



Personalised medicine in child and Adolescent Psychiatry: Focus on omega-3 polyunsaturated fatty acids and ADHD



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ABSTRACT

Attention deficit hyperactivity disorder, or ADHD, is a common childhood disorder with a prevalence rate of 5–10%. There have been many theories proposed to explain ADHD, and one of them focuses on the deficiency of essential fatty acids (EFA), particularly omega-3 polyunsaturated fatty acids (n-3 PUFAs) including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Studies have shown that there is a positive correlation between EFA deficiency severity and ADHD symptoms, and a negative association between blood PUFAs levels and ADHD symptoms. Moreover, clinical studies have shown a promising effect of n-3 PUFAs in the treatment of both clinical and cognitive symptoms in children with ADHD. In addition, with the more relatively safe and tolerable properties of n-3 PUFAs when comparing with the standard pharmacotherapy, n-3 PUFAs may be a potential treatment option for children with ADHD. Of note, the association between n-3 PUFAs deficiency and ADHD has been suggested to involve several biological systems, including inflammation, dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS), and an imbalanced gut-microbiota axis (GBA). Thus, the biomarkers from these biological systems may serve as possible treatment response predictors of n-3 PUFAs in children with ADHD.

1. Attention deficit hyperactivity disorder (ADHD)

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder that has high comorbidity with other psychiatric disorders, including conduct disorders (Biederman et al., 1991a), mood disorders (Biederman et al., 1991b), anxiety disorders, and substance use disorders (Wilens and Biederman, 2006). The global prevalence rate is around 5–10% (Biederman and Faraone, 2005). Untreated ADHD has been reported to have an overwhelming impact on society, including an increase in work absenteeism, school drop-outs, motor vehicle accidents, substance use problems and lower economic growth of the society as a whole (Volkow and Swanson, 2013). Moreover, children with ADHD tend to have a more impaired relationship with their mothers and less family support (Chang and Gau, 2017; Gau and Chang, 2013). Although current pharmacotherapy, including methylphenidate and atomoxetine, has a good efficacy of around 60–80%, there are still about 20–40% of patients with ADHD either respond poorly to the current treatments or suffer from medication side effects (Childress and Sallee, 2014). On the other hand, nutritional interventions such as n-3 PUFAs supplementation, have emerged in recent years as a potential alternative

treatment option for children with ADHD (Chang et al., 2018c, 2019; Chang et al., 2019b) (see Fig. 1).

2. N-3 PUFAs

The two main types of polyunsaturated fatty acids (PUFAs) in the human body are the omega-6 (n-6) PUFAs from the cis-linoleic acid (LA, 18:2n-6) and the omega-3 (n-3) PUFAs from the α -linolenic acid (ALA, 18:3n-3). Not only are they important constituents of cell membranes, but they are also called essential fatty acids (EFAs) since they are crucial for the survival of humans; they cannot be synthesized by the human body and can only be obtained from diets (Das, 2006). The PUFAs appear to have biological functions, and these functions require their conversion into metabolites including eicosanoids. Linoleic acid can be converted to gamma-linolenic acid (GLA, 18:3n-6) and GLA can be elongated to form dihomo-GLA (20:3n-6), which is the precursor of the prostaglandin (PG)-1s. Dihomo-GLA can also be converted to arachidonic acid (AA, 20:4n-6), which is the precursor of the pro-inflammatory PG-2s, thromboxanes (Tx) and the Leukotriene (LT)-4s. On the other hand, ALA can be converted to eicosapentaenoic acid (EPA; 20:5n-3) and EPA forms the

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precursor of anti-inflammatory PG-3s and LT-5s. EPA can also be converted to docosahexaenoic acid (DHA; 22:6n-3) (See Fig. 2). Both PG-2s and LT-4s have pro-inflammatory action and are known to be involved in the pathophysiology of inflammation-associated disorders, such as atherosclerosis, asthma, cardiovascular diseases, cerebrovascular diseases, inflammatory bowel syndrome, neurological diseases and metabolic syndrome (Connor, 2000; Das, 2006; Torpy et al., 2006). Moreover, Phospholipase A2 (PLA2) and cyclooxygenase 2 (COX2) are the two key enzymes of the PUFA metabolism and PGE2 synthesis (Rao et al., 2008). PLA2 is a large family of enzymes, with Ca²⁺-independent phospholipase A2 (iPLA2) preferentially on DHA metabolism and cytosolic PLA2 (cPLA2) preferentially on AA and EPA metabolism (Strokin et al., 2003, 2004). COX2 converts AA to PGE2, and PGE2 relates to the development of mental and physical disorders such as depression and cardiovascular diseases (CVDs) via its actions in immunomodulation (Su, 2008). COX2 and PLA2 polymorphisms have been reported to be associated with risk for depression and increased inflammation (Chang et al., 2018b; Su et al., 2010).

N-3 PUFAs have been reported to be important for several brain disorders (Hibbeln et al., 2007; Su et al., 2008, 2014). DHA and EPA as mentioned earlier are EFAs crucial for the brain and the body, thus the deficiency of both may impair brain development and attribute to the development of several brain disorders including depression. Moreover, DHA deficiency has been associated with neuronal membrane instability and abnormal transmission of serotonin, norepinephrine and dopamine (Chalon, 2006; Su et al., 2003), associated with the mood and cognitive



Fig. 1. Jane Pei-Chen Chang

Jane is currently the director of the Child and Adolescent Psychiatry Division and the PI at the Mind-Body Interface (MBI)-Lab of China Medical University (CMU) Hospital and the assistant professor at CMU in Taiwan. Jane received her MD and MSc from CMU and her PhD in Psychological Medicine at the Institute of Psychiatry, Psychology and Neuroscience (IoPPN) at King's College London (KCL). Jane is also the visiting researcher and part of the Stress, Psychiatry and Immunity (SPI)-Lab at IoPPN. Her research interests include in search for novel treatments and biomarkers for depression and attention deficit hyperactivity disorder (ADHD), with a special focus on omega-3 polyunsaturated fatty acids. Jane has published more than 50 SCI articles, including a recent clinical guideline of omega-3 in child and adolescent psychiatric disorders, in high impact factor journals such as *Brain Behavior and Immunity* (BBI), *Neuropsychopharmacology* and *Translational Psychiatry*. She currently serves on the Editorial Board of BBI. Her research has successfully attracted grants from Ministry of Science and Technology in Taiwan and National Institute of Health Research and Biomedical Research Centre in UK. Jane has received several recognitions for her work from several prestigious and distinguished associations globally, including The World Psychiatric Association (WPA) Young Psychiatrists Award, The International Association of Child and Adolescent Psychiatry and Allied Professions (IACAPAP) Donald J Cohen Fellowship Award, The Junior Clinical British Association for Psychopharmacology (BAP) Psychopharmacology Award, The World Federation of Societies of Biological Psychiatry (WFSBP) Young Researcher's Award, The Association of Asian Child and Adolescent Psychiatry and Allied Professions (ASCAPAP) Future of Asian Child and Adolescent Psychiatry Award, and recently, two Dr. Paul Janssen Research Awards in 2020 from The Taiwanese Society of Child and Adolescent Psychiatry and The Taiwanese Society of Biological Psychiatry and Neuropsychopharmacology.

symptoms in depression. On the other hand, N-3 PUFAs have been shown in clinical trials to improve and prevent symptoms of depression (Chang et al., 2019a; Lin and Su, 2007; Su et al., 2003, 2008, 2014) and cognitive function in mild cognitive impairment (Chiu et al., 2008).

3. N-3 PUFAs and ADHD

3.1. N-3 PUFAs deficiency and ADHD

Deficiency in n-3 PUFAs has been suggested to underpin part of the mechanisms in ADHD (Stevens et al., 1995). For example, mothers who have lower seafood intake during pregnancy are at risk of having children with suboptimal developmental outcomes for prosocial behaviors, fine motor coordination, verbal communication and social development (Hibbeln et al., 2007). Moreover, our recent study showed that children with ADHD have greater severity of EFA deficiency, a clinical syndrome associated with insufficient fatty acid levels and comprising symptoms such as dry and scaly skin, eczema, and dry eyes (Chang et al., 2016). In addition, EFA deficiency in children with ADHD has been associated negatively with plasma DHA levels (Stevens et al., 1995) and positively with ADHD symptoms (Chang et al., 2016).

ADHD, compared to typically developing (TD) children, also has lower levels of red blood cells (RBCs) PUFAs (Stevens et al., 1995) and higher n-6/n-3 ratios (Stevens et al., 2003), while lower n-3 PUFAs levels have been positively associated with the severity of ADHD symptoms in children (Colter et al., 2008; Stevens et al., 2003). Our recent meta-analysis further indicated that children with ADHD have lower blood levels of DHA, EPA and total n-3 PUFAs when compared with TD children (Chang et al., 2018c).

It is also interesting to note that ADHD has been associated with the single nucleotide polymorphisms (SNPs) of *FADS* (*fatty acid desaturase*)1 and *FADS*2 genes, genes responsible for coding the enzymes (delta-5 desaturase and delta-6 desaturase) responsible for the metabolism of PUFAs (Brookes et al., 2006). For example, ADHD has been associated with SNP rs498793 in the *FADS*2 gene, while the two *FADS*1 gene SNPs rs174545 and rs174548 have been associated with ADHD in a group of children prenatally exposed to alcohol (Brookes et al., 2006).

3.2. N-3 PUFAs supplementation in ADHD

Although n-3 PUFAs have recently received attention as a possible treatment for ADHD, several issues have not been addressed in the current literature. For example, there is a lack of information on n-3 PUFAs supplementation. For example, should the supplementation be DHA or EPA monotherapy, or a combined formula of EPA and DHA? Moreover, how much dosage and how long should n-3 PUFAs be prescribed to treat ADHD?

The findings supporting n-3 PUFAs for ADHD have been controversial. For example, some clinical trials with n-3 PUFAs supplementation in ADHD have shown improvement in clinical symptoms (Manor et al., 2012; Perera et al., 2012; Richardson and Puri, 2002) and cognitive performances (Sinn et al., 2008; Vaisman et al., 2008; Voigt et al., 2001), while others reported negative findings (Widenhorn-Muller et al., 2014). Moreover, when reviewing clinical trials of n-3 PUFAs in children with ADHD, one would find that most of the trials used DHA, rather than EPA, as the main component of the n-3 PUFAs (Richardson and Puri, 2002; Voigt et al., 2001) and used a relatively low dosage of n-3 PUFAs (DHA + EPA < 500 mg/d) (Sinn et al., 2008; Vaisman et al., 2008; Voigt et al., 2001). See Table 1 for the characteristics and Table 2 for the challenges of the current n-3 supplementation studies in children with ADHD.

The previous meta-analyses findings investigating the effects of n-3 PUFAs in ADHD (Cooper et al., 2015; Gillies et al., 2012; Hawkey and Nigg, 2014; Puri and Martins, 2014; Sonuga-Barke et al., 2013), consists of shortcomings including heterogeneity in the clinical sample (including both children and adult subjects (Hawkey and Nigg, 2014) or subjects

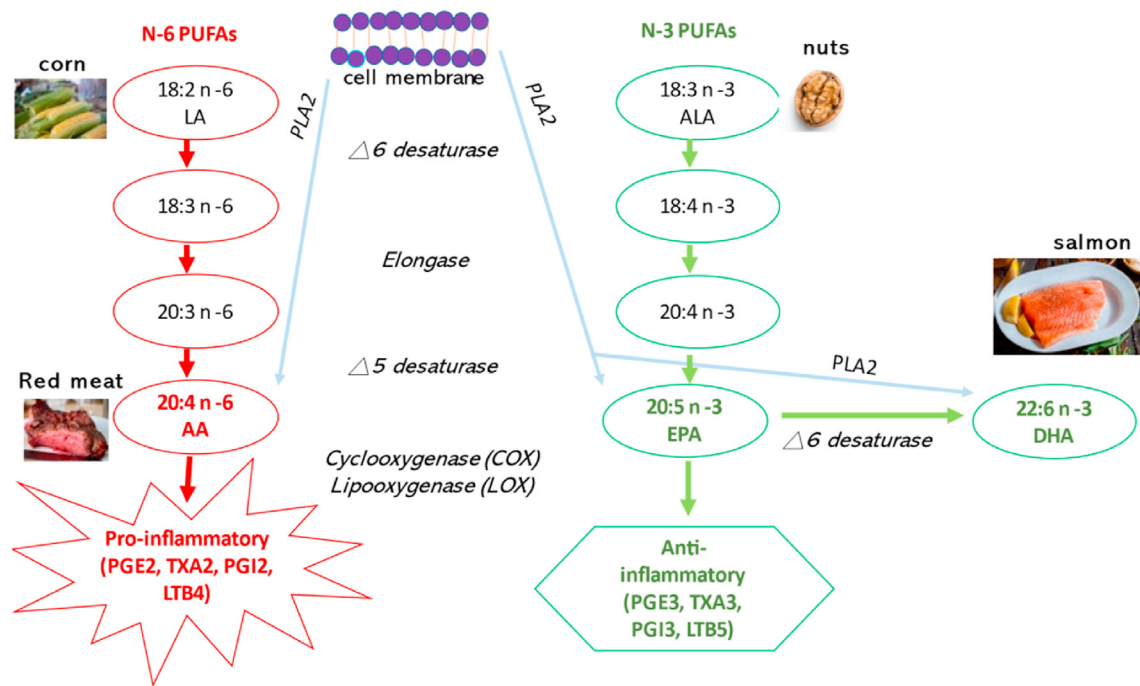


Fig. 2. Metabolism of N-3 and N-6 PUFAs. The sources of n-3 and n-6 PUFAs can either be obtained from food (such as nuts and deep-sea oily fish for n-3 PUFAs; corn and red meat for n-6 PUFAs) or from the cell membrane (iPLA2 preferentially on DHA metabolism and cPLA2 preferentially on AA and EPA metabolism). N-6 PUFAs derive from LA (18:2n-6) and n-3 PUFAs derive from ALA (18:3n-3). LA can be converted to GLA (18:3n-6) and GLA can be elongated to form dihomogamma-Linolenic acid (20:3n-6). Dihomogamma-Linolenic acid can also be converted to AA (20:4n-6); and ALA can be converted to EPA (20:5n-3). COX and LOX then convert AA and EPA to pro-inflammatory PG-2s, TXs and the LT-4s, and anti-inflammatory PG-3s and LT-5s, respectively. EPA can also be converted to DHA (22:6n-3). N-3 and n-6 PUFAs compete for the same enzymes in elongation and desaturation. Abbreviations: AA, arachidonic acid; ALA, α -linolenic acid; cPLA2, cytosolic phospholipase 2; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GLA, gamma-linolenic acid; iPLA2, Ca²⁺-independent phospholipase A2; LT, leukotrienes; n-3, omega-3; n-6, omega-6; PUFAs, PG, prostaglandins; polyunsaturated fatty acid; Tx, thromboxanes. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Summary of Supplementation Studies of n-3 PUFAs in Children with ADHD.

Study	Indication	Doses (mg)	Dur (wk)	Main Outcome	Safety Concerns/Idiosyncrasies
Voigt et al. (2001)	ADHD	DHA: 345	16	CBCL/CCTT/CRS/TOVA: No Diff	No AE
Richardson et al. (2002)	ADHD	EPA:186 DHA:480	12	Improved CPRS-L ADHD Subscales & DSM inattention, DSM global total	AE: N-3 (Digestive:1); Placebo (Digestive:1)
Sinn et al. (2008)	ADHD	EPA:93 DHA:29	15	Improved TEA-ch creature counting accuracy	AE (did not indicate whether n-3 or placebo): Nausea:2 Nosebleeds:1
Vaisman et al. (2008)	ADHD	EPA: 153 DHA: 96	12	Improved TOVA scores	AE (did not indicate whether n-3 or placebo, but no difference in attrition rates between groups): GI:3, rash:1
Manor et al. (2012)	ADHD	EPA:560 DHA: 40	15	Improved CRS-P: RI subscale + CHQ PE subscale scores	AE: N-3 (GI:6; AD:1; Elevated GOT:1; Hyperactivity:1; Nausea:1; Tantrums:2; Tics:1); Placebo (GI:4; Headache:1)
Perera et al. (2012)	ADHD	EPA:560	24	Improved in inattention, impulsiveness, and cooperation with teachers and parents	No AE
Widenhorn-Muller et al. (2014)	ADHD	EPA:600 DHA:120	16	Improved CBCL-P: thought problems, CBCL-T aggressive behaviors, HAWIK-IV: WMI, DS, DBW	No AE
Chang et al. (2019)	ADHD	EPA: 1200	12	Improved in CPT (Focused attention, Vigilance)	No AE

Note: AD, atopic dermatitis; ADHD, attention deficit hyperactivity disorder; AE, adverse events; CBCL, Child Behavior Checklist; CBCL-P, parent rated; CBCL-T, teacher rated; CCTT, Children's Color Trails test; CHQ, Child Health Questionnaire; CPRS-L & CRS-P, Conner's Parent Rating Scale; CRS, Conner's Rating Scale; DBW, digit backward task; DHA: docosahexaenoic acid; Diff, difference; DS, digit span; DSM, The Diagnostic and Statistical Manual of Mental Disorders; EPA, eicosapentaenoic acid; GI, gastrointestinal; GOT, glutamic oxaloacetic transaminase, HAWIK, Hamburg Wechsler Intelligence Scales for Children; N-3, omega-3 fatty acids; PE, Parent impact-emotional subscale; RI, Restless/Impulsive subscale; TEA-ch, Test of Everyday Attention for Children; TOVA, Test of Variables of Attention; Wk, weeks; WMI, working memory index.

with a diagnosis other than ADHD (Cooper et al., 2015; Puri and Martins, 2014)), as well as by the inclusion of non-parallel trials (Hawkey and Nigg, 2014; Puri and Martins, 2014), and as well as mixed supplementation interventions including n-3 PUFAs together with vitamins and

nutrients (Gillies et al., 2012; Sonuga-Barke et al., 2013). We have tried to address the limitation of the previous meta-analyses and recently conducted a meta-analysis on the effects of randomised controlled trials of n-3 PUFAs monotherapy in children with pure ADHD (involving 6

Table 2
Challenges of n-3 PUFAs Supplementation Studies in Children with ADHD.

Shortcomings	Studies
DHA as main component EPA < 500 mg	Voigt et al., (2001); Richardson et al., (2002) Voigt et al., (2001); Richardson et al., (2002); Sinn et al., (2008); Vaisman et al., (2008)
Low n-3 PUFAs (DHA + EPA) dosage < 500 mg	Voigt et al., (2001); Sinn et al., (2008); Vaisman et al., (2008)
Duration < 16 wks	Richardson et al., (2002); Sinn et al., (2008); Vaisman et al., (2008); Manor et al., (2012); Chang et al., (2019)

Note: DHA: docosahexaenoic acid; EPA, eicosapentaenoic acid; N-3 PUFAs, omega-3 polyunsaturated fatty acids; Wks, weeks.

trials with 524 children) and found that n-3 PUFAs have greater improvement in both inattention and total ADHD scores and cognitive function (Chang et al., 2018c). In addition, the subanalysis showed that n-3 PUFAs supplementation with EPA > 500 mg/d improved clinical hyperactivity/impulsivity symptoms (Chang et al., 2018c). The content of EPA as the main component of the n-3 PUFAs is further emphasized in another study examining 10 ADHD clinical trials with 699 children with ADHD (predominantly males, 60–87%), which suggested that a high dose of EPA (1–2g) supplementation is required to show significant improvement of clinical symptoms in ADHD (Bloch and Qawasmi, 2011). In addition, EPA has been suggested to be the “active” component with antidepressant effects among the n-3 PUFAs supplementation in depression (Lin et al., 2012). This may be due to the effect of EPA to counteract the actions of AA, and with its anti-inflammatory effects (see section 2), and with inflammation as a potential mechanism involved in ADHD, the anti-inflammatory properties of EPA may help improve ADHD symptoms via immunomodulation. Thus, a higher ratio of EPA to DHA (e.g., 2:1 ratio) in the combined formula or even EPA monotherapy should be considered for n-3 PUFAs supplementation in ADHD.

Our meta-analysis further showed that the duration of most of the trials in this area range between 12 and 16 weeks to show an effect on clinical symptoms (Chang et al., 2018c). Moreover, it has been reported that it requires at least 16 weeks to have an effect on cognitive performance (Stonehouse, 2014), about 24 weeks to reach a steady level in the RBC (Katan et al., 1997), and sometimes up to 52 weeks to show behavioural changes (Raine et al., 2015).

Identifying the clinical characteristics of children with ADHD who responded well to n-3 PUFAs treatment may further maximize the treatment efficacy of n-3 PUFAs. N-3 PUFAs in depression studies showed an increase in effect size in patients with inflammation (Rapaport et al., 2016), suggesting that inflammation may be a potential treatment target for n-3 PUFAs treatment. This concept was further supported by our recent clinical trial, showing a high EPA dosage of 1200 mg/d improved cognitive function (focused attention and vigilance) *only* in those children with ADHD with a low endogenous EPA level (<0.91%, *more inflamed*), but did not improve cognitive function in those children with moderate (between 0.91 and 1.98%) or high ($\geq 1.08\%$) endogenous EPA level (Chang et al., 2019a,b). The groups were defined with the stratification based on the tertiles of the EPA levels of the children enrolled in the study, thus generalisation of the values of different EPA levels may be limited. However, the findings of this pioneering study implicated that by subtyping ADHD with inflammation status or endogenous n-3 PUFAs level may contribute to the personalised medicine in ADHD with n-3 PUFAs as treatment; where endogenous n-3 PUFAs levels and inflammation status can be used as a treatment response predictor.

Depression in adulthood has also been reported to be associated with untreated childhood ADHD and persistent ADHD symptoms (Ginsberg et al., 2014). Although there have been no clinical trials of n-3 PUFAs in adult ADHD measuring clinical symptoms as the outcome, it has been shown that adults with ADHD also have a deficiency in n-3 PUFAs, including lower erythrocyte total n-3 PUFAs (Young et al., 2004) and a higher n-6/n-3 ratio (Laasonen et al., 2009); the deficiency in n-3 PUFAs

has been associated with cognitive decline in normal adults (Young et al., 2005). On the other hand, n-3 PUFAs supplementation has been shown to enhance not only cognition in healthy adults (Fontani et al., 2005), but also increase total n-3 PUFAs and decrease n-6 PUFAs and n-6/n-3 ratio in adults with ADHD (Young et al., 2005). Since adults with persistent ADHD, have a higher chance of comorbid depression (Yoshimasu et al., 2018), n-3 PUFAs may serve as a potential treatment option for this group of patients to help improve both ADHD and depression symptoms.

4. N-3 PUFAs: the missing link in ADHD?

N-3 PUFAs have been suggested to be involved in several mechanisms potentially underpinning ADHD. These mechanisms include inflammation, the hypothalamus-pituitary-adrenal (HPA) axis stress response, the gut microbiota composition, and the autonomic nervous system (ANS) activity.

4.1. Inflammation

Inflammation has recently been widely discussed in ADHD. Previous epidemiological and clinical studies have shown high comorbidity of ADHD with inflammatory and autoimmune disorders and the differences in biomarkers between ADHD and TD youth. ADHD has been associated with several allergy-related disorders including asthma, atopic dermatitis (Miyazaki et al., 2017; Schans et al., 2017) and psoriasis (Hegvik et al., 2018). Moreover, a personal and maternal history of autoimmune diseases, such as thyrotoxicosis, type 1 diabetes, autoimmune hepatitis, psoriasis and ankylosing spondylitis, has been associated with an increased risk for ADHD (Nielsen et al., 2017).

The inflammatory and autoimmune disorders may be associated with the continuous release of cytokines that further impact the functions of the prefrontal cortex, which are often impaired in ADHD (Sebastian et al., 2014). Cytokines produced by systematic inflammation may pass the blood-brain barrier, affect synaptic plasticity and neurogenesis, and may even induce T-cell mediated neuroinflammation (Buske-Kirschbaum et al., 2013; Oades et al., 2010a), which then contribute to the pathogenesis of ADHD. Moreover, ADHD has been shown to have higher comorbidity with T-cell mediated neuroinflammation (Gungor et al., 2013; Schmitt et al., 2010).

ADHD has also been suggested as the result of an exaggerated central nervous system (CNS) inflammatory response in fetus associated with maternal inflammation (Lefka et al., 2018). Infections associated with inflammatory responses during the first postnatal month have been associated with the risk for developing ADHD at the age of 10 (Allred et al., 2017). Moreover, a similar genetic signature between ADHD and depression in genes related to inflammation has also been reported (de Jong et al., 2016). However, the studies regarding inflammatory biomarkers in ADHD have been inconclusive. For example, some studies, including our own study, reported a higher immunoreactivity and higher levels of pro-inflammatory cytokines such as interleukin(IL)-6 (Chang et al., 2020) and anti-inflammatory cytokines such as IL-10 in ADHD (Donfrancesco et al., 2016; Passarelli et al., 2013), while others found no differences in IL-1 β , IL-6, IL-10 levels between ADHD and TD groups (Corominas-Roso et al., 2017; Oades et al., 2010b). Our recent study also reported higher levels of high-sensitivity c-reactive protein (hs-CRP) in ADHD when compared with TD children (Chang et al., 2020).

N-3 PUFAs, especially EPA, is important in balancing the immune functions and physical health by reducing membrane AA (an n-6 PUFAs) and PGE2 synthesis (Faroqui et al., 2006), which might be associated with medical comorbidity and somatic symptoms in depression (Su, 2009). Moreover, EPA and DHA have been shown to increase anti-inflammatory action via inhibition of free radical generation and oxidant stress (Das, 2006), and to regulate neurotransmitter and immune functions via the modulation of lipid rafts signaling platforms on the cell membrane (Chang et al., 2010). A recent animal study further showed that n-3 supplementation is essential during the gestation period,

especially in those pregnant mice with maternal immune activation (MIA), where the pregnant mice were injected with lipopolysaccharide to induce inflammation reaction. The study showed that a diet deficient of n-3 PUFAs exacerbated inflammation in the pregnant mice with MIA, and induces spatial memory deficits in the adult offspring; while the adult offspring of the mice fed with n-3 balanced diet during gestation period have no memory deficits (Labrousse et al., 2018).

4.2. HPA axis stress response

HPA axis dysregulation has been reported in children with ADHD, but the findings have not been consistent. For example, one study comparing ADHD and TD children reported a lower morning salivary cortisol level in children with ADHD (Isaksson et al., 2012), while another study reported no such differences (van West et al., 2009). Moreover, some studies were able to demonstrate a correlation between low basal cortisol levels and total ADHD symptoms (Wang et al., 2011) or hyperactivity symptoms (Kaneko et al., 1993; Wang et al., 2011), while other studies failed to report such an association (Pesonen et al., 2011). To date, four studies measured salivary cortisol levels in children with ADHD at 3 or more time points throughout the day, where two studies reported lower awakening cortisol together with a lower 1800h cortisol (Angeli et al., 2018) or lower bedtime cortisol (Chang et al., 2020; Isaksson et al., 2012), while one reported higher bedtime cortisol (Imeraj et al., 2012). On the other hand, medications for ADHD, such as methylphenidate, have been shown to increase cortisol levels by triggering dopamine release (Wilens, 2008).

4.3. Gut dysbiosis and ANS activity

Other biological systems that may be involved in the pathogenesis of ADHD include the dysregulation of the gut-brain axis (or gut dysbiosis) and the ANS. Several conditions associated with the risk of ADHD have been associated with gut dysbiosis. ADHD was associated with a decrease in *Faecalibacterium* (Jiang et al., 2018), while a decrease in *Faecalibacterium* has been associated with increased ADHD symptoms and allergic conditions (Bull-Larsen and Mohajeri, 2019). Furthermore, a decreased microbial diversity (alpha diversity) has also been reported in ADHD (Prehn-Kristensen et al., 2018), which may contribute to a 'leaky gut' and low-grade systemic inflammation reported in ADHD. Gastrointestinal (GI) microbes will also affect the brain via activation of the vagus nerve and alteration of the ANS. Interestingly, alteration of ANS has been reported in ADHD (Negrao et al., 2011). Children with ADHD have been reported to have ANS dysregulation with reduced vagally-mediated heart rate variability (HRV) (Robe et al., 2019), while n-3 PUFAs supplementation has been shown to decrease the mean heart rate and increase HRV (Buchhorn et al., 2018).

Overall, studies have supported the potential involvement of inflammation, HPA axis dysregulation, gut dysbiosis and ANS hyperactivity in ADHD. N-3 PUFAs, on the other hand, may mediate via these biological systems to improve ADHD symptoms. However, more studies will be needed to elucidate the specific mechanisms involved with these biological systems. Moreover, the mixed findings of the inflammatory biomarker and the cortisol studies may be attributed to small sample sizes, heterogeneity between the biomarkers and heterogeneity of ADHD. Thus, future n-3 supplementation studies are warranted to evaluate its effects on the inflammatory biomarkers and the HPA axis with larger sample sizes, and subtyping the ADHD subjects with their clinical presentation, e.g., inattentive subtype or hyperactive-impulsive subtype or combined subtype, or biological presentation, e.g., inflammation severity. As for the gut dysbiosis and ANS hyperactivity theories, future studies should examine the effects of n-3 PUFAs on the gut microbiome and the changes in HRV in children with ADHD to further support the proposed mechanisms of actions.

5. Safety and tolerability of N-3 PUFAs

N-3 PUFAs have been widely reported for their tolerability and relative fewer adverse effects when compared with standard treatment in ADHD, however, there are still some potential adverse effects associated with n-3 PUFAs that require our attention. Our recent meta-analysis showed that although there was no evidence for any prescription n-3 PUFAs products (RxOME3FAs), RxOME3FAs were associated with treatment-related dysgeusia (fishy taste), skin abnormalities (eczema, itching), and mild changes on non-lipid blood profiles including fasting glucose, elevated alanine transaminase, while EPA + DHA combination was associated with more treatment-related eructation, nausea and elevation of low-density lipoprotein (LDL) cholesterol (Chang et al., 2018a). Therefore, it is recommended to monitor adverse effects systematically and to obtain a comprehensive metabolic panel in patients receiving higher doses of n-3 PUFAs. In addition, the quality of the n-3 PUFAs is also an important factor that may affect the adverse effects of n-3 PUFAs, and it has been shown that RxOME3FAs have fewer adverse effects than regular n-3 PUFAs supplementations.

Of note, the concerns regarding bleeding with high doses of n-3 PUFAs may have been exaggerated from previous literature, and the ex-vivo hemostatic effect of n-3 PUFAs may not necessarily translate into a clinically significant increased risk of bleeding (Wachira et al., 2014). Recent data have suggested that even with the concurrent usage of antiplatelet or anticoagulant agents and doses up to 4g of n-3 PUFAs/day have not been associated with increased risks for major bleeding (Mori, 2014). Recent meta-analyses focused on pregnancy (Middleton et al., 2018) and perioperative periods (Akintoye et al., 2018) also supported that n-3 PUFAs have similar safety profiles as the placebo in bleeding-related adverse events. In vivo studies also suggested that n-3 PUFAs do not affect platelet aggregation or adhesion in healthy subjects (Bagge et al., 2018). As for the pediatric population, two retrospective studies with chart reviews showed that *neither* oral n-3 PUFAs supplementation (EPA 1267.28 mg + DHA 698.74 mg) over a median duration of (2.5 years) in renal transplant recipients *nor* intravenous fish oil monotherapy (Omegaven: EPA 13–26% & DHA 14–17%) 1 g/kg/day over 8–24 h in patients with intestinal failure-associated liver disease (IFALD) increased risk of bleeding (Filler et al., 2012).

6. Clinical implication

Children with ADHD have been shown to have lower levels of DHA, EPA and total n-3 PUFAs. N-3 PUFAs, on the other hand, are shown to be neuroprotective during the perinatal period, in the context of inflammation or immune activation. Moreover, n-3 PUFAs supplementation, with a combination of DHA and EPA, has been shown to improve clinical and cognitive symptoms in ADHD with a minimum duration of 12 weeks. In addition, inflammatory biomarkers or endogenous levels of n-3 PUFAs may serve as a potential treatment response predictor of n-3 PUFAs in children with ADHD. Thus, n-3 PUFAs may be a potential treatment option for a subpopulation of children with ADHD, e.g., *more inflamed*.

Our recently published clinical guideline of n-3 PUFAs in children with ADHD suggested that if a child would like to use n-3 PUFAs for his/her ADHD: 1) a thorough consultation with the child's primary psychiatrist, 2) if the child is responding well to the current medication, then n-3 PUFAs should be considered as an augmentation strategy to maximize the treatment efficacy, 3) The quality, the dosage, and the EPA/DHA ratio should be examined if the responses to the n-3 PUFAs were not reached optimally, and 4) Periodical monitoring of the child's adverse effects including laboratory changes, skin and GI symptom manifestations is highly recommended (Chang and Su, 2020).

Declaration of competing interest

No conflicts of Interest.

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Appendix A. Supplementary data

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