UNIVERSITY OF SAO PAULO

FCF/FSP/FEA

Interunit Graduate Program in Applied Human Nutrition- PRONUT

Nutritional Strategies in the Management of Alzheimer's Disease: Systematic Review and Meta-analysis.

Shirley Steffany Muñoz Fernández

A dissertation submitted in conformity with the requirements for the degree of Master of Science.

Supervisor: Prof. Dr. Sandra Maria Lima Ribeiro

Sao Paulo

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"The doctor of the future will no longer treat the human frame with drugs, but will rather cure and prevent disease with nutrition".
Thomas A. Edison

ABSTRACT

MUÑOZ, S.S. **Nutritional strategies in the management of Alzheimer's disease: Systematic review and meta-analysis.** 2016. 145p Dissertation (Master's degree) - Interunit Graduate Program in Applied Human Nutrition PRONUT, University of Sao Paulo, Sao Paulo, 2016.

Alzheimer's disease (AD) is one of the main causes of dependency and disability in the elderly population. A number of investigations have been seeking its prevention and/or management. In this context, it is important to highlight the role of modifiable risk factors, such as nutrition. This study aims to conduct a systematic review and subsequent meta-analysis, to assess the effect of food and/or nutrients for the management of AD at different stages. This work was steered based on the Cochrane Handbook for systematic reviews of interventions and the PRISMA Statement. Electronic databases were searched up to 2014, in Portuguese, English or Spanish. Relevant publications were identified by title and abstract using key search terms referring to Alzheimer's disease, nutrition interventions and type of study. Trials' risk of bias was appraised by applying the Cochrane's tool for assessing risk of bias. The main outcome measures comprise neuropsychological tests such as MMSE, ADCS-ADL, NPI and CDR-sob, biomarkers and brain imaging. Pairwise meta-analyses were performed in a random-effect model by estimating the weighted mean differences between treatment and placebo groups, with 95% confidence intervals for outcome measures by treatment. Network meta-analysis and the ranking probability of treatment for each nutrition intervention were undertaken on cognitive outcome. The strength and quality of evidence were rated according to the GRADE approach. From the whole research, 182 studies met the systematic review's purpose. Thirty-five clinical trials complied with eligibility criteria and risk of bias assessment. Included studies utilized: antioxidants, B-vitamin complex, carbohydrates, lipids, omega-3 fatty acids, polymeric formulas, polypeptide and vitamin D. Estimates treatment effects from pairwise meta-analyses show a significant positive effect from the supplementation with proline-rich polypeptide (WMD 12.00 [95% CI 10.20, 13.80] $P < 0.00001$) and B-vitamin complex (WMD 0.44 [95% CI 0.09, 0.79] $P = 0.01$) on cognitive function measured by the MMSE. Remaining nutrients supplementation did not show any significant effect on functional, behavioral, global performance, biomarkers or brain imaging outcomes. Isolated nutrient supplementations show no convincing evidence of providing a significant benefit on clinical manifestations or neuropathology of AD. As a treatment strategy, nutrients did not show any effect when delivered individually, probably due to their synergistic work on brain function at different domains. Nevertheless, nutrients represent a potential preventive approach and an adjuvant treatment for patients with AD at earlier stages.

Key-words: Alzheimer's Disease, nutrition, systematic review, meta-analysis.

RESUMO

MUÑOZ, S.S. **Nutrição e alimentação no manejo da doença de Alzheimer: Revisão sistemática and meta-análise.** 2016. 145p. Dissetação (Mestrado) - Programa de Pós-Graduação Interunidades em Nutrição Humana Aplicada PRONUT, Universidade de São Paulo, São Paulo, 2016.

A doença de Alzheimer (DA) é uma das maiores causas de dependência e incapacidade na população idosa, o que tem levado a inúmeras investigações sobre sua prevenção e ou manejo. Neste contexto, é importante destacar o papel desempenhado pelos fatores de risco modificáveis, como a nutrição. Este estudo trata de uma revisão sistemática e meta-análise, para avaliar o efeito das intervenções nutricionais no manejo da DA, em seus diferentes estágios. Este trabalho segue as propostas da Colaboração Cochrane e a declaração PRISMA. Bases de dados eletrônicas foram pesquisadas a partir do seu início até o 2014, em Português, Inglês ou Espanhol. Estudos relevantes foram identificados por título e resumo usando as palavras-chave referente à doença de Alzheimer, intervenções nutricionais e tipo de estudo. A qualidade dos estudos foi avaliada mediante a ferramenta da Cochrane para avaliação do risco de viés. As principais medidas de desfechos compreenderam os testes neuropsicológicos MEEM, AVD, NPI e CDR-sob, biomarcadores e neuroimagem. As meta-análises em pares foram realizadas em modelo de efeito aleatório pela estimativa de diferença de médias ponderadas entre os grupos de tratamento e placebo, com 95% de intervalo de confiança para as medidas de desfecho segundo a intervenção. A meta-análise em rede e a probabilidade da posição do tratamento para cada intervenção nutricional foi realizada para o desfecho cognitivo. A força e a qualidade da evidência foram avaliadas de acordo com o método GRADE. Da busca total inicial, 182 estudos cumpriam com o propósito desta revisão sistemática. Ainda, 35 ensaios clínicos preencheram os critérios de elegibilidade e avaliação de risco de viés. Os estudos incluídos usaram: antioxidantes, vitaminas do complexo B, carboidratos, lipídeos, ácidos graxos ômega-3, formula poliméricas, polipeptídios e vitamina D. As estimativas de efeito do tratamento das meta-análises em pares mostraram um efeito positivo significativo a partir da suplementação com um polipeptídio rico em prolina (MD 12.00 [95% IC 10.20, 13.80] $P < 0.00001$) e com as vitaminas do complexo B (MD 0.44 [95% IC 0.09, 0.79] $P = 0.01$) na função cognitiva avaliada pelo MEEM. A suplementação com os demais nutrientes não mostrou um efeito significativo na funcionalidade, comportamento, desempenho global, biomarcadores da DA, nem desfechos de imagem. A suplementação com nutrientes isolados não mostrou um efeito significativo nas manifestações clínicas ou neuropatologicas da DA. Como estratégia de tratamento, os nutrientes não demonstraram um efeito separadamente, provavelmente devido a seu trabalho sinérgico nos diferentes domínios da função cerebral. Ainda assim, os nutrientes representam uma abordagem preventiva potencial e um tratamento adjuvante nas pessoas com DA nos estágios iniciais.

Palavras-chave: Doença de Alzheimer, nutrição, revisão sistemática, meta-análise.

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LIST OF ABBREVIATIONS

Aβ: β-amyloid peptide
AβPP: amyloid precursor protein
AchE-Is: Acetylcholinesterase Inhibitors
AD: Alzheimer's disease
ADI: Alzheimer's Disease International
ADAS-cog: Alzheimer's Disease Assessment Scale – Cognitive
ADL: Activities of Daily Living
ADCS-ADL: Alzheimer's Disease Cooperative Study Activities of Daily Living
BBB: Blood Brain Barrier
BRSD: Behavior Rating Scale for Dementia
CAMDEX: Cambridge Mental Disorders of the Elderly Examination
CDR: Clinical Dementia Rating
CDR-sob: Clinical Dementia Rating sum of boxes
CNS: Central nervous system
CRP: C-reactive protein
CSF: Cerebrospinal fluid
DAD: Disability Assessment in Dementia Questionnaire
DHA: Docosahexaenoic acid
EPA: Eicosapentaenoic acid
F2-IsoPs: F2-isoprostanes
Hcy: Homocysteine
Hs-CRP: High sensitive
IADL: Instrumental Activities of Daily Living
IU: International Units
MRI: Magnetic resonance imaging
MCI: Mild Cognitive Impairment
MD: Mean difference
MMSE: Mini-Mental State Examination
NAC: N-acetylcysteine
NFT: neurofibrillary tangles
NMA: network Meta-analysis
NPI: Neuropsychiatric Inventory
P-Tau: phosphor-tau
PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses
PUFA: Polyunsaturated fatty acid
SD: Standard Deviation
T-Tau: total tau
WHO: World Health Organization

1. INTRODUCTION

1.1 Aging and Alzheimer's disease

Recent global statistics prove that the demographic transition has led to a rapid growth of the elderly population in recent years (1). This demographic transition is also associated with nutritional transition, characterized by changes in life styles, such as inadequate dietary patterns, physical inactivity, tobacco smoking and alcohol abuse. These changes usually result in a high prevalence of chronic diseases, which are often associated with the elderly population (2). With regard to non-communicable age-related diseases, it is important to include neurodegenerative diseases, specifically dementia, whose rate of occurrence increases with age. Dementia is defined as a syndrome, usually of chronic and progressive nature, caused by a brain disease. This syndrome disrupts multiple cortical functions, causing intellectual and cognitive impairment, affecting memory, language, orientation, reasoning, calculation, comprehension, judgment and learning processes (3). Thence, dementia can be considered one of the major causes of disabilities and dependence in aging. Alzheimer's disease (AD) is the most common form of dementia, comprising 50 to 75% of all cases (4). It is imperative to highlight that the dementia is not part of a thriving aging, and imply great suffering for families and high costs to public health (5).

Epidemiological projections indicate that the number of people with dementia has been growing continuously in the last decade. In 2005 an article concerning the global prevalence of dementia in 14 regions in the world was published, the Delphi Consensus Study (6). This study determined a prevalence of 24.3 million people in 2001, with an increase of 4.6 million new cases annually, mostly in developing countries. This prevalence was reappraised in 2010 by the Global Burden of Disease study (7) in 21 world regions, which estimated a total of 35.6 million cases of dementia. A recent report published by the Alzheimer's Disease International (ADI) estimated 46.8 million people living with dementia in 2015. The number of people with dementia is projected to double every 20 years to 74.7 million by 2030 and 131.5 million by 2050. A higher fraction of the increase of these projections is expected to occur in low and middle-income countries, currently estimated at 58%. The overall new cases of dementia are about 9.9 million each year worldwide, suggesting a new case every 3.2 seconds (8).

The WHO ranked AD in the twentieth global position in 2012, and in the region of the Americas moved up to the third position from tenth in 2000, in the 20 leading causes of death (9). Brazil is among countries with the largest number of cases, moving from the nine position in 2010 to the fifth in 2015 with 1.6 million people (8,10). In 2010, the ADI estimated a total yearly costs worldwide of dementia at US$604 billion (11) that augmented by US$818 billion in 2015 (8) constituting an enormous impact over the world's economy. Thus, investigating strategies that may prevent or delay the onset of dementia is a matter of the utmost importance (4,12).

1.2 Physiopathology of AD

The AD is a continuum pathological disorder of the brain characterized by a progressive synaptic lost, dysfunction and neuronal death, caused by the deposition of pathologic markers inducers of lesions in the brain tissue, amyloidopathy and tauopathy (13). Recent studies have focused in the comprehension of this hallmarks, neuritic plaques composed by amyloid β peptide (Aβ) and extracellular neurofibrillary tangles (NFT) by hyperphosphorylated Tau protein, with a preferential distribution along the medial temporal-lobe structures (entorhinal-hippocampal region) (14,15).

The β-amyloid plaques arise from a transmembrane neuronal protein; Aβ peptide is cleaved from the proteolysis of the large amyloid precursor protein (AβPP) by the action of the α-secretase enzyme into Aβ1–40 and Aβ1–42 peptides and the Aβ oligomer that in some cases are able to accumulate in the brain. According to the amyloid cascade hypothesis, the Aβ aggregation occurs because of the reduction of its degradation, increased production, enhanced aggregation or decreased clearance from the brain to the blood/cerebrospinal fluid (CSF); reflected in reduced Aβ CSF levels. Until now, therapies attempting to diminish amyloid-β production or aggregation have not obtained permanent successful results (16). The other component of Alzheimer's pathology, the NFT, are constituted of an abnormally hyperphosphorylated and aggregated form of Tau protein, whose magnitude is regulated by enzymatic reaction. Normally, this is a soluble protein associated to microtubules and vesicle transport in axons; as a disease sign, it accumulates in insoluble paired helical filaments, breaking down the structures and neuronal functions. These tangles can be displaced to other brain regions (17). In addition, it has been proposed that changes in Tau are promoted by the toxic effect of Aβ aggregation; as well as, the predisposition to AD is triggered by inherited mutations in genes encoding amyloid precursor protein (APP),

presenilin 1 (PSEN1) and PSEN2. The apolipoprotein E (APOE) gene constitutes the main genetic risk factor in the early onset of the development of AD, especially the possession of an APOE4 allele (18). All these alterations are linked to synaptic dysfunction, neuron loss and vascular toxicity that precede the beginning of clinical symptomatologies, characteristics of AD (19,20).

The neuropathogenesis of AD has been associated to a sequence of complex molecular events. Processes such as mitochondria dysfunction, inflammation, abnormal accumulation of transition metals, Aβ and tau protein accumulation, induce to a disruption in the redox homeostasis of reactive oxygen species (ROS) and reactive nitrogen species (RNS), destabilizing the antioxidative defense, resulting in oxidative stress. The brain, due to its composition and to the high, metabolic rate, is very susceptible organ to oxidative damage (oxidation of glucose, lipids, protein and DNA). In turn, oxidative stress increases the Aβ production and deposition and promotes the phosphorylation and polymerization of tau and the consequent synapse loss and repressed neuronal survival, therefore creating a vicious cycle that boosts the beginning and progression of AD (21,22).

Albeit currently AD can only be diagnosed post mortem, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA), established some criteria for a probable diagnosis of AD, that requires a careful and comprehensive medical assessment comprising clinical, cognitive and neuropathological examination and diagnostic techniques (23).

1.3 Nutrition and DA

An adequate intake of nutrients is necessary to the formation, development, operation, maintenance of the brain structures, and the production of molecules such as neurotransmitter, precluding thus, the senility. In the situations of nutritional deficiencies, brain function may be altered, favoring the occurrence of neurological diseases, particularly during aging (24).

Recently, nutrition has emerged as an important modifiable determinant of chronic diseases. The scientific evidence increasingly corroborates that nutritional adjustments have strong effects, both positives and negatives, on health throughout lifetime (25). Such evidences

indicate that nutrients might have a preventive effect in neurodegenerative diseases (26). Extensive research over the past years supports the promising beneficial effects of nutrients in AD that implies a safe, cost-effective, ease of administration and socially acceptable approach (27). Among modifiable risk factors involved in the prevention of AD, some dietary exposures have been identified as protective factors and showed a lower incidence of AD; namely, low fat and calorie intake, high consumption of folate, fish, antioxidants (vitamin E/C, polyphenols), coffee and Mediterranean diet. In addition, some nutrition-related conditions (hyperhomocysteine, hypertension, frailty, type 2 diabetes mellitus, high body mass index in mid-life and late low BMI) increase the risk, suggesting that effective dietary interventions may reduce the growing incidence of AD (28,29).

1.3.1 Carbohydrates

The brain uses glucose as the primary source of energy, and its utilization is estimated in about 100 g/day or 20% of the food energy ingestion, given its oxygen consumption of 15-20% of the total body uptake at rest. Such rate reaches higher values in children and infants. It is possible that alterations in carbohydrates consumption do not influence the uptake of glucose by the brain, since this organ has the ability to adapt to glucose supplies, increasing the activity of glucose transporter proteins in the Blood Brain Barrier (BBB). Although in some exceptional cases, such as starvation, chronic ingestion of very high fat diets, or in rapid hypoglycemia in diabetes patients, induce the brain to use ketone bodies as source of energy. However, the continued use of glucose seems to be mandatory and it is provided via hepatic gluconeogenesis (30,31). Low concentrations of blood glucose (under 50 mg/dl) trigger neurological symptoms, coma and death, demonstrating the importance of glucose for brain (32). Therefore, appropriate brain function depends on quality and quantity of dietary intake of carbohydrates; it has been shown, for instance, that the ingestion of the first meal of the day is determinant for the memory performance; increase in blood glucose levels might be one of the mechanism involved (33). The brain regulates blood glucose concentration and assures energy supply by controlling eating behavior, as the body has limited carbohydrate reserves (34).

Some studies support that glucose participates in part in the regulation, and possibly in the enhancement of the processes of memory and learning formation; however, the mechanisms involved in these processes remains quite uncertain (35,36). It is thought that glucose affects

memorization by acting on the cholinergic system (37). Conversely, impairments in glucose regulation lead to brain disruptions, mainly in elderly (38). Individuals with Diabetes Mellitus have been associated to a decrease in memory, attention and other cognitive domains, compared to a healthy control counterpart, wherein glycemic control (or raised insulin levels) possibly play a part in this relationship (39). It is shown that inadequate regulation of blood glucose induces to reduced memorization, and can be enhanced after ingestion of glucose (40). In addition, moderate hypoglycemia also gives rise to general cognitive dysfunctions, which are not immediately recovered after glycemic levels restoration, and such damage can become permanent as long as the effects of hypoglycemia persist in a long-term, especially in the brain regions more vulnerable to such glucose variations (41).

1.3.2 Amino acid and proteins

The brain needs a steady supply of amino acids (AAs) to synthesize peptides, enzymes and neurotransmitters, which are essential for the adequate functioning of the central nervous system (CNS). AAs neuronal uptake is determined by the properties of carriers located in the brain capillary endothelial cell surfaces of BBB (42). These compounds are readily influenced by the quality and quantity of the dietary proteins consumed. Insufficient provision of protein leads to several brain disturbances at structural and functional level, such as alteration in the cerebral monoaminergic function, and might influence psychosocial behavior and pathologies influenced by neurotransmitters. Those damages can be observed in individuals suffering from protein-energy malnutrition (43). Seemingly, two brain structures are more susceptible to the protein deficiency, the hippocampus and the cortex (44).

Some studies have found that individuals with poor cognitive function, and even in dementia, reported considerably lower protein intake compared to healthy control, showing a positive correlation between dietary protein intake and cognitive function (45).

Large neutral amino acids (LNAAs), notably tryptophan (Trp), phenylalanine (Phe), tyrosine (Tyr), and histidine (His), are the main substrates involved in the synthesis of neurotransmitters, particularly serotonin and the catecholamines (dopamine, norepinephrine and epinephrine) (46). Trp, precursor of serotonin, execute a modulator role in the processes of appetite and satiety, sleep, pain sensibility, blood pressure regulation, pituitary hormone secretion

and behavior. Brain Trp concentration is directly influenced by the Trp plasma levels and its LNAAs transport competitors; in turn, LNAAs concentrations in plasma hinge on their dietary ingestion, which influence the rate of serotonin synthesis. Low concentrations of Trp, and therefore serotonin, are associated with mood and cognitive impairments (47). Similarly, Tyr stimulates the neuronal catecholamines biosynthesis, particularly dopamine, and its concentration depends on the amount of dietary protein ingested; hence, variations in Tyr concentrations give rise to alterations in catecholamines, affecting brain functions that operate under this physiological pathway. In addition, Phe, in conjunction with its derived Tyr, serves as a co-substrate for the enzyme Tyr hydroxylase (TH) required in the catecholamine production (46). When it comes to cross the BBB, transport is shared by several LNAAs, the aforementioned AAs and the branch chain amino acids (BCAAs), and is competitive. Given this condition, BCAAs influence brain function by modifying the Trp and Tyr conveyance. Thus, as a higher intake of BCAA rise their brain concentrations, the Trp and Tyr levels drop, reducing, as a result, the synthesis and the release of serotonin and catecholamines. However, the amount of BCAA needed to evoke a specific effect remains unknown (48).

With regard to other relevant AAs in the CNS, glutamate, a non-essential one, is found in larger amounts in the CNS compared to other amino acids; it directly exerts an excitatory neurotransmitter function, and is ready to be used by most nerve terminals in the synaptic process. Glutamatergic neurons are recognized for their participation in learning and memory, in the regulation of the blood pressure and in the pituitary hormone secretion. Nonetheless, for its excitatory trait, glutamate is related to excitotoxicity, occurring when neurons are exposed to elevated concentrations of this amino acid, which can set off an over arousal causing neuron death. Still, the brain has mechanisms of protection against such events, it is not a coincidence that transport of glutamate in the brain leans toward the output instead of input (49).

On the other hand, Acetyl-L-carnitine (ALC), an acetyl derived of L-carnitine synthesized from S-adenosylmethionine and L-lysine, may stimulate the production and delivery of ACh in the cholinergic system by acting as a cholinergic receptor agonist; as well as preserves and restores neurons from injury and contributes to the cellular energy production by carrying substrates through the membrane of mitochondria. In animal studies, ALC has been found to increase brain synaptic function and as a result improves memory and learning capacity in aging

conditions (50). For example, ALC modulates brain energy metabolism and phospholipid metabolism, improves spatial learning and long-term memory performance, and elevates levels and modulates the activity of neurotrophins such as nerve growth factor (NGF) in the CNS of rats (51).

N-acetylcysteine (NAC), derivative of the amino acid cysteine synthetized from the essential amino acid L-methionine, is precursor to the antioxidant glutathione (GSH) the most important primary endogenous antioxidant. The oxidative stress is probably induced from the abnormal accumulation of Aβ and tau proteins; sequentially this oxidative process may boost the production and aggregation of Aβ and the phosphorylation and polymerization of tau, thus forming a vicious cycle and contributing in great manner to the onset and progression of AD (21). This leads cholinergic neurons to impairments of the membrane integrity, cellular dysfunction, neurotoxicity and apoptosis. As a glutathione precursor, the NAC's antioxidant potent activity concedes its beneficial effect by preventing somewhat the lipid peroxidation and the protein oxidation, acting as cellular defense mechanisms upon the elevated amounts of reactive oxygen species (ROS). Thereby restoring the membrane integrity and the normal levels of oxidative markers, acetylcholinesterase (AChE), choline acetyltransferase (ChAT) and acetylcholine (Ach) and inhibiting the cell apoptosis, regulating in this way the cholinergic system, which results in learning and memory improvements (52). Increasing glutathione has been proposed as a potential therapeutic strategy to slow or prevent AD (53). *In vitro* studies have observed the protective action of NAC against glutamate-induced death of oligodendrocytes and tumor necrosis factor α (TNF-α)-induced death of oligodendrocytes and L929 fibroblasts (54) and reduction of phospho-tau levels in SHSY5Y neuroblastoma cells exposed to oxidative stress inducing/cytotoxic compounds (H2O2, UV light and toxic Aβ peptides) (55). The NAC appears to have a lower toxicity than the cysteine in the CNS. Variations in NAC levels can influence neurotransmitter pathways since it modulates a number of neurotransmitter correlated to different psychiatric conditions, including glutamate and dopamine. Cysteine levels regulate the cysteine-glutamate antiporter. This process determines the neuronal extra and intracellular exchange of glutamate. With glutamate, ensuring adequate cysteine availability via NAC is essential for healthy brain function. NAC levels can also regulate dopamine release (56). Some clinical trial NAC treatment appears to show favorable effects for depressive symptoms in bipolar disorder (57) and schizophrenia (58).

1.3.3 Lipids and Fatty acids

Fatty acids (FA) do not represent a source of energy directly used by the brain; instead, these substances constitute approximately 10% of its dry weight and perform a functional and structural role shaping the cell membranes, and contributing to the configuration and the anatomic architecture of the CNS, likewise offering protection against bumps and injuries. A high amount of polyunsaturated fatty acids (PUFA) can be found in the neurons and in the organelles of retina and brain tissues; these amounts seem to decrease with aging. The most abundant are the omega 3 (n-3) FA docosahexaenoic acid (DHA) and the omega 6 (n–6) FA arachidonic acid (ARA); necessarily they must come from the diet and the type and concentration in brain are determined by their ingestion. Such deficiencies are detrimental for brain, for instance, the generation of abnormalities in its composition affecting its functionality during perinatal period; in animal studies, chronic deficiency of n-3 FAs in developmental stage decreases brain levels of DHA, while n-6 FAs rises, including docosapentaenoic acid (DPA), and decline in behavioral tasks of learning. Conversely, epidemiological evidences have associated the higher intake n–3 PUFA with a protective effect and decreased the risk of cognitive decline (59,60).

Furthermore, n–3 PUFA may exert neuroprotective mechanism against inflammation and oxidative stress in the CNS, important factors contributing to the initiation and progression of AD, which influence brain function related to neurotransmission; membrane fluidity; ionic exchange, given that DHA content of membranes determines molecular activity of the sodium pump; enzymatic activities, like ATPase; and gene expression. The modulator effect of n-3 Long-chain fatty acids (LCPUFAs) on inflammation is mediated according to their composition, LCPUFAs mainly constituted from EPA and DHA (leukotrienes, resolvins, neuroprotectin D1 [NPD1] DHA-derived mediators) are anti-inflammatory, whereas those from the n-6 PUFA, ARA, are pro-inflammatory. The Aβ accumulation actives microglia and astrocytes, both release pro-inflammatory cytokines and chemokines, coming to an inflammatory response, which in turn, stimulate Aβ synthesis and deposition, starting a vicious circle of exacerbation of inflammation that may result in neuronal damage fomenting the progression of the disease. The microglia activation result in their aggregation around Aβ plaques, and express scavenger receptors to interact with Aβ, causing ROS secretion. This neuroprotection is also meaningful against Aβ accumulation, synaptic marker loss, and hyperphosphorylation of tau. DHA has been shown to

mitigate Aβ secretion in animal models and cultured cells by means of the anti-apoptotic and neuroprotective gene-expression programs that inhibit Ab42-induced neurotoxicity stimulated by the action of the NPD1, promoting brain cell survival and protecting them from apoptosis induced by the Aβ (61).

The n–3 PUFAs have been known for being prone to oxidation, through lipid peroxidation reactions, due to their high degree of unsaturation. However, the reduced production of ROS and the low excretion of lipid peroxidation metabolites after n–3 PUFAs supplementation in in vivo and in vitro studies have suggested an antioxidant activity; it appears to trigger antioxidant defense enzymes as an indirect mechanism. Moreover, n-3 LCPUFAs have shown a direct superoxide scavenging capacity. Inflammation also participates in the oxidation process, brain cytokines increases oxidative stress by overproduction of ROS and hereafter the risk of neurodegeneration that could be counteracted by the anti-inflammatory effects of n-3 PUFA. In this manner, n–3 PUFAs may reduce oxidative damage, markedly elevated in AD (62,63).

A vast quantity of in vitro and animal studies proposes the indirect influence of other classes of lipids in the pathogenesis of AD. Even though cholesterol has a significant function in neurotransmission and symptogenesis in brain cell membranes, high levels have been involved in the Aβ formation via amyloid cascade pathway in neuronal tissues. Cholesterol also may be linked to AD by account of vascular dementia, a risk for developing this disease. Lipid-lowering medications in some cases have shown to attenuate the production of amyloid plaques when administered in animals or decrease the incidence of dementia in humans under certain circumstances, for example age, but had no positive effects at all, since this medication had failed to show this impact in other studies. Hypertriglyceridemia has been correlated to negative neuropsychological outcomes as well. On one side, triglycerides diminish transport of leptin across the BBB – this hormone has an effect on hippocampus and is thought to influence positively memory and learning processes – and on the other increase the transport of ghrelin and insulin, which also have positive effects on cognition, even in AD. Accordingly, this lipid model is still inconclusive (64).

Neurotransmitter ACh is synthesized by cholinergic neurons from acetyl coenzyme A and choline, derived from glucose and the methylation of phosphatidylethanolamine and hidrolization of the phosphatidylcholine, respectively. Choline may be finally derived from serine and

methionine (converted to S-adenosylmethionine), since phosphatidylethanolamine is partially synthesized from phosphatidylserine (65).

1.3.4 Vitamins

Brain tissues have the same vitamin needs than the rest of the body. These organic compounds have several functions into the nervous cells, such as cofactors in enzyme-mediated reactions; they are readily converted to their active form once entered into the brain. A large number of epidemiological studies display significant association of vitamin status and cognitive domains.

Water-soluble vitamins

1.3.4.1 B-vitamins

B-vitamins group include eight vitamins (B1, B2, B3, B5, B6, B7, B9, B12,) carry out vital functions as co-enzymes and precursors of cofactors in several biochemical reactions in the brain required altogether for the adequate physiological and neurological functioning. These functioning includes the synthesis of neurotransmitters and myelination of the nervous system, and different aspects involved in the energy metabolism, the synthesis of numerous neurochemicals and signaling molecules and DNA/RNA synthesis, repair and methylation, important in the formation and maintenance of neuronal and glial cell membranes (66). Folic acid (vitamin B9), for example, is required for the appropriate development of brain and the neural tube in the fetus before conception, and thus prevents defects such as spina bifida. This vitamin might participate in the methylation of phospholipids in cell membranes and influence the membrane receptors, second messenger systems and ion channels. Folate deficiency entails a risk for depression in adults, which has been a very frequent endpoint observed in persons with megaloblastic anemia; and those diagnosed with depression have been found to have low plasma and red blood cell folate levels. Folate supplementation has shown improvement of mood in depression. This might be explained through the mechanism by which folate supplies the methyl group for the conversion of methionine to S-adenosylmethionine (SAM) that has a role in the methylation step in the synthesis of serotonin and catecholamine neurotransmitters, which in turn are important to regulate mood (60,67).

Through different ways, vitamin B-12 has been associated with cognition some data display that low levels of this vitamin can affect cognition negatively among elderly, even within the normal range, these changes may lead to brain atrophy and white matter damage. However, a threshold of low concentrations of B12, that could indicate the beginning of this atrophy cannot be exactingly defined (68). In the same way as folic acid, B12 deficiency entails a risk for depression in adults and neural tube defects during pregnancy. In earlier stages, vitamin B12 deficiency is also linked to adverse outcomes in brain development. Deficiency of both vitamins, B12 and folate, is related to pernicious anemia, affecting cognitive in the same manner than in iron deficiency anemia. This deficiency, when severe, also leads to neurological abnormalities through degeneration of nerve fibers, and irreversible brain damage, maybe due to inflammation and demyelination, which results from a deficient methylation of myelin basic protein, possibly occasioning cognition disturbances. Another proposed mechanism by which low B12 affects cognition is via homocysteine (Hcy) metabolism; the combination of B12 deficiency and low concentrations of vitamin B6 and folate, brings about to an augmentation of Hcy levels. Besides to the vascular effects, Hcy is associated to neurotoxicity and oxidation; folate and B12 play a part in the remethylation of Hcy, and B6 acts as a coenzyme in the conversion of Hcy to cysteine. Vitamin B12 is presumed to exert a neuroprotection against neurotoxin-induce damage (60,67).

In turn, vitamin B6, available in form of pyridoxal, pyridoxamine, and pyridoxine, is implicated in the synthesis of several neurotransmitters, comprising dopamine, serotonin, γ-aminobutyric acid (GABA), noradrenaline and the hormone melatonin; and regulation of serotonin levels; serves as a cofactor for aromatic l-amino acid decarboxylase, an enzyme that catalyzes the decarboxylation of a variety of aromatic l-amino acids (69). The vitamin B1, thiamine, is a crucial cofactor in glucose metabolism, which is reduced in AD; and in the pentose phosphate pathway, a key phase for the synthesis the aromatic amino acid precursors of some neurotransmitters, nucleic acids, lipids, steroids, and glutathione. It contributes to the neuro-modulation of the acetylcholine neurotransmitter system, and the structure and function of neurons and glia cell membranes (70), and such deficiency produces a cholinergic deficit and induces excess glutamate release. Thiamine deficiency also sets off an array of neurological problems, including cognitive deficits and encephalopathy. The most common disease caused by the B1 deficiency, beriberi, and the first breakthrough concerning vitamins, encompasses a remarkable neurological issue. The Korsakoff's psychosis, a manifestation of brain lesions that

brings memory disturbances, hallucinations, apathy and emotional blandness; and the Wernicke's encephalopathy, a neuropsychiatric disorder characterized by confusion, nystagmus, ataxia, recent memory loss and ophthalmoplegia; thiamine supplementation result in recovery of these conditions, concurring with the cognitive changes in AD. Authors propose that a long-term thiamine deficiency might constitute a progressive detrimental outcome that eventually results in the formation of neuritic plaques and NFT. Furthermore, in animal studies has shown that B1 deficiency has a positive correlation with learning and memory impairment (71).

Among the other B-vitamins, Riboflavin (Vitamin B2) has a role in most cellular enzymatic activities by means of its derivatives the flavoproteins FMN and FAD; they also act as a co-factor in the upregulation of glutathione and in the metabolism of essential brain fatty acids; B2 deficiency can lead to deleterious events in the brain functioning. Pantothenic Acid (Vitamin B5) plays an important part in the production of the coenzyme A (CoA) involved in the synthesis of cholesterol, amino acids, phospholipids and fatty acids supporting the structure and function of neuronal cells; and the synthesis of a set of neurotransmitters and steroid hormones. The different forms of Niacin (Vitamin B3), nicotinamide adenine dinucleotide (NAD) and NAD phosphate (NADP) are needed to carry out a range of biochemical processes and enzymes implicated in all features of peripheral and brain cell function (70).

1.3.4.2 Vitamin C

Ascorbic acid (vitamin C) is considered one of the most powerful antioxidants in the organism, it reaches the brain via the Sodium-dependent Vitamin C Transporter-2 (SVCT2); this transporter is found in large quantities in neuron-rich areas, such as the hippocampus, cortex and cerebellum, which correspond nearly with regional distributions of this vitamin in brain. Vitamin C has several functions in the CNS; it participates as a co-factor in the synthesis of tyrosine, carnitine, catecholamine neurotransmitters, cholesterol, peptide hormones, collagen production and regulation of HIF-1α. Moreover, vitamin C contributes to the neural maturation and the neuromodulation of the activity of acetylcholine, glutamate, GABA, dopamine and the catecholamine neurotransmitters and related behaviors. In AD, PD and other neurodegenerative diseases that implicate high oxidative activity, ascorbic acid has been hypothesized to exert an effective therapeutic action against the oxidative-induced damage (72).

Vitamin C absorption and biological utilization rely on modulating factors, genetic (SVCT1 and SVCT2 SNPs) and non-genetic (for example age, intake), that might influence its needs in later stages of lifecycle, and especially in persons with an AD. Studies performed in humans and animals exhibit a correlation between vitamin C deficiency and oxidative stress markers, noticeably increased in AD (73). A study in AD models observed that a moderate vitamin C deficiency, mostly during initial stages of disease development, has a significant effect in accelerating amyloid pathogenesis, which may be modulated by oxidative stress pathways (74). In another study performed with normal rats supplemented in a long-term with two different dosages of ascorbic acid, it was found that in the lowest dose supplementation the anxiolytic effects of ascorbic acid were more typical, while memory improvement seemed to be confined to the highest dose (75). To further support the vitamin C effects on brain functions, other animal experiments demonstrated the harmful effect of vitamin C inadequacy to survival in neonatal period and brain volume growth, producing reduced spatial cognition in perinatal phase (76).

On the other hand, in the Cache Country Study, a large cross-sectional and prospective study of dementia, it was observed an association between the supplementation of ascorbic acid in conjunction with vitamin E and a reduced AD prevalence and incidence (77). Later, these results were confronted by other study of dementia, the Adult Changes in Thought study, which showed no reduction of the AD risk in self-reported users of vitamins C or E supplements (78). Among these controversial results, epidemiological studies have failed to draw consistent conclusions about the role of this vitamin in cognitive functions, this fact has been attributed to the research methods has not been accurately designed (79,80). These results altogether could show that, whilst a wide range of studies had evidenced the likely protective function of upholding adequate levels of vitamin C against age-related cognitive decline and AD, precluding deficiency through a normal healthy diet is worthwhile rather than taking supplements on upper levels.

Fat-soluble vitamins

1.3.4.3 Vitamin A

Vitamin A turns into its bioactive forms, retinoid acids, and promptly gains access to the brain. This molecule has a significant role in maintaining dopaminergic cognitive function and

signaling, synaptic plasticity, gene regulation, neurogenesis modulation, neuronal differentiation and regeneration (81). Despite vitamin A deficiency is a very common form of malnutrition and a great public health concern, its role in human cognition has not been definitely elucidated. Dietary retinoic acid (RA) supplementation improves learning and memory; enhance cognitive declines associated with normal aging in vitamin-A-deficient post-embryonic and adult models (82). Also, cultured cells experiments indicated RA to take part in the regulation of dopamine D2 receptor expression (83) and to bind to retinoic acid receptors all over the brain areas involved in cognitive processes, and may perhaps suggest a role in the maturation and function of the CNS (84).

1.3.4.4 Vitamin D

Vitamin D (active form 1,25 $(OH)_2D_3$) is thought to be have a modulator role in the development of the brain and in neuropsychiatric disorders. Among the raft of brain functions associated to vitamin D are neurotransmission, neuroprotection given by the modulation of the production of nerve growth factor, vasoprotection and the amyloid phagocytosis and clearance. As well as, the control of neuronal calcium homeostasis; up-regulation of GSH, controlling the toxicity of ROS; upregulation of neurotrophic factors such as nerve growth factor, glial cell-derived neurotrophic factor and nitric oxide synthase. Moreover, this vitamin has pro-apoptotic, antimitotic and pro-differentiation properties. Human and animal studies have found Vitamin D derivatives in CSF and vitamins D receptor protein expression in the whole brain including hippocampus. Vitamin D deficiency has been found to be a common condition in older population due to both inadequate dietary intake and cutaneous synthesis. Some studies have correlated this status of deficiency with depression, cognitive decline, AD and Parkinson's disease (PD); symptoms seems to be improved by supplementation, but it is uncertain if this relationship has a causal factor or is due to chance alone, because the mechanism involved has not been deciphered. Additionally, this condition (vitamin D deficiency) entails a risk factor for schizophrenia and autism in developing stages (85–87). Experiments with severe vitamin D-deficient maternal models have shown alteration in the brain anatomical and physiological development of their offspring, which support the hypothesis of the vitamin D role in the CNS (88). Other experiments showed that chronic hypovitaminosis D along with hypocalcaemia result

in increased levels of catecholamine in the brain, whereas in non-induced hypocalcaemia affects the ontogeny of dopamine systems during development (89).

1.3.4.5 Vitamin E

This vitamin comprises 8 chemical forms 4 tocotrienols and 4 tocopherols: α, β, γ and δ; however, most studies testing vitamin E in brain has been with regard to α-tocopherol. This form has a predominant antioxidant and free radical scavenger function, protects PUFA within biological membranes and in plasma lipoproteins (90). The mechanisms of vitamin E in brain function are still undefined. Animal studies posited an ancillary participation in gene expression and in activation and suppression of different enzymatic reactions that may influence cognitive processes; it is deemed necessary for normal neurological functions. Reduced plasma concentrations of different vitamin E forms, altogether, with a simultaneous augmentation in the indexes of vitamin E oxidative/nitrosative damage were found to be related to AD and mild cognitive impairment in senior individuals; this fact insinuates a key role of vitamin E in neurodegeneration (91,92). Although vitamin E deficiencies are exceptional, this depletion manifested neurological and visual disorders including peripheral nerve degeneration, spinocerebellar ataxia, psychomotor abnormalities and retinopathy (93). Vitamin E forms also participate in the regulation of membrane-bound enzymes, gene expression, cell signaling processes, cellular proliferation, possess anti-inflammatory properties and contribute to the brain protection against the glutamate-induced neurotoxicity through the modulation of phospholipase A_2 (91). Moreover, it must be noticed that some evidences have reported the involvement of vitamin E in memory, cognition, and emotional functions (94).

1.3.4.6 Vitamin K

Vitamin K appears as two active forms, phylloquinone or vitamin K1 (K1), from plant-based dietary origin, and the menaquinones or vitamin K2 (VK2), from animal and bacterial origin. The extensive presence of the vitamin K-dependent growth factor/tyrosine kinase receptor – Gas6, implicated in cell growth, survival, myelination and apoptosis – and the vitamin K-dependent carboxylase expressed in the CNS during the early embryonic stages, has revealed the presence and a possible role of the vitamin K in the brain development. The brain vitamin K form correspond to the menaquinone-4 (MK-4), actually it is synthetized from dietary K1 in an

enzymatic process mediated by the UbiA prenyltransferase containing 1 (UBIAD1). Moreover, vitamin K also plays a part in the production of sphingolipids, a type of lipids abundantly found in neuronal cell membranes that further to their structural role, contribute to proliferation, differentiation, senescence, transformation and interactions among cells. Some evidences have correlated changes presented in the sphingolipids metabolism with age-related cognitive decline, for instance AD and PD. Even so, the likelihood that vitamin K may exert an effect in psychomotor functions and cognitive performance has been scarcely investigated. MK-4 also has been related to neuroprotection against oxidative stress and inflammation; in cultured cells, it was shown to inhibit glutathione depletion and to limit the production of IL-6 and prostaglandins. In observational studies, it has been associated to reduced levels of the IL-6, intracellular adhesion molecule-1, tumor necrosis factor receptor 2, and C-reactive protein (95,96). Vitamin K has a well-defined role in the blood clotting; the vitamin K-dependent enzyme mediates the activation of liver proteins, including prothrombin, by the conversion of glutamate to γ-carboxyglutamate (Gla). Then, Gla binds to calcium, which is also essential for the enzymatic activity of blood coagulation. Moreover, vitamin K-dependent γ-carboxylation of glutamate has been found to influence the synthesis of extrahepatic proteins, such as osteocalcin, an indicator of bone development. Pregnant women exposed to anticoagulants run a substantial risk of fetal detrimental consequences, among them bone formation and calcium metabolism alterations, known as warfarin embryopathy, and abnormalities in the CNS and mental retardation. In view of the fact that anticoagulants, warfarin, inhibit the γ-carboxylation of blood-clotting proteins by preventing the renewal of vitamin K from the corresponding epoxide. It also has been hypothesized that vitamin K may be associated to a lessened neuronal damage arisen from cardiovascular disease (97).

1.3.5 Minerals

Minerals are inorganic elements essential for the development and electrophysiological function of the brain. Generally, minerals are classified according to their concentration in the body into two main groups; the macroelements and the microelements, found in larger and lower amounts in the body respectively (98). Their imbalance, both deficiency and excess, can cause severe damages to brain development, mainly during pregnancy and initial postnatal periods that are reflected later in childhood and adolescence in learning difficulties and neuropsychological

impairments (99). Neurons generate ionic currents from sodium and potassium to conduct brain information as electrical impulses through the membrane depolarization, that is, the potential of action; in addition, this sodium/potassium pump has been proposed to have a function in brain coding and computation tasks by Purkinje neurons in the cerebellum (100).

Calcium (Ca) acts as an important component in neuronal function, since it participates in metabolic activity and cell growth, influences the transmission of the depolarizing signal and the release of neurotransmitter regulating synapsis activity (101). Neurons have highly developed Ca^{2+} signaling systems responsible for regulating synaptic transmission, depolarization, learning processes and the formation and consolidation of memory, processes on which underlie the neuronal survival. The aging process yields to a slight Ca^{2+} dyshomeostasis resulting from the oxidative stress and the accumulation of energy metabolism remnants. Dysfunction of these Ca^{2+} signaling pathways in the brain is implicated in neurodegenerative disease, among these AD, PD, cerebellar ataxia, amyotrophic lateral sclerosis (ALS), Huntington's disease (HD) and familial hemiplegic migraine (FHM) (102,103). It has been hypothesized that the aggregation of Aβ in AD induces a progressive increase in the resting level of Ca^{2+} causing a deregulation of Ca^{2+} signaling via direct effects on neurons and indirectly by inflammatory responses in microglia and astrocytes, which possibly influence cognition by interfering with the rhythm rheostat that controls the sleep/wake cycle. This interference affects mainly memory formation by a rapid erasure of memories acquired during the wake period before they can be consolidated during sleep. Vitamin D is proposed to ameliorate some of these deleterious effects of Aβ (104)

Other essential macro-element found in large amounts in the body is magnesium (Mg). This ion has several physiological and metabolic functions, from which depend hundreds of enzymatic reactions. Mg is required for the synthesis of nucleic acids and proteins, and for particular activities in the neuromuscular and cardiovascular systems, for example myocardial/muscle contraction, potential of action conduction and neurotransmitter release, and its deficiency is manifested in neuromuscular and neuropsychiatric disturbances including migraine, depression, epilepsy, hyperexcitability, tremor, fasciculations and tetany (105). Mg also has been associated to neuroprotective properties; it regulates oxidative stress and the release of calcitonin gene-related peptide (CGRP) and substance P, an inflammatory neuropeptide whose release is increased by Mg deficiency; this release stimulates the secretion of inflammatory

mediators e.g., some interleukins and TNF. Brain Mg has an inhibitory function on N-methyl-D-aspartate (NMDA) receptor regulating its excitability, which rises at a Mg deficient state. Such receptor is implicated in the excitatory synaptic transmission, neuronal plasticity, and excitotoxicity, and thus, participate in learning and memory processes (106). Experiments conducted in rats showed the effects of magnesium supplementation in the improvement of hippocampal frequency potentiation and learning and memory functions (107,108), reduction of tau hyperphosphorylation and protection of synaptic plasticity (109). Patients with AD have been associated with low levels of Mg (110). Indeed, Mg deficiency has been hypothesized to have a role in the pathogenesis of AD (111) and a modulator role of the AβPP (112,113) suggesting a potential component in the treatment of dementia (114), as well as other neuropsychiatric disorders, such as depression and anxiety (115–117). Unlike specific conditions, Mg deficiency are not common, even though in elderly has been observed relatively low dietary intakes of magnesium, which might represent a risk for this population (118).

Iron is an essential trace element carried to the brain by the transferrin protein; it serves to a number of enzymes that mediate the synthesis of neurotransmitters. In aging, it is common to observe an abnormal iron accumulation in the *substantia nigra,* accounting for a high susceptibility to generate free radical and oxidative damage that has been postulated to lead to neurodegenerative diseases, including PD and AD (119). Conversely, iron deficiency is a more prevalent concern, the principal cause of anemia, the critical hazard of this deficiency takes place in developing periods (120). This condition represents a risk for permanent cognitive deficits and behavioral affections, which might be attributable to role of iron in the neurochemistry and neurobiology of myelination, neuronal networks, and neurotransmitters inducing to changes in the implicated biochemical processes (121). There are evidences demonstrating poorer academic performance of people that suffered from iron deficiency, with or without anemia, in their childhood, even after recovery treatment. Some other experiments also conducted in children, showed improvement of motor and neuropsychological outcomes after iron supplementation, while others have found no effects; even though, these results are inconsistent, the favorable benefits acquired from preventing deficits are prevalent. Thus, the importance of protecting the developing brain from early iron deprivation is highly emphasized (122,123).

Gestational deficiency of Iodine is known to brings on irretrievable deleterious neurological and cognitive events on the fetus, is the case of cretinism, a syndrome manifested as arrested physical and mental development, diplegia and subnormal intelligence. In addition, deficits in cognitive functioning have been observed in children living in iodine-deficient areas; other data indicate that postnatal iodine deficiency is associated with cognitive deficits, despite the fact, conclusions are still controversial (124).

Selenium (Se) constitutes an essential component of selenoproteins, comprising several enzymes that have antioxidant and anti-inflammatory effects, serving as modulator in brain function. Some of them are glutathione peroxidases (GPx), methionine-sulfoxide-reductase and thioredoxin reductases. The activity of those enzymes is altered by Se inadequacy promoting loss of cells in neurodegenerative disease models (125). Deficient Se state leads to negatives outcomes in immune and cognitive function, manifesting irreversible brain harm. Experiments in mice lacking selenoprotein P (SEPP1), responsible for transporting Se to the brain, demonstrated neurological symptoms (twitching, spasticity and seizures). Similarly, in humans it was observed and thus established a possible association with seizure episodes, coordination, PD and cognitive decline in those with low serum concentrations of selenium. Not only deficiency of selenium, but also overload, are deleterious for human health. SEPP1 offers neuroprotection to brain cells against the amyloid-β-induced oxidative damage inhibiting neuronal apoptosis (126). A clinical trial evaluating supplementation and dietary Se intake on mood in healthy subjects, identified that the lower ingestion of dietary Se presented an increase of anxiety, depression and tiredness that improved after 5 weeks of Se treatment (127), whereas another clinical trial showed no effects of Se supplementation in this same outcome (128).

Zinc is a vital element in the organism for growth, maturation, and function during initial stages of life. It is required for a vast number of biochemical activities belonging to neuronal development and functioning. In the CNS, a large quantity of zinc is fastened to metalloproteins in neurons and glial cells. Also, it has been found in synaptic vesicles of some glutamatergic cerebral areas – zinc-containing neurons – associated with the episodic memory function and behavior, emotional expression, and cognitive-mnemonic operations, such as the hippocampus and the amygdala, indicating a neuromodulator role in plasticity and glutamatergic synapses, thus, linked to a role in learning and memory (129). Zinc is also attributed to an antioxidant role

and such alterations in its homeostasis is been implicated in neurodegenerative conditions, in which oxidative stress has been identified as a triggering factor (130). The main manifestations of dietary zinc deprivation are anorexia and stunted growth; still, behavior and cognitive functioning are influenced by zinc deficiency during development and adulthood, causing alterations in attention, motor development and neuropsychological behavior. In children from developing countries, it was observed improvement in mental functions and psychomotor development after Zinc treatment. Nonetheless, there is no data of this influence in aging. In animals at early stage, dietary zinc deficiency severely affected some aspects of memory, behavior and learning, and diminished the spontaneous motor activity, somewhat reflected in older ages (131). Likewise, this depletion is associated to set off teratogenic effects and neurogenesis, migration and synaptogenesis impairments being more detrimental in periods of growth and development. Zinc deficiency is suggested to disrupt calcium channels, generating a lower intracellular calcium concentration that inhibits gene expression of growth factors and production of nucleic acids and proteins. Zinc-deficient models have expressed almost permanent disruptions of learning and memory and minimal odds of neuronal survival (132). In contrast, despite the low toxicity of zinc compared to other transition metals, experiments *in vitro* have revealed neurotoxic effect at excessive levels in the brain extracellular fluid, which might boost the deposition of Aβ, stimulated by the α-helical structure of Aβ, given rise to the cerebral amyloid plaques, reversible with chelation. Furthermore, zinc preserves the nontoxic characteristics of Aβ (133).

Another trace element, manganese (Mn) is likely to have a role in synaptic neurotransmission in glutamatergic neurons. Mn is part of Mn-metalloproteins, i.e., glutamine synthetase. Insufficient intake of this metal through the diet may influence cerebral Mn homeostasis and trigger neurologic dysfunctions. Inadequate levels of brain Mn are linked to neurological disorders like PD. Alternatively, higher levels of Mn are neurotoxic since it induces oxidative activity (134). Some brain enzymatic activities also depend on copper, which perform a co-factor function; one of them is the dopamine β-monoxygenase reaction that converts dopamine into norepinephrine. However, due to its redox activity, copper can also induce oxidative stress. Due to both the essential function of Cu and toxicity effect of higher levels in brain, it is tightly regulated, a modulator role performed by astrocytes. Dyshomeostasis of copper has been attributed to the development of neurodegenerative diseases, including AD (135).

2. HYPOTHESIS AND RESEARCH QUESTIONS

This work hypothesized that clinical and neuropathological manifestations of AD can be prevented or corrected, partial or totally, through the ingestion of specific nutrients and/or food, likewise by specific dietary patterns. Due to its importance, many studies about nutrients and cognitive impairment have arisen through the last years, and there is a plethora to be identified (136).

Unarguably, the amount of scientific information about this issue is growing. For their use in the clinical practice, it is essential to transform this information into knowledge, namely, this information have to be gathered, organized, critically assessed and quantitatively measured. Clinical guidelines based in systematic reviews are enabling this transformation. Although some systematic reviews and meta-analysis with particular nutrients related to AD have been found in the literature, none of them comprised at the same time, different ways of ingestion of nutrients, foods and dietary patterns, in the development and progression of AD.

Thereby, the present study addresses the following questions:

1- Nutrition interventions, including nutrients, foods or dietary patterns, are capable of slowing down or decreasing some symptoms of Alzheimer's disease in elderly?
2- Is there any therapeutic association between consumption of specific nutrients, food or dietary patterns with the pathological manifestations of Alzheimer disease in elderly?

3. OBJETIVES

This work aims:

- To synthesize the current evidence through a systematic review and subsequent meta-analysis of clinical trials examining the use of nutrients, foods and/or dietary patterns, in the treatment of AD at different stages, in elderly;

- To associate the scientific finding effects of nutrients with outcomes regarding cognitive domains, functional abilities, neuropsychiatric symptoms and neuronal structures compared to other active or inactive control interventions.

The findings of this review will allow appraising the extent of nutrition in the management of AD and planning future studies.

4. METHODS

Systematic review is an objective, efficient and replicable scientific technique, which allows extrapolating findings, assessing the consistency and explaining possible inconsistencies and conflicts in data from single studies. Furthermore, this technique increases the accuracy of results and improves the precision of the estimated treatment effect of a clinical intervention (137). This study was steered in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (Appendix 2) (138), and the handbook set by the Cochrane Collaboration (139). Thereby, the methods used to carry out this work are described stepwise as follows.

3.1 Eligibility Criteria

Inclusion Criteria

Inclusion criteria were specified in accordance with the characteristics of the study:

- Clinical situation: studies performed in patients with AD at any stage (mild, moderate, advanced), with or without association to chronic diseases, such as hypertension, diabetes or dyslipidemias.
- Type of participants: studies conducted in elderly population (aged over 60 years old) both gender, regardless of race/ethnicity or geographical location.
- Type of intervention: studies that have investigated any type of nutrient, food, special diet or dietary pattern; at all doses or ingested amounts, no restriction in the duration of intervention, compared to placebo.
- Type of studies: well design blinded clinical trials or open label and epidemiological cohort studies, concluded, without restriction in the publication data.
- Type of outcomes: selection of dependent variables assessed in the studies:

Primary outcomes of interest:

  - Cognitive tests- mini mental state examination scale; neuropsychological test batteries scales (categorical- classification- or numerical- score- interpretation);

- Imaging tests- structural or functional neuroimaging, from nuclear magnetic resonance imaging or computerized tomography (PET or SPECT), or other imaging methods (categorical- classified as normal or not- or numerical- hippocampal volume- interpretation).

Secondary outcomes:

- Biochemical tests- AD biomarkers in CSF or plasma (Aβ-42, total tau, phospho-tau, BDNF);
- Inflammation and/or oxidative stress biomarkers (pro and anti-inflammatory cytokines, C-reactive protein, isoprostane).

Exclusion Criteria:

Studies were ineligible for this systematic review whether:

- Participants with cognitive decline or other types of dementia non-Alzheimer type
- Published in languages different from English, Portuguese or Spanish
- Carried out in animal models, *in vivo*, or *in vitro*
- Nutrition intervention studies in AD evaluating food intake, plasma nutrient levels or nutritional status, but not the disease situation or progression itself
- Studies examining early AD, that is, familial Alzheimer initiated before 50 years old, and AD related to other genetic diseases e.g., Trisomy 21 (Down syndrome).

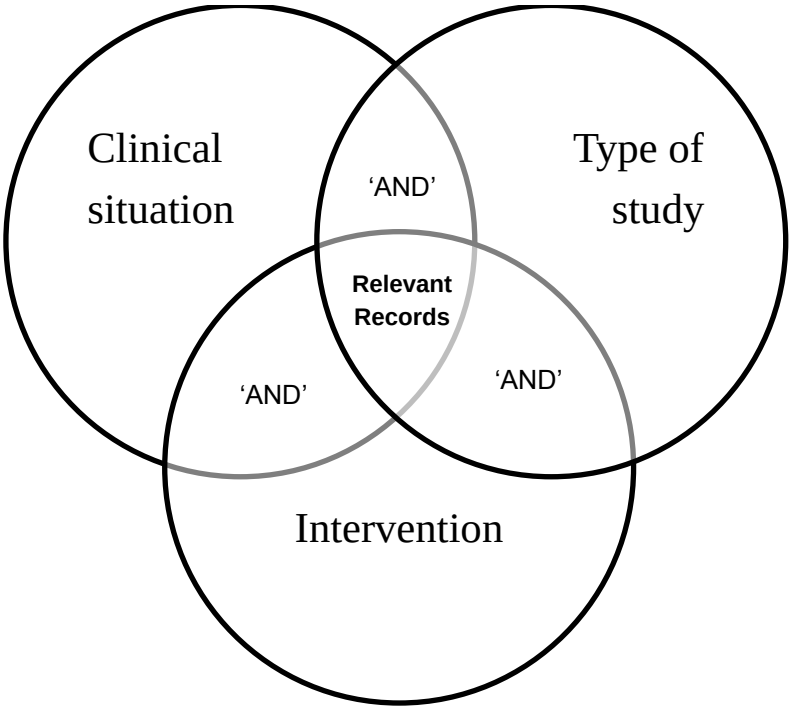
3.2 Screening and search Strategy

Electronic databases were exhaustively searched (Cochrane Controlled Trial Registered (CCTR), EMBASE (Biomedical Database*),* PubMed/MEDLINE, Virtual Health Library *(*VHL*)* and the Web of Science) for potentially relevant studies examining the association of nutrients and/or food and/or dietary patterns with AD, published up to December 2014 in English, Portuguese or Spanish languages. The search strategy was built by crossing key search terms for each component of the review question: clinical situation, type of intervention and type of study (Chart 1), joining every word together within each other of the three components with the Boolean operator ‘AND’, shown in Figure 1.

Chart 1. General plan to build up search strategy

CLÍNICAL SITUATION	INTERVENTION	TYPE OF STUDY
#1 Alzheimer`s Disease	#4 nutrients	#22 clinical trial
#2 Alzheimer	#5 carbohydrate	#23 randomized
#3 Dementia Type Alzheimer	#6 glucose	#24 controlled trial
	#7 lipids	#25 epidemiological
	#8 fatty acids	#26 incidence study
	#9 Omega-3	#27 longitudinal study
	#10 protein	#28 follow-up study
	#11 amino acids	
	#12 vitamin	
	#13 mineral	
	#14 zinc	
	#15 Selenium	
	#16 phytochemical	
	#17 antioxidant	
	#18 diet	
	#19 food Pattern	
	#20 dietary pattern	
	#21 Mediterranean diet	

Figure 1. Intersection of concepts as a search sets



3.3 Study selection and Data extraction

The first author screened and evaluated primary studies by title and abstract for inclusion and exclude obviously irrelevant reports. Studies that matched clinical situation, type of intervention and study design of interest for this research were selected and documented in a spreadsheet writing down reasons for exclusion (Appendix 1). Duplicated studies were identified simultaneously to the database searches. Afterward, the second author accessed the study records to carry out the same process for inclusion, by filling out a separated spreadsheet. Both spreadsheets were examined in the first consensus meeting to reach a final decision on study selection, where there were no discrepancies. Both reviewers applied the selection criteria to assess the quality of the studies.

After the consensus for study inclusion, the first author retrieved full text of preliminary relevant studies identified in the preceding step. Once publications were obtained, complete reading of the studies was performed for a thorough evaluation by the eligibility criteria and data extraction. Studies were classified into two categories: clinical trials and observational studies. After discussion with the second author, it was decided the exclusion of observational studies from this work, for further analysis of a preventive approach. Clinical trials were characterized in

a spreadsheet developed according to the recommendations of the Cochrane Collaboration (139), comprising general information, eligibility criteria for inclusion, methods (study design), characteristics of participants, intervention details, types of outcomes, results of outcomes (dichotomous or continuous), adverse events and other relevant information necessary for assessment of quality and risk of bias. Items of data extraction are specified in more details in Appendix 3.

3.4 Risk of bias assessment

According to the PRISMA statement, the quality of a systematic review depends on the quality of single studies and the absence of bias for its inclusion, thence it is used as a tool to contribute in the improvement of clarity and transparence of the present study (140). The quality analysis was conducted to decide the inclusion of each clinical trial in the systematic review, and the possibility of meta-analysis, by applying the risk of bias assessment tool available in the Cochrane's website (http://handbook.cochrane.org/). The assessment was performed at study level and categorized by domains: Selection bias (Random sequence generation, Allocation concealment), Performance bias (Blinding of participants and personnel), Detection bias (Blinding of outcome assessment), Attrition bias (Incomplete outcome data), Reporting bias (Selective reporting) and other bias (Other sources of bias). Two authors performed the assessment based on their judgment according to the information provided by the article, grading domains as 'low risk', 'unclear risk' and 'high risk'.

Details of study assessments were recorded in a spreadsheet table, specifying the source of bias in each domain; supports for judgment were based on findings in each study and the Cochrane's tool criteria (Appendix 4). The overall clinical trials assessment was presented in a risk of bias summary figure. The decision for inclusion of studies in the systematic review and the possibility of meta-analysis was determined by the quality for the main domains as follows:

- Random sequence generation and concealment allocation
    - Low risk: randomization and concealment allocation processes adequately described through: referring to a random number table; using a computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization. Central allocation (including telephone, web-based

and pharmacy-controlled randomization); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.

- Unclear risk: sequence generation and concealment allocation methods were not described or were not described in sufficient details to allow judgment, but the text reports that the study is randomized, indicating the allocation seems to be adequate despite there is no other information available.
- High risk: sequence generation and concealment allocation methods based on strategies that possibly may introduce selection bias, for example a non-random approach. Sequence generated by: odd or even date of birth; some rule based on date (or day) of admission; some rule based on hospital or clinic record number. As well as; allocation by: judgment of the clinician; preference of the participant; based on the results of a laboratory test or a series of tests; availability of the intervention. The allocation was done by: using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. if envelopes were unsealed, non-opaque, or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure; or the study was not randomized.

- Incomplete outcome data
  - Low risk: no missing outcome data; reasons for missing outcome data unlikely to be related to true outcome; missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups. For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
  - Unclear risk: when reporting of attrition/exclusions is insufficient to permit judgment of bias (e.g. number randomized not stated, no reasons for missing data provided); or the study did not address this outcome.
  - High risk: reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups. For continuous outcome data, plausible effect size (difference in means or

standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; potentially inappropriate application of simple imputation.

- Other bias:
    - Low risk: The study appears to be free of other sources of bias
    - Unclear risk: There is insufficient information to identify a possible risk of bias
    - High risk: There is a potential source of bias related to the specific study design used or some other problem, in this study for example, sample size power and conflicts of interest- researcher will discuss the inclusion of studies presenting competing interests.

For some articles, it was necessary to contact study authors to request details about missing or unclear data in the publication.

Disagreements about whether a study should be included were resolved by consensus. Authors defined the final bias assessments of studies for inclusion as follows:

- Low risk study: for low risk of bias in all main domains.
- Unclear risk study: whether one or more main domains are appraised as unclear risk of bias.
- High-risk study: for high risk of bias classification in one or more main domains.

Articles graded as low and unclear risk of bias were included. On the other hand, articles classified as high risk were excluded due to the possibility of introducing bias, thus enabling a more reliable comparison among selected studies.

1.4.1 Statistical analysis

Meta-analyses of data were undertaken whether the included studies were comparable enough to be grouped; this is, if participants, intervention and clinical outcomes were homogeneous. We run different meta-analyses for each outcome and nutrient intervention; at least two similar studies were deemed suitable to carry out statistical analysis (141).

Afterwards, multiple treatments comparison meta-analysis was performed for cognitive outcome measure. The network Meta-analysis (NMA) method enables us to make direct and indirect comparison of the magnitude of effect among different interventions all together, based on a common comparator, placebo in this study, to estimate treatment effects among interventions in the combined analysis and figure out whether from this evidence there is a best nutrient intervention of several options.

3.5.1 Treatment effect measures

Statistical analyses were performed to increase the likelihood of achieving a significant treatment effect estimate, if it exists, by calculating the summary treatment effect estimate, the weighted mean difference (MD) or standardized mean difference (SMD); and improve precision in the estimation of treatment effect, obtained by calculating the confidence interval (CI) of the summary statistic, or its variance. Results of meta-analysis (the pooled treatment effect estimate) are the weighted average of the treatment effects estimated in the individual studies.

Pairwise meta-analyses of continuous variables were performed using the method of inverse variance in a random effect model (DerSimonian and Laird method) to calculate the estimative of treatment effect. All outcomes were estimated based on the change from baseline to follow-up, and pooled effects were presented as MDs with 95% CIs for neuropsychological scales and biomarkers outcome measures (142). In included studies, there were identified four types of neuropsychological outcome measures, namely cognition, behavioral disturbances, functional and global performance. However, this type of outcomes was measured through different assessment scales. In an initial pilot analysis, these different assessment scales were combined per type of outcome measure to make them suitable to be pooled in the meta-analyses. Owing to the scales used in the studies had different scoring systems with different distributions of results, the result MD of each scale was transformed in SMD, by using the equation 1. Because some outcomes improve as the scale increases whilst others worsen, to unify the scales to the same direction, some mean values were multiply by -1 (143).

Equation 1

$$\boldsymbol{SMD} = \frac{\boldsymbol{MD}}{\boldsymbol{SD_{pooled}}}$$

Where SD pooled,

$$SD_{pooled} = \sqrt{\frac{SD_E^2 + SD_C^2}{2}}$$

SD_E referring to the variability in experimental group, and SD_C in the control group.

However, the use of the global estimative SMD resulted in a higher imprecision in the estimation of treatment effects. Given that most studies used a common assessment scale for cognition, the MMSE, then we used this scale as the primary outcome measure to assess cognition; the ADAS-cog was the second most used scaled in studies, though it was not considered in the analysis since it measures the same outcome, cognition, in the same population. For the remaining neuropsychological outcome measures, the most common assessment scales were the ADCS-ADL to assess functional capacity, the NPI to assess behavioral disturbances and the CDR-sob to assess global performance. Trials that assessed these neuropsychological outcomes with different scales were not excluded, but were not included in the statistical analysis. Using a single scale to run meta-analysis enables the use of the MD, preserving non-transformed values is assumed to provide a more accurate pooled effect in order to diminish the likelihood of obtaining spurious effects, introducing bias or misusing the global estimative.

Variability among studies in a systematic review is known as heterogeneity. Variability in the participants, interventions and outcomes examined is defined as clinical diversity (clinical heterogeneity), and methodological diversity occurs when there is a variability in study design and risk of bias (methodological heterogeneity). Variability in the intervention effects assessed in the different studies describes a statistical heterogeneity, and is a consequence of clinical or methodological diversity, or both, among the studies. Heterogeneity of studies was appraised with I^2 statistic that expresses results in percentage; less than 40% represent a low heterogeneity, 30 - 60% moderate, 50 - 90% substantial, and 75 - 100% a considerable heterogeneity, and the Chi-square (Chi^2) test with significance (p-value) at the level of 0.10 for difference between groups. Heterogeneity was explored and explained if significant, this is I^2 >30% and Chi^2 p

<0.10. Statistical analyses were carried out using the software Review Manager (RevMan) version 5.3 (144).

Multiple comparison treatment meta-analyses were accomplished in a Bayesian framework using Markov Chain Monte Carlo (MCMC) methods with a random effect model using ADDIS release 1.16.6 (145) to analyze the consistency of relative effects and estimate the rank probability of a intervention to be the best treatment, the second best and so on. The model generated 50,000-simulation iterations (4 chains) to provide an accurate estimate of the statistical model; this is known as convergence (assuming comparable interstudy variances for all treatment effects for the same outcome). Convergence was assessed by comparing within-chain and between-chain variance to calculate the Potential Scale Reduction Factor (PSRF) (Brooks-Gelman-Rubin diagnostic method). The model converges when all the chains are similar. A PSRF close to one indicates approximate convergence has been reached. If the PSRF is large, it means that the between-chains variance can be decreased by running additional iterations (146).

Since this analysis owns a more complex evidence structure, the inconsistency analysis needs to be assessed. Inconsistency arises when a treatment C exhibits different effect when it is compared with A or B (i.e., studies comparing A and C are systematically different from studies comparing B and C).

3.5.2 Managing missing data

Undertaking meta-analysis hinge upon a summary statistic and its variability, however some authors and editors overlooked this data, even though is assumed essential in reporting research. When this information was not published, it was made available by the authors on request. However, some study authors did not respond to our request at all. Thus, we deal with missing data in the following manner.

The change of outcome measure from the baseline is required in order to run meta-analysis. Some studies did not report this value, in such cases calculation of difference in means was obtain from the initial and final means using the equation 2.

Equation 2

$$\boldsymbol{M_{change} = M_{final} - M_{baseline}}$$

Given the missing mean change, its standard deviation was not reported as expected; hence, the standard deviation (SD) difference was calculated from change comparator data that could be available by means of the designated techniques. SD change for group means was calculated with equation 3 when 95% confidence interval (CI) for means was on hand, if the study's sample size was large (greater than 100 participants in each group), the 3.92 standard errors wide of 95% CI (3.92 = 2 × 1.96) was used as divisor. Whilst in moderate and small sample sizes (between 60 and 100 and less than 60 in each group respectively), the divisor, 3.92, in the equation 3 was replaced by the value obtain from the t distribution in the equation 4.

Equation 3

$$\boldsymbol{SD = \sqrt{N} \times (upper\ limit - lower\ limit)/3.92}$$

Equation 4

$$\boldsymbol{Divisor = TINV(1 - 0.95, N - 1) \times 2}$$

From studies reporting standard errors, the standard deviation was calculated by,

Equation 5

$$\boldsymbol{SD = SE \times \sqrt{N}}\ .$$

In most studies with missing SD of change, there was not enough data to calculate SD for mean changes. SD was imputed from the initial value through a correlation coefficient (Corr); in studies that reported initial and final SD in the equation 6, in turn the Corr used was imputed, for both intervention groups; from others similar studies included in the meta-analysis in which all SDs were available (initial, final and change) by replacing equation 7. Corr could be calculated only for one study with omega 3, which provided all data necessary for this imputation, for the remaining studies it was used 0,5 as Corr (139,141,147).

Equation 6

$$\boldsymbol{SD_{change} = \sqrt{SD_{baseline}^2 + SD_{final}^2 - \left(2 \times Corr \times SD_{baseline} \times SD_{final}\right)}}$$

Equation 7

$$\boldsymbol{Corr = \frac{SD_{baseline}^2 + SD_{final}^2 - SD_{change}^2}{2 \times SD_{baseline} \times SD_{final}}}$$

Additional to the missing SD of change, in some studies it was reported either baseline or final SD, hampering the use of the above equation to calculate SD of change. In this case, the missing SD, typically final SD, was imputed from the average of two or more similar studies; this is, studies assessing the same outcome in the same type of intervention treatment, measured in similar time-point. Alternatively, we used the SD of the baseline value in this case, under the assumption that it would be equal to the SD of the final value. Because only one RCT included in the meta-analysis was handled in this manner, we did not expect this to have major effects on the interpretation of the overall pooled effect.

A very small number of trials reported results expressed in median and the range, instead of mean and SD, or variance. To make this data available, the median was assumed to best estimate the mean, as sample size exceeded 25. If the study had a small sample size, ≤25, the equation 8 was used to estimate the mean ($\bar{X}$) using the values of the median (m), low and high end of the range (a and b, respectively). To estimate the variance for trials with very small sample size, up to 15, the variance was estimated using the equation 9, for moderate sample, 15< n ≤70, Range/4 was used to best estimate the standard deviation (and variance), and Range/6 for large samples, >70, where range is: R = b - a, we. (148)

Equation 8

$$\bar{X} \approx \frac{a+2m+b}{4}$$

Equation 9

$$S^2 \approx \frac{1}{12}\left(\frac{(a-2m+b)^2}{4} + (b-a)^2\right)$$

In some studies, the baseline SD and the SD of change were reported, when necessary to calculate SMD in the pilot analysis, and the final SD was calculated using the equation 10.

Equation 10

$$SD_{final} = \frac{-2\times Corr\times SD_{baseline} \pm \sqrt{(2\times Corr\times SD_{baseline})^2 - 4\times\left(SD_{baseline}^2 - SD_{change}^2\right)}}{2}$$

Because SDs of change values tend to be less than the SDs of final values, in some circumstances when this postulation was not in compliance, this formula could not be used. Then

under the same assumption, the missing SD was imputed from the average of similar studies or from another time point in the self-study within the same outcome, if available; otherwise we presumed that the intervention does not alter the variability of the outcome measure and used the baseline SD.

When data could not be obtained from other reported values, or there was a “great scarcity” of data, the study was excluded from the analysis due to reporting bias.

3.5 Sensibility analysis

The sensibility of results in the meta-analyses was determined through sensibility analysis by altering or removing entries that might influence the pooled estimative of treatment effect, by characteristics of the population (i.e. severity of disease) or study design (139), this enable us to evaluate the degree of reliability of results in situations of uncertain decisions or assumptions about the data.

3.6 Results presentation and final report

Results of this systematic review were distributed in three parts:

- Description of studies;
- Quality of studies;
- Result of variables.

In the possibility of undertake the meta-analysis, funnel plot, and/or forest plot were built to visualize analyses. In the interpretation of results, the strength of evidence found was determined according to the Grading of Recommendations Assessment, Development and Evaluation system (GRADE) (149), the applicability of results, information about costs, current practice and everything else that would be relevant for clear determination of limits between risk and benefits.

4. RESULTS

In the first step, authors contacted the Cochrane Dementia and Cognitive Improvement Group to register this systematic review in the library and enroll in the review group, to allow the continue updating of this study, as well as to access appropriate resources in order to contribute with greater support and consolidation. Nevertheless, the approach adopted in this study differed from the working program of the group for reviews on modifiable risk factors in dementia.

4.1 Study identification

Succeeding the cross matching of key search terms in all databases, a total of 35327 records were identified at first and registered in the spreadsheet, among these records, in this first article screening, 5212 duplicates were found in the searched databases. After removal of clearly irrelevant articles and duplicates, 456 out of 30115 studies were related to the research topic, and were pre-selected by title and abstract (Table 1). Pre-selected studies were organized in a spreadsheet where title and abstracts of articles were registered. From these studies, 182 studies – 101 clinical trial and 81 observational– were selected and classified by nutrients to be evaluated (Table 2); most of studies were based in dietary patterns instead of specific nutrients. At this point 274 were excluded, because they did not meet the eligibility criteria for this systematic review. There were excluded: studies *in vitro*, animal models, pharmacological studies, plasma nutrient level measurement, metabolism of nutrients in the physiopathology of AD, nutritional status or food intake in people with dementia; review articles, systematic reviews, monographies, books and chapters of books, however, they were utilized as literature reference to identify other studies that possibly meet the criteria. From the 182 selected studies for examination of full texts, 168 full-article publications could be accessed, where 90 were clinical trials and 78 were observational studies. The identification process and study selection is shown in the PRISMA flow diagram (Figure 2) (140).

Table 1. Results screening of primary studies for systematic review

Databases	**N° identified studies**	**N° duplicated studies**	**N° pre-selected studies**
PubMed	2881	110	230
CENTRAL Cochrane	656	62	16
Web of Science	17397	2646	166
Virtual Health Library	13343	2368	41
Embase	1050	26	2
Other websites	1	0	1
Total	**35328**	**5212**	**456**

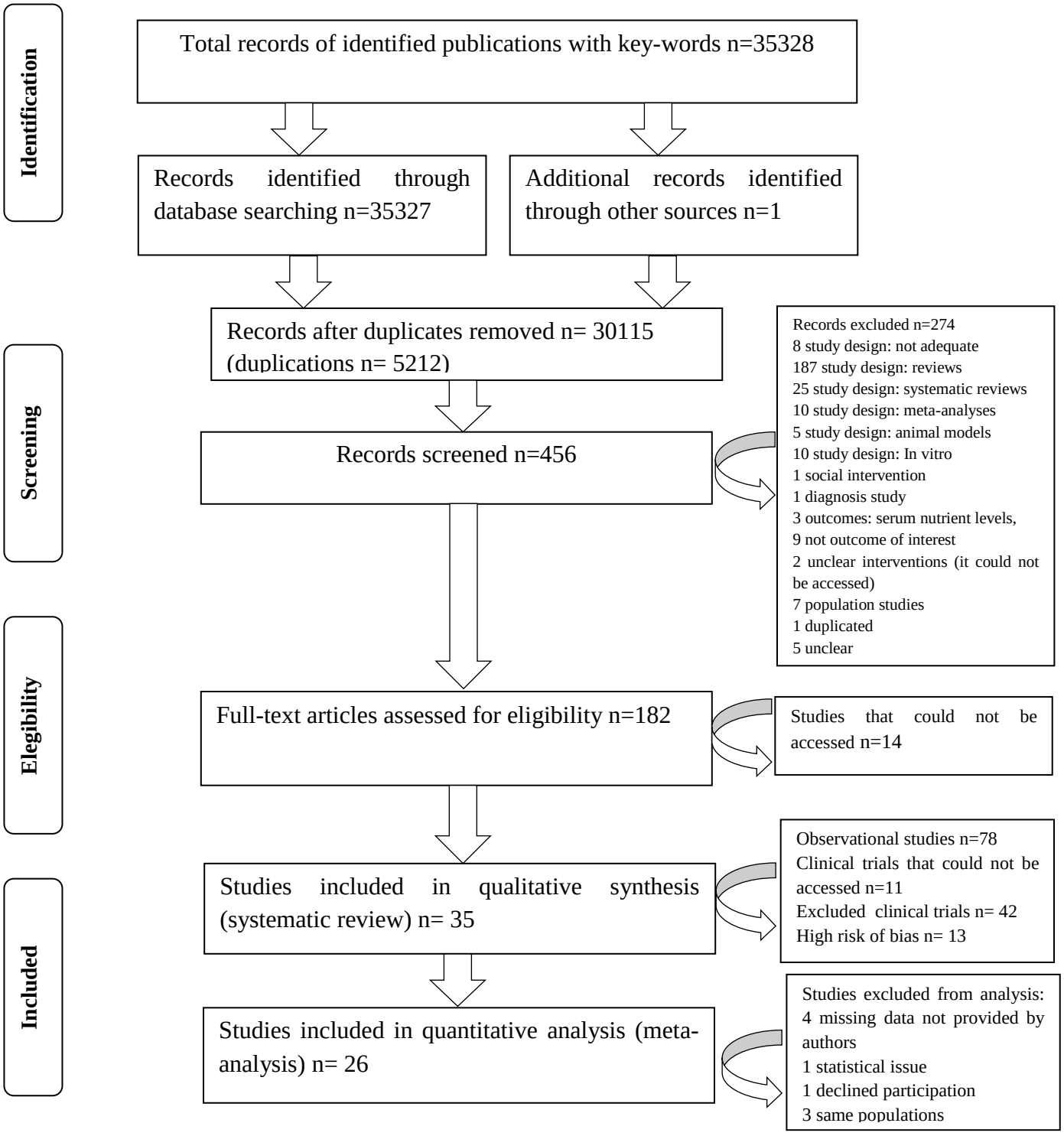
Table 2. Pre-selected studies classified by nutrient

Nutrient	**N° Clinical trials**	**N° Observational**	**N° total publication**
Amino acids	2	0	2
Carbohydrates	1	1	2
Lipids	3	6	9
Omega 3	18	5	23
Antioxidants	9	7	16
Dietary patter/Food	6	32	38
Micronutrients	7	7	14
Nutrients (supplements)	18	4	22
Vitamin B	13	8	21
Vitamin C + E	2	4	6
Vitamin D	4	1	5

Vitamin E	13	3	16
Vitamin E + B	1	0	1
Vitamin K	0	1	1
Others	4	2	6
Total	**101**	**81**	**182**

Figure 2. PRISMA flow diagram, illustration of the stages of study

(PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses). [1]



[1] Excluded clinical trials: 6 duplicated studies, 8 healthy population, 14 mild cognitive impairment population or no Alzheimer dementia, 4 no outcomes of interest, 3 ongoing studies, 7 study design

4.2 Characterization of studies

As stated by the authors' decision in the consensus meeting, observational studies were excluded from the systematic review, at least in this final stage of the dissertation.

Ninety clinical trials were thoroughly assessed by the eligibility criteria and the Cochrane risk of bias tool, at the same time of data extraction to conduct the systematic review. From these trials, forty-two clinical trials were excluded by the following reasons: participants do not meet clinical situation criteria (mild cognitive impairment and other dementias n= 14 (150–163), non-demented elderly n= 8 (164–171)), ongoing studies n= 3 (172–174), study design: article review n=2 (175,176), retrospective studies n= 2 (177,178), report/protocol n= 3 (179–181)), duplication n= 6 (182–187), studies that outcomes did not address the review question n= 4 (188–191).

From clinical studies, which matched eligibility criteria, 13 studies were classified as high risk of bias by the Cochrane's tool (see Appendix 5), with a total of 35 selected clinical trials left for inclusion in the systematic review.

Included studies in the systematic review are characterized in Table 4. Briefly, 28 randomized double-blind controlled trials (one with cross-sectional longitudinal analysis of 3 subgroups), one prospective randomized double-blind controlled trial, two pilot studies, one open randomized double-blind controlled trial, one crossover clinical trial, and two secondary analysis of randomized double-blind controlled trial.

Sample sizes of included studies ranged from eleven to 561 subjects, with a total of 3527 individuals. The diagnosis of dementia in most studies was based on accepted standardized criteria, such as the Diagnostic and Statistical Manual of Mental Disorders third or fourth edition DSM-III/IV (American Psychiatric Association); and the National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). Additionally, two studies used Mini Mental State Examination scores; one study used Telephone Interview for Cognitive Status and the International Classification of Diseases (ICD-10) to diagnose patients. Main clinical diagnosis or health conditions of selected population were mild to moderate AD (15 studies), moderate to severe AD (two studies), probable AD without specification the disease stage (16 studies), AD and MCI (Mild cognitive impairment) (one study), dementia and cognitive impairment (1 study). The mean age was 74.7 y (range: 66.5–81.6 y), except for two studies that did not make this data available (192,193).

Interventions were performed comparing a group of intervention with a control group or placebo. Studies were classified into 9 types of nutrient interventions that were found: antioxidants 4, carbohydrates 1, lipids 1, micronutrients 2, polymeric formula 8, polypeptide 1, omega-3 8, B-vitamin 4, vitamin D 1 and vitamin E 5. In 19 studies, overall, participants used medication as co-intervention, mostly acetyl-cholinesterase inhibitors (AChE-Is), either in the initial phase or during whole time of follow up. The shorter time of intervention was 4 weeks, and the longer time was 24 months. These studies were found to examine the effect of nutrient intervention principally on neuropsychological scales, and less often on biomarkers of Alzheimer's disease, oxidative and inflammation biomarkers, and brain-imaging outcome measures (Table 3).

Table 3. Classification of outcomes according to intervention

Nutrient Classification	**Number of Studies per Outcome**				**Total studies**
	Tests/Scales	Oxidative/ inflammatory Markers	AD Biomarkers	Brain Imaging	
Antioxidants	2 (1)[oa]	1	1[c]	-	4
Carbohydrates	1	-	-	-	1
Lipids except w-3	1	-	-	-	1
Micronutrients	1	-	1	-	2
Polymeric formula	6	-	-	2(1[c])	8
Polypeptide	1				1
Omega 3	4	2[c]	1[o]	1[c]	8
B-vitamins	3	-	1[c]	-	4
D-vitamin	1	-	-	-	1
Vitamin E	3	1[c]	-	1[c]	5
Total	23	4	4	4	35

[a] AD markers outcomes

[c] Cognitive outcomes

[o] Oxidative/inflammatory outcomes

Table 4. Characteristics of clinical trials eligible for systematic review[1]

First author, year of publication (Country)	Study design (name of study)	Principal health problem	Population Age in years	Gender	Final sample size	Intervention	Duration	Co-interventions	Comparison	Main Outcome	Funding source	Findings	Risk of bias
ANTIOXIDANTS													
Ringman et al, 2012 (USA)(194)	Randomized, double blind, placebo-controlled study	Mild to moderate AD	Average 73.5	F= 63%	30	Placebo, 2 gm or 4 gm of Curcumin C3 Complex® four 500 mg capsules twice daily in a 1:1:1 ratio.	24 weeks, with an open-label extension to 48 weeks.	AchE-Is (93%) and memantine (77%)	2mg curcumin vs 4mg curcumin vs placebo	ADAS-Cog, NPI, MMSE, ADCS-ADL; plasma levels of: Ab1-40, Ab1-42; CSF levels of: Ab1-42, T-tau, P-tau, F2-IsoPs	Not reported	There were no significant effects of treatment group on change in plasma Ab1-40 and Ab1-42, CSF Ab1-42, CSF tau or p-tau or F2-IsoPs. This study was unable to demonstrate clinical or biochemical evidence of efficacy against AD.	Low
Adair JC, et al 2001 (USA)(192)	double-blind fashion	Probable AD, NINCDS-ADRDA criteria	Not reported	Data not shown	43	NAC (N-acetylcysteine) group received 50 mg/kg/day compounded into capsules that matched the placebo in size and color.	6 months	Not reported	Active (NAC) vs Placebo	MMSE, ADL, BNT, Gesture to Command, WMS Figure Reproduction (immediate), HVLT Recall (immediate), HVLT recognition, Letter fluency, Category fluency, Judgment of Line Orientation	Alzheimer's Disease and Related Disorders Association, the Veterans Affairs Research Service, and the General Clinical Research Center at the University of New Mexico.	Active treatment with NAC failed to significantly change the primary outcome measures. Positive results in reducing oxidant stress in AD.	Unclear

J.M. Rubio-Perez & J.M. Morillas-Ruiz, 2013 (Spain)(195)	double-blind study with cross-sectional and longitudinal analysis	Probable AD, NINCDS-ADRDA criteria	mean±SD Patients 76.5±3.5 (AD initial phase 76±4; AD moderate phase 77±3); Control group 79±4	F/M= Patients 35/13 (AD initial phase 17/7; AD moderate phase 18/6), control 40/12	100	Antioxidant Beverage (AB): 84.29% water, 10.16% apple concentrate, 4.80% trehalose, 0.42% lemon concentrate, 0.16% green tea extract, 0.08% apple extract, 0.05% vit C, 0.01% apple flavoring, <0.01% vit E, <0.01% niacin, < 0.01% acesulfame K, <0.01% vitB12, <0.01% Zn, <0.001% Cu, <0.001% folic acid and <0.001% Se. Placebo beverage (PB): 99.32% water, 0.50% apple flavouring, 0.15% tea flavouring, 0.01% citric acid, 0.009% caramel coloring, 0.006% acesulfame K and 0.005% sucralose.	8 months	Not reported	Control group vs; AD initial phase; AD moderate phase	IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IFN-γ, TNF-α, monocyte chemotactic protein-1 (MCP-1)	Seneca Foundation. Directorate General of Investigation, Ministry of Education and Culture of the Autonomous Community of the Region of Murcia, Spain.	The AB did not produce a significant change in serum levels of the anti-inflammatory cytokines IL-4 and IL-10; but, significantly decreased serum levels of the pro-inflammatory cytokines IL-2, IFN-γ and TNF-α in AD patients. AB was more effective against inflammation in the early AD.	Unclear
Galasko et al, 2012 (USA)(196)	Double-blind, placebo-controlled clinical trial.	Mild to moderate AD	Mean (SD) E/C/ALA 73.6 (9.1) CoQ 71.4 (8.4) Placebo 73.2 (9.5)	F= 78	62	Vitamin E 800 IU, vitamin C 200 mg, and alpha-lipoic acid (α-LA) 600 mg into three capsules, 1 capsule 3 times/day. CoQ 400 mg, as a wafer, 2 wafers 3 times/day.	16 weeks	AChE-I , Memantine, Concomitant vitamin or supplement (allowed only if contained vitamin E, vitamin C, α-LA, or CoQ in amounts much lower than the doses used in this trial).	E/C/ALA vs CoQ vs Placebo	F2-IsoPslevel CSF, A342 level, Tau level, P-tau181, MMSE, ADL	NIA	These antioxidants did not affect CSF Aβ, tau, or P-tau biomarkers; suggesting that this combination did not improve indices of neurodegeneration. E/C/ALA significantly	Unclear

												decrease CSF F2-isoprostanes levels, it is unclear whether this reduction may lead to clinical benefits in AD. Increased cognitive decline in the E/C/ALA group raises a concern that this combination could adversely affect cognition in AD.	
VITAMIN E													
Dysken MW, et al, 2014 (USA)(197)	Double-blind, placebo-controlled, parallel-group, randomized clinical trial	Mild to moderate AD	Mean (SD) [range], y VitE 78.6 (7.2) [55-93] MEM 78.8 (7.2) [53-92] vit E + MEM 78.3 (7.0) [54-94] plac 79.4 (7.0) [61-96]	M= 594	561	α-tocopherol (dl-α-tocopheryl acetate) 1000 IU twice a day. Memantine 10 mg twice a day.	4 years	AChEI, No. (%) Donepezil 104 (68) 100 (65) 100 (65) 96 (63) Galantamine 43 (28) 47 (30) 49 (32) 55 (36) Rivastigmine 5 (3) 8 (5) 4 (3) 1 (1)	Vitamin E, Memantine, Vit E + Memantine	ADCS-ADL, MMSE, ADAS-cog, NPI, CAS time, Dependence Scale level.	Veterans Affairs Cooperative Studies Program. Forest Research Institute (Forest Laboratories). DSM Nutritional Products	A dosage of 2000 IU/d of α- tocopherol was effective in slowing the functional decline of patients with mild to moderate AD taking an AChEI and was also effective in reducing caregiver burden. Neither memantine nor the combination of alpha tocopherol and memantine	Low

												showed clinical benefit in these patients.	
Sano M, et al, 1997 (USA)(198)	Double-blind, placebo-controlled, 2x2 factorial, pararelled group desing. randomized, multicenter trial (Alzheimer's Disease Cooperative Study)	Moderate probable AD	means ± SD. Placebo 73.5±8.3 Seleg 72.7±8.9 a-toc 73.4±7.8 Seleg + a-toc 73.9±7.1	F (%)= 65.5 Seleg 67.8 a-toc 65.9 Seleg + a-toc 60.0	318	Selegiline 5 mg twice a day, dl - alpha-tocopherol 1000 IU twice a day	2 years	Not reported	Selegiline vs α-tocopherol vs selegiline + α-tocopherol vs placebo	MMSE, ADAS, Blessed Dementia Scale, Equivalent Institutional Service, Dependence Scale, BRSD, Unified Parkinson's Disease Rating Scale	NIH	In AD patients treated with α-tocopherol significantly delay institutionalization, deterioration of functional performance, and the need for care. There was no improvement in cognitive test scores in any of the treatment groups. Both selegiline and α-tocopherol delay functional deterioration. The use of selegiline or α-tocopherol may delay clinically important functional deterioration in patients with AD.	Unclear
M. Onofrj et al, 2002 (Italy)(199)	Double-blinded Randomized Controlled Trial	Mild and with moderate–severe AD	Mean (SE) Group I DPZ 65.2 ± 1.8 Group I VIT E 65.5 ± 1.7 Group II DPZ 66.7 ± 1.5 Group II VIT E 66.5 ± 1.6. Control SE, 68.9 ± 0.9	M/F (27/33)	60	Singledaily dose 5 mg DPZ and 1000 IU Vit E during 14 days of titration, followed by 10 mg DPZ and 2000 IU Vit E for 6 months.	6 months	Not reported	Group I DPZ, Group II DPZ, Group I Vit E, Group II Vit E	WAIS score, MMSE, ADAS-cog, P300 Recordings	Not reported	Vit E Group II patients underwent a more severe deterioration of P3 and Neuropsychological test scores than DPZ Group II patients.	Unclear

			[57–78]										
A. Thomas et al, 2001 (Italy)(200)	26-week study, randomized in double-blind branches (DPZ vs. vitamin E) and in an open controlled study (Riv).	Probable AD, DSM-IV and the NINCDS-ADRDA criteria	Mean ± SD [range]: control 67.5 ± 14.85 [57–78] DPZ 66.5 ± 9.19 [60–73] Riv 65.0 ± 8.49 [59–71] Vit E 65.5 ± 10.61 [58–73]	M/F= 53/67	54	DPZ: single dose 5 mg/d/1 mo and 10 mg/d/ remaining months. Vit E: 2,000 IU single dose. Riv: 1.5 mg/d /1st mo; 1.5 mg twice/day (total 3 mg) 2 mo; 3 mg twice/day (total 6 mg) 3 mo; 4.5 mg twice/day (total 9 mg) 4 mo; and 6 mg twice/day (total 12 mg) following months.	6 months	Not reported	DPZ vs Riv vs Vit E	MMSE, ADAS-cog, WAIS, NPI	Not reported	Patients with AD receiving vitamin E instead of DPZ or Riv did not undergo improvements in P300 or neuropsychol ogic test results. Vitamin E might have slowed the progression of disturbances; however, a regression of symptoms was neither expected nor found. It might be suggested that with short-term (DPZ and Riv) and long-term (vitamin E) effects in AD, the two classes of drugs might act synergically and should be administered together.	Unclear
A. Lloret et al., 2009 (Spain)	Prospective, double blind, placebo controlled study.	Probable AD, NINCDS-ADRA criteria	We checked that all patients had similar age and gender distribution in all groups	Not reported	33	vitamin E (800 IU per day), or placebo	6 months	cholinesterase drugs	Vitamin E vs Placebo	MMSE, Blessed-Dementia Scale, CDT, Oxidized glutathione (GSSG), plasma MDA	RETICEF, Instituto de Salud Carlos III.	This paper show that systemic oxidative stress occurs in AD patients and correlates with the	Unclear

												cognitive status of these patients. Not all patients responded equally to antioxidant treatment. There were two groups of patients: “respondents” and “nonresponde nts”. In respondents, vitamin E treatment the GSSG levels were reduced. The non-respondent group of patients did not improve their cognitive functions.	
POLYPEPTIDE													
J. Leszek et al., 1999 (Poland)(201)	Double-blind placebo-controlled one-year trial	Probable AD, DSM-III-R and NINCDS-ADRDA criteria	Female age (mean, range) A= 68.5 (45–83) B= 69.8 (50–82) C= 68.9 (61–75). Male age (mean, range) A= 73 (72–74) B= 71.7 (69–76) C= 66.7 (59–76)	F/M= 34/12	42	Group A: every second day one tablet 100 µg of Colostrinin. Group B: selenium (100 mg) tablets. Group C: placebo tablets.	1 year	Not reported	Proline rich polypeptide (Colostrinin) vs Selenium or Placebo	MMSE	Not reported	Colostrinin was more effective in patients at the initial stages of disease. The immunomodu latory properties of Colostrinin may induce changes which may improve brain functions.	Unclear
OMEGA-3 PUFA													

G. Faxén-Irving et al, 2013 (Sweden)(202)	Randomized double blind placebo-controlled study	Mild to moderate AD	Omega-3 72.6 ± 9.0. Placebo 72.9 ± 8.6	M/F= 84/90	174	Four 1-g capsules daily, of 430 mg of DHA and 150 mg of EPA, 4 mg of tocopherol	12 months	Not reported	Omega3 vs Placebo	MMSE, Plasma and CSF transthyretin, hs-CRP	Stockholm County Council. Karolinska Institute. PronovaBiocare A/S, Lysaker..	A DHA-rich n−3 FA supplementation appeared to preserve TTR in plasma in mild to moderate AD patients. Plasma TTR correlated to MMSE and inversely to ADAS-Cog, which may indicate a potential mechanism for possible positive cognitive effects of n−3 FA treatment.	Low
Freund-Levi et al., 2009 (Sweden)(203)	part of a larger randomized, double-blind placebo-controlled trial (OmegAD Trial)	AD, DSM-IV criteria	Age, years n-3FA 72.2±8.8, Pl 68.3±7.3	F= n-3FA 8 (44%), Pbo 6 (30%)	35	four 1-gram capsules daily, each containing either 430 mg DHA (22: 6 n-3 FA) and 150 mg EPA (20: 5 n-3 FA), or an isocaloric placebo oil (1 g of corn oil, including 0.6 g of linoleic acid). 4 mg of vitamin E (tocopherol) was added to each capsule.	6 months	Acetylsalicylicacid, n n-3FA 4 (22%), Pl 2 (10%) 0.3. All patients in the present study were on standard treatment with AchE-Is	n-3FAsvs Placebo	Aβ 1 –42, CSF T-tau, CSF P-tau level, IL-6 in plasma and CSF, TNF-α in CSF, TNF-α in Plasma, hs-CRP in plasma	Stockholm County Council, Karolinska Institutet, Funds of Capio, Swedish Alzheimer Foundation, Odd Fellow, Swedish Nutrition Foundation, Gun ochBertilStohnesStiftelse, Swedish Society of Physicians and PronovaBiocare A/S, Lysaker.	Treatment with n-3 FAs resulted in null effects on CSF and plasma inflammatory markers nor on dementia biomarkers compared to placebo. Plasma levels of IL-1 and TNF- were indicated as strong predictors for development of AD. The concomitant treatment with AChEIs may have masked a smaller anti-	Unclear

												inflammatory effect of the n-3 FAs.	
Quinn JF et al, 2010 (USA)(184)	Randomized, double-blind, placebo-controlled trial	Mild to moderate AD	Mean (SD) 76 (8.7)	F= 210 (52.2%)	298	Algal DHA capsules 1 g twice per day.	18 months	AchE-Is use at baseline. Memantine use at baseline	DHA / Placebo	ADAs-cog, CDR, MMSE, ADCS-ADL, NPI, Quality of Life AD scale. Rate of brain atrophy by volumetric MRI	NIA. Study drugs were provided by Martek Biosciences .	There was no evidence of benefit of DHA supplementation in this population. In the subgroup with paired MRI scans, DHA had no effect on change in volume of hippocampus, whole brain, or ventricles.	Low
Freund-levi et al, 2008 (Sweden)(204)	Randomized, double-blind, placebo-controlled clinical trial	Mildtomoderate AD	Omega 3= 72.6 ± 9.0. Placebo= 72.9 ± 8.6	F= 90	174	four 1-g capsules daily, of 430 mg of DHA and 150 mg of EPA, 0.6 g of linoleic acid and 4 mg of tocopherol	12 months	AchEI, n (%) Donepezil Galantamine Rivastigmine Antidepressants Neuroleptics Herbal medication	Omega3 vs Placebo	NPI, MADRS, DAD, CGB Emotional overload, Economic overload, Captured in a role	Funds of Capio, Swedish Alzheimer Foundation, Odd Fellow, Swedish Society of Physicians and Lion's Sweden.	Supplementation of 1.7 g DHA and 0.6 g EPA given daily for 6 months to patients with mild to moderate AD did not seem to influence neuropsychiatric, behavior or functional ability.	Unclear
L. Shinto et al, 2014 (USA)(182)	3-arm, parallel group, randomized, double-blind, placebo-controlled pilot clinical trial	Probable AD, NINCDS-ADRDA criteria	Mean (SEM) placebo 75.2 (10.8) ω3 75.9 (8.1) ω3+LA 76.7 (10.6)	F/M= 21/18 (F= pbo 54% w-3 39% w-3 + LA 39%)	34	ω-3 group: fish oil concentrate in the triglyceride form at 3 gr/day (3 capsules), DHA 675 mg and EPA 975 mg/day . ω-3 + LA group: LA in the racemic form at 600 mg/day in one tablet. Placebo group: placebo LA: no LA (excipients:	12 months	AchE-Isor memantine (Pbo 77% ω-3 92% ω-3+LA 77%), vitamin E, and ginkgo biloba.	ω-3 vs ω-3+LA vs placebo	F2-IsoPs, ADAS-cog, MMSE, ADL, IADL	NIH/NIA and NIH General Clinical Research	In a small pilot study combining ω-3 with LA slowed both cognitive and functional decline in mild to moderate AD participants over 12 months. There was no difference	Low

						lactose, hypromellose, silicon dioxide, microcristalline cellulose, polyethylene glycol, povidone, corn starch, talc, and magnesium stearate). Placebo oil: soybean oil with 5% fish oil.						between groups at 12 months in peripheral F2-isoprostane levels. The combination appears to be safe at the doses evaluated.	
C.-C. Chiu et al, 2008 (Taiwan)(205)	Randomized double-blind placebo-controlled study	Mild or moderate AD, Amnesic MCI	Mean, 95% CI Omega-3 74.0 (70.1–77.8) Placebo 76.5 (71.8–81.1)	F % Omega-3 65.0 Placebo 46.7	29	Omega-3 as 3 capsules twice/day (EPA 1080 mg and DHA 720 mg). Placebo capsules twice/day with olive oil esters.	24 weeks	Tertiary-butyl hydroquinone 0.2 mg/g, and tocopherols 2 mg/g.	Omega3 vs Placebo	ADAS-cog, CIBIC-plus, MMSE, HDRS, Hachinski's Ischemic Scale.	Department of Health. National Science Council. Taipei City Hospital in Taiwan.	Omega-3 fatty acids may improve general clinical function in patients with mild or moderate AD and MCI, but not their cognitive function. The cognitive effects of omega-3 FAs might be favored in patients with MCI rather than those with AD.	Unclear
Freund-Levi et al, 2006 (Sweden)(206)	Randomized, double-blind, placebo-controlled clinical trial.	Mild to moderate AD	Omega-3 72.6 ± 9.0. Placebo 72.9 ± 8.6	F= 90	174	Four 1-g capsules daily, of 430 mg of DHA and 150 mg of EPA, 4 mg of tocopherol (EPAX1050TG; Pronova Biocare A/S, Lysaker, Norway) .	12 months	AChE-I: Donepezil, Galantamine, Rivastigmine, Antidepressant agents, Neuroleptic agents, Statin drugs.	All patients (ω-3 vs placebo)	MMSE, ADAS-COG, CDR Global Score, CDR Scale Sum of Boxes	PronovaBiocare A/S Funds of Capio, GamlaTja¨narinnor, Swedish Alzheimer Foundation, Odd Fellow, Swedish Society of Physicians, and Lion's Sweden.	Supplementation with n-3 in mild to moderate AD patients found no significant overall treatment effects on neuropsychiatric symptoms, on activities of daily living or on caregiver's burden,	Unclear

												except for possible positive effects on depressive symptoms in non-APOEv4 carriers and agitation symptoms in APOEv4 carriers.	
S. Kotani et al., 2006 (Japan)	Pilot clinical study	MCI, modified criteria of Petersen et al. (1999) and the total score of 12 indexes being less than mean minus 1.5 S.D. Early AD, NINCDS-ADRDA and NINDSAIREN criteria.	years old mean ± SD, MCI 68.1 ± 6.3. Organic brain lesions 57.5 ± 12.4. AD 67.0 ± 6.3	MCI-A; 9 M/ 3 F; MCI-P; 3 M/ 6 F; organic brain lesions 4 M/ 6 F; AD 3 M/ 5 F	39	Aravita (comercially Suntory) 40 mg/capsule of ARA and DHA, and 0.16 mg/capsule of asthaxanthin (antioxidant of PUFA). Placebo: 40 mg/capsule of olive oil (major content is oleic acid). 6 capsules/day, daily intake (ARA and DHA, or olive oil) was 240 mg, respectively.	90 days	Not reported	ARA and DHA supplementation vs Placebo	Immediate memory list learning, immediate memory story learning, visuospatial/constructional figure copy, visuospatial/constructional line orientation, language picture naming, language semantic fluency. attention digit span, attention coding, delayed memory list recall, delayed memory list recognition, delayed memory story recall, delayed memory figure recall	Japan Foundation for Ageing and Health, and Narishige Neuroscience Research Foundation (to SK), and the Japan Ministry of Education, Science and Technology (to TY).	This pilot study of ARA and DHA supplementation showed remarkable memory improvements in the human patients with organic brain lesion or MCI-A. There were no significant improvements in AD and MCI-P groups	Unclear
B-VITAMIN COMPLEX													
Ford, AH. et al, 2010	Randomized, double-blind	Cognitive impairment	Mean (SD) Placebo 78.7	M= 100%	241	400 µg B12, 2 mg folic acid, and 25	2 years	Not reported	vitamin - placebo	ADAS-cog, CVLT (List A	National Health and	There was no difference	Low

(Australia)(207)	controlled clinical trial (Health in Men Study)	and dementia	(2.7) Vitamins79.3 (2.8)			mg B6, 1 capsule daily.				immediate free recall trials1–5 total), CVLT (List A long-delay free recall), MMSE, Digit cancellation test, CDT CAMDEX, TICS, SF36–mental health, SF36–vitality, social functioning, role emotional.	Medical Research Council of Australia, Blackmores Ltd.	in the ADAS-cog change from baseline to 24 months between the placebo and vitamins group. The results of this trial indicate that the use of vitamins B6, B12, and folate for 2 years does not change the rate of cognitive decline among men with hypertension aged 75 years or older. Neither seems to benefit these men in terms of mortality or a later diagnosis of dementia.	
Connelly et al, 2008 (United Kingdom)(208)	double-blind placebo-controlled study	Probable AD, NINCDS-ADRDA criteria	76.27 SD 6.23 Folicacid [n=23] 75.65 SD 5.94Placebo [n=18] 77.60 SD 6.89	M/F= 12/29	41	1 mg of folic acid or placebo daily	6 months	donepezil n= 35, rivastigmine n= 12, galantamine n= 10.	Folate vs Placebo	MMSE, IADL, Social Behaviour (SB), DSST, Combined IADL/SB	NHS Tayside Grant.	After 6 months a significant difference was seen in the change from baseline in combined IADL and SB between arms but not change in MMSE. This pilot study indicates that supplementation of ChI with folic	Low

												acid may be useful in the treatment of AD.	
Y. Sun et al, 2007 (Taiwan)(209)	Randomized, double-blind, placebo controlled trial	Mild to moderate AD	mean [SD] 75 [7.3]	M/F = 45 / 44	63	Mecobalamin (0.5 mg) + multivitamin supplement. In addition to folic acid and pyridoxine HCl, the supplement contained iron ferrous 60 mg, nicotinamide 10 mg, calcium carbonate 250 mg, riboflavin 2 mg, thiamine mononitrate 3 mg, calcium pantothenate 1 mg, ascorbic acid 100 µg, iodine 100 µg, copper 150 µg, vitamin B12 3 µg, vit A 4000 IU, and vit D3 400 IU.	26 weeks	AchE-I Donepezil [Aricept®] (all participants), Rivastigmine [Exelon®](multivitamin group n= 1)	Multivitamin vs Placebo	ADAS-Cog, MMSE, CASI, ADL Index, IADL Scale	National Science Council. En Chu Kong Hospital. Genovate Biotechnology Co., Ltd. Eisai Co., Ltd.	Patients with mild to moderate AD and normal serum levels of vit B12 and folic acid, combination treatment with mecobalamin + a multivitamin decreased homocysteine concentration, however, statistically significant beneficial effects on cognition or ADL function were not found at 26 weeks.	Low
Aisen et al, 2008 (USA)(210)	multicenter, randomized, double-blind 2-group parallel design controlled clinical trial (VITAL)	Probable AD, NINDS-ADRDA criteria	mean (SD), y Treatment 75.7 (8.0) Placebo 77.3 (7.9) All participants 76.3 (8.0)	F= Treatment 138 (57.5%) Placebo 91 (53.9%) All 229 (56.0%)	344	5mg/d of folic acid, 1mg/d of vitamin B12 (cyanocobalamin), and 25 mg/d of vitaminB6 (pyridoxine hydrochloride).	18months	Stable use (for at least 3 months) of AchE-I sand memantine was allowed	high-dose vitamin supplements vs placebo	ADAS-cog, MMSE, CDR sob, ADCS-ADL, NPI	NIA, General Clinical Research Center Program of the National Center for Research Resources, NIH. Supplements were donated by Roche Inc.	High-dose supplement intervention reduced homocysteine levels but, in the study population as a whole, there was no evidence of benefit on any outcome measure. This study does not support the treatment of individuals with mild to moderate AD	Low

												and normal vitamin levels with B vitamin supplements.	
VITAMIN D													
M.S. Stein et al, 2011 (Australia)(211)	Double-blinded Randomized Controlled Trial	Mild to moderate AD	77.5 69–80 (Median, Interquartile range)	F/M= 15/ 17	31	Low-dose (1000 IU) vit D2, 2 capsules 3 times/ day, and then 0 to 2 capsules 3 times/day, adjustment based on serum 25OHD (130–175 nM). High-dose D/ placebo capsules (6000 IU vit D2). Human insulin: Humulin-R 100 IU per ml. Three sprays per nostril (total 60 IU insulin) 4 times/ day.	16 weeks	16 donepezil, 1 Rivastigmine, 8 Galantamine and 1 Galantamine and memantine	High-dose D vs Placebo high-dose D. Insulin vs Placebo	ADAS-cog (word recognition, word recall sub-scores), WMS-R LM immediate recall, WMS-R LM 30 min delayed, GDS, DAD, BPI, DAD sub-scores of activities of daily living	The Shepherd Foundation	This RCT found no benefit for cognition or disability from adding high-dose vitamin D to ongoing low-dose vitamin D supplementation. Nor benefit from nasal insulin acutely or over 48 h. The ADAS-cog score was not significantly changed after 16 weeks of low-dose vitamin D supplementation (during 8 weeks of which half the participants were randomized to high-dose vitamin D as well) is consistent with the proposition that low-dose vitamin D may retard progression of AD.	Unclear
POLYMERIC FORMULA													

P. Scheltens et al, 2010 (The Netherlands, Germany, United Kingdom, and United States)	Double-blind, randomized, controlled, multicenter trial	Mild AD	mean age 73.7	M= 106	161	Fortasyn Connect 125 mL/day: EPA 300 mg, DHA 1200 mg, Phospholipids 106 mg, Choline 400 mg, UMP 625 mg, Vit E (alpha-TE) 40 mg, Vit C 80 mg, Selenium 60 µg, Vit B12 3 µg, Vit B6 1 mg, Folic acid 400 µg.	12 weeks, with possible extension of 12 weeks.	Not reported	Active vs Control	WMS-r delayed verbal memory test, modified ADAS-cog, WMS-r immediate verbal memory test, ADCS-ADL, NPI-12, Quality of life–AD (composite score), CIBIC-plus	Danone Research–Centre for Specialized Nutrition (part of Group Danone).	This proof-of-concept study showed that supplementation with the multi-nutrient drink Souvenaid for 12 weeks is well-tolerated and results in an improvement in memory in patients with mild AD.	Unclear (author decline participation)
P.J.G.H. Kammpuis, et al, 2011 (The Netherlands, Germany, United Kingdom, and United States)(212)	Secondary analyses from a double-blind, randomized, controlled, multicenter, proof-of-concept trial	Mild AD	mean age 73.7	M= 106	161	Fortasyn Connect 125 mL/day: EPA 300 mg, DHA 1200 mg, Phospholipids 106 mg, Choline 400 mg, UMP 625 mg, Vit E (alpha-TE) 40 mg, Vit C 80 mg, Selenium 60 µg, Vit B12 3 µg, Vit B6 1 mg, Folic acid 400 µg.	12 weeks, with possible extension of 12 weeks.	Not reported	Active vs Control	ADCS-ADL, MMSE,	Nutricia advanced medical Nutrition, Danone Research, Centre for specialized Nutrition.	ADCS-ADL performance was significantly improved in a subgroup of mild AD patients with 'low' baseline BMI. the data indicated that patients with lower BMI at baseline may benefit more from souvenaid, with respect to functional outcome, than those with higher baseline BMI.	Low
P.J.G.H. Kammpuis. et al, 2011 (The Netherlands, Germany, United Kingdom, and United States)(213)	Secondary analyses from a double-blind, randomized, controlled, multicenter, proof-of-concept trial	Mild AD	Age ± sd, yr Control 73.3 ± 7.8 Active 74.1 ± 7.3	M= 105	161	Fortasyn Connect 125 mL/day: EPA 300 mg, DHA 1200 mg, Phospholipids 106 mg, Choline 400 mg, UMP 625 mg, Vit E (alpha-TE) 40 mg, Vit C 80 mg,	12 weeks, with possible extension of 12 weeks.	Not reported	Active vs Control	13-item ADAS-cog	Nutricia advanced medical Nutrition, Danone Research.	Results from this study demonstrated that dietary supplementation with souvenaid yields improvements in the	Low

						Selenium 60 µg, Vit B12 3 µg, Vit B6 1 mg, Folic acid 400 µg.						memory of patients with mild and very mild AD. Patients with higher ADAS-cog scores at baseline, souvenaid significantly improved ADAS-cog scores compared with the control group.	
Scheltens P. et al, 2014 (The Netherlands, Germany, Belgium, Spain, Italy, and France)	Randomized, controlled, double-blind, parallel-group, multi-country trial (The Souvenir II study)	Probable AD	years [range] Control 73.2 (8.4) [51–88] Active 74.4 (6.9) [55–89]	M= 132	238	Fortasyn Connect 125 mL/day: EPA 300 mg, DHA 1200 mg, Phospholipids 106 mg, Choline 400 mg, UMP 625 mg, Vit E (alpha-TE) 40 mg, Vit C 80 mg, Selenium 60 µg, Vit B12 3 µg, Vit B6 1 mg, Folic acid 400 µg.	24 weeks	Not reported	Active vs Control	EEG, NTB memory domain, RAVLT immediate recall, RAVLT delayed recall, RAVLT recognition performance, WMS-VPA immediate recall, WMS-VPA delayed recall, NTB executive function domain, WMS digit span, TMT condition A and B, Category fluency, COWAT, NTB total composite, ADAS-cog orientation task, LDST.	Danone Research BV, on behalf of Nutricia Advanced Medical Nutrition, Danone's specialized healthcare unit. NL Food & Nutrition Delta project.	The EEG outcomes show a significant biological effect that could be interpreted in terms of changes in functional connectivity, supporting the hypothesis that the intervention enhances synapse formation and function in mild AD. The limited evidence for the degree of cognitive change as measured by the NTB makes it more difficult to relate the memory	Low

												effects in terms of clinical effectiveness.	
Planas et al 2004 (Spain)	randomized double-blind placebo-controlled study	Probable AD, NINCDS-ADRDA criteria	Mean age (year) S= 72.52±10.72 C= 76.71±5.53	M/F= 20/24	39	250 ml energy dense and protein-rich liquid supplement 2 times/ day (total: 500 kcal/day, 45% carbohydrates, 25% fat, and 30% proteins)	6 months	Not reported	Study-group (S) vs Control-group (C)	Blandford scale, MMSE, Isaacs Set Test	Instituto de Salud Carlos III. Nutricia, S.A. provided the study drugs.	No positive effects on disease progression were observed with supplementation. After 6 months, no improvement and no significant deterioration in eating behaviour disorders or in cognitive measures, as observed within groups as well as between groups.	Unclear
Shah et al. 2013(214)	24-week, double-masked, parallel, randomized, controlled clinical study (S-Connect study)	Probable AD, NINCDS-ADRDA criteria	76.7 years (SD = 8.2). Age (years) Active 76.6 (8.2) Control 76.9 (8.2)	F= Active 139 (52%) Control 135 (52%)	254	Fortasyn Connect or an iso-caloric control product that lacked Fortasyn Connect, as a 125 ml (125 kcal)/day.	24 weeks	Duration of AD medication use (months): Active 28.8 (22.9) Control 31.5 (28.7)	Active vs Control	ADAS-cog, Cognitive test battery (Digit Span from the WMS, Concept Shifting Test, Letter Digit Substitution, Category Fluency), ADCS-ADL Scale, CDR-sob	Nutricia Research	This trial establishes that Souvenaid as an add-on intervention does not slow overall cognitive decline and is safe and well tolerated in persons with mild-to-moderate AD using AD medication.	Low
De Waal et al 2014 (The Netherlands, Germany, Belgium, Spain, Italy,	A 24-week randomized, controlled, double-blind, parallel-group, multi-	Probable AD, NINCDS-ADRDA criteria	Age, y [range] Control 72.5 (8.0) [52–85] Active 74.1 (6.8) [55–87]	M= Control 47 (50.5%) Active 45	159	Fortasyn Connect (DHA, EPA, phospholipids, choline, UMP, vitamin B12, B6, and folate,	24 weeks	Not reported	Active vs Control	EEG Phase Lag Index (PLI)	Danone Research BV, on behalf of Nutricia Advanced	Findings from this study indicate that Souvenaid preserves the organisation	Low

and France)(215)	country study (Souvenir II study)			(52.3%)		vitamins C and E, and selenium), or an isocaloric control product that lacked Fortasyn Connect, as a 125mL/day.					Medical Nutrition, Danone's specialized healthcare unit. NL Food & Nutrition Delta project.	of brain networks in patients with mild AD within 24 weeks.	
Remington et al, 2015 (USA)(216)	A double-blind, multi-site, phase II study	Moderate to late-stage probable AD, NINCDS, and MMSE score of 11.9 ± 2.5	77.8±9.3	Not reported	106	Nutraceutical formulation: folic acid (400 mg), B12 (6 mg), α-tocopherol (30 IU), SAM (400 mg), NAC (600 mg), and ALCAR (500 mg).	9 months	Not reported	Treatment vs Placebo	DRS-2, CLOX-1, 12-item NPI, ADCS-ADL	Awards from the Alzheimer's Association, No corporate funds	Participants receiving NF improved Clox-1 and DRS vs placebo within 3 months and those receiving placebo exhibited a decline in cognitive performance.. Caregivers reported non-significant improvements in NPI. ADL did not change for either cohort	Low
MICRONUTRIENTS													
H. Kessler et al. 2008 II (Germany)	monocentric, prospective, double-blind, placebo-controlled, parallel-group randomized design	Probable AD, NINCDS–ADRDA criteria	(years) PBO 69.48 ± 1.39 VERUM 70.37 ± 1.12	M/F= 29/39	57	Cu orotate 51.62 mg (8 mg Cu) once daily.	12 months	5–10 mg donepezil daily	Verum vs placebo	CSF Ab42, Tau level, P-Tau level	HOMFOR program of the Saarland University Medical Faculty. International Copper Association.	CSF biomarker analysis demonstrates that long-term oral intake of Cu can be excluded as a risk factor for AD. CSF Ab42 levels declined significantly within 12 months indicating its	Unclear

												value as a prognostic biomarker.	
H. Kessler et al. 2008 (Germany)	monocenter, prospective, double-blind, placebo-controlled, parallel-group randomized design	Probable AD, NINCDS-ADRDA criteria	Mean ± SD 69.4 ± 8.1 69.6 ± 6.6	M/F= 25/32	57	Cu-(II)-orotate-dihydrate 51.62 mg (8 mg Cu) once daily.	12 months	Donepezil 5–10 mg 2 months prior to recruitment and during the study.	Verumvs Placebo	ADAS-cog, MMSE	HOMFOR program of the Saarland University Medical Faculty. International Copper Association	This study shows that Long-term oral intake of Cu is well-tolerated and has no effect on the progression of AD.	Unclear
LIPIDS													
Henderson ST. et al, 2009 (USA)(217)	Randomized, double-blind, placebo-controlled, parallel-group study	Mild to moderate AD	Mean (± SD) AC1202 76.9 (± 8.9) Placebo 76.8 (± 7.4) Median AC1202 78.0 Placebo 78.0 Range AC102 (52 – 93) Placebo (51 – 89)	M/F= 67/85	124	30 gr powder sachets [10 gr of AC-1202, a MCT of glycerin and caprylic acid (C8:0) 33% AC-1202, 64% gum Acacia and 2.6% syloid]. First 7 days one 30 gr sachet/day. Day 8, two 30 gr sachets/day (20 gr AC-1202), to 90 day.	90 days	AD medications: Aricept™, Exelon™, Namenda™, Reminyl™/Razadyne™	AC-1202 vs Placebo	ADAS-Cog, MMSE, ADCS-CGIC	Accera, Inc Broomfield, CO.	AC-1202 elevated serum ketone bodies in AD patients and resulted in significant differences in ADAS-Cog scores compared to Placebo. Effects were most notable in APOE4(-) subjects who were dosage compliant.	Unclear
CARBOHYDRATES													
Y. Barak et al., 1996 (Israel)(218)	double-blind controlled crossover trial	Dementia of the Alzheimer type, DSM-III-R	mean age 81.6 years	F= 100%	12	inositol 6 gm daily or placebo (dextrose)	4 weeks (8 weeks cross-over)	No medications were permitted, except for oxazepam up to 15 mg/ day, or an equivalent benzodiazepine if the patients had been taking it before the study.	INOSITOL vs PLACEBO	CAMDEX (CAMCOG Subscales: Orientation, Language, Attention, Praxis, Perception, Abstraction, Memory, N And Total CAMCOG)	Not reported	Supplementation with inositol does not improve AD measured by the CAMCOG. A trend in favor of inositol was not statistically significant. The language and orientation subscales improved	Unclear

												significantly during inositol treatment.	

[1]AD: Alzheimer's disease, MCI: Mild Cognitive Impairment, SD: Standard Deviation, BMI: Body Mass Index, MMSE: Mini-Mental State Examination. F: Female, M: Male, ADAS-cog: Alzheimer's Disease Assessment Scale – Cognitive, GDS: Global DeteriorationScale, SIB: SevereImpairment Battery, NPI: Neuropsychiatric Inventory,NPI-NH: Neuropsychiatric Inventory Nursing Home version, LPRS: London Psychogeriatric Rating Scale, ADCS-ADL: Alzheimer's Disease Cooperative Study Activities of Daily Living, AchE-Is: Acetylcholinesterase Inhibitors. DHA: Docosahexaenoic acid , EPA:Eicosapentaenoic acid, Hs-CRP: High sensitive C-reactive protein, CDR: Clinical Dementia Rating. CDR-sob: Clinical Dementia Rating sum of boxes,MADRS: Montgomery Asberg Depression Rating Scale, ADL: Activities of Daily Living, IADL: Instrumental Activities of Daily Living, PUFA: Polyunsaturated fatty acid, CIBIC: Clinician's Interview-Based Impression of Change Scale, HDRS: Hamilton Depression Rating Scale, IU: International Units. CAS: CaregiverActivity Survey, MIS: Memory Impairment Screen, CSF: Cerebrospinal fluid. CVTL: California Verbal Learning Test, CAMDEX: Cambridge Mental Disorders of the Elderly Examination, TICS: Telephone interview of cognitive status, SF36: Short Form (36), CVD: Cardiovascular diseases, NSAIDs: Non-steroidal anti-inflammatory drugs, MRI: Magnetic resonance imaging, tHcy: Total Homocysteine, IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly, HVLT-DR: Hopkins Verbal Learning Test - Delayed Recall, CLOX: Clox-drawing test, WMS-R LM: Wechsler Memory Scale-Revised Logical Memory, DAD: Disability Assessment in Dementia Questionnaire, BPI: Brief Pain Inventory, CASI: Cognitive Abilities Screening Instrument, Aβ: β-amyloid peptide, DRS: Dementia Rating Scale, BDS: Blessed Dementia Scale, DPZ: Donepezil, Riv: Rivastigmine; WAIS: Wechsler Adult Intelligent Scale–Revised, APOE: Apolipoprotein E, EBS: Eating Behavior Scale, MNA: Mini Nutritional Assessment, NTB: Neuropsychological Test Battery, TMT: Trail Making Test, COWAT: Controlled Oral Word Association Test, LDST: Letter Digit Substitution Test, VR: Visual reproduction, RAVLT: Rey Auditory Verbal Learning Test, CDT: Clock drawing test, ADCS-CGIC: Alzheimer's Disease Cooperative Study - Clinician's Global Impression of Change, UPDRS: Unified Parkinson's Disease Rating Scale, BRSD: Behavior Rating Scale for Dementia, UMP: Uridine monophosphate, P-Tau: phosphor-tau, T-Tau: total tau, F2-IsoPs: F2-isoprostanes, BNT: Boston Naming Test, DSST: Digit Symbol Substitution Test. MDA: malondialdehyde. NIH/NIA: National Institutes of Health/National Institute of Aging.

4.3 Risk of bias assessment of included studies

The quality of single studies was independently evaluated by two authors using the Cochrane Risk of Bias Tool, as a criteria for judging each domain based on the information provided by the original papers and supplements (see Appendix 4), followed by a consensus meeting to define the ultimate assessment of bias for inclusion. The general grading of risk of bias summary of included studies is presented in graphs produced through the RevMan software (Figures 3 and 4).

Allocation (selection bias), random sequence generation and allocation concealment: Most studies indicated that randomization and allocation processes were performed and described in the method utilized; studies that do not report sufficient details were classified as unclear. Studies with 'inadequate' processes, according to the Cochrane, were graded as high risk of bias, and thus, excluded from the analysis. Random sequence allocation was appropriate for 60% [n= 21] studies and unclear for 40% [n= 14]. On the other hand, allocation concealment was appropriate for 28.6% [n= 10] studies and unclear for 71.4% [n= 25].

Blinding (performance bias), 60% [n= 21] of included studies described the method of blinding of both participants and personnel, those which just mentioned that the study was double blind controlled randomized were classified as unclear 40% [n= 14]. Non-blinded studies were excluded, due to, based in the assessment tool, the outcome is more likely to be influenced by the lack of blinding and consequently it might induce performance bias.

Blinding of outcome assessment (detection bias) were suitable in 37.2% [n= 13] and 62.8% [n= 22] were unclear.

Incomplete outcome data (attrition bias) revealed a high risk of bias in 2.9% [n= 1], a good number of studies were appropriate 80% [n= 28] and 17.1% [n= 6] unclear.

Selective reporting (reporting bias), to the publications found with selective reporting of results, the study authors were contacted to request the incomplete or missing information. Though some authors responded to our request and provided the data; however, in 17.1% [n= 6] studies, missing results could not be obtained due to lack of response by authors or decline in participation (one study), and therefore were classified as high risk of bias. Missing data in outcome measure was because either the outcome measure values were not published or the

means utilized to report results do not enable the extraction of values (for instance, graphs). In addition, 82.9% [n= 29] studies were adequate for this domain.

In other sources of bias, 91.4% [n= 32] studies were appropriate and 8.6% [n= 3] were unclear on account of the insufficient information to assess whether an important risk of bias existed.

Figure 3. Risk of bias graph

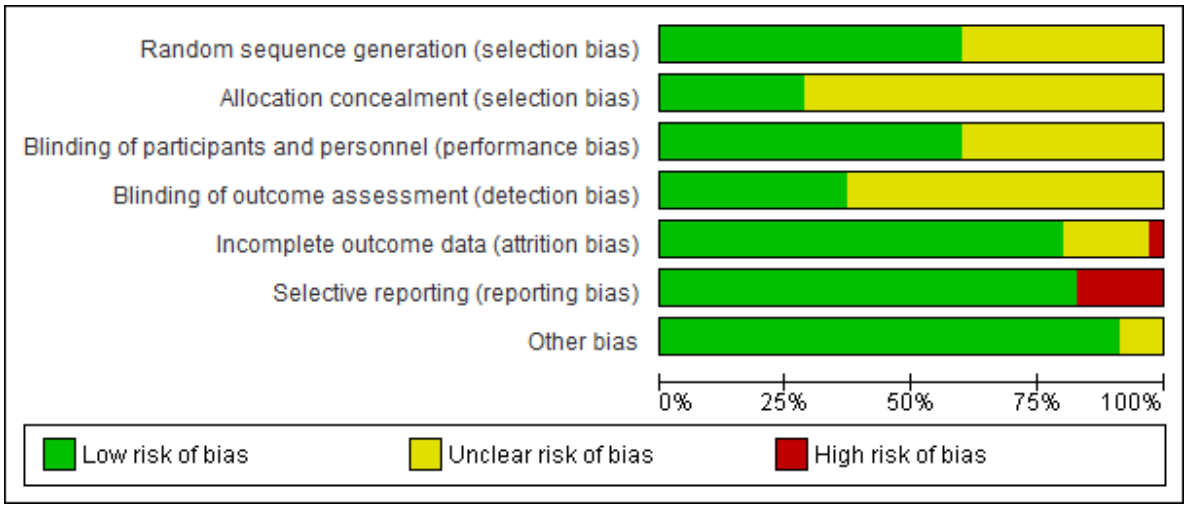
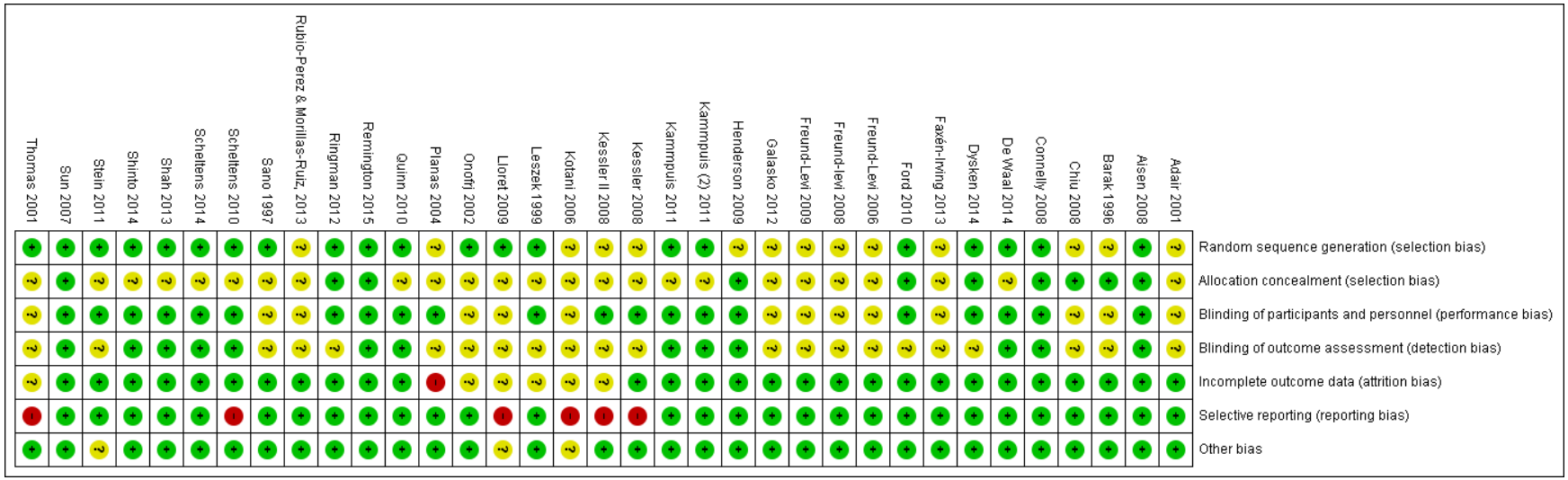


Figure 4. Risk of bias summary



4.4 OUTCOME MEASURES

From the included studies, the outcome with the higher number of measures was related to neuropsychological scales, especially for cognition and functional performance. In turn, outcome measures behavioral disturbances and global performance have few evaluations.

Fewer studies evaluating AD markers and biomarkers for oxidation and inflammation were found, and even less measuring brain structures. The following neuropsychological batteries were used to evaluate cognitive and mood performance on participants in included studies

4.4.1 Primary Outcomes

4.4.1.1 Assessment scales

4.4.1.1.1 Cognitive outcome measures

- Mini Mental State Examination (MMSE): a test used to measure cognitive aspects of mental functions. The total score ranges from zero to 30 points, where 30 is the least impaired. Commonly practitioner use cutoffs of 24-18 and 17-10 to estimate mild and moderate cognitive impairment, respectively. The test is divided into two sections; one of them evaluates orientation, memory and attention, and the other one evaluates naming, comprehension, repetition, concentration, and ability to create a sentence and to copy 2 intersecting polygons (219). A minimal important mean difference for the MMSE was defined in 3.72 (95% CI 3.50-3.95) points to interpret the clinical significance of the results of trials assessing the efficacy of AD therapy (220).
- Alzheimer's disease Assessment Scale - Cognitive Subscale (ADAS-cog): ADAS is a rating instrument that evaluates the severity of cognitive and non-cognitive behavioral dysfunctions characteristic of persons with AD. The cognitive subscale, 11-items form, assesses multiple domains including memory, language, praxis, and orientation, the total score range from zero to 70 points (48 for the first 9 items, and 22 for the last two items), where 70 is the most impaired. A clinically significant change have been considered since four-point difference between treatment groups (221,222). Albeit, a cutoff score has not been establish for dementia, a study showed a reliable and valid cutoff defined in $\geq$ 12

points (223). Since higher scores represent increased impairment, a negative score in change from Baseline represents an improvement in cognitive performance.

- Clock drawing test (CDT), a suitable and rapid screening assessment for dementia, appraises a small portion of cognitive dysfunction, wherein individuals ought to draw a clock with numbers and hands pointing at a requested time. Different variants of this test have been reported, still scoring methods are easily managed, e.g., the Shulman method ranges from one to six, higher score indicates worse performance; CLOX-1 scores range from 0–15, lower scores reflect greater impairment. (224,225).
- Cambridge Mental Disorders of the Elderly Examination (CAMDEX) focuses on the diagnosis of dementia, with particular reference to its mild forms and to the identification of specific types of dementia. It comprises a number of sections, where: Section A: patient's current physical and mental state; section B: cognitive examination (CAMCOG); section C: interviewer's observations patient's appearance; section D: physical examination; section E: laboratory and radiological investigations. The CAMCOG consists of 67 items with a maximum possible score of 107. Scores lower than 80 are considered indicative of dementia. The CAMDEX is primarily a diagnostic instrument and has not been used in psychopharmacological trials. Although the CAMCOG encompasses similar areas of cognition as those more widely used Alzheimer's Disease Assessment Scale, it has yet to be proven to be sensitive to changes affected by drug treatment (226).
- Neuropsychological Test Battery (NTB): a psychometric scale measures cognitive changes in patients with mild to moderate AD. NTB consists of 9 validated components evaluating memory and executive function domains. The memory domain comprises the Wechsler Memory Scale (WMS) visual immediate (score range, 0-18) and visual delayed (score range, 0-6), WMS verbal immediate (score range, 0-24) and verbal delayed (score range, 0-8), Rey Auditory Verbal Learning Test (RAVLT) immediate (score range, 0-105) and RAVLT delayed (score range, 0-30), composed of delayed recall and recognition performance. In addition, the WMS Digit Span (score range, 0-24); Controlled Word Association Test (COWAT) and Category Fluency Test (CFT) measure the executive function domain. The overall NTB score is a composite z score calculated

from the average of the resultant z scores for each of the 9 NTB components, higher scores are better (227).

4.4.1.1.2 Functional capacity outcome measures

- Activities of Daily Living scale (ADCS-ADL): assesses functional performance, activities that normal elderly regularly execute and may be relevant in patients with AD. It uses a structured interview of the study partner, including ADL necessary for personal care, communicating and interacting with other people, maintaining a household, conducting hobbies and interests, and making judgment and decisions. Score ranges from 0 (nonperformance or need for extensive help) to 78 (independent performance or less functional impairment) (228)
- The Barthel Index: this index assesses the functional ability for older people focused on ADL in 10 domains, possible score are from 0 to 100 higher is better (229).
- Instrumental Activities of Daily Living (IADL) assesses ability in eight complex daily living tasks such as telephone use, shopping, housekeeping and finances. These abilities are more complex than the more basic abilities of daily living, and therefore more sensitive to the cognitive changes seen in dementia (230). Ranges 0-6 mean intact functioning in ADL measured by the IADL (male: ≥4, female: ≥6),
- Disability Assessment for Dementia scale (DAD) assesses functional disability through the appraisal of the ability to perform basic self-care, instrumental and leisure activities in community-dwelling persons with dementia, suitable for research or clinical practice. Functional disability is defined as any restriction in the ability to perform an activity, a task, or any behavior of everyday life. Scores range from 0 to 46, higher scores indicates less disability (231).
- Blessed Dementia Scale (BDS): 22-items clinical rating scale divided in two parts IADL and basic ADL evaluating functional abilities, intermittent incapacity is given a half-point total scores range from 0 (preserved capacity) to 28 (extreme incapacity). The cognitive subscale, excludes personality questions (12–22), scores range from 0 (normal) to 17 (severe dementia) (232).

- The Nurses' Observation Scale for Geriatric Patients (NOSGER): a rating scale of the most frequent behavioral disturbances in geriatric patients. It evaluates six dimensions comprising 5 items: Mood, Disturbing behavior, Social behavior, Memory, ADL, and IADL. Each item account for 1 (always) to 5 (never) points. The total score ranges from 30 (no impairment) to 150 (greater impairment) (233).

4.4.1.1.3 Behavior disturbances outcome measures

- Neuropsychiatric Inventory (NPI): assesses the frequency and severity of ten behavioral domains (delusions; hallucinations; agitation/aggression; dysphoria; anxiety; euphoria; apathy; disinhibition; irritability/lability; and aberrant motor activity) in patients with dementia, through the use of screening questions. Range 0-144, where 144 is the most impaired (234).
- NOSGER Subscale Social Behavior (SB), measure impairment in disturbing behavior, rating is based on direct observation of daily behavior by the nurse/caregiver over a two-week period. Number of points possible 25 where lower is better, pathological score >8 in women and >9 in men (235).
- Behavior Rating Scale for Dementia (BRSD): an instrument to measure the incidence and severity of psychopathological behavior in persons with dementia or cognitive impairment, based on information from an informant with good knowledge of the patient. In 11 of the 37 items rating the severity of the symptoms, the rating of frequency on a 5-point scale ranges from 0 (no occurrence since the onset of the disease) to 4 (occurrence over half of the month's days). Subscale ratings are for all 45 items summed for obtaining total score (item 46 is not scored), ranging from 0 to 167, where the higher number indicates worse performance (236).

4.4.1.1.4 Global impression outcome measures

- Clinical Dementia Rating Scale (CDR): is a clinical staging assessment of global performance in subjects with dementia, using structured interviews of the participant and a study partner. It rates the subject on the six following cognitive and behavioral domains: memory, orientation, judgment and problem solving, community affairs, home and

hobbies, and personal care. Rating patients as non-demented (CDR 0), questionable dementia (CDR 0.5), mild (CDR 1), moderate (CDR 2), or severe dementia (CDR 3). (237).

- CDR Sum of boxes (CDR-sob) version is derived from the scores in each of the six former domains ("box scores"), it measures the severity of dementia based on caregiver accounts of problems in daily functional and cognitive tasks and ranges from 0 to 18, where 18 is the most impaired (238).
- Clinician Interview Based Impression of Change plus Caregiver Input (CIBIC-plus) is an exhaustive global measure of detectable change in cognition, function and behavior, usually requiring separate interviews with patients and caregivers. It is an appealing instrument for assessing progression, but may take long time to apply and requires a trained clinician (239). Scoring consists in a 7-point Likert-type scale, in which 1 represents improved; 4, no change; and 7, worse.

The different cognitive domains measured by the psychometric scales are specified in Table 5. Other scales least used in trials included in the systematic review but not included in the meta-analysis due to the fact of being an alternative scale measuring the same outcome; or even due to reporting bias:

Measures of cognition

- Letter Digit Substitution Test (LDST)
- Wechsler Memory Scale (WMS)
- Wechsler Adult Intelligence Scale (WAIS)
- Cognitive Test Battery
- Rey Auditory Verbal Learning Test (RAVLT)
- Dementia Rating Scale 2 (DRS-2)
- Isaacs Set Test
- California Verbal Learning Test (CVLT)
- Digit Cancellation Test,
- Digit span
- Digit Symbol Substitution Test (DSST)
- VR visual reproduction

- Cognitive Abilities Screening Instrument (CASI)

Measures of global performance

- AD Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC)

The following scales, in spite of the importance on measuring these outcomes to evaluate the disease progress, were found just once in the very few studies:

Measures of dependence

- Dependence Scale: rates the need for supervision and care, assesses functional dependence.

Measures of caregiver burden

- CGB [Emotional overload, Economic overload, Captured in a role]
- Caregiver Activity Survey (CAS)

Measures of quality of life

- Quality of Life in Alzheimer's disease
- Quality of life (Short Form [SF]–36)

Measures of eating disorders

- Blandford scale

Table 5. Domains assessed in the most common psychometric scales in dementia

	MMSE	ADAS-cog	ADL	NPI	CDR	IADL	DAD	NBT
Attention	X	X						
Calculation	X							
Community affairs					X			
Executive function								X
Home & hobbies					X			
Judgment problem solving					X			
Language	X	X						
Memory	X	X			X			X
Neuropsychiatric disturbances				X				
Orientation	X	X			X			
Personal care/functional performance			X		X	X	X	
Praxis		X						
Reasoning		X						
Recall	X							
Registration	X							

4.4.1.2 Brain imaging outcome measure

- Volumetric Magnetic Resonance Imaging (MRI): Structural and functional imaging are valuable diagnostic methods of AD, implemented to determine differences in brain morphometry between controls and demented elderly, mainly for neuroanatomical degeneration (cerebral atrophy). Based on the physiopathology of AD in this quantitative image-based volume measurement the primary neuroanatomical structures of interest are medial temporal lobe limbic structures (hippocampal formation, amygdala, and parahippocampal gyrus) (240,241).
- Electroencephalogram (EEG), a procedure to measure the electrical activity of the brain reflecting synaptic activity, probably involved in cognitive processing. This method has been used as a helpful tool in the diagnosis of AD (242). EEG signal analysis allows the construction of functional networks and has benefit in studies of subjects suffering from cognitive problems (243).
- P300 (P3) is an electrophysiological technique that allows analyzing the association between CNS function and age-related changes. P3 is a component of the event-related brain potentials (ERPs), measured by quantifying the amplitude (size) and latency (timing), which is thought to result from neural activity associated with attentional and memory processes. The latency reflects the time processing before the response occurs, shorter latencies reflects faster processing speed, meaning greater cognitive performance (244).

4.4.2 Secondary Outcomes

4.4.2.1 Biomarker measures related to AD

- Aβ42: the 42 amino acid form of Aβ peptide is a biochemical marker found in the cerebrospinal fluid (CSF), reflecting the key pathogenic process and a worthwhile tool for clinical workup of AD. The variants for Aβ encompass their N- or C-terminal shorter form Aβ1-39 (ending at Val-39) or Aβ1-40 (ending at Val-40) and the longer form Aβ1-42 (ending at Ala-42); this last one is the more toxic and susceptible to aggregation, but also the major form of Aβ in the brain. CSF-Aβ42 levels are altered as the dementia severity progresses, and patients with AD have low levels of this biomarker (245). In turn,

plasma Aβ1-40 and Aβ1-42 levels may be increased (246). Cutoff Aβ42 for 85% sensitivity in identified as 550 ng/L (95% CI 531–570) and 83% specificity (95% CI 76–89) (247)

- Total Tau (t-Tau) and phosphorylated Tau (P-tau) proteins: CSF t-tau and p-tau levels are supportive biomarkers for the diagnosis and differentiation of AD from other neurodegenerative disorders, as well as the identification of those at high risk for AD and MCI, and as indicators of disease progression and response to treatments. There are six different isoforms and numerous phosphorylation sites of tau protein in the human brain. Tau expression is elevated in non-myelinated cortical axons, particularly in the limbic cortex region including the hippocampus, and is the first protein that will be released into the CSF and their levels maybe reveal the severity of neuronal degeneration. Thus, Tau is thought to be a possible potential measurement for Alzheimer-type axonal degeneration and NFT formation (248–250). Evidences show a relationship of low Aβ42 and high Tau in CSF levels of AD patients (251,252). CSF t-tau cutoff for 85% sensitivity 375 ng/L (95% CI 325–405) and 78% specificity (95% CI 70–85), CSF p-tau Cutoff for 85% sensitivity 52 ng/L (95% CI 48–56) 68% specificity (95% CI 60–77) (247).

4.4.2.2 Inflammation/ Oxidative stress biomarkers

- Cytokines: Pro-inflammatory cytokines are produced by activate macrophages and take part in up-regulation of inflammatory reactions. Some of the more frequently found in plasma were IL-1β, IL-6, and TNF-α (cachectin). Chemokines inducing chemotaxis: IL-8 (GRO/kc), Lymphotactin, Fractalkine, MCP-1, MIP-1α, MIP-1β, Rantes. Anti-inflammatory cytokines are immunoregulatory molecules that regulate the pro-inflammatory cytokine's response. Their physiologic role in inflammation and pathologic role in systemic inflammatory states are increasingly recognized: IL-1 (receptor antagonist), IL-4, IL-10, IL-11, IL-13. Cytokines categorized as anti-inflammatory or pro-inflammatory under various circumstances: Leukemia inhibitory factor, INF-α, IL-G, TGF-β. Function as inhibitor for pro-inflammatory cytokines: Specific cytokine receptor for IL-1, TNF-α (253). The inflammatory response occurring in the AD revealed by a higher peripheral concentrations of cytokines, particularly IL-6, TNF- α, IL-1β, TGF-β, IL-12 and IL-18 and higher CSF concentrations of TGF-β (254).

- F_2-isoprostanes (F_2-IsoPs): a series of prostaglandin F_2-like compounds derivate from the peroxidation of arachidonic acid, a free radical-generating reaction catalyzed by the cyclooxygenase enzyme. F_2-IsoPs CSF levels, a measure of lipid peroxidation to quantify oxidative damage, have been found as considerably high in AD patients compared with control subjects, signifying a useful tool to determine oxidative damage in the CNS (255).

- High sensitive C-reactive protein (Hs-CRP) is a nonspecific acute-phase hepatic protein used as a more sensitive marker of systemic inflammation, infection, and tissue damage, some data associate its high levels (>3 mg/dl) with increased risk of cerebrovascular, neurodegenerative diseases and impaired cognition. The evidence shows that serum hs-CRP levels have been found considerably augmented in patients with AD compared to healthy controls (256–258).

Other biomarkers merely assessed by one study not comparable among them: Transthyretin, Malondialdehyde, Oxidized glutathione (GSSG)

4.5 INTERVENTION EFFECTS

Pair-wise and network meta-analyses were undertaken for the different nutrition interventions –classified in eight categories: antioxidants (single and composite), carbohydrates, lipids, polymeric formula, polypeptide, omega 3 fatty acid, B-vitamins complex and vitamin D – assessing the change on the above related outcomes over the treatment duration from the baseline, all included studies are graded as low or unclear risk of bias. As describe in methods, the main neuropsychological outcome measures analyzed and plotted correspond to the most used assessment scales in studies within the same nutrient intervention, the MMSE for cognition, the ADCS-ADL for functional capacity, the NPI for behavioral disturbances and the CDR-sob for global performance.

Studies with missing data not provided by authors (193,259,259–261) or evaluating similar outcomes in the same population and intervention were excluded from analysis (199,213,215). Data analyses show the following results.

4.5.1 PAIR-WISE META-ANALYSIS

4.5.1.1 Antioxidants

Eight studies using nutrient interventions associated to antioxidant function were classified in this category. In turn, this category was divided into two branches, single antioxidants and composite antioxidants, this last one for treatments using more than one nutrient. Interventions included in the meta-analysis are summarized in Table 6, all of them compared with placebo. The first analysis evaluated the single antioxidant effect of curcumin, vitamin E, co-enzyme Q, selenium and N-acetylcysteine on cognitive outcome measures, evaluated by using the MMSE, in a sample size of 270 in experimental and 304 in placebo group of probable AD patients from mild-to-moderate to unspecified stage. The pooled effect in a random model was -0.00 [95% CI -0.85, 0.84] Z = 0.01 (p = 0.99), which means a non-significant or null response across trials pointing out to opposite directions (Figure 5a, 6a). The analysis presented a moderate heterogeneity I^2 = 46%; Chi^2 = 11.14, df = 6 (p = 0.08), which may be attributed to the intervention variability in trials duration, type of compound and dosage, due to the different biological and physiological mechanism of each compound, regardless their antioxidant function. Results did not change after a sensitivity analysis using only vitamin E trials intervention, where

overall effect was-0.16 [95% CI -1.06, 0.75], Z = 0.34 (p = 0.73). Individual results of vitamin E trials did not match among them; treatment effects point to different directions, while one study was beneficial, the other showed no effect and the third was deleterious, which may explain the moderate heterogeneity of the sensitivity analysis I^2 = 44%; Chi^2 = 3.56, df = 2 (p= 0.17).

In the functional capacity measured in four studies with the ADCS-ADL scale, with changes evaluated at 4 and 6 months, and sample size of 192 in intervention and 191 in placebo group; there was no significant effect favoring antioxidants 0.43 [95% CI -2.06, 2.92], Z = 0.34 (p = 0.73). Included trials presented a moderate heterogeneity I^2 = 52%; Chi^2 = 6.25, df = 3 (P = 0.10), as well as in cognitive outcome (Figure 5b, 6b). Analysis of behavioral disturbances using the NPI scale in two studies, did not show significant trend toward active treatment on change at 6 months -2.04 [95% CI -4.90, 0.82] Z = 1.40 (p = 0.16) (Figure 5c, 6c). Despite the variability of interventions (curcumin 4 mg and vitamin E 2000 IU), in this case there was not found significant heterogeneity I^2 = 0%; Chi^2 = 0.73, df = 1 (p = 0.39).

In the second analysis, the examination of composite antioxidants, α-lipoic acid, omega-3, selegiline, and vitamins C and E, with 120 participants in the active group and 114 in the placebo group, no effect on cognition was found 0.10 [95% CI -2.34, 2.54]. Test for overall effect: Z = 0.08 (p = 0.93) by MMSE (Figure 7, 8). It was found a considerable heterogeneity among studies I^2 = 81%; Chi^2 = 10.44, df = 2 (p = 0.005); evidently explained by the variability of components, dosage and trial duration. One study assessing the effect of vitamin E and selegiline in behavioral outcome measured with the Behavioral Rating Scale of Dementia in a sample size of 158 subjects revealed a statistically significant effect of -10.00 [95% CI -13.59, -6.41] Z = 5.45 (p< 0.00001). The use of different scales to measure functional capacity does not allow undertaking meta-analysis. Outcomes evaluating global performance were not obtained. Most reported adverse events that appeared during the course of studies were not relevant neither were judged to be associated with study treatments. Co-intervention with medication was not informed.

There were not found any difference between single antioxidant intervention (n=28) and placebo (n= 32) group in biomarkers. CSF levels of Aβ-42 (-4.10 [95% CI -19.90, 11.69], Z = 0.51 (p = 0.61)); T-tau (2.55 [95% CI -8.80, 13.90], Z = 0.44 (p = 0.66)); P-tau (-0.70 [95% CI -7.79, 6.39], Z = 0.19 (p = 0.85)); or F2-isoprostanes (2.67 [95% CI -4.00, 9.33], Z = 0.78 (P = 0.43)). One study measured inflammatory markers IL-6 (0.29 [95% CI -4.89, 5.47], Z = 0.11 (p =

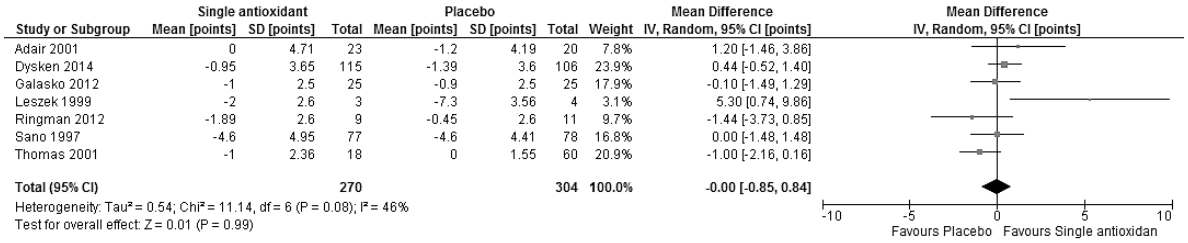
0.91)), TNF-α (-0.05 [95% CI -0.66, 0.56], Z = 0.16 (p = 0.87)). Therefore, none of those measures presented any significance.

Table 6. RCTs examining antioxidants included in the meta-analysis

Study	Severity of disease	Arms	Dosage	Outcome measures analyzed	Timepoint-change	Category
Ringman et al, 2012	Mild-to-moderate probable AD	Curcumin	2 mg	MMSE	24 weeks	Single
		Curcumin	4 mg	ADL, NPI, biomarkers		
Shinto et al, 2014	Probable AD	Lipoic acid + Omega 3	600 mg/day + 3 gr/day	MMSE	12 months	Composite
Dysken et al, 2014	mild to moderate probable AD	α-tocopherol	1000 IU twice/day	MMSE	12 months	Single
				ADL, NPI	6 months	
Galasko et al, 2012	mild to moderate probable AD	α-tocopherol + vitamin C + α-lipoic acid	800 IU + 200 mg + 600 mg 3 times/day	MMSE	16 weeks	Composite
		Coenzyme Q	800 mg 3 times/day	MMSE, ADL, biomarkers	16 weeks	Single
Sano et al, 1997	moderate probable AD	Selegiline	5 mg twice/day	-	months	Single
		α-tocopherol	1000 IU twice/ day	MMSE	15.6 months	
		Selegiline + α-tocopherol	5 mg + 1000 IU twice/day	MMSE	15.6 months	Composite
Leszek et al, 1999	probable mild AD	Selenium	100 mg	MMSE	Approx. 1 year	Single
Thomas et al, 2001	probable AD	Vitamin E	2000 IU single dose	MMSE	6 months	Single
Adair et al, 2001	probable AD	N-acetylcysteine	50 mg/kg/day	MMSE, ADL	6 month	Single

Figure 5. Random-effects meta-analysis of data on effects of single antioxidants compared to placebo on outcome measures in patients with AD.

a.



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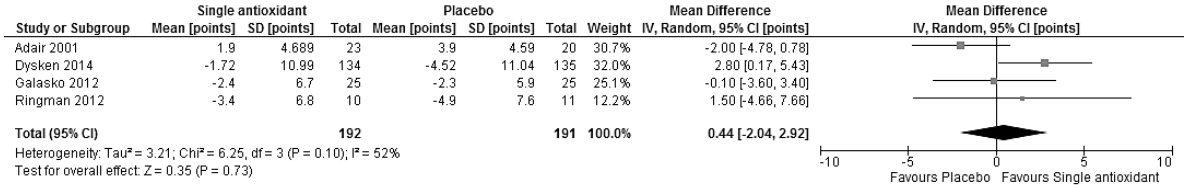

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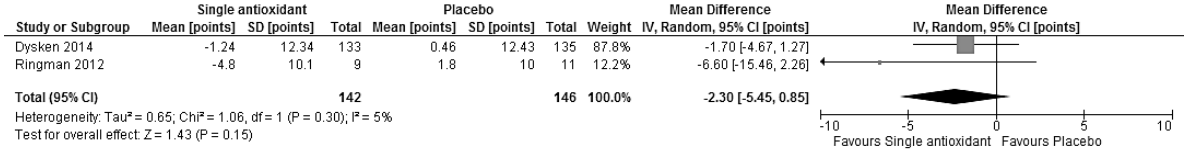
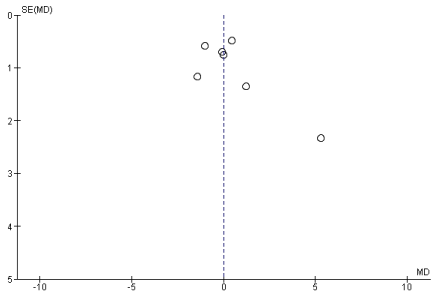


Forest plots. The overall effect size was estimated by the MD. Dark square sizes represent weights of studies in the meta-analysis. The horizontal lines represent 95% CIs. The vertical line represents the line of no effect. Diamonds represent overall pooled estimates of effects of dietary interventions on cognition measured with MMSE. (a) Cognitive; (b) functional (c) behavioral. IV, inverse variance.

Figure 6. Publication bias in antioxidant interventions on outcome measures

a.



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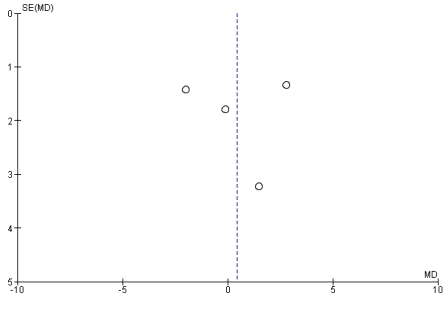
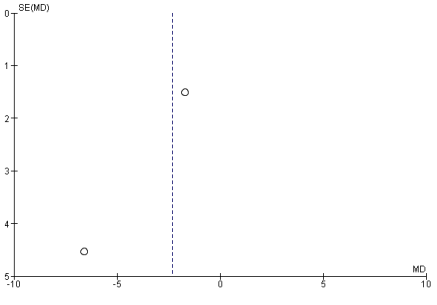
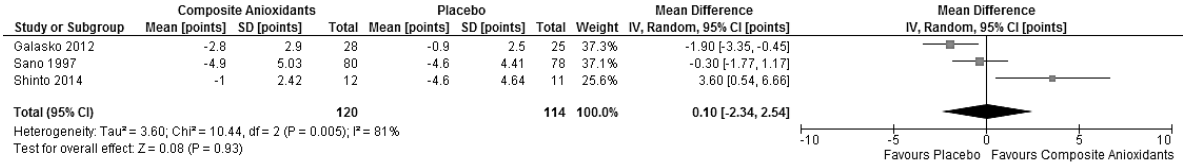


c.



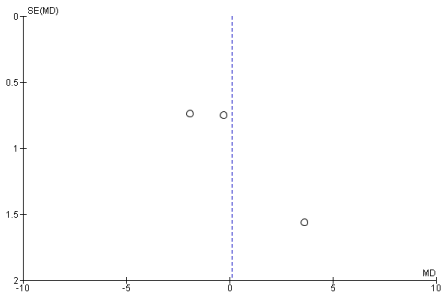
Funnel plots. Intervention effect estimates from individual studies on the horizontal scale (MD), and the measure of study size on the vertical axis (SE). (a) Cognitive; (b) functional; (c) behavioral.

Figure 7. Random-effects meta-analysis of data on effects of composite antioxidants compared to placebo on cognitive outcome in patients with AD.



Forest plots. The overall effect size was estimated by the MD. Dark square sizes represent weights of studies in the meta-analysis. The horizontal lines represent 95% CIs. The vertical line represents the line of no effect. Diamonds represent overall pooled estimates of effects of dietary interventions on function. IV, inverse variance.

Figure 8. Publication bias in composite antioxidants on cognition



Funnel plots. Intervention effect estimates from individual studies on the horizontal scale (MD), and the measure of study size on the vertical axis (SE).

4.5.1.2 B-Vitamins Complex

We identified B-group vitamins supplementation in four studies (Table 7), three of them in co-intervention with AChE-Is and memantine, performed in sample size of 436 intervention and 355 placebo groups; these studies were explored on cognitive status in the MMSE change at 6 months. A statistically significant benefit was detected in the pooled WMD 0.44 [95% IC 0.09, 0.79] Z = 2.44 (P = 0.01) with low heterogeneity I^2 = 0%; Chi^2 = 1.54, df = 3 (p = 0.67) (Figure 9a, 10a). To confirm this data in a more specific way, we conducted a sensitivity analysis excluding the trial without a well-defined AD diagnosis (207), since it may incur in a variability in the clinical condition of the sample population, which also was the only one study which did not report use of AD medication. There was still an important tendency favoring B-vitamins intervention 0.52 [95% CI -0.05, 1.09] Z = 1.79 (P = 0.07) with no heterogeneity I^2 = 0%.

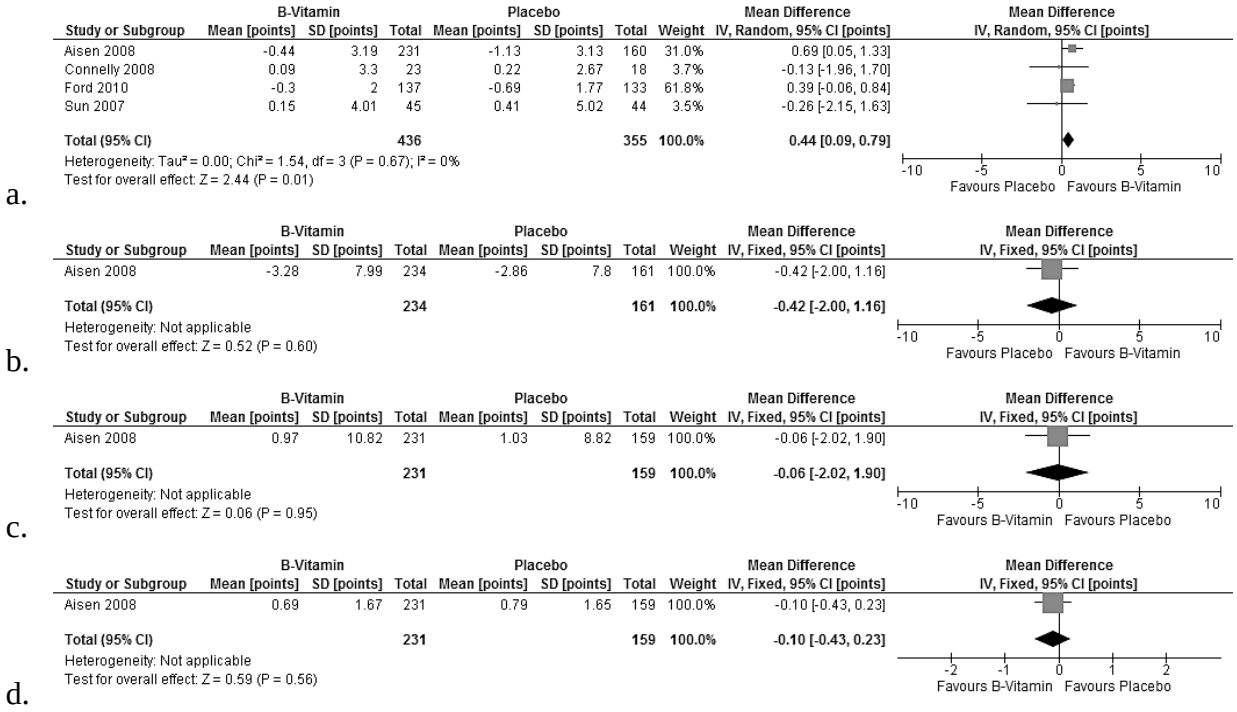
There were no found enough evidence for functional performance behavior, disturbances and global clinical state assessed by the ADCS-ADL, NPI and CDR-sob, respectively. A single study with 395 participants; these few data do not support significant results for none of the outcomes: function (-0.42 [95% CI -2.00, 1.16], Z = 0.52 (p = 0.60)) (Figures 9b, 10b), behavior (-0.06 [95% CI -2.02, 1.90], Z = 0.06 (p = 0.95)) (Figure 9c, 10c) and global performance (-0.10 [95% CI -0.43, 0.23], Z = 0.59 (p = 0.56)) (Figure 9d, 10d).

Table 7. Studies with B-vitamins complex included in meta-analysis

Study	Severity of disease	Arms	Dosage	Outcome measures analyzed	Time point-change
Ford et al, 2010	Cognitive impairment and dementia	B12 + folic acid + B6	400 µg + 2 mg + 25 mg/day	MMSE	6 months
Sun et al, 2007	mild to moderate AD	B-complex + multivitamin supplement[1]	0.5 mg	MMSE	26 weeks
Connelly et al, 2008	probable AD	folic acid	1 mg/day	MMSE	6 months
Aisen et al, 2008	probable AD	folic acid + vitaminB12	5mg/d + 1mg/d	MMSE, ADL, NPI, CDR-sob	6 months

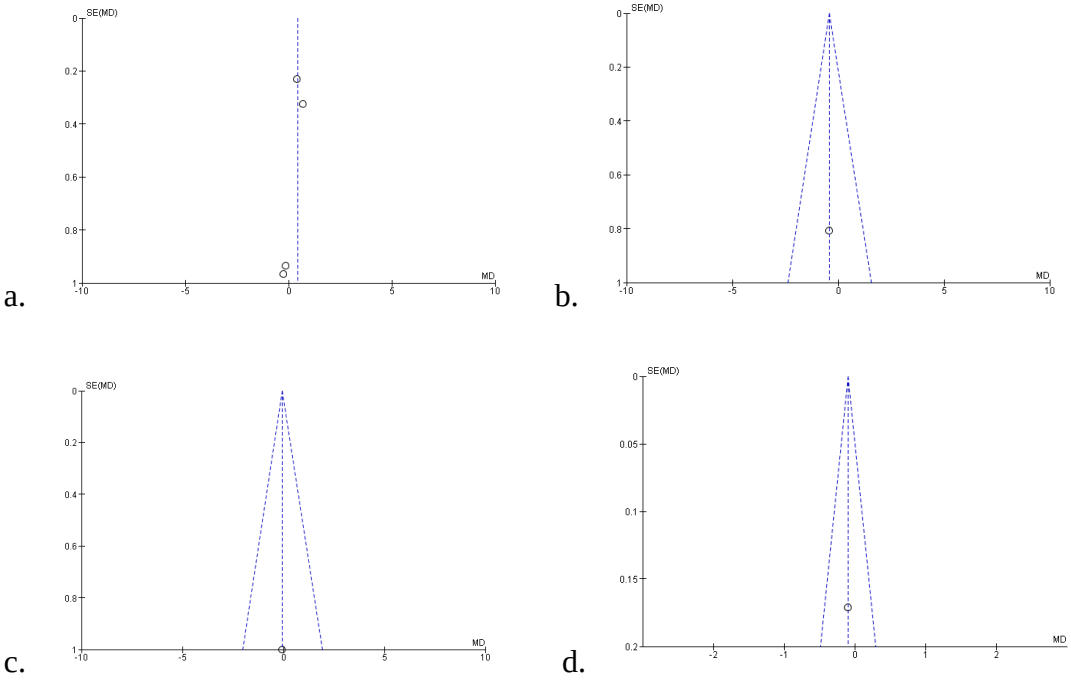
[1] Mecobalamin (B12 form) 0.5 mg, folic acid 5 mg and pyridoxine HCl 5 mg. The multivitamin supplement contained iron ferrous 60 mg, nicotinamide 10 mg, calcium carbonate 250 mg, riboflavin 2 mg, thiamine mononitrate 3 mg, calcium pantothenate 1 mg, ascorbic acid 100 µg, iodine 100 µg, copper 150 µg, vitamin B12 3 µg, vitamin A 4000 IU, and vitamin D3 400 IU.

Figure 9. Random-effects meta-analysis of data on effects of B-vitamin complex compared to placebo on outcome measures in patients with AD.



Forest plots. The overall effect size was estimated by the MD. Dark square sizes represent weights of studies in the meta-analysis. The horizontal lines represent 95% CIs. The vertical line represents the line of no effect. Diamonds represent overall pooled estimates of effects of dietary interventions on cognition measured with MMSE. (a) Cognitive; (b) functional; (c) behavioral; (d) global. IV, inverse variance.

Figure 10. Publication bias in B-vitamin complex on outcome measures



Funnel plots. Intervention effect estimates from individual studies on the horizontal scale (MD), and the measure of study size on the vertical axis (SE). (a) Cognitive; (b) functional; (c) behavioral; (d) global.

4.5.1.3 Carbohydrates

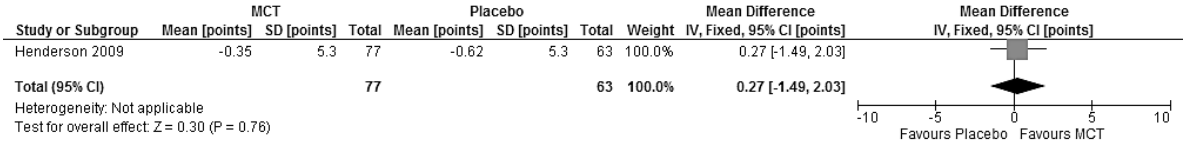
A double blind crossover trial with Inositol, 6 mg/day (n= 11) for 4 weeks, compared to glucose as placebo, evaluated cognitive abilities measured by the CAMDEX cognitive subscale, CAMCOG, in AD patients at different stages (218), revealed no significant total improvement in favor of treatment intervention overall effect 5.36 [-14.92, 25.64], Z = 0.52 (p= 0.60). Only in the stratification by domains, treatment intervention revealed a significant improvement in language and orientation ($P < 0.05$). No other medications were permitted in this trial. Harmful side effects were not reported.

4.5.1.4 Lipids

A 90-days treatment RCT with a ketogenic agent (n= 140), 10 grams of a Medium-chain triglyceride (MCT) of glycerin and caprylic acid (AC-1202), in mild to moderate AD patients had no significant effects on cognition assessed by MMSE at 104 days, two weeks following the last product administration. The pooled WMD was 0.27 [95% CI -1.49, 2.03], Z = 0.30 (p = 0.76) in a fixed effect model analysis (Figure 11, 12). In this trial, supplementation was provided in

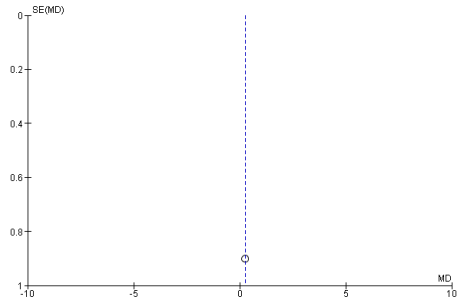
conjunction with AD medication, the most common adverse event reported corresponds to gastrointestinal events in both groups.

Figure 11. Random-effects meta-analysis of data on effects of medium chain triglycerides compared to placebo on cognitive outcomes in patients with AD.



Forest plots. The overall effect size was estimated by the MD. Dark square sizes represent weights of studies in the meta-analysis. The horizontal lines represent 95% CIs. The vertical line represents the line of no effect. Diamonds represent overall pooled estimates of effects of dietary interventions on cognition measured with MMSE. IV, inverse variance.

Figure 12. Publication bias in medium chain triglycerides on cognition



Funnel plots. Intervention effect estimates from individual studies on the horizontal scale (MD), and the measure of study size on the vertical axis (SE).

4.5.1.5 Omega 3

Interventions with omega 3 fatty acid, summarized in Table 8, ranging from larger to lower doses of EPA and DHA, with a mean of 663.75±422.72 mg and 903.75±552.38 mg respectively, from algal-derived or fish oil source, in AD patients, lasting above 6 months, showed no significant effects in any outcome. Four studies, with sample size of 355 in omega 3 group and 272 in control group, measuring cognition evaluated by MMSE, had a null overall effect -0.00 [95% CI -0.62, 0.62], Z= 0.01 (P = 0.99) with low heterogeneity I^2 = 0%; Chi^2 = 2.32, df = 3 (p = 0.51) (Figure 13a, 14a). One study (n= 308) using the ADCS-ADL scale displayed no treatment effect in functional capacity 1.08 [95% CI -1.72, 3.88], Z= 0.76 (p = 0.45) (Figure 13b, 14b). Behavioral disturbance outcome was assessed by two studies (n= 479) that also failed to demonstrate an effect -0.33 [95% CI -4.29, 3.63] Z = 0.16 (p = 0.87) with the NPI scale (Figure 13c, 14c). In this outcome we found a moderate heterogeneity between studies I^2 =

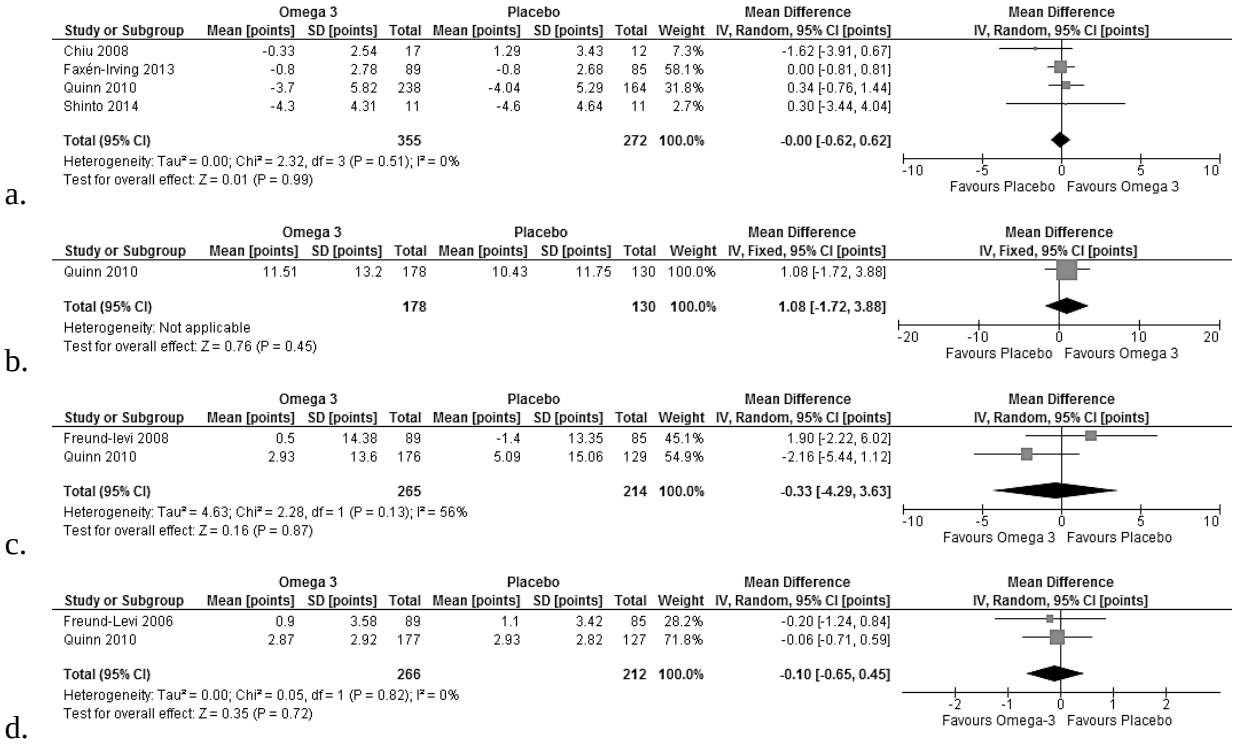
56%; Chi^2 = 2.28, df = 1 (p = 0.13). Probably this variability was attributed to substances of intervention, time point and dosage. One study used DHA and EPA at higher amounts and shorter duration, whereas the other study only use DHA at lower doses and extended duration of 6 months of difference. This heterogeneity was not detected in the cognitive outcome; it may be lessened by the inclusion of the other two studies using similar intervention, both DHA and EPA. Two studies provide data for assessing global performance with the CDR-sob, which were insufficient to observe a significant influence in this outcome (-0.10 [95% CI -0.65, 0.45], Z = 0.35 (p = 0.72); Heterogeneity I^2 = 0%, Chi^2 = 0.05, df = 1 (p = 0.82)) (Figure 13d, 14d).

One study found no significant differences in AD biomarkers between omega-3 and placebo Aβ1-42(9.10 [-51.94, 70.14], Z = 0.29 (P = 0.77)), T-tau (104.70 [95% CI -89.06, 298.46], Z = 1.06 (P = 0.29)), P-tau (11.00 [95% CI -9.80, 31.80], Z = 1.04 (P = 0.30)). Neither on inflammatory biomarkers hs-CRP (-0.40 [95% CI -1.86, 1.06], Z = 0.54 (P = 0.59)), IL-6 (-0.30 [95% CI -0.93, 0.33], Z = 0.94 (P = 0.35)), TNF-α (3.50 [95% CI -132.78, 139.78], Z = 0.05 (P = 0.96)).

Table 8. Studies with omega 3 included in meta-analysis

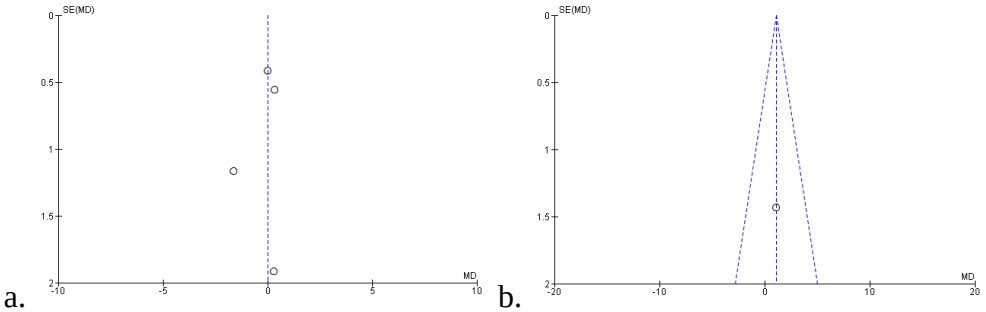
Study	**Severity of disease**	**Arms**	**Dosage**	**Outcome measures analyzed**	**Timepoint-change**
Faxén-Irving et al, 2013	Mild to moderate AD	DHA-EPA	4 g/day	MMSE	6 months
Freund-Levi et al, 2006	Mild to moderate AD	DHA-EPA	4 g /day	CDR-sob	6 months
Freund-Levi et al, 2009	Mild to moderate AD	DHA-EPA	4 g/day	Biomarkers	6 months
Freund-levi et al, 2008	Mild to moderate AD	DHA-EPA	4 g/day	NPI	12 months
Quinn et al, 2010	Mild to moderate AD	DHA	2 g/day	MMSE, ADL, NPI, CDR-sob	18 months
Shinto et al, 2014	Probable AD	DHA-EPA	3 gr/day	MMSE	12 months
Chiu et al, 2008	Mild or moderate AD, Amnesic MCI	DHA-EPA	3 capsules twice/day	MMSE	24 weeks

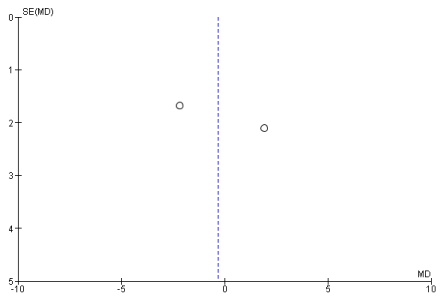
Figure 13. Random-effects meta-analysis of data on effects of omega-3 compared to placebo on outcome measures in patients with AD.

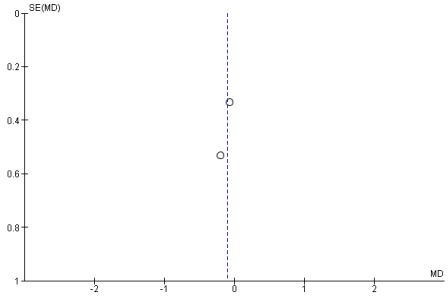


Forest plots. The overall effect size was estimated by the MD. Dark square sizes represent weights of studies in the meta-analysis. The horizontal lines represent 95% CIs. The vertical line represents the line of no effect. Diamonds represent overall pooled estimates of effects of dietary interventions on cognition measured with MMSE. (a) cognitive; (b) functional; (c) behavioral; (d) global. IV, inverse variance.

Figure 14. Publication bias in omega-3 on outcome measures



c. 

d. 

Funnel plots. Intervention effect estimates from individual studies on the horizontal scale (MD), and the measure of study size on the vertical axis (SE). (a) cognitive; (b) functional; (c) behavioral; (d) global.

4.5.1.6 Polymeric formula

Two studies using polymeric formula in mild to moderate AD patients, evaluated cognitive status through the MMSE changes at 3 and 6 months. The sample size (n=237) had a non-significant trend toward treatment intervention, with WMD of 0.33 [95% CI -0.53, 1.19], Z = 0.76 (P = 0.45) manifesting low heterogeneity: I^2 = 0%; Chi^2 = 0.31, df = 1 (P = 0.58) (Figure 15a, 16a). Three studies with low heterogeneity: I^2 = 0%; Chi^2 = 0.12, df = 2 (p = 0.94) completed a sample size of 377 in the active and 356 in control group were not able to demonstrate an effect on functional performance 0.06 [95% CI -1.39, 1.50], Z = 0.08 (P = 0.94) measured by ADCS-ADL (Figure 15b, 16b). One study analyzed behavioral disturbances (n=49 in active n= 34 control) by the NPI -2.80 [95% CI -31.07, 25.47], Z = 0.19 (P = 0.85) (Figure 15c, 16c), and other assessed global performance (n=226 in active n= 222 control) using the CDR-sob scale 0.08 [95% CI -0.28, 0.44], Z = 0.44 (P = 0.66) (Figure 15d, 16d). These studies were also unsuccessful in obtaining significant results. Studies did not reported serious adverse events that were unrelated to study products, with no important differences in the incidence of adverse events between groups over the trial duration. Only one study reported consumption of AChE-Is and/or memantine. Table 9 summarizes the studies with polymeric formulas.

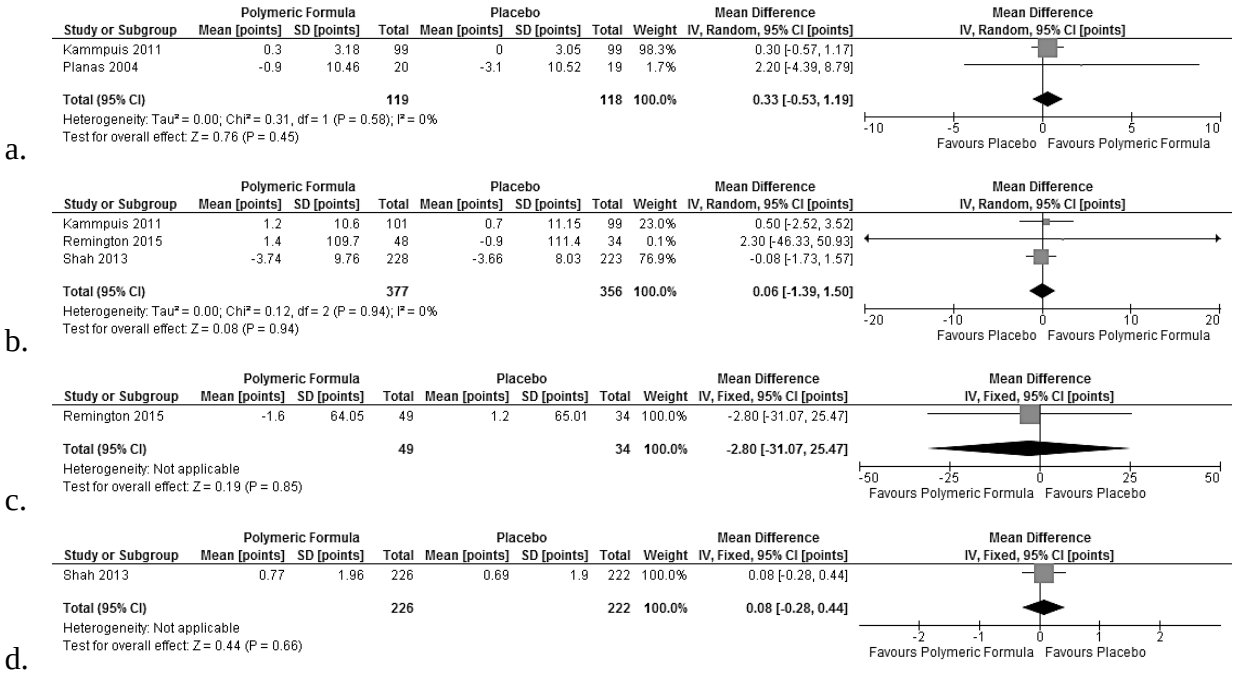
Table 9. Studies with polymeric formulas included in meta-analysis

Study	Severity of disease	Arms	Dosage	Outcome measures analyzed	Timepoint-change
Kammpuis, et al, 2011	mild AD	Fortasyn Connect[1]	125 ml/day	MMSE, ADL	12 weeks
Shah et al. 2013	probable AD	Fortasyn Connect[1]	125 ml/day	ADL, CDR-sob	24 weeks
Planas et al 2004	probable AD	Energy dense and	250 ml twice/day	MMSE	6 months

		protein-rich liquid supplement[2]			
Remington et al, 2015	moderate to late-stage AD	Nutraceutical formulation[3]	2 tablets/day	ADL, NPI	3 months

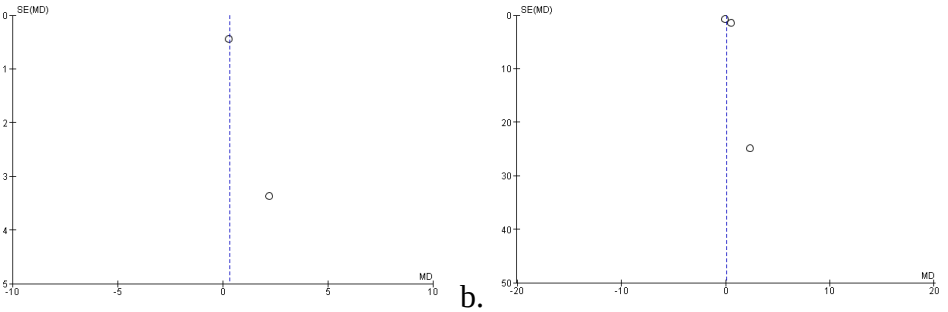
[1] EPA 300 mg, DHA 1200 mg, Phospholipids 106 mg, Choline 400 mg, UMP (uridine monophosphate) 625 mg, Vitamin E (alpha-TE) 40 mg, Vitamin C 80 mg, Selenium 60 µg, Vitamin B12 3 µg, Vitamin B6 1 mg, Folic acid 400 µg,
[2] Alpha-tocopherol (mg) 38, Vitamin C (mg) 250, Vitamin B12 (mg) 1.5, Folate (mg) 200, Zinc (mg) 10, Copper (mg) 1.500, Manganese (mg) 3, Whey protein 15(% of protein content), Arginine (g) 3.5, total: 500 kcal/day, as 45% carbohydrates, 25% fat, and 30% proteins.
[3] 400 g folic acid, 6 g B12, 30 I.U. alpha-tocopherol, 400mg SAM (200mg active ion), 600 mg NAC, and 500 mg ALCAR.

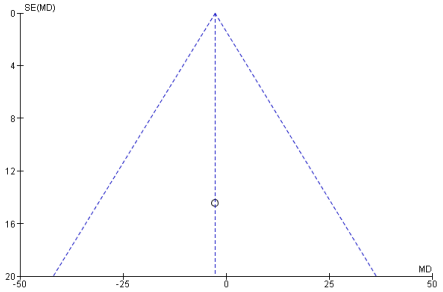
Figure 15. Random-effects meta-analysis of data on effects of polymeric formulas compared to placebo on cognitive outcomes in patients with AD.

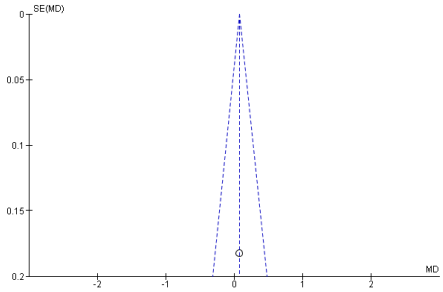


Forest plots. The overall effect size was estimated by the MD. Dark square sizes represent weights of studies in the meta-analysis. The horizontal lines represent 95% CIs. The vertical line represents the line of no effect. Diamonds represent overall pooled estimates of effects of dietary interventions on cognition measured with MMSE. (a) cognitive; (b) functional; (c) behavioral; (d) global. IV, inverse variance.

Figure 16. Publication bias in polymeric formulas on outcome measures



c. 

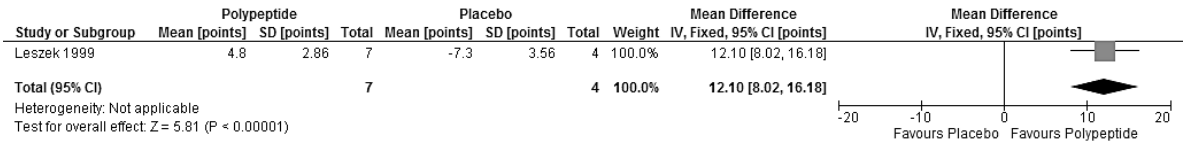
d. 

Funnel plots. Intervention effect estimates from individual studies on the horizontal scale (MD), and the measure of study size on the vertical axis (SE). (a) cognitive; (b) functional; (c) behavioral; (d) global.

4.5.1.7 Polypeptide

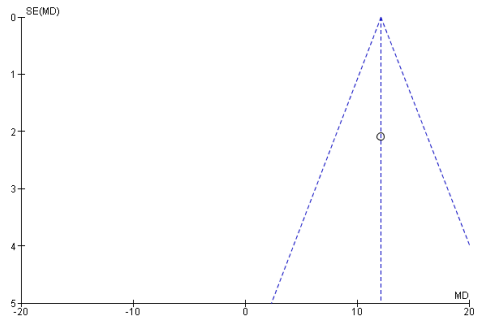
One study used a proline-rich polypeptide in a dosage of 100 µg (Colostrinin) during 10 cycles of treatment; each cycle consisted of 3 weeks separated by a 2-week hiatus without treatment, accounting for one year of treatment, in probable AD patients, which were stratified by stages according to the MMSE in mild, moderate and severe. A very small sample size of mild AD supplemented participants (n=7), against placebo (n= 4) showed a significant large effect on cognition 12.10 [95% CI 8.02, 16.18], Z = 5.81 (P < 0.00001) by using the MMSE (Figure 17, 18). This result, due to the small sample size and the sole study included in the meta-analysis, induced to an overestimation of the treatment effect, very wide CI draw attention to the little accuracy about the effect. In a second analysis using cumulative results to prove this result, mild, moderate and severe subgroups were explored altogether; herein it was obtained an average of the subgroups MD for active and placebo, getting a simple size of 15 and 16 individuals, respectively. The pooled WMD of 12.00 [95% CI 10.20, 13.80], Z = 13.05 (p < 0.00001) still support the large overall effect this time with a narrower CI, however further information is needed to draw reliable conclusions. The treatment product was well tolerated and reported mild transient non-toxic side effects.

Figure 17. Random-effects meta-analysis of data on effects of rich-proline polypeptide compared to placebo on cognitive outcomes in patients with AD.



Forest plots. The overall effect size was estimated by the MD. Dark square sizes represent weights of studies in the meta-analysis. The horizontal lines represent 95% CIs. The vertical line represents the line of no effect. Diamonds represent overall pooled estimates of effects of dietary interventions on cognition measured with MMSE. IV, inverse variance.

Figure 18. Publication bias in rich-proline polypeptide on cognition



Funnel plots. Intervention effect estimates from individual studies on the horizontal scale (MD), and the measure of study size on the vertical axis (SE).

4.5.1.8 Vitamin D

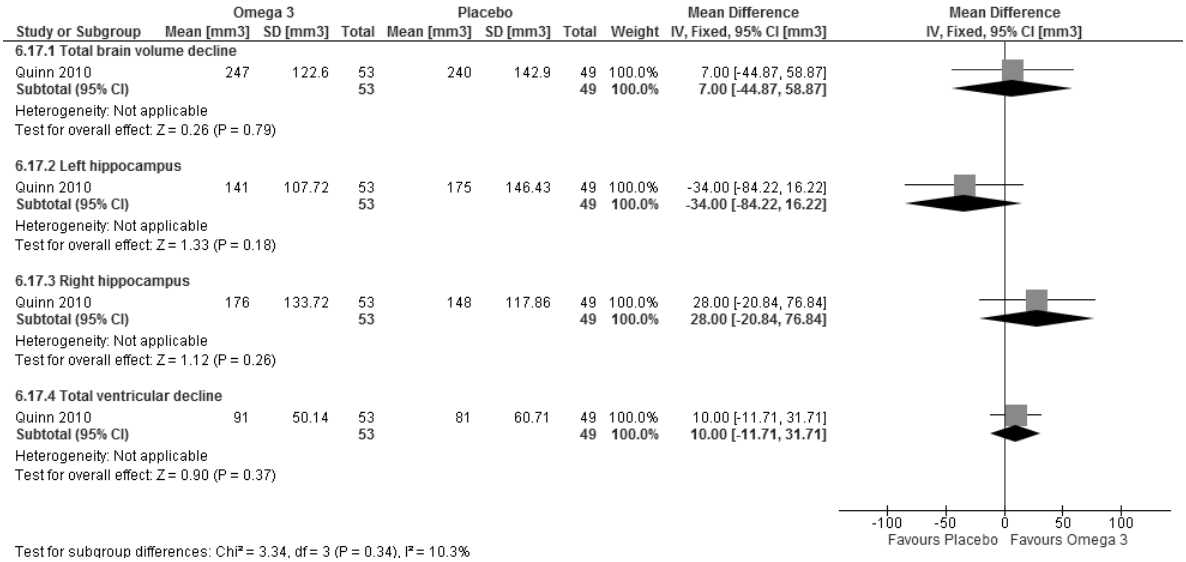
Analysis was carried out by estimating mean and standard deviation from median and interquartile range (see methods), in a small RCT of subjects with mild to moderate AD (n= 16) treated with high-dose of vitamin D (6000 IU vitamin D2) and n= 15 with low-dose (1000 IU vitamin D2) as placebo, in co-intervention with AChE-Is and/or memantine. Vitamin D supplementation for 16 weeks was unable to present a significant effect on cognition measured with the ADAS-cog subscale obtaining a WMD -0.25 [95% CI -2.26, 1.76], Z = 0.24 (P = 0.81); neither on functional capacity -1.25 [95% CI -6.16, 3.66], Z = 0.50 (P = 0.62) by using the DAD scale. Significant adverse events ware not reported.

4.5.1.9 Nutrients on Brain Imaging

There were merely found four studies assessing brain image in different outcomes measure methodically incomparable among them, and therefore there were not possible to perform a suitable statistical analysis. Briefly, in one research the eighteen months supplementation of DHA in 107 mild to moderate AD patients, had no effect on brain volume by paired MRI scans. The WMD in total volume decline was 0.70 [95% CI -4.49, 5.89], Z = 0.26 (p = 0.79), in left hippocampus volume -34.00 [95% CI -84.22, 16.22], Z = 1.33 (P = 0.18), right hippocampus volume 28.00 [95% CI -20.84, 76.84], Z = 1.12 (P = 0.26) and total ventricular decline 10.00 [95% CI -11.71, 31.71], Z = 0.90 (p = 0.37) (Figure 19) (184). In a small sample of moderate–

severe AD patients it was displayed a severe deterioration of P3 recordings in the vitamin E treatment group (199). Finally, drug-naıve AD patients supplemented with a polymeric formula exhibited an effect in the EEG, and the authors explained it as a possible influence of the intervention product in functional connectivity, improving synapse formation and function, on the EEG relative and absolute power in frequency bands and peak frequency (262) and a EEG-based functional network analysis (215).

Figure 19. Fixed-effects meta-analysis of data on effects of DHA interventions compared to placebo on volume change for MRI outcome in patients with AD.



Forest plots. The overall effect size was estimated by the MD. Dark square sizes represent weights of studies in the meta-analysis. The horizontal lines represent 95% CIs. The vertical line represents the line of no effect. Diamonds represent overall pooled estimates of effects of dietary interventions on global performance. IV, inverse variance.

4.5.2. NETWORK META-ANALYSES

Multiple treatment comparisons were subdivided in two separate groups of interventions: “single nutrient” and “composite nutrients”, according to whether the supplementation was provided using only one isolated form of nutrient or in a mixed supplementation.

Nutrients on cognition

The indirect comparisons among single nutrient interventions show the MD with 95% credible intervals of the treatment effects on cognition measured by the MMSE. Proline-rich polypeptide appears to show a significant higher efficacy in improving mental status when

compared with remaining interventions, MD 8.46 (95% CI 5.13, 12.24) compared with MCT and MD 8.41 (95% CI 5.39, 11.66) when compared with B-vitamins. In the indirect comparison between MCT and B-vitamins, the last one shows a small non-significant higher efficacy over MCT (MD 0.07 95% CI -1.91, 1.95) (Figure 20). Nutrients were ranked for the probability of having the best treatment effect (Figure 21). Proline-rich polypeptide showed the highest probability of being the most effective treatment of improvement in cognitive status (100%), however this data is controversial due to the reduced number of studies and small sample size. Followed by the MCT ranked as the second probable best treatment 43% were also controversial, and B-vitamins has 34% probability of being the third effective treatment intervention, whereas omega-3 was ranked as the probable worst treatment 37%.

In composite nutrients analysis, polymeric formula showed a higher non-significant efficacy compared with composite antioxidants in the improvement of cognition (MD 0.55 95% CI -2.39, 2.80) obtaining a 56% probability of being the best treatment, while antioxidants 60% probability of being worst treatment.

These results are relatively consistent with pairwise meta-analysis where it was observed a prevalent treatment effect by the proline rich polypeptide followed by B-vitamins, polymeric formula and MCT, and the no effect of omega-3 on cognitive outcomes (Table 10). Results of the network meta-analysis present potential confounding factors found in pairwise meta-analyses, for example, trials duration are different among interventions, as well as dosage, severity of diseases. This heterogeneity may lead to differences between comparisons; this is the inconsistency in results.

Figure 20. Network meta-analysis of cognitive effect of nutrient interventions

a.

B-vitamins	-0.07 (-1.95, 1.91)	-0.46 (-1.35, 0.47)	-0.41 (-0.96, 0.20)	8.41 (5.39, 11.66)	-0.21 (-1.05, 0.71)
0.07 (-1.91, 1.95)	MCT	-0.42 (-2.37, 1.64)	-0.38 (-2.25, 1.50)	8.46 (5.13, 12.24)	-0.19 (-2.04, 1.77)
0.46 (-0.47, 1.35)	0.42 (-1.64, 2.37)	Omega-3	0.05 (-0.68, 0.78)	8.85 (5.81, 12.15)	0.28 (-0.73, 1.27)
0.41 (-0.20, 0.96)	0.38 (-1.50, 2.25)	-0.05 (-0.78, 0.68)	Placebo	8.82 (5.85, 11.96)	0.20 (-0.46, 0.84)
-8.41 (-11.66, -5.39)	-8.46 (-12.24, -5.13)	-8.85 (-12.15, -5.81)	-8.82 (-11.96, -5.85)	Polypeptide	-8.61 (-11.80, -5.50)
0.21 (-0.71, 1.05)	0.19 (-1.77, 2.04)	-0.28 (-1.27, 0.73)	-0.20 (-0.84, 0.46)	8.61 (5.50, 11.80)	Single antioxidant

b.

B-vitamins	-0.05 (-2.05, 1.85)	-0.45 (-1.41, 0.54)	-0.44 (-0.94, 0.23)	8.78 (5.64, 11.81)	-0.24 (-1.03, 0.67)
0.05 (-1.85, 2.05)	MCT	-0.41 (-2.35, 1.65)	-0.38 (-2.17, 1.50)	8.82 (5.49, 12.16)	-0.18 (-2.03, 1.86)
0.45 (-0.54, 1.41)	0.41 (-1.65, 2.35)	Omega-3	-0.00 (-0.72, 0.87)	9.27 (6.10, 12.27)	0.21 (-0.73, 1.28)

0.44 (-0.23, 0.94)	0.38 (-1.50, 2.17)	0.00 (-0.87, 0.72)	Placebo	9.20 (6.13, 12.18)	0.20 (-0.43, 0.83)
-8.78 (-11.81, -5.64)	-8.82 (-12.16, -5.49)	-9.27 (-12.27, -6.10)	-9.20 (-12.18, -6.13)	Polypeptide	-9.01 (-12.01, -6.03)
0.24 (-0.67, 1.03)	0.18 (-1.86, 2.03)	-0.21 (-1.28, 0.73)	-0.20 (-0.83, 0.43)	9.01 (6.03, 12.01)	Single antioxidant

c.

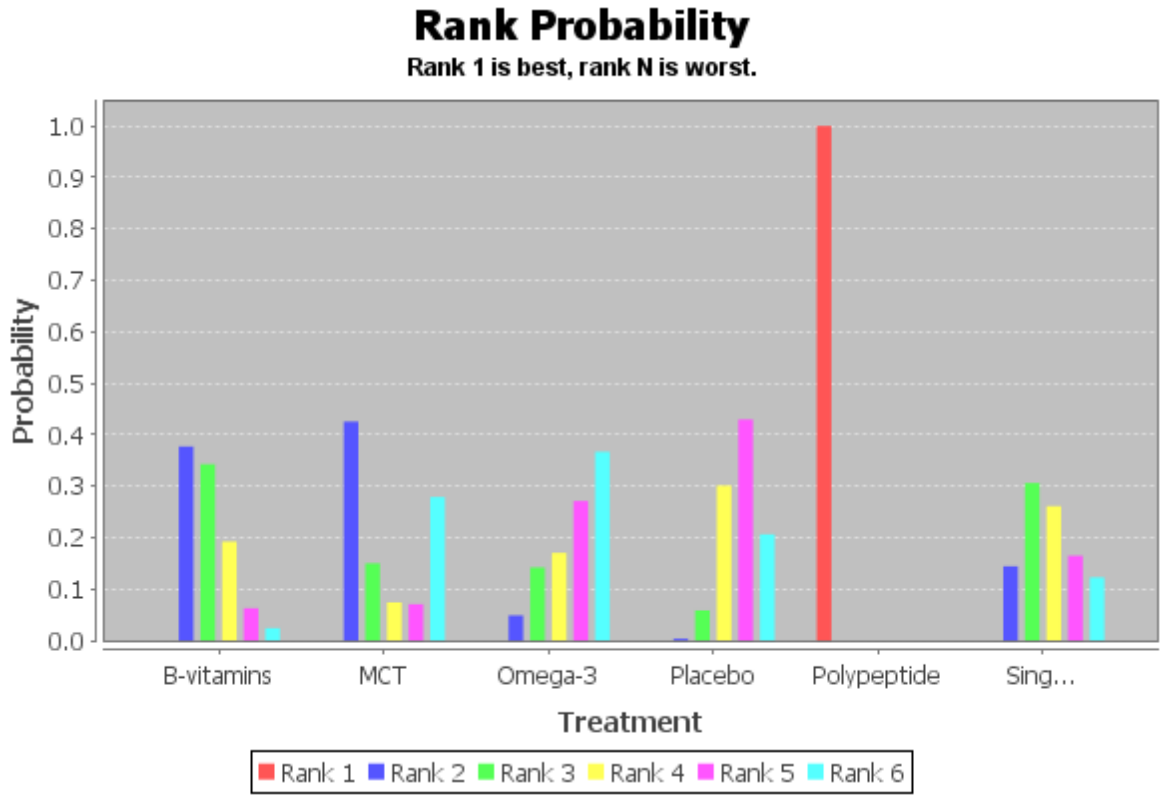
Composite antioxidants	0.36 (-2.09, 2.03)	0.55 (-2.39, 2.80)
-0.36 (-2.03, 2.09)	Placebo	0.16 (-1.43, 1.91)
-0.55 (-2.80, 2.39)	-0.16 (-1.91, 1.43)	Polymeric formula

d.

Composite antioxidants	0.31 (-2.17, 2.04)	0.50 (-2.56, 2.95)
-0.31 (-2.04, 2.17)	Placebo	0.16 (-1.49, 1.97)
-0.50 (-2.95, 2.56)	-0.16 (-1.97, 1.49)	Polymeric formula

Treatments effects are reported in MD and 95% credible interval, organization is given alphabetically. Consistency model of single nutrients (a); Inconsistency model of single nutrients (b); Consistency model of composite nutrients (c); Inconsistency model of composite nutrients (d).

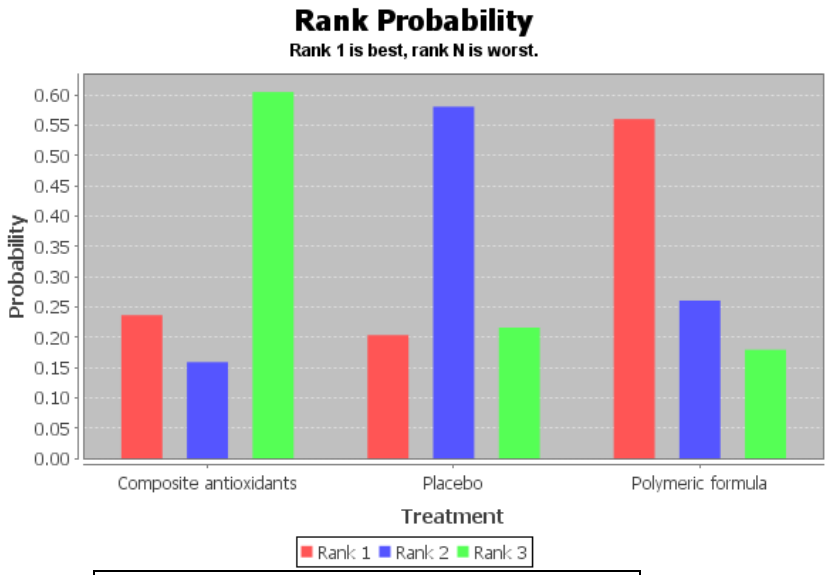
Figure 21. Rank probability of cognitive effect and network of nutrient interventions



a.

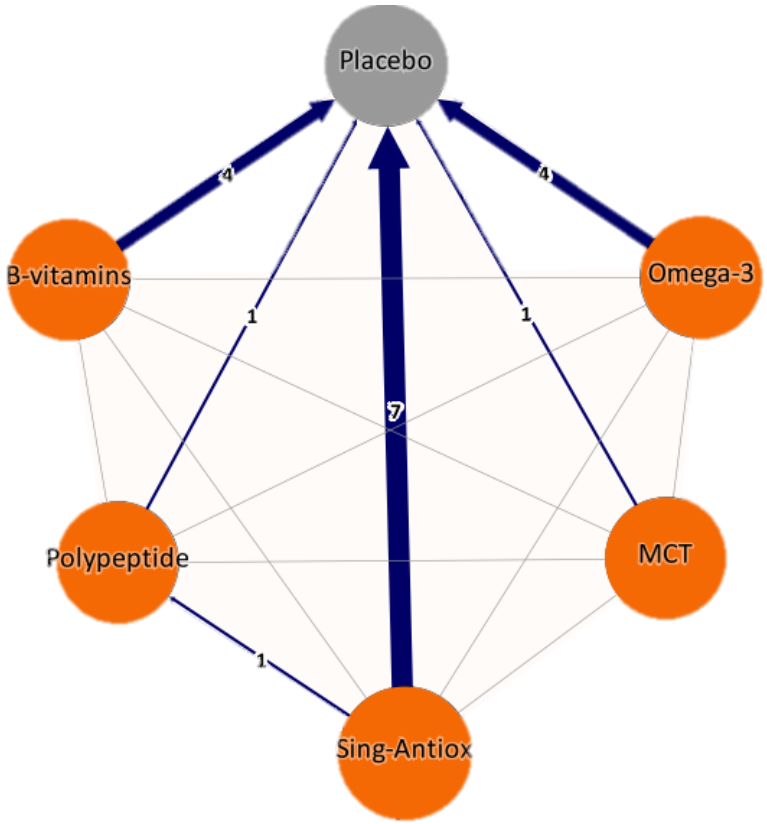
Nutrient Intervention	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6
B-vitamins	0.00	0.38	0.34	0.19	0.06	0.02
MCT	0.00	0.43	0.15	0.07	0.07	0.28
Omega-3	0.00	0.05	0.14	0.17	0.27	0.37
Placebo	0.00	0.00	0.06	0.30	0.43	0.21
Polypeptide	1.00	0.00	0.00	0.00	0.00	0.00
Single antioxidant	0.00	0.14	0.31	0.26	0.17	0.12

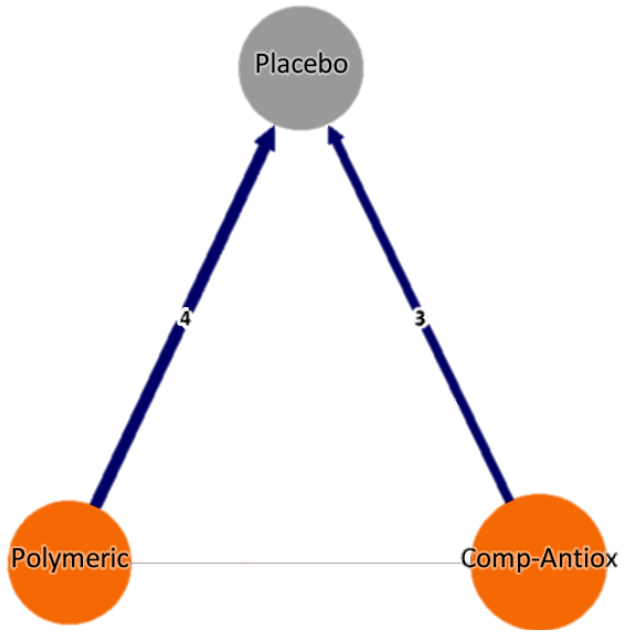
b.



Nutrient Intervention	Rank 1	Rank 2	Rank 3
Composite antioxidants	0.24	0.16	0.60
Placebo	0.20	0.58	0.22
Polymeric formula	0.56	0.26	0.18

c.





d.

Probability of each nutrient being ranks as best treatment effect on cognitive status in AD patients. Rank 1 is the best and rank N is worst. (a) Single nutrient intervention; (b) composite nutrient intervention; (c) network single nutrient intervention; (d) network composite nutrient intervention. Network graphs: Arrows link the interventions that have been analyzed in direct comparisons among trials. The numbers on the edge of the arrows denote the number of trials or trial arms. The widths of the arrows represent the cumulative number of trials for each comparison. MCT, medium chain triglycerides; Sing-Antiox, single antioxidants; Polypeptide, Proline-rich polypeptide; Comp-Antiox, composite antioxidants; Polymeric, polymeric formulas.

Table 10. Summary effects estimates on cognition from pairwise and network meta-analysis

Nutrient intervention	N° Studies/ arms	Sample size	Weight	Pairwise (MD)	Network (MD)	Rank probability
Polypeptide	1	31	1,18%	12.10 (8.02, 16.18)	8.82 (5.85, 11.96)	1
B-vitamins	4	791	30,03%	0.44 (0.09, 0.79]	0.41 (-0.20, 0.96)	3
Polymeric formula	2	237	9,00%	0.33 [-0.53, 1.19]	0.16 (-1.43, 1.91)	4
MCT	1	140	5,32%	0.27 [-1.49, 2.03]	0.38 (-1.50, 2.25)	2
Composite antioxidants	3	234	8,88%	0.10 [-2.34, 2.54]	-0.36 (-2.03, 2.09)	7
Single antioxidants	7	574	21,79%	-0.00 [-0.85, 0.84]	0.20 (-0.46, 0.84)	5
Omega 3	4	627	23,80%	-0.00 [-0.62, 0.62]	-0.05 (-0.78, 0.68)	6

4.6 Quality of the evidence

This work uses the GRADE approach (263) to grade the quality of evidence and strength of recommendation for the use of nutrient interventions to support the management of AD which is presented in the summary of findings (Table 11). This tool offers a structured and transparent process in the development and presentation of evidence in systematic reviews and guidelines. The system for rating the quality of this evidence consist of applying thoroughly five – factors risk of bias, inconsistency, indirectness, imprecision and publication bias – that influence the

quality of evidence and strength of recommendations for each outcome across all the studies from randomized trials that may lead to rating down the quality of evidence.

All the included studies were well designed with a strong methodology that contributes to not downgrade for risk of bias. The consistency in the magnitude of intervention effect may be affected by the heterogeneity identified by the statistical test Chi^2 and a large I^2, given the variability in population, intervention and outcomes, along with the extent of overlap of CI. In general, the evidence was not rated down by indirectness, unless for studies, in which important outcomes of interest were surrogated, in diseases such as dementia, important endpoints encompass behavioral disturbances, function and caregiver burden, frequently substitute for cognition or not comprised to the integral assessment. The precision was primarily affected by whether the 95% confidence intervals (CI) around the pooled effect is sufficiently narrow to represent the true effect or overlaps the no effect, including both no effect and appreciable benefit or harm. Limitations of the CIs was potentiated by the optimal information size (OIS), this following means whether the total number of individuals included in the systematic review is less than the number of participants for a conventional sample size calculation in a single adequately powered trial. The OIS criterion was calculated at http://www.stat.ubc.ca/~rollin/stats/ssize/b2.html. An OIS not met, due to small sample size, implicate the downgrade of the quality. Visual inspection of funnel plots of each intervention for asymmetry of distribution found no enough evidence to detect possible publication bias and reporting of negative results suggested a lower risk of reporting bias. However, the no inclusion of unpublished studies and gray literature may have introduced publication bias to our results, as well as, the language restriction in the screening of studies also may have overlooked relevant records. Thus, reduce the overall quality of this evidence.

Table 11. Summary of findings

Single antioxidant compared to placebo in AD

Patients or population: Elderly diagnosed with mild to moderate probable AD

Settings: University, medical center

Intervention: Single antioxidants (curcumin 2/4 mg, vitamin E 2000 UI, coenzyme Q 24mg, selenium 100 mg, N- acetylcysteine 50 mg/kg)

Comparison: Placebo

Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Anticipated absolute effects	
							Risk with placebo	Risk with single antioxidant	Risk with placebo	Risk difference with single antioxidant
Cognitive performance (follow up: range 4 months to 15.6 months; assessed with: MMSE; Scale from: 0 to 30)										
574 (7 RCTs) range 4 months to 15.6 months	not serious	serious [1,2]	not serious	serious [3]	publication bias strongly suspected[5]	⨁◯◯◯ VERY LOW	304	270	The mean cognitive performance was-**2.26** points	MD **0 points** (0.85 lower to 0.84 higher)
Functional capacity (follow up: range 4 months to 6 months; assessed with: ADL; Scale from: 0 to 78)										
383 (4 RCTs) range 4 months to 6 months	not serious	serious [1,2]	not serious	serious [3,4]	publication bias strongly suspected [5]	⨁◯◯◯ VERY LOW	191	192	The mean functional capacity was **0**	MD **0.44 higher** (2.04 lower to 2.92 higher)
Behavioral disturbances (follow up: 6 months; assessed with: NPI; Scale from: 0 to 144)										
289 (2 RCTs) 6 months	not serious	serious [1,2]	not serious	serious [3,4]	publication bias strongly suspected [5]	⨁◯◯◯ VERY LOW	146	143	The mean behavioral disturbances was**0**	MD **2.04 lower** (4.9 lower to 0.82 higher)

[1] Point estimates vary widely across studies, CIs show minimal overlap
[2] Heterogeneity in intervention (dose and co-interventions), outcome follow up measurement
[3] OIS is not met and 95% CI overlaps the no effect
[4] Wide CI
[5] Missing unpublished trials/gray literature

Composite antioxidant compared to placebo in AD

Patients or population: Elderly diagnosed with mild to moderate probable AD

Settings: University, medical center

Intervention: Composite antioxidants (vitamin E 2400 UI + vitamin C 600 mg + α-lipoic acid 1800 mg; selegiline 10 mg + vitamin E 2000 UI; lipoic acid 600 mg + omega-33gr)

Comparison: Placebo

Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Anticipated absolute effects	
							Risk with placebo	Risk with composite antioxidants	Risk with placebo	Risk difference with composite antioxidants
Cognition (follow up: range 4 months to 15.6 months; assessed with: MMSE; Scale from: 0 to 30)										
234 (3 RCTs) range 4 months to 15.6 months	not serious	very serious [1,2,3]	not serious	serious [4]	publication bias strongly suspected [5]	⊕◯◯◯ VERY LOW	114	120	The mean cognition was-**3.36** points	MD **0.1 points higher** (2.34 lower to 2.54 higher)

[1] Significant Heterogeneity: Tau² = 3.60; Chi² = 10.44, df = 2 (P = 0.005); I² = 81%
[2] Point estimates vary widely across studies and CIs show minimal overlap. Differences in directions.
[3] Heterogeneity in intervention (dose, co-intervention) and outcome follow up measurement
[4] OIS is not met and wide 95% CI overlaps the no effect
[5] Missing unpublished trials/gray literature

B-vitamins complex compared to placebo in AD

Patients or population: Elderly diagnosed with probable AD and cognitive impairment/dementia

Settings: Community, hospital, clinical research sites

Intervention: B-vitamins complex (B12 400 µg + folic acid 2 mg+ B6 25 mg; B-12 0.5 mg + multivitamin supplement; folic acid 1 mg; folic acid 5mg + vitaminB12 1 mg)

Comparison: Placebo

Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Anticipated absolute effects	
							Risk with placebo	Risk with B-vitamins complex	Risk with placebo	Risk difference with B-vitamins complex
Cognition (follow up: 6 months; assessed with: MMSE; Scale from: 0 to 30)										
791 (4 RCTs) 6 months	not serious	not serious[4]	not serious	not serious	publication bias strongly suspected [1,2]	⊕⊕⊕◯ MODERATE	355	436	The mean cognition was-**0.297** points	MD **0.44 points higher** (0.09 higher to 0.79 higher)
ADL										
395	not serious	not serious	not serious	serious [3]	publication bias	⊕⊕◯◯	161	234	The mean ADL was **0**	MD **0.42 lower**

B-vitamins complex compared to placebo in AD

Patients or population: Elderly diagnosed with probable AD and cognitive impairment/dementia

Settings: Community, hospital, clinical research sites

Intervention: B-vitamins complex (B12 400 µg + folic acid 2 mg+ B6 25 mg; B-12 0.5 mg + multivitamin supplement; folic acid 1 mg; folic acid 5mg + vitaminB12 1 mg)

Comparison: Placebo

Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Anticipated absolute effects	
							Risk with placebo	Risk with B-vitamins complex	Risk with placebo	Risk difference with B-vitamins complex
(1 RCT)					strongly suspected [2]	LOW				(2 lower to 1.16 higher)
NPI										
390 (1 RCT)	not serious	not serious	not serious	serious [3]	publication bias strongly suspected [2]	⊕⊕◯◯ LOW	159	231	The mean NPI was **0**	MD **0.06 lower** (2.02 lower to 1.9 higher)
CDRsob										
390 (1 RCT)	not serious	not serious	not serious	not serious	publication bias strongly suspected [2]	⊕⊕⊕◯ MODERATE	159	231	The mean cDRsob was **0**	MD **0.1 lower** (0.43 lower to 0.23 higher)

[1] Small number of studies, some reported conflict of interest
[2] Missing unpublished trials/gray literature
[3] Wide Cis
[4] Variability in severity of disease and dosage of intervention, heterogeneity not detected

Medium chain triglycerides compared to placebo in AD

Patients or population: Elderly diagnosed with mild to moderate AD

Settings: clinical sites based within the U.S.

Intervention: AC1202 (10 grams of MCT glycerin and caprylic acid [C8:0])

Comparison: Placebo

Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Anticipated absolute effects	
							Risk with placebo	Risk with medium chain triglycerides	Risk with placebo	Risk difference with medium chain triglycerides
Cognition (follow up: 104 days; assessed with: MMSE; Scale from: 0 to 30)										
140 (1 RCT)	not serious	not serious	serious [1]	very serious [2,3]	publication bias strongly suspected [4,5]	⊕◯◯◯ VERY LOW	63	77	The mean cognition was-**0.62** points	MD **0.27 points higher**

Medium chain triglycerides compared to placebo in AD

Patients or population: Elderly diagnosed with mild to moderate AD

Settings: clinical sites based within the U.S.

Intervention: AC1202 (10 grams of MCT glycerin and caprylic acid [C8:0])

Comparison: Placebo

Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Anticipated absolute effects	
							Risk with placebo	Risk with medium chain triglycerides	Risk with placebo	Risk difference with medium chain triglycerides
104 days										(1.49 lower to 2.03 higher)

[1] Surrogate outcome
[2] CI: very wide, overlaps the no effect
[3] Do not met OIS
[4] Missing unpublished trials/gray literature
[5] Small number of studies, some reported as industry sponsored/conflict of interest

Omega 3 compared with placebo for people with AD

Patients or population: Elderly diagnosed with Mild to moderate AD

Settings: University, hospital and medical research centers

Intervention: DHA 903.75±552.38 mg, EPA 663.75±422.72 mg

Comparison: Placebo

Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Anticipated absolute effects	
							Risk with placebo	Risk with omega-3	Risk with placebo	Risk difference with omega-3
Cognition (follow up: range 6 months to 18 months; assessed with: MMSE; Scale from: 0 to 30)										
627 (4 RCTs) range 6 months to 18 months	not serious [1]	not serious [2]	not serious	serious [3]	publication bias strongly suspected [4,5]	⊕⊕◯◯ LOW	272	355	The mean cognition was**-2.04** points	MD **0 points** (0.62 lower to 0.62 higher)
Functional capacity (follow up: 18 months; assessed with: ADL; Scale from: 0 to 78)										
308 (1 RCT) 18 months	not serious	not serious	not serious	not serious [6]	publication bias strongly suspected [4,5]	⊕⊕⊕◯ MODERATE	130	178	The mean functional capacity was **0**	MD **1.08 higher** (1.72 lower to 3.88 higher)
Behavioral disturbances (follow up: range 12 months to 18 months; assessed with: NPI; Scale from: 0 to 144)										
479 (2 RCTs)	not serious	serious [2,7]	not serious	not serious [6]	publication bias strongly suspected [4,5]	⊕⊕◯◯	214	265	The mean behavioral disturbances was**0**	MD **0.33 lower** (4.29 lower to 3.63

Omega 3 compared with placebo for people with AD

Patients or population: Elderly diagnosed with Mild to moderate AD

Settings: University, hospital and medical research centers

Intervention: DHA 903.75±552.38 mg, EPA 663.75±422.72 mg

Comparison: Placebo

Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Anticipated absolute effects	
							Risk with placebo	Risk with omega-3	Risk with placebo	Risk difference with omega-3
range 12 months to 18 months						LOW				higher)
Global performance (follow up: range 12 months to 18 months; assessed with: CDR-sob; Scale from: 0 to 18)										
478 (2 RCTs) range 12 months to 18 months	not serious	not serious [2]	not serious	not serious [6]	publication bias strongly suspected [5]	⊕⊕⊕◯ MODERATE	212	266	The mean global performance was**0**	MD **0.1 lower** (0.65 lower to 0.45 higher)

[1] Selective outcome reporting
[2] Moderate heterogeneity, variability in dosage and follow-up assessment
[3] OIS is met and 95% CI overlaps the no effect
[4] Small number of studies, some reported as industry sponsored/conflict of interest
[5] Missing unpublished trials/gray literature
[6] 95% CI overlaps the no effect

Polymeric formula compared to placebo in AD

Patients or population: Elderly diagnosed with mild and moderate to late-stage probable AD

Settings: Medical centers, nursing home and clinics

Intervention: Polymeric formula (Fortasyn Connect 125 ml, Energy dense and protein-rich liquid supplement 500 ml, Nutraceutical formulation 2 tablets)

Comparison: Placebo

Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Anticipated absolute effects	
							Risk with placebo	Risk with polymeric formula	Risk with placebo	Risk difference with polymeric formula
Cognition (follow up: range 3 months to 6 months; assessed with: MMSE; Scale from: 0 to 30)										
237 (2 RCTs) range 3 months to 6 months	not serious	serious [1]	not serious	serious [2]	publication bias strongly suspected [3,4]	⊕◯◯◯ VERY LOW	118	119	The mean cognition was-**1.55** points	MD **0.33 points higher** (0.53 lower to 1.19 higher)

Polymeric formula compared to placebo in AD

Patients or population: Elderly diagnosed with mild and moderate to late-stage probable AD

Settings: Medical centers, nursing home and clinics

Intervention: Polymeric formula (Fortasyn Connect 125 ml, Energy dense and protein-rich liquid supplement 500 ml, Nutraceutical formulation 2 tablets)

Comparison: Placebo

Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Anticipated absolute effects	
							Risk with placebo	Risk with polymeric formula	Risk with placebo	Risk difference with polymeric formula
Functional capacity (follow up: range 3 months to 6 months; assessed with: ADL; Scale from: 0 to 78)										
733 (3 RCTs) range 3 months to 6 months	not serious	serious [1]	not serious	serious [2]	publication bias strongly suspected [3,4]	⨁◯◯◯ VERY LOW	356	377	The mean functional capacity was **0**	MD **0.06 higher** (1.39 lower to 1.5 higher)
Behavioral disturbances (follow up: 3 months; assessed with: NPI; Scale from: 0 to 144)										
83 (1 RCT) 3 months	not serious	not serious	not serious	serious [2]	publication bias strongly suspected [3,4]	⨁⨁◯◯ LOW	34	49	The mean behavioral disturbances was**0**	MD **2.8 lower** (31.07 lower to 25.47 higher)
Global performance (follow up: 6 months; assessed with: CDR-sob; Scale from: 0 to 18)										
448 (1 RCT) 6 months	not serious	not serious	not serious	serious [2]	publication bias strongly suspected [3,4]	⨁⨁◯◯ LOW	222	226	The mean global performance was**0**	MD **0.08 higher** (0.28 lower to 0.44 higher)

[1] Heterogeneity in outcome assessment follow up
[2] OIS is no met and 95% CI overlaps the no effect
[3] Small number of studies industry sponsored/conflict of interest
[4] Missing unpublished trials/gray literature

Polypeptide compared to placebo in Alzheimer's disease

Patients or population: Elderly diagnosed with probable AD at mild, moderate and severe stage

Settings: Outpatients

Intervention: Proline-rich polypeptide 100 µg (Colostrinin)

Comparison: Placebo

Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Anticipated absolute effects	
							Risk with placebo	Risk with polypeptide	Risk with placebo	Risk difference with polypeptide

Polypeptide compared to placebo in Alzheimer's disease

Patients or population: Elderly diagnosed with probable AD at mild, moderate and severe stage

Settings: Outpatients

Intervention: Proline-rich polypeptide 100 µg (Colostrinin)

Comparison: Placebo

Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Anticipated absolute effects	
							Risk with placebo	Risk with polypeptide	Risk with placebo	Risk difference with polypeptide
Polypeptide on cognition (follow up: 1 year; assessed with: MMSE; Scale from: 0 to 30)										
11 (1 RCT) 1 year	not serious	not serious	serious [1]	serious [2]	publication bias strongly suspected [3]	⊕◯◯◯ VERY LOW	15	16	The mean polypeptide on cognition was **-5.6** points	MD **12 points higher** (10.2 higher to 13.8 higher)

[1] Surrogate outcome
[2] Do not meet OIS, wide CI. Initial small trial with impressive positive results.
[3] Possible risk of over-estimation of the underlying beneficial effect due to small sample size. Missing unpublished trials/gray literature

5. DISCUSION

5.1 Summary of main results, agreements and disagreements with other studies or reviews

Nutrients play an important role in the adequate formation, physiological and anatomical development and maintenance of brain, and this is reflected in brain functioning including cognition, mood, behavior and aging, important features affected by the physiopathology of AD. Findings from a large body of evidence from cell culture, animal models, observational and epidemiological studies suggest a protective effect of different nutrients, such as vitamin E and other antioxidants, B-vitamin complex, omega 3, among others, against dementia; arising the probability of analogous preventive benefits in humans (264–267). This systematic review and meta-analysis synthesized data from published trials of different nutrient interventions on cognitive, behavioral and functional outcomes in AD at different stages. The insufficient evidence found in this comprehensive research, judged as exempt of risk of bias, was unable to prove clinical or statistical significance of the efficacy of isolated and/or mixed nutrients supplementation on the related outcomes. There is a noticeable incongruence between the clear portrait of the impact of nutrients on AD that come from biological evidence and the contradictory outcomes of clinical trials. In general, considering the small number of studies, the small sample sizes and short duration of these studies, notably the attempt for achieving significant impact on clinical indicators was abortive; therefore, these findings do not provide consistent evidence to establish conclusive statements whether nutrients can slow down or decrease neuropathological manifestations of AD. We must highlight that most AD outcomes in the evidence included in this research were mainly restricted to cognitive state and functional abilities, outcomes concerning neuropsychiatric behavior, global clinical state, biomarkers and neuroimaging were limited. Until data from more high-quality well-design randomized trials become available for analysis, there is no suitable evidence to support our hypothesis of the use of dietary supplementation for the management of AD.

Nevertheless, limited evidence suggests a possible association between nutrient and reduced risk of dementia. In the estimation analyses, supplementations with proline-rich polypeptide and B-vitamin complex somehow provided protection against cognitive decline in

AD persons. In spite of the positive large estimated effect of the polypeptide complex, described as having psychotropic and immunomodulatory activity, results may be biased due to the single study with unrepresentative sample producing a possible spurious effect. Even though, these promising results were reproduced in a larger scale albeit during a reduced period, and the results of the same cognitive outcome measure (MMSE) showed no significant benefit, but did in the ADAS-cog (268). More trials are needed to reach unarguable, robust and consistent results.

A positive treatment effect on cognition was also observed in the intervention with B-vitamin complex, albeit it shows a faintly lower decline in mental status compared with control group, rather than the improvement of symptoms. It still represents an advantageous outcome in a progressive neurodegenerative disease such as AD. Thus, until this available data, B-vitamins offer to some extent predominant evidence over proline-rich polypeptide supplementation in demonstrating a noteworthy efficacy in lower impairment of cognitive status compared with placebo. Compared with proline-rich polypeptide, the treatment with B-vitamins was outweighed by larger number of studies and sample size, outcome measured at the same time point and assessment scale, similar intervention components and sequential point estimates, leading to better quality of evidence. B-vitamins are well known by their mutual main role in the CNS (66). Note that B-vitamins intervention may have been enhanced by co-adjuvant effect with AD medication, or vice-versa. In contrast with these results, a systematic review of cross-sectional, cohort studies and randomized double-blind clinical studies looking at the benefit and risks of serum and erythrocyte folate levels, folate intake and related nutrients on cognitive function in older people; did not support a positive effect of folic acid supplementation on cognition in this population. However, it was shown that people with low folate serum levels are prone to greater risk of cognitive impairment while high folate levels in conjunction with low vitamin B12 levels are able to promote a higher decline (269). A meta-analysis of RCTs of folic acid supplementation with or without other B vitamins during nearly to 6 months showed no effect on the prevention cognitive decline (270). A Cochrane review found no trials examining the efficacy of vitamin B6 in reducing the risk of developing cognitive impairment by healthy elderly or improving cognitive function of those diagnosed with cognitive decline or dementia, regardless vitamin B6 deficiency, only two trials in elderly people had no beneficial effects on mood or mental function (271). They also conducted a systematic review assessing the efficacy of vitamin B1 for AD, in which three studies with inadequate reporting results and a sample size of not more

than 50 subjects were not sufficient to support any effect of this vitamin in any outcome (272). Another Cochrane review with small number of included studies, with high variability in participants, dosage and outcome measure, evaluating the effect of Folic acid with or without vitamin B12 for the prevention or delay of cognitive impairment in healthy or demented older adults does not achieve adequate evidence of this supplementation benefit on cognition. The treatment was effective in some measures of cognition in participants with higher levels of serum homocysteine, and also in reducing its concentrations, as well as folic acid displayed a favorable improvement in behavioral response to AChE-Is in AD patients (273). On the other hand, the Cochrane review of B12 supplementation alone in the same target population, also failed to showed significant evidence of the treatment with vitamin B12 for cognition in cognitive impairment or dementia and low serum vitamin B12 levels (274). Concurrently to this, other systematic review of randomized controlled trials and prospective cohort studies from different authors evaluating vitamin B12 intake and status in elderly reported no association between vitamin B12 intake and cognitive function or serum/plasma vitamin B12 and risk of dementia, global cognition or memory. Unlike to sensitive markers of vitamin B12 status showed that significant associations with risk of dementia, AD, or global cognition (275). Finding from a similar systematic review analyzed the association B-vitamins and fatty acid levels with the risk of developing dementia from prospective cohort studies, and the treatment effect of B-vitamins and fatty acid supplementation on cognitive function from RCT were inconsistent. While some observational studies resulted in a positive correlation in higher serum levels or dietary intake of folate and fish/fatty acids and low serum levels of homocysteine with a reduced risk of incident AD and dementia, other studies did not support this correlation (276). At this point, summary evidence from B-vitamins is insufficient for making recommendations in the nutritional management of AD. Nevertheless, the controversial findings of this meta-analysis evaluating the efficacy of B-vitamin complex as a whole in contrast with the existent similar work evaluating this vitamins independently, lead us to consider that this vitamins have narrowly interrelated roles and may work together in cooperation, the citric acid cycle is the epitome of their unified functions (66), and should not be evaluated distinctly in the management or prevention of neurodegenerative conditions.

Since several studies have proved a strong association with oxidative stress in the pathogenesis and progress of AD, promoting the exacerbation of pathological hallmarks, Aβ and

Tau plaques, which induces to neuronal damage and subsequent clinical manifestations. Some authors have used several nutrients with known antioxidant and free radical scavenger functions that would be expected to ameliorate oxidation and in consequence contribute to the delay of deterioration in the course of the disease. In this study, all RCTs included in the meta-analyses of antioxidants as treatment intervention had different doses or forms of active compound, different or unspecified stage of disease severity in populations studied, different follow-up times, and different assessment scales to assess the same neuropsychological outcome that could not be combined. Therefore, we were not surprised that, when these studies were pooled in a meta-analysis, an important heterogeneity was detected among studies. This predictable large heterogeneity somewhat might prevent the examination from bringing about to a result different from a null effect. Perhaps, a homogeneous population of mild-to-moderate probable AD enables a more direct comparative analysis. In a parallel relationship to our findings, a systematic review of epidemiological studies evaluating the association between the ingestion of dietary antioxidants (vitamins C, E, flavonoids, carotenoids) on cognition and risk for dementia do not get at consistent results in the evidence to draw definite assumptions whether antioxidants have an effect in this association, authors attributed this inconsistency to the difficulties in the study designs (277).

Concerning individual analysis of antioxidant results, curcumin, beyond the small sample size and short duration of the study, authors refer to an extensive metabolism in the gastrointestinal tract suggesting limited bioavailability and a possible interference in the biological mechanism of its effect (194). A trial arm supplemented with selenium showed a significant stabilization in 90% of patients, instead of an improvement, on cognitive state compared with placebo and no discernible side-effects, in agreement with the suggested possible preventive, but no a role in the treatment of AD presented in a systematic review of RCT, prospective, cross-sectional, case control, animals, cells and autopsy studies. Authors did not find consistent data regarding beneficial effect of selenium supplementation and in the treatment or prevention of AD. However, an association of selenium status and cognitive function was observed in epidemiological studies, while in molecular biology was detected a pivotal role in the pathogenesis of AD (278).

The included clinical trial using N-acetyl-L-cysteine did not attain significantly improvement on cognition. Despite it has been shown auspicious results in other psychiatric diseases (279,280) there is no sufficient data of the use this compound in the management of AD. Coenzyme Q (CoQ), a naturally occurring antioxidant in mitochondria, did not affect cognitive and functional outcome or biomarkers; there is unclear scientific evidence for any benefit of CoQ in AD. Whereas, the combination of vitamin E and C with α-lipoic acid, a mitochondrial coenzyme with antioxidant actions, revealed a decline in the cognitive outcome measure and no effect in function or biomarkers. This is inconsistent with the reduced prevalence and incidence of AD from a very large (n = 4470) cross-sectional prospective study associated to the combined use of vitamins C and E (77), but congruent with a prospective cohort study (n = 2969) that showed no reduced risk of dementia with both supplementation (78). In the combination of vitamin E with selegiline, a monoamine oxidase inhibitor, it was not observed a substantial benefit on cognition or dependence, but behavioral symptoms were significantly decreased.

The exploratory analysis using only vitamin E also was futile, certainly attributed to the inconsistent results of individual trials, where the direction of treatment estimative effects across studies varied widely. A Cochrane review found no evidence assessing the efficacy of Vitamin E in the prevention or treatment of AD and prevention of progression of MCI to AD, neither of the 2 included studies showed significant difference (281). Another review of clinical trials evaluating the safety and efficacy of vitamin E supplementation in AD, among other diseases, do not recommend vitamin E supplementation for preventing or delaying AD due to the controversial results from different reviewed studies, instead promote the consumption of vitamin E–rich foods (282). Possibly, vitamin E might failed to show positive results in conducted trials because of the restriction to the chemical form α-tocopherol (90), and it properly exerts its antioxidant function working synergistically with other nutrients such as selenium, copper, zinc, manganese and riboflavin, thus depends on the adequate levels and it would be convenient to verify the action of these additional nutrients (283).

Despite all the evidence supporting the important participation of omega-3 in the CNS PUFA and its neuroprotective effect against inflammation and oxidative processes incurring in the pathology of AD, high quality trials recruited and combined in the meta-analysis showed a lack of effect of omega-3 supplementation in patients with AD. Our results are congruent with

others systematic review examining the efficacy of omega-3 in cognitive outcomes. A meta-analysis of RCTs examining the benefits of omega-3 fatty acids on neuropsychological cognitive performance in healthy, cognitive impairment no dementia (CIND), or AD people was unable to demonstrate effects of n-3 FAs on composite memory, neither on cognition of AD patients as measured by the MMSE or ADAS–cog. An analysis by domain exhibited a favorable effect in CIND subjects for immediate recall, attention and processing speed but not healthy individuals (284). A Cochrane review did not find evidence of omega 3 PUFA dietary intake or supplementation longer than 6 months for the prevention of cognitive impairment or dementia in non-demented older population (285). Other systematic review of clinical trials and observational studies measured the efficacy of omega–3 PUFA on cognitive function in normal aging and dementia. One cohort study found no association of fish or omega-3 total consumption on cognition; and four studies of omega–3 fatty acids on incidence and treatment of dementia had a limited trend toward the reduction of the risk of dementia and improvement of cognitive function (286). Moreover, a study reported a positive association between the dietary omega-6/omega-3 ratio and the risk of AD, though this evidence in supported by animal studies in which this dietary ratio manifest an influence in the AD pathology, behavior and brain structure; and limitedly by observational and epidemiological human studies, and one controlled trial, where the dietary omega-6/3 ratio was related to cognitive decline, and incidence of dementia (287).

We found insufficient well-designed studies using multi-nutrient product intervention, polymeric formula including macro and micronutrients, those which match eligibility criteria used different assessment outcome scales that do not allow making a comparison among them. Studies coinciding in the same outcome measure for cognition and functional capacity were analyzed, but significant effects were not observed between them. A systematic review examining the effect of different nutritional supplementations when combined with cholinesterase inhibitors on cognitive and functional improvement showed no convincing evidence of a beneficial effect (288). The supplementation of Souvenaid (Fortasyn Connect) in patients with AD was evaluated in a meta-analysis of three published RCTs, general results revealed non-significant beneficial effect of this product compared with placebo on cognition, functional ability, behavior, or global clinical change (289).

Regardless of the growing data concerning the role of vitamin D in the neurophysiology and the association of its deficient state and cognitive decline among other neuropsychiatric disorder, results from this comprehensive research suggest that there is scarce evidence to support vitamin D supplementation for symptoms in AD. Herein, one high quality trial using a low dose of vitamin D supplementation during 8 weeks in a relatively small sample following a high-dose supplementation versus low-dose as placebo up to 16 weeks failed to show a benefit on cognitive or functional abilities. Authors considered the possibility that an effect of high-dose vitamin D could be prevented by a protective effect of low-dose D.

A sole study using Inositol, an isomer of glucose, in AD patients at different stages in a double blind crossover fashion, did not reach a significant improvement in cognition measured by the CAMCOG. Among other psychiatric disorders, inositol has reported significant benefits in small control trials the therapeutic strategy of depression, panic disorder and obsessive-compulsive disorder but not in schizophrenia, autism, attention deficit disorder, electroconvulsive therapy-induced memory impairment (290).

Ketogenic diet has been used to treat different neurological conditions, in a trial of medium chain triglyceride containing C8:0 fatty acids supplementation inducing ketosis in AD was not observed significant change in cognition measured by the MMSE or in global performance measured by the CGIC at any time point of follow up. The ADAS-cog exhibited a significant change at 45 days of treatment, after the treatment supplementation and after the two-week washout; there was no significant difference between active group and placebo. AD models fed with a high-fat/low-carbohydrate ketogenic diet improved motor performance but did not show any effect on Aβ accumulation (291). In contrast, another study testing high saturated fat/low-carbohydrate diet on a transgenic mouse model of AD found reduced Aβ brain levels but did not change behavioral measures (292). In human studies, a very low carbohydrate diet during 6 week in elderly with MCI displayed improved memory function, however did not exert an effect on depressive symptoms authors attributed this benefit to some mechanism involved with ketosis including adjustment of hyperinsulinemia, reduced inflammation and enhanced energy metabolism (293).

Across studies, there was observed inconclusive treatment effect of nutrients on clinical and neuropathological outcomes in patients diagnosed with AD at different stages, which may be

attributed to the fact of using separated nutrient supplementation overlooking the role of their counterpart to exert an appropriate physiological function in every metabolic pathway of the body. As it has been emphasized, nutrients have specific roles and are essential at some physiological level, but they work mutually in a complex sequential network system enhancing, boosting or even preventing the action among them. That also depends on many other components and factors, such as overall health status, biological use, interactions with medication and between nutrients, quality, amount and combination of food ingested. The slight tendency toward favoring nutrients intervention suggests that an approach joining nutrients altogether may offer strengthened benefits. The major embodiment of this concept is that nutrients are comprised as a unit, food. Despite the study of isolated nutrients function in the physiopathology have made significant contributions in understanding their individual roles and may be beneficial in states of insufficiency, treatment strategies cannot be focused in such manner. Single nutrient intervention is a narrowed approach putting aside the concept of food and nutrients synergy. The interrelation between constituents in foods is a remarkable fundament demonstrating that they act synergistically to influence the risk of several chronic diseases, it is well known that single nutrients naturally cannot exert functions independently, which is the basis for promoting consumption of food variety and selecting nutrient-rich foods (294–297). Our findings confirm that a nutrient-based perspective is limited and does not reach significant effects resulting in the observed abject results, while a food-based strategy may lead to more convincing and effective results in delaying or improving pathological sings and clinical manifestation. The proof that the association between nutrients and disease lies in the combination of foods within diet patterns and of nutrients in single foods is the Mediterranean diet. A higher adherence to this diet pattern is associated with better cognitive function, lower rates of cognitive decline, and reduced risk of developing MCI and AD (298,299). This same protective effect has been observed in the Dietary Approaches to Stop Hypertension (DASH) diet (300), and in a hybrid Mediterranean-DASH diets termed MIND diet (301). Evidently, these dietary patterns consist in well-balanced natural plant-based foods and limited intakes of animal, excluding fish that is consumed frequently, and high saturated fat foods. On other side, the western diet, comprising higher intake of unhealthy foods and poorer intake of nutrient-dense foods, has shown an association with a smaller hippocampus (302) implying a higher atrophy of brain structures involved in the neuropathology of AD, supporting the significant influence of diet in the brain health. Since AD has no cure but can be

prevented (303), nutrition needs to be implemented as a potential preventive approach and as an adjuvant treatment for AD patients at earlier stages, at the time that represent a cost-effective and safe strategy without the high costs (8), adverse effects and limited effectiveness of AD medication in a long term (304–309). Future studies may focus on identifying the foods or groups of food that might interact in a coordinate manner to improve or maintain brain function in the deteriorative process of this pathology.

5.2 Overall completeness and applicability of evidence

All studies were performed in developed countries, in the minority of studies that report participant's ethnicity or race, a higher percent correspond to Caucasian people. These observations might implicate a disadvantage since most people suffering from dementia live in low and middle-income countries, 58% worldwide, in the event that the biology of this population will differs substantially from the other one influencing the manner in which AD affects people from different race, genetic and environmental conditions. Nonetheless, as these interventions are based on nutrients that can be reached through an adequate dietary ingestion, populations living in developing countries are more prone to inadequate food intake and consequently subclinical nutrient deficient state, even more in vulnerable people such as elderly. This condition is likely to exert an impact in the nutrient supplementation treatment that could be reflected in improvement, deterioration or no effects. Unless a research is conducted, it is not possible to conclude whether these findings can be efficiently applied, and in which magnitude, or whether will be as the same beneficial, unresponsive or deleterious to those populations. Since nutritional treatments represent an inexpensive and ease of access strategy, we would expect that their beneficial effects are not restricted to lower socioeconomic groups; however, there are some implicit issues determined by limiting aspects for example concomitant diseases, and external factors like food security and healthcare systems, economic, and political affairs.

5.3 Potential biases and limitations in the review process

The principal limitation in the analysis of results was the variety of measurement scales used to assess neuropsychological outcomes and incomplete reporting of results (reporting bias) that we could not obtain from study authors, generating difficulties in pooling the results of trials.

There were limitations in the retrieval of unpublished or gray literature that limit the extent of our results.

Several studies assessing single nutrients have small sample size what may introduce bias in the statistical analysis, indeed few studies match type of compound, dosage and time point measurement leading to heterogeneity in results. Some of the trial duration may be too short for the intervention to bring about noteworthy differences in cognitive domains and functions that comprises acquiring knowledge and skills that might not be affected following the nutritional supplementation on the shorter term. We also find some limitations in which cognitive domain nutrients could exert an influence, and not enough data for adjustment of possible important confounding variables, for example education level or dietary nutrients intake. It is noteworthy that most studies found regarding to nutrient intervention in dementia were conducted in healthy elderly or with MCI, few studies assessed patients diagnosed with AD, in which there were found these large variabilities among them.

CONCLUSION

This study examined whether nutrients, food and/or specific dietary patterns would improve or stave off, partial or totally, clinical and neuropathological manifestations in elderly patients diagnosed with AD. Throughout all nutrients have been described as having a modulator, functional and structural role in the CNS as previously indicated, thus supplementation with nutrients would lead to synergistic improvements in mental performance. Through this employed method, it was possible to observe that most interventions somewhat lean toward favoring nutrient active group, however, no compelling evidence of a substantial effect on cognitive, functional, behavioral or global outcomes was found in AD patients at different stages supplemented with isolated or some combined nutrients in scant well design clinical trials.

These findings do not support our hypothesis and lead us to assume that as a treatment strategy for AD, the mutual interaction of nutrients enhancing the action of each other on brain function, at cognitive or behavioral level, should not be segregated. Future studies regarding single nutrients may focus on their role or behavior in the pathological process of this disease and possibly in other body systems affected by the altered brain neurological functions, as well as their interaction with other nutrients, or medications; rather than their isolated supplementation as a treatment. In such cases, we encourage monitoring dietary nutrients ingestion and related factors. Thus, nutrients may arise as a preventive approach and an adjuvant treatment for persons with AD at earlier stages.

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APPENDICES

Appendix 1: Articles screened and abstracts description

Number of study	Reference (authors, title and source of publication)	Abstract	Clinical situation	Intervention	Type of study	Inclusion (Y or N)	Justification for rejection of the study
1							
2							
3							
4							
5							
6							
7							

OBS.: Study variables are not considered as criteria for inclusion or exclusion in this first stage of the systematic review

Appendix 2: PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	i
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	vii
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	22
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	23
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	n.a.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	24-25
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	25
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	25-27
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	27
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	27
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	28
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	28-30
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	31-32
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	33-36

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	92-93
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	36
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	37-40
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	41-46
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	62-64
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	74-92
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	74-92
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	77-87
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	74-75,78,86
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	94-100
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	109-110
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	101-111
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	v

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Appendix 3. Data extraction from studies

DATA COLLECTION FORM (Adapted from the Cochrane Public Health Group Form of Data Extraction and Assessment Template)

1. General Information

Date Extraction	Study funding sources
Study ID *(first author, year of publication)*	Possible conflicts of interest
Citation	Country of study
Report title	Report IDs of other reports of this study *(e.g. duplicate publications)*
Publication type	Abstract
Report author contact details	Classification Nutrient

2. Study Eligibility

Study Characteristics	Eligibility criteria *(Insert eligibility criteria for each characteristic as defined in the Protocol)*	Meet criteria			Location in text
		Yes	No →Exclude	Unclear	
Type of study	RCT / Controlled Clinical Trial / Non-RCT				
Participants	specific social or cultural characteristics geographic boundary defined				
Types of intervention	Strategies included in the intervention Focus of the intervention/assessment				
Duration of intervention	Start date / Stop date / Duration				
Outcome measures	(measured at a population or individual level)				
INCLUDE ☐ EXCLUDE ☐					
Independently assessed, and then compared?					
Differences resolved					
Request further details?					
Notes: (Reason for exclusion)					

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

3. Methods

	Description/ Location in text		Description/ Location in text
Intervention/observation group		Type of randomization	
Setting		Representativeness of sample	
Method/s of recruitment of participants		Assumed risk estimate	
Inclusion criteria		Unit of analysis	
Exclusion criteria		Statistical methods	
Control or placebo?		Calculation sample size (power)	

4. Participants

	Description/ Location in text		Description/ Location in text
Total num. randomized		Age and Gender	
% individuals agreed to participate		Race/Ethnicity	
N° allocated to each group		Co-morbidities	
Diagnostic criteria		Other relevant sociodemographic	
Principal health problem (stage of illness)		Subgroups	

5. Intervention

Intervention Group

	Description/ Location in text		Description/ Location in text
Intervention assessment		Duration of intervention	
Delivery *(e.g. mechanism, intensity, etc)*		Duration of follow up	
Providers *(e.g. profession, training, etc.)*		Co-interventions	

Dose *(amount, frequency, consistency)*		Economic variables	
Via administration		Intervention-control subgroups	

6. Outcomes Description/ Location in text

Measure application	

Primary Outcomes		**Secondary Outcomes**	
Test/scales		Biochemical test	
Upper and lower limits, cut-off		Upper and lower limits, cut-off	
Is outcome/tool validated?	Yes No Unclear	Inflammation/ Oxidative stress markers	
Imaging test		Upper and lower limits, cut-off	
Details of brain imaging			

7. Results

Dichotomous outcome	Description/ Location in text	***Continuous outcome***	Description/ Location in text
Comparison		Comparison	
Outcome		Outcome	
Timepoint		Timepoint	
Results (Intervention and Comparison)	No. events/ participants	Results (Intervention and Comparison)	Mean SD (Initial, Final Change from baseline), N
Result of analyses		Test (differences between changes during treatment intervention vs. comparison groups)	
Sample size: initial and final		Sample size initial and final	
No. dropouts and reasons		No. dropouts and reasons	
Any other results reported		Subgroup results (Intervention and Comparison)	Mean SD (Initial, Final Change from baseline), N
Reanalysis required?	Yes No Unclear	Reanalysis required?	Yes No Unclear

8. Other information Description/ Location in text Description/ Location in text

Intention-to-treat		Key conclusions of study authors	
Adverse events/ effects		References to other relevant studies	

Appendix 4. Risk of bias assessment

The Cochrane Collaboration's tool for assessing risk of bias

Source of Bias (Domain)	Support for judgement	Cochrane Criteria	Review authors' judgment Low risk	High risk	Unclear
Random sequence generation *(selection bias)*					
Allocation concealment *(selection bias)*					
Blinding of participants and personnel *(performance bias)*					
Blinding of outcome assessment *(detection bias)*					
Incomplete outcome data *(attrition bias)*					
Selective outcome reporting? *(reporting bias)*					
Other bias					

Appendix 5. High risk of bias studies

RISK OF BIAS ASSESSMENT OF EXCLUDED STUDIES								
Study ID	**Summarizing risk of bias for a study**	**Selection bias**		**Performance bias**	**Detection bias**	**Attrition bias**	**Reporting bias**	**Other bias**
		Random sequence generation	**Allocation concealment**	**Blinding of participants and personnel**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective reporting**	**Other sources of bias**
Manders et al, 2009 (the Netherlands)	High risk of bias	Allocation based on the results of a laboratory test or a series of tests	the method of concealment is not described or not described in sufficient detail to allow a definite judgement	Insufficient information to permit judgement	Insufficient information to permit judgement	Insufficient information to permit judgement	All of the study's pre-specified outcomes that are of interest in the review have been reported	Insufficient information to assess whether an important risk of bias exists
		High risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk
Young et al, 2004 (Canada)	High risk of bias	Allocation by availability of the intervention.	Sequentially numbered, opaque, sealed envelopes.	No blinding, Insufficient information to permit judgement	Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.??	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups	All of the study's pre-specified outcomes that are of interest in the review have been reported	The study appears to be free of other sources of bias.
		High risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk
Arlt et al, 2012 (Germany)	High risk of bias	Insufficient information about the sequence generation process to judge	No concealment	No blinding, Insufficient information to permit judgement	No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding	The study did not address this outcome	All of the study's pre-specified outcomes that are of interest in the review have been reported	Had a potential source of bias related to the specific study design used
		Unclear risk	High risk	Unclear risk	Low risk	Unclear risk	Low risk	High risk
Chan et al, 2009 (USA)	High risk of bias	Non-randomized trial	No concealment	non-blinded	Insufficient information to judge	The study did not address this outcome	One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis	Insufficient information to assess whether an important risk of bias exists
		High risk	High risk	Unclear risk	Unclear risk	Unclear risk	High risk	High risk
Petersen RC, et al, 2005 (USA and Canada)	High risk of bias	Allocation based on the results of a laboratory test or a series of tests	the method of concealment is not described or not described in sufficient detail to allow a definite judgement	Insufficient information to judge	Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.	Missing data have been imputed using appropriate methods	All of the study's pre-specified outcomes that are of interest in the review have been reported	The study appears to be free of other sources of bias
		High risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
Parrott et al, 2006 (Canada)	High risk of bias	Allocation by availability of the intervention.	Sequentially numbered, opaque, sealed envelopes.	No blinding or incomplete blinding, Insufficient information to judge	Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken	Missing data have been imputed using appropriate methods.	One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis;	The study appears to be free of other sources of bias.
		High risk	Low risk	Unclear risk	Low risk	Low risk	High risk	Low risk

A. Salva et al, 2011 (Spain)	High risk of bias	Allocation by judgement of the clinician	No concealment	No blinding	Insufficient information to permit judgement	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups	All of the study's pre-specified outcomes that are of interest in the review have been reported	The study appears to be free of other sources of bias.
		High risk	High risk	High risk	Unclear risk	Low risk	Low risk	Low risk
J. Salas-Salvado´ et al. 2005 (Spain)	High risk of bias	Insufficient information about the sequence generation process to judge	Central allocation, but does not report if including telephone, web-based and pharmacy-controlled randomization	Insufficient information to permit judgement	Insufficient information to permit judgement	Insufficient reporting of attrition/exclusions to permit judgement	One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis;	The study appears to be free of other sources of bias.
		High risk	Unclear risk	High risk	Unclear risk	Unclear risk	High risk	Low risk
K. Hager et al., 2007 (Australia)	High risk of bias	Allocation by availability of the intervention	Not concealment of allocations prior to assignment	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding	The study did not address this outcome	Insufficient reporting of attrition/exclusions to judge	All of the study's pre-specified outcomes that are of interest in the review have been reported	The study appears to be free of other sources of bias.
		High risk	High risk	High risk	Unclear risk	Unclear risk	Low risk	Low risk
Apostolova et al.2013 (USA)	High risk of bias	Allocation based on the results of a laboratory test or a series of tests	Insufficient information about allocation concealment	Insufficient information to permit judgement	Insufficient information to permit judgement	Insufficient reporting of attrition/exclusions to judge	One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis;	Insufficient information to assess whether an important risk of bias exists
		High risk	Unclear risk	Unclear risk	Low risk	Unclear risk	High risk	Unclear risk
C.R. Jack Jr. et al. 2008 (USA)	High risk of bias	Allocation based on the results of a laboratory test or a series of tests	The method of concealment is not described or not described in sufficient detail to allow a definite judgement	Insufficient information to permit judgement	Insufficient information to permit judgement	Insufficient information to permit judgement	All of the study's pre-specified outcomes that are of interest in the review have been reported	The study appears to be free of other sources of bias.
		High risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk
Lauque et al. 2004 (Frace)	High risk of bias	Drawing of lots	The method of concealment does not ensure the blindness in participants and personnel	Insufficient information to permit judgement	Insufficient information to permit judgement	Missing data have been imputed using appropriate methods.	All of the study's pre-specified outcomes that are of interest in the review have been reported	The study appears to be free of other sources of bias
		Low risk	High risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
Remington et al, 2010 (USA)	High risk of bias	Insufficient information about the sequence generation process	No concealment	No blinding and the study did not address this outcome	Insufficient information to permit judgement	No missing outcome data	All of the study's pre-specified outcomes that are of interest in the review have been reported	Open label
		High risk	High risk	High risk	Unclear risk	Low risk	Low risk	High risk

Appendix 6. Ficha do aluno

Janus - Sistema Administrativo da Pós-Graduação

Universidade de São Paulo
Interunidades em Nutrição Humana Aplicada
Documento sem validade oficial
FICHA DO ALUNO

89131 - 8846589/1 - Shirley Steffany Muñoz Fernandez

Email:	shirleymf@usp.br
Data de Nascimento:	27/07/1989
Cédula de Identidade:	RNE - V998726-U - DF
Local de Nascimento:	Colômbia
Nacionalidade:	Colombiana
Graduação:	Nutricionista Dietista - Universidad Del Atlántico - Atlántico - Colômbia - 2011

Curso:	Mestrado
Programa:	Nutrição Humana Aplicada (1)
Data de Matrícula:	31/03/2014
Início da Contagem de Prazo:	31/03/2014
Data Limite para o Depósito:	30/09/2016
Orientador:	Prof(a). Dr(a). Sandra Maria Lima Ribeiro - 31/03/2014 até o presente. Email: smlribeiro@usp.br
Proficiência em Línguas:	Inglês, Aprovado em 31/03/2014
Data de Aprovação no Exame de Qualificação:	Aprovado em 01/10/2015
Data do Depósito do Trabalho:	
Título do Trabalho:	
Data Máxima para Aprovação da Banca:	
Data de Aprovação da Banca:	
Data Máxima para Defesa:	
Data da Defesa:	
Resultado da Defesa:	
Histórico de Ocorrências:	Primeira Matrícula em 31/03/2014

Aluno matriculado no Regimento da Pós-Graduação USP (Resolução nº 5473 em vigor de 18/09/2008 até 19/04/2013).
Última ocorrência: Matrícula de Acompanhamento em 18/07/2016
Impresso em: 18/08/2016 18:24:53

Janus - Sistema Administrativo da Pós-Graduação

Universidade de São Paulo
Interunidades em Nutrição Humana Aplicada
Documento sem validade oficial
FICHA DO ALUNO

89131 - 8846589/1 - Shirley Steffany Muñoz Fernandez

Sigla	Nome da Disciplina	Início	Término	Carga Horária	Cred.	Freq.	Conc.	Exc.	Situação
MNE5718-6/2	Estratégias de Pesquisa Clínica em Demência (Faculdade de Medicina - Universidade de São Paulo)	14/04/2014	27/04/2014	60	4	100	B	N	Concluída
FBA5712-6/1	Fisiologia da Nutrição I (Faculdade de Ciências Farmacêuticas - Universidade de São Paulo)	19/05/2014	29/06/2014	90	6	100	A	N	Concluída
HNT5711-6/3	Recursos Alimentares para Populações (Faculdade de Saúde Pública - Universidade de São Paulo)	05/08/2014	25/08/2014	30	0	-	-	N	Turma cancelada
EAE5876-5/2	Economia da Alimentação e Nutrição (Faculdade de Economia, Administração e Contabilidade - Universidade de São Paulo)	08/08/2014	05/12/2014	120	8	88	B	N	Concluída
FBC5722-2/3	Controle Hormonal da Resposta Inflamatória (Faculdade de Ciências Farmacêuticas - Universidade de São Paulo)	02/09/2014	22/09/2014	60	4	100	A	N	Concluída
HNT5705-5/4	Consumo Alimentar de Populações (Faculdade de Saúde Pública - Universidade de São Paulo)	03/03/2015	17/04/2015	60	4	100	A	N	Concluída
HEP5800-3/10	Bioestatística (Faculdade de Saúde Pública - Universidade de São Paulo)	03/03/2015	14/05/2015	90	6	100	A	N	Concluída
EDM5100-2/1	A Formação do Professor Universitário (Faculdade de Educação - Universidade de São Paulo)	10/03/2015	01/06/2015	120	0	-	-	N	Pré-matrícula indeferida
NEC5719-3/1	Preparação Pedagógica (Instituto de Psicologia - Universidade de São Paulo)	11/03/2015	29/04/2015	30	2	100	A	N	Concluída
NHA5706-1/1	Fragilidade no Idoso: Prevenção e Intervenções Relacionadas à Nutrição e Atividade Física	02/04/2015	22/04/2015	30	2	100	A	N	Concluída
FBA5728-3/11	Aprimoramento Didático (Faculdade de Ciências Farmacêuticas - Universidade de São Paulo)	14/04/2015	11/05/2015	60	0	-	-	N	Pré-matrícula indeferida
HNT5762-1/3	Revisão Sistemática e Meta-Análise (Faculdade de Saúde Pública - Universidade de São Paulo)	10/08/2015	16/08/2015	30	2	100	A	N	Concluída

	Créditos mínimos exigidos		Créditos obtidos
	Para exame de qualificação	Para depósito da dissertação	
Disciplinas:	25	25	38
Estágios:			
Total:	25	25	38

Créditos Atribuídos à Dissertação: 71

Observações:

1) Unidades de Ensino responsáveis pelo programa: Faculdade de Saúde Pública - Faculdade de Ciências Farmacêuticas - Faculdade de Economia, Administração e Contabilidade..

Conceito a partir de 02/01/1997:

A - Excelente, com direito a crédito; B - Bom, com direito a crédito; C - Regular, com direito a crédito; R - Reprovado; T - Transferência.

Um(1) crédito equivale a 15 horas de atividade programada.

Última ocorrência: Matrícula de Acompanhamento em 18/07/2016

Impresso em: 18/08/2016 18:24:53