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NUTRITION AND THE BRAIN (J NASSER, SECTION EDITOR)

Dietary Sources of Omega-3 Fatty Acids Versus Omega-3 Fatty Acid Supplementation Effects on Cognition and Inflammation

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Abstract

Purpose of Review This review summarises previous literature and recent findings on omega-3 fatty acids in cognition and inflammation in humans, comparing the effects of dietary omega-3 with supplemental omega-3.

Recent Findings Whilst some omega-3 studies, both dietary and supplementation, show positive benefits of omega-3s in cognition, particularly memory function, and supplementation studies show reduction in markers of inflammation, including IL-6 and TNF-α, some studies also show no clear benefits on cognition and inflammation, particularly in healthy populations. Most consistency in beneficial cognition outcomes has been in populations with MCI.

Summary Many clinical trials have investigated omega-3 supplements and cognition outcomes in healthy populations across the lifespan; however, omega-3 dietary interventions are limited to studies in children and adolescents. Future studies should compare the effects of dietary omega-3 with omega-3 supplementation before further conclusions can be drawn.

Keywords Omega-3 · Fish · Supplementation · Cognition · Inflammation · Review

Introduction

In an ageing population research focus on the longevity of our cognitive function, including an understanding of the dysfunctions associated with cognition, such as mild cognitive impairment (MCI) and Alzheimer's disease (AD), has emerged. Additionally, maximising cognitive performance is of interest in modern society. For these reasons, nutritional science has begun to explore dietary approaches which provide improved cognition performance and increased duration of cognitive function, as well as approaches that may treat dysfunctions such as MCI and AD.

A number of cognitive domains are included in the term 'cognition', and these domains cover aspects such as our ability to focus attention, to recall information, to think abstractly, and to be aware of relationships, amongst other cognitive domains [1]. It has been shown that as we age, a decline occurs within some of these cognitive domains, evident already from 45 years onwards [2], with prevalence of MCI reportedly between 16 and 20% in majority of studies on people over 60 years of age [3]. It has been suggested that the association between age and cognitive decline may be due to an increased state of inflammation which occurs with the ageing process.

Whilst inflammation is often protective and involved in healing processes, prolonged inflammation can also be damaging to tissues and initiate the release of reactive oxygen species (ROS), further inciting oxidative damage and a chronic pro-inflammatory response [1]. Furthermore, a review of the evidence reveals inflammatory markers, frequently including C-reactive protein (CRP) and interleukin-6 (IL-6), to have a role in cognitive decline [4]. Additionally, evidence suggests a link between increased inflammation in diseased states and cognitive decline, including in chronic kidney disease patients [4] and in obesity [5].

Evidence reported on the link between inflammation and cognition suggests a possibility for anti-inflammatory agents as potentially therapeutic with omega-3 fatty acids previously

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shown to exert anti-inflammatory effects [6]. The typical western diet has been seen to increasingly contain more of foods high in omega-6s rather than omega-3s, with studies showing higher concentrations of linolenic acid (LA) in subcutaneous adipose tissue over time [7]. Additionally, evidence suggests that a higher omega-6 to omega-3 ratio is associated with an increased risk of AD [8]. As LA leads to increased arachidonic acid and hence pro-inflammatory effects, a higher consumption of anti-inflammatory omega-3s may help reduce risks of inflammation [9].

Sources of Omega-3 Fatty Acids

Omega-3 fatty acids are essential fatty acids (EFAs), which cannot be synthesised in sufficient amounts by the human body and, hence, are an essential part of our diet. Omega-3s are polyunsaturated fatty acids (PUFA), as they are comprised of two or more double bonds. Omega-3 fatty acids include alpha-linolenic acid (ALA), which is found in canola oils and margarines, linseed oils, certain nuts such as walnuts, and legumes, and in small amounts in leafy vegetables [10]. Omega-3 fatty acids also include a group of long-chain (LC) fatty acids, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and docosapentaenoic acid (DPA), mostly found in oily fish such as mackerel, herrings, sardines, salmon, tuna [10], trout, sea brass, and sea bream [11] amongst other seafoods. Hence, omega-3 supplements used in the food industry are obtained predominantly from fish [12].

Role of Omega-3 Fatty Acids in Cognition and Inflammation

DHA is also the most abundant omega-3 fatty acid membrane lipid in the human brain [13], and plays an important role in some fundamental membrane properties including conformational flexibility, which are associated with cognitive processes [14]. This influence of DHA on conformational flexibility is due to the high number of double bonds within the structure of DHA. Changes in fatty acid composition of membranes can thus have an impact on brain functioning and such alterations have been shown to be associated with several neurodegenerative diseases, such as AD, motor system–mediated Parkinson's disease, and major depression [15].

Dietary Omega-3 or Supplementation?

Whilst it is evident there is a role for omega-3s in cognition and inflammation, there is also the consideration of the source of omega-3s. Studies have investigated the effect of omega-3s obtained through dietary sources, such as fish, and also investigated omega-3s taken in supplementation form. Therefore, a point to consider is whether dietary sources or supplementation of omega-3s is superior or of equal benefit in cognition and inflammation outcomes.

Prior Literature on Dietary or Supplementation of Omega-3 Fatty Acids

A number of intervention studies have investigated the effects of omega-3 supplementation and cognition, leading to several recent systematic literature reviews (SLRs) investigating overall outcomes of individual studies on omega-3s in cognitive decline [16, 17] and omega-3s on cognition [18••]. Very few intervention studies have investigated dietary sources of omega-3s, namely fish, and the effects on cognition, leading to two recent SLRs of prospective cohort studies on the association between high fish consumption and cognitive decline [19, 20] and no SLRs on dietary intervention studies. A brief overview of the findings of these SLRs in the field is given below.

Findings from SLRs on Omega-3 Supplementation and Cognition Studies

An SLR by Alex et al. [16••] reporting on 25 studies conducted with omega-3 supplementation in adults free of dementia, with or without MCI, reported that overall, there was no effect on global cognitive function; however, memory function showed a small benefit. A similar review by Marti Del Moral and Fortique [17••] reporting on 14 omega-3 supplementation studies in aged/elderly adults, with or without MCI, and with no previous fish oil supplementation, reported an improvement in at least one domain of cognitive function (e.g. working memory, executive function, verbal memory, short-term memory, perceptual speed) in 10 out of the 14 studies included in the review. The authors stated that supplementation may have positive effects on cognitive function and that evidence suggests the possibility for omega-3 use as preventative or therapeutic treatment in older adults. Rangel-Huerta and Gil [18••] deemed it unclear whether omega-3 supplementation can improve cognitive development or inhibit cognitive decline in either young or older adults after reviewing 51 articles in healthy individuals with mild or moderate MCI and AD. Overall, difficulty in comparing studies utilising a range of different cognitive tests was reported by the authors. However, authors highlighted a possibility that duration may have impacted outcomes, stating that limited effects of intervention on cognition in patients with AD was shown after 4 months, maintained cognitive function after 6 months, and delayed progression of functional impairment after 12 months of intervention.

These three SLRs suggest some evidence for a possible role for omega-3 supplementation in cognition, but highlight some potential factors involved in positive outcomes, such as age of participants, duration of intervention, and cognitive measures used to assess outcomes.

However, there is still insufficient consistency in the evidence for an effect of omega-3 supplementation on cognitive outcomes based on these reviews.

Findings from SLRs on Dietary Sources of Omega-3 and Cognition Studies

An SLR and meta-analyses conducted by Zhang et al. [19••] to investigate findings from 21 cohort studies on fish consumption and risk of dementia showed that 1 serve of fish per week lowered the risk of dementia and that an increase of 0.1 g/day of DHA in the diet was associated with decreased risk of dementia and AD. The authors also reported a curvilinear relationship between omega-3 intake from marine source and mild cognitive decline. Another SLR of epidemiological studies on dietary intake of fish and cognition was conducted by Zeng et al. [20••], reporting on nine prospective studies on older adults. When authors compared the highest and lowest cohorts of fish consumption, higher intake of fish was shown to reduce the relative risk of dementia of the Alzheimer's type (DAT) by 20%. Furthermore, that a 100-g/week increase in fish intake reduced the risk of DAT by an additional 12% in dose-response analyses. However, when analysing cohorts with MCI, the results were non-significant.

Whilst both Zhang et al. [19••] and Zeng et al. [20••] report a positive relationship between fish intake and cognition in populations with AD or dementia, only findings from Zhang et al. [19••] show a relationship in populations with MCI.

Comparison of Omega-3 Sources and Cognition Outcomes

The literature review findings above suggest omega-3s from dietary sources and supplementation both show some evidence of an effect on cognition; however, both diet and supplementation studies show some conflicting results. Additionally, a review on data from 2015 to 2016 compared fish studies and omega-3 supplementation studies on cognitive decline, dementia, and AD in older adults using observational data from prospective cohort studies [21]. Overall, the author concluded that older adults with either memory complaints or MCI, and possibly some subgroups with AD, may have cognitive benefits from either fish intake or omega-3 supplementation. One other study, comparing a 100-g serving of fish (estimated to provide 150–200 mg DHA) per weekday to school children (aged 9–10 years) for 12 weeks compared with DHA supplement (403 mg/day DHA), showed a significant difference in improvement only in the trail making test, representative of cognitive improvements, with the DHA supplement being more effective than fish intake [22]. However, the dose of DHA in the fish treatment group was less than half the DHA dose in the supplement group.

A limitation of the reviewed literature to date is the absence of data on omega-3 dietary intervention studies in adults, forcing comparisons to be made between clinical interventions with omega-3 supplementations and observational omega-3 dietary studies. Whilst several SLRs exist in the field of omega-3s and cognition, the current review aims to include data from dietary and supplementation clinical trial studies to make a comparison of cognition outcomes. Additionally, it aims to give an overview of inflammatory marker outcomes reported within these studies and to evaluate whether a link between cognition changes and inflammation is evident in the current literature. This review will identify any gaps in the knowledge and provide insight into further studies required on this topic.

Search Strategy and Selection Criteria

For an update of the literature given in the current review, PubMed was searched using the following search terms to explore the literature on omega-3 and cognition: "omega 3 *OR* fish *OR* DHA *OR* EPA *AND* cogni*". Original clinical trial articles and systematic literature reviews published in English over the last 10 years, from 2010 to 2020 with last search dated February 25, 2020, were evaluated for relevant publications; reference lists of prior SLRs were also searched for any additional studies. Studies on healthy adults and healthy teenagers were included; also, studies on adults with subjective cognitive impairment (SCI) or MCI were included. Studies on infants, children 12 years and under, pregnant or lactating women, patients with AD, or dementia were not included.

Search Results

The search resulted in 297 articles which were screened for inclusion or exclusion. After refining the outcomes based on the selection criteria described above, 30 articles were included in the current review. These consisted of 29 studies on omega-3 supplementation intervention and one dietary omega-3 intervention. The remainder of the dietary studies on fish and cognition retrieved were prospective cohort studies, which were not eligible for inclusion as this review focusses on the clinical trial data available for both treatment groups, dietary and supplementation. Table 1 below outlines the clinical trial evidence on both dietary and supplementation forms of omega-3 and cognition outcomes and provides any findings on markers of inflammation reported within these trials. Studies have been categorised in Table 1 by participant populations, including healthy study populations (20 studies, 3253 participants), participants with SCI (four studies, 1863 participants), and participants with MCI (five studies, 897 participants).

Table 1 Clinical studies on omega-3s and cognition outcomes

Reference	Study pop, age; no.	Intervention	Duration	Cognitive measures	Inflammatory measures	Outcomes
Healthy participant population						
Amen et al. [23]	Healthy adults, age n.s.; ($n = 30$)	Intervention: fish oil 860 mg/day of EPA and 580 mg/day of DHA Control: comprised olive oil, soybean oil, palm oil, coconut oil, canola oil, natural lemon flavour, and natural mixed tocopherols	2 months	MicroCog, WebNeuro	None reported	(+) Significant improvements were observed after fish oil supplementation on MicroCog: reasoning, memory, information processing accuracy, and on WebNeuro: executive function, information processing efficiency.
Bauer et al. [24]	Healthy young adults, 20–34 years; ($n = 13$)	The study utilised two different fish oil diets. High EPA:DHA formulation (3:1) providing 590 mg/day EPA, 137 mg/day DHA High DHA:EPA (4:1) formulation providing 159 mg/day EPA and 417 mg/day DHA Participants supplemented with 6 capsules daily (3 mornings and 3 nights)	30 days	SCWT, spatial WMT	None reported	(−) No change after DHA-rich supplementation in actual performance and no improvement in time or accuracy on the Stroop and Spatial Working Memory tasks. However, supplementation significantly increased functional activation in the right precentral gyrus during tasks.
Dangour et al. [25]	Healthy older adults, 70–79 years; ($n = 867$)	Intervention: 500 mg/day DHA and 200 mg/day EPA Control: olive oil	24 months	CVLT	None reported	(−) Omega-3 supplementation led to no changes in cognitive function scores.
Danthiir et al. [26]	Healthy older adults, 65–90 years old; ($n = 390$)	Intervention: fish oil equivalent to 1720 mg/day DHA and 600 mg EPA/day Control: olive oil capsules plus 1.8 mg/day EPA and 1.2 mg/day DHA (for blinding, to cover possible aftertaste)	18 months	Variables measured included reasoning, working memory, short-term memory, retrieval fluency, inhibition, simple and choice-reaction time, perceptual speed, odd-man-out reaction time, speed of memory scanning, and psychomotor speed MMSE	High-sensitivity C-reactive protein (hs-CRP) Homocysteine	(−) Fish oil supplementation did not maintain or improve cognitive performance. A small negative main effect was found on psychomotor speed. (−) No significant differences in inflammatory markers hs-CRP and homocysteine compared to the control group were reported.
Dretsch et al. [27]	Healthy adults, 18–55 years; ($n = 78$)	Intervention: 950 mg/day DHA and 1175 mg/day EPA Control: corn oil	60 days	CNS-VS	None reported	(−) Omega-3 supplementation had no significant effect on neurocognitive functioning.
Giles et al. [28]	Healthy young adults; ($n = 72$)	Intervention: 1120 mg/day DHA and 1680 mg/day EPA Control: olive oil	35 days	EIT, MFT	Interleukin-1β (IL-1β)	(+) Rated confusion remained stable in fish oil supplemented participants but increased with stress in the olive oil group. However, fish oil had no

Table 1 (continued)

Reference	Study pop, age; no.	Intervention	Duration	Cognitive measures	Inflammatory measures	Outcomes
						further effects on cognitive function. (−) No effect on or IL-1β
Handeland et al. [29•]	Healthy adolescents, 14–15 years; ($n = 426$)	Three groups received one of the following: Fatty fish meal (total weight 230 g) three times per week, providing approximately 259 mg/day DHA and 150 mg/day EPA Meat meal (total weight 230 g) three times per week, containing 3.2 mg/100 g EPA, 5.0 mg/100 g DHA, and 6.0 mg/100 g DPA Fish oil supplement providing approximately 315 mg/day DHA and 474 mg/day EPA	12 weeks	D2 test of attention, concentration performance, processing speed, omission errors, commission errors and overall performance	None reported	(+) A small beneficial effect of fatty fish consumption was reported for processing speed compared to meat meals and the fish oil supplement. However, low dietary compliance was also reported for fish consumption.
Jackson et al. [30]	Healthy young adults, 18–29 years; ($n = 159$)	Intervention: 896 mg/day DHA and 128 mg/day EPA Control: olive oil	6 months	CDB, COMPASS	None reported	(−) No changes in cognitive performance despite significantly increased concentrations of oxyhaemoglobin and total levels of haemoglobin in the prefrontal cortex during tasks.
Jaremka et al. [31] Keicolt-Glaser et al. [32]	Healthy older adults; 40–85 years; ($n = 132$)	Intervention: fish oil capsules—two groups; low dose (1.25 g/day fish oil) and a high dose (2.5 g/days fish oil) providing either: 174/348 mg/day DHA and 1042.5/2085 mg/day EPA Control: consisted of palm, olive, soy, canola, and cocoa butter oils	4 months	CVLT-II, three tests from the Wechsler Memory Scale Third Edition, Digit Span and Letter-Number Sequencing tasks Spatial Span task, TMT, Controlled Oral Word Association Task	IL-6 and TNF-α (reported in separate publication Kiecolt-Glaser et al., 2012)	(+) Omega-3 supplementation attenuated loneliness-related verbal episodic memory declines over time [31]. (+) Serum interleukin-6 decreased by 10% and 12% in low and high dose omega-3 groups, respectively, compared to a 36% increase in the control group [32]. (+) Omega-3 groups showed modest 0.2% (low dose) and −2.3% (high dose) changes in serum TNF-α, compared with a 12% increase in the control group [32].
Karr et al. [33]	Healthy college aged adults; ($n = 41$)	Intervention: fish oil capsules equivalent to 480 mg/day DHA and 720 mg/day EPA	4 weeks	RAVLT, SCWT, TMT, PANAS	None reported	(−) No significant benefits of fish oil on cognition reported.

Table 1 (continued)

Reference	Study pop, age; no.	Intervention	Duration	Cognitive measures	Inflammatory measures	Outcomes
		Control: coconut oil capsules				
Konagai et al. [34]	Healthy elderly, males in their 60s and 70s; ($n = 45$)	Intervention: krill oil equivalent to 193 mg/day EPA + 92 mg DHA; or sardine oil equivalent to 491 mg/day EPA + 251 mg/day DHA Control: medium chain triglycerides	3 months	WMT (2-back numeric task), Calculation task-conducted using Uchida-Kraepelin test paper	None reported	(−) No change in cognitive test performance reported although significantly greater changes in KO and SO group in oxyhaemoglobin concentrations in dorsolateral prefrontal cortex in response to performance of the Working Memory test.
Külzow et al. [35]	Healthy older adults, 50–75 years; ($n = 44$)	Intervention: fish oil 2.2 g/day equivalent to 880 mg/day DHA and 1320 mg/day EPA Control: sunflower oil	26 weeks	LOCATO object-location-memory task, RAVLT	None reported	(+) Fish oil supplementation significantly improved recall of object locations compared with control. However, performance in the RAVLT was not significantly affected by intervention.
Mahmoudi et al. [36]	Healthy older adults, 65 years or older; ($n = 199$)	Intervention: 180 mg/day DHA and 120 mg/day EPA Control: coconut oil	6 months	MMSE, AMT	hs-CRP	(+) Omega-3 supplement reduced the amount of decline in AMT in participants with normal cognition compared with the placebo group. No other cognition changes were reported. (−) No change in hs-CRP reported.
Narendran et al. [37]	Healthy young adults, 18–25 years; ($n = 13$)	Intervention: 750 mg/day DHA and 930 mg/day EPA No control group	6 months	WMT (verbal N-back task)	None reported	(+) Improvement after omega-3 supplementation on AHR performance on the 3-back test.
Nilsson et al. [38]	Healthy adults, 51–72 years; ($n = 44$)	Intervention: 1500 mg/day EPA and 1050 mg/day DHA Control: contained in total 366 mg dicalcium phosphate, 150 mg microcrystalline cellulose, and 4 mg magnesium salts of fatty acids	5 weeks	WMT	TNF-α	(+) Omega-3 supplementation led to better performance in the Working Memory test compared with control. (−) No change in TNF-α post supplementation
Pase et al. [39]	Healthy adults, 50–70 years; ($n = 160$)	Intervention: fish oil providing 480 mg/day EPA and 480 mg/day DHA without micronutrient supplement Two fish oil groups with a micronutrient supplement:	16 weeks	Measured by a set of cognitive composite scores, including reaction time, cognitive processing speed, short-term memory, and visual memory using SUCCAB	None reported	(−) No effect of treatment on any of the primary cognitive endpoints. However, increased omega-3/6 ratio in blood was associated with improvements

Table 1 (continued)

Reference	Study pop, age; no.	Intervention	Duration	Cognitive measures	Inflammatory measures	Outcomes
		240/480 mg/day EPA + 240/480 mg/day DHA Control: sunola oil				in spatial working memory but no other cognitive domains
Schättin et al. [40]	Healthy older adults, 65 years or older; ($n = 58$)	Both groups received exergame training for the intervention period. Intervention: fish oil (13.5 ml per day) equivalent to 1471.5 mg/day EPA and 162 mg/day DHA Control: olive oil	26 weeks	MMSE	None reported	(−) No additional benefits of fish oil, combined with exergame training, above exergame, and placebo.
Stonehouse et al. [41]	Healthy young adults; 18–45 years with low DHA intake (less than 200 mg/week EPA + DHA); ($n = 228$)	Intervention: 1160 mg/day DHA and 170 mg/day EPA Control: sunflower oil	6 months	COMPASS, finding As task (from the Kit of Factor-Referenced Cognitive Tests), Letter-number sequencing task	None reported	(+) DHA supplementation improved memory and the response time of memory in healthy, young adults whose habitual diets were low in DHA.
Stough et al. [42]	Healthy older adults, 45–77 years; ($n = 74$)	Intervention: 252 mg/day DHA and 60 mg/day EPA Control: soybean oil	3 months	CDR-CAS	None reported	(−) No significant effects of DHA supplementation on cognitive function
Tokuda et al. [43]	Healthy older adults, 55–64 years; ($n = 115$).	Intervention: 300 mg of DHA, 100 mg of EPA, and 120 mg of ARA Control: olive oil	1 month	Measurement of ERPs using an auditory oddball paradigm	None reported	(−) No change in cognitive test performance reported although changes in electroencephalograph latency were significantly different in relation to the placebo group (+ 13.6 ms) and the LCPUFA group (− 1.8 ms) after supplementation
Witte et al. [44]	Healthy older adults, 50–75 years; ($n = 65$)	Intervention: 1320 mg EPA + 880 mg DHA per day Control: sunflower oil	26 weeks	TMT, SCWT, RAVLT, Forward and backward digit spans, verbal fluency	hs-CRP, TNF-α, IL-6	(+) Omega-3 supplementation improved executive functions by 26%. Also, significant increases in regional grey matter volume compared with control. (−/+) Both the placebo and intervention groups exhibited lower levels of inflammatory markers (TNF-α and IL-6). No change in hs-CRP was reported.
Participant populations with SCI						
Andrieu et al. [45]			3 years		None reported	(−) Omega-3 capsules alone or in combination with a multi

Table 1 (continued)

Reference	Study pop, age; no.	Intervention	Duration	Cognitive measures	Inflammatory measures	Outcomes
	Older adults, 70 years or older with memory complaints; ($n = 1680$)	A multidomain intervention with or without omega-3 supplementation/placebo. Intervention: 800 mg/day DHA and 225 mg/day EPA Control: flavoured paraffin oil		Free and total recall of the Free and Cued Selective Reminding test, MMSE orientation items, Digit Symbol Substitution Test, Category Naming Test		domain intervention had no significant effects on cognitive decline over 3 years in elderly people with memory complaints.
Boespflug et al. [46]	Older adults, 62–80 years with subjective memory impairment; ($n = 21$)	Intervention: fish oil 1600 mg/day EPA and 800 mg/day DHA Control: corn oil	24 weeks	Working memory task (sequential letter n-back)	None reported	(+) Fish oil supplementation improved working memory performance.
Jackson et al. [47]	Healthy older adults, 50–70 years with subjective memory complaints; ($n = 86$)	Intervention: fish oil supplementation providing 896 mg DHA and 128 mg EPA A multinutrient supplement (phosphatidylserine, gingko biloba, folic acid, vitamin B_{12}) also containing fish oil providing 964.4 mg/day DHA + 160 mg/day EPA Control: high oleic acid sunflower oil and 120 mg fish oil (32 mg DHA + EPA) for masking purposes	6 months	CDB, RVIP All the tasks were presented using the COMPASS cognitive assessment system	None reported	(−) No effect of fish oil treatment on either cognitive function or cerebral haemodynamics
McNamara et al. [48]	Older adults, 62–80 years with subjective cognitive impairment; ($n = 76$)	Intervention: fish oil providing 1600 mg/day EPA + 800 mg/day DHA Blueberry powder 12 g Combined FO and Blueberry supplementation Control: unspecified powder	24 weeks	DEX, TMT, Controlled Oral Word Production, Hopkins Verbal Learning test	None reported	(+) Fish oil supplementation reduced cognitive symptoms in everyday activities as measured by the dysexecutive test. No effect for motor speed, working memory, learning and retention, and lexical access
Participant populations with MCI						
Bo et al. [49•]	Elderly subjects, 60 years and older with MCI; ($n = 86$)	Intervention: 480 mg/day DHA and 720 mg/day EPA Control: olive oil	6 months	BCATs	IL-6, IL-10, TNF-α	(+) Omega-3 supplementation improved total BCAT scores, perceptual speed, space imagery efficiency. and working memory (+) IL-6 and TNF-α were significantly reduced after omega-3 supplementation
Lee et al. [50]	Elderly people, 60 years and older with MCI; ($n = 36$)	Intervention: fish oil 1300 mg/day DHA and 0.45 mg/day EPA Control: corn oil	12 months	Visual reproduction I and II subtests from WMS-R, RAVLT, Digit span backward from WAIS-R, CDT, Digit span forward, Digit symbol	None reported	(+) Fish oil intervention led to significant improvement in short-term and working memory, immediate verbal memory and delayed recall

Table 1 (continued)

Reference	Study pop, age; no.	Intervention	Duration	Cognitive measures	Inflammatory measures	Outcomes
				substitution test and Matrix reasoning and Block design from WAIS-III, MMSE		capability. Change in memory was significantly improved in the fish oil group after 12 months.
Sinn et al. [51]	Healthy older adults; 65 years or older with MCI; ($n = 50$)	Intervention: two fish oil groups, high EPA providing 1.67 g/day EPA and 160 mg/day DHA, or high DHA providing 1.55 g/day DHA and 400 mg/day EPA Control: Safflower oil	6 months	RAVLT, TMT, Letter fluency	None reported	(+) High DHA intervention led to improved verbal fluency (Initial Letter Fluency) compared with the control group. There were no treatment effects on other cognitive parameters.
Yurko-Mauro et al. [52]	Healthy older adults, 55 years and older with cognitive decline; ($n = 485$)	Intervention: 900 mg/day DHA Control: corn and soy oil	6 months	CANTAB Paired Associate Learning, SCWT	None reported	(+) DHA supplementation improved learning and memory function compared with placebo.
Zhang et al. [53]	Elderly subjects with MCI; ($n = 240$)	Intervention: 2000 mg/day DHA Control: corn oil	12 months	WAIS-RC	None reported	(+) DHA supplementation group had a significant improvement in the Full-Scale Intelligence Quotient, Information, and Digit Span compared with placebo group.

AHR, adjusted hit rate; *AMT*, Abbreviated Mental Test; *BCATs*, Basic Cognitive Aptitude Tests; *CDB*, Cognitive Demand Battery; *CDR-CAS*, Cognitive Drug Research-computerised assessment system; *CDT*, Clock drawing test; *CNV-CS*, Central Nervous System-Vital Signs; *COMPASS*, Computerised Mental Performance Assessment System; *CVLT*, California Verbal Learning Test; *CVLT-II*, California Verbal Learning Test Second Edition; *DEX*, Dysexecutive Questionnaire; *DHA*, docosahexaenoic acid; *EIT*, emotional interference task; *EPA*, eicosapentaenoic acid; *ERPs*, event-related potentials; *IL*, interleukin; *MCI*, mild cognitive impairment; *MFT*, Morphed Faces Task; *MMSE*, Mini Mental State Examination; *n.s.*, non-specified; *PANAS*, Positive and Negative Affect Schedule; *RAVLT*, Rey Auditory Verbal Learning Test; *RVIP*, Rapid Visual Information Processing; *SCI*, subjective cognitive impairment; *SCWT*, Stroop Colour and Word Test; *SUCCAB*, Swinburne University Computerised Cognitive Assessment Battery; *TMT*, Trail Making Test; *TNF-a*, tumour necrosis factor-alpha; *WAIS-R*, Wechsler Adult Intelligent Scale–Revised; *WMS-R*, Wechsler Memory Scale–Revised; *WAIS-RC*, Chinese version of the Wechsler Adult Intelligence Scale–Revised; WMT, working memory task; (+), improvement in outcome; (−) no improvement in outcome

Omega-3 Dietary Sources Versus Supplementation in Cognition Outcomes

Whilst only one dietary omega-3 study [29•] was suitable for inclusion in the review of recent findings, results showed improvements in processing speed in the fatty fish treatment group, compared with meat meals and supplements groups. Dose of DHA and EPA in the fish and supplement groups were approximately 259 mg/day DHA and 150 mg/day EPA versus 315 mg/day DHA and 474 mg/day EPA, respectively. In comparison, the remaining studies used omega-3 in supplementation form and were conducted in adults. Of the 19 supplementation studies in the healthy population [23–28, 30, 31, 33, 34] nine studies (accounting for 827 participants of the 2827) showed some positive effects of omega-3 supplementation on cognition [23, 28, 31, 35–38, 41, 44]. Of the four studies in participants with SCI [45–48], two studies (accounting for 97 participants of the 1863) showed positive cognition effects of supplementation [46, 48]. All five studies conducted in participants with predetermined MCI (897 participants) showed positive cognition outcomes [49–53]. The cognitive domain most frequently reported to have improved outcomes across all participant population categories was memory function (including working memory, immediate verbal memory, delayed recall response time of memory, recall of object locations, loneliness-related verbal episodic memory).

Outcomes in Healthy Participants

In the nine supplementation studies conducted in healthy participants which reported beneficial effects of omega-3 on cognition, duration was as short as 35 days [28] and as long as 26 weeks [35, 44]. Duration did not appear to be the main influencer of outcome, with other trials running as long as 18 months [26] and 24 months [25] and no significant effects reported on cognition. Overall, the average dose appeared to be higher for DHA and for EPA within studies with positive effects (showing an average dose of 712.2 mg/day DHA and 1102.8 mg/day EPA compared with an average dose of 510.5 mg/day DHA and 489.8 mg/day EPA in the studies with no effects). Outcomes reported most often across studies with positive effects were evident in memory-based tests and also included improvement in reasoning, information processing accuracy and efficiency, executive function, rated confusion, and improved verbal fluency.

Outcomes in Participants with SCI

In the two studies in participants with SCI, both dose and duration appeared to be of importance. Studies showing benefit [46, 48] were of similar DHA doses but higher EPA doses (both 800 mg/day DHA, 1600 mg/day EPA) than the other two studies (800/896 mg/day DHA and 128/225 mg/day EPA), but of equivalent duration (6 months) to one [47] and longer by 3 months to another [45]. Improvements were reported in memory-related testing [46] and in tasks of the dysexecutive test [48].

Outcomes in Participants with MCI

In the five studies on participants with MCI, duration was of either 6 months [49, 51, 52] or 12 months [50, 53] and dosage included 900–2000 mg/day DHA alone [52, 53], 160 mg/day DHA plus 1670 mg/day EPA [51], 1550 mg/day DHA plus 400 mg/day EPA [51], 480 mg/day DHA plus 720 mg/day EPA [49•], and 1300 mg/day DHA plus 0.45 mg/day EPA [50]. Amongst the five studies with positive outcomes, memory was reportedly improved within three of these studies [49, 50, 52]. Improvements were also reported in the full-scale intelligence quotient, total basic cognitive aptitude, perceptual speed, space imagery efficiency, learning, and verbal fluency.

Omega-3 and Inflammation in Cognition Studies

Several markers of inflammation were assessed within the included omega-3 studies on cognition. These included interleukins (IL); IL-1b [28], IL-6 [32, 44, 49], IL-10 [49•], tumour necrosis factor-alpha (TNF-α) [32, 38, 44, 49], homocysteine [26], and high-sensitivity C-reactive protein (hs-CRP) [26, 36, 44]. All studies were based on supplementation forms of omega-3 fatty acids only, and included six studies in healthy adults and one study in adults with MCI. None of the studies in adults with SCI reported on inflammatory markers.

Of the inflammatory markers reported on in these studies, no beneficial effects of omega-3 supplementation were reported for IL-1b [28], IL-10 [49•], homocysteine [26], and hs-CRP [26, 36, 44]. Beneficial effects were reported for all three studies on the inflammatory markers IL-6 [32, 44, 49], with studies ranging in duration from 4 to 6 months and with the lowest and highest cumulative dose of omega-3s (DHA plus EPA) ranging from 1216.5 mg/day to 2433 mg/day (174 mg/day DHA plus 104.2 mg/day EPA and 348 mg/day DHA and 2085 mg/day EPA, respectively). Beneficial effects were reported in three [32, 44, 49] of the four studies on TNF-α, with the one study which showed no change in TNF-α having a duration of 5 weeks and dose of 1050 mg/day DHA plus 1500 mg/day EPA [38], whilst the other studies had duration and dose as given above for IL-6. Both the intervention and placebo group showed reductions in IL-6 and TNF-α in one study; hence, there was no significant difference in comparison with the control, despite the reductions in inflammatory markers [44].

Studies with Reduced Markers of Inflammation and Improved Cognitive Outcomes

Of the seven studies reporting on inflammatory markers, three studies reported positive inflammatory outcomes in response to omega-3 supplementation; of these three studies, two were in healthy populations which showed improvements in cognition [32, 44] and one was in a population with MCI reporting improvements in cognition [49•]. Of the studies which had no positive outcomes in inflammatory markers [26, 28, 36, 38], only one showed cognitive benefits [26]; two showed benefits in cognition but not inflammatory markers, but did not investigate either IL-6 or TNF-α [28, 36]; and one showed improvement in cognition but no improvement in TNF-α [38]; however, this study was for a shorter duration of 5 weeks.

Summary of Omega-3 Studies and Outcomes for Cognition and Markers of Inflammation

Overall, in all studies with positive effects on cognition from omega-3 supplementation, memory function appeared to be the most frequently reported benefit, also most consistent beneficial outcomes were found in participants with MCI. Overall, in studies with a positive impact on markers of inflammation from omega-3 supplementation, IL-6 and TNF-α appeared to be the most frequently reported inflammatory markers and were mostly associated with positive outcomes in cognition in healthy populations and those with MCI.

Additional Considerations

Although the present review aims to compare cognition and inflammatory outcomes of omega-3 dietary and supplementation studies, other considerations should be addressed between these two types of interventions. Additional health benefits can be found when diet is the source of omega-3 intervention, these include displacement of less healthful options, increased protein intake, and other benefits of micronutrients found in fish beyond omega-3s, i.e. iron and vitamin B_{12}. Alternatively, additional benefits of using supplements as the source of omega-3s include the ability to control for contaminants (such as heavy metals found in fish like mercury), ease of prescription, improved dose control and compliance, and hence the greater number of RCTs investigating supplements.

Numerous clinical trials conducted across different phases of the lifespan for omega-3 supplementation studies on cognition were identified in the current review; however, the search yielded zero clinical trials in healthy adults or adults with SCI/ MCI and only one trial in healthy adolescents where the intervention was dietary omega-3s with cognition as an outcome. Aside from a handful of intervention studies in children and adolescents showing mixed outcomes, there is insufficient data on dietary omega-3 interventions in adults and cognition outcomes, hence creating difficulty in making adequate conclusions on the topic. More omega-3 dietary intervention clinical trials measuring cognition outcomes in healthy adults, with or without MCI, should be conducted. Comparison studies between omega-3 supplementation and dietary intervention are also required in these populations.

Conclusion

Together, previous SLRs, meta-analyses, and data reported from recent clinical trials highlight a potential for omega-3s, both dietary and supplemental, in cognition outcomes in healthy populations, and in patients with SCI or MCI. The present review also indicates a possible relationship between changes in the inflammatory markers IL-6 and TNF-α and successful cognition outcomes. However, there continues to be inconsistency in cognition outcomes in omega-3 clinical trials. Important considerations for future studies should include dose, duration, and population and also measure inflammatory markers, particularly IL-6 and TNF-α, as possible indicators for improved cognition outcomes. Additional factors influencing outcomes may also include pre-intervention intake of omega-3s, through diet or supplementation. Also, omega-6 intake during the intervention period should be reported, as higher ratios of omega-6 to omega-3 may increase inflammation and negate beneficial effects of omega-3 interventions. Furthermore, a focus on the importance of which cognitive tests are selected to measure cognition outcomes may lead to more consistent findings.

Whilst some omega-3 supplementation studies show beneficial effects on cognition and observational studies show positive associations between fish consumption and cognition, overall, there is inconsistency in findings on the effect of omega-3 fatty acids (dietary or supplemental) on cognition. With a growing body of work in this field and considerations taken from SLRs, more studies comparing the effects of dietary omega-3s and omega-3 supplementation are required to determine differences in inflammatory and cognition outcomes. Also, studies providing a comparison of the two omega-3 interventions on the relationship between inflammatory markers, such as IL-6 and TNF-α, in cognition outcomes, particularly memory domains, would provide further clarity on the role of inflammation in cognition outcomes.

Compliance with Ethical Standards

Conflict of Interest Jessica E. Singh has a patent on Easy Access IP issued and licenced to La Trobe University for a herb spice mix and weight loss.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Tangestani Fard M, Stough C. A review and hypothesized model of the mechanisms that underpin the relationship between inflammation and cognition in the elderly. Front Aging Neurosci. 2019;11:56. https://doi.org/10.3389/fnagi.2019.00056.
2. Singh-Manoux A, Kivimaki M, Glymour MM, Elbaz A, Berr C, Ebmeier KP, et al. Timing of onset of cognitive decline: results from Whitehall II prospective cohort study. BMJ. 2012;344:d7622. https://doi.org/10.1136/bmj.d7622.
3. Roberts R, Knopman DS. Classification and epidemiology of MCI. Clin Geriatr Med. 2013;29(4):753–72. https://doi.org/10.1016/j.cger.2013.07.003.
4. Kaltsatou A. The impact of inflammation on cognitive impairment in chronic kidney disease patients. J Clin Exp Nephrol. 2016;1:20. https://doi.org/10.21767/2472-5056.100020.
5. Spyridaki EC, Avgoustinaki PD, Margioris AN. Obesity, inflammation and cognition. Curr Opin Behav Sci. 2016;9:169–75.
6. Massaro M, Scoditti E, Carluccio MA, Campana MC, De Caterina R. Omega-3 fatty acids, inflammation and angiogenesis: basic mechanisms behind the cardioprotective effects of fish and fish oils. Cell Mol Biol. 2010;56(1):59–82.
7. Guyenet S, Carlson SE. Increase in adipose tissue linoleic acid of US adults in the last half century. American Society for Nutrition Adv Nutr. 2015;6:660–4. https://doi.org/10.3945/an.115.009944.
8. Loef M, Walach H. The omega-6/omega-3 ratio and dementia or cognitive decline: a systematic review on human studies and biological evidence. J Nutr Gerontol Geriatr. 2013;32(1):1–23. https://doi.org/10.1080/21551197.2012.752335.
9. Saini RK, Keum YS. Omega-3 and omega-6 polyunsaturated fatty acids: dietary sources, metabolism, and significance-a review. Life Sci. 2018;203:255–67. https://doi.org/10.1016/j.lfs.2018.04.049.
10. Nutrient Reference Values for Australia and New Zealand. Fats: total fat and fatty acids: https://www.nrv.gov.au/nutrients/fats-total-fat-fatty-acids (2006). Accessed on 10 March 2020.
11. Tocher DR, Betancor MB, Sprague M, Olsen RE, Napier JA. Omega-3 long-chain polyunsaturated fatty acids, EPA and DHA: bridging the gap between supply and demand. Nutrients. 2019;11:89.
12. Rubio-Rodríguez N, Beltrán S, Jaime I, de Diego SM, Sanz MT, Carballido JR. Production of omega-3 polyunsaturated fatty acid concentrates: a review. Innovative Food Sci Emerg Technol. 2010;11:1–12. https://doi.org/10.1016/j.ifset.2009.10.006.
13. Innis S. Dietary omega 3 fatty acids and the developing brain. Brain Res. 2008;1237:35–43.
14. Stillwell W, Wassall SR. Chemistry and physics of lipids docosahexaenoic acid: membrane properties of a unique fatty acid. Chem Phys Lipids. 2003;126(1):1–27.
15. Bazinet RP, Layé S. Polyunsaturated fatty acids and their metabolites in brain function and disease. Nat Rev Neurosci. 2014;15:771–85. https://doi.org/10.1038/nrn3820.
16.•• Alex A, Abbott KA, McEvoy M, Schofield PW, Garg ML. Long-chain omega-3 polyunsaturated fatty acids and cognitive decline in non-demented adults: a systematic review and meta-analysis. Nutrition Reviews. 2019:1–16. https://doi.org/10.1093/nutrit/nuz073. **This systematic review contributes valuable data through meta-analyses of omega-3 intervention studies, pooling data from 25 intervention studies. Outcomes led to the conclusion that omega-3 supplementation could provide a mild benefit in improving memory function in adults free of dementia.**
17.•• Martí Del Moral A, Fortique F. Omega-3 fatty acids and cognitive decline: a systematic review. Nutr Hosp. 2019;36(4):939–49. https://doi.org/10.20960/nh.02496. **This systematic review looked at interventional studies on aged adults and elderly subjects with or without MCI and with no previous intake of fish oil supplements. Ten of the 14 studies included showed positive outcomes on cognition.**
18.•• Rangel-Huerta O, Gil A. Effect of omega-3 fatty acids on cognition: an updated systematic review of randomized clinical trials. Nutrition Reviews. 2017;76(1):1–20. https://doi.org/10.1093/nutrit/nux064. **This systematic review provides an overview of the largest number of studies from all the reviews on the topic, reporting on 51 studies across all ages and covering healthy individuals with mild or moderate cognitive impairment and also patients with Alzheimer's disease. Findings led to the conclusion that evidence on improvement of cognitive function from omega-3s during childhood and youth is inconclusive. Furthermore, in adults (both young and older), it is still unclear if omega-3s can improve cognition or prevent cognitive decline.**
19.•• Zhang Y, Chen J, Qui J, Li Y, Wang J, Jingjing J. Intakes of fish and polyunsaturated fatty acids and mild-to-severe cognitive impairment risks: a dose-response meta-analysis of 21 cohort studies. Am J Clin Nutr. 2016;103:330–40 The meta-analysis conducted in this systematic review highlights the impact of dietary intake of omega-3s based on data from 21 cohort studies and including 181,580 participants. A curvilinear relationship was reported between fish consumption and risk of AD, also between total PUFAs and risk of MCI.
20.•• Zeng L-F, Cao Y, Liang W-X, Bao W-H, Pan J-K, Wang Q, et al. An exploration of the role of a fish-oriented diet in cognitive decline: a systematic review of the literature. Oncotarget. 2017;8(24):39877–95. **This systematic review analyses data from nine studies containing 28,754 participants and reports reduced relative risk of DAT in highest categories of fish consumption compared with the lowest categories.**
21. Cederholm T. Fish consumption and omega-3 fatty acid supplementation for prevention or treatment of cognitive decline, dementia or Alzheimer's disease in older adults–any news? Current Opinion in Clinical Nutrition and Metabolic Care. 2017;20(2):104–109(6).
22. Al-Ghannami SS, Al-Adawi S, Ghebremeskel K, Hussein IS, Min Y, Jeyaseelan L, et al. Randomized open-label trial of docosahexaenoic acid-enriched fish oil and fish meal on cognitive and behavioral functioning in Omani children. Nutrition. 2019;57:167–72. https://doi.org/10.1016/j.nut.2018.04.008.
23. Amen DG, Taylor DV, Ojala K, Kaur J, Willeumier K. Effects of brain-directed nutrients on cerebral blood flow and neuropsychological testing: a randomized, double-blind, placebo-controlled, crossover trial. Adv Mind Body Med. 2013;27(2):24–33.

24. Bauer I, Hughes M, Rowsell R, Cockerell R, Pipingas A, Crewther S, et al. Omega-3 supplementation improves cognition and modifies brain activation in young adults. Hum Psychopharmacol. 2014;29(2):133–44.
25. Dangour AD, Allen E, Elbourne D, Fasey N, Fletcher AE, Hardy P, et al. Effect of 2-y n-3 long-chain polyunsaturated fatty acid supplementation on cognitive function in older people: a randomized, double-blind, controlled trial. Am J Clin Nutr. 2010;91(6):1725–32. https://doi.org/10.3945/ajcn.2009.29121.
26. Danthiir V, Hosking DE, Nettelbeck T, Vincent AD, Wilson C, O'Callaghan N, et al. An 18-mo randomized, double-blind, placebo-controlled trial of DHA-rich fish oil to prevent age-related cognitive decline in cognitively normal older adults. Am J Clin Nutr. 2018;107(5):754–62. https://doi.org/10.1093/ajcn/nqx077.
27. Dretsch MN, Johnston D, Bradley RS, MacRae H, Deuster PA, Harris WS. Effects of omega-3 fatty acid supplementation on neurocognitive functioning and mood in deployed U.S. soldiers: a pilot study. Mil Med. 2014;179(4):396–403. https://doi.org/10.7205/MILMED-D-13-00395.
28. Giles GE, Mahoney CR, Urry HL, Brunyé TT, Taylor HA, Kanarek RB. Omega-3 fatty acids and stress-induced changes to mood and cognition in healthy individuals. Pharmacol Biochem Behav. 2015;132:10–9.
29.• Handeland K, Øyen J, Skotheim S, Graff IE, Baste V, Kjellevold M, et al. Fatty fish intake and attention performance in 14–15 year old adolescents: FINS-TEENS-a randomized controlled trial. Nutr J. 2017;16(1):64. https://doi.org/10.1186/s12937-017-0287-9. **This is the only study on cognition in healthy adolescents that compares fish intake with omega-3 supplementation. The results suggest further studies comparing fish intake to omega-3 supplementation should be conducted.**
30. Jackson PA, Reay JL, Scholey AB, Kennedy DO. DHA-rich oil modulates the cerebral haemodynamic response to cognitive tasks in healthy young adults: a near IR spectroscopy pilot study. Br J Nutr. 2012;107(8):1093–8. https://doi.org/10.1017/S0007114511004041.
31. Jaremka LM, Derry HM, Bornstein R, Prakash RS, Peng J, Belury MA, et al. Omega-3 supplementation and loneliness-related memory problems: secondary analyses of a randomized controlled trial. Psychosom Med. 2014;76(8):650–8. https://doi.org/10.1097/PSY.0000000000000104.
32. Kielcolt-Glaser JK, Belury MA, Andridge R, Malarkey WB, Hwang BS, Glaser R. Omega-3 supplementation lowers inflammation in healthy middle-aged and older adults: a randomized controlled trial. Brain Behav Immun. 2012;26(6):988–95. https://doi.org/10.1016/j.bbi.2012.05.011.
33. Karr JE, Grindstaff TR, Alexander JE. Omega-3 polyunsaturated fatty acids and cognition in a college-aged population. Exp Clin Psychopharmacol. 2012;20(3):236–42. https://doi.org/10.1037/a0026945.
34. Konagai C, Yanagimoto K, Hayamizu K, Han L, Tsuji T, Koga Y. Effects of krill oil containing n-3 polyunsaturated fatty acids in phospholipid form on human brain function: a randomized controlled trial in healthy elderly volunteers. Clin Interv Aging. 2013;8:1247–57. https://doi.org/10.2147/CIA.S50349.
35. Külzow N, Witte AV, Kerti L, Grittner U, Schuchardt JP, Hahn A, et al. Impact of omega-3 fatty acid supplementation on memory functions in healthy older adults. J Alzheimers Dis. 2016;51(3):713–25. https://doi.org/10.3233/JAD-150886.
36. Mahmoudi MJ, Hedayat M, Sharifi F, Miraefin M, Nazari N, Mehrdad N, et al. Effect of low dose ω-3 poly unsaturated fatty acids on cognitive status among older people: a double-blind randomized placebo-controlled study. Journal of Diabetes & Metabolic Disorders. 2014;13:34 http://www.jdmdonline.com/content/13/1/34.
37. Narendran R, Frankle WG, Mason NS, Muldoon MF, Moghaddam B. Improved working memory but no effect on striatal vesicular monoamine transporter type 2 after omega-3 polyunsaturated fatty acid supplementation. PLoS One. 2012;7(10):e46832. https://doi.org/10.1371/journal.pone.0046832.
38. Nilsson A, Radeborg K, Salo I, Björck I. Effects of supplementation with n-3 polyunsaturated fatty acids on cognitive performance and cardiometabolic risk markers in healthy 51 to 72 years old subjects: a randomized controlled cross-over study. Nutr J. 2012;11:99. https://doi.org/10.1186/1475-2891-11-99.
39. Pase MP, Grima N, Cockerell R, Stough C, Scholey A, Sali A, et al. The effects of long-chain omega-3 fish oils and multivitamins on cognitive and cardiovascular function: a randomized, controlled clinical trial. J Am Coll Nutr. 2015;34(1):21–31. https://doi.org/10.1080/07315724.2014.880660.
40. Schättin A, Baier C, Mai D, Klamroth-Marganska V, Herter-Aeberli I, de Bruin ED. Effects of exergame training combined with omega-3 fatty acids on the elderly brain: a randomized double-blind placebo-controlled trial. BMC Geriatr. 2019;19(1):81. https://doi.org/10.1186/s12877-019-1084-4.
41. Stonehouse W, Conlon CA, Podd J, Hill SR, Minihane AM, Haskell C, et al. DHA supplementation improved both memory and reaction time in healthy young adults: a randomized controlled trial. Am J Clin Nutr. 2013;97(5):1134–43. https://doi.org/10.3945/ajcn.112.053371.
42. Stough C, Downey L, Silber B, Lloyd J, Kure C, Wesnes K, et al. The effects of 90-day supplementation with the omega-3 essential fatty acid docosahexaenoic acid (DHA) on cognitive function and visual acuity in a healthy aging population. Neurobiol Aging. 2012;33(4):824.e1–3. https://doi.org/10.1016/j.neurobiolaging.2011.03.019.
43. Tokuda H, Sueyasu T, Kontani M, Kawashima H, Shibata H, Koga Y. Low doses of long-chain polyunsaturated fatty acids affect cognitive function in elderly Japanese men: a randomized controlled trial. J Oleo Sci. 2015;64(6):633–44. https://doi.org/10.5650/jos.ess15009.
44. Witte AV, Kerti L, Hermannstädter HM, Fiebach JB, Schreiber SJ, Schuchardt JP, et al. Long-chain omega-3 fatty acids improve brain function and structure in older adults. Cereb Cortex. 2014;24(11):3059–68. https://doi.org/10.1093/cercor/bht163.
45. Andrieu S, Guyonnet S, Coley N, Cantet C, Bonnefoy M, Bordes S, et al. MAPT Study Group. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multi domain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. Lancet Neurol. 2017;16(5):377–89. https://doi.org/10.1016/S1474-4422(17)30040-6.
46. Boespflug EL, McNamara RK, Eliassen JC, Schidler MD, Krikorian R. Fish oil supplementation increases event-related posterior cingulate activation in older adults with subjective memory impairment. J Nutr Health Aging. 2016;20(2):161–9. https://doi.org/10.1007/s12603-015-0609-6.
47. Jackson PA, Forster JS, Bell JG, Dick JR, Younger I, Kennedy DO. DHA supplementation alone or in combination with other nutrients does not modulate cerebral hemodynamics or cognitive function in healthy older adults. Nutrients. 2016;8(2):86. https://doi.org/10.3390/nu8020086.
48. McNamara RK, Kalt W, Shidler MD, McDonald J, Summer SS, Stein AL, et al. Cognitive response to fish oil, blueberry, and combined supplementation in older adults with subjective cognitive impairment. Neurobiol Aging. 2018;64:147–56. https://doi.org/10.1016/j.neurobiolaging.2017.12.003.
49.• Bo Y, Zhang X, Wang Y, You J, Cui H, Zhu Y, et al. The n-3 polyunsaturated fatty acids supplementation improved the cognitive function in the Chinese elderly with mild cognitive impairment: a double-blind randomized controlled trial. Nutrients. 2017;9(1).

https://doi.org/10.3390/nu9010054. **This intervention study shows improved cognition outcomes and also reports significant reductions in the inflammatory markers IL-6 and TNF-alpha.**

50. Lee LK, Shahar S, Chin AV, Yusoff NA. Docosahexaenoic acid-concentrated fish oil supplementation in subjects with mild cognitive impairment (MCI): a 12-month randomised, double-blind, placebo-controlled trial. Psychopharmacology. 2013;225(3):605–12. https://doi.org/10.1007/s00213-012-2848-0.
51. Sinn N, Milte CM, Street SJ, Buckley JD, Coates AM, Petkov J, et al. Effects of n-3 fatty acids, EPA v. DHA, on depressive symptoms, quality of life, memory and executive function in older adults with mild cognitive impairment: a 6-month randomised controlled trial. Br J Nutr. 2012;107(11):1682–93. https://doi.org/10.1017/S0007114511004788.
52. 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. https://doi.org/10.1016/j.jalz.2010.01.013.
53. Zhang YP, Miao R, Li Q, Wu T, Ma F. Effects of DHA supplementation on hippocampal volume and cognitive function in older adults with mild cognitive impairment: a 12-month randomized, double-blind, placebo-controlled trial. J Alzheimers Dis. 2017;55(2):497–507.