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BIOMEDICAL SCIENCES

The Benefit of Omega-3 Fatty Acid-Based Diets on Attention-Deficit Hyperactivity Disorder through the Brain-Gut Axis: A Systematic Review of Randomized Controlled Trials

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Abstract

Attention-Deficit Hyperactivity Disorder (ADHD) is one of the most prevalent mental conditions in children and young adolescents. While stimulants are the first-line treatment, diet-based supplements, particularly omega-3 fatty acids, are being investigated for their additional benefits. Omega-3 fatty acids influence the microbiota-gut-brain axis through anti-inflammatory and antioxidant properties, modulation of gut microbes, and stimulation of the immune system, highlighting their potential as crucial dietary supplements for individuals with ADHD. This review aims to comprehensively summarize current evidence on the benefits of omega-3 fatty acids in patients with ADHD, both clinically and in terms of biological markers, to elucidate their advantages and underlying mechanisms for future research applications. A comprehensive literature search of relevant studies available in English was conducted on PubMed/MEDLINE, Web of Science, and Wiley Online Library databases from 1987 until December 2023. Articles were selected based on inclusion and exclusion criteria, resulting in thirty-six studies being included in this review. Twenty-one of the thirty-six studies reported benefits of omega-3, showing improvements in rating scales, behavioral functions, or both. However, two studies indicated that omega-3 supplementation could worsen adverse effects on behavior or aggression rating scales, particularly in pregnant women and newborns with long-term follow-up. Most of the studies focused on children diagnosed with ADHD documenting a reduction in ADHD symptoms among individuals supplementing with omega-3 fatty acids. Our systematic review provides evidence that omega-3 polyunsaturated fatty acids are beneficial in improving clinical symptoms of ADHD in adolescents and adults, potentially by increasing beneficial gut microorganisms, and removing endotoxins that cause pro-inflammatory responses. Future research should involve larger sample sizes, longer durations, and determination of optimal omega-3 sources for ADHD treatment.

Keywords: Attention Deficit Disorder with Hyperactivity; Fatty Acids, Omega-3; Behavioral Symptoms; Mechanism of Action; Review, Systematic

Introduction

Attention-deficit hyperactivity disorder (ADHD) is one of the most common psychological disorders among children and young adolescents, with a prevalence of one in 11 children being diagnosed [1]. This condition can affect patients' social relationships, learning abilities, functional development, and daily life. It is a neuropsychological disorder that can happen to anyone regardless of their gender, race, or ethnicity. Based on the "National Survey of Children's Health" data, 6 million diagnosed children in the United States were currently diagnosed from ages 3 to 17 in 2016-2019. ADHD is more common in boys than girls, 12% versus 6%, and in some patients, the disease may be carried into adulthood. The number of adults diagnosed is also on the rise because, as of 2020, the global prevalence of symptomatic adult ADHD was 6.76% or 366.33 million [2]. According to Diagnostic and Statistical Manual of Mental Disorders-5 criteria, the diagnosis of ADHD can be established by patterns of six or more symptoms of inattention and/or hyperactivity-impulsivity that hinder daily functions or normal development for six months or longer [3]. Unlike the pediatric population, ADHD diagnosis in adulthood requires five or more symptoms only, and the impact on quality of life can be varied. Only two-thirds of ADHD adolescents are on pharmacological therapies based on a 2016 data report [4], and a subset of the patient population has received behavioral therapies or alternative non-pharmacological treatments. Though stimulants are first-line treatment, recent medication shortages challenge patients and providers to receive

adequate care. Recent studies also suggest that long-term use of medication for ADHD is associated with an increased risk of cardiovascular disease. Therefore, seeking an effective supplement is an urgent issue [5]. To resolve this ongoing matter, we have looked into dietary approaches in ADHD - particularly omega-3 fatty acids (FAs), focusing on the brain-gut axis, the connection between the nervous system, the intestine, and microbiota. An omega-3-based diet includes foods high in omega-3 FAs, mainly fish, seafood, nuts, etc. In contrast with different diets, such as a few foods or an elimination diet, this diet has no food restrictions. As such, it is possible for ADHD patients to start on an omega-3-based diet even with diet limitations or to add omega-3 as a dietary supplement on top of stimulants. Omega-3 has been proven to help reduce symptoms in ADHD patients in studies. This review aims to comprehensively summarize current evidence on the benefits of omega-3 fatty acids in patients with ADHD, both clinically and in terms of biological markers, to elucidate their advantages and underlying mechanisms for future research applications.

Review Methodology

Search strategy

Our research question was to determine the effect if omega-3 based diet in reduced symptoms or outcomes of patients with attention deficit hyperactivity disorder. A comprehensive literature search of relevant studies available in English was conducted on PubMed/MEDLINE, Web of Science, and Wiley Online Library database from 1987 till December 2023 in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [6]. The following terms were used on all databases: “Omega-3 fatty acid” and “attention deficit hyperactivity disorder”.

The search query was shown as below: ("fatty acids, omega 3"[MeSH Terms] OR ("fatty"[All Fields] AND "acids"[All Fields] AND "omega 3"[All Fields]) OR "omega-3 fatty acids"[All Fields] OR "omega 3 fatty acid"[All Fields]) AND ("attention deficit disorder with hyperactivity"[MeSH Terms] OR ("attention"[All Fields] AND "deficit"[All Fields] AND "disorder"[All Fields] AND "hyperactivity"[All Fields]) OR "attention deficit disorder with hyperactivity"[All Fields] OR ("attention"[All Fields] AND "deficit"[All Fields] AND "hyperactivity"[All Fields] AND "disorder"[All Fields]) OR "attention deficit hyperactivity disorder"[All Fields]).

Inclusion and Exclusion Criteria

In order to conduct a rigorous analysis, we employed inclusion and exclusion criteria to choose high-quality studies specifically. Studies unrelated to the impact of omega-3 fatty acids on individuals with ADHD, those focusing on animal models, or lacking original data were excluded. Additionally, studies without accessible full-text versions were excluded.

Regarding the study types, we selectively included randomized controlled trials (RCTs) with a minimum of two arms, where one arm involved the administration of Omega-3 and the other a placebo. Excluded from consideration were case reports, case series, dissertations, book chapters, abstracts, posters, oral presentations, protocol articles, guidelines, reviews, news articles, conference abstracts, letters to the editor or commentary letters, editorials, systematic reviews, meta-analyses, cross-sectional studies, and cohort studies.

Types of intervention: We selected only studies which evaluated the impact of omega-3 based supplement/diet including alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and phosphatidylserine.

Outcomes: The included studies should report relevant outcomes including symptoms, clinical score/index (reading score, aggression score, spelling score…), brain activity, Omega-3 concentration, inflammatory biomarker.

Selection of studies

After an initial screening relying on the title and abstract, two reviewers (AET and PNLB) independently identified trials for inclusion in this review, adhering to pre-established inclusion and exclusion criteria. Any disagreement regarding the inclusion of studies was resolved through consensus between the two reviewers, with consultation from a third review author (HDNT) if needed.

Results

Across the databases, we identified 659 studies. After a careful examination and screening process. We selected 36 studies for final review. The study selection process is illustrated in Figure 1. All the selected studies were included in Table 1. We found that two studies were conducted in the United States, one in Mexico, fifthteen in Europe, six in Australia, one in Africa, and eleven in Asia.

Twenty-one out of thirty-six studies reported benefits of omega-3 with improvement in either rating scales or behavioral functions or both. Because of the variations in rating scales, each study was determined to measure progress, omega-3 doses, and supplementation sources; it is impractical to generalize whether one study demonstrates more significant results than another. Nonetheless, notable mentions include the study of Perera et al. [7], which showed a significant improvement in inattention and impulsiveness in patients already on medication and behavior therapy. Hariri et al. illustrated that reduced blood concentrations of C-reactive proteins and interleukin-6 substantiate the anti-inflammatory advantages of omega-3 fatty acids [8]. Mcnamara et al. reported an increased percentage of DHA composition in erythrocyte membranes and assessed brain regions (more activation of the dorsolateral prefrontal cortex and less activation of the occipital cortex and cerebellar cortex) [9].

Eight out of 36 studies reported no significant improvement with omega-3 supplementation com-

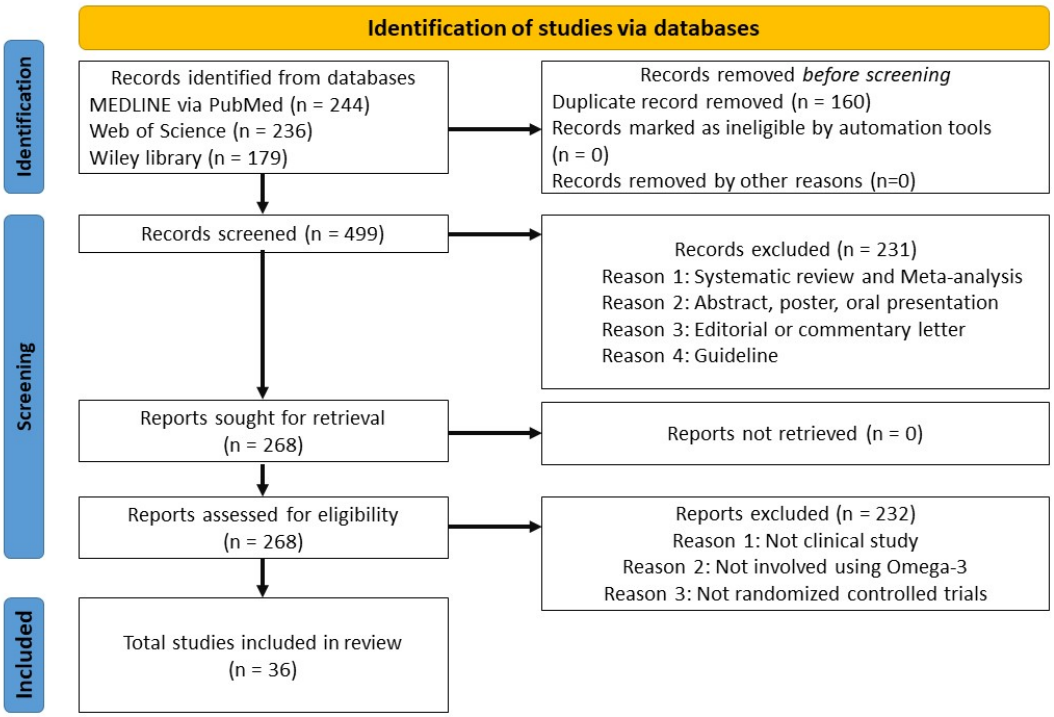

Figure 1: PRISMA flow diagram of study selection. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis

pared to the placebo group. Such studies found no symptomatic improvements or changes in score ratings in experimental and placebo groups before and after the intervention. Possibilities of these studies not meeting the significance threshold include but are not limited to small sample sizes and low daily doses of omega-3. Different supplementation types did not impact the results as taking omega-3 or being part of the diet still did not improve the symptoms. The other three studies presented partial improvement in subgroups, increased ratings in certain categories, or behavioral improvement observed in a limited window. Two studies of Raz and Rodriguez reported improvements in both groups yet no superiority to placebo [10, 11].

On the other hand, Dean and Gould stated that omega-3 supplementation could worsen adverse effects on behaviors or aggression rating scales [12, 13]. The latter study focused on a special population of pregnant women and newborns with long-term follow-up. The fact that prenatal DHA supplementation can potentially worsen the behaviors of children, as reported in this study, is intriguing because DHA is one of the strongly recommended fats to be consumed during pregnancy for fetal development benefits [13].

Twenty-three studies focused on children with diagnosed ADHD. Still, only a few studies mentioned whether the sample population had prior medication treatments or were excluded from the study if they were previously on treatment, such as Perera's study, which was the only study specifying that patients were on methylphenidate and standard behavior therapy [7]. The status of the official diagnosis does not hold the data, as there were studies with no improvement, even in the undiagnosed population. Most studies focused on diagnosed children/adolescents starting at 6 to 18 years old, males and females, with the youngest starting at age 4 in Hirayama's study [14]. Eleven studies reported their studies with a healthy or undiagnosed population as the baseline measurement to determine omega-3 benefits. Age groups in those studies were similar to the above studies with the diagnosed population. The studies of Ramakrishnan and Gould were the only two that solely included a special population of pregnant and postpartum women and their children [13, 15]. Compared to Gould's study, Ramakrishnan did have improvements in rating scores at the follow-up of 5 years after postpartum [15]. Conflicting results between the two studies should be studied further due to the same study population and large sample sizes.

The sample size in most studies was relatively small due to the nature of the disorder and the age of the population. Twenty studies were conducted with a small sample size of less than 100 participants. Unlike these, twelve studies had larger sample sizes of > 100 with an average of 200 people, with Pinarmarti 's research with nearly 800 participants [16]. As mentioned above, studies with a special population even had greater sample sizes as both studies of Ramakrishnan and Gould conducted their studies on a thousand participants [13, 15]. The majority of studies also framed their study duration to be $\leq$3 months or 12 weeks, as found in 15 studies. On the other hand, twenty studies had a longer than 3-month period, with some studies extending to 12 months. Such factors have no strong influence on the results or

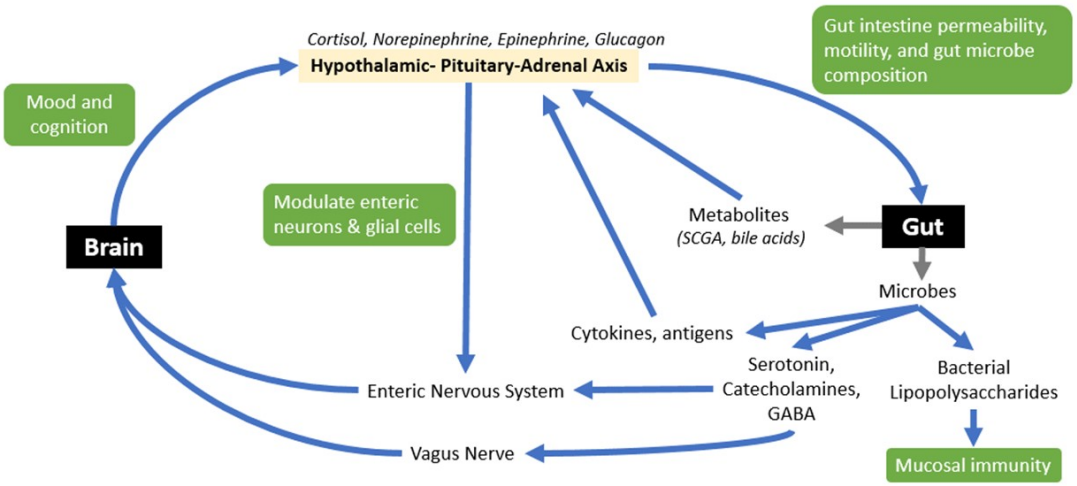

Figure 2: Molecular mechanisms and functions of microbiota-gut-brain-axis. The hypothalamic pituitary adrenal (HPA) axis releases stress hormones like cortisol and epinephrine, affecting gut permeability, motility, and microbiota. The gut's enteric nervous system and gut microbes modulate the production of neurotransmitters including serotonin, catecholamines, Gamma-aminobutyric acid (GABA) that communicate with the brain, influencing mood and cognition. Gut microbial metabolites like short-chain fatty acids (SCFA) and bile acids regulate neurotrophic factors, the HPA axis, and hormonal balance.

improvements in reported studies, but longer study durations or larger sample sizes may or may not influence the results.

In these studies, supplementation of omega-3 is more common than being part of the diet. Twenty-four studies reported using omega-3 supplements such as gel capsules or pills, but each study had unique daily doses of DHA and EPA and did not specify the source of omega-3. Fourteen studies had omega-3 as part of the diet, such as raw walnut kernels and margarine. A few studies mentioned a target of 3.6 grams of DHA per week, but not every study outlined it in the same manner. Vitamin E, a fat-soluble vitamin with antioxidant and anti-inflammatory properties, was used as both the supplementation and placebo. Unlike other studies, Kean's study specifically catered the trial using marine oil extract, PCSO-524, which was reported as "an inflammatory modulator inhibits the 5'-lipoxygenase and cyclooxygenase pathways and decreases concentrations of the pro-inflammatory arachidonic acid (AA)" [17]. Due to the positive benefits mentioned in the study and its similarity to omega-3, further research on PCSO-524 is encouraged.

Microbiota-gut-brain-axis and underlying beneficial mechanisms of Omega 3

Microbiota-gut-brain-axis (MGBA) is a concept that the emotional and cognitive centers of the brain are linked with intestinal functions and microorganisms residing in our guts (Figure 2) [18]. By bidirectional communication, both the gut and the brain influence each other. Under stressful conditions, the hypothalamic pituitary adrenal axis (HPA) from central nervous system (CNS) releases stress hormones like cortisol, epinephrine, norepinephrine, and glucagon which modify intestinal permeability, motility, and gut microbiota composition [18]. Conversely, the gut comprises the enteric nervous system (ENS) that facilitates G.I. tract movements. Gut microbes modulate the production of chemical neurotransmitters like serotonin, catecholamines, and Gamma-aminobutyric acid which stimulate the ENS and the vagus nerve to communicate with the brain regions such as the hippocampus, amygdala, and prefrontal cortex, consequently affecting mood and cognition. The gut also produces microbial metabolites such as short-chain fatty acids and bile acids, which influence neurotrophic factors, regulate the HPA axis, and regulate hormonal homeostasis.

This ideology has broadened beyond the former simplex pathophysiological perspective on mental disorders. Modifying the gut microbiome composition to the optimal level can improve clinical symptoms of mental health disorders; thus, eating a healthy diet or taking probiotics are trending patterns in hopes of enhancing clinical benefits. So far, studies that focus on diets in ADHD patients include but are not limited to polyunsaturated fatty acids (PUFA), artificial food additives (colors and flavors), few-food diets, minerals such as zinc and magnesium, and others [19]. Omega-3 can be only supplemented by dietary means and is differentiated into ALA, EPA, and DHA. Consuming omega-3 fatty acids is essential as our bodies cannot synthesize ALA. DHA and EPA may be converted from ALA; but the amount is insufficient for actual benefits. Fatty fish, oysters, flaxseeds, and soybeans are a few food examples rich in omega-3, and for those who prefer to take it as a medication, over the counter or by-prescription products sell the ingredient in gel or capsule forms. Fish oils are widely used for

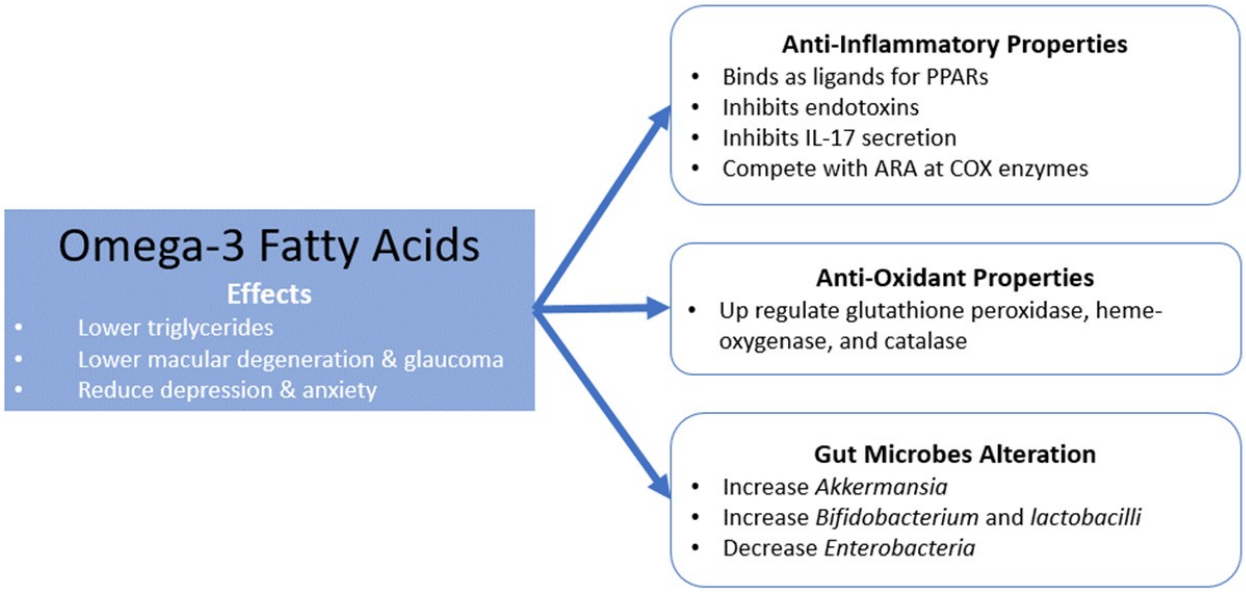

Figure 3: Proposed benefits of omega-3 fatty acids. Omega-3 fatty acids enhance anti-inflammatory responses by activating peroxisome proliferator-activated receptors (PPARs) and inhibiting endotoxins and Interleukin-17A (IL-17). They also interfere with arachidonic acid (ARA) and cyclooxygenase enzymes (COX). Additionally, omega-3 FAs have antioxidant properties, upregulating genes for glutathione peroxidase, heme oxygenase 1, and catalase. They also increase beneficial gut bacteria.

omega-3 supplements as they are reported to exhibit the most significant benefit in the gut flora [20].

Despite its positive effect on cholesterol levels already approved by healthcare professionals and the public, the benefits of omega-3 fatty acids are far beyond (Figure 3). Notable mentions include depression and anxiety benefits, and anti-inflammatory response. When intestinal microbiomes digest omega-3 FAs, they serve as endogenous ligands for peroxisome proliferator-activated receptors to enhance anti-inflammatory responses in the body under stressful conditions. They alter pro-inflammatory mediators via the inhibition of endotoxins and Interleukine-17A secretions. Non-steroidal anti-inflammatory drugs (NSAIDs) are known for their anti-inflammatory responses via blocking activities of cyclooxygenase enzymes (COX) from binding to arachidonic acid. In comparison, omega-3 FAs serve as the alternative substrate by competing with AA to bind to COX enzymes. This competitive inhibition increases the production of leukotriene B5 and prostaglandine E3, anti-inflammatory mediators. NSAIDs are preferable for acute treatment due to quick enzymatic blockage; meanwhile, omega-3 FAs are better for long-term treatment because of slow substrate competition [21]. Moreover, omega-3 FAs are recognized for antioxidant properties for upregulating genes that express glutathione peroxidase, heme oxygenase 1, and catalase enzymes [20]. Since ADHD is found to be linked with possible immunological and inflammatory mechanisms, anti-inflammatory characteristics of omega-3 can contribute to controlling symptoms. This unique action could further treat the disorder from a different perspective and deviate from the standard treatments with stimulating agents.

Omega-3 alters balances of gut microbes, such as increasing beneficial bacteria like Akkermansia while decreasing Enterobacteria, suppressing endotoxins, which leads to another anti-inflammatory action. Though the mechanism of ADHD is not directly linked to inflammatory consequences to the brain, modification in the latter can cause imbalances in neurotransmitters and lead to clinical symptoms. Evidence has also been found that omega-3 PUFAs increase the gut microorganisms such as bifidobacterium and lactobacilli [20]. These bacteria are known for their beneficial health effects and are used as probiotic supplements for regulating the immune system, facilitating nutrient absorption, and promoting psychological health. These findings regarding modification in gut microbiome are crucial because an increase in gut microbes prevents activation of inflammatory pathways, again proving the role of MGBA. Per one study, supplementing probiotics Bifidobacterium bifidum itself is linked to improvement in clinical symptoms and weight gain in ADHD youths [22]. Thus, we can hypothesize that omega-3 can also reduce negative symptoms of ADHD by indirect means. On the other hand, Aartes reported that the abundance of Bifidobacterium bacteria in ADHD patients correlates to an increased number of cyclohexadienyl dehydratase enzymes involved in dopamine precursor synthesis. The article outlined that such an increase in dopamine precursors relates

to "decreased neural reward anticipation, one of the hallmarks of ADHD" [23].

Limitations and Potentials

In comparison to medications, literature analysis for dietary supplements in mental disorders is often limited. Nevertheless, the trending change in perspective on using supplements, vitamins, and probiotics, along with behavioral and pharmacological treatments, has opened more doors for researchers to study each beneficial supplement. Omega-3 FAs are already widely used for cardiovascular effects, and they are expected to be utilized further in psychological disorders as well for their results on gut microbiome and anti-inflammatory purposes. Currently, the proven benefits of omega-3 FAs are limited compared to its proposed properties: 1) Reported randomized controlled trials had small sample sizes and short study durations, and short-term results can be challenging to fully assess the long-term effect of omega-3 supplements for a larger population. 2) Each study utilized various sources of omega-3 FAs with different doses, so it is tough to determine the equivalency of omega-3 at baseline and aftereffects. 3) Some trials openly reported that patients not being on ADHD medications during the trials or excluded those populations; however, some trials disregarded the information. As such, whether the supplement itself is efficacious alone or as an add-on is still being determined. Even with limited evidence, the potential of omega-3 FAs to reduce symptoms in ADHD patients goes far beyond. Researchers are encouraged to collect more data in the future, such as comparisons with first-line treatments or behavioral treatments, to showcase how supplements like omega-3 may take command of treating psychological disorders to resolve drug shortages and provide quality healthcare.

Conclusion

Our systematic review provides the evidence that omega-3 PUFAs are beneficial in improving clinical symptoms of ADHD in adolescents and adults, increasing gut microorganisms, and removing endotoxins that cause pro-inflammatory responses. Future research should involve a larger sample size and longer duration and determine optimal omega-3 sources for ADHD treatment.

List of Abbreviations

ADHD: Attention-deficit hyperactivity disorder
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCTs: Randomized controlled trials
ALA: Alpha-linolenic acid
EPA: Eicosapentaenoic acid
DHA: Docosahexaenoic acid
AA: Arachidonic acid
MGBA: Microbiota-gut-brain-axis
HPA: Hypothalamic pituitary adrenal axis
CNS: Central nervous system
ENS: Enteric nervous system
PUFA: Polyunsaturated fatty acids
NSAIDs: Non-steroidal anti-inflammatory drugs
COX: Cyclooxygenase enzymes

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Ethics approval and consent to participate

Not applicable

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Competing interests

The authors declare that they have no competing interests.

Table 1: Characteristics of Randomized Controlled Trials Included in This Review.

Author	Study Type	Sample	Time	Omega-3 Source	Results
Voigt et al., 2001 [24]	Randomized, double-blind, placebo-controlled trial	6 to 12 years old Children with ADHD N = 32 for DHA and 31 for placebo	16 weeks	345 mg/d DHA or placebo	No statistically significant improvement in any objective or subjective measure of ADHD symptoms
Hirayama et al., 2004 [25]	Double-blind, placebo-controlled study	6 to 12 years old Children with ADHD N = 20 for taking active foods containing fish oil and 20 for indistinguishable food without fish oil	8 weeks	fermented soybean milk, bread rolls and steamed bread; 3.6 g DHA/week from these foods Or no fish oil	No intragroup and intergroup difference reported for ADHD symptoms
Itomura et al., 2005 [26]	Double-blind, placebo-controlled study	9 to 12 year-old school children N = 83 for fish oil group and 83 for control	12 weeks	Fish oil-fortified foods providing 3600 DHA + 840 EPA/ week	No change in physical aggression scores (13 to 13, n = 43) in fish oil group, score increase observed in control group (13 to 15, n = 42) in female population .
Sinn et al., 2008 [27]	Randomized Controlled Trial	7 to 12 years old children with symptoms $\geq$ 2 S.D. on Conners' ADHD Index N = 129	30 weeks	PUFA, PUFA with multivitamins or placebo	Improvements in ability to switch and control attention in the first 15 weeks, (ANOVA score on ADHD index: p<0.01,F = 7.38, $\eta^2 p = 0.067$) but improvements also observed in placebo in week 16-30
Johnson et al., 2009 [28]	Randomized Placebo-Controlled Trial	8 to 18 years old adolescents with diagnosed ADHD N = 75	3-month, omega 3/6 placebo-controlled, one-way crossover trial Followed with 3-months with omega 3 for all	First 3 month: a daily dose of 558 mg EPA, 174 mg DHA (both are omega-3 fatty acids), 60 mg gamma linoleic acid (an omega 6 fatty acid), and 10.8 mg Vitamin E Or placebo (olive oil)	Only a subgroup of 26% responded with > 25% reduction of ADHD symptoms and a drop of CGI scores to the near-normal range vs 7% in placebo after 3 months
Raz et al., 2009 [10]	Randomized, double-blind, placebo-controlled study	7 to 13 years old with diagnosed ADHD N = 39 for experimental (N = 32 for analysis), N = 39 for placebo (N = 31 for analysis)	7 week	480 mg of linoleic acid, 120mg of ALA, as softgel capsules BID (daily essential fatty acid 600 mg) placebo: 1000mg of vitamin C	Both groups demonstrated benefits but no significant differences between the two Parent DSM inattention score: EFA (before 4.05 $\pm$ 0.91 vs. after 3.80 $\pm$ 0.9), P 0.0987 Placebo (before 4.43 $\pm$ 0.93 vs. after 3.84 $\pm$ 0.98)
Mcnamara et al., 2010 [9]	Double blinded, placebo -controlled trial	8 to 10 years old healthy boys with no history of Axis 1 psychiatric disorders N = 33 (n = 10 for placebo, n = 10 for low dose DHA, n = 13 for high dose DHA)	8 weeks	1 of 2 doses of algal triglyceride DHA (400 or 1200 mg/day) Placebo: corn oil	Increase in erythrocyte membrane DHA composition from baseline: 47% in low dose and 70% in high dose More activation of dorsolateral prefrontal cortex and fewer activation of occipital cortex and cerebellar cortex compared to placebo
Hariri et al., 2012 [8]	randomized, double-blind, placebo-controlled clinical trial	6 to 12 years old children with ADHD N = 103	8 weeks	n-3 group received n-3 fatty acids (635 mg eicosapentaenoic acid (EPA), 195 mg docosahexaenoic acid (DHA)), placebo: olive oil capsules	Significant reduction in the levels of C-reactive protein(P<0.05, 95% CI = 0.72-2.02) and IL-6 (P<0.001, 95% CI = 1.93-24.33) in the omega-3 group. also significant increase in activity of superoxide dismutase and glutathione-reductase (P<0.001) and in the ASQ-P scores (P<005)
Johnson et al., 2012 [29]	Randomized, placebo-controlled clinical trial	8 to 18 years old children and adolescents with DSM-IV ADHD N = 75	3 months of RCT, followed by 3 months of open phase	Omega 3/6 preparation Equazen eye q (daily dose of 558 mg EPA, 174 mg DHA, 60 mg gamma linoleic acid) or placebo containing olive oil	Increased fatty acid composition of plasma phosphatidylcholine in active vs. placebo (3.7 vs 0.17, p < 0.001) No correlation to ADHD rating scale scores

Table 1 (continued)

Author	Study Type	Sample	Time	Omega-3 Source	Results
Manor et al., 2012 [30]	Double-blind, placebo-controlled Phase 1 and Open-label Phase 2	6 to 13 years old children with ADHD N=200, 67% boys, 33% girls	30 weeks	300 mg of Phosphatidylserine + EPA (80mg) /DHA (40mg) or placebo	Significant reduction in Conners' teacher DSM-Inattentive subscale score of boys compared to placebo (mean change from baseline S.D; 2.62 $\pm$ 7.59 and 0.46 $\pm$ 6.54, respectively; p = 0.031)
Milte et al., 2012 [31]	Randomized controlled trial	7 to 12 years old Australian children with ADHD symptoms higher than 90th percentile on Conners Rating Scales N = 25 for EPA-rich oil group, N = 20 for DHA-rich oil group, N = 20 for LA-rick oil	4 months	4 x 500 mg capsules daily containing EPA-rich fish oil with 1109 mg EPA and 108mg DHA, DHA-rich fish oil with 264 mg EPA and 1032 mg DHA, or placebo with safflower oil with LA 1467 mg/ day	Improved word reading (r = 0.394, P <0.01) and lower parent ratings of oppositional behavior (r = 0.392, P <0.05) in DHA-rich oil group
Richardson et al., 2012 [32]	Randomized controlled trial	7 to 9 years old children underperforming in reading ($\leq$33 Percentile) N = 179 for active, N = 182 for placebo	16 weeks	600 mg/ day of DHA from algal oil or corn/soybean oil placebo	DHA effect reported in certain sub-group only, change in reading scores in $\leq$20th percentile group: 2 in active vs 0.9 in placebo (p = 0.041), Change in reading scores in $\leq$10th percentile group: 3.1 in active vs 0.9 in placebo (p = 0.011)
Perera et al., 2012 [7]	Randomized controlled trial	6 to 12 years old with ADHD on methylphenidate and standard behavior therapy N = 48 for active treatment, N = 46 for placebo	6 months	EPA (560mg) Combined omega-3 and omega-6 or placebo	Statistically significant improvement in majority of symptoms after 6 months (>80% improved in active group compared to 17.4-30.4% improved in placebo, P < 0.05)
Hirayama et al., 2013 [14]	Randomized double-controlled trial	4 to 14 years old ADHD children without prior drug treatment N = 17 for placebo, N = 19 for active	2 months	100 mg of soy-derived phosphatidylserine cocoa-flavored chews, 2 chews per day or placebo chews	Improved scores in DSM IV- TR: (11.4 pre-supplementation vs 7.2 post, p 0.01) in PS group and (11.5 pre-supplementation vs 10.9, p 0.53) in placebo
Milte 2013 et al., [33]	Randomized three-way crossover trial	6 to 13 years old with ADHD symptoms N = 96 with 90 receiving allocated intervention and 6 not receiving allocated intervention	12 months	4 x 500 mg capsules daily containing EPA-rich fish oil with 1109 mg EPA and 108mg DHA, DHA-rich fish oil with 264 mg EPA and 1032 mg DHA, or placebo with safflower oil with LA 1467 mg/ day	Improved spelling scores in EPA+DHA group (r= 0.365, p<0.001), sky search scores (r=-0.540, p <0.001), reduced oppositional behavior (r = -0.301, p <0.003) and hyperactivity (r = -0.310, p<0.001)
Dean et al., 2014 [12]	Randomized, Controlled, Crossover Trial	7.1 to 14.2 years old children with impulsive aggression N = 21	12 weeks (6 weeks for each inter-vention)	4g of fish oil daily: 400 mg EPA and 2000 mg DHA Placebo: polyphenol olive oil and 10 mg standard fish oil	No influence on primary aggression rating score (F = 0.05, p = 0.82), worsened secondary aggression rating score reported in fish oil group (F = 4.34, p = 0.056)
Dubnov-raz et al., 2014 [34]	Randomized controlled double-blind study	Untreated children with ADHD, aged 6 to 16 years N = 40 (17 completed the study: 8 in supplementation and 9 in placebo)	8 weeks	2 g/day of oil containing 1 g ALA placebo	No significant difference found in any of the measured variables tested before and after supplementation, in both study groups (p = 0.79 for change in parent Conners' index)
Raine et al., 2014 [35]	Randomized, double-blind, placebo-controlled, stratified, parallel-group trial	8 to 16 year old healthy children N = 100 for active, N = 100 for placebo	6 months	1 g/day of omega-3 supplementation consisting of fruit drink or placebo	41.6% reduction in parent-rated child externalizing behavior and 68.4% in internalizing behavior in supplemented group

Table 1 (continued)

Author	Study Type	Sample	Time	Omega-3 Source	Results
Widenhorn-Muller et al., 2014 [36]	Double-blind RCT	6 to 12 years old with DSM-IV ADHD diagnosis N = 95,78% boys and 22% girls	16 weeks	720 mg daily dose of supplement (600 mg EPA, 120 mg DHA) and 15 mg of Vit E as antioxidant or placebo (olive oil)	Increased EPA and DHA concentrations and improved working memory index score in EPA/DHA group (F = 5.54, p = 0.019) No statistically improvements on ratings
Bos et al., 2015 [37]	Double-blind RCT	8 to 14 years old boys with DSM-IV diagnosis with ADHD N = 40 for ADHD and 39 for placebo	16 weeks	10 g of margarine daily, enriched with either 650 mg of EPA/DHA each or placebo	Reduced scores on child behavior checklist attention problems after supplementation (ANCOVA score, F(1,67) = 14.99, p<0.001)
Matsudaira et al., 2015 [38]	Randomized, placebo-controlled, clinical trial	12 to 16 years old male adolescents with ADHD N = 25 for active and 23 for placebo	12 weeks	558 mg EPA, 174 mg DHA of omega-3 FA or placebo	No improvement on Barratt-Impulsiveness scale before and after intervention between groups (Control: 80.48 vs 76.75, active: 79.04 vs 81.42, p = 0.024)
Wu et al., 2015 [39]	Randomized control trial	7 to 12 years old children with lower IQs or ADHD N = 90 for control, N = 89 for active	3 months	Eggs rich in omega-3, EPA and DHA or ordinary egg	Improved visual acuity of study group after intervention compared to control group (p = 0.013)
Johnson et al., 2016 [40]	Randomized, double-blind, placebo-controlled trial	9 to 10 years old school children without ADHD diagnosis N = 78 for active and N = 76 for placebo	3 month	Omega 3/6 capsules: 558 mg EPA, 174 mg DHA, 60 mg gamma-linolenic acid Placebo: palm oil	Improvement in phonologic decoding time between groups (difference -0.16, 95% CI -0.03, -0.29, ES 0.44, p = 0.005)
Kean et al., 2016 [17]	Randomized, double-blind, placebo-controlled trial	6 to 14 years old with DSM-IV diagnosed ADHD N = 54 in PCSO-524 gp, N = 58 in placebo	14 weeks	3 or 4 capsules (based on weight) of PCSO-524 (marine oil abstract) or placebo	No improvement in parental reports of hyperactivity, inattention and impulsivity over placebo but changes in inattention score in non-combined CPRS scores: PCSO-524: (74.57 baseline vs 61.61 after 14 weeks) and Placebo: (74.1 baseline vs 67.55 after 14 weeks) P = 0.11, and changes in inattention score in combined CPRS scores: PCSO-524: (83.59 baseline vs 77.34 after 14 weeks) and Placebo: (83.56 baseline vs 71.03 after 14 weeks) P = 0.04
Ramakrishnan et al., 2016 [15]	Randomized, placebo-controlled trial	1094 women and 797 offsprings at age 5 years N = 547 for placebo, N = 547 for DHA	18th to 22nd week of pregnancy until delivery	400 mg of either DHA or placebo	No differences reported in McCarthy Scales of Children's abilities but improved T scores in DHA group (DHA: 47.6 $\pm$ 10.3, placebo: 49.5 $\pm$ 11.2, P < 0.01)
Cornu et al., 2017 [41]	Double-blind RCT	6 to 15 years old children with diagnosed ADHD N = 71 for DHA/EPA and 77 for placebo	12 weeks	DHA + EPA or Placebo for children aged 6–8 years, 336 mg EPA and 84 mg of DHA; for children aged 9–11 years, 504 mg EPA and 126 mg DHA, and for children aged 12–15 years 672 mg EPA and 168 mg DHA	No benefits of omega-3 observed in children with mild ADHD symptoms, mean difference in ADHD total score between active and placebo: 9.3 (0.3, 18.3), p = 0.039
Al-ghannami et al., 2018 [42]	Randomized open-label trial	9 to 10 years old N = 132 (Two group: fish oil and grilled fish meal: 66 in each groups)	12 weeks	DHA-enriched fish oil capsule (403 mg DHA) or 100g grilled fish meal (150-200 mg DHA)	Increased DHA levels by 72% in fish oil (Mean: 3.6% to 6.2%) and 64 % in fish meal (Mean: 3.4% to 5.6%) group, p=0.000.
Montgomery et al., 2018 [43]	Randomized double-blind, placebo-controlled trial, parallel group, fixed dose	7 to 9 years old healthy children who underperform in reading (<20th percentile) N = 187 for active supplement, N = 189 for placebo	16 weeks	600 mg/day DHA (from algal oil), and placebo	No differences between intervention and placebo group; Change in T score: 9.3% in active vs 9.8% in placebo (p = 0.356, t = 0.925)

Table 1 (continued)

Author	Study Type	Sample	Time	Omega-3 Source	Results
Crippa et al., 2019 [44]	Randomized, placebo-controlled trial	7 to 14 years olds, drug-naive children with ADHD N = 25 for DHA and 25 for Placebo	16 - 24 weeks	2 soft gelatin pearls per day providing a dose of 500 mg algal DHA low-concentration of Vitamin E as placebo	No superiority of DHA supplement to placebo observed on ADHD-RS-IV rating scale (11.29 in DHA vs 11.38 in placebo after 6 months supplementation), small positive effects on other behavioral and cognitive difficulties reported
Rodriguez et al., 2019 [11]	Double-blind placebo-controlled randomized clinical trial	6 to 18 years boys and girls with DSM-5 diagnosis of ADHD N = 32 in DHA group, N = 34 in placebo)	6 months	1000 mg DHA, 90 mg EPA, 150mg DHA	Increased total test effectiveness reported in both groups, DHA gp: 316.1 to 373.5 ($p < 0.001$) and Placebo gp: 330.1 to 381.8 ($p<0.001$)
Lee et al., 2020 [45]	Open-label trial	6 to 12 years diagnosed with ADHD N = 40 (77% boys, 23% girls)	12 weeks	500 mg of omega-3 (EPA, 294 mg; DHA, 206 mg) and and 3 mg of Korean red ginseng extract (combination of ginsenoside Rg1, Rb1, and Rg3)	Improvements on ADHD-Rating Scale (31.12 ± 8.82 at baseline, 24.15 ± 11.45 at endpoint; $p < 0.001$)) Improvements on Clinical Global Impression-Severity (3.38 ± 1.18 at baseline, 2.94 ± 1.00 at endpoint; $p < 0.001$)
Dopfener et al., 2021 [46]	Randomized Placebo-Controlled Trial	3 to 6 years old preschool children at risk for ADHD, N= 16 for active, and 15 for placebo	16 weeks	Two capsules of Omega-3/Omega-6 twice daily dose of 372 mg EPA, 116 mg DHA, and 40 mg GLA Placebo: no Omega-3/Omega-6	Experienced reliable improvement in active group vs placebo (60% vs 25%) and clinical improvement (67% vs 19%) in teacher-rated ADHD symptoms but not in parent-rated symptoms
Gould et al., 2021 [13]	Double-blind, randomized controlled trial	Women with singleton pregnancy < 21 weeks' gestation at trial entry N= 726 mother-child pairs (DHA = 351; Placebo = 375) N= 638 mother-child pairs at 7-year follow-up (DHA = 310; Placebo = 328)	Until birth	800 mg DHA/day placebo	No positive advantage to childhood behavior in DHA supplementation group, instead more adverse effects reported on behavioral functioning
Carucci et al., 2022 [47]	Double-blind, RCT Phase-1 and Phase-2 Open-label trial	6 to 12 years old children with inattentive-ADHD N = 160	6 months for each phase	2 capsules containing 279 mg EPA, 87 mg DHA, 30 mg GLA	Phase-1: no superiority of omega-3 supplementation on ADHD-RS-inattention score observed (46.3% in omega-3/6 group and 45.6% in placebo) Slight improvements on ADHD-RS-total score in omega-3/6 group (ANOVA score: $p = 0.041$; $\eta^2 p = 0.067$)
San Mauro Martin et al., 2022 [48]	Randomized controlled trial	6 to 16 years-old boys and girls N = 60 divided into 4 groups (control group, mediterranean diet, omega-3, mediterranean + omega-3)	8 weeks	137.5 g EPA and 56.25 mg DHA per softgel, daily dose: 550 mg EPA and 225 mg DHA per day	Significant drop in Barratt Impulsiveness Scale scores in omega-3 group: 49 to 45.1 points, P = 0.049
Pinar-marti et al., 2023 [16]	Multi-school-based Randomized controlled trial	11 to 16 years old healthy teenagers N = 386 for intervention and 385 for control	6 months	30 grams/day of raw walnut kernels (9 grams of ALA per 100 g) into regular diet	No improvement in neuropsychological function but improved attention score (n = 669, beta coefficient 1.74, 95% CL (-7.97, 11.46) , P = 0.73) and ALA (n = 270, beta coefficient 0.04, 95% CL (0.03, 0.06), P < 0.0001)

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