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Review

Dietary intervention and prevention of cognitive-related outcomes in healthy older adults without cognitive dysfunction

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In the last decade, the association between diet and cognitive function/dementia has been largely investigated in observational studies, while there was a lack of evidence from randomized clinical trials (RCTs) on the prevention of late-life cognitive disorders though dietary intervention in cognitively healthy older adults. In the present article, we reviewed RCTs published in the last three years (2014-2016) exploring nutritional intervention efficacy in preventing the onset of late-life cognitive disorders and dementia in cognitively healthy subjects aged over 60 years using different levels of investigation (i.e., dietary pattern changes/medical food/nutraceutical supplementation/multidomain approach and dietary macro- and micronutrient approaches). From the included RCTs, there was moderate evidence that intervention through dietary pattern changes, medical food/nutraceutical supplementation, and multidomain approach improved specific cognitive domains or cognitive-related blood biomarkers. Moreover, there was high evidence that protein supplementation improved specific cognitive domains. For fatty acid supplementation, mainly long-chain polyunsaturated fatty acids, there was emerging evidence suggesting an impact of this approach in improving specific cognitive domains, MRI findings, and/or cognitive-related biomarkers also in selected subgroups of older subjects although some results were conflicting. Moreover, there was convincing evidence of an impact of non-flavonoid polyphenol and flavonoid supplementations in improving specific cognitive domains and/or MRI findings. Finally, there was only low evidence suggesting efficacy of intervention with homocysteine-related vitamins in improving cognitive functions, dementia incidence, or cognitive-related biomarkers in cognitively healthy older subjects.

Key words: Alzheimer's disease, Dementia, Dietary pattern, Medical food, Nutraceuticals, Healthy diet, Mediterranean diet, Macronutrients, Micronutrients, Mild cognitive impairment, Prevention

INTRODUCTION

Given the absence of available disease-modifying therapies for the treatment of Alzheimer's disease (AD) [1], there is a great need in preventing and delaying the onset of cognitive impairment in healthy older subjects. In the last decade, many observational studies have shown a wide variety of potentially modifiable risk factors for cognitive impairment, that have been proposed as targets for preventive strategies [2]. In addition to cardiovascular risk factors, psychological conditions, education level, engagement

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in social and mentally stimulating activities, sensory changes, lifestyle including diet, physical activity and voluptuary habits has obtained a crucial role [2 3]. In particular, in the last years, a growing body of evidence has been focused on the association between dietary habits and cognitive performance [3]. Several nutritional supplements have been studied for their potential role as neuroprotective interventions useful in delaying the onset of cognitive decline in older adults [4-7]. Observational studies have showed that specific micro- or macronutrients such as polyunsaturated fatty acids (PUFAs), vitamins, flavonoids are associated with a significantly reduced risk of dementia [3 8]. This protective effect could be mediated by several pathobiological pathways involved in AD development as amyloid-β (Aβ) deposition, neurofibrillary degeneration, synapse loss, inflammation, oxidative stress, mitochondrial dysfunction, loss of vascular integrity and neuronal injury [8]. Furthermore, several evidences underlined that foods and nutrients properly combined into specific dietary patterns may act synergistically amplifying the health effects of single components [3 9-14]. In particular, the Mediterranean dietary pattern has been the first and widely well studied and proposed in epidemiological studies, showing a strong protective role in cardiovascular and cognitive aging [3 9-11]. Considering these promising results and the growing interest in this field, several randomized clinical trials (RCTs) investigated nutritional interventions as preventive or therapeutic approaches for cognitive function obtaining contrasting results. Furthermore, in the last few years, the approach to the study of the relationship between diet and cognitive impairment has been changed. In fact, according to the National Institute on Aging-Alzheimer's Association (NIA-AA) guidelines for AD and cognitive decline due to AD pathology [15], it has been suggested a direct impact of nutrition to brain structure and activity changes. This consideration in addition to the need to objectively quantify the effects of nutrients on cognitive outcomes not only in terms of neuropsychological test scores o clinical scales, has opened the era of brain imaging biomarkers in nutritional research. Another feature to underline was the emerging use of objective measures of dietary habits, not only in terms of daily questionnaires, but also biomarkers in order to achieve more reliable findings. The aim of the present article was to provide a comprehensive and updated review focusing on the RCTs published in the past 3 years (2014-2016) exploring nutritional interventions efficacy in preventing the onset of late-file cognitive disorders and dementia in cognitively healthy subjects aged 60 years and older.

NUTRITIONAL INTERVENTION THROUGH DIETARY PATTERN CHANGES, MEDICAL FOOD/ NUTRACEUTICAL SUPPLEMENTATION AND MULTIDOMAIN APPROACH

Dietary pattern changes

We used a narrative synthesis to summarize the findings of the included studies, subdividing the articles for the three principal diet-based approaches (dietary patterns/medical food/nutraceutical supplementation/ multidomain approach, macronutrients, and micronutrients), specifying sample size and the cognitive outcomes of the included studies (Tabs. I-III) [16-43]. Table I shows selected RCTs published in the last three years (2014-2016) that evaluated the efficacy of nutritional intervention through dietary pattern changes, medical food/nutraceutical supplementation, and multidomain approach in preventing the onset of late-life cognitive disorders and dementia in cognitively healthy subjects aged over 60 years [16-23]. The Mediterranean diet (MeDi), the typical dietary pattern of Mediterranean countries, has been the most studied dietary pattern, with a proposed protective role against cognitive decline and dementia. The main components of the MeDi pattern are fruits, vegetables, legumes, cereals and olive oil as the main added lipid, associated with a moderate consumption of red wine and low consumption of red meat and dairy products. In particular, the findings from prospective observational studies and very recent systematic reviews and meta-analyses of pooled studies suggested that higher adherence to the MeDi fulfilling the whole-diet approach was associated with a reduced risk of cognitive impairment, MCI and AD, as well as the transition from MCI to AD [3 9-11]. Moreover, a recent systematic review on this issue suggested that also other emerging healthy dietary patterns such as the Dietary Approach to Stop Hypertension (DASH) and the Mediterranean-DASH diet Intervention for Neurodegenerative Delay (MIND) diets were associated with slower rates of cognitive decline and significant reduction of AD rate [3]. Despite observational studies showed a positive significant association of certain healthy dietary patterns with cognitive impairment, only few interventional studies have been conducted on dietary patterns, particularly on MeDi, reporting contrasting findings. In fact, in a RCT including 447 cognitively normal participants randomly assigned to a MeDi supplemented with extra-virgin olive oil (EVOO) or with mixed nuts, or a control diet for a 4.1 years follow-up, those allocated to a MeDi plus EVOO scored better on the episodic memory and attention tasks compared with the control group. Furthermore, compared with controls, this RCT showed a significant improvement in memory composite in the

MeDi plus nuts group and a significant improvement in frontal and global cognition composites in the MeDi plus EVOO group (Tab. I) [16]. Furthermore, in a large RCT recruiting 48,835 women (50-79 years) for a follow-up of mean length of 8.1 years, dietary intervention based on caloric fat restriction and increasing consumption of vegetables, fruit and grain had no significant effects on cognition, with small significant improvements in three health-related quality of life subscales: general health, physical functioning, and vitality at one year follow-up (Tab. I) [17].

Medical food/nutraceutical supplementation

In the last decade, several RCTs have proposed medical foods/nutraceuticals as preventive or therapeutic approaches for cognitive decline and dementia, according to the increasing knowledge about the potential beneficial effect of specific nutrients properly combined in selected dietary patterns.[44] In the last three years, some medical foods/nutraceuticals have been tested in cognitively healthy subjects in order to delay cognitive impairment obtaining good results only in specific cognitive domains (Tab. I) [18-21]. In a RCT, 105 cognitively intact adults were randomized to receive a pill-based nutraceutical (NT-020), a proprietary formulation of blueberry, green tea extract (95% polyphenols), carnosine, blueberry extract (40% polyphenolics, 12.5% anthocyanins), and vitamin D3 (2000 IU per serving) and also contains grape polyphenolics, including 5% resveratrol or placebo using a battery of neuropsychological tests assessing six broad cognitive domains (episodic memory, processing speed, verbal ability, working memory, executive functioning, and complex speed) at baseline and eight weeks later. The NT-020 group exhibited better performance on two measures of processing speed than the placebo group at eight weeks of follow-up (Tab. I) [18]. Among nutraceutical compounds and combinatorial formulations, Ginkgo biloba extract is probably the most widely studied and used herbal-based medication for the prevention and treatment of AD and late-life cognitive decline [45]. Notwithstanding negative meta-analytic findings and the discouraging results of preventive trials against AD, some RCTs focusing particularly on dementia, AD, and MCI subgroups with neuropsychiatric symptoms and some recent meta-analyses have suggested a renowned role for Ginkgo biloba extract for cognitive impairment and dementia [45]. A RCT on 97 cognitively healthy older adults with no history of significant cognitive deficits reported modest effects of Ginkgo biloba plus choline-based formula on specific cognitive domains (executive functioning and verbal fluency) and immune functioning (Tab. I) [19]. An interesting RCT including 116 healthy cognitively older participants investigated the effects of supplementation with two multivitamin, mineral and herbal supplements, a women's formula and a men's formula in women and men, respectively. Assessments at baseline and post-supplementation included computerized cognitive tasks and blood biomarkers relevant to cognitive aging. After 16 weeks of follow-up, no cognitive improvements were observed after supplementation with either formula, while several significant improvements were observed in cognitive-related blood biomarkers including increased levels of vitamins B6 and B12 in women and men, reduced C-reactive protein in women, reduced homocysteine (Hcy) and marginally reduced oxidative stress in men, as well as improvements to the lipid profile in men (Tab. I) [20]. Finally, in one RCT, 27 postmenopausal women received either a combination of 1 g docosahexaenoic acid (DHA), 160 mg eicosapentaenoic acid (EPA), 240 mg Ginkgo biloba, 60 mg phosphatidylserine, 20 mg d-α tocopherol, 1 mg folic acid, and 20 µg vitamin B12 per day or placebo for 6 months. The intervention resulted in significant effects in two of the four cognitive tests, with shorter mean latencies in a motor screening task, and more words remembered, and one of the three primary mobility measures with improved habitual walking speed. Compared with the placebo group, supplementation also resulted in significantly higher blood DHA levels (Tab. I) [21].

Multidomain approach

Considering the great interest on the relationships between an healthy lifestyle including optimal dietary habits and physical activity and an healthy cognitive aging, some studies have proposed a multidomain approach as an effective preventive approach for cognitive impairment or dementia (Tab. I) [22 23]. 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 [46], but these results have seldom been replicated in larger samples. In two 24-week RCTs carried out in parallel, 127 older subjects performed a resistance-type physical exercise program or not and, in both studies, subjects were randomly allocated to either a protein drink (2×15 g daily) or a placebo one. In frail and pre-frail older adults, resistance-type exercise training combined with protein supplementation significantly improved information processing speed, whereas exercise training alone had significant good effects on attention and working memory. There were no significant differences among the intervention groups on the other cognitive tests or domain scores (Tab. I) [22]. Finally, in 2015, a successful 2-year multi-domain lifestyle intervention was completed aiming at prevention of cognitive decline, the Finnish Geriatric Intervention Study to Prevent Cognitive

Table I. Randomized clinical trials evaluating the efficacy of nutritional intervention through dietary pattern changes, medical food/nutraceutical supplementation, and multidomain approach in preventing the onset of late-life cognitive disorders and dementia in cognitively healthy subjects aged over 60 years (2014-2016).

Reference	Study sample	Intervention(s)	Duration	Cognitive-related outcomes and nutritional assessment	Principal results
Dietary pattern changes					
Valls-Pedret et al., 2015 [16]	447 cognitively healthy older subjects Mean age: 68.2 ± 6.3 years for the intervention group and 68.8 ± 6.5 years for the placebo group	MeDi + EVOO (1L/week) MeDi + mixed nuts (30 g/day) Control diet (advice to reduce dietary fat)	4.1 years (median)	MMSE, AVLT, ASF, DS-WAIS, VPA-WAIS, CTT	In an older population, a MeDi supplemented with EVOO or nuts was associated with improved episodic memory and frontal and global cognition
Assaf et al., 2016 [17]	48.835 older women Aged: 50-79 years	Intervention group: reduced calories from fat to 20%, increased vegetables and fruit to 5+ servings, and increased grain servings to 6+ servings a day Placebo	8.1 ± 1.7 years (max. 11.2 yeas)	3MSE, RAND36 WHI FFQ.	No significant improvement in cognitive functions. Small significant improvements in three health-related quality of life subscales: general health, physical functioning, and vitality at 1 year follow-up
Medical food/nutraceutical supplementation					
Small et al., 2014 [18]	105 cognitively intact adults Aged: 65-85 years	Nutraceutical NT-020 Placebo	8 weeks	MMSE, AVLT, IPT, NC, TMT-A and –B, FBDS-WAIS, CF, COWAT, DST	Better performance for the NT-020 group in two measures of processing speed (IPT and NC) compared to placebo group
Lewis et al., 2014 [19]	97 cognitively healthy older subjects MMSE ≥ 23 Aged ≥ 60 years	Nutraceutical formulation with: Ginkgo biloba leaf (120 mg/day), Ginkgo biloba whole extract (80 mg/day), grape seed extract (40 mg/day), Gotu kola leaf (Centella asiatica), dried buckwheat leaf juice, buckwheat seed, and soybean lecithin powder + Choline (700 mg/day) Nutraceutical formulation with: grape seed extract (100 mg/day), green tea extract (50 mg/day, 60% catechins), bilberry fruit (50 mg/day, 25% anthocyanins), dried buckwheat leaf and juice, green tea leaf powder, and dried carrot root + nutraceutical formulation with: vitamin D (312 IU/day), vitamin A (1,600 IU/day), vitamin C (5.3 mg/day), thiamine (0.3 mg/day), riboflavin (0.3 mg/day), vitamin B6 (1.3 mg/day), defatted wheat germ, carrot (root), calcium lactate, nutritional yeast, bovine adrenal, bovine liver, magnesium citrate, bovine spleen, ovine spleen, bovine kidney, dried pea (vine) juice, dried alfalfa (whole plant) juice, mushroom, oat flour, soybean lecithin, and rice bran Placebo	6 months	MMSE, SCWT, TMT-A and -B, COWAT, DS-WAIS-III, HVLT-R Immune function markers	Isolated and modest effects of a Ginkgo biloba plus choline-based formula on cognitive (executive functioning and verbal fluency) and immune functioning among healthy older adults with no history of significant cognitive deficits

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Reference	Study sample	Intervention(s)	Duration	Cognitive-related outcomes and nutritional assessment	Principal results
Multidomain approach					
Harris et al., 2015 [20]	116 healthy older participants Aged: 55-65 years	Multivitamin, mineral and herbal supplements Placebo	16 weeks	CRT, IDRM, SI, SWM, and CM, blood biomarkers relevant to cognition	In cognitively healthy older people, multivitamin supplementation improved a number of cognitive-related blood biomarkers, but these biomarker changes were not accompanied by no significant improvement in cognitive functions
Strike et al., 2016 [21]	27 postmenopausal women Aged: 60-84 years	Nutraceutical formulation providing: DHA (1 g/day), EPA (160 mg/day), Ginkgo biloba, phosphatidylserine, α-tocopherol, folic acid, and vitamin B12 Placebo	6 months	MOT, VRM, and PAL, mobility was assessed by VICON 9 motion capture camera system synchronized with Kistler force plates; blood fatty acid levels by pin-prick analysis	In this RCT, multinutrient supplementation improved cognition and mobility in healthy older females suggesting a potential role in reducing the decline to frailty
Van de Rest et al., 2014 [22]	127 frail or pre-frail older subjects Mean age: 79 years	Protein (30g/day) Protein + physical exercise Placebo Placebo + physical exercise	24 weeks	MMSE, TMT-A and -B, WLT, SCWT, FBDS-WAIS, VFT, and reaction time tasks 3 day dietary record	Significant improvement of information processing speed in the protein plus physical exercise group
Ngandu et al., 2015 [23]	1260 nondemented older subjects Aged: 60-77 years	Multidomain lifestyle intervention Control group	2 years	A comprehensive NTB Z score	Findings from this long-term, RCT suggested that a multidomain intervention could improve or maintain cognitive functioning in at-risk older people

MeDi: Mediterranean diet; EVOO: extravirgin olive oil; MMSE: Mini-Mental State Examination; AVLT: Rey Auditory Verbal Learning Test; ASF: Animals Semantic Fluency; DS-WAIS: Digit Span subtest from the Wechsler Adult Intelligence Scale; VPA-WAIS: Verbal Paired Associates from the Wechsler Memory Scale; CTT: Color Trail Test; 3MSE: modified Mini-Mental State Examination; RAND36: RAND 36-Item Health Survey; WHI: Women's Health Initiative; FFQ: food frequency questionnaires; IPT: Identical Pictures Test; NC: Number Comparison task; TMT-A: Trail Making Test - A; TMT-B: Trail Making Test -B; FBDS-WAIS: Forward and Backward Digit Span task; CF: Category Fluency; COWAT: Controlled Oral Word Association Test; DST: Digit Symbol Tests; SCWT: Stroop Color-Word Test; DS-WAIS-III: Digit Symbol subtest from the Wechsler Adult Intelligence Scale- III; HVLT-R: the Hopkins Verbal Learning Test-Revised; CRT: Choice Reaction Time; IDRM: Immediate and Delayed Recognition Memory; SI: Stroop Interference tasks; SWM: Spatial Working Memory; CM: Contextual Memory; MOT: psychomotor response latency; VRM: Verbal Recognition Memory; PAL: paired associate learning; WLT: Word Learning Test, SCWT: Stroop Color-Word Test, VFT: Verbal Fluency Test; PUFAs: polyunsaturated fatty acids; NTB: neuropsychological test battery

Impairment and Disability (FINGER) (Tab. I) [23], with dietary counselling as one of the intervention domains (diet, exercise, cognitive training, vascular risk monitoring) and a control group (general health advice). Intervention goals were based on Finnish dietary recommendations. This 2-year multidomain lifestyle intervention was conducted on 631 participants in the intervention and 629 in the control group, aged 60-77 years at baseline with an estimated mean change in neuropsychological test battery total Z score at 2 years of 0.2 in the intervention group and 0.16 in the control group. These findings from the FINGER suggested that a multidomain intervention could improve or maintain cognitive functioning in at-risk older people from the general population (Tab. I) [23].

NUTRITIONAL INTERVENTION THROUGH MACRONUTRIENT CHANGES

Table II shows selected RCTs published in the last three years (2014-2016) that evaluated the efficacy of nutritional intervention through supplementation of dietary macronutrients in preventing the onset of late-life cognitive disorders and dementia in cognitively healthy subjects aged over 60 years [24-34]. In particular, many interventional RCTs evaluated the cognitive impact of macronutrient intakes such as proteins and PUFAs with promising results.

Proteins

Many RCTs evaluated protein intake as a supplementation in nondemented older adults showing significant improvement in specific cognitive domains (Tab. II) [24-27]. Interestingly, these RCTs reported also promising results not only in terms of cognitive outcomes, but also magnetic resonance imaging (MRI) findings. In one RCT on 65 frail or pre-frail cognitively healthy older subjects randomly assigned to protein drink or placebo for 24 weeks, protein supplementation improved reaction time performance, but did not improve the cognitive domains of episodic memory, attention and working memory, information processing speed, and executive functioning (Tab. II) [24]. Promising results have been reported in a trial including 51 cognitively healthy older subjects [Mini-mental State Examination (MMSE) > 15] randomly assigned to dietary carnosine and anserine (carnosine related compounds, CRC) supplementation (chicken meat extract) or placebo. In this trial, a significant improvement

Table II. Randomized clinical trials evaluating the efficacy of nutritional intervention using a macronutrient approach in preventing the onset of late-life cognitive disorders and dementia in cognitively healthy subjects aged over 60 years (2014-2016).

Reference	Study sample	Intervention(s)	Duration	Cognitive-related outcomes and nutritional assessment	Main Results Cognitive results
Protein supplementation					
Van der Zwaluw et al., 2014 [24]	65 frail or pre-frail older subjects Mean age: 79 years	Proteins (30 g/day) Placebo	24 weeks	MMSE, TMT-A and -B, WLT, SCWT, FBDS-WAIS, VFT, and reaction time tasks 3 day dietary record	Protein supplementation improved reaction time performance in pre-frail and frail older adults, but did not improve other cognitive functions
Szcześniak et al., 2014 [25]	51 older subjects MMSE ± 15 Mean age: 81 ± 7 years in CRC group and 80.5 ± 7.5 years in placebo group	CME containing 40% of CRC (2:1 ratio of anserine to carnosine) was administered 2.5 g/day Placebo	13 weeks	MMSE, STMS, and CDR	A significant improvement was found after supplementation in specific subscores of STMS, a test evaluating global cognitive functions, such as construction/copying, abstraction, and recall
Rokicki et al., 2015 [26]	31 cognitively healthy participants Aged: 42-78 years	Twice-daily doses of the imidazole dipeptide formula (500 mg) Placebo	3 months	ADAScog, WMSLM 1 and 2, and BDI Functional MRI	In the CRC group, better verbal episodic memory performance and decreased connectivity on functional MRI were found
Hisatsune et al., 2016 [27]	39 cognitively healthy participants Mean age: 69.2 years	Twice-daily doses of the imidazole dipeptide formula (500 mg) Placebo	3 months	ADAScog, WMSLM 1 and 2, BDI, SF-36, MMSE Serum concentrations of 27 cytokines Perfusion MRI	CRC supplementation showed a significant beneficial effect on verbal episodic memory and brain perfusion in older adults
Fatty acid supplementation					
Witte et al., 2014 [28]	65 cognitively healthy older subjects MMSE ± 26 Mean Age: 63.9 ± 6.6 years	n-3 PUFA group received fish oil capsules with 2.2 g of n-3 PUFAs (1320 mg EPA + 880 mg DHA, given as 1000 mg fish oil and 15 mg vitamin E) Placebo (sunflower oil)	26 weeks	VF, TMT-A and -B, SCWT, AVLT, FBDS-WAIS, STAI 1 and 2 Erythrocyte membrane fatty acid composition MRI	Supplementation with high levels of n-3-PUFAs demonstrated enhanced executive functions in healthy older adults after 26 weeks and improved white matter microstructural integrity, regional gray matter volume, and vascular parameters
Jaremka et al., 2014 [29]	138 cognitively healthy older subjects Mean age: 51.0±7.8 years	1.25 g/day of n-3 PUFAs 2.50 g/day of n-3 PUFAs Placebo The fish oil supplements contained a 7:1 ratio of EPA to DHA	4 months	20-item UCLA loneliness scale, CVLT -II, DS-WMS-III, LNS-WMS-III, SS- WMS-III, TMT, COWAT Plasma levels of n-6 and n-3 PUFAs.	Lonelier people within the placebo condition had poorer verbal episodic memory post-supplementation, as measured by immediate and long-delay free recall, than their less lonely counterparts. The plasma n-6 PUFAs: n-3 PUFAs ratio data mirrored these results
Mahmoudi et al., 2014 [30]	199 older individuals with normal or mild to moderate cognition impairment Aged ≥ 65 years	180 mg of DHA + 120 mg of EPA Placebo	6 months	MMSE, AMT Plasma cholesterol, CRP, fasting blood sugar	No significant effects on cognitive outcomes
Chew et al., 2015 [31]	3741 partecipants Mean Age: 72.7 years	n-3 PUFAs (1 g) and/or lutein (10 mg)/zeaxanthin (2 mg) Placebo All participants were also given varying combinations of vitamins C, E, beta carotene, and zinc	5 years	HHI, CES-D, TICS-M, TICS-M Recall, AC, LF, AF, LM-WMS-III-1 & 2, DB, and DR-WMS-III-RP	No significant effects on cognitive outcomes

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Reference	Study sample	Intervention(s)	Duration	Cognitive-related outcomes and nutritional assessment	Main Results Cognitive results
Fatty acid supplementation					
Pase et al., 2015 [32]	160 cognitively healthy older volunteers Aged: 50-70 years	Multivitamin combined with fish oil (3 g) Multivitamin combined with fish oil (6 g) Placebo multivitamin combined with fish oil (6 g) Placebo multivitamin combined with placebo fish oil (Sunola oil)	16 weeks	SUCCAB measuring reaction time, cognitive processing speed, short-term memory, and visual memory BP variables	Absolute increases in the red blood cell n-3/n-6 ratio were associated with improvements in spatial working memory. The 6 g fish oil without the multivitamin group displayed a significant decrease in aortic pulse pressure and aortic augmentation pressure, two measures of aortic BP and aortic stiffness
Tokuda et al., 2015 [33]	113 older nondemented Japanese men Mean age: 59.6 years	LC-PUFA-containing oil (including ARA 120 mg/die, DHA 300 mg/die and EPA 100 mg/die) Purified olive oil	4 weeks	Event-related potential P300 and POMS LC PUFA plasma analysis Diet history questionnaire, semi-quantitative FFQ, and study diary	Changes in P300 latency were significantly different between the placebo group and the LC PUFA group after supplementation
Külzow et al., 2016 [34]	44 cognitively healthy individuals Mean age: 62 ± 6 years	n-3 PUFAs (2.2 g/day) Placebo	26 weeks	LOCATO assessing OLM in older adults, AVLT, and PANAS Erythrocyte membrane fatty acid composition, serum biomarkers and APOE genotyping Dietary habit questionnaire	Performance in cued recall in a OLM task was sensitive in detecting beneficial effects of n-3 PUFA supplementation. Omega-3-index significantly increased in the n-3 PUFA group and decreased in the placebo group

MMSE: Mini-Mental State Examination; TMT-A: Trail Making Test - A; TMT-B: Trail Making Test -B; WLT: Word Learning Test; SCWT: Stroop Color-Word Test; FBDS-WAIS: Forward and Backward Digit Span task from the Wechsler Adult Intelligence Scale; VFT: Verbal Fluency Test; CRC: carnosine related compounds; CME: chicken meat extract; STMS: Short Test of Mental Status; CDR: Clinical Dementia Rating; ADAS-cog: Alzheimer's Disease Assessment Scale-Cognition; LM-1 & 2-WMS-: Logical Memory 1 & 2 from Wechsler Memory Scale; BDI: Beck Depression Inventory; MRI: magnetic resonance imaging; SF-36: Medical Outcomes Study, 36-item Short Form; MCS: Mental Health Component Summary score; PCS: Physical Health Component Summary; n-3 PUFA: n-3 polyunsaturated fatty acids; VF: Verbal Fluency; AVLT: Auditory Verbal Learning Test; STAI 1 and 2: Spielberger's State-Trait Angst Inventar; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; CVLT: California Verbal Learning Test, Second Edition; DS-WMS-III: Digit Span subtest from the Wechsler Memory Scale – Third Edition; LNS-WMS-III: Letter-Number Sequencing subtest from the Wechsler Memory Scale – Third Edition; SS-WMS-III: Spatial Span subtest from the Wechsler Memory Scale – Third Edition; COWAT: Controlled Oral Word Association Test; AMT: Abbreviated Mental Test score; CRP: C-reactive protein; CES-D: Center for Epidemiologic Studies' Depression Scale; TICS-M: Telephone Interview Cognitive Status-Modified; AC: Animal Category; LF: Letter Fluency; AF: Alternating Fluency; LM-WMS-III-1 & 2: Logical Memory 1 & 2 from Wechsler Memory Scale – Third Edition; DB: Digits Backward; DR-WMS-III-RP: Delayed Recall from Wechsler Memory Scale – Third Edition Recall Paragraph; SUCCAB: Swinburne University Computerised Cognitive Assessment Battery; BP: blood pressure; LC PUFA: long-chain polyunsaturated fatty acids; ARA: arachidonic acid; POMS: Profile of Mood Status; FFQ: food frequency questionnaires; OLM: object-location memory; PANAS: Positive and Negative Affect Schedule; APOE; apolipoprotein E

after supplementation was found in specific subscores of a test evaluating global cognitive functions, such as construction/copying, abstraction, and recall (Tab. II) [25]. After 3 months of imidazole dipeptide formula supplementation containing 500 mg of CRC supplementation (carnosine and anserine, ratio 1/3) to 31 healthy participants, the CRC group had not only a better verbal episodic memory performance but also, at functional MRI, a decreased connectivity in the default mode network, the posterior cingulate cortex and the right fronto-parietal network, as compared with the placebo group. Furthermore, there was a correlation between the extents of cognitive and neuroimaging changes suggesting that daily CRC supplementation could impact cognitive function and that network connectivity changes may be associated with its effects (Tab. II) [26]. These findings were confirmed in another RCT including 39 healthy older adults assigned to a CRC supplementation (carnosine and anserine) or placebo for three months. CRC group showed significant preservation in delayed recall verbal memory compared to the placebo group, but not in the immediate recall test, suggesting that CRC supplementation may have a beneficial effect on verbal memory registration, but not on short-term working verbal memory. Blood analysis revealed a decreased secretion of inflammatory cytokines in the CRC group, including CCL-2 (MCP-1) and interleukin (IL)-8. Furthermore, perfusion MRI analysis using arterial spin labeling showed a suppression of the age-related decline in brain blood flow in the posterior cingulate cortex area in the CRC group compared to the placebo group suggesting a protective role of CRC supplementation on brain perfusion (Tab. II) [27].

Fatty acids

In AD brains, it has been reported the lack of enzyme responsible for converting choline into acetylcholine,

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 [47]. However, results from clinical trials were contrasting and further RCTs are required to evaluate their role as therapeutic supplements in order to delay cognitive impairment. 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 [48]. In particular, an increasing body of epidemiological evidence suggested that elevated saturated fatty acids (SFAs) 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 [49]. Despite the strong evidence in cognitive decline prevention coming from observational studies, findings coming from RCTs were controversial considering the great heterogeneity of samples and outcome measures as well as neuropsychological tools or MRI findings (Tab. II) [28-34]. Interesting data have been suggested from one RCT on 65 healthy subjects showing not only a significant increase in executive functions and letter fluency in the n-3-PUFA group compared with placebo, but also neuroimaging modifications after supplementation suggesting a pathobiological effect of n-3 PUFAs (Tab. II) [28]. In fact, n-3 PUFA supplementation led to significant beneficial effects on white matter microstructural integrity and significant increases in regional gray matter volume compared with placebo in specific regions as left hippocampus, precuneus, superior temporal, inferior parietal and postcentral gyri, and in the right middle temporal gyrus and beneficial effects on carotid intima media thickness and diastolic blood pressure. Improvements in executive functions correlated positively with changes in omega-3-index and peripheral brain-derived neurotrophic factor, and negatively with changes in peripheral fasting insulin (Tab. II) [28]. In another RCT, n-3 PUFA supplementation was effective on immediate and long-delayed free recall only in healthy lonelier participants. In fact, lonelier people within the placebo condition had poorer verbal episodic memory post-supplementation, as measured by immediate and long-delay free recall, than their less lonely counterparts. This effect was not observed in the n-3 PUFA 1.25 g/day and n-3 PUFA 2.5 g/day supplementation groups. The plasma n-6 PUFAs: n-3 PUFAs ratio data mirrored these findings (Tab. II) [29]. However, findings from two RCTs showed that oral supplementation with n-3 PUFAs had no statistically significant effect on cognitive functions (Tab. II) [30 31]. In particular, in a RCT on 199 older subjects with normal or mild to moderate cognition impairment, low dose n-3 PUFAs (180 mg of DHA + 120 mg of EPA) for 6 months had no significant beneficial effects on improvement of cognition or prevention of cognitive decline in older people. However, considering only the cognitively healthy subjects, authors noticed near significant less decrement in global cognitive scores in n-3 PUFA group compared to placebo (Tab. II) [30]. Moreover, in a large RCT including 3741 older participants, randomized to receive n-3 PUFAs (1 g) and/or lutein (10 mg)/zeaxanthin (2 mg) *vs* placebo for 5 years no statistically significant differences in change of cognitive scores between groups were reported (Tab. II) [31]. Furthermore, several RCTs reported promising findings only in specific cognitive domains evaluated with several neuropsychological tests. In fact, in a RCT including 160 healthy participants randomized to multivitamins with fish oil for 16 weeks, the red blood cell n-3/n-6 ratio increases were associated with improvements in spatial working memory (Tab. II) [32]. Some trials reported promising results in specific cognitive domains with higher doses of LC PUFAs compared to general dietary intake levels. Interestingly, a RCT suggested a potential role in improving cognitive function of LC PUFAs also at low doses of supplementation similar to general dietary intake. In fact, in 113 non-demented older Japanese participants, after 4 weeks of supplementation with LC PUFA-containing oil (DHA 300 mg/day, EPA 100 mg/day, and ARA 120 mg/day) or purified olive oil as placebo, changes in P300 latency, a measure of cognitive processes, were significantly different between the placebo group and the LC PUFA group. Significant increases in DHA and ARA contents in plasma phospholipids were observed in the LC PUFA group, while no changes were observed in the placebo group (Tab. II) [33]. In another RCT conducted on 44 cognitively healthy individuals, the recall of object locations was significantly better after n-3 PUFA supplementation (daily dose of 1.320 mg EPA + 880 mg DHA for 26 weeks) compared with placebo. No significant correlation between changes in memory performance and omega-3-index were observed, suggesting that memory benefits were not associated in a simple linear fashion with changes in omega-3-index (Tab. II) [34].

NUTRITIONAL INTERVENTION THROUGH MICRONUTRIENT CHANGES

Non-flavonoid polyphenols

Table III shows selected RCTs published in the last three years (2014-2016) that evaluated the efficacy of

nutritional intervention through supplementation of dietary micronutrients in preventing the onset of late-life cognitive disorders and dementia in cognitively healthy subjects aged over 60 years [35-43]. Several classes of polyphenols have been investigated for their potential anti-ageing and neuroprotective properties, including flavonoids, commonly found in berries, grapes and red wine, and non-flavonoids, i.e., curcumin from turmeric and resveratrol from grapes and red wine [50]. An increasing body of evidence suggested that consumption of polyphenols such as resveratrol and flavonoids may have potential beneficial effects on cognition, particularly on declarative and spatial memory, mainly in cognitively healthy individuals [50]. However, results from RCTs were contrasting considering also the methodological inconsistencies of studies. On the other hand, findings from observational studies suggested that moderate consumption of red wine, rich in specific polyphenolic compounds such as quercetin, myricetin, catechins, tannins, anthocyanidins, resveratrol, and ferulic acid, has been associated with a lower incidence of cognitive decline, suggesting a protective role against dementia [51]. These data were confirmed from a recent RCT (Tab. III) [35]. In fact, a trial including 46 cognitively healthy older adults randomly assigned to receive a daily intake of 200 mg of resveratrol and 320 mg of quercetin or placebo showed that supplementary resveratrol over a period of 26 weeks improved retention of words over a 30 min delay and functional connectivity of the hippocampus with frontal, parietal, and occipital areas in healthy older overweight adults compared with placebo (Tab. III) [35]. Among non-flavonoid polyphenols, curcumin has been extensively reported to demonstrate many beneficial biological effects including anti-cancer, antioxidant and anti-inflammatory activities [52].

For the prevention of cognitive-related outcomes in older age, promising results were reported in a one-year RCT in 96 cognitively normal subjects randomized to receive placebo or 1500 mg/d of bioenhanced preparation of curcumin (BCM-95®CG). A significant time×treatment group interaction was observed for global cognitive function, explained by a function decline in the placebo group at 6 months that was not found in the intervention group (Tab. III) [36].

Flavonoids

Flavonoids [flavanols (catechin, epicatechin, epigallocathechin, 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 [45 53]. Recent RCTs showed significant improvements in some cognitive domains after flavonoid interventions [54]. However, the great heterogeneity in sample, flavonoid dose, follow-up and cognitive tests used led to inconsistent findings [54]. In a very interesting RCT on 37 healthy older adults who consumed a high cocoa flavanol-containing diet (900 mg cocoa flavanols and 138 mg of epicatechin) or a low-dose one (10 mg cocoa flavanols and < 2 mg epicatechin) with or without aerobic exercise for 12 weeks, the high-flavanol intervention was found to enhance dentate gyrus (DG) function measured by functional MRI and by cognitive testing, suggesting the crucial role of DG dysfunction in age-related cognitive decline and the potential beneficial effects of flavonoid supplementation on DG function (Tab. III) [37]. On the contrary, in a trial including 300 cognitively healthy postmenopausal women randomized to receive 25 grams of isoflavone-rich soy protein for 2.7 years, long-term changes in isoflavonoids were not associated with global cognition and episodic memory, although greater isoflavonoid exposure was associated with decrements in general intelligence (Tab. III) [38]. Promising results come from other two trials with a 8 week follow-up (Tab. III) [39 40]. In particular, in a RCT including 37 healthy participants randomized to receive two different flavanone-rich supplementations, high flavanone and low flavanone orange juice drinks, global performance, executive function, and episodic memory, and immediate recall were significantly better after the high flavanone drink than the low flavanone drink (Tab. III) [39]. Similar positive findings were found in the second RCT for a drink containing a high dose of cocoa flavanols (993 mg/day) compared to a low dose drink (993 mg/day) in cognitively healthy participants for specific cognitive domains (i.e., executive function and verbal fluency) suggesting a possible protective role in age-related cognitive dysfunction, possibly through an improvement in insulin sensitivity (Tab. III) [40].

Homocysteine-related vitamins

A possible modifiable risk factor of dementia is an elevated plasma Hcy level. In fact, Hcy may be toxic for neurons and vascular endothelial cells [55], and cross-sectional and prospective studies have shown associations between elevated Hcy levels and cognitive decline and dementia [56]. Hcy levels can be lowered by supplementation with folic acid (vitamin B9) and vitamin B12 [57]. 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 (Tab. III) [41-43]. In fact, in two RCTs, no significant effect of supplementation of Hcy-related vitamins on cognitive function were found (Tab. III) [41 42]. In particular, in a large RCT

Table III. Randomized clinical trials evaluating the efficacy of nutritional intervention using a micronutrient approach in preventing the onset of late-life cognitive disorders and dementia in cognitively healthy subjects aged over 60 years (2014-2016).

Reference	Study sample	Intervention(s)	Duration	Cognitive-related outcomes and nutritional assessment	Main results
Non-flavonoid polyphenols					
Witte et al., 2014 [35]	46 cognitively healthy overweight older individuals Aged: 50-75 years	Daily intake of four capsules (in total 200 mg of resveratrol and 320 mg of quercetin) Placebo All subjects received a 13 week supply of capsules and another 13 week supply after 3 months	26 weeks	AVLT Functional MRI and DTI MRI Lipid metabolism, inflammation, neurotrophic factors, and vascular parameters	Significant positive effect of resveratrol on retention of words over 30 minutes and functional connectivity of the hippocampus with frontal, parietal, and occipital areas in healthy older overweight adults compared with placebo
Rainey-Smith et al., 2016 [36]	96 community-dwelling older adults without significant cognitive impairments Mean age: 66 ± 6.6 years	1500 mg/day of bioenhanced preparation of curcumin (BCM-95®CG) Placebo	12 months	CCRT, DASS, SF-36, PRMQ-16, MoCA; AVLT, COWAT, WDSS-WAIS-R, and the computerized CogState battery APOE genotyping	A significant time×treatment group interaction for global cognition, explained by a function decline in the placebo group at 6 months that was not found in the intervention group. No differences for all other clinical and cognitive measures
Flavonoids					
Brickman et al., 2014 [37]	37 cognitively healthy, sedentary older subjects Aged: 50-69 years	High flavanol intake + aerobic exercise High flavanol intake Low flavanol intake + aerobic exercise Low flavanol intake	12 weeks	ModBent task, AVLT Functional MRI	High dietary flavanol consumption enhanced dentate gyrus function in the aging human hippocampal circuit, independently of exercise
St John et al., 2014 [38]	300 cognitively healthy women Mean age: 61 years	25 g of isoflavone-rich soy protein (91 mg of aglycone weight isoflavones: 52 mg genistein, 36 mg daidzein, and 3 mg glycitein) Milk protein-matched placebo provided daily	2.7 years	WTAR, CES-D; neuropsychological test battery evaluating general intelligence (executive/expressive/visuospatial tasks), verbal episodic memory (list learning/logical memory), and visual episodic memory Overnight urine excretion of isoflavonoids and fasting plasma levels of isoflavonoids	Long-term changes in isoflavonoids were not associated with global cognition. Increasing isoflavonoid exposure from dietary supplements was, however, associated with decrements in general intelligence but not memory
Kean et al. 2015 [39]	37 cognitively healthy older subjects Mean age: 66.7 years	High flavanone drink (305 mg/day) Low flavanone drink (37 mg/day)	8 weeks	CERAD immediate and delayed verbal recalls and serial sevens, SWM, DSST-WAIS, VPA-WMS-III, LM, LF, and Go-NoGo	Daily consumption of high dose flavanone-rich orange juice was associated with benefits for global cognitive function, executive function, and episodic memory, mainly immediate recall
Mastroiacovo D et al. 2015 [40]	90 cognitively healthy older subjects Mean age: 69.5 years	993 mg flavanols/day 520 mg flavanols/day 48 mg flavanols/day	8 weeks	MMSE, TMT-A and -B, and VFT	High dose flavanol consumption caused significant effects on executive function and verbal fluency
Van der Zwaluw et al., 2014 [41]	2.919 older participants with Hcy levels between 12 and 50 µmol/L Mean age: 74.1 + 6.5 years	Daily either a tablet with 400 µg folic acid and 500 µg vitamin B12 Placebo Both tablets contained 15 µg vitamin D3	2 years	MMSE, AVLT, FBDS-WAIS, TMT-A and –B, SCWT, SDMT, and LF Blood biomarkers	This large RCT did not reveal beneficial effects of supplementation with vitamin B12 and folic acid on the cognitive domains of episodic memory, attention and working memory, information processing speed, and executive function

▶

Reference	Study sample	Intervention(s)	Duration	Cognitive-related outcomes and nutritional assessment	Main results
Homocysteine-related and antioxidant vitamins					
Dangour et al., 2015 [42]	201 older subjects with moderate vitamin B-12 deficiency (serum vitamin B-12 concentrations: 107-210 pmol/L) in the absence of anemia Mean age: 80 years	1 mg crystalline vitamin B-12 Placebo	12 months	CVLT, SLMT, simple and choice reaction time, and VFT Peripheral motor and sensory nerve conduction and central motor conduction assessment	No evidence of an effect on peripheral nerve or central motor function outcome or on cognitive function
Cheng et al., 2016 [43]	104 older participants with hyperhomocysteinemia Mean age: 71.7 ± 8.8 years	Vitamin B group, which received 800 µg/day of folate, with 10 mg of vitamin B6 and 25 µg of vitamin B12 Placebo	14 weeks	BCATs Serum measure of tHcy, vitamin B6, vitamin B12, and folate	Improvement with vitamin B supplementation in global cognitive scores and four subtests (mental speed, visuo-spatial ability, working memory, and visual memory)

AVLT: Auditory Verbal Learning Test; DTI: diffusion tensor imaging; MRI: magnetic resonance imaging; CCRT: Cambridge Contextual Reading Test; DASS; Depression Anxiety Stress Scales; PRMQ-16: 16 item self-report Prospective and Retrospective Memory Questionnaire; MoCA: Montreal Cognitive Assessment; WDSS-WAIS-R: Wechsler Digit Symbol Scale from Wechsler Adult Intelligence Scale revised; APOE; apolipoprotein E; Mod Bent; modified Benton Visual Retention Test; WTAR: Wechsler Test of Adult Reading; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; SWM: Spatial Working Memory; DSST-WAIS: Digit Symbol Substitution Test from the Wechsler Adult Intelligence Scale; VPA-WMS-III: Verbal Paired Associates from the Wechsler Memory Scale– Third Edition; LM: Letter Memory; LF: Letter Fluency; TMT-A: Trail Making Test - A; TMT-B: Trail Making Test -B; VFT: Verbal Fluency Test; Hcy: homocysteine; FBDS-WAIS: Forward and Backward Digit Span task from the Wechsler Adult Intelligence Scale; SCWT: Stroop Color-Word Test; SDMT: Symbol Digit Modalities Test; CVLT: California Verbal Learning Test, Second Edition; SLMT: symbol letter modality test; BCATs: Basic Cognitive Aptitude Tests

on 2.919 older participants with elevated Hcy levels, a 2-year folic acid and vitamin B12 supplementation did not significantly improve cognitive performance in all four cognitive domains investigated (episodic memory, attention and working memory, information processing speed, and executive function). Interestingly it was reported a small difference in global cognition, that the authors concluded as attributable to chance (Tab. III) [41]. The other RCT included 201 healthy cognitive older adults with moderate vitamin B12 deficiency. In this one-year follow-up trial, there was no effect of B12 supplementation peripheral nerve or central motor function outcome or cognitive function (Tab. III) [42]. However, another RCT suggested more promising findings with a supplementation containing 800 µg/day of folate, 10 mg of vitamin B6 and 25 µg of vitamin B12 in 104 older patients with hyperhomocysteinemia. This supplemtation improved cognitive function in terms of global cognitive scores and four subtests (mental speed, visuo-spatial ability, working memory, and visual memory) (Tab. III) [43].

CONCLUSIONS AND FUTURE DIRECTIONS

In the last decade, while the association between diet and cognitive function or dementia has been largely investigated in observational studies, there was a lack of evidence from RCTs dealing with the prevention of late-life cognitive disorders though dietary intervention in older adults without cognitive dysfunction. In the present article, we reviewed RCTs published in the last three years (2014-2016) exploring nutritional intervention efficacy in preventing the onset of late-life cognitive disorders and dementia in cognitively healthy subjects aged over 60 years and using different levels of investigation (i.e., dietary pattern changes/medical food/nutraceutical supplementation/multidomain approach and dietary macro- and micronutrient approaches). From the reviewed RCTs, there was moderate evidence that nutritional intervention through dietary pattern changes, medical food/nutraceutical supplementation, and multidomain approach improved specific cognitive domains or cognitive-related blood biomarkers. Furthermore, there was convincing evidence that protein supplementation improved specific cognitive domains. For fatty acid supplementation, mainly LC PUFAs, there was emerging evidence suggesting an impact of this approach in improving specific cognitive domains, MRI findings, and/or cognitive-related biomarkers also in selected subgroups of older subjects although some results were conflicting. Among selected RCTs that evaluated the efficacy of nutritional intervention through supplementation of dietary micronutrients, there was evidence of an impact of non-flavonoid polyphenol and flavonoid supplementations in improving specific cognitive domains and/or MRI findings. Finally, there was only low evidence suggesting efficacy of intervention with homocysteine-related vitamins in improving cognitive functions, dementia incidence, or cognitive-related biomarkers in cognitively healthy older subjects.

In the last five 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 [4-7]. However, these meta-analyses and systematic/scoping reviews investigated also observational studies and not only RCTs [4 7], included also younger subjects [5], and were limited to specific macronutrients (i.e., n-3 PUFAs) [4-7], micronutrients [5 6], or dietary pattern changes/nutraceuticals [4 7]. In particular, some of these studies found that n-3 PUFAs were associated with better global cognition and some specific cognitive domains [4 6 7]. B vitamins, and vitamin E supplementations did not affect cognition [5] or had limited efficacy [6 7], while adherence to the MeDi was significantly associated with better cognitive performance and less cognitive decline [4].

The absence of disease-modifying treatment for AD patients leads to the investigation of a multimodal alternative therapeutic or preventive approaches by targeting modifiable risk factors. Therefore, in the last years, a growing interest has concerned the relation between nutrients and cognitive impairment in the earlier phases, considering the multifactorial effects of nutrition in human diseases. In fact, it is well known that dietary habits may influence several cardiometabolic risk factors, as visceral adiposity, blood pressure, glucose-insulin metabolism, lipids levels, but also hepatic function, endothelial health, microbiome function, and several biological processes as oxidative stress, inflammation, both involved in human aging. Despite several promising findings coming from observational studies [3], evidence suggesting a potential preventive effectiveness of nutritional intervention in healthy olders to delay the onset of cognitive decline are still scarce and quite contrasting. Considering that is unlikely that a single nutrient could significantly improve cognition and delay cognitive impairment, several observational studies and RCTs proposed combination of micro/macronutrients or medical foods/nutraceuticals as potential preventive approaches in olders with promising results [3 4 6 7] Furthermore, a multidimensional approach consisting in healthy life style (healthy dietary habits in combination with physical activity) seems the best intervention in olders. In fact it is well known that there is a strong bidirectional interaction between cognitive performance and other main outcomes in olders that have to be considered as physical and cognitive frailty and disability [58]. 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 questionnaire but also biomarkers dosage 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 significant and objective results. Therefore, in addition to clinical scales and cognitive tests, serum and cerebrospinal fluid (CSF) biomarkers, neuroimaging and other cognitive-related biomarkers have been proposed. As a result, these findings could give us the possibility to better understand and quantify the nutrition-related impact on cognitive impairment and AD pathobiology. In conclusion, dietary pattern change/multidomain approaches, macronutrient (i.e., proteins and LC PUFAs) and micronutrient (i.e., non-flavonoid polyphenols and flavonoids) supplementations could be really effective in achieving cognitive-related outcomes in healthy older subjects without cognitive dysfunction. 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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