Omega-3 Fatty Acid Supplementation for the Treatment of Children With Attention-Deficit/Hyperactivity Disorder Symptomatology: Systematic Review and Meta-Analysis

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Objective: Several studies have demonstrated differences in omega-3 fatty acid composition in plasma and in erythrocyte membranes in patients with attention-deficit/hyperactivity disorder (ADHD) compared with unaffected controls. Omega-3 fatty acids have anti-inflammatory properties and can alter central nervous system cell membrane fluidity and phospholipid composition. Cell membrane fluidity can alter serotonin and dopamine neurotransmission. The goal of this meta-analysis was to examine the efficacy of omega-3 fatty acid supplementation in children with ADHD. **Method:** PubMed was searched for randomized placebo-controlled trials examining omega-3 fatty acid supplementation in children with ADHD symptomatology. The primary outcome measurement was standardized mean difference in rating scales of ADHD severity. Secondary analyses were conducted to determine the effects of dosing of different omega-3 fatty acids in supplements. **Results:** Ten trials involving 699 children were included in this meta-analysis. Omega-3 fatty acid supplementation demonstrated a small but significant effect in improving ADHD symptoms. Eicosapentaenoic acid dose within supplements was significantly correlated with supplement efficacy. No evidence of publication bias or heterogeneity between trials was found. **Conclusion:** Omega-3 fatty acid supplementation, particularly with higher doses of eicosapentaenoic acid, was modestly effective in the treatment of ADHD. The relative efficacy of omega-3 fatty acid supplementation was modest compared with currently available pharmacotherapies for ADHD such as psychostimulants, atomoxetine, or α_2 agonists. However, given its relatively benign side-effect profile and evidence of modest efficacy, it may be reasonable to use omega-3 fatty supplementation to augment traditional pharmacologic interventions or for families who decline other psychopharmacologic options. J. Am. Acad. Child Adolesc. Psychiatry, 2011;50(10):991–1000. **Key Words:** attention-deficit disorder with hyperactivity, polyunsaturated fatty acids, omega-3 fatty acids, eicosapentaenoic acid, meta-analysis

Attention-deficit/hyperactivity disorder (ADHD) is characterized by developmentally inappropriate and impairing inattention, impulsivity, and hyperactivity (*DSM*).[1] ADHD is one the most common and impairing health conditions affecting school-age children.[2,3] Several pharmacotherapies have demonstrated

significant short-term efficacy for the treatment of ADHD. More than 70% of children with ADHD respond to psychostimulant medications (i.e., methylphenidate and dextroamphetamine derivatives).[4] Other medications such as atomoxetine, α_2 agonists, and desipramine have also demonstrated efficacy in treating ADHD.[5-7] However, many families elect not to use traditional pharmacotherapies to treat ADHD. This decision is often related to concerns over possible short-term side effects or doubts regarding long-term efficacy or effects of these medications on development.[8-11]

Instead, alternative and complementary treatments such as natural supplements are often used by families to treat ADHD.[12]

Omega-3 fatty acid supplementation is one of the most studied alternative treatments for ADHD.[13] Omega-3 fatty acids cannot be synthesized de novo by humans and instead are required in the diet. In the Western diet, omega-6 fatty acids or their precursors (e.g., linoleic acid) are much more abundant than omega-3 fatty acids or their precursors (e.g., α-linolenic acid).[14] A high ratio of omega-6 to omega-3 can alter cell membrane properties and increase production of inflammatory mediators because arachidonic acid, an omega-6 fatty acid found in cell membranes, is the precursor of inflammatory eicosanoids, such as prostaglandins and thromboxanes.[15] In contrast, omega-3 fatty acids are anti-inflammatory.[15] Therefore, a high dietary ratio of omega-6 to omega-3 fatty acid could promote neuroinflammation. Increased omega-3 fatty acid concentration in the diet may also act by altering central nervous system cell membrane fluidity and phospholipid composition, which may alter the structure and function of the proteins embedded in it.[16] By this mechanism, increased omega-3 fatty acid concentrations in cell membranes have been shown to affect serotonin and dopamine neurotransmission, especially in the frontal cortex.[17]

Through these mechanisms omega-3 fatty acid consumption has been hypothesized to alter risk for different psychiatric conditions including psychosis, depression, dementia, and ADHD.[18,19] Several studies have demonstrated differences in omega-3 fatty acid composition in plasma and in erythrocyte membranes in patients with ADHD compared with unaffected controls.[20-26] Furthermore, omega-3 fatty acid supplementation has been consistently demonstrated to alter cell membrane composition in vivo.[25,27]

Several double-blind, placebo-controlled trials have been conducted to assess the efficacy of omega-3 fatty acid supplementation in the treatment of children with ADHD. The results of these trials have been mixed, leading to considerable confusion and controversy in the field. For instance, one recent systematic review published in the previous year described the results of current trials in the area as "very disappointing" and "most randomized trials have clearly demonstrated lack of superiority or arbitrary findings (which may be a result of multiple analyses without appropriate statistical correction) compared with placebo."[13] Another recent review, evaluating the same literature, stated "that the administration of specific combinations of long chain-polyunsaturated fatty acids (LC-PUFAs) can have a positive effect in children with ADHD" but that the "optimum LC-PUFA composition and dose needs to be established."[28]

To our knowledge, no meta-analysis has been conducted to determine the efficacy of omega-3 fatty acid supplementation for children with ADHD. The present goal was to conduct a meta-analysis to determine the efficacy of omega-3 fatty acid supplementation in ADHD. Given the considerable heterogeneity expected in the literature, meta-regression was used to examine how the use of different omega-3 fatty acid compositions in supplementation affected treatment efficacy.

METHOD

Search Strategy

All meta-analytic methods and sensitivity analyses were specified before conducting the meta-analysis but were not registered online. PubMed (1965 through December 2010) was searched by two reviewers (M.H.B. and A.Q.) for relevant trials using the search strategy (Attention Deficit Disorder with Hyperactivity"[Mesh] AND "Fatty Acids, Unsaturated"[Mesh]). The results of the search were further limited to randomized control trials and meta-analyses. The references of eligible trials for this meta-analysis and any appropriate review articles in this area were also searched for citations of further relevant published and unpublished research. In addition, unpublished or ongoing trials were searched on the ClinicalTrials.gov Web site using the search terms *fatty acid*, *omega-3* or *omega-6* and *ADHD*. There were no language limitations.

Criteria for Inclusion of Studies in This Review

Studies were included in this meta-analysis if they were randomized placebo-controlled trials examining the efficacy of omega-3 fatty acid supplementation in children with ADHD or targeting ADHD symptoms in other children (undiagnosed or with comorbid conditions) and used a validated rating scale to measure ADHD severity during the trial. Trials were considered randomized when investigators explicitly represented them as such in the Methods section of their published study. Trials in which other psychoactive substances were started at the same time as omega-3 fatty acid supplementation were also excluded.

Meta-Analytic Method

Data extraction was performed on specially designed Excel (Microsoft, Redmond, WA) spreadsheets. Data were also collected on methods, participants, intervention and outcome measurements, and other relevant attributes and results of the studies. Any missing information was requested from the study investigators when possible.

The outcome measurement selected from each included trial was the difference in mean improvement between a group with omega-3 fatty acid supplementation and a placebo group in a clinical rating scale measuring ADHD severity over the course of the trial. Preferred rating scales for rating of ADHD severity (in order of preference) were the ADHD Rating Scale, the Conner's Rating Scales for Teachers or Parents, and the Disruptive Behavior Disorder Rating Scale. When parents and teachers completed the same rating scale, the responding group that had the largest number of completed rating scales was used. A hierarchy of preferred ADHD rating scales for the primary outcome was established a priori (as opposed to using the ADHD rating scale identified as primary by the trial investigator) to avoid any possible inflation of treatment effects caused by possible reporting bias toward measurements that showed the greatest efficacy. Because many rating scales have excellent psychometric properties in evaluating ADHD, this hierarchy of preferred rating scales for ADHD is not meant to reflect the relative merit of these measurements. When the standard deviation of the mean improvement on placebo or omega-3 fatty acid supplementation was not reported in individual studies, this was imputed based on the standard deviation of reported baseline and endpoint ADHD severity using Cochrane methodology.[29]

Standard mean difference (SMD) was chosen as the summary statistic for meta-analysis and calculated by pooling the standardized mean improvement of each study using RevMan 5 (The Cochrane Collaboration, Copenhagen). SMD was favored over weighted mean difference because rating scales differed across studies. A fixed-effects model was chosen for meta-analysis because this method is favored when testing for subgroup differences in stratified meta-analysis. Publication bias was assessed by plotting the effect size against the sample size for each trial (funnel plot).[30] Publication bias was also statistically tested by testing the association between sample size and effect size in meta-regression. Heterogeneity of treatment response was assessed visually from the forest plot of weighted mean differences and relative risk of individual studies. Statistical estimates of heterogeneity were also assessed using the I^2 heterogeneity statistic in RevMan. A sensitivity analysis was conducted to examine the decision to use a random-effects rather than a fixed-effects model for meta-analysis.

For secondary analysis, the same methodology was used to examine the effect of omega-3 supplementation on symptoms of inattention and hyperactivity/impulsivity separately. The effect of omega-3 supplementation on parent ratings of ADHD symptoms also was examined. The effects of supplementation on teacher ratings of ADHD could not be examined because a minority of trials reported on this outcome. Several subgroup analyses and meta-regression were performed. For subgroup analyses, trials were stratified based on whether the omega-3 supplement was given as monotherapy or as an augmentation agent to pharmacologic treatment, methodologic quality of trials, diagnosis (undiagnosed population, confirmed ADHD, and ADHD symptoms in comorbid condition), analysis method (intention-to-treat or completers analysis), and type of placebo. Overall methodologic quality of the trials was assessed using the Jadad Scale.[31,32] The test for subgroup differences in RevMan was used to determine whether subgroups decreased overall heterogeneity.[33]

Meta-regression was performed in SPSS 19.0 (SPSS, Inc., Chicago, IL) using linear regression. Trials were weighted using the generic inverse variance method. Effect size (SMD) of trials was entered as the dependent variable with the variables of interest being the independent variable. Meta-regression techniques were used to examine the association between omega-3 and naturally continuous variables such as trial duration, proportion of dropouts in trials using completers analysis, and doses of omega-3 fatty acids in supplementation preparations. Doses of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and α-linolenic acid in omega-3 fatty acid preparations were examined. For the primary analysis examining the efficacy of omega-3 fatty acids for ADHD symptoms, a significance threshold of $p < .05$ was used. For all subgroup analyses and meta-regression, the same threshold for statistical significance was used. Any significant findings should be regarded as exploratory because the study did not adjust for inflation of false-positive error from the 13 secondary analyses.

RESULTS

Selection of Studies

The PubMed search identified 18 articles that were potentially eligible for inclusion in this meta-analysis. Four potentially eligible trials were identified from the references of relevant reviews. Figure 1 presents a flow diagram depicting the selection procedure for this meta-analysis. One randomized controlled trial was excluded because it included supplementation with additional psychoactive substances (including *Gingko biloba*, [scap]l[r]-glutamate, Grapine, *Melissa*

FIGURE 1 Flow chart depicting selection of studies. Note: ADHD = attention-deficit/hyperactivity disorder.
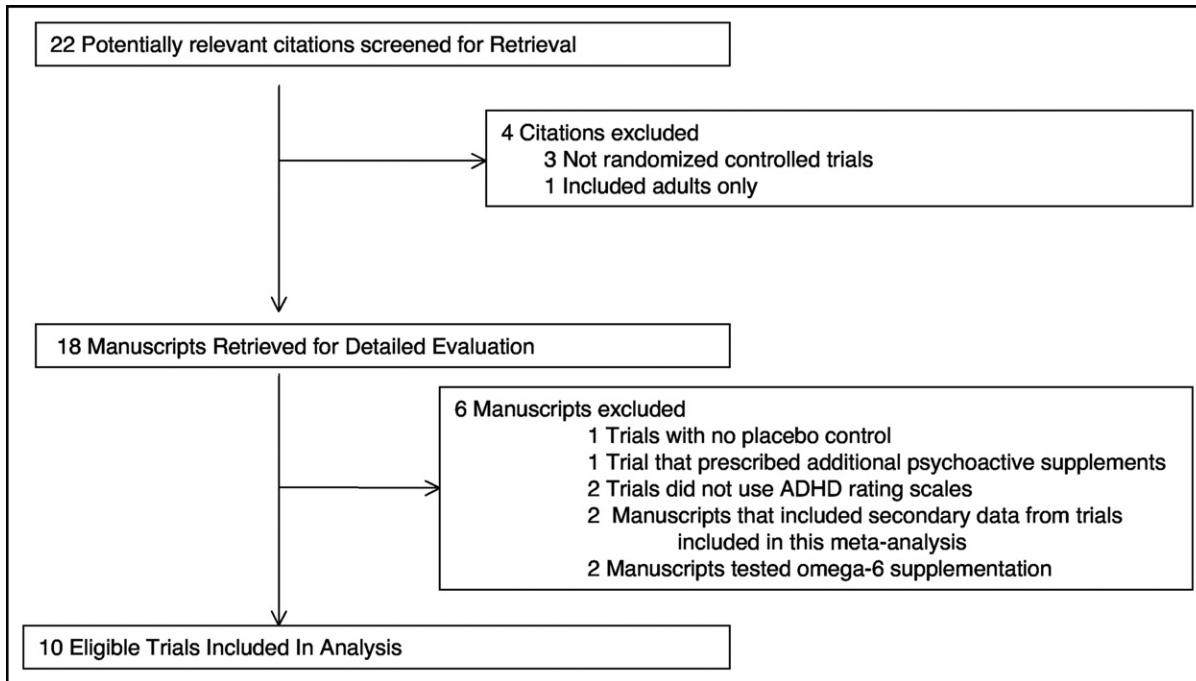
officinalis, and dimethylaminoethanol).[34] Two randomized controlled trials were excluded because they used the number of *DSM* ADHD symptoms present rather than a rating scale to assess ADHD severity.[35,36] Two trials also were excluded because they studied omega-6 rather than omega-3 fatty acid supplementation.[37,38]

Ten eligible trials with 11 appropriate treatment arms were identified for inclusion in this review. Table 1 presents the characteristics of included trials.[25,38-47] Only two of these 10 trials reported a statistically significant benefit of omega-3 fatty acid supplementation.[41,45] Six trials showed no benefit of omega-3 fatty acid supplementation compared with placebo.[25,37-40,43,44,46] Two trials demonstrated a benefit on some but not most ADHD rating scales when no measurement was specified a priori.[42,47]

Efficacy of Omega-3 Fatty Acid Supplementation for ADHD

Overall meta-analysis of 10 trials involving 699 participants demonstrated a small but significant effect of omega-3 fatty acid supplementation on ADHD (SMD = 0.31, 95% confidence interval [CI] 0.16–0.47, $z = 4.04$, $p < .0001$). Figure 2 provides a forest plot depicting the significant

benefit of omega-3 fatty acid supplementation in the treatment of ADHD. There was no evidence of significant heterogeneity (heterogeneity: $\chi^2_{10} = 3.68$, $p = .96$, $I^2 = 0\%$). A funnel plot indicated no evidence of publication bias in the literature. A regression of sample size versus trial effect size also showed no evidence of publication bias ($\beta = 0$, 95% CI -0.004 to 0.005, $t = 0.20$, $p = .84$). Sensitivity analysis demonstrated that the findings were identical when using a random-effects model. In addition, when parental ratings of ADHD were used from each trial, omega-3 supplementation showed similar benefits compared with placebo (SMD = 0.29, 95% CI 0.14–0.44, $z = 3.72$, $p = .0002$). Teacher ratings of ADHD were not analyzed as an outcome because a minority of trials reported on this outcome.

Meta-analysis also demonstrated similar effect sizes of omega-3 fatty acid supplementation in the treatment of inattentive (SMD = 0.29, 95% CI 0.07–0.50, $z = 2.63$, $p = .009$) and hyperactivity (SMD = 0.23, 95% CI 0.07–0.40, $z = 2.78$, $p = .005$) symptoms separately. Data were available for only eight of 10 eligible trials for these analyses and involved 602 participants. There was no significant heterogeneity or publication bias evident for these measurements.
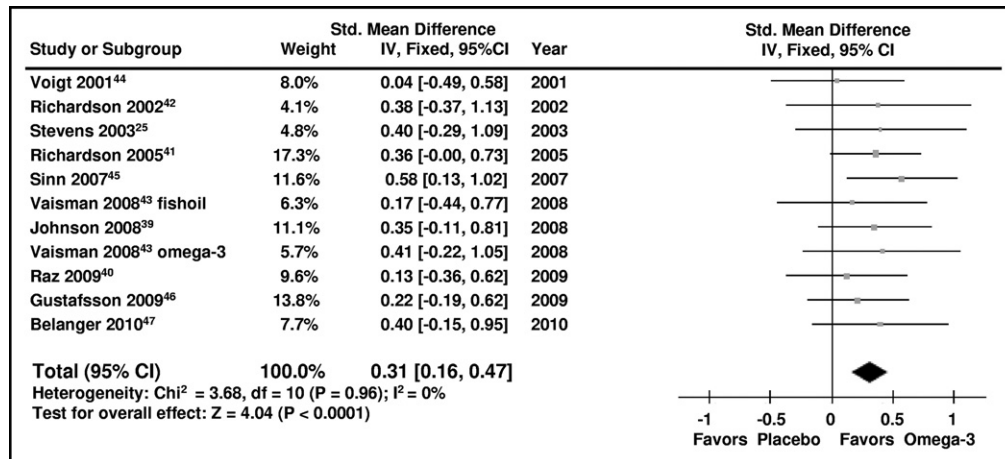
TABLE 1 Characteristics of Included Trials

Study	Year	Design	Study Duration	Monotherapy vs. Augmentation	N	Mean Age	Gender (% Male)	Rating	Jadad Score	Analysis	EPA Dose (mg)	DHA Dose) (mg)	ALA Dose (mg)	Placebo
Voigt et al.[44]	2001	parallel	4 mo	augmentation	63	9.3	78	CBCL Attention subscale	5	completer	0	345	0	—
Richardson et al.[42]	2002	parallel	12 wk	monotherapy	41	10.3	85	CPRS-L	4	completer	186	480	0	olive oil
Stevens et al.[25]	2003	parallel	4 mo	augmentation	47	9.8	87	ASQ (DBD–teacher)[b]	3	completer[a]	80	480	0	olive oil
Richardson et al.[41]	2005	parallel	3 mo	monotherapy	117	8.8	67	CTRS-L	5	ITT	558	174	0	olive oil
Sinn and Bryan[45]	2007	parallel	15 wk	monotherapy	104	9.4	74	CPRS-L	2	completer	558	174	0	palm oil
Johnson et al.[39]	2009	parallel	3 mo	monotherapy	75	12.0	85	ADHD-RS	5	modified ITT	558	174	0	olive oil
Vaisman et al.[43]	2008	parallel	3 mo	monotherapy	55	9.2	77	CPRS-R-S	4	completer	156	95	1	canola oil
Vaisman et al.[43]	2008	parallel	3 mo	monotherapy	54	9.4	71	CPRS-R-S	4	completer	153	96	2	canola oil
Belanger et al.[47]	2009	crossover	16 wk	monotherapy	26	9.2	69	CPRS-L	3	completer	750	300	0	sunflower oil
Gustafsson et al.[46]	2010	parallel	15 wk	monotherapy	92	7–12	—	CTRS	5	modified ITT	500	2.7	0	canola oil
Raz et al.[40]	2009	parallel	7 wk	monotherapy	78	10.5	60	ADHD-RS	3	completer	0	0	120	vitamin C

Note: Twelve trials involving 735 children with attention-deficit/hyperactivity disorder (ADHD) were included in this meta-analysis. ADHD-RS = ADHD rating scale; ALA = α-linolenic acid; ASQ = Connors' Parental Abbreviated Symptom Questionnaire; CBCL = Connors' Behavioral Checklist; CPRS-L = Connors' Parents Rating Scale–Long Version; CPRS-R-S = Connors' Parents Rating Scale-Revised Short Version; CTRS-L = Connors' Teachers Rating Scale-Long Version; DBD = Disruptive Behavior Disorders Scale; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; ITT = intention-to-treat; N = number of individuals contributing data to meta-analysis from trial.
[a]Presented data for completers analysis only but reported p values for ITT sample.
[b]For inattention and hyperactivity measurements, the DBD scale was used.

FIGURE 2 Omega-3 fatty acid supplementation for attention-deficit/hyperactivity disorder (ADHD). Note: Forest plot depicts the efficacy of omega-3 fatty acid supplementation compared with placebo in the treatment of children with ADHD symptoms. Ten studies involving 699 participants contributed to this analysis. There was a significant benefit of omega-3 supplementation compared with placebo and no evidence of heterogeneity or publication bias. CI = confidence interval.

Study or Subgroup	Weight	Std. Mean Difference IV, Fixed, 95%CI	Year
Voigt 2001[44]	8.0%	0.04 [-0.49, 0.58]	2001
Richardson 2002[42]	4.1%	0.38 [-0.37, 1.13]	2002
Stevens 2003[25]	4.8%	0.40 [-0.29, 1.09]	2003
Richardson 2005[41]	17.3%	0.36 [-0.00, 0.73]	2005
Sinn 2007[45]	11.6%	0.58 [0.13, 1.02]	2007
Vaisman 2008[43] fishoil	6.3%	0.17 [-0.44, 0.77]	2008
Johnson 2008[39]	11.1%	0.35 [-0.11, 0.81]	2008
Vaisman 2008[43] omega-3	5.7%	0.41 [-0.22, 1.05]	2008
Raz 2009[40]	9.6%	0.13 [-0.36, 0.62]	2009
Gustafsson 2009[46]	13.8%	0.22 [-0.19, 0.62]	2009
Belanger 2010[47]	7.7%	0.40 [-0.15, 0.95]	2010
Total (95% CI)	**100.0%**	**0.31 [0.16, 0.47]**	

Heterogeneity: $Chi^2 = 3.68$, df = 10 (P = 0.96); $I^2 = 0\%$
Test for overall effect: Z = 4.04 (P < 0.0001)

Std. Mean Difference IV, Fixed, 95% CI
Favors Placebo — Favors Omega-3 (scale: -1, -0.5, 0, 0.5, 1)

Dosing of Omega-3 Fatty Acid Supplementation

Higher doses of EPA within omega-3 fatty acids supplements were significantly associated with increased efficacy in treating ADHD symptoms ($\beta = 0.36$, 95% CI 0.01–0.72, $t = 2.30$, $p = .04$, $R^2 = 0.37$). Figure 3 shows a scatterplot that depicts the relation between EPA dose and effect size of supplementation for individual trials.

Doses of other omega-3 fatty acids within supplements such as DHA ($\beta = 0.24$, 95% CI −0.54 to 1.02, $t = 0.70$, $p = .50$) and α-linolenic acid ($\beta = -1.71$, 95% CI −4.62 to 1.19, $t = -1.33$, $p = .22$) were not significantly associated with the measured efficacy of supplements.

Augmentation versus Monotherapy

No significant difference was found in the efficacy of omega-3 fatty acid supplementation based on whether it was given as monotherapy versus augmentation to other traditional ADHD medications (test for subgroup differences: $\chi^2_1 = 0.45$, $p = .50$, $I^2 = 0\%$). There was no significant difference in efficacy when omega-3 fatty acid supplementation was given as monotherapy (SMD = 0.33, 95% CI 0.17–0.50, $z = 4.01$, $p < .0001$) compared with augmentation (SMD = 0.18, 95% CI −0.25 to 0.60, $z = 0.82$, $p = .41$).

Primary Psychiatric Diagnosis of Subjects

The efficacy of omega-3 fatty acid supplementation did not significantly (test for subgroup dif-

ferences: $\chi^2_1 = 0.12$, $p = .73$, $I^2 = 0\%$) differ whether ADHD was the subjects' primary diagnosis (SMD = 0.30, 95% CI 0.13–0.47, $z = 3.42$, $p = .0006$) or whether ADHD symptoms were being targeted in another psychiatric condition (SMD = 0.36, 95% CI 0.04–0.69, $z = 2.18$, $p = .03$).

Trial Duration

Trial duration ranged from 4 weeks to 4 months in the included trials. Meta-regression demonstrated no significant relation between trial duration and measured efficacy of supplementation ($\beta = 0.002$, 95% CI −0.004 to 0.007, $t = 0.63$, $p = .55$).

Type of Placebo

No significant effect of type of placebo was found on the measured effect of omega-3 supplementation in trials (test for subgroup differences: $\chi^2_4 = 2.26$, $p = .69$, $I^2 = 0\%$). Four trials that used olive oil as the placebo demonstrated a modest effect size (SMD = 0.36, 95% CI 0.12–0.61, $z = 2.87$, $p = .004$)[25,41,42] similar to that seen in trials using canola oil as a placebo (SMD = 0.25, 95% CI −0.05 to 0.55, $z = 1.62$, $p = .11$)[43,46] and individual trials that used vitamin C,[40] sunflower oil,[47] and palm oil[45] as placebo.

Study Quality

No significant effect of study quality was found on the measured efficacy of omega-3 fatty acid

FIGURE 3 Eicosapentaenoic acid (EPA) dose and efficacy of omega-3 fatty acid supplementation for attention-deficit/hyperactivity disorder (ADHD). Note: Scatterplot displays the measured efficacy of omega-3 fatty acid supplementation in trials as a function of EPA dose used. Trials were weighted (size of circles) using the generic inverse variance method. Higher doses of EPA within essential fatty acid supplements were significantly associated with increased efficacy in treating ADHD symptoms ($\beta = 0.36$, 95% CI: 0.01–0.72, $t = 2.34$, $p = .04$, $R^2 = 0.38$). Two trials, by Johnson et al.[39] (effect size = 0.35, EPA dose = 558 mg, weight = 11.1%) and Richardson et al.[41] (effect size = 0.36, EPA dose = 558 mg, weight = 17.3%), had overlapping point estimates on this figure. CI = confidence interval.
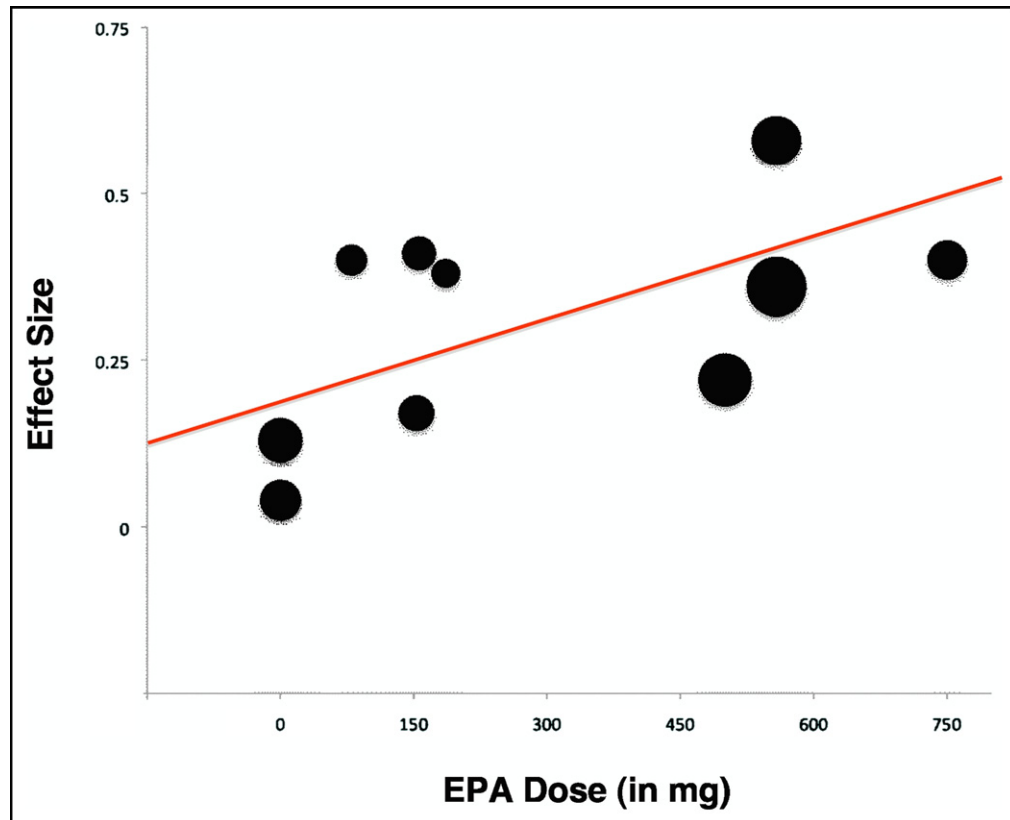
supplementation in the treatment of ADHD (test for subgroup differences: $\chi^2_1 = 0.41$, $p = .52$, $I^2 = 0\%$). Lower-quality studies (Jadad score = 2 or 3: SMD = 0.38, 95% CI 0.12–0.64, $z = 2.87$, $p = .004$) did not show a significantly greater efficacy of omega-3 fatty acid supplementation than higher-quality studies (Jadad score = 4 or 5: SMD = 0.28, 95% CI 0.09–0.46, $z = 2.92$, $p = .004$).

Method of Analysis

Trials that relied on completers analysis (SMD = 0.32, 95% CI 0.12–0.52, $z = 3.09$, $p = .002$) did not demonstrate a significantly greater efficacy (test for subgroup differences: $\chi^2_1 = 0$, $p = 0.98$, $I^2 = 0\%$) of omega-3 fatty acid supplementation than trials that used intention to treat or modified intention-to-treat analysis methods (SMD = 0.31, 95% CI 0.08–0.55, $z = 2.6$, $p = .009$).

Effects of Subject Dropouts

The proportion of dropouts within trials employing completers analysis was not significantly associated with measured efficacy of supplementation ($\beta = 0.51$, 95% CI −0.28 to 1.29, $t = 1.46$, $p = .18$).

DISCUSSION

In this meta-analysis, a small but significant benefit of omega-3 fatty acid supplementation was found. Meta-analysis found no evidence of publication bias or of significant heterogeneity between trials. In secondary analysis, no evidence indicated that poor study quality or inappropriate treatment of study dropouts in some studies affected overall findings.

These results reporting a significant benefit of omega-3 supplementation stand in contrast to the

conclusions of most individual trials included in the meta-analysis. The effect size of 0.31 reported for omega-3 fatty acid supplementation, although significant, is quite modest. To have sufficient power ($\beta = 80\%$, two-sided $\alpha = 0.05$) to detect a significant benefit of omega-3 fatty acid supplementation compared with placebo assuming the effect size observed in this meta-analysis, clinical trials would require a sample of approximately 330 children. In contrast, the omega-3 fatty acid supplementation trials examining childhood ADHD employed 26 to 117 participants. Thus, insufficient power in the original trials likely account for the different conclusion reached in this meta-analysis.

The statistically significant benefits of omega-3 fatty acid supplementation are modest compared with the efficacy of currently available pharmacologic treatments for ADHD. For example, recent meta-analyses have estimated the effect sizes of commonly prescribed pharmacologic treatments for ADHD such as methylphenidate (effect size = 0.78, 95% CI 0.64–0.91), clonidine (effect size = 0.58, 95% CI 0.27–0.89), and atomoxetine (effect size = 0.64, 95% CI 0.51–0.76) to be higher.[5-7] Based on the currently available evidence, using omega-3 fatty acid supplementation in lieu of traditional pharmacologic treatments is not recommended in children with significant ADHD symptoms. However, given the evidence of modest efficacy of omega-3 fatty acid supplementation and its relatively benign side-effect profile, omega-3 fatty acid supplementation, particularly with higher doses of EPA, is a reasonable treatment strategy as augmentation to traditional pharmacotherapy or for those families reticent to use psychopharmacologic agents.

Meta-regression also demonstrated a significant association between efficacy and dose of EPA given in supplements. EPA and DHA are omega-3 fatty acids. Omega-3 fatty acids have anti-inflammatory properties.[15] Omega-3 fatty acids are also known to alter cell membrane fluidity in the central nervous system, which affects dopamine and serotonin neurotransmission.[17] It remains unclear why supplementation with EPA may improve ADHD symptoms, whereas supplementation with DHA may not to the same degree. Of note, EPA and not DHA supplementation has also been demonstrated to effective in omega-3 supplementation to treat depression.[48] Oxidized derivatives of DHA are known to have pro-inflammatory effects, whereas oxidized derivatives of EPA have anti-inflammatory effects.[49] Thus, in a situation of excess supplementation with omega-3 fatty acids, EPA would still produce anti-inflammatory effects, whereas DHA would not.

Although there was a significant effect of omega-3 fatty acid supplementation in treating ADHD symptomatology, there are several weaknesses and limitations to the present meta-analysis. In general, the clinical trials conducted in this area have been of rather poor quality, many with Jadad scores of 2 or 3, indicating potential issues with randomization, blinding, and/or tracking dropouts. In addition, many trials included in this analysis did not account for dropouts in their analysis method, which could introduce further bias into the results. Questions have been raised regarding the adequacy of blinding in early trials using fish oil because of a fishy aftertaste when the active formulations are refluxed.[50] Based on the data presented in the articles, it is not possible to evaluate the effectiveness of blinding in these trials. Inadequate blinding has the potential to introduce bias and can inflate estimates of efficacy. Despite these limitations of individual trials, overall meta-analysis demonstrates no evidence of publication bias, heterogeneity between trials, and effect of subject dropout or poor study quality. Likely some evidence of each of these phenomena would be present if any of these types of bias were driving the results. Statistical measurements of heterogeneity, publication bias, and the effects of subject dropout and study quality were not only statistically insignificant, they were negligible.

Overall this meta-analysis demonstrates a small but statistically significant benefit of omega-3 fatty acid supplementation in the treatment of ADHD. Furthermore, there was a significant association between EPA dose in supplements and its measured efficacy. Because of poor quality and potential issues of blinding in many of the included trials, further clinical trials are needed to replicate the results of this meta-analysis. In particular, clinical trials involving at least 330 children with ADHD are needed to demonstrate efficacy of these supplements. In addition, these trials should use supplements with high concentrations of EPA, an omega-3 fatty acid, given the evidence of a dose-response relation in meta-regression. Given omega-3 fatty acid supplementation's modest efficacy compared with other available pharmacologic treatments for ADHD, its use in lieu of traditional psychopharmacologic agents for ADHD is not recommended. However, given its relatively benign side-effect profile and evidence of modest efficacy, it may be reasonable to use omega-3 fatty supplementation to augment traditional pharmacologic interven-

tions or for families who decline all other psychopharmacologic options. &

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