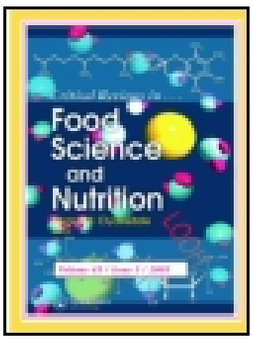

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REVIEW

The role of marine omega-3 in human neurodevelopment, including Autism Spectrum Disorders and Attention-Deficit/Hyperactivity Disorder – a review

Bárbara P. Martins[a], Narcisa M. Bandarra[b], and Margarida Figueiredo-Braga[a,c]

[a]Department of Clinical Neurosciences and Mental Health, Medical Psychology, Faculty of Medicine, University of Porto, Porto, Portugal; [b]Department of Sea and Marine Resources, Portuguese Institute for the Sea and Atmosphere (IPMA, IP), Lisbon, Portugal; [c]Research Group: Metabolism, Nutrition & Endocrinology, i3S Instituto de Investigação e Inovação em Saúde, Porto, Portugal

ABSTRACT

Autism Spectrum Disorders (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD) are two increasingly prevalent neurodevelopmental disorders. This rise may 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 DHA in children neurodevelopment, in order to elicit its role in the prevention and mitigation of ASD and ADHD. As main finding, a low DHA supply seems to negatively affect childhood neurodevelopment in specific conditions 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 DHA provision through maternal diet or breastfeed may promote some neuronal protection in specific offspring's populations, suggesting that DHA may act as a modifiable risk factor for ASD and ADHD.

KEYWORDS

Neurodevelopment; docosahexaenoic acid; n-3 Polyunsaturated Fatty Acids; maternal seafood intake; pregnancy; lactation

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 (American Psychiatric Association (APA) 2013; Modabbernia, Velthorst, and Reichenberg 2017).

ASD displays deficits in social communication and reciprocal social interaction and restricted repetitive activities, behaviors and interests, frequently starting before three years of age (Faras, Al Ateeqi, and Tidmarsh 2010). 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 (APA 2013). One in each 68 children (1.5%) in United States was affected in 2012, 4.5 times more frequent in boys than girls (Christensen et al. 2016). Others studies in Europe, Asia, and North America reported a prevalence of ASD of 1–2% (Centers for Disease Control and Prevention (CDC) 2016).

Although ASD is highly heritable (last estimates 38–54%), environmental factors are crucial in its etiology, especially those affecting fetal and early-life development (Madore et al. 2016). Advanced parental age and birth complications related to ischemia, trauma and hypoxia have shown solid links to ASD (Modabbernia, Velthorst, and Reichenberg 2017). 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 (Modabbernia, Velthorst, and Reichenberg 2017).

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 (Cortese and Castellanos 2015; National Institute of Mental Health, NIH 2016). 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 (APA 2013; Cortese and Castellanos 2015; NIH 2016). Like in ASD, genetic factors play an important etiological role, but other external factors, such as alcohol, tobacco or toxins exposure during pregnancy, emotional difficulties, premature or post mature delivery, low birth weight and pre- or postnatal brain injury have been shown to contribute to ADHD (Guney, Cetin, and Iseri 2015).

CONTACT Margarida Figueiredo-Braga mmfb@med.up.pt Department of Clinical Neurosciences and Mental Health, Medical Psychology, Faculty of Medicine, University of Porto, Alameda Prof. Hernâni Monteiro, Porto, 4200-319, Portugal.

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The clinical and etiological similarities between the two diseases are remarkable and their prevalence identically has increased at an alarming rate (Dougherty et al. 2016). A change to a Western diet, characterized by an increase in dietary pro-inflammatory omega-6 polyunsaturated fatty acids (n-6 PUFAs), through 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 (Akerele and Cheema 2016). 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 (Morgese and Trabace 2016; Van Elst et al. 2014).

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 (Van Elst et al. 2014). In particular, Docosahexaenoic acid (DHA) constitutes 90% of the n-3 PUFAs in the human brain and about 10–20% of total lipids (Weiser, Butt, and Mohajeri 2016), being associated with a number of positive effects on maternal and infant health (Morgese and Trabace 2016). Higher DHA intake appears to reduce the risk of schizophrenia, bipolar disorder, depression, anxiety, and behavior disorders, while suboptimal DHA levels seem to be a potentially risk factor for mental illness (Bozzatello et al. 2016).

DHA is quickly incorporated into the retina and brain nervous tissue during the third trimester of pregnancy until two years of age (Cardoso, Afonso, and Bandarra 2017). 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 (Larque et al. 2012). 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 (Carlson et al. 2013; Larque et al. 2012; Meher et al. 2016; Ramakrishnan et al. 2010). However, neurodevelopmental improvements, especially for cognitive function, remain controversial and need further clarification (Osendarp 2011).

PUFA levels in blood are considered consistent biomarkers of their status (Mazahery et al. 2017). Considering 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 to 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.

Neurodevelopment and functionally brain changes in ASD and ADHD

Several studies indicated that individuals with ASD and ADHD have differences in anatomy, function and brain connectivity compared to healthy controls, resulting in changes in many neurodevelopmental outcomes (Donovan and Basson 2017; Dougherty et al. 2016; Polsek et al. 2011).

In patients with ASD, some level of intellectual disability is detected in 70% (Srivastava and Schwartz 2014), and about 5–44% could have a seizure disorder (Lee, Smith, and Paciorkowski 2015). Anxiety, delays in learning, attention, sensory processing and motor activity deficits may also be present (CDC 2016).

An early postnatal brain overgrowth, with an increase in head circumference, is one of the most important morphological changes reported in ASD brain (Donovan and Basson 2017; Dougherty et al. 2016; Hazlett et al. 2005; Polsek et al. 2011), described as a possible predictor of its diagnosis in infants of high risk families (Hazlett et al. 2017). Anterior temporal region and frontal cortex appear to be the most affected (Geschwind 2009), 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 (Dougherty et al. 2016). 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 (Ecker 2017). 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 (Ismail et al. 2016).

A problem in long-range connectivity is now known as an emerging theory in ASD. Dinstein et al. (2011) 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 have found a significantly reduction in the volume of corpus callosum, the major white matter bundle in the brain (Dougherty et al. 2016; Frazier and Hardan 2009). 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 (Baron-Cohen and Belmonte 2005).

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 (Basson and Wingate 2013; Fatemi et al. 2012). Most of the studies have found a larger size of cerebellum in ASD children, particularly prominent in its posterior lobe (Donovan and Basson 2017; Polsek et al. 2011). Although vermis has already been reported as smaller or larger compared to controls (Polsek et al. 2011; Stanfield et al. 2008), a consistent finding was a significant lower number and size of Purkinje cells in post-mortem studies (Stanfield et al. 2008; Won, Mah, and Kim 2013).

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 (Hadjikhani et al. 2007; Schumann et al. 2009). 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 (Kennedy and Courchesne 2008).

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 (Madore et al. 2016; Onore, Careaga, and Ashwood 2012; Rossignol and Frye 2014). 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 (Patterson 2011).

Lastly, regarding the neurotransmission changes in ASD, the excitation/inhibition imbalance theory stands out (Polsek et al. 2011). These subjects have high glutamate (excitatory) (Shinohe et al. 2006) and low Gamma-Aminobutyric Acid (GABA) (inhibitory) blood levels, and a decreased density of GABAA receptors (Fatemi et al. 2009), with a possible relation between glutamate upregulation and ASD severity (Shinohe et al. 2006). 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 (Polsek et al. 2011). Other studies pointed out that ASD behavior arises from a dysfunction in the midbrain dopaminergic system (Paval 2017). 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 (Bernardi et al. 2011).

ADHD symptoms, on the other hand, arise from a deficit in executive function, including attention and inhibitory control, and working memory (NIH 2016). These children are also predisposed to present delays in language and motor development, associated with impaired brain activity in several neuronal networks (NIH 2016).

Patients with ADHD seem to experience normal steps of cortical maturation but slower than healthy controls (Dougherty et al. 2016). A volume reduction and a cortical thinning in certain brain regions, mainly in frontal and prefrontal regions, was found in children with ADHD (Batty et al. 2010), but the most replicable abnormalities are in basal ganglia, being associated with the severity of the symptoms (Nakao et al. 2011).

Dougherty et al. (2016), comparing the structural imaging of the ASD and ADHD brain, have 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 magnetic resonance imaging and decreased FA in DTI), and superior longitudinal fasciculus (reduced FA) abnormalities, supporting the idea that white matter integrity is also affected in ADHD (Dougherty et al. 2016; Wu et al. 2017). 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 (Dougherty et al. 2016).

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) (Morgese and Trabace 2016). 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 (Nikolas et al. 2010). Serotonin also modulates dopamine release and its interaction seems to affect impulsivity; however, further studies are needed to confirm its link to ADHD pathology (Nikolas et al. 2010).

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 (Dagai, Peri-Naor, and Birk 2009; Janssen and Kiliaan 2014). This accumulation continues up to the postnatal period, being dependent on breastmilk (Janssen and Kiliaan 2014).

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. In the liver, ALA undergoes 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, which is again desaturated to 24:6n-3. Finally, in peroxisome, 24:6n-3 is β-oxidized to DHA (22:6n-3) (Domenichiello, Kitson, and Bazinet 2015). In humans, the ability to convert ALA to DHA is extremely limited – less than 0.1% (Weiser, Butt, and Mohajeri 2016) –, especially in the fetus, making them highly dependent on the transfer of maternal DHA through the placenta. This is influenced by maternal DHA synthesis, mobilization from adipose stores, and dietary intake (Lauritzen and Carlson 2011). 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 (Morgese and Trabace 2016).

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 (Morgese and Trabace 2016). They are also important for dendritic growth and neuronal synaptogenesis and can regulate inflammation (Cardoso, Afonso, and Bandarra 2017). EPA and ARA are precursors of eicosanoids (prostaglandins, thromboxanes and leukotrienes), but while ARA shows proinflammatory properties, EPA exerts anti-inflammatory effects (Janssen and Kiliaan 2014). 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 (Cardoso, Afonso, and Bandarra 2017; Janssen and Kiliaan 2014). 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 the mother and fetus (Janssen and Kiliaan 2014). Low DHA levels could be harmful for neurodevelopment, especially in preterm infants, who are deprived of maternal stores in the third trimester (Dunstan et al. 2008; Hall 2016). 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 should be implemented (Global Organization for EPA and DHA omega-3s 2017).

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 insecure (Starling et al. 2015). 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 (Hibbeln et al. 2007). 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 (Strain et al. 2015). 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 (Strain et al. 2015). 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 (Gale et al. 2008; Mendez et al. 2009; Oken et al. 2008a; Oken et al. 2008b; Strain et al. 2015).

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 (Jacobson et al. 2008), better motor development and fewer internalizing behavior problems at 7 years (Krabbendam et al. 2007), and higher verbal and full-scale IQ at 8 years (Steer et al. 2013). Some observational studies reported no association between maternal fish consumption (Valent et al. 2013), DHA in mothers' red blood cell (RBC) (Bernard et al. 2013; Valent et al. 2013) 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, King, and Innis (2014) showed that infants in the placebo group had an increased risk of developing language problems, 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 to 20 weeks' gestation until birth (Gustafson et al. 2013), and better problem solving in infants of mothers who received 214 mg/day of DHA in same period (Judge, Harel, and Lammi-Keefe 2007). In Gustafson's study (2013), 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, other studies found interesting results (Campoy et al. 2011; Dunstan et al. 2008; Escolano-Margarit et al. 2011; Gould, Smithers, and Makrides 2013; Makrides et al. 2010; Makrides et al. 2014; Meldrum et al. 2015). For example, in a study with high level of methodological rigor with low attrition, Makrides et al. (2010) studied preterm infants whose mothers were supplemented with 800 mg DHA + 100 mg 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, supporting the evidence that DHA supplementation is effective at preventing developmental delay in early childhood. However, they did not find differences between groups in any scales of the Behavior Rating Inventory of Executive Function at 4 years of age (Makrides et al. 2014). Note that although this study was not a pure DHA test, since it used fish oil capsules containing both DHA and EPA, DHA is present in the brain at levels 50 and 200-fold higher than EPA and ALA, respectively (Domenichiello, Kitson, and Bazinet 2015).

Tables S1 and S2 (Supplementary material) 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 (Gould, Smithers, and Makrides 2013; Newberry et al. 2016). 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 (Campoy et al. 2011; Escolano-Margarit et al. 2011; Hurtado et al. 2015; Makrides et al. 2010; Makrides et al. 2014; Meldrum et al. 2015; Ramakrishnan et al. 2015; Van Goor et al. 2011), with few showing a negative effect (Gould et al. 2016; Gould et al. 2017), some found that children with better neurodevelopment outcomes individually had higher DHA levels (Campoy et al. 2011; Escolano-Margarit et al. 2011; Makrides et al. 2010; Ostadrahimi et al. 2017; Van Goor et al. 2011). Furthermore, two of these studies (Campoy et al. 2011; Escolano-Margarit et al. 2011), 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 (Escolano-Margarit et al. 2011). 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 be a proxy for socio-economic background and healthy life-style factors, that may synergically improve brain development (Gould et al. 2016; Van Goor et al. 2011).

It is also important to maintain optimal DHA levels during postnatal period. At this time, breastmilk is the main source of DHA in infant́s RBC (Harslof et al. 2013), being dependent on maternal DHA consumption (Lauritzen and Carlson 2011).

DHA from breastmilk seems to be crucial for better language and cognitive function (Belfort et al. 2013; Quigley et al. 2012; Whitehouse et al. 2011), social behavior with fewer attentional symptoms, and better global psychosocial health (Hayatbakhsh et al. 2012; Oddy et al. 2010). Oddy et al. (2010) 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 on neurodevelopment (Mendez et al. 2009). However, other studies did not find significant effects of breastfeeding on children's neurodevelopment (Belfort et al. 2016; Bernard et al. 2017; Gale et al. 2010; Girard, Doyle, and Tremblay 2017; Jacobson et al. 2008; Kramer et al. 2008; Lind et al. 2014) (see Supplementary material, 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 (Gale et al. 2010; Girard, Doyle, and Tremblay 2017). Women who were more intelligent or better educated seem to be more receptive to breastfeeding promotion (Gale et al. 2010).

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 (Lapillonne et al. 2013). 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 (Colombo et al. 2011; Colombo et al. 2013; Drover et al. 2011; Willatts et al. 2013).

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 (Birch et al. 2007; Drover et al. 2011; Willatts et al. 2013) (see Supplementary material, 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 (Birch et al. 2007). Moreover, Drover et al. (2011) 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 benefit of intaking DHA (Colombo et al. 2011; Colombo et al. 2013; Drover et al. 2011). 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 (Gale et al. 2010). Other studies, however, did not find short- (Colombo et al. 2013; Pivik et al. 2009) or long-term (de Jong et al. 2010; Willatts et al. 2013) 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.

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 (Constable et al. 2008; Tam et al. 2016), presenting a higher risk for ASD and ADHD, mood, and psychotic disorders (McNamara, Vannest, and Valentine 2015). Their lower DHA levels may be partially responsible for this impaired neurodevelopment (McNamara, Vannest, and Valentine 2015; Tam et al. 2016).

Recent studies have shown that a short-term high DHA dose (0.86–1% of total PUFAs) seems to be helpful for an optimal neurodevelopment in preterm infants (Henriksen et al. 2008; Makrides et al. 2009; Smithers et al. 2008), mostly in very low birth weight (VLBW) babies (<1500 g) (Henriksen et al. 2008; Westerberg et al. 2011) (see Supplementary material, Table S3). For example, Makrides et al. (2009) 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. (2008) found also that a high-DHA supplementation (0.86% DHA plus 0.91% ARA) in VLBW infants, during nine weeks, led to better 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. (2011) 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 (Almaas et al. 2015). Other long-term studies did not report significant benefits in infancy, including for executive functions, ADHD and ASD symptoms, and emotional or behavior problems (Collins et al. 2015; Isaacs et al. 2011; Molloy et al. 2016; Smithers et al. 2010).

Overall, some meta-analysis concluded that there is insufficient evidence to recommend DHA supplementation in preterm (Schulzke, Patole, and Simmer 2011), and also in full-term infants (Koletzko et al. 2008; Qawasmi et al. 2012; Simmer 2011), 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 (Parellada et al. 2017).

How can DHA be related to ASD and ADHD?

Potential mechanistic pathways of DHA in ASD

Women appear to have a higher conversion rate of ALA into DHA, associated with higher hepatic expression of PUFA desaturase enzymes, and probably longer DHA half-life in the plasma compared to men (Domenichiello, Kitson, and Bazinet 2015). This could indicate that DHA have an important role in ASD since it is more frequent in boys (Hall 2016; Morgese and Trabace 2016). 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 (Cardoso, Afonso, and Bandarra 2017). 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 (Mazahery et al. 2017). Parletta, Niyonsenga, and Duff (2016) showed that a worse PUFA profile, especially in relation to this PUFA ratio, is associated with clinical severity in children with ASD or ADHD. Additionally, a mechanistic model linking the ASD phenotype and DHA deficiency has been proposed recently, together with a testing strategy to verify this connection (Hall 2016).

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 (Das 2013; Van Elst et al. 2014). However, their potential biological pathways in ASD are not yet fully understood (Das 2013).

A deficit of DHA during perinatal period was shown to be associated with a reduction in neurogenesis and delays in neuronal migration (McNamara et al. 2017), and it has recently been implicated in synaptic plasticity (Delorme et al. 2013) – a new research field in ASD (Delorme et al. 2013; Ebert and Greenberg 2013). ASD is also characterized by changes in myelination and by an abnormal long-range brain connectivity. Additionally, the formation of white matter tract appears to be very susceptible to the n-6 to n-3 PUFA ratio (Durand et al. 2013). 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 (Lukiw and Bazan 2008; Taurines et al. 2014). Children with ASD have lower BDNF levels, associated with more severe disease (Taurines et al. 2014), and a supplementation with DHA could normalize BDNF in some brain areas affected in ASD (Wu, Ying, and Gomez-Pinilla 2011).

From a neurochemical point of view, there are studies that point to the effect of DHA deficiency on the modulation of GABA-ergic receptor functions, especially in specific GABAA receptor subunits (Hamazaki and Hamazaki 2008), or to an interaction between PUFAs and PLA2 (Phospholipase A2), present in the plasma membrane (Van Elst et al. 2014). PLA2 is able to inhibit GABAA receptor function and high n-6 ARA levels may increase its activation, resulting in increased neuronal excitability (Van Elst et al. 2014). 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 glutamatergic system in offspring female rats (Kodas et al. 2004; Moreira et al. 2010; Zimmer et al. 1998). Then, a DHA supplementation increased synaptic plasticity in hippocampal neurons and improved glutamatergic neurotransmission (Kim, Spector, and Xiong 2011). However, following its supplementation, DHA levels increase differently in the various brain regions (Van Elst et al. 2014). 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 (Pardo and Eberhart 2007).

Regarding the problem of systemic immune dysfunction present in up to 60% of autistic patients (Pardo and Eberhart 2007), Weiser, Butt, and Mohajeri (2016) 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 (Careaga, Van de Water, and Ashwood 2010; Madore et al. 2016; Onore et al. 2013), and the increase in the n-6 to n-3 PUFA ratio is one of the possible reasons for this (Van Elst et al. 2014). 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 (Van Elst et al. 2014). Mostafa, El-Khashab, and Al-Ayadhi (2015) found also higher serum levels of brain-specific autoantibodies, namely anti-myelin basic protein, in autistic patients, probably linked to a lower plasma DHA and higher 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 (Madore et al. 2016). N-3 PUFA deficiency during perinatal period alters intestinal microbial balance in offspring, inducing dysbiosis, with a reduction in bacterial density and a decrease in the proportion of Firmicutes to Bacteroidetes (Gibson et al. 2015; Madore et al. 2016). N-3 PUFA supplementation showed to promote an increase in gut Lactobacillus and Bifidobacterium species and a decrease in potential pathobionts, such as in Enterobacteriaceae family (Madore et al. 2016). On the other hand, microbial overgrowth can affect the uptake and metabolism of PUFAs and other molecules (Madore et al. 2016). 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 of about 1-2:1, in the prevention or symptomatic improvement of ASD, recently indicating the gut:brain axis as a potential target for intervention in ASD.

Potential mechanistic pathways of DHA in ADHD

The study of Stevens et al. (1995) 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 (Chang et al. 2018) 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 compared to controls, showing that while RBCs PUFAs are strongly correlated with dietary intake of the previous month (Sun et al. 2007), and their brain levels (Pivik et al. 2009), plasma levels only reflect its intake in the last days (Chang et al. 2018).

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 (McNamara et al. 2017).

The most studied mechanism relating DHA intake to the pathophysiology of ADHD is the alteration in cortical dopamine neurotransmission (Cardoso, Afonso, and Bandarra 2017; Morgese and Trabace 2016). 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 (Zimmer et al. 2002).

Other authors have also found a pro-inflammatory status in ADHD, supporting the idea that n-3 PUFAs present benefits in controlling ADHD symptoms by its anti-inflammatory action. For example, Hariri et al. (2012) 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 (Gould et al. 2017). Indeed, it should be noted that low DHA intake has been associated with anxiety disorders (Liu et al. 2013), a risk factor for ASD and ADHD, while its supplementation has shown anxiolytic effects (Jacka et al. 2012). 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.

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

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, all damaged in ASD. However, how maternal intake of DHA additionally affects the development of ASD is less clear, and research dedicated to this topic is scarce (see Supplementary material, Table S4). Recently, Julvez et al. (2016) reported that maternal seafood intake during pregnancy, particularly fish with a high fat content, confers 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 previously 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. (2013) 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 were 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 (Graaff et al. 2016). However, Gao et al. (2016) and Julvez et al. (2016) found a protective effect of fish intake during or before pregnancy against ASD diagnosis, respectively. Note that in all of these studies, the information associated with the type of fish consumed and the culinary process is missing.

DHA requirement during pregnancy has to be combined with an optimal postnatal and early childhood dietary intake of it, important for cortical circuits' maturation (Van Elst et al. 2014). 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 (Al-Farsi et al. 2013).

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 (Al-Farsi et al. 2012; Boucher et al. 2017; Julvez et al. 2007; Schultz et al. 2006; Shafai et al. 2014), others did not (Husk and Keim 2015). For example, Al-Farsi et al. (2012) 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 (Tseng et al. 2017). Boucher et al. (2017) 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. (2006) 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 (Tseng et al. 2017). 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 not only with worse neurodevelopmental outcomes (Bernard et al. 2013; Valent et al. 2013) but also with higher number of autism traits in offspring (Graaff et al. 2016). Graaff et al. (2016) 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. On the other hand, 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 be only the increasing of n-3 PUFA intake but also the reduction of food intake with high content of n-6 PUFAs.

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 (Morgese and Trabace 2016) (see Supplementary material, Table S5).

Some studies reported that higher maternal DHA levels at birth were associated with lower ADHD symptoms, such as inattention in toddlers (Kannass, Colombo, and Carlson 2009) and hyperactivity/inattention during school age (Kohlboeck et al. 2011). Gale et al. (2008) also showed that children whose mothers had eaten fatty fish, rich in EPA and DHA, early in pregnancy had a lower risk of hyperactivity compared to those whose mothers did not eat fatty fish. In addition, Sagiv et al. (2012) 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 (Hibbeln et al. 2007). Once again, in ADHD studies, no author has included information regarding seafood intake as doses and culinary treatment.

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 (Jensen et al. 2010; Ramakrishnan et al. 2016), others did not find any association (Gould et al. 2014). Although these studies addressed healthy population, Ramakrishnan et al. (2016) 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 (Groen-Blokhuis et al. 2013; Mimouni-Bloch et al. 2013; Park et al. 2014; Stadler et al. 2016). 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 (Mimouni-Bloch et al. 2013; Park et al. 2014; Stadler et al. 2016).

In summary, the present review included 73 studies, reported in Supplementary material, Tables S1–S5. Of these, 59 studies reported the effect of DHA on various neurodevelopmental outcomes in the offspring and only 9 and 5 studies concerned individuals with ASD and ADHD, respectively.

Of the 9 ASD studies, DHA was measured in biological samples in 2 cases. Three categories were used to summarize the conclusions (Supplementary material, Table S4): "positive association", when there was a statistically significant positive association with the clinical diagnosis of ASD ($n = 5$); "inconsistent association", when a positive association was detected with autism traits but no clinical diagnosis was established ($n = 2$); and "no association", when no statistically significant association was found between the two variables ($n = 2$).

In the 5 ADHD studies (Supplementary material, Table S5) DHA was not measured. All of 5 studies reported a positive association between breastfeeding and ADHD diagnostic.

In the 59 studies addressing the normal neurodevelopmental (Supplementary material, Tables S1–S3): in the observational studies ($n = 24$) DHA was measured in biological samples in 9 cases. Thirteen showed a "positive association", 4 showed "inconsistent association", 6 showed "no association" and 1 showed "conflicting results"; in the prenatal RCTs studies ($n = 17$), 2 showed a "positive association", 5 showed "inconsistent association", 9 showed "no association" and 1 showed "conflicting results"; in the postnatal RCTs studies in full-term infants ($n = 9$), 1 showed a "positive association", 4 showed "inconsistent association" and 4 showed "no association"; in the postnatal RCTs studies in preterm infants ($n = 9$), 1 showed a "positive association", 3 showed "inconsistent association" and 5 showed "no association"."

Discussion

ASD and ADHD arise from interactions between genetic and environmental factors that influence neurobiological systems beginning in the prenatal period. It is unlikely that a single neuroanatomical 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 fatty fish and other seafood consumption. 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 population study. 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. Breastfeeding is a natural and efficient DHA source. However, DHA content of human milk is highly variable, it depends on mother's diet and her FADS genetic make-up (Brenna et al. 2007; Fidler et al. 2000; Hall 2016; Xie and Innis 2008). 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. Additionally, in this period, it seems to be more important to have an optimal n-6 to n-3 PUFA ratio than ideal levels of DHA. Although these results were found in healthy children, collectively, these findings may 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 seems 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.

In conclusion, DHA and EPA-rich food, particularly in pre- and postnatal period, appear to have a positive impact in some populations of offspring. Particularly in very preterm infants and very low birth weight infants, research has shown the role of DHA in neurodevelopmental outcomes and the importance of having an optimal n-6 to n-3 PUFA ratio. Early deficits of DHA in fetal brain may possibly impinge normal development and represent a modifiable risk factor for ASD and ADHD. In order to clarify this role, more and better-quality studies, especially focused on ASD and ADHD diagnosed populations, are necessary. It is also

important to include the individual baseline intake/status of DHA to predict who will benefit from an intervention through diet supplementation or optimization. Recently, the Food and Drug Administration (FDA) and the Environmental Protection Agency, recommend that pregnant women, women who might become pregnant, and breastfeeding mothers eat 2–3 servings of lower-mercury fish or 8–12 ounces (227–340 g) per week, while avoiding fish intake that is high in mercury (FDA 2017; EPA 2017). 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 (Costa et al. 2015), sardine (Bandarra et al. 2004), mackerel, horse mackerel, tilapia), (2) "Good choices" (eat 1 time/week; e.g. hake, meager (Afonso et al. 2015; Costa et al. 2013), halibut, mahi-mahi, snapper) and (3) "Fish to avoid"; e.g. swordfish, tilefish, blue shark (Matos et al. 2015). On the other hand, DHA supplementation could be an alternative to optimize maternal DHA levels in women who do not achieve optimal level of fish intake, such as poorly nourished mothers, those on vegan diets or those with a family history of mental illness. Moreover, n-3 PUFAs supplements and fortified formulas seem to be well tolerated. Newberry et al. (2016), 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. In infants, adverse events were also limited to GI symptoms, with most serious adverse events related to morbidities associated with prematurity.

In summary, our results point to the need of more methodological sound research particularly addressing clinically diagnosed ASD and ADHD populations to convey more robust conclusions and inform good practice.

Disclosure statement

The authors declare no conflict of interest.

ORCID

Narcisa M. Bandarra http://orcid.org/0000-0002-7563-9226
Margarida Figueiredo-Braga http://orcid.org/0000-0003-2374-4371

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