The Efficacy of Omega 3 Supplements in Improving Symptoms of Attention-Deficit/Hyperactivity Disorder in Children: A Systematic Review

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Abstracts

Introduction: Attention-deficit/hyperactivity disorder (ADHD) is characterized by symptoms of inattention, hyperactivity, and impulsivity, impacting daily functioning in children. Genetic and environmental factors contribute to its prevalence, affecting about 8% of children. Treatment typically involves medication and behavioral therapy. Dietary factors, including omega-3 fatty acids, have been studied for their impact on ADHD. While some evidence suggests omega-3s may help, systematic reviews show insufficient support for their effectiveness in treating ADHD symptoms. This research aims to evaluate omega-3 supplements' effectiveness in improving ADHD symptoms in children.

Method: A search strategy using PubMed and Medline with keywords "ADHD," "children," and "omega 3 fatty acid" followed PRISMA guidelines (2020). The PICO model targeted children with ADHD, comparing omega-3 fatty acids to placebo, measuring improvement in ADHD-RS-IV scores by parents. Inclusion criteria: RCTs from 2017-2024, children with ADHD, and English-language studies. Exclusion criteria: non-RCTs, studies before 2017, on adolescents/adults, and non-English studies. Primary outcome was changes in ADHD parent ratings, and secondary outcome was side effects.

Results: All five randomized studies showed reductions in ADHD scores (ADHD-RS-IV) after their trials, with varying degrees of improvement between intervention and placebo groups. One study reported a larger reduction in the placebo group compared to the intervention group. Another found no significant differences between DHA supplementation and placebo. A third study saw similar decreases in ADHD scores for both groups without significant differences. In another trial, there was an improvement in the DHA group and worsening in the placebo group. One study reported significant reductions in both groups. For secondary outcomes, side effects like decreased appetite, restlessness, headaches, nausea, vomiting, and diarrhea were noted, with no significant differences between groups.

Conclusion: The extensive research into omega-3 supplements for managing ADHD has shown

they are not effective as a primary treatment. This systematic review of five RCTs consistently found no significant difference between omega-3 supplementation and placebo in reducing ADHD symptoms in children.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is defined by symptoms of inattention and hyperactivity-impulsivity that appear before the age of 12 and disrupt daily functioning in at least two different situations, such as at home and in school, it can be identified in one of three distinct forms. The Combined forms includes a blend of inattentive and hyperactive-impulsive symptoms. In the Inattentive form, the focus is mainly on pronounced symptoms of inattention. On the other hand, the Hyperactive-Impulsive forms is characterized by a more significant presence of hyperactive and impulsive behaviours (Polanczyk et al, 2007). It is associated with increased risks of academic difficulties, challenges in peer relationships, family tensions, depression, a higher likelihood of accidental fatalities and various health issues (Tuscano et al, 2010).

The causes of ADHD and the factors influencing its progression are diverse and complex. Research has indicated that the genetic predisposition for ADHD symptoms is between 65% to 75%. However, it's important to note that part of this genetic influence might result from interactions between genes and environmental factors (Purcell et al, 2002) (Nigg et al, 2010). The estimated occurrence of ADHD in children and adolescents stands approximately at 8.0%. Notably, the prevalence rate is double in boys, at 10%, compared to girls, where it is 5% (Ayano et al, 2023).

One of the most common tools used to assess ADHD symptoms is the ADHD Rating Scale IV (ADHD RS IV), it is a tool administered and scored by clinicians to evaluate the severity of ADHD symptoms in children and adolescents. The scale consists of 18 items, each reflecting specific ADHD symptoms. Each item is rated from 0 to 3, where 0 means "none" (never or rarely), 1 means "mild" (sometimes), 2 means "moderate" (often), and 3 means "severe" (very often). The total score is obtained by summing the scores of all 18 items. The scale can be further divided into two subscales: inattention and hyperactivity/impulsivity. This scale is highly effective for assessing the severity of ADHD symptoms in various clinical settings and research studies (Zhang et al, 2005).

The treatment of ADHD can include medication, behavioral therapy, or a combination of both. Regardless of the chosen method, it is advised that all children receive treatment, as early and effective intervention has been shown to result in better outcomes and fewer issues in adulthood (Sharma and Couture, 2014). One of the most common stimulant is Methylphenidate for treating ADHD It effectively alleviates ADHD symptoms in children at home and school, while also enhancing their social skills. For healthy children, methylphenidate is safe and has been shown to cause no cardiac side effects (Golmirzaei et al, 2016). But there are some Common adverse effects of methylphenidate, include a loss of appetite, irritability, difficulty falling asleep, and weight loss (Greydanus et al, 2021). Also Lifestyle factors, including diet and nutrition, have been proposed to influence the pathophysiology and management of ADHD (Lange, 2018). For

instance, a recent case control study from Iran by Darabi et al. (2022) involving 360 children and adolescents, comprising 120 cases and 240 controls aged 7 to 13 years, discovered that a higher dietary phytochemical score, which reflects the percentage of daily energy intake from phytochemical-rich foods (including fruits, vegetables, legumes, whole grains, nuts, soy products, seeds, and olive oil), was linked to a reduced risk of ADHD. Another example is what was found in a study in China by Park et al. (2012), demonstrating that High consumption of sweetened desserts, fried foods, and salt has been associated with an increase in learning, attention, and behavioral problems. On the other hand, a balanced diet that includes regular meals with plenty of dairy products and vegetables is related to a decrease in these problems.

ESPEN guidelines emphasizes the importance of controlling saturated fats intake in studies on omega-3 supplementation for ADHD, as high saturated fats levels in omega-3 supplements can negate their benefits. It recommends prioritizing supplements with a high omega-3/ saturated fats ratio to ensure efficacy. Discrepancies in study results may be due to the confounding presence of saturated fats in supplements, suggesting future research should rigorously control for saturated fats levels. Additionally, choosing high-quality omega-3 supplements and broader dietary interventions reducing saturated fats while increasing omega-3 intake may improve ADHD symptoms and neurodevelopmental outcomes (Morandini et al, 2022). As for NICE guidelines they indicate that while omega-3 supplements, particularly those with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), may offer modest improvements in attention and behavior in some instances, other studies do not show significant differences when compared to a placebo. The quality of evidence ranges from high to very low, with low-quality evidence suggesting short-term functional status improvements favoring omega-3s. Due to these inconsistent findings, omega-3 supplements are not widely recommended as a primary treatment for ADHD but may be considered as a supplementary option in certain cases (NICE, 2016).

In a recent systematic review by Gillies et al. (2023), to assess the effectiveness of polyunsaturated fatty acid (PUFA) supplementation in treating ADHD symptoms in children and adolescents included 13 trials with 1011 participants, their findings revealed limited evidence of improvement with omega-3/6 PUFA supplementation and no significant benefits in parent or teacher-rated ADHD symptoms, behavior, quality of life, or side effects. They concluded that there is insufficient evidence to support PUFA supplementation for ADHD. Another systematic review by Händel et al. (2021), they identified and critically assessed 31 randomized controlled trials involving 1755 patients. The study found no significant effects of PUFAs on ADHD core symptoms, behavioral difficulties, or quality of life, as rated by parents or teachers. Additionally, PUFAs did not increase the occurrence of side effects. The overall certainty of the evidence was low to very low, and the study concluded that there is insufficient evidence to support the use of PUFAs as a treatment for ADHD in clinical practice.

As for this research rational, it widely known that omega 3 supplements because of their unique properties the supplementation of polyunsaturated fatty acids has been suggested to influence the etiology and treatment of many mental disorders (Lange, 2020). The aim is to evaluate whether omega 3 supplements are effective in improving ADHD symptoms in children.

2. Methods

The search strategy was implemented across two databases: PubMed and Medline. The keywords used in the search were: (ADHD), (children), and (omega-3 fatty acid). The studies included were chosen following the Preferred Reporting Items for Systematic Reviews (PRISMA, 2020) guidelines, as illustrated in Figure 1.

The PICO model was followed in this review:

- Population: children diagnosed with ADHD.
- Intervention: omega 3 fatty acid.
- Comparison: placebo.
- Outcome: improvement in ADHD symptoms which is measure by ADHD-RS-IV score by parents.
- Inclusion Criteria

1. RCTs.
2. Published between 2017 and 2024.
3. children patients.
4. ADHD patients.
5. Studies written and published in English.

- Exclusion Criteria:

1. Non-RCT studies.
2. Published before 2017.
3. Studies on adolescents and adults.
4. Studies that are not in English.

Primary Outcome

Changes in ADHD rating parent score.

Secondary Outcome

side effects

3. Results:

The quality assessment was performed using the modified Cochrane Collaboration tool to evaluate the risk of bias in randomized controlled trials (RCTs) across five domains: the randomization process, intended intervention, missing outcomes, outcome measurement, and

selection of results. The risk of bias was categorized as high, low, or unclear (Sterne et al., 2019). Refer to Table 1 for details.

Table1.

Biases / Authors	Randomization process	Intended intervention	Missing outcome	Outcome measurement	Selection of results	Overall risk of bias
Assareh et al, 2017	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Cornu et al, 2018	Low risk	Low risk	Some concerns	Low risk	Low risk	Some concerns
Crippa et al, 2019	Low risk	Low risk	Some concerns	Low risk	Low risk	Some concerns
Mohammadzadeh et al, 2019	Low risk	Low risk	Some concerns	Low risk	Low risk	Some concerns
Rodríguez et al, 2019	Low risk	Low risk	Some concerns	Low risk	Low risk	Some concerns

From 5 RCTs reviewed in this paper published between 2017-2024 in different countries that compared the effect omega 3 fatty acid supplements in improving ADHD symptoms.

All the studies measured the symptoms using the ADHD-RS-IV score by parents, with a total number of 376 patients as shown in table2.

Table2:

Author's	Location	N of participants	Duration	Intervention	Outcome
Assareh et al, 2017	Iran	40	10 weeks	1 omega 3+omega 6 capsule per day and placebo	ADHD total score decreased by 65.7% in intervention and 62.7% in placebo.
Cornu et al, 2018	France	162	3 months	Omega3 supplements (both EPA and DHA) per day and placebo	ADHD total score decreased in placebo(19%) more than treatment group(9.70%).
Crippa et al, 2019	Italy	48	6 months	500 mg DHA per day and placebo	ADHD total score decreased in placebo(17.10%) more than treatment group(15.70%).
Mohammadzadeh et al, 2019	Iran	60	8 weeks	1 Omega 3 supplement capsule per day in the first week and 2 after that and placebo	ADHD total score decreased in placebo(63%) more than treatment group(58%).
Rodríguez et al, 2019	Spain	66	6 months	1 omega 3 supplement capsule per day and placebo	ADHD total score decreased by 11.76% in intervention and 6.74% in placebo.

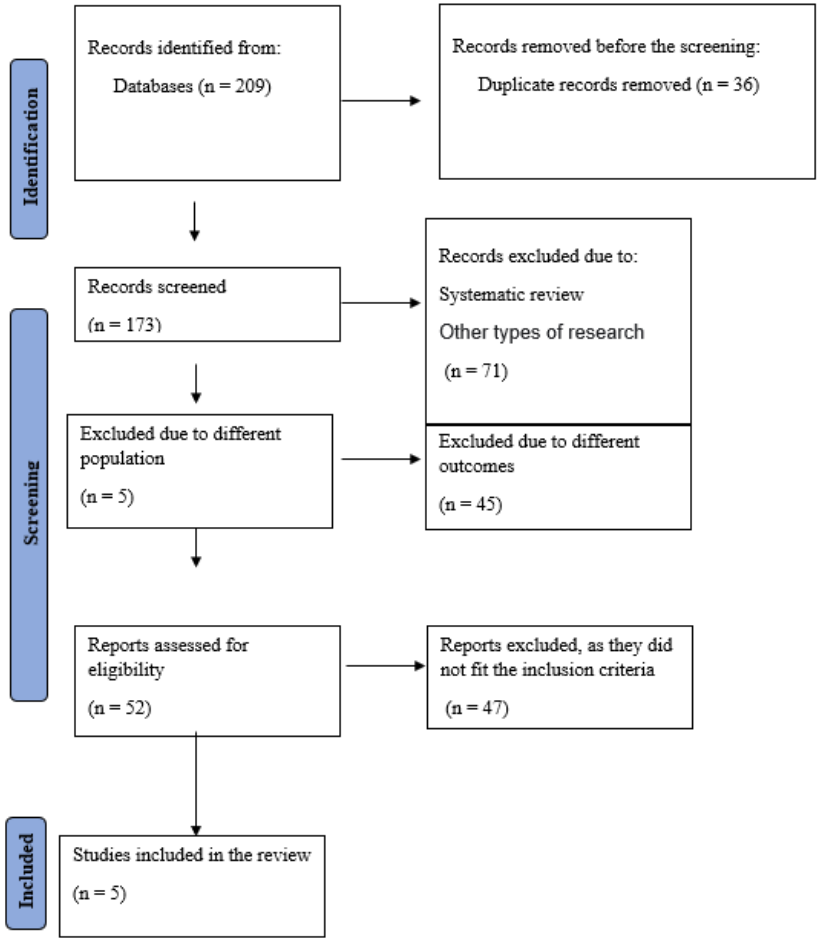

Figure 1: PRISMA flowchart demonstrating the selection of articles included in the review

Primary outcome:

All 5 RSTs showed some reductions in the ADHD score (ADHD-RS-IV) after the end of each trial, in Cornu et al. (2018) trial, at baseline, the ADHD scores were 36.5 in the intervention group and 38.1 in the placebo group. After three months, both groups saw a reduction in scores, with the placebo group experiencing a larger decrease to 30.6 compared to the intervention group's 32.8.

In the randomized clinical trial conducted by Crippa et al. (2019) the ADHD Rating Scale was used to evaluate changes in symptoms over a six-month period. The study involved two groups, one receiving docosahexaenoic acid (DHA) supplementation and the other a placebo. At baseline, the DHA group had a mean total score of 29.56, while the placebo group had 31.76.

After six months, the DHA group's mean score decreased to 24.92, and the placebo group's mean score dropped to 26.33. Despite these improvements, no significant differences were found between the two groups.

While in Mohammadzadeh et al. (2019), the initial ADHD scores at baseline (week 0) were similar between the methylphenidate + placebo group and the methylphenidate + omega-3 group, with an average of around 42.6 in both. By the 2-week mark, scores fell to 34.9 in the placebo group and 35.8 in the omega-3 group. At week 4, the scores further decreased to 25.6 for the placebo group and 25.8 for the omega-3 group. By week 8, they dropped even more, reaching 15.8 for the placebo group and 17.8 for the omega-3 group.

While ADHD scores decreased significantly from baseline to the end of the study in both groups, there wasn't a statistically significant difference in the reduction between those who received omega-3 supplementation and those who took a placebo.

In Rodríguez et al. (2019) in the DHA group, the ADHD scores showed a reduction over time, starting at 18.7 at baseline, dropping to 16.6 at 3 months, and then slightly decreasing to 16.5 after 6 months. Meanwhile, the placebo group exhibited an increase in ADHD scores, beginning at 17.0 at baseline, rising to 17.7 at 3 months, and climbing further to 18.1 at the 6-month mark. This suggests an improvement in ADHD symptoms in the DHA group, contrasted by a worsening in the placebo group.

Finally, in Assareh et al, (2017) Over the 10-week study period, both the treatment and control groups experienced a significant reduction in scores, demonstrating progress from the beginning to the 10th week. Specifically, the treatment group's overall score fell from 34 to 13, a decline of 65.7%, and the control group's score decreased from 37 to 13, showing a 62.7% reduction.

Secondary Outcome:

As for the secondary outcome, Assareh et al, (2017) mentioned side effects but without any specific numbers such as decreased appetite, restlessness, and headaches were the predominant side effects observed in both groups. There was no significant difference between the two groups in terms of the number or kind of side effects experienced during the study ($p > .05$)

In Mohammadzadeh et al. (2019) trial, the study reported side effects such as nausea occurred in 1 child (2%) in the methylphenidate with placebo group and in 2 children (2.9%) in the methylphenidate with omega-3 group; vomiting was observed in 1 child (2%) in the placebo group and in 4 children (5.9%) in the omega-3 group; diarrhea was reported in 10 children (20%) in the placebo group and in 8 children (11.8%) in the omega-3 group. None of these differences were statistically significant ($P > 0.05$).

4. Discussion:

The primary outcomes of the five randomized controlled trials (RCTs) indicate reductions in ADHD symptoms, as measured by the ADHD Rating Scale-IV (ADHD-RS-IV), across all studies, regardless of the intervention. For instance, in Cornu et al. (2018), both the intervention and placebo groups saw decreases in ADHD scores after three months. Interestingly, the placebo

group experienced a larger reduction (from 38.1 to 30.6) compared to the intervention group (from 36.5 to 32.8). This outcome suggests that the intervention did not have significant effect on the symptoms, In Crippa et al. (2019), participants were evaluated over six months with one group receiving DHA supplementation and the other a placebo. Both groups exhibited decreases in ADHD scores, with the DHA group's scores reducing from 29.56 to 24.92 and the placebo group's from 31.76 to 26.33. Despite these reductions, there was no significant difference between the groups, indicating that DHA supplementation was not more effective than placebo in managing ADHD symptoms over the study period which was for 6 months. Moreover, Crippa et al. (2019) acknowledged the small sample size as a primary limitation, which may have resulted in an underpowered study unable to detect smaller but clinically significant effects. There were also significant between-group differences at baseline, particularly in the focused attention task, which could bias the results. Additionally, adherence to treatment was not confirmed through blood samples, which raises concerns about the reliability of self-reported compliance.

Mohammadzadeh et al. (2019) investigated the effects of omega-3 supplementation in conjunction with methylphenidate. Both groups showed significant reductions in ADHD scores from baseline to week 8. The placebo group's scores dropped from 42.6 to 15.8, and the omega-3 group's from 42.6 to 17.8. The similar reductions suggest that omega-3 did not provide additional benefits beyond those of the placebo even when combined with methylphenidate, which can significantly improve children's behavior across various measures in both recreational and classroom settings. This included better compliance with activity rules, reduced disruptive behavior, and increased on-task behavior (Pelham et al, 2002).

Rodríguez et al. (2019) reported that the DHA group experienced a reduction in ADHD scores from 18.7 at baseline to 16.5 after six months, while the placebo group saw an increase from 17.0 to 18.1. This indicates a potential benefit of DHA supplementation in reducing ADHD symptoms compared to placebo, though the changes were relatively modest. However, the small sample size and potential confounding factors reduce the robustness of the findings. The study underscores the need for larger, more controlled trials that can better account for these variables and provide a more comprehensive understanding of the effects of omega-3 supplementation on ADHD.

Assareh et al. (2017) observed significant reductions in ADHD scores over a 10-week period in both the treatment and control groups. The treatment group's scores decreased by 65.7% (from 34 to 13), and the control group's scores decreased by 62.7% (from 37 to 13). The similar magnitude of reduction suggests more placebo effect, meaning no significant benefit from the intervention, this study has several key limitations. Firstly, the sample size is relatively small, which may impact the generalizability of the findings. Another significant limitation is the absence of teacher assessments; the study relies solely on parent-reported outcomes due to the timing of the study during the school year, which could lead to biased results. Additionally, the study did not measure blood levels of essential fatty acids, which would have strengthened the interpretation of the data regarding the physiological impact of PUFA supplementation. The study duration was relatively short at 10 weeks, which might be insufficient to observe long-term effects of supplementation.

Regarding secondary outcomes, side effects were reported but showed no significant differences between intervention and placebo groups. Assareh et al. (2017) noted side effects such as decreased appetite, restlessness, and headaches in both groups, without significant differences in their incidence. Similarly, Mohammadzadeh et al. (2019) reported nausea, vomiting, and diarrhea in both the methylphenidate + placebo and methylphenidate + omega-3 groups, with no statistically significant differences.

The findings suggest a consistent trend across the studies, both intervention and placebo groups experienced significant reductions in symptoms, but the interventions did not demonstrate a clear, significant advantage over placebos. This pattern suggests the substantial symptom reductions observed in placebo groups across multiple studies underscore the powerful placebo effect in ADHD treatment trials. This highlights the psychological and contextual factors that may influence the perception of symptom improvement.

The findings of this systematic review align with Gillies et al. (2023) findings which showed minimal benefit from PUFA supplementation, with slight improvement observed in a few trials using a combination of omega-3 and omega-6 PUFAs. However, their findings suggest that PUFA supplementation does not significantly benefit children and adolescents with ADHD.

Other dietary interventions could help reduce the risk of ADHD. For example, a recent systematic review in ESPEN found that a healthy diet, including fruits and vegetables, fish, and foods rich in PUFAs, magnesium, zinc, and phytochemicals, appears to lower the risk of ADHD by 37%. In contrast, dietary patterns common among children, such as the Western diet and junk food, increase the risk. The Western diet, high in red and processed meats, refined grains, soft drinks, and hydrogenated fats, was associated with a 92% increased risk of ADHD. Similarly, the junk food diet, high in processed foods with artificial food coloring and sugar, increased the risk by 51% (Shareghfarid et al, 2020).

To the best of our knowledge regarding the use of omega 3 supplements in children diagnosed with ADHD, it is highly unlikely that this intervention has promising effects on improving ADHD symptoms. However, other dietary interventions could be useful in this disease as mentioned earlier.

5. Conclusion

The extensive research into the role of omega 3 supplements in managing ADHD has provided valuable insights, though the evidence does not support their efficacy as a primary treatment. This systematic review of five randomized controlled trials (RCTs) highlights the consistent finding that omega-3 supplementation does not significantly outperform other approaches in reducing ADHD symptoms in children. While omega 3 have been theorized to offer neurodevelopmental benefits due to their anti-inflammatory properties and role in cell membrane function, the clinical trials reviewed here do not substantiate their effectiveness in this context. Given the lack of significant benefits from omega-3 supplementation in treating ADHD, future research and clinical practice should pivot towards exploring alternative and complementary approaches. A key recommendation is to conduct longer-term and larger-scale studies that

evaluate the sustained impact of dietary changes and omega-3 supplementation on ADHD symptoms. These studies should meticulously account for varying adherence levels and monitor blood levels of essential fatty acids to gain a deeper understanding of the physiological effects of supplementation. Such comprehensive research is essential to ascertain the long-term viability and effectiveness of dietary interventions in managing ADHD.

Moreover, a multimodal approach to treatment could prove more beneficial in managing ADHD symptoms. This involves combining dietary interventions with established behavioral therapies and pharmacological treatments. By integrating diet, behavior modification, and medication into a cohesive treatment plan, practitioners can address the multifaceted nature of ADHD more effectively. Tailored multimodal treatment plans are likely to yield better outcomes than relying on single interventions, as they cater to the diverse needs of individuals with ADHD and leverage multiple therapeutic avenues.

Public health initiatives also play a crucial role in this broader strategy. While omega-3 supplements may not be highly effective on their own, other dietary interventions have the potential to reduce the risk of ADHD and improve overall health. Enhancing the overall nutrition of children through educational campaigns that encourage the reduction of processed food consumption and an increase in whole food intake can be highly beneficial. A diet rich in fruits, vegetables, fish, and foods high in PUFAs, magnesium, zinc, and phytochemicals may lower the risk of ADHD and contribute to better health outcomes. Public health campaigns should aim to raise awareness about the importance of healthy eating habits and their impact on mental and physical well-being. Continued support for research into dietary interventions and their impact on ADHD and mental health conditions is essential. Exploring the complex interactions between diet, genetics, and environmental factors can provide deeper insights into the etiology and management of ADHD. There is a critical need for funding large-scale, high-quality randomized controlled trials to establish more definitive evidence on effective dietary strategies. Such research can pave the way for more informed clinical practices and policy decisions, ultimately leading to better health outcomes for children with ADHD.

In conclusion, while omega-3 supplements do not appear to significantly improve ADHD symptoms, adopting a broader approach to dietary management and public health interventions holds considerable promise. By focusing on enhancing overall nutrition and integrating multiple treatment modalities, we can significantly improve the well-being of children with ADHD. This comprehensive strategy not only addresses the symptoms of ADHD more effectively but also promotes better health outcomes on a larger scale, benefiting children and communities alike.

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