Lead Article

Effect of omega-3 fatty acids on cognition: an updated systematic review of randomized clinical trials

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Context: *The increasing number of studies on the effects of n-3 long-chain polyunsaturated fatty acids (LC-PUFAs) on health, particularly cognition, in the last 5 years reflects the growing interest in this area of research.* ***Objective:*** *The aim for this systematic review was to evaluate the scientific evidence published in the last 5 years (2012–2017) on the effects of n-3 LC-PUFA intake on cognition, cognitive development, and cognitive decline to determine whether n-3 LC-PUFAs support cognitive development and prevent cognitive decline.* ***Data Sources:*** *The PubMed database was searched.* ***Study Selection:*** *The 51 articles included in this systematic review reported on healthy individuals with mild or moderate cognitive impairment and patients with Alzheimer's disease. Risk of bias was assessed using Cochrane methodology.* ***Data Extraction:*** *The number of study participants, the type of study, the type and dose of n-3 LC-PUFAs, and the key results are reported here.* ***Results:*** *Current evidence indicates that n-3 LC-PUFAs administered during pregnancy or breastfeeding have no effect on the skills or cognitive development of children in later stages of development. Evidence regarding the improvement of cognitive function during childhood and youth or in attention deficit/hyperactivity disorder is inconclusive. Moreover, it is still unclear if n-3 LC-PUFAs can improve cognitive development or prevent cognitive decline in young or older adults.*

INTRODUCTION

In recent years, long-chain polyunsaturated fatty acids (LC-PUFAs) have been the subject of increased research. Known to be the main components of cell membranes, including[1] neurons in the brain, they are involved in energy transformation and the regulation of information flow between cells.

Omega-3 (n-3) and omega-6 (n-6) LC-PUFAs are essential for infant and child development because they participate in several neuronal processes, including the regulation of membrane fluidity and gene expression.[1] The accumulation of docosahexaenoic acid (DHA) in the brain begins in utero, mainly in the second half of pregnancy, when growth of gray matter accelerates.[2] For instance, the deficiency or imbalance of LC-PUFAs has been associated with poorer child development reflected in domains such as language ability, communication, gross motor and fine motor skills, problem solving, and personal/social and verbal fluency.[3]

In 2007, Eilander et al.[4] reported a beneficial effect of maternal n-3 LC-PUFA supplementation during pregnancy and lactation on the cognitive development of infants and children. However, there was no reported benefit for visual development as measured using electrophysiological tests. Furthermore, their work could

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not confirm previous evidence of a beneficial effect of supplementation given to preterm and term infants and children older than 2 years of age. Nonetheless, Campoy et al.[6] reported that term infants supplemented with a daily dose of 100 mg of DHA plus 200 mg of arachidonic acid showed improved visual development. In 2012, the *British Journal of Nutrition* published a supplemental issue on the role of LC-PUFAs in the prevention and treatment of disease. In particular, the effect of n-3 fatty acids on cognition was evaluated.[5–7] Campoy et al.[6] conducted a systematic review and reported that supplementation with DHA during pregnancy or lactation had a beneficial effect on visual acuity outcomes. However, they noted that evidence from the randomized clinical trials (RCTs) included in the review did not demonstrate a clear and consistent beneficial effect of LC-PUFA supplementation during pregnancy and lactation on the growth or neurodevelopment of term infants.

The responsiveness of the brain, mainly the frontal lobes, to supplementation with DHA during developmental stages is very sensitive.[8] The optimal level of DHA is of great importance because the frontal lobe supports diverse functions such as those required for executive and high-order cognitive activities, and the prefrontal lobe supports social, emotional, and behavioral development.[8] The accumulation of DHA slows down during infancy, and thus dietary intake of DHA and eicosapentaenoic acid (EPA), a precursor of DHA, might help maintain optimal levels in the brain and improve cognitive function during infancy.[9]

Several studies reported an association between DHA levels and cognitive performance. For example, Escolano-Margarit et al.[10] reported that higher DHA levels in cord blood might be related to better neurological outcomes at 5.5 years of age. Furthermore, Campoy et al.[11] reported that maternal DHA status at delivery was associated with a Mental Processing Composite Score (MPCS) above the 50th percentile in the offspring at 6.5 years. Nevertheless, none of the authors reported a significant beneficial effect of LC-PUFA supplementation. In 2003, Helland et al.[12] studied the effect of maternal n-3 LC-PUFA supplementation during pregnancy on 4-year-old children. They reported that supplementation might be beneficial for later mental development of children, as assessed by the MPSC of the Kaufman Assessment Battery for Children. Later, Ryan and Nelson[13] found that, in 4-year-old children, DHA levels in blood are associated with increased scores on the Peabody Picture Vocabulary Test. Recently, Brew et al.[14] investigated the effect of n-3 LC-PUFA supplementation during the first 5 years of life during later academic performance. They found no significant results to support the academic enhancement attributable to the supplementation. Nonetheless, they observed an association between the n-3 LC-PUFA concentration at 8 years of age and academic performance evaluated from 8 to 14 years of age.[14]

Evidence from cross-sectional studies in children in the age range of 7 to 9 years showed an association between regular intake of n-3 LC-PUFAs and cognitive health.[15,16] For example, Montgomery et al.[16] found that lower DHA concentrations in whole blood were linked to poorer reading ability and working memory performance as well as oppositional behavior.

Studies of the effect of n-3 LC-PUFAs in adolescents and young adults are scarce, and therefore the effect of supplementation is unclear. For instance, it has been shown that supplementation with n-3 LC-PUFAs in college-aged individuals had limited beneficial effects.[17,18] On the other hand, data from cross-sectional studies in healthy postmenopausal women found an association between a higher n-3 index and larger total normal brain volume and hippocampal volume.[19]

The influence of the administration of n-3 LC-PUFAs varies across the life span, but it is known to be amplified during the earlier and the latest periods of life.[20] The research, however, has shown mixed results in adults and the elderly. For example, after a secondary analysis of data from the Women's Health Initiative Study of Cognitive Aging study,[21] which included women with a cognitive health condition, the authors reported no significant association between DHA plus EPA levels in red blood cells and age-related cognitive decline. Titova et al.[22] reported that dietary intake of EPA plus DHA assessed using a self-report questionnaire might be linked to enhanced cognitive health in later life, but there was no relationship between dietary data and brain volume. On the contrary, data from dementia-free Framingham Study participants[23] revealed that lower red blood cell DHA levels are associated with a smaller brain volume and, interestingly, a cognitive impairment pattern, even in persons free of clinical dementia.

Several studies have shown a neuroprotective effect of n-3 LC-PUFAs and have also observed an association between high levels of n-3 LC-PUFAs and a lower incidence of some mental illnesses such as depression[24] and of neurodegenerative diseases such as Alzheimer's disease (AD).[25] For instance, the analysis of retrospective data from the Alzheimer's Disease Neuroimaging Initiative showed that the use of fish oil supplements was associated with less atrophy of cerebral cortex gray matter and the hippocampus and better performance on the Alzheimer's Disease Assessment Scale–Cognitive subscale and the Mini-Mental State Examination.[26]

Recognition of the importance of DHA in the development of the central nervous system has also contributed to increased interest in LC-PUFAs, which have been correlated with diverse functions such as neurogenesis, neurotransmission, and protection against oxidative stress.[27] The inclusion of n-3 LC-PUFAs in the diet seems to have a neuroprotective effect and might have modulatory effects on the nervous system, both of which are of keen interest in the aging process.[28] A meta-analysis conducted by Wu et al.[29] concluded that a higher intake of fish was associated with a lower risk of AD, while data from Raji et al.[30] showed that fish consumption was related to brain structural integrity, mainly in the gray matter in the hippocampus, precuneus, posterior cingulate, and orbital cortex. Similarly, a recent meta-analysis of 21 studies[31] reported that fish products are recommended as dietary sources and are associated with a lower risk of cognitive impairment. Indeed, marine-derived DHA was associated with a lower risk of dementia and AD, though without a linear dose–response relation. Additionally, Zhang et al.[32] indicated that n-3 fatty acids might help to prevent cognitive decline in the elderly, while Gu et al.[33] suggested that increased consumption of LC-PUFAs and vitamin E–rich foods is associated with better white matter integrity. In contrast, Forbes et al.[34] suggested that n-3 fatty acids did not affect cognition in nondemented middle-aged and older adults. Likewise, Dangour et al.[5] concluded there was no evidence to support the routine use of LC-PUFA supplements for the prevention or amelioration of cognitive decline in later life.

The increasing number of studies on the effects of n-3 LC-PUFAs on health, particularly cognition, published in the last 5 years reflects the growing interest in this area of research. Therefore, the aim of this review was to evaluate the effects of n-3 LC-PUFA intake on cognitive development and cognitive decline at different stages of life. For this purpose, a systematic review of the scientific evidence published during the peroid 2012–2017 was conducted.

METHODS

This systematic review was designed with the aim of generating an updated review of RCTs conducted to assess the effect of n-3 LC-PUFAs on cognition, including cognitive performance, following previous work.[5–7,35,36] It summarizes evidence of the effect of n-3 LC-PUFAs over the life span in a single publication. It was developed according to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) statement,[37] and the PICOS (Population, Intervention, Comparison, and Outcomes) (Table 1) criteria were used to define the following research question: Do n-3 LC-PUFAs benefit cognitive development and prevent cognitive decline? Randomized clinical trials that studied the effect of n-3 LC-PUFAs on cognitive skills, cognitive development, or cognitive impairment in humans, both healthy and ill, were included. Prospective, parallel, and crossover designs were considered. There was no restriction on sample size. Articles, or at least the abstract, had to be written in English. No ecological or case–control studies were included.

Table 1 **PICOS criteria for inclusion of studies**

Parameter	Inclusion criteria
Population	All populations, with no restrictions for age or sex
Intervention	Supplementation with n-3 long-chain polyunsaturated fatty acids
Comparison	Treatment vs control
Outcome	Cognitive development and cognitive decline
Setting	Randomized controlled trial

Inclusion and exclusion criteria

To be considered for inclusion in the systematic review, studies had to administer dietary supplementation or a specific diet. Studies that used dietary recommendations or self-reporting alone were excluded. Studies were also excluded if a supplement that could potentially confound the effects of n-3 LC-PUFAs was administered or if no ethical approval had been received. Since previous systematic reviews and meta-analyses have already examined evidence of the effect of n-3 fatty acids on cognition,[5–7] only studies published between January 1, 2012, and June 27, 2017, were included.

Participants

Eligible participants were individuals of all ages, either healthy or with acute or chronic disease. There were no restrictions regarding gender, ethnicity, or study setting.

Types of interventions

The n-3 LC-PUFA treatments selected included EPA and DHA, individually or in combination with each other or with another pharmacological treatment (or vitamin supplementation), provided the study design allowed the effects of n-3 LC-PUFAs to be isolated. There were no restrictions on dosage or dosing regimen.

Primary outcome measures

The following primary outcomes were considered for inclusion in cognitive studies: evaluation of the

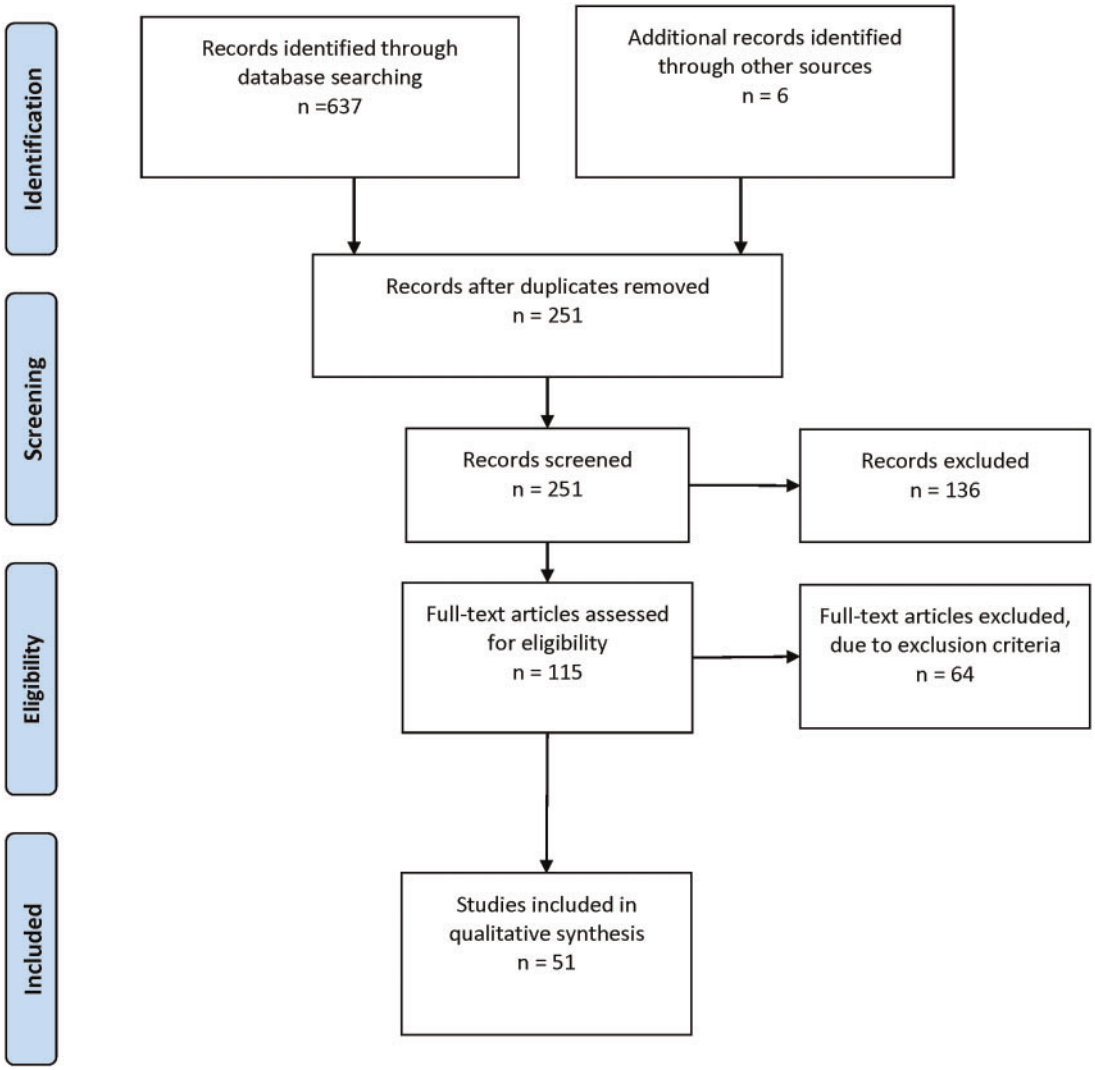

Figure 1 **Flow diagram of the literature search process.**

involvement of the senses; learning ability; test of cognitive development; structural alterations in brain white matter; visual evoked potentials; and the performance of executive and motor functions.

Literature search

Figure 1 shows the main steps of the literature search. Studies were identified in the PubMed database by applying the limit date from January 1, 2012, to June 27, 2017, using the following medical subject headings (MeSH) search terms: ("Fatty Acids, omega-3" AND cognitive development) AND "Humans"; ("Fatty Acids, omega-3" AND cognitive impairment) AND "Humans"; ("Fatty Acids, omega-3" AND brain development) AND "Humans"; ("Fatty Acids, omega-3" AND cognitive decline) AND "Humans"; ("Mild Cognitive Impairment" AND "Fatty Acids, omega-3") AND "Humans"; ("Cognition" AND "Fatty Acids, omega-3") AND "Humans"; ("Learning disorders" AND "Fatty Acids, omega-3") AND "Humans"; ("Cognition disorders" AND "Fatty Acids, omega-3" AND "Humans").

Study selection

Abstracts of publications yielded by the search were examined by O.D.R.H., who eliminated all publications that were obviously ineligible for inclusion.

Data extraction

Two reviewers (O.D.R.H. and María José Soto) input the data into a database; a third reviewer (A.G.) resolved any discrepancies.

Assessment of risk of bias

Both authors (A.G. and O.D.R.H.) independently assessed the risk of bias following the Cochrane Collaboration's methodology.[38] The Cochrane tool includes different domains related to randomization and allocation concealment (selection bias), blinding (performance and measurement bias), loss to follow-up and adherence to the intention-to-treat principle (attrition bias), and selective outcome publication (reporting bias). In addition, other potential sources of bias, such as private or public funding, were included. Risk of bias was tabulated for each study and was classified as low, high, or unclear, as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions*.[38]

RESULTS

Table 1, Table 2,[14,39–58] and Table 3[17,59–71] list the 51 publications selected for inclusion in the systematic review. The articles are grouped by study population. Tables 1–3 also show the sample size, the type of study, the dose of n-3 LC-PUFAs administered, the tests used to evaluate cognitive condition, and the primary outcomes.

n-3 LC-PUFA supplementation during pregnancy, lactation, or early life: association with cognitive development

Seven of the 51 selected studies reported on n-3 supplementation during pregnancy[39–45] (Table 2). All 7 were performed in healthy pregnant women who were supplemented between weeks 18 and 20 of gestation until delivery (sample size ranged between 50 and 973). The doses ranged between 150 and 1100 mg of EPA per day and between 400 and 2200 mg of DHA per day and were delivered in fish oil. All RCTs included a placebo. The studies focused mainly on the follow-up of children whose mothers had received LC-PUFA supplementation during pregnancy. Objectives included the assessment of mental and psychomotor development at 6 and 20 months[40] and the auditory and visual evoked responses in the brainstem at 3 and 6 months, respectively.[41] In the longer interventions, the primary outcomes were as follows: evaluation of cognitive function after follow-up of children for 2 years[42] and 5 years,[39] study of general conceptual ability at age 4 years,[43] and assessment of the attention networks after 8.5 years of maternal supplementation.[44] Language and motor control were evaluated in 12-year-old children.[45] Finally, behavior was evaluated in 5-year-old children[39] and 12-year-old children.[45] Only Ramakrishnan et al.[39] reported a significant improvement in attention using the Conners' Kiddie Continuous Performance test after supplementation of 5-year-old children with DHA at 400 mg/d. Otherwise, there was no significant effect on other parameters evaluated after supplementation with EPA or DHA.

Another 5 studies investigated n-3 LC-PUFA supplementation of infants during lactation[46–50] (Table 2). The intervention period began at birth in 4 of the studies and at 3 months after birth in the fifth study. The intervention period in these studies ranged from 9 weeks to 9 months, and the study population ranged between 98 and 654. The doses of DHA and EPA ranged from 20 to 300 mg/d and from 32 to 300 mg/d, respectively. The aims of the studies included the investigation of long-term cognitive function after 8 years of LC-PUFA supplementation; the verification of general intellectual ability; the assessment of neurodevelopment and language; and the examination of the cognitive development at 12 months after supplementation. None of the interventions was shown to be effective, although Henriksen et al.[46] reported that the concentration of DHA in blood could predict IQ.

Nine of the RCTs included were designed to study the effect of LC-PUFA supplementation through childhood or adolescence (Table 2).[14,51–57] The population size in these studies ranged between 59 and 362, with participants aged between 3 and 13 years. In 4 studies, the children included were described as healthy. One study recruited children who were rated as having a low reading level; in another study, participants were iron deficient; and in the remaining 3 studies, participants presented attention-deficit/hyperactivity disorder (ADHD). The duration of the intervention ranged from 3 to 9 months in 8 RCTs and was 5 years in the other 1. The reported doses ranged from 32 to 1109 mg/d for EPA and between 135 and 1032 mg/d for DHA. The findings were mixed: a 40-week intervention had positive effects on cognitive development[51]; in contrast, supplementation for 4 to 8 months showed no significant benefit.[52,55,56] Nevertheless, daily supplementation with at least 210 mg of DHA alone or with 120 mg of DHA plus 600 mg of EPA (EPA/DHA ratio: 1:5) for 3 months or more might improve the speed of information processing[52,53] and the reading speed.[56]

The RCTs that studied n-3 LC-PUFA supplementation in children with ADHD (Table 2) found no effects of supplementation compared with placebo. However, the increased concentration of EPA and DHA in red blood cells was associated with improved working memory, reading speed, and behavior.[56–58] In the only long-term intervention, Brew et al.[14] studied the cognitive function in 14-year-old adolescents after supplementation with LC-PUFAs during the first 5 years of

Table 2 **Randomized clinical trials (published between 2012 and 2016) of interventions with n-3 long-chain polyunsaturated fatty acids (LC-PUFAs) to evaluate effects on cognition in children and adolescents**

Reference	Timing of intervention, age group tested	*N*	Dosage	Period of intervention	Outcome (test)	Conclusion
Ramakrishnan et al. (2016)[39]	Prenatal supplementation, NB to 6 mo	973	DHA, 400 mg	Gestation week 18–22 through delivery	Global cognition, behavior, and attention (MSCA, BASC-2, K-CPT) (follow-up period, up to age 5 y)	Significant improvement observed only in attention (K-CPT)
Campoy et al. (2015)[40]	Prenatal supplementation, NB to 6 mo	118	Group 1: Fish oil containing DHA 500 mg/d + EPA 150 mg/d EPA:DHA ratio: 3:1 Group 2: 5-MTHF, 400 μg Group 3 Fish oil + 5-MTHF	Gestation week 20 through delivery	Mental and psychomotor development at 6 and 20 mo (BSID)	No effect of intervention
Stein et al. (2012)[41]	Prenatal supplementation, NB to 6 mo	900	DHA, 400 mg/d	Gestation week 18–22 through delivery	Auditory- and visual-evoked potentials at 3 and 6 mo (SWI)	No effect of intervention
Catena et al. (2016)[44]	Prenatal supplementation, children 2–12 y	270	Group 1: Fish oil containing DHA 500 mg/d + EPA 150 mg EPA:DHA ratio, 3:1 Group 2: 5-MTHF, 400 μg Group 3: Fish oil + 5-MTHF	Gestation week 20 through delivery	Attention networks (follow-up period, up to age 8.5 y) (ANT)	No effect of the interventions that included fish oil
Meldrum et al. (2015)[45]	Prenatal supplementation, children 2–12 y	50	DHA, 2200 mg/d EPA, 1100 mg/d EPA:DHA ratio, 1:2	Gestation week 20 through delivery	Cognitive function, language, behavior, and motor control (follow-up period, up to age 12 y) (WISC)	No effect of intervention
Gould et al. (2014)[42]	Prenatal supplementation, children 2–12 y	184	DHA, 800 mg/d	Gestation week 20 through delivery	Cognitive function, (follow-up period, up to age 2 y) (a lentil-box version of the A-not-B task)	No effect of intervention
Makrides et al. (2014)[43]	Prenatal supplementation, children 2–12 y	646	DHA, 800 mg/d	Gestation week 20 through delivery	General conceptual ability (follow-up period, up to age 4 y) (DAS)	No effect of intervention
Henriksen et al. (2016)[46]	Supplementation during lactation, NB to 8 y	98	DHA, 32 mg/d AA, 31 mg/d in 100 mL of breastmilk	From birth to 9 wk	Long-term cognitive function (follow-up period, up to age 8 y) (WASI, Full-Scale IQ)	No significant effect. Blood DHA concentration can predict IQ

(continued)

Table 2 **Continued**

Reference	Timing of intervention, age group tested	*N*	Dosage	Period of intervention	Outcome (test)	Conclusion
Collins et al. (2015)[48]	Supplementation during lactation, NB to 8 y	654	DHA diet: DHA, 20 mg/kg/d DHA-rich diet: DHA, 50 mg/kg/d	From birth to 40 wk	Cognitive development(WISC)	No effect of intervention
Almaas et al. (2015)[47]	Supplementation during lactation, NB to 8 y	98	DHA, 32 mg/d + AA, 31 mg/d in 100 mL of breastmilk	From birth to 9 wk	Long-term cognitive function (follow-up period, up to age 8 y) (WISC)	No effect of intervention
Meldrum et al. (2012)[49]	Supplementation during lactation, NB to 8 y	420	DHA, 250 mg/d EPA, 60 mg/d EPA:DHA ratio, 1:4	From birth to 6 mo	Neurodevelopment and language (BSID, TDC, CBCL TVMI)	No effect of intervention
van der Merwe et al. (2013)[50]	Supplementation during lactation, NB to 8 y	172	DHA, 200 mg/d EPA, 300 mg/d EPA:DHA ratio, 1:0.6	From 3 to 9 mo	Cognitive development at 12 mo (2-step measured problem-solving, WIP, TDC)	No effect of intervention
Brew et al. (2015)[14]	Supplementation during lactation, children 3–12 y	239	DHA, 135 mg/d EPA, 32 mg/d EPA:DHA ratio, 1:4	Until 5 y old	Long-term cognitive function (follow-up period, up to age 14 y) (NAPLAN)	No effect of intervention
Portillo-Reyes et al. (2014)[53]	Supplementation during lactation, children 3–12 y	59	DHA, 180 mg/d EPA, 270 mg/d DHA:EPA ratio, 1:1.3	3 mo	Neuropsychological function (WISC, ENI)	More than 70% of omega-3–supplemented children showed improvement in processing speed, visual-motor coordination, perceptual integration, attention, and executive function
Parletta et al. (2013)[51]	Supplementation during lactation, children 3–12 y	227	EPA, 558 mg/d DHA, 174 mg/d EPA:DHA ratio, 3:1	40 wk	Reading, spelling, and nonverbal cognitive development (DAP, CRS)	Improvement in cognitive development but not in literacy
Willatts et al. (2013)[52]	Supplementation during lactation, children 3–12 y	235	LC-PUFA formula: DHA, 210 mg/d in 100 g of fat	4 mo	Cognitive development (follow-up period, up to age 6 y) (WPPSI-R IQ test, DNT, MFFT)	No difference in IQ between groups after intervention. However, individuals supplemented with LC-PUFA were faster and more efficient at processing information
Richardson et al. (2012)[54]		362	DHA, 600 mg/d	16 wk	Reading, working memory, and behavior (BSID, CRS)	Improvement in reading skills

(continued)

Table 2 **Continued**

Reference	Timing of intervention, age group tested	*N*	Dosage	Period of intervention	Outcome (test)	Conclusion
	Supplementation during lactation, children 3–12 y					
Baumgartner et al. (2012)[55]	Supplementation during lactation, children 3–12 y	321	Group 1: Iron, 50 mg/d, 4 times/wk Group 2: Iron placebo Group 3: DHA, 420 mg/d + EPA, 80 mg/d EPA:DHA ratio, 1:5 Group 4: DHA + EPA placebo	8.5 mo	Cognitive development (KABC-II, HVLT)	No effect of intervention
Milte et al. (2015)[58]	Supplementation during lactation, children with ADHD aged 3–13 y	90	EPA-rich oil: EPA, 1109 mg/d + DHA, 108 mg/d EPA:DHA ratio, 10:1 DHA-rich oil: EPA, 264 mg/d + DHA, 1032 mg/d EPA:DHA ratio, 1:5	4 mo	Literacy, behavior, attention, and inhibition (WIAT, WISC, CRT)	No effect of intervention. Higher concentration of DHA and EPA in erythrocytes was associated with better behavior, attention, and literacy
Widenhorn-Müller et al. (2014)[56]	Supplementation during lactation, children with ADHD aged 3–13 y	95	EPA, 600 mg/d DHA, 120 mg/d EPA:DHA ratio, 1:0.2 Vitamin E, 120 mg/d	4 mo	Behavior and cognitive function (DISYPS-II)	Improvement in working memory associated with an increase in EPA and DHA and a decrease in AA
Milte et al. (2012)[57]	Supplementation during lactation, children with ADHD aged 3–13 y	87	EPA-rich oil: EPA, 1109 mg/d + DHA, 108 mg/d EPA:DHA ratio, 10:1 DHA-rich oil: EPA, 264 mg/d + DHA, 1032 mg/d EPA:DHA ratio, 1:5	4 mo	Literacy and behavior (WISC, CRT)	No difference between treatments. However, increase in LC-PUFA was associated with better behavior and improved reading skills

Abbreviations: AA, arachidonic acid; ADHD, attention deficit hyperactivity disorder; ANT, Attention Network Test; BASC-2, Behavioral Assessment System for Children, Second Edition; BSID, Bayley Scales of Infant Development; CBCL, Child Behavior Checklist; CRS, Conners' Rating Scale; CRT, choice reaction time; DAP, Draw-a-Person test; DAS, Differential Ability Scales; DIPSYS, Diagnostik-System für psychische Störungen; DHA, docosahexaenoic acid; DNT, Day-Night Test; EPA, eicosapentaenoic acid; ENI, Evaluación Neuropsicológica Infantil; HVLT, Hopkins Verbal Learning Test; K-CTP, Conners' Kiddie Continuous Performance Test; KABC-II, Kaufman Assessment Battery for Children, Second Edition; MFFT, Matching Family Figures Test; MSCA, McCarthy Scales of Children's Abilities; NAPLAN, National Assessment Program Literacy and Numeracy; NB, newborn; SWI, Sierra Wave instrument; TDC, Toddler Development Checklist; TVMI, Test of Visual-Motor Integration; WASI, Wechsler Abbreviated Scale of Intelligence; WIAT, Weschler Individual Achievement Test; WIP, Willats' Infant Planning; WISC, Weschler Intelligence Scales for Children; WPPSI-R, Wechsler Preschool and Primary Scale of Intelligence–Revised; 5-MTHF, methyltetrahydrofolate.

Table 3 **Randomized clinical trials (published between 2012 and 2016) of interventions with n-3 long-chain polyunsaturated fatty acids (LC-PUFAs) to evaluate effects on cognition in adults**

Reference	Timing of intervention, age group	*N*	Dosage	Duration of intervention	Outcome (test)	Conclusion
Giles et al. (2015)[60]	Healthy young adults,18–34 y	72	EPA, 1680 mg/d DHA, 120 mg/d DHA:EPA ratio, 1:1.5	35 d	Mood, psychosocial stress test, and cognitive function (POMS, STICSA, TSST, EIT, MFT)	No effect of intervention
Bauer et al. (2014)[61]	Healthy young adults,18–34 y	11	EPA-rich oil: EPA, 590 mg/d + DHA, 137 mg/d DHA:EPA ratio, 1:4 DHA-rich oil: EPA, 159 mg/d + DHA, 417 mg/d EPA:DHA ratio, 1:4	1 mo	Cognitive function (Stroop test, SMT)	EPA-rich formula improved cognitive function
Jackson et al. (2012)[59]	Healthy young adults,18–34 y	159	Group 1: DHA, 450 mg/d EPA, 90 mg/d EPA:DHA ratio, 1:5 Group 2: EPA, 300 mg/d DHA, 200 mg/d DHA:EPA ratio, 1:1.5	12 wk	Cognitive function and mood (COMPASS)	No effect of intervention
Jackson et al. (2012)[63]	Healthy young adults,18–34 y	65	Group 1: DHA, 450 mg/d EPA, 90 mg/d EPA:DHA, 1:5 Group 2: EPA, 300 mg/d DHA, 200 mg/d DHA:EPA ratio, 1:1.5	12 wk	Cognitive function (COMPASS)	No effect of intervention
Jackson et al. (2012)[62]	Healthy young adults,18–34 y	22	Group 1: DHA, 450 mg/d EPA, 90 mg/d EPA:DHA ratio, 1:5 Group 2: EPA, 300 mg/d DHA, 200 mg/d DHA:EPA ratio, 1:1.5	12 wk	Cognitive function (COMPASS)	Increased cerebral blood flow (associated with cognitive tasks) observed in the DHA group
Karr et al. (2012)[17]	Healthy young adults,18–34 y	41	DHA, 480 mg/d EPA, 720 mg/d DHA:EPA ratio, 1:1.5	4 wk	Cognitive function (RAVLT, Stroop test, TMT, PANAS)	No effect of intervention

(continued)

Table 3 **Continued**

Reference	Timing of intervention, age group	*N*	Dosage	Duration of intervention	Outcome (test)	Conclusion
Mazereeuw et al. (2016)[64]	Healthy adults up to 75 y	92	DHA, 1200 mg/d EPA, 600 mg/d EPA:DHA ratio, 1:2 Other LC-PUFAs, 100 mg/d	12 wk	Cognitive performance, verbal memory (CVLT), attention and processing, and executive function (animal naming test, CWAT, and TMT, part B)	No effect of intervention
Pase et al. (2015)[70]	Healthy adults up to 75 y	160	Group 1: EPA, 240 mg/d DHA, 240 mg/d (EPA:DHA ratio, 1:1) + MV Group 2: EPA, 480 mg/d DHA, 480 mg/d (EPA:DHA ratio, 1:1) + MV Group 3: EPA, 480 mg/d DHA, 480 mg/d EPA:DHA ratio, 1:1	4 mo	Cognitive function (Swinburne University test)	No effect of intervention
Witte et al. (2014)[71]	Healthy adults up to 75 y	121	EPA, 1320 mg/d DHA, 880 mg/d DHA:EPA ratio, 1:1.5	26 wk	Cognitive function, brain structure (TMT, AVLT, Stroop test)	Improvement in executive function, gray mass volume, and microstructural integrity of white mass
Dretsch et al. (2014)[66]	Healthy adults up to 75 y	106	EPA, 1175 mg/d DHA, 950 mg/d DHA:EPA ratio, 1:1.2	2 mo	Neurocognitive evaluation, mood, and sleepiness (CNS-VS, Stroop test, PSQI, ESS)	No effect on neurocognitive function. EPA + DHA levels in blood were associated with a reduction in daytime sleepiness
Stonehouse et al. (2013)[65]	Healthy adults up to 75 y	176	DHA, 1160 mg/d EPA, 170 mg/d EPA:DHA ratio, 1:7	6 mo	Cognitive function (COMPASS)	Improvement in memory and reaction time
Antypa et al. (2012)[67]	Healthy adults up to 75 y	71	EPA, 1740 mg/d DHA, 250 mg/d DHA:EPA ratio, 1:7	4 wk	Cognitive function (Go/No-Go task, POMS, FERT)	No effect of intervention
Stough et al. (2012)[68]	Healthy adults up to 75 y	74	DHA, 252 mg/d EPA, 60 mg/d EPA:DHA ratio, 1:4 Vitamin E, 10 mg/d	90 d	Cognitive function and visual acuity	No effect on cognitive function. Improvement in visual acuity observed in adults with a diminishment
Nilsson et al. (2012)[69]	Healthy adults up to 75 y	40	EPA, 1500 mg/d DHA, 1050 mg/d DHA:EPA ratio, 1:1.5	5 weeks	Cognitive function (working memory test)	No effect of intervention

Abbreviations: AVLT, Auditory Verbal Learning Test; COMPASS, Computerized Mental Performance Assessment System; CNS-VS, central nervous system vital signs; CVLT, California Verbal Learning Test; CWAT, Controlled Word Association Test; DHA, docosahexaenoic acid; EIT, emotional interference task; EPA, eicosapentaenoic acid; ESS, Epworth Sleepiness Scale; FERT, Facial Expression Recognition Task; MFT, Morphed Faces Task; MV, multivitamin; PANAS, Positive and Negative Affect Schedule; POMS, Profile of Mood States; PSQI, Pittsburgh Sleep Quality Index; RAVLT, Rey Auditory Verbal Learning Test; SMT, spatial memory task; STICSA, State-Trait Inventory for Cognitive and Somatic Anxiety; TMT, Trail Making Test; TSST, Trier Social Stress Test.

life. The authors found no effects from the administration of LC-PUFAs, but they reported an association between plasma n-3 LC-PUFA levels and academic performance between the ages of 8 and 14 years.

n-3 LC-PUFA supplementation in young people and adults: association with cognitive development

Table 3[17,59–63] shows the 6 RCTs that assessed the effect of n-3 LC-PUFAs on cognitive development in young adults between 18 and 34 years of age. The intervention lasted between 1 and 3 months, and all studies included healthy individuals (n = 11–159 participants). The dose ranged from 159 to 1680 mg/d for EPA and from 137 to 1120 mg/d for DHA. Five studies did not report significant effects on cognitive function after n-3 supplementation.[17,59,60,62,63] However, Bauer et al.[61] concluded that an EPA-rich dose (590 mg/d, with a 4:1 ratio of EPA:DHA) administered for 1 month is adequate to improve cognitive function as assessed by the Stroop test. Jackson et al.[62] reported that supplementation with DHA (450 mg/d, with a 5:1 ratio of DHA:EPA) significantly increased the cerebral blood flow associated with various cognitive tasks related to reaction time and visual information processing, but performance in the Stroop test was not affected. Finally, Jackson et al.[59] and Giles et al.[60] investigated the effect of n-3 LC-PUFAs on mood and situations of psychosocial stress but found no significant results.

A further 7 RCTs included healthy adults aged 18 to 75 years (Table 3).[64–71] The length of the intervention ranged from 2 months to 26 weeks, and the daily doses ranged between 170 and 1740 mg of EPA and between 250 and 1200 mg of DHA. The primary objective in all studies was to assess cognitive function; improvements in memory and reaction time were reported after supplementation with n-3 LC-PUFAs for 6 months[65] and improvements in executive function after 26 weeks.[71] Additionally, mood, sleep, and brain structure were analyzed. Benefits reported included the association of EPA and DHA in blood with a reduction in daytime sleepiness[66] and the preservation of both the integrity of the microstructure of white mass and the volume of gray mass with a dose of 1320 mg of EPA plus 880 mg of DHA per day for 26 weeks.[71]

n-3 LC-PUFA supplementation in older adults: protection against cognitive decline

This review included 17 studies in older or elderly adults (≥50 y) (Table 4[25,72–87]). Seven were conducted in cognitively healthy or presumptively healthy individuals (1 that included women only and 2 that included men only),[72–78] 7 in patients with mild or moderate cognitive deficit,[79–85] and 3 in patients with a probable or confirmed diagnosis of AD.[25,86,87] The studies in healthy participants (n = 27–3073) had an intervention length ranging between 1 and 40 months, with an EPA dosage of 100 to 491 mg/d and a DHA dosage of 92 to 964 mg/d. Cognitive function was assessed in all studies. Various beneficial effects on cognitive function have been reported with EPA + DHA supplementation above 285 mg/d, mainly enhancements in reaction time, verbal memory, recall of object location, and evoked potentials.[75–77,79] However, in the 2 interventions with the largest number of participants[74,78] and the 1 with second-longest duration (3 years),[72] no improvement in cognitive function or delay in cognitive decline was observed.

The duration of the intervention in the 7 studies conducted in patients with cognitive impairment[79–85] ranged from 9 days to 12 months, while the dosage of EPA ranged from 120 to 1670 mg/d and the dosage of DHA from 180 to 1550 mg/d. The primary goal in all interventions was the assessment of cognitive function. In addition, 3 studies were designed to study brain structure or hemodynamics.[80–82] The administration of EPA at 480 mg/d plus DHA at 720 mg/d (EPA:DHA ratio, 1:1.5) for 9 days improved cognitive function significantly, as evaluated using the Basic Cognitive Aptitude Test.[79] Moreover, the consumption of EPA at 1600 mg/d plus DHA at 800 mg/d (EPA:DHA ratio, 2:1) was associated with an improvement in certain memory tasks.[80] Köbe et al.[82] indicated that the combination of EPA/DHA intake, aerobic exercise, and cognitive stimulation reduced gray matter atrophy in brain regions associated with AD. Furthermore, Boespflug et al.[80] reported an increase in cortical blood-oxygen-level–dependent activity after 24 weeks in the right posterior cingulate and left superior frontal regions during memory loading. This activity was correlated with memory performance, as evaluated with the 2-back task.

Finally, the duration of intervention in 3 studies conducted in patients in whom AD was suspected or confirmed was 4, 6, and 12 months, respectively, with doses ranging between 600 and 975 mg of EPA per day and between 625 and 1720 mg of DHA per day (n = 34–174 participants). Cognitive function was assessed at the end of each intervention. After 4 months, the effect of supplementation with n-3 LC-PUFAs was limited.[86] After 6 months, cognitive function was maintained (with a dose richer in DHA),[25] and after 12 months, the progression of functional impairment had been delayed (with a dose richer in EPA).[87]

Assessment of risk of bias

All articles were assessed for risk of bias. They were classified into 3 age groups: children, adults, and older

Table 4 **Randomized clinical trials (published between 2012 and 2016) of interventions with n-3 long-chain polyunsaturated fatty acids (LC-PUFAs) to evaluate effects on cognitive impairment in older adults**

Reference	Timing of intervention, age group	*N*	Dosage	Duration of intervention	Outcome (test)	Conclusion
Andrieu et al. (2017)[72]	Healthy adults (≥ 50 y)	1680	DHA, 800 mg/d EPA, 225 mg/d EPA:DHA ratio, 1:3.5	3 y	Cognitive decline (WAIS, MMSE)	No effect of intervention
Külzow et al. (2016)[73]	Healthy adults (≥ 50 y)	44	EPA, 1320 mg/d DHA, 800 mg/d DHA:EPA ratio, 1:1.65	26 wk	Cognitive function (OLM task, AVLT)	Improvement in cognitive function
Chew et al. (2015)[74]	Healthy adults (≥ 50 y)	3073	LC-PUFAs 1 g/d + lutein 10 mg/d or zeaxanthin 2 mg/d	3 mo	Cognitive function (ARED cognitive battery tests)	No effect of intervention
Strike et al. (2015)[75]	Healthy adults (≥ 50 y)	27	Multivitamin (DHA-rich fish oil, 2 g/d) (DHA, 964 mg/d + EPA, 160 mg/d; EPA:DHA ratio, 1:7) + phosphatidylserine (88 mg), ginkgo biloba (240 mg), folic acid (1 mg), and vitamin B_{12} (24 mg)	6 mo	Mobility (walking speed) and cognitive function (CANTAB)	Improvement in cognitive function and mobility
Tokuda et al. (2015)[76]	Healthy adults (≥ 50 y)	113	DHA, 300 mg/d EPA, 100 mg/d EPA:DHA ratio, 1:3 ARA, 120 mg/d	1 mo	Cognitive function (P300 test)	Improvement in cognitive function
Konagai et al. (2013)[77]	Healthy adults (≥ 50 y)	45	Krill oil: DHA, 92 mg/d EPA, 193 mg/d DHA:EPA ratio, 1:2 Sardine oil: DHA, 251 mg/d + EPA, 491 mg/d DHA:EPA ratio, 1:2	3 mo	Cognitive function (P300 test)	Both groups showed improvement in cognitive function
Geleijnse et al. (2012)[78]	Healthy adults (≥ 50 y)	2911	Group 1: EPA + DHA, 400 mg/d EPA:DHA ratio, 3:2 Group 2: EPA + DHA, 400 mg/d + ALA, 2 g/d EPA:DHA ratio, 3:2 Group 3: ALA, 2 g/d	40 mo	Cognitive function (MMSE)	No effect of intervention
Boespflug et al. (2016)[80]	Adults with mild or moderate CI	21	EPA, 1600 mg/d DHA, 800 mg/d EPA:DHA ratio, 2:1	24 wk	Cortical BOLD response. 0-, 1-, and 2-back working memory task	Increase in BOLD response and improvement in 2-back memory task accuracy
Bo et al. (2017)[79]	Adults with mild or moderate CI	86	EPA, 720 mg/d DHA, 480 mg/d EPA:DHA ratio, 1.5:1	9 d	Cognitive function (BCAT)	Improvement in BCAT scores, perceptual speed, space imaginary efficiency, and working memory

(continued)

Table 4 **Continued**

Reference	Timing of intervention, age group	*N*	Dosage	Duration of intervention	Outcome (test)	Conclusion
Jackson et al. (2016)[81]	Adults with mild or moderate CI	85	Group 1: DHA, 896 mg/d EPA, 128 mg/d EPA:DHA ratio, 1:7 Group 2: Multivitamin with phosphatidylserine (88 mg), ginkgo biloba (240 mg), folic acid (1 mg) and vitamin B_{12} (24 mg) DHA, 964 mg/d EPA, 160 mg/d EPA:DHA ratio, 1:6	6 mo	Cerebral hemodynamics and cognitive function. (CDB, RVIP, COMPASS)	No effect of intervention
Köbe et al. (2015)[82]	Adults with mild or moderate CI	26	EPA, 1320 mg/d DHA, 880 mg/d DHA:EPA, 1:1.5 Vitamin E, 15 mg/d	6 mo	Cerebral structure and function (AVLT, TMT, Stroop test, mini MMSE)	n-3 LC-PUFA + aerobic exercise + cognitive stimulation reduced gray matter atrophy in regions associated with AD
Mahmoudi et al. (2014)[83]	Adults with mild or moderate CI	199	DHA, 180 mg/d EPA, 120 mg/d EPA:DHA, 1:1.5	6 mo	Cognitive function (MMSE, AVLT)	No effect of intervention
Lee et al. (2012)[84]	Adults with mild or moderate CI	36	DHA, 1300 mg/d EPA, 450 mg/d EPA:DHA, 1:3	12 mo	Cognitive function (MMSE, DRS, RAVLT, WAIS, CDT)	No effect of intervention
Sinn et al. (2012)[85]	Adults with mild or moderate CI	50	Group 1: EPA, 1670 mg/d DHA, 160 mg/d DHA:EPA ratio, 1:10 Group 2: EPA, 400 mg/d DHA, 1550 mg/d EPA:DHA, 1:3.5	6 mo	Depression symptoms, life quality, and cognitive function (Stroop test, MFQ, RAVLT, WAIS BMT)	No effect of intervention
Phillips et al. (2015)[86]	AD patients	76	DHA, 625 mg/d EPA, 600 mg/d EPA:DHA ratio, 1:1	4 mo	Cognitive function, visual acuity, and mood (MMSE, HVLT-R, BASDEC, BADLS)	No effect of intervention
Eriksdotter et al. (2015)[25]	AD patients	174	DHA, 1720 mg/d EPA, 600 mg/d EPA:DHA ratio, 1:2.1	6 mo	Cognitive function (ADAS-Cog test)	Maintenance of cognitive function

(continued)

Table 4 **Continued**

Reference	Timing of intervention, age group	*N*	Dosage	Duration of intervention	Outcome (test)	Conclusion
Shinto et al. (2014)[87]	AD patients	34	Group 1: DHA, 675 mg/d EPA, 975 mg/d DHA:EPA ratio, 1:1.4 Group 2: DHA, 675 mg/d EPA, 975 mg/d DHA:EPA ratio, 1:1.4 LA, 600 mg/d	12 mo	Cognitive function (ADAS-Cog, MMSE) and functional ability	No effect in cognitive function according to the ADAS-Cog test. Both groups showed a delay in progression of functional impairment. Group 2 showed decreased global CI as reflected in the MMSE

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale cognitive subscale; ALA, alpha-linolenic acid; ARA, arachidonic acid; ARED, Age-Related Eye Disease Study; AVLT, auditory verbal learning test; BADLS, Bristol Activities of Daily Living Scale; BASDEC, Brief Assessment Schedule Depression Cards; BCAT, Basic Cognitive Aptitude Tests; BOLD, cortical blood oxygen level-dependent; CANTAB, Cambridge Neuropsychological Test Assessment Battery; CDB, cognitive demand battery; CDT, clock-drawing test; CI, cognitive impairment; COMPASS, Computerized Mental Performance Assessment System; DHA, docosahexaenoic acid; DRS, Dementia Rating Scale; EPA, eicosapentaenoic acid; HVLT-R, Hopkins Verbal Learning Test–Revised; LA, alpha-lipoic acid; MFQ, Memory Functioning Questionnaire; OLM, object location memory; MMSE, Mini-Mental State Examination; RAVLT, Rey Auditory Verbal Learning Test; RVIP, Rapid Visual Information Processing; TMT, Trail Making Test; WAIS, Weschler Adult Intelligence Scale.

individuals with cognitive impairment or AD. The process for evaluating and determining the risk of bias for each article is shown in Figure S1 in the Supporting Information online. Figures S2A, S2B, and S2C in the Supporting Information online show the distribution of the risk of bias according to each category and domain specified by the Cochrane Collaboration tool. With regard to studies conducted in children (see Figure S2A in the Supporting Information online), the categories related to random sequence generation, blinding of participants, and outcomes showed a low risk of bias. However, allocation concealment was unclear in 38% of the studies. The domain associated with attrition bias presented 28% of unclear or high risk of bias. Evaluation of the studies that included adults and older adults (Figure S2B and S2C in the Supporting Information online) revealed that random sequence generation and allocation concealment were unclear in a high percentage of studies (>25% in the former and >50% in the latter), owing mainly to vague reporting. Furthemore, the assessment of attrition bias (25% of studies had unclear or high risk) in studies conducted in older individuals suggests a potential for high risk of bias.

In addition, authors of 45 of the 51 included studies either declared a collaboration with private companies to develop the research or disclosed that at least 1 author had a relationship with the funding source. Nevertheless, the majority of the authors declared independence with regard to the design, development, and publication of the studies.

DISCUSSION

Although n-3 LC-PUFA intake during pregnancy and lactation has been reported to benefit the development of visual acuity and verbal learning in infants,[6] current evidence indicates that n-3 LC-PUFA intake by pregnant or breastfeeding women does not influence the cognitive skills or development of children. This is reflected in the results of the RCTs conducted during the last 5 years, which are consistent with a 2012 review by Gould et al.,[88] who reported that previous findings were insufficient to demonstrate the benefit of LC-PUFA supplementation during pregnancy for the future cognitive development of children.

Taken together, studies in children or infants showed mixed results. While studies of n-3 LC-PUFA supplementation for more than 40 weeks demonstrated positive results, studies with interventions of 4 to 8 months reported limited improvement.[52,55,56] Interestingly, 2 studies agreed that n-3 LC-PUFA supplementation with at least 100 mg/d for more than 3 months improved the speed of information

processing,[52,53] and 1 study reported an enhancement in working memory.[56] Portillo-Reyes et al.[53] and Parletta et al.[51] concurred that children aged 6 to 12 years who lived in unfavorable conditions (such as poverty, malnutrition, and low education) showed an enhanced response to n-3 LC-PUFA supplementation. The findings of the present review are in accordance with those of Eilander et al.[4] and reflect the lack of evidence to support a benefit of LC-PUFA supplementation on cognition in children in aged 2 to 7 years. In fact, few authors have reported findings for this age group over the last 5 years. Moreover, as noted by Weiser et al.,[8] there is considerable inconsistency between studies. Hence, the evidence is inconclusive, which indicates the need for more RCTs focused on children, particularly those aged 4 to 7 years. If studies were designed to assess cognitive functions independently, it might be possible to isolate the effect of LC-PUFAs on specific tasks. In addition, it might be useful to investigate the effect of n-3 LC-PUFAs in children in hostile environments who do not consume optimal amounts of LC-PUFAs. Thus, increasing the availability of DHA might affect all cognitive functions. Moreover, it is necessary to set new standards for baseline concentrations of DHA in order to increase comparability of results from different interventions.

The administration of n-3 LC-PUFAs seems to have a null effect on cognitive development as the primary outcome in children with ADHD, as indicated by reviews of long-term interventions. In a recently published meta-analysis[89] that included some of the studies reviewed here, the authors concluded that there is scarce evidence to support an effect of n-3 LC-PUFAs on cognitive performance. Additionally, Sinn et al.[85] found no evidence to support a possible benefit of n-3 LC-PUFAs in patients with ADHD. Although recent studies addressed the limitations of previous trials, mainly by increasing both the length of the intervention and the doses,[56,58] there is still a lack of evidence to support the role of n-3 LC-PUFAs in cognitive development. Nevertheless, it seems that n-3 LC-PUFA consumption may be associated with behavior improvement, but additional studies with larger populations are needed.[57,58] Altogether, these findings indicate the need for further RCTs to strengthen the existing evidence in children and adolescents.

Only a few publications included healthy young adults, and results were weak and inconsistent. On one hand, 4 of the included studies[17,59,60,63] found no effects associated with the consumption of LC-PUFAs, even though doses exceeded the daily recommendation. On the other hand, the 2 studies that reported an enhancement in cognitive function had fewer participants.[61,62]

In their 2014 review of 15 articles, Jiao et al.[90] concluded that n-3 LC-PUFA supplementation does not promote improvement in memory, executive function, or processing speed. In the current review, several authors of RCTs conducted in cognitively healthy adults agreed that supplementation with n-3 LC-PUFAs had a limited effect on cognitive function.[65–70] Nonetheless, supplementation with LC-PUFAs at more than 1.2 mg/d for at least 5 months might enhance executive function and reaction time[65,71]; clearly, further studies are required to confirm this. Overall, however, there is limited evidence to support the effect of n-3 LC-PUFAs on cognitive function in young people and adults.

Studies in older, cognitively healthy adults showed that interventions longer than 1 month and daily doses greater than 92 mg of EPA and 50 mg of DHA appear to be effective in enhancing cognitive function. However, in order to validate the effects reported thus far, more studies with greater numbers of participants are needed. In contrast, the evidence from studies in older adults has shown that n-3 LC-PUFAs seem to be ineffective in influencing cognitive function.[90] Likewise, the results included in this review are not robust enough to support a recommendation of n-3 LC-PUFA supplementation to prevent cognitive impairment or decline. In fact, the recent 3-year RCT from Andrieu et al.[72] shows that PUFA supplementation is ineffective in preventing cognitive decline. Evidence from previous reviews and meta-analyses also has shown no apparent beneficial effects. For instance, Sydenham et al.,[91] Forbes et al.,[34] and Wu et al.[29] all concluded that n-3 LC-PUFAs do not prevent cognitive impairment; however, Zhang et al.[32] reported that n-3 LC-PUFAs may help prevent cognitive decline in older adults. Likewise, the meta-analysis by Zhang et al.,[31] which included data from 21 cohorts, demonstrated that 1 serving of fish per week was associated with a lower risk of dementia. In support of this finding,[31] a DHA increment of 0.1 g/d in the diet was associated with a decreased risk of dementia and AD. They also observed a curvilinear relationship between fish consumption and the risk of AD and between n-3 LC-PUFA intake and mild cognitive decline. Intake of LC-PUFAs from a marine source was associated with a lower risk of dementia and AD; interestingly, there seems to be a dose–response relationship.

The present report includes 3 RCTs conducted in AD patients, and the response appears to be associated with the length of the intervention. In fact, while a 4-month intervention showed limited results,[86] a 6-month intervention showed maintenance of cognitive function[25] and a 12-month intervention showed a delay in the progression of functional impairment.[87] DHA is a precursor of neuroprotectins, the molecules that modulate the activity of glial cells and may help to limit the accumulation of protein β-amyloid in the brain.[92] More studies of longer duration and more robust design are

needed to investigate cognitive decline in healthy adults and in adults with neurodegenerative diseases. Furthermore, it is important to develop meta-analyses with more clearly defined and homogeneous criteria to enable objective comparisons.

Authors of 2 previous reviews were unable to compare outcomes because it was impossible to pool the results of multiple studies in a single analysis.[93,94] Such is the case when specific types of memory are assessed, because it is difficult to define which tests measure each type of memory.[93] The findings of the present review show that it is remains challenging to compare results between different interventions because of the diverse tests use to assess cognitive function and, in some cases, to pinpoint the overall cognitive performance. Otherwise, as suggested by Cheatham et al.,[94] it might be interesting to evaluate cognitive functions independently, since different interventions may have different effects on cognitive outcomes.

It seems that many of the tests chosen to assess cognitive development may not be sensitive to dietary changes. Therefore, it is important to consider that cognitive development is associated with the maturation of specific brain regions that are related to the development of different specific cognitive functions, and thus the administration of LC-PUFAs might affect some areas of cognition, but not others. Jackson et al.[81] developed noteworthy research. They designed their study and chose tasks on the basis of previous evidence showing activation of the prefrontal cortex when cerebral hemodynamics were assessed by near-infrared spectroscopy. The assessment included 4 repetitions of the Cognitive Demand Battery, which comprises 2 mathematical tasks and 1 questionnaire to evaluate mental fatigue, although the authors noted that these tasks might not be sensitive to changes in n-3 LC-PUFA intake in healthy older adults.

Another tool, the Bayley Scales of Infant Development (BSID), is a globally standardized measure of development, but it was developed for the assessment of neurodevelopmental delays or disorders; hence, it might not be appropriate for evaluating the effect of dietary interventions on healthy individuals. The use of the BSID may take into account the target population, mainly because this tool was based on the study of European and US populations. Therefore, the BSID needs to be standardized for the population being studied in order to avoid possible bias related to different socioeconomic or geographic conditions.

Other alternatives such as the MacArthur Communicative Development Inventory or the Child Behavior Checklist are cost effective and highly validated tools for the assessment of specific tasks of cognitive functions. The MacArthur Communicative Development Inventory and the Child Behavior Checklist are instruments designed to assess behavioral development, vocabulary growth, and parental perception of a child's mental health. Researchers administering these tests should recognize that these tools have been shown to be influenced by the test taker's knowledge of the group assignment in dietary interventions and the family background.[49]

It is unlikely that specific effects of dietary manipulations can be detected when assessing overall cognitive function. For example, when designing studies in older people, the age ranges must be narrow enough so that similar ranges of healthy and undiagnosed nonhealthy individuals can be examined together. In addition, the inclusion criteria must be strict and objective; ideally, they should include a previous genetic screening, since certain genetic factors (ie, the *APOE* gene) might confound the potential effect of supplementation. Hence, potential confounding factors must be considered when selecting the tests to measure cognitive function. For instance, instruments such as the Stroop test or the A-not-B task have been shown to be age sensitive and possibly not challenging enough for certain age groups.[42,95] The Stroop test assesses the ability of the individual to resist to verbal interference, which is a measure of selective attention.

Similarly, the widely used Hopkins Verbal Learning Test (HVLT) is not standardized for use in children, and thus results must be adjusted by age. Baumgartner et al.[55] reported that the heterogeneity of HVLT results when comparing different time points might be related to the different set of words used at each time point. Nevertheless, the HVLT has been shown to be reliable in screening for mild dementia and as an adjunct in the clinical assessment of older people.[96] In fact, a comparison between the HVLT and the Mini-Mental State Examination for detecting patients with mild dementia revealed better sensitivity of the former and better specificity of the latter.[96] Moreover, Phillips et al.[86] concluded that the use of the Brief Assessment Schedule Depression Cards is inappropriate for assessing mood in individuals with AD because such patients lack awareness. Neither is the Bristol's Activities of Daily Living Scale the right tool to detect a change in cognitive function in persons with cognitive impairment but no dementia. The authors suggest the use of the AD Cooperative Study Scale for Activities of Daily Living in Mild Cognitive Impairment might provide more relevant data for the analysis of more complex everyday tasks.[86]

Numerous systematic reviews and meta-analyses over the past 5 years have studied n-3 supplementation in cognition and cognitive development.[89,90,93,97] Some authors, however, reported a number of limitations, in

some cases related to study design, such as insufficient statistical power, small sample size, and the inclusion of broad age ranges.[90,97] In the present review, it was found that several authors of more recent studies addressed key methodological issues, such as increasing the intervention duration, the population, and the n-3 dose (above 1.5 mg/d). In addition, as mentioned above, some researchers focused on studying specific cognitive outcomes independently (such as attention, processing speed, or problem-solving).[14,25,44,49,51,52,70,83] Others[41,76,77] included the use of electrophysiological tests, which may provide a more objective approach than traditional and more subjective tests such as the BSID. Clearly, future studies should consider using independent tests when trying to isolate the specific effects of LC-PUFAs on different cognitive processes. For instance, as reported here, LC-PUFAs are involved in increasing the speed with which information is acquired[52,53]; this might improve synaptic efficiency or transmission speed or enhance the function of *N*-methyl-aspartate channels.[94]

The use of improved technologies such as functional magnetic resonance imaging (fMRI), for instance, also might provide new insights. The use of fMRI has been reported in a study of the brain's response to taste, aroma, and flavor perceptions[98] and a study of the early stages of AD.[99] Functional MRI has been shown to be an excellent tool to assess network dysfunction; therefore, it might be useful as a complementary technique to study the cerebral response to dietary manipulations.

The present review notes that researchers who are developing studies in certain populations, such as older adults or patients with AD, are starting to use similar tools to evaluate cognitive enhancement or decline, thus permitting the comparison of results between interventions. And, while there is still a broad range of approaches used to assess effects in infants and adolescents, researchers seem to be focusing on those aims that seem promising, for instance, the effect of n-3 supplementation on information processing speed.

Other authors are designing studies in which n-3 LC-PUFAs are included in the daily diet through the intake of fish products. This approach should provide data to better understand both the impact of an entire diet on cognitive function and the interactions between different dietary components and n-3 LC-PUFAs.

Finally, another limitation noted in previous reviews was related to RCT methodology, such as the vague descriptions of allocation concealment and blinding methods, which can be a potential source of bias. Thus, risk of bias in this review was assessed using the Cochrane tool designed for this purpose, and allocation concealment was found to be unclear in a high percentage of the studies included. Hence, it is not possible to determine whether the process of allocation and blinding was done incorrectly due to a lack of report rather than the use of an incorrect method. Another potential source of bias detected in the studies in children is related to incomplete outcome data: several studies are follow-up interventions in which the reported results correspond to secondary analyses. Thus, the initial power calculation might not be applicable because of dropouts from these secondary analyses. This must be taken into account when designing new follow-up studies. Reports for elderly individuals tend to be unclear, and thus the description and reporting in most of the domains need to be improved to ensure the findings are valid.

CONCLUSION

Supplementation with n-3 LC-PUFAs during pregnancy, lactation, or the early years of life does not appear to provide benefits to cognitive development beyond those previously described for visual acuity and language outcomes in infants. Evidence of the effects of supplementation with LC-PUFAs during childhood and youth on cognitive function appears inconclusive, but more RCTs with a larger number of participants are needed. Furthermore, the study of supplementation in children under unfavorable conditions, such as malnourishment, might be a promising path for future research. In addition, it is unclear whether the administration of n-3 LC-PUFAs can improve cognitive development or prevent cognitive decline in young or older adults. Indeed, longer and better-designed studies with lower risk of bias are needed in adults, elderly individuals, and AD patients to investigate the potentially beneficial effects of n-3 fatty acids on cognition.

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Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

Appendix 1 **PRISMA guidelines checklist**

Figure S1 **Risk of bias summary: review author's judgements about each risk of bias item for each included study**

Figure S2 **(a) Risk of bias graph: review author's judgement about each risk of bias item presented as percentages across the studies in children (b) Risk of bias graph: review author's judgement about each risk of bias item presented as percentages across the studies in adults (c) Risk of bias graph: review author's judgement about each risk of bias item presented as percentages across the studies in older subjects**

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