Omega-3 Polyunsaturated Fatty Acids for Core Symptoms of Attention-Deficit/Hyperactivity Disorder:

A Meta-Analysis of Randomized Controlled Trials

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Abstract

Objective: Previous studies have shown conflicting results for the effectiveness of omega-3 polyunsaturated fatty acids (PUFAs) in improving attention-deficit/hyperactivity disorder (ADHD) symptoms. This inconsistency may be due to differences in dosage, composition, and treatment duration. The current meta-analysis aims to address this inconsistency by improving subtype analyses and focusing on heterogeneity in treatment duration, omega-3 PUFA composition, and eicosapentaenoic acid (EPA) dose.

Data Sources and Study Selection: We searched PubMed, EMBASE, PsycINFO, and Cochrane Library for randomized controlled trials of omega-3 PUFAs for ADHD, without publication year or language limitations, up to November 27, 2022. The primary outcome was the improvement of ADHD core symptoms. Subgroup analyses were conducted based on the formula, dosages, and composition ratios of omega-3 PUFAs. To ensure methodological quality, the Cochrane Risk-of-Bias Tool 1.0 was utilized to assess the risk of bias for each study included in the analysis. The pooled data were then analyzed using the random-effect meta-analysis, and the inverse variance method was employed.

Data Extraction: The outcomes of interest were extracted using a data extraction form developed for this study.

Results: Twenty-two studies with 1,789 participants were included in the analysis. Overall, omega-3 PUFAs did not significantly improve ADHD core symptoms compared to placebo (standardized mean difference [SMD]: −0.16; 95% CI, −0.34 to 0.01; $P=.07$). However, in the subgroup of studies with a treatment duration of at least 4 months, omega-3 PUFAs were significantly more effective than placebo (SMD: −0.35; 95% CI,−0.61 to −0.09; $P=.007$). Neither high eicosapentaenoic acid (EPA) dosage nor high EPA/docosahexaenoic acid (DHA) ratio was found to improve ADHD symptoms.

Conclusions: Our findings indicate that omega-3 PUFAs did not improve ADHD core symptoms, but long-term supplementation may have potential benefits. The main limitation of the study was the moderate heterogeneity and small sample sizes in subgroup analyses and the lack of dietary pattern information.

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Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder with persistent symptoms of difficulty sustaining attention, hyperactivity, and impulsivity that interfere with functioning or development.[1] It is a chronic condition that affects approximately 5% of children and adolescents globally.[2] According to the American Academy of Pediatrics recommendations for children aged 4 to 5 years, treatment should begin with parent- or teacher-administered behavioral therapy.[3] Simulants such as methylphenidate should be considered if behavioral interventions fail. For children aged 6 to 11 years, initial treatment should consider the combination of stimulants and behavioral therapy. However, some parents are concerned about the side effects of stimulants. Thus, it is necessary to evaluate alternative treatments in children with ADHD. In recent decades, there has been a growing interest in dietary interventions of polyunsaturated fatty acids (PUFAs), including omega-3 and omega-6. PUFAs are used in diverse medical conditions for their anti-inflammatory, antithrombotic, antiatherogenic, and vasodilation effects.[4,5] In addition, studies found lower

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Clinical Points

- This meta-analysis aims to resolve conflicting results regarding the effectiveness of omega-3 polyunsaturated fatty acids (PUFAs) in treating attention-deficit/hyperactivity disorder (ADHD) by analyzing subtypes and heterogeneity in dosage, composition, and treatment duration.
- Omega-3 PUFAs did not help improve ADHD core symptoms, but long-term omega-3 PUFA supplementation (≥4 months) might be effective in improving ADHD core symptoms.
- Selecting less severely ill ADHD patients is crucial for omega-3 PUFAs intervention, as they may have less urgency to achieve desired outcomes.

plasma levels of omega-3 PUFAs in children with ADHD, and omega-3 PUFAs supplementation may play a role in improving clinical symptoms in children with ADHD.[6,7]

Current evidence shows conflicting results for using omega-3 PUFAs to improve ADHD symptoms. A number of randomized controlled trials (RCTs) have been designed specifically to provide an evaluation of the effects of treatment with omega-3 PUFAs in children with ADHD.[8–30] Still, conflicting findings have been found on this issue. Inconsistency among systematic reviews and meta-analyses of RCTs might be explained by several factors.[31–34] First, in the included RCTs, the dose, composition, and source of omega-3 PUFAs varied, which may result in a heterogeneous effect. Second, the outcome of interest and methods were different among the studies. Finally, inconsistency between the findings of systematic reviews and meta-analyses may also derive from a wide variation of treatment duration across studies. Some of them performed treatment for as short as 1 month, while others investigated long-term PUFAs treatment.[14]

In the present study, we aimed to combine all the data from RCTs of omega-3 PUFAs intervention for children with ADHD using a meta-analysis to provide reliable and quantitative results of reducing ADHD symptoms with omega-3 PUFAs supplementation in children. Also, this study intends to clarify the effects of omega-3 PUFA doses, components (eicosapentaenoic acid [EPA] to docosahexaenoic acid [DHA] ratio), and duration of treatment on ADHD core symptoms.

METHODS

Inclusion and Exclusion Criteria

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered in PROSPERO (registration number CRD42022340218).[35] Only RCTs that assessed the clinical efficacy of omega-3 PUFAs for children with ADHD were included. No limitations were imposed regarding age, sex, race or ethnicity, types of omega-3 PUFAs, or duration of treatment. Studies were included if they met the following criteria: (i) included children with ADHD; (ii) used omega-3 EPA or DHA as an intervention; (iii) used a placebo, standard care, or other alternative treatment as a comparator; and (iv) reported clinical efficacy as a study outcome. The following were excluded: (i) non–double-blinded RCTs, (ii) studies that did not report the outcomes of interest, and (iii) nonhuman studies. In addition, studies that are still ongoing and do not have publication data were also excluded.

Search Strategy and Study Selection

PubMed, Embase, PsycINFO, Cochrane Central Register of Controlled Trials, and Airiti Library were searched from their inception to November 27, 2022. We also manually searched for additional eligible articles from the reference lists of relevant articles. Keywords were selected according to the PICO (population, intervention, comparison, outcome) method and Medical Subject Headings (MeSH) terms and were input for literature searching using Boolean operators. The detailed search strategies are listed in Supplementary Table 1. Two investigators (T.-H.L and J.-Y.W.) independently screened the titles and abstracts of the records collected using the aforementioned search strategies to identify and assess potentially eligible studies. Disagreements were resolved by a third investigator (P.-Y.H.). Full-text copies of potentially relevant articles were obtained and reviewed for eligibility.

Data Extraction

The following information was extracted: study design, study site, study duration, number of included patients, clinical symptoms, and risk of adverse events (AEs). The primary outcome was defined as the changes in ADHD core symptoms, according to various ADHD core symptoms scales. Two investigators (T.-H.L. and J.-Y.W.) independently collected the data for each included study.

Assessment of Study Quality and Risk of Bias

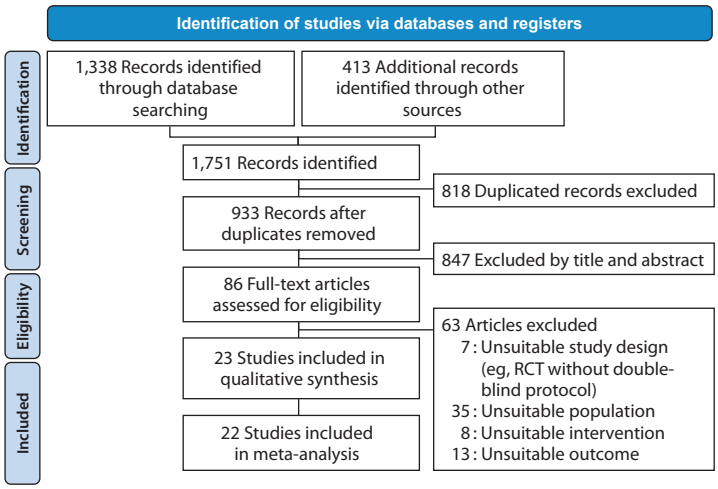
Two investigators (T.-H.L. and J.-Y.W.) independently assessed the risk of bias for each included study using the Cochrane Risk-of-Bias Tool 1.0.[36] Disagreements were resolved through discussion and consensus with a third investigator (P.-Y.H.). The overall certainty of the evidence was evaluated using Grading of Recommendations Assessment, Development, and Evaluation (GRADE).[37]

Statistical Analysis

We calculated the standardized mean difference (SMD) with a 95% confidence interval (CI) for the primary outcome and risk ratio (RR) for the risk of adverse effects. We conducted a subgroup analysis to explore how sensitive results were to reasonable changes in assumptions made if significant heterogeneity existed

Figure 1.

Meta-Analysis Flow-Chart Diagram According to the PRISMA Guideline



Abbreviation: RCT = randomized controlled trial.

in the primary outcome. Random-effect meta-analyses using the inverse variance method were performed to pool the data.[38,39] Heterogeneity was assessed using the Cochran *Q* test and quantified with the I^2 statistic. Heterogeneity was categorized as low ($I^2 \leq 25\%$), moderate ($25\% < I^2 < 75\%$), or high ($I^2 \geq 75\%$).[40,41] All *P* values were 2-tailed, with a significance level set at .05 except for the determination of a statistical test for heterogeneity that employed .1. All analyses were performed using Review Manager software version 5.4 (Nordic Cochrane Centre, Cochrane Collaboration) and STATA (Version 16; 2019; College Station, TX; Stata Corp LP).

RESULTS

Search Results

Initially, 1,751 studies were identified from PubMed, Embase, PsycINFO, Cochrane Central Register of Controlled Trials, and Airiti Library. After exclusion of 818 duplicate articles, 933 articles were screened, 847 of which were excluded based on the title and abstract. The 86 remaining articles underwent a full-text review to assess their eligibility. Finally, 23 RCTs met our inclusion criteria, and 22 RCTs with 1,789 participants provided quantitative data for meta-analysis. The algorithm for study selection is shown in Figure 1.[8–25,27–30]

Characteristics of Included Studies

The main characteristics of the selected studies are listed in Table 1. In the 22 studies eligible for primary outcome analysis, the age of children with ADHD ranged from 7 to 12 years old. The omega-3 PUFAs supplement was administered orally in all 22 RCTs, with either DHA, EPA, or combined supplements with both types of omega-3 PUFAs. The intervention duration lasted between 4 weeks and 12 months. In 6 studies,[10,20–22,24,29] the children were also treated with stimulants in both intervention and control groups, with omega-3 PUFAs as an add-on treatment.

Risk of Bias Assessment

The risk of bias assessment of the included RCTs was illustrated in Supplementary Figure 1. One study[18] demonstrated a high risk of bias in 3 domains, while 1 study[25] demonstrated a high risk of bias in 2 domains, and 4 studies[11,15,22,27] demonstrated a high risk of bias in only 1 domain. Incomplete outcome reporting, selective reporting, and methods of blinding for outcome assessment were the major sources of bias. Studies that did not adequately describe the methods of random sequence generation and allocation concealment were rated as having an unclear risk of bias in these domains.[9–11,13,14,16,22–27,29,30]

Primary Outcome: Effects of Omega-3 PUFAs in Improving ADHD Core Symptoms

Twenty-two RCTs with 1,789 participants provided data for this outcome. Omega-3 PUFAs did not significantly improve the parent-rated ADHD core symptoms compared to the control group (SMD: −0.16; 95% CI, −0.34 to 0.01; $P = .07$) (Figure 2). The statistical heterogeneity across the included RCTs was significant ($I^2 = 69\%$; $P < .001$).

Secondary Outcome: Comparison of ADHD Core Symptoms at Baseline and the End of the Study

In both the omega-3 PUFAs group and the control group, the parent-rated ADHD core symptoms were significantly improved at the end of the study compared

Table 1.
Summary of the Baseline Characteristics of the Included Studies

First Author, Year	Country	Sample Size, n (% Male)	EPA, mg/d	DHA, mg/d	Omega-3, mg/d	Intervention Duration, mo	Age, Mean ± SD, y	Clinical Symptom Measurements
Carucci, 2022[8]	Italy	160 (74%)	558	174	732	12	9.7 ± 1.9	ADHD-RS-IV total
Chang, 2019[9]	Taiwan	92 (86%)	1,200	0	1,200	3	9.5 ± 3.1	SNAP-IV
Crippa, 2019[13]	Italy	50 (92%)	0	1,000	1,000	6	O: 11.1 ± 1.9; P: 10.9 ± 1.4	ADHD-RS-IV Parent
Döpfner, 2021[15]	Germany	40 (70%)	372	116	488	4	5.6 ± 0.6	FBB-ADHS-V
Mohammadzadeh, 2019[21]	Iran	O: 33 (70%); P: 33 (79%)	360	240	600	2	O: 7.7 ± 1.7; P: 8.2 ± 1.7	ADHD-RS-IV Parent
Rodriguez, 2019[23]	Spain	66 (71%)	180	2,000	2,180	6	11.7 ± 3.1	EDAH version for families
Cornu, 2018[12]	France	162 (78%)	504	126	630	3	9.9 ± 2.6	ADHD-RS-IV
Assareh, 2017[10]	Iran	40 (67%)	33	241	274	2.5	9.1 ± 2.0	ADHD-RS-IV
Kean, 2017[17]	Australia	144 (85%)	29.2	22	51.2	3.5	8.7 ± 2.2	CPRS scores
Moghaddam, 2017[20]	Iran	40 (83%)	360	240	600	2	O: 9.5 ± 2.0; P: 8.9 ± 1.6	ADHD-RS-IV
Salehi, 2016[24]	Iran	150 (74%)	200	0	200	2	O: 8.6 ± 1.7; P: 9.1 ± 2.2	CPRS
Anand, 2016[29]	India	50 (70%)	NR	120	120	4	6.0 ± 2.1	CPRS
Bos, 2015[11]	Netherlands	40 (100%)	650	650	1,300	4	10.3 ± 2.0	CBCL for ADHD
Milte, 2015[19]	Australia	90 (77%)	1,373	1,140	2,513	4	8.9 ± 1.7	CPRS
Dashti, 2014[14]	Iran	56 (55%)	1,000	0	1,000	1	8.2 ± 1.7	CPRS
Widenhorn-Müller, 2014[28]	Germany	95 (79%)	1,200	240	1,440	4	O: 8.9 ± 1.5; P: 8.9 ± 1.2	DISYPS-II questionnaire
Behdani, 2013[30]	Iran	69 (80%)	360	240	600	2	8.7 ± 1.7	ADHD-RS-IV
Perera, 2012[22]	Lanka	O: 48 (71%); P: 46 (76%)	NR	NR	592.74	6	O: 9.4 ± 1.5; P: 9.2 ± 1.5	SNAP-IV
Manor, 2012[18]	Israel	O: 100 (72%); P: 47 (68%)	80	40	120	3.75	O: 9.2 ± 2.0; P: 9.2 ± 1.8	CPRS
Gustafsson, 2010[16]	Sweden	92 (83%)	500	2.7	502.7	3.75	7–12 years were recruited	CPRS
Vaisman, 2008[27]	Israel	42 (71%)	NR	NR	250	3	O: 9.4 ± 1.1; P: 9.3 ± 1.3	CPRS
Sinn, 2007[25]	Australia	104 (74%)	558	174	732	3.75	O: 9.4 ± 1.9; P: 9.7 ± 1.9	Conners ADHD Index

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ADHD-RS-IV = ADHD Rating Scale-IV, CBCL = Child Behavior Checklist, CPRS = Conners' Parent Rating Scale, DISYPS II = Diagnostic System for Psychiatric Disorders in Children and Adolescents II, DHA = docosahexaenoic acid, EDAH version for families = Escala de Déficit de Atención e Hiperactividad Scale of Attention Deficit and Hyperactivity, EPA = eicosapentaenoic acid, FBB-ADHS-V = the German ADHD Rating scale, NR = not reported, O = omega-3 polyunsaturated fatty acids group, P = placebo group, SNAP-IV = Swanson, Nolan and Pelham Questionnaire.

with baseline. The SMD was 0.81 (95% CI, 0.71 to 0.82; $P < .001$) and 0.75 (95% CI, 0.68 to 0.83; $P < .001$) in the omega-3 PUFAs and control groups, respectively (Figure 3). There were no significant differences between the omega-3 PUFAs and the control group ($P = .107$).

Adverse Effects

Six RCTs provided data concerning this outcome (Supplementary Figure 2). Only minor adverse effects, such as diarrhea and abdominal discomfort, were reported. Overall, there were no significant differences in the incidence of adverse effects between the omega-3 PUFAs group and the control group (diarrhea: RR = 0.89; 95% CI, 0.27 to 2.94; $P = .84$; abdominal discomfort: RR = 0.73; 95% CI, 0.17 to 3.21; $P = .68$).

Subgroup Analysis

The heterogeneity of the results prompted further subgroup analyses of the meta-analysis of parent-rated ADHD core symptoms. In the subgroup analysis of patients receiving ≥ 4 months of treatment, omega-3 PUFAs were associated with a significantly more improvement of parent-rated ADHD core symptoms than placebo (SMD: −0.35; 95% CI, −0.61 to −0.09; $P = .007$) (Figure 4A). However, no statistically significant differencewas observed between the two groups in the subgroup analysis of those receiving treatment less than 4 months of treatment (SMD: −0.04; 95% CI, −0.26 to −0.18; $P = .73$) (Figure 4A). Meanwhile, a significant difference was found in the parent-rated ADHD core symptoms between the different subgroups of treatment duration ($P = .07$).

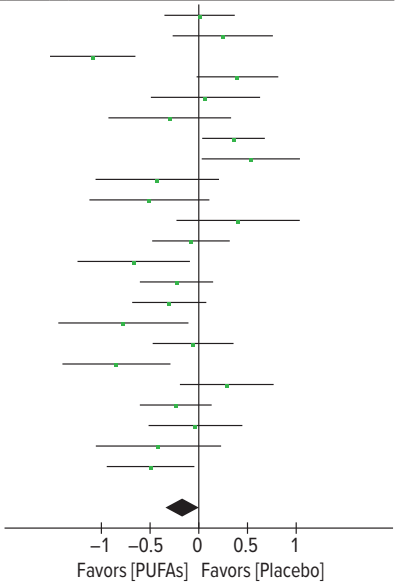
In addition, we also performed subgroup analysis according to the dosage of EPA (≥ 500 mg and < 500 mg; ≥ 1,000 mg and < 1,000 mg) and the ratio of EPA/DHA (≥ 2 and < 2). Neither of the subgroups found significant differences between omega-3 PUFAs and placebo (EPA dosage ≥ 500 mg: SMD: −0.14; 95% CI, −0.41 to 0.12; $P = .3$; EPA dosage < 500 mg: SMD: −0.16; 95% CI, −0.41 to 0.09; $P = .92$; EPA dosage ≥ 1,000 mg: SMD: −0.22; 95% CI, −0.67 to 0.22; $P = .33$; EPA dosage < 1,000 mg: SMD: −0.14; 95% CI, −0.34 to 0.06; $P = .18$; EPA/DHA ratio ≥ 2: SMD: −0.11; 95% CI, −0.31

Figure 2.

The Forest Plot Depicts the Efficacy of Omega-3 Polyunsaturated Fatty Acids Supplements in Improving Parent-Rated Attention-Deficit/Hyperactivity Disorder Core Symptoms

Study or Subgroup (First Author)	PUFAs Mean	PUFAs SD	PUFAs Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std Mean Difference IV, Random [95% CI]
Carucci, 2022[8]	−4.48	9.08	62	−4.56	9.89	60	5.2%	0.01 [0.35 to 0.36]
Mohammadzadeh, 2019[21]	−24.8	8.66	31	−26.84	7.63	29	4.2%	0.25 [−0.26 to 0.75]
Rodriguez, 2019[23]	−3.3	4.91	46	1.6	4	49	4.7%	−1.09 [−1.52 to −0.66]
Chang, 2019[9]	−4.37	10.12	48	−8.41	10.07	44	4.8%	0.40 [−0.02 to 0.81]
Crippa, 2019[13]	−4.64	9.9	25	−5.43	12.57	25	4.0%	0.07 [−0.49 to 0.62]
Döpfner, 2019[15]	−0.33	0.54	20	−0.15	0.64	20	3.6%	−0.30 [−0.92 to 0.33]
Cornu, 2018[12]	−3.7	9.2	77	−7.5	11.8	80	5.4%	0.36 [0.04 to 0.67]
Kean, 2017[17]	−6.89	11.71	29	−13.39	12.26	36	4.3%	0.53 [0.04 to 1.03]
Moghaddam, 2017[20]	−8.8	7.86	20	−6.3	2.09	20	3.6%	−0.43 [−1.05 to 0.20]
Kean, 2017[17]	−10.74	11.92	23	−4.7	11.43	20	3.7%	−0.51 [−1.12 to 0.10]
Assareh, 2017[10]	−21	7.94	20	−24	6.56	20	3.6%	0.40 [−0.22 to 1.03]
Salehi, 2016[24]	−19.6	9.21	50	−18.9	8.06	50	4.9%	−0.08 [−0.47 to 0.31]
Anand, 2016[29]	−2.5	2.17	25	−1	2.25	25	3.9%	−0.67 [−1.24 to −0.10]
Milte, 2015[19]	−8.2	8.78	56	−6.2	8.59	57	5.1%	−0.23 [−0.60 to 0.14]
Milte, 2015[19]	−10.3	14.83	54	−6.2	11.95	57	5.0%	−0.30 [−0.68 to 0.07]
Bos, 2015[11]	−1.2	3.05	19	1.1	2.76	19	3.4%	−0.77 [−1.44 to −0.11]
Widenhorn-Müller, 2014[28]	-0.33	0.54	45	−0.3	0.48	47	4.8%	−0.06 [−0.47 to 0.35]
Dashti, 2014[14]	−7.45	9.26	28	0.08	8.28	28	4.0%	−0.85 [−1.39 to −0.30]
Behdani, 2013[30]	−12.44	5.34	36	−14	5.4	33	4.4%	0.29 [−0.19 to 0.76]
Manor, 2011[18]	−5.36	9.46	98	−3.1	9.61	42	5.1%	−0.24 [−0.60 to 0.13]
Gustafsson, 2010[16]	−7.2	17.64	46	−6.6	17.1	27	4.4%	−0.03 [−0.51 to 0.44]
Vaisman, 2008[27]	−5	8.32	18	−2.35	3.73	21	3.5%	−0.41 [−1.05 to 0.22]
Sinn, 2007[25]	−4.9	6.69	77	−1.7	5.54	27	4.6%	−0.50 [−0.94 to −0.05]
Total (95% CI)			953			836	100.0%	-0.16 [−0.34 to 0.01]

Heterogeneity: Tau' = 0.12; $X^2 = 71.36$, $df = 22$ ($P < .00001$); $I^2 = 69\%$
Test for overall effect: $Z = 1.83$ ($P = .07$)

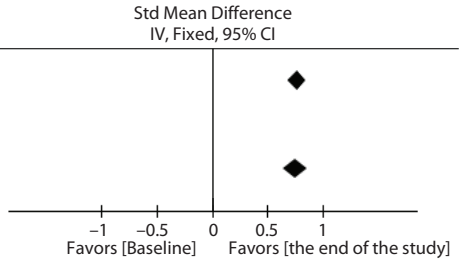


Abbreviations: PUFA = polyunsaturated fatty acid, Std = standardized.

Figure 3.

Forest Plots Demonstrate the Secondary Outcomes Comparing Attention-Deficit/Hyperactivity Disorder Core Symptoms at the Baseline and the end of the Study

Study or Subgroup	Std Mean Difference IV, Fixed, 95% CI
2.1. PUFAs group	0.81 [0.71 to 0.82]
Heterogeneity: $X^2 = 103.02$, $df = 18$ ($P < .001$); $I^2 = 82.6\%$	
Test for overall effect: $Z = 14.43$ ($P < .001$)	
2.2. Placebo group	0.75 [0.68 to 0.83]
Heterogeneity: $X^2 = 210.41$, $df = 18$ ($P < .001$); $I^2 = 91.1\%$	
Test for overall effect: $Z = 11.22$ ($P < .001$)	
Test for subgroup differences: $df = 1$ ($P = .107$)	



Abbreviations: IV = inverse variance, PUFA = polyunsaturated fatty acid, Std = standardized.

to 0.09; $P = .29$; EPA/DHA ratio < 2: SMD: −0.20; 95% CI, −0.53 to 0.13; $P = .64$) (Figures 4B, 4C, and 4D).

Publication Bias and Certainty of Evidence (GRADE)

The funnel plot was symmetric (Supplementary Figure 3) by visualization, and no potential publication bias was observed among the included RCTs. Based on the GRADE (Supplementary Figure 4) framework, the primary outcome was judged to be low certainty of evidence.

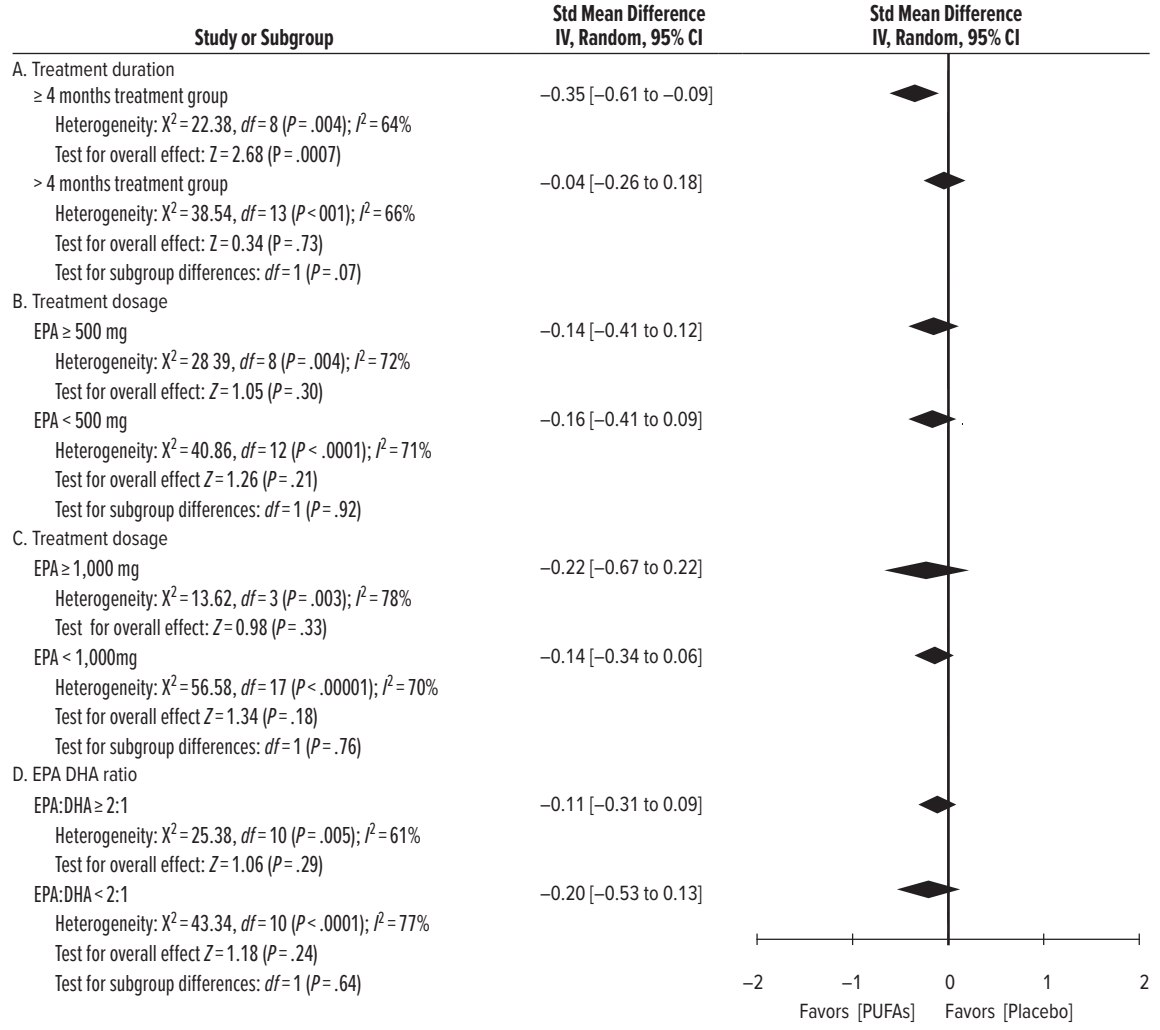
DISCUSSION

This study investigating the clinical efficacy of omega-3 PUFAs in treating ADHD had several significant findings. First, the meta-analysis involving 22 RCTs demonstrated that the omega-3 PUFAs supplement did not significantly improve ADHD core symptoms. Second, the subgroup analysis of patients receiving omega-3 PUFAs supplementation greater than or equal to 4 months showed a significant improvement in the parent-rated ADHD core symptoms compared to the control group. Finally, there was no significant difference in increasing the risk of adverse effects following the use of omega-3 PUFAs, including diarrhea and gastrointestinal discomfort, so omega-3 PUFAs are as tolerable as the comparator in this clinical entity.

The findings from studies of omega-3 PUFAs in children with ADHD have been controversial. Some studies have shown no beneficial effects, while others

Figure 4.

The Forest Plot Shows Subgroup Analyses of the Parent-Rated Attention-Deficit/Hyperactivity Disorder Core Symptoms According to Treatment Duration, Omega-3 Polyunsaturated Fatty Acids (PUFAs) Dosage, and Omega-3 PUFAs Components



Abbreviations: DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, IV = inverse variance, Std = standardized.

have found improvement in clinical symptoms. Our result was consistent with that of the Cochrane review by Gilles et al published in 2012.[34] Although an increased number of RCTs investigating the use of omega-3 PUFAs as a treatment for ADHD and with larger sample sizes were included in the present study, the overall conclusion remains the same. The latest meta-analysis from Händel et al[32] found a statistically small but positive effect on the improvement of parent-rated ADHD core symptoms (SMD: −0.17; 95% CI, −0.32 to −0.02; $P = .02$), which was different from our finding (SMD: −0.16; 95% CI, −0.34 to 0.01; $P = .07$). This discrepancy may be due to the fact that they included all studies using PUFAs, while we focused specifically on omega-3 EPA and DHA. Additionally, while they used post-intervention scores for their analysis, our study adopted change-from-baseline scores. Change-from-baseline outcomes are more efficient and powerful than the comparison of post-intervention values, as they remove a component of between-person variability from the analysis.[38] When comparing our study with others showing that omega-3 PUFAs improve ADHD symptoms, we found methodological differences. In 2 reviews[42,43] and a RCT[9] showing beneficial effects, we found a lack of methodological quality assessment of the included studies, which may lead to the misinterpretation of the results and could not provide certainty of evidence using the GRADE approach.

In the subgroup analysis according to the duration of omega-3 PUFAs treatment, significant ADHD core symptom improvement was observed in the long-term treatment group. Though no previous study focused on the optimal omega-3 PUFAs treatment duration in children with ADHD, animal studies suggested long-term omega-3 PUFAs supplementation might be more effective in

improving cognitive function in patients with Alzheimer's disease compared to short-term treatment.[44] Moreover, a previous study[45] has shown that the long-term effect of omega-3 PUFAs supplementation may be beneficial for the onset of cardiac death, sudden death, and myocardial infarction. This finding may be due to the change in tissue lipid composition as well as to the fact that the beneficial antioxidant, anti-inflammatory, and antiatherogenic properties of omega-3 PUFAs may take time to manifest. As the red blood cell survives about 120 days in the body, less than 120 days of supplementation might not be long enough to change the omega-3 PUFAs compositions.[33] In addition, the turnover of fatty acids in the brain of 6- to 12-year-old children is relatively low, which might require a more extended period of supplementation or more supplementation to change the concentration of fatty acids in the central nervous system.[46] However, the pathway and how long it takes for optimal levels of omega-3 PUFAs to be reached in the brain remained unclear.

Omega-3 PUFAs supplementation dosage in our meta-analysis ranged from 2.7 to 2,000 mg of DHA and 29 to 1,373 mg of EPA, with 3 studies using EPA and 1 using DHA as the only source of omega-3 PUFAs supplementation. Subgroup analysis found that neither EPA dosage greater than 500 mg, EPA dosage greater than 1,000 mg, nor a combination of EPA/ DHA at a ratio higher than 2 improved ADHD core symptoms significantly. This finding was consistent with those of the study by Chang et al,[9] which showed that high EPA dosage of 1,200 mg/d did not improve core symptoms but improved cognitive function instead. Some trials focusing on personalized medicine found that omega-3 PUFAs supplementation might benefit only children with ADHD with low EPA levels.[31] Further studies with larger sample sizes are needed to clarify the optimal dosage and the effectiveness of omega-3 PUFAs.

Strengths and Limitations of the Current Review

Our study provides a comprehensive meta-analysis of the latest RCTs that addresses the important clinical question of whether omega-3s should be considered as a part of the armamentarium for ADHD. Second, we conducted subgroup analyses based on treatment duration, intervention dosage, and PUFAs components to shed light on the potential sources of controversy in past research. To our knowledge, this meta-analysis is the first to investigate the effects of long-term omega-3 PUFAs supplementation and EPA dosage greater than 1,000 mg on ADHD core symptoms. Third, our findings have important implications for clinicians and caregivers, as they can assist in measuring the possible benefits and cost-effectiveness of using omega-3 PUFAs as a supplement to treat children with ADHD. Fourth, this study could provide valuable guidance for the treatment of ADHD. Our findings indicate that short-term supplementation with omega-3 PUFAs may not result in a significant improvement in core symptoms of ADHD. In contrast, stimulant agents are known to produce faster and more noticeable improvements, which are evident within a few days and can be observed by parents and teachers in children. Therefore, if omega-3s are considered as a treatment option, it is crucial to inform patients and their parents that the effects may take longer to appear compared to those of standard stimulants. Additionally, the selection of patients for this intervention is of paramount importance, with individuals having a less severe form of ADHD being more suitable candidates, as they may have less urgency to achieve desired outcomes.

Nevertheless, our study results should be interpreted cautiously because of the following limitations. First, moderate to high heterogeneity was noticed among the included studies. Thus, we performed subgroup analyses according to EPA dosage, omega-3 PUFAs components, and treatment duration to elucidate the heterogeneity. However, heterogeneity remained moderate. Second, a trial sequential analysis (TSA) can help assess whether further trials need to be conducted. However, due to various ADHD core symptoms scales, pooled results have been expressed as SMD, and the TSA program does not facilitate meta-analysis of SMDs.[47] Third, the lack of dietary pattern information and baseline serum EPA levels might lead us to underestimate the efficacy of omega-3 PUFAs. Finally, while we used a 4-month cutoff point, we recognize that this may have limitations and encourage further exploration of different cutoff points in future investigations. Nonetheless, this systematic review and meta-analysis strictly followed the guidelines of the Cochrane Collaboration and PRISMA, and the protocol was pre-registered at PROSPERO to ensure high methodological quality.

CONCLUSION

Based on low certainty of evidence, omega-3 PUFAs may not improve ADHD core symptoms. However, long-term supplementation (≥ 4 months) can be effective. Therefore, we recommend careful selection of patients for this intervention. Individuals who have a less severe form of ADHD may be more suitable candidates, as they may have less urgency to achieve desired outcomes. In addition, omega-3 PUFAs are also tolerable in children with ADHD. However, further research with larger samples and longer treatment duration is needed to clarify the duration, efficacy, and optimal dosage of omega-3 PUFAs in children with ADHD.

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The Journal of Clinical Psychiatry

Supplementary Material

Article Title: Omega-3 Polyunsaturated Fatty Acids for Core Symptoms of Attention-Deficit/Hyperactivity Disorder: A Meta-Analysis of Randomized Controlled Trials

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

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Supplementary Table 1. Search Strategy **Database:**

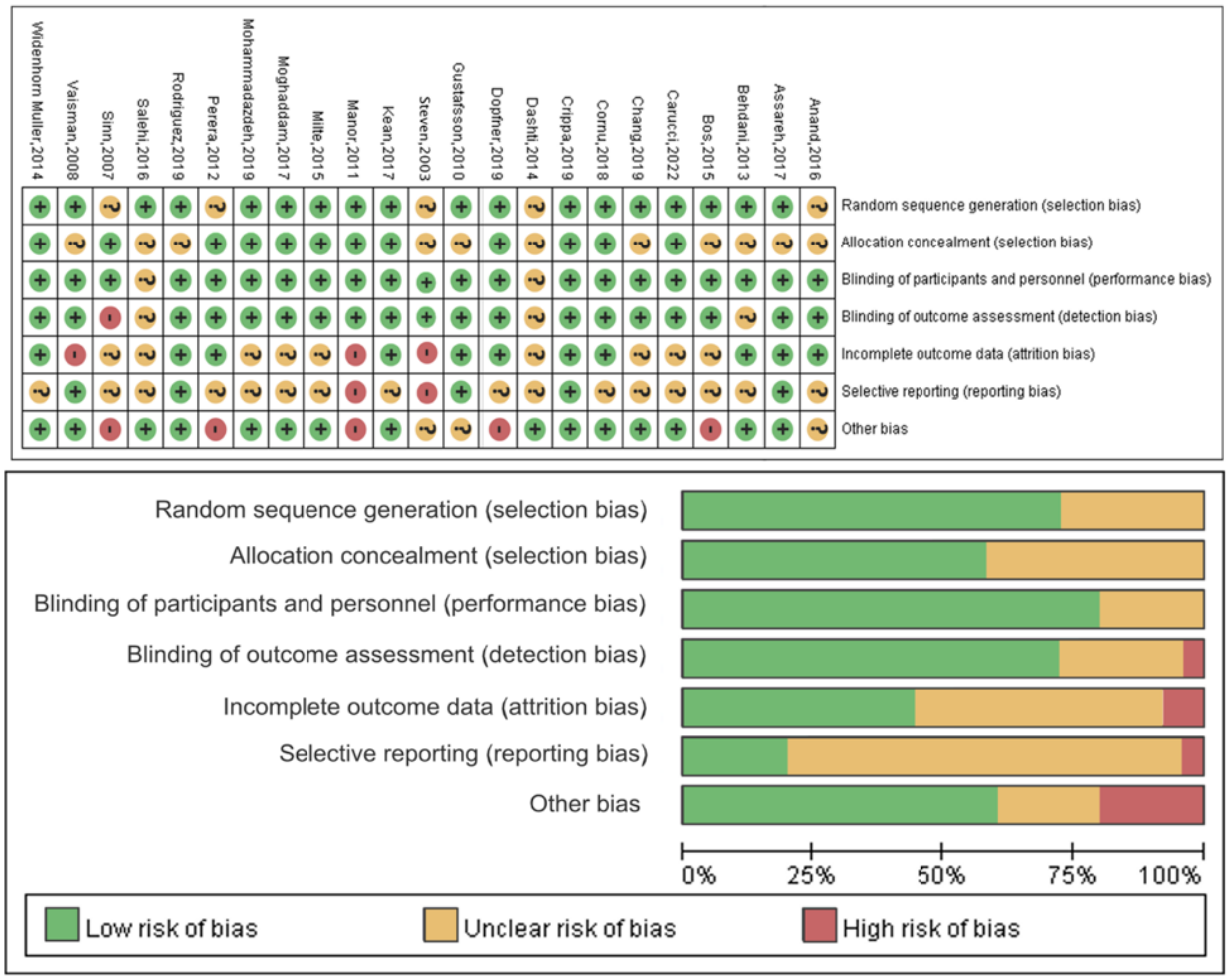
PubMed

No	Query	Results
#1	"fatty acids, omega 3"[MeSH Terms] OR "fatty acids, unsaturated"[MeSH Terms]	239, 043
#2	"fatty acids, unsaturated"[MeSH Terms] OR ("fatty"[All Fields] AND "acids"[All Fields] AND "unsaturated"[All Fields]) OR "unsaturated fatty acids"[All Fields] OR "pufas"[All Fields] OR "pufa s"[All Fields] OR "Polyunsaturated fatty acid"[All Fields] OR "omega-6"[All Fields] OR ("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"[All Fields]) OR "Docosahexaenoic acid"[All Fields] OR "Eicosapentaenoic acid"[All Fields] OR ("eur policy anal"[Journal] OR "epa"[All Fields]) OR "DHA"[All Fields]	286,550
#3	"Attention Deficit Disorder with Hyperactivity"[All Fields] OR ("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 "adhd"[All Fields])	46, 514
#4	("fatty acids, unsaturated"[MeSH Terms] OR ("fatty"[All Fields] AND "acids"[All Fields] AND "unsaturated"[All Fields]) OR "unsaturated fatty acids"[All Fields] OR "pufas"[All Fields] OR "pufa s"[All Fields] OR "Polyunsaturated fatty acid"[All Fields] OR "omega-6"[All Fields] OR ("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"[All Fields]) OR "Docosahexaenoic acid"[All Fields] OR "Eicosapentaenoic acid"[All Fields] OR ("eur policy anal"[Journal] OR "epa"[All Fields]) OR "DHA"[All Fields] OR ("fatty acids, omega 3"[MeSH Terms] OR "fatty acids, unsaturated"[MeSH Terms])) AND ("Attention Deficit Disorder with Hyperactivity"[All Fields] OR ("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 "adhd"[All Fields]))	362

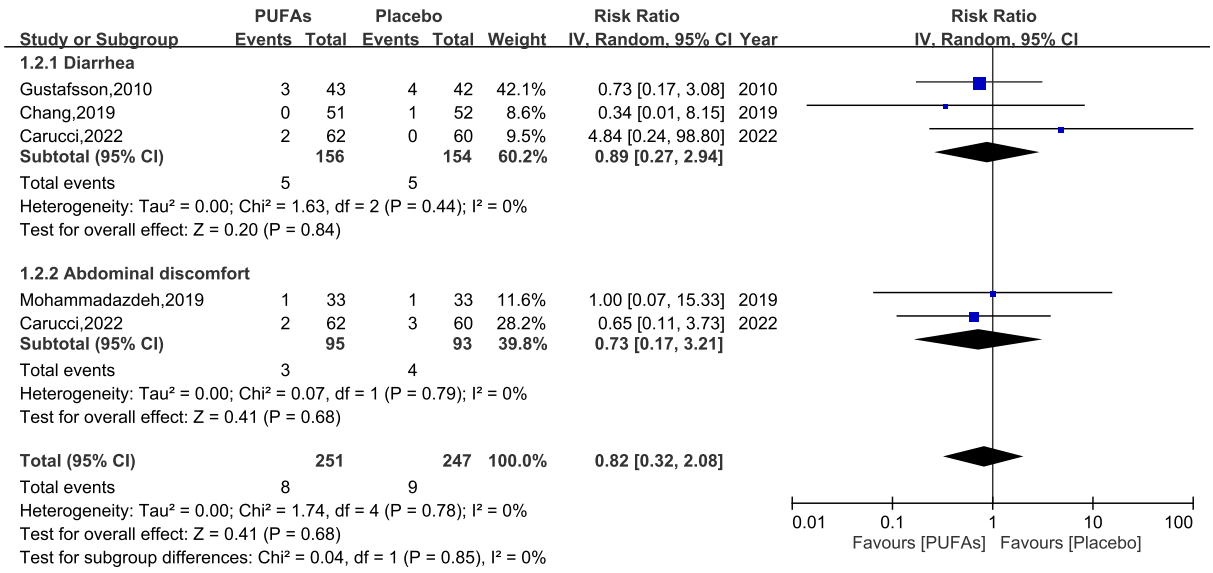
Database: Embase

No	Query	Results
#1	'attention deficit hyperactivity disorder'/exp OR 'adhd' OR 'attention deficit' OR 'attention deficit and disruptive behavior disorders' OR 'attention deficit and disruptive behaviour disorders' OR 'attention deficit disorder' OR 'attention deficit disorder with hyperactivity' OR 'attention deficit hyperactivity disorder'	81, 024
#2	'omega 3 fatty acid'/exp OR 'bilantin omega' OR 'conchol	98, 675

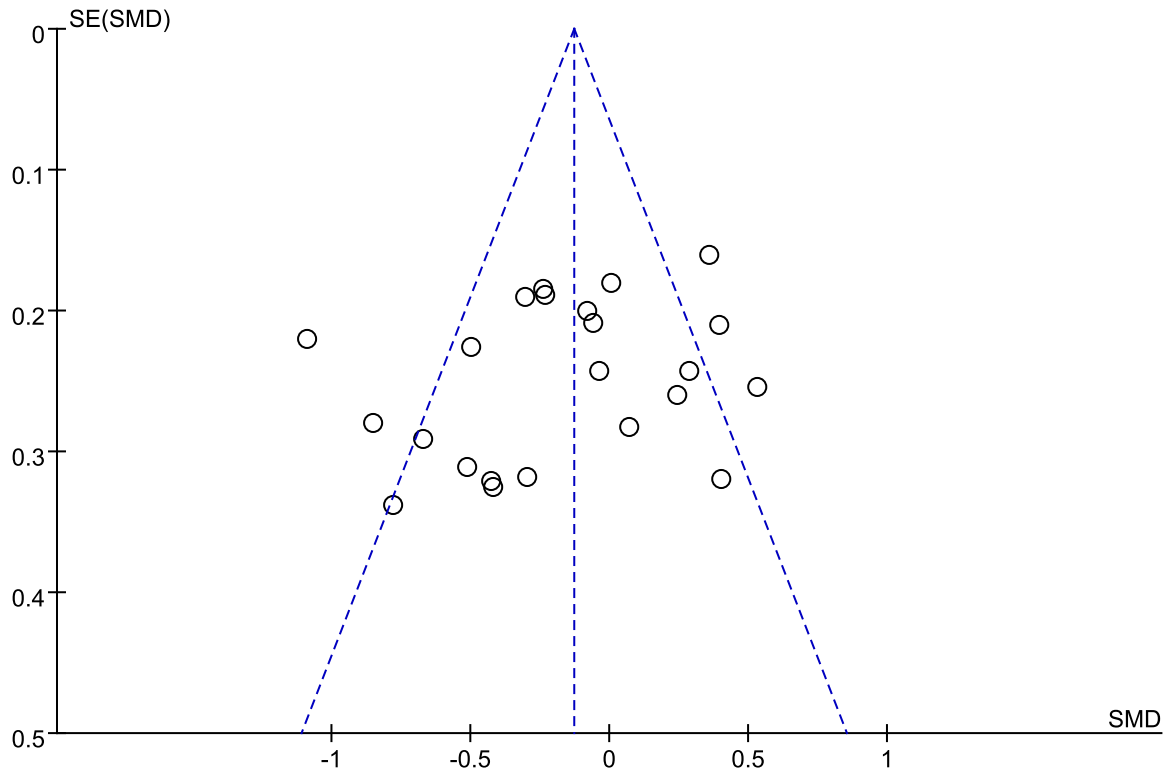
	36' OR 'eicosae' OR 'eicosapen' OR 'epaisdin' OR 'epanova' OR 'fatty acids, omega 3' OR 'fatty acids, omega-3' OR 'n 3 fatty acid' OR 'n 3 polyunsaturated fatty acid' OR 'omega 3' OR 'omega 3 carboxylic acid' OR 'omega 3 carboxylic acids' OR 'omega 3 fatty acid' OR 'omega 3 feingold' OR 'omega 3 plus'OR 'omega 3 polyunsaturated fatty acid' OR 'omega forte' OR 'omega-3-carboxylic acids' OR 'omega3 polyunsaturated fatty acid' OR 'sakana' OR 'sanhelios omega 3' OR 'docosahexaenoic acid'/exp OR 'dhasco' OR 'docosahexaenoate' OR 'docosahexaenoic acid' OR 'docosahexaenoic acids' OR 'docosahexenoic acid' OR 'fish oil'/exp OR 'ameu' OR 'efamed'OR 'epax' OR 'epax 5000' OR 'feniko' OR 'fish oil' OR 'fish oils' OR 'himega' OR 'k 85' OR 'k 85 fish oil preparation' OR 'lachs 550' OR 'lipitac' OR 'maxepa' OR 'olemar' OR 'omegaven' OR 'optimepa' OR 'pikasol' OR 'promega' OR 'super epa'OR 'superepa' OR 'tuna oil' OR 'polyunsaturated fatty acid'/exp OR 'fatty acid polyunsaturation' OR 'fatty acid, polyunsaturated' OR 'poly unsaturated fatty acid' OR 'polyunsaturated fat' OR 'polyunsaturated fatty acid'	
#3	**(**'attention deficit hyperactivity disorder'/exp OR 'adhd' OR 'attention deficit' OR 'attention deficit and disruptive behavior disorders' OR 'attention deficit and disruptive behaviour disorders' OR 'attention deficit disorder' OR 'attention deficit disorder with hyperactivity' OR 'attention deficit hyperactivity disorder') AND ('omega 3 fatty acid'/exp OR 'bilantin omega'OR 'conchol 36' OR 'eicosa e' OR 'eicosapen' OR 'epaisdin' OR 'epanova' OR 'fatty acids, omega 3' OR 'fatty acids, omega-3' OR 'n 3 fatty acid' OR 'n 3 polyunsaturated fatty acid' OR 'omega 3' OR 'omega 3 carboxylic acid' OR 'omega 3 carboxylic acids' OR 'omega 3 fatty acid' OR 'omega 3 feingold' OR 'omega 3 plus' OR 'omega 3 polyunsaturated fatty acid' OR 'omega forte' OR 'omega-3-carboxylic acids' OR 'omega3 polyunsaturated fatty acid' OR 'sakana' OR 'sanhelios omega 3' OR 'docosahexaenoic acid'/exp OR 'dhasco' OR 'docosahexaenoate' OR 'docosahexaenoic acid' OR 'docosahexaenoic acids' OR 'docosahexenoic acid' OR 'fish oil'/exp OR 'ameu' OR 'efamed' OR 'epax' OR 'epax 5000' OR 'feniko' OR 'fish oil' OR 'fish oils' OR 'himega' OR 'k 85' OR 'k 85 fish oil preparation' OR 'lachs 550' OR 'lipitac' OR 'maxepa' OR 'olemar' OR 'omegaven' OR 'optimepa' OR 'pikasol' OR 'promega' OR 'super epa' OR 'superepa' OR 'tuna oil'OR 'polyunsaturated fatty acid'/exp OR 'fatty acid polyunsaturation' OR 'fatty acid, polyunsaturated' OR 'poly unsaturated fatty acid' OR 'polyunsaturated fat' OR 'polyunsaturated fatty acid')	758



Supplementary Figure 1. Methodological quality assessment of the included studies (Cochrane risk-of-bias tool 1.0).



Supplementary Figure 2. Forest plots demonstrate the risk of adverse effect (delete total here because one patient may have diarrhea and abdominal discomfort at the same time)



Supplementary Figure 3. The funnel plot shows the visual check for publication bias on the risk of incidence of delirium.

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With [comparison]	With [intervention]		Risk with [comparison]	Risk difference with [intervention]
Parent-rated ADHD core symptoms											
1789 (22 RCTs)	serious	serious	not serious	not serious	none	⨁⨁◯◯ Low	836	953	-	-	SMD **0.16 SD lower** (0.34 lower to 0.01 higher)

CI: confidence interval; **SMD:** standardised mean difference

Supplementary Figure 4. GRADE assessment