

Alzheimer's Disease: An Epidemiologic Disaster From Nutritional Perspective

Magda Antal¹, Szabolcs Péter^{2*}, Manfred Eggersdorfer^{2,3}

¹Pannónia Street 66, Budapest 1133, Hungary

²DSM Nutritional Products Ltd., Wurmisweg 576, Kaiseraugst 4303, Switzerland

³University Medical Center Groningen, University of Groningen, Hanzeplein 1, The Netherlands

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***Corresponding author:** Szabolcs Péter MD, PhD, Principal Scientist, DSM Nutritional Products Ltd., P.O. Box 2676, 4002 Basel, Switzerland, Tel.: +41 61 815 8966; Fax: +41 61 815 8540; E-mail: szabolcs.peter@dsm.com

Abstract

Alzheimer disease (AD) is a progressive, multifactorial, untreatable neurodegenerative disease with worldwide increasing incidence and prevalence in the ageing societies. Besides pharmaceutical drug development there is also a need for alternative solutions for both prevention and treatment. The major objective of this article is to summarize the non-modifiable and some modifiable risk factors of AD, including nutrition and diet, and to discuss different aspects of AD prevention. Optimizing the nutritional status of the general population as a preventive measure may provide additional support to therapeutic concepts as they become available. Already several randomized controlled trials demonstrated promising results for certain nutrients to decrease the risk of developing AD and maintaining cognitive performance. Moreover, symptoms of AD such as neuroinflammation, glucose dysregulation, homocysteine accumulation and neuronal loss can be considerably influenced by nutrition. Thus, lifelong optimal supply of essential micro- and macronutrients may contribute to delay the onset of AD. However, currently the scientific evidence regarding the effects of nutrients on AD is incomplete and there are many opportunities for nutrition scientists to contribute to the clarification of the conflicting results and adjust guidelines accordingly.

Keywords: Alzheimer's Disease; Public Health; Nutrition; Vitamins; Polyunsaturated Fatty Acids.

Introduction

In 2015, globally the average Life Expectancy (LE) at birth was 71.4 years, while the healthy life expectancy at birth was 63.1 years [1]. However, there are great differences in LE among countries and between genders: For example in the US men live 76.9 years on average, while women live 81.6 years; these data in the UK are 79.4 and 83.0 years, respectively; while Japan has one of the highest LE in the world for men (80.5 years) and for women (86.8 years) as well [2].

The share of population aged 65 and over is increasing in every EU member state: In 2014 the 65-79 years age group represented 13.4% of the population, while the rate of people aged 80 years

and over was 5.1%. The estimated ratio of these two age groups in the 28 EU countries for 2040 is 17.9% and 9.9%, and for 2050 it is projected to be 17.2% and 10.9%, respectively [3] (Figure 1).

Based on the data available, LE during the 20th century increased by more than 30 years. By the year 2040 more than a quarter of the Europeans will be older than 65 years and one in seven will be at least 75 years of age. More importantly, health expectancy on average is 8-11 years shorter than LE and loss of cognitive functions and increase in dementia are major contributors of disability and disease during these last couple years of life [4, 5].

Alzheimer's Disease (AD) is the most common cause of dementia in people aged 60 years or older, representing approximately 60-70% of all cases [6].

Currently at least 35 million people are affected by AD worldwide and this number is expected to quadruple by the year 2050. Although mortality due to HIV, stroke and heart disease decreased between 2000 and 2013 by 52%, 23% and 14%, respectively, death cases related to AD increased by 71% within the same timeframe, making AD the fourth leading cause of death in developed countries [7].

The prevalence of AD increases with age, for example the proportion of people with AD in the US in 2015 was estimated as follows: <65 years: 4%; 65-74 years: 15%; 75-84 years: 43%; 85+ years: 38% [7].

Definition of AD

Alois Alzheimer identified the first case of AD in a 51 year old woman, whose brain autopsy showed plaques and tangles that characterize AD [8].

AD is a degenerative brain disease of unknown origin, usually developing slowly during the late middle age or in old age and worsens with time. AD results in progressive memory loss, impaired thinking, disorientation, changes in personality and mood. These symptoms are leading to profound decline in

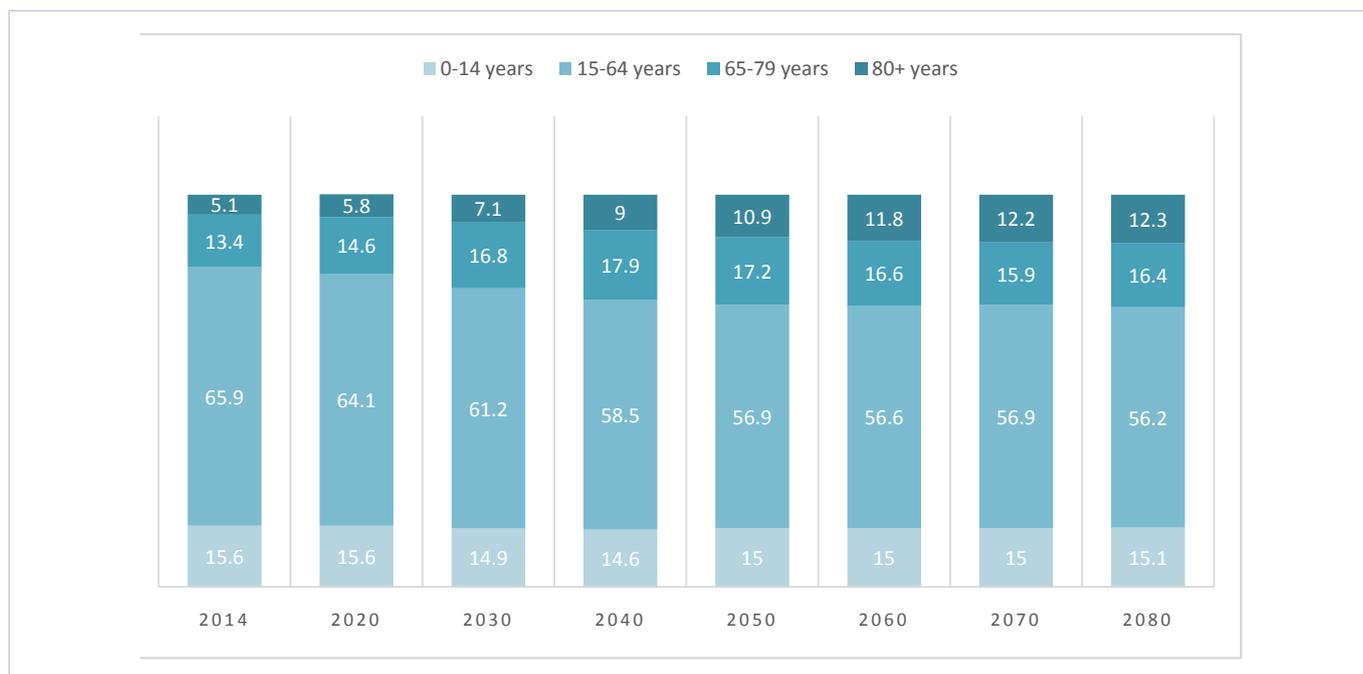


Figure 1: Population structure by major age groups, EU-28, 2014–80 (% of total population) [3]

cognitive and physical functioning, which is histopathologically characterized by degeneration of brain neurons, especially in the central cortex, and by the presence of neurofibrillary tangles and plaques containing β amyloid [7, 9, 10] (Table 1).

Risk factors and protective circumstances

Given the presence of numerous interconnected genetic and environmental factors, AD is unquestionably considered as a complex multifactorial disease. However, its cause or causes are not known. Risk factors are grouped into two categories: Those that cannot be altered and others that are possible to modify [11].

Non modifiable risk factors

Age: AD is not part of the normal ageing process, but age is the strongest independent risk factor for the development of AD. This does not mean that most people develop AD as they age, and in fact most do not. However, some younger people still in their 40s and 50s can be diagnosed with the early onset form of the disease. Over the age of 65 years the risk of developing AD doubles ca. every five years. In the US for example the incidence of AD within the age group of 65-74 years is 2 per 1,000 people, in the age group of 75-84 years it is 13 and in the >85 years group 39 per 1,000 people. According to the Framingham study, the estimated lifetime risk for AD is 9.1% for men and 17.2% for women at age of 65 years; 10.2% and 18.5% at 75 years; 12.1% and 20.3% at 85 years, respectively [7].

Gender: Age related loss of sex steroid hormones is an established risk factor for the development of AD in both men and women. Estrogens and androgens exert general neuroprotective properties, including protection from neuronal death, increase spine density, facilitate synaptic plasticity and improve certain

aspects of cognition. In addition, estrogens and androgens regulate key processes implicated in AD pathogenesis. Due to the loss of estrogen and progesterone, β amyloid protein ($A\beta$) accumulation and tau phosphorylation are increasing.

Evidence suggests that AD pathogenesis is regulated by estrogen and progesterone in females, but primarily by androgens in males [12, 13].

Menopause: It is known that AD is more prevalent in women, than in men. The higher prevalence of AD in women can be partly explained by the differences in life expectancy, however according to several studies, the incidence of AD is also higher in women. Moreover, AD pathology and AD-related cognitive decline are more marked in women than in men. This can be partly justified by the relatively abrupt loss of oestrogen and progesterone in women and the more gradual decrease of testosterone level in men. The 17 β -estradiol concentration in the female brain decreases sharply at menopause, but with very little additional decrease with ageing afterwards. Moreover, there is a stronger association with apolipoprotein E ϵ 4 Allele (APOE ϵ 4) in AD in women than in men, and this association correlates with greater hippocampal atrophy in women. The underlying cause for increased vulnerability of females to AD-like pathology is ambiguous.

Hormone Replacement Therapy (HRT) in menopausal women seems to offer promising results in reducing the risk of AD. Controversially, according to a prospective study, HRT may even increase the risk of dementia. Recent clinical data suggest that AD risk is reduced when HRT is initiated in midlife, but is exacerbated by HRT administration in late life [12, 13].

Table 1: Stages of Alzheimer's disease [10]

Mild Alzheimer's disease (early-stage) lasts for 2-4 years	Moderate Alzheimer's disease (middle-stage) lasts for 2-10 years	Severe Alzheimer's disease (late stage) lasts for 1-3+ years
In the early stages of AD the patient may function independently	As the disease progresses, the patient will require a greater level of care	As memory and cognitive skills continue to worsen, personality changes may occur and patients need extensive help with daily activities
<ul style="list-style-type: none"> - Difficulty by performing tasks in social or work settings - Forgetting text that one has just read - Losing or misplacing objects - Increasing problems with planning or organizing 	<ul style="list-style-type: none"> - Forgetting events or own personal history - Feeling unpredictable or withdrawn in socially or mentally challenging situations - Unable to recall own address or phone number - Confusion about present time and location - Need for help choosing proper clothing for the season or occasion - Trouble controlling bladder and bowels - Changes in sleep patterns (e.g. sleeping during the day and becoming restless at night) - Increased risk of wandering and becoming lost - Personality and behavioral changes (incl. suspiciousness and delusions, compulsive, repetitive behaviour etc.) 	<ul style="list-style-type: none"> - Full-time assistance needed with daily personal care - Lose awareness of recent experiences and surroundings - High levels of assistance required with daily activities and personal care - Experience changes in physical abilities (incl. the ability to walk, sit, swallow) - Increasing difficulty communicating - Vulnerable to infections, esp. pneumonia

Genetics: AD can be categorized into two subtypes: Early onset AD (EOAD) or familial AD (FAD) and late onset AD (LOAD) [14].

I. Familial AD

FAD is expressed as a Mendelian trait with dominant inheritance, and around 2-5% of all AD cases belong to this category. If a person has FAD, each of their children have 50% chance of inheriting the disease; when both partents have FAD, their children will develop AD in adulthood. FAD cases occur in people between the age of 30-60 years. Characteristic pathological features in the brain include progressive accumulation of Aβ in the form of senile plaques outside the neurons, and twisted strands of protein (neurofibrillary tangles, hyperphosphorylated tau protein) inside the neurons. These changes are eventually accompanied by low-grade chronic inflammation and oxidative stress, causing neuron damage and cerebral cortical atrophy, which in the long run leads to dementia [14, 15].

a. Amyloid Cascade Hypothesis (ACH): According to the ACH, the deposition of Aβ is the initial event in AD, leading to the formation of extracellular senile plaques and then to neurofibrillary tangles, neural cell death and ultimately clinical dementia [16].

Specially three mutations in the genes of the Amyloid Precursor Protein (APP), Presenilin1 (PSEN1) and Presenilin2 (PSEN2) result in the alteration of Aβ, and cells produce Aβ peptides of variable length: A peptide of 40 amino acids (Aβ40) is the most prevalent, whereas the longer Aβ42 isomer appears

to be the key pathogenic form for FAD. During physiological circumstances, APP is cleared by α-secretase, producing a dissolved form (amyloid α) which is released into the extracellular compartment [17, 18].

Neuronal microtubules transports nutrients, molecules and information to other cells. Tau protein plays a key role in keeping the microtubule system stable. In AD the threads of tau become tangled and twisted, thus the microtubule become instable and disintegrated, collapsing the entire neuronal transport system. Plaques and highly Phosphorylated Neurofibrillary Tangles (NFT) lead to functional failure of synapses, synaptic loss and finally neural death [19].

However, the current hypothesis of amyloid cascade and tau pathology only partially explains the pathophysiology of AD, which is considered to have a multifactorial etiology. Musiek and Holtman argued that Aβ acts primarily as a trigger of other downstream processes, particularly tau aggregation, which mediate neurodegeneration: Thus Aβ appears to be necessary, but not sufficient to cause AD by itself. At the same time Herrup also rejects the ACH and suggests that amyloid is not even necessary for AD development. Most probably a "multiple reason" hypothesis will be able to account for all the various aspects that underline the disease process, and to differentiate between normal and pathological brain ageing [20, 21].

A comprehensive review by Morris et al. summarized the pros and cons of the amyloid cascade hypothesis. They concluded that Aβ in the AD brain is a consequence rather than the primary

cause of the disease. Since the amyloid hypothesis is still incomplete and also highly debated, it is worthwhile to consider other alternative theories [22].

b. A β Clearance Systems: It has been hypothesized that A β accumulation results from an imbalance between A β production and clearance. A β clearance seems to be impaired in both early and late forms of AD. Recently, the clearance systems of the brain were described in relation with AD pathology, and with a special focus on A β : the blood-brain barrier clearance, the intra- and extracellular degradation clearance, the interstitial fluid bulk flow clearance and the cerebrospinal fluid adsorption clearance. The precise understanding of the mechanisms of clearance dysfunction in AD is essential for developing strategies to reduce excess deposition of neurotoxic proteins and to stop the related pathological changes. It still remains a question whether the observed clearance defect in AD is a cause or a consequence of the pathology or merely a coincidence. Further examination of the A β clearance defect might provide a useful biomarker for the reversible clinical pathology of AD [23].

II. Late Onset AD (LOAD)

LOAD usually develops in patients older than 60 years of age. The causes are not completely understood yet, but genetic, environmental and lifestyle factors may contribute to the progression and severity of this form of the disease. Nevertheless, based on clinical evaluation of a community population sample, the prevalence is strongly associated with age: 3% between 65-74 years; 18,7% between 75-84 years; and 47,2% over 85 years [24].

Apolipoprotein E (APOE) is a major determinant of the fat soluble vitamin transport in blood to the peripheral tissues, as well as in the central nervous system to neurons via APOE receptors. APOE is polymorphic with three major alleles: ϵ 2, ϵ 3, and ϵ 4. The APOE ϵ 2 form is carried by 8%, ϵ 3 about 77% and ϵ 4 around 15% of the population, respectively. It has been proposed that APOE ϵ 2 may provide some protection against AD, while APOE ϵ 3, the most frequent allele is believed to play a neutral role in the disease, although both APOE ϵ 2 and ϵ 3 may enhance the clearance of A β . There are data showing that APOE ϵ 2 reduces the risk of dementia in persons older than 90 years. APOE ϵ 4 probably increases the risk of AD by initiating and accelerating A β accumulation in the brain. This allele is present in 40% of patients with LOAD, and it is considered to be the major genetic risk factor of AD. However, inheriting an APOE ϵ 4 allele does not necessarily mean a definitive development of AD, but the risk of LOAD is ca. 8-10 times higher in homozygous individuals as compared to the risk in heterozygous persons [18, 25-27]. Furthermore it has been demonstrated that APOE ϵ 4 accelerates age dependant cognitive decline and worsens memory performance and functional activities as well as hippocampal atrophy [26, 28].

Epidemiological, in vitro and animal studies suggested that APOE ϵ 4 causes neuronal disturbances and behavioural deficits in vivo via multiple ways, either independently or in combination with other factors, such as A β and tau. APOE ϵ 4 contributes to the impairment of the oxidative defence system, dysregulation of

neuronal signalling pathways, increased phosphorylation of tau and formation of neurofibrillary tangles. [26, 27, 29].

Modifiable risk factors, life-course concept

This theory aims to understand how risk factors and protective circumstances interact during gestation, childhood, adolescence, and adult life to influence the development of later disease [30].

Intrauterine life is important for the maturation and development of the brain and the nervous system. In turn, brain development may influence the risk of cognitive impairment and dementia in older age.

The brain reaches 95% of its final size at age 6, the maximal brain size and skull circumference are reached between 11 and 15 years. Thereafter brain size decreases, while skull circumference remains constant. Thus the circumference of the adult skull reflects the brain size at its peak [30]. The individual capacity to withstand pathological alterations is usually referred to as Brain Reserve (BR) or Cognitive Reserve (CR) [31].

BR refers to qualitative measures, such as brain size, number of neurons and synapses. BR is a passive protection against the consequences of brain damage, mediated by larger brain or more neurons and synaptic connections [31]. Epidemiological and clinical studies have consistently shown that at similar levels of AD pathology, higher estimates of BR and greater Intracranial Volume (ICV) were related to less severe symptoms. Perneczky et al. involved in the Mirage study suggested that larger head circumference is associated with less cognitive impairment. The larger brains contain more neurons, synaptic connections and bigger brain size is mostly determined in early childhood. The results suggest that optimal neural development in the first couple of years provides a buffer against cerebral pathology in late life [31]. Although greater premorbid brain size seems to protect against clinical deterioration in AD related brain atrophy in Mild Cognitive Impairment (MCI), the protective effects of morphologic reserve seem to be limited to early clinical AD [32].

CR is characterized by active processes through alternative neural pathways, helping to compensate the effect of brain pathology in its clinical presentation. CR includes compensatory strategies like education, Intelligence Quotient (IQ), literacy and the integrity of social networks. Epidemiological data suggest that persons with higher education, occupational competence and participation in leisure activities have a lower risk for developing AD [33]. It is widely accepted that CR is an important protective factor against AD, but the question remains how to maximize CR of individuals. In this regard several suggestions have been proposed by Stern, such as the extension of the person's social network, early life education and cognitive activities in later life [34].

Nutrition

There is an increasing interest to clarify the role of nutrition in AD. This review is focusing on certain key nutritional compounds and a few diseases/disorders that may be connected to AD. It also takes these factors into account concerning the development and

progression of AD, and their role in prevention. As AD is currently incurable, these factors need to be very carefully investigated.

I. Vitamin E: Significant positive association was found for the beneficial effect of vitamin E and the prevention of AD: Grade I. evidence indicates that vitamin E may decrease the risk for the development of AD [35].

Vitamin E is a fat soluble vitamin with eight isoforms: α -, β -, γ -, δ -tocopherol and α -, β -, γ -, δ -tocotrienol. All forms have a chromanol ring with a hydroxyl group that can serve hydrogen atom to reduce free radicals, and a hydrophobic side chain which allows its penetration into biological membranes. The human body preferentially uses α -tocopherol; this form is found in the largest quantities in the blood and the tissues [36].

a. Function of α -tocopherol:

1.) Antioxidant activity: Alpha-tocopherol is a chain breaking antioxidant preventing the propagation of Reactive Oxygen Species (ROS) in membranes and in plasma lipoprotein. When a molecule of α -tocopherol neutralizes ROS, it oxidizes to a less active tocopherol radical, which is reduced by a hydrogen donor such as vitamin C. In this way the chain reaction of lipid peroxidation is broken [36].

It has been suggested that vitamin E may prevent hyperphosphorylated tau protein dysfunction. Additionally, vitamin E has been related to reduced rate of neuronal death induced by A β protein in cultures of hippocampal and cortical cells [37].

2.) Anti-inflammatory activity: Recent studies indicate that γ - and δ -tocopherols and γ -tocotrienol have unique anti-inflammatory properties that are superior to those of α -tocopherol in prevention and therapy against chronic diseases. These vitamin E forms scavenge reactive nitrogen species, inhibit cyclooxygenase- and 5-lipoxygenase-catalysed eicosanoids and suppresses pro-inflammatory signalling. Animal and human studies show that γ -tocopherol and tocotrienols may be useful against inflammation associated diseases [38].

3.) Enzymatic activity regulator: Protein Kinase C (PKC) plays a role in smooth muscle growth and can be inhibited by α -tocopherol: α -tocopherol has a stimulatory effect on protein phosphatase 2A, which in turn cleaves phosphate groups from PKC, leading to its deactivation, bringing the smooth muscle growth to a halt [39, 40].

4.) Protective role of vitamin E during oxidative stress: Oxidative stress is a risk factor for AD. In healthy individuals the generation of ROS should be in balance with antioxidant defences.

Growing evidence suggests that vitamin E has a neuroprotective effect by inhibiting oxidative stress and scavenging A β -associated free radicals [41].

b. Clinical trials concerning vitamin E supplementation: Compared to cognitively normal subjects, AD and MCI patients have lower blood concentrations of total tocopherols, total tocotrienol and total vitamin E [41].

According to the Cochrane database, only three studies met the inclusion criteria to investigate the effect of vitamin E in the treatment of MCI or AD [42].

Sano et al. investigated the effect of selective monoamine oxidase inhibitor selegiline (10 mg/d), α -tocopherol (2,000 IU/d) or both and placebo for two years. In patients with moderately severe impairment form of AD, treatment with selegiline, α -tocopherol or their combination slowed the progression of the disease [43].

Lloret et al. treated patients with 800 IU vitamin E/d or placebo for six months. Blood oxidized glutathione (GSSG) was measured and cognitive tests were analyzed. Patients were divided in two groups: In the "respondents" to vitamin E, GSSG levels were lower after treatment and scores of cognitive tests were unchanged. In the "non-respondent" group, vitamin E was not effective in preventing oxidative stress, and cognition decreased sharply. Authors suggested that vitamin E supplementation in AD patients cannot be recommended without the determination of its antioxidant effect in each patient [44].

Petersen et al. administered 2,000 IU vitamin E daily, 10 mg of donepezil daily or placebo to patients with amnesic subtype of MCI for three years. They concluded that vitamin E had no benefit for patients with MCI [45].

According to the conclusion of the Cochrane group, there is no convincing evidence that vitamin E is beneficial for the treatment of AD and MCI, and future trials assessing vitamin E treatment in AD should not be restricted to α -tocopherol [42].

One of the largest and longest treatment trials, involving patients with mild to moderate AD, studied the effect of α -tocopherol (2,000 IU/day) or memantine (20 mg/d) alone or in combination, versus the combination of placebo and Acetylcholinesterase (ACE) inhibitor medication) over a period of six months to four years. The results showed that a dosage of 2,000 IU/d α -tocopherol significantly delayed the progression of AD symptoms in mild to moderate AD and decreased caregiver burden. Moreover, the authors found no safety concern associated with vitamin E supplementation compared to the control group [46].

There are several ideas to explain the inconsistent results on the effect of vitamin E supplementation. According to Brewer's hypothesis, the antioxidant vitamin E is ineffective because the oxidized vitamin E is not removed from the membranes and is not reduced by vitamin C or any other antioxidant. Therefore it will either accumulate or pass the electron to another lipid, further damaging the membrane [47]. However, there is another possibility. Generally, α -tocopherol is used as a supplement in clinical trials, but γ -tocopherol was found more effective in scavenging free radicals and nitrogen oxygen species that cause inflammation. Moreover, α -tocopherol supplements significantly

reduces serum γ -tocopherol concentration and this may have important biological effects. Therefore, α -tocopherol may eliminate the favourable effects of other forms of vitamin E in MCI and AD [48, 49].

Recently it was discussed in a comprehensive review that the difficulty in performing precise and uniform human studies is mostly responsible for the inconsistent outcomes reported in the literature. Therefore more standardized clinical research is needed to identify a clear effect of vitamin E on cognitive decline observed during aging and AD progression from early to late phase [50].

Nutrition epidemiologic studies indicate that vitamin E from food sources may be more effective at preventing age related neurodegenerative disorders than dietary supplements. This could be partly explained by the fact that vitamin E from foods comprises all four tocopherols and four tocotrienols with different properties. Besides this, the combination of nutrients from food may have synergic effects [48, 49].

II. Vitamin C: The beneficial effect of high vitamin C intake on AD and MCI has grade I. evidence [35].

Vitamin C (ascorbic acid, the γ -lactone of hexonic acid) is a water soluble vitamin. It is a very unstable compound and readily undergoes oxidation to dehydroascorbic acid. Vitamin C has a huge redox potential. It is a potent antioxidant and essential cofactor in numerous enzymatic reactions, e.g. in the biosynthesis of collagen, carnitine and catecholamine and is involved in the metabolism of cholesterol. It also increases the intestinal absorption of non-hem iron.

Sodium dependent adsorption of vitamin C is limited, 100% adsorption is observed at dose of 200 mg. When plasma vitamin C level reaches saturation, additional vitamin C is largely excreted into urine [51].

The effect of vitamin C was investigated on A β formation and behaviour in an AD mice model. Due to the effect of vitamin C, the reduction of A β oligomerization was accompanied by marked decrease in brain oxidative damage and in the ratio of soluble A β 42 to A β 40, a typical indicator of AD progression. Moreover, vitamin C attenuated the phosphorylation of tau, but brain plaque deposition was not altered [52].

It has been shown, that as compared to control subjects, plasma vitamin C concentration is lower in AD patients and is negatively associated with the degree of cognitive impairment. This correlation seems to be independent of age, gender, Body Mass Index (BMI), diet, and vitamin C intake. AD subjects have increased lipid peroxidation levels and free radicals may cause damage in the neural tissue [53, 54].

However, the literature implicating vitamin C and other antioxidants in the promotion of cognitive function and the prevention of AD are conflicting. The relationship between AD and intake of vitamin C and/or E was investigated in elderly, who were free of dementia at baseline, and were followed on average for three years. The intake of vitamin C and/or E was

not associated with a decreased risk of dementia or AD [55]. The Rotterdam prospective study had the same conclusion, namely vitamin C intake was not associated with dementia risk [56]. Two of eight studies, providing data from well characterized cohorts and epidemiologic populations, suggested benefit of vitamin C intake [54]. On the contrary, results of another prospective study suggested that combined use of vitamin C and E for at least three years was associated with the reduction of AD prevalence and incidence [57]. Harrison's comprehensive review on vitamin C for prevention of age-related cognitive decline and AD concluded that there are several unsolved problems in the published study results. For example, the classification of participants according to vitamin C status is inaccurate, the use of vitamin C supplements is sometimes erroneously recorded, vitamin C levels in plasma are not always reported and the estimated daily intake in food diaries may not be accurately assessed. Overall, maintaining optimal levels of vitamin C may have a protective effect against age-related cognitive decline and development of AD [58].

The Team of Alzheimer Drug Discovery Foundation summarized the effect of vitamin C and E supplements on dementia and AD as follows: It remains unclear whether vitamin C and E supplementation alone and in combination prevent cognitive decline or dementia; maintaining healthy levels of vitamin C and E with the diet may be more beneficial than supplementation [59].

Few studies have measured vitamin C in the Cerebrospinal Fluid (CSF). Higher CSF to plasma vitamin C ratio at baseline was associated with a slower rate of cognitive decline at a one year follow up study. The strength of this relationship was modified by CSF albumin index, a marker of Blood-Brain-Barrier (BBB) integrity. The CSF albumin index attenuated the association of CSF-plasma ascorbic acid ratio with cognitive outcomes. It has been suggested that BBB dysfunction may lead to diffusion of vitamin C from the Central Nervous System (CNS) and may impair the brain's ability to maintain the high CSF-plasma ratio in AD [60].

Epidemiological studies confirmed the relevance of the relationship between vascular disease and AD. Polidori et al. investigated the connection between the level of several antioxidants and Carotid Intima-Media-Thickness (C-IMT), as an indirect index of vascular damage. They established that higher vitamin C plasma levels appears to be protective against elevated C-IMT values in elderly. In the light of increased risk of cardiovascular disease, cerebrovascular disease and cognitive impairment shown in patients with increased C-IMT, the achievement of better antioxidant status in general and vitamin C in particular should be always encouraged in the elderly [61].

III. Folate: Folate is a generic term, referring to both natural folates (pteroyl glutamate) in the food and folic acid (pteroyl-l-glutamic acid), the synthetic form used in supplements and fortified food. Folate is a coenzyme and its principal role is to accept or donate one-carbon units. Vitamin B2 (riboflavin), vitamin B6 (pyridoxine) and vitamin B12 (cyanocobalamin) are required for the folate metabolism to serve one-carbon units [62, 63].

One of the key enzymes in the folate metabolism is 5,10-Methylene Tetrahydro Folate Reductase (MTHFR) that catalyzes the reduction of 5,10-methylenetetrahydrofolate to 5-methylenetetrahydrofolate, the methyl donor for methionine synthesis from homocysteine [62].

MTHFR is a rate-limiting enzyme in the methyl cycle, and it is encoded by the MTHFR gene. The MTHFR nucleotide at position 677 in the gene has two variants: C (cysteine) or T (thymine). C at position 677 is the normal allele, the 677 T allele encodes a thermolabile enzyme with reduced activity. Homozygous individuals with two copies of 677C (677C/C) have the most frequent genotype, while people with the 677T/T variant have lower MTHFR activity than C/T or C/C individuals. Thus homozygous 677T/T persons have higher Homocysteine (Hct) concentrations, and Hct shows negative (grade I.) association with AD as shown below [35].

Depending on the population, 20-53% of individuals may have inherited one T copy (677C/T genotype) and 3-32% of the individuals may have inherited two T copies (677T/T) for the MTHFR gene, compared to individuals with the most frequent 677 C/C homozygous genotype [64, 65].

There are numerous studies investigating the association between MTHFR genotypes, folate, vitamin B6, B12 intake and serum levels and Hct concentrations in connection with AD. Religa et al. found that the concentration of plasma total Hct is increased in AD patients and this may be associated with T/T genotype in the MTHFR gene [66]. Recently, a comprehensive meta-analysis was performed involving in total 68 studies. Hct, folic acid and vitamin B12 levels in AD patients in comparison with controls, and their association with the risk of AD were evaluated. According to the results, AD patients may have lower levels of folate and vitamin B12 and higher level of Hct in plasma than controls. An age-subgroup analysis showed no age effect for Hct levels in plasma between AD patients and matched controls, while the differences in folate and vitamin B12 levels further expanded with increasing age. Data also suggested that high Hct and low folate levels may correlate with increased risk of AD occurrence [67].

Another comprehensive review and meta-analysis examined the role of vitamin B supplementation on MCI and AD. Results showed moderate beneficial effects of vitamin B supplementation on memory, whereas no significant difference on general cognitive function, executive function and attention were found in MCI patients. No significant cognitive benefits on the AD Assessment Scale and Mini Mental State Examination, functional, behavioural or global change were observed in AD patients. Collectively weak evidence of benefits were observed for the domains of memory in patients with MCI. Recent data does not yet provide adequate evidence of an effect of vitamin B on general cognitive function, executive function and attention in people with MCI. Similarly, folic acid alone or vitamin B in combination were unable to stabilize or slow down decline in cognition, function, behaviour and global change of AD patients [68].

A third meta-analysis investigated the effects of Hct lowering

effect of B vitamin treatment on cognitive function and on the rate of cognitive age. According to the results, B vitamins lowered Hct concentrations, but had no significant effect on individual cognitive domains or global cognitive function or cognitive ageing [69].

IV. Vitamin D: Vitamin D is a fat-soluble seco-steroid hormone. It exists in two isomorphs: Vitamin D3 (cholecalciferol) is synthesized in the skin, and vitamin D2 (ergocalciferol) is photosynthesized in plants. These inactive precursors are metabolized in the liver and kidneys. Following synthesis in the epidermis or dietary intake, both forms enter the circulation and are transported to the liver by the vitamin D binding protein. In the hepatocytes the inactive form is converted to 25-Hydroxyvitamin D3 or D2 (25(OH)D) which is activated in the kidney. The metabolically active form, 1,25-Dihydroxy Vitamin D (1,25(OH)₂D) is binding to Vitamin D Receptor (VDR) and directly or indirectly regulate hundreds of genes.

The major circulating form of vitamin D is the sum of 25(OH)D3 and 25(OH)D2 and used as a biomarker of vitamin D nutritional status [70]. VDRs are present in all the brain regions that are essential for cognition. Annweiler summarised the potential roles of vitamin D mediated by VDRs in the central nervous system as follows: Clearance of Aβ peptide; regulation of the intraneuronal calcium; anti-inflammatory action; anti-oxidative action; primary prevention and reduction of ischemic zone size; regulation of cholinacetyltransferase; regulation of neuro trophic agents [71].

a. Observational studies: Epidemiologic studies indicated that people with AD have lower vitamin D status than controls. A meta-analysis on the 25(OH)D status involving six studies proved that AD patients had lower levels of 25(OH)D than aged matched controls [71, 72]. Cross sectional and case control studies confirmed also that vitamin D concentrations are lower in individuals with cognitive impairment and dementia [73]. Recently published meta-analyses indicated that lower vitamin D status may be associated with an increased risk of developing dementia and AD [74].

b. Supplementation studies: Annweiler et al. studied the effect of vitamin D or memantine alone or combined in 43 outpatients (mean age 84.7 ± 6.3 years; 65.1% women) with new diagnosis of AD. Patients who took memantine plus vitamin D for six months had statistically and clinically increased cognitive improvement, meanwhile vitamin D or memantine alone showed no effect [75]. These results suggest that vitamin D supplementation is not sufficient to prevent AD by itself and so the development of a multi-target drug is necessary, using vitamin D supplements as an adjunct to standard anti-dementia treatments [71]. Based on the available data, the Vitamin D Council also concluded that other treatment should not be replaced by vitamin D in AD patients [76].

New theories for the development of AD

Vitamin D hypothesis: In early 2014, Gezen-Aket et al. presumed that long-term-hypovitaminosis D or inefficient

utilization of vitamin D may be a prime inducer of neurodegeneration in ageing and AD, which results in a long term hormonal imbalance. They hypothesized that vitamin D has protective effects in the central nervous system, because it is involved in the regulation of neurotrophic factor production, neurotransmitter levels, oxidative stress metabolism, calcium homeostasis, immune system function and induction of A β clearance. The term of insufficient utilization of vitamin D was suggested. According to the theory, vitamin D deficiency/hypovitaminosis has the potential result of accumulation of A β . On the other hand, A β may disrupt the utilization of vitamin D even if the systemic level of vitamin D is sufficient. Due to the accumulation of A β , the number of VDRs decrease and 24-hydroxylase concentration increase. This may result in the alteration of vitamin D related genes and the consequence may be the inefficient utilization of vitamin D [77].

The role of arginine: Kan et al. studied the immune system of the CVN-AD mouse, a model of human AD. In the brain of the mouse model plaques, tangles and hippocampal neuron death are present, resulting in rodent memory loss. Areas of hippocampal neuron death were associated with the immunosuppressive CD11c+ microglia and extracellular arginase, resulting in arginine catabolism and reduced level of total brain arginine. Difluoromethyl-Ornithine (DFMO) was used to block arginase before the symptoms of AD appeared. As a result, fewer plaques could be identified and the mice performed better on memory tests. This study suggests that in AD certain immune cells that normally protect brain begin to abnormally consume arginine. The data indicate that immune suppression and arginine catabolism lead to a loss of arginine and its deprivation is followed by cell death. Authors concluded, that in contrast to previous views which considered AD as driven by immunity and inflammation, it is rather associated with an immunosuppressive pattern [78].

The study of Kan et al. has been commented by several experts [79]: Spiers-Jones highlighted that the results need to be confirmed in other models as well before moving into human studies. According to Pickett, the next step would be to show that targeting arginine metabolism in the brain can reduce the death of brain cells. Phipps warned that clinical trials are essential before any potential new treatment can be given to people. The question arises, whether arginine supplementation can prevent AD. Arginine supplementation is not recommended, because the blood-brain barrier would prevent arginine to go into the brain, and even if it does get through, arginine would be still degraded by the arginase enzyme [80].

The best way to maintain a healthy brain throughout the life is to ensure a balanced diet, no smoking, being mentally and physically active with regular exercise, and to keep blood pressure and cholesterol level controlled, as summarised by Phipps.

It is undeniable that the hypothesis of Kan generated a new idea in Alzheimer research, but it needs more data to prove it [79].

The role of Polyunsaturated Fatty Acids (PUFAs):

More than half of the solid brain matter is composed of membrane lipids, which are predominantly phospholipids. A large proportion of phospholipids are PUFAs, that belong to the ω -6 and ω -3 classes. AA, (arachidonic acid C20:4,n-6) and DHA, (docosahexaenoic acid C22:6,n-3) are the main components of these classes.

Eonic EPA (eicosapentaenoic acid C20:5,n-3) quickly disappears from the system.

The effects of PUFAs on the brain functions are the following: They modify neuronal membrane fluidity, membrane activity, the number and affinity of receptors, the function of neuronal membrane ionic channels, and the production of neurotransmitters and brain peptides.

Free ω -6 and ω -3 PUFAs are precursors to the local hormones, i.e. eicosanoids. Eicosanoids are involved in numerous brain functions, sometimes with conflicting or opposing effects. For example prostaglandins derived from ω -6 PUFAs are highly potent and proinflammatory, but ω -3 products have an anti-inflammatory effect. Eicosanoids exert important effects on vascularity, including increased blood flow and permeability of various membranes. In the aging brain the concentration of ω -6 PUFAs decrease, while ω -3 PUFAs increase. It is suggested that the optimal ratio of ω -6/ ω -3 is 4:1 in the brain to protect and stabilize the neuronal membrane in health and disease [81, 82].

Several studies examined the effect of ω -3 PUFAs on cognition and AD. In AD animal model, DHA has been demonstrated to reduce A β production and pathological changes. However, the results in human studies are contradictory. Some studies suggest that supplementation or higher dietary intake of ω -3 fatty acids are related to reduced risk of dementia and AD, while other studies failed to find this association [5, 41, 83-85]. In a study the connection among serum Hcy, ω -3 fatty acids and B vitamins (folic acid, vitamins B6 and B12) was investigated. Participants with MCI with low ω -3 status at the baseline showed no effect from B vitamin treatment, while those in highest tertile for ω -3 fatty acid or DHA, B vitamins significantly slowed the rate of cognitive and clinical decline. Results call the attention to the necessity to investigate the interactions of different nutrients [86, 87]. Recently, a meta-analysis was conducted to review the association of dietary intake of ω -3 PUFAs or fish, an important source of ω -3 fatty acids, and the incidence of dementia and AD. According to the results, dietary intake of ω -3 PUFAs was not associated with lower risk of dementia or AD in any case.

Higher intake of fish did not have a significant association with lower risk of dementia, but a borderline significant 36% lower risk of AD was demonstrated for those with the highest fish intake. A dose-response meta-analysis showed that each 100 g/week intake of fish was associated with an 11% lower risk of AD. The protective effect of fish intake may have several reasons: Fish is a good source of ω -3 PUFAs, especially DHA. Fish is also a good source of other nutrients such as vitamins, essential amino acids and trace elements, and these may also contribute

to cognitive function improvement. Generally, fish intake maybe associated with a healthier dietary pattern, and high fish intake maybe associated with lower intake of other types of fat, such as saturated fat. This meta-analysis also showed that the higher intake of fish was associated with lower risk of AD, while ω -3 PUFAs intake did not influence the risk of dementia and AD [88].

The role of diabetes: Some papers suggest a connection between Type 2 Diabetes Mellitus (T2DM) and dementia and AD [89-91]. However, the findings are inconsistent. Some studies state that there is no direct relationship between AD and diabetes. It seems that diabetes is more strongly and consistently associated with vascular form of cognitive impairment rather than with AD like neurodegenerative forms [92, 93].

A recently issued meta-analysis showed no evidence based association between T2DM and AD in western population, however there is a significant association between T2DM and AD in Asian population [35].

To absolve this inconsistency, a concept has been proposed that AD might represent a specific form of brain diabetes and so de La Monte and Wands put forward the term 'type 3 diabetes' that selectively involves the brain. They proved with human and experimental animal studies that CNS impairments in Insulin/Insulin Like Growth Factor (IGF) signalling mechanism can occur in the absence of Type 1 And 2 Diabetes Mellitus (T1DM and T2DM2). T2DM was not sufficient to cause AD, although it could be possible serve as a cofactor in its pathogenesis or progression. They concluded that AD is a neuro endocrine disease caused by selective impairments in insulin and IGF signalling mechanism, including deficiencies in local insulin and IGF production. The accompanying inflammatory response, oxidative stress, DNA damage and mitochondrial dysfunction have also been proposed to contribute to the degenerative cascade causing brain damage [94].

Obesity: A recent meta-analysis estimated grade I. evidence for high BMI in midlife as well as low BMI to be correlated with AD [35]. However, the available evidence from epidemiological studies associated with overweight and obesity as measured by BMI in midlife is still conflicting. The relationship between BMI in midlife and late-life and dementia was investigated in another meta-analysis. According to the follow-up prospective study in midlife, Underweight, overweight and obese BMIs were associated with increased risk of dementia as compared to the normal BMI. Risks appeared to be the highest for underweight and obese BMI. An U-shaped relationship was suggested between midlife BMI and late-life risk of dementia. Findings were similar for AD as well. But in late-life continuous BMI was not associated with dementia, probably because of some methodological factors, such as the insufficient length of follow-up and the small size of the groups [95].

According to a prospective population-based cohort with a 26 years follow-up study, higher midlife (mean age: 50.2 \pm 6.0 y) BMI was related to higher risk of dementia and AD. Steeper decrease of BMI and low late-life (mean age: 71.2 \pm 4.9 y) BMI were associated with higher risk of dementia and AD [96].

Luchsinger et al. compared the predictive value of BMI to dementia. Hazard ratios relating quartiles of BMI to dementia in persons <76 years old and persons \geq 76 years old were characterized. In persons <76 years old the association between BMI and dementia resembled an U-shape, the second and third quartiles were related to lower risk, while the fourth was similar to the reference. In older people, the risk of dementia decreased with increasing BMI. Continuing this study authors explored whether measures of central obesity were better predictors of AD compared to BMI in elderly. They established that the association between adiposity and dementia differs depending on anthropometric measures used and is modified by age. It has been shown that BMI loses predictive ability in the elderly and Waist To Hip Ratio (WHR) is a better predictor of AD compared to other measures. It also helps to explain the apparent discrepancies in studies reporting on obesity in elderly and AD [97, 98].

The effects of some modifiable risk factors for AD and dementia are highlighted in Table 2.

Dietary patterns and guidelines

Diet and nutrition might be important modifiable risk factors of AD. Single nutrients are not consumed in isolation but as part of a diet. Examining the role of a single nutrient is difficult also due to the interaction between the different nutrients. Therefore examining foods, rather than single nutrients might be more useful [41]. Recently dietary pattern analysis was introduced, as a way for examining diet-disease relations in AD. Dietary pattern is defined as quantities, proportions, variety or combination of different foods, drinks and nutrients in diets and frequency, with which they are habitually consumed [99]. Among dietary patterns, Mediterranean, Japanese and healthy diets have been reported to be associated with lower risk of AD. However, further studies are needed to explore the importance of diets in dementia and AD [41].

A subgroup of the Dietary Guidelines Advisory Committee (DGACS2) assessed the connection between several dietary patterns, food and nutrients and dementia and AD. They concluded that patterns higher in fruits, vegetables, nuts, legumes and seafood were generally associated with reduced risk; patterns higher in red and/or processed meats were generally associated with greater risk; relatively few studies reported on refined sugar and added salt, but patterns including these nutrients tended to report greater risk [99].

At the International Conference on Nutrition and Brain, experts recommended guidelines for AD prevention as follows [100]:

- 1.) Minimize saturated trans-fat intake
- 2.) Vegetables, fruits, legumes and whole grains should replace meat and dairy products
- 3.) Vitamins should come from food, however, recommended intake and adequate status is difficult to achieve
- 4.) A reliable source of vitamin B12 providing at least the recommended daily allowance

Table 2: Effect of some modifiable risk factors for AD and dementia

Reference	Study selection	Purpose	Number of studies included, sample size	Main outcome	Conclusion
Farina et al. 2012 [42]	Double-blind randomized trials	To assess the efficacy of Vitamin E in the treatment of AD and prevention of progression of MCI to dementia	Two studies analyzed in AD and one in MCI population	First of the AD studies: reported some benefit from Vitamin E (Sano); Second AD treatment study: patients whose oxidative stress markers were lowered by Vitamin E showed no improvement in cognitive status (Lloyd); Third study: Vitamin E had no beneficial effect on progression from MCI to AD.	No convincing evidence that Vitamin E treatment is beneficial in the treatment of AD or MCI. In some cases increased mortality. Vitamin E should not be used for the treatment of MCI and AD. More trials are needed and these should include different forms of Vitamin E.
ADDF 2014 [59], Li et al. 2012 [103]	n/a	Evaluate the association between dietary intake of Vitamin C, E, β Carotene and risk of AD	n/a	Dietary intake of these antioxidants can lower the risk of AD. Vitamin E exhibiting the most pronounced protective effects.	Findings will be of significance in the prevention and interventional treatment of AD.
Shen & Ji 2015 [67]	Comprehensive meta-analysis	To evaluate: 1) Hcy, folic acid and Vitamin B12 levels in AD patients; 2) the association between Hcy, folic acid and B12 levels and risk of AD	68	1) AD patients may have higher level of Hcy and lower levels of folate and Vitamin B12. 2) No age effect for Hcy level in plasma.	Analyses 1) confirmed higher Hcy, lower folic acid and B12 levels are in AD patients; 2) Data suggests that high Hcy and low folic acid levels may be risk factors of AD.
Li et al. 2014 [68]	n/a	To assess the efficacy of Vitamins B supplementation in slowing the rate of cognitive, behavioral, functional and global decline in MCI and AD patients	5 trials were analyzed	1) Moderate beneficial effects of Vitamins B supplementation in memory, no significant difference in cognitive and executive functions, and attention in MCI 2) No significant benefits on cognitive functions in AD.	Data does not provide adequate evidence of an effect of Vitamins B on general cognitive and executive functions and attention in people with MCI. Folic acid alone or Vitamins B alone or in combination are unable to stabilize or slow decline in cognition, function, behaviour and global change in AD.
Clarke et al. 2014 [69]	Placebo-controlled randomized trials	To assess the effects of treatment with Vitamins B administered for several years, compared to placebo on composite domains of cognitive functions, global cognitive functions and cognitive aging	11 large randomized trials in 22,000 patients. Domain-based Z scores (memory, speed and executive function) before and after treatment (mean ~2.3y) in the 4 cognitive domain trials (n=1,340) MMSE-Type tests at the end of treatment (mean ~5y) in 7 global cognition trials (n=20,431)	Domain-composite and MMSE-type global cognitive function Z scores decreased with age. B vitamins lowered Hct in cognitive-domain trials, but no significant effects on the Z scores differences from baseline for individual domains or for global cognitive function - similar effect in the global cognition trials.	Hcy lowering with B vitamins has no effect on individual cognitive domains or global cognitive functions nor cognitive aging.
Zhao et al. 2013 [72]	n/a	To examine the 25(OH) D status in AD patients	6 studies, 319 patients and 573 controls	AD patients had lower levels of 25(OH)D levels than controls	Despite the similar mean age of AD patients and controls, patients had lower levels of 25(OH)D than controls.

Shen & Ji 2015 [74]	Random-effect model	To estimate the association between vitamin D deficiency and risk of developing AD and dementia	Flowchart selection from 526 references, 5 studies included	Subjects with deficient vitamin D status (25(OH) D<50nmol/l were at increased risk of developing AD and dementia.	Data indicate that vitamin D deficiency may be associated with increased risk of developing AD and dementia. Studies are needed to evaluate the beneficial effects of vitamin D supplementation.
WU et al. 2015 [88]	Prospective cohort	To review the association between dietary intake of long-chain n-3 fatty acids (FA), fish and the incidence of dementia and AD	1,361 potentially relevant articles; 6 studies included	1) Higher dietary intake of n-3 FAs was not associated with lower risk of AD or dementia. 2) Higher intake of fish was associated with lower risk of dementia.	Most studies confirmed an inverse relationship between higher fish intake and AD, but statistically significant association between long chain n-3FA intake and AD risk was not evident.
Anstey et al. 2011 [95]	Prospective cohort	Evaluate the association of BMI with risk of dementia in midlife and late life	15 prospective studies	Underweight, overweight and obese individuals have increased dementia risk. Risks appeared to be the highest for underweight and obese BMI, suggesting a U-shaped relationship between midlife BMI and dementia risk. Findings were similar for AD and any other dementia.	Reducing the impact of obesity on dementia prevalence and incidence should be priority to governments, health providers and the general public.

- 5.) If using multivitamins, choose those without iron, copper
- 6.) Although aluminium's role in AD remains a matter of investigations those who desire to minimize their exposure can avoid to use products that contain aluminium
- 7.) Include aerobic exercise in your routine

Conclusion

Considering that the incidence and prevalence of currently incurable AD is constantly and rapidly increasing in the ageing societies worldwide, besides pharmaceutical drug development there is an urgent need for alternative solutions for both prevention and treatment. Optimizing the nutritional status of the general population as a preventive measure may provide additional support to therapeutic concepts as they become available [5]. However, currently the scientific evidence regarding the effects of diet and nutrients on AD is incomplete and there are still a lot of opportunities for the nutrition scientists to contribute to the clarification of the conflicting results and adjust guidelines accordingly [100, 101]. Nevertheless, pathophysiological characteristics of AD such as neuroinflammation, glucose dysregulation, homocysteine accumulation and neuronal loss can be considerably and positively influenced by proper nutrition [102]. Moreover, already several RCTs have demonstrated promising results for nutrients to decrease the risk of developing AD and maintaining cognitive performance. Thus, lifelong optimal supply of essential micro- and macronutrients may greatly contribute to delay the onset of AD.

Conflict of Interest

MA received an honorarium from DSM Nutritional Products Ltd. for writing the article. SP and ME are employees of DSM Nutritional Products Ltd.

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