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Bárbara Pinto Martins

Papel do ómega-3 marinho nas Perturbações do Espectro do Autismo e Perturbações de Hiperatividade e Défice de Atenção - uma revisão focada na dieta das mães

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NOME

Bárbara Pinto Martins

NÚMERO DE ESTUDANTE | E-MAIL

201201156 | barbarapmartins6@gmail.com

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Dedico este trabalho a todos os que me ajudam a traçar o meu caminho:

Aos meus pais, pelo apoio incondicional em todos os momentos.

Ao meu irmão, pelo exemplo de trabalho e conquista.

Ao meu namorado, pela confiança e valorização em tudo o que sou no mínimo que faço.

A todos os médicos que o são por amor à profissão e a quem cuidam.

Review

The role of marine omega-3 in Autism Spectrum Disorders and Attention-Deficit/Hyperactivity Disorder - a review focused on mothers' diet

Bárbara P. Martins[1], Narcisa Bandarra[2] and Margarida Figueiredo-Braga[1,3*]

[1] Department of Clinical Neurosciences and Mental Health, Medical Psychology, Faculty of Medicine, University of Porto, Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal

[2] Department of Sea and Marine Resources, Portuguese Institute for the Sea and Atmosphere (IPMA, IP), Rua Alfredo Magalhães Ramalho 1495-006 Lisbon, Portugal

[3] I3S Instituto de Investigação e Inovação em Saúde, Porto, Portugal

[*] Correspondence to: mmfb@med.up.pt; Tel.: +351917514681

Abstract: Autism Spectrum Disorders (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD) are two increasingly prevalent neurodevelopmental disorders. This rise appears to be associated with a higher dietary intake of n-6 polyunsaturated fatty acids (PUFAs) and lower of n-3 PUFAs. Docosahexaenoic acid (DHA), a key nutritional n-3 PUFA, is crucial for an optimal offspring's neurodevelopment through the last trimester of pregnancy. Recently, lower DHA levels have been reported in children with ASD and ADHD. The present review summarizes the main research achievements concerning the effect of maternal DHA intake in children neurodevelopment, in order to elicit its role in the prevention and mitigation of ASD and ADHD. As main finding, a low maternal marine DHA intake seems to negatively affect childhood neurodevelopment and increase the risk and the severity of ASD or ADHD. Higher DHA status at birth was associated with better childhood neurodevelopmental, but controversial results found in prenatal supplementation raised the hypothesis that the benefits of DHA may be influenced by other factors as socio-economic background and life-style. In conclusion, an optimal maternal consumption of marine products and being breastfeed may promote some neuronal protection in offspring, confirming the essential role of DHA as a modifiable risk factor for ASD and ADHD.

Keywords: Autism Spectrum Disorders; Attention-Deficit/Hyperactivity Disorder; neurodevelopment; docosahexaenoic acid; n-3 Polyunsaturated Fatty Acids; maternal seafood intake; pregnancy; lactation.

1. Introduction

Autism Spectrum Disorders (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD) are two neurodevelopmental disorders, that evolve as a result of interactions between genetic and environmental factors [1, 2].

ASD displays deficits in social communication and reciprocal social interaction and restricted repetitive activities, behaviors and interests, frequently starting before three years of age [3]. In the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), the terms Autistic disorder, Asperger disorder, Childhood disintegrative disorder, and Pervasive developmental disorder - not otherwise specified are included in ASD, also called Pervasive Developmental Disorder [1]. One in each 68 children (1.5%) in United States was

affected in 2012, 4.5 times more frequent in boys than girls [4]. Others studies in Europe, Asia, and North America reported a prevalence of ASD of 1-2% [5].

Although ASD is highly heritable (last estimates 38–54%), environmental factors are crucial in its etiology, especially those affecting fetal and early-life development [6]. Advanced parental age and birth complications related to ischemia, trauma and hypoxia have shown solid links to ASD [2]. Other pregnancy-related factors such as extremely preterm delivery, very low birthweight, maternal infection, use of infertility treatments, maternal exposure to environmental pollutants or specific medications, maternal obesity and diabetes, have shown a less strong, but significant, association with the risk of ASD [2].

Despite the growing research interest in ASD, ADHD remains the most studied pediatric mental disorder, affecting 5-7% of children and being 3 times more frequent in boys [7, 8]. It is defined by ongoing pattern of inattention, problems in controlling impulsive behaviors or be overly active, with an onset at 7-12 years of age [1, 7, 8]. Like in ASD, genetic factors play an important etiological role, but other external factors, such as alcohol, tobacco or pollutants exposure during pregnancy, emotional difficulties, premature delivery, very low birth weight and pre- or postnatal brain injury have been shown to contribute to ADHD [9].

The clinical and etiological similarities between the two diseases are remarkable and their prevalence identically has increased at an alarming rate [10]. A change to a Western diet, characterized by an increase in dietary pro-inflammatory omega-6 polyunsaturated fatty acids (n-6 PUFAs), though meat and processed food, and a decrease in anti-inflammatory omega-3 (n-3 PUFAs), present mainly in seafood, caused a dramatic increase in the n-6 to n-3 PUFA ratio from the optimal 1-2:1 of the Paleolithic diet to about 20-30:1 [11]. This change could be one of the explanations for the increased prevalence of these diseases, as a high ratio seems to be unfavorable for the proper function of central nervous system [12, 13].

N-3 PUFAs play a central role in the brain function and structure of the neuronal cell membranes, and also in the development of myelin sheath and retina [12]. In particular, docosahexaenoic acid (DHA) overcomes 90% of the n-3 PUFAs in the human brain and about 10 to 20% of total lipids [14], being associated with a number of positive effects on maternal and infant health [13]. Higher DHA intake appears to reduce the risk of schizophrenia, bipolar disorder, depression, anxiety, and behavior disorders, while suboptimal DHA levels seems to be a potentially risk factor for mental illness [15].

DHA is quickly incorporated into the retina and brain nervous tissue during the third trimester of pregnancy until two years of age [16]. Since the synthesis of DHA in fetus is low, maternal DHA intake and status, and placental function, are critical for its supply to the fetus [17]. Several observational studies and randomized clinical trials showed that higher prenatal levels of DHA might improve pregnancy outcomes, such as birthweight and gestation duration, and offspring neurodevelopment [17-20]. However, neurodevelopmental improvements, especially for cognitive function, remain controversial and need further clarification [21].

PUFA levels in blood are considered consistent biomarkers of their status [22]. Knowing that children with ASD and ADHD have lower DHA and lower total n-3 PUFA serum levels compared to neurotypical controls, the determination of whether maternal DHA intake alters the risk for these diseases is a reasonable and informative next step for research. The present paper reviews ASD and ADHD neuroanatomy and physiology, relating them with marine n-3 PUFAs, especially DHA, from mother’s diet. It also aims to review present knowledge about the

impact of DHA levels in prenatal and postnatal neurodevelopment, especially in children at higher risk for these diseases, such as preterm and very low birth weight infants.

2. Neurodevelopment and functionally brain changes in ASD and ADHD

Several studies indicated that ASD and ADHD have differences in anatomy, function and brain connectivity compared to healthy controls, resulting in changes in many neurodevelopmental outcomes [10, 23, 24].

In patients with ASD, some level of intellectual disability is detected in 70% [25], and about 5% to 44% could have a seizure disorder [26]. Anxiety, delays in learning, attention, sensory processing and motor activity deficits may also be present [5].

An early postnatal brain overgrowth, with an increase in head circumference, is one of the most important morphological changes reported in ASD brain [10, 23, 24, 27], described as a possible predictor of its diagnosis in infants of high risk families [28]. Anterior temporal region and frontal cortex appear to be the most affected [29], highlighting the growth of prefrontal cortex – a crucial area in ASD and ADHD physiopathology due to its role in attention, impulse control and cognitive function [10]. This overgrowth seems to persist up to 5–6 years of age, after which no important volume increase is denoted, probably representing a deviated maturational trajectory in ASD brain [30]. However, focal areas of reduced gray matter's volume, such as in fronto-striatal networks, and reduced white matter's volume in cerebellum and cerebral fornices are also described in these children [31].

A problem in long-range connectivity is now known as an emerging theory in ASD. Dinstein et al. [32] showed that toddlers with Autism displayed a weaker "functional connectivity" between brain hemispheres in language areas (including the superior temporal gyrus and the inferior frontal cortex), with an abnormal right lateralized processing of language, present since the age of 14 months. Other studies found a significantly reduction in the volume of corpus callosum, the major white matter bundle in the brain [10, 33]. Overall, ASD patients appear to have a reduction in long-range connectivity, but normal or increased short-range neuronal connections, which could clarify some of their better processing functions, like visual perception or some attention to detail [34].

On the other hand, it has recently been discovered that cerebellum plays a role in cognitive functions, making it an important research area for ASD and ADHD [35, 36]. Most of the studies found a larger size of cerebellum in ASD children, particularly prominent in its posterior lobe [23, 24]. Although vermis has already been reported as smaller or larger compared to controls [24, 37], a consistent finding was a significant lower number and size of Purkinje cells in postmortem studies [37, 38].

In these patients, there is also a hypoactivation in social brain regions (important for facial recognition, empathy, social cognition and behavior), including the inferior frontal gyrus, anterior insula, anterior cingulate cortex, interparietal sulcus, fusiform gyrus and amygdala, with an enlargement of this last region [39, 40]. However, recent studies pointed out that the problem in ASD may not be the social isolation, but a difficulty in the separation of consciousness of self and others, as they showed an abnormal activation of the ventromedial prefrontal cortex

in non-self performing tasks, while in unaffected children it is only activated in self-referential processing [41].

Another topic of discussion is the neuroinflammatory phenomenon found in ASD, characterized by an activation of microglia, higher pro-inflammatory cytokines brain levels, autoantibody generation, and increased blood-brain barrier permeability, which favors the migration of leukocytes to brain tissue [6, 42, 43]. Animal models showed that the exposure to toxic substances or infections during pregnancy led to an activation of the maternal immune system and neuroinflammation in offspring, presenting a negative impact on neurodevelopment and subsequently contributing to ASD [44].

Lastly, regarding the neurotransmission changes in ASD, the excitation/inhibition imbalance theory stands out [24]. These subjects have high glutamate (excitatory) [45] and low Gamma-Aminobutyric Acid (GABA) (inhibitory) blood levels, and a decreased density of GABAA receptors [46], with a possible relation between glutamate upregulation and ASD severity [45]. The serotonin and dopamine neurotransmission are also altered in these patients. Some of them have higher blood levels of serotonin, which can impair language learning and intelligence quotient (IQ) level, and promote self-aggression [24]. Other studies pointed out that ASD behavior rises up from a dysfunction in the midbrain dopaminergic system [47]. In fact, the use of dopamine D2 receptor antagonists showed to be efficient in ameliorating autistic symptoms, and this could be due to the mediation of glutamate release via D2, confirming the excitation/inhibition imbalance theory [48].

ADHD symptoms, on the other hand, arise from a deficit in executive function, including attention and inhibitory control, and working memory [7]. These children are also predisposed to present delays in language and motor development, associated with impaired brain activity in several neuronal networks [7].

Patients with ADHD seem to experience normal steps of cortical maturation but slower than healthy controls [10]. A volume reduction and a cortical thinning in certain brain regions, mainly in frontal and prefrontal regions, was found in children with ADHD [49], but the most replicable abnormalities are in basal ganglia, being associated with the severity of the symptoms [50].

Dougherty et al. [10], comparing the structural imaging literature about ASD and ADHD brain, found differences in total brain volume, amygdala, and internal capsule. For this last alteration, the results in ASD were unclear, while in ADHD were a reduction in Fractional Anisotropy (FA), using diffusion tensor images (DTI). However, ASD and ADHD seem to have an overlap in the corpus callosum and vermis cerebellar (lower volume in MR images and decreased FA in DTI), and superior longitudinal fasciculus (reduced FA) abnormalities, supporting the idea that white matter integrity is also affected in ADHD [10, 51]. In ADHD, the amygdala volume has already been reported as normal or decreased; so, these authors pointed out that amygdala could serve as a marker for discriminating both disorders [10].

Finally, ADHD patients have an abnormal neurotransmission with lower levels of norepinephrine (particularly in predominantly inattentive ADHD) and dopamine (mainly in predominantly hyperactivity-impulsive ADHD) [52]. As these neurotransmitters are associated with reward processing, but not with the emotional dysregulation, some authors have suggested that serotonin neurotransmission is also altered in ADHD. Serotonin also modulates dopamine release and its interaction seems to affect impulsivity; however, further studies are needed to confirm its link to ADHD pathology [52].

3. The role of maternal DHA intake in offspring neurodevelopment

The human brain growth spurt begins in the third trimester of pregnancy, at which point the fetal brain begins to accumulate DHA [53, 54]. This accumulation continues up to the postnatal period, being dependent on breastmilk [53].

DHA can be obtained from diet or synthesized from α-linolenic acid (ALA, 18:3n-3), a n-3 PUFA found in walnut, chia, flax seeds, rapeseed and soy [55]. In the liver, ALA suffers a desaturation by Δ6-desaturase, an elongation, and another desaturation by Δ5-desaturase to finally form Eicosapentaenoic acid (EPA, 20:5n-3). EPA is elongated to 22:5n-3 and 24:5n-3, and then, this last compost suffers a new desaturation to 24:6n-3. Finally, in peroxisome, 24:6n-3 is β-oxidized to DHA (22:6n-3) [55]. In humans, the ability to convert ALA to DHA is extremely limited (less than 0.1 [14]), especially in fetus, making them highly dependent on the transfer of maternal DHA through the placenta, influenced by maternal DHA synthesis, mobilization from adipose stores, and dietary intake [56]. Furthermore, the desaturase enzymes are not only responsible for the conversion of ALA into DHA, but also of Linoleic acid (LA, an n-6 PUFA) into Arachidonic acid (ARA), the second most important PUFA, next to DHA, for brain growth [13].

DHA, EPA and ARA, also known as Long Chain (LC)-PUFAs, modulate phospholipids composition, involved in membrane fluidity, being able to control the functions of enzymes, ion channels and receptors, and to regulate neurotransmission [13, 16]. They are also important for dendritic growth and neuronal synaptogenesis, and can regulate inflammation [16]. EPA and ARA are precursors of eicosanoids (prostaglandins, thromboxanes and leukotrienes), but while ARA shows proinflammatory properties, EPA exerts anti-inflammatory effects [53]. On the other hand, DHA cannot produce eicosanoid, but it is a source of docosanoids, metabolites that can have the ability to inactivate pro-inflammatory and pro-apoptotic signaling [16, 53]. In addition to have a general pro-inflammatory effect, higher consumption of n-6 PUFAs increases the competition between LA and ALA, as substrates of the enzymes stated above, resulting in a lower conversion of ALA to DHA and a lower DHA levels in mothers and fetus [53]. Low DHA levels could be harmful for neurodevelopment, especially in preterm infants, who are deprived of maternal stores in the third trimester [57]. Overall, an optimal DHA intake during pregnancy and postnatal period appears essential, and global recommendations for pregnant and lactating women to have a minimum DHA intake of 200 mg/day are being implemented [58].

The necessary amount of dietary DHA can be obtained mainly through fish and other seafood intake. However, recent studies indicate that pregnant women do not have enough information about the importance of fish consumption, since guidelines emphasizing the health risks of methyl-mercury (MeHg) can make them doubtful and unsecure [59]. A large observational study showed that children whose mothers consumed lower seafood (<340 g/week) during pregnancy had increased risk of having lower verbal IQ and lower fine motor ability, and suboptimum outcomes for social behavior, communication and social development at 6 months to 8 years of age, compared to children whose mothers consumed high seafood diets [60]. Currently, although it is known that MeHg is neurotoxic at high levels, the effect in neurodevelopment of its exposure in low-level from fish intake remains controversial [61]. This effect appears to be influenced by n-6 to n-3 PUFA ratio, suggesting that the balance of this ratio may reflect the capability of these LC-PUFAs, at higher levels, to increase or protect, respectively, inflammation induced by MeHg [61]. Furthermore, the benefits of fish consumption, probably

due to its high DHA composition, may overcome or mask the potential MeHg's adverse effects on neurodevelopmental outcomes [61-65].

Other authors reported that a high DHA status in umbilical cord blood were associated with longer gestation, better visual acuity and higher levels of novelty preference at 6 months, and higher cognitive scores at 11 months [66], better motor development and fewer internalizing behavior problems at 7 years [67], and higher verbal and full-scale IQ at 8 years [68]. Few observational studies reported no association between maternal fish consumption [69], DHA in mothers' red blood cell (RBC) [69, 70] and improvement in neurodevelopmental outcomes of healthy children. Note that although these studies were performed in healthy children, these symptoms are also present in ASD and some in ADHD.

Regarding the randomized clinical trials (RCTs), Mulder et al. [71] showed that infants in the placebo group had an increased risk of developing a worse language, an important symptom of ASD, than those whose mothers received 400 mg/day of DHA during pregnancy. Two other studies, with DHA supplementation alone, reported higher scores on autonomic and motor skills scales at 14 days of age, when mothers were supplemented with 600 mg/day of DHA from 12-20 weeks' gestation until birth [72], and better problem solving in infants of mothers who received 214mg/day of DHA in same period [73]. In Gustafson's study [72], a more mature autonomic function indicates greater flexibility and integrity of the Autonomic Nervous System, probably reflecting a better physiological reactivity of the newborn to the environment. However, this study had a significantly low rate of completion (78%) and the majority of enrollees were non-White, but African American, reporting higher pre-DHA status.

In DHA plus EPA prenatal supplementation's group, four studies found positive results [57, 74-79]. For example, in a study with high level of methodological rigor with low attrition, Makrides et al. [74] studied preterm infants whose mothers were supplemented with 800mg DHA + 100mg EPA per day, from <21 weeks of gestation until birth. These authors found that few children in the DHA group had scores indicative of mildly delayed cognitive development, evidencing that DHA supplementation is effective at preventing developmental delay in early childhood. However, these authors did not find differences between groups in any scales of the Behavior Rating Inventory of Executive Function at 4 years of age [78]. Note that although this study was not a pure DHA test, since it used fish oil capsules that contains DHA and EPA levels, DHA is present in the brain at levels 50 and 200-fold higher than EPA and ALA, respectively [55].

Supplementary tables S1 and S2 show the results of observational and RCTs' studies regarding the association between maternal DHA intake during pregnancy and infant neurodevelopmental outcomes. Overall, RCTs results from maternal supplementation still appear inconclusive and some meta-analyses concluded that maternal n-3 PUFA supplementation (DHA or DHA+EPA) had no consistent effect on children neurodevelopment [79, 80]. Note that the majority of these studies have important limitations, particularly high attrition rates, small sample sizes, and poor statistical design. Moreover, although several authors did not generally demonstrate a positive effect of maternal prenatal n-3 PUFA supplementation [74-78, 81-83], with few showing a negative effect [84, 85], some found that children with better neurodevelopment outcomes individually had higher DHA levels [74-76, 82, 86]. Furthermore, two of these studies [75, 76], gathering information from 3 European countries with high seafood intakes, found that 84.4% of the mothers at the start of supplementation had already achieved the recommended DHA intake of 200 mg per day, and that, in this group, parental level of education was also relatively high. These authors concluded that, possibly, the positive effects of DHA supplementation during prenatal period are less

apparent in mothers who already have an optimal dietary DHA supply. The responsiveness to prenatal DHA could be related to the characteristics of the specific population groups studied, and DHA status could to be a proxy for socio-economic background and healthy life-style factors, that may synergically improve brain development [82, 85].

It is also important to maintain optimal DHA levels during postnatal period. At this time, breastmilk is the main responsible for the amount of DHA in infant´s RBC [87], being dependent on maternal DHA consumption [56].

DHA from breastmilk seems to be crucial for better language and cognitive function [88-90], social behavior with fewer attentional symptoms and better global psychosocial health [91, 92]. Oddy et al. [91] showed that breastfeeding for less than 6 months was an independent predictor of mental health problems, such as behavior problems, through childhood and adolescence. In the cases of shorter duration of breastfeeding, a maternal fish intake at least 2 fish times/week could have a protective effect in neurodevelopment [64]. However, other studies did not find significant effects of breastfeeding on children's neurodevelopment [66, 93-98] (see supplementary table S1). This discrepancy in studies' results could be due to level of control for potential confounders such the heterogeneous composition of breast milk, maternal IQ, education level, social economic status, home environment and child care, and/or different methods of assessment of outcomes [95, 96]. Women who were more intelligent or better educated seem to be more receptive to breastfeeding promotion [96].

However, even if all of breastmilk is consumed by the baby, the DHA intake is only 13-26 mg/day (0.2–0.4% of total fatty acids), clearly below the rate of uterine accretion of ≈45-50 mg/kg/day [99]. This amount appears to be sufficient for normal brain development in full-term infants, as long as mother consumes optimal amounts of DHA during peri-natal period [100-103].

Some clinical evidence proposed that supplementing both DHA and ARA instead of DHA alone is critical to optimal influence on neuronal development of full-term infants [100, 101, 104] (see supplementary table S3). For example, verbal IQ and visual acuity at 4 years of age was comparable between infants receiving both 0,36% DHA and 0,72% ARA during the first 4 months of life and breastfed infants, whereas verbal IQ was lower in infants receiving DHA alone [104]. Moreover, Drover et al. [100] showed that a DHA-standard concentration of 0.32% was adequate to improve cognitive function while higher concentrations (about 0.96% of total fatty acids) did not confer additional benefit, and may also contribute to competing and lower ARA levels. This could mean that there is possibly an upper limit to the benefits of intaking DHA [100, 102, 103]. Although these benefits may be due exclusively to ARA supplementation, no study to date has investigated the effects of ARA supplementation alone on cognitive development, while studies with only DHA-enriched formula have already reported positive effects of this supplementation [96]. Other studies, however, did not find short- [102, 105] or long-term [101, 106] benefits in some cognition measures using LC-PUFA supplements.

On the other hand, the standard amount of DHA may not be an adequate approach for preterm infants, who appear to be more sensitive to the effects of maternal DHA intake.

4. The clinical example of preterm infants, a risk factor for ASD and ADHD

Preterm infants appear to have deficits in myelin integrity and connectivity of the cortical circuits [107, 108], presenting a higher risk for ASD and ADHD, mood, and psychotic disorders [109]. Their lower DHA levels may be partially responsible for this impaired neurodevelopment [108, 109].

In the last years, studies showed that a short-term high DHA dose (0,86-1% of total PUFAs) seems to be helpful for an optimal neurodevelopment in preterm infants [110-112], mostly in very low birth weight (VLBW) babies (<1500g) [110, 113] (see supplementary table S3). For example, Makrides et al. [111] found that a DHA supplementation of about 1% of total PUFAs, from day 2 to 4 until term-corrected age, reduced cognitive delay, improved the neurological development of girls and was strongly indicative of improved neurodevelopment in very preterm infants (≤33 weeks gestation) at 18 months of age, compared to those with a standard-DHA diet (0.3% of total fatty acids). In this study, ARA intake was the same in both groups (0.6% of total fatty acids). Henriksen et al. [110] found also that a high-DHA supplementation (0,86% DHA plus 0,91% ARA) in VLBW infants, during nine weeks, led to better capacity to problem solving and recognition memory at 6 months of age. This latter function is essential to focus attention, learning and information processing. Lastly, Westerberg et al. [113] reported a better-sustained attention at 20 months of age in these high-DHA group, but did not find differences in mental and motor development scores between the groups. However, their plasma DHA concentration was positively correlated with Bayley Mental Developmental Index, showing that this nutrient may be one of the factors that influence the development of VLBW babies. Nevertheless, at 8 years of age, these children had no differences in brain macrostructure (volume, area and thickness through imaging data), behavioral outcome and cognitive functions [114]. Other long-term studies did not report significant benefits in infancy, including for executive functions, ADHD and ASD symptoms, and emotional or behavior problems [115-118].

Overall, some meta-analysis concluded that there is insufficient evidence to recommend DHA supplementation in preterm [119], and also in full-term infants [120-122], with respect to potential long term neurodevelopmental benefits. Nevertheless, it cannot be ignored that the studies stated above showed that a high DHA dose in preterm infants could reduce, in short-term, the typical symptoms found in ASD and ADHD, diseases that are also characterized by lower levels of this nutrient. However, the differential effect of this nutrient on healthy versus ASD/ADHD states is one of the most important issues to be addressed [123].

5. How can DHA be related to ASD and ADHD?

5.1 Potential mechanistic pathways of DHA in ASD

The conversion of ALA into DHA is insignificant in males while occurring in girls at 9%. This could indicate that DHA have an important role in this disorder since ASD is more frequent in boys [13]. The higher conversion capacity in females may be due to the importance of maintaining optimal DHA levels for their offspring's development during pre- and postnatal period [16]. Actually, several studies reported that children with ASD have lower DHA, EPA and

ARA levels and higher total n-6 to n-3 PUFA ratio compared to unaffected children [22]. Parletta et al. [124] showed that a worse PUFA profile, especially in relation to this PUFA ratio, is associated with clinical severity in children with ASD or ADHD.

The low n-3 PUFA levels in ASD can be explained by defects in enzymes involved in the DHA and EPA production from ALA, known as fatty acid desaturase (FADS), by deficiencies in its process of cell membrane incorporation, or an alteration in its metabolism, for example through a possible dysfunction in mitochondrial PUFA oxidation [12, 16, 125]. However, their potential biological pathways in ASD are not yet fully understood [125].

A deficit of DHA during perinatal period was shown to be associated with a reduction in neurogenesis and delays in neuronal migration [126], and it has recently been implicated in synaptic plasticity [127] - a new research field in ASD [127, 128]. ASD is also characterized by changes in myelination and by an abnormal long-range brain connectivity, and the formation of white matter tract appear to be very susceptible to the n-6 to n-3 PUFA ratio [129]. Moreover, a low maternal intake of DHA was associated with a decrease in brain-derived neurotrophic factor (BDNF), a protein that protect neurons and glia from death [130, 131]. Children with ASD have lower BDNF levels, associated with more severe disease [131], and a supplementation with DHA could normalize BDNF in some brain areas affected in ASD [132].

From a neurochemical point of view, there are studies that point to an effect of DHA deficiency on the modulation of GABA-ergic receptor functions, especially in specific GABAA receptor subunits [133], or to an interaction between PUFAs and PLA_2 (Phospholipase A2), present in the plasma membrane [12]. PLA_2 is able to inhibit GABAA receptor function and high n-6 ARA levels may increase its activation, resulting in increased neuronal excitability [12]. In addition, a lower n-3 PUFA intake in rats has shown to reduce dopamine levels in frontal cortex, increase basal synaptic release of serotonin and change glutamergic system in offspring female rats [134-136]. Then, a DHA supplementation increase synaptic plasticity in hippocampal neurons and improved glutamatergic neurotransmission [137]. However, following its supplementation, DHA levels increase differently in the various brain regions [12]. As the hippocampus and frontal cortex are the brain regions that take the longest time to recover normal DHA levels after its prenatal deficit, it may be difficult to restore its concentration in the absence of a postnatal dietary intervention [138].

Regarding the problem of systemic immune dysfunction present in up to 60% of autistic patients [138], Weiser et al. [139] showed that a high maternal dietary DHA in mouse protect offspring from the deleterious effects of maternal infection on ASD behavior symptoms, and later on immune system reactivity in adulthood. Furthermore, neuro-inflammation in the autistic brain has been reported several times [6, 140, 141], and the increase in the n-6 to n-3 PUFA ratio is one of the possible reasons for this [12]. In addition to its pro-inflammatory action, n-6 PUFA derived prostaglandins may be associated with initiation of preterm labor, with an increased risk of ASD in susceptible children [12]. Won et al. [38] found also high autoantibodies levels to neuronal and glial molecules in ASD patients, probably linked to a n-6 to n-3 PUFA ratio.

Finally, the gut:brain axis was recently pointed as an alternative pathway for the n-3 PUFA action against ASD [6]. N-3 PUFA deficiency during perinatal period alters intestinal microbial balance in offspring, with a reduction in bacterial density and a decrease in the proportion of Firmicutes to Bacteroidetes [142]. On the other hand, microbial overgrowth can affect the uptake and metabolism of PUFAs and other molecules [143]. As this axis is different

among people, its variation in ASD patients may be one of the explanations for the inconsistent results in n-3 PUFA supplementation studies.

Overall, the majority of these studies underscore the important role of n-3 PUFAs, especially DHA, with an optimal n-6 to n-3 PUFA ratio, in the prevention or symptomatic improvement of ASD, recently indicating the gut:brain axis as a potential target for intervention in ASD.

5.2 Potential mechanistic pathways of DHA in ADHD

The study of Stevens et al. [144] was the first to show a link between ADHD and n-3 PUFAs. These authors found lower DHA and EPA plasma levels in ADHD children, with an overlap of PUFA deficiency and ADHD symptoms: thirst, frequent urination, dry skin and hair and nail weakness. Recently, a meta-analysis [145] showed that youth with ADHD have lower RBCs DHA, EPA and total n-3 PUFAs but not lower levels of total n-6 PUFAs. However, no differences were reported in PUFA plasma levels comparing to controls, showing that while RBCs PUFAs are strongly correlated with dietary intake of the last month [146], and their brain levels [105], plasma levels only reflect its intake in the last days [145].

Several authors suggested that, as a deficient fetal DHA level results in deficits in white matter integrity and in a reduction of functional connectivity in fronto-basal glial circuits (found in preterm infants), it could increase the risk of developing ADHD symptoms in childhood [126].

The most studied mechanism relating DHA intake to the pathophysiology of ADHD is the alteration in cortical dopamine neurotransmission [13, 16]. Dopamine levels and its binding to D2 receptors could be reduced, mainly in frontal cortex, in chronic n-3 PUFA deficiencies, associated with symptoms similar to those observed in ADHD [147].

Other authors have also found a pro-inflammatory status in ADHD, supporting the idea that n-3 PUFAs enhance ADHD symptoms by its anti-inflammatory action. For example, Hariri et al. [148] showed that 8 weeks of EPA plus DHA supplementation decreased plasma inflammatory mediators (C-reactive protein and IL-6) and oxidative stress in children with ADHD, although its impact on ADHD symptoms was not evaluated.

Overall, there is relatively little research regarding the mechanisms of DHA in ADHD, compared to ASD information. Recently, the gut:brain axis was also reported to influence ADHD symptoms and diagnosis [84]. Indeed, it should be noted that low DHA intake has been associated to anxiety disorders [149], a risk factor for ASD and ADHD, while its supplementation has shown anxiolytic effects [150]. Therefore, an adequate DHA intake during pregnancy may lead to beneficial effects in children with ADHD or ASD also by reducing anxiety symptoms in their mothers.

6. The role of maternal intake of DHA in the prevalence and risk of ASD and ADHD

6.1. The importance in ASD

Several authors showed the importance of optimal DHA levels in healthy children in neurological and motor development, verbal IQ, social behavior, inattention and hyperactivity,

both damaged in ASD. However, how maternal intake of DHA additionally affect the development of ASD is less clear, and research dedicated to this topic is scarce (see supplementary table S4). Recently, Julvez et al. [151] reported that maternal seafood intake during pregnancy, particularly large fatty fish, confer some protection against autism spectrum characteristics in offspring at 5 years of age, with a moderate attenuation after adjustment for LC-PUFA (including DHA) levels in cord blood. Associations remained positive above the previous recommended level of 340 g/week of fish during pregnancy, which appear to confirm the importance of optimal maternal DHA levels in preventing or ameliorating ASD symptoms in their children. Notably, in this study, cord-blood mercury acted as an important biomarker of seafood intake rather than having a neurotoxic association. Lyall et al. [152] also showed that women with the lowest total n-3 PUFA intake (the lowest 5% of the distribution) had a 53% increase in risk of having a child with ASD as compared with women in the highest 90% of the distribution. However, these authors did not find this association when DHA levels were assessed specifically. Indeed, no significant associations were found between n-3 PUFA intake in the upper quartiles, or maternal fish intake, and ASD risk, suggesting that once the minimum requirements of total n-3 PUFA intake for normal development are met, a higher intake may provide little or no benefit. Note that a major bias in this study relies on the fact that ASD diagnoses was not performed by a clinical evaluation and, therefore, the results should be interpreted with caution. Also, since maternal fish consumption had no significant impact on ASD risk, other dietary sources of n-3 PUFA may have contributed to the results. In fact, the relation between maternal consumption of fish, the main source of DHA and EPA, and the risk of ASD remain controversial, with other studies reporting no association between them [151, 153]. However, Julvez et al. [151], and Gao et al. [154] found a protective effect of fish intake during or before pregnancy against ASD diagnosis, respectively.

DHA requirement during pregnancy has to be combined with an optimal postnatal and early childhood dietary intake of it, important for cortical circuits' maturation [12]. If it does not happen, it appears to become a risk factor that acts synergistically with other factors in the promotion of the pathogenesis of ASD among susceptible children [155].

Few studies have investigated the potential protective effects of breastfeeding against behavioral problems such as ADHD symptoms, and even fewer on ASD traits. Studies in this area found mixed results: while some showed a positive association between breastfeeding and ASD [156-160], others did not [161]. For example, Al-Farsi et al. [157] found that, in ASD, there are more suboptimal breastfeeding practices comparing to the control group. In agreement, a recent meta-analysis provides evidence that breastfeeding may protect against ASD [162]. Boucher et al. [159] reported that each additional month (>6 months) of breastfeeding was associated with a small improvement in cognitive function and with slightly fewer autistic traits, and more mitigated effects were found on ADHD symptoms and attention function. However, these authors did not find significant association between breastfeeding duration and the occurrence of scores within the clinical range for ASD and ADHD diseases. Finally, Schultz et al. [156] found that the use of infant formula without DHA plus ARA supplementation versus exclusive breastfeeding was associated with a significant increase in the odds of autistic disorder. Nevertheless, DHA is only one of the factors that contribute to the beneficial effects of breastmilk in childhood neurodevelopment; other potential molecules, such as oxytocin and serum insulin-like growth factor (IGF), are increased in breastmilk and could influence the risk

of ASD [162]. These findings may be useful for maternal counseling, especially in cases of risk of having ASD.

Other studies further indicated that more than a deficit of DHA intake, a higher maternal n-6 to n-3 PUFA ratio during pregnancy was associated with a higher number of autism traits in offspring [153]. Graff et al. [153] pointed out that these associations were independent of child intelligence, suggesting that the PUFAs distribution specifically affects the development of autistic traits in addition to general neurodevelopment, but maternal n-3 PUFA status and prenatal intake of fish were not associated with child autistic traits. These findings suggest that, possibly, the focus of dietary interventions should not only be the increasing of n-3 PUFA intake but also the reduction of food intake with high content of n-6 PUFAs.

6.2. The importance in ADHD

As in ASD, it was proposed that maternal DHA intake during pregnancy and lactation influences the neurodevelopment of susceptible children to ADHD [13] (see supplementary table S5).

Some studies reported that higher maternal DHA levels at birth were associated with lower ADHD symptoms, such as inattention in toddlers [163] and hyperactivity/inattention during school age [164]. Gale et al. [65] also showed that children whose mothers had eaten fatty fish early in pregnancy, the type of fish richer in DHA and EPA, had a lower risk of hyperactivity compared to those whose mothers did not eat fatty fish. In addition, Sagiv et al. [165] found a protective association of ingestion of more than 2 times/week of fish with ADHD-related behaviors, particularly DSM-IV Impulsive/Hyperactive behaviors. However, other studies did not detect any benefits of prenatal seafood intake in attention, once confounders were taken into consideration [60].

Regarding supplementation studies, there are also mixed results: while some authors reported a beneficial effect of prenatal DHA supplementation on measures of attention and executive function at preschool age [166, 167], others did not find any association [168]. Although these studies addressed healthy population, Ramakrishman et al. [167] showed that the same results were present in children with ADHD.

Breastfeeding is one of the factors that could be related to ADHD and the prevalence of ADHD among patients not fed with breastmilk, but with artificial formula, is significantly higher compared to those who are fed with breastmilk [169-172]. Moreover, breastmilk seems to prevent ADHD, once breastfeeding of shorter duration appears to be associated with an increased internalizing, externalizing, and overall behavioral problems as well as the diagnosis of ADHD [169, 171, 172].

7. **Discussion**

ASD and ADHD arise from interactions between genetic and environmental factors that influence neurobiological systems since the prenatal period. It is unlikely that a single neuroanatomic or neurophysiological change is responsible for all the pathogenesis of ASD and ADHD. An alteration in brain volume is one of the more consistent features of ASD and ADHD,

but other problems, such as in myelin integrity, connectivity of the cortical circuits, neurotransmission and neuroinflammation, were also described.

N-3 PUFAs, especially DHA, are necessary for neurodevelopment. Their tissue concentrations in fetal plasma and brain are dependent on maternal diet intake, mainly through fish and other seafood. This intake is particularly important during the third trimester of pregnancy until the first six months of life. In fact, the current review shows that a low maternal intake of fish (or low DHA levels) during pregnancy can affect the neurodevelopment of their offspring, resulting in lower cognitive and language function, motor ability, poorer social and communication skills, and behavior problems. However, RTCs and other controlled studies have not shown the same consistent positive results as found in observational studies. Indeed, although the results from maternal supplementation RCTs still appear inconclusive, some studies pointed that DHA status in cord and maternal blood are associated with better childhood neurodevelopmental outcomes. One possible explanation for this is that, during pregnancy, DHA is not the unique factor to intervene in this development, as other factors such as birth weight, maternal education, maternal IQ, and smoking may mask the benefits of this intervention. In addition, the baseline DHA intake/status is not systematically included in the characterization of the study population. As this status could affect the response to changes in DHA intake, this may also be one of the reasons for the lack of significant association found in these studies.

Besides DHA deficits in prenatal period, an optimal DHA intake during the postnatal period may represent a safe and efficacious strategy to mitigate these deficits. In this period, it is more important to have an optimal n-6 to n-3 PUFA ratio than ideal levels of DHA. Additionally, preterm infants need higher DHA levels than full-term infants. They seem to have a higher risk for ASD and ADHD, and a high dose of DHA could reduce the typical symptoms found in ASD and ADHD at short-term but not in long-term. Although these results were found in healthy children, collectively, these findings provide support for the proposition that reduced perinatal DHA accrual in brain may represent a risk factor for ASD and ADHD.

Recent studies in ASD found that an optimal maternal consumption of fish and breastfeed for 6 months or more, could confer some protection against autism spectrum characteristics in offspring, while a higher maternal n-6 to n-3 PUFA ratio seem to be associated with higher autism traits in offspring. In addition, the brain-microbiota axis is a future tool for finding more effective strategies to prevent or treat ASD, and probably ADHD. These results were similar for ADHD, also showing positive findings of maternal DHA intake in the reduction of ADHD symptoms, although other studies did not demonstrate this association. Together, it suggests that early deficits of DHA in fetal brain may represent a modifiable risk factor for ASD and ADHD and could therefore be crucial for early intervention and prevention strategies.

In conclusion, DHA-rich food, particularly in pre- and postnatal period, could improve the health and well-being of pregnant woman, and reduce the risk for having a child with ASD and ADHD, especially in those with a positive family history. Recently, the Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA), recommend that pregnant women, women who might become pregnant, and breastfeeding mothers eat 2-3 servings of lower-mercury fish or 8-12 ounces (227 to 340 g) per week, while avoiding fish intake that is high in mercury [173, 174]. The novelty comparing to the recommendations of 2014 was a creation of three categories of fish: 1) “Best choices” (eat 2-3 times/week; e.g. salmon, tilapia, scallop, shrimp); 2) “Good choices” (eat 1 time/week; e.g. halibut, mahi-mahi, snapper) and 3) “Fish to avoid”; e.g. swordfish, king mackerel, tilefish.

Finally, DHA supplementation appear to be an alternative to optimize maternal DHA levels in women who do not achieve optimal level of fish intake, such as poorly nourished mothers or those on vegan diets. N-3 PUFAs supplements and fortified formulas seems to be well tolerated. Newberry et al. [80], in a recent systematic review including 21 RCTs studies, found that the adverse effects of these supplementation in pregnant and lactating women were limited to mild gastrointestinal (GI) symptoms, with no serious adverse events reported. Indeed, in preterm and full-term infants, adverse events were also limited to GI symptoms, with most serious adverse events related to morbidities associated with prematurity.

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References:

1. American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders, 5th ed.; APA; Washington DC, 2013.
2. Modabbernia, A.; Velthorst, E.; Reichenberg, A. Environmental risk factors for autism: an evidence-based review of systematic reviews and meta-analyses. *Mol Autism.* 2017, 8, 13, DOI: 10.1186/s13229-017-0121-4.
3. Faras, H.; Al Ateeqi, N.; Tidmarsh, L. Autism spectrum disorders. *Ann Saudi Med*. 2010, 30(4), 295-300, DOI: 10.4103/0256-4947.65261.
4. Christensen, D.L.; Baio, J.; Braun, K.V.; et al. Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2012. *MMWR Surveill Summ*. 2016, 65(3), 1–23, DOI: http://dx.doi.org/10.15585/mmwr.ss6503a1.
5. Autism Spectrum Disorder [updated July 11, 2016. Division of Birth Defects, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention]. Available online: https://www.cdc.gov/ncbddd/autism/data.html (accessed on 20 March 2018).
6. Madore, C.; Leyrolle, Q.; Lacabanne, C.; Benmamar-Badel, A.; Joffre, C.; Nadjar, A.; et al. Neuroinflammation in Autism: Plausible Role of Maternal Inflammation, Dietary Omega 3, and Microbiota. *Neural Plast.* 2016, 1-15, DOI: 10.1155/2016/3597209.
7. Attention Deficit Hyperactivity Disorder [updated March, 2016. National Institute of Mental Health] Available online: https://www.nimh.nih.gov/health/topics/attention-deficit-hyperactivity-disorder-adhd/index.shtml#part_145444 (accessed on 20 March 2018).
8. Cortese, S.; Castellanos, F.X. Attention Deficit/Hyperactivity Disorder. *Neurob Brain Disord.* Academic Press, San Diego, 2015, pp. 42-58, DOI: 10.1016/B978-0-12-398270-4.00004-5.
9. Guney, E.; Cetin, F.H.; Iseri, E. The Role of Environmental Factors in Etiology of Attention-Deficit Hyperactivity Disorder, ADHD - New Directions in Diagnosis and Treatment. InTech, Rijeka, 2015. Ch. 02, DOI: 10.5772/61025.
10. Dougherty, C.C.; Evans, D.W.; Myers, S.M.; Moore, G.J.; Michael, A.M. A Comparison of Structural Brain Imaging Findings in Autism Spectrum Disorder and Attention-Deficit Hyperactivity Disorder. *Neuropsychology Rev.*, 2016, 26(1), 25-43, DOI: 10.1007/s11065-015-9300-2.
11. Akerele, O.A.; Cheema, S.K. A balance of omega-3 and omega-6 polyunsaturated fatty acids is important in pregnancy. *JNIM*, 2016, 5, 23-33, DOI: 10.1016/j.jnim.2016.04.008.
12. van Elst, K.; Bruining, H.; Birtoli, B.; Terreaux, C.; Buitelaar, J.K.; Kas, M.J. Food for thought: dietary changes in essential fatty acid ratios and the increase in autism spectrum disorders. *Neurosci Biobehav. Rev.*, 2014, 45, 369-78, DOI: 10.1016/j.neubiorev.2014.07.004.
13. Morgese, M.G.; Trabace., L. Maternal Malnutrition in the Etiopathogenesis of Psychiatric Diseases: Role of Polyunsaturated Fatty Acids. *Brain Sci.*, 2016, 6(3), DOI: 10.3390/brainsci6030024.

14. Weiser, M.J.; Butt, C.M.; Mohajeri, M.H. Docosahexaenoic Acid and Cognition throughout the Lifespan. *Nutrients*, 2016, 8(2), 99, DOI: 10.3390/nu8020099.
15. Bozzatello, P.; Brignolo, E.; De Grandi, E., Bellino, S. Supplementation with Omega-3 Fatty Acids in Psychiatric Disorders: A Review of Literature Data. *J Clin Med.* 2016, 5(8), DOI: 10.3390/jcm5080067.
16. Cardoso, C.; Afonso, C.; Bandarra, N.M. Dietary DHA, bioaccessibility, and neurobehavioral development in children. *Crit Rev Food Sci Nutr.* 2017, 1-15, DOI: 10.1080/10408398.2017.1338245.
17. Larque, E.; Gil-Sanchez, A.; Prieto-Sanchez, M.T.; Koletzko, B. Omega 3 fatty acids, gestation and pregnancy outcomes. *Br J Nutr* 2012, 107 (Suppl 2), 77-84, DOI: 10.1017/S0007114512001481.
18. Carlson, S.E.; Colombo, J.; Gajewski, B.J.; Gustafson, K.M.; Mundy, D.; Yeast, J.; et al. DHA supplementation and pregnancy outcomes. *Am J Clin Nutr.* 2013, 97(4), 808-15, DOI: 10.3945/ajcn.112.050021.
19. Meher, A.; Randhir, K.; Mehendale, S.; Wagh, G.; Joshi, S. Maternal Fatty Acids and Their Association with Birth Outcome: A Prospective Study. *PloS one* 2016, 11(1), e0147359, DOI: 10.1371/journal.pone.0147359.
20. Ramakrishnan, U.; Stein, A.D.; Parra-Cabrera, S.; Wang, M.; Imhoff-Kunsch, B.; Juarez-Marquez, S.; et al. Effects of docosahexaenoic acid supplementation during pregnancy on gestational age and size at birth: randomized, double-blind, placebo-controlled trial in Mexico. *Food Nutr Bull.* 2010, 31(Suppl 2), 108-16, DOI: 10.1177/15648265100312S203.
21. Osendarp, S.J.M. The role of omega-3 fatty acids in child development. *OCL* 2011, 18(6), 307-313, DOI: 10.1684/ ocl.2011.0417.
22. Mazahery, H.; Stonehouse, W.; Delshad, M.; Kruger, M.C.; Conlon, C.A.; Beck, K.L.; et al. Relationship between Long Chain n-3 Polyunsaturated Fatty Acids and Autism Spectrum Disorder: Systematic Review and Meta-Analysis of Case-Control and Randomised Controlled Trials. *Nutrients* 2017, 9(2), DOI: 10.3390/nu9020155.
23. Donovan, A.P.; Basson, M.A. The neuroanatomy of autism - a developmental perspective. *J Anat*. 2017, 230(1), 4-15, DOI: 10.1111/joa.12542.
24. Polsek, D.; Jagatic, T.; Cepanec, M.; Hof, P.R.; Simic, G. Recent developments in neuropathology of autism spectrum disorders. *Transl Neurosci*. 2011, 2(3), 256-64. DOI: 10.2478/s13380-011-0024-3;
25. Srivastava, A.K.; Schwartz, C.E. Intellectual disability and autism spectrum disorders: causal genes and molecular mechanisms. *Neurosci Biobehav Rev.* 2014, 46 Pt 2, 161-74, DOI: 10.1016/j.neubiorev.2014.02.015.
26. Lee, B.H.; Smith, T.; Paciorkowski, A.R. Autism spectrum disorder and epilepsy: Disorders with a shared biology. *Epilepsy Behav.* 2015, 47, 191-201, DOI: 10.1016/j.yebeh.2015.03.017.
27. Hazlett, H.C.; Poe, M.; Gerig, G.; Smith, R.G.; Provenzale, J.; Ross, A.; et al. Magnetic resonance imaging and head circumference study of brain size in autism: birth through age 2 years. *Arch Gen Psychiatry*. 2005, 62(12), 1366-76, DOI: 10.1001/archpsyc.62.12.1366.
28. Hazlett, H.C.; Gu, H.; Munsell, B.C.; Kim, S.H.; Styner, M.; Wolff, J.J.; et al. Early brain development in infants at high risk for autism spectrum disorder. *Nature* 2017, 542(7641), 348-351, DOI: 10.1038/nature21369.
29. Geschwind, D.H. Advances in autism. *Annu Rev Med.* 2009, 60, 367-80, DOI: 10.1146/annurev.med.60.053107.121225.
30. Ecker, C. The neuroanatomy of autism spectrum disorder: An overview of structural neuroimaging findings and their translatability to the clinical setting. *Autism* 2017, 21(1), 18-28, DOI: 10.1177/1362361315627136.
31. Ismail, M.T.; Keynton, R.S.; Mostapha, M.O.; ElTanboly, A.H.; Casanova, M.F.; Gimel'farb, G.L.; El-Baz, A. Studying Autism Spectrum Disorder with Structural and Diffusion Magnetic Resonance Imaging: A Survey. *Front Hum Neurosci*. 2016, 10, 211, DOI: 10.3389/fnhum.2016.00211.
32. Dinstein, I.; Pierce, K.; Eyler, L.; Solso, S.; Malach, R.; Behrmann, M.; et al. Disrupted neural synchronization in toddlers with autism. *Neuron*. 2011, 70(6), 1218-25, DOI: 10.1016/j.neuron.2011.04.018.
33. Frazier, T.W.; Hardan, A.Y.; A meta-analysis of the corpus callosum in autism. *Biol. Psychiatry* 2009, 66(10), 935-41, DOI: 10.1016/j.biopsych.2009.07.022.
34. Baron-Cohen, S.; Belmonte, M.K. Autism: a window onto the development of the social and the analytic brain. *Annu Rev Neurosci.* 2005, 28, 109–26, DOI: 10.1146/annurev.neuro.27.070203.144137.

35. Basson, M.A.; Wingate, R.J. Congenital hypoplasia of the cerebellum: developmental causes and behavioral consequences. *Front Neuroanat*. 2013, 7, 29, DOI: 10.3389/fnana.2013.00029.
36. Fatemi, S.H.; Aldinger, K.A.; Ashwood, P.; Bauman, M.L.; Blaha, C.D.; Blatt, G.J.; et al. Consensus paper: pathological role of the cerebellum in autism. *Cerebellum* 2012, 11(3), 777-807, DOI:10.1007/s12311-012-0355-9.
37. Stanfield, A.C.; McIntosh, A.M.; Spencer, M.D.; Philip, R.; Gaur, S.; Lawrie, S.M. Towards a neuroanatomy of autism: a systematic review and meta-analysis of structural magnetic resonance imaging studies. *Eur Psychiatry* 2008, 23, 289–299, DOI: 10.1016/j.eurpsy.2007.05.006.
38. Won, H.; Mah, W.; Kim, E. Autism spectrum disorder causes, mechanisms, and treatments: focus on neuronal synapses. *Front Mol Neurosci.* 2013, 6, 19, DOI: 10.3389/fnmol.2013.00019.
39. Hadjikhani, N.; Joseph, R.M.; Snyder, J.; Tager-Flusberg, H. Abnormal activation of the social brain during face perception in autism. *Hum Brain Mapp.* 2007, 28, 441–449, DOI: 10.1002/hbm.20283.
40. Schumann, C.M.; Barnes, C.C.; Lord, C., et al. Amygdala enlargement in toddlers with autism related to severity of social and communication impairments. *Biol Psychiatry* 2009, 66, 942–949, DOI: 10.1016/j.biopsych.2009.07.007.
41. Kennedy, D.P.; Courchesne, E. Functional abnormalities of the default network during self- and other-reflection in autism. *Soc Cogn Affect Neurosci*. 2008, 3, 177–190, DOI: 10.1093/scan/nsn011.
42. Onore, C.; Careaga, M.; Ashwood, P. The role of immune dysfunction in the pathophysiology of autism. *Brain Behav Immun.* 2012, 26(3), 383-92, DOI: 10.1016/j.bbi.2011.08.007.
43. Rossignol, D.A., Frye, R.E. Evidence linking oxidative stress, mitochondrial dysfunction, and inflammation in the brain of individuals with autism. *Front Physiol.* 2014, 5, 150, DOI: 10.3389/fphys.2014.00150.
44. Patterson, P.H. Maternal infection and immune involvement in autism. *Trends Mol Med.* 2011, 17(7), 389-94, DOI: 10.1016/j.molmed.2011.03.001.
45. Shinohe, A.; Hashimoto, K.; Nakamura, K.; Tsujii, M.; Iwata, Y.; Tsuchiya, K.J.; et al. Increased serum levels of glutamate in adult patients with autism. *Prog Neuropsych Biol Psychiatry.* 2006, 30, 1472–1477, DOI: 10.1016/j.pnpbp.2006.06.013.
46. Fatemi, S.H.; Reutiman, T.J.; Folsom, T.D.; Thuras, P.D. GABA(A) receptor downregulation in brains of subjects with autism. *J Autism Dev Disord*. 2009, 39, 223–230, DOI: 10.1007/s10803-008-0646-7.
47. Paval, D. A Dopamine Hypothesis of Autism Spectrum Disorder. *Dev Neurosci.* 2017, 39(5), 355-360, DOI: 10.1159/000478725.
48. Bernardi, S.; Anagnostou, E.; Shen, J.; Kolevzon, A.; Buxbaum, J.D.; Hollander, E., et al. In vivo 1H-magnetic resonance spectroscopy study of the attentional networks in autism. *Brain Res*. 2011, 1380, 198-205, DOI: 10.1016/j.brainres.2010.12.057.
49. Batty, M.J.; Liddle, E.B.; Pitiot, A.; Toro, R.; Groom, M.J.; Scerif, G.; et al. Cortical gray matter in attention-deficit/hyperactivity disorder: a structural magnetic resonance imaging study. *J Am Acad Child and Adol Psychiatry* 2010, 49(3), 229-38, DOI: 10.1097/00004583-201003000-00006.
50. Nakao, T.; Radua, J.; Rubia, K.; Mataix-Cols, D. Gray matter volume abnormalities in ADHD: voxel-based meta-analysis exploring the effects of age and stimulant medication. *Am J Psychiatry* 2011, 168(11), 1154-63, DOI: 10.1176/appi.ajp.2011.11020281.
51. Wu, Z.M.; Bralten, J.; Cao, Q.J.; Hoogman, M.; Zwiers, M.P.; An L., et al. White Matter Microstructural Alterations in Children with ADHD: Categorical and Dimensional Perspectives. *Neuropsychopharma*. 2017, 42(2), 572-580, DOI: 10.1038/npp.2016.223.
52. McNamara, R.K.; Carlson, S.E. Role of omega-3 fatty acids in brain development and function: potential implications for the pathogenesis and prevention of psychopathology. *Prostaglandins Leukot Essent FA* 2006, 75(4-5), 329-49, DOI: 10.1016/j.plefa.2006.07.010.
53. Janssen, C.I.; Kiliaan, A.J. Long-chain polyunsaturated fatty acids (LCPUFA) from genesis to senescence: the influence of LCPUFA on neural development, aging, and neurodegeneration. *Prog Lipid Res.* 2014, 53, 1-17, DOI: 10.1016/j.plipres.2013.10.002.
54. Dagai, L.; Peri-Naor, R.; Birk, R.Z. Docosahexaenoic acid significantly stimulates immediate early response genes and neurite outgrowth. *Neurochem Res.* 2009, 34(5), 867-75, DOI: 10.1007/s11064-008-9845-z.
55. Domenichiello, A.F.; Kitson, A.P., Bazinet, R.P. Is docosahexaenoic acid synthesis from α-linolenic acid sufficient to supply the adult brain? *Prog Lipid Res.* 2015, 59, 54-66, DOI: 10.1016/j.plipres.2015.04.002.

56. Lauritzen, L.; Carlson, S.E. Maternal fatty acid status during pregnancy and lactation and relation to newborn and infant status. *Matern Child Nutr.* 2011, 7 (Suppl 2), 41-58, DOI: 10.1111/j.1740-8709.2011.00303.x.
57. Dunstan, J.A.; Simmer, K.; Dixon, G.; Prescott, S.L. Cognitive assessment of children at age 2(1/2) years after maternal fish oil supplementation in pregnancy: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed.* 2008, 93, 45–50, DOI: 10.1136/adc.2006.099085.
58. Global Recommendations for EPA and DHA Intake [revised April 3, 2017; Global Organization for EPA and DHA omega-3s]. Available online: http://goedomega3.com/index.php/intake-recommendations (accessed on 20 March 2018).
59. Starling, P.; Charlton, K.; McMahon, A.T.; Lucas, C. Fish intake during pregnancy and foetal neurodevelopment - a systematic review of the evidence. *Nutrients* 2015, 7(3), 2001-14, DOI: 10.3390/nu7032001.
60. Hibbeln, J.R.; Davis, J.M.; Steer. C.; Emmett, P.; Rogers, I.; Williams, C.; et al. Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. *Lancet* 2007, 369(9561), 578-85, DOI: 10.1016/s0140-6736(07)60277-3.
61. Strain, J.J.; Yeates, A.J.; van Wijngaarden, E.; et al. Prenatal exposure to methyl mercury from fish consumption and polyunsaturated fatty acids: associations with child development at 20 mo of age in an observational study in the Republic of Seychelles. *Am J Clin Nutr*. 2015, 101(3), 530–537, DOI: 10.3945/ajcn.114.100503.
62. Oken, E.; Osterdal, M.L.; Gillman, M.W.; Knudsen, V.K.; Halldorsson, T.I.; Strom, M.; et al. Associations of maternal fish intake during pregnancy and breastfeeding duration with attainment of developmental milestones in early childhood: a study from the Danish National Birth Cohort. *Am J Clin Nutr.* 2008, 88(3), 789-96. PMCID: PMC2875187.
63. Oken, E.; Radesky, J.S.; Wright, R.O.; Bellinger, D.C.; Amarasiriwardena, C.J.; Kleinman, K.P.; et al. Maternal fish intake during pregnancy, blood mercury levels, and child cognition at age 3 years in a US cohort. *Am J Epidemiol.* 2008, 167(10), 1171-81, DOI: 10.1093/aje/kwn034.
64. Mendez, M.A.; Torrent, M.; Julvez, J.; Ribas-Fito, N.; Kogevinas, M.; Sunyer, J. Maternal fish and other seafood intakes during pregnancy and child neurodevelopment at age 4 years. *Public Health Nutr.* 2009, 12(10), 1702-10, DOI: 10.1017/S1368980008003947.
65. Gale, C.R.; Robinson, S.M.; Godfrey, K.M.; Law, C.M.; Schlotz, W.; O'Callaghan, F.J. Oily fish intake during pregnancy—association with lower hyperactivity but not with higher full-scale IQ in offspring. *J Child Psychol Psychiatry.* 2008, 49(10), 1061-8, DOI: 10.1111/j.1469-7610.2008.01908.x.
66. Jacobson, J.L.; Jacobson, S.W.; Muckle, G.; Kaplan-Estrin, M.; Ayotte, P.; Dewailly, E. Beneficial effects of a polyunsaturated fatty acid on infant development: evidence from the inuit of arctic Quebec. *J. Pediatrics* 2008, 152(3), 356-64, DOI: 10.1016/j.jpeds.2007.07.008.
67. Krabbendam, L.; Bakker, E.; Hornstra, G.; van Os, J. Relationship between DHA status at birth and child problem behaviour at 7 years of age. *Prostaglandins Leukot Essent FA* 2007, 76(1), 29-34, DOI: 10.1016/j.plefa.2006.09.004.
68. Steer, C.D.; Lattka, E.; Koletzko. B.; Golding, J.; Hibbeln, J.R. Maternal fatty acids in pregnancy, FADS polymorphisms, and child intelligence quotient at 8 y of age. *Am J Clin Nutr*. 2013, 98(6), 1575-82, DOI: 10.3945/ajcn.112.051524.
69. Valent, F.; Mariuz, M.; Bin, M.; Little, D.; Mazej, D.; Tognin, V.; et al. Associations of prenatal mercury exposure from maternal fish consumption and polyunsaturated fatty acids with child neurodevelopment: a prospective cohort study in Italy. *J Epidemiol.* 2013, 23(5), 360-70, DOI: 10.2188/jea.JE20120168.
70. Bernard, J.Y.; De Agostini, M.; Forhan, A.; de Lauzon-Guillain, B.; Charles, M.A.; Heude. B. The dietary n6:n3 fatty acid ratio during pregnancy is inversely associated with child neurodevelopment in the EDEN mother-child cohort. *J Nutrition* 2013, 143(9), 1481-8, DOI: 10.3945/jn.113.178640.
71. Mulder, K.A.; King, D.J.; Innis, S.M. Omega-3 fatty acid deficiency in infants before birth identified using a randomized trial of maternal DHA supplementation in pregnancy. *PloS one* 2014, 9(1), e83764, DOI: 10.1371/journal.pone.0083764.
72. Gustafson, K.M.; Carlson, S.E.; Colombo, J.; Yeh, H.W.; Shaddy, D.J.; Li, S.; et al. Effects of docosahexaenoic acid supplementation during pregnancy on fetal heart rate and variability: a randomized clinical trial. *Prostaglandins Leukot Essent FA* 2013, 88(5), 331-8, DOI: 10.1016/j.plefa.2013.01.009.

73. Judge, M.P.; Harel, O.; Lammi-Keefe, C.J. Maternal consumption of a docosahexaenoic acid-containing functional food during pregnancy: benefit for infant performance on problem-solving but not on recognition memory tasks at age 9 mo. *Am J Clin Nutr*. 2007, 85(6), 1572-7, DOI: 10.1093/ajcn/85.6.1572.
74. Makrides, M.; Gibson, R.A.; McPhee, A.J.; Yelland, L.; Quinlivan, J.; Ryan, P. Effect of DHA supplementation during pregnancy on maternal depression and neurodevelopment of young children: a randomized controlled trial. *JAMA* 2010, 304(15), 1675-83, DOI: 10.1001/jama.2010.1507.
75. Escolano-Margarit, M.V.; Ramos, R.; Beyer, J.; Csabi, G.; Parrilla-Roure, M.; Cruz, F.; et al. The Prenatal DHA status and neurological outcome in children at age 5.5 years are positively associated. J. *Nutrition* 2011, 141(6), 1216-23, DOI: 10.3945/jn.110.129635.
76. Campoy, C.; Escolano-Margarit, M.V.; Ramos, R.; Parrilla-Roure, M.; Csabi, G.; Beyer, J.; et al. Effects of prenatal fish-oil and 5-methyltetrahydrofolate supplementation on cognitive development of children at 6.5 y of age. *Am J Clin Nutr*. 2011, 94 (Suppl 6), 1880s-8s, DOI: 10.3945/ajcn.110.001107.
77. Meldrum, S.; Dunstan, J.A.; Foster, J.K.; Simmer, K.; Prescott, S.L. Maternal fish oil supplementation in pregnancy: a 12 year follow-up of a randomised controlled trial. *Nutrients* 2015, 7(3), 2061-7, DOI: 10.3390/nu7032061.
78. Makrides, M.; Gould, J.F.; Gawlik, N.R.; Yelland, L.N.; Smithers, L.G.; Anderson, P.J.; et al. Four-year follow-up of children born to women in a randomized trial of prenatal DHA supplementation. *JAMA* 2014, 311(17), 1802-4, DOI: 10.1001/jama.2014.2194.
79. Gould, J.F.; Smithers, L.G.; Makrides, M. The effect of maternal omega-3 (n-3) LCPUFA supplementation during pregnancy on early childhood cognitive and visual development: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr*. 2013, 97(3), 531-44, DOI: 10.3945/ajcn.112.045781.
80. Newberry, S.J.; Chung, M.; Booth, M.; et al. Omega-3 fatty acids and maternal and child health: An updated systematic review. *Ag Healthcare Res and Quality (US)* 2016; 224, 16(17)-E003-EF, DOI: 10.23970/AHRQEPCERTA224.
81. Ramakrishnan, U.; Stinger, A.; DiGirolamo, A.M.; Martorell, R.; Neufeld, L.M.; Rivera, J.A.; et al. Prenatal Docosahexaenoic Acid Supplementation and Offspring Development at 18 Months: Randomized Controlled Trial. *PloS one* 2015, 10(8), e0120065, DOI: 10.1371/journal.pone.0120065.
82. van Goor, S.A.; Dijck-Brouwer, D.A.; Erwich, J.J.; Schaafsma, A.; Hadders-Algra, M. The influence of supplemental docosahexaenoic and arachidonic acids during pregnancy and lactation on neurodevelopment at eighteen months. *Prostaglandins Leukot Essent FA* 2011, 84(5-6), 139-46, DOI: 10.1016/j.plefa.2011.01.002.
83. Hurtado, J.A.; Iznaola, C.; Pena, M.; Ruiz, J.; Pena-Quintana, L.; Kajarabille, N.; et al. Effects of Maternal Omega-3 Supplementation on Fatty Acids and on visual and Cognitive Development. *J Pediatr Gastroenterol Nutr.* 2015, 61(4), 472-80, DOI: 10.1097/MPG.0000000000000864.
84. Gould, J.F.; Treyvaud, K.; Yelland, L.N.; Anderson, P.J.; Smithers, L.G.; McPhee, A.J.; et al. Seven-Year Follow-up of Children Born to Women in a Randomized Trial of Prenatal DHA Supplementation. *JAMA* 2017, 317(11), 1173-5, DOI: 10.1001/jama.2016.21303.
85. Gould, J.F.; Anderson, A.J.; Yelland, L.N.; Gibson, R.A.; Makrides, M. Maternal characteristics influence response to DHA during pregnancy. *Prostaglandins Leukot Essent FA* 2016, 108, 5-12, DOI: 10.1016/j.plefa.2016.03.011.
86. Ostadrahimi, A.; Salehi-Pourmehr, H.; Mohammad-Alizadeh-Charandabi, S.; Heidarabady, S.; Farshbaf-Khalili, A. The effect of perinatal fish oil supplementation on neurodevelopment and growth of infants: a randomized controlled trial. *Eur J Nutr.* 2017, DOI: 10.1007/s00394-017-1512-1.
87. Harslof, L.B.; Larsen, L.H.; Ritz, C.; Hellgren, L.I.; Michaelsen, K.F.; Vogel, U.; et al. FADS genotype and diet are important determinants of DHA status: a cross-sectional study in Danish infants. *Am J Clin Nutr*. 2013, 97(6), 1403-10, DOI: 10.3945/ajcn.113.058685.
88. Belfort, M.B.; Rifas-Shiman, S.L.; Kleinman, K.P.; Guthrie, L.B.; Bellinger, D.C.; Taveras, E.M.; et al. Infant feeding and childhood cognition at ages 3 and 7 years: Effects of breastfeeding duration and exclusivity. *JAMA Pediatr.* 2013, 167(9), 836-44, DOI: doi:10.1001/jamapediatrics.2013.455.
89. Quigley, M.A.; Hockley, C.; Carson, C.; Kelly, Y.; Renfrew, M.J.; Sacker, A. Breastfeeding is associated with improved child cognitive development: a population-based cohort study. *J Pediatr.* 2012, 160(1), 25-32, DOI: 10.1016/j.jpeds.2011.06.035.

90. Whitehouse, A.J.; Robinson, M.; Li, J.; Oddy, W.H. Duration of breast feeding and language ability in middle childhood. *Paediatr Perinat Epidemiol.* 2011, 25(1), 44-52, DOI: 10.1111/j.1365-3016.2010.01161.x.
91. Oddy, W.H.; Kendall, G.E.; Li, J.; Jacoby, P.; Robinson, M.; de Klerk, N.H.; et al. The long-term effects of breastfeeding on child and adolescent mental health: a pregnancy cohort study followed for 14 years. *J Pediatr.* 2010, 156(4), 568-74, DOI: 10.1016/j.jpeds.2009.10.020.
92. Hayatbakhsh, M.R.; O'Callaghan, M.J.; Bor, W.; Williams, G.M.; Najman, J.M. Association of breastfeeding and adolescents' psychopathology: a large prospective study. *Breastfeed Med.* 2012, 7(6), 480-6, DOI: 10.1089/bfm.2011.0136.
93. Kramer, M.S.; Fombonne, E., Igumnov, S.; Vanilovich, I., Matush, L.; Mironova, E.; et al. Effects of prolonged and exclusive breastfeeding on child behavior and maternal adjustment: evidence from a large, randomized trial. *Pediatrics* 2008, 121(3), e435-40, DOI: 10.1542/peds.2007-1248.
94. Belfort, M.B.; Rifas-Shiman, S.L.; Kleinman, K.P.; Bellinger, D.C.; Harris, M.H.; Taveras, E.M.; et al. Infant Breastfeeding Duration and Mid-Childhood Executive Function, Behavior, and Social-Emotional Development. *J Dev Behav Pediatr.* 2016, 37(1), 43-52, DOI: 10.1097/DBP.0000000000000237.
95. Girard, L.C.; Doyle, O.; Tremblay, R.E. Breastfeeding, Cognitive and Noncognitive Development in Early Childhood: A Population Study. *Pediatrics* 2017, 139(4), DOI: 10.1542/peds.2016-1848.
96. Gale, C.R.; Marriott, L.D.; Martyn, C.N.; Limond, J.; Inskip, H.M.; Godfrey, K.M.; et al. Breastfeeding, the use of docosahexaenoic acid-fortified formulas in infancy and neuropsychological function in childhood. *Arch Dis Child.* 2010, 95(3), 174-9, DOI: 10.1136/adc.2009.165050.
97. Bernard, J.Y.; Armand, M.; Peyre, H.; Garcia, C.; Forhan, A.; De Agostini, M.; et al. Breastfeeding, Polyunsaturated Fatty Acid Levels in Colostrum and Child Intelligence Quotient at Age 5-6 Years. *J Pediatr.* 2017, 183, 43-50.e3, DOI: 10.1016/j.jpeds.2016.12.039.
98. Lind, J.N.; Li, R.; Perrine, C.G.; Schieve, L.A. Breastfeeding and later psychosocial development of children at 6 years of age. *Pediatrics* 2014, 134 (Suppl 1), S36-41, DOI: 10.1542/peds.2014-0646G.
99. Lapillonne, A.; Groh-Wargo, S.; Gonzalez, C.H.; Uauy, R. Lipid needs of preterm infants: updated recommendations. *J. Pediatr.* 2013, 162 (Suppl 3), S37-47, DOI: 10.1016/j.jpeds.2012.11.052.
100. Drover, J.R.; Hoffman, D.R.; Castaneda, Y.S.; Morale, S.E.; Garfield, S.; Wheaton, D.H.; et al. Cognitive function in 18-month-old term infants of the DIAMOND study: a randomized, controlled clinical trial with multiple dietary levels of docosahexaenoic acid. *Early Hum Dev.* 2011, 87(3), 223-30, DOI: 10.1016/j.earlhumdev.2010.12.047.
101. Willatts, P.; Forsyth, S.; Agostoni, C.; Casaer, P.; Riva, E.; Boehm, G. Effects of long-chain PUFA supplementation in infant formula on cognitive function in later childhood. *Am J Clin Nutr.* 2013, 98(2), 536S-42S, DOI: 10.3945/ajcn.112.038612.
102. Colombo, J.; Carlson, S.E.; Cheatham, C.L.; Shaddy, D.J.; Kerling, E.H.; Thodosoff, J.M.; et al. Long-term effects of LCPUFA supplementation on childhood cognitive outcomes. *Am J Clin Nutr.* 2013, 98(2), 403-12, DOI: 10.3945/ajcn.112.040766.
103. Colombo, J.; Carlson, S.E.; Cheatham, C.L.; Fitzgerald-Gustafson, K.M.; Kepler, A.; Doty, T. Long-chain polyunsaturated fatty acid supplementation in infancy reduces heart rate and positively affects distribution of attention. *Pediatr Res* 2011, 70, 406–10, DOI: 10.1203/PDR.0b013e31822a59f5.
104. Birch, E.E.; Garfield, S.; Castaneda, Y.; Hughbanks-Wheaton, D.; Uauy, R.; Hoffman, D. Visual acuity and cognitive outcomes at 4 years of age in a double-blind, randomized trial of long-chain polyunsaturated fatty acid-supplemented infant formula. *Early Hum Dev.* 2007, 83(5), 279-84, DOI: 10.1016/j.earlhumdev.2006.11.003.
105. Pivik, R.T.; Dykman, R.A.; Jing, H.; Gilchrist, J.M.; Badger, T.M. Early infant diet and the omega 3 fatty acid DHA: effects on resting cardiovascular activity and behavioral development during the first half-year of life. *Dev Neuropsychol.* 2009, 34(2), 139-58, DOI: 10.1080/87565640802646726.
106. de Jong, C.; Kikkert, H.K.; Fidler, V.; Hadders-Algra, M. The Groningen LCPUFA study: no effect of postnatal long-chain polyunsaturated fatty acids in healthy term infants on neurological condition at 9 years. *Br J Nutr.* 2010, 104(4), 566-72, DOI: 10.1017/S0007114510000863.
107. Constable, R.T.; Ment, L.R.; Vohr, B.R.; Kesler, S.R.; Fulbright, R.K.; Lacadie, C.; et al. Prematurely born children demonstrate white matter microstructural differences at 12 years of age, relative to term control subjects: an investigation of group and gender effects. *Pediatrics* 2008, 121(2), 306-16, DOI: doi: 10.1542/peds.2007-0414.

108. Tam, E.W.; Chau, V.; Barkovich, A.J.; Ferriero, D.M.; Miller, S.P.; Rogers, E.E.; et al. Early postnatal docosahexaenoic acid levels and improved preterm brain development. *Pediatr. Res.* 2016, 79(5), 723-30, DOI: doi: 10.1038/pr.2016.11.
109. McNamara, R.K.; Vannest, J.J.; Valentine, C.J. Role of perinatal long-chain omega-3 fatty acids in cortical circuit maturation: Mechanisms and implications for psychopathology. *World J Psychiatry* 2015, 5(1), 15-34, DOI: 10.5498/wjp.v5.i1.15.
110. Henriksen, C.; Haugholt, K.; Lindgren, M.; Aurvag, A.K.; Ronnestad, A.; Gronn, M.; et al. Improved cognitive development among preterm infants attributable to early supplementation of human milk with docosahexaenoic acid and arachidonic acid. *Pediatrics* 2008, 121(6), 1137-45, DOI: 10.1542/peds.2007-1511.
111. Makrides, M.; Gibson, R.A.; McPhee, A.J.; Collins, C.T.; Davis, P.G.; Doyle, L.W.; et al. Neurodevelopmental outcomes of preterm infants fed high-dose docosahexaenoic acid: a randomized controlled trial. *JAMA* 2009, 301(2), 175-82, DOI: 10.1001/jama.2008.945.
112. Smithers, L.G.; Gibson, R.A.; McPhee, A.; Makrides, M. Higher dose of docosahexaenoic acid in the neonatal period improves visual acuity of preterm infants: results of a randomized controlled trial. *Am J Clin Nutr.* 2008, 88(4), 1049-56, DOI: 10.1093/ajcn/88.4.1049.
113. Westerberg, A.C.; Schei, R.; Henriksen, C.; Smith, L.; Veierod, M.B.; Drevon, C.A.; et al. Attention among very low birth weight infants following early supplementation with docosahexaenoic and arachidonic acid. *Acta Paediatr.* 2011, 100(1), 47-52, DOI: 10.1111/j.1651-2227.2010.01946.x.
114. Almaas, A.N.; Tamnes, C.K.; Nakstad, B.; Henriksen, C.; Walhovd, K.B.; Fjell, A.M.; et al. Long-chain polyunsaturated fatty acids and cognition in VLBW infants at 8 years: an RCT. *Pediatrics* 2015, 135(6), 972-80, DOI: 10.1542/peds.2014-4094.
115. Isaacs, E.B.; Ross, S.; Kennedy, K.; Weaver, L.T.; Lucas, A.; Fewtrell, M.S. 10-year cognition in preterms after random assignment to fatty acid supplementation in infancy. *Pediatrics* 2011, 128(4), e890-8, DOI: 10.1542/peds.2010-3153.
116. Smithers, L.G.; Collins, C.T.; Simmonds, L.A.; Gibson, R.A.; McPhee, A.; Makrides, M. Feeding preterm infants milk with a higher dose of docosahexaenoic acid than that used in current practice does not influence language or behavior in early childhood: a follow-up study of a randomized controlled trial. *Am J Clin Nutr.* 2010, 91(3), 628-34, DOI: 10.3945/ajcn.2009.28603.
117. Collins, C.T.; Gibson, R.A.; Anderson, P.J.; McPhee, A.J.; Sullivan, T.R.; Gould, J.F.; et al. Neurodevelopmental outcomes at 7 years' corrected age in preterm infants who were fed high-dose docosahexaenoic acid to term equivalent: a follow-up of a randomised controlled trial. *BMJ open* 2015, 5(3), e007314, DOI: 10.1136/bmjopen-2014-007314.
118. Molloy, C.S.; Stokes, S.; Makrides, M.; Collins, C.T.; Anderson, P.J.; Doyle, L.W. Long-term effect of high-dose supplementation with DHA on visual function at school age in children born at <33 wk gestational age: results from a follow-up of a randomized controlled trial. *Am J Clin Nutr.* 2016, 103(1), 268-75, DOI: 10.3945/ajcn.115.114710.
119. Schulzke, S.M.; Patole, S.K.; Simmer, K. Long-chain polyunsaturated fatty acid supplementation in preterm infants. *Cochrane Database Syst Rev.* 2011, (2), CD000375, DOI: 10.1002/14651858.CD000375.pub4.
120. Simmer, K. Long-chain polyunsaturated fatty acid supplementation in infants born at term. The *Cochrane Database Syst Rev.* 2011, (12), CD000376, DOI: 10.1002/14651858.CD000376.pub3.
121. Qawasmi, A.; Landeros-Weisenberger, A.; Leckman, J.F.; Bloch, M.H. Meta-analysis of long-chain polyunsaturated fatty acid supplementation of formula and infant cognition. *Pediatrics* 2012, 129(6), 1141-9, DOI: 10.1542/peds.2011-2127.
122. Koletzko, B.; Lien, E.; Agostoni, C.; Bohles, H., Campoy, C.; Cetin, I., et al. The roles of long-chain polyunsaturated fatty acids in pregnancy, lactation and infancy: review of current knowledge and consensus recommendations. *J Perinat Med.* 2008, 36(1):5-14, DOI: 10.1515/JPM.2008.001.
123. Parellada, M.; Llorente, C.; Calvo, R.; Gutierrez, S.; Lazaro, L.; Graell, M.; et al. Randomized trial of omega-3 for autism spectrum disorders: Effect on cell membrane composition and behavior. *Eur Neuropsychopharmacol.* 2017, 27(12), 1319-1330, DOI: 10.1016/j.euroneuro.2017.08.426.
124. Parletta, N.; Niyonsenga, T.; Duff, J. Omega-3 and Omega-6 Polyunsaturated Fatty Acid Levels and Correlations with Symptoms in Children with Attention Deficit Hyperactivity Disorder, Autistic Spectrum Disorder and Typically Developing Controls. *PloS one* 2016, 11(5), e0156432, DOI: 10.1371/journal.pone.0156432.

125. Das, U.N. Nutritional factors in the pathobiology of autism. *Nutrition* 2013, 29(7-8), 1066-9, DOI: 10.1016/j.nut.2012.11.013.

126. McNamara, R.K.; Asch, R.H.; Lindquist, D.M.; Krikorian, R. Role of polyunsaturated fatty acids in human brain structure and function across the lifespan: An update on neuroimaging findings. *Prostaglandins Leukot Essent FA* 2017, pii: S0952-3278(16)30219-8, DOI: 10.1016/j.plefa.2017.05.001.
127. Delorme, R.; Ey, E.; Toro, R.; Leboyer, M.; Gillberg, C.; Bourgeron, T. Progress toward treatments for synaptic defects in autism. *Nat. Med.* 2013, 19(6), 685-94, DOI: 10.1038/nm.3193.
128. Ebert, D.H.; Greenberg, M.E. Activity-dependent neuronal signalling and autism spectrum disorder. *Nature* 2013, 493(7432), 327-37, DOI: 10.1038/nature11860.
129. Durand, T.; De Felice, C.; Signorini, C.; Oger, C.; Bultel-Ponce, V.; Guy, A.; et al. F(2)-Dihomo-isoprostanes and brain white matter damage in stage 1 Rett syndrome. *Biochimie.* 2013, 95(1), 86-90, DOI: 10.1016/j.biochi.2012.09.017.
130. Lukiw, W.J.; Bazan, N.G. Docosahexaenoic acid and the aging brain. *J. Nutr.* 2008, 138(12), 2510-4, DOI: 10.3945/jn.108.096016.
131. Taurines, R.; Segura, M.; Schecklmann, M.; Albantakis, L.; Grunblatt, E.; Walitza, S; et al. Altered peripheral BDNF mRNA expression and BDNF protein concentrations in blood of children and adolescents with autism spectrum disorder. *J. Neural. Transm*. 2014, 121(9), 1117-28, DOI: 10.1007/s00702-014-1162-x.
132. Wu, A.; Ying, Z.; Gomez-Pinilla, F. The salutary effects of DHA dietary supplementation on cognition, neuroplasticity, and membrane homeostasis after brain trauma. *J. Neurotrauma.* 2011, 28(10), 2113-22, DOI: 10.1089/neu.2011.1872.
133. Hamazaki, T.; Hamazaki, K. Fish oils and aggression or hostility. *Prog Lipid Res.* 2008, 47(4), 221-32, DOI: 10.1016/j.plipres.2008.02.001.
134. Moreira, J.D.; Knorr, L.; Ganzella, M.; Thomazi, A.P.; de Souza, C.G.; de Souza, D.G.; Pitta, C.F.; Mello e Souza, T.; Wofchuk, S.; Elisabetsky, E.; et al. Omega-3 fatty acids deprivation affects ontogeny of glutamatergic synapses in rats: Relevance for behavior alterations. *Neurochem. Int.* 2010, 56, 753–759, DOI: 10.1016/j.neuint.2010.02.010.
135. Kodas, E.; Galineau, L.; Bodard, S.; Vancassel, S.; Guilloteau, D.; Besnard, J.C.; Chalon, S. Serotoninergic neurotransmission is affected by n-3 polyunsaturated fatty acids in the rat. *J. Neurochem.* 2004, 89, 695–702, DOI: 10.1111/j.1471-4159.2004.02401.x.
136. Zimmer, L.; Hembert, S.; Durand, G.; Breton, P.; Guilloteau, D.; Besnard, J.C.; Chalon, S. Chronic n-3 polyunsaturated fatty acid diet-deficiency acts on dopamine metabolism in the rat frontal cortex: A microdialysis study. *Neurosci. Lett.* 1998, 240, 177–181, DOI: 10.1016/S0304-3940(97)00938-5.
137. Kim, H.-Y.; Spector, A.A.; Xiong, Z.-M. A synaptogenic amide N-docosahexaenoylethanolamide promotes hippocampal development. *Prostaglandins Other Lipid Mediat.* 2011, 96, 114–120, DOI: 10.1016/j.prostaglandins.2011.07.002.
138. Pardo, C.A.; Eberhart, C.G. The neurobiology of autism. *Brain Pathol.* 2007, 17(4), 434-47, DOI: 10.1111/j.1750-3639.2007.00102.x.
139. Weiser, M.J.; Mucha, B.; Denheyer, H.; Atkinson, D.; Schanz, N.; Vassiliou, E.; et al. Dietary docosahexaenoic acid alleviates autistic-like behaviors resulting from maternal immune activation in mice. *Prostaglandins Leukot Essent FA* 2016, 106, 27-3, DOI: 10.1016/j.plefa.2015.10.005.
140. Careaga, M.; Van de Water, J.; Ashwood, P. Immune dysfunction in autism: a pathway to treatment. *Neurotherapeutics* 2010, 7(3), 283-92, DOI: 10.1016/j.nurt.2010.05.003.
141. Onore, C.E.; Careaga, M.; Babineau, B.A.; Schwartzer, J.J.; Berman, R.F.; Ashwood, P. Inflammatory macrophage phenotype in BTBR T+tf/J mice. *Front Neurosci.* 2013, 7, 158, DOI: 10.3389/fnins.2013.00158.
142. Gibson, D.L.; Gill, S.K.; Brown, K.; Tasnim, N.; Ghosh, S.; Innis, S.; et al. Maternal exposure to fish oil primes offspring to harbor intestinal pathobionts associated with altered immune cell balance. *Gut Microbes.* 2015, 6(1), 24-32, DOI: 10.1080/19490976.2014.997610.
143. Wall, R.; Marques, T.M.; O'Sullivan, O.; Ross, R.P.; Shanahan, F.; Quigley, E.M.; et al. Contrasting effects of Bifidobacterium breve NCIMB 702258 and Bifidobacterium breve DPC 6330 on the composition of murine brain fatty acids and gut microbiota. *Am J Clin Nutr.* 2012, 95(5), 1278-87, DOI: 10.3945/ajcn.111.026435.

144. Stevens, L.J.; Zentall, S.S.; Deck, J.L.; Abate, M.L.; Watkins, B.A.; Lipp, S.R.; et al. Essential fatty acid metabolism in boys with attention-deficit hyperactivity disorder. *Am J Clin Nutr.* 1995, 62(4), 761-8, DOI: 10.1093/ajcn/62.4.761.
145. Chang, J.C.; Su, K.P.; Mondelli, V.; Pariante, C.M. Omega-3 Polyunsaturated Fatty Acids in Youths with Attention Deficit Hyperactivity Disorder (ADHD): A Systematic Review and Meta-Analysis of Clinical Trials and Biological Studies. *Neuropsychopharma.* 2018, 43(3), 534-545, DOI: 10.1038/npp.2017.160.
146. Sun, Q.; Ma, J.; Campos, H.; Hankinson, S.E.; Hu, F.B. Comparison between plasma and erythrocyte fatty acid content as biomarkers of fatty acid intake in US women. *Am J Clin Nutr.* 2007, 86(1), 74-81, DOI: 10.1093/ajcn/86.1.74.
147. Zimmer, L.; Vancassel, S.; Cantagrel, S.; Breton, P.; Delamanche, S.; Guilloteau, D.; et al. The dopamine mesocorticolimbic pathway is affected by deficiency in n-3 polyunsaturated fatty acids. *Am J Clin Nutr.* 2002, 75(4), 662-7, DOI: 10.1093/ajcn/75.4.662.
148. Hariri, M.; Djazayery, A.; Djalali, M.; Saedisomeolia, A.; Rahimi, A.; Abdolahian, E. Effect of n-3 supplementation on hyperactivity, oxidative stress and inflammatory mediators in children with attention-deficit-hyperactivity disorder. *Malays J Nutr.* 2012, 18(3), 329-35, PMID: 24568073.
149. Liu, J.J.; Galfalvy, H.C.; Cooper, T.B.; Oquendo, M.A.; Grunebaum, M.F.; Mann, J.J.; et al. Omega-3 polyunsaturated fatty acid (PUFA) status in major depressive disorder with comorbid anxiety disorders. *J Clin Psychiatry* 2013, 74(7), 732-8, DOI: 10.4088/JCP.12m07970.
150. Jacka, F.N.; Maes, M.; Pasco, J.A.; Williams, L.J.; Berk, M. Nutrient intakes and the common mental disorders in women. *J Affect Disord.* 2012, 141(1), 79-85, DOI: 10.1016/j.jad.2012.02.018.
151. Julvez, J.; Mendez, M.; Fernandez-Barres, S.; Romaguera, D.; Vioque, J.; Llop, S.; et al. Maternal Consumption of Seafood in Pregnancy and Child Neuropsychological Development: A Longitudinal Study Based on a Population With High Consumption Levels. *Am J Epidemiol.* 2016, 183(3), 169-82, DOI: 10.1093/aje/kwv195.
152. Lyall, K.; Munger, K.L.; O'Reilly, E.J.; Santangelo, S.L.; Ascherio, A. Maternal dietary fat intake in association with autism spectrum disorders. *Am J Epidemiol.* 2013, 178(2), 209-20, DOI: 10.1093/aje/kws433.
153. Steenweg-de Graaff, J.; Tiemeier, H.; Ghassabian, A.; Rijlaarsdam, J.; Jaddoe, V.W.; Verhulst, F.C.; et al. Maternal Fatty Acid Status During Pregnancy and Child Autistic Traits: The Generation R Study. *Am J Epidemiol.* 2016, 183(9), 792-9, DOI: 10.1093/aje/kwv263.
154. Gao, L.; Cui, S.S.; Han, Y.; Dai, W.; Su, Y.Y.; Zhang, X. Does Periconceptional Fish Consumption by Parents Affect the Incidence of Autism Spectrum Disorder and Intelligence Deficiency? A Case-control Study in Tianjin, China. *Biomed Environ Sci.* 2016, 29(12), 885-892, DOI: 10.3967/bes2016.118.
155. Al-Farsi, Y.M.; Waly, M.I.; Deth, R.C.; Al-Sharbati, M.M.; Al-Shafaee, M.; Al-Farsi, O.; et al. Impact of nutrition on serum levels of docosahexaenoic acid among Omani children with autism. *Nutrition* 2013, 29(9), 1142-6, DOI: 10.1016/j.nut.2013.03.009.
156. Schultz, S.T.; Klonoff-Cohen, H.S.; Wingard, D.L.; Akshoomoff, N.A.; Macera, C.A.; Ji, M.; et al. Breastfeeding, infant formula supplementation, and Autistic Disorder: the results of a parent survey. *Int Breastfeed J.* 2006, 1, 16, DOI: 10.1186/1746-4358-1-16.
157. Al-Farsi, Y.M.; Al-Sharbati, M.M.; Waly, M.I.; Al-Farsi, O.A.; Al-Shafaee, M.A.; Al-Khaduri, M.M.; et al. Effect of suboptimal breast-feeding on occurrence of autism: a case-control study. *Nutrition* 2012, 28(7-8), e27-32, DOI: 10.1016/j.nut.2012.01.007.
158. Shafai, T.; Mustafa, M.; Hild, T.; Mulari, J.; Curtis, A. The association of early weaning and formula feeding with autism spectrum disorders. *Breastfeed Med.* 2014, 9(5), 275-6, DOI: 10.1089/bfm.2013.0104.
159. Boucher, O.; Julvez, J.; Guxens, M.; Arranz, E.; Ibarluzea, J.; Sanchez de Miguel, M.; et al. Association between breastfeeding duration and cognitive development, autistic traits and ADHD symptoms: a multicenter study in Spain. *Pediatr Res.* 2017, 81(3), 434-442, DOI: 10.1038/pr.2016.238.
160. Julvez, J.; Ribas-Fito, N.; Forns, M.; Garcia-Esteban, R.; Torrent, M.; Sunyer, J. Attention behaviour and hyperactivity at age 4 and duration of breast-feeding. *Acta Paediatr.* 2007, 96(6), 842-7. 10.1111/j.1651-2227.2007.00273.x
161. Husk, J.S.; Keim, S.A. Breastfeeding and Autism Spectrum Disorder in the National Survey of Children's Health. *Epidemiology* 2015, 26(4), 451-7, DOI: 10.1097/EDE.0000000000000290.

162. Tseng, P.T.; Chen, Y.W.; Stubbs. B.; Carvalho, A.F.; Whiteley, P.; Tang, C.H.; et al. Maternal breastfeeding and autism spectrum disorder in children: A systematic review and meta-analysis. *Nutr Neurosci.* 2017, 1-9, DOI: 10.1080/1028415X.2017.1388598.
163. Kannass, K.N.; Colombo, J.; Carlson, S.E. Maternal DHA levels and toddler free-play attention. *Dev Neuropsychol.* 2009, 34(2), 159-74, DOI: 10.1080/87565640802646734.
164. Kohlboeck, G.; Glaser, C.; Tiesler, C.; Demmelmair, H.; Standl, M.; Romanos, M.; et al. Effect of fatty acid status in cord blood serum on children's behavioral difficulties at 10 y of age: results from the LISAplus Study. *Am J Clin Nutr.* 2011, 94(6), 1592-9, DOI: 10.3945/ajcn.111.015800.
165. Sagiv, S.K.; Thurston, S.W.; Bellinger, D.C.; Amarasiriwardena, C.; Korrick, S.A. Prenatal exposure to mercury and fish consumption during pregnancy and attention-deficit/hyperactivity disorder-related behavior in children. *Arch Pediatr Adolesc Med.* 2012, 166(12), 1123-31, DOI: 10.1001/archpediatrics.2012.1286.
166. Jensen, C.L.; Voigt, R.G.; Llorente, A.M.; Peters, S.U.; Prager, T.C.; Zou, Y.L.; et al. Effects of early maternal docosahexaenoic acid intake on neuropsychological status and visual acuity at five years of age of breast-fed term infants. *J Pediatr.* 2010, 157(6), 900-5, DOI: 10.1016/j.jpeds.2010.06.006.
167. Ramakrishnan, U.; Gonzalez-Casanova, I.; Schnaas, L.; DiGirolamo, A.; Quezada, A.D.; Pallo, B.C.; et al. Prenatal supplementation with DHA improves attention at 5 y of age: a randomized controlled trial. *Am J Clin Nutr.* 2016, 104(4), 1075-1082, DOI: 10.3945/ajcn.114.101071.
168. Gould, J.F.; Makrides, M.; Colombo, J.; Smithers, L.G. Randomized controlled trial of maternal omega-3 long-chain PUFA supplementation during pregnancy and early childhood development of attention, working memory, and inhibitory control. *Am J Clin Nutr.* 2014, 99(4), 851-9, DOI: 10.3945/ajcn.113.069203.
169. Mimouni-Bloch, A.; Kachevanskaya, A.; Mimouni, F.B.; Shuper, A.; Raveh, E.; Linder, N. Breastfeeding may protect from developing attention-deficit/hyperactivity disorder. *Breastfeed Med.* 2013, 8(4), 363-7, DOI: 10.1089/bfm.2012.0145.
170. Groen-Blokhuis, M.M.; Franic, S.; van Beijsterveldt, C.E.; de Geus, E.; Bartels, M.; Davies, G.E.; et al. A prospective study of the effects of breastfeeding and FADS2 polymorphisms on cognition and hyperactivity/attention problems. *Am J Med Genet B Neuropsychiatr Genet.* 2013, 162B(5), 457-65, DOI: 10.1002/ajmg.b.32175.
171. Park, S.; Kim, B.N.; Kim, J.W.; Shin, M.S.; Yoo, H.J.; Cho, S.C. Protective effect of breastfeeding with regard to children's behavioral and cognitive problems. *Nutr J.* 2014, 13(1), 111, DOI: 10.1186/1475-2891-13-111.
172. Stadler, D.D.; Musser, E.D.; Holton, K.F.; Shannon, J.; Nigg, J.T. Recalled initiation and duration of maternal breastfeeding among children with and without ADHD in a well characterized case-control sample. *J Abnorm Child Psychol.* 2016, 44(2), 347-355, DOI:10.1007/s10802-015-9987-9.
173. Eating Fish: What Pregnant Women and Parents Should Know [FDA - U.S. Food and Drug Administration]. Available online: https://www.fda.gov/Food/ResourcesForYou/Consumers/ucm393070.htm (accessed on 10 February 2017).
174. Choose Fish and Shellfish Wisely [EPA - United States Environmental Protection Agency]. Available online: https://www.epa.gov/fish-tech (accessed on 10 February 2017).

Supplementary Materials

Table S1: Observational studies addressing the impact of maternal prenatal fish/DHA intake and breastfeeding in the offspring neurodevelopmental outcomes

Author	N	PUFAs measure (time; biological samples)	Food intake assessment	Neurodevelopment assessment (years)	Results
Bernard et al. 2017 [97]	1080 mother-child pairs (very preterm infants excluded)	Lactating mothers; colostrum	Breastfeeding - mothers' questionnaire	WPPSI-III at 5-6 y	Longer breastfeeding duration associated with higher verbal IQ, but not with total and performance IQ. Exposure to colostrum high in LA and low in DHA associated with lower IQ (compared to colostrum high in DHA or low in LA and DHA).
Girard et al. 2017 [95]	7478 mother-child pairs (full-term infants)	--	Breastfeeding - mothers' questionnaire	BAS: Pictures similarities scale and Naming vocabulary scale; SDQ; at 3 and 5 y	Breastfeeding for ≥6 mo associated with lower child's hyperactivity. No significant differences post-matching on any outcome.
Belfort et al. 2016 [94]	1000 mother-child pairs (preterm and full-term infants)	--	Breastfeeding - mothers' questionnaire	BRIEF; SDQ; in mid-childhood	No association between longer breastfeeding duration, or exclusive breastfeeding, and better executive function, behavior, or social-emotional development in mid-childhood.
Strain et al. 2015 [61]	1265 mother-child pairs (preterm and full-term infants)	28 weeks' gestation; maternal serum	Fish Use Questionnaire	BSID-II MDI and PDI; MacArthur CDI; IBQ-R; at 1.7 y	Higher prenatal DHA levels associated with better child's language function, but with worse mental development. Higher n-6:n-3 ratio associated with poorer social communication and language development. No associations between PUFA status and IBQ-R scores.
Lind al. 2014 [98]	1442 mother-child pairs (preterm and full-term infants)	--	Breastfeeding - mothers' questionnaire	SDQ at 6 y	No associations between breastfeeding for ≥6 mo, and exclusively breastfed for ≥3 mo,

					and better emotional symptoms, conduct problems, and total difficulties, after adjustment.
Belfort et al. 2013 [88]	1312 mother-child pairs (preterm and full-term infants)	--	Breastfeeding - mothers' questionnaire FFQ, 6 mo pp - estimate prenatal fish intake	PPVT-III at 3 y; WRAVMA at 3 and 7 y; KBIT and WRAML at 7 y	Longer duration and exclusivity of breastfeeding associated with better receptive language and verbal and non-verbal IQ, with no changes in visual motor skills and visual memory. Higher benefit on visual motor ability with ≥2 fish times/week.
Steer et al. 2013 [68]	2839 mother-child pairs (preterm and full-term infants)	Throughout pregnancy; mothers' RBCs	--	WISC at 8 y	Low prenatal DHA levels associated with lower IQ.
Bernard et al. 2013 [70]	1335 mother-child pairs (very preterm infants excluded)	--	FFQ, days pp - estimate maternal prenatal PUFA intake	MacArthur CDI at 2 y; ASQ, PMT 5, a test of design copying, and the verbal fluency test; at 3 y	No associations between prenatal DHA intake and neurodevelopment. In never-breastfed children: Higher maternal n-6:n-3 ratio associated with worse CDI, ASQ and verbal fluency scores. In the group of higher prenatal n6:n3 ratio, breastfeeding duration had a stronger positive effect in language domain.
Valent et al. 2013 [69]	606 mother-child pairs (full-term infants)	20-22 or 32 weeks' gestation; maternal serum	FFQ, 1 mo pp - to estimate prenatal fish and PUFA intake.	BSID III at 1.5 y	No associations between prenatal fish intake and child neurodevelopment. No associations between maternal DHA, EPA and total n-3 PUFAs and child neurodevelopment. Higher n-6:n-3 ratio associated with lower language score.
Quigley et al. 2012 [89]	11 879 mother-child pairs (preterm and full-term infants)	--	Breastfeeding - mothers' questionnaire	BAS: Vocabulary, pattern construction and picture similarities subscales; at 5 y	Breastfeeding associated with better cognitive development, mainly in preterm infants.

					Improvements appeared when breastfeeding ≥4-6 mo in term and ≥2 mo in preterm infants.
Hayatbakhsh et al. 2012 [92]	4502 mother-adolescent pairs (preterm and full-term infants)	--	Breastfeeding - mothers' questionnaire	Youth Self Report - CBCL at 14 y	Breastfeeding for ≥4 mo associated with fewer anxiety/depression symptoms, social or attention problems, and aggressive/delinquent behavior.
Whitehouse et al. 2011 [90]	1195 mother-child pairs (full-term infants)	--	Breastfeeding - mothers' questionnaire	PPVT at 10 y	Breastfeeding for ≥6 mo associated with higher language outcomes.
Oddy et al. 2010 [91]	2900 mother-child pairs (preterm and full-term infants)	--	Breastfeeding - mothers' questionnaire	CBCL at 2, 6, 8, 10 and 14 y	Breastfeeding for <6 mo associated with higher mental health problems, including behavior problems, through childhood and into adolescence.
Mendez et al. 2009 [64]	392 mother-child pairs (full-term infants)	--	FFQ, 3 mo pp - estimate prenatal fish intake.	MCSA at 4 y	In children breast-fed for <6 mo, prenatal fish intake >2–3 times/week associated with higher cognitive and motor development (compared to intake of ≤1 times/week). No association between fish >3 times/week and better scores. In children breast-fed for >6 mo, no association between maternal fish intake and development scores.
Oken et al. 2008 [62]	25446 mother-child pairs (preterm and full-term infants)	--	FFQ, 25 weeks' gestation - estimate prenatal fish intake.	Mothers' interview - total, motor, social and cognitive scores at 1.5 y	Higher prenatal fish intake (particularly ≥3 times/week) associated with higher developmental scores. Breastfeeding for >6 mo, particularly >10, associated with higher developmental scores.
Oken et al. 2008 [63]	341 mother-child pairs (preterm and full-term infants)	2nd trimester of pregnancy; mothers' RBCs	FFQ, 2nd trimester of pregnancy - estimate fish, DHA and EPA prenatal intake.	PPVT and WRAVMA at 3 y	Prenatal fish intake >2 times/week, but not below,

					associated with higher language and visual motor skills. No associations between DHA+EPA dietary intake (and RBCs levels) and child cognition.
Gale et al. 2008 [65]	217 mother-child pairs (preterm and full-term infants)	--	FFQ, 15 and 32 weeks' gestation - estimate prenatal fish intake	SDQ and WASI at 9 y	Eat oily fish in early or late pregnancy associated with lower risk of child hyperactivity. Eat fish (oily or not) at ≥1 times/week, in late pregnancy, associated with higher verbal IQ.
Jacobson et al. 2008 [66]	109 mother-child pairs (full-term infants)	At birth; cord and maternal plasma phospholipids. 1 mo pp; total maternal milk lipids	--	TVACT and FTII at 0.5 and 0.92 y; BSID-II at 0.92 y	Higher cord DHA levels associated with longer gestation, better visual acuity, higher scores of novelty preference, and better mental and psychomotor scores. No associations between DHA from maternal milk and neurodevelopmental scores.
Krammer et al. 2008 [93]	13889 mother-child pairs (full-term infants)	--	Breastfeeding - mothers' questionnaire	SDQ Canadian NLSCY at 6.5 y	No association between longer breastfeeding duration, or exclusive breastfeeding, and child social-emotional scores.
Krabbendam et al. 2007 [67]	393 mother-child pairs (preterm and full-term infants)	Late gestation; umbilical venous plasma phospholipids	--	Dutch version of CBCL at 7 y	Higher DHA status at birth associated with lower levels of internalizing problem behavior (not with externalizing problem).
Hibbeln et al. 2007 [60]	11875 mother-child pairs (preterm and full-term infants)	--	FFQ, 32 weeks' gestation - estimate prenatal fish intake.	WISC-III at 8 y; SDQ at 6.75 y; Development questionnaire at 0.5, 1.5, 2.5 and 3.5 y	Low prenatal seafood intake (<340 g or <3 times/week) associated with lower verbal IQ and fine motor ability, less pro-social behavior, and poorer social and communication skills.

Legend: DHA = Docosahexaenoic acid; PUFAs = polyunsaturated fatty acids; Very preterm infants = gestational age <33 weeks; y = years; WPPSI-III = Wechsler Preschool and Primary Scale of Intelligence, Third Edition; IQ = Intelligence Quotient; LA = linoleic acid, an n-6 PUFA; BAS = British Abilities Scale; SDQ = Strengths and Difficulties Questionnaire; mo = months; BRIEF = Behavior Rating Inventory of Executive Function; BSID II = Bayley Scales of Infant Development, Second Edition; MDI = Mental Development Index, in BSID-II; PDI = Psychomotor Developmental Index, in BSID-II; CDI = Communicative Development Inventories; IBQ-R = Infant Behavior Record–Revised; FFQ = Food Frequency Questionnaire; pp = postpartum; PPVT = Peabody Picture Vocabulary Test; WRAVMA = Wide-Range Assessment of Visual Motor Abilities; KBIT = Kaufman Brief Intelligence Test; WRAML = Wide Range Assessment of Memory and Learning; RBCs = Red Blood Cells; WISC = Wechsler Intelligence Scale for Children; ASQ = Ages and Stages Questionnaire; PMT = Peg Moving Task;

BSID-III = Bayley Scales of Infant and Toddler Development, Third Edition; EPA = Eicosapentaenoic acid; CBCL = Child Behavior Checklist; MCSA = McCarthy Scales of Children's Abilities; WASI = Wechsler Abbreviated Scale of Intelligence; TVACT = Teller Visual Acuity Card Test; FTII = Fagan Test of Infant Intelligence; NLSCY = National Longitudinal Survey of Children and Youth.

Supplementary Materials

Table S2: RCTs studies addressing the impact of maternal DHA supplementation during pregnancy and offspring neurodevelopmental outcomes

Author	N	Supplementation Type; dose (daily)	Supplementation Weeks (mean)	Neurodevelopment assessment (years)	Results
Ostadrahimi et al. 2017 [86]	150 Preterm and full-term	120 mg DHA + 180 mg EPA	24 weeks (20 weeks' gestation - 1 mo pp)	ASQ at 0.3 and 0.5 y	Supplementation associated only with higher communication skills at 0.3 y.
Gould et al. 2017 [84]	543 Preterm and full-term	800 mg DHA	> 19 weeks (<21 weeks' gestation – birth)	WASI-II; FST and ReyCF; TEACh; RAVL; CELF-4; WRAT-4; Parent report-behavior: Conners 3 (ADHD) and SDQ; at 7 y	No differences in IQ, language, academical abilities, executive function or in the diagnosis of neurodevelopmental disorders, but slightly higher reasoning scores in DHA group. Supplementation associated with more behavior problems and executive dysfunction.
Gould et al. 2016 [85]	2399 Preterm and full-term	800 mg DHA	> 19 weeks (<21 weeks' gestation – birth)	BSID III at 1.5 y; DAS II at 4 y.	Supplementation associated with higher cognitive scores when mothers did not complete further education, but with lower language scores at 1.5 y and cognitive development at 4 y when education was completed. Smoking nullified the benefits of DHA supplementation in neurodevelopment.
Ramakrishnan et al. 2016 [167]	797 Preterm and full-term	400 mg DHA	18-22 weeks (18-22 weeks' gestation – birth)	MSCA; BASC-2; K-CPT; at 5 y	No differences in cognitive and behavioral outcomes. Supplementation associated with better sustained attention.
Meldrum et al. 2015 [77]	50 Full-term	220 mg DHA + 110 mg EPA	20 weeks (20 weeks' gestation – birth)	WISC-IV; CBCL; Beery-Buktenica TVMI;	No differences in cognition, language and fine motor skills.

				CCC; at 12 y	Higher RBCs' DHA levels associated with higher cognitive scores in WISC-IV.
Hurtado et al. 2015 [83]	110 Full-term	392 mg (DHA + EPA)	28 weeks (28 weeks' gestation - 4 mo pp)	VEPs at 0.2 and 0.63 y; BSID-II at 1 y	No differences in VEPs, cognitive and psychomotor development.
Ramakrishnan et al. 2015 [81]	730 Full-term	400 mg DHA	18-22 weeks (18-22 weeks' gestation – birth)	BSID-II at 1.5 y	No differences in cognitive, motor, or behavioral development.
Gould et al. 2014 [168]	158 Full-term	800 mg DHA	20 weeks (20 weeks' gestation – birth)	Single-object task; Multiple-object task; Distractibility task; WMIC task; at 2.25 y.	No differences in attention, working memory and inhibitory control. No association between cord plasma DHA and neurodevelopmental outcomes.
Mulder et al. 2014 [71]	270 Full-term	400 mg DHA	24 weeks (16 weeks' gestation – birth)	TAC at 0.17 and 1 y; McArthur CDI 1.17 and 1.5 y; BSID-III at 1.5 y	Placebo group associated with higher risk of lower language development at 1.17 and 1.5 y, and lower visual acuity at 0.17 y, but not at 1 y.
Makrides et al. 2014 [78]	646 Preterm	800 mg DHA + 100 mg EPA	> 19 weeks (<21 weeks' gestation – birth)	BRIEF; CELF Preschool–2; DAS II; at 4 y	No differences in cognition, language, and executive functioning.
Gustafson et al. 2013 [72]	52 Full-term	600 mg DHA	20-28 weeks (12-20 weeks' gestation – birth)	NBAS at 1-14 days pp	Supplementation associated with higher autonomic and motor scores.
van Goor et al. 2011 [82]	114 Full-term	1) 220 mg DHA 2) 220 mg DHA + 220 mg ARA	32-38 weeks (14-20 weeks' gestation - 3 mo pp)	BSID-II and Hempel examination at 1.5 y	No differences between groups in mental and psychomotor scores. Children with simple MND had lower DHA in umbilical venous compared to normal children.

Escolano-Margarit et al. 2011 [75]	270 Full-term	500 mg DHA + 150 mg EPA	20 weeks (20 weeks' gestation – birth)	Hempel examination at 4 y; Touwen examination at 5.5 y	No differences in neurodevelopmental scores. Higher prenatal DHA levels in fetal and maternal blood, and lower maternal ARA:DHA ratio, associated with better performance on neurological examinations.
Campoy et al. 2011 [76]	315 Full-term	500 mg DHA + 150 mg EPA	20 weeks (20 weeks' gestation – birth)	K-ABC at 6.5 y of age	No differences in cognitive function. Higher maternal RBCs' DHA levels at delivery associated with higher mental processing scores.
Makrides et al. 2010 [74]	694 Preterm	800 mg DHA + 100 mg EPA	> 19 weeks (<21 weeks' gestation – birth)	BSID-III at 1.5 y	No differences in cognitive, language and motor development.
Dunstan et al. 2008 [57]	98 Full-term	220 mg DHA + 110 mg EPA	20 weeks (20 weeks' gestation – birth)	GMDS; PPVT; CBCL; at 2.5 y	Supplementation associated with higher scores for eye and hand coordination. Cord RBCs' n-3 PUFA levels positively correlated with eye and hand coordination.
Judge et al. 2007 [73]	29 Full-term	214 mg DHA	16 weeks (24 weeks' gestation – birth)	2-step problem-solving test: support step and search step; FTII; at 0.75 y	Supplementation associated with better problem solving but not with recognition memory.

Legend: RCTs = Randomized controlled trials; DHA = Docosahexaenoic acid; EPA = Eicosapentaenoic acid; mo = months; pp = postpartum; ASQ = Ages and Stages Questionnaire; mo = months; WASI-II = Wechsler Abbreviated Scale of Intelligence, Second Edition; FST = Fruit Stroop Test; ReyCF = Rey Complex Figure; TEACh = Test of Everyday Attention for Children; RAVL = Rey Auditory Verbal Learning Test; CELF = Clinical Evaluation of Language Fundamentals; WRAT-4 = Wide Range Achievement Test, Fourth Edition; SDQ = Strengths and Difficulties Questionnaire; y = years; BSID-III = Bayley Scales of Infant and Toddler Development, Third Edition; DAS II = Differential Ability Scales; MSCA = McCarthy Scales of Children's Abilities; BASC-2 = Behavioral Assessment System for Children, Second Edition; K-CPT = Conners' Kiddie Continuous Performance Test; WISC-IV = Wechsler Intelligence Scale for Children-IV; CBCL = Child Behavior Checklist; TVMI = Test of Visual-Motor Integration; CCC = Children's Communication Checklist; RBCs = Red Blood Cells; VEPs = Visual Evoked Potentials; BSID-II = Bayley Scales of Infant Development, Second Edition; WMIC = Working Memory and Inhibitory Control; TAC = Teller Acuity Card; CDI = Communicative Developmental Inventory; BRIEF = Behavior Rating Inventory of Executive Function; NBAS = Neonatal Behavioral Assessment Scale; ARA = Arachidonic Acid; MND = Minor Neurological Dysfunction; Simple MND = presence of 1 dysfunctional domain; K-ABC = Kaufman Assessment Battery for Children; GMDS = Griffiths Mental Development Scales; PPVT = Peabody Picture Vocabulary Test; PUFAs = polyunsaturated fatty acids; FTII = Fagan Test of Infant Intelligence.

Supplementary Materials

Table S3: RCTs studies addressing the impact of postnatal DHA supplementation in neural development in full-term and preterm infants

Author	N	Supplementation Type; dose (daily)	Supplementation length Weeks	Neurodevelopment assessment (years)	Results
Full-term infants					
Willatts et al. 2013 [101]	147	0.21 g/100g DHA + 0.35g/100g ARA; (Infant formula)	15-16 weeks (<7 days pp - 4 mo pp)	WPPSI-R; Day-Night Test; MFFT; at 6 y	No differences in IQ and attention control. Supplementation associated with faster and more efficient information processing.
Colombo et al. 2013 [102]	81	1) 0%DHA (control group) 2) 0.32% DHA 3) 0.64% DHA 4) 0.96% DHA All + 0.64% ARA; (Infant formula)	48 weeks (birth - 12 mo pp)	BSID-II at 1.5 y; MacArthur-Bates CDI at 1.5 y; SDRT at 2, 2.5, and 3 y; Bear-Dragon Go/No-Go Task at 3, 3.5, and 4y; Stroop tasks and DCCS at 3, 3.5, 4, and 5 y; Tower of Hanoi task at 3, 5, and 6 y; PPVT-III at 5 y; WPPSI-III at 6y.	Supplementation associated with better executive function and verbal scores at 5 and 6 y. Higher supplementation (0.96% DHA) associated with less impact on neurodevelopment than 0.32 or 0.64% DHA groups (exception Stroop tasks).
Drover et al. 2011 [100]	131	1) 0% DHA (control group) 2) 0.32% DHA 3) 0.64% DHA 4) 0.96% DHA All + 0.64% ARA; (Infant formula)	47-48 weeks (1-9 days pp - 12 mo pp)	BSID-II at 1.5 y	Supplementation associated with higher cognitive function. No differences between DHA groups in mental, psychomotor or behavior development.
Colombo et al. 2011 [103]	122	1) 0% DHA (control group) 2) 0.32% DHA 3) 0.64% DHA 4) 0.96% DHA All + 0.64% ARA; (Infant formula)	48 weeks (birth - 12 mo pp)	Visual habituation protocol (at 0.3, 0.6 and 0.75 y)	Supplementation with 0.32% or 0.64% of DHA associated with longer attention activity. Supplementation with 0.96% of DHA associated with less impact on neurodevelopment than 0.32 and 0.64% groups.

Gale et al. 2010 [96]	241	6.8 to 18 mg/100 ml DHA; (Infant formula)	24 weeks (birth – 6 mo pp)	WPPSI-III; NEPSY; TVPS; at 4 y	Supplementation associated with higher total and verbal IQ. DHA intake from milk (breastmilk plus formula) no associated with any neurodevelopmental outcome.
De Jong et al. 2010 [106]	341	0.30% DHA + 0.45% ARA; (Infant formula)	8 weeks (birth – 2 mo pp)	Touwen examination at 9 y	No differences in neurological functioning. Breastfeeding associated with less often fine manipulative dysfunction than formula-feeding.
Jensen et al. 2010 [166]	160	200 mg DHA; (Mothers' supplementation)	15-16 weeks (5 days pp – 4 mo pp)	VEP and ETDRS/Bailey-Lovie chart; Bayley PDI, MSCA, PPT, K-ABC; WPPSI-R; Sustained Attention scale of the Leiter-R; At 5 y	Supplementation associated with better sustained attention. No differences in visual function and other neuropsychological domains.
Pivik et al. 2009 [105]	71	1) 0% DHA or ARA 2) 0.15% DHA + 0.40% ARA 3) 0.32% DHA + 0.64% ARA; (Infant formula)	24 weeks (birth – 6 mo pp)	BSID; PLS; at 0.25 and 0.5 y	In the 3 groups, developmental function and language measures were in the normal range. No differences in neurodevelopmental outcomes.
Birch et al. 2007 [104]	52	1) 0.35% DHA 2) 0.36% DHA + 0.72% ARA (Infant formula)	16-17 weeks (<5 days pp – 17 weeks pp)	WPPSI-R; ATS protocol and EVA system; at 4 y	DHA+ARA supplementation associated with better visual acuity and verbal IQ than DHA supplementation alone. Supplementation only with DHA associated with lower verbal IQ than breast-fed group. No differences between DHA+ARA supplementation and breast-fed group.
Preterm infants					
Molloy et al. 2016 [118]	104 Very preterm infants	1) 1.0% DHA + 0.6% ARA 2) 0.35% DHA + 0.6% ARA;	Day 2-4 pp – estimated due date	FrACT; Vernier Acuity Test;	No differences in visual-processing.

		(Infant formula)		RPST; Judgment of line orientation; TVPS-3; at 7 y.	
Collins et al. 2015 [111]	604 Very preterm infants	1) 1.0% DHA + 0.6% ARA 2) 0.35% DHA + 0.6% ARA (Infant formula)	Day 2-4 pp – estimated due date	WASI; TEA-Ch; RCFT, Fruit Stroop Test, BRIEF; RAVLT; TVPS-3; Parent questionnaires: Conners 3 (ADHD) and SDQ; at 7 y	No differences in IQ, attention, executive function, behavior, visual-spatial perceptual skills and educational progress. No differences in the diagnosis of ADHD, ASD or cerebral palsy.
Almaas et al 2015 [114]	98 VLBW infants	0.86% DHA + 0.91% ARA (Infant formula)	9 weeks (birth – 9 weeks pp)	WASI, WISC-III; CVLT-II; Grooved Pegboard test; at 8 y	No differences in cognitive and MRI data on brain volumes or cortical surface volume, area and thickness.
Isaacs et al. 2011 [115]	107	0.5 g/100g DHA + 0.1g/100g EPA + 0.04g/100g ARA (Infant formula)	36 weeks (birth – 9 mo pp)	WASI; CMS, Word Pairs instrument; Neuropsychological Test for Children; WIAT-II; TEA-Ch; BADS-C; at 10 y	No differences in IQ, memory, language, learning skills, academic attainment, attention and executive function.
Westerberg et al. 2011 [113]	92 VLBW infants	0.86% DHA + 0.91% ARA (Infant formula)	9 weeks (birth – 9 weeks pp)	BSID MDI; ASQ; Free-play session test; at 1.7 y.	Supplementation associated with better attention capacity, but no differences in MDI and ASQ scores. Plasma DHA at delivery associated with better sustained attention and MDI.
Smithers et al. 2010 [116]	128 Very preterm infants	1) 1.0% DHA + 0.6% ARA 2) 0.35% DHA + 0.6% ARA (Infant formula)	Day 2-4 pp – estimated due date	MacArthur CDI at 2.2 y; SDQ and STSC at 3 and 5 y.	No differences in language development and child's behavior.
Makrides et al. 2009 [111]	657 Very preterm infants	1) 1.0% DHA + 0.6% ARA 2) 0.35% DHA + 0.6% ARA (Infant formula)	Day 2-4 pp – estimated due date	BSID at 1.5 y	No differences in mental, psychomotor or behavior development.

					For infants weigh <1250g, group 1 associated with higher mental scores, but no statistical significant.
Smithers et al. 2008 [112]	168 Very preterm infants	1) 1.0% DHA + 0.6% ARA 2) 0.35% DHA + 0.6% ARA (Infant formula)	Day 2-4 pp – estimated due date	VEP at 0.17 and 0.3 y	No differences in visual acuity at 0.17 y, but supplementation associated with higher visual acuity at 0.3 y.
Henriksen et al. 2008 [110]	105 VLBW infants	0.86% DHA + 0.91% ARA (Infant formula)	8 weeks (1 week pp – 9 weeks pp)	ASQ; Event-Related Potentials; at 0.5 y	Supplementation associated with better problem-solving skills and recognition memory.

Legend: RCTs = Randomized controlled trials; DHA = Docosahexaenoic acid; ARA = Arachidonic Acid; pp = postpartum; WPPSI-R= Wechsler Preschool and Primary Scale of Intelligence –Revised; MFFT = Matching Familiar Figures Test; IQ = Intelligence Quotient; BSID-II = Bayley Scales of Infant Development, Second Edition; CDI = Communicative Development Inventories; SDRT = Spatial Delayed Response task; DCCS = Dimensional Change Card Sort; PPVT = Peabody Picture Vocabulary Test; NEPSY = Developmental NEuroPSYchological Assessment; TVPS = Test of Visual-Perceptual Skills (non-motor); VEP = Visual evoked potential; PDI = Psychomotor Development Index; MSCA = McCarthy Scales of Children's Abilities; PPT = Purdue Pegboard Test; K-ABC = Kaufman Assessment Battery for Children; Leiter-R = Leiter International Performance Scale-Revised; PLS = Preschool Language Scales; ATS = Amblyopia Treatment Study; EVA = Electronic Visual Acuity; Very preterm infants = <33 weeks' gestational age; FrACT = Freiburg Visual Acuity Test; RPST = Randot Preschool Stereoacuity Test; TVPS-3 = Test of Visual Perceptual Skills, Third Edition; WASI = Wechsler Abbreviated Scale of Intelligence; TEA-Ch = Test of Everyday Attention for Children; RCFT = Rey Complex Figure Test; BRIEF = Behavior Rating Inventory of Executive Function; RAVLT = Rey Auditory Verbal Learning Test; SDQ = Strengths and Difficulties Questionnaire; VLBW = Very Low and Extremely Low Birth Weight, <1500g; WISC = Wechsler Intelligence Scale for Children; CVLT-II = California Verbal Learning Test II; MRI = Magnetic Resonance Imaging; EPA = Eicosapentaenoic acid; CMS = Children's Memory Scale; WIAT-II = Wechsler Individual Achievement Test, Second Edition; BADS-C = Behavioural Assessment of the Dysexecutive Syndrome for Children; MDI = Mental Development Index; ASQ = Ages and Stages Questionnaire; STSC = Short Temperament Scale for Children.

Supplementary Materials

Table S4: Overview of the studies addressing the impact of maternal fish and DHA intake and offspring ASD diagnosis

Author	N	PUFAs measure (time; biological samples)	Food intake assessment	Neurodevelopment assessment (years)	Results
Boucher et al. 2017 [159]	1346 mother-child pairs (term infants)	--	Breastfeeding - mothers' questionnaire	MSCA; K-CPT; ADHD: DSM-IV; Autistic traits: CAST; at 4 y	Longer breastfeeding duration (for each additional month) associated with better cognitive outcomes and fewer autistic traits. More mitigated effects for ADHD symptoms. No association between breastfeeding duration and ASD and ADHD in the clinical range*.
Julvez et al. 2016 [151]	1892 mother-child pairs (term infants)	At birth; cord-blood	FFQ at 10-13 and 28-32 weeks' gestation	BSID at 1.17 y; MSCA at 5 y; Autistic traits: CAST at 5 y	Maternal seafood intake, particularly within the highest quantile (>238 g/week), associated with moderate child neurodevelopment benefits, with a better cognition and fewer autistic traits. Part of the associations reduced by adjustments for PUFA levels.
Graff et al. 2016 [153]	4624 mother-child pairs (preterm and term infants)	Midpregnancy (median: 20.6 weeks' gestation); maternal plasma	FFQ, early pregnancy (median, 13.8 weeks) and at 1.2 y pp	Autistic traits: SRS and CBCL at 6 y	Lower prenatal n-3:n-6 PUFA ratio associated with more autistic traits. No association between maternal n-3 PUFA levels (or prenatal dietary fish intake) and child autistic traits.
Gao et al. 2016 [154]	926 mother-child pairs	--	Parental questionnaire: diet from 0.5 y before pregnancy to birth.	ASD: DSM-IV and CARS score ≥ 30.	Parental fish intake before pregnancy associated with lower risk of child autism.

Husk et al. 2015 [161]	37901 mother-child pairs (preterm and term infants)	--	Breastfeeding - mothers' questionnaire	ASD: parental report and DSM-IV	No association between any measure of breastfeeding history and ASD.
Shafai et al. 2014 [158]	145 mother-child pairs	--	Breastfeeding - mothers' questionnaire	ASD: parental report	Longer breastfeeding duration, especially ≥12 mo, associated with less ASD diagnosis. Lack of breastfeeding associated with higher risk of having ASD in genetically susceptible children.
Lyall et al. 2013 [152]	18045 mother-child pairs	--	FFQ, during pregnancy or until 1–2 y pp	ASD: parental report Validation: ADI-R by phone and SRS.	Very low maternal n-3 PUFA intake associated with higher risk of ASD (RR=1.53). No associations between maternal fish intake and ASD.
Al-Farsi et al. 2012 [157]	204 mother-child pairs	--	Breastfeeding - mothers' questionnaire	ASD: DSM-IV-R	Late initiation of breastfeeding, non-intake of colostrum, prelacteal feeding**, and formula-feeding associated with higher prevalence of ASD. Longer exclusive breastfeeding and continued breastfeeding during the first 2 y associated with lower ASD risk.
Schultz et al. 2006 [156]	984 mother-child pairs	--	Breastfeeding - mothers' questionnaire	ASD: parental report using online internet survey	Lack of breastfeeding associated with higher risk for AD (OR=2.48), compared to breastfeeding for > 6 mo. Infant formula without DHA and ARA associated with higher risk for AD (OR=4.41), compared to exclusive breastfeeding.

Legend: DHA = Docosahexaenoic acid; MSCA = McCarthy Scales of Children's Abilities; K-CPT = Kiddie Continuous Performance Test; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; CAST = Childhood Asperger Syndrome Test; FFQ = Food Frequency Questionnaire; BSID = Bayley Scales of Infant Development; PUFAs = polyunsaturated fatty acids; pp = postpartum; SRS = Social Responsiveness Scale; CBCL = Child Behavior Checklist; CARS = Childhood Autism Rating Scale; ADI-R = Autism Diagnostic Interview-Revised; AD = Autistic Disorder.

* ADHD in the clinical range estimated by recording ratings of options 0 and 1 as "symptom absent, and ratings of 2 and 3 as "symptom present", and using the DSM-IV criteria for ADHD (≥ six symptoms within a single category). For ASD: Score in the clinical range (≥ 15).

** Prelacteal feeds: food or liquid received before the initiation of breastfeeding.

Supplementary Materials

Table S5: Overview of the studies addressing the impact of maternal fish and DHA intake and offspring ADHD diagnosis

Author	N	PUFAs measure (time; biological samples)	Food intake assessment	Neurodevelopment assessment (years)	Results
Stadler et al. 2016 [172]	474 mother-child pairs	--	Breastfeeding - mothers' questionnaire	ADHD: DSM-V at 7-13 y	Breastfeeding <6 mo associated with higher prevalence of ADHD.
Park et al. 2014 [171]	874 mother-child pairs	--	Breastfeeding - mothers' questionnaire	ADHD: DISC-IV; CBCL; KEDI-WISC; at 8-11 y	Lack of breastfeeding associated with higher internalizing, externalizing and other behavioral problems, lower child's IQ, and increased ADHD prevalence.
Groen et al. 2013 [170]	1739 mother-child pairs	--	Breastfeeding - mothers' questionnaire	CBCL at 3, 7, 10 and 12 y; RAKIT at 5, 7 and 10 y; WISC-R and WISC-R-III at 10 and 12 y; CITO at 12 y	Breastfeeding associated with higher educational attainment, less overactive behavior and a trend toward higher IQ.
Mimouni-Bloch et al. 2013 [169]	159 mother-child pairs	--	Breastfeeding - mothers' questionnaire	ADHD: clinical diagnosis not specified at 6-12 y	ADHD associated with less frequent breastfeeding at 3 and 6 mo.
Sagic et al. 2012 [165]	515 mother-child pairs	--	FFQ, days after birth - estimate prenatal fish intake.	ADHD symptoms: CRS-T and DSM-IV; WISC-III; CPT; at 8 y	Fish intake >2 times/week associated with better ADHD-related behaviors, mainly Impulsive/Hyperactive behaviors. Maternal fish intake associated with higher cognitive scores.

Kohlboeck et al. 2011 [164]	416 mother-child pairs (term infants)	At birth; cord blood serum	--	SDQ at 10 y	Higher cord blood DHA associated with lower hyperactivity/inattention scores and fewer emotional symptoms.
Kannass et al. 2009 [163]	45 mother-child pairs	At birth; Maternal RBCs phospholipids	--	Free-play tasks, including the multiple-object task at 1 and 1,5 y	Higher maternal DHA status at birth associated with higher attention, and lower distractibility.
Julvez et al. 2007 [160]	500 mother-child pairs	--	Breastfeeding - mothers' questionnaire	ADHD: DSM-IV; MSCA; CPSCS; at 4 y	Breastfeeding > 3 mo associated with fewer attention and hyperactivity symptoms and better socio-behavioural outcomes. Breastfeeding > 5 mo associated with higher executive function scores.

Legend: DHA = Docosahexaenoic acid; FFQ = Food Frequency Questionnaire; DSM= Diagnostic and Statistical Manual of Mental Disorders; DISC-IV = Diagnosis Interview Schedule for Children Version-IV; CBCL = Child Behavior Checklist; KEDI-WISC = Korean Educational Development Institute's-Wechsler Intelligence Scales for Children; IQ = Intelligence Quotient; RAKIT = Revised Amsterdamse Kinder Intelligentie children; WISC-R = Wechsler Intelligence Scales for Children – Revised; CITO = CITO-elementary Test for Educational attainment; CRS-T = Conners' Rating Scale-Teachers; CPT = Continuous Performance Test; SDQ = Strength and Difficulties Questionnaire; RBCs = Red Blood Cells; CPSCS = California Preschool Social Competence Scale.

ANEXOS

Anexo I. Normas de escrita e submissão à revista *Nutrients*
Anexo II. Agradecimentos

ANEXO I:

Preparation of a Manuscript

General Considerations

- **Research manuscripts** should comprise:
  - Front matter: Title, Author list, Affiliations, Abstract, Keywords;
  - Research manuscript sections: Introduction, Materials and Methods, Results, Discussion, Conclusions (optional);
  - Back matter: Supplementary Materials, Acknowledgments, Author Contributions, Conflicts of Interest, References.
- **Review manuscripts** should comprise the front matter, literature review sections and the back matter. The template file can also be used to prepare the front and back matter of your review manuscript. It is not necessary to follow the remaining structure. Structured reviews and meta-analyses should use the same structure as research articles and ensure they conform to the PRISMA guidelines.
- **Case reports** should include a succinct introduction about the general medical condition or relevant symptoms that will be discussed in the case report; the case presentation including all of the relevant de-identified demographic and descriptive information about the patient(s), and a description of the symptoms, diagnosis, treatment, and outcome; a discussion providing context and any necessary explanation of specific treatment decisions; a conclusion briefly outlining the take-home message and the lessons learned.
- **Abstract graphic:** Authors are encouraged to provide a graphical abstract as a self-explanatory image to appear alongside with the text abstract in the Table of Contents. Figures should be a high quality image in any common image format. Note that images displayed online will be up to 11 by 9 cm on screen and the figure should be clear at this size.
- **Abbreviations** should be defined in parentheses the first time they appear in the abstract, main text, and in figure or table captions.
- **SI Units** (International System of Units) should be used. Imperial, US customary and other units should be converted to SI units whenever possible.
- **Accession numbers** of RNA, DNA and protein sequences used in the manuscript should be provided in the Materials and Methods section. Please also see the section on Deposition of Sequences and of Expression Data.
- **Equations:** If you are using Word, please use either the Microsoft Equation Editor or the MathType add-on. Equations should be editable by the editorial office and not appear in a picture format.
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Please disclose at the submission stage any restrictions on the availability of materials or information. Read the information about Supplementary Materials and Data Deposit for additional guidelines.

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Front Matter

These sections should appear in all manuscript types

- **Title:** The title of your manuscript should be concise, specific and relevant. It should identify if the study reports (human or animal) trial data, or is a systematic review, meta-analysis or replication study. When gene or protein names are included, the abbreviated name rather than full name should be used.

- **Author List and Affiliations:** Authors' full first and last names must be provided. The initials of any middle names can be added. The PubMed/MEDLINE standard format is used for affiliations: complete address information including city, zip code, state/province, country, and all email addresses. At least one author should be designated as corresponding author, and his or her email address and other details should be included at the end of the affiliation section. Please read the criteria to qualify for authorship.

- **Abstract:** The abstract should be a total of about 200 words maximum. The abstract should be a single paragraph and should follow the style of structured abstracts, but without headings: 1) Background: Place the question addressed in a broad context and highlight the purpose of the study; 2) Methods: Describe briefly the main methods or treatments applied. Include any relevant preregistration numbers, and species and strains of any animals used. 3) Results: Summarize the article's main findings; and 4) Conclusion: Indicate the main conclusions or interpretations. The abstract should be an objective representation of the article: it must not contain results which are not presented and substantiated in the main text and should not exaggerate the main conclusions.

- **Keywords:** Three to ten pertinent keywords need to be added after the abstract. We recommend that the keywords are specific to the article, yet reasonably common within the subject discipline.

Back Matter

- **Supplementary Materials:** Describe any supplementary material published online alongside the manuscript (figure, tables, video, spreadsheets, etc.). Please indicate the name and title of each element as follows Figure S1: title, Table S1: title, etc.
- **Acknowledgments:** All sources of funding of the study should be disclosed. Clearly indicate grants that you have received in support of your research work and if you received funds to cover publication costs. Note that some funders will not refund article processing charges (APC) if the funder and grant number are not clearly and correctly identified in the paper. Funding information can be entered

separately into the submission system by the authors during submission of their manuscript. Such funding information, if available, will be deposited to FundRef if the manuscript is finally published.

- **Author Contributions:** Each author is expected to have made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work; or have drafted the work or substantively revised it; AND has approved the submitted version (and version substantially edited by journal staff that involves the author's contribution to the study); AND agrees to be personally accountable for the author's own contributions and for ensuring that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and documented in the literature.
  For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "X and Y conceived and designed the experiments; X performed the experiments; Y analyzed the data; Y wrote the paper." **Authorship must include and be limited to those who have contributed substantially to the work. Please read the section concerning the criteria to qualify for authorship carefully.**
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- Citations and References in Supplementary files are permitted provided that they also appear in the main text and in the reference list. In the text, reference numbers should be placed in square brackets [ ], and placed before the punctuation; for example [1], [1–3] or [1,3]. For embedded citations in the text with pagination, use both parentheses and brackets to indicate the reference number and page numbers; for example [5] (p. 10). or [6] (pp. 101–105).The reference list should include the full title, as recommended by the ACS style guide. Style files for Endnote and Zotero are available.

References should be described as follows, depending on the type of work:

→ Journal Articles:
1. Author 1, A.B.; Author 2, C.D. Title of the article. *Abbreviated Journal Name* **Year**, *Volume*, page range, DOI. Available online: URL (accessed on Day Month Year).
→ Books and Book Chapters:

2. Author 1, A.; Author 2, B. *Book Title*, 3rd ed.; Publisher: Publisher Location, Country, Year; pp. 154–196; ISBN.
3. Author 1, A.; Author 2, B. Title of the chapter. In *Book Title*, 2nd ed.; Editor 1, A., Editor 2, B., Eds.; Publisher: Publisher Location, Country, Year; Volume 3, pp. 154–196; ISBN.
→ Unpublished work, submitted work, personal communication:
4. Author 1, A.B.; Author 2, C. Title of Unpublished Work. status (unpublished; manuscript in preparation).
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9. Title of Site. Available online: URL (accessed on Day Month Year).
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Preparing Figures, Schemes and Tables

- File for Figures and schemes must be provided during submission in a single zip archive and at a sufficiently high resolution (minimum 1000 pixels width/height, or a resolution of 300 dpi or higher). Common formats are accepted, however, TIFF, JPEG, EPS and PDF are preferred.
- *Nutrients* can publish multimedia files in articles or as supplementary materials. Please contact the editorial office for further information.
- All Figures, Schemes and Tables should be inserted into the main text close to their first citation and must be numbered following their number of appearance (Figure 1, Scheme I, Figure 2, Scheme II, Table 1, *etc.*).
- All Figures, Schemes and Tables should have a short explanatory title and caption.
- All table columns should have an explanatory heading. To facilitate the copy-editing of larger tables, smaller fonts may be used, but no less than 8 pt. in size. Authors should use the Table option of Microsoft Word to create tables.
- Authors are encouraged to prepare figures and schemes in color (RGB at 8-bit per channel). There is no additional cost for publishing full color graphics.

ANEXO II:

Agradecimentos

"O sucesso é a soma de pequenos esforços repetidos dia após dia"

Robert Collier

Ao se aproximar o fim de mais uma etapa, talvez uma das mais importante da minha vida, não poderia deixar de agradecer a todas as pessoas que me apoiaram e contribuíram para o meu percurso académico e conclusão deste trabalho.

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