

## REVIEW

## Nutritional interventions in patients with Alzheimer's disease and other late-life cognitive disorders

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Given the impact of nutrition on neuroprotection largely investigated in observational studies, in the present article, we reviewed evidence from randomized clinical trials (RCTs) published in the last three years (2014-2016) exploring nutritional intervention efficacy in slowing cognitive impairment progression and achieving cognitive-related outcomes in patients aged 60 years and older with mild cognitive impairment (MCI), preclinical Alzheimer's disease (AD), prodromal AD, AD, unspecified dementia, and vascular dementia using different levels of investigation (i.e., medical food/nutraceutical supplementation/multidomain approach and dietary food/macro- and micronutrient approaches). From the reviewed RCTs, there was emerging evidence that nutritional intervention through medical food/nutraceutical supplementation (Fortasyn Connect<sup>®</sup> and another similar nutraceutical formulation) and multidomain approach improved magnetic resonance imaging findings and other cognitive-related biomarkers, but without clear effect on cognition in mild AD and MCI. Moreover, there was some evidence of a positive effect of antioxidant-rich foods (nuts) in improving specific cognitive domains and cognitive-related outcomes in MCI and mild-to-moderate dementia, but only in small samples. There was also convincing evidence for fatty acid supplementation, mainly n-3 polyunsaturated fatty acids (PUFAs), in improving specific cognitive domains and/or cognitive-related biomarkers in MCI and AD. Furthermore, antioxidant vitamin and trace element supplementations improved only cognitive-related outcomes and biomarkers, without effect on cognitive function in AD and MCI patients. Finally, high-dose B vitamin supplementation in AD and MCI patients improved cognitive outcomes but only in the subjects with a high baseline plasma n-3 PUFA, while folic acid supplementation had positive impact on specific cognitive domains.

**Key words:** Alzheimer's disease, Dementia, Medical food, Nutraceuticals, Macronutrients, Micronutrients

### INTRODUCTION

By 2050, the number of people living with Alzheimer's disease (AD), an age-related neurodegenerative disorder, or other dementias in the United States is projected to nearly double from 48 million to 88 million<sup>1</sup>. Therefore, considering the public health impact of AD and

the absence of available disease-modifying therapies for AD treatment<sup>2</sup>, there is a great need in preventing the onset of the disease and slowing AD progression. In the last two decades, in addition to cardiovascular risk factors, several observational studies suggested a wide variety of potentially modifiable risk factors for late-life cognitive impairment and AD such as psychological

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conditions, education level, engagement in social and mentally stimulating activities, sensory changes, and lifestyle including diet, physical activity and voluptuary habits<sup>3,4</sup>. In particular, several nutritional supplements have been studied for their potential role as neuroprotective interventions in AD and cognitive disorders in older age.<sup>5</sup> This protective effect could be mediated by several pathobiological pathways involved in AD development such as amyloid- $\beta$  (A $\beta$ ) deposition, neurofibrillary degeneration, synapse loss, inflammation, oxidative stress, mitochondrial dysfunction, loss of vascular integrity, and neuronal injury. In particular, late-life cognitive disorders were associated with synaptic abnormalities and dysfunction<sup>6</sup>, the last currently considered as one of the pathological hallmarks of AD<sup>7</sup>. Therefore, several observational studies and randomized clinical trials (RCTs) have proposed nutritional interventions as preventive or therapeutic approaches in order to slow the progression of cognitive impairment in older subjects or reducing AD risk and progression. In particular, several meta-analyses and systematic/scoping reviews investigated the efficacy of different nutritional supplementations in preventing late-life cognitive disorders in cognitively healthy older adults with encouraging findings<sup>8-12</sup>. Some of these studies found that n-3 polyunsaturated fatty acids (PUFAs) were associated with improved global cognition and some specific cognitive domains, magnetic resonance imaging (MRI) findings, and/or cognitive-related biomarkers<sup>9-12</sup>. B vitamins, and vitamin E supplementations did not affect cognition<sup>8</sup> or had limited efficacy<sup>9,11,12</sup>, while adherence to the Mediterranean diet was significantly associated with better cognitive performance and less cognitive decline<sup>10,12</sup>. Moreover, for patients with mild cognitive impairment (MCI), AD, or dementia, there were fewer systematic reviews and meta-analyses investigating RCTs conducted on nutritional intervention<sup>13-16</sup>.

Furthermore, in the last years, according to the National Institute on Aging-Alzheimer's Association (NIA-AA) guidelines for AD due to AD pathology<sup>17</sup> and International Working Group (IWG)-1<sup>18</sup> and IWG-2 criteria for AD<sup>19</sup>, it has been suggested a direct impact of nutrition on brain structure and activity changes<sup>4</sup>. Furthermore, there was an increased need to objectively quantify the effects of nutrients on cognitive-related outcomes not only in terms of cognitive scores or clinical scales, so opening the era of brain imaging biomarkers also for nutritional epidemiology<sup>20</sup>. Finally, the use of objective measures of dietary habits, not only using daily semi-quantitative food frequency questionnaires, but also biochemical markers (e.g., serum concentration or red blood cells levels), also emerged to achieve more reliable findings. The present study sought to provide a comprehensive systematic review of the RCTs published in the past

three years (2014-2016) about nutritional intervention efficacy in slowing cognitive impairment progression and achieving cognitive-related outcomes in patients aged 60 years and older with late-life cognitive disorders, i.e., MCI, preclinical AD, prodromal AD, AD, unspecified dementia, and vascular dementia (VaD), using different levels of investigation (i.e., medical food/nutraceutical supplementation/multidomain approach and dietary food/macro- and micronutrient approaches).

## NUTRITIONAL INTERVENTION THROUGH MEDICAL FOOD/NUTRACEUTICAL SUPPLEMENTATION AND MULTIDOMAIN APPROACH

### MEDICAL FOODS/NUTRACEUTICALS

Table I shows selected RCTs published in the last three years that evaluated the efficacy of nutritional intervention through medical foods/nutraceutical supplementation and multidomain approach in the treatment of patients with late-life cognitive disorders aged over 60 years<sup>21-27</sup>. Therefore, it is likely that the potency of single nutrients may be insufficient to achieve a clinically relevant benefit<sup>5</sup>. Based on the increasing body of evidence about the potential beneficial effect of specific nutrients properly combined, several RCTs investigated medical foods and nutraceutical supplementations characterized by a specific well studied combination of nutrients in different phases of cognitive dysfunction. Several medical foods and multinutrient interventions have been tested showing promising findings, not only in earlier phases of cognitive impairment<sup>5</sup>.

#### *Fortasyn Connect*<sup>®</sup>

The medical food Fortasyn Connect<sup>®</sup> contains a specific nutrient combination of docosahexaenoic acid (DHA) 1200 mg, eicosapentaenoic acid (EPA) 300 mg, uridine monophosphate 625 mg, choline 400 mg, folic acid 400 mcg, vitamin B6 1 mg, vitamin B12 3 mcg, vitamin C 80 mg, vitamin E 40 mg, selenium 60 mcg, and phospholipids 106 mg, designed to ameliorate synapse loss, synaptic dysfunction, and other pathological pathways affected in AD patients<sup>28</sup>. In fact, several neuroprotective effects of Fortasyn Connect<sup>®</sup> have been reported in preclinical studies such as increases in markers of synaptogenesis<sup>29</sup>, neurotransmitter synthesis and release<sup>29</sup>, and cerebral blood flow<sup>30</sup>, preservation in matter integrity<sup>30</sup>, reduction in A $\beta$  production and toxicity<sup>31</sup>, and restoration of neurogenesis<sup>32</sup>. In two previous RCTs, Souvenir I<sup>33</sup> and Souvenir II<sup>34</sup>, Fortasyn Connect<sup>®</sup> improved memory performance in mild AD patients not taking AD medications. In particular, in

Souvenir I, Fortasyn Connect® significantly improved delayed verbal recall test of the Wechsler Memory Scale revised edition (WMS-r) in mild AD patients [Mini Mental State Examination (MMSE) score 20-26] after 12 weeks of intervention *versus* placebo without effects on the 13-item modified Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog)<sup>33</sup>. In Souvenir II, significant improvements on the memory domain composite z-score based on a Neuropsychological Test Battery (NTB) during the 24 weeks were observed in mild AD patients (MMSE score  $\geq$  20)<sup>34</sup>. In addition, an exploratory analysis of results from a 24-week open-label extension (OLE) of Souvenir II suggested that memory function improved throughout 48 weeks in patients with mild AD taking Fortasyn Connect®<sup>35</sup>. However, a third RCT, the S-Connect study, in patients with mild-to-moderate AD (MMSE score 14-24) receiving AD medications did not show any Fortasyn Connect® effects on cognition<sup>36</sup>. In a recent effect size analysis conducted on Souvenir I, Souvenir II, S-Connect, and the OLE of Souvenir II, in patients with mild AD, effect sizes were 0.21 [95% confidence interval (CI): -0.06, 0.49] for the primary outcome in Souvenir II (NTB z-score) and 0.20 (95% CI: 0.10, 0.34) for the co-primary outcome of Souvenir I (WMS-r delayed recall). No effect was shown on cognition in patients with mild-to-moderate AD (S-Connect)<sup>37</sup>. Recently, a biomarker panel of ten plasma lipids, including 8 phosphatidylcholine species, showed to predict conversion from cognitive normal aged adults to amnesic MCI or AD within 2-3 years with > 90% accuracy<sup>38</sup>, with the reduced levels of these plasma phospholipids reflecting altered phospholipid metabolism in the brain and periphery. Using data from the Souvenir II<sup>34</sup>, a 24-week intervention with Fortasyn Connect® in 96 drug-naïve patients with very mild to mild AD significantly increased 5 of the 7 measured biomarker phosphatidylcholine species (Tab. I)<sup>21</sup>, suggesting that this nutritional intervention could be useful in asymptomatic subjects with a plasma lipid biomarker profile prognostic of AD. Considering synaptic loss as an early pathological hallmark in AD related to memory impairment, macroscopic brain activity modifications measured with electro- and magnetoencephalography (EEG and MEG) might indicate synaptic changes in AD and has been proposed to identify nutritional intervention effects in clinical trials. In an interesting RCT was investigated the Fortasyn Connect® effects on synaptic integrity and function, assessed by advanced EEG analysis, considering brain activity-based networks as a derivative of underlying synaptic function (Tab. I)<sup>22</sup>. In this RCT, 179 drug-naïve mild AD patients were randomised to receive Fortasyn Connect® or placebo for 24 weeks. The network measures in the beta band were significantly different between groups. In fact, it

decreased in the control group, but remained relatively unchanged in the supplemented one, suggesting Fortasyn Connect® role in preventing the progressive network disruption in AD patients. However, these network measures were not related to memory performance (Tab. I)<sup>22</sup>. Using cumulative data from the Souvenir I (n = 212), Souvenir II (n = 259), S-Connect (n = 527), and the OLE of Souvenir II (n = 201), Rijpma et colleagues showed that circulating levels of micronutrients and fatty acids, including uridine, selenium, folate, vitamin B12, vitamin E, vitamin C, DHA and EPA, decreased in the AD population and can be increased by 12-48-week oral supplementation with Fortasyn Connect®<sup>23</sup>. In the OLE study, similar levels were reached in former control product/initial active product users, whereas 24-week continued active product intake showed no suggestion of a further increase in nutrient levels (Tab. I)<sup>23</sup>. Furthermore, in another RCT, comparing quantitative markers regarding spectral properties, functional connectivity, and graph theoretical aspects of MEG from the Souvenir II MEG sub-study in 55 drug-naïve mild AD patients, no significant intervention effects were found between the Fortasyn Connect® group and the placebo one (Tab. I)<sup>24</sup>.

#### Other nutraceutical formulations

Two trials reported significant and promising findings on a nutraceutical multinutrient formulation [400 ug folic acid, 6 ug B12, 30 I.U. alpha-tocopherol, 400 mg S-adenosyl methionine (SAM), 600 mg N-acetyl cysteine, and 500 mg acetyl-L-carnitine] in AD and MCI patients (Tab I)<sup>25,26</sup>. In the first RCT, including 106 AD patients randomized to the nutraceutical formulation or placebo for 3 or 6 months, followed by an additional nutraceutical formulation supplementation of 6 months, participants in the intervention group improved statistically *versus* baseline and placebo in cognitive performance evaluated by CLOX-1 (Clock Drawing Test sensitive to executive control) and age- and education-adjusted Dementia Rating Scale (DRS), and in the memory domain of the age-education-adjusted DRS (Tab. I)<sup>25</sup>. In the second RCT, 34 MCI subjects were randomized for 6 months to the nutraceutical formulation or placebo and then, for another 6-month period, all individuals received nutraceutical formulation. Interestingly, the nutraceutical formulation cohort improved in the age- and education-adjusted DRS and maintained baseline performance in CLOX-1, while the placebo cohort did not improve in the age- and education-adjusted DRS and declined in CLOX-1, but during the open-label extension improved in the age- and education-adjusted DRS and ceased declining in CLOX-1 (Tab. I)<sup>26</sup>.

#### MULTIDOMAIN APPROACH

According to the increasing interest on healthy lifestyle

**Table I.** Randomized clinical trials evaluating the efficacy of nutritional intervention through medical food/nutraceutical supplementation and multidomain approach in the treatment of patients with late-life cognitive disorders aged over 60 years (2014-2016).

Reference	Study sample	Intervention(s)	Duration	Cognitive-related outcomes and nutritional assessment	Principal results
<b>Medical food/nutraceutical supplementation</b>					
Hartmann et al., 2014 <sup>21</sup>	96 drug-naïve mild AD patients  Mean age: not reported	Fortasyn Connect® Placebo	24 weeks	Plasma concentration of specific PC species	Five of the 7 measured PC species were significantly increased following the 24-week treatment with this multinutrient combination
de Waal et al., 2014 <sup>22</sup>	179 drug-naïve mild AD patients  Mean age: 73.3 years	Fortasyn Connect® Placebo	24 weeks	NTB and EEG	Significant effects on network measures in the beta band without significant effects on cognitive outcomes
Rijpmma et al., 2015 <sup>23</sup>	1199 drug-naïve mild and mild-to moderate AD patients  Mean age: 74.5 years	Fortasyn Connect® Placebo	12-24 weeks	Plasma levels of B vitamins, choline, vitamin E, selenium, uridine and homocysteine and proportions of DHA, EPA and total n-3 PUFAs in plasma and erythrocytes	12-24-week active product intake increased plasma and/or erythrocyte micronutrients: uridine, choline, selenium, folate, vitamins B6, B12 and E, and levels of DHA and EPA
van Straaten et al., 2016 <sup>24</sup>	55 drug-naïve patients with mild AD  Mean age: 69.0 years	Fortasyn Connect® Placebo	24 weeks	EEG and MEG	No statistically significant intervention effects
Remington et al., 2015a <sup>25</sup>	106 AD patients  Mean age: 77.8 years	Nutraceutical formulation (400 ug folic acid, 6 ug B <sub>12</sub> , 30 I.U. alpha-tocopherol, 400 mg S-adenosyl methionine (200 mg active ion), 600 mg N-acetyl cysteine, and 500 mg acetyl-L-carnitine) Placebo	12 months (3 or 6 months with a 6-month open-label extension study)	CLOX-1, DRS, NPI, and ADCS-ADL	At 3 months, there was cognitive improvement for the intervention group in CLOX-1 and the DRS total score and memory domain score
Remington et al., 2015b <sup>26</sup>	34 MCI patients  Mean age: 62.0 years	Nutraceutical formulation (400 ug folic acid, 6 ug B <sub>12</sub> , 30 I.U. alpha-tocopherol, 400 mg S-adenosyl methionine (200 mg active ion), 600 mg N-acetyl cysteine, and 500 mg acetyl-L-carnitine) Placebo	12 months (6 months with a 6-month open-label extension study)	CLOX-1 and DRS	The nutraceutical formulation cohort improved in the DRS and maintained baseline performance in CLOX-1. The placebo cohort did not improve in DRS and declined in CLOX-1, but during the open-label extension study improved in DRS and ceased declining in CLOX-1



Reference	Study sample	Intervention(s)	Duration	Cognitive-related outcomes and nutritional assessment	Principal results
<b>Multidomain approach</b>					
Köbe et al., 2016 <sup>27</sup>	22 MCI patients  Mean age: 70 years	Multidomain intervention with n-3 PUFA, aerobic exercise and cognitive stimulation Control group	6 months	AVLT, TMT-A-B, SCWT, forward and backward digit spans, verbal fluency (semantic and phonemic)  Erythrocyte membrane fatty acid compositions, anthropometric measures, serum vascular, metabolic and inflammatory parameters, and structural MRI	Gray matter volume decreased in the frontal, parietal and cingulate cortex of patients in the control group, while 39 gray matter volume in these areas was preserved or even increased after the multidomain intervention. No significant differences in cognitive performance or other vascular, metabolic and inflammatory parameters were observed between groups

AD: Alzheimer's disease; PC: phosphatidylcholine; EEG: electroencephalography; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; PUFAs: polyunsaturated fatty acids; MEG: magnetoencephalography; MRS: magnetic resonance spectroscopy; PME: phosphomonoester; PDE: phosphodiester; tCho: choline-containing compounds; MRI: magnetic resonance imaging; CLOX-1: clock drawing task sensitive to executive control; DRS: Dementia Rating Scale; NPI: Neuropsychiatric Inventory; ADCS-ADL: Alzheimer's Disease Cooperative Study – Activities of Daily Living; AVLT: Auditory Verbal Learning Test; TMT-A-B: Trail Making Test part A and B; SCWT: Stroop Color-Word Test

including good dietary habits and physical activity as an effective multidomain therapeutic approach for cognitive impairment, several studies investigated the efficacy of physical exercise programs combined with nutrient supplementations. Epidemiological studies demonstrated that links exist between nutrition, physical activity, and cognitive and social stimulation that help to improve brain health <sup>5</sup>. The findings of several RCTs have suggested that some single-domain interventions, i.e., antihypertensives, nutritional supplements, cognitive training, and physical activity, had protective effects on cognitive decline <sup>39</sup>, but these results have seldom been replicated in larger samples. As prevention has been advocated as an effective way to reduce the burden of AD <sup>40</sup>, multidomain interventions seem therefore appropriate to target the multiple factors involved in cognition and ageing. In the last years, some European multidomain intervention trials with nutritional guidance, physical exercise, cognitive training and social activities, and management of vascular/metabolic risk factors conducted in subjects at risk of cognitive decline [Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability

(FINGER) <sup>41</sup> and the Prevention of Dementia by Intensive Vascular care (preDIVA) trial <sup>42</sup>] or with subjective memory complaints [Multi-domain Alzheimer Preventive Trial (MAPT) <sup>43</sup>] showed some promising findings with beneficial effects on cognition in an at-risk older general population <sup>41</sup> and some benefits on dementia incidence in at-risk subgroups (i.e., preDIVA participants with untreated hypertension at baseline who adhered to the intervention) <sup>42</sup>. However, we had only limited data on patients with established cognitive dysfunction. In a recent RCT, the effect of combined n-3 PUFA supplementation, aerobic exercise and cognitive stimulation *versus* n-3 PUFA supplementation and non-aerobic exercise was evaluated on cognitive function and gray matter volume at MRI in patients with MCI (Tab. I) <sup>27</sup>. This trial demonstrated that n-3 PUFA intake combined with aerobic exercise and cognitive stimulation over six months led to reduced atrophy in AD-related brain regions of MCI patients, compared to n-3 PUFA intake plus the control condition of stretching and toning. No significant group differences emerged for cognitive parameters over time (Tab. I) <sup>27</sup>.

## NUTRITIONAL INTERVENTION THROUGH FOOD AND MACRONUTRIENT SUPPLEMENTATION

### Foods

Table II shows selected RCTs published in the last four years evaluating the efficacy of nutritional intervention using a food or macronutrient approach in the treatment of patients with late-life cognitive disorders aged over 60 years<sup>44-52</sup>.

### Nuts

Considering the known links among late-life cognitive decline, AD, and oxidative stress<sup>53,54</sup>, Brazil nuts, the best food source of an important antioxidant trace element, i.e., selenium<sup>55</sup>, have been recently investigated as a possible source of supplementation for late-life cognitive disorders. However, only a few studies have investigated whether selenium supplementation can benefit cognitive performance, and in most of them, selenium was part of a multinutrient supplementation<sup>33,34,56</sup>. Furthermore, none of these RCTs have used foods rich in selenium as a source of supplementation. Recently, in a small RCT on 31 MCI patients randomly assigned to ingestion of Brazil nuts or placebo for 6 months, verbal fluency, and constructional praxis were the cognitive domains significantly improved in the supplemented group (Tab. II)<sup>44</sup>.

### MACRONUTRIENTS

#### Lipids

In AD brains, it has been reported a reduction in choline acetyltransferase, a biosynthetic enzyme of acetylcholine responsible for converting choline into acetylcholine<sup>57</sup>. Therefore, the first dietary lipids proposed as potential therapeutic agents in AD were lecithin, the major dietary source of choline, and alpha lipoic acid, both able to increase acetylcholine production<sup>58</sup>. However, the first studies documented how use of lecithin, after the first exciting results, has not really helped to improve the cognitive deficits of treated patients in a significant manner<sup>59</sup>. Furthermore, a decline of phospholipids in neuronal membranes, particularly phosphatidylserine (PS), has been associated with memory impairment and deficits in mental cognitive abilities<sup>60,61</sup>, leading to the proposal that administration of endogenously occurring phospholipids may prevent or reverse age-related neurochemical deficits. Recently, early pilot studies performed with a brain-health food supplement containing a proprietary blend of 100 mg PS and 80 mg phosphatidic acid (PA) produced from soy lecithin have been proposed<sup>45</sup>. Among these studies, a 2-month RCT assessed the effect of three PS/PA capsules/day (300 mg PS plus 240 mg PA/day) or placebo on daily

functioning, mental health, emotional state, and self-reported general condition in patients with AD (Tab. II)<sup>45</sup>. In AD patients, daily functioning (i.e., 7 activities of daily living) under PS/PA (n = 53) remained unchanged, but declined from 5.62 to 4.90 under placebo (n = 39), with significant group difference. The PS/PA group had 3.8% deterioration and 90.6% stability in daily functioning, compared to 17.9% and 79.5% under placebo. The PS/PA patients reported positive trend with a 49% improved general condition, compared to 26.3% under placebo (Tab. II)<sup>45</sup>.

#### Fatty acids

Many epidemiological studies have demonstrated that dietary fatty acids may play a key role in several pathological conditions. Long-chain (LC) PUFAs, such as DHA, EPA, and arachidonic acid (ARA) are among the most studied macronutrients in late-life cognitive disorders and neurodegeneration<sup>62</sup>. In particular, an increasing body of epidemiological evidence suggested that elevated saturated fatty acids could have negative effects on MCI, while a clear reduction of risk for cognitive decline has been found in population samples with elevated fish consumption, high intake of monounsaturated fatty acids (MUFAs) and LC PUFAs, particularly n-3 PUFAs<sup>63</sup>. Despite the strong evidence in cognitive decline prevention coming from observational studies, findings coming from RCTs in cognitively healthy older adults were controversial considering the great heterogeneity of samples and outcome measures as well as neuropsychological tools or MRI findings<sup>12</sup>. In a RCT, 39 AD patients were randomized for 12 months to placebo, n-3 PUFA supplementation (fish oil concentrate containing a daily dose of 675 mg DHA and 975 mg EPA), or the same n-3 PUFA supplementation plus alpha lipoic acid (600 mg/day). No difference in ADAS-cog between placebo and n-3 PUFA supplementation or between placebo and n-3 PUFA supplementation plus alpha lipoic acid was reported. For MMSE, there was no difference between placebo and n-3 PUFA supplementation, but a significant difference between placebo and n-3 PUFA supplementation plus alpha lipoic acid was found (Tab. II)<sup>46</sup>. In the OmegaAD study, systemic oxidative stress and inflammatory biomarkers were evaluated following oral supplementation of dietary n-3 PUFA (1.7 g DHA and 0.6 g EPA) or placebo for 6 months. In this RCT, F<sub>2</sub>-isoprostane in urine increased in the placebo group after 6 months, but there was no clear difference in treatment effect between supplemented and non-supplemented patients on the urinary levels of F<sub>2</sub>-isoprostanes and 15-keto-dihydro-PGF<sub>2α</sub>. At baseline, the levels of 15-keto-dihydro-PGF<sub>2α</sub>, a major metabolite of PGF<sub>2α</sub> and biomarker of inflammatory response, showed negative correlative relationships with

**Table II.** Randomized clinical trials evaluating the efficacy of nutritional intervention using a food/macronutrient approach in the treatment of patients with late-life cognitive disorders aged over 60 years (2014-2016).

Reference	Study sample	Intervention(s)	Duration	Cognitive-related outcomes and nutritional assessment	Principal results
<b>Food supplementation</b>					
Cardoso et al., 2016 <sup>44</sup>	31 older subjects with MCI Mean age: 77.7 years	Daily Brazil nut intake (estimated 288.75 µg of selenium) Placebo	6 months	CERAD neuropsychological test battery total score, CERAD subtests (verbal fluency, BNT, constructional praxis, word list learning test, and word list recall) Blood selenium concentrations, erythrocyte glutathione peroxidase activity, oxygen radical absorbance capacity, and malondialdehyde	In the supplemented group there were significant improvement of some cognitive domains, i.e., verbal fluency and constructional praxis
<b>Macronutrient approach</b>					
<b>Lipids</b>					
Moré et al., 2014 <sup>45</sup>	96 patients with AD Aged 50-90 years	100 mg phosphatidylserine plus 80 mg phosphatidic acid in lecithin three times daily Placebo (starch)	2 months	7-ADL, MMSE, and RDT	Significant positive effect of this supplementation on daily functioning, positive trends on emotional state and on self-reported general condition. No adverse effects were reported
<b>Fatty acids</b>					
Shinto et al., 2014 <sup>46</sup>	39 AD patients Mean age: 75.9 years	n-3 PUFAs n-3 PUFAs + alpha-lipoic acid Placebo	12 months	ADAS-cog, MMSE, ADL, and IADL	No difference in ADAS-cog between placebo and n-3 PUFA supplementation or between placebo and n-3 PUFA supplementation plus alpha lipoic acid was reported. For MMSE, there was no difference between placebo and n-3 PUFA supplementation, but a significant difference between placebo and n-3 PUFA supplementation plus alpha lipoic acid was found



Reference	Study sample	Intervention(s)	Duration	Cognitive-related outcomes and nutritional assessment	Principal results
<b>Fatty acids</b>					
Freund-Levi et al., 2014a <sup>47</sup>	40 moderate AD patients  Mean age: 70.5 years	n-3 PUFA (1.7 g DHA and 0.6 g EPA) Placebo	6 months	Urinary levels of F2-isoprostane, 8-iso-PGF <sub>2α</sub> , and 15-keto-dihydro-PGF <sub>2α</sub>	F2-isoprostane in urine increased in the placebo group after 6 months, but there was no clear difference in treatment effect between supplemented and non-supplemented patients on the urinary levels of F2-isoprostanes and 15-keto-dihydro-PGF <sub>2α</sub>
Freund-Levi et al., 2014b <sup>48</sup>	33 mild-to-moderate AD patients  Age: over 65 years	n-3 PUFA (1.7 g DHA and 0.6 g EPA) Placebo	6 months	CSF PUFA levels, plasma PUFA levels, and CSF biomarkers of AD and inflammation	The n-3 PUFA supplemented group displayed significant increases in CSF and plasma EPA, DHA and total n-3 PUFA levels, whereas no changes were found in the placebo group. Changes in DHA levels in CSF were inversely correlated with CSF levels of total and phosphorylated tau, and directly correlated with soluble interleukin-1 receptor type II
O'Callaghan et al., 2014 <sup>49</sup>	33 MCI patients  Age: over 65 years	EPA-rich fish oil (1.67 g EPA plus 0.16 g DHA/day), DHA-rich fish oil (1.55 g DHA plus 0.40 g EPA/day) LA (safflower oil, LA 2.2 g/day)	6 months	Telomere length	Telomere shortening was greatest in the LA group than in the DHA and EPA groups. Increased erythrocyte DHA levels were associated with reduced telomere shortening in the DHA group
Eriksdotter et al., 2015 <sup>50</sup>	165 AD patients Mean age: 72.5 years	n-3 PUFA (1.7 g DHA and 0.6 g EPA) Placebo  Subsequently, all patients received the n-3 PUFA formulation for the next 6 months	12 months	ADAS-cog, MMSE, and plasma PUFA levels	A significant positive association between the changes of plasma DHA levels and changes of total scores of ADAS-cog. No significant correlation between changes of n-3 PUFA levels and changes of MMSE scores nor any of its sub-items



Reference	Study sample	Intervention(s)	Duration	Cognitive-related outcomes and nutritional assessment	Principal results
<b>Fatty acids</b>					
Phillips et al., 2015 <sup>51</sup>	76 participants with CIND or AD Mean age: 71.1 years	n-3 PUFAs (600 mg EPA and 625 mg DHA per day) Placebo (olive oil)	4 months	MMSE, HVLT-R, MMSES7, MMSEWB, BASDEC, other neuropsychological measures of executive functioning, language, verbal reasoning, visual memory, and BADLS	No significant effects on cognitive, depressive, and functional outcomes
Yassine et al., 2016 <sup>52</sup>	70 AD patients Mean age: not reported	Algae-derived DHA oil (2 g/day of DHA) Placebo (corn/soy oil)	18 months	Plasma and CSF DHA levels, CSF A $\beta_{1-42}$ , tau, and phosphorylated tau.  APOE genotype	After 18 months of DHA supplementation, APOE $\epsilon$ 4 allele and lower CSF A $\beta_{1-42}$ levels were associated with less transport of DHA to CSF. These findings may suggest that brain amyloid pathology may limit the delivery of DHA to the brain in AD

MCI: mild cognitive impairment; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; ADAS-Cog: Alzheimer's disease Assessment scale, Cognitive subscale; VLT: Verbal Learning Test-Revised; MMSE: Mini Mental State Examination; FCSRT: Free and Cued Selective Reminding Test; PS: phosphatidylserine; PA: phosphatidic acid; AD: Alzheimer's disease; ADL: activities of daily living; RDT: Tel-Aviv University Rosen Target Detection test; PUFAs: polyunsaturated fatty acids; IADL: instrumental activities of daily living; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; CSF: cerebrospinal fluid; LA: linoleic acid; CIND: cognitive impairment no dementia; HVLT-R: Hopkins Verbal Learning Test-Revised; MMSES7: mini mental state examination Serial Sevens; MMSEWB: mini-mental state examination World Backwards; BASDEC: Brief Assessment Schedule Depression Cards; BADLS: Bristol's Activities of Daily Living Scale; A $\beta$ : amyloid B; APOE: apolipoprotein E

n-3 PUFAs, and a positive correlation to the n-6 PUFA linoleic acid (LA), while 8-iso-PGF<sub>2 $\alpha$</sub> , a consistent *in vivo* biomarker of oxidative stress, correlated negatively to the n-6 PUFA ARA (Tab. II)<sup>47</sup>. Findings from the same RCT, the OmegaAD study, on 33 moderate AD patients suggested that at 6 months the n-3 PUFA supplemented group (1.7 g DHA and 0.6 g EPA) showed significant increases in cerebrospinal fluid (CSF) and plasma EPA, DHA and total n-3 PUFA levels, whereas no changes were observed in the placebo group. Changes in CSF and plasma levels of EPA and n-3 PUFA docosapentaenoic acid were strongly correlated, in contrast to those of DHA. Changes in DHA levels in CSF were inversely correlated with CSF levels of total and phosphorylated tau, and directly correlated with soluble interleukin-1 receptor type II (Tab. II)<sup>48</sup>. In 33 MCI patients aged over 65 years, randomized to receive a supplement rich in the long-chain n-3 PUFAs EPA (1.67 g EPA plus 0.16 g DHA/day) or DHA (1.55 g DHA plus 0.40 g EPA/day) versus n-6 PUFA LA (2.2 g/day) for 6 months, telomere shortening, a marker of accelerated aging also linked to cognitive ability and MCI<sup>64</sup>, was greater in the LA group than in the DHA and EPA groups. Increased erythrocyte DHA levels were associated with reduced

telomere shortening in the DHA group. These findings suggested that telomeric shortening may be attenuated by n-3 PUFA supplementation (Tab. II)<sup>49</sup>. Other findings from the OmegaAD study on 165 AD patients showed a significant positive association between the changes of plasma DHA levels and changes of total ADAS-cog scores suggesting a potential protective role of increasing plasma n-3 PUFA levels in preservation of cognitive functioning. However, changes of plasma n-3 PUFA levels and changes MMSE scores and its sub-items were not significantly related (Tab. II)<sup>50</sup>. On the other hand, no significant findings on cognitive, depressive, and functional domains have been reported in another RCT including 76 participants [57 with cognitive impairment no dementia (CIND) and 19 with AD] randomized to receive either n-3 PUFAs (600 mg EPA and 625 mg DHA per day) or placebo for 4 months (Tab. II)<sup>51</sup>. Finally, in the Alzheimer's Disease Cooperative Study (ADCS)-sponsored DHA clinical trial, at baseline, there were no significant differences between CSF or plasma DHA levels by CSF A $\beta_{1-42}$  tertiles or apolipoprotein E (APOE)  $\epsilon$ 4 status in AD patients supplemented with 2 g/day of DHA or AD patients assuming placebo (Tab. II)<sup>52</sup>. After 18 months of DHA supplementation, participants

at the lowest  $A\beta_{1-42}$  tertile had significantly lower CSF DHA levels and lower CSF-to-plasma DHA ratios compared to the other tertiles. Baseline CSF  $A\beta_{1-42}$  levels were significantly lower in APOE  $\epsilon 4$  carriers than in APOE  $\epsilon 4$  noncarriers. Participants carrying the  $\epsilon 4$  allele demonstrated a less pronounced increase in CSF DHA level compared with noncarriers, with a possible interaction effect between treatment and APOE genotype. These findings suggested that APOE  $\epsilon 4$  allele and lower CSF  $A\beta_{1-42}$  levels were associated with less transport of DHA to CSF (Tab. II) <sup>52</sup>.

## NUTRITIONAL INTERVENTION THROUGH MICRONUTRIENT CHANGES

### ANTIOXIDANTS VITAMINS AND TRACE ELEMENTS

Table III shows selected RCTs published in the last four years evaluating the efficacy of nutritional intervention through supplementation of dietary micronutrients in the treatment of patients with late-life cognitive disorders aged over 60 years <sup>65-73</sup>. Given the suggested relationship between cognitive impairment and oxidative stress <sup>53 54</sup>, and consequently cell death, membranes peroxidation, and  $A\beta$  deposition, several antioxidant vitamins or minerals and trace elements with antioxidant properties have been proposed for the treatment of AD, MCI, and other late-life cognitive disorders <sup>56</sup>. However, findings coming from RCTs were contrasting <sup>16</sup>. In a RCT including 561 AD patients assigned to receive 2000 IU/day of vitamin E (alpha tocopherol), 20 mg/d of memantine, the combination, or placebo, no significant findings have been reported on cognitive outcomes (MMSE, ADAS-cog). However, ADCS-Activities of Daily Living Inventory scores declined significantly less in the vitamin E group compared with the placebo one, suggesting a beneficial effect in slowing functional decline in AD patients (Tab. III) <sup>65</sup>. Furthermore, in another trial including 256 MCI subjects assigned to receive either 300 mg of vitamin E plus 400 mg vitamin C per day or placebo for one year, no significant differences in MMSE score were reported, despite significant improvement in most of the oxidative stress biomarkers measured (Tab. III) <sup>66</sup>. Among trace elements with antioxidant properties, selenium was part of multinutrient supplementations in AD <sup>33 34 56</sup>. In a 24-week Phase IIa RCT, 40 mild-to-moderate AD patients (MMSE 14-26) with a mean age of 70.5 years were randomized to a supranutritional sodium selenate group (VEL015 10 mg three times per day), chosen for its selenium content and high solubility, or control (VEL015 320  $\mu$ g three times per day) or placebo groups. Exploratory biomarkers included cognitive tests, neuroimaging (diffusion

MRI and FDG-PET), and CSF (p-tau, t-tau, and  $A\beta_{1-42}$ ). No significant differences between the supranutritional and control groups were observed for cognition, CSF, and FDG-PET biomarkers. Only one secondary biomarker, diffusion MRI measures, showed group differences, with less deterioration in the supranutritional group (Tab. III) <sup>67</sup>.

### HOMOCYSTEINE-RELATED VITAMINS

A possible modifiable risk factor of dementia is an elevated plasma homocysteine (Hcy) level. In fact, Hcy may be toxic for neurons and vascular endothelial cells <sup>74</sup>, and cross-sectional and prospective studies have shown associations between elevated Hcy levels and cognitive decline and dementia <sup>75</sup>. Hcy levels can be lowered by supplementation with folic acid (vitamin B9) and vitamin B12 <sup>76</sup>. Although observational studies have shown a strong association between poor vitamin B6, B12, and folate levels and increased risk of dementia, suggesting a preventive and protective role of these micronutrients, evidence from RCTs appeared to be unclear <sup>12</sup>. Findings from the Homocysteine and B Vitamins in Cognitive Impairment (VITACOG) trial on 168 MCI patients, randomly assigned either to placebo (n = 83) or to daily high-dose B vitamin supplementation (folic acid, 0.8 mg; vitamin B6, 20 mg; vitamin B12, 0.5 mg) (n = 85) suggested that after 2 years of supplementation there was a significant interaction between B vitamin treatment and plasma combined n-3 PUFA (EPA and DHA) on brain atrophy rates at MRI (Tab. III) <sup>68</sup>. In MCI subjects with high plasma concentrations of n-3 PUFA (EPA+DHA 0.590 mmol/L), B vitamin supplementation slowed the mean brain atrophy rate by 40% compared with subjects in the placebo group. In contrast, in MCI subjects with low n-3 PUFA concentrations (0.390 mmol/L), there was no beneficial effect of B vitamins on brain atrophy (Tab. III) <sup>68</sup>. Other findings from the VITACOG trial including 266 MCI subjects randomized to B vitamins (folic acid, vitamins B6 and B12) or placebo for 2 years, final scores for verbal delayed recall (episodic memory), global cognition, and CDR-SB scores were better in the B vitamin-treated group according to increasing baseline plasma concentrations of n-3 PUFAs, whereas in the placebo group scores were similar across these concentrations. These findings suggested that at low n-3 PUFA concentrations, B vitamin treatment had no effect on cognitive decline in MCI. However, at n-3 PUFA plasma levels in the upper normal range, B vitamins might slow cognitive decline. In particular, DHA in this study was more effective than EPA in enhancing the cognitive effects of B vitamins (Tab. III) <sup>69</sup>. In another RCT including 159 MCI subjects randomized to a daily intervention of 400  $\mu$ g folic acid *versus* placebo for 6 months, folic

**Table III.** Randomized clinical trials evaluating the efficacy of nutritional intervention using a micronutrient approach in the treatment of patients with late-life cognitive disorders aged over 60 years (2014-2016).

Reference	Study sample	Intervention(s)	Duration	Cognitive-related outcomes and nutritional assessment	Principal results
<b>Antioxidant vitamins and trace elements</b>					
Dysken et al., 2014 <sup>65</sup>	561 AD patients Mean age: 78.8 years	2000 IU/d of vitamin E (alpha tocopherol) 20 mg/d of memantine 2000 IU of vitamin E (alpha tocopherol) + 20 mg/d of memantine Placebo	5 years (mean follow up: 2.3 years)	ADCS-ADL Inventory, ADAS-cog, MMSE, NPI, CAS, and Dependence Scale	No significant effects on cognitive outcomes
Naeini et al., 2014 <sup>66</sup>	256 subjects with MCI Mean age: 66.4 years	300 mg of vitamin E plus 400 mg of vitamin C/day Placebo	1 year	MMSE  Serum oxidative stress markers  Three-day dietary record forms	Despite significant improvement in most of the oxidative stress biomarkers, no significant effects on cognitive outcomes
Malpas et al., 2015 <sup>67</sup>	40 mild-to-moderate AD patients Mean age: 70.5 years	Supranutritional sodium selenate group (VEL015 10 mg three times per day) Control group (VEL015 320 µg three times per day) Placebo	24 weeks	MMSE, ADAS-Cog, COWAT, CFT, and 3 tests from the CogState computerized battery: OCL, IDN, and DET  Diffusion MRI and FDG-PET  CSF biomarkers	Only one secondary biomarker, diffusion MRI measures, showed group differences, with less deterioration in the supranutritional group
<b>Homocysteine-related vitamins</b>					
Jernerén et al., 2015 <sup>68</sup>	168 subjects with MCI Mean age: 76.6 years	Daily high-dose B vitamin supplementation (folic acid, 0.8 mg; vitamin B6, 20 mg; vitamin B12, 0.5 mg) Placebo	2 years	Structural MRI  Plasma n-3 PUFA	A significant interaction effect between high-dose B vitamin treatment and n-3 PUFA concentrations on rate of atrophy of the whole brain was found. The beneficial effect of high-dose B vitamin supplementation was augmented by a high baseline status of plasma n-3 PUFA
Oulhaj et al., 2016 <sup>69</sup>	266 subjects with MCI Mean age: 76.8 years	Daily high-dose B vitamin supplementation (folic acid, 0.8 mg; vitamin B6, 20 mg; vitamin B12, 0.5 mg) Placebo	2 years	HVLT-DR, TICS-M, and CDR  Plasma n-3 PUFA  APOE genotype	When n-3 PUFA concentrations were low, B vitamin treatment had no effect on cognitive decline in MCI, but when n-3 PUFA levels were in the upper normal range, B vitamins interacted to slow cognitive decline



Reference	Study sample	Intervention(s)	Duration	Cognitive-related outcomes and nutritional assessment	Principal results
<b>Homocysteine-related vitamins</b>					
Ma et al., 2016 <sup>70</sup>	159 subjects with MCI Mean age: 74.7 years	Folic acid (400 µg/day) Placebo	6 months	WAIS-RC and MMSE  Serum Hcy, SAM, SAH, folic acid, and vitamin B12	Folic acid group had statistically significant increase in global cognitive function (WAIS-RC) and some WAIS-RC sub-tests investigating short-term verbal memory and visuoconstructional ability
Chen et al., 2016 <sup>71</sup>	121 patients with AD Mean age: 67.9 years	Donepezil /10 mg / day) plus folic acid (1.25 mg/day) Donepezil /10 mg /day)	6 months	MMSE Serum folate, Aβ, IL-6, TNFα, plasma Hcy, SAM, SAH, and the mRNA levels of PS, IL-6, and TNF-α in leukocytes	The mean MMSE was slightly increased in the intervention group compared to that in the control group. Post-treatment plasma SAM and SAM/SAH levels were significantly higher, while Aβ <sub>1-40</sub> , PS1-mRNA, and TNFα-mRNA levels were lower in the intervention group than in the control group. The Aβ <sub>1-42</sub> /Aβ <sub>1-40</sub> ratio was also higher in the intervention group
<b>Flavonoids and carotenoids</b>					
Gleason et al., 2015 <sup>72</sup>	65 AD patients Mean age: 79 years	Soy isoflavones (100 mg/day) Placebo	6 months	List Learning, Paragraph Recall, BVRT, CFR, phonemic fluency, animal fluency, Digit Symbol, Digit Span, SCWT, Mazes, TMT-A-B, CFC, and GPB  APOE genotype and plasma isoflavone levels	No cognitive benefits over placebo after 6 months of supplementation, and global cognition declined at similar rates in both treatment and control groups
Nolan et al., 2016 <sup>73</sup>	31 AD patients and 31 age-similar control subjects Mean age: 78 years	Carotenoids (10 mg meso-zeaxanthin, 10 mg lutein, 2 mg zeaxanthin) Placebo (sunflower oil)	6 months	MMSE, phonemic fluency, animal fluency, and three tasks from the CANTAB	No significant effects on all cognitive outcomes

AD: Alzheimer's disease; ADCS-ADL: Alzheimer's Disease Cooperative Study-Activities of Daily Living; ADAS: Alzheimer's Disease Assessment Scale; MMSE: Mini Mental State Examination; NPI: Neuropsychiatric Inventory; CAS: Caregiver Activity Survey; MCI: mild cognitive impairment; COWAT: Controlled Oral Word Association Test; CFT: Category Fluency Test; OCL: one-card learning memory task; IDN: identification reaction time task; DET: detection reaction time task; MRI: magnetic resonance imaging; FDG-PET: fluorodeoxyglucose positron emission tomography; CSF: cerebrospinal fluid; PUFA: polyunsaturated fatty acids; HVLT-DR: Hopkins verbal learning test with delayed recall; TICS-M: telephone inventory for cognitive status-modified; CDR: Clinical Dementia Rating; APOE: apolipoprotein E; WAIS-RC: Chinese version of the Wechsler Adult Intelligence Scale-Revised; Hcy: homocysteine; SAM: S-adenosylmethionine; SAH: S-adenosyl homocysteine; Aβ: amyloid β; PS: presenilin; IL-6: interleukin-6; TNF-α: tumor necrosis factor α; BVRT: Benton Visual Retention test; CFR: Complex Figure Recall; SCWT: Stroop Color Word test; TMT-A-B: trail making test part A and B; CFC: Complex Figure Copy; GPB: Grooved Peg Board; CANTAB: Cambridge Neuropsychological Test Automated Battery

acid supplementation was associated with a significant increase in global cognitive function (Chinese version of the Wechsler Adult Intelligence Scale-Revised, WAIS-R) and some WAIS-RC sub-tests investigating short-term verbal memory and visuoconstructional ability, probably related to reduced Hcy levels also observed in this trial after six months, and even after 3 months of supplementation (Tab. III) <sup>70</sup>. Finally, in another RCT, 121 AD being treated with donepezil were randomly assigned into two groups with (intervention group) or without (control group) supplemental treatment with folic acid (1.25 mg/d) for 6 months. The mean MMSE was slightly increased in the intervention group compared to that in the control group. Folic acid supplementation improved also markers of inflammation suggesting that folic acid may be beneficial in patients with AD in concert with donepezil and that inflammation may play an important role in the interaction between folic acid and AD (Tab. III) <sup>71</sup>.

#### FLAVONOIDS

Flavonoids [flavanols (catechin, epicatechin, epigallocatechin, and epigallocatechingallate-EGCG), flavonols (quercetin and kaempferol), flavones (luteolin and apigenin), isoflavones (daidzein and genistein), flavanones (esperetin and naringenin), and anthocyanidins (pelargonidin, cyanidine, and malvidin) have also been proposed to prevent or treat cognitive impairment or dementia <sup>77-78</sup>. The polyphenol subgroups of flavanols, anthocyanins and flavanones have been shown to be the most beneficial in terms of neuroprotection <sup>79</sup>. Recent RCTs showed significant improvements in some cognitive domains after flavonoid interventions <sup>80</sup>. However, the great heterogeneity in sample, flavonoid dose, follow-up and cognitive tests used led to inconsistent findings <sup>80</sup>. In a RCT, 65 AD patients over the age of 60 were treated with 100 mg/day soy isoflavone, or matching placebo capsules for six months. Although no significant differences in treatment effects emerged on cognitive outcomes between treatment groups or genders, among individuals who were effectively able to metabolize the soy isoflavone daidzein to equol, data suggested an association between plasma levels of equol and performance on verbal fluency and speeded manual dexterity (Tab. III) <sup>72</sup>.

#### CAROTENOIDS

Carotenoids lutein and zeaxanthin are found in certain fruits and vegetables (i.e., spinach, broccoli, peppers, melon) <sup>81</sup>, while meso-zeaxanthin has been identified in fish <sup>82</sup> and is also believed to be generated from lutein at the retina <sup>83</sup>. High carotenoid intake has been found to result in a reduced risk of AD <sup>84</sup>. Nonetheless, recent interventional studies administering lutein and zeaxanthin

have shown improvement in different domains of cognition in patients free of AD <sup>85-86</sup>. Indeed, a RCT in 31 patients with AD and 31 age-similar control subjects who were supplemented with carotenoids (10 mg meso-zeaxanthin, 10 mg lutein, 2 mg zeaxanthin) or placebo (sunflower oil) found no benefit in measures of cognitive function performed in the trial. However, the active supplement improved visual function (contrast sensitivity) in AD and control groups (Tab. III) <sup>73</sup>.

## DISCUSSION

The association between diet and cognitive function or dementia has been largely investigated in observational studies <sup>4</sup>, while there was a lack of evidence from RCTs dealing with the treatment of AD and other late-life cognitive disorders through dietary interventions. Indeed, in the last four years, several meta-analyses and systematic/scoping reviews investigated the efficacy of different nutritional supplementations in preventing late-life cognitive disorders in cognitively healthy older adults <sup>8-12</sup>. However, there were fewer similar studies on patients with dementia, AD, or MCI <sup>13-16</sup>. In the present article, we systematically reviewed RCTs published in the last four years exploring nutritional intervention efficacy in slowing cognitive impairment progression and achieving cognitive-related outcomes in patients aged 60 years and older with late-life cognitive disorders, using different levels of investigation (i.e., medical food/nutraceutical supplementation/multidomain approach and dietary food/macro- and micronutrient approaches). In the present systematic review, we included studies focusing on dementia, AD, prodromal AD, MCI, and different models of late-life cognitive impairment/decline, but we did not find studies focusing in particular on nutritional intervention for VaD. From the reviewed RCTs, there was emerging evidence that nutritional intervention through medical food/nutraceutical supplementation (Fortasyn Connect<sup>®</sup>) and multidomain approach improved MRI findings and cognitive-related biomarkers (plasma lipid biomarker profile prognostic of AD, EEG findings, and circulating levels of supplemented micro- and macronutrients), but without clear effect on cognition in mild AD and MCI and with one substantially negative MEG study. However, another nutraceutical formulation showed positive effects on specific cognitive domains in AD and MCI patients (Tab. I). Moreover, for food supplementation, there was some evidence of a positive effect of antioxidant-rich foods (nuts) in improving specific cognitive domains and cognitive-related outcomes in MCI and mild-to-moderate dementia, but only in small samples (Tab. II). For lipid supplementation, there were only

limited effects of phospholipids in MCI and mild AD, while there was convincing evidence for fatty acid supplementation, mainly n-3 PUFAs, in improving specific cognitive domains and/or cognitive-related biomarkers in MCI and AD (Tab. II). Furthermore, among selected RCTs that evaluated the efficacy of nutritional intervention through supplementation of dietary micronutrients, there was evidence for antioxidant vitamin and trace element supplementations of an impact in improving only cognitive-related outcomes and biomarkers, without effect on cognitive function in AD and MCI patients (Tab. III). For Hcy-related vitamin supplementation, there was evidence of an impact of high-dose B vitamin supplementation in AD and MCI patients in improving cognitive outcomes but only in the subjects with a high baseline status of plasma n-3 PUFA, and of folic acid supplementation in improving specific cognitive domains. Finally, there was no evidence of significant improvement in cognitive outcomes after flavonoid and carotenoid supplementations (Tab. III).

In the last four years, some meta-analyses and systematic reviews investigated the efficacy of different nutritional supplementations for the treatment of AD and other late-life cognitive disorders<sup>13-16 78</sup>. For patients with MCI, AD, or dementia, other recent systematic reviews and meta-analyses investigating less recent RCTs suggested some efficacy of medical foods/nutraceuticals in specific cognitive domains at early stage of AD<sup>15</sup> or in patients with dementia, AD, and MCI with also neuropsychological symptoms<sup>78</sup>. An increasing body of evidence suggested that Fortasyn Connect® could have clinically detectable effects in early AD patients<sup>37</sup>. In fact, considering that synapses formation is compromised by the neurodegeneration characterizing the later stages of AD, the potential beneficial effect on neuroprotection and synaptogenesis of Fortasyn Connect® may be limited in later AD stages compared with earlier ones<sup>37</sup>. Furthermore, other systematic reviews found no convincing evidence for the efficacy of n-3 PUFA supplements in the treatment of mild to moderate AD, at least on cognitive outcomes<sup>14</sup>, or vitamin E supplementations in people with MCI to prevent progression to dementia, or improve cognitive function in people with MCI or dementia due to AD<sup>16</sup>. Finally, another systematic review and meta-analysis found weak evidence of benefits with vitamins B supplementation for the domain of memory in patients with MCI, with no significant cognitive benefits in AD patients<sup>13</sup>. Therefore, while there were encouraging findings with specific dietary supplementations in the earlier phases of AD or MCI, results from RCTs were contrasting for moderate AD patients probably based also on a great heterogeneity in sample size.

In the last years, considering the known less efficacy of single nutrients *versus* combined ones in improving cognitive function and the bidirectional interaction between cognitive and physical dimensions in older age<sup>87</sup>, several studies proposed medical foods or a multidimensional approaches, including supplements and physical activity, with some promising results in subjects with and without cognitive impairment<sup>27 41-43</sup>, particularly in at-risk subgroups. Considering evidence showing a greater efficacy of nutritional intervention in earlier stage of AD, it is necessary to increase disease biomarkers use in order to allow diagnosis in the earlier phase of cognitive dysfunction, i.e., subjective memory decline<sup>88</sup>, so identifying subjects at risk of developing AD and dementia.

However, some limitations should be reported for the present systematic review article. An important limitation was linked to the great heterogeneity of included RCTs not only in terms of study samples and trial durations, but also in relation to the outcome measures and nutrients intake quantification. This heterogeneity made really difficult to give clear answers about the efficacy of dietary intervention in older adults without cognitive dysfunction. However, there are several interesting concepts coming from the reviewed RCTs to underline. The first one was the emerging use of innovative measures of dietary habits, not only daily semi-quantitative food frequency questionnaires but also biomarker dosages such as blood exams or urinary excretion. This resulted into an objective quantification of nutrient supplementation but also of nutritional status of patients at baseline. Furthermore, as shown in the present systematic review, recent RCTs underlined the importance to consider emerging cognitive-related outcomes in order to achieve more clinically focused and reliable findings. Therefore, in addition to clinical scales and neuropsychological tests, serum, CSF, neuroimaging, and other cognitive-related biomarkers have been proposed. The result was an objective quantification of dietary habits and nutritional state of patients at baseline and of the nutrition-related impact on cognitive impairment and AD pathobiology to achieve more clinically focused and reliable findings. In conclusion, medical food/nutraceutical supplementation (Fortasyn Connect® and another similar combinatorial formulation), nutritional interventions with antioxidant-rich foods (nuts), and macronutrient (n-3 PUFAs) and micronutrient (antioxidant and Hcy-related vitamins) supplementations could be really effective in achieving cognitive-related outcomes in MCI and AD patients. However, to obtain more statistically significant and reliable results, RCTs would be conducted in larger selected samples characterized by well defined cognitive function status, nutritional and dietary habits at baseline, with longer follow-up, and would include further objective measures of

cognitive-related outcomes as blood or CSF biomarkers and neuroimaging findings.

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#### CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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