.e1–9.
[30] Irizarry MC, Soriano F, McNamara M, Page KJ, Schenk D, Games D, et al. Abeta deposition is associated with neuropil changes, but not with overt neuronal loss in the human amyloid precursor protein V717 F (PDAPP) transgenic mouse. J Neurosci 1997;17:7053–9.
[31] Bazan NG, Molina MF, Gordon WC. Docosahexaenoic acid signalolipidomics in nutrition: Significance in aging, neuroinflammation, macular degeneration, Alzheimer's, and other neurodegenerative diseases. Annu Rev Nutr 2011;31:321–51.
[32] Lichtlen P, Mohajeri MH. Antibody-based approaches in Alzheimer's research: safety, pharmacokinetics, metabolism, and analytical tools. J Neurochem 2008;104:859–74.
[33] Moyer MW. Alzheimer's researchers call for clinical revamp. Nat Med 2011;17:235.
[34] Fotuhi M, Mohassel P, Yaffe K. Fish consumption, long-chain omega-3 fatty acids and risk of cognitive decline or Alzheimer disease: a complex association. Nat Clin Pract Neurol 2009;5:140–52.
[35] Obrenovich ME, Li Y, Parvathaneni K, Yendluri BB, Palacios HH, Leszek J, et al. Antioxidants in health, disease and aging. CNS Neurol Disord Drug Targets 2011;10:192–207.
[36] O'Brien MM, Kiely M, Harrington KE, Robson PJ, Strain JJ, Flynn A. The North/South Ireland Food Consumption Survey: Vitamin intakes in 18 to 64-year-old adults. Public Health Nutr 2001;4:1069–79.
[37] Perry G, Nunomura A, Raina AK, Smith MA. Amyloid-beta junkies. Lancet 2000;355:757.
[38] Rottkamp CA, Atwood CS, Joseph JA, Nunomura A, Perry G, Smith MA. The state versus amyloid-beta: the trial of the most wanted criminal in Alzheimer disease. Peptides 2002;23:1333–41.
[39] Webber KM, Bowen R, Casadesus G, Perry G, Atwood CS, Smith MA. Gonadotropins and Alzheimer's disease: the link between estrogen replacement therapy and neuroprotection. Acta Neurobiol Exp (Wars) 2004;64:113–8.
[40] Furman JL, Sama DM, Gant JC, Beckett TL, Murphy MP, Bachstetter AD, et al. Targeting astrocytes ameliorates neurologic changes in a mouse model of Alzheimer's disease. J Neurosci 2012;32:16129–40.
[41] Casadesus G, Moreira PI, Nunomura A, Siedlak SL, Bligh-Glover W, Balraj E, et al. Indices of metabolic dysfunction and oxidative stress. Neurochem Res 2007;32:717–22.
[42] Perry G, Sayre LM, Atwood CS, Castellani RJ, Cash AD, Rottkamp CA, et al. The role of iron and copper in the aetiology of neurodegenerative disorders: therapeutic implications. CNS Drugs 2002;16:339–52.
[43] Perry G, Castellani RJ, Hirai K, Smith MA. Reactive oxygen species mediate cellular damage in Alzheimer disease. J Alzheimers Dis 1998;1:45–55.
[44] Pogocki D. Alzheimer's beta-amyloid peptide as a source of neurotoxic free radicals: the role of structural effects. Acta Neurobiol Exp (Wars) 2003;63:131–45.
[45] Avila J. Tau aggregation into fibrillar polymers: taupathies. FEBS Lett 2000;476:89–92.
[46] Burton TR, Dibrov A, Kashour T, Amara FM. Antiapoptotic wild-type Alzheimer amyloid precursor protein signaling involves the p38 mitogen-activated protein kinase/MEF2 pathway. Brain Res Mol Brain Res 2002;108:102–20.
[47] Drewes G, Lichtenberg-Kraag B, Doring F, Mandelkow EM, Biernat J, Goris J, et al. Mitogen activated protein (MAP) kinase transforms tau protein into an Alzheimer-like state. EMBO J 1992;11:2131–8.
[48] Trojanowski JQ, Clark CM, Arai H, Lee VM. Elevated levels of tau in cerebrospinal fluid: Implications for the antemortem diagnosis of Alzheimer's disease elevated levels of tau in cerebrospinal fluid: implications for the antemortem diagnosis of Alzheimer's disease. J Alzheimers Dis 1999;1:297–305.
[49] USDA's my plate- Daily Food Plan. http://www.choosemyplate.gov/myplate/index.aspx. Accessed February 3, 2013.
[50] Kant AK. Consumption of energy-dense, nutrient-poor foods by adult Americans: nutritional and health implications. The third National Health and Nutrition Examination Survey, 1988–1994. Am J Clin Nutr 2000;72:929–36.
[51] Deutsche Gesellschaft für Ernährung e. V. . Ernährung älterer Menschen in stationären Einrichtungen (ErnSTES-Studies). In: Ernährungsbericht 2008. Bonn: Deutsche Gesellschaft für Ernährung e. V; 2008. p. 157–204.
[52] Blumberg J. Nutritional needs of seniors. J Am Coll Nutr 1997;16:517–23.
[53] Hansen RG. An index of food quality. Nutr Rev 1973;31:1–7.
[54] Darmon N, Ferguson EL, Briend A. A cost constraint alone has adverse effects on food selection and nutrient density: an analysis of human diets by linear programming. J Nutr 2002;132:3764–71.

[55] NHANES 2003–2004. Data, documentation, codebooks, SAS code. Dietary interview. Individual foods, total nutrient intakes first and second day. Available at: http://www.cdc.gov/nchs/nhanes/nhanes2003–2004/diet03_04.html. Accessed October 1, 2010.
[56] NHANES 2005–2006. Data, documentation, codebooks, SAS code. Dietary interview. Individual foods, total nutrient intakes first and second day. Available at: http://www.cdc.gov/nchs/nhanes/nhanes2005–2006/diet05_06.html. Accessed October 1, 2010.
[57] NHANES 2007–2008. Data, documentation, codebooks, SAS code. Dietary interview. Individual foods, total nutrient intakes first and second day. Available at: http://www.cdc.gov/nchs/nhanes/nhanes2007–2008/diet07_08.html. Accessed October 1, 2010.
[58] Troesch B, Hoeft B, McBurney M, Eggersdorfer M, Weber P. Dietary surveys indicate vitamin intakes below recommendations are common in representative Western countries. Br J Nutr 2012;108:692–8.
[59] Max Rubner-Institut: Nationale Verzehrsstudie II. Ergebnisbericht Teil 2. Die bundesweite Befragung zur Ernährung von Jugendlichen und Erwachsenen. Karlsruhe 2008. Accessed at: http://www.was-esse-ich.de/uploads/media/NVSII_Abschlussbericht_Teil_2.pdf. Accessed February 7, 2011.
[60] Elmadfa I, Meyer A, Nowak V, Hasenegger V, Putz P, Verstraeten R, et al. European nutrition and health report 2009. Basel: Karger; 2009.
[61] Norman K, Pichard C, Lochs H, Pirlich M. Prognostic impact of disease-related malnutrition. Clin Nutr 2008;27:5–15.
[62] Ljungqvist O, de Man F. Under nutrition: a major health problem in Europe. Nutrición Hospitalaria 2009;24:369–70.
[63] Lenders CM, Deen DD, Bistrian B, Edwards MS, Seidner DL, McMahon MM, et al. Residency and specialties training in nutrition: a call for action. Am J Clin Nutr 2014;99:1174 S–83 S.
[64] Rock CL. Multivitamin-multimineral supplements: who uses them? The Am J Clin Nutr 2007;85:277 S–9 S.
[65] Fulgoni VL, Keast DR, Bailey RL, Dwyer J. Foods, fortificants, and supplements: where do Americans get their nutrients? J Nutr 2011;141:1847–54.
[66] Flynn A, Hirvonen T, Mensink GB, Ocke MC, Serra-Majem L, Stos K, et al. Intake of selected nutrients from foods, from fortification and from supplements in various European countries. Food Nutr Res 2009;53:1–51.
[67] Krasinski SD, Russell RM, Samloff IM, Jacob RA, Dallal GE, McGandy RB, et al. Fundic atrophic gastritis in an elderly population. Effect on hemoglobin and several serum nutritional indicators. J Am Geriatr Soc 1986;34:800–6.
[68] Lane L, Rojas-Fernandez C. Treatment of vitamin b(12)-deficiency anemia: oral versus parenteral therapy. Ann Pharmacoth 2002;36:1268–72.
[69] Bailey RL, Carmel R, Green R, Pfeiffer CM, Cogswell ME, Osterloh JD, et al. Monitoring of vitamin B-12 nutritional status in the United States by using plasma methylmalonic acid and serum vitamin B-12. Am J Clin Nutr 2011;94:552–61.
[70] Sahota O. Osteoporosis and the role of vitamin D and calcium-vitamin D deficiency, vitamin D insufficiency and vitamin D sufficiency. Age Ageing 2000;29:301–4.
[71] Sebastian RS, Cleveland LE, Goldman JD, Moshfegh AJ. Older adults who use vitamin/mineral supplements differ from nonusers in nutrient intake adequacy and dietary attitudes. J Am Diet Assoc 2007;107:1322–32.
[72] Raichle ME, Gusnard DA. Appraising the brain's energy budget. PNAS 2002;99:10237–9.
[73] Malinin NL, West XZ, Byzova TV. Oxidation as “the stress of life.” Aging (Albany NY) 2011;3:906–10.
[74] Lu T, Pan Y, Kao SY, Li C, Kohane I, Chan J, et al. Gene regulation and DNA damage in the ageing human brain. Nature 2004;429:883–91.
[75] Gustafson D. A life course of adiposity and dementia. Eur J Pharmacol 2008;585:163–75.
[76] Lazarczyk MJ, Hof PR, Bouras C, Giannakopoulos P. Preclinical Alzheimer disease: identification of cases at risk among cognitively intact older individuals. BMC Med 2012;10:127.
[77] Moreira PI, Nunomura A, Nakamura M, Takeda A, Shenk JC, Aliev G, et al. Nucleic acid oxidation in Alzheimer disease. Free Radic Biol Med 2008;44:1493–505.
[78 Shigenaga MK, Hagen TM, Ames BN. Oxidative damage and mitochondrial decay in aging. Proc Natl Acad Sci USA 1994;91:10771–8.
[79] Liu J, Killilea DW, Ames BN. Age-associated mitochondrial oxidative decay: Improvement of carnitine acetyltransferase substrate-binding affinity and activity in brain by feeding old rats acetyl-L-carnitine and/or R-alpha-lipoic acid. Proc Natl Acad Sci USA 2002;99:1876–81.
[80] Moreira PI, Siedlak SL, Wang X, Santos MS, Oliveira CR, Tabaton M, et al. Increased autophagic degradation of mitochondria in Alzheimer disease. Autophagy 2007;3:614–5.
[81] Venkateshappa C, Harish G, Mahadevan A, Srinivas Bharath MM, Shankar SK. Elevated oxidative stress and decreased antioxidant function in the human hippocampus and frontal cortex with increasing age: implications for neurodegeneration in Alzheimer's disease. Neurochem Res 2012;37:601–14.
[82] Klunk WE. Amyloid imaging as a biomarker for cerebral beta-amyloidosis and risk prediction for Alzheimer dementia. Neurobiol Aging 2011;32(Suppl 1):S20–36.
[83] Hedden T, Mormino EC, Amariglio RE, Younger AP, Schultz AP, Becker JA, et al. Cognitive profile of amyloid burden and white matter hyperintensities in cognitively normal older adults. J Neurosci 2012;32:16233–42.
[84] Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. Cold Spring Harb Perspect Med 2011;1:a006189.
[85] Hedden T, Van Dijk KR, Shire EH, Sperling RA, Johnson KA, Buckner RL. Failure to modulate attentional control in advanced aging linked to white matter pathology. Cereb Cortex 2012;22:1038–51.
[86] Reiman EM, Quiroz YT, Fleisher AS, Chen K, Velez-Pardo C, Jimenez-Del-Rio M, et al. Brain imaging and fluid biomarker analysis in young adults at genetic risk for autosomal dominant Alzheimer's disease in the presenilin 1 E280 A kindred: a case-control study. Lancet Neurol 2012;11:1048–56.
[87] Coley N, Andrieu S, Gardette V, Gillette-Guyonnet S, Sanz C, Vellas B, et al. Dementia prevention: methodological explanations for inconsistent results. Epidemiol Rev 2008;30:35–66.
[88] Mangialasche F, Kivipelto M, Mecocci P, Rizzuto D, Palmer K, Winblad B, et al. High plasma levels of vitamin E forms and reduced Alzheimer's disease risk in advanced age. J Alzheimers Dis 2010;20:1029–37.
[89] Huskisson E, Maggini S, Ruf M. The role of vitamins and minerals in energy metabolism and well-being. J Int Med Res 2007;35:277–89.
[90] Huskisson E, Maggini S, Ruf M. The influence of micronutrients on cognitive function and performance. J Int Med Res 2007;35:1–19.
[91] Zhuo JM, Wang H, Pratico D. Is hyperhomocysteinemia an Alzheimer's disease (AD) risk factor, an AD marker, or neither? Trends Pharmacol Sci 2011;32:562–71.
[92] Refsum H, Nurk E, Smith AD, Ueland PM, Gjesdal CG, Bjelland I, et al. The Hordaland Homocysteine Study: a community-based study of homocysteine, its determinants, and associations with disease. J Nutr 2006;136:1731S–40S.
[93] Ellinson M, Thomas J, Patterson A. A critical evaluation of the relationship between serum vitamin B, folate and total homocysteine with cognitive impairment in the elderly. J Hum Nutr Diet 2004;17:371–83.
[94] Adunsky A, Arinzon Z, Fidelman Z, Krasniansky I, Arad M, Gepstein R. Plasma homocysteine levels and cognitive status in long-term stay geriatric patients: a cross-sectional study. Arch Gerontol Geriatr 2005;40:129–38.
[95] Tucker KL, Qiao N, Scott T, Rosenberg I, Spiro A 3rd. High homocysteine and low B vitamins predict cognitive decline in aging men: the Veterans Affairs Normative Aging Study. Am J Clin Nutr 2005;82:627–35.
[96] Pietrzik K. Concept of borderline vitamin deficiencies. Int J Vitam Nutr Res Suppl 1985;27:61–73.
[97] Ames BN. Low micronutrient intake may accelerate the degenerative diseases of aging through allocation of scarce micronutrients by triage. Proc Natl Acad Sci U S A 2006;103:17589–94.
[98] Spinazzi M, Angelini C, Patrini C. Subacute sensory ataxia and optic neuropathy with thiamine deficiency. Nat Rev Neurol 2010;6:288–93.
[99] Prakash R, Gandotra S, Singh LK, Das B, Lakra A. Rapid resolution of delusional parasitosis in pellagra with niacin augmentation therapy. Gen Hosp Psychiatry 2008;30:581–4.
[100] Plecko B, Stockler S. Vitamin B6 dependent seizures. Can J Neurol Sci 2009;36(Suppl 2):S73–7.
[101] Chome J, Paul T, Pudel V, Bleyl H, Heseker H, Huppe R, et al. Effects of suboptimal vitamin status on behavior. Bibl Nutr Dieta; 1986:94–103.
[102] Midttun O, Hustad S, Schneede J, Vollset SE, Ueland PM. Plasma vitamin B-6 forms and their relation to transsulfuration metabolites in a large, population-based study. Am J Clin Nutr 2007;86:131–8.
[103] Kaufman S. Dopamine-beta-hydroxylase. J Psychiatr Res 1974;11:303–16.
[104] Levine M, Dhariwal KR, Washko P, Welch R, Wang YH, Cantilena CC, et al. Ascorbic acid and reaction kinetics in situ: a new approach to vitamin requirements. J Nutr Sci Vitaminol (Tokyo) 1992;Spec No:169–72.
[105] Padayatty SJ, Katz A, Wang Y, Eck P, Kwon O, Lee JH, et al. Vitamin C as an antioxidant: evaluation of its role in disease prevention. J Am Coll Nutr 2003;22:18–35.
[106] Wang X, Quinn PJ. Vitamin E and its function in membranes. Prog Lipid Res 1999;38:309–36.
[107] Muller DP. Vitamin E and neurologic function. Mol Nutr Food Res 2010;54:710–8.
[108] Brigelius-Flohe R, Traber MG. Vitamin E: function and metabolism. FASEB J 1999;13:1145–55.
[109] Azzi A, Gysin R, Kempna P, Ricciarelli R, Villacorta L, Visarius T, et al. The role of alpha-tocopherol in preventing disease: from epidemiology to molecular events. Mol Aspects Med 2003;24:325–36.
[110] Azzi A, Stocker A. Vitamin E: non-antioxidant roles. Prog Lipid Res 2000;39:231–55.
[111] Devaraj S, Hugou I, Jialal I. Alpha-tocopherol decreases CD36 expression in human monocyte-derived macrophages. J Lipid Res 2001;42:521–7.
[112] Villacorta L, Graca-Souza AV, Ricciarelli R, Zingg JM, Azzi A. Alpha-tocopherol induces expression of connective tissue growth factor and antagonizes tumor necrosis factor-alpha-mediated downregulation in human smooth muscle cells. Circ Res 2003;92:104–10.
[113] Schneider C. Chemistry and biology of vitamin E. Mol Nutr Food Res 2005;49:7–30.

[114] Cellini E, Piacentini S, Nacmias B, Forleo P, Tedde A, Bagnoli S, et al. A family with spinocerebellar ataxia type 8 expansion and vitamin E deficiency ataxia. Arch Neurol 2002;59:1952–3.
[115] Doerflinger N, Linder C, Ouahchi K, Gyapay G, Weissenbach J, Le Paslier D, et al. Ataxia with vitamin E deficiency: Refinement of genetic localization and analysis of linkage disequilibrium by using new markers in 14 families. Am J Hum Genet 1995;56:1116–24.
[116] Mangialasche F, Xu W, Kivipelto M, Costanzi E, Ercolani S, Pigliautile M, et al. Tocopherols and tocotrienols plasma levels are associated with cognitive impairment. Neurobiol Aging 2012;33:2282–90.
[117] Ravaglia G, Forti P, Lucicesare A, Pisacane N, Rietti E, Mangialasche F, et al. Plasma tocopherols and risk of cognitive impairment in an elderly Italian cohort. Am J Clin Nutr 2008;87:1306–13.
[118] Lansdowne AT, Provost SC. Vitamin D3 enhances mood in healthy subjects during winter. Psychopharmacology (Berl) 1998;135:319–23.
[119] Buell JS, Dawson-Hughes B. Vitamin D and neurocognitive dysfunction: preventing "D"ecline? Mol Aspects Med 2008;29:415–22.
[120] Annweiler C, Llewellyn DJ, Beauchet O. Low serum vitamin D concentrations in Alzheimer's disease: a systematic review and meta-analysis. J Alzheimers Dis 2013;33:659–74.
[121] Annweiler C, Rolland Y, Schott AM, Blain H, Vellas B, Beauchet O. Serum vitamin D deficiency as a predictor of incident non-Alzheimer dementias: a 7-year longitudinal study. Dement Geriatr Cogn Disord 2011;32:273–8.
[122] Annweiler C, Rolland Y, Schott AM, Blain H, Vellas B, Herrmann FR, et al. Higher vitamin D dietary intake is associated with lower risk of alzheimer's disease: a 7-year follow-up. J Gerontol A Biol Sci Med Sci 2012;67:1205–11.
[123] Nimitphong H, Holick MF. Vitamin D, neurocognitive functioning and immunocompetence. Curr Opin Clin Nutr Metab Care 2010;14:7–14.
[124] Mohajeri MH, Winwwod RJ. The role of DHA in cognitive performance of children. AgroFOOD industry hi-tech 2012;23:22–4.
[125] Jicha GA, Markesbery WR. Omega-3 fatty acids: potential role in the management of early Alzheimer's disease. Clin Interv Aging 2010;5:45–61.
[126] Ramesh BN, Rao TS, Prakasam A, Sambamurti K, Rao KS. Neuronutrition and Alzheimer's disease. J Alzheimers Dis 2010;19:1123–39.
[127] Gemma C, Bachstetter AD, Bickford PC. Neuron-microglia dialogue and hippocampal neurogenesis in the aged brain. Aging Dis 2010;1:232–44.
[128] Yaffe K, Lindquist K, Schwartz AV, Vitartas C, Vittinghoff E, Satterfield S, et al. Advanced glycation end product level, diabetes, and accelerated cognitive aging. Neurology 2011;77:1351–6.
[129] Benton D. Neurodevelopment and neurodegeneration: are there critical stages for nutritional intervention? Nutr Rev 2010;68(Suppl 1):S6–10.
[130] Gray SL, Hanlon JT, Landerman LR, Artz M, Schmader KE, Fillenbaum GG. Is antioxidant use protective of cognitive function in the community-dwelling elderly? Am J Geriatr Pharmacother 2003;1:3–10.
[131] Meertens L, Solano L. Vitamin B12, folic acid and mental function in the elderly. Invest Clin 2005;46:53–63.
[132] Calvaresi E, Bryan J. B vitamins, cognition, and aging: a review. J Gerontol B Psychol Sci Soc Sci 2001;56:P327–39.
[133] Ortega RM, Requejo AM, Andres P, Lopez-Sobaler AM, Quintas ME, Redondo MR, et al. Dietary intake and cognitive function in a group of elderly people. Am J Clin Nutr 1997;66:803–9.
[134] Annweiler C, Allali G, Allain P, Bridenbaugh S, Schott AM, Kressig RW, et al. Vitamin D and cognitive performance in adults: a systematic review. Eur J Neurol 2009;16:1083–9.
[135] Nelson C, Wengreen HJ, Munger RG, Corcoran CD. Dietary folate, vitamin B-12, vitamin B-6 and incident Alzheimer's disease: the cache county memory, health and aging study. J Nutr Health Aging 2009;13:899–905.
[136] Luchsinger JA, Tang MX, Miller J, Green R, Mayeux R. Relation of higher folate intake to lower risk of Alzheimer disease in the elderly. Arch Neurol 2007;64:86–92.
[137] Corrada MM, Kawas CH, Hallfrisch J, Muller D, Brookmeyer R. Reduced risk of Alzheimer's disease with high folate intake: the Baltimore Longitudinal Study of Aging. Alzheimers Dement 2005;1:11–8.
[138] Rosenberg IH, Miller JW. Nutritional factors in physical and cognitive functions of elderly people. Am J Clin Nutr 1992;55:1237 S–43 S.
[139] Institute of Medicine. Dietary reference intakes for calcium and vitamin D. Washington DC: The National Academies Press; 2011.
[140] Institute of Medicine. Dietary reference intakes for vitamin C, vitamin E, selenium and varotenoids. Washington DC: The National Academies Press; 2000.
[141] Institute of Medicine. Dietary reference intakes for thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin and cholin. Washington DC: The National Academies Press; 1998.
[142] Faux NG, Ellis KA, Porter L, Fowler CJ, Laws SM, Martins RN, et al. Homocysteine, vitamin B12, and folic acid levels in Alzheimer's disease, mild cognitive impairment, and healthy elderly: baseline characteristics in subjects of the Australian Imaging Biomarker Lifestyle study. J Alzheimers Dis 2011;27:909–22.
[143] Park S, Johnson MA. What is an adequate dose of oral vitamin B12 in older people with poor vitamin B12 status? Nutr Rev 2006;64:373–8.
[144] Harrison FE. A critical review of vitamin C for the prevention of age-related cognitive decline and Alzheimer's disease. J Alzheimers Dis 2012;29:711–26.
[145] Rinaldi P, Polidori MC, Metastasio A, Mariani E, Mattioli P, Cherubini A, et al. Plasma antioxidants are similarly depleted in mild cognitive impairment and in Alzheimer's disease. Neurobiol Aging 2003;24:915–9.
[146] Li FJ, Shen L, Ji HF. Dietary intakes of vitamin E, vitamin C, and beta-carotene and risk of Alzheimer's disease: a meta-analysis. J Alzheimers Dis 2012;31:253–8.
[147] Polidori MC, Pratico D, Mangialasche F, Mariani E, Aust O, Anlasik T, et al. High fruit and vegetable intake is positively correlated with antioxidant status and cognitive performance in healthy subjects. J Alzheimers Dis 2009;17:921–7.
[148] Morris MC, Evans DA, Bienias JL, Tangney CC, Wilson RS. Vitamin E and cognitive decline in older persons. Arch Neurol 2002;59:1125–32.
[149] Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Aggarwal N, et al. Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. JAMA 2002;287:3230–7.
[150] Xu Q, Parks CG, DeRoo LA, Cawthon RM, Sandler DP, Chen H. Multivitamin use and telomere length in women. Am J Clin Nutr 2009;89:1857–63.
[151] Hemila H, Kaprio J. Vitamin E may affect the life expectancy of men, depending on dietary vitamin C intake and smoking. Age Ageing 2011;40:215–20.
[152] Klapcinska B, Derejczyk J, Wieczorowska-Tobis K, Sobczak A, Sadowska-Krepa E, Danch A. Antioxidant defense in centenarians (a preliminary study). Acta Biochim Pol 2000;47:281–92.
[153] Muldoon MF, Ryan CM, Sheu L, Yao JK, Conklin SM, Manuck SB. Serum phospholipid docosahexaenonic acid is associated with cognitive functioning during middle adulthood. J Nutr 2010;140:848–53.
[154] Wurtman RJ, Cansev M, Sakamoto T, Ulus I. Nutritional modifiers of aging brain function: Use of uridine and other phosphatide precursors to increase formation of brain synapses. Nutr Rev 2010;68(Suppl 2):S88–101.
[155] Grima NA, Pase MP, Macpherson H, Pipingas A. The effects of multivitamins on cognitive performance: a systematic review and meta-analysis. J Alzheimers Dis 2012;29:561–9.
[156] Durga J, Verhoef P, Anteunis LJ, Schouten E, Kok FJ. Effects of folic acid supplementation on hearing in older adults: a randomized, controlled trial. Ann Intern Med 2007;146:1–9.
[157] Aisen PS, Schneider LS, Sano M, Diaz-Arrastia R, van Dyck CH, Weiner MF, et al. High-dose B vitamin supplementation and cognitive decline in Alzheimer disease: a randomized controlled trial. JAMA 2008;300:1774–83.
[158] Nilsson K, Gustafson L, Hultberg B. Plasma homocysteine, cobalamin/folate status, and vascular disease in a large population of psychogeriatric patients. Dement Geriatr Cogn Disord 2006;22:358–66.
[159] Morillas-Ruiz JM, Rubio-Perez JM, Albaladejo MD, Zafrilla P, Parra S, Vidal-Guevara ML. Effect of an antioxidant drink on homocysteine levels in Alzheimer's patients. J Neurol Sci 2010;299:175–8.
[160] Smith AD, Smith SM, de Jager CA, Whitbread P, Johnston C, Agacinski G, et al. Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: a randomized controlled trial. PLoS One 2010;5:e12244.
[161] de Jager CA, Oulhaj A, Jacoby R, Refsum H, Smith AD. Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: a randomized controlled trial. Int J Geriatr Psychiatry 2012;27:592–600.
[162] Douaud G, Refsum H, de Jager CA, Jacoby R, Nichols TE, Smith SM, et al. Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment. Proc Natl Acad Sci U S A 2013;110:9523–8.
[163] Morris MC, Evans DA, Tangney CC, Bienias JL, Wilson RS, Aggarwal NT, et al. Relation of the tocopherol forms to incident Alzheimer disease and to cognitive change. Am J Clin Nutr 2005;81:508–14.
[164] Dysken MW, Sano M, Asthana S, Vertrees JE, Pallaki M, Llorente M, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA cooperative randomized trial. JAMA 2014;311:33–44.
[165] Sano M, Ernesto C, Thomas RG, Klauber MR, Schafer K, Grundman M, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. the Alzheimer's Disease Cooperative Study. N Engl J Med 1997;336:1216–22.
[166] Kidd PM. Alzheimer's disease, amnestic mild cognitive impairment, and age-associated memory impairment: current understanding and progress toward integrative prevention. Altern Med Rev 2008;13:85–115.
[167] Quinn JF, Raman R, Thomas RG, Yurko-Mauro K, Nelson EB, Van Dyck C, et al. Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: a randomized trial. JAMA 2010;304:1903–11.
[168] Yurko-Mauro K. Cognitive and cardiovascular benefits of docosahexaenoic acid in aging and cognitive decline. Curr Alzheimer Res 2010;7:190–6.
[169] Yurko-Mauro K, McCarthy D, Rom D, Nelson EB, Ryan AS, Blackwell A, et al. Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline. Alzheimers Dement 2010;6:456–64.
[170] Chiu CC, Su KP, Cheng TC, Liu HC, Chang CJ, Dewey ME, et al. The effects of omega-3 fatty acids monotherapy in Alzheimer's disease and mild cognitive impairment: a preliminary randomized double-blind placebo-controlled study. Prog Neuropsychopharmacol Biol Psychiatry 2008;32:1538–44.

[171] Freund-Levi Y, Basun H, Cederholm T, Faxen-Irving G, Garlind A, Grut M, et al. Omega-3 supplementation in mild to moderate Alzheimer's disease: effects on neuropsychiatric symptoms. Int J Geriatr Psychiatry 2008;23:161–9.
[172] Kotani S, Sakaguchi E, Warashina S, Matsukawa N, Ishikura Y, Kiso Y, et al. Dietary supplementation of arachidonic and docosahexaenoic acids improves cognitive dysfunction. Neurosci Res 2006;56:159–64.
[173] Sinn N, Milte CM, Street SJ, Buckley JD, Coates AM, Petkov J, et al. Effects of n-3 fatty acids, EPA v. DHA, on depressive symptoms, quality of life, memory and executive function in older adults with mild cognitive impairment: a 6-mo randomised controlled trial. Br J Nutr 2012;107:1682–93.
[174] O'Callaghan N, Parletta N, Milte CM, Benassi-Evans B, Fenech M, Howe PR. Telomere shortening in elderly people with mild cognitive impairment may be attenuated with omega-3 fatty acid supplementation: a randomised controlled pilot study. Nutrition 2014;30:489–91.
[175] Johnson EJ, McDonald K, Caldarella SM, Chung HY, Troen AM, Snodderly DM. Cognitive findings of an exploratory trial of docosahexaenoic acid and lutein supplementation in older women. Nutr Neurosci 2008;11:75–83.
[176] Grodstein F, Kang JH, Glynn RJ, Cook NR, Gaziano JM. A randomized trial of beta carotene supplementation and cognitive function in men: the Physicians' Health Study II. Arch Intern Med 2007;167:2184–90.
[177] Golde TE, Schneider LS, Koo EH. Antiabeta therapeutics in Alzheimer's disease: the need for a paradigm shift. Neuron 2011;69:203–13.
[178] Koffie RM, Hyman BT, Spires-Jones TL. Alzheimer's disease: synapses gone cold. Mol Neurodegener 2011;6:1–9.
[179] Obrenovich ME, Joseph JA, Atwood CS, Perry G, Smith MA. Amyloid-beta: a (life) preserver for the brain. Neurobiol Aging 2002;23:1097–9.
[180] Moser U. Vitamins—wrong approaches. Int J Vitam Nutr Res 2012;82:327–32.
[181] Guallar E, Stranges S, Mulrow C, Appel LJ, Miller ER 3rd. Enough is enough: stop wasting money on vitamin and mineral supplements. Ann Intern Med 2013;159:850–1.
[182] Grodstein F, O'Brien J, Kang JH, Dushkes R, Cook NR, Okereke O, et al. Long-term multivitamin supplementation and cognitive function in men: a randomized trial. Ann Intern Med 2013;159:806–14.
[183] Institute of Medicine. Dietary reference intakes of vitamin C, vitamin E, selenium, and carotenoids. Washington, DC: National Academic Press; 2000.
[184] Institute of Medicine. Dietary reference intakes of vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington, DC: National Academic Press; 2001.
[185] Deutsche Gesellschaft für Ernährung, Österreichische Gesellschaft für Ernährung, Schweizerische Gesellschaft für Ernährung, Schweizerische Vereinigung für Ernährung: Referenzwerte für die Nährstoffzufuhr. Frankfurt/Main: Umschau Verlag; 2008.
[186] Referenzwerte für die Nährstoffzufuhr- Vitamin D (Calciferole) Available at: http://www.dge.de/modules.php?name=Content&pa=showpage&pid=4&page=12. Accessed October 1, 2010.
[187] Joosten E, Lesaffre E, Riezler R, Ghekiere V, Dereymaeker L, Pelemans W, et al. Is metabolic evidence for vitamin B-12 and folate deficiency more frequent in elderly patients with Alzheimer's disease? J Gerontol A Biol Sci Med Sci 1997;52:M76–9.
[188] Clarke R, Smith AD, Jobst KA, Refsum H, Sutton L, Ueland PM. Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease. Arch Neur 1998;55:1449–55.
[189] Fekkes D, Van Der Cammen TJM, Van Loon CPM, Verschoor C, Van Harskamp F, De Koning I, et al. Abnormal amino acid metabolism in patients with early stage Alzheimer dementia. J Neural Transm 1998;105:287–94.
[190] Leblhuber F, Walli J, Artner-Dworzak E, Vrecko K, Widner B, Reibnegger G, et al. Hyperhomocysteinemia in dementia. J Neural Transm 2000;107:1469–74.
[191] Postiglione A, Milan G, Ruocco A, Gallotta G, Guiotto G, Di Minno G. Plasma folate, vitamin B12, and total homocysteine and homozygosity for the C677 T mutation of the 5,10-methylene tetrahydrofolate reductase gene in patients with Alzheimer's dementia: a case-control study. Gerontology 2001;47:324–9.
[192] Hogervorst E, Ribeiro HM, Molyneux A, Budge M. David Smith A. Plasma homocysteine levels, cerebrovascular risk factors, and cerebral white matter changes (leukoaraiosis) in patients with Alzheimer disease. Arch Neur 2002;59:787–93.
[193] McIlroy SP, Dynan KB, Lawson JT, Patterson CC, Passmore AP. Moderately elevated plasma homocysteine, methylenetetrahydrofolate reductase genotype, and risk for stroke, vascular dementia, and Alzheimer disease in northern Ireland. Stroke 2002;33:2351–6.
[194] Mizrahi EH, Jacobsen DW, Debanne SM, Traore F, Lerner AJ, Friedland RP, et al. Plasma total homocysteine levels, dietary vitamin B6 and folate intake in AD and healthy aging. J Nutr Health Aging 2003;7:160–5.
[195] Religa D, Styczynska M, Peplonska B, Gabryelewicz T, Pfeffer A, Chodakowska M, et al. Homocysteine, apolipoproteine E and methylenetetrahydrofolate reductase in Alzheimer's disease and mild cognitive impairment. Dement Geriatr Cogn Dis 2003;16:64–70.
[196] Gallucci M, Zanardo A, De Valentin L, Vianello A. Homocysteine in Alzheimer disease and vascular dementia. Arch Gerontol Geriatr 2004;38:195–200.
[197] Malaguarnera M, Ferri R, Bella R, Alagona G, Carnemolla A, Pennisi G. Homocysteine, vitamin B12 and folate in vascular dementia and in Alzheimer disease. Clin Chem Lab Med 2004;42:1032–5.
[198] Mizrahi EH, Bowirrat A, Jacobsen DW, Korczyn AD, Traore F, Petot GJ, et al. Plasma homocysteine, vitamin B12 and folate in Alzheimer's patients and healthy Arabs in Israel. J Neurol Sci 2004;227:109–13.
[199] Nilsson K, Gustafson L, Hultberg B. Plasma homocysteine concentration relates to the severity but not to the duration of Alzheimer's disease. Int J Geriatr Psychiatry 2004;19:666–72.
[200] Quadri P, Fragiacomo C, Pezzati R, Zanda E, Forloni G, Tettamanti M, et al. Homocysteine, folate, and vitamin B-12 in mild cognitive impairment, Alzheimer disease, and vascular dementia. Am J Clin Nutr 2004;80:114–22.
[201] de Silva HA, Gunatilake SB, Johnston C, Warden D, Smith AD. Medial temporal lobe atrophy, apolipoprotein genotype, and plasma homocysteine in Sri Lankan patients with Alzheimer's disease. Exp Aging Res 2005;31:345–54.
[202] Da Silva VC, Ramos FJ, Freitas EM, De Brito-Marques PR, Cavalcanti MN, D'Almeida V, et al. Alzheimer's disease in Brazilian elderly has a relation with homocysteine but not with MTHFR polymorphisms. Arq Neuropsiquiatr 2006;64:941–5.
[203] Bottiglieri T, Parnetti L, Arning E, Ortiz T, Amici S, Lanari A, et al. Plasma total homocysteine levels and the C677 T mutation in the methylenetetrahydrofolate reductase (MTHFR) gene: a study in an Italian population with dementia. Mech Ageing Dev 2001;122:2013–23.
[204] Nägga K, Rajani R, Mardh E, Borch K, Mardh S, Marcusson J. Cobalamin, folate, methylmalonic acid, homocysteine, and gastritis markers in dementia. Dement Geriatr Cogn Disord 2003;16:269–75.
[205] Köseoglu E, Karaman Y. Relations between homocysteine, folate and vitamin B12 in vascular dementia and in Alzheimer disease. Clin Biochem 2007;40:859–63.
[206] Storey SG, Suryadevara V, Aronow WS, Ahn C. Association of plasma homocysteine in elderly persons with atherosclerotic vascular disease and dementia, atherosclerotic vascular disease without dementia, dementia without atherosclerotic vascular disease, and no dementia or atherosclerotic vascular disease. J Gerontol A Biol Sci Med Sci 2003;58:M1135–6.
[207] Folin M, Baiguera S, Gallucci M, Conconi M, Liddo R, Zanardo A, et al. A Cross-sectional study of nomocysteine-, NO-levels, and CT-findings in Alzheimer dementia, vascular dementia and controls. Biogerontology 2005;6:255–60.
[208] Quadri P, Fragiacomo C, Pezzati R, Zanda E, Tettamanti M, Lucca U. Homocysteine and B vitamins in mild cognitive impairment and dementia. Clin Chem Lab Med 2005;43:1096–100.
[209] Miller JW, Green R, Mungas DM, Reed BR, Jagust WJ. Homocysteine, vitamin B6, and vascular disease in AD patients. Neurology 2002;58:1471–5.
[210] Renvall MJ, Spindler AA, Ramsdell JW, Paskvan M. Nutritional status of free-living Alzheimer's patients. Am J Med Sci 1989;298:20–7.
[211] BourdelMarchasson I, Delmas-Beauvieux MC, Peuchant E, Richard-Harston S, Decamps A, Reignier B, et al. Antioxidant defences and oxidative stress markers in erythrocytes and plasma from normally nourished elderly Alzheimer patients. Age Ageing 2001;30:235–41.
[212] Jiménez-Jiménez FJ, Molina JA, de Bustos F, Ortí-Pareja M, Benito-León J, Tallón-Barranco A, et al. Serum levels of β-carotene, α-carotene and vitamin A in patients with Alzheimer's disease. Eur J Neurol 1999;6:495–7.
[213] Sato Y, Asoh T, Oizumi K. High prevalence of vitamin D deficiency and reduced bone mass in elderly women with Alzheimer's disease. Bone 1998;23:555–7.
[214] Martyn CN, Singh S, Wood PJ. Calcium metabolism in Alzheimer's disease. Gerontology 1989;35:153–7.
[215] Sato Y, Kanoko T, Satoh K, Iwamoto J. Menatetrenone and vitamin D2 with calcium supplements prevent nonvertebral fracture in elderly women with Alzheimer's disease. Bone 2005;36:61–8.
[216] Evatt ML, Delong MR, Khazai N, Rosen A, Triche S, Tangpricha V. Prevalence of vitamin d insufficiency in patients with Parkinson disease and Alzheimer disease. Arch Neurol 2008;65:1348–52.
[217] Buell JS, Dawson-Hughes B, Scott TM, Weiner DE, Dallal GE, Qui WQ, et al. 25-Hydroxyvitamin D, dementia, and cerebrovascular pathology in elders receiving home services. Neurology 2010;74:18–26.
[218] Ferrier IN, Leake A, Taylor GA, McKeith IG, Fairbrairn AF, Robinson CJ, et al. Reduced gastrointestinal absorption of calcium in dementia. Age Ageing 1990;19:368–75.
[219] Kipen E, Helme RD, Wark JD, Flicker L. Bone density, vitamin D nutrition, and parathyroid hormone levels in women with dementia. J Am Geriatr Soc 1995;43:1088–91.
[220] Tully AM, Roche HM, Doyle R, Fallon C, Bruce I, Lawlor B, et al. Low serum cholesteryl ester-docosahexaenoic acid levels in Alzheimer's disease: a case-control study. Br J Nutr 2003;89:483–9.