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Omega-3 Polyunsaturated Fatty Acids in Children with Attention Deficit Hyperactivity Disorder: A Systematic Review

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Abstract

Introduction *Attention Deficit-Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder that affects a significant population of children. Omega-3 supplementation is being explored since standard pharmacological treatments cause bothersome side effects. Our objective is to examine the impact of Omega-3 fatty acids on the symptoms of ADHD in children.*

Methods: *We conducted a systematic review, searching for randomized clinical trials in MEDLINE, Embase, and Web of Science from April 17th until May 1st, 2024. Studies were included if they involved children aged 6-18 with ADHD who consumed Omega-3 fatty acids through diet or supplementation. Studies were excluded if they included individuals without an ADHD diagnosis, used animal models, or supplements alongside Omega-3. Data extraction and Cochrane Risk-of-Bias (RoB2-tool) analysis were performed using Covidence. Findings were described in tables and analyzed.*

Results: *A total of thirty-one eligible randomized clinical trials were included, evaluating 2,494 individuals with an average age of 8.93 years (SD = 1.39). Most studies (90.3%) followed a two-arm design comparing Omega-3 supplementation to placebo. While fourteen studies (45.1%) reported statistically significant benefits of Omega-3 supplementation in overall ADHD symptoms, the sub-analysis on hyperactivity/impulsivity and inattention symptoms showed no significant effects or differences between groups. Studies were highly heterogeneous in design, interventions, trial duration, dosage, and outcome measurement tools.*

Conclusion: *Overall, Omega-3 may not have a significant effect on ADHD symptoms to recommend its use. Future research should address the limitations, such as the main dose and comparator and also ideal treatment time.*

Introduction

Attention Deficit-Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder that affects children globally (Xu et al., 2018). This disorder is characterized by inattention, hyperactivity, and impulsivity, leading to impairments in the child's social interactions, academic performance, and overall well-being (Händel et al., 2021).

The prevalence of ADHD in children under 18 years has increased over time, from 7.2% in 2015 to 8.7% in the United States (Thomas et al., 2015). This rise is attributed to increased awareness, changes in diagnostic criteria, and improved access to care (Abdelnour et al., 2022).

Effective interventions are crucial, given their impact on a child's development and quality of life. Methylphenidate (MPH) is currently the most widely used medication and is considered safe for long-term use in children and adolescents. However, concerns remain about modest increases in blood pressure and pulse rate (Man et al., 2023; ADDUCE study, 2023), among other side effects that are acknowledged by clinicians, patients, and family (Berger et al., 2008; Man et al., 2023). Other options, like amphetamines, atomoxetine, and non-pharmacological therapies, vary in availability and usage across countries due to differing healthcare access and regulations (Felt et al., 2014).

As a result, new treatments, such as Omega-3 fatty acids, are being explored for their potential benefits without these side effects, and have gained considerable attention as complementary or alternative treatments for ADHD. Omega-3 fatty acids are essential components of brain cell membranes and play a critical role in neurotransmission and brain development. Children with ADHD often exhibit lower levels of these fatty acids in their blood (Hawkey & Nigg, 2014). While the mechanisms by which they influence ADHD symptoms are not fully understood, they may involve modulation of neurotransmitter systems, reduction of inflammation (Bagga et al., 2003; Das, 2006), and enhancement of neuronal communication (Chang & Su, 2010).

However, despite the promising findings regarding Omega-3 supplementation, a knowledge gap remains in understanding the full extent of its efficacy and the mechanisms underlying its effects on ADHD symptoms. Several systematic reviews and meta-analyses have examined the impact of Omega-3 supplementation on ADHD (Abdullah et al., 2019; Agostoni et al., 2017a; Bloch& Qawasmi, 2011; J. et al., 2018; Cooper et al., 2015; Gillies et al., 2023a; Händel et al., 2021b). The findings suggest that, while not as effective as traditional pharmacological treatments, Omega-3 supplements, particularly those high in eicosapentaenoic acid (EPA), show slight improvements in hyperactivity, impulsivity, and inattention. These benefits are more pronounced in children with lower baseline Omega-3 levels, suggesting a potential for biomarker-based personalized treatment. Despite their modest efficacy, Omega-3 supplements have a favorable side effect profile, making them a viable supplementary option to conventional ADHD medications. The discrepancies in findings, along with emerging new data, highlight the need for a new review.

Therefore, we conducted this systematic review to evaluate the current evidence on the impact of Omega-3 fatty acids on ADHD symptoms in children, including their relationship with different types and dosages of Omega-3. We also incorporate recent randomized clinical trials (RCTs) to provide comprehensive guidance for clinicians and families considering non-pharmacological interventions.

Materials and Methods

Search strategy

We conducted a search in the MEDLINE, Embase, and Web of Science electronic databases (Bramer et al., 2017) between April 17th and May 1st, 2024. An a priori search strategy was developed using Medical Subject Headings (MeSH) terms and free-text keywords, following recommended guidelines (Aromataris & Riitano, 2014), and refined based on our population, intervention, control, and outcomes (PICO) framework. Key search terms included "attention deficit disorder with hyperactivity" OR "ADHD" OR "attention deficit hyperactivity disorder" OR "Hyperkinetic disorder" OR "Inattentiveness" OR "Hyperactivity" AND "minority groups" OR "minors" OR "kids" OR "child" OR "children" OR "pediatric" AND "fatty acids, omega 3" OR "Omega-3" OR "alpha-linolenic acid" OR "docosahexaenoic acids"OR "eicosapentaenoic acid" OR "N-3 fatty acids" OR "Polyunsaturated fatty acids" OR "PUFA* OR "DHA" OR "n 3 oil" OR "Fish oil" OR "EPA" AND "randomized controlled trial" OR "controlled clinical trial" OR "trial" NOT ("animals" NOT "humans").

We did not conduct additional manual searches of reference lists from the retrieved articles or gray

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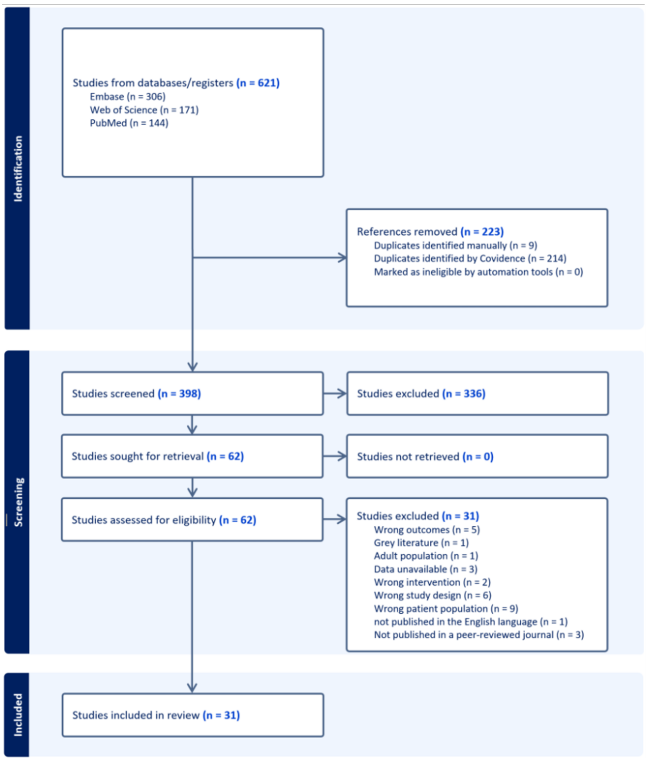

Figure 1: *PRISMA Flow diagram representing the study selection process.*

literature sources (e.g., Google Scholar, Dissertation, and Theses).

Selection of the studies

Our review adheres to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021), and the selection process is outlined in Figure 1. Authors (GPR and NCP) independently assessed the results from the electronic searches for each database using the same search strategy. References were stored in Covidence, a web-based software (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org). All authors participated as first, second, and third reviewers. Covidence was used for title and abstract screening by two independent investigators. Studies meeting the inclusion criteria were retrieved in full text and assessed for eligibility. Any disagreements between the two reviewers were resolved through discussion, and, if necessary, a third investigator was consulted to reach a consensus.

Inclusion criteria

Studies were included if they involved preschoolers, children, and adolescents (less than or equal to 18 years old), diagnosed with ADHD, investigating the intake of Omega-3 fatty acids through diet or supplementation and its impact on the severity of ADHD symptoms. Only RCTs published in peer-reviewed journals in English or Spanish over the past 30 years were considered.

Exclusion criteria

Studies were excluded if they involved animal models, adults (>18 years old), individuals without an ADHD diagnosis, or if they used herbal or vitamin supplements alongside Omega-3, with the exception of vitamin E supplementation due to its synergistic properties with Omega-3 and its common prescription alongside it. In terms of study design, meeting abstracts, prospective and retrospective cohort studies, case-control studies, systematic reviews, meta-analyses, narrative reviews, editorials, opinion articles, and comments were also excluded.

Data extraction

For the extraction phase, we followed the recommendations outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2024). All authors contributed to extract the following information for each trial: the first author's name, year of the study, country, setting, blinding, arms, interventions and controls, total sample size, outcomes assessed, and measurement scores on specified rating scales. We also collected participants' baseline characteristics, such as age, as well as any adverse events. The main data are summarized in Table 1.

Risk of bias assessment

The risk of bias in the included studies was assessed using the Cochrane Risk-of-Bias Tool 2 (Sterne et al., 2019). All authors acted as first, second, and third reviewers. Two investigators independently evaluated each study, examining domains such as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Discrepancies were resolved through discussion, and a third investigator was involved if consensus could not be reached. All articles that met the inclusion criteria were considered for the result, regardless of the quality of the study.

Data synthesis

We included results from all the studies that met the inclusion criteria and reported relevant information. The findings were exported from Covidence to an Excel sheet (Microsoft Excel®) and summarized descriptively in Table 1. A narrative synthesis was performed to summarize the findings from the included studies, given the heterogeneity in study designs, interventions, and outcomes, which highlights the complexity of the research findings. We did not contact the authors to get additional information; when data were unavailable in the trials, it was recorded as "NA".

Results

Description of the studies

In this review, a total of 621 studies were obtained from Embase (n=306), Web of Science (n=171), and Pubmed (n=144). Following title and abstract screening, as well as full-text screening on the Covidence platform, duplicate and ineligible studies were excluded from the data extraction process. Figure 1 shows the PRISMA flow diagram detailing this process.

A total of 31 eligible articles (Chang et al., 2019; Bos et al., 2015; Carucci et al., 2022; Cornu et al., 2018; Milte et al., 2012; Voigt et al., 2001; Salehi et al., 2016; Rodríguez et al., 2019; Stevens et al., 2003; Gustafsson et al., 2010; Barragán et al., 2017; Mohammadzadeh et al., 2019; Crippa et al., 2019; Widenhorn-Müller et al., 2014; Johnson et al., 2009; Mohammadzadeh et al., 2019; Dubnov-Raz et al., 2014; Milte et al., 2015; Behdani et al., 2013; Hariri et al., 2012; Anand & Sachdeva 2016; Matsudaira et al., 2015; Raz et al., 2009; Hirayama et al., 2004; Sinn & Bryan 2007; Perera et al., 2012; Dashti et al., 2014; Manor et al., 2012; Vaisman et al., 2008; Assareh et al., 2017; Bélanger 2009; Voigt et al., 2001) were included in this systematic review, all of which were RCTs.

Study design

Out of these, 26 (83.8%) (Voigt et al., 2001; Stevens et al., 2003; Hirayama et al., 2004; Vaisman et al., 2008; Belanger, 2009; Raz et al., 2009; Gustafsson et al., 2010; Hariri et al., 2012; Manor et al., 2012; Milte et al., 2012; Perera et al., 2012; Behdani et al., 2013; Dashti et al., 2014; Dubrov-Raz 2014; Widenhorn-Muller 2014; Matsudaira et al., 2015; Anand & Sachdeva 2016; Salehi et al., 2016; Assareh et al., 2017; Moghaddam et al., 2017; Cornu et al., 2018; Chang et al., 2019; Crippa et al., 2019; Rodriguez 2019; Mohammadzadeh et al., 2019; Carucci et al., 2022), utilized parallel design, four studies (12.9%) used a cross-over design (Sinn & Bryan, 2007; Belanger 2009; Johnson et al., 2009; Milte et al., 2015), and one study (3.2%) used a factorial study design (Bos et al., 2015). A summary of the study designs is shown in Table 2. The total number of patients evaluated in this systematic review was 2,494, with an average sample size of 88.3 participants (SD = 41.9) and an average age of 8.93 years (SD = 1.39).

Intervention and comparators

Twenty-five studies (87%) (Voigt et al., 2001; Stevens et al., 2003; Sinn & Bryan, 2007; Vaisman et al., 2008; Bélanger 2009; Johnson et al., 2009; Raz et al., 2009; Gustafsson et al., 2010; Hariri et al., 2012; Manor et al., 2012; Perera et al., 2012; Behdani et al., 2013; Dashti et al., 2014; Widenhorn-Müller et al., 2014; Bos et al., 2015; Matsudaria 2015; Milte et al., 2015; Salehi et al., 2016; Assareh et al., 2017; Moghaddam 2017; Cornu et al., 2018; Crippa et al., 2019; Rodríguez et al., 2019; Mohammadzadeh et al., 2019; Carucci et al., 2022), compared Omega-3 versus placebo. Some of these studies included various combinations of interventions, such as Omega-3 versus fish oil versus placebo (Vaisman et al., 2008); Omega-3/6 + MPH versus placebo + MPH (Perera et al., 2012); MPH+Omega-3 versus MPH + placebo (Behdani et al., 2013; Assareh et al., 2017; Moghaddam 2017; Mohammadzadeh et al., 2019); Omega-3 versus MPH versus placebo (Dashti et al., 2014); and MPH+zinc versus MPH + Omega-3 versus MPH + placebo (Salehi et al., 2016). The median duration of treatment was 14 weeks (IQR 12), ranging from seven weeks to 48 weeks. Details of the interventions and comparators are presented in Table 1.

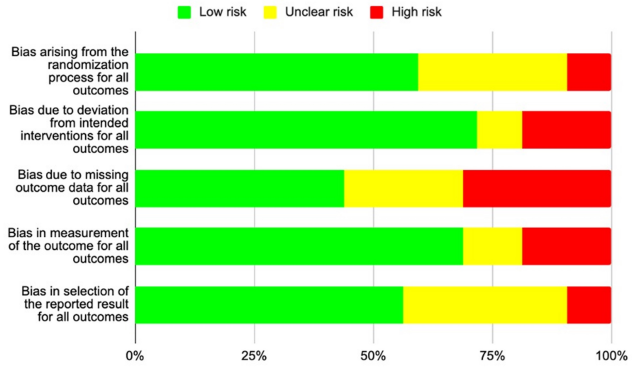

Figure 2: *Risk of bias assessment.*

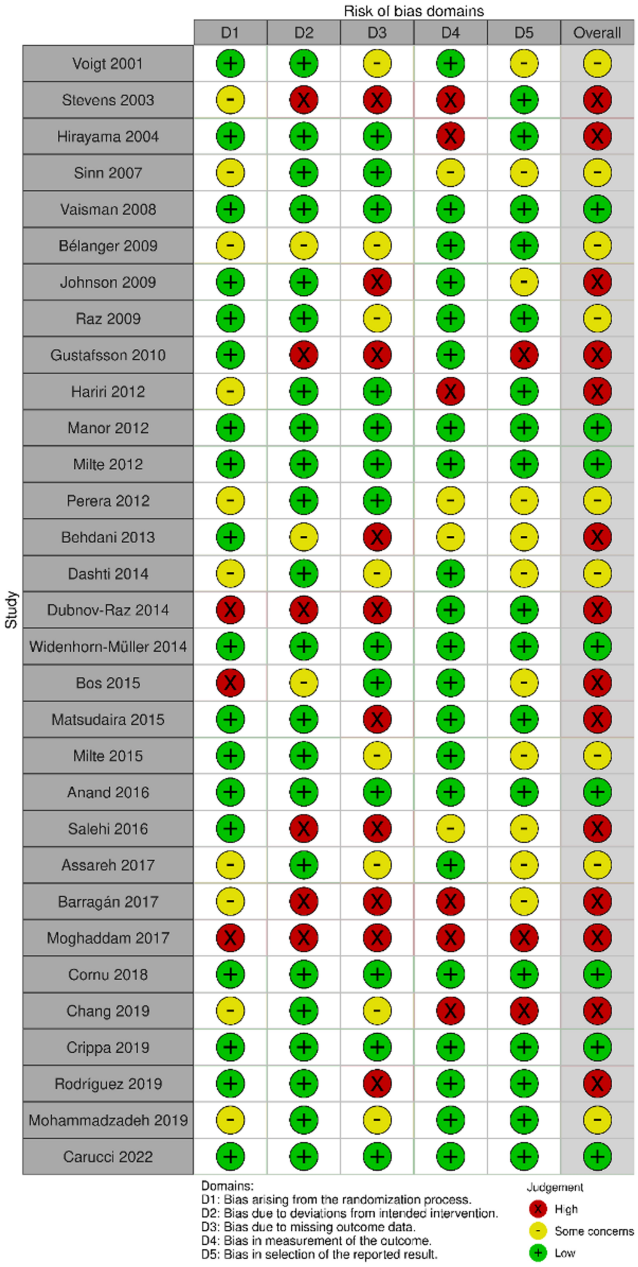

Figure 3: *Risk of bias assessment domains.*

The most commonly used combination of Omega-3 and Omega-6 fatty acids included EPA, DHA, and GLA, as reported by five studies (16.13%) (Sinn & Bryan, 2007; Johnson et al., 2009; Matsudaira et al., 2015; Barragán et al., 2017; Carucci et al., 2022). Of these, four studies (12.9%) also incorporated vitamin E into the regimen (Sinn & Bryan, 2007; Johnson et al., 2009; Matsudaira et al., 2015; Carucci et al., 2022). Other combinations included DHA+EPA or DHA+EPA+AA+GLA with vitamin E (Stevens et al., 2003; Widenhorn-Müller et al., 2014). Most treatments were administered in the form of prescribed capsules, although a few studies referenced natural sources of Omega-3 and -6, such as primrose oil and fish oil (Sinn & Bryan, 2007; Vaisman et al., 2008). The dosage of Omega-3 and Omega-6 varied across studies. The total daily EPA dosage ranged from 180 mg to 1.2g, while DHA ranged from 120 mg to 1,032 mg. Vitamin E dosages ranged from 8 to 10.8 mg. One commonly used daily dosage combination was 6 capsules of 93 mg of EPA (558 mg/day), 29 mg of DHA (174 mg/day), 10 mg of GLA (60 mg/day), and 1.8 mg of vitamin E (10.8 mg/day). Some studies prescribed PUFA doses based on the child's age or body weight (Assareh et al., 2017; Barragán et al., 2017; Dashti et al., 2014; Matsudaira et al., 2015; Salehi et al., 2016; Cornu et al., 2018).

In the comparator arms, three studies used standard ADHD treatment such as MPH or Atomoxetine (Dashti et al., 2014; Anand & Sachdeva 2016; Barrágan 2017). Twenty-eight studies employed placebos in the form of vegetable oils like olive, sunflower, palm, soybean, safflower, rapeseed, or cellulose (Voigt et al., 2001; Stevens et al., 2003; Hirayama et al., 2004; Sinn & Bryan, 2007; Vaisman et al., 2008; Johnson et al., 2009; Bélangerer 2009; Raz et al., 2009; Gustafsson et al., 2010; Milte et al., 2012; Hariri et al., 2012; Perera et al., 2012; Manor et al., 2012; Behdani et al., 2013; Widenhorn-Müller et al., 2014; Dubnov-Raz et al., 2014; Dashti et al., 2014; Bos et al., 2015; Milte et al., 2015; Matsudaira et al., 2015; Moghaddam 2017; Assareh et al., 2017; Cornu et al., 2018; Chang et al., 2019; Rodríguez et al., 2019; Mohammadzadeh et al., 2019; Crippa et al., 2019; Carucci et al., 2022). All trials except one were double-blinded (Barragán et al., 2017). Two studies included an open-label extension (Carucci et al., 2022; Johnson et al., 2009).

Outcomes

The studies included in this review focused primarily on assessing the effect of Omega-3 supplementation on two primary outcomes related to ADHD symptoms: overall ADHD symptoms and subtype symptoms (impulsivity/hyperactivity and inattention). These outcomes were measured using a variety of standardized tools, with ADHD-Rating Scale (ADHD-RS) and Conners' Parent and Teacher Rating Scales (CPRS and CTRS) being the most commonly used scores.

Effect of Intervention on Outcomes

Overall ADHD symptoms

Fourteen of the thirty-one trials reported a statistically significant ($p<0.05$) improvement in at least one subscale in the Omega-3 group (Stevens et al., 2003; Sinn & Bryan, 2007; Vaisman et al., 2008; Johnson et al., 2009; Gustafsson et al., 2010; Hariri et al., 2012; Manor et al., 2012; Perera et al., 2012; Dashti et al., 2014; Bos et al., 2015; Barragán et al., 2017; Moghaddam 2017; Rodríguez et al., 2019, Chang et al., 2019). In contrast, 17 trials reported no statistically significant effects after treatment (Voigt et al., 2001; Hirayama et al., 2004; Bélanger 2009; Raz et al., 2009; Milte et al., 2012; Behdani et al., 2013; Dubnov-Raz et al., 2014; Widenhorn-Müller et al., 2014; Matsudaira et al., 2015; Milte et al., 2015; Anand & Sachdeva 2016; Salehi et al., 2016; Assareh et al., 2017; Cornu et al., 2018; Crippa et al., 2019; Mohammadzadeh et al., 2019; Carucci et al., 2022)

ADHD subtype symptoms

Impulsivity/Hyperactivity

Twenty-three (74.2%) trials reported results for hyperactivity and impulsivity, utilizing various scales such as ADHD-RS (Assareh et al., 2017; Barragán et al., 2017; Carucci et al., 2022; Cornu et al., 2018; Crippa et al., 2019; Mohammadzadeh et al., 2019), CTRS (Carucci et al., 2022; Dashti et al., 2014; Gustafsson et al., 2010; Manor et al., 2012; Milte et al., 2012), CPRS (Bélanger 2009; Carucci et al., 2022; Crippa et al., 2019; Dashti et al., 2014; Gustafsson et al., 2010; Manor et al., 2012; Milte et al., 2012; Sinn & Bryan, 2007), DISYPS-II (Widenhorn-Müller et al., 2014), MOXO performance test (Dubnov-Raz et al., 2014), EDAH version for families (Rodríguez et al., 2019), Self-made Checklist (Perera et al., 2012), Continuous Performance Test (CPT) (J. P.-C. Chang et al., 2019; Hirayama et al., 2004) and Barratt-Impulsiveness Scale (Matsudaira et al., 2015).

The effect of Omega-3 on hyperactivity and impulsivity varied across the trials, with 15 studies showing no effect from Omega-3 supplementation (Assareh et al., 2017; Bélanger 2009; Cornu et al., 2018; Hirayama et al., 2004; Matsudaira et al.,

Article and N N Included (n completed)	Country and setting	Intervention vs. control	Age (years)	Study Design and Duration	Summary
Voigt 2001 n= 63 (54)	United States Single	Omega-3 vs. Placebo	6-12.	Parallel 17.4 weeks	No statistically significant improvement observed in any objective or subjective measure of ADHD symptoms after the 4-month supplementation.
Stevens 2003 n= 50; 33	United States Single	Omega-3 vs Placebo	6-13.	Parallel 17 weeks	Improvement of PUFA group in most outcomes compared to placebo, but reached significance only in conduct (42.7% decrease vs 9.9%, P=0.05) and attention (14.8% improvement vs -3.4%, P=0.05)
Hirayama 2004 n= 40	Japan Single	DHA supplement in specific foods vs. Placebo	6-12.	Parallel 9 weeks	No changes were seen in 5 out of 7 criteria: attention deficit, hyperactivity and impulsivity, aggression, visual perception, visual-motor integration, and impatience. The control group showed improvement over the intervention group in visual and auditory short-term memory, and continuous performance.(P < 0.02 and 0.001, respectively)
Sinn 2007 n= 167 n= 104	Australia Single	Omega-3vs. Placebo	7-12.	One-way crossover 30 weeks	PUFA supplementation improved parent ratings of inattention, hyperactivity, impulsivity, and oppositional behavior compared to placebo, with medium to large effect sizes. These findings were also replicated after crossover. Statistical significance reached in 9 out of 14 subscales at 15 weeks.
Vaisman 2008 n= 83 n= 60	Israel Single	Omega-3 vs. Fish oil vs. Placebo	8-13.	Parallel 13 weeks	Total Test of Variables of Attention score showed greater improvements in attention in Omega-3 and Fish Oil groups compared to placebo, with Omega-3 showing the most improvement (p < 0.001)
Bélanger 2009 n= 37 n= 26	Canada Single	Omega-3 vs. Placebo	6-11.	One-way Crossover 26 weeks	The SWAN questionnaire showed no significant differences. Conners' revealed improvements in inattention and impulsivity in both groups, with greater but non-significant improvement in Omega-3.
Johnson 2009 n= 75 n= 59	Sweden Multi-center	Omega-3 vs. Placebo	8-18.	One-way Crossover 8 and 16* weeks	In Phase I, 26% of participants in the active group showed a >25% reduction in ADHD symptoms, compared to 7% in the placebo group(p = .04). In Phase II, 47% of participants were responders (p = .03), with 12% achieving >50% symptom reduction.
Raz 2009 n= 73 n= 63	Israel Single	Omega-3 vs. Placebo	7-13.	Parallel 7 weeks	No between-group difference was found in the changes of the various measures of ADHD symptoms.
Gustafsson 2010 n= 92 n= 82	Sweden Multi-center	Omega-3 vs. Placebo	7-12.	Parallel 15 weeks	EPA supplementation improved inattention/cognitive scores (p = 0.04) but not Conners' total score. In oppositional children, 48% showed ≥25% improvement in total score with EPA versus 9% for placebo (p = 0.01).
Hariri 2012 n= 120 n = 103	Iran Single	Omega-3 vs. Placebo	6-11.	Parallel 17.4 weeks	The intervention group showed significant improvement in Conners' Abbreviated Questionnaires (p = 0.001), while the placebo group showed no significant improvement (p = 0.251). Note: Statistical analysis used unpaired t-tests instead of paired t-tests.
Manor 2012 n=200 n= 147	Israel Single	Omega-3 vs. Placebo	6-13.	Parallel with open label extension 8 weeks	Phosphatidylserine with Omega-3 showed no significant improvements in any subscale, except for CPRS parent-rated restless/impulsive symptoms (p < 0.05) and CHQ Emotional impact on parent (p<0.05)
Milte 2012 n= 90 n= 70	Australia Multi-center	Omega-3 vs. Fish oil	7-12.	Parallel 26 weeks	No significant differences in primary outcomes after 16 weeks. However, increased erythrocyte DHA levels improved several scales.
Perera 2012 n=98 n= 94	Sri Lanka Single	Omega-3 + 6 + MPH vs. Placebo +MPH	6-12.	Parallel 26 weeks	Significant improvement in inattention, impulsiveness, and cooperation (p<0.05) at 24 weeks in an unvalidated scale. Effect sizes ranged from 0.3 to 1.1 at 12 weeks and 0.2 to 1.4 at 24 weeks.
Behdani 2013 n= 75 n= 69	Iran Single	MPH + Omega-3vs. MPH + Placebo	7-15.	Parallel 9 weeks	No significant differences between experimental and control groups at baseline or at weeks 2, 4, and 8.

Table 1: *Characteristics of the included studies.*

Dashti 2014 n= 85	Iran Single	Omega-3 vs. MPH vs. Placebo	6-12.	Parallel 16 weeks	Omega-3 demonstrated significant efficacy comparable to MPH in reducing symptoms of hyperactivity-impulsivity in combined subtypes of ADHD. The placebo group in the study did not exhibit significant changes.
Dubnov-Raz 2014 n= 40 n= 17	Israel Single	ALA-rich sage oil vs. Placebo	6-16.	Parallel 8 weeks	Of 40 patients, only 17 (42.5%) completed the study. No significant differences in ADHD symptoms were found before or after supplementation in either group
Widenhorn-Müller 2014 n= 110 n= 95	Germany NA	Omega-3vs. Placebo	6-12.	Parallel 8 weeks	Omega-3 levels improved working memory function, but had no effect on ADHD symptoms or behavior ratings.
Bos 2015 n= 79 n= 77	Netherlands Single	Omega-3vs. Placebo	8-14.	2 × 2 factorial design 16 weeks	Omega-3 PUFAs reduced parent-rated inattention compared to placebo (p<0.001). No changes in fMRI were found. The treatment effect varied over time, influenced by ADHD diagnostic status.
Matsudaira 2015 n= 76 n= 69	United Kingdom Single	Omega-3vs. Placebo	12-16.	Parallel 17.4 weeks	Despite increased EPA and DHA erythrocyte levels, the treatment group showed no significant improvement in ADHD symptoms or related psychological measures compared to the placebo group.
Milte 2015 n= 93 n= 53	Australia Multi-center	Omega-3 vs. Placebo	6-13.	Crossover 12 weeks	No significant treatment effects on literacy, cognition, or behavior among EPA, DHA, and LA groups.
Anand 2016 n= 50 n= 50	India Single	Omega-3 + Atomoxetine vs. Atomoxetine alone	4-11.	Parallel 8.7 weeks	While the study group showed a greater reduction in ADHD scores compared to the control group, the difference was not statistically significant (p = 0.08). The improvement was more notable among male participants with the combined type of ADHD.
Salehi 2016 n= 150 n= ?	Iran Single	MPH + zinc vs. MPH + Omega-3 vs. MPH + Placebo	6-15.	Parallel 17 weeks	No significant differences in Conners' scale scores among groups before treatment (P = 0.07) or at any point during treatment (P > 0.05).
Assareh 2017 n= 40	Iran Single	Omega-3 + MPH vs. Placebo + MPH	6-12.	Parallel 52 weeks	Inattention, and hyperactivity scores showed no significant difference between groups. Impulsivity scores decreased significantly more in the PUFAs group after adjusting for age, sex, and MPH dose. The study could not confirm the beneficial effect of PUFAs for ADHD treatment.
Barragán 2017 n= 90 n= 69	México Single Unblinded	Omega-3 + MPH vs. MPH alone	6-12.	Parallel 8 weeks	Combination of MPH + Omega-3/6 was superior to Omega-3/6 alone for ADHD Total and Hyperactivity-Impulsivity subscales but similar for Inattention. CGI-
Moghaddam 2017 n= 40 n= 40	Iran Single	Omega-3 + MPH vs. MPH + Placebo	6-12.	Parallel 10 weeks	Mean ADHD-RS reduction: 19.7±5.9 (MPH + Omega-3) vs. 15.1±9.3 (MPH + placebo, p<0.067). Response rate (≥25% reduction): 90% (MPH + Omega-3) vs. 60% (MPH + placebo, p=0.028). Authors conclude PUFA is effective.
Cornu 2018 n= 162 n= 148	France Multi-center	Omega-3vs. Placebo	6-15.	Parallel 13 weeks	ADHD-RS score reduction was greater in the placebo group (p < 0.05)
Chang 2019 n= 103 n= 92	China Single	High-dose EPA vs. Placebo	8-18.	Parallel 12 weeks	Improved attention and vigilance scores (p < 0.05) but worsened impulsivity in high baseline EPA participants.
Crippa 2019 n= 50 n= 48	Italy Single	Omega-3 vs. Placebo	7-14.	Parallel 26 weeks	Within-group differences on the Conners' scale showed ADHD symptoms decreased in the DHA group and increased in the placebo group. No between-group differences were observed.
Rodríguez 2019 n= 95 n= 66	Spain Single	Omega-3 vs. Placebo	6-18.	Parallel 8 weeks	Improvements in the Omega-3 group when compared to placebo reached statistical significance in 2 of 3 scales (p<0.05).
Mohammadzadeh 2019 n= 66 n= 60	Iran Single	Omega-3 + MPH vs. Placebo + MPH	6-12.	Parallel 26 weeks	No superiority of Omega-3 over placebo was observed in ADHD-RS and CPRS.
Carucci 2022 n= 160 n= 135	Italy Multi-center	Omega-3 vs Placebo	6-12.	Parallel with open-label extension 52 weeks	No statistically significant differences were noted between Omega-3 and Placebo groups on the blinded phase of the trial.

Characteristics of the included studies. **Abbreviations:** CGI-S = Clinical Global Impressions–Severity"; ADHD-RS = Attention Deficit Disorder Rating Scale; CBCL = Child Behavior Checklist, CPRS = Conners' Parent Rating Scale; CTRS = Conner's Teacher Rating Scale; SWAN = The Strengths and Weaknesses in ADHD and Normal Behaviors; CGAS = Children's Global Assessment Scale; MPH = Methylphenidate; Alpha linolenic acid = ALA; Eicosapentanoic acid = EPA; Docosahexaenoic acid = DHA; PUFA.

Table 1: *(continued) Characteristics of the included studies.*

Study design	Number analyzed
Two-arm RCT	**28 (90.3%)**
Omega-3 vs. Placebo	17 (60.71%)
Omega-3 + Methylphenidate vs Placebo + Methylphenidate	4 (14,30%)
Omega-3 + Methylphenidate vs Methylphenidate alone	1 (3.57%)
DHA supplement in specific foods vs. Placebo	1 (3.57%)
Omega-3 vs Fish Oil	1 (3.57%)
Omega-3 + 6 + Methylphenidate vs Placebo + Methylphenidate	1 (3.57%)
ALA rich sage oil vs Placebo	1 (3.57%)
Omega-3 + atomoxetine vs atomoxetine alone	1 (3.57%)
High dose EPA vs Placebo	1 (3.57%)
Three-arm RCT	**3 (9.7%)**
Omega-3 vs. Fish oil vs. Placebo	1 (33.3%)
Omega-3 vs. Methylphenidate vs. Placebo	1 (33.3%)
MPH + zinc vs. MPH + Omega-3 vs. MPH + Placebo	1 (33.3%)
Total	**31**

Table 2: *Study designs.*

2015; Milte et al., 2012; Widenhorn-Müller et al., 2014; Perera et al., 2012; Dubnov-Raz et al., 2014; Rodríguez et al., 2019; Sinn & Bryan, 2007; Vaisman et al., 2008; Salehi et al., 2016; Crippa et al., 2019; Carucci et al., 2022). Conversely, 6 studies reported significantly positive results (Barragán et al., 2017; Moghaddam 2017; Dashti et al., 2014; Gustafsson et al., 2010; Manor et al., 2012; Anand & Sachdeva 2016), while two studies indicated a worsening of symptoms (Chang et al., 2019; Johnson et al., 2009).

Sub-analysis: Inattention

Twenty-four studies (77.4%) assessed attention through various scales, including the CPT (Chang et al., 2019), Parent-rated Child Behavior Checklist (Bos et al., 2015), ADHD-RS (Assareh et al., 2017; Carucci et al., 2022; Crippa et al., 2019; Johnson et al., 2009; Milte et al., 2012; Mohammadzadeh et al., 2019), CPRS and CTRS (Bélanger 2009; Anand & Sachdeva, 2016; Carucci et al., 2022; Gustafsson et al., 2010; Rodríguez et al., 2019; Salehi et al., 2016), Test of Everyday Attention for Children (Milte et al., 2012), Test of Variables of Attention (Voigt et al., 2001), D2+AULA Nesplora executive function test (Rodríguez et al., 2019), DBD Rating Scale (Stevens et al., 2003), ANCOVAs (Barragán et al., 2017), DISYPS-II (Widenhorn-Müller et al., 2014), CGI (Johnson et al., 2009), MOXO-CPT (Dubnov-Raz et al., 2014), DSM-IV ADHD Rating Scale (Hirayama et al., 2004; Manor et al., 2012; Sinn & Bryan, 2007), 11-item checklist (Perera et al., 2012), TOVA (Vaisman et al., 2008) CPRS-L (Sinn & Bryan, 2007).

Among these studies, 7 (29.1%) reported statistically significant improvements in attention symptoms (Bos et al., 2015; Chang et al., 2019; Gustafsson et al., 2010; Perera et al., 2012; Sinn & Bryan, 2007; Stevens et al., 2003; Vaisman et al., 2008). However, 17 studies (70.7%) found no significant effects or differences among groups (Voigt et al., 2001; Hirayama et al., 2004; Assareh et al., 2007; Johnson et al., 2009; Bélanger 2009; Manor et al., 2012; Milte et al., 2012; Dubnov-Raz et al., 2014; Widenhorn-Müller et al., 2014; Milte et al., 2015; Salehi et al., 2016; Anand & Sachdeva 2016; Barragán et al., 2017; Crippa et al., 2019; Mohammadzadeh et al., 2019; Rodríguez et al., 2019; Carucci et al., 2022). Specific scales, such as the CBCL attention problems subscale (Bos et al., 2015) and CTRS (Gustafsson et al., 2010), showed notable improvements. Mixed results were noted with scales like ADHD-RS, with Carucci et al. (2022) reporting statistical differences slightly favoring Omega-3/6 during the open-label phase, while other authors (Crippa et al., 2019; Johnson et al., 2009) found no significant differences overall.

Risk of bias in individual studies:

The risk of bias across the studies was assessed in five

key domains: bias arising from the randomization process (D1), bias due to deviations from intended intervention (D2), bias due to missing outcome data (D3), bias in the measurement of the outcome (D4), and bias in the selection of the reported result (D5). The overall risk of bias is depicted in Figure 2, which shows the proportion of studies categorized as low risk (green), having some concerns (yellow), or high risk (red) across these five domains. Figure 3 provides a detailed breakdown of the risk level for each individual study, allowing for a comparison of bias across all domains.

The studies exhibited variability in terms of bias risk. Among the thirty-one included studies, eight studies (26%) were rated as having a low risk of bias across all domains (Vaisman et al., 2008; Manor et al., 2012; Milte et al., 2012; Widenhorn-Müller et al., 2014; Anand & Sachdeva 2016; Cornu et al., 2018; Crippa et al., 2019; Carucci et al., 2022). Nine studies (29%) were assessed as having "some concerns" in at least one domain, with particular emphasis on domains D1, D3, and D5 (Voigt et al., 2001; Sinn & Bryan, 2007; Bélanger 2009; Raz et al., 2009; Perera et al., 2012; Dashti et al., 2014; Milte et al., 2015; Assareh et al., 2017; Mohammadzadeh et al., 2019). Fourteen studies (45%) were classified as having a high risk of bias, predominantly influenced by issues in domains D2, D3, and D4 (Stevens et al., 2003; Hirayama et al., 2004; Johnson et al., 2009; Gustafsson et al., 2010; Hariri et al., 2012; Behdani et al., 2013; Dubnov-Raz et al., 2014; Bos et al., 2015; Matsudaira et al., 2015; Salehi et al., 2016; Barragán et al., 2017; Moghaddam 2017; Chang et al., 2019; Rodríguez et al., 2019). This qualitative analysis highlights the overall integrity of the included studies and the need for cautious interpretation of the findings, especially in those with identified risks of bias.

Discussion

This review included 31 RCTs published between 2003 and 2022, summarizing a total of 2,494 patients aged 4-18 years. The main objective was to evaluate the impact of Omega-3 supplementation on ADHD symptoms of children and adolescents. Overall, the results are highly heterogeneous in terms of study design, interventions, trial duration, dosage, and outcome measurement tools. This complexity makes it difficult to compare studies and to arrive at a confident conclusion regarding the effects of Omega-3 on ADHD clinical manifestations.

Some studies reported that Omega-3 significantly reduced inattention scores and performed similarly to MPH in reducing ADHD symptoms, including hyperactivity-impulsivity (Bélanger 2009; Anand & Sachdeva 2016; Barragán et al., 2017; Bos et al., 2015; Chang et al., 2019; Crippa et al., 2019; Moghaddam et al., 2017; Gustafsson et al., 2010; Hariri et al., 2012; Milte et al., 2015; Perera et al., 2012; Sinn & Bryan, 2007; Stevens et al., 2003; Vaisman et al., 2008). However, these studies had limitations, such as small sample sizes and statistical flaws, which challenge the reliability of their findings. On the other hand, several studies found no significant benefit of Omega-3 supplementation on ADHD symptoms, with some showing better results in the placebo group or no enhancement when combined with MPH (Assareh et al., 2017; Barragán et al., 2017; Carucci et al., 2022; Cornu et al., 2018; Crippa et al., 2019; Dubnov-Raz et al., 2014; Hirayama et al., 2004; Johnson et al., 2009; Matsudaira et al., 2015; Mohammadzadeh et al., 2019; Raz et al., 2009; Salehi et al., 2016; Voigt et al., 2001; Widenhorn-Müller et al., 2014). Three studies concluded that DHA supplementation had no beneficial effect, while four studies with EPA showed significant improvements in ADHD symptom measures (Chang et al., 2019; Crippa et al., 2019, Gustafsson et al., 2010; Hirayama et al., 2004; Milte et al., 2015; Vaisman et al., 2008; Voigt et al., 2001).

In the sub-analysis, hyperactivity-impulsivity outcomes were more negative, with 14 out of 23 studies showing no effect of Omega-3 supplementation (Assareh et al., 2017; Bélanger 2009; Cornu et al., 2018; Hirayama et al., 2004; Matsudaira et al., 2015; Milte et al., 2012; Widenhorn-Müller et al., 2014; Perera et al., 2012; Dubnov-Raz et al., 2014; Rodríguez et al., 2019; Sinn & Bryan, 2007; Vaisman et al., 2008; Salehi et al., 2016; Crippa et al., 2019). Inattention outcomes were similar, with 14 studies showing no significant effect of Omega-3 supplementation (Voigt et al., 2001; Hirayama et al., 2004; Assareh et al., 2007; Johnson et al., 2009; Manor et al., 2012; Milte et al., 2012; Dubnov-Raz et al., 2014; Widenhorn-Müller et al., 2014; Salehi et al., 2016; Barragán et al., 2017; Crippa et al., 2019; Mohammadzadeh et al., 2019; Rodríguez et al., 2019; Carucci et al., 2022). Although some studies suggest the benefits of Omega-3 in managing ADHD impulsivity/hyperactivity and inattention symptoms, the evidence remains inconsistent, highlighting the need for further research to reach clearer conclusions (Bélanger 2009; Anand & Sachdeva 2016; Barragán et al., 2017; Bos et al., 2015; Chang et al., 2019; Crippa et al., 2019; Moghaddam et al., 2017; Gustafsson et al., 2010; Hariri et al., 2012; Milte et al., 2015; Perera et al., 2012; Sinn & Bryan, 2007; Stevens et al., 2003; Vaisman et al., 2008).

Previous systematic reviews, such as those by Bloch& Qawasmi (2011), Agostoni et al. (2017), and Chang et al. (2018), reported a small but significant benefit of Omega-3 supplementation in managing

ADHD. Bloch & Qawamis's review included 10 RCTs with 699 patients and concluded favorable results for Omega-3, though only two studies within this review showed beneficial effects of omega-3 treatment (Bloch & Qawasmi 2011). Chang et al.'s 2018 review also reported a positive effect but acknowledged that excluding a particular trial led to these conclusions, which makes the results less reliable (Chang et al., 2018). On the other hand, Gillies et al.'s 2012 and 2023 reviews found no significant effect of Omega-3 on ADHD symptom management (Gillies et al., 2023; Gillies et al., 2012). Importantly, all these previous reviews relied on RCT data, which is consistent with the studies included in this systematic review.

Comparing these findings to our review, it is evident that newer studies continue to demonstrate mixed results. While earlier reviews suggested a small, potentially beneficial effect, the methodological limitations (such as bias and small sample sizes) present in these earlier trials continue to challenge the reliability of the evidence. The statistical significance of the results across the studies varies considerably, and clinically, even where statistical significance was achieved, the improvements in ADHD symptoms, such as inattention or hyperactivity, were often modest and may not represent meaningful changes in real-world functional outcomes.

In our systematic review, almost half of the included studies had a high overall risk of bias (n=14, 42%), primarily due to deficiencies in trial design and high dropout rates, which are common in RCTs involving children and adolescents (Barragán et al., 2017; Behdani et al., 2013; Bos et al., 2015; Chang et al., 2019; Dubnov-Raz et al., 2014; Moghaddam et al., 2017; Gustafsson et al., 2010; Hariri et al., 2012; Hirayama et al., 2004; Johnson et al., 2009; Matsudaira et al., 2015; Rodríguez et al., 2019; Salehi et al., 2016; Stevens et al., 2003). Therefore, while the previous reviews highlighted potential benefits, our updated analysis suggests the evidence remains inconsistent and unreliable due to persistent methodological issues.

A significant source of heterogeneity between studies is the variability in interventions. Studies included in this review utilized a wide range of interventions, including combinations of fish oil, placebo, Omega-3 and Omega-6, or Omega-3 alone. However, even within this subset, there was substantial variability in the daily dosages administered, which ranged from 180 mg to 10 g, with 1 g being a common dosage selection. Additionally, administration methods varied, with most studies using fixed daily dosages while some provided dosages based on the child's age or body weight (Assareh et al., 2017; Barragán et al., 2017; Dashti et al., 2014; Matsudaira et al., 2015; Salehi et al., 2016; Cornu et al., 2018). Notably, studies that used daily doses ranging from 300 mg to 1 g tended to report positive results, particularly in trials lasting longer than 12 weeks (Anand & Sachdeva 2016; Barragán et al., 2017; Behdani et al., 2013; Carucci et al., 2022; Crippa et al., 2019; Dashti et al., 2014; Moghaddam et al., 2017; Gustafsson et al., 2010; Hariri et al., 2012; Hirayama et al., 2004; Johnson et al., 2009; Matsudaira et al., 2015; Mohammadzadeh et al., 2019; Raz et al., 2009; Sinn & Bryan, 2007; Vaisman et al., 2008; Voigt et al., 2001; Widenhorn-Müller et al., 2014). However, these inconsistencies in dosages prevent the ability to accurately assess the efficacy of the interventions. Trial duration also contributed to heterogeneity. Longer trials were more likely to report positive effects, while shorter-duration studies frequently yielded negative results. This suggests that the duration of supplementation may play a role in its effectiveness in reducing ADHD symptoms.

Due to the high heterogeneity in study design, intervention types, dosages, and trial durations, a clear recommendation regarding the use of Omega-3 for ADHD management cannot be made. The evidence included in this review suggests little to no consistent statistical or clinical effect of Omega-3 supplementation on ADHD symptoms. Future research needs to address these methodological challenges and better standardize interventions to determine if there is a definitive role for Omega-3 in ADHD treatment.

Strengths and limitations

Our review exclusively included peer-reviewed randomized controlled trials (RCTs), which, along with the large number of studies and patients analyzed, strengthens the power and internal validity of our findings. Additionally, the inclusion of participants from diverse nationalities enhances the external validity of the review. By identifying and documenting the time duration and dosage of interventions, we were able to categorize the trials, observe general patterns, and reduce heterogeneity in the analysis.

The limitations of this review stem from the differences between the studies in aspects such as dosages, follow-up periods (ranging from 7 to 48 weeks), and the age range of the study populations, all of which may influence the results and limit the external validity of the findings. Additionally, missing information across the studies highlights potential sources of bias. Key data, such as variations in socioeconomic status and parental educational level, were not reported in most studies, despite their significant influence on dietary habits, healthcare access, and overall well-being,

as well as awareness and understanding of ADHD. Furthermore, variables like height and weight, which are essential in evaluating growth patterns and determining appropriate dosages in pediatric populations, were also largely absent from the studies.

Our review includes studies published between 2003 and 2022. A key change during this period was the introduction of the DSM-V criteria in 2013, which expanded the diagnostic parameters for ADHD. Notably, conditions like autism are no longer exclusionary under the new guidelines, potentially leading to an increase in ADHD diagnoses. This broader criterion, along with heightened public and physician awareness of ADHD, may have contributed to over- or misdiagnosis in recent years. These factors, in turn, could lead to greater heterogeneity in the sample populations, with patients presenting different neuro-genetic and environmental characteristics that may account for varied responses to interventions (Abdelnour et al., 2022).

Conclusion

This systematic review extends the ongoing research on the controversial and unresolved topic of Omega-3 supplementation, either as a standalone treatment or combined with MPH, Omega-6, and/or vitamin E, for managing ADHD symptoms in children and adolescents. Despite the publication of new studies, it remains difficult to establish a definitive contribution to the field. The limitations outlined in this review present opportunities for future experimental trials that address the key shortcomings, such as implementing stratified randomization, ensuring proper blinding, and using clinically relevant scales for outcome measurement.

Abbreviations

AA: Arachidonic acid
ADHD: Attention Deficit-Hyperactivity Disorder
ALA: Alpha linolenic acid
DHA: Docosahexaenoic acid
DPA: Decosapentatoneic acid
EFA: Essential fatty acids
EPA: Eicosapentaenoic acid
FO: Fish oil
GLA: Gamma linolenic acid
LA: Linolenic acid (a precursor of n-6 PUFA)
MPH: Methylphenidate
n-3 PUFA: Omega-3 polyunsaturated fatty acid
n-6 PUFA: Omega-6 polyunsaturated fatty acid
Omega-3 (n-3 PUFA) consists of the following PUFAs: ALA, EPA, DHA
Omega-6 (n-6 PUFA) consists of the following PUFAs: GLA, AA, DPA
PL: Phospholipid
PUFA: Polyunsaturated fatty acids
RCTs: Randomized clinical trials

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Conflicts of Interest

The authors declare no conflict of interest.

References

Abdelnour, E., Jansen, M. O., & Gold, J. A. (2022). *ADHD Diagnostic Trends: Increased Recognition or Overdiagnosis?* Missouri Medicine, 119(5), 467–473.

Abdullah, M., Jowett, B., Whittaker, P. J., & Patterson, L. (2019). *The effectiveness of omega-3 supplementation in reducing ADHD associated symptoms in children as measured by the Conners' rating scales: A systematic review of randomized controlled trials*. Journal of Psychiatric Research, 110, 64–73. https://doi.org/10.1016/j.jpsychires.2018.12.002

Ageranioti Bélanger, S., Vanasse, M., Spahis, S., Sylvestre, M.-P., Lippé, S., Ghadirian, P., Vanasse, C.-M., Levy, E., & Bélanger, S. (2009). *Omega-3 fatty acid treatment of children with attention-deficit hyperactivity disorder: A randomized, double-blind, placebo-controlled study*. Paediatr Child Health, 14(2).

Agostoni, C., Nobile, M., Ciappolino, V., Delvecchio, G., Tesei, A., Turolo, S., Crippa, A., Mazzocchi, A., Altamura, C. A., & Brambilla, P. (2017). *The Role of Omega-3 Fatty Acids in Developmental Psychopathology: A Systematic Review on Early Psychosis, Autism, and ADHD*. International Journal of Molecular Sciences, 18(12). https://doi.org/10.3390/ijms18122608

Anand, P., & Sachdeva, A. (2016). *Effect of poly unsaturated fatty acids administration on children with attention deficit hyperactivity disorder: A randomized controlled trial*. Journal of Clinical and Diagnostic Research, 10(9), OC01–OC05.

https://doi.org/10.7860/JCDR/2016/20423.8471

Aromataris, E., & Riitano, D. (2014). *Systematic Reviews*. AJN, American Journal of Nursing, 114(5), 49–56. https://doi.org/10.1097/01.NAJ.0000446779.99522.f6

Assareh, M., Davari Ashtiani, R., Khademi, M., Jazayeri, S., Rai, A., & Nikoo, M. (2017). *Efficacy of Polyunsaturated Fatty Acids (PUFA) in the Treatment of Attention Deficit Hyperactivity Disorder*. Journal of Attention Disorders, 21(1), 78–85. https://doi.org/10.1177/1087054712463962

Bagga, D., Wang, L., Farias-Eisner, R., Glaspy, J. A., & Reddy, S. T. (2003). *Differential effects of prostaglandin derived from omega-6 and omega-3 polyunsaturated fatty acids on COX-2 expression and IL-6 secretion*. PNAS, 100(4), 1751–1756. https://doi.org/10.1073/pnas.0334211100

Barragán, E., Breuer, D., & Döpfner, M. (2017). *Efficacy and Safety of Omega-3/6 Fatty Acids, Methylphenidate, and a Combined Treatment in Children With ADHD*. Journal of Attention Disorders, 21(5), 433–441. https://doi.org/10.1177/1087054713518239

Behdani, F., Hebrani, P., Naseraee, A., Haghighi, M. B., & Akhavanrezayat, A. (2013). *Does omega-3 supplement enhance the therapeutic results of methylphenidate in attention deficit hyperactivity disorder patients?* Journal of Research in Medical Sciences, 18(8), 653–658.

Bélanger, S. A., Vanasse, M., Spahis, S., Sylvestre, M. P., Lippé, S., L'heureux, F., Ghadirian, P., Vanasse, C. M., & Levy, E. (2009). *Omega-3 fatty acid treatment of children with attention-deficit hyperactivity disorder: A randomized, double-blind, placebo-controlled study*. Paediatrics & Child Health, 14(2), 89–98. https://doi.org/10.1093/pch/14.2.89

Berger, I., Dor, T., Nevo, Y., & Goldzweig, G. (2008). *Attitudes toward attention-deficit hyperactivity disorder (ADHD) treatment: parents' and children's perspectives*. Journal of Child Neurology, 23(9), 1036–1042. https://doi.org/10.1177/0883073808317726

Bloch, M. H., & Qawasmi, A. (2011). *Omega-3 Fatty Acid Supplementation for the Treatment of Children With Attention-Deficit/Hyperactivity Disorder Symptomatology: Systematic Review and Meta-Analysis*. Journal of the American Academy of Child & Adolescent Psychiatry, 50(10), 991–1000. https://doi.org/10.1016/j.jaac.2011.06.008

Bos, D. J., Oranje, B., Veerhoek, E. S., Van Diepen, R. M., Weusten, J. M. H., Demmelmair, H., Koletzko, B., De Sain-Van Der Velden, M. G. M., Eilander, A., Hoeksma, M., & Durston, S. (2015). *Reduced Symptoms of Inattention after Dietary Omega-3 Fatty Acid Supplementation in Boys with and without Attention Deficit/Hyperactivity Disorder*. Neuropsychopharmacology, 40(10), 2298–2306. https://doi.org/10.1038/npp.2015.73

Bramer, W. M., Rethlefsen, M. L., Kleijnen, J., & Franco, O. H. (2017). *Optimal database combinations for literature searches in systematic reviews: a prospective exploratory study*. Systematic Reviews, 6(1), 245. https://doi.org/10.1186/s13643-017-0644-y

Carucci, S., Romaniello, R., Demuru, G., Curatolo, P., Grelloni, C., Masi, G., Liboni, F., Mereu, A., Contu, P., Lamberti, M., Gagliano, A., & Zuddas, A. (2022). *Omega-3/6 supplementation for mild to moderate inattentive ADHD: a randomized, double-blind, placebo-controlled efficacy study in Italian children*. European Archives of Psychiatry and Clinical Neuroscience, 272(8), 1453–1467. https://doi.org/10.1007/s00406-022-01428-2

Chang, J. P.-C., Su, K.-P., Mondelli, V., Satyanarayanan, S. K., Yang, H.-T., Chiang, Y.-J., Chen, H.-T., & Pariante, C. M. (2019). *High-dose eicosapentaenoic acid (EPA) improves attention and vigilance in children and adolescents with attention deficit hyperactivity disorder (ADHD) and low endogenous EPA levels*. Translational Psychiatry, 9(1), 303. https://doi.org/10.1038/s41398-019-0633-0

Chang, J. P.-C., Su, K.-P., Mondelli, V., & Pariante, C. M. (2018). *Omega-3 Polyunsaturated Fatty Acids in Youths with Attention Deficit Hyperactivity Disorder: a Systematic Review and Meta-Analysis of Clinical Trials and Biological Studies*. Neuropsychopharmacology, 43(3), 534–545. https://doi.org/10.1038/npp.2017.160

Chang, J. P. C., & Su, K.-P. (2010). *The lipid raft hypothesis: the relation among omega-3 fatty acids, depression and cardiovascular diseases*. Taiwanese Journal of Psychiatry (Taipei), 24(3). https://www.researchgate.net/publication/285763041

Cooper, R. E., Tye, C., Kuntsi, J., Vassos, E., & Asherson, P. (2015). *Omega-3 polyunsaturated fatty acid supplementation and cognition: A systematic review and meta-analysis*. Journal of Psychopharmacology, 29(7), 753–763. https://doi.org/10.1177/0269881115587958

Cornu, C., Mercier, C., Ginhoux, T., Masson, S., Mouchet, J., Nony, P., Kassai, B., Laudy, V., Berquin, P., Franc, N., Le Heuzey, M. F., Desombre, H., & Revol, O. (2018). *A double-blind placebo-controlled randomized trial of omega-3 supplementation in children with moderate ADHD symptoms*. European Child and Adolescent Psychiatry, 27(3), 377–384. https://doi.org/10.1007/s00787-017-1058-z

Crippa, A., Tesei, A., Sangiorgio, F., Salandi, A., Trabattoni, S., Grazioli, S., Agostoni, C., Molteni, M., & Nobile, M. (2019). *Behavioral and cognitive effects of docosahexaenoic acid in drug-naïve children with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled clinical trial*. European Child and Adolescent Psychiatry, 28(4), 571–583. https://doi.org/10.1007/s00787-018-1223-z

Das, U. N. (2006). *Essential fatty acids: biochemistry, physiology and pathology*. Biotechnology Journal, 1(4), 420–439. https://doi.org/10.1002/biot.200600012

Dashti, N., Hekmat, H., Soltani, H. R., Rahimdel, A., & Javaherchian, M. (2014). *Comparison of Therapeutic Effects of Omega-3 and Methylphenidate (Ritalin ®) in Treating Children With Attention Deficit Hyperactivity Disorder*. Iran J Psychiatry Behav Sci, 8. www.ijpbs.mazums.ac.ir

Dubnov-Raz, G., Khoury, Z., Wright, I., Raz, R., & Berger, I. (2014). *The effect of alpha-linolenic acid supplementation on ADHD symptoms in children: a randomized controlled double-blind study*. Frontiers in Human Neuroscience, 8. https://doi.org/10.3389/fnhum.2014.00780

Felt, B. T., Biermann, B., Christner, J. G., Kochhar, P., & Harrison, R. V. (2014). *Diagnosis and management of ADHD in children*. American Family Physician, 90(7), 456–464.

Gillies, D., Leach, M. J., & Perez Algorta, G. (2023). *Polyunsaturated fatty acids (PUFA) for attention deficit hyperactivity disorder (ADHD) in children and adolescents*. Cochrane Database of Systematic Reviews, 2023(4). https://doi.org/10.1002/14651858.CD007986.pub3

Gillies, D., Sinn, J. K., Lad, S. S., Leach, M. J., & Ross, M. J. (2012). *Polyunsaturated fatty acids (PUFA) for attention deficit hyperactivity disorder (ADHD) in children and adolescents*. Cochrane Database of Systematic Reviews, 2012(7), CD007986. https://doi.org/10.1002/14651858.CD007986.pub2

Gustafsson, P. A., Birberg-Thornberg, U., Duchén, K., Landgren, M., Malmberg, K., Pelling, H., Strandvik, B., & Karlsson, T. (2010). *EPA supplementation improves teacher-rated and oppositional symptoms in children with ADHD*. Acta Paediatrica, 99(10), 1540–1549. https://doi.org/10.1111/j.1651-2227.2010.01871.x

Händel, M. N., Rohde, J. F., Rimestad, M. L., Bandak, E., Birkefoss, K., Tendal, B., Lemcke, S., & Callesen, H. E. (2021). *Efficacy and Safety of Polyunsaturated Fatty Acids Supplementation in the Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in Children and Adolescents: A Systematic Review and Meta-Analysis of Clinical Trials*. Nutrients, 13(4), 1226. https://doi.org/10.3390/nu13041226

Hariri, M., Djazayery, A., Djalali, M., Saedisomeolia, A., Rahimi, A., & Abdolahian, E. (2012). *Effect of n-3 supplementation on hyperactivity, oxidative stress and inflammatory mediators in children with attention-deficit-hyperactivity disorder*. Malaysian Journal of Nutrition, 18(3), 329–335.

Higgins, J.P.T., Thomas, J., Chandler, J., Cumpston. M., Li, T., Page, M.J., Welch, V.A. (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.5 (updated August 2024). Cochrane, 2024. Available from www.training.cochrane.org/handbook.

Hirayama, S., Hamazaki, T., & Terasawa, K. (2004). Effect of docosahexaenoic acid-containing food administration on symptoms of attention-deficit/hyperactivity disorder – A placebo-controlled double-blind study. European Journal of Clinical Nutrition, 58(3), 467–473. https://doi.org/10.1038/sj.ejcn.1601830

Hogan, E., Akpan, M., Ijezie, E., & Edem, K. (2022). Prevalence of attention deficit hyperactivity disorder symptoms among primary school children in Nigeria: a comparison of teachers and parent reports. International Journal of Research in Medical Sciences, 10(5), 1021. https://doi.org/10.18203/2320-6012.ijrms20221172

Johnson, M., Östlund, S., Fransson, G., Kadesjö, B., & Gillberg, C. (2009). Omega-3/omega-6 fatty acids for attention deficit hyperactivity disorder: A randomized placebo-controlled trial in children and adolescents. Journal of Attention Disorders, 12(5), 394–401. https://doi.org/10.1177/1087054708316261

Man, K. K. C., Häge, A., Banaschewski, T., Inglis, S. K., Buitelaar, J., Carucci, S., Danckaerts, M.,

Dittmann, R. W., Falissard, B., Garas, P., Hollis, C., Konrad, K., Kovshoff, H., Liddle, E., McCarthy, S., Neubert, A., Nagy, P., Rosenthal, E., Sonuga-Barke, E. J. S., … Uebel-von Sandersleben, H. (2023). Long-term safety of methylphenidate in children and adolescents with ADHD: 2-year outcomes of the Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects (ADDUCE) study. The Lancet Psychiatry, 10(5), 323–333. https://doi.org/10.1016/S2215-0366(23)00042-1

Manor, I., Magen, A., Keidar, D., Rosen, S., Tasker, H., Cohen, T., Richter, Y., Zaaroor-Regev, D., Manor, Y., & Weizman, A. (2012). The effect of phosphatidylserine containing Omega3 fatty-acids on attention-deficit hyperactivity disorder symptoms in children: A double-blind placebo-controlled trial, followed by an open-label extension. European Psychiatry, 27(5), 335–342. https://doi.org/10.1016/j.eurpsy.2011.05.004

Matsudaira, T., Gow, R. V., Kelly, J., Murphy, C., Potts, L., Sumich, A., Ghebremeskel, K., Crawford, M. A., & Taylor, E. (2015). Biochemical and Psychological Effects of Omega-3/6 Supplements in Male Adolescents with Attention-Deficit/Hyperactivity Disorder: A Randomized, Placebo-Controlled, Clinical Trial. Journal of Child and Adolescent Psychopharmacology, 25(10), 775–782. https://doi.org/10.1089/cap.2015.0052

Milte, C. M., Parletta, N., Buckley, J. D., Coates, A. M., Young, R. M., & Howe, P. R. C. (2012). Eicosapentaenoic and docosahexaenoic acids, cognition, and behavior in children with attention-deficit/hyperactivity disorder: A randomized controlled trial. Nutrition, 28(6), 670–677. https://doi.org/10.1016/j.nut.2011.12.009

Milte, C. M., Parletta, N., Buckley, J. D., Coates, A. M., Young, R. M., & Howe, P. R. C. (2015). Increased erythrocyte eicosapentaenoic acid and docosahexaenoic acid are associated with improved attention and behavior in children with adhd in a randomized controlled three-way crossover trial. Journal of Attention Disorders, 19(11), 954–964. https://doi.org/10.1177/1087054713510562

Moghaddam, M. F., Shamekhi, M., & Rakhshani, T. (2017). Effectiveness of methylphenidate and PUFA for the treatment of patients with ADHD: A double-blinded randomized clinical trial. Electronic physician, 9(5), 4412–4418. https://doi.org/10.19082/4412

Mohammadzadeh, S., Baghi, N., Yousefi, F., & Yousefzamani, B. (2019). Effect of omega-3 plus methylphenidate as an alternative therapy to reduce attention deficit-hyperactivity disorder in children. Korean Journal of Pediatrics, 62(9), 360–366. https://doi.org/10.3345/kjp.2018.06982

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ (Clinical Research ed.), 372, n71. https://doi.org/10.1136/bmj.n71

Perera, H., Jeewandara, K. C., Seneviratne, S., & Guruge, C. (2012). Combined ω3 and ω6 supplementation in children with attention-deficit hyperactivity disorder (ADHD) refractory to methylphenidate treatment: A double-blind, placebo-controlled study. Journal of Child Neurology, 27(6), 747–753. https://doi.org/10.1177/0883073811435243

Pingault, J.-B., Barkhuizen, W., Wang, B., Hannigan, L. J., Eilertsen, E. M., Corfield, E., Andreassen, O. A., Ask, H., Tesli, M., Askeland, R. B., Davey Smith, G., Stoltenberg, C., Davies, N. M., Reichborn-Kjennerud, T., Ystrom, E., & Havdahl, A. (2023). Genetic nurture versus genetic transmission of risk for ADHD traits in the Norwegian Mother, Father and Child Cohort Study. Molecular Psychiatry, 28(4), 1731–1738. https://doi.org/10.1038/s41380-022-01863-6

Raz, R., Carasso, R. L., & Yehuda, S. (2009). The Influence of Short-Chain Essential Fatty Acids on Children with Attention-Deficit/Hyperactivity Disorder: A Double-Blind Placebo-Controlled Study. Journal of Child and Adolescent Psychopharmacology, 19(2), 167–177. https://doi.org/10.1089/cap.2008.070

Rodríguez, C., García, T., Areces, D., Fernández, E., García-Noriega, M., & Domingo, J. C. (2019). Supplementation with high-content docosahexaenoic acid triglyceride in attentiondeficit hyperactivity disorder: A randomized double-blind placebo-controlled trial. Neuropsychiatric Disease and Treatment, 15, 1193–1209. https://doi.org/10.2147/NDT.S206020

Salehi, B., Mohammadbeigi, A., Sheykholeslam, H., Moshiri, E., & Dorreh, F. (2016). Omega-3 and Zinc supplementation as complementary therapies in children with attention-deficit/hyperactivity disorder. Journal of Research in Pharmacy Practice, 5(1), 22. https://doi.org/10.4103/2279-042x.176561

Sinn, N., & Bryan, J. (2007). Effect of supplementation with polyunsaturated fatty acids and

micronutrients on learning and behavior problems associated with child ADHD. Journal of developmental and behavioral pediatrics : JDBP, 28(2), 82–91. https://doi.org/10.1097/01.DBP.0000267558.88457.a5

Sterne, J. A. C., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., Cates, C. J., Cheng, H.-Y., Corbett, M. S., Eldridge, S. M., Emberson, J. R., Hernán, M. A., Hopewell, S., Hróbjartsson, A., Junqueira, D. R., Jüni, P., Kirkham, J. J., Lasserson, T., Li, T., … Higgins, J. P. T. (2019). RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ, l4898. https://doi.org/10.1136/bmj.l4898

Stevens, L., Zhang, W., Peck, L., Kuczek, T., Grevstad, N., Mahon, A., Zentall, S. S., Arnold, L. E., & Burgess, J. R. (2003). EFA supplementation in children with inattention, hyperactivity, and other disruptive behaviors. *Lipids, 38(10), 1007–1021.* https://doi.org/10.1007/s11745-006-1155-0

Thomas, R., Sanders, S., Doust, J., Beller, E., & Glasziou, P. (2015). Prevalence of Attention-Deficit/Hyperactivity Disorder: A Systematic Review and Meta-analysis. Pediatrics, 135(4), e994–e1001. https://doi.org/10.1542/peds.2014-3482

Vaisman, N., Kaysar, N., Zaruk-Adasha, Y., Pelled, D., Brichon, G., Zwingelstein, G., & Bodennec, J. (2008). Correlation between changes in blood fatty acid composition and visual sustained attention performance in children with inattention: effect of dietary n-3 fatty acids containing phospholipids. *The American journal of clinical nutrition, 87(5),* 1170–1180. https://doi.org/10.1093/ajcn/87.5.1170

Voigt, R. G., Llorente, A. M., Jensen, C. L., Fraley, J. K., Berretta, M. C., & Heird, W. C. (2001). A randomized, double-blind, placebo-controlled trial of docosahexaenoic acid supplementation in children with attention-deficit/hyperactivity disorder. Journal of Pediatrics, 139(2), 189–196. https://doi.org/10.1067/mpd.2001.116050

Widenhorn-Müller, K., Schwanda, S., Scholz, E., Spitzer, M., & Bode, H. (2014). Effect of supplementation with long-chain ω-3 polyunsaturated fatty acids on behavior and cognition in children with attention deficit/hyperactivity disorder (ADHD): A randomized placebo-controlled intervention trial. Prostaglandins, Leukotrienes and Essential Fatty Acids, 91(1–2), 49–60. https://doi.org/10.1016/j.plefa.2014.04.004

Xu, G., Strathearn, L., Liu, B., Yang, B., & Bao, W. (2018). Twenty-Year Trends in Diagnosed Attention-Deficit/Hyperactivity Disorder Among US Children and Adolescents, 1997-2016. *JAMA Network Open, 1(4), e181471.* https://doi.org/10.1001/jamanetworkopen.2018.1471