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1 **Omega-3 Polyunsaturated Fatty Acids in Youths with Attention Deficit**
2 **Hyperactivity Disorder (ADHD): A Systematic Review and Meta-analysis of**
3 **Clinical Trials and Biological Studies**

4
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1 ABSTRACT

2 The role of omega-3 polyunsaturated fatty acids (omega-3 or n-3 PUFAs) in the
3 pathogenesis and treatment of children and adolescents with attention deficit
4 hyperactivity disorder (ADHD) is unclear. A systematic review followed by
5 meta-analysis was conducted on: 1) randomized controlled trials (RCTs) assessing the
6 effects of n-3 PUFAs on clinical symptoms and cognition in children and adolescent
7 with ADHD; and 2) case-control studies assessing the levels of n-3 PUFAs in blood
8 and buccal tissues of children and adolescents with ADHD. In seven RCTs, totalling
9 $n=534$ randomised youth with ADHD, n-3 PUFAs supplementation improves ADHD
10 clinical symptom scores ($g=.38$, $p<.0001$); and in three RCTs, totalling $n=214$
11 randomised youth with ADHD, n-3 PUFAs supplementation improves cognitive
12 measures associated with attention ($g=1.09$, $p=.001$). Moreover, children and
13 adolescents with ADHD have lower levels of DHA (seven studies, $n=412$, $g=-.76$,
14 $p=.0002$), EPA (seven studies, $n=468$, $g=-.38$, $p=.0008$), and total n-3 PUFAs (six
15 studies, $n=396$, $g=-.58$, $p=.0001$). In summary, there is evidence that n-3 PUFAs
16 supplementation monotherapy improves clinical symptoms and cognitive
17 performances in children and adolescents with ADHD, and that these youth have a
18 deficiency in n-3 PUFAs levels. Our findings provide further support to the rationale
19 for using n-3 PUFAs as a treatment option for ADHD.

- 1 **Keywords:** ADHD, adolescents, attention deficit hyperactivity disorder children,
- 2 cognition DHA, EPA, meta-analysis, omega-3, PUFAs levels

1 INTRODUCTION

2 Deficiency in omega-3 polyunsaturated fatty acids (n-3 PUFAs) has recently
3 been investigated as a potential pathogenetic mechanism in ADHD (Stevens *et al*,
4 1995). Although current pharmacotherapies, such as methylphenidate and
5 atomoxetine, are able to improve ADHD symptoms (MTA 1999; Quintana *et al*,
6 2007), there is still about 20-40% of patients with ADHD who do not benefit from
7 these medications (Pliszka *et al*, 2006). Therefore, novel treatments with clear
8 efficacy and measurable biological mechanisms are essential. At cognitive levels,
9 ADHD has been suggested to be a disorder involving an impaired inhibition control
10 system (Barkley, 1997) and a disrupted feedback of the rewarding and motivational
11 system (Barkley, 1997), and n-3 PUFAs have been associated with cognitive function
12 and learning (Milte *et al*, 2011), including in patients with ADHD (Sinn *et al*, 2008;
13 Vaisman *et al*, 2008; Voigt *et al*, 2001). Hence, n-3 PUFAs may be considered one of
14 such novel treatments.

15 Several lines of evidence support the importance of n-3 PUFAs in brain disorders
16 (Hibbeln *et al*, 2007; Su *et al*, 2008; Su *et al*, 2014). The n-3 PUFAs series include
17 docosahexaenoic acid (DHA or 22:6 n-3) and eicosapentaenoic acid (EPA or 20:5
18 n-3), which are essential fatty acids (EFA) that cannot be efficiently synthesized by
19 the human body and have to be obtained through dietary intake. EPA and DHA have

1 an anti-inflammatory action via inhibition of free radical generation and oxidant stress
2 (Das, 2006), and have also been shown to regulate neurotransmitter and immune
3 functions via the modulation of lipid rafts signalling platforms on the cell membrane
4 (Chang *et al*, 2010). Moreover, n-3 PUFAs also improve symptoms of depression
5 (Lin and Su, 2007; Su *et al*, 2003; Su *et al*, 2008; Su *et al*, 2014) and Alzheimer's
6 Disease (Chiu *et al*, 2008).

7 There is promising evidence that n-3 PUFAs may be relevant to ADHD. In
8 epidemiological studies, children of mothers who have lower seafood intake during
9 pregnancy are at risk of suboptimal outcomes for prosocial behaviours, fine motor
10 coordination, verbal communication and social development (Hibbeln *et al*, 2007).
11 Moreover, we have shown that children with ADHD have greater severity of EFA
12 deficiency, a clinical syndrome associated with insufficient fatty acid levels and
13 comprising symptoms such as dry and scaly skin, eczema, and dry eyes (Chang *et al*,
14 2016). In addition, EFA dietary deficiency in children with ADHD correlates
15 negatively with plasma DHA levels (Stevens *et al*, 1995), and we have recently
16 shown that EFA deficiency positively correlates with ADHD symptoms (Chang *et al*,
17 2016). However, several case-control studies have reported no dietary differences, or
18 even higher dietary PUFAs intake, in ADHD (Chen *et al*, 2004; Colter *et al*, 2008;
19 Gow *et al*, 2013; Stevens *et al*, 1995). Interestingly, some clinical trials with n-3

1 PUFAs supplementation in ADHD have shown improvement in clinical symptoms
2 (Manor *et al*, 2012; Perera *et al*, 2012; Richardson and Puri, 2002) and cognitive
3 performances (Sinn *et al*, 2008; Vaisman *et al*, 2008; Voigt *et al*, 2001), but others
4 have found no beneficial effects (Widenhorn-Muller *et al*, 2014). Hence our decision
5 to conduct the present meta-analysis.

6 In terms of PUFAs levels, lower red blood cells (RBCs) PUFAs (Stevens *et al*,
7 1995) and a higher n-6/n-3 ratio (Stevens *et al*, 2003) have been reported in ADHD,
8 and lower n-3 PUFAs levels are positively associated with the severity of ADHD
9 symptoms in children (Colter *et al*, 2008; Stevens *et al*, 2003). However, some studies
10 could not replicate the differences in n-3 PUFAs levels between children with ADHD
11 and controls (Gow *et al*, 2013; Stevens *et al*, 2003). Again, this inconsistency in the
12 literature has prompted us to conduct the present meta-analysis.

13 Although there were previous meta-analyses on this topic (Cooper *et al*, 2015;
14 Gillies *et al*, 2012; Hawkey and Nigg, 2014; Puri and Martins, 2014; Sonuga-Barke *et*
15 *al*, 2013), their findings might be confounded by heterogeneity in the clinical samples,
16 including both children and adult subjects (Hawkey *et al*, 2014) or subjects with
17 diagnosis other than ADHD (Cooper *et al*, 2015; Puri *et al*, 2014), as well as by the
18 inclusion of non-parallel trials (Hawkey *et al*, 2014; Puri *et al*, 2014) as well as
19 mixed supplementation interventions including n-3 PUFAs together with vitamins and

1 nutrients (Gillies *et al*, 2012; Sonuga-Barke *et al*, 2013). To address these issues, we
2 have performed a systematic review and meta-analyses to examine both the efficacy
3 of n-3 PUFAs supplementation *and* the levels of n-3 PUFAs, specifically in young
4 (children and adolescents) subjects with ADHD. We have also examined the factors
5 potentially modulating these findings, such as the EPA and DHA dosages in the
6 supplementations trials, and the source tissue (RBCs, plasma, buccal cells) for the
7 measurements of n-3 PUFAs levels.

8

9 **MATERIALS AND METHODS**

10 We conducted a systematic review and meta-analysis in accordance with the
11 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)
12 guidelines (Moher *et al*, 2009).

13

14 *Literature Search*

15 To identify eligible studies for this meta-analysis, a computerized search was
16 performed for all publications available up to 31st March 2017 through Cochrane
17 Central Register of Controlled Trials, Embase, Ovid Medline, PsychInfo, limited to
18 literature in English and human studies. The search terms used are listed in
19 Supplementary Table S1. References of eligible trials and appropriate reviews were

1 searched for additional citations. Unpublished or ongoing trials were searched on
2 ClinicalTrials.gov website and authors contacted to request relevant data. Our initial
3 search identified 4415 studies (Fig 1).

4

5 *Inclusion Criteria of Studies in the Meta-analysis*

6 The characteristics of included articles are described in Table 1,
7 Supplementary Tables S2 and S3.

8 N-3 PUFAs Supplementations and Clinical Symptoms

9 Our criteria were: 1) studies were randomized, double-blind, placebo-
10 controlled trials of n-3 PUFAs supplementation with DHA and EPA alone or in
11 combination; 2) participants were school-aged children (4-12 years) and adolescents
12 (13-17 years) who had a diagnosis of ADHD; 3) the study measured clinical
13 symptoms of ADHD as reported by parents; 4) the data allowed to calculate an effect
14 size; and 5) the publications were in peer-reviewed journals.

15 We identified 8 studies (Bos *et al*, 2015; Gustafsson *et al*, 2010; Manor *et al*,
16 2012; Perera *et al*, 2012; Richardson *et al*, 2002; Sinn *et al*, 2008; Vaisman *et al*, 2008;
17 Widenhorn-Muller *et al*, 2014), totalling 628 subjects: 366 received n-3 PUFAs and
18 262 received placebo. Seven studies were included in the meta-analysis for total
19 ADHD clinical symptoms totalling 534 subjects: 318 received n-3 PUFAs and 216

1 received placebo. Seven studies were included in the meta-analysis for inattention
2 clinical symptoms (Bos *et al*, 2015; Gustafsson *et al*, 2010; Manor *et al*, 2012; Perera
3 *et al*, 2012; Richardson *et al*, 2002; Sinn *et al*, 2008; Widenhorn-Muller *et al*, 2014),
4 totalling 590 subjects: 348 received n-3 PUFAs and 242 received placebo. Six studies
5 were included in the meta-analysis for hyperactivity clinical symptoms (Gustafsson *et*
6 *al*, 2010; Manor *et al*, 2012; Perera *et al*, 2012; Richardson *et al*, 2002; Sinn *et al*,
7 2008; Widenhorn-Muller *et al*, 2014), totalling 551 subjects: 328 received n-3 PUFAs
8 and 223 received placebo.

9 N-3 PUFAs Supplementation and Cognitive Performance

10 Our criteria were: 1) studies were randomized, double-blind, placebo-
11 controlled trials of n-3 PUFAs supplementation with DHA and EPA alone or in
12 combination; 2) participants were school-aged children (4-12 years) and adolescents
13 (13-17 years) who had a diagnosis of ADHD; 3) the studies measured cognitive
14 performance defined as omission errors, commission errors, forward memory,
15 backward memory, and information processing; 4) the data allowed to calculate an
16 effect size; and 5) the publications were in peer-reviewed journals.

17 We identified 4 studies (Sinn *et al*, 2008; Vaisman *et al*, 2008; Voigt *et al*,
18 2001; Widenhorn-Muller *et al*, 2014), totalling 309 subjects: 178 received n-3 PUFAs

1 and 131 received placebo. Three studies were included in the meta-analysis for
2 omission errors (Sinn *et al*, 2008; Vaisman *et al*, 2008; Voigt *et al*, 2001), totalling
3 214 subjects: 134 received n-3 PUFAs and 80 received placebo. Two studies were
4 included in the meta-analysis for commission errors totalling 85 subjects: 43 received
5 n-3 PUFAs and 42 received placebo. Two studies were included in the meta-analysis
6 for memory (Sinn *et al*, 2008; Widenhorn-Muller *et al*, 2014), totalling 224 subjects:
7 137 received n-3 PUFAs and 87 received placebo. Four studies were included in the
8 meta-analysis for information processing (Sinn *et al*, 2008; Vaisman *et al*, 2008;
9 Voigt *et al*, 2001; Widenhorn-Muller *et al*, 2014), totalling 309 subjects: 178 received
10 n-3 PUFAs and 131 received placebo.

11 N-3 PUFAs Levels

12 Our criteria were: the studies 1) measured levels of DHA, EPA, AA, total n-3
13 or total n-6; and 2) used samples from RBCs membrane, blood phospholipids and
14 cholesteryl esters, or buccal cells; 3) participants were school-aged children (4-12
15 years) and adolescents (13-17 years) who had a diagnosis of ADHD; 4) the data
16 allowed to calculate an effect size; and 5) the publications were in peer-reviewed
17 journals.

1 Nine studies were included in the meta-analysis on n-3 PUFAs levels (Bos *et al*
2 *al*, 2015; Chen *et al*, 2004; Colter *et al*, 2008; Germano *et al*, 2007; Gow *et al*, 2009;
3 Gow *et al*, 2013; Mitchell *et al*, 1987; Stevens *et al*, 2003; Stevens *et al*, 1995),
4 totalling 558 subjects: 297 youths with ADHD and 261 controls. Eight studies were
5 included in the meta-analysis for DHA level (Bos *et al*, 2015; Chen *et al*, 2004; Colter
6 *et al*, 2008; Germano *et al*, 2007; Gow *et al*, 2009; Mitchell *et al*, 1987; Stevens *et al*,
7 2003; Stevens *et al*, 1995), totalling 486 subjects: 268 youth with ADHD and 218
8 controls. Eight studies were included in the meta-analysis for EPA levels (Chen *et al*,
9 2004; Colter *et al*, 2008; Germano *et al*, 2007; Gow *et al*, 2009; Gow *et al*, 2013;
10 Mitchell *et al*, 1987; Stevens *et al*, 2003; Stevens *et al*, 1995), totalling 542 subjects:
11 285 youth with ADHD and 257 controls. Seven studies were included in the
12 meta-analysis for total n-3 PUFAs levels (Bos *et al*, 2015; Chen *et al*, 2004; Colter *et*
13 *al*, 2008; Germano *et al*, 2007; Gow *et al*, 2013; Stevens *et al*, 2003; Stevens *et al*,
14 1995), totalling 470 subjects: 250 youth with ADHD and 220 controls. Eight studies
15 were included in the meta-analysis for AA levels (Bos *et al*, 2015; Chen *et al*, 2004;
16 Colter *et al*, 2008; Germano *et al*, 2007; Gow *et al*, 2013; Mitchell *et al*, 1987;
17 Stevens *et al*, 2003; Stevens *et al*, 1995), totalling 567 subjects: 298 youth with
18 ADHD and 269 controls. Eight studies were included in the meta-analysis for total
19 n-6 PUFAs levels (Bos *et al*, 2015; Chen *et al*, 2004; Colter *et al*, 2008; Germano *et*

1 *al*, 2007; Gow *et al*, 2009; Gow *et al*, 2013; Stevens *et al*, 2003; Stevens *et al*, 1995),
2 totalling 499 subjects: 270 youth with ADHD and 229 controls. If a study had
3 measurements of both RBCs and plasma levels for PUFAs (DHA, EPA, AA, n-3, n-6),
4 only measurement of RBCs level were included in the meta-analysis, since plasma
5 levels reflect more recent fluctuations (e.g., days) in phospholipids while RBCs levels
6 reflect more long term changes (e.g., months).

7 Studies that included and reanalysed the same data set as previously published
8 studies were not regarded as independent, and only the study with the highest number
9 of participants was included. See Fig 1 for the flow chart showing the selection of
10 included studies.

11

12 *Meta-Analytic Methods*

13 In our analysis, the primary outcomes were comparisons of 1) clinical symptoms
14 and cognitive performance in RCTs (omission errors, commission errors, memory and
15 information processing) between n-3 and placebo groups; and 2) levels of DHA, EPA,
16 AA, total n-3 PUFAs and total n-6 PUFAs, between ADHD and controls.

17 For each identified study, the effect size (*ES*) expressing the difference in clinical
18 symptoms and cognitive performance between n-3 and placebo group, or the

1 difference in the PUFAs levels between ADHD and controls, were described as
2 standardized mean difference (SMD) on the basis of Hedge's adjusted g , in which a
3 value greater than 0 indicated n-3 PUFAs were superior than placebo, or levels were
4 higher in ADHD subjects. When these data could not be retrieved from the
5 publications, we contacted the authors to acquire the data of derived ES from other
6 measures of variability. The results of individual studies were synthesized by the
7 random effects model (Shadish, 1994), but which ES s were pooled and 95%
8 confidence intervals (CIs) were calculated. The significance of the pooled effect size
9 was determined by the z test. Sensitivity analyses were performed to determine
10 whether any individual study was responsible for the significant results. Moreover,
11 each study was individually removed and the significance was retested. The I^2 statistic
12 assessed heterogeneity between studies. Publication bias was assessed using the Egger
13 regression asymmetry tests (and inspection of the regression asymmetry plot) and the
14 Begg adjusted rank correlation test. Meta-analyses were conducted by applying
15 STATA (Stata Corp, 2009) and Forest Plots were created by using Review Manager
16 5.3 (Cochrane Collaboration, 2014). Two-sided p values $<.05$ were considered
17 statistically significant.

18 **RESULTS**

19 *N-3 PUFAs Improves Clinical Symptoms in ADHD*

1 The major finding of our study is that n-3 PUFAs supplementation significantly
2 improves parental reports of total symptom scores (7 studies, $n=534$, $g=.38$, $p<.0001$),
3 inattention (7 studies, $n=590$, $g=.42$, $p<.0001$), and hyperactivity (6 studies, $n=551$,
4 $g=.48$, $p=.04$) (see Fig 2). We also did a subanalysis looking at effects of n-3 PUFAs
5 using two specific measurements, the Conner's cognition subscale (Richardson *et al*,
6 2002; Sinn *et al*, 2008) and the Conner's DSM-IV inattention subscale (Manor *et al*,
7 2012; Richardson *et al*, 2002; Sinn *et al*, 2008): n-3 PUFAs have a significant effect
8 on both scores (2 studies, $n=159$, $g= .49$, $p=.01$; 3 studies, $n=306$, $g= .36$, $p=.007$,
9 respectively). For both inattention (Figure 2A) and total ADHD score (Figure 2C),
10 these effects are significant also in the subgroup analyses testing separately studies
11 with EPA dosage of 500mg/day or greater, and studies with EPA dosage less than
12 500mg. However, for hyperactivity (Figure 2B), only studies with EPA dosage of
13 500mg/day or greater (Gustafsson *et al*, 2010; Perera *et al*, 2012; Widenhorn-Muller
14 *et al*, 2014) show a significant effect, but not those with smaller dosages (Manor *et al*,
15 2012; Richardson *et al*, 2002; Sinn *et al*, 2008). Interestingly, only one study (Perera
16 *et al*, 2012) in our meta-analysis used EPA as the sole source for omega-3
17 supplementation, and showed a significant effect for both inattention ($n=93$, $g=.69$,
18 $p=.001$,) and hyperactivity symptoms ($n=93$, $g=1.22$, $p<.00001$).

1 Of note, n-3 PUFAs have no significant effect on teacher's reports of
2 inattention, hyperactivity or total scores (Gustafsson *et al*, 2010; Manor *et al*, 2012;
3 Widenhorn-Muller *et al*, 2014) (3 studies, $n=334$, $p=.20$).

4

5 *N-3 PUFAs Improves Cognitive Performance in ADHD*

6 The second main finding of our study is that n-3 PUFAs supplementation is
7 superior to placebo in terms of cognitive performance for omission errors (3 studies,
8 $n= 214$, $g=1.09$, $p=.001$) and commission errors (2 studies, $n=85$, $g=2.14$, $p<.00001$)
9 (Fig 3), but not forward memory (2 studies, $n=224$, $p=.66$), backward memory (2
10 studies, $n=224$, $p=0.08$) or information processing (4 studies, $n=309$, $p=.23$)
11 (Supplementary Fig S1).

12

13 *Youth with ADHD Have Lower Levels of N-3 PUFAs*

14 In the overall meta-analysis, irrespective of tissue source, youth with ADHD
15 have lower levels of DHA (8 studies, $n=486$, $g=-.56$, $p=.05$), but no group differences
16 are present for EPA, AA, n-3 PUFAs and n-6 PUFAs levels (Figure 4).

17 We also performed a secondary analysis by excluding the study by Stevens *et*
18 *al*. (2003), which was different from all other studies in their participants' inclusion
19 criteria (see Figure 4 and Discussion). In this analysis, we found that youth with

1 ADHD indeed have lower levels not only of DHA (7 studies, $n=412$, $g=-.76$, $p=.0002$),
2 but also of EPA (7 studies, $n=468$, $g=-.38$, $p=.0008$), total n-3 (6 studies, $n=396$,
3 $g=-.58$, $p=.0001$) and AA (7 studies, $n=493$, $g=-.41$, $p<.0001$), but not of n-6 PUFAs
4 (7 studies, $n=425$, $p=.80$) (Figure 4).

5 We also performed subanalyses looking at levels of the RBCs and plasma
6 PUFAs separately. Youth with ADHD have lower RBCs DHA (5 studies, $n=277$,
7 $g=-.77$, $p<.0001$), EPA (4 studies, $n=196$, $g=-.55$, $p=.01$) and n-3 PUFAs (4 studies,
8 $n=245$, $g=-.70$, $p=.0002$) (Supplementary Fig S2). However, the subanalysis showed
9 that there is no difference in plasma PUFAs levels (Supplementary Fig S3).

10

11 **DISCUSSION**

12 This is the first meta-analysis to examine the roles of n-3 PUFAs as both
13 interventions and biomarkers in youth with ADHD, and to separately analyse RBCs
14 and plasma levels of n-3 PUFAs in these individuals. We show that n-3 PUFAs
15 supplementation improves total ADHD symptoms compared with placebo, with a
16 modest effect size ($g=.38$). Moreover, n-3 PUFAs also improve omission and
17 commission errors compared with placebo, with a large effect size ($g= 1.09$ to 2.14).
18 Lastly, youth with ADHD have lower levels of DHA, EPA, n-3 PUFAs, and AA than
19 control youth, with moderate to large effect size ($g=-.38$ to $-.76$).

1

2 *N-3 PUFAs Improve Clinical Symptoms*

3 N-3 PUFAs supplementation improves clinical symptoms in youth with
4 ADHD in this meta-analysis, measured as parental reports of total ADHD, inattention
5 and hyperactivity symptom scores. In contrast, we found no effects of PUFAs on the
6 teacher-reported ADHD severity (Gustafsson *et al*, 2010; Manor *et al*, 2012;
7 Widenhorn-Muller *et al*, 2014). Parental and teachers' ratings provide unique clinical
8 information regarding ADHD symptoms in different settings, and in general show
9 only weak to moderate correlations (Narad *et al*, 2015). For example, parents are
10 more likely to detect changes in the child's daily activities, such as getting ready for
11 school, getting dressed, getting ready for bed, eating meals and completing their
12 homework. In contrast, teachers' reports are more representative of the child's
13 behavior at school, such as peer interactions and talking in class. This could explain
14 why only symptoms measured by parental reports seem to improve following
15 treatment with PUFAs. However it is also important to highlight that the sample size
16 is smaller for studies using teacher reports (n= 344 with teacher reports vs. n=
17 534-590 with parental reports), which could also contribute to the negative findings.

18 The dosage of n-3 PUFAs supplementation included in our meta-analysis ranges
19 from 2.7mg to 640mg of DHA and 80mg to 650mg of EPA, with one study using

1 EPA (560mg) as the sole source of n-3 PUFAs supplementation. Our paper
2 demonstrates that all trials included in the meta-analysis improve inattention and total
3 ADHD symptoms scores, regardless of the EPA supplementation dosage. However,
4 only studies with EPA doses of ≥ 500 mg improve hyperactivity symptoms. Thus, our
5 paper shows that EPA supplementation dosage ≥ 500 mg should be considered when
6 treating youth with ADHD, especially those with predominantly
7 hyperactivity/impulsivity presentation.

8

9 *N-3 PUFAs Improve Cognitive Performance*

10 The second finding of this meta-analysis is that n-3 PUFAs supplementation
11 shows efficacy in improving omission and commission errors, but not memory and
12 information processing, in children with ADHD. This is consistent with
13 epidemiological studies, where EFA deficiency correlates with cognitive impairment
14 and increased impulsivity (associated with commission errors) (Chang *et al*, 2016).
15 N-3 PUFAs are crucial for optimal neurotransmitter function: for example,
16 incorporating more EPA and DHA in the cell membrane can increase cholesterol
17 efflux (Chang *et al*, 2010), modulate lipid raft clustering and disruption (Chang *et al*,
18 2010), and affect the function of the dopamine transporter (DAT) (Foster *et al*, 2008),

1 which in turn may affect attention and executive function by regulating synaptic
2 dopamine levels (Foster *et al*, 2008).

3

4 *Youth with ADHD Have Lower Levels of N-3 PUFAs*

5 Our overall meta-analysis, including all studies and irrespective of tissue
6 source, shows that youth with ADHD have lower levels of DHA. DHA has been
7 implicated in the brain development of infants and children, since lower maternal
8 intake of n-3 PUFAs during pregnancy is associated with worse developmental
9 outcomes in the offspring, including lower fine motor and communication scores and
10 lower social development scores (Hibbeln *et al*, 2007). Children with developmental
11 disorders also have lower levels of DHA (Milte *et al*, 2011).

12 When we excluded the study by Stevens *et al*. (2003) from the meta-analysis,
13 we found that youth with ADHD also have lower EPA, n-3 PUFAs and AA levels. In
14 the study by Stevens *et al*. (2003), children with ADHD had higher RBCs levels of
15 AA and DHA when compared with healthy children, which is different from all other
16 studies. We would argue that we are justified to exclude Stevens *et al*. (2003), as in
17 this study the diagnosis of ADHD was not strictly defined, and the subjects
18 self-referred and enrolled in the ADHD group if they reported to have been given a
19 diagnosis of ADHD from a paediatrician, psychologist or psychiatrist. In contrast, in

1 all the other studies the diagnosis was confirmed by standardised clinical interviews,
2 and/or subjects had an ADHD symptoms rating scale score of moderate severity. In
3 fact, the enrolment criteria in Stevens's study (2003) are also different from a
4 previous study from the same authors (Stevens *et al*, 1995), where the subjects had a
5 clinical diagnosis of ADHD and severity confirmed by the Parent/Teacher Conner's
6 Rating Questionnaire; and indeed, in this first study they found that ADHD children
7 do have lower levels of plasma and/or RBCs DHA, EPA, n-3 PUFAs and AA. Taken
8 together, these lines of evidence justify our decision to present the findings with and
9 without this study (Stevens *et al*, 2003).

10 Furthermore, in our meta-analysis youth with ADHD also have lower levels of
11 AA, while no difference in n-6 PUFAs levels were present. AA, derived from
12 linolenic acid, is the precursor of a wide range of biologically and clinically important
13 eicosanoids, including prostaglandins, thromboxanes and leukotrienes; it is also one of
14 the most abundant fatty acids, after DHA, in the brain. Indeed, lower levels of DHA
15 and AA have been associated with more anxiety, impulsivity and hyperactivity
16 symptoms in ADHD (Stevens *et al*, 1995), while low dose dietary supplementation of
17 AA had been shown to possibly improve cognition (Okaichi *et al*, 2005; Ishikura *et al*,
18 2009). The deficiency of AA in ADHD, may be due to a reduced ability to convert
19 linolenic acid to AA (Kinsella *et al*, 1990; Burgess *et al*, 2000). Possible steps

1 associated with inefficient conversion include desaturase steps, the
2 malonyl-CoA-dependent elongation steps, and the peroxisomal β -oxidation steps
3 (Burgess *et al*, 2000). Moreover, ratio of linolenic acid to AA was greater in a
4 subgroup of youth with ADHD with a greater severity of EFA deficiency (Burgess *et*
5 *al*, 2000). Another explanation for the low AA levels may be an increased metabolism
6 of AA to the eicosanoids via nonenzymatic oxidation, due to impaired cellular
7 defense mechanism (Burgess *et al*, 2000).

8 It is also of note that a subanalysis of RBCs levels of n-3 PUFAs shows that
9 youth with ADHD have lower levels of RBCs, but not plasma, DHA, EPA, n-3 and
10 AA. Both RBCs and plasma PUFAs are common biomarkers used to reflect fatty acid
11 intake/status in clinical studies (Chang *et al*, 2015; Chang *et al*, 2017; Lin *et al*, 2010;
12 Su *et al*, 2014). Of note, RBCs and plasma PUFAs levels are measured with standard
13 gas chromatography in the studies included in the meta-analysis. The units are
14 presented as percentage, which is more reliable in cross-study comparison (Lin *et al*,
15 2010; Lin *et al*, 2017). Although the PUFAs levels from the meta-analysis were not
16 directly from brain tissues, thus the results can not be directly applied to brain tissue
17 PUFAs levels, peripheral RBCs and plasma DHA and EPA levels do highly correlate
18 with brain DHA and EPA levels in animal studies (Connor *et al*, 1990; Lapillonne *et*
19 *al*, 2002; Stark *et al*, 2008). In addition, RBCs PUFAs are more strongly correlated

1 with dietary intake (Sun *et al*, 2007), and reflect longer-term fatty acid consumption
2 (e.g., months) (Sun *et al*, 2007), while plasma PUFAs reflect recent fluctuations of
3 fatty acid consumptions (e.g., days). We also included buccal cells PUFAs
4 measurements, a non-invasive measurement that correlates significantly with RBCs,
5 plasma and brain PUFAs (Lapillonne *et al*, 2002). However, since only one study
6 (Bos *et al*, 2015) in the meta-analysis used buccal cells PUFAs measurement, more
7 studies using this method will be needed to support its role as a biomarker.

8

9 *Biological Mechanisms and Clinical Impact*

10 EPA is the most common form of fatty acids stored in our body, and will
11 convert to DHA when needed, thus the low EPA level identified in the meta-analysis
12 may indicate an attempt of the body to compensate for the low DHA levels. DHA is
13 crucial for neurodevelopment, and its supplementation has been associated with
14 learning (Milte *et al*, 2011). In contrast, EPA have been associated with mood
15 regulation (Lin *et al*, 2010), and EPA supplementation has stronger antidepressant
16 effects than DHA (Su *et al*, 2014), although higher DHA and EPA levels are both
17 associated with lower anxiety and shyness (Milte *et al*, 2011).

1 In the context of ‘personalised medicine’, it is tempting to speculate that a
2 subpopulation of youth with ADHD and with low levels of n-3 PUFAs may respond
3 better to n-3 PUFAs supplementation, but there are no studies to date attempting this
4 stratification approach. However, we have shown that individuals at genetic risk of
5 developing depression in the context of the immune challenge, interferon-alpha (IFN-
6 α), have lower levels of RBCs n3-PUFAs (Su *et al*, 2010), and that n-3 PUFAs
7 supplementation prevents the onset of IFN- α -induced depression, arguably by
8 replenishing the endogenously low anti-inflammatory PUFAs in the ‘at risk’
9 individuals (Su *et al*, 2014). Moreover, a recent study by Rapaport has stratified
10 patients with major depressive disorder into a ‘high’ and a ‘low’ inflammation group,
11 and shown that the ‘high inflammation’ group has a better responses to EPA
12 (Rapaport *et al*, 2016). Indeed, some studies have found inflammatory abnormalities
13 in ADHD, and this would support the theoretical model that PUFAs affect ADHD
14 symptoms via an anti-inflammatory action (Su *et al*, 2014). For example, one study
15 has shown that ADHD children have higher IL-6 and IL-10 levels (Donfrancesco *et al*,
16 2016), while another study has shown that n-3 supplementation in ADHD children
17 reduces IL-6 and C-reactive protein (CRP) levels (Hariri *et al*, 2012). Therefore,
18 stratification of ADHD children by n-3 PUFAs levels or by immune biomarkers could
19 be one approach to optimise the therapeutic effects of n-3 PUFAs supplementation.

1

2 *Limitations and Conclusions*

3 This meta-analysis is limited by paucity of original data in some of the
4 investigated comparisons. For example, all studies examining efficacy in clinical
5 symptoms had parental, but only some had teacher, ratings of ADHD symptoms.
6 Similarly, fewer studies measured memory function and information processing,
7 which again may have contributed to the negative findings. The other limitation is that
8 there are no actual data linking DHA/EPA baseline levels and EPA/DHA
9 concentrations after treatment and response. Another limitation is that some of our
10 analyses have been conducted only on 2-3 studies, which is not ideal for
11 meta-analysis. Nevertheless, the conclusions remain reliable in that we have
12 conducted the systematic review and meta-analyses in accordance with the Preferred
13 Reporting Items for Systematic Reviews and Meta-analysis (PRISM) guidelines.
14 Moreover, supporting literature has suggested that two studies are adequate to
15 perform a meta-analysis (Valentine *et al*, 2010). Finally, our decision to exclude
16 Stevens's study (2003), extensively discussed above, is scientifically justified, but
17 does partly contravene the meta-analysis model. Notwithstanding these limitations,
18 however, we provide strong evidence supporting a role for n3-PUFAs deficiency in
19 ADHD, and for advocating n-3 PUFAs supplementation as a clinically relevant

- 1 intervention in this group, especially if guided by a biomarker-based personalisation
- 2 approach.
- 3
- 4

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3

4

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23

1 **FIGURE LEGENDS**

2

3 Figure 1. PRISMA Flow Diagram.

4

5 Figure 2. Forest plots showing effect sizes (Hedges's g) and 95% confidence intervals
6 (CIs) from individual studies and pooled results comparing ADHD clinical symptoms,
7 (A) inattention symptom scores, (B) hyperactivity symptom scores, (C) total ADHD
8 symptom scores, between n-3 and placebo group.

9

10 Figure 3. Forest plots showing effect sizes (Hedges's g) and 95% confidence intervals
11 (CIs) from individual studies and pooled results comparing cognitive function, (A)
12 Omission and (B) Commission, between n-3 group and placebo group.

13

14 Figure 4. Forest plots showing effect sizes (Hedges's g) and 95% confidence intervals
15 (CIs) from individual studies and pooled results comparing n-3 PUFAs Levels, (A)
16 DHA, (B) EPA, (C) n-3, (D) AA, (E) n-6, between ADHD population and control
17 group.