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Review

Long-chain polyunsaturated fatty acids (LCPUFA) from genesis to senescence: The influence of LCPUFA on neural development, aging, and neurodegeneration

Carola I.F. Janssen, Amanda J. Kiliaan *

Department of Anatomy, Radboud University Medical Center, Donders Institute for Brain, Cognition, and Behaviour, PO Box 9101, 6500 HB Nijmegen, The Netherlands

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ABSTRACT

Many clinical and animal studies demonstrate the importance of long-chain polyunsaturated fatty acids (LCPUFA) in neural development and neurodegeneration. This review will focus on involvement of LCPUFA from genesis to senescence. The LCPUFA docosahexaenoic acid and arachidonic acid are important components of neuronal membranes, while eicosapentaenoic acid, docosahexaenoic acid, and arachidonic acid also affect cardiovascular health and inflammation.

In neural development, LCPUFA deficiency can lead to severe disorders like schizophrenia and attention deficit hyperactivity disorder. Perinatal LCPUFA supplementation demonstrated beneficial effects in neural development in humans and rodents resulting in improved cognition and sensorimotor integration.

In normal aging, the effect of LCPUFA on prevention of cognitive impairment will be discussed. LCPUFA are important for neuronal membrane integrity and function, and also contribute in prevention of brain hypoperfusion. Cerebral perfusion can be compromised as result of obesity, cerebrovascular disease, hypertension, or diabetes mellitus type 2.

Last, we will focus on the role of LCPUFA in most common neurodegenerative diseases like Alzheimer's disease and Parkinson's disease. These disorders are characterized by impaired cognition and connectivity and both clinical and animal supplementation studies have shown the potential of LCPUFA to decrease neurodegeneration and inflammation. This review shows that LCPUFA are essential throughout life.

Contents

Abbreviations: 5-LOX, 5-lipoxygenase; AD, Alzheimer's disease; ADAS-cog, cognitive subscale of the Alzheimer's disease assessment scale; ADHD, attention deficit hyperactivity disorder; ADP, adenosine diphosphate; ALA, α-linolenic acid; AMI, acute myocardial infarction; ARA, arachidonic acid; ATP, adenosine triphosphate; Aβ, β-amyloid; B12, vitamin B12; B6, vitamin B6; BBB, blood brain barrier; BDNF, brain-derived neurotrophic factor; BSID, Bayley Scales of Infant Development; cAMP, cyclic adenosine monophosphate; CDP-choline, cytidine diphosphate choline; CDR, clinical dementia rating; CIBIC-plus, clinician's interview-based impression of change scale which included caregiver-supplied information; CK, choline kinase; COX, cyclooxygenase; CPT, 1,2 diacylglycerol choline phosphotransferase; CREB, cAMP response element binding protein; CT, cytidine triphosphate-phosphocholine cytidyl transferase; CTP, cytidine triphosphate; DAG, diacylglycerol; DBS, deep brain stimulation; DHA, docosahexaenoic acid; DMII, diabetes mellitus type 2; EPA, eicosapentaenoic acid; FADS, fatty acid desaturase; GDNF, glial cell-derived neurotrophic factor; GLA, γ linolenic acid; I-DOPA, I-dihydroxyphenylalanine; IQ, intelligence quotient; LA, linoleic acid; LCPUFA, long-chain polyunsaturated fatty acids; LDL, low density lipoprotein; LT, leukotrienes; MCI, mild cognitive impairment; MDI, mental development index; MetS, metabolic syndrome; MMSE, mini-mental state examination; MPTP, 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine; n-3 PUFA, omega-3 polyunsaturated fatty acids; n-6 PUFA, omega-6 polyunsaturated fatty acids; NPD1, neuroprotectin D1; NPI, neuropsychiatric inventory; p.p., post partum; PC, phosphatidylcholine; PD, Parkinson's disease; PDI, psychomotor development index; PE, phosphatidylethanolamine; PG, prostaglandins; PPAR, peroxisome proliferator-activated receptor; PS, phosphatidylserine; RAR, retinoic acid receptor; RBANS, repeatable battery for the assessment of neuropsychological status; rdbpc, randomized double blind placebo controlled; RXR, retinoid X receptor; SFA, saturated fatty acids; SNpc, substantia nigra pars compacta; Trk B, tyrosine kinase B; TX, thromboxanes; UTP, uridine triphosphate; VEP, visual evoked potential; VLDL, very low density lipoprotein.

* Corresponding author. Tel.: +31 24 3614378; fax: +31 24 3613789.
E-mail addresses: Carola.Janssen@radboudumc.nl (C.I.F. Janssen), Amanda.Kiliaan@radboudumc.nl (A.J. Kiliaan).

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1. Introduction

Long-chain polyunsaturated fatty acids (LCPUFA) are lipids which are mainly derived from diet and important in maintaining human health. With the industrial revolution, the Western dietary intake has drastically changed from an omega-3 polyunsaturated fatty acids (n-3 PUFA) rich diet to an almost n-3 PUFA deficient diet accompanied by a sedentary lifestyle [1]. Regarding fatty acid content, Western dietary intake has shifted to an increase in omega-6 polyunsaturated fatty acids (n-6 PUFA), saturated fatty acids (SFA) and *trans* fatty acids, and a decrease in n-3 PUFA [1]. The current diets are also associated with large cultural differences in health. For example, the traditional Greenland Inuit diet was based on whale, seal, fish, and wildfowl, which was demonstrated to result in lower risk for ischemic heart disease [1–3]. The Mediterranean diet is not only based on fish, but also fruits, vegetables, and whole grain and it has been shown that it leads to a lower risk of cardiovascular disease and contributes to a healthy brain [4–10]. The common factor between these diets is that they are low in saturated fats and refined grains.

Over the years, the importance of LCPUFA in neural development, aging, and neurodegeneration has been shown in both clinical and animal studies [11–18]. Supplementation with LCPUFA has shown to be beneficial in the development of both children and (young) rodents. Several animal studies and studies in children revealed an improvement in cognition and motor skills after LCPUFA supplementation [18–20]. On the other hand, LCPUFA deficiency can lead to neurodevelopmental disorders such as schizophrenia, ADHD, or mood disorders [21–25]. LCPUFA have also been shown to be advantageous in neurodegenerative disorders. For example, dietary LCPUFA supplementation showed an attenuation of cognitive impairment and decreased anxiety in both human and animal studies [26–28].

In this review, we will focus on the involvement of LCPUFA from genesis to senescence. We will cover the stages of neural development, normal aging, and neurodegeneration. In all these stages, the role of LCPUFA in the brain will be discussed with emphasis on synaptic plasticity, neurogenesis, cognition, and vascular health.

We searched the PubMed database for original articles published in English from 1995 until August 31, 2013. The main search topics concerned LCPUFA, influence of LCPUFA in neural development of preterm and full term infants, influence of LCPUFA in disorders such as autism, attention deficit hyperactivity disorder (ADHD), mild cognitive impairment (MCI), cerebrovascular disease, Alzheimer's disease (AD), and Parkinson's disease (PD). The search strategy was based on the following search terms: LCPUFA, neural development, cognition, autism, ADHD, healthy aging, MCI, cerebrovascular disease, AD, PD, filter: clinical trials. Moreover, to identify potentially relevant new papers we filtered our total list of relevant papers by hand. Based on the title and abstract, we selected the studies. If these two components were not sufficient for selection, we evaluated the total publication.

2. LCPUFA in neural development

During the embryonic phase in humans (until 7 weeks) the structure of the brain is defined, while growth during the fetal phase (start at 8 weeks) is characterized by functional development [29,30]. At birth, the brain is fully developed but only 25% of its definitive volume; postnatally, the brain expands by an increase in glial cells, outgrowth of axons and dendrites, and myelination of nerve fibers. This human brain growth spurt starts prenatally in the third trimester of pregnancy [31]. At this time, the infant brain starts accumulating docosahexaenoic acid (DHA, 22:6n-3) *in utero* and this continues up to the first 24 months of neonatal brain growth, although the postnatal DHA accumulation occurs at a slower rate [31,32]. In this period, neural development is most dependent on an adequate supply of LCPUFA.

LCPUFA are essential nutrients in the development and functioning of brain and visual system [12,17,33]. The most abundant LCPUFA in the brain are DHA which is mainly derived from fish, and arachidonic acid (ARA, 20:4n-6) from animal sources like meat and eggs. Linoleic acid (LA, 18:2n-6) is the precursor molecule of ARA which is derived from LA by desaturation and elongation of the carbon chain. DHA is derived from α-linolenic acid (ALA, 18:3n-3), forming eicosapentaenoic acid (EPA, 20:5n-3) in the process. The placental fatty acid composition is dependent on the supply from maternal plasma fatty acids. After birth, breast-fed infants are subsequently supplied with n-3 and n-6 fatty acids from breast milk, which support the rapid growth and development of the infant brain [17,34–36]. The most important LCPUFA responsible for the growth of the brain are DHA and ARA. Aside from inflammation and cardiovascular health, LCPUFA are important building blocks of neuronal membranes. The lipid bilayer of neuronal membranes consists of phospholipids, with DHA, ARA, and EPA as their main components. Three compounds are important for the membrane formation as shown in the Kennedy cycle (Fig. 1): a uridine source, a fatty acids source, and a choline source [37,38]. Other phospholipids are also synthesized via the Kennedy cycle and incorporate LCPUFA, such as phosphatidylethanolamine (PE) that uses ethanolamine instead of choline [39]. Phosphatidylserine (PS) exchanges a serine molecule for choline in phosphatidylcholine (PC) or ethanolamine in PE [39].

Humans, like all mammals, can synthesize saturated and monounsaturated fatty acids, but they are not able to synthesize the n-3 fatty acid ALA and the n-6 fatty acid LA due to lack of the conversion enzyme n-3-desaturase, making ALA and LA essential fatty acids [40]. Humans are able to convert EPA to DHA, and ARA to all-cis-4,7,10,13,16-docosapentaenoic acid (osbond acid), but the conversion rate by the responsible delta-5- and delta-6-desaturase is very slow [41,42]. These n-3 and n-6 PUFA are obtained by dietary intake or endogenous conversion of the parent precursors. LA and ALA require the same conversion enzymes, which means that there is competitive inhibition between these 2 substrates. Especially delta-6-desaturase favors the conversion of n-3 fatty acids to that of n-6 fatty acids [40,43]. Despite the preference for conversion of n-3 PUFA, a high LA intake may shift the balance towards conversion of n-6 PUFA and can interfere with the desaturation and elongation of ALA [44]. This imbalance can also lead to inhibition of the conversion of ALA to DHA, by slowing down the conversion rate of ALA into EPA and of EPA into DHA by delta-6-desaturase. The fatty acid desaturase (FADS) 1 and FADS2 genes are responsible for the expression of the conversion enzymes delta 5 desaturase and delta 6 desaturase making them a rate limiting factor in the LCPUFA conversion [41,42,45]. Thus, polymorphisms

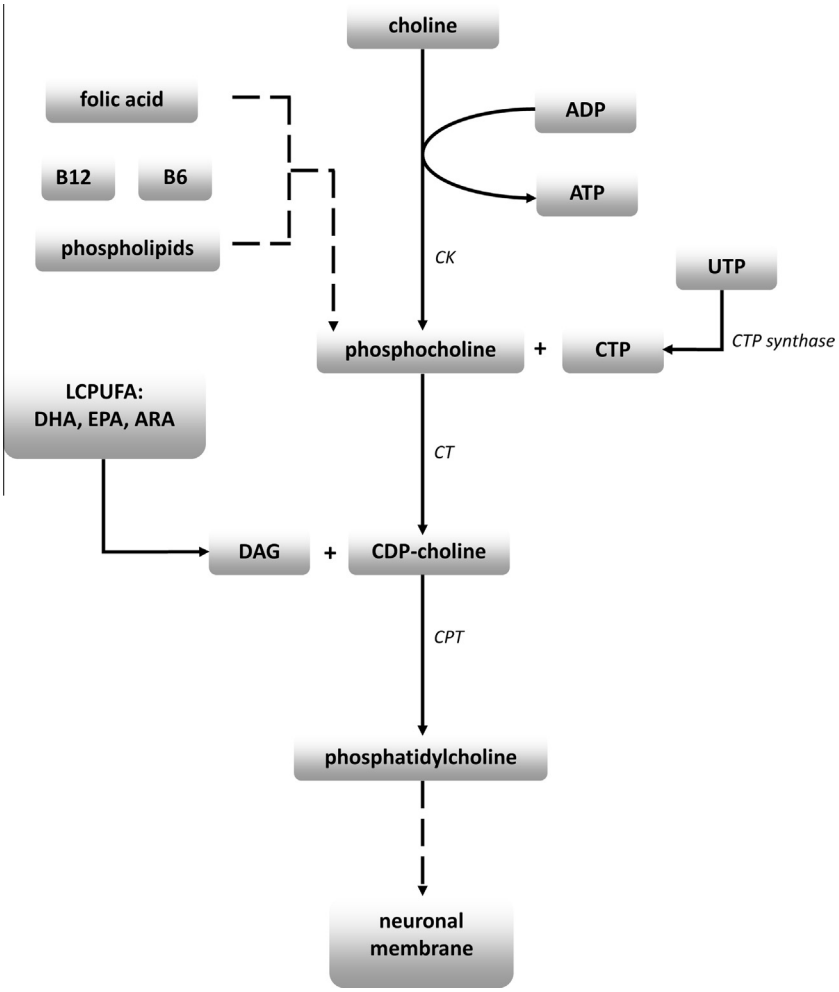

Fig. 1. Formation of neuronal membranes. Schematic overview of the formation of neuronal membranes from LCPUFA, also known as the Kennedy pathway [37,38,240,241]. ADP, adenosine diphosphate; ARA, arachidonic acid; ATP, adenosine triphosphate; B12, vitamin B12; B6, vitamin B6; CDP-choline, cytidine diphosphate choline; CK, choline kinase; CPT, 1,2 diacylglycerol choline phosphotransferase; CT, cytidine triphosphate-phosphocholine cytidyl transferase; CTP, cytidine triphosphate; DAG, diacylglycerol; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LCPUFA, long-chain polyunsaturated fatty acids; UTP, uridine triphosphate.

in these genes are able to influence the conversion of LCPUFA. Some studies suggest that these polymorphisms may increase the sensitivity of LCPUFA intervention, which recommend investigation of the genetic variation when performing a supplementation study [41,45,46].

EPA and ARA are also important during this period for the production of eicosanoids (prostaglandins, thromboxanes, leukotrienes) and their involvement in inflammation (Fig. 2). Eicosanoids are lipid mediators that are involved in a wide array of physiological functions, some of which are vasoreactivity, platelet aggregation, and inflammation [43,47]. The eicosanoids derived from LCPUFA exert effects that are involved in inflammation, for example the regulation of arrhythmia, platelet activation, vasoreactivity, and inflammation, resulting in either enhanced or compromised immunity [1,43,47]. Prostaglandins, leukotrienes and thromboxanes are metabolites that regulate inflammatory mediation and they are metabolized by cyclooxygenase (COX) and 5-lipoxygenase (5-LOX) [48,49]. ARA is the precursor for the 2-series of prostaglandins and thromboxanes, and the 4-series of leukotrienes. EPA is a precursor for the 3-series of prostaglandins and thromboxanes, and the 5-series of leukotrienes and these eicosanoids are less pro-inflammatory [43]. The prostaglandin 2-series therefore exert pro-arrhythmic effects, while the 3-series shows anti-arrhythmic effects and the thromboxane 2-series act as platelet activator and vasoconstrictor, while the 3-series performs as a platelet inhibitor and vasodilator. Furthermore, leukotrienes of the 4-series have pro-inflammatory effects, while the 5-series exert anti-inflammatory effects. As a result, ARA shows typical pro-inflammatory properties opposed to EPA that overall exerts anti-inflammatory effects [43]. Furthermore, 5-LOX is responsible for the generation of anti-inflammatory eicosanoids that are derived from DHA and EPA, the resolvins, and neuroprotectins [48,49]. Neuroprotectin D1 (NPD1) induces signaling for homeostatic maintenance of cellular integrity, and also has the ability to inactivate pro-apoptotic and pro-inflammatory signaling [43]. Besides regulation of inflammation, these physiological properties of LCPUFA contribute to cardiovascular health. EPA and DHA have the potential to prevent arrhythmia, lower blood pressure, reduce plasma triglycerides, improve vasoreactivity, increase plaque stability, reduce platelet aggregation, and decrease inflammation [50–52]. This will be discussed in more detail in Section 3 *LCPUFA in normal aging*.

Several studies in humans and rodents have shown that an n-3 PUFA deficiency may lead to a variety of neuronal abnormalities, such as ADHD, depression, schizophrenia, autism spectrum disorders, and anxiety [20,24,53–57]. It is proposed that an n-3 PUFA deficiency reduces neurotransmission processes, especially the dopaminergic and serotonergic system, by affecting membrane fluidity and related receptor functions and thereby ultimately

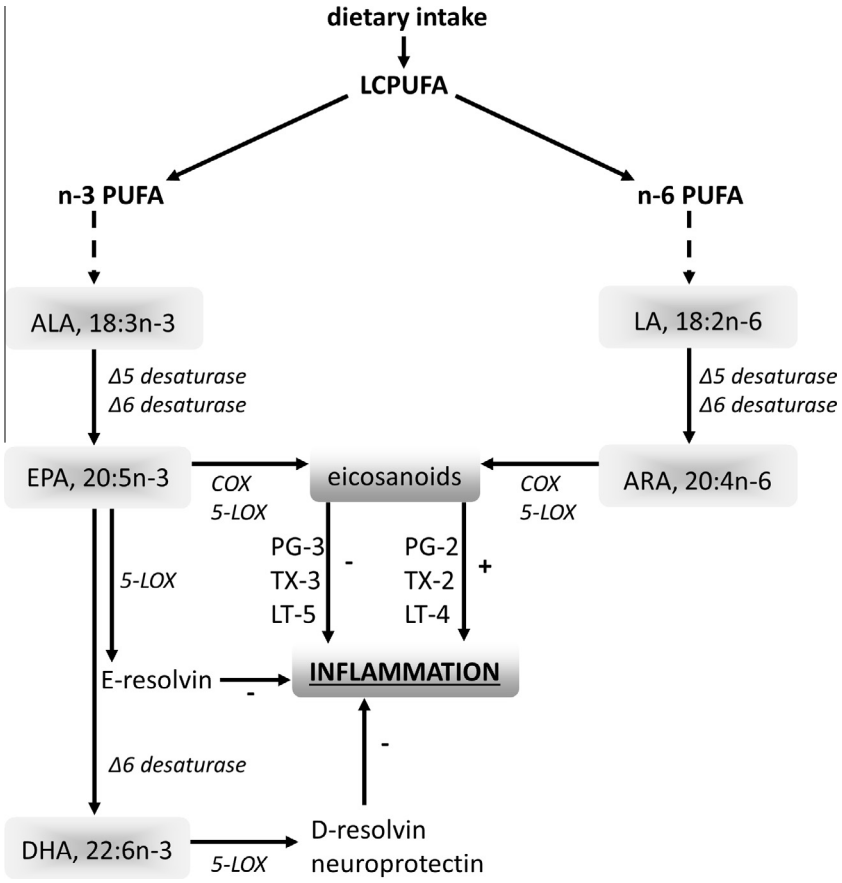

Fig. 2. Involvement of LCPUFA in inflammation. Schematic overview of involvement of EPA, ARA, and DHA in inflammation. ALA, α-linolenic acid; ARA, arachidonic acid; COX, cyclooxygenase; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LA, linoleic acid; LCPUFA, long-chain polyunsaturated fatty acids; LOX, lipoxygenase; LT, leukotrienes; n3-PUFA, omega-3 polyunsaturated fatty acids; n6-PUFA, omega-6 polyunsaturated fatty acids; PG, prostaglandins; TX, thromboxanes.

affecting brain structure and function [1,53]. Studies in n-3 PUFA deficient rodents indicate that this deficiency may result in hyperactivity which underlies disorders such as ADHD and schizophrenia [53,55–57]. ADHD is the most common developmental disorder occurring during childhood and has been shown to persist into adulthood [21,58]. ADHD often shows comorbidity with behavioral and learning disorders in childhood, while it is linked to mood disorders during adulthood [1,21,59]. A genetic association has been found between the occurrence of ADHD and disorders such as dyslexia, antisocial behavior, mood disorders, and schizophrenia. Studies have also shown that environment, in particular nutrition, strongly influences genetic expression [21,60]. It has been demonstrated that LCPUFA and their metabolites are involved in regulating gene expression such as cAMP response element binding protein (CREB), which plays an important role in long term potentiation [61,62]. But also in the retinoid signaling pathways regulating synaptic plasticity, learning, and memory involving the retinoic acid receptor (RAR), retinoid X receptor (RXR), and peroxisome proliferator-activated receptor (PPAR) [63–65].

In short, LCPUFA have the ability to influence human health in many different ways. DHA, EPA and ARA are important components of neuronal membranes, while DHA and EPA also contribute to cardiovascular health, and finally ARA and EPA act as precursors in the production of eicosanoids. As mentioned before, ARA (n-6) tends to lead to more pro-inflammatory eicosanoids, while EPA (n-3) leads to mostly anti-inflammatory eicosanoids. For this reason, the balance between n-3 and n-6 PUFA is critical in maintaining a healthy LCPUFA status and it has been suggested that a n-6/n-3 ratio of 1/1 or 2/1 would be the optimal ratio [47]. A balanced ratio is very important for many bodily and brain functions like in inflammation, endocrine and cardiovascular system and (lipid) metabolism [17,18,40,66,67].

2.1. Clinical studies

Tables 1A–1C show an overview of LCPUFA supplementation studies during pregnancy and/or lactation in pre- and full-term infants, and postnatal supplementation in patients that are diagnosed with either autism spectrum disorders or ADHD (Tables 1A–1C).

The influence of LCPUFA in the neural development of preterm infants is being studied more and more over the last decade (Table 1A). Only one study investigated prenatal supplementation, while most other studies focused on postnatal supplementation [68–77]. The results of these studies have been ambiguous, with some studies indicating slight beneficial effects [73–77] and others demonstrating no neurodevelopmental effects [68–72] and none showing major adverse effects. Overall, the preterm supplementation studies show beneficial effects of the supplementation when the n-6/n-3 ratio is at an optimal balance of 1/1 to 2/1.

The problem with studies on preterm infants is that these infants cannot fully benefit from the accumulation of LCPUFA which start in the last trimester of gestation, because of their preterm birth. Thus, the nutritional LCPUFA status of preterm infants needs to be optimal in order to complement the LCPUFA accumulation. Makrides et al. demonstrated that prenatal supplementation did not affect neural development in preterm infants (Table 1A) [68]. They supplemented preterm infants starting before 21 weeks of

Table 1A
Overview of supplementation studies in neural development, perinatal supplementation in preterm infants.

Author	Year	N	Prenatal versus postnatal	Start supplementation	Duration supplementation	Daily dose					Primary outcome
						DHA	EPA	ARA	ALA	LA	
Preterm infants											
Isaacs et al. [69]	2011	107	Postnatal	Birth	9 months	0.5 g/100 g	0.1 g/100 g	0.04 g/100 g	–	–	No overall change in cognitive measures at 10 years
Westerberg et al. [73]	2011	92	Postnatal	Birth	9 weeks	32 mg	–	31 mg	–	–	Increased attention at 20 months
Makrides et al. [68]	2010	694	Prenatal	<21 weeks of gestation	Birth	800 mg	100 mg	–	–	–	No difference BSID at 18 months
Smithers et al. [70]	2010	125	Postnatal	Birth – 5 days commencing enteral feeds	Estimated due date	1%	–	–	–	–	No difference language development at 26 months; no difference in behavior between 3 and 5 years
Henriksen et al. [74]	2008	105	Postnatal	Birth	9 weeks	32 mg/100 ml	–	31 mg/100 ml	11 mg/100 ml	88 mg/100 ml	Increased problem-solving skills and discrimination of familiar/unfamiliar objects at 6 months
Smithers et al. [75]	2008	143	Postnatal	Birth – 5 days commencing enteral feeds	Estimated due date	1%	–	–	–	–	No difference VEP acuity at 2 months, improvement at 4 months
Fang et al. [76]	2005	27	Postnatal	Birth	6 months	0.05%	–	0.10%	–	–	Improved PDI and MDI between 6 and 12 months. No difference visual acuity
Fewtrell et al. [71]	2004	298	Postnatal	Birth	9 months	0.5 g/100 g	0.1 g/100 g	0.04 g/100 g	–	–	No difference BSID at 9 and 18 months
Fewtrell et al. [72]	2002	174	Postnatal	⩽10 days p.p.	⩾3 weeks until discharge neonatal unit	0.17 g/100 g	0.04 g/100 g	0.31 g/100 g	–	–	No difference BSID at 9 and 18 months
O'Connor et al. [77]	2001	463	Postnatal	⩽28 days p.p.	12 months (corrected age)	1) 0.16–0.27 g/100 g 2) 0.15–0.24 g/100 g	1) 0.08 g/100 g 2) –	1) 0.43 g/100 g 2) 0.41 g/100 g	– –	– –	Increased BSID at 12 months in group 1

ALA, α-linolenic acid; ARA, arachidonic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LA, linoleic acid; MDI, mental development index; PDI, psychomotor development index; VEP, visual evoked potential.

Table 1B
Overview of supplementation studies in neural development, perinatal supplementation in healthy full term subjects.

Author	Year	N	Prenatal versus postnatal	Start supplementation	Duration supplementation	Daily dose					Primary outcome
						DHA	EPA	ARA	ALA	LA	
Full term infants											
Willatts et al. [105]	2013	147	Post	⩽7 days p.p.	4 months	0.21 g/100 g	–	0.35 g/100 g	–	–	No difference IQ at 6 years; improvement of information processing
van Goor et al. [85]	2011	114	Pre + post	Gestational week 14–20	Until 3 months p.p.	220 mg	–	220 mg	–	–	No difference BSID at 18 months
Firmansyah et al. [86]	2011	290	Post	12 months p.p.	Until 24 months p.p.	23 mg/100 g		24 mg/100 g	0,48 mg/100 g	4,3 mg/100 g	No difference BSID at 24 months
Smithers et al. [87]	2011	183	Pre	18–20 weeks of gestation	Birth	800 mg	100 mg	–	–	–	No difference VEP acuity and latency at 4 months
de Jong et al. [88]	2010	341	Post	Birth	2 months p.p.	0.30%	–	0.45%	–	–	No difference neurological functioning at 9 years
Birch et al. [89]	2010	244	Post	⩽9 days p.p.	12 months p.p.	1) 0.32% 2) 0.64% 3) 0.96%	– – –	1) 0.64% 2) 0.64% 3) 0.64%	– – –	– – –	Increased VEP acuity at 12 months
Pivik et al. [90]	2009	28–44	Post	Birth	6 months p.p.	1) 0.15% 2) 0.32%	– –	1) 0.40% 2) 0.64%	– –	– –	No difference BSID at 3 and 6 months
Dunstan et al. [91]	2008	83	Pre	20 weeks of gestation	Birth	2200 mg	1100 mg	–	–	–	Higher eye and hand coordination at 2.5 years
Innis et al. [92]	2008	135	Pre	16 weeks of gestation	Birth	400 mg	–	–	40 mg	–	Higher visual acuity at 60 days
Birch et al. [106]	2007	52	Post	⩽5 days p.p.	17 weeks	1) 0.35% 2) 0.36%	– –	1) – 2) 0.72%	– –	– –	Improvement of visual acuity and verbal IQ at 4 years in group 2
Judge et al. [94]	2007	29	Pre	<20 weeks of gestation	Birth	214 mg	–	–	–	–	Better problem solving at 9 months
Judge et al. [93]	2007	30	Pre	<20 weeks of gestation	Birth	294 mg	–	–	–	–	Higher visual acuity at 6, but not 4 months
Bouwstra et al. [95]	2006	270	Post	Neonatal age	2 months p.p.	0.30%	–	0.45%	–	–	No difference BSID at 18 months
Jensen et al. [96]	2005	160	Post	Birth	4 months p.p.	200 mg	–	–	–	–	Higher PDI at 30 months
Lauritzen et al. [97]	2005	89	Post	<14 days p.p.	4 months p.p.	900 mg	–	–	–	–	No difference problem solving, lower early language acquisition at 1 year
Auestad et al. [98]	2003	210	Post	<7 days p.p.	12 months	1) 0.12 g/100 g 2) 0.23 g/100 g	– –	1) 0.43 g/100 g 2) –	– –	– –	No difference in cognition and visual acuity at 39 months
Helland et al. [35]	2003	83	Pre + post	18 weeks of gestation	3 months p.p.	1183 mg	803 mg	–	–	–	Improved cognition at 4 years
Hoffman et al. [99]	2003	61	Post	4–6 months p.p.	until 12 months p.p.	0.36%	–	0.72%	–	–	Higher VEP acuity at 1 year
Malcolm et al. [100]	2003	55	Pre	15 weeks of gestation	birth	40.4% (200 mg)	4.1%	0.1%	0.8%	1.2%	No difference VEP at 6 months
Auestad et al. [101]	2001	294	Post	Birth – ⩽ 11 days	12 months	1) 0.14 g/100 g 2) 0.13 g/100 g	1) – 2)⩽0.4 g/100 g	1) 0.45 g/100 g 2) 0.46 g/100 g	– –	– –	No difference BSID or visual acuity at 6 and 12 months
Birch et al. [107]	2000	56	Post	⩽5 days p.p.	17 weeks	1) 0.35% 2) 0.36%	– –	1) – 2) 0.72%	– –	– –	Improvement MDI at 18 months in both groups
Lucas et al. [102]	1999	354	Post	1st week p.p.	6 months	0.32%	–	0.30%	–	–	No difference BSID at 18 months
Hørby–Jørgensen et al. [103]	1998	37	Post	<30 days p.p.	4 months	0.3%	0.4%	–	–	–	No difference VEP at 4 months
Scott et al. [104]	1998		Post	<7 days p.p.	12 months	1) 0.12 g/100 g 2) 0.23 g/100 g	– –	1) 0.43 g/100 g 2) –	– –	– –	No difference BSID at 14 months; lower vocabulary scores in group 2

ALA, α-linolenic acid; ARA, arachidonic acid; BSID, Bayley Scales of Infant Development; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; IQ, intelligence quotient; LA, linoleic acid; PDI, psychomotor development index; p.p., post partum; VEP, visual evoked potential.

Table 1C
Overview of supplementation studies in neural development, supplementation in autism spectrum disorders and ADHD.

Author	Year	N	Start supplementation	Duration supplementation	Daily dose					Primary outcome
					DHA	EPA	ARA	ALA	LA	
Autism spectrum disorders										
Yui et al. [120]	2012	13	6–28 years	16 weeks	120–240 mg	–	120–240 mg	–	–	Improvement of social impairment
Bent et al. [117]	2011	25	3–8 years	12 weeks	460 mg	700 mg	–	–	–	No difference in hyperactivity and core symptoms of autism
Politi et al. [119]	2008	19	18–40 years	6 weeks	DHA + EPA: 930 mg					No difference in behavior
Meguid et al. [118]	2008	60	3–11 years	3 months	240 mg	52 mg	20 mg	–	–	Improvement of concentration, eye contact, language development, and motor skills
Amminger et al. [116]	2007	12	5–17 years	6 weeks	700 mg	940 mg	–	–	–	No difference in aberrant behavior
ADHD										
Perera et al. [128]	2012	94	6–12 years	6 months	n-3 PUFA: 592.74 mg n-6 PUFA: 361.5 mg					Improvement of learning and behavior
Milte et al. [127]	2012	67	7–12 years	4 months	1) 108 mg 2) 1032 mg 3) –	1) 1109 mg 2) 264 mg 3) –	– – –	– – –	1) – 2) – 3) 1467 mg	No differences between groups. Increased erythrocyte DHA improves literacy and behavior within ADHD group
Gustafsson et al. [124]	2010	74	7–12 years	15 weeks	2.7 mg	500 mg	–	–	–	Improvement of oppositional behavior, hyperactivity, and impulsivity
Bélanger et al. [123]	2009	26	6–12 years	8 weeks rdbpc 8 weeks open label	200–400 mg	500–1000 mg	–	–	–	Improvement of ADHD core symptoms
Johnson et al. [126]	2009	59	8–18 years	3 months rdbpc 3 months open label	174 mg	558 mg	–	–	–	No difference in ADHD core symptoms
Raz et al. [129]	2009	63	7–13 years	7 weeks	–	–	–	120 mg	480 mg	No difference in ADHD core symptoms
Sorgi et al. [130]	2007	9	8–16 years	4 weeks open label 4 weeks open label	5400 mg 2700–4000 mg	10800 mg 5400–8100 mg	– –	– –	– –	Improvement of ADHD core symptoms
Hirayama et al. [125]	2004	40	6–12 years	2 months	3600 mg per week	700 mg per week	–	–	–	No difference in ADHD core symptoms
Voigt et al. [131]	2001	63	6–12 years	4 months	345 mg	–	–	–	–	No difference in ADHD core symptoms

ADHD, attention deficit hyperactivity disorder; ALA, α-linolenic acid; ARA, arachidonic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GLA, γ linolenic acid; LA, linoleic acid; rdbpc, randomized double blind placebo controlled.

gestation until birth [68]. However, these infants are born in the last trimester of gestation, missing the supplementation at a crucial time point. Another issue is that the preterm infants in this study were supplemented with n-3 PUFA only [68]. It is important in preterm infants that they are supplemented with both n-3 and n-6 PUFA. It is also advisable to add the n-6 ARA to n-3 PUFA supplements, because n-3 PUFA are known to decrease the plasma concentrations of ARA due to the competition for conversion by delta-6 desaturase [78–84].

The postnatal supplementation studies in preterm infants show more beneficial effects of LCPUFA than in the prenatal phase (Table 1A). These studies started supplementation at birth or directly after birth, a time point that would originally mark the last trimester of gestation when DHA accumulation begins. Table 1A shows that in only one cohort the supplementation was aborted at the estimated due date [70,75]. Smithers et al. reported no difference in visual acuity at 2 months, but they did find an improvement at 4 months of age [75]. In the same cohort no differences in language development were shown at 26 months, and there was no difference in behavior between 3 and 5 years of age [70]. In this study only n-3 PUFA was supplemented. As shown in Table 1A, the other postnatal supplementation studies continued supplementation ranging from 3 weeks up until 12 months (corrected age) with both n-3 and n-6 PUFA [69,71–74,76,77]. These studies stress the importance of an optimal n-6/n-3 ratio (1/1 to 2/1). A 9 months supplementation with a LCPUFA ratio of 1/15 did not affect cognition at 9 months, 18 months, or 10 years of age [69,71]. Studies using a ratio of 1/1 or 2/1 did show long term improvement of cognitive functions starting already with 9 weeks of supplementation [73,74,76,77]. However, Fewtrell et al. used a "healthy" n-6/n-3 ratio of 1.5/1 but did not find positive effects on cognition at 9 or 18 months of age. In this study the duration of supplementation was 33 days on average which appears to be too short to establish an effect on cognition. These studies indicate that apart from a balanced n-6/n-3 ratio, the duration of supplementation is another key factor contributing to beneficial effects of LCPUFA supplementation.

Numerous studies have been performed investigating the impact of LCPUFA supplementation on general and neurological development of full term infants (Table 1B) [35,85–107]. However, there are only few studies exceeding the age of 18 months [35,86,88,91,95,96,98,105,106]. Often, clinical supplementation studies show little to no effect of LCPUFA supplementation [85–88,90,95,98,100–103] and the few effects found showed just slight improvements in cognition, visual function, or motor skills [35,89,91–94,96,99,105–107]. Two studies reported decreased language skills at 12 and 14 months of age after supplementation with only n-3 PUFA after 4 and 12 months of supplementation respectively [97,104]. Table 1B demonstrates the overall finding that both pre- and postnatal supplementation are potent in achieving effects on LCPUFA supplementation of full term infants. This is in line with the finding in preterm infants that it is important to start supplementation in the last trimester of gestation. However, in contrast to preterm supplementation where the n-6/n-3 ratio was of importance, full term supplementation studies remain inconclusive whether only n-3 PUFA or both n-3 and n-6 PUFA supplementation are more suitable. Overall, n-3 PUFA show beneficial effects prenatally, while both n-3 and n-6 PUFA demonstrate to be favorable during postnatal supplementation (Table 1B).

Several studies and reviews have made recommendations for a healthy LCPUFA intake in preterm and full term infants based on the available data from randomized controlled trials [108–112]. In these studies a DHA intake of 0.35–1% in preterm infants and 0.2–0.32% for full term infants is suggested. The advised concentration of ARA is 0.4–0.8% for preterm infants and 0.35% for full term infants. It should be noted that these concentrations are quite conservative as they reflect the average concentrations in maternal milk from Western countries.

A key factor that one has to keep in mind while interpreting supplementation studies on full term infants is that it is plausible that the effect of LCPUFA supplementation is limited in a healthy (LCPUFA sufficient) full term cohort. Prenatal supplementation studies have shown to be most likely to show beneficial effects, because supplementation already starts at the critical time point which is the start of the last trimester of gestation.

It is difficult to study underlying mechanisms in humans due to limited parameters. In infants, the outcomes are limited to non invasive parameters. It is possible that the tests used (mainly Bayley scales of infant development and visual acuity tests) are not sensitive enough to measure all effects caused by LCPUFA supplementation [110,113]. Animal studies have the advantage that they enable invasive techniques and to perform histological and biochemical techniques on for example brain tissue, unlike studies on infants. Furthermore, animal supplementation studies are less time consuming and long term effects can be studied in a broader lifespan. When studying the effect of perinatal supplementation in later childhood and beyond in humans, there is a large timeframe that makes the study vulnerable to external influences. However, animal studies indicate that it is important to take into account multigenerational influences. In order to reach a model for n-3 PUFA depletion, several studies use a multigenerational animal model [20,114,115]. Moriguchi et al. point out stronger effects of n-3 PUFA deficiency when comparing F3 generation to F2 generation rats [115].

Multiple studies have investigated the effect of n-3 PUFA supplementation in neurodevelopmental disorders (Table 1C). As mentioned before, it is thought that n-3 PUFA deficiency impairs neurotransmission processes, by affecting membrane fluidity and related receptor functions [1,53]. This suggests that ADHD patients and autism spectrum disorders may benefit from LCPUFA supplementation as well. Studies on n-3 PUFA supplementation in autism spectrum disorders are scarce and do not show significant results due to small sample sizes [116–120]. However, there are indications that supplementation may be able to decrease hyperactivity symptoms [121,122]. Table 1C shows that studies on n-3 PUFA supplementation as treatment of ADHD remain inconclusive whether supplementation can be used as a treatment for ADHD for the same reason [123–131]. Gustafsson et al. show some improvement in clinical symptoms of ADHD patients, whereas Voigt et al. did not find effects on attention and impulsivity [124,131]. Milte et al. found that the improvement in cognition was associated with n-3 PUFA levels in erythrocyte phospholipids and suggest that not only the dose of supplementation should be taken into account, but especially the erythrocyte n-3 PUFA status of the patient [127]. They demonstrated that patients with an increased erythrocyte n-3 PUFA status were more likely to show improvements in cognitive function [127]. The overall weak points in these studies seem to be the small sample size, short duration of supplementation, and short follow-up periods [121,122].

All in all, the supplementation studies performed during neural development produce inconclusive findings. More research has to be done to elucidate the influence of LCPUFA in neural development in health and disease.

3. LCPUFA in normal aging

LCPUFA concentration in the brain decreases with age in both humans and rodents. In elderly subjects, LCPUFA have the potential to act as neuroprotective mediators and intervene in the mechanisms resulting in cognitive impairment or inflammation [132]. DHA, for example, has the ability to act as a neurotrophic factor

[133]. It increases the level of brain-derived neurotrophic factor (BDNF), which is predominantly synthesized by hippocampal neurons. BDNF can act on tyrosine kinase B (Trk B) receptor signaling, resulting in activation of synaptic proteins such as synapsin-1 [133]. This protein may contribute in enhancing synaptic plasticity and cognitive function. Synapsin-1 increases the synthesis of synaptic membranes leading to elevated levels of phosphatides and specific pre- and postsynaptic proteins [134]. Via this pathway DHA increases the number of dendritic spines and possibly synapses on hippocampal neurons, particularly on excitatory glutamatergic synapses [134]. These neurons are involved in learning and memory. Wu et al. have shown a synergistic effect of DHA and physical exercise on synaptic plasticity [133]. Agrawal and Gomez-Pinilla have also demonstrated that an n-3 PUFA deficiency decreased synaptophysin and phosphorylation of synapsin-1 [135]. They showed that n-3 PUFA supplementation has the ability to normalize this effect, thereby restoring cognitive function [135].

Normal aging is often accompanied by a decline in cognition, marked by decreased synaptic density, a decrease in neuronal survival, and loss of both gray and white matter volume [136–142]. The number of aging individuals experiencing cognitive impairment is increasing rapidly worldwide. Age-related cognitive impairment is strongly correlated to the development of dementia [143]. Factors contributing to this cognitive decline are obesity, cardio- and cerebrovascular disease, hypertension, and diabetes mellitus type 2 (DMII). All these factors are risk factors for vascular disorders and dementia as well and have in common that they can derive from the metabolic syndrome (MetS) that afflicts modern Western society [144]. These risk factors can derive separately from MetS, though they can also act synergistically on each other exerting combined effects. A low n-3 PUFA intake and a high intake of n-6 PUFA, saturated fatty acids, or *trans* fatty acids are also risk factors in developing MetS [135,144,145]. This leads to a high ratio between ARA and EPA/DHA that activates a pro-inflammatory state resulting in low-grade inflammation [1].

A sedentary lifestyle is another major risk factor for the development of MetS, besides a low n-3 PUFA intake, and is often accompanied by a high cholesterol intake [144]. Cholesterol is absorbed from food or synthesized in the liver, intestine, or brain. It is required for the formation of bile acids, steroid hormones, and membrane synthesis, but excessive levels lead to hypercholesterolemia. Cholesterol circulating in the blood is not able to cross the blood brain barrier (BBB). Yet, the brain is the organ in the human body that contains the most cholesterol [146]. It is mainly synthesized by astrocytes and especially present in the myelin sheath and membranes of neurons and astrocytes [147]. In general, increased serum levels of cholesterol (hypercholesterolemia) lead to increased blood levels of low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) [148]. LDL and VLDL invade the endothelium and start accumulating, initiating a state commonly known as atherosclerosis [148]. The damage to the endothelium initiates an inflammatory response and monocytes and macrophages start accumulating, while platelets adhere to the affected area [148]. Eventually, this will evolve into a chronic inflammatory state if the cholesterol intake is not changed. This situation increases hypoperfusion and ultimately the risk of cardiovascular disease.

Important causes of cardiovascular disease are hypertension and atherosclerosis. Atherosclerosis is induced by accumulation of cholesterol within the arterial walls, leading to plaques and consequently to narrowed arterial lumen and, occasionally, resulting in an acute myocardial infarction (AMI) or a cerebral stroke due to a stenosis, or rupture of a blood vessel in case of hemorrhages. Hypertension is thereby also a risk factor for stroke, ischemic white matter lesions, silent infarcts, general atherosclerosis, myocardial infarction, and often co-exists with other vascular risk factors, such as diabetes mellitus, obesity and hypercholesterolemia. Hypertension can predict both vascular dementia and Alzheimer's disease (AD) already 20 years before onset [149–152]. Atherosclerosis like hypertension, is a process that precedes dementia symptoms by many years. Both hypertension and atherosclerosis cause impaired blood flow and blood brain barrier function, hypoperfusion and blood vessel wall pathology which may initiate the underlying neurodegenerative processes leading to cognitive impairment and ultimately AD [152–156].

As mentioned before, consumption of the n-3 PUFA protects against cardiovascular disease [51,157,158]. These beneficial effects have been explained by the capacity to prevent arrhythmias, improving vasoreactivity, decreasing blood pressure and inflammation and decreasing atherosclerosis [52,159–164]. This was already reported over 30 years ago in 1976 when studies on Greenland Inuit suggested that ingestion of n-3 PUFA protects against cardiovascular diseases [165]. The Inuit consumed diets with large quantities of the long-chain polyunsaturated fatty acids EPA and DHA present in traditional Inuit food of seals, whales, and fish [166]. In other studies it has been found that eating fish once a week significantly decreased coronary heart disease mortality rates [167]. Omega-3 fatty acids from fish oil might beneficially influence cardiovascular disease by decreasing blood pressure, and atherosclerosis formation [160,163,168,169]. Growing evidence in literature points to the benefits of the Mediterranean diet on human health: it has been shown recently that extra-virgin olive oil containing diets rich in LCPUFA reduce the risk of not only cardiovascular disease, but also cancer, AD, and PD [4,170]. All these findings suggest that LCPUFA containing diets resulted in a substantial reduction in the risk of major cardiovascular events among high-risk persons and support the benefits of the Mediterranean diet for the primary prevention of cardiovascular disease.

3.1. Clinical studies

Supplementation studies performed in healthy elderly subjects, and patients with either MCI or cerebrovascular disease are very scarce. Table 2 demonstrated that the studies of Yurko-Mauro et al., Witte et al., and Nilsson et al. are the only ones that show an effect of LCPUFA supplementation on cognition in healthy elderly [10,171,172]. Yurko-Mauro et al. demonstrated that DHA supplementation during 24 weeks improved episodic memory in healthy elderly subjects [172]. Witte et al. showed enhanced executive functions in healthy elderly after 26 weeks of supplementation, accompanied by improvements in white matter integrity, gray matter volume, and vascular parameters [171]. Nilsson et al. found an improvement in working memory in a cross-over study after already 5 weeks of supplementation with n-3 PUFA [10]. Stough et al. did not find effects on cognition after DHA supplementation during 90 days, but an improvement of visual acuity in elderly subjects with corrected vision was revealed [173]. The studies performed by van de Rest et al. and Dangour et al. failed to show an effect of DHA + EPA on cognition in healthy elderly, both on a short (13 or 26 weeks) or long (24 months) supplementation period (Table 2) [143,174]. A possible explanation may lie in the relatively short duration of supplementation, and in addition starting supplementation earlier in life may have a stronger effect. Danthiir et al. describe the trial design and methodology of the ongoing study on the influence of n-3 PUFA supplementation in healthy elderly [175]. They will supplement a large group of healthy elderly with 1720 mg DHA and 600 mg EPA daily during 18 months. Cognitive performance is assessed every 6 months. Other factors, such as dose of administration and mini-mental state examination (MMSE), differ between the studies, making it difficult to compare them to each other. In contrast to clinical studies on neural development, the clinical studies in normal aging only supplemented

Table 2
Overview of supplementation studies in normal aging, supplementation in healthy subjects, MCI patients, and patients with a history of cerebrovascular disease.

Author	Year	N	Duration supplementation	Daily dose					Primary outcome
				DHA	EPA	ARA	ALA	LA	
Healthy subjects									
Witte et al. [171]	2013	65	26 weeks	800 mg	1320 mg	–	–	–	Enhanced executive functions after 26 weeks; improvement of white matter integrity, grey matter volume and vascular parameters
Nilsson et al. [10]	2012	40	5 weeks	1050 mg	1500 mg	–	–	–	Improved working memory
Stough et al. [173]	2012	74	90 days	252 mg	–	–	–	–	No difference in cognitive function after 90 days; improvement in visual acuity in participants with corrected vision
Danthiir et al. [175]	2011	391	18 months	1720 mg	600 mg	–	–	–	Ongoing study
Dangour et al. [174]	2010	867	24 months	500 mg	200 mg	–	–	–	No difference in cognitive function after 24 months
Yurko-Mauro et al. [172]	2010	485	24 weeks	900 mg	–	–	–	–	Improved episodic memory and learning after 24 weeks
Van de Rest et al. [143]	2008	299	26 weeks	1) 847 mg 2) 176 mg	1) 1093 mg 2) 226 mg	– –	– –	– –	No difference in cognitive function after 13 and 26 weeks
MCI									
Sinn et al. [177]	2012	40	6 months	1) 160 mg 2) 1550 mg 3) –	1) 1670 mg 2) 400 mg 3) –	– – –	– – –	1) – 2) – 3) 2200 mg	Reduction of depressive symptoms; improvement of cognition
Lee et al. [178]	2013	35	12 months	1300 mg	450 mg	–	–	–	Improvement of memory after 12 months
Chiu et al. [176]	2008	29 (MCI + AD)	24 weeks	720 mg	1080 mg	–	–	–	Improvement in CIBIC-plus
Cerebrovascular disease									
Andreeva et al. [179]	2011	1748	4 years	200 mg	400 mg	–	–	–	No difference in cognitive function in patients with a history of cardio- or cerebrovascular disease
Terano et al. [180]	1999	20	12 months	720 mg	–	–	–	–	Improvement of dementia scores in moderately severe dementia from thrombotic cerebrovascular disorder

ALA, α-linolenic acid; ARA, arachidonic acid; CIBIC-plus, clinician's interview-based impression of change scale which included caregiver-supplied information; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LA, linoleic acid; MCI, mild cognitive impairment.

the subjects with n-3 PUFA. At adult age, ARA is no longer required for growth of the brain and high doses will only lead to the formation of pro-inflammatory eicosanoids.

Supplementation of LCPUFA in patients with MCI looks very promising, as (minor) improvements in cognition have been shown (Table 2) [176–178]. There are a few studies that have looked into the benefits of n-3 PUFA supplementation in patients with a history of cerebrovascular disease [179,180]. While Terano et al. demonstrated a reduction of depressive symptoms in patients with thrombotic cerebrovascular disease, Andreeva et al. found no difference in cognition in patients with a history of cardio- and cerebrovascular disease [179,180].

Overall, duration of supplementation is again essential in setting a proper design for these types of studies. In general, the clinical studies performed in healthy elderly and MCI patients indicate that supplementation should persist for at least 6 months. Furthermore, again it should be noted that differences in outcomes may occur to large variances in and between study populations.

4. LCPUFA in neurodegeneration

Life expectancy has increased enormously in the last century, from around 50 years to over 80 due to better medical care and better living conditions. However, increasing age is also the main risk factor for major life-threatening conditions, such as cardiovascular disease and neurodegenerative and age-related cognitive disorders. Both cerebrovascular and neurodegenerative diseases increase significantly after 60 years of age in almost all populations worldwide. Understanding exactly how aging increases the risk of disease is necessary to fight this growing societal problem. The most frequent age related neurodegenerative diseases are AD and PD, characterized by the abnormal deposition of insoluble protein aggregates, and progressive death of neurons and loss of brain structures, associated with progressive, age-related decline in neuronal function.

AD is the most common age related neurodegenerative disorder and is widely recognized as the most important cause of dementia, while the second most common form of brain degenerative disorder leading to dementia, is caused by cerebrovascular disease. Vascular lesions are frequently found to co-exist with AD-type pathologies in older subjects and it is now evident that vascular and neurodegenerative lesions intensify each other, accelerating pathological mechanisms and increasing the risk that individuals with Alzheimer lesions will exhibit dementia [181]. In agreement with these findings, major risk factors for AD are vascular related risk factors like hypertension and atherosclerosis [182,183]. Future preventative interventions should take the proper time-window for intervention into account and the multifactorial nature of AD [184].

A decreased level of plasma DHA is associated with cognitive impairment with aging [185–187]. Many animal, epidemiological and clinical studies have shown that high DHA consumption is associated with reduced AD risk [60,188–193]. In rat, a DHA containing diet enhanced the effects of exercise on cognition and BDNF-related synaptic plasticity [133,194]. More recent studies showed that dietary DHA could be protective against β-amyloid (Aβ) production, deposition in plaques and cerebral amyloid angiopathy in an aged AD mouse model and increases cerebral blood volume [16,195]. In other transgenic AD mouse models DHA also protects against dendritic pathology [196,197].

Both AD patient brain and the 3xTg-AD mouse exhibit reductions in DHA and the DHA derived NPD1 [198]. As mentioned, it has been shown that NPD1 has anti-inflammatory and neuroprotective, but also anti-amyloidogenic bioactivity [199]. Large multicentre randomized trials should still be executed, because studies performed up until now include various populations (for example Mediterranean, Australian, Dutch, and North American populations). These geographical differences cause a broad variation of dietary habits which may lead to large baseline differences. Many observational studies in elderly indicate that development of cognitive decline and dementia can be inhibited via healthy foods and dietary supplements [132,200–204]. Furthermore, consumption of fish is related to lower risk of AD, maybe via inhibition of inflammation and enhancing vascular health and countering atherosclerosis [205–208].

PD is the second most common neurodegenerative disease after AD. It has been estimated that 9 million individuals aged over 50 will have PD worldwide in 2030 [209]. PD is a complex age related neurodegenerative disorder resulting in movement, balance, and fine motor control changes as a consequence of cell death of dopamine-containing neurons of the substantia nigra pars compacta (SNpc) [210]. The dopaminergic cell death is induced by oxygen reactive free radicals overproduction and mitochondrial dysfunction among other factors. This process can be mimicked by the 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) model which affects mitochondria by inhibiting mitochondrial complex I or complex III, which induces specifically neuronal cell death in the SNpc [210].

Currently, the main clinical treatment for PD is dopamine replacement therapy using l-dihydroxyphenylalanine (l-DOPA) and/or dopamine receptor agonists [211]. In the early phase of the disease, treatment is generally highly effective, but medication becomes increasingly inadequate in controlling motor fluctuations and dyskinesia as the disease progresses. Moreover, pharmacotherapy cannot postpone the progression of the loss of dopaminergic neurons, and also cannot recover the lost dopaminergic neurons. Deep brain stimulation (DBS) is also seen as an alternative treatment suggested earlier in life and not just late in life as used nowadays [212–214]. However, still many surgical complications from the DBS procedure are reported such as infection, bleeding, stroke, neuropsychiatric adverse effects including depression, aggression, apathy, and anxiety [212]. Another possible beneficial clinical option for PD treatment could be cell transplantation therapy, but development of this therapy is still very premature [215].

It has been shown that n-3 PUFA have a modulatory effect on BDNF and glial cell-derived neurotrophic factor (GDNF) [216]. In line with the positive effect of n-3 PUFA on BDNF regulation, is the finding that an ALA deficient diet decreased striatal BDNF content in mice [217]. Moreover, it has recently been shown that BDNF expression decreases in n-3 PUFA deficient rats and the upregulation of BDNF and its receptor has been recognized as a potential mechanism of action of n-3 PUFA as demonstrated in MPTP treated mice [218,219]. Animals with MPTP-induced impaired balance and motor coordination showed diminished Parkinsonism symptoms and decreased dopaminergic neuronal death when fed a DHA diet [220]. Furthermore, it has been indicated that DHA supplementation may protect dopaminergic neurons in experimental PD models by targeting inflammatory signaling pathways and by enhancing the expression of GDNF and Neurturin (member of the same protein family as glial cell-derived neurotrophic factor). Both have been shown to benefit the dopaminergic neurons in the substantia nigra which is affected in PD [216,220–224]. DHA supplementation in a nonhuman primate (MPTP) model reduces levodopa-induced dyskinesia, suggesting an innovative and safe approach to improve the quality of life of PD patients [225]. Administration of n-3 PUFA could therefore be used as therapeutic strategy against PD via stimulation of cerebral BDNF production, which is supported by the observation of decreased post-mortem levels of BDNF in the brains of PD patients, and that neurotrophic factors are not able to cross the BBB [226,227].

Higher adherence to the Mediterranean diet consisting of whole grains, fish and olive oil and moderate consumption of alcohol is also associated with significant improvement in incidence of neurodegenerative disorders.

4.1. Clinical studies

Table 3 shows the LPCUFA supplementation studies that were performed in AD and PD patients. Strikingly, these studies show only slight improvement or no effect on cognition after

Table 3
Overview of supplementation studies in neurodegeneration, supplementation in AD and PD patients.

Author	Year	N	Duration supplementation	Daily dose					Primary outcome
				DHA	EPA	ARA	ALA	LA	
AD									
Scheltens et al. [231]	2012	258	24 weeks	1200 mg	300 mg	–	–	–	Improvement in memory performance in mild AD
Quinn et al. [230]	2010	295	18 months	2000 mg	–	–	–	–	No difference in ADAS-cog No difference in CDR
Chiu et al. [176]	2008	29 (AD + MCI)	24 weeks	720 mg	1080 mg	–	–	–	No difference in ADAS-cog (AD) Improvement in CIBIC-plus (AD + MCI)
Freund-Levi et al. [15]	2008	174	6 months rdbpc 6 months open label	1720 mg	600 mg	–	–	–	No difference in NPI
Freund-Levi et al. [228]	2006	174	6 months rdbpc 6 months open label	1720 mg	600 mg	–	–	–	No difference in ADAS-cog No difference in MMSE
Kotani et al. [229]	2006	8	90 days	240 mg	–	240 mg	–	–	No difference in RBANS
Boston et al. [232]	2004	19	12 weeks rdbpc 12 weeks open label	–	1000 mg ethyl-EPA	–	–	–	No difference in ADAS-cog
Yehuda et al. [234]	1996	100	4 weeks rdbpc	–	–	–	LA/ALA: 4.5/1		Improvement of short term memory
PD									
da Silva et al. [233]	2008	29	3 months	480 mg	720 mg	–	–	–	Antidepressant effect in PD patients with depression

AD, Alzheimer's disease; ADAS-cog, cognitive subscale of the Alzheimer's disease assessment scale; ALA, α-linolenic acid; ARA, arachidonic acid; CDR, clinical dementia rating; CIBIC-plus, clinician's interview-based impression of change scale which included caregiver-supplied information; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LA, linoleic acid; MCI, mild cognitive impairment; MMSE, mini-mental state examination; NPI, neuropsychiatric inventory; PD, Parkinson's disease; RBANS, repeatable battery for the assessment of neuropsychological status; rdbpc, randomized double blind placebo controlled.

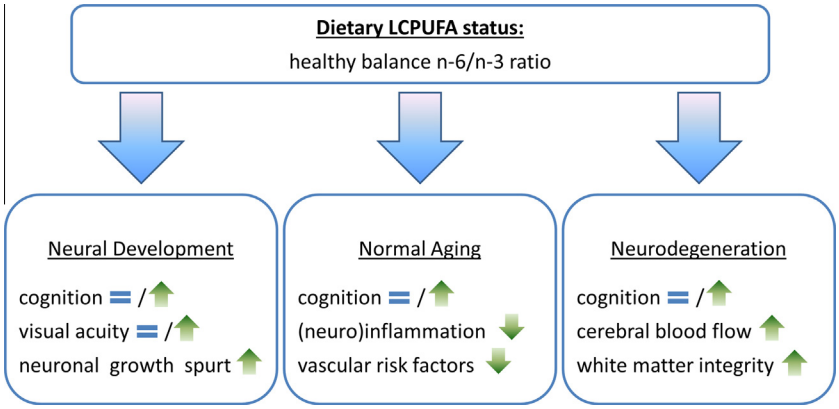

Fig. 3. Concluding overview. Schematic overview of findings from clinical studies on LCPUFA supplementation in neural development, normal aging, and neurodegeneration. This review has shown that there are indications that LCPUFA (mainly a healthy balance n-6/n-3) support and improve brain structure and functioning. In neural development there is evidence that LCPUFA might improve cognition and visual acuity. Subsequently, LCPUFA are required during the perinatal neuronal (out)growth when the number of glial cells increase, outgrowth of axons and dendrites takes place, as well as the myelination of nerve fibers. During normal aging LCPUFA supplementation may improve cognition, decrease (neuro)inflammation, and reduce vascular risk factors. Furthermore, LCPUFA have also shown to improve white matter integrity and cerebral blood flow in neurodegeneration. LCPUFA, long-chain polyunsaturated fatty acids; n-3, n-3 fatty acids; n-6, n-6 fatty acids.

supplementation [15,176,228–234]. Chiu et al. were the only group to show a minor improvement in a clinician's interview-based impression of change scale which included caregiver-supplied information (CIBIC-plus). Though, no effect on the cognitive subscale of the Alzheimer's disease assessment scale (ADAS-cog) could be observed [176]. However, this study combined AD patients with patients with MCI and the improvement in CIBIC-plus was only found in the combined group. The AD patients did not show a difference in ADAS-cog after LCPUFA supplementation [176]. In a study performed by Freund-Levi et al., 174 AD patients (mean age of 74 years) were supplemented daily with 1.7 g DHA and 0.6 g EPA for 12 months, and tested on a number of standard cognitive assessments (Table 3) [228]. In a subgroup with very mild cognitive dysfunction, a significant reduction in the cognitive decline rate was observed compared to placebo, suggesting that those with milder cognitive impairment may benefit from n-3 PUFA supplementation.

da Silva et al. were the only group to study supplementation in PD patients and found that LCPUFA act as antidepressants in PD patients that were experiencing depression (Table 3) [233]. Overall, the clinical trials applied relatively short supplementation periods, with an exception of the trial performed by Quinn et al. [230]. They supplemented mild to moderate AD patients with DHA for 18 months, but still did not find an effect on ADAS-cog. Two other studies supplementing both DHA and EPA did find slight improvements in cognition after only 24 weeks of supplementation [176,231].

Studies with transgenic mice and Aβ-infused rats did show improvements in cognition after LCPUFA supplementation [195,235–239]. The duration of supplementation in these animal studies is relatively longer compared to the clinical studies. This may indicate that the supplementation should start earlier on in clinical studies to obtain LCPUFA effects on cognition in AD patients.

5. Conclusion

The wide range of studies available have shown that LCPUFA are able to influence the brain in many ways throughout life (Fig. 3). In general, LCPUFA are essential in membrane fluidity and their function as inflammatory mediators. They are important at the start of life to support neural development and prevent neurodevelopmental disorders, and remain important throughout life for membrane fluidity, the prevention of inflammatory states, and cardiovascular health. Supplementation studies starting early in life show more potent results than those starting during aging or AD. This suggests that it is important to achieve a healthy LCPUFA status early on in life and maintain this status throughout life in order to have a beneficial effect.

The Mediterranean diet fits very well with a healthy LCPUFA status. Not only does it enclose a balanced n-6/n-3 ratio, due to the fact that it is rich in fish and lean meat, but it also contains other important nutrients, such as vitamins and antioxidants, originating from fruit, vegetables, and whole grains. This in contrast to Western diets that are rich in saturated fats, *trans* fats, sugar, and refined grains. Therefore, implementation of a Mediterranean diet contributes to a healthy lifestyle.

The overall weaknesses in clinical LCPUFA supplementation studies throughout life are the relatively short duration of supplementation, variance in populations, and the limitations of testing variables. In rodent studies, LCPUFA have shown potential to contribute to a healthy life, but in clinical studies they could not yet demonstrate their full potential due to these shortcomings.

This review shows that LCPUFA have a beneficial effect on health, but the n-6/n-3 ratio is most important to establish a healthy and balanced diet. The key message in maintaining this healthy LCPUFA status is finding the proper n-6/n-3 balance, with a ratio of about 1/1 to 2/1.

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