Current evidence and future directions for research with omega-3 fatty acids and attention deficit hyperactivity disorder

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Purpose of review
Nutritional insufficiencies of nutrients such as omega-3 highly unsaturated fatty acids (HUFAs), vitamins and minerals have been linked to suboptimal developmental outcomes including attention deficit hyperactivity disorder (ADHD). Although the predominant treatment is currently psychostimulant medications, randomized clinical trials with omega-3 HUFAs have reported small-to-modest effects in reducing symptoms of ADHD in children despite arguable individual methodological and design misgivings.

Recent findings
This review presents, discusses and critically evaluates data and findings from meta-analytic and systematic reviews and clinical trials published within the last 12 months. Recent trajectories of this research are discussed, such as comparing eicosapentaenoic acid and docosahexaenoic acid and testing the efficacy of omega-3 HUFAs as an adjunct to methylphenidate. Discussion includes highlighting limitations and potential future directions such as addressing variable findings by accounting for other nutritional deficiencies and behavioural food intolerances.

Summary
The authors conclude that given the current economic burden of ADHD, estimated in the region of $77 billion in the USA alone, in addition to the fact that a proportion of patients with ADHD are either treatment resistant, nonresponders or withdraw from medication because of adverse side-effects, the investigation of nonpharmacological interventions including omega-3 HUFAs in clinical practice warrants extrapolating.

Keywords
attention deficit hyperactivity disorder, docosahexaenoic acid, eicosapentaenoic acid, highly unsaturated fatty acids, omega-3 fatty acids

INTRODUCTION

The neural developmental stages are complex and closely intertwined with a number of processes occurring simultaneously including neuronal migration, neurogenesis, synaptogenesis and myelination, all of which implicate the role of omega-3 highly unsaturated fatty acids (HUFAs). These sensitive processes are mediated by a multitude of factors including genetic and metabolic diseases, immune disorders, infectious diseases, deprivation, physical trauma, toxicity, environmental and undoubtedly nutritional factors. Any interruption in neurodevelopment as a result of any of the factors listed may result in adverse developmental outcomes. Neurodevelopmental disorders occur as a result of impairments in the growth and development of the brain or central nervous system and attention deficit hyperactivity disorder (ADHD), characterized by inattention, hyperactivity and impulsivity, is one of the most pervasive.

EVIDENCE FROM HUMAN STUDIES

Omega-3 HUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the end products of omega-3 polyunsaturated fatty acid (PUFA) elongation and desaturation. Their role in alleviating learning and behaviour problems associated with ADHD is an area of hot debate. A 2011 meta-analysis of 699 children across 10 randomized, placebo-controlled clinical trials demonstrated a small-modest

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KEY POINTS

- Omega-3 HUFA levels appear to be lower in individuals with ADHD compared with unaffected counterparts but the reasons for this are unclear.
- Several meta-analytic reviews have found that omega-3 HUFA supplementation has a small-medium effect size in improving clinical symptoms of ADHD despite methodological shortcomings and/or inconsistencies in research trials to date.
- Omega-3 HUFAs may be a useful adjunct to medication and an alternative intervention for parents who choose not to medicate their children.
- Recent reviews suggest that EPA has greater clinical efficacy; however, based on methodological considerations of included studies, the body of work to date and differential mechanisms of action, it is likely that both EPA and DHA are important.
- Other nutritional deficiencies and in particular behavioural food intolerances should be considered in the symptomatology of ADHD.
- Children with learning and behavioural difficulties without a diagnosis of ADHD may benefit from omega-3 HUFA supplementation; further work needs to identify likely responders.

effect size in reducing clinical symptoms of ADHD, with EPA appearing to have greater efficacy [1] – possibly because many of the better-designed studies employed a supplement containing a high EPA/DHA ratio. A critical observation of existing studies was raised by Bloch and Qawasmi [1] regarding adequate power and sample size. They noted that to have sufficient power (β 80%, two-sided, $\alpha = 0.05$) to detect an effect size of 0.31, clinical trials would need samples of approximately 330 children. Therefore, trials to date are considerably underpowered, likely to contribute to inconsistent findings in addition to wide variation in methodology, formulation and dose in previously published literature.

ADHD is purported to be associated with an exaggerated fetal central nervous system inflammatory response to a prenatal insult such as maternal inflammatory disease or fetal infection [2]. Therefore, the role of omega-3 HUFAs as a potential preventive risk factor for ADHD is an area of increasing clinical interest. It is well established that omega-3 HUFAs DHA and EPA limit neuroinflammation, whereas diets rich in the omega-6 arachidonic acid promote inflammation. We have published previous in-depth reviews [3,4], therefore, the purpose of this article is to provide updated commentary in the context of recent clinical trials of omega-3 HUFAs in ADHD.

INDIVIDUAL RESEARCH STUDIES

We conducted searches on Clinicaltrials.gov and *PubMed* databases for studies published in the last 12 months using key words including 'ADHD and omega-3 fatty acids' or 'attention deficit and fish oil' which yielded nine results appropriate for the purpose of this review.

Milte *et al.* [5▪] investigated erythrocyte fatty acid composition in relation to attention and behaviour in children with symptoms of ADHD in the context of a randomized, controlled, three-way crossover trial. Ninety children aged 6–13 years of age were randomized by process of minimization on the basis of sex and age to receive EPA-rich oil providing 1109 mg of EPA, 108 mg of DHA; DHA-rich oil providing 264 mg of EPA and 1032 mg of DHA; or safflower oil containing 1467 mg of linoleic acid per day for 4 months each in a cross-over design. The results showed no significant differences in treatment effects between groups. The study was limited by insufficient statistical power because of challenges with recruiting eligible children and a 37% drop-out rate. However, using regression analyses, significant associations were observed between elevated omega-3 HUFA levels and improved literacy scores, attention and parent-rated measures of oppositional, hyperactive behaviour and cognitive problems. These changes, reported at 4 months [6] and across the 12 months, were most pronounced for DHA and for the ratio of omega-6 to omega-3 HUFA. Inverse associations were observed between elevated omega-6 and various outcome variables.

ADHD is often comorbid with oppositional behaviours, and callous-unemotional personality traits represent a distinct developmental vulnerability to persistent antisocial behaviour [7,8]. Gow *et al.* [9] recruited a sample of 29 young male adolescents (ages 12–16 years) with ADHD and found a significant association between low EPA levels and callous-unemotional traits ($r = -0.597$, $P = 0.009$) [10,11]. Additionally, the ADHD group showed a correlation between high callous-unemotional scores and oppositional behaviours ($r = 0.464$, $P = 0.011$) and with low total omega-3 PUFA levels ($r = -0.498$, $P = 0.027$), and trends towards a correlation between low DHA levels and high callous-unemotional scores ($r = -0.436$, $P = 0.054$). A trend toward an association of low total omega-3 PUFA levels and antisocial behaviours was also observed. These findings are unique and further research with larger samples is needed to investigate whether early intervention with omega-3 HUFAs may benefit youths with callous-unemotional traits and help prevent the subsequent emergence of conduct disorder.

In the Mauritius study, Raine *et al.* [12▪▪] examined potential effects of omega-3 PUFA

supplementation in a randomized controlled trial for reduction of behaviour problems such as those commonly found in ADHD in 200 children aged between 8 and 16. The children received 1 g omega-3 (300 mg DHA, 200 mg EPA, 400 mg α-linolenic acid, and 100 mg DPA; $n = 100$) daily in a vitamin D and antioxidant-enriched fruit drink or placebo ($n = 100$) drink for 12 months. Assessments were conducted at baseline, 6 and 12 months (6 months post-treatment). Primary outcome measures were externalizing (characterized as aggressive and rule breaking) and internalizing (e.g. anxious/depressed, withdrawn depressed and somatic complaints) behaviours. These problems were reported by caregivers and children at baseline, 6 and 12 months, with secondary outcome measures of parental antisocial behaviour. Six months of omega-3 PUFA supplementation resulted in 42–68% reduction in parent-reported externalizing and internalizing behaviour problems. This is one of the few studies to conduct longer term follow-up, with improvements continuing 6 months after treatment cessation. A medium effect size ($d = -0.58$) was also observed for long-term improvement in callous-unemotional traits, and significant reductions were reported in parental psychopathy and reactive aggression in the parents of treated children. Interestingly, improvement in parental behaviour accounted for 60.9% of the improvement in child antisocial behaviour.

Widenhorn-Müller *et al.* [13] examined the effects of omega-3 HUFA supplementation (2 fish oil capsules/day providing 600 mg EPA and 120 mg DHA) or placebo for 16 weeks on behaviour and cognition in 97 children aged 6–12 years meeting the Diagnostic and Statistical Manual of Mental Disorders-IV criteria for ADHD. Blood samples were taken to measure fatty acid composition and compliance. Fish oil supplementation led to significantly increased erythrocyte EPA and DHA and decreased arachidonic acid compared with placebo. The findings revealed no effects on teacher or parent ADHD rating scales after 16 weeks. Improved working memory was observed in the active group compared with placebo, and these improved scores were significantly associated with increased blood levels of EPA and DHA and decreased arachidonic acid. The study had several limitations, for example, there was no control group and a proportion of the children were taking psychostimulant medication.

OMEGA-3 HUFA AS AN ADJUNCT TO METHYLPHENIDATE

A recent comparison between methylphenidate (MPH) and omega-3/6 HUFAs (558 mg EPA, 174 mg DHA and 60 mg γ-linolenic acid/day) or a combination for treating symptoms in 90 children with ADHD was made in an unblinded controlled trial [14▪]. The children ($M = 8.27$ years) were randomized to receive MPH, MPH and omega-3/6 or omega-3/6 for 12 months. The results demonstrated that omega-3/6 HUFAs were an effective and well tolerated monotherapy for children with ADHD, although slightly less effective than MPH alone. Combined omega-3/6 and MPH provided no increased benefit over MPH monotherapy but did permit lower doses of MPH. Reductions in symptom scale scores were initially lower in both the omega-3/6 and MPH and omega-3/6 groups compared with MPH alone; however, these scores levelled off towards week 8 suggesting long-term stabilization with omega-3/6 either alone or in combination with MPH. Longer term comparisons are needed as prior research suggests that omega-3 HUFA treatment benefits may increase over time, with no plateauing observed after 30 weeks of supplementation [15].

A similar randomized, double-blind, clinical trial by Behdani *et al.* [16] examined whether 2000 mg of omega-3 containing 240 mg of DHA and 360 mg of EPA would enhance therapeutic effects of MPH in 69 children aged 7–15 years with ADHD. The experimental group received 2 g omega-3 HUFAs and MPH per day for 8 weeks, whereas the control group received MPH and matching placebo. Significant reductions in both parent and teacher ADHD rating scales across both groups were observed but there was no significant difference between groups suggesting omega-3 was unable to improve the therapeutic effects of MPH in this group of children [16]. Given that omega-3 HUFA supplementation may correct an underlying deficiency, with minimal side-effects, rather than merely treating symptoms, it warrants further investigation as a single or adjunctive treatment.

SYSTEMATIC AND META-ANALYTIC REVIEWS

Hawkey and Nigg [17▪] conducted a blood level analysis and meta-analysis of supplementation trials in the field of omega-3 and ADHD. Their results demonstrated that out of nine studies ($n = 586$), individuals with ADHD had significantly lower blood levels of omega-3 PUFA compared with controls. However, to date, this concept has not been advanced in the scientific literature and reasons for this finding remain unclear. Future studies should explore the possibility of impaired delta 6 and 5 enzyme activity using stable isotopes which can map and trace the absorption and synthesis of HUFAs. These authors then examined 16 intervention studies ($n = 1408$) and found that omega-3

HUFAs improved overall symptoms of ADHD. Improved parent and teacher ratings of hyperactivity were significant, whereas inattention was significant only for parent reports. Despite finding a modest effect size of omega-3 HUFA efficacy, the authors choose to err on the side of caution and conclude 'not enough evidence to recommend omega-3 fatty acids as an alternative to existing empirically supported pharmacological and behavioural treatments . . .'. They do suggest that omega-3 HUFA supplementation is justified to use given its mild side-effect profile, although it remains unclear which children are most likely to benefit.

Puri and Martins [18] recognized the wide variation in results reported in the existing literature pool of omega-3 HUFA supplementation trials in children and adolescents with ADHD. To address some of the variations in differential efficacy, formulas and rater blinding, they conducted an exploratory meta-regression analysis with no *a priori* direction concerning which PUFA may be effective in alleviating symptoms of ADHD. The results, pooled from 18 studies, demonstrated that combined ADHD symptoms decreased with PUFA supplementation across all raters. When analyzed by individual rater, only parent-rated symptoms decreased significantly. Factors such as longer supplementation duration and the interaction between γ-linolenic acid and EPA were linked to significant decreases in attention. The authors observed modest efficacy of PUFA supplementation for symptoms of inattention. However, the authors note that the generalizability of their findings is limited by evidence of reporting bias, quality of design and potentially psychoactive placebos.

Sonuga-Barke *et al.* [19▪] examined nonpharmacological interventions for ADHD in a systematic review and meta-analysis of randomized controlled trials of dietary and psychological treatments. They reported that supplementation with fatty acids (n-3 HUFA) and artificial food colour exclusions appeared to have beneficial effects in reducing symptoms of ADHD. They noted that for fatty acids the effect was small and for artificial food colourings effects may be limited to individuals with food sensitivities. These three meta-analytic reviews are in support of a modest effect size of n-3 HUFAs which is important given methodological shortcomings of individual trials. This supports previous reviews reporting that fish oil supplements and elimination diets (avoiding specific-food elements) are to date the most promising nonpharmacological dietary interventions in reducing symptoms of ADHD [20▪,21]. However, the authors note that further investigations are needed to ascertain their efficacy as part of a treatment programme for ADHD.

LIMITATIONS OF EXISTING RESEARCH

There are several key limitations of existing studies which arguably have proved cumbersome for replication. Sample size has continued to result in a significant number of published research trials being underpowered and, hence, may negatively impact findings. An exception is the study by Raine *et al.* [12▪▪] ($n = 200$) and supplementation over 6 months – yielding a stronger effect size than that found across other studies. Additionally, the majority of research has been inconsistent in both dose and formula resulting in an eclectic assortment of trials, including the rationale for some formulas. For example, Raz *et al.* [22] supplemented children with short chain fatty acids rich in linoleic acid with no clear rationale for their unusual choice of formula given that the average Western diet already contains excess omega-6 to the detriment of omega-3 and biochemically both compete for absorption. Furthermore, there is a clear distinction between omega-3 and 6 HUFAs and their respective mechanistic actions in neuronal membranes. Recent meta-analyses have provided insights into the potentially enhancing effects of EPA but EPA-rich trials in this area are still limited. The one study to date that compared EPA-rich with DHA-rich oil [5▪,6] suggests that both may be effective, highlighting also the importance of taking blood samples to better inform findings. An additional limitation is recruiting children with ADHD whose symptoms are already normalized by stimulant medication, which can be recognized by evaluating baseline Conner's ADHD rating scores. If symptoms are already controlled, there leaves little room for any improvement such as a previous study that used a DHA supplement [23].

CONCLUSION

Despite numerous intervention studies in ADHD and omega-3 HUFAs, many unanswered questions remain. These questions are largely concerned with individual variation; in other words, why some children with ADHD respond to omega-3 HUFAs, whereas others appear not to. Baseline erythrocyte omega-3 HUFA levels should be tested via finger prick tests if venous samples are not possible prior to supplementation. This may help ascertain normative standards, predict potential responders and variation in dose if appropriate. Given the complexity of other nutritional deficiencies and behavioural food intolerances identified in children with ADHD [21,24], this is also likely to contribute to variability in treatment response. A possible treatment approach could be to screen children firstly for low omega-3 HUFA levels, identify those

with untreated behavioural food intolerances, then test and correct other nutritional deficiencies before randomizing to omega-3 HUFA treatment or placebo.

The jury is still out regarding relative efficacy of EPA versus DHA. The body of results and differential mechanisms of action suggests that both are important. It is also unclear why some children and adults with ADHD have lower blood levels of omega-3 HUFA. Future research directions need to investigate this further in order to advance the field in an informed manner. An important consideration is that a small collection of studies seem to suggest greater improvement in symptoms [6,25–27] as well as lower omega-3 HUFA levels [28] in subgroups of children with learning difficulties although conduct disorder/callous and unemotional traits may also be improved [9,12▪▪]. The latter studies also suggest that children who have learning and/or behaviour problems but not necessarily a diagnosis of ADHD may benefit from omega-3 HUFA supplementation, suggesting possible benefits with a symptomatic rather than diagnostic approach. The identification of responders within the cohort is a useful practice; helps better shape the pooled literature, reduce heterogeneity of samples and guide future research trials. Longer term supplementation trials are required to test extended benefits.

Taking into consideration the relatively mild side-effect profile and evidence of modest efficacy, we conclude that it may be reasonable to use omega-3 supplementation to augment traditional pharmacologic interventions or to treat young people whose families decline other psychopharmacologic options in addition to recommending fish consumption at least twice a week in accordance with US Dietary Guidelines.

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Conflicts of interest

None.

This manuscript represents only the views of the authors and should not be interpreted as representing any policy of position of the National Institutes of Health, Department of Health and Human Services, the US Federal Government or any other entity.

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