Javier Olivera-Pueyo[1,3]
Carmelo Pelegrín-Valero[2,3]

Dietary supplements for cognitive impairment

[1]Programa de Psicogeriatría, Servicio de Psiquiatría, Hospital San Jorge. Huesca
[2]Jefe de Servicio de Psiquiatría, Hospital San Jorge. Huesca
[3]Profesor Asociado. Universidad de Zaragoza

Alzheimer disease and the other neurodegenerative dementias as yet have no curative treatment. For this reason, the prevention of these conditions and non-pharmacological treatments are important fields of research at present.

The Mediterranean diet (rich in fruits, vegetables, legumes, and olive oil, with regular fish consumption and low consumption of dairy products and meats) has been shown to reduce the incidence of mild cognitive impairment (MCI) and, probably, the conversion of MCI to dementia. Vitamins, especially vitamin E and the vitamins of the B group, have also been associated with the prevention of cognitive impairment due to their antioxidant effects. Ginkgo biloba is one of the most widely used supplements in the world for cognitive improvement because of its possible effects as a vasodilator and facilitator of cerebral vascularization. Green tea polyphenols have shown beneficial effects in different diseases, including cognitive impairment. Cerebral aging is associated with changes in the lipid composition of neuronal membranes, so it has been suggested that treatment with phospholipids like phosphatidylcholine and phosphatidylserine could favor cognitive improvement. Similarly, polyunsaturated and omega-3 fatty acids, and docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) supplements are associated with a beneficial effect on cognitive function due to the cumulative summation of factors that ultimately favor membrane permeability and neuronal functioning.

Key words: Cognitive impairment, Dementia, Diet, Polyunsaturated fatty acids

Actas Esp Psiquiatr 2017;45(Suppl. 1):37-47

Suplementos nutricionales para el deterioro cognitivo

Tanto la enfermedad de Alzheimer como el resto de demencias neurodegenerativas carecen, a día de hoy, de un tratamiento curativo. Por ello la prevención y los tratamientos no farmacológicos representan, en este momento, importantes focos de investigación.

La adherencia a la dieta mediterránea (rica en frutas, verduras y legumbres, así como en aceite de oliva, con un consumo regular de pescado, con bajo consumo de lácteos y carnes) se ha demostrado que reduce la incidencia de deterioro cognitivo leve (DCL) y probablemente la conversión del DCL a demencia. Las vitaminas, especialmente la vitamina E y las del grupo B, también se han asociado con la prevención del deterioro cognitivo gracias a sus efectos antioxidantes. El Ginkgo biloba es uno de los suplementos más utilizados en el mundo para la mejoría cognitiva debido a sus posibles efectos vasodilatadores y facilitadores de la vascularización cerebral. Los polifenoles del té verde han demostrado efectos beneficiosos en diferentes enfermedades incluido el deterioro cognitivo. El envejecimiento cerebral se asocia con cambios en la composición de los lípidos en las membranas neuronales, por ello se ha sugerido que el tratamiento con fosfolípidos como la fosfatidilcolina y la fosfatidilserina podrían favorecer la mejoría cognitiva. Del mismo modo los ácidos grasos poliinsaturados, omega-3, y los suplementos de ácido docosahexanoico (DHA) y ácido eicosapentanoico (EPA) se asocian con un efecto beneficioso para las funciones cognitivas debido a una suma acumulativa de factores que finalmente favorecen la permeablidad de las membranas y el funcionamiento neuronal.

Palabras clave: Deterioro cognitivo, Demencia, Dieta, Ácidos grasos poliinsaturados

Correspondence:
Javier Olivera Pueyo
Servicio de Psiquiatría
Hospital San Jorge
Avd. Martínez de Velasco, nº 36
22004, Huesca (Spain)
E-mail: joliverp@aragon.es

INTRODUCTION: THE MEDITERRANEAN DIET: MYTH OR REALITY?

Cognitive impairment and dementia continue to be complex processes with multiple causes for which there is no curative treatment in most patients.[1] For that reason, patients, family members, and the healthcare professionals who work with these patients demand the use of complementary forms of treatment that include nutritional supplements to improve cognitive health.[2]

In recent decades, it has been hypothesized that the Mediterranean diet could be the most adequate for human health. The Mediterranean diet is understood to be a diet containing large amounts of fruit, vegetables, and legumes, olive oil rich in polyphenols, regular fish consumption, low consumption of meats and dairy products, and moderate consumption of red wine.[3] Numerous studies have shown that following the Mediterranean diet reduces the incidence of mild cognitive impairment in the population and can also reduce the rate of conversion of mild cognitive impairment to Alzheimer disease.[4,5] The benefit of this diet may be due to a set of summative effects: the antioxidant effect of fruits and vegetables, the effect of the omega-3 fatty acids of oily fish, and the neuroprotective effect of olive oil,[6] but follow-up studies clarifying these effects are still pending.[5] In any case, the majority of studies suggest that cognitive health improves with greater adherence to the Mediterranean diet.[7,8] Cognitive function seems to be favored still more when the Mediterranean diet is supplemented with extra virgin olive oil.[9]

However, other studies suggest that the "diet" is not the only protective factor, but that it is probably the Mediterranean "lifestyle" that really favors good cognitive health: an important framework of frequent social relationships, a healthy diet, frequent exercise,[10] and, possibly, other factors that we cannot yet define precisely, but might refer to more complex and profound issues, such as the way of life, relationship with the environment, and other factors.[11]

Nevertheless, according to extensive and reasoned reviews of the available studies to date, it seems that the strongest and most consistent evidence supports adherence to the Mediterranean diet as a factor in maintaining cognitive health.[7,12]

VITAMINS AND MINERALS

The antioxidant and neuroprotective effect associated with most vitamins has recently focused interest on the possible benefits of different vitamin types and groups as coadjuvant treatment for Alzheimer disease.[13] This interest is related to the current focus on the theory that associates oxidative stress with synaptic dysfunction and the accumulation of beta-amyloid and hyperphosphorylated Tau protein in Alzheimer disease.[14]

- Vitamin E

  This group includes the tocopherol and tocotrienol derivatives. Alpha-tocopherol is the usual form for medical use. Vitamin E is a fat-soluble vitamin found in many foods: vegetable oils, grains, meat, poultry, eggs, fruit, vegetables, and wheat germ oil. It can also be provided as a pharmacological supplement. It may have an important role in preventing the peroxidation of the polyunsaturated fatty acids found in membrane phospholipids and in plasma lipoproteins.[15]

  In studies of the possible effect of vitamin E (dose of 2000 IU/day) in patients with Alzheimer disease, some of these patients showed some improvement in the basic activities of daily living and general functioning compared to patients treated with placebo.[16] Oxidative stress markers have also been shown to decrease following treatment. However, there is insufficient evidence of its overall long-term effect on mild cognitive impairment to justify the use of vitamin E according to the Cochrane Review.[17] In any case, it is recommended that the external supply of vitamin E should not exceed 4000 IU/day, and that this precaution should be increased in people with cardiac or vascular problems. However, other studies in older women suggest that high doses of vitamin E and other antioxidants may be associated with a lower risk of vascular dementia and better cognitive function.[18]

- Group B vitamins (B6, B9, B12)

  Although the studies are not conclusive, vitamin B supplements have been commonly used to improve cognition.[19] In previous studies, the effect of vitamin B supplements on cognition has been examined, including vitamin B6, vitamin B9 (folates) and B12 (cyanocobalamin). These studies were based on the hypothesis that elevated homocysteine levels are associated with a higher risk of dementia and one of the most common causes of elevated homocysteine levels is B6, B9 or B12 deficiency.[20]

  However, systematic reviews that include clinical trials with not very extensive samples in people receiving vitamin B supplements to prevent the progression of cognitive impairment have not demonstrated efficacy in either healthy individuals or in patients with previous cognitive impairment.[21-23]

  High doses of vitamin B have not been shown to slow the progression of cognitive impairment in patients with dementia.[24] Some authors have even suggested

that high doses of vitamin B might increase depressive symptoms in patients with Alzheimer disease.[25]

- Vitamins A and C

  Although vitamin A and vitamin C are common in nutritional supplements and both have been attributed antioxidant activity, they do not appear to have demonstrated efficacy in the treatment of cognitive impairment.[2] A diet with sufficient vitamin C intake is recommended to associate its beneficial antioxidant effect to a possible prevention of this oxidative factor also present in cerebral aging and in Alzheimer disease.[26]

- Vitamin D

  The effects of vitamin D can be localized in the bones, as well as outside the musculoskeletal system. It is synthesized in the skin as vitamin D3 (cholecalciferol), but it is also obtained from the diet or from supplements such as vitamin D3 or D2 (ergocalciferol). In the brain, vitamin D receptors have been identified in the cerebral cortex and in the hippocampus, areas which are linked to cognitive functions. Vitamin D is attributed anti-neurodegenerative actions associated with anti-inflammatory, antioxidant and anti-ischemic effects. In a systematic review of five observational studies it was concluded that high levels of 25-hydroxy vitamin D were associated with improved cognitive function,[27] while low levels of vitamin D (25-hydroxy vitamin D less than 75 nmol/L) are associated with an increased risk of cognitive impairment,[28] and other studies have found an association between low doses of vitamin D with worse cognitive function evaluated with the Short Portable Mental State Questionnaire.[29]

- Minerals

  We have studied the ingestion of different minerals, especially calcium, potassium, and magnesium, with the development of dementia related to both Alzheimer disease and vascular dementia.[30]

  The most conclusive findings seem to suggest that magnesium supplements could reduce the risk of cognitive impairment, while high potassium and iron ingestion could encourage increased development of cognitive impairment.[31] It appears that magnesium plays an important role in different cellular processes, such as oxidative phosphorylation, glycolysis, cellular respiration and protein synthesis.[32] It is suspected that a decrease in magnesium, particularly in the hippocampus, may be related to the pathogenesis of Alzheimer disease.[33] Magnesium supplements in animal models of Alzheimer disease have improved cognitive function and synaptic plasticity.[34]

GINKGO BILOBA

This herbal product comes from a deciduous tree of Asian origin. An extract of leaves, which contain flavonoids and terpenoids (bilobalides and ginkgolides A, B, C and J), is obtained for medicinal use.[35] Ginkgo biloba is one of the supplements for cognitive health most widely used worldwide. The usual dose is 120-240 mg/day. Ginkgo biloba is assumed to improve brain function through mechanisms that include improving cerebrovascular circulation by facilitating cerebral vasodilation, reducing blood viscosity, reducing free radical oxidation, and reducing the decrease in neurotransmitter receptors associated with age.[36,37] Some studies have suggested that the benefits of Ginkgo biloba supplements are insufficient in preventing dementia.[38]

However, for the Cochrane Review, there is cumulative evidence suggesting that Ginkgo biloba could improve cognitive decline associated with aging and dementia.[39] In any case, its use should be carefully evaluated in patients at risk of bleeding or who receive treatment with drugs that are metabolized by cytochrome CYP2C19, such as omeprazole or valproic acid, since Ginkgo biloba induces this enzyme.[40]

GINSENG

Ginseng is also one of the most widely used herbal supplements in the world for cognitive enhancement.[41,42] Ginsenosides are the active component. They appear to attenuate the toxicity of β-amyloid protein and could be of interest in treating Alzheimer disease.[43] Open-label studies have been conducted in very specific populations that have shown cognitive improvement after up to 2 years of follow-up in patients with Alzheimer disease treated with doses of Korean red ginseng between 4.5 and 9 g/day.[44]

In systematic reviews, it has been concluded that studies of different ginseng supplements are too heterogeneous in terms of dose, measurement instruments, and sample size to extract conclusive results regarding their benefit in improving cognition in healthy adults, mild cognitive impairment, or dementia. In any case, it appears that no serious adverse effects have been reported with ginseng supplements in any of these studies.[42]

POLYPHENOLS

The tea beverage originated in China 4000 to 5000 years ago. All the cultivated tea variants come from the species *Camelia sinensis*. The main differences and the relevance for health issues between different teas are based on the degree of fermentation and oxidation of the polyphenols in fresh tea leaves. During fermentation,

polyphenols (theoflavins and theorubigins) are oxidized; polyphenol content varies according to the degree of fermentation of the tea. Black tea is fermented and green tea is unfermented. The antioxidant and anti-inflammatory effects of tea are attributed to its polyphenols.[45]

In recent decades numerous studies, both experimental and epidemiological, have highlighted the health benefits of tea consumption for various conditions ranging from cardiovascular disease to cancer, and even its influence on general mortality.[46,47] The neuroprotective effect of tea associated with its polyphenol content has also been studied.[48,49] Green tea consumption has subsequently been associated with a lower prevalence of cognitive impairment in the Japanese and Chinese populations.[45,50]

The benefits of tea consumption on mild cognitive impairment and age-associated cognitive decline have been confirmed in prospective studies[51] and in recent meta-analyses.[52]

PHOSPHOLIPIDS: PHOSPHATIDYLCHOLINE AND PHOSPHATIDYLSERINE

Aging is associated with changes in cerebral lipid composition. Phospholipids are fundamental components of the neuronal membranes and it has been suggested that they could contribute to an effective therapy for the treatment and prevention of cognitive decline.[53]

- Phosphatidylcholine

  Citicoline (cytidine 5'-diphosphocholine) is a compound synthesized by all mammalian cells and it is an intermediate compound in the main pathway of transformation from choline to phosphatidylcholine. Citicoline is a precursor and activates the synthesis of the structural phospholipids of the neuronal membrane, increasing cerebral metabolism and slightly raising dopamine and noradrenaline levels. Citicoline may protect the neuronal membrane through a double mechanism[54]:

  - accelerating the re-synthesis of phosphatidylcholine
  - suppressing free fatty acid release.

  Phosphatidylcholine (for which citicoline is a precursor) is one of the membrane phospholipids that breaks down during cerebral ischemia, forming free radicals. It is therefore thought that citicoline administration might protect neuronal membranes by accelerating phospholipid re-synthesis. For that reason, it has been used for more than three decades for the treatment of brain processes that occur with neuronal deterioration, both acute (cerebral infarction, traumatic brain injury) and chronic (neurodegenerative diseases).

  Adverse effects of citicoline are uncommon and include hallucinations, headache, vertigo, reduced or increased blood pressure, nausea and vomiting, dyspnea, flushing, rash, edema, or purpura.

  In the case of mild cognitive impairment, the use of citicoline would be especially indicated in cognitive impairment of vascular origin because studies carried out in patients with cerebrovascular diseases have yielded positive results.[54] Citicoline also probably improves chronic cerebral vascular damage or "cerebrovascular insufficiency", which is a common element in the cognitive deterioration of the elderly, as stated by the Cochrane review. It is suggested that doses of citicoline between 600 and 1000 mg daily could have a positive effect on memory and behavior in the short and medium term in people who have cognitive impairment associated with cerebrovascular disease.[55]

- Phosphatidylserine

  Since the 1990s, the results of various studies with oral phosphatidylserine supplements suggest cognitive and behavioral improvement in patients with cognitive impairment.[56] The U.S. Food and Drug Administration (FDA) acknowledges that "supplemental phosphatidylcholine use may reduce the risk of cognitive dysfunction in the elderly."[57]

  Phosphatidylserine is a structural phospholipid of the cell membranes, especially in the cells of the brain and nervous system. It is probably the most important phospholipid in all the membranes of the human body, constituting between 2% and 20% of all the phospholipids in plasma of adult humans and intracellular membranes. Myelin is rich in phosphatidylserine (PS) and the content of this phospholipid doubles in the cerebral gray matter from birth to old age.[58] The phosphatidylserine content in the cerebral omega-3 fatty acid docosahexaenoic acid (DHA) is of transcendental importance.[59] It has been shown that a reduction in DHA phosphatidylserine content in the cerebral cortex is associated with progression from mild cognitive impairment to Alzheimer disease.[60]

  Young people are thought to synthesize enough phosphatidylserine to meet their needs and maintain functions. However, the risk of phospholipid deficiency increases starting in the fourth or fifth decade. It has also been shown that during aging the phosphatidylserine content diminishes and the proportion of cholesterol increases in neuronal membranes, leading to neurochemical changes that contribute to increasing cell membrane viscosity by reducing enzymatic activity.[61,62]

Phosphatidylserine is very abundant in the brains of animals, as well as in viscera (liver, kidney, heart, spleen, offal ...), but it is also found in blue fish (mackerel, herring, eel, tuna ...), some vegetables such as soy, and in egg yolk.

In the first studies carried out with phosphatidylserine, this phospholipid was obtained from the distillation of bovine brains, which had the greatest concentration of this phospholipid. However, the spread of bovine spongiform encephalopathy ("mad cow disease") stopped the use of this source of extraction. Therefore, all study materials and commercially marketed forms of phosphatidylserine are currently derived from soy lecithin.

Phosphatidylserine derived from soy has been established as a safe alternative and is used as a nutritional supplement, also for the elderly, at a dose of 100 mg to 200 mg taken three times a day.

In humans, the incorporation of exogenous FS (supplements) in brain structures is functionally relevant. In studies using positron emission tomography (PET) to investigate the use of cerebral glucose in patients diagnosed with Alzheimer disease, there is a significant increase in glucose utilization following the administration of phosphatidylserine supplements, especially in the temporal and parietal areas most affected by the disease.[63]

In a number of open-label clinical trials using dietary supplements of phosphatidylserine 300 mg/day (100 mg three times daily) in patients with mild cognitive impairment or very early stage dementia, significant improvement in learning, memory, and verbal fluency, as well as visual learning, attention, communication, initiative and socialization, have been observed.[64-67]

The efficacy of oral phosphatidylserine supplements has been demonstrated in double-blind, placebo-controlled studies, especially in patients with memory impairment without dementia, improving verbal recall, attention, vigilance, and even initiative and apathy.[68,69]

In the case of depressed elderly patients with frequent association of memory loss, the administration of phosphatidylserine 300 mg/day reduced apathy, increased motivation and interest, and improved memory.[70]

OMEGA-3 FATTY ACIDS

Since the 1990s numerous studies have been published on the health benefits of fish oils due to their high fatty acid content. These health effects have been demonstrated in different areas: cardiovascular diseases, inflammatory diseases, brain development and function, as well as mental illness and cognitive decline.[71,72]

Omega-3 fatty acids are essential fatty acids that humans cannot synthesize efficiently from other substances. They are always supplied externally by either diet or specific supplements.

The omega-3 fatty acids are polyunsaturated fatty acids and include:

- Alpha-linolenic acid (ALA)
- Eicosapentaenoic acid (EPA)
- Docosahexaenoic acid (DHA)

Docosahexaenoic acid (DHA) is the center of attention because it is considered a fatty acid essential for development and maintaining health. Adequate DHA levels are essential for cognitive functioning throughout the life cycle, from conception to the end of life.[73] However, EPA is essential in the synthesis and metabolism of DHA and, in turn, there must be an adequate balance in the body between the synthesis of Omega-3 and Omega-6 polyunsaturated fatty acids, facilitating inflammation phenomena when required by cellular organisms and an anti-inflammatory effect in processes such as aging or in neurodegenerative diseases (Figure 1).

The main natural sources of DHA are some oily fish (mainly mackerel and herring), oils derived from these fish and some seaweeds. DHA is found in photosynthetic heterotrophic microalgae that are ingested by oily fish. Polyunsaturated fatty acids are ingested through plant derivatives with alpha-linoleic acid (ALA), fish and marine products rich in omega-3 fatty acids, or through DHA and EPA supplements.

DHA is the main long-chain polyunsaturated fatty acid present in the brain. DHA concentration is very high in the cerebral areas richest in synapses and neuronal proliferation, constituting 30% to 40% of all polyunsaturated fatty acids in cerebral gray matter.

DHA appears to be essential for the proper development of the human brain.[74] It has been shown that DHA concentrations progressively increase from the last trimester of pregnancy to peak levels at the age of 2 years.[75] Consequently, adequate intake of a diet rich is omega-3 polyunsaturated fatty acids is also very important in pregnant women.[76]

DHA levels appear to stabilize later on in childhood and into adulthood, eventually decreasing during aging. This progressive decrease in DHA has also been shown to be more pronounced in patients with cognitive impairment. It has been observed, for example, that patients with Alzheimer disease had 60% to 70% less docosahexaenoic acid (DHA) in serum and brain compared to other healthy persons of the same age.[77,78] Low serum DHA levels appear to be associated

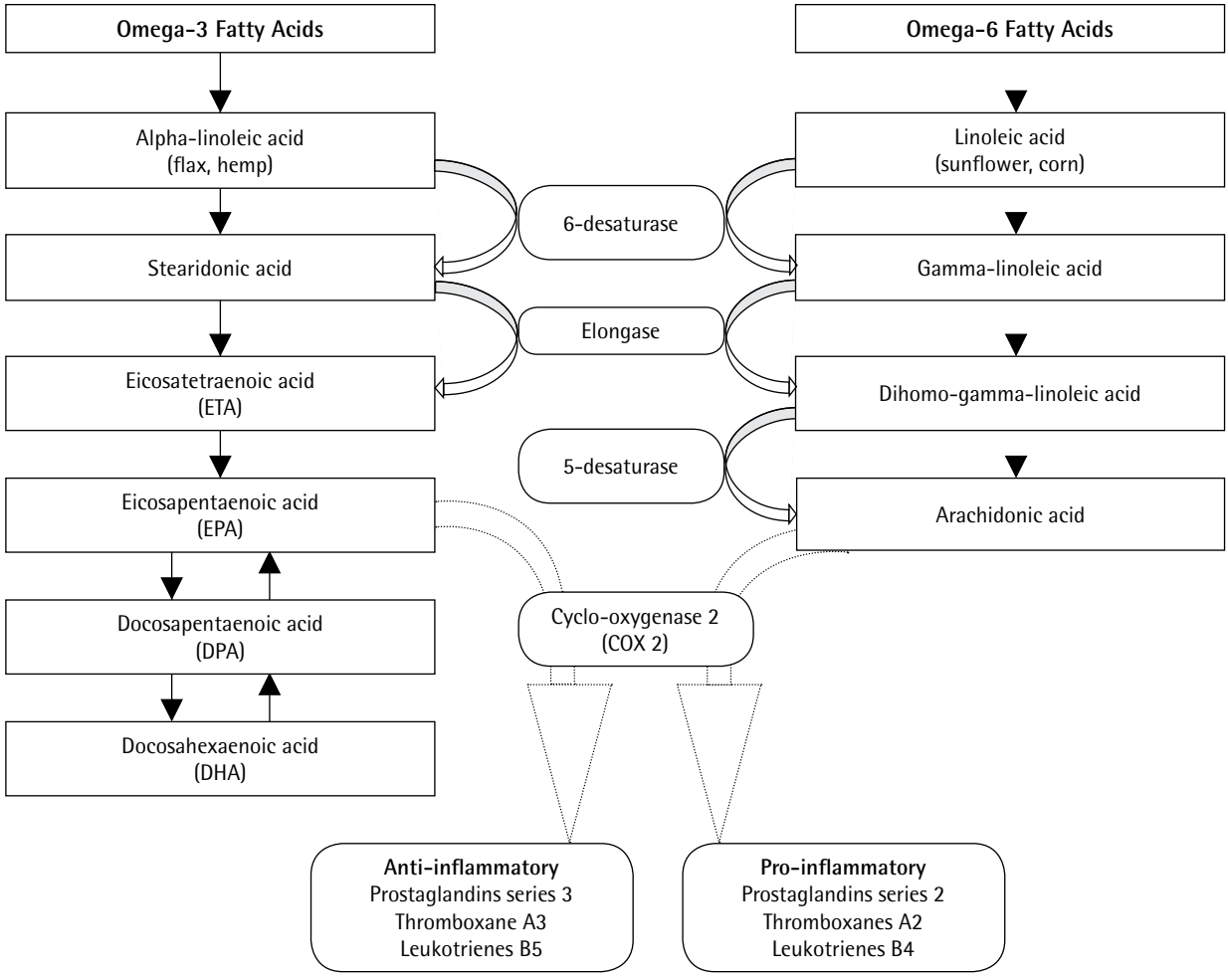

Figure 1 | *Metabolism of Omega-3/Omega-6 Polyunsaturated Fatty Acids*

more with cognitive impairment than EPA levels, which were not found to be significant for this.[79]

DHA is also involved in multiple brain functions, including[80]:

- increased activity of membrane-bound enzymes
- modification of the number and affinity of membrane receptors
- modification of ion channel function
- modification of the neurotransmitter production and activity.

Finally all these effects tend to favor the permeability of the neuronal membrane, favoring its activity, speed of response, and action capacity.

In animal models it has been demonstrated that increasing dietary DHA facilitated the excitability of the neuronal membrane, increasing neurotransmitter levels and reducing brain damage. Because of these actions, its beneficial effect in humans in improving cognitive dysfunction associated with brain damage or aging also has been demonstrated.[81]

Prospective studies have associated the consumption of fish rich in polyunsaturated fatty acids with a lower risk for developing Alzheimer disease.[82-84] After reviewing published studies, it is thought that both DHA and EPA may play a role in preventing Alzheimer disease and may be involved in its pathophysiology, although further studies to confirm this premise are recommended.[85] In the famous Framingham study it was observed that low levels of plasma phosphati-

dylcholine and DHA were associated with an increased risk for the development of dementia.[86]

The Cochrane Library conducted reviews in 2006 and 2012 on the effect of Omega-3 fatty acids on the prevention of dementia and cognitive impairment, although it was concluded that the results are scarce and more prospective studies are needed. They recognize that "the cumulative sum of several small protective effects of Omega-3 polyunsaturated fatty acids may have a significant protective effect against the risk of dementia and age-related cognitive decline; in addition, they have very few adverse effects, limited to mild gastrointestinal discomfort".[87,88]

In the MIDAS study, a randomized, double-blind, placebo-controlled clinical trial, 485 patients with age-related cognitive impairment (MMSE > 26 out of 30) were given a supplement of 900 mg/day of DHA or placebo for 24 weeks. After this 6-month period, significant improvement in learning was observed, as well as significant improvement in verbal recognition memory scores. No serious adverse events related to treatment were recorded, and it was concluded that DHA supplements improved learning and memory in the cognitive decline associated with age and thus can be considered a beneficial supplement for healthy aging.[80] In a double-blind, placebo-controlled clinical trial it was concluded that long-chain polyunsaturated fatty acids (DHA and EPA) combined with lutein and zeaxanthin did not have a significant beneficial effect on cognitive function. However, this study has important limitations since its initial objectives were not the treatment of mild cognitive impairment but assessment of the effect of this combination of supplements in preventing ocular macular degeneration; cognitive assessment was limited to a simple telephone interview.[89]

DHA has also been studied in combination with EPA, a polyunsaturated fatty acid with a prominent anti-inflammatory effect. In a study in which DHA and EPA were associated, improvement in the cognitive function of patients with Alzheimer disease and mild cognitive impairment was shown; the study concluded that patients with mild cognitive impairment (considered MMSE > 27 out of 30) treated with DHA and EPA showed a significant reduction in cognitive impairment.[90] On the other hand, the results of a randomized, double-blind, placebo-controlled study in patients with cognitive impairment associated with age showed that the group treated with the DHA and EPA combination had a higher level of improvement in cognition.[91]

In double-blind placebo-controlled clinical trials, fish oil supplements with high concentrations of DHA and EPA have improved short-term memory, immediate verbal memory, working memory, and 12-month delayed verbal recall in patients with mild cognitive impairment, although fewer than 20 patients were studied.[92] It is therefore recommended to strengthen these studies by increasing the sample size.[92]

DHA and EPA have also been tested together in nutritional complexes that include uridine, a nucleoside that forms part of RNA and appears to have a prominent role in the formation and maintenance of neuronal membranes.[93] It appears that these supplements, which also include choline, could favor synapsis formation in the brain.[94]

In a recent meta-analysis in which the results of 21 cohort studies on the effect of fish and polyunsaturated fatty acid intake on mild and moderate-to-severe cognitive impairment, it was concluded that the association of marine fish-derived DHA supplements is associated with a lower risk of developing dementia and Alzheimer disease.[95]

In another meta-analysis of six controlled trials involving more than 1000 patients it was concluded that omega-3 fatty acids may help prevent cognitive impairment in older adults.[96]

Although the mechanisms linking the benefit of omega-3 fatty acids on cognitive impairment and dementia are not well known, the findings of experimental studies suggest that they may be associated with an increase in neuronal differentiation and synaptic plasticity associated with the reduction in inflammation attributed to these polyunsaturated fatty acids.[97,98]

The use of supplements rich in DHA and EPA can improve memory and cognitive function in mild cognitive impairment, and it can even delay the risk of progression to dementia, although the most appropriate doses and the duration of supplementation necessary to achieve the most beneficial effect should be studied more carefully.[99]

The effective dose of DHA ranges from 250 mg to 1800 mg/day.

CONCLUSIONS

To date, no really effective treatment for Alzheimer disease and other neurodegenerative dementias has been identified.[100] Because of this situation, "non-pharmacological" interventions such as providing nutritional supplements have been, and continue to be, one of the most explored therapeutic possibilities.[101,102] The possibilities of nutritional supplements for cognitive maintenance and improvement are summarized in Table 1.

The importance of other actions, such as physical activity[103-105] or directed cognitive stimulation,[106,107] must be emphasized.

In the same way that protein ingestion is of little use for muscular development if it is not accompanied by physical

Table 1 Dietary supplements for cognitive impairment

Nutrition Group	Supplements	Dose	Mechanism of action
Vitamins	Vitamin E	2000 – 4000 IU	Antioxidant
Minerals	Magnesium	1 – 2 g/day	Oxidative phosphorylation
Ginkgo biloba	Ginkgo biloba	120 – 240 mg/day	Vasodilator and antiplatelet aggregant
Ginseng	Ginseng	4.5 – 9 g/day	Neurotransmitter potentiation
Polyphenols	Green tea	2 – 4 g/day	Antioxidant
Phospholipids	Phosphatidylcholine Phosphatidylserine	500 – 1000 mg/day 100-200 mg/8 hours	Neural membrane components
Polyunsaturated fatty acids	DHA EPA	250 – 1800 mg/day 50 – 300 mg/day	Membrane permeability

DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid

exercise, nutritional supplementation to improve the neuron and the neuronal membrane is of little use if the necessary stimulus associated with neuroplasticity is not provided to favor the creation of new branches and neural connections. It has been demonstrated in recent studies combining modern neuroimaging techniques that what is really effective for improving cognitive health is the combination of omega-3 fatty acid supplementation (mainly DHA) with aerobic physical exercise and cognitive stimulation, which may even prevent the decrease in gray matter volume in the frontal and parietal lobes and cingulate cortex compared to controls.[108]

Therefore, the final conclusion for better cognitive health would be Mediterranean diet with DHA supplements, cognitive stimulation, and regular physical exercise.

REFERENCES

1. Olivera-Pueyo J, Pelegrín-Valero C. Prevención y tratamiento del deterioro cognitivo leve. Psicogeriatría. 2015;5(2):45–55.
2. Gestuvo MK, Hung WW. Common dietary supplements for cognitive health. Aging Health. 2012;8(1):89–97.
3. Tapsell LC. Foods and food components in the Mediterranean diet: supporting overall effects. BMC Medicine. 2014; 12(100):1–3.
4. Scarmeas N, Stern Y, Mayeux R, Manly JJ, Schupf N, Luchsinger JA. Mediterranean diet and mild cognitive impairment. Arch Neurol. 2009;66:216–25.
5. Huhn S, Karabian Masouleh S, Stumvoll M, Villringer A, Witte AV. Components of Mediterranean diet and their impact on cognitive functions in agings. Front Aging Neurosci. 2015;7:1–10.
6. Martínez-Lapiscina EH, Clavero P, Toledo E, Estruch R, Salas-Salvadó J, San Julián B, et al. Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial. J Neurol Psychiatry. 2013;84(12):1318–25.
7. Lourida I, Soni M, Thompson-Coon J, Purandare N, Lang IA; Ukoumunne OC et al. Mediterranean diet, cognitive function, and dementia: a systematic review. Epidemiology. 2013;24(4):479–89.
8. León-Caballero MP, Alcolea-Martínez E. Estado nutricional en personas mayores y su influencia sobre el deterioro cognitivo y la demencia. Psicogeriatría. 2016;6(3):99–109.
9. Martínez-Lapiscina EH, Clavero P, Toledo E, Estruch R, Salas-Salvadó J, San Julián B et al. Virgin oliver oil supplementation and long-term cognition: the PREDIMED-NAVARRA randomized trial. J Nutr Health Aging. 2013;17(6):544–52.
10. Scarmeas N, Luchsinger JA, Schupf N, Brickman AM, Consentino S, Tang MX, et al. Physical activity, diet, and risk of Alzheimer disease. JAMA. 2009;302:627–37.
11. Yannakoulia M, Kontogianni M, Scarmeas N. Cognitive health and Mediterranean diet: just diet or lifestyle pattern? Ageing Res Rev. 2015;20:74–8.
12. Prince M, Albanese E, Guerchet M, Prina M. Nutrición y demencia. Una revisión de estudios disponibles. Resumen ejecutivo. Alzheimer´s Disease International (ADI). Londres; 2014.
13. Bhatti AB, Usman M, Ali F, Satti SA. Vitamin Supplementation as an Adjuvant Treatment for Alzheimer´s Disease. J Clin Diagn Res. 2016;10(8):OE07-11.
14. Tönnies E, Trushina E. Oxidative Stress, Synaptic Dysfunction, and Alzheimer´s Disease. J Alzheimers Dis. 2017;57(4):1105-21.
15. Wang X, Qinn PJ. The location and fucntion of vitamin E in membranas (review). Mol Membr Biol. 2000;17(3):143–56.
16. Sano M, Ernesto C, Thomas RG, Klauber MR, Schafer K, Grundman M, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. N Engl J Med.

1997;336:1216-22.
17. Farina N, Isaac MG, Clark AR, Rusted J, Tabet N. Vitamin E for Alzheimer´s dementia and mild cognitive impairment. Cochrane Database Syst Rev. 2012;(11):CD002854.
18. Grodstein F, Chen J, Willett WC. High dose antioxidant supplements and cognitive function in community dwelling elderly women. Am J Clin Nutr. 2003;77:975-84.
19. Nahin RL, Pecha M, Welmerink DB, Sink K, Dekosky ST, Fitzpatrick AL. Concomitant use of prescription drugs and dietary supplements in ambulatory elderly people. J Am Geriatr Soc. 2009;57(7):1197–205.
20. Tucker KL, Qiao N, Scott T, Rosenberg I, Spiro A. High homocysteine and low B vitamins predict cognitive decline in aging men: the Veterans Affairs Normative Aging Study. A J Clin Nutr. 2005;82(3):627–35.
21. Malouf R, Areosa Sastre A. Vitamin B12 for cognition. Cochrane Database Syst Rev. 2003;3:CD004326.
22. Malouf R, Grimley Evans J. Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people. Cochrane Database Syst Rev. 2008;4:CD004514.
23. Malouf R, Grimley Evans J. The effect of vitamin 6 on cognition. Cochrane Database Syst Rev. 2003;82(3):627–35.
24. Connelly P. High dose vitamin B supplementation does not slow cognitive decline in mild to moderate Alzheimer´s disease. Evid Based Ment Health. 2009;12(3):86.
25. Aisen PS, Schneider LS, Sano M, Díaz-Arrastia R, Van Dyck CH, Weiner MF, et al. High-dose B vitamin supplementation and cognitive decline in Alzheimer disease: a randomized controlled trial. JAMA. 2008;300(15):1774–83.
26. Harrison FE. A critical review of Vitamin C for the prevention of age-related cognitive decline and Alzheimer´s disease. J Alzheimers Dis. 2012;29(4):711–26.
27. Annweiler C, Allali G, Allain P, Brindenbaugh S, Schott AM, Kressig RW, et al. Vitamin D and cognitive performance in adults: a systematic review. Eur J Neurol. 2009;16(10):1083–89.
28. Soni M, Kos K, Lang IA, Jones K, Melzer D, Llewellyn DJ. Vitamin D and cognitive function. Scand J Clin Lab Invest Suppl. 2012;243:79–82.
29. Annweiler C, Schott AM, Rolland Y, Blain H, Hermann FR, Beauchet O. Dietary intake of vitamin D and cognition in older women. Neurology. 2010;75(2):1810–16.
30. Ozawa M, Ninomiya T, Ohara T, Hirakawa Y, Doi Y, Hata J, et al. Self-reported diatary intake of potassium, calcium, and magnesium and risk of dementia in the Japanese: the Hisayama Study. J Am Geriatr Soc. 2012;60:151–20.
31. Cherbuin N, Kumar R, Sachdev PS, Anstey. Dietary Mineral Intake and Risk of Mild Cognitive Impairment: The PATH through Life Project. Front Aging Neurosci. 2014;6(4):1–8.
32. Ebel H, Günther T. Magnesium metabolism: a review. J Clin Chem Clin Biochem. 1980;18(5):257–70.
33. Durlach J. Magnesium depletion and pathogenesis of Alzheimer´s disease. Magnes Res. 1990;3(3):217–8.
34. Xu Z-P, Li L, Bao J, Wang Z-H, Zeng J, Liu E-J, et al. Magnesium Protects Cognitive Functions and Synaptic Plasticity in Streptozotocin-Induced Sporadic Alzheimer´s Model. PLoS One. 2014;9(9):e108645.
35. Kleijnen J, Knipschild P. Ginkgo biloba. Lancet. 1992; 340(8833):174.
36. Snitz BE, O´Meara ES, Carlson MC, Arnold AM, Ives DG, Rapp SR, et al. Ginkgo biloba for preventing cognitive decline in older adults: a randomized trial. JAMA. 2009;302(24):2663–70
37. Maclennan KM, Darlington CL, Smith PF. The CNS effects of Ginkgo biloba extracts and ginkgolide B. Prog Neurobiol. 2002;67(3):235–57.
38. Dekosky ST, Williamson JD, Fitzpatrick AL, Kronmal RA, Ives DG, Saxton JA, et al. Ginkgo biloba for prevention of dementia: a randomized controlled trial. JAMA. 2008;300(19):2253–62.
39. Birks J, Grimley EV, Evans J. Ginkgo biloba for cognitive impairment and dementia. Cochrane Database Syst Rev. 2009; 1:CD003120.
40. Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: an updated systematic review. Drugs. 2009;69(13):1777–98.
41. Serby MJ, Yhap C, Landron EY. A study of herbal remedies for memory complaints. J Neuropsychitary Clin Neurosci. 2010; 22(3):345–7.
42. Geng J, Dong J, Ni H, Lee MS, Wu T, Jiang K, et al. Ginseng for cognition. Cochrane Database Syst Rev. 2010;12:CD007769.
43. Lee MS, Yang EJ, Kim JI, Ernst E. Ginseng for cognitive function in Alzheimer´s disease: a systematic review. J Alzheimers Dis. 2009;18(2):339–44.
44. Heo JH, Lee ST, Oh MJ, Park HJ, Shim JY, Chu K, Kim M. Improvement of Cognitive Deficit in Alzheimer´s Disease Patients by Long Term Treatment with Korean Red Ginseng. J Ginseng Res. 2011;35(4):457–61.
45. Ng T-P, Feng L, Niti M, Kua E-H, Yap K-B. Tea consumption and cognitive impairment and decline in older Chinse adults. Am J Clin Nutr. 2008;88:224–31.
46. Gardner EJ, Ruxton CH, Leeds AR. Balck tea – helpful or hamful? A review of the evidence. Eur J Clin Nutr. 2007;61(1):3–18.
47. Saito E, Inoue M, Sawada N, Shimazu T, Yamaji T, Iwasaki M, et al. Association of green tea consumption with mortality due to all causes and major causes of death in a Japanese population: the Japan Public Health Center-based Prospective Study (JPHC). Ann Epidemiol. 2015;25(7):512–8.
48. Mandel S, Youdim MB. Catechin polyphenols: neurodegeneration and neuroprotection in neurodegenerative diseases. Free Radic Biol Med. 2004;37(3):304–17.
49. Weinreb O, Mandel S, Amit T, Youdim MB. Neurological mechanisms of green tea polyphenols in Alzheimer´s and Parkinson´s diseases. J Nutr Biochem. 2004;15(9):506–16.
50. Kuriyama S, Hozawa A, Ohmori K, Shimazu T, Matsui T, Ebihara S, et al. Green tea consumption and cognitive function: a cross-sectional study from the Tsurugaya Project 1. Am J Clin Nutr. 2006.83(2):355–61.
51. Ide K, Yamada H, Takuma N, Park M, Wakamiya N, Nakase J, et al. Green Tea Consumption Affects Cognitive Dysfunction in the Elderly: A Pilot Study. Nutrients. 2014;6:4032–42.
52. Ma QP, Huang Ch, Cui QY, Yang DJ, Sun K, Chen X, Li XH. Meta-Analysis of the Association between Tea Intake and the Risk of Cognitive Disorders. PloS One. 2016;11(11):e0165861.
53. Vakhapova V, Cohen T, Richter Y, Herzog Y, Korczyn AD. Phosphatidylserine containing omega-3 fatty acids may improve memory abilities in non-demented elderly with memory complaints: a double-blind placebo-controlled trial. Dement Geriatr Cogn Disord. 2010;29(5):467–74.
54. Abad-Santos F, Novalbos-Reina J, Gallego-Sandín S, García AG. Tratamiento del deterioro cognitivo leve: utilidad de la citicolina. Rev Neurol. 2002;35:675–82.
55. Fiovaranti M, Yanagi M. Cytidinephosphocholine (CDP – choline) for cognitive and behavioural disturbances associated with chronic cerebral disorders in the elderly. Cochrane Database Syst Rev. 2005;18(2):CD000269.
56. Cenacchi T, Bertoldin T, Farina C, Fiori MG, Crepaldi G. Cognitive decline in the elderly: a double-blind, placebo-controlled multicenter study on efficacy of phosphatidylserine administration. Aging (Milano). 1993;5(2):123–33.

57. Taylor CL. Letter regarding phosphatidylserine and cognitive dysfunction and dementia. Bethesda. MD: US Food and Drug Administration (FDA); 2003.
58. Glade MJ, Smith K. Phosphatidylserine and the human brain. Review. Nutrition. 2015;31:781–6.
59. Tanaka K, Farooqui AA, Siddiqi NJ, Alhomida AS, Ong WY. Effects of docosahexaenoic acid on neurotransmission. Biomol Ther. 2012;20:152–7.
60. Cunnane SC, Schneider JA, Tangney C, Tremblay-Mercier J, Fortier M, Bennett DA, et al. Plasma and brain fatty acid profiles in mild cognitive impairment and Alzheimer´s disease. J Alzheimers Dis. 2012;29:691–7.
61. Crook TH, Tinklenberg J, Yesavage J, Petrie W, Nunzi MG, Massari DC. Effects of phosphatidylserine in age-associated memory impairment. Neurology. 1991;41:644–9.
62. Marra C, Silveri MC, Gainotti G. Predictors of cognitive decline in the early stage of probable Alzheimer´s disease. Dement Geriatr Cogn Disord. 2000;11:212–8.
63. Klinkhammer P, Szelies B, Heiss WD. Effect of phosphadidylserine on cerebral glucose metabolism in Alzheimer´s disease. Dementia. 1990;1:197–201.
64. Caffara P, Santamaria V. The effects of phosphatidylserine in patients with mild cognitive decline. An open trial. Clin Trials J. 1987;24:109–14.
65. Engel RR. Double-blind crossover study of phosphatidylserine versus placebo in subjects with early cognitive deterioration of the Alzheimer type. Eur Neuropsychopharmacol. 1992;2:149–55.
66. Richter Y, Herzog Y, Cohen T, Steinhart Y. The effect of phosphatidylserine containing omega-3 fatty acids on memory abilities in subjects with subjective memory complaints: a pilot study. Clin Interv Aging. 2010;5:313–6.
67. Vakahpova V, Cohen T, Richter Y, Herzog Y, Kam Y, Korczyn AD. Phosphatidylserine containing omega-3 fatty acids may improve memory abilities in nondemented elderly individuals with memory complaints: results from an open-label extension study. Dement Geriatr Cogn Disord. 2014;38:39–45.
68. Villardita C, Grioli S, Salmeri G, Nicoletti F, Pennisi G. Multicentre clinical trial of brain phosphatidylserine in elderly patients with intellectual deterioration. Clin Trials J. 1987;24:84–93.
69. Palmieri G, Palmieri R, Inzoli MR, Lombardi G, Sottini C, Tavolato B, et al. Double-blind controlled trial of phosphatidylserine in patients with senile mental deterioration. Clin Trials J. 1987;24:73–83.
70. Magglioni M, Picotti GB, Bondiolotti GP, Panerai A, Cenarcchi T, Nobile P, et al. Effects of phosphatidylserine therapy in geriatric patients with depressive disorders. Acta Psychiatr Scand. 1990;81:265–70.
71. Ruxton CHS, Reed SC, Simpson MJA, Millington KJ. The health benefits of omega-3 polynsaturated fatty acids: a review of the evidence. J Hum Nutr Dietet. 2004;17:449–59.
72. Caballer-García J, Jiménez-Treviño L. Ácidos grasos omega-3 en psicogeriatría: implicaciones en depresión y demencia. Psicogeriatría. 2010;2(2):83-92.
73. Weiser MJ, Butt CM, Mohajeri MH. Docosahexaenoic Acid and Cognition throughout the Lifespan. Nutrients. 2016;8(2):99.
74. Crawford MA, Hassam AG, Stevens PA. Essential fatty acid requirements in pregnancy and lactation with special reference to brain development. Prog Lip Res. 1981;20:31–40.
75. Lauritzen L, Brambilla P, Mazzocchi A, Haslof LBS, Ciappolino V, Agostino C. DHA Effects in Brain Development and Function. Nutrients. 2016;8(6):2–17.
76. Ozias MK, Carlson SE, Levant B. Maternal parity and diet (n-3) polyunsaturated fatty acid concentration influence accretion of brain phospholipid docosahexaenoic acid in developing rats. J Nutr. 2007;137(1):125–9.
77. Conquer JA, Tierney MC, Zecevic J, Bettger WJ, Fisher RH. Fatty acid analysis of blood plasma of patients with Alzheimer´s disease, other types of dementia and cognitive impairment. Lipids. 2000;35:1305–12.
78. Huang TL. Omega-3 fatty acids, cognitive decline, and Alzheimer´s disease: acritical review and evaluation of the literature. J Alzheimer Dis. 2010;21:673–90.
79. Otsuka R, Tange C, Insita Y, Kato Y, Imai T, Ando F, et al. Serum docosahexaenoic and eicosapentaenoic acid and risk of cognitive decline over 10 years among elderly Japanese. Eur J Clin Nutr. 2014;68(4):503–9.
80. Yurko-Mauro K, McCarthy D, Rom D, Nelson EB, Ryan AS, Blackwell A, et al. MIDAS investigators. Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline. Alzheimers Dement. 2010;6(6):456–64.
81. Kotani S, Sakaguchi E, Warashina S, Matsukawa N, Ishikura Y, Kiso Y, et al. Dietary supplementation of arachidonic and docosahexaenoic acids improves cognitive dysfunction. Neurosci Res. 2006;56(2):159–64.
82. Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Wilson RS, et al. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. Arch Neurol. 2003;60:940–6.
83. Barberger-Gateau P, Raffaitin C, Letenneur L, Berr C, Tzourio C, Dartigues JF, et al. Dietary patterns and risk of dementia: the Three-City cohort study. Neurology. 2007;69:1921–30.
84. Devore EE, Grodstein F, van Rooij FJA, Hofman A, Rosner B, Stampfer MJ, et al. Dietary intake of fish and omega-3 fatty acids in relation to long-term dementia risk. Am J Clin Nutr. 2009;90:170–6.
85. Oliveira G, Soriguer F. Papel de los ácidos grasos docosahexaenoico (DHA) y eicosapentaenoico (EPA) en la prevención de la enfermedad de Alzheimer. Med Clin (Barc). 2010;11(1):7–12.
86. Schaefer EJ, Bongard V, Beiser AS, Lamon-Fava S, Robins SJ, Au R, et al. Plasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer disease: the Framingham Heart Study. Arch Neurol. 2006;63:1545–50.
87. Lim WS, Gammack JK, Van Niekerk J, Dangour AD. Omega 3 fatty acid for the prevention of dementia. Cochrane Database Syst Rev. 2006;25(1):CD005379.
88. Sydenham E, Dangour AD, Lim WS. Omega 3 fatty acid for the prevention of cognitive decline and dementia. Cochrane Database Syst Rev. 2012;6:CD005379.
89. Chew EY, Clemons TE, Agrón E, Launer LJ, Grodstein F, Bernstein PS; for AREDS2 Research Group. Effect of Omega-3 Fatty Acids, Lutein/Zeaxanthin, or Other Nutrient Supplementation on Cognitive Function: The AREDS2 Randomized Clinical Trial. JAMA. 2015;314(8):791–801.
90. Freund-Levi Y, Eriksdotter-Jönhagen M, Cederholm T, et al. Omega-3 fatty acid treatment in 174 patients with mild to moderate Alzheimer disease: OmegaAD study: a randomized double-blind trial. Arch Neurol. 2006;63(10):1402–8.
91. Chiu CC, Su KP, Cheng TC, Liu HC, Chang CJ, Dewey ME, et al. The effects of omega-3 fatty acids monotherapy in Alzheimer´s disease and mild cognitive impairment: a preliminary randomized double-blind placebo-controlled study. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(6):1538–44.
92. Lee LK, Shahar S, Chin AV, Mohd Yusoff NA. Docosahexaenoic acid-concentrated fish oil supplementation in subjects with mild cognitive impairment (MC): a 12-month randomised, double-blind, placebo-controlled trial. Psychopharmacology.

2013;225:605–12.
93. Wijk NV, Broersen LM, de Wilde MC, Hageman RJJ, Groenendijk M, Sijben JWC, et al. Targeting Synaptic Dysfunction in Alzheimer´s Disease by Administering a Specific Nutrient Combination. J Alzheimer Dis. 2014;459–79.
94. Wurtman RJ. A Nutrient Combination that Can Affect Synapse Formation. Nutrients. 2014;6:1701–10.
95. Zhan XW, Hou WS, Li M, Tang ZY. Omega-3 fatty acids and risk of cognitive decline in the elderly: a meta-analysis of randomized controlled trials. Aging Clin Exp Res. 2016;28(1):165–6.
96. Zhang Y, Chen J, Qiu J, Li Y, Wang J, Jiao J. Intakes of fish and polyunsaturated fatty acids and mild-to-severe cognitive impairment risk: a dose-response meta-analysis of 21 cohort studies. Am J Clin Nutr. 2016;103:330–40.
97. Dyall SC, Michael GJ, Michael-Titus AT. Omega-3 fatty acids reverse age-related decreases in nuclear receptors and increase neurogenesis in old rats. J Neurosci Res. 2010;88(10):2091–2102.
98. Cutuli D, De Bartola P, Caporali P, Laricchiuta D, Foti F, Ronci M, et al. n-3 polyunsaturated fatty acids supplementation enhances hippocampal functionality in aged mice. Front Aging Neurosci. 2014;6:220.
99. Waitzberg DL, Garla P. Contribución de los Ácidos Grasos Omega-3 para la Memoria y la Función Cognitiva. Nutr Hosp. 2014;30(3):467–77
100. Eshkoor SA, Hamid TA, Mun CY, Ng CK. Mild cognitive impairment and its management in older people. Clin Interv Aging. 2015;10:687–93.
101. Gómez-Pinilla F. Brain foods: the effects of nutrients on brain function. Nat Rev Neurosci. 2008;9:568–78.
102. Hooijmans CR, Pasker-de Jong PC, de Vries RB, Ritskes-Hoitinga M. The effects of long-term omega-3 fatty acid supplementation on cognition and Alzheimer´s pathology in animal models of Alzheimer´s disease: a systematic review and meta-analysis. J Alzheimer´s Dis. 2012;28:191–209.
103. Colcombe SJ, Erickson KI, Scalf PE, Kim JS, Prakash R, McAuley E, et al. Aerobic exercise training increases brain volume in aging humans. J Gerontol Biol Sci Med. 2006;61:1166–70.
104. Lautenschlager NT, Cox KL, Flicker L, Foster JK, Van Bockxmeer FM, Xiao J, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. JAMA. 2008;300:1027–37.
105. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, et al. Exercise training increases size of hippocampus and improves memory. Proc Nat Acad Sci. 2011;108:3017–22.
106. Sitzer DI, Twamley EW, Jeste DV. Cognitive training in Alzeimer´s disease: a meta-analysis of the literature. Acta Psychiatr Scand. 2006;114:75–90.
107. Rebok GW, Ball K, Buey LT, Jones RN, Kim HY, King JW, Group AS, et al. Ten-year effects of the advanced cognitive training for independent and vital elderly cognitive training trial on cognition and everyday functioning in older adults. J Am Geriatr Soc. 2014;62:16–24.
108. Köbe T, Witte AV, Schnelle A, Lesemann A, Fabian S, Tesky VA, et al. Combined omega-3 fatty acids, aerobic exercise and cognitive stimulation prevents decline in gray matter volume of the frontal, parietal and cingulate cortex in patients with mild cognitive impairment. Neuroimage. 2016;131:226