Review

Nutritional approaches in the risk reduction and management of Alzheimer's disease

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ARTICLE INFO

ABSTRACT

Alzheimer's disease (AD) is a heterogeneous and devastating neurodegenerative disease with increasing socioeconomic burden for society. In the past 30 y, notwithstanding advances in the understanding of the pathogenesis of the disease and consequent development of therapeutic approaches to novel pathogenic targets, no cure has so far emerged.

This contribution focuses on recent nutritional approaches in the risk reduction and management of AD with emphasis on factors providing a rationale for nutritional approaches in AD, including compromised nutritional status, altered nutrient uptake and metabolism, and nutrient requirements for synapse formation. Collectively these factors are believed to result in specific nutritional requirement in AD. The chapter also emphasizes investigated nutritional interventions in patients with AD, including studies with single nutrients and with the specific nutrient combination Fortasyn Connect and discusses the current shift of paradigm to intervene in earlier stages of AD, which offers opportunities for investigating nutritional strategies to reduce the risk for disease progression.

Fortasyn Connect was designed to enhance synapse formation and function in AD by addressing the putative specific nutritional requirements and contains docosahexaenoic acid, eicosapentaenoic acid, uridine-5'-mono-phosphate, choline, phospholipids, antioxidants, and B vitamins. Two randomized controlled trials (RCTs) with the medical food Souvenaid, containing Fortasyn Connect, showed that this intervention improved memory performance in mild, drug-naïve patients with AD. Electroencephalography outcome in one of these clinical studies suggests that Souvenaid has an effect on brain functional connectivity, which is a derivative of changed synaptic activity. Thus, these studies suggest that nutritional requirements in AD can be successfully addressed and result in improvements in behavioral and neuro-physiological alterations that are characteristic to AD.

The recent advance of methodologies and techniques for early diagnosis of AD facilitates the investigation of strategies to reduce the risk for AD progression in the earliest stages of the disease. Nutrition-based approaches deserve further investigation as an integral part of such strategies due to their low risk for side effects and their potential to affect pathological processes of very early AD.

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Introduction

Alzheimer's disease (AD), the most common form of dementia, is estimated to reach 100 million cases worldwide by 2050 [1,2]. It imposes a significant burden on patients, caregivers, and health care systems—the estimate in the United States alone is for an increase in health care budget for AD and other dementias from $200 billion in 2012 to $1.1 trillion in 2050 [3].

Thus, more effective therapies and novel strategies leading to improved disease management or risk reduction would have enormous socioeconomic effect.

Although AD was first identified more than 100 y ago, mechanistic studies and therapeutic developments for this devastating disease have gained momentum mostly in the past 30 y. Extraneuronal senile plaques and intraneuronal neurofibrillary tangles are two hallmarks of disease pathology in AD brain. Clinical manifestations include cognitive impairment and dementia. However, more subtle synaptic changes may occur years before such pathological and clinical symptoms manifest. Such

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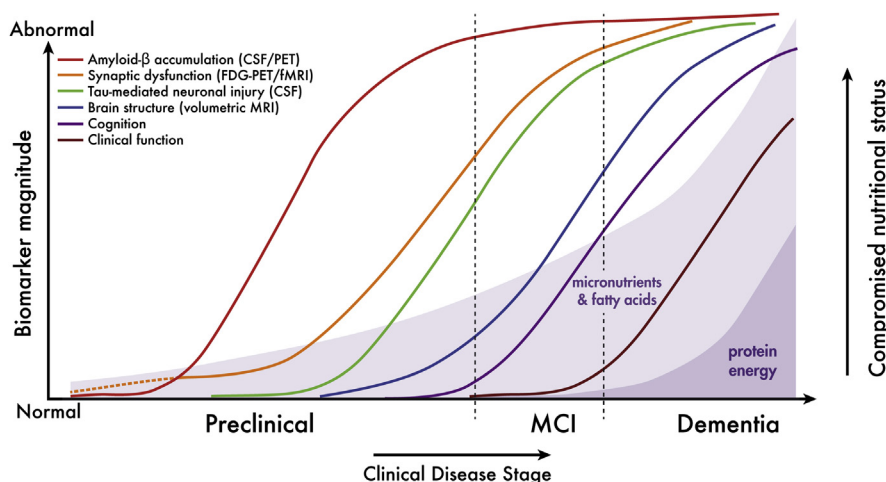E-mail address: patrick.kamphuis@danone.com (P. JGH. Kamphuis).

Fig. 1. Hypothetical model of dynamic biomarkers and nutritional status across the AD spectrum (adapted from Sperling et al, 2011 [8], with permission from Elsevier). Biomarkers including Aβ, synaptic dysfunction, tau-mediated neuronal injury and brain structure, change from normal to maximally abnormal (left y-axis) as disease progresses (details referred to [8]). The temporal trajectory of two key indicators for clinical stages of disease, cognition and clinical function, are also included. Compromised nutritional status has been highlighted with purple shades. Compromised micronutrients and fatty acids status have been implicated throughout the whole disease spectrum. Such compromised nutrient status may result from alterations in nutrient intake, reduced endogenous biosynthesis of nutritional compounds, and compromised nutrient absorption and uptake. With the disease progression, protein-energy malnutrition becomes prevalent at the demented stage of AD and the resulting weight loss is a common problem at this stage. Protein-energy malnutrition has been reported to be present in 50% of AD patients with severe AD [16].

a continuum of synaptic loss is strongly correlated with cognitive impairment [4–7]. With the recent advance in methodologies and techniques for early diagnosis of AD, especially the continuing maturation of structural, functional, and molecular imaging (i.e., magnetic resonance imaging [MRI], positron emission tomography [PET] or single-photon emission computed tomography [SPECT]) and identification of reliable cerebrospinal fluid (CSF)/plasma biomarkers, the research focus has shifted to the earliest stages of AD and strategies to reduce the risk for disease progression [8].

Mounting evidence points to the important role of nutrition in relation to cognitive function, especially during aging [9]. The maintenance of healthy neurons relies on adequate supply of nutritional compounds, which are mostly acquired from the diet. For instance, docosahexaenoic acid (DHA) from dietary intake is important for the formation of neuronal membranes. Choline is a precursor for the neurotransmitter acetylcholine and it also is used in the synthesis of neuronal membrane. For other nutrients' roles in the structure and function of the nervous system one can refer to a review by Bourre [10]. Furthermore, lower intakes of certain nutrients (i.e., DHA, B vitamins, and antioxidants) have been linked to increasing risk for AD and a diet rich in the aforementioned nutrients has shown to decrease the risk for AD [11–14]. Hence, in addition to pharmaceutical therapeutic approaches and lifestyle modification, we postulate that nutritional approaches are set to play an important role in future management options for AD. This contribution focuses on nutritional approaches investigated so far and their potentials as risk reduction measures of AD.

Rationale for nutritional approaches in AD

Protein-energy malnutrition in AD

Impaired nutritional status has been reported in AD. Protein-energy malnutrition is prevalent at the demented stage of AD and increases with disease severity (Fig. 1). In mild to moderate AD, 3% of the patients were reported to be malnourished [15], whereas another study indicated that 50% of patients with severe

AD had protein-energy malnutrition [16]. Such compromised protein-energy status could be due to worsening of appetite, taste, and smell, which lead to reduced food consumption, food neglect, and changes in food preferences [17–19]. Additionally, compromised nutritional status has been shown in older individuals with AD living at home with their spouses; and among them weight loss and malnutrition (undernutrition) are a common problem [20–22]. Body mass index (BMI) and mini-nutritional assessment (MNA) are two widely accepted screening tools for the indication of malnutrition in the elderly [23,24].

Lower micronutrients and fatty acid status in AD

In addition to the fact that patients with AD are at risk for a compromised protein-energy status at the demented stage, there also might be compromised micronutrients/ω-3 fatty acids during the entirety of disease progression (Fig. 1). Recent meta-analysis has shown significantly lower plasma levels of vitamins A, C, E, folate, and vitamin B$_{12}$ in patients with AD compared with cognitively intact elderly controls [25]. A trend toward lower levels of vitamin D and zinc also was observed [25]. Plasma levels of other nutrients and vitamins have been reported low in AD compared with age-matched healthy individuals (i.e., ω-3 polyunsaturated fatty acids [PUFAs] [26–29] and selenium [30,31]). Reduced uridine has been reported in the CSF of patients with mild AD [32], whereas a trend toward lower plasma uridine levels in mild AD compared with healthy controls has been reported for the first time in a recent study [33]. Interestingly, increased cysteine associated with decreased uridine is the best-paired combination to identify mild AD with specificity and sensitivity levels of above 75% [32]. Furthermore, lower nutrient status has been shown in subjects with mild cognitive impairment (MCI), that is, DHA content in phospholipids [26]; vitamins A, C, and E, lutein, zeaxanthin, and α-carotene [34,35]; and folate [36]. Taken together, observational studies suggest that lower nutrient status is a consistent finding during disease progression: It not only is a risk factor for onset of AD, but also

presents in the early stage of AD including MCI, in the absence of protein-energy malnutrition.

Compromised nutrient intake, uptake, and metabolism

Such lower nutrient status may result from various factors including alterations in nutrient intake, reduced endogenous biosynthesis of nutritional compounds, and compromised nutrient absorption and uptake. For instance, it has been reported that *de novo* synthesis of DHA in the liver is reduced in patients with AD [37,38]. Endogenous uridine-5'-monophosphate (UMP; a source of uridine) synthesis in the liver may decline with aging and be further impaired in AD, which may be attributed to aging-related decline in liver function and accelerated loss of liver function in AD [32,39]. The uptake of choline from the circulation into the brain decreases with aging and such reduced uptake of choline from the plasma may result in increased degradation of membrane phosphatidylcholine (PC; the most abundant phospholipid in the brain) in order to produce sufficient amounts of the neurotransmitter acetylcholine [40–42]. In a recent systematic review, the pooled data from nine case–control studies showed that patients with AD have low serum levels of folate and vitamin B_{12}, which are associated with increased homocysteine (Hcy) levels [43]. Increased Hcy and low B vitamin status are associated with reduced mobilization of DHA from liver to plasma and peripheral tissue [44,45], and with reduced choline synthesis and increased choline utilization [46–48].

Nutrient requirements for synapse formation

In addition to altered uptake, synthesis, and metabolism of nutrients in AD, the need for specific nutrients might be higher due to AD specific pathology (i.e., synapse loss). Thus, it is important to maintain optimal levels of such nutrients during diseased states. Phospholipids account for approximately 20% to 25% of the adult brain's dry weight and form the backbone of neuronal membranes including synaptic membranes [49]. Therefore, they are functionally essential for providing a suitable environment to facilitate membrane-dependent processes, like receptor activity and enzyme function [50,51]. Numerous studies from the lab of Dr. Wurtman (MIT, Cambridge/USA) have shown that membrane phospholipid synthesis can be increased through administration of substrates of the Kennedy pathway (i.e., uridine, DHA, or eicosapentaenoic [EPA], and choline [52,53]). Furthermore, data have shown uridine can stimulate phospholipid synthesis without diminishing acetylcholine synthesis or release in rat brain slices; and dietary supplementation with UMP increases acetylcholine level and release in striatum of aged rat [54,55]. Supplemental intakes of B vitamins (folate and vitamins B_{12} and B_6) and dietary phospholipids may serve as cofactors to increase the availability of choline and DHA for neuronal membrane phospholipid synthesis [45,46,56]. Uridine or DHA, which promote phospholipids' synthesis, also have been shown to increase synaptic protein levels, enhance neurite outgrowth, and increase dendrite spine density, all indicative of synapse formation [52,57–60]. Chronic dietary supplementation with UMP and DHA can ameliorate the hippocampal-dependent memory deficits in environmentally impoverished rats or normal adult gerbils [61–63]. Combined uridine and choline administration ameliorates cognitive deficits in spontaneously hypertensive rats, a model with deficiency in visual selective attention and spatial learning [64]. The largest effect on the aforementioned phenomenon was observed with administration of DHA, UMP, and
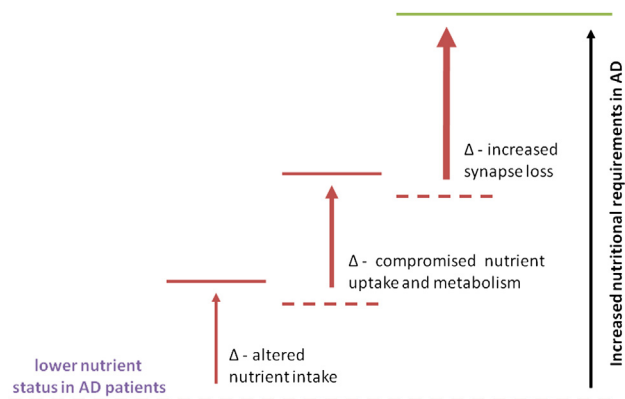

Fig. 2. Hypothetical model of increased nutrient requirements throughout the whole AD stages. Lower nutrient status (e.g. of DHA, vitamins A, C, E, folate, and vitamin B_{12}) has been reported in patients with AD compared with cognitively intact elderly controls. Such compromised nutritional status may result from alteration in nutrient intake, uptake, metabolism, and utilization. First, worsening of appetite, altered taste and smell might lead to smaller portions of food being consumed, to food neglect, and to changes in food preferences, resulting in lower intake of specific nutrients. Second, compromised nutrient uptake and metabolism (e.g., due to compromised liver function) result in lower concentration in the circulation. Third, AD-specific pathology may result in higher utilization and needs of specific nutrients (e.g., for neuronal membrane and synapse formation). Collectively, these factors result in a putative increased nutrient requirement that is specific to AD.

choline in combination [65]. Furthermore, lower levels of DHA in the brain make dendrites more vulnerable to Aβ toxicity [66]. Supplementation of ω-3 PUFAs or DHA can reduce Aβ production both in vitro and in vivo [67–69]. Chronic administration of DHA ameliorates the impairment of spatial cognition learning ability in Aβ-infused rats [70].

Together, these data indicate that certain nutrients are rate-limiting precursors for the formation of neuronal membranes, synapses, and synaptic function. Because progressive loss of synapses is an early and characteristic feature of AD, the requirements for renewal of synapses might be higher in AD than in healthy individuals.

Putative increased nutritional requirements in AD

The dietary factors in AD described in the previous sections are hypothesized to result in a micronutrient and fatty acid insufficiency, leading to a disease-specific nutritional requirement in AD, that is, a nutrient intake needed to compensate for the lower nutrient status in AD and concurrently meeting the higher nutrient needs resulting from the pathophysiological processes. The major factors that contribute to the putative increased nutritional requirement in AD are changes in eating behavior, alterations in nutrient uptake and metabolism, and increased needs for renewal of synapses (Fig. 2). Based on the previously mentioned observations, the specific nutrient combination Fortasyn® Connect, has been designed to enhance synapse formation and function, by addressing the putative specific nutritional requirements in AD [71]. It comprises the combination of nutritional precursors and cofactors for membrane synthesis, including DHA, EPA, UMP, choline, phospholipids, folic acid, vitamins B_6, B_{12}, C, E, and selenium [71]. B vitamins, vitamins C and E, and selenium act as cofactors by increasing the availability of membrane precursors or by directly affecting the neuronal membrane or membrane synthesis, and are all reported to be lower in AD. Fortasyn Connect's
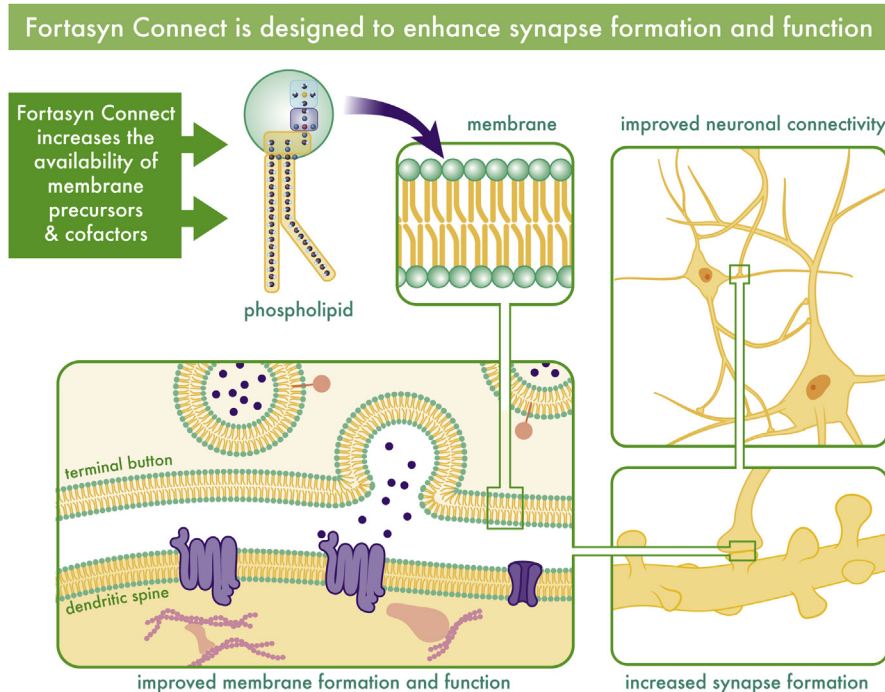
Fig. 3. Fortasyn Connect, present in the medical food Souvenaid, is designed to enhance synaptic formation and function. Fortasyn Connect comprises the nutritional precursors and cofactors for the formation of phospholipids and neuronal membranes, the principal and rate-limiting constituents for the dendritic spines that, together with presynaptic boutons form new synapses. Animal studies have shown that dietary enrichment with these constituents increases neuronal membrane formation, synaptic protein levels, dendritic spine density, neurite outgrowth, neurotransmission, and receptor function [71]. Clinical studies have shown that the medical food Souvenaid, improved memory performance in mild, drug-naïve patients with AD [89,90]. EEG data in one of these studies suggest that Souvenaid improves brain functional connectivity, a derivative of changed synaptic activity [90]. Figure 3 was designed in collaboration with Medical Visuals, Maartje Kunen.

hypothesized mode of action on enhancing synaptic formation and function, and neuronal connectivity can be referred to Figure 3. Preclinical studies showed that this specific nutrient combination can enhance M1 muscarinic acetylcholine receptor responses in vitro, and protect the central cholinergic system against Aβ-42–induced toxicity in a rat Aβ-42 infusion model [72,73]. Furthermore, dietary enrichment with Fortasyn Connect can reduce AD pathology in young adult APP$_{swe}$/PS1$_{dE9}$ mice [74]. Additional data have confirmed the efficacy of dietary intervention with Fortasyn Connect in alleviating spatial learning deficits in APP$_{swe}$/PS1$_{dE9}$ mice [75]. Investigations on the effects of this nutrient combination and other nutritional approaches in AD are summarized in the next two sections.

Nutritional interventions studied in AD

Protein-energy supplementation by oral nutritional supplements in AD

Nutritional approaches have been implicated in the management of AD [76]. For instance, oral nutritional supplements (ONS) using protein and energy supplementation have been applied in AD patients at risk for malnutrition in hospital and day-care centers; this resulted in significant improvements in energy intake with ONS versus usual care [77,78].

Single- or multinutrient approaches in AD

Nutritional interventions using micronutrients/fatty acids targeting cognition so far have shown contrasting results [79]. Although the majority of observational studies indicate that ω-3

fatty acids (especially DHA) have beneficial effects in cognition, meta-analysis has not shown that DHA supplementation can slow the rate of cognitive and functional decline in AD patients [80]. A positive effect of ω-3 fatty acids was observed within specific cognitive domains (i.e., immediate recall, attention, and processing speed) in cognitively impaired non-demented participants, but not in healthy or AD patients [80]. A single-center, RCT has shown that Hcy-lowering B vitamins in very high does can slow the rate of accelerated brain atrophy in individuals with MCI [81]. In the same study, B vitamins have shown to slow cognitive and clinical decline (secondary outcome) in individuals with MCI, in particular in those with elevated Hcy [82]. However, a meta-analysis on RCTs with folic acid has shown lowered Hcy levels without significant benefit on cognitive decline [83]. Nevertheless, supplementation with vitamins B$_{12}$, B$_6$, and folic acid alone or in combination did not improve cognitive function in individuals with or without existing cognitive impairment, as indicated by a recent meta-analysis [84]. No overall benefit has been observed in antioxidant trials with vitamins E and C, α-tocopherol and β-carotene, either as single-nutrient supplements or in combination [85–88].

Nutritional interventions using Souvenaid

The medical food Souvenaid® (Nutricia N.V., Zoetermeer, The Netherlands) contains Fortasyn Connect, and has been investigated in several RCTs. Souvenaid showed improved performance in the delayed verbal memory task derived from the Wechsler Memory Scale-revised in a 12-wk, RCT (Souvenir I) with 225 drug-naïve, mild AD patients [79,89]. This finding on memory performance in mild AD has been confirmed and extended in

a second double-blind RCT involving 259 drug-naïve patients (Souvenir II) with longer duration of 24 wk [90]. During this trial, Souvenaid significantly improved the memory domain Z score of the Neuropsychological Test Battery. Electroencephalography (EEG) measures, as a secondary outcome for derivative synaptic connectivity, also were significantly improved in the Souvenaid group, providing first support to the hypothetical mode of action in patients [90]. An open-label extension (OLE) study to Souvenir II showed that the use of Souvenaid for 48 wk is safe, well tolerated, with intake adherence of ≥95%. Additionally, the OLE demonstrated memory improvement during Souvenaid intervention from 24 to 48 wk in both the active–active and control–active groups [91]. A 24-wk, RCT with Souvenaid in 527 patients with mild to moderate AD in combination with stable use of acetylcholinesterase inhibitors and/or N-methyl-D-aspartate receptor antagonist showed good safety profile but no improvement on the Alzheimer's Disease Assessment Scale—Cognition subscale (S-Connect) [92]. The results of S-Connect study in mild to moderate AD, the positive outcomes in mild AD from Souvenir I and II and the view that synaptic dysfunction is a very early event, suggest that this nutritional intervention targeting synapse formation and function might offer the greatest potential when applied to earlier stages of AD, for example, in those individuals with MCI due to AD.

Future directions: toward nutrition as integrated part of strategies to reduce the risk for AD

Preventive initiatives

With the advance of diagnostic methodology and technology, in combination with the understanding of the disease pathogenesis, a paradigm shift to earlier diagnosis and treatment of AD is occurring [79]. Such a paradigm shift is a strategic continuum from disease management in AD, to early diagnosis and treatment in subjects in the prodromal/preclinical stages of AD and eventually to risk reduction in the general aging population. Three ongoing, US-led prevention initiatives have formed a new group: the Collaboration for Alzheimer's Prevention (CAP). These initiatives, including A4 (Anti-Amyloid Treatment in Asymptomatic AD), DIAN (Dominantly Inherited Alzheimer Network), and API (Alzheimer's Prevention Initiative), serve as a platform to search for reliable biomarkers in presymptomatic populations and to develop treatment strategies for such populations [93–95]. Additionally, Zinfandel-Takeda Pharmaceuticals Alliance's Phase III primary prevention study in cognitively normal elderly participants (∼ 5000 individuals, 5 y study) has been announced [96]. With a similar goal, The Alzheimer's Disease Neuroimaging Initiative (ADNI) is also aiming to validate the use of biomarkers and MRI/PET imaging for AD clinical trials and early diagnosis.

Nutrition-based approaches for reduction of AD risk

In alignment with such preventive initiatives, nutrition can make an important contribution [97]. Epidemiologic evidence shows that moderate intake of unsaturated fats during midlife may be protective, whereas a moderate intake of saturated fats may increase the risk for dementia and AD, especially among ApoE4 carriers [98,99]. Additionally, the Mediterranean diet (a diet rich in fish, fresh fruit, and vegetables) is associated with a lower risk for developing MCI and AD [100–102]. In the Framingham Heart Study with 9.1 y of prospective follow-up, the greater mean fish intake was associated with greater plasma PC

DHA content, which was associated in turn with decreased risk for AD as well as all-cause dementia [103]. Several nutritional prevention studies have been completed and the outcomes are not consistent [79]. For instance, the results of ω-3 PUFAs/DHA supplementation on behavioral outcomes in the elderly deserve cautious interpretation, with one study reporting a benefit on cognitive performance in healthy elderly individuals with age-related cognitive decline [104], whereas the other did not show a benefit in cognitively healthy elderly people due to lack of cognitive decline during the 24-mo intervention period [105]. This suggests ω-3 PUFAs used in isolation might be efficacious only in a carefully chosen target population and with a longer intervention period.

Folic acid fortification was originally introduced to prevent neural tube defects in infants; however, serum folate and vitamin B_{12} status also have been suggested to influence cognitive decline in elderly [106,107]. Studies have shown that in elderly with normal vitamin B_{12} status, high serum folate status through fortified food and/or supplementation is associated with protection against cognitive decline [108,109]. However in elderly with low serum vitamin B_{12} levels, high serum folate is associated with cognitive impairment [108,110]. A 3-y double-blind RCT showed folic acid supplementation in the elderly with normal serum vitamin B_{12} levels improved domains of cognitive function that tend to decline with age [111]. Overall, although no definite conclusion can be drawn at the moment, high serum folate in combination with normal vitamin B_{12} status can potentially reduce cognitive decline in elderly individuals [107].

The FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) study is an ongoing multicenter RCT involving 1200 participants ages 60 to 77 y. This 2-year, multidomain lifestyle intervention study includes nutritional guidance, exercise, cognitive training, increased social activity, and intensive monitoring and management of metabolic and vascular risk factors. It aims to prevent cognitive impairment, dementia, and disability among high-risk individuals [112]. The MAPT (French Multi-domain Alzheimer Preventive Trial) also aims to evaluate the efficacy of an integrated intervention (nutritional, physical, and cognitive training) and ω-3 supplementation in the reduction of cognitive decline in frail elderly persons aged ≥70 y; the final result is expected to be known this year [113]. Other ongoing nutritional interventions in cognitive aging or MCIs are presented in Table 1.

Souvenaid in prodromal AD

Although administration of ω-3 fatty acid (DHA and EPA) in patients with mild to moderate AD did not delay the rate of cognitive decline, positive effects were observed in a very small subgroup with very mild cognitive dysfunction (Mini–Mental State Examination [MMSE] > 27 points) [114], suggesting that interventions early in the disease might have a higher chance of success. Similarly, the Souvenir I clinical trial reported the greatest effect of Souvenaid in the prespecified population of patients with very mild AD (mean baseline MMSE = 25.61) [89]. These observations together with epidemiologic data of dietary patterns on risk reduction of AD, suggest a greater opportunity to intervene successfully in very early stage of AD. A double-blind RCT is ongoing within LipiDiDiet program (FP7-211696) to study the effect of Souvenaid in prodromal AD with Neuropsychological Test battery as primary outcome (LipiDiDiet, NTR1705, Table 1) [115]. Approximately 300 patients are to be recruited and given Souvenaid for a minimum of 2 y, and measures will be taken on well-established cognitive, pathologic,

Table 1
Ongoing nutritional interventions in individuals with cognitive aging or mild cognitive impairment (MCIs)

Ongoing studies	Participants	Mean follow up	Nutrients	1) Primary outcome 2) Secondary outcome
LIPIDIDIET NTR1705	1) 300 Prodromal AD as defined by episodic memory disorder and evidence for underlying AD pathology (Dubois et al, 2007) 2) 55 - 85 years 3) MMSE $\geq$ 20	2 y	125 mL of Souvenaid®, once daily	1) Cognitive performance during 24 mo of intervention as measured by a modified version of the NTB (Harrison et al, 2007) 2) Progression to dementia; cognitive performance (MMSE, 13-item ADAS-cog); functional abilities (ADCS-ADL); occurrence of depressive symptoms (MADRS); plasma biomarkers; atrophy rates on MRIs; nutritional (blood) parameters; tolerance and safety
BERRY NCT01515098	1) 132 MCIs 2) $\geq$ 65 y	6 mo	35 g freeze-dried blueberries	1) Change in cognitive test performance 2) Change in body mass distribution; change in oxidative stress and inflammatory markers as measured in blood and urine
NCT00599508	1) 60 MCIs 2) $\geq$ 66 y	16 wk	Purple grape juice	1) Memory performance 2) Cortisol
NCT01571193	1) 212 nondemented participants with either normal cognition or amnestic MCIs 2) 50–75 y	1 y	1000 mg pomegranate extract	1) Improved cognitive performance
NCT01219244	1) 330 participants with mild cognitive impairment 2) 50–80 y 3) Moderate to heavy weight (BMI 25–35 kg/m^2)	Dietary intervention: 6 moExercise/ cognitive training: NA	Dietary intervention (caloric restriction, ω-3 fatty acids and resveratrol) and in combination with exercise and cognitive training	1) ADAS-cog 2) Functional/structural brain changes and plasma biomarkers
MAPT NCT00672685 [113]	1) 1200 frail elderly with subjective memory complaints 2) $\geq$ 70 y	3 y	Multidomain intervention (nutritional, physical, and cognitive training) and DHA (800 mg/d)	1) Changes in memory function scores determined by Gröber and Buscke test 2) Changes in other cognitive functions; changes in functional capacities. To study the long-term safety and tolerability of DHA treatment. To study compliance and adhesion to "multidomain" intervention program
Efalex Active 50+ NCT01185379	1) 250 healthy elderly 2) 50–70 y 3) MMSE >24; 4) Participants suffering from a memory complaint (MAC-Q score > 24)	6 mo	Efalex Active 50+, a dietary supplement containing DHA, phosphatidylserine, vitamin B$_{12}$, folic acid and Ginkgo biloba	1) Cognitive performance (attention, memory, executive function) 2) Cerebral hemodynamics; mood/well-being
Alois de Montauban study	1) 4000 individuals 2) $\geq$ 67 y	5 y	DHA	1) Prevent development of neurodegenerative disease 2) Prevent development of AD
EPOCH ACTRN 12607000278437 [116]	1) 400 elderly; 2) 65–90 y; 3) Score $\geq$ 24	1.5 y	ω-3 PUFAs430 mg DHA + 150 mg EPA	1a) Rate of cognitive decline b) Change in well-being measures; 2) Plasma fatty acid changes, blood pressure, oxidative stress, and inflammation
PREADVISE NCT00040378	1) 10 400 males with no neurologic or psychiatric illness 2) 60–90 y	7–12 y	Vitamin E + Selenium (400 IU + 200 mcg/d)	1) Prevention of AD as measured by Memory Impairment Screen
NCT00996229	1) 300 healthy adults; 2) 50–80 y; 3) Moderate to heavy weight (BMI 25–30 kg/m^2)	6 mo	Caloric restriction or dietary supplementation (2 g/d DHA/EPA or resveratrol)	1) Auditory verbal learning task 2) Functional/structural brain changes and plasma biomarkers
B-PROOF NCT00696514 [117]	1) 3000 healthy elderly 2) $\geq$ 65 y 3) Fasting plasma homocysteine $\geq$12 and <50 µmol/L	2 y	Folic acid (400 mcg) + vitamin B$_{12}$ (500 µg) + vitamin D$_3$ (600 IU); placebo (vitamin D$_3$ 600 IU)	1) Fractures 2) Cognitive decline; bone health; physical performance; QoL; nutritional status
NCT01164020	1) 80 healthy women 2) $\geq$ 60 y	23–24 wk	Creatine supplementation (20 g/d for 7 d followed by 5 g/d for 23 wk) in combination with resistance training	1) Cognitive function 2) Physical capacity, muscle strength, and function

Table 1 (Continued)

Ongoing studies	Participants	Mean follow up	Nutrients	1) Primary outcome 2) Secondary outcome
Oxi-Stress NCT01234506 [118]	1) 154 healthy adults 2) 60–80 years	24 wk	Flax lignan SDG (300 mg SDG/d) + 1000 IU vitamin D;placebo (1000 IU vitamin D)	1) Safety of 300 mg/d SDG consumption; effect of SDG on oxidative stress and inflammation 2) Effect of SDG on QoL including cognitive function; effect of SDG supplement on blood levels of flax lignan metabolites, bone resorption, and blood lipids
MOP201109 NCT01625195	1) 300 healthy adults; 2) 20–80 y	6 mo	1.2 g/d of DHA and 2.4 g/d of EPA	1) Change from baseline in cognition 2) DHA level in plasma at baseline, monthly DHA metabolism
WAHA NCT01634841	1) 700 healthy adults; 2) 65–75 y	2 y	30–45 g/d walnuts	1) Change in cognitive decline from baseline 2) Change in macular degeneration from baseline
NCT01620567	1) 44 healthy adults 2) ≥ 50 y 3) MMSE > 24	6 mo	1 avocado/d; placebo: equivalent calories of chickpeas/potatoes	1) Cognition 2) Inflammation (markers in plasma)

AD, Alzheimer's disease; ADAS, Alzheimer's Disease Assessment Scale; ADL, activities of daily living; BMI, body mass index; DHA, docosahexaenoic acid; EPA, eicosapentaenoic; MADRS, Montgomery–Åsberg Depression Rating Scale; MCI, mild cognitive impairment; MIS, Memory Impairment Screen; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NTB, Neuropsychological Test Battery; SDG, secoisolariciresinol diglucoside; QoL, quality of life.

and biomarkers. The outcome of this study will be a first indication of whether Souvenaid is efficacious in slowing down cognitive decline in the most dominant and relevant risk group who have amnestic MCI due to AD. Furthermore, this study will give guidance on future investigation of nutritional interventions on an earlier stage of presymptomatic AD.

Conclusion

Current advances in earlier diagnosis of AD facilitates investigation of the idea that interventions targeting prodromal stage or even earlier stages of AD might be more effective than at more advanced clinical stages, when damaging pathophysioligical changes may have accumulated to an irreversible degree. Effective, nutrition-based approaches would be of great benefit due to a relatively low risk for side effects in a presymptomatic or prodromal, and relatively healthy population allied to the necessarily long exposure time. Based on results so far, and the notion that synaptic dysfunction is an early phenomenon in the AD spectrum, a nutritional approach targeting synaptic dysfunction deserves further investigation as an integral part of strategies to reduce the risk for AD progression.

Acknowledgments

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