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Polyunsaturated fatty acids (PUFA) for attention deficit hyperactivity disorder (ADHD) in children and adolescents (Review)

Gillies D, Leach MJ, Perez Algorta G

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[Intervention Review]

Polyunsaturated fatty acids (PUFA) for attention deficit hyperactivity disorder (ADHD) in children and adolescents

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ABSTRACT

Background

Attention deficit hyperactivity disorder (ADHD) is a major problem in children and adolescents, characterised by age-inappropriate levels of inattention, hyperactivity, and impulsivity, and is associated with long-term social, academic, and mental health problems. The stimulant medications methylphenidate and amphetamine are the most frequently used treatments for ADHD, but these are not always effective and can be associated with side effects. Clinical and biochemical evidence suggests that deficiencies of polyunsaturated fatty acids (PUFA) could be related to ADHD. Research has shown that children and adolescents with ADHD have significantly lower plasma and blood concentrations of PUFA and, in particular, lower levels of omega-3 PUFA. These findings suggest that PUFA supplementation may reduce the attention and behaviour problems associated with ADHD. This review is an update of a previously published Cochrane Review. Overall, there was little evidence that PUFA supplementation improved symptoms of ADHD in children and adolescents.

Objectives

To compare the efficacy of PUFA to other forms of treatment or placebo in treating the symptoms of ADHD in children and adolescents.

Search methods

We searched 13 databases and two trials registers up to October 2021. We also checked the reference lists of relevant studies and reviews for additional references.

Selection criteria

We included randomised and quasi-randomised controlled trials that compared PUFA with placebo or PUFA plus alternative therapy (medication, behavioural therapy, or psychotherapy) with the same alternative therapy alone in children and adolescents (aged 18 years and under) diagnosed with ADHD.

Data collection and analysis

We used standard Cochrane methods. Our primary outcome was severity or improvement of ADHD symptoms. Our secondary outcomes were severity or incidence of behavioural problems; quality of life; severity or incidence of depressive symptoms; severity or incidence of anxiety symptoms; side effects; loss to follow-up; and cost. We used GRADE to assess the certainty of evidence for each outcome.

Main results

We included 37 trials with more than 2374 participants, of which 24 trials were new to this update. Five trials (seven reports) used a cross-over design, while the remaining 32 trials (52 reports) used a parallel design. Seven trials were conducted in Iran, four each in the USA and

Israel, and two each in Australia, Canada, New Zealand, Sweden, and the UK. Single studies were conducted in Brazil, France, Germany, India, Italy, Japan, Mexico, the Netherlands, Singapore, Spain, Sri Lanka, and Taiwan. Of the 36 trials that compared a PUFA to placebo, 19 used an omega-3 PUFA, six used a combined omega-3/omega-6 supplement, and two used an omega-6 PUFA. The nine remaining trials were included in the comparison of PUFA to placebo, but also had the same co-intervention in the PUFA and placebo groups. Of these, four trials compared a combination of omega-3 PUFA plus methylphenidate to methylphenidate. One trial each compared omega-3 PUFA plus atomoxetine to atomoxetine; omega-3 PUFA plus physical training to physical training; and an omega-3 or omega-6 supplement plus methylphenidate to methylphenidate; and two trials compared omega-3 PUFA plus dietary supplement to dietary supplement. Supplements were given for a period of between two weeks and six months.

Although we found low-certainty evidence that PUFA compared to placebo may improve ADHD symptoms in the medium term (risk ratio (RR) 1.95, 95% confidence interval (CI) 1.47 to 2.60; 3 studies, 191 participants), there was high-certainty evidence that PUFA had no effect on parent-rated total ADHD symptoms compared to placebo in the medium term (standardised mean difference (SMD) −0.08, 95% CI −0.24 to 0.07; 16 studies, 1166 participants). There was also high-certainty evidence that parent-rated inattention (medium-term: SMD −0.01, 95% CI −0.20 to 0.17; 12 studies, 960 participants) and hyperactivity/impulsivity (medium-term: SMD 0.09, 95% CI −0.04 to 0.23; 10 studies, 869 participants) scores were no different compared to placebo.

There was moderate-certainty evidence that overall side effects likely did not differ between PUFA and placebo groups (RR 1.02, 95% CI 0.69 to 1.52; 8 studies, 591 participants). There was also moderate-certainty evidence that medium-term loss to follow-up was likely similar between groups (RR 1.03, 95% CI 0.77 to 1.37; 13 studies, 1121 participants).

Authors' conclusions

Although we found low-certainty evidence that children and adolescents receiving PUFA may be more likely to improve compared to those receiving placebo, there was high-certainty evidence that PUFA had no effect on total parent-rated ADHD symptoms. There was also high-certainty evidence that inattention and hyperactivity/impulsivity did not differ between PUFA and placebo groups.

We found moderate-certainty evidence that overall side effects likely did not differ between PUFA and placebo groups. There was also moderate-certainty evidence that follow-up was similar between groups.

It is important that future research addresses the current weaknesses in this area, which include small sample sizes, variability of selection criteria, variability of the type and dosage of supplementation, and short follow-up times.

PLAIN LANGUAGE SUMMARY

Polyunsaturated fatty acids (PUFA) supplements for attention deficit hyperactivity disorder (ADHD) in children and adolescents

What is ADHD?

Attention deficit hyperactivity disorder (ADHD) is a common problem in children and adolescents. Those affected may struggle to concentrate, feel restless, or act on impulse. As a result of these difficulties, ADHD can cause long-term social, academic, and mental health problems. Medicines are the most frequently used treatments for ADHD, but they are not always effective and can cause unwanted side effects.

What are polyunsaturated fatty acids (PUFA)?

Polyunsaturated fatty acids (PUFA) are a type of fat. They are necessary for normal brain development and are found in foods such as fish (omega-3 PUFA) and vegetable oils (omega-6 PUFA).

How could PUFA be useful in ADHD?

There is some evidence that ADHD could be related to low levels of PUFA, in particular omega-3 PUFA. PUFA supplements may therefore improve ADHD symptoms, behavioural problems, and related mental health symptoms such as anxiety and depression.

What did we want to find out?

We wanted to know whether PUFA supplements improve ADHD symptoms in children and adolescents with ADHD.

Although there were some limited data in the original review that suggested PUFA improved symptoms of ADHD, there is currently little evidence that PUFA supplementation is beneficial. It was important to update the evidence to incorporate new studies that have been published since the original review.

What did we do?

We searched for all trials that compared PUFA to placebo (dummy pill), medicines, or psychological or medical therapies in children or adolescents with ADHD. We searched 13 databases and two trials registers up to October 2021.

What did we find?

We found 24 new studies in this update, bringing the total number of studies included in the review to 37, which involved more than 2374 children and adolescents with ADHD. Seven studies were conducted in Iran; four each in the USA and Israel; two each in Australia, Canada, New Zealand, Sweden, and the UK; and one each in Brazil, France, Germany, India, Italy, Japan, Mexico, the Netherlands, Singapore, Spain, Sri Lanka, and Taiwan.

Thirty-six studies compared PUFA to placebo. Treatment with PUFA lasted between two weeks and six months.

Although there was some evidence that PUFA could improve ADHD symptoms in children and adolescents, most of the evidence indicated that PUFA did not improve ADHD symptoms such as inattention or hyperactivity-impulsivity. PUFA probably makes little to no difference to overall side effects or whether a person drops out of a study (i.e. does not complete it).

How confident are we about what we found?

We are confident that PUFA has no effect on ADHD symptoms when compared to placebo. Although there was some evidence that ADHD symptoms may be more likely to improve in children and adolescents receiving PUFA compared to those receiving placebo, we have little confidence in this finding.

We are fairly confident that there are no differences between PUFA and placebo groups in overall side effects or dropout.

Limitations of the analyses included small sample sizes, variability of selection criteria, variability of the type and dosage of supplementation, and short follow-up times.

Summary of findings 1. Summary of findings table - PUFA compared to placebo for children and adolescents with ADHD

PUFA compared to placebo for children and adolescents with ADHD

Patient or population: children and adolescents with ADHD
Setting: All settings
Intervention: PUFA
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with PUFA				
ADHD symptoms – improvement – medium term	319 per 1000	**621 per 1000** (468 to 829)	**RR 1.95** (1.47 to 2.60)	191 (3 RCTs)	⊕⊕⊝⊝ Low[a,b]	
ADHD symptoms – total, parent-rated – medium term	-	SMD **0.08 SD lower** (0.24 lower to 0.07 higher)	-	1166 (16 RCTs)	⊕⊕⊕⊕ High	
ADHD symptoms – inattention, parent-rated – medium term	-	SMD **0.01 lower** (0.2 lower to 0.17 higher)	-	960 (12 RCTs)	⊕⊕⊕⊕ High	
ADHD symptoms – hyperactivity/impulsivity, parent-rated – medium term	-	SMD **0.09 higher** (0.04 lower to 0.23 higher)	-	869 (10 RCTs)	⊕⊕⊕⊕ High	
Side effects – overall	190 per 1000	**194 per 1000** (131 to 289)	**RR 1.02** (0.69 to 1.52)	591 (8 RCTs)	⊕⊕⊕⊝ Moderate[c]	
Loss to follow-up – medium term	138 per 1000	**142 per 1000** (106 to 189)	**RR 1.03** (0.77 to 1.37)	1121 (13 RCTs)	⊕⊕⊕⊝ Moderate[c]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio; **SMD:** standardised mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_425001674858162955.

[a] Downgraded one level for risk of bias concerns: less than 50% of risk of bias domains across all studies were rated low risk.
[b] Downgraded one level for serious imprecision: data came from only three RCTs with 191 participants.
[c] Downgraded one level for serious imprecision: wide confidence interval.

BACKGROUND

Description of the condition

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; APA 2013), people with attention deficit hyperactivity disorder (ADHD) show developmentally inappropriate levels of inattention or hyperactivity–impulsivity, or both, before 12 years of age, that persist for at least 6 months; negatively affect social, school, or work function; and are not explained by another mental disorder (APA 2013). A diagnosis of ADHD requires six or more symptoms in children aged up to 16 years, and five or more symptoms in those aged 17 years or older (APA 2013).

According to the International Classification of Diseases (ICD-11; WHO 2018), ADHD is characterised by a persistent pattern (at least six months) of inattention and/or hyperactivity-impulsivity that has a direct negative impact on academic, occupational, or social functioning. Additionally, there is evidence of significant inattention and/or hyperactivity-impulsivity symptoms prior to age 12. The ICD-11 definition of ADHD supersedes the ICD-10 hyperkinetic disorders which similarly included developmentally inappropriate levels of inattention, hyperactivity, and impulsivity (WHO 2010).

ADHD is a common neurodevelopmental disorder with a worldwide prevalence of approximately 5% to 7% in children and adolescents (Polanczyk 2007; Polanczyk 2014; Thomas 2015; Willcutt 2012). Boys are more commonly diagnosed than girls, with an approximate ratio of two boys to one girl (Polanczyk 2007; Willcutt 2012). Approximately 50% to 75% of children with ADHD will continue to have symptoms into adulthood (Targum 2014; Willcutt 2012).

Children and adolescents with ADHD can have academic impairments (Arnold 2020; Loe 2007), social dysfunction (Carpenter Rich 2009; Nijmeijer 2008), and poor self-esteem (Cooper 2015; Cueli 2020; Houck 2011). ADHD is frequently comorbid with other mental health disorders, such as anxiety and depression (Chung 2019; Katzman 2017; Rowland 2002), and is associated with a higher risk of negative effects such as substance abuse (Daley 2004; Davis 2015; Polanczyk 2014; Rowland 2002.

Aetiology

A range of factors may contribute to the onset and maintenance of ADHD symptoms, including genetic factors (Swanson 2000; Swanson 2007); neuroanatomical abnormalities (Biederman 2005); psychosocial factors (Biederman 2005; Morrell 2003); pregnancy and delivery complications (Biederman 2005; Zappitelli 2001); and environmental factors, such as prenatal cigarettes or alcohol (Linnet 2003; Langley 2005), and artificial food colouring (Schab 2004). However, the most significant factor associated with ADHD is heritability, which contributes approximately 75% to the aetiology of ADHD (Biederman 2005; Froehlich 2011).

There is good evidence that the neurotransmitter dopamine may be implicated in the pathogenesis of ADHD. Stimulant drugs that are used in the management of ADHD symptoms increase the availability of dopamine in the brain (Biederman 2005), and a number of genes related to the dopamine pathway have been implicated in ADHD, in particular the dopamine D4 and D5 receptor, dopamine-β-hydroxylase and dopamine transporter genes (Faraone 2000; Li 2006). In addition, imaging studies have shown differences in the dopamine pathway in children and adults with ADHD (Biederman 2005; Krause 2003; Swanson 2007).

Diagnosis of ADHD

The diagnosis of ADHD in children and adolescents should be based on validated criteria, such as DSM-5, APA 2013, DSM-IV, APA 1994, or DSM-IV-TR, APA 2000, for ADHD, or ICD-11, WHO 2018, or ICD-10 for hyperkinetic disorder, WHO 2010. Assessment should be through diagnostic interviews and supported by behaviour rating scales, direct observations of behaviour, and clinic-based testing (NICE 2018).

Treatment for ADHD

The most frequently used treatment used for ADHD is the stimulant medication methylphenidate (Beau-Lejdstrom 2016); the stimulant dexamfetamine is also used (Beau-Lejdstrom 2016; Punja 2016). Meta-analyses of stimulant medications have shown them to be effective in improving inattention and behavioural symptoms, although their effectiveness for improving cognition and achievement is more modest (Punja 2016; Storebø 2015). However, as many as 30% of children do not respond to stimulants (Banaschewski 2004). Stimulants may also be associated with a number of serious adverse events such as psychosis and arrhythmias (Storebø 2018), as well as a range of non-serious adverse events including decreased appetite, weight loss, insomnia, stomachache, headache, and irritability (Punja 2016; Storebø 2018), and may also be associated with longer-term adverse effects such as decreased growth (Storebø 2019).

The most commonly used non-stimulant medications used for ADHD are atomoxetine (Beau-Lejdstrom 2016; Hales 2018; Renoux 2016), clonidine, and guanfacine (Hales 2018). Non-stimulant medications may also be preferable to stimulants treatment of ADHD as stimulants can exacerbate comorbidities such as epilepsy, Eaton 2022, and tics, Osland 2018. However, non-stimulants may be less effective in treating the core symptoms of ADHD compared to stimulants (Nijmeijer 2008; Verbeeck 2017).

As alternatives to medication, there is some limited evidence that non-pharmacological therapies may be effective in improving symptoms and associated behaviours in ADHD (Lopez 2018; Zwi 2011), while evidence for the effectiveness of other non-pharmacological therapies is lacking (Bjornstad 2005; Krisanaprakornkit 2010; Storebø 2019).

Because of the limitations associated with the available treatments for ADHD, particularly the stimulant medications, families often look for alternative treatments (NIH 2000; Daley 2004). The use of polyunsaturated fatty acids (PUFA) is one such potential alternative (Brue 2001; Daley 2004).

Description of the intervention

Human infants require omega-6 and omega-3 PUFA for neural development and to maintain neural integrity and function (Innis 2000; Haag 2003). The omega-3 PUFA, alpha-linolenic acid (ALA) is found in green-leaved plants, while eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA) are found in high concentrations in fish oil; the omega-6 PUFA precursor linoleic acid is found in vegetable oils (Haag 2003; Assisi 2006). Omega-3 PUFA, which include ALA, EPA, and DHA, are associated with brain development

(Innis 2000; Richardson 2000; Haag 2003), and DHA is the major PUFA in the adult mammalian brain (Innis 2000). Arachidonic acid is the most abundant omega-6 PUFA in the human brain (Agostoni 2008). The ratio of omega-3 to omega-6 PUFA is also considered important to normal development and function of the human brain (Innis 2000; Haag 2003), with a ratio of 1:4 considered optimal (Assisi 2006; Borsonelo 2008).

How the intervention might work

Children and adults with ADHD have been shown to have significantly lower plasma and blood concentrations of PUFA (Bonvicini 2016; Chang 2018; Lange 2017; Tesei 2017), and, in particular, lower levels of omega-3 PUFA (Burgess 2000; Chen 2004; Yonezawa 2018). There is also some evidence that PUFA supplementation can improve neurodevelopmental indicators in preterm infants (Moon 2016), but not full-term infants (Jasani 2017). Taken together, these findings suggest that PUFA supplementation may reduce the attention and behaviour problems associated with ADHD.

Why it is important to do this review

This review is an update of the original Cochrane Review of PUFA for ADHD in children and adolescents (Gillies 2012). In the original review, we found little evidence that PUFA supplementation improved ADHD symptoms in children and adolescents. However, our conclusions were limited by potential weaknesses such as small sample sizes in the included trials, variation in participants and in types of supplementation, and short follow-up times.

Since the original review was conducted there has been a steady increase of trials in this area, therefore it was important that this large body of data be integrated into a current Cochrane Review update.

OBJECTIVES

To compare the efficacy of polyunsaturated fatty acids (PUFA) to other forms of treatment or placebo in treating the symptoms of attention deficit hyperactivity disorder (ADHD) in children and adolescents.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and quasi-randomised controlled trials comparing PUFA with placebo or PUFA plus alternative therapy (medication, behavioural therapy, or psychotherapy) with the same alternative therapy alone in children and adolescents (up to and including 18 years of age) diagnosed with ADHD.

Quasi-randomised trials are trials that use allocation methods that are not truly random, for example allocation based on the last number of medical identifier numbers or last number of the date of birth.

Types of participants

Children or adolescents (up to and including 18 years of age) diagnosed with ADHD using validated criteria, such as the ICD-10, WHO 2010, or DSM-5, APA 2013, or scores on related scales with high sensitivity and specificity for a diagnosis of ADHD. We included children and adolescents with comorbidities.

Types of interventions

We were interested in the following four comparisons.

1. PUFA versus placebo
2. PUFA versus medication, e.g. methylphenidate, amphetamine
3. PUFA versus behavioural therapy*
4. PUFA versus psychotherapy*

*We included trials where participants continued with their usual medication as long as this was consistent in all groups.

Types of outcome measures

Primary outcomes

1. Severity or improvement of ADHD symptoms measured by validated scales such as the Child Behavior Checklist, Achenbach 1983, or Conners Rating Scales, Conners 1998. Severity was a continuous measure based on endpoint or change scores, while improvement was a dichotomous outcome based on author-defined improvements in scores.

N.B. We only included outcome data that were measured using a scale or questionnaire if the scale or questionnaire was reported to be valid and reliable in a peer-reviewed journal. In addition, we only included improvement if the clinician making the judgement was blinded to the participant's treatment group, or if it was unclear whether they were blinded.

Secondary outcomes

1. Severity or incidence of behavioural problems, e.g. oppositional behaviour or conduct disorder (measured by scales such as the Child Behavior Checklist (Achenbach 1983)).
2. Quality of life (measured by, for example, Pediatric Quality of Life Inventory Version 4.0 (Varni 2001)).
3. Severity or incidence of depressive symptoms (measured by, for example, Children's Depression Inventory (Kovacs 1992)).
4. Severity or incidence of anxiety symptoms (measured by, for example, State-Trait Anxiety Inventory for Children (Spielberger 1973)).
5. Side effects, such as gastrointestinal symptoms, allergies, changes in weight, changes in appetite or sleep pattern.
6. Loss to follow-up.
7. Cost.

We analysed data for parent, teacher, clinician, and self-reported outcomes separately.

We collected data for all time points. We subgrouped data as short term (up to three months of PUFA treatment), medium term (from three months up to one year of PUFA treatment), and long term (one year or more of PUFA treatment); see Data synthesis.

Search methods for identification of studies

For this update, the Information Specialist of Cochrane Developmental, Psychosocial and Learning Problems searched the following databases on 20 September 2016. Top-up searches were run in November 2019, October 2020, and October 2021. We did

not impose any date or language restrictions. The search strategies used for this update and the previous version of the review are listed in Appendix 1 and Appendix 2, respectively.

Electronic searches

We searched the following databases.

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 10) in the Cochrane Library. Searched 6 October 2021.
2. MEDLINE Ovid (1946 to 4 October 2021).
3. MEDLINE E-Pub Ovid (4 October 2021).
4. MEDLINE In-Process Ovid (1946 to 4 October 2021).
5. Embase Ovid (1974 to 4 October 2021).
6. APA PsycINFO Ovid (1806 to September Week 4 2021).
7. CINAHL Plus EBSCOhost (Cumulative Index to Nursing and Allied Health Literature) (1937 to 6 October 2021).
8. Web of Science Core Collection Clarivate (Science Citation Index; Social Science Citation Index; Conference Proceedings Citation Index - Science; Conference Proceedings Citation Index - Social Sciences & Humanities; 1970 to 6 October 2021).
9. Cochrane Database of Systematic Reviews (CDSR; 2021, Issue 10) in the Cochrane Library. Searched 6 October 2021.
10. Epistemonikos (www.epistemonikos.org; searched 7 October 2021).
11. ProQuest Dissertations & Theses (all available years; searched 7 October 2021).
12. TROVE (limited to theses; all available years, last searched 25 November 2019).
13. WorldCat (limited to theses; all available years, last searched 25 November 2019).
14. ClinicalTrials.gov (clinicaltrials.gov/; searched 7 October 2021).
15. World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; who.int/trialsearch/Default.aspx; searched 7 October 2021).

Searching other resources

We checked the reference lists of relevant studies and reviews for additional references to potentially relevant studies. We included trials in languages other than English; where possible, these were translated by members of the author team; where this was not possible, we used translation software.

Data collection and analysis

In the following sections, we describe the methods we undertook. Methods we had proposed to use in the protocol but could not undertake because of inadequate data are listed in Appendix 3.

Selection of studies

Two review authors (DG, ML, GPA) independently assessed the records yielded by the searches for eligibility using a two-step process. First, two review authors independently screened all titles and abstracts. Any records that appeared to meet the inclusion criteria were moved through to the second step where full texts were obtained and screened for inclusion. Any disagreements regarding the selection of studies were resolved through consensus or by consulting a third member of the review team if necessary. The study selection process is illustrated in a PRISMA diagram (Moher 2009).

Data extraction and management

We developed and piloted a data extraction form for the original version of this review (Gillies 2012). Two review authors (DG, ML, GPA) independently extracted details of participants, setting, interventions, methodology, and outcome data from each trial. We then compared the data for any differences. If differences were identified, we resolved them by consensus or referral to a third member of the team, when necessary. Where further clarification or missing data from trial authors were needed, we made all reasonable attempts at contact.

Assessment of risk of bias in included studies

Using the Cochrane risk of bias tool as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), two review authors (DG, ML, GPA) independently assessed trials based on the following risk of bias domains:

1. adequacy of sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessors;
5. incomplete outcome data; and
6. selective outcome reporting.

We rated these criteria as at low, high, or unclear risk of bias (for further details, please see Appendix 4). We also collected information on any other sources of bias (e.g. baseline imbalance, cross-over design, differential loss to follow-up, inappropriate administration of an intervention or co-intervention, early stopping, and selective reporting of subgroups).

We collected details on how each of these criteria were addressed from the trial reports. Any disagreements regarding risk of bias criteria were resolved by consensus or by referral to a third member of the review team.

Measures of treatment effect

Dichotomous data

For binary outcomes, we calculated the risk ratio (RR) and 95% confidence interval (CI) using a random-effects model because of the significant clinical heterogeneity between studies.

Continuous data

For continuous outcomes, we used endpoint data in preference to change data if both were available. We calculated the standardised mean difference (SMD) between groups and 95% CI using a random-effects model because there was significant clinical heterogeneity between studies. We used SMDs because more than one scale was used for each of these continuous outcomes.

Unit of analysis issues

Because of the potential for carry-over of effects in cross-over trials (Higgins 2022, Section 23.3.2), we used first-phase data were these were available. If first-phase data were not available, we used data for both phases if reported and conducted sensitivity analysis for such trials.

Dealing with missing data

We used intention-to-treat data where available, and collected information on how the intention-to-treat analysis was calculated, which we reported in Characteristics of included studies. Where the reporting of data appeared to be incomplete, we made all reasonable efforts to contact the trial authors to request the missing data.

We reported loss to follow-up and the reasons for missing data where this information was available. If outcome data were reported as a median or range, or as a mean without a variance, we reported them in Additional tables.

We considered the potential impact of missing data on the results in the interpretation of the results of the review.

Assessment of heterogeneity

We used a Tau^2 test and I^2 statistic to evaluate heterogeneity. We interpreted a P value of less than 0.10 for the Tau^2 test of heterogeneity or an I^2 value of greater than 50% (or both) as significant heterogeneity.

A rough guide to interpretation in the context of meta-analyses of randomised trials is as follows:

1. 0% to 40%: might not be important;*
2. 30% to 60%: may represent moderate heterogeneity;*
3. 50% to 90%: may represent substantial heterogeneity;*
4. 75% to 100%: considerable heterogeneity.*

*(Deeks 2022, Section 10.10.2)

Assessment of reporting biases

Where data from at least 10 trials were available, we entered primary outcome data into a funnel plot to assess for asymmetry, which may indicate publication bias (Page 2022, Section 13.3.5.2).

Data synthesis

In the case of sufficient data, we synthesised similar interventions and outcomes in a meta-analysis. Where the same co-interventions were used in both groups (e.g. methylphenidate), these trials were included in meta-analysis.

We created a summary of findings table using the primary outcome of ADHD symptoms - improvement, parent rated, teacher rated, and clinician rated.

Data collection intervals

We collected data for all time points. All outcome data were subgrouped as short term (up to three months of PUFA treatment), medium term (from three months up to one year of PUFA treatment), and long term (one year or more of PUFA treatment). If a study reported data for more than one time point within any of these predefined intervals (e.g. data at three months and six months), then data for only one of these time points were used. The decision of which time point to use was based on the following criteria in order of priority: i) completeness of data; ii) loss to follow-up; and iii) longer treatment intervals.

Skewed data

As a meta-analysis is based on assumptions of normality, we checked all continuous data for skew before inclusion. We considered data to be skewed if the standard deviation was greater than half the mean (Altman 1996). It was not possible to check change data, as these can include positive and negative values. We found no endpoint data to be skewed.

Subgroup analysis and investigation of heterogeneity

We aimed to undertake subgroup analyses for the type of PUFA supplement that was used, that is omega-3 only, omega-6 only, or a combination of omega-3 and omega-6. However, we were only able to compare omega-3 with omega 3/omega-6 PUFA, as there were inadequate data for omega-6 PUFA. We used medium-term total parent-rated ADHD scores for this subgroup analysis.

Sensitivity analysis

We used sensitivity analyses to compare studies that used a clinician diagnosis of ADHD as an inclusion criterion to those that included participants based on ADHD symptom scale scores.

We also conducted sensitivity analyses for any cross-over studies that were included but that did not report first-phase data, and based on attrition bias.

All sensitivity analyses were conducted for comparisons of PUFA versus placebo. We used the primary outcome of parent-reported symptoms for all sensitivity analyses except for the sensitivity analysis for the one cross-over trial for which first-phase data was not available (Aman 1987), for which parent-rated inattention as total scores were not available.

Summary of findings and assessment of the certainty of the evidence

We generated a summary of findings table employing GRADEpro GDT integrated with RevMan Web (GRADEpro GDT; RevMan Web 2022; Schünemann 2022), using as the main comparison PUFA versus placebo for the medium-term outcomes of improvement, parent-rated total, inattention and hyperactivity-impulsivity symptoms, overall side effects, and loss to follow-up.

The GRADE Working Group grades of evidence are as follows.

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Using the GRADE approach, two review authors (DG, ML) independently rated the certainty of the evidence as high, moderate, low, or very low according to the presence of the following criteria: risk of bias, imprecision, inconsistency, indirectness, and publication bias. We downgraded the certainty of the evidence for risk of bias where only 50% of risk of bias

domains were rated low risk. We downgraded the certainty of the evidence for serious imprecision when the evidence was based on few studies with few participants or resulted in a wide confidence interval. Any discrepancies between authors were resolved by discussion.

RESULTS

Description of studies

Results of the search

We identified 2081 records in total in this update, of which 2073 records were retrieved by the electronic searches and 8 were records of studies that had been classified as ongoing studies in the previous version of the review. We discarded 751 duplicates before screening the titles and abstracts of the remaining 1330 records. We excluded 1259 irrelevant records and retrieved full text of the remaining 71 records for closer examination, from which we identified 24 new included studies (from 39 reports). We found 6 additional reports of studies included in the previous version of the review (Bélanger 2009; Brue 2001; Gustafsson 2010; Johnson 2009; Vaisman 2008); identified 10 studies as awaiting classification (from 13 reports); and classified 1 report as an ongoing study. We also excluded 9 studies (from 12 reports). See Figure 1. The review now has a total of 37 included studies (from 62 reports).

Figure 1. Study flow diagram for review update.

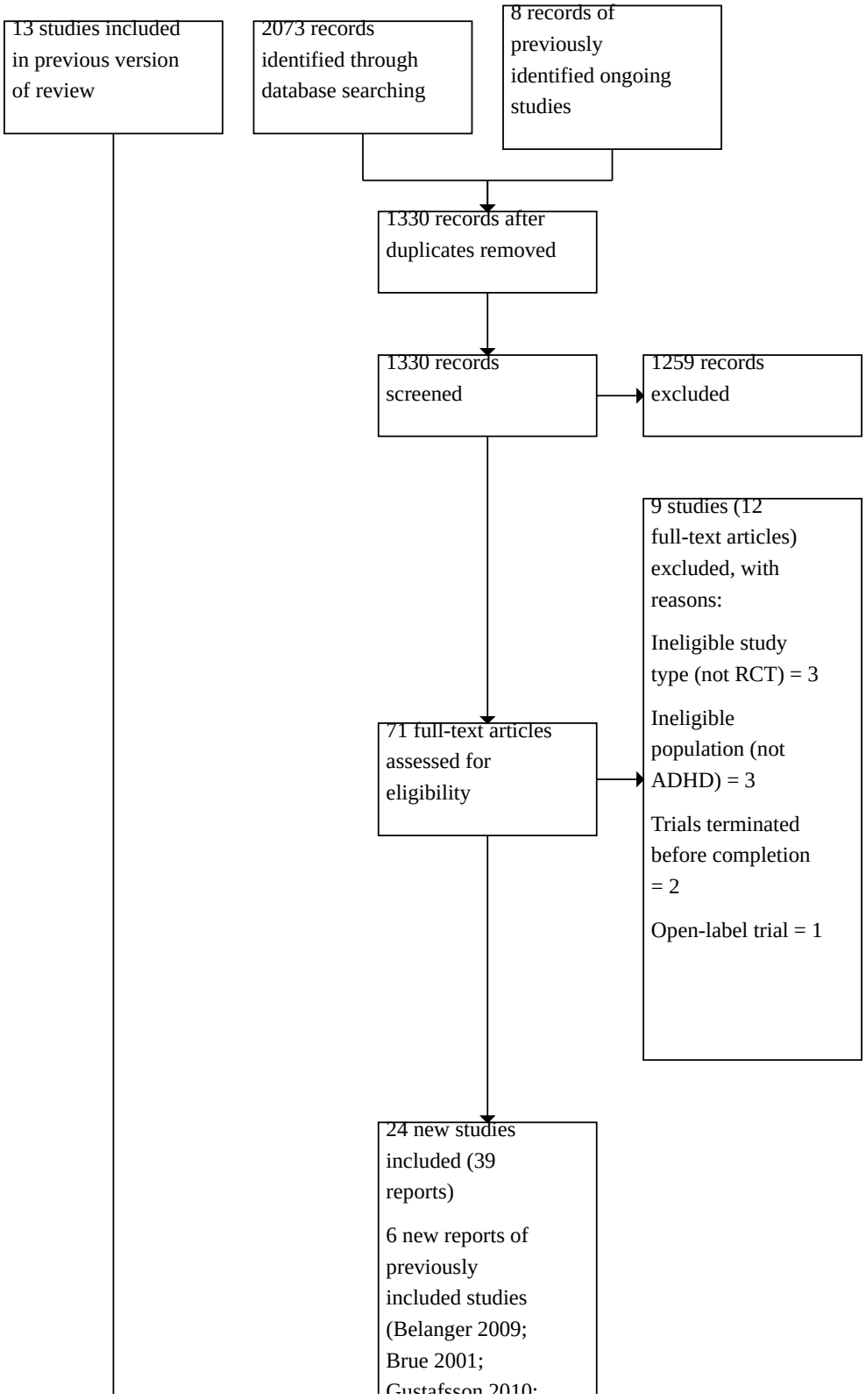
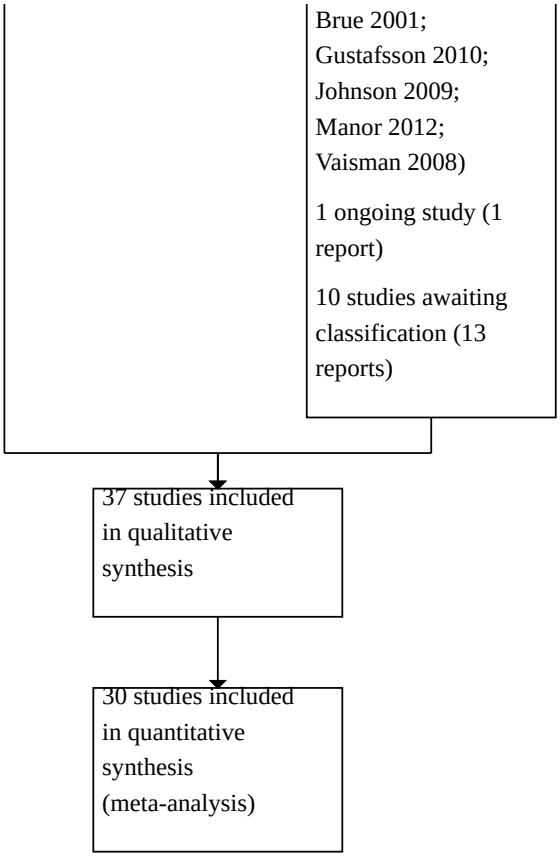


Figure 1. (Continued)



Included studies

Study design

Five trials (seven reports) had a cross-over design (Aman 1987; Arnold 1989; Bélanger 2009; Johnson 2009; Sinn 2007). First-phase data from cross-over trials were integrated with data from parallel trials where first-phase data were reported. Where first-phase data were not reported separately (Aman 1987), data from cross-over trials were included in the meta-analysis but a sensitivity analysis was conducted.

The 32 remaining trials (52 reports) all had a parallel-group design.

See Appendix 5.

Location/setting

Seven trials were conducted in Iran, four each in the USA and Israel, two each in Australia, Canada, New Zealand, Sweden, and the UK, and one each in Brazil, France, Germany, India, Italy, Japan, Mexico, the Netherlands, Singapore, Spain, Sri Lanka, and Taiwan.

Participants

We included 37 studies with more than 2374 participants. It is not possible to be exact about the number of participants as this was not always clearly reported. The number of participants ranged from 17 to 160, and the age of participants was between six and 18 years, with a mean study age of 6 to 11 years. In most trials, the diagnosis of ADHD was made by a clinician, except for the studies by Aman 1987, Arnold 1989, Sinn 2007, Gow 2012, Hariri 2012, Dashti 2014, and Moghaddam 2017, which used scale cut-offs with high sensitivity for a diagnosis of ADHD. Only one study used inclusion criteria that could be indicative of PUFA deficiency, that is thirst or skin symptoms (Stevens 2003).

Funding

Seven studies were funded by the company that produced PUFA supplements (Aman 1987; Arnold 1989; Barragán 2017; Crippa 2019; Johnson 2009; Manor 2012; Voigt 2001). Four appeared to be sponsored by a pharmaceutical company, but it was unclear whether the sponsor produced the PUFA used in the trial (Bos 2015; Cornu 2018; Kean 2017; Perera 2012). Studies were funded by research grants from charitable institutions (Matsudaira 2015), government (Dubnov-Raz 2014; Milte 2012; Sinn 2007; Widenhorn-Müller 2014), and universities (Assareh 2017). Three studies received mixed funding from a government agency or university and pharmaceutical company (Bélanger 2009; Gow 2012; Stevens 2003). The remaining studies provided no information on funding.

Interventions and comparators

We aimed to include studies for the four main comparisons:

1. PUFA versus placebo;
2. PUFA versus medication, e.g. methylphenidate, amphetamine;

3. PUFA versus behavioural therapy; and
4. PUFA versus psychotherapy.

However, data were only available for the following three comparisons:

1. PUFA versus placebo;
2. PUFA versus medication;
3. omega-3 versus omega-6 PUFA. This comparison was a post hoc analysis, as it was not prespecified in the protocol (Differences between protocol and review).

Twenty-seven studies compared PUFA alone to placebo alone. Of these, 19 compared an omega-3 PUFA supplement to placebo (Bos 2015; Chang 2019; Cornu 2018; Crippa 2019; Dashti 2014; Gow 2012; Gustafsson 2010; Hariri 2012; Hirayama 2004; Ivity 2015; Kean 2017; Lim-Ashworth 2013; Manor 2012; Matsudaira 2015; Milte 2012; Rodriguez 2019; Vaisman 2008; Voigt 2001; Widenhorn-Müller 2014); two compared an omega-6 PUFA to placebo (Aman 1987; Arnold 1989); and six compared a combined omega-3 and omega-6 supplement to placebo (Assareh 2017; Dubnov-Raz 2014; Johnson 2009; Perera 2012; Raz 2009a; Stevens 2003).

Nine additional trials compared PUFA to placebo but also had the same co-intervention in both the PUFA and placebo groups; these studies were included in comparison 1. Four studies compared omega-3 PUFA plus methylphenidate to methylphenidate (Behdani 2013; Moghaddam 2017; Mohammadzadeh 2019; Salehi 2016); two trials compared omega-3 PUFA plus dietary supplement to dietary supplement (Brue 2001; Sinn 2007); one trial each compared omega-3 plus atomoxetine to atomoxetine (Anand 2016); omega-3 PUFA plus physical training to physical training (NCT01807299); and an omega-3 or omega-6 supplement plus methylphenidate to methylphenidate (Barragán 2017).

Three studies compared PUFA to medication, in this case stimulants. One study compared omega-3 to methylphenidate (Dashti 2014); one study compared an omega-3 or omega-6 supplement to methylphenidate (Barragán 2017), and one study compared omega-6 PUFA to dexamfetamine (Arnold 1989). One study compared omega-3 to omega-6 PUFA (Bélanger 2009).

See Appendix 5.

The omega-3 PUFA used in supplements was DHA (2.7 to 3600 mg/day, 22 studies), EPA (33 to 1039 mg/day, 22 studies), and ALA (60 to 1080 mg/day, 2 studies). The omega-6 PUFA was arachidonic acid (40 to 60 mg/day, 2 studies), linoleic acid (240 to 360 mg/day, 5 studies), and gamma-linoleic acid (6 to 345 mg/day, 8 studies). Supplements were given for a period of between two weeks and six months.

Outcomes

Improvement

Six studies reported improvement rated by parents (Assareh 2017; Barragán 2017; Perera 2012; Stevens 2003), clinicians (Johnson 2009; Moghaddam 2017), and teachers (Stevens 2003). All of these studies used the ADHD Rating Scale to measure improvement, except for Moghaddam 2017, who did not state which scale was used.

ADHD symptoms

Twenty-two studies reported parent-rated total ADHD symptom scores (Anand 2016; Assareh 2017; Barragán 2017; Behdani 2013; Bélanger 2009; Bos 2015; Chang 2019; Cornu 2018; Crippa 2019; Dashti 2014; Dubnov-Raz 2014; Gustafsson 2010; Lim-Ashworth 2013; Manor 2012; Matsudaira 2015; Milte 2012; Mohammadzadeh 2019; Perera 2012; Salehi 2016; Sinn 2007; Stevens 2003; Widenhorn-Müller 2014). Six studies used the ADHD Rating Scale (Barragán 2017; Behdani 2013; Cornu 2018; Crippa 2019; Mohammadzadeh 2019; Perera 2012); one used the Strengths and Weaknesses of ADHD symptoms and Normal behavior scale (SWAN) (Bos 2015); one used the DISYPS-II (Widenhorn-Müller 2014); one used the SNAP-IV (Chang 2019); and the remaining studies used the Conners Rating Scale.

Three studies reported clinician-rated total symptom scores. One study used the ADHD Rating Scale (Johnson 2009); one used the Conners Rating Scale (Hariri 2012); and one did not state which measure was used (Moghaddam 2017).

Nine studies reported teacher-rated total symptoms. One study used the ADHD Rating Scale (Behdani 2013); one used the DISYPS-II (Widenhorn-Müller 2014); one used the SNAP-IV (Chang 2019); and the remaining studies used the Conners Rating Scale (Dubnov-Raz 2014; Gustafsson 2010; Manor 2012; Matsudaira 2015; Raz 2009a; Stevens 2003).

Seven studies reported hyperactivity/impulsivity or inattention (or both), which in all studies was rated by parents (Aman 1987; Brue 2001; Chang 2019; Hirayama 2004; Kean 2017; Vaisman 2008; Voigt 2001). Four of these studies also reported teacher-rated symptoms (Aman 1987; Brue 2001; Chang 2019; Hirayama 2004). All studies used the Conners Rating Scale, except for Chang 2019, who used the SNAP-IV; Hirayama 2004, who reported the number of DSM-IV-symptoms; and Voigt 2001, who reported the Child Behavior Checklist - Attention.

Behaviour

Four studies reported that aggression was measured (Aman 1987; Bos 2015; Hirayama 2004; Perera 2012); however, Hirayama 2004 and Perera 2012 did not use a validated scale. Aman 1987 used the parent-rated Revised Behavior Problem Checklist subscales for conduct and aggression and teacher-rated Conners subscale for conduct. Bos 2015 used the parent-rated Child Behavior Checklist to measure aggression.

In addition to Aman 1987, parent-rated conduct problems were also reported by Crippa 2019 and Matsudaira 2015, both of whom used the Strengths and Difficulties Questionnaire. Parent- and teacher-rated conduct problems were also reported by Stevens 2003, using the Disrupted Behavior Disorders Rating Scale.

Stevens 2003 also used the Disrupted Behavior Disorders Rating Scale to report teacher-rated oppositional behaviour. The Conners Rating Scale was used for teacher-rated oppositional behaviour by Gustafsson 2010 and Manor 2012, and for parent-rated oppositional behaviour by Manor 2012, Milte 2012, and Sinn 2007. Parent- and teacher-rated oppositional behaviour was also measured using the SNAP-IV by Chang 2019.

Internalising and externalising behaviour was also reported by Voigt 2001 and Widenhorn-Müller 2014, both of whom used the parent-rated Child Behavior Checklist.

Higher scores are related to more severe or more frequent behavioural problems for all of these measures.

Follow-up

Fourteen studies only reported short-term outcomes (Aman 1987; Arnold 1989; Assareh 2017; Behdani 2013; Bélanger 2009; Dashti 2014; Dubnov-Raz 2014; Hariri 2012; Hirayama 2004; Ivity 2015; Moghaddam 2017; Mohammadzadeh 2019; Raz 2009a; Salehi 2016), with only one study reporting long-term outcomes (Barragán 2017). The remaining 22 studies reported medium-term outcomes.

Data not used in meta-analyses

Data from several studies could not be used in meta-analyses. Outcome data were not reported in Arnold 1989, Gow 2012, and Lim-Ashworth 2013, and only the median number of ADHD symptoms were reported in Hirayama 2004. We could not include data for any outcome for Brue 2001 and Bélanger 2009 in meta-analysis because variances were not reported. Data from Milte 2012 were only reported as correlations and effect difference. We have therefore reported data for ADHD symptoms in Brue 2001, Bélanger 2009, and Milte 2012 separately in Table 1. In addition, not all outcomes in Sinn 2007 could be included in meta-analyses as data for anxiety, oppositional behaviour, and social problems were skewed.

Excluded studies

We excluded a total of 14 studies, five in the previous review and a further nine in this update. We excluded two studies because they were found to be literature reviews upon full-text assessment (Anonymous 2009; Doebel 2005); four studies that were not randomly allocated trials (Harding 2003; Joshi 2006; Meguid 2016; San Mauro Martin 2019); and one study that was an open-label trial (Wilens 2017). We excluded three studies because participants did not have ADHD (Döpfner 2021; Greeff 2011; Johnson 2017). Despite attempts to contact the authors of Richardson 2002, we could not obtain further details on their inclusion criteria. Tan 2014 only reported data for a subgroup of participants with ADHD from a larger randomised controlled trial in children with disruptive behaviour disorders. Two trials were terminated before completion (NCT01777048; NCT01778647).

Studies awaiting classification

Ten studies (from 13 reports) are awaiting classification, as the results of these studies are not yet available, although the studies appear to have been completed. All are parallel, randomised trials, and one is a multicentre trial (Carucci 2017). Four studies compare omega-3 to placebo (NCT00770627; NCT02348073; NCT02986672; NCT03542643); three compare omega-3/omega-6 PUFA to placebo (Carucci 2017; NCT02114632; NCT02248948); and three compare omega-3 plus stimulant to stimulant alone (IRCT201104166201N1; IRCT201304035393N3; IRCT2016050918927N2). All of these studies have listed ADHD symptoms as an outcome.

Ongoing studies

One ongoing cluster-randomised trial, CTRI/2020/05/025267, is comparing omega-3 PUFA plus methylphenidate therapy to methylphenidate alone in children aged 6 to 12 years who have ADHD and who have not previously received methylphenidate.

Risk of bias in included studies

The risk of bias assessment based on the six risk of bias domains is provided below. See Figure 2 for the overall risk of bias, and Figure 3 for risk of bias ratings for each of the included studies.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

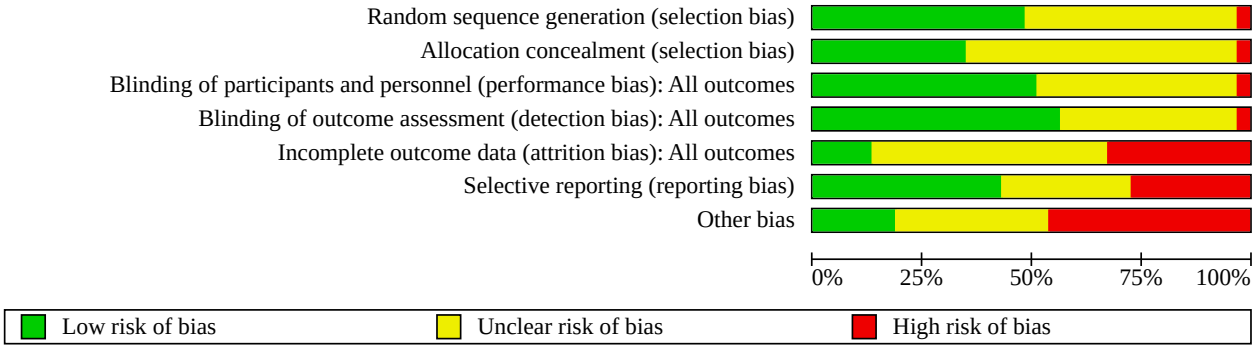


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

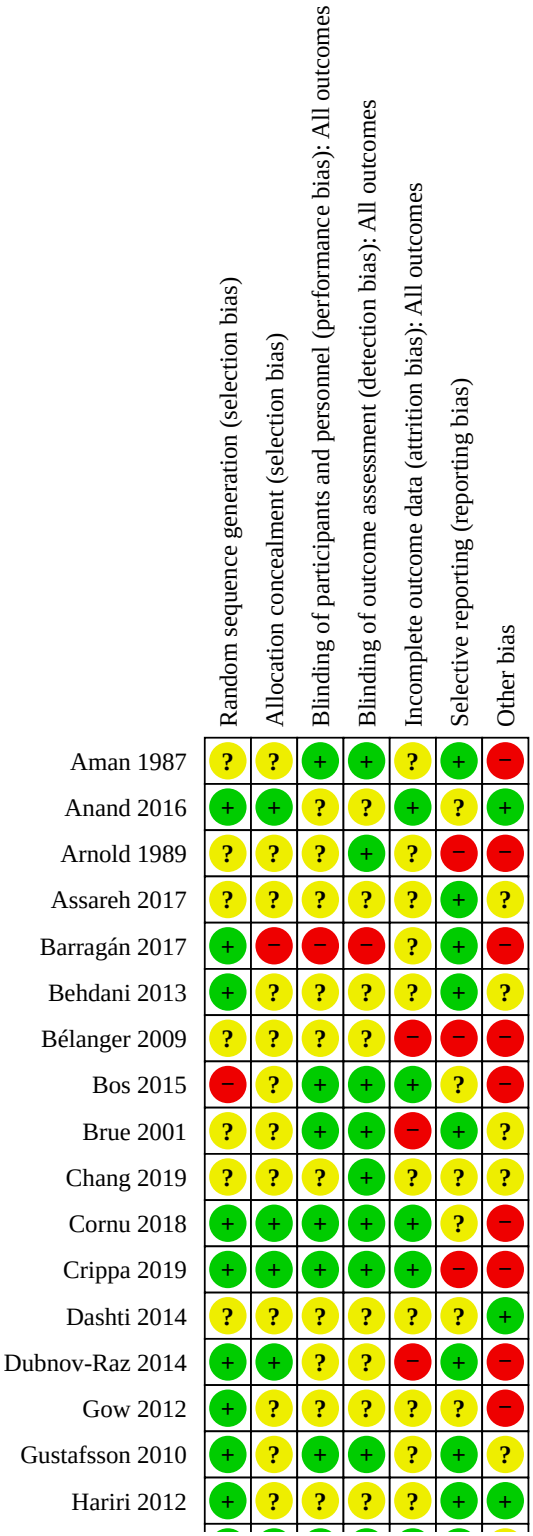
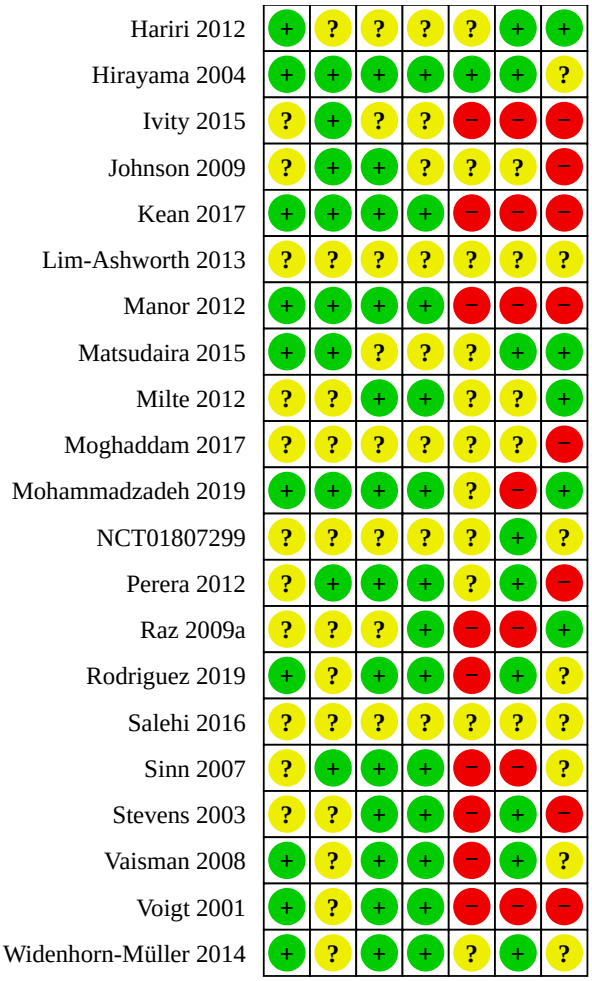


Figure 3. (Continued)



Allocation

Random sequence generation

We assessed 19 trials as at low risk of bias for random sequence generation (Anand 2016; Barragán 2017; Behdani 2013; Bos 2015; Cornu 2018; Crippa 2019; Dubnov-Raz 2014; Gow 2012; Gustafsson 2010; Hariri 2012; Hirayama 2004; Kean 2017; Manor 2012; Matsudaira 2015; Mohammadzadeh 2019; Rodriguez 2019; Vaisman 2008; Voigt 2001; Widenhorn-Müller 2014), and the remaining 18 trials as at unclear risk due to inadequate information.

Allocation concealment

We assessed 13 trials as at low risk of bias for allocation concealment (Anand 2016; Cornu 2018; Crippa 2019; Dubnov-Raz 2014; Hirayama 2004; Ivity 2015; Johnson 2009; Kean 2017; Manor 2012; Matsudaira 2015; Mohammadzadeh 2019; Perera 2012; Sinn 2007), one trial at high risk of bias (Barragán 2017), and the remaining trials at unclear risk of bias.

Blinding

Participants and personnel

The majority (19) of the included trials described methods used to blind participants and personnel and were therefore assessed as at a low risk of performance bias. However, we rated 17 studies as at unclear risk of performance bias (Anand 2016; Arnold 1989; Assareh 2017; Behdani 2013; Bélanger 2009; Chang 2019; Dashti 2014; Dubnov-Raz 2014; Gow 2012; Hariri 2012; Ivity 2015; Lim-Ashworth 2013; Matsudaira 2015; Moghaddam 2017; NCT01807299; Raz 2009a; Salehi 2016), and one study at high risk (Barragán 2017).

Outcome assessors

We considered the majority of trials (21) to be at low risk of detection bias because the intervention and placebo were described as identical, and because parent- or teacher-rated measures (or both) were used (Aman 1987; Arnold 1989; Bos 2015; Brue 2001; Chang 2019; Cornu 2018; Crippa 2019; Gustafsson 2010; Hirayama 2004; Kean 2017; Manor 2012; Milte 2012; Mohammadzadeh 2019; Perera 2012; Raz 2009a; Rodriguez 2019; Sinn 2007; Stevens 2003; Vaisman 2008; Voigt 2001; Widenhorn-Müller 2014). We rated Barragán 2017 as at high risk of bias, and the remaining 15 studies as at unclear risk of detection bias because of insufficient information.

Incomplete outcome data

We considered only five studies to be at low risk of attrition bias (Anand 2016; Bos 2015; Cornu 2018; Crippa 2019; Hirayama 2004). We assessed 12 trials as at high risk of attrition bias because data

were only reported for participants who were not lost to follow-up (Bélanger 2009; Brue 2001; Dubnov-Raz 2014; Ivity 2015; Kean 2017; Manor 2012; Raz 2009a; Rodriguez 2019; Sinn 2007; Stevens 2003; Vaisman 2008; Voigt 2001). We considered the remaining studies as at unclear risk of bias because of insufficient information.

Selective reporting

We assessed 16 studies as at low risk of reporting bias as all outcomes appear to have been reported (Aman 1987; Assareh 2017; Barragán 2017; Behdani 2013; Brue 2001; Dubnov-Raz 2014; Gustafsson 2010; Hariri 2012; Hirayama 2004; Matsudaira 2015; NCT01807299; Perera 2012; Rodriguez 2019; Stevens 2003; Vaisman 2008; Widenhorn-Müller 2014). There was a high risk of reporting bias in seven trials because the result of at least one outcome was not reported (Arnold 1989; Bélanger 2009; Manor 2012; Mohammadzadeh 2019; Raz 2009a; Sinn 2007; Voigt 2001). We assessed the remaining studies as at unclear risk of bias.

Other potential sources of bias

We considered 11 studies as at high risk of other bias as they were fully (Aman 1987; Arnold 1989; Barragán 2017; Bos 2015; Cornu 2018; Crippa 2019; Johnson 2009; Kean 2017; Manor 2012; Perera 2012; Voigt 2001) or partly (Bélanger 2009; Gow 2012; Stevens 2003) funded by a company that produced PUFA supplements.

There were other potential confounding variables in five studies. In Aman 1987, it was not clear whether the additional five children included in the trial would have met the original inclusion criteria. The PUFA group in Brue 2001 had received an additional 12 weeks of dietary supplementation before the PUFA trial was started. In Stevens 2003, although both groups were comparable over a large range of variables, the Conners Parent score and reaction time were significantly lower in the PUFA group. There were fewer children with Asperger's syndrome and more children with a learning disorder in the PUFA group in the trial reported by Hirayama 2004, although this was not significant. More than half of the children in the PUFA group in Sinn 2007 also received a multivitamin. Sinn 2007 also reported that baseline scores for ADHD symptoms were significantly higher in the group lost to follow-up.

We considered six studies to be at low risk of other potential sources of bias as they reported that there were no apparent differences between groups in potentially confounding characteristics, and there were no other apparent sources of bias (Dashti 2014; Hariri 2012; Matsudaira 2015; Milte 2012; Mohammadzadeh 2019; Raz 2009a).

Effects of interventions

See: **Summary of findings 1** Summary of findings table - PUFA compared to placebo for children and adolescents with ADHD

Comparison 1: PUFA versus placebo

ADHD symptoms

There were seven data sets from six trials looking at ADHD symptoms. Improvement was more likely in the group receiving PUFA compared to placebo at short term: risk ratio (RR) 1.22, 95% confidence interval (CI) 0.85 to 1.76; 2 studies, 80 participants; Tau^2 = 0.04; Chi^2 = 2.68, df = 1 (P = 0.10); I^2 = 63%; medium term: RR 1.95, 95% CI 1.47 to 2.60; 3 studies, 191 participants; Tau^2 = 0.00; Chi^2 = 1.34, df = 2 (P = 0.51); I^2 = 0%; or in the long term: RR 1.67, 95% CI 0.70 to 3.95; 2 studies, 141 participants; Tau^2 = 0.36; Chi^2 = 15.41, df = 1 (P < 0.001); I^2 = 94%; Analysis 1.1. We assessed the evidence that children and adolescents receiving PUFA were more likely to improve compared to those receiving placebo as of low certainty (Summary of findings 1).

There were no differences between groups in parent ratings of overall ADHD symptoms at any time point (short term: standardised mean difference (SMD) 0.17, 95% CI −0.25 to 0.59; 7 studies, 442 participants; Tau^2 = 0.27; Chi^2 = 30.80, df = 7 (P < 0.001); I^2 = 77%; medium term: SMD −0.08, 95% CI −0.24 to 0.07; 16 studies, 1166 participants; Tau^2 = 0.04; Chi^2 = 24.62, df = 15 (P = 0.06); I^2 = 39%; long term: SMD −0.30, 95% CI −0.81 to 0.21; 1 study, 60 participants; Tau^2 = 0.04; I^2 = 0%; Analysis 1.2). Likewise, there were no differences for parent-rated inattention (short term: SMD 0.01, 95% CI −0.31 to 0.33; 5 studies, 283 participants; Tau^2 = 0.06; Chi^2 = 7.57, df = 4 (P = 0.11); I^2 = 47%; medium term: SMD −0.01, 95% CI −0.20 to 0.17; 12 studies, 960 participants; Tau^2 = 0.04; Chi^2 = 17.16, df = 10 (P = 0.07); I^2 = 42%; long term: SMD −0.39, 95% CI −0.90 to 0.12; 1 study, 60 participants; I^2 = 0%; Analysis 1.3) and parent-rated hyperactivity/impulsivity (short term: SMD 0.15, 95% CI −0.20 to 0.50; 5 studies, 283 participants; Tau^2 = 0.08; Chi^2 = 8.63, df = 4 (P = 0.07); I^2 = 54%; medium term: SMD 0.09, 95% CI −0.04 to 0.23; 10 studies, 869 participants; Tau^2 = 0.00; Chi^2 = 4.77, df = 9 (P = 0.85); I^2 = 0%; long term: SMD −0.21, 95% CI −0.72 to 0.29; 1 study, 60 participants; I^2 = 0%; Analysis 1.4). We assessed the evidence that PUFA had no effect on total ADHD symptoms, inattention, and hyperactivity/impulsivity as of high certainty (Summary of findings 1).

There were no clear differences in teacher ratings of overall ADHD symptoms in the short term: SMD 0.35, 95% CI −0.30 to 1.00; 4 studies, 185 participants; Tau^2 = 0.32; Chi^2 = 12.70, df = 3 (P = 0.005); I^2 = 76%; or the medium term: SMD 0.06, 95% CI −0.12 to 0.24; 5 studies, 598 participants; Tau^2 = 0.00; Chi^2 = 5.10, df = 5 (P = 0.40); I^2 = 2%; Analysis 1.5. There was also no difference in teacher-rated inattention at any of the recorded time points (short term: SMD 0.02, 95% CI −0.40 to 0.44; 2 studies, 86 participants; Tau^2 = 0.00; Chi^2 = 0.04, df = 1 (P = 0.85); I^2 = 0%; medium term: SMD 0.17, 95% CI −0.14 to 0.49; 4 studies, 428 participants; Tau^2 = 0.07; Chi^2 = 9.67, df = 4 (P = 0.05); I^2 = 59%; Analysis 1.6) or in hyperactivity/impulsivity ratings in the short term: SMD 0.00, 95% CI −0.51 to 0.51; 1 study, 60 participants; I^2 = 0%; or medium term: SMD 00.15, 95% CI −0.03 to 0.34; 5 studies; 462 participants; Tau^2 = 0.00; Chi^2 = 4.30, df = 5 (P = 0.51); I^2 = 0%; Analysis 1.7.

Three trials reported clinician ratings of overall ADHD symptoms. Total symptom scores rated by clinicians were lower in the PUFA group in the short term (SMD −0.74, 95% CI −1.08 to −0.40; 2 studies, 143 participants; I^2 = 0%) but not in the medium term (SMD −0.35, 95% CI −0.84 to 0.15; 1 study, 64 participants; Tau^2 = 0.00; Chi^2 = 0.01, df = 1 (P = 0.91); I^2 = 0%; Analysis 1.8). There were no differences between groups for clinician-rated inattention (short term: SMD −0.05, 95% CI −1.00 to 0.90; 1 study, 17 participants; I^2 = 0%; medium term: SMD −0.29, 95% CI −0.65 to 0.07; 2 studies, 124 participants; Tau^2 = 0.00; Chi^2 = 0.01, df = 1 (P = 0.93); I^2 = 0%; Analysis 1.9) or for hyperactivity/impulsivity (short term: SMD 0.36, 95% CI −0.18 to 0.91; 2 studies, 53 participants; I^2 = 0%; medium term: SMD −0.28, 95% CI −0.77 to 0.21; 1 study, 64 participants; Tau^2 = 0.00; Chi^2 = 0.05, df = 1 (P = 0.82); I^2 = 0%; Analysis 1.10).

Severity of behavioural problems

There were no differences between groups in parent-rated internalising behaviour recorded at medium term (SMD 0.16, 95% CI −0.09 to 0.42; 3 studies, 237 participants; $Tau^2 = 0.00$; $Chi^2 = 0.05$, df = 1 (P = 0.82); $I^2 = 0\%$; Analysis 1.11) or externalising behaviour in both the short term: SMD 0.02, 95% CI −0.49 to 0.52; 1 study, 60 participants; $I^2 = 0\%$; and medium term: SMD 0.07, 95% CI −0.26 to 0.41; 5 studies, 340 participants; $Tau^2 = 0.08$; $Chi^2 = 9.36$, df = 4 (P = 0.05); $I^2 = 57\%$; Analysis 1.12). Likewise, there were no clear differences in parent ratings of conduct in the short term: SMD −0.10, 95% CI −0.60 to 0.41; 1 study; 60 participants; $I^2 = 0\%$; or medium term: SMD 0.16, 95% CI −0.05 to 0.38; 5 studies, 332 participants; $Tau^2 = 0.00$; $Chi^2 = 1.14$, df = 4 (P = 0.89); $I^2 = 0\%$; Analysis 1.13. Similarly, there was no evidence of a difference in oppositional behaviour at medium term (SMD 0.02, 95% CI −0.17 to 0.21; 6 studies, 527 participants; $Tau^2 = 0.01$; $Chi^2 = 5.69$, df = 5 (P = 0.34); $I^2 = 12\%$; Analysis 1.14) or socialisation behaviour also in the medium term (SMD 0.27, 95% CI −0.06 to 0.60; 2 studies, 145 participants; $Tau^2 = 0.00$; $Chi^2 = 1.02$, df = 1 (P = 0.31); $I^2 = 2\%$; Analysis 1.15).

There were no differences between groups in teacher ratings of conduct (short term: SMD −0.03, 95% CI −0.54 to 0.48; 1 study, 60 participants; $I^2 = 0\%$; medium term: SMD −0.03, 95% CI −0.39 to 0.34; 2 studies, 118 participants; $Tau^2 = 0.00$; $Chi^2 = 0.06$, df = 1 (P = 0.80); $I^2 = 0\%$; Analysis 1.16); oppositional behaviour (medium term: SMD 0.10, 95% CI −0.18 to 0.37; 2 studies, 224 participants; $Tau^2 = 0.00$; $Chi^2 = 0.80$, df = 1 (P = 0.37); $I^2 = 0\%$; Analysis 1.17); or socialisation behaviour (medium term: SMD −0.16, 95% CI −0.58 to 0.27; 1 study, 85 participants; Analysis 1.18).

Quality of life

There was no clear difference between omega-3 PUFA and placebo groups in the medium term: SMD −0.01, 95% CI −0.37 to 0.35; 1 study, 138 participants; Analysis 1.19.

Side effects

Side effects were reported at any time during the duration of the study.

There was moderate-certainty evidence that overall side effects did not differ between PUFA and placebo groups (RR 1.02, 95% CI 0.69 to 1.52; 8 studies, 591 participants; $Tau^2 = 0.06$; $Chi^2 = 6.97$, df = 5 (P = 0.22); $I^2 = 28\%$; Summary of findings 1). There was also no apparent difference between groups in appetite loss (RR 0.48, 95% CI 0.27 to 0.83; 1 study, 60 participants); anxiety (RR 0.38, 95% CI 0.11 to 1.28; 1 study, 60 participants); dermatitis (RR 1.43, 95% CI 0.06 to 34.36; 1 study, 147 participants); diarrhoea (RR 0.71, 95% CI 0.36 to 1.42; 3 studies, 207 participants; $Tau^2 = 0.00$; $Chi^2 = 0.00$, df = 1 (P = 0.96); $I^2 = 0\%$); gastrointestinal discomfort (RR 0.73, 95% CI 0.24 to 2.23; 3 studies, 269 participants; $Tau^2 = 0.00$; $Chi^2 = 0.02$, df = 1 (P = 0.88); $I^2 = 0\%$); headache (RR 0.54, 95% CI 0.30 to 0.97; 2 studies, 207 participants; $Tau^2 = 0.00$; $Chi^2 = 0.65$, df = 1 (P = 0.42); $I^2 = 0\%$); hyperactivity (RR 1.43, 95% CI 0.06 to 34.36; 1 study, 147 participants); insomnia (RR 0.27, 95% CI 0.07 to 1.12; 2 studies, 122 participants; $Tau^2 = 1.85$; $Chi^2 = 2.22$, df = 1 (P = 0.14); $I^2 = 55\%$); irritability (RR 0.07, 95% CI 0.00 to 1.12; 1 study, 60 participants); nausea (RR 1.00, 95% CI 0.43 to 2.33; 5 studies, 428 participants; $Tau^2 = 0.00$; $Chi^2 = 1.33$, df = 4 (P = 0.86); $I^2 = 0\%$); nose bleed (RR 0.75, 95% CI 0.16 to 3.58; 2 studies, 158 participants; $Tau^2 = 0.58$; $Chi^2 = 1.32$, df = 1 (P = 0.25); $I^2 = 24\%$); palpitations (RR 0.71, 95% CI 0.25 to 2.00; 1 study, 60 participants); tics (RR 0.46, 95% CI 0.07 to 3.27; 2 studies, 207 participants; $Tau^2 = 0.00$; $Chi^2 = 0.78$, df = 1 (P = 0.38); $I^2 = 0\%$); or tremor (RR 0.33, 95% CI 0.01 to 7.87; 1 study, 60 participants). See Analysis 1.20.

Loss to follow-up

Loss to follow-up likely did not differ between the PUFA and placebo groups (short term: RR 1.05, 95% CI 0.78 to 1.41; 10 studies, 785 participants; $Tau^2 = 0.00$; $Chi^2 = 3.51$, df = 7 (P = 0.83); $I^2 = 0\%$; medium term: RR 1.03, 95% CI 0.77 to 1.37; 13 studies, 1121 participants; $Tau^2 = 0.00$; $Chi^2 = 10.49$, df = 11 (P = 0.49); $I^2 = 0\%$; Analysis 1.21). We assessed the evidence that follow-up was similar between groups as of moderate certainty (Summary of findings 1).

No studies provided data on depressive or anxiety symptoms or cost.

Comparison 2: PUFA versus medication (stimulants)

Two trials compared PUFA to medication, in this case stimulants. One trial each compared PUFA with dexamfetamine, Arnold 1989, and with methylphenidate, Barragán 2017.

ADHD symptoms

In the short and medium term, total ADHD symptoms (short term: SMD 0.75, 95% CI 0.31 to 1.19; 2 studies, 96 participants; $Tau^2 = 0.01$; $Chi^2 = 1.13$, df = 1 (P = 0.29); $I^2 = 11\%$; medium term: SMD 0.62, 95% CI 0.10 to 1.13; 1 study, 60 participants; Analysis 2.1); inattention (short term: SMD 0.88, 95% CI 0.35 to 1.41; 1 study, 60 participants; medium term: SMD 0.47, 95% CI −0.04 to 0.98; 1 study, 60 participants; Analysis 2.2); and hyperactivity-impulsivity scores (short term: 0.66, 95% CI 0.25 to 1.07; 2 studies, 96 participants; $Tau^2 = 0.00$; $Chi^2 = 0.38$, df = 1 (P = 0.54); $I^2 = 0\%$; medium term: SMD 0.58, 95% CI 0.07 to 1.10; 1 study, 60 participants; Analysis 2.3) were lower in the group receiving stimulants. However, there was no difference in the long term for total ADHD symptoms (SMD 0.30, 95% CI −0.21 to 0.81; 1 study, 60 participants; Analysis 2.1); inattention (SMD 0.06, 95% CI −0.45 to 0.57; 1 study, 60 participants; Analysis 2.2); or hyperactivity/impulsivity (not estimable; 1 study, 60 participants; Analysis 2.3).

Neither study provided data on behavioural problems, quality of life, depressive or anxiety symptoms, side effects, loss to follow-up, or cost.

Comparison 3: omega-3 versus omega-6 PUFA

ADHD symptoms

Bélanger 2009 reported a cross-over trial of omega-3 PUFA versus omega-6 PUFA in 26 participants. Because variance was not reported and could not be calculated, mean data are presented in Table 1. The authors reported no clear differences between omega-3 and omega-6 PUFA groups in parent ratings of overall ADHD symptoms, inattention, or hyperactivity.

No studies provided data on behavioural problems, quality of life, depressive or anxiety symptoms, side effects, loss to follow-up, or cost.

Subgroup analyses

There was no difference between subgroups of studies that compared omega-3 PUFA to placebo and those that compared combined omega-3/omega-6 supplements to placebo in total parent-rated ADHD symptoms (Chi^2 = 1.23, df = 1, P = 0.27, I^2 = 18.8%; Analysis 3.1).

Sensitivity analyses

We used the primary outcome of parent-reported symptoms for the sensitivity analyses for bias and inclusion criteria. However, the primary outcome of symptoms could not be used to conduct sensitivity analysis for cross-over trials that did not report first-phase data, therefore the outcome of parent-rated inattention was used.

Bias

We conducted a sensitivity analysis for attrition bias. There was no difference between PUFA and control groups in parent symptom ratings, regardless of whether attrition bias was low risk (SMD −0.19, 95% CI −0.63 to 0.24; 4 studies, 295 participants; I^2 = 66%); unclear risk (SMD 0.01, 95% CI −0.20 to 0.22; 12 studies, 789 participants; I^2 = 54%); or high risk (SMD 0.06, 95% CI −0.65 to 0.78; 4 studies, 278 participants; I^2 = 82%) (Analysis 4.1).

Inclusion criteria

We also conducted a sensitivity analysis to evaluate whether there were any differences in findings in studies that used a clinician diagnosis of ADHD as an inclusion criterion compared to those that used scale cut-offs. Dashti 2014, Sinn 2007, and Moghaddam 2017 used scale cut-offs, but there was no difference in the effects of PUFA on ADHD total symptoms (SMD −0.59, 95% CI −0.90 to −0.27; 3 studies, 183 participants; I^2 = 0%) when these studies were compared to studies that only included participants with a clinician diagnosis of ADHD (SMD 0.04, 95% CI −0.15 to 0.23; 17 studies, 1179 participants; I^2 = 58%; Analysis 4.2).

Cross-over trials

There was no difference in short-term parent-rated inattention (Analysis 1.3) when sensitivity analyses were conducted without data from Aman 1987, the cross-over study for which first-phase data were unavailable (SMD 0.13, 95% CI −0.16 to 0.43; 5 studies, 223 participants), compared to parent-rated inattention when data from Aman 1987 were included (SMD 0.01, 95% CI −0.31 to 0.33; 5 studies, 283 participants).

Funnel plots

We undertook funnel plots for the three primary outcomes: parent-rated total ADHD symptoms (Figure 4), inattention (Figure 5), and hyperactivity/impulsivity (Figure 6). However, there was no obvious asymmetry of these plots that may have indicated publication bias.

Figure 4. Funnel plot for the comparison of PUFA versus placebo for ADHD symptoms - total, parent rated. *Footnotes* ADHD: attention deficit hyperactivity disorder; PUFA: polyunsaturated fatty acids; SE: standard error; SMD: standardised mean difference.

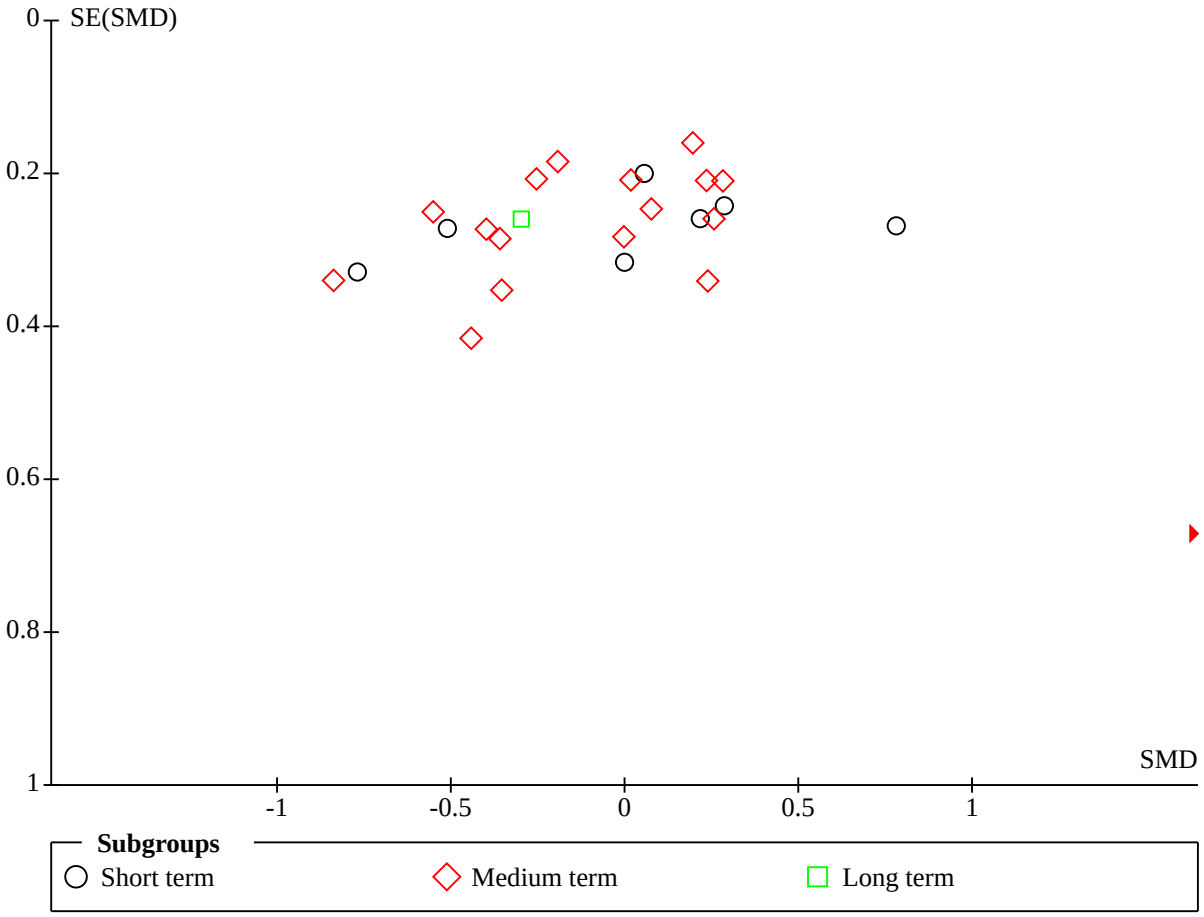


Figure 5. Funnel plot for the comparison of PUFA versus placebo for ADHD symptoms - inattention, parent rated.
Footnotes
ADHD: attention deficit hyperactivity disorder; PUFA: polyunsaturated fatty acids; SE: standard error; SMD: standardised mean difference.

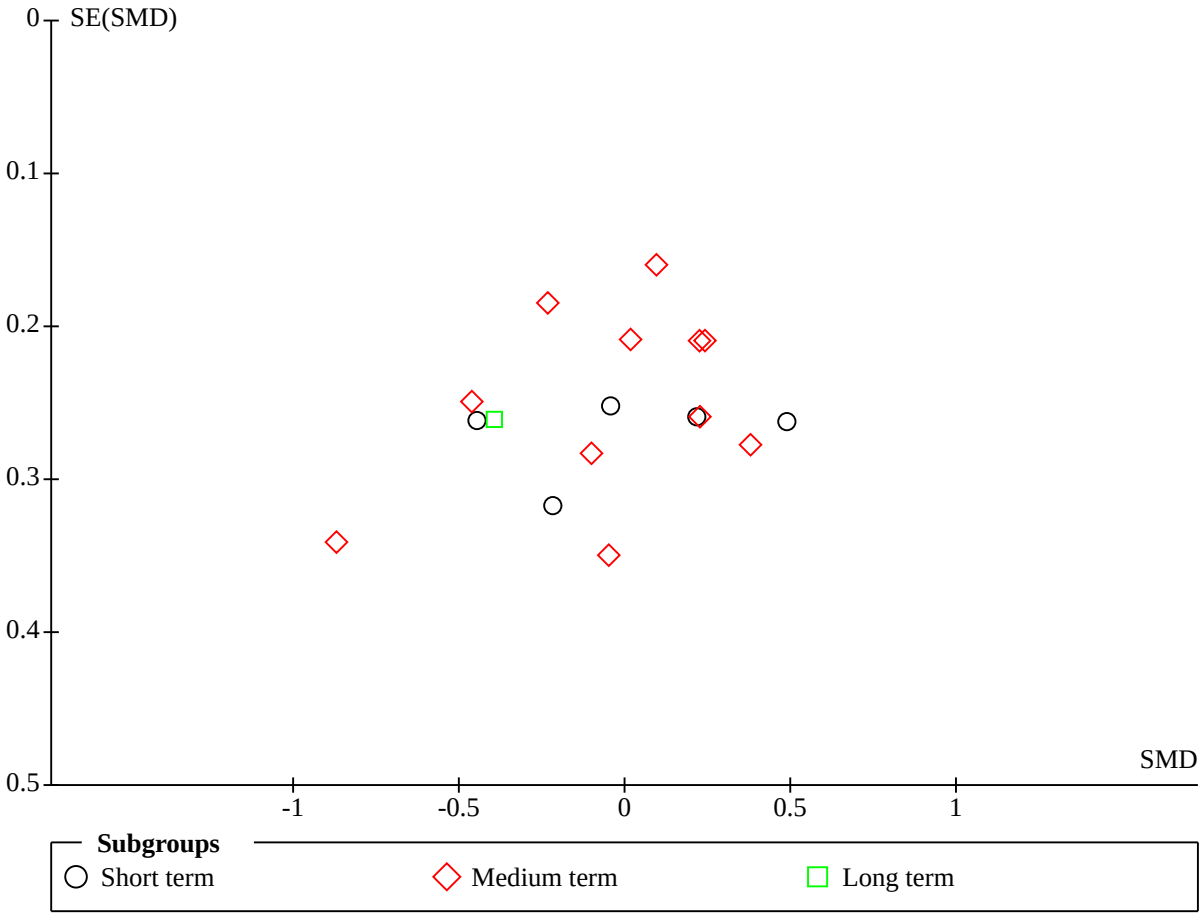
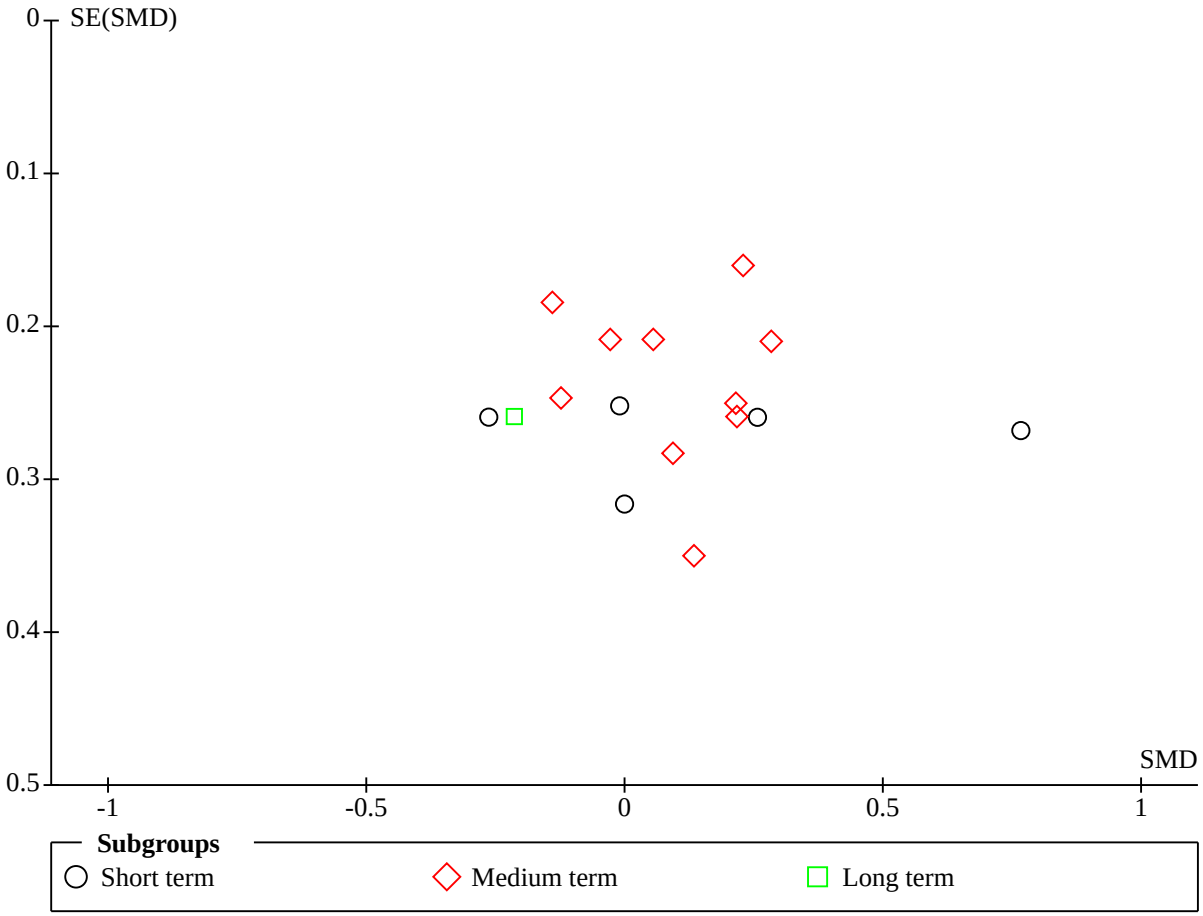


Figure 6. Funnel plot for the comparison of PUFA versus placebo for ADHD symptoms - hyperactivity/impulsivity, parent rated. *Footnotes*
ADHD: attention deficit hyperactivity disorder; PUFA: polyunsaturated fatty acids; SE: standard error; SMD: standardised mean difference.



DISCUSSION

Summary of main results

The number of trials of the effects of PUFA in children and adolescents with ADHD since our original review in 2012 has increased from 13 to 37 trials. Despite a nearly three-fold increase in the number of included trials, there remains little evidence that PUFA supplementation provides any benefit for the symptoms of ADHD in children and adolescents compared to placebo. As with the original review, there was low-certainty evidence that PUFA supplementation resulted in overall symptom improvement compared to placebo; however, there is now high-certainty evidence that PUFA does not improve overall ADHD symptoms or the inattention or hyperactivity/impulsivity symptoms domains compared to placebo.

Overall completeness and applicability of evidence

Compared to the earlier version of this review (Gillies 2012), there has been a marked increase in the number of randomised controlled trials investigating the effectiveness of PUFA supplementation in children and adolescents with ADHD, although there are still very few that are of high quality. Most trials still have small sample sizes and highly variable selection criteria; use supplements that vary greatly in terms of dosage and constituents; do not address the use or non-use of stimulant medications; and follow up participants for short periods.

There was large variation in the constituents and dosages of PUFA supplements. Supplements used in the included trials included omega-3 alone, omega-6 alone, and combinations of omega-3 and omega-6 PUFA. The number of trials that investigated the effects of omega-6 PUFA (in the absence of omega-3 PUFA) was surprising given that the evidence for a role of PUFA in ADHD points to omega-3 supplements rather than omega-6 PUFA (Raz 2009b; Richardson 2000; Richardson 2006). In addition, pure PUFA supplements were not used in most studies, and non-PUFA constituents were not replicated in the placebo. For example, PUFA supplements commonly include vitamin E as an antioxidant, but in most cases this was not included in the placebo. In future trials, more attention needs to be given to the constituents of PUFA supplements and placebos so that any beneficial effects, or lack thereof, may be more clearly attributed to PUFA supplementation. There also needs to be more consideration in the type and dosage

of PUFA that is used. It may be most appropriate to base the type of supplement and dosages on supplements that have previously resulted in significant increases in plasma PUFA; for example, see Voigt 2001, Stevens 2003, and Gustafsson 2010.

A particular limitation was that follow-up in all studies was very short, with most trials conducted for 16 weeks or less. Because it may take up to three months for the brain to recover from a chronic PUFA deficiency (Richardson 2000), most of these trials may have been too short to demonstrate a benefit. Future trials should therefore ensure that follow-up extends beyond three months and preferably is considerably longer.

Although the premise for the effectiveness of supplementation is a deficiency of PUFA in children and adolescents with ADHD, it is unclear how long-lasting any effects of supplementation would be. Parallel-design trials may therefore be more appropriate than cross-over studies, which may be associated with carry-over effects of PUFA.

Compliance is also likely to be an issue in these trials because participants were commonly expected to take multiple capsules each day (up to eight), and loss to follow-up was reported because participants could not swallow capsules. Although compliance was quite high in the five trials where it was reported (88% to 97% in the PUFA group and 86% to 100% in the placebo group, Table 2), in future trials it may be preferable to identify supplements that can deliver an appropriate dose in a smaller number of capsules.

The importance of including learning-related outcomes was identified by one of the editors during completion of this review. It is therefore important that such outcomes are included in future updates of this review.

Quality of the evidence

We assessed the evidence that children and adolescents receiving PUFA were more likely to improve compared to those receiving placebo to be of low certainty due to imprecision and overall risk of bias. We downgraded the certainty of evidence for improvement by two levels: one level for high risk of bias, as only 50% of risk of bias domains across all studies were rated low risk; and one level for serious imprecision, as data came from only three randomised controlled trials with 191 participants. However, there was high-certainty evidence that PUFA had no effect on total ADHD symptoms.

There was also high-certainty evidence that inattention and hyperactivity/impulsivity did not differ between PUFA and placebo groups. There was moderate-certainty evidence that overall side effects did not differ between PUFA and placebo groups. There was also moderate-certainty evidence that follow-up was similar between groups. We downgraded the certainty of evidence for both overall side effects and medium-term loss to follow-up by one level for serious imprecision, as meta-analytic estimates had very wide confidence intervals.

Ensuring adequate blinding may be crucially important in this area of research. Despite overall negative findings in a systematic review of essential fatty acids and ADHD (Raz 2009b), positive findings of PUFA supplementation were reported in all four open-label trials. A major difficulty with omega-3 PUFA supplementation is masking the distinctive smell and taste of fish oil (Schachter 2005). It is therefore likely that parents were aware when their children were receiving an omega-3 supplement, which could explain why parent ratings were more much likely to show improvement than teacher ratings.

The risk of attrition and reporting bias was high in the majority of included trials, which may have resulted in overestimates of benefits associated with PUFA supplementation.

Systematic reviews of the literature have shown that industry-funded research that identifies a beneficial effect of the industry product is more likely to be published (Golder 2008; Lexchin 2003). Because most of the included trials were funded by the suppliers of the supplement being tested, this may indicate a publication bias in the identified literature.

Potential biases in the review process

As fewer than half of the included trials contributed to any of the meta-analyses in this review, there are substantial risks of reporting bias. A potential bias is the possibility that relevant studies may not have been identified, particularly studies that are not published in English. A major potential bias is the lack of available data from studies that have been identified from clinical trials registers but do not yet appear to have reported data or made data available.

Agreements and disagreements with other studies or reviews

In our original review, Gillies 2012, several narrative reviews of the effectiveness of PUFA in ADHD were identified (Raz 2009b; Richardson 2006; Schachter 2005). All of these reviews found no conclusive evidence of a beneficial role of omega-3 or omega-6 PUFA in people with ADHD.

Since 2012, several additional systematic reviews and meta-analyses covering this topic have been published. In addition to the meta-analysis by Bloch 2011, which was published while we were completing our original review (Gillies 2012), seven further systematic reviews and meta-analyses of the effects of omega-3 supplementation have been published (Agostoni 2017; Calderón-Moore 2012; Chang 2018; Cooper 2015; Derbyshire 2017; Goode 2018; Kemper 2018).

Four of these reviews found no evidence of an effect of supplementation. In a systematic review of omega-3 and omega-6 fatty acid supplementation in developmental neurological disorders in paediatric patients, Calderón-Moore 2012 found no significant difference in ADHD symptoms in the five identified trials. Kemper 2018 reported that a meta-analysis of seven identified trials comparing omega-3 and omega-6 PUFA to placebo showed no effect on ADHD symptoms in children and adolescents. Cooper 2015 identified 24 studies evaluating the effectiveness of omega-3 PUFAs on cognitive outcomes in children and adults with and without ADHD but found no benefits of PUFA. In meta-analyses of seven trials of children and adolescents, Goode 2018 also found no significant effects of omega-3 or omega-6 PUFA on parent- or teacher-rated total ADHD symptoms.

A beneficial effect of PUFA was reported in meta-analyses by Bloch 2011, Chang 2018, and Sonuga-Barke 2013. Bloch 2011 found a small improvement in ADHD symptoms in the group receiving omega-3 supplementation (10 studies with 699 children). Sonuga-Barke 2013 reported a beneficial effect of omega-3 and omega-6 PUFA across 11 studies of children and

adolescents, and Chang 2018 found that omega-3 PUFAs decreased symptom scores in children and adolescents with ADHD (7 studies with 534 participants). Two other systematic reviews without meta-analyses reported a notable proportion of studies that reported benefits of PUFA. These included Derbyshire 2017, who reported that, of 16 trials of omega-3/6 fatty acids in children and adolescents, 13 reported favourable benefits on ADHD symptoms, and Agostoni 2017, who reported that positive results were identified in nine of 25 trials of omega-3 PUFA in all ages.

Stevenson 2014 compared our original meta-analyses, Gillies 2012, with two other reviews by Bloch 2011 and Sonuga-Barke 2013, which had found a significant effect of PUFA. Stevenson 2014 noted that the effect was not significant in our review because the number of trials included in our analysis was fewer than that reported by Sonuga-Barke 2013. However, we had included all 10 studies included by Bloch 2011 and all 11 studies included by Sonuga-Barke 2013. Rather, the difference in effect was due to the fact that Bloch 2011 had pooled measures of ADHD symptoms reported by different raters, and Sonuga-Barke 2013 had synthesised data across raters and also used domain scores where total scores were not available.

AUTHORS' CONCLUSIONS

Implications for practice

Although there has been a substantial increase in the number of trials since our original review, we did not find evidence that attention deficit hyperactivity disorder (ADHD) symptoms are likely to improve in children and adolescents with ADHD receiving polyunsaturated fatty acids (PUFA) supplements. We found high-certainty evidence that PUFA had no effect on total parent-rated ADHD symptoms, inattention, or hyperactivity/impulsivity, with only low-certainty evidence of improvement. Consequently, even with moderate-certainty evidence that side effects and loss to follow-up were not increased by PUFA, there is little evidence to recommend PUFA supplementation as a treatment for ADHD in children and adolescents.

Implications for research

Despite the large increase in the number of trials, data are still inadequate to conclude whether PUFA supplementation in children and adolescents with ADHD is effective. Overall, there is moderate- to high-certainty evidence that PUFA supplementation does not provide any benefit for the symptoms of ADHD in children and adolescents.

It seems unlikely that future high-quality research will identify any benefits of PUFA on ADHD symptoms without more consistent approaches to supplementation. Given the lack of consistency in PUFA types and dosages, future studies could focus on active PUFA supplements at dosages that have previously been shown to significantly increase circulating PUFA. In addition, given evidence indicating that the ratio of omega-3 to omega-6 PUFA may be more important than omega-3 supplements alone, trials of omega-3 and omega-6 PUFA at optimal ratios may be more effective. Furthermore, because follow-up in the included studies was short term, longer-term trials of PUFA may be more able to identify beneficial effects. Future trials should also prevent potential biases that were identified in the included trials, such as inadequate sample sizes and follow-up, valid and reliable selection criteria, and complete reporting of outcomes.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aman 1987

Study characteristics	
Methods	**Design:** cross-over trial **Comparison:** omega-6 PUFA vs placebo
Participants	**Inclusion criteria:** 1. children with scores on the Attention Problem subscale of the Revised Behavior Problem Checklist (RBPC) and Inattention subscale of the Conners Teacher questionnaire above the 90th percentile (n = 26; note, 5 additional children diagnosed with DSM-III ADD by a child psychiatrist were also included, therefore the total sample size was 31 children) **Exclusion criteria:** not stated **Number of participants:** 31 **Mean age:** 8.86 years **Gender:** 27 boys and 4 girls **ADHD subtypes:** not stated **Using ADHD drugs at baseline:** 0% **Baseline scores:** IQ = 101.07; Conners' inattention subscale = 3.08; Conners' hyperactivity subscale = 2.80; RBPC attention problem scale = 20.42; and motor excess = 6.23 **Setting:** Auckland, New Zealand, year/s not stated **Funding:** supported by grants from Efamol Research
Interventions	**Intervention (31 participants):** omega-6 PUFA for 4 weeks; 3 capsules of Efamol, containing 360 mg of linoleic acid and 45 mg of gamma-linoleic acid, after 1-week washout **Control (31 participants):** placebo for 4 weeks; 3 capsules of 500 mg of liquid paraffin taken twice daily, after a 1-week washout
Outcomes	1. ADHD symptoms at 4 weeks a. Parent-rated Revised Behavior Problem Checklist (RBPC) subscales: attention and motor excess b. Teacher-rated Conners Questionnaire subscales: inattention and hyperactivity c. ADD-H Comprehensive Teacher Rating Scale (ACTeR) subscales: attention and hyperactivity 2. Behaviour at 4 weeks a. Parent-rated RBPC subscales: conduct; socialised aggression b. Teacher-rated Conners Questionnaire subscales: conduct c. ACTeR (Comprehensive Teacher Rating Scale) subscales: oppositional behaviour
Notes	**Comment:** variances were estimated from baseline data

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Aman 1987 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	**Comment:** not stated
Allocation concealment (selection bias)	Unclear risk	**Comment:** not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment:** The authors stated that the trial was double-blind and that the intervention and control were given as "indistinguishable capsules" (p78).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** capsules "indistinguishable" (p78), and parent and teacher-rated scales used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** Unclear how many participants were randomised
Selective reporting (reporting bias)	Low risk	**Comment:** data reported for all outcomes listed in paper
Other bias	High risk	**Comment:** It was not clear whether the additional 5 children included in the trial would have met the original inclusion criteria. Baseline characteristics of each group were not reported. The trial was funded by Efamol Research Inc.

Anand 2016

Study characteristics	
Methods	**Design:** parallel trial **Comparison:** omega-3 PUFA + atomoxetine vs atomoxetine
Participants	**Inclusion criteria:** 1. children aged 4 to 11 years with ADHD; 2. screened by a psychiatrist using DSM-IV criteria and Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (K-SADS-PL) **Exclusion criteria:** 1. acute physical illness, requiring hospital admission; 2. autism; 3. mental retardation; 4. chronic physical disability; 5. psychosis; 6. on other medication or nutritional supplements or using street drugs **Number of participants:** 50 **Mean age:** 6 years **Gender:** 35 boys and 15 girls **ADHD subtypes:** combined = 33; inattentive = 9; hyperactive = 8 **Using ADHD drugs at baseline:** 0% **Baseline scores:** Conners Parent Rating Scale - Revised scores: omega-3 = 39.1 (SD 2.12), placebo = 38.4 (SD 2.31) **Setting:** paediatric and psychiatry departments of a tertiary care hospital, India, year/s not stated **Funding:** not stated

Anand 2016 *(Continued)*

Interventions	**Intervention (25 participants):** omega-3 PUFA + atomoxetine for 4 months; 180 mg of EPA plus 120 mg of DHA plus 0.5 mg/kg/day of atomoxetine **Control (25 participants):** atomoxetine for 4 months; 0.5 mg/kg/day
Outcomes	1. ADHD symptoms at 4 months a. Conners Parent Rating Scale - Revised
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** generated by “Computer generated table” (p2)
Allocation concealment (selection bias)	Low risk	**Comment:** The drugs allocations were stored in an envelope and “assigned by an independent pharmacist” (p2)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** states it is “double-blinded” (quote)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** states it is “double blind” (p1)
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** appears to have been 100% follow-up - no one dropped out
Selective reporting (reporting bias)	Unclear risk	**Comment:** data only reported for 4 months but collected every 2 weeks up to 4 months
Other bias	Low risk	**Comment:** no apparent difference between groups in age, gender or type of ADHD

Arnold 1989

Study characteristics

Methods	**Design:** cross-over trial **Comparison:** omega-6 PUFA vs dexamfetamine vs placebo
Participants	**Inclusion criteria:** 1. children of normal intelligence; 2. aged between 6 and 12 years; 3. with a DSM-III diagnosis of ADHD by a child psychiatrist; 4. a score of at least 18 on the Conners Hyperactivity Index; and 5. a score of at least 24 on the first 6 items of David's Hyperkinetic Rating Scale **Exclusion criteria:** 1. psychoactive drug use in the preceding week; 2. history of seizures **Number of participants:** 18

Arnold 1989 *(Continued)*

	Mean age: not reported; median = 9 years **Gender:** all 18 participants were boys **ADHD subtypes:** not stated **Using ADHD drugs at baseline:** 0% within previous week **Baseline scores:** not stated **Setting:** Ohio, USA, year/s not stated **Funding:** grant from the Efamol Research Institute
Interventions	**Intervention** 1. **Omega-6 PUFA (18 participants):** 4 capsules, twice daily for 1 month, of Efamol capsules containing 500 mg of evening primrose oil, which provides 350 mg of linoleic acid and 40 mg of gamma linolenic acid, and 13 IU of vitamin E as a preservative 2. **Dexamfetamine for 1 month (18 participants):** 4 capsules, twice daily for 1 month, of a 10- or 15-milligram time-released capsule **Control:** placebo for 1 month; 4 capsules, twice daily, of paraffin oil
Outcomes	1. ADHD symptoms at 2 and 4 weeks a. Teacher-rated Conners total score and Hyperactivity Index
Notes	Outcome data were not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** not stated
Allocation concealment (selection bias)	Unclear risk	**Comment:** not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** placebo was described as matched
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** behavioural ratings were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** unclear how many were enroled, 18 participants completed
Selective reporting (reporting bias)	High risk	**Comment:** Teacher-rated Conners' total score and Hyperactivity scores were not reported. Unclear what other outcomes were used. A parent rating of the Conners scale appears to have been used but was not reported.
Other bias	High risk	**Comment:** baseline characteristics of each group were not reported. Results for a Psychiatrists' Global Rating scale were reported but this scale was not described. Study funded by Efamol Research Institute

Assareh 2017

Study characteristics	
Methods	**Design:** parallel trial **Comparison:** omega-3 or omega-6 + MPH PUFA vs MPH
Participants	**Inclusion criteria:** 1. children with ADHD aged between 6 and 12 years; 2. with DSM-IV diagnosis by 2 subspecialists in child and adolescent psychiatry; 3. scored more than 20 on the Parent ADHD Rating Scale **Exclusion criteria:** 1. psychiatric disorder other than oppositional defiant disorder or learning disability; 2. IQ < 70; 3. use of any psychotropic, opioid, or other drugs affecting the CNS in the previous 2 weeks; 4. any significant neurologic disease; 5. PUFAs more than once a week **Number of participants:** 40 **Mean age:** 9.1 years **Gender:** not stated **ADHD subtypes:** not stated **Using ADHD drugs at baseline:** 0% within previous 2 weeks **Baseline scores:** ADHD Rating Scale total score: omega-3 = 34 (SD 6); placebo = 37 (SD 6) **Setting:** hospital clinic, Iran, 2009 to 2010 **Funding:** supported in part by a grant from the Behavioral Sciences Research Center of Shahid Beheshti University of Medical Sciences (Tehran, Iran)
Interventions	**Intervention (no. of participants unclear):** omega-3/omega-6 PUFA + MPH over 2 weeks; 80 mg of omega-6, 241 mg of DHA, and 33 mg of EPA, given once daily, plus MPH **Control (no. of participants unclear):** MPH over 2 weeks; 1 mg/kg/day of MPH (increased from 0.3 mg/kg/day over 2 weeks) in 2 daily divided doses
Outcomes	1. ADHD improvement at 2, 4, 6, 9, and 10 weeks a. 25% decrease in Parent ADHD Rating Scale 2. ADHD symptoms at 2, 4, 6, 9, and 10 weeks a. Parent ADHD Rating Scale: total score and inattention and hyperactivity subscale scores
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Comment:** Patients were given numbers on attendance and “desired numbers were included” but states they were “randomly assigned” (p79).
Allocation concealment (selection bias)	Unclear risk	**Comment:** Patients were given numbers on attendance and “desired numbers were included” (p79).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** states it was double-blind

Assareh 2017 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** states it was double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** not clear how many were enroled and not clear how many were in each group
Selective reporting (reporting bias)	Low risk	**Comment:** all outcomes listed in paper and protocol IRCT138803122000N1 were reported
Other bias	Unclear risk	**Comment:** no significant difference between groups in age, gender or ODD

Barragán 2017

Study characteristics	
Methods	**Design:** parallel trial **Comparison:** omega-3/omega-6 PUFA + MPH vs MPH
Participants	**Inclusion criteria:** 1. aged 6 to 12 years; 2. newly diagnosed with ADHD of any subtype; 3. diagnosed according to DSM-IV-TR criteria **Exclusion criteria:** 1. neurologic disorders; 2. autism; 3. pervasive developmental disorder; 4. hypersensitivity to omega-3 or omega-6; 5. previous pharmacotherapy for ADHD; 6. chronic conditions; 7. medications for chronic conditions; 8. not receiving school assistance **Number of participants:** 107 (60 completed) **Mean age:** 8.27 years **Gender:** not stated **ADHD subtypes:** combined = 51; inattentive = 32; hyperactive-impulsive = 7 **Using ADHD drugs at baseline:** 0% **Baseline scores:** ADHD Rating Scale: omega-3 + MPH or omega-6 + MPH = 42.03 (SD 4.00), MPH = 41.43 (SD 4.3) **Setting:** neurology department, children's hospital, Mexico, 2009 to 2010 **Funding:** funded within the scope of an unrestricted grant provided by Vifor Pharma
Interventions	**Intervention (30 participants):** omega-3/omega-6 PUFA + MPH for 12 months; Equazen capsules contained 558 mg of EPA, 174 mg of DHA, and 60 mg of gamma-linolenic acid **Control (30 participants):** MPH for 12 months; 0.5 mg/kg/day (titrated weekly over 2 weeks from 0.3 mg/kg/day) Mean doses were higher (1 mg/kg) in the MPH group than in the omega-6 + MPH group (0.8 mg/kg).
Outcomes	1. Parent-rated ADHD improvement at 12 months a. 30% or more decrease in ADHD total score 2. Parent- and investigator-rated ADHD symptoms at 1, 3, 6, 12 months a. ADHD Rating Scale

Barragán 2017 *(Continued)*

b. Clinical Global Impressions scale

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Comment:** A random numbers table was used to allocate participants
Allocation concealment (selection bias)	High risk	**Quote:** the authors stated the study was "unblinded" (p4)
Blinding of participants and personnel (performance bias) All outcomes	High risk	**Quote:** allocation was not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	**Quote:** allocation was not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** analysis based on last observation carried forward; total loss to follow-up: 13/60
Selective reporting (reporting bias)	Low risk	**Comment:** all outcomes listed in paper appear to have been reported
Other bias	High risk	**Comment:** doses off MPH were statistically lower in omega-3/omega-6 group. Funded by Vifor Pharma.

Behdani 2013

Study characteristics	
Methods	**Design:** parallel trial **Comparison:** omega-3 PUFA + MPH vs placebo + MPH
Participants	**Inclusion criteria:** 1. children aged 7 to 15 years; 2. diagnosed with ADHD (DSM-IV-TR) by a child and adolescent psychiatrist; 3. at least 1.5 SD above norms for ADHD-RS-IV **Exclusion criteria:** 1. patients with a comorbid psychiatric diagnosis; 2. history or current diagnosis of pervasive developmental disorder; 3. evidence of suicide risk; 4. IQ < 70; 5. hypertension; 6. hypotension; 7. serious organic problems, 8. already under treatment **Number of participants:** 69 **Mean age:** 8.7 (SD 1.7) years **Gender:** 55 boys and 14 girls **ADHD subtypes:** inattentive = 15; hyperactive = 26; mixed = 28

Behdani 2013 *(Continued)*

	Using ADHD drugs at baseline: 0% **Baseline scores:** Parents' ADHD rating score: omega-3 + MPH = 27, placebo + MPH = 30; Teachers' score: omega-3 + MPH = 18, placebo + MPH = 28 **Setting:** outpatient child and adolescent psychiatry clinic, Dr Sheikh Pediatric Hospital, Mashhad city, Iran, 2007 **Funding:** not stated
Interventions	**Intervention (36 participants):** omega-3 + MPH* for 8 weeks; omega-3 (2000 mg/day, Novartis) given as 2 1000-milligram capsules (containing 240 mg of DHA and 360 mg of EPA) per day **Control (33 participants):** placebo + MPH* for 8 weeks; placebo given in similar capsules to the omega-3 capsules *The initial dose of methylphenidate (Novartis) was 2.5 to 5 mg/day titrated weekly, to a final dose of 1 mg/kg (maximum dose = 60 mg/day) in 2 or 3 divided doses.
Outcomes	1. ADHD symptoms at 2, 4, and 8 weeks a. Parent and Teacher ADHD Rating Scale IV
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** randomised using computer-generated code
Allocation concealment (selection bias)	Unclear risk	**Comment:** not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Quote:** "all investigational staff members who performed efficacy and tolerability rating scales were blind to the patient treatment group" (p654-5)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** analysis done on 69/75 enroled participants who completed the trial
Selective reporting (reporting bias)	Low risk	**Comment:** all outcomes listed in paper were reported
Other bias	Unclear risk	**Comment:** baseline teacher-rated ADHD score was 18 in experimental group and 28 in placebo group, but 27 and 30, respectively on the parent-rated scale

Bos 2015

Study characteristics

Methods	**Design:** parallel trial

Bos 2015 *(Continued)*

	Comparison: omega-3 PUFA nutritional supplement vs placebo
Participants	**Inclusion criteria:** 1. boys between 8 and 14 years of age; 2. with a DSM-IV diagnosis or ADHD, confirmed via Diagnostic Interview Schedule for Children-Parent Version (DISC-P); 3. were medication naïve or using psychostimulant medication **Exclusion criteria:** 1. any DISC-P-confirmed diagnosis of a psychiatric condition in children or first-degree relatives **Number of participants:** 40 (38 completed) **Mean age:** 10.3 years **Gender:** 40 boys and 0 girls **ADHD subtypes:** not stated **Using ADHD drugs at baseline:** some children were using MPH, but it is not clear how many **Baseline scores:** Child Behavior Checklist ADHD scores: omega-3 = 8.8, placebo = 9.0 **Setting:** Department of Psychiatry, University Medical Center, Utrecht, the Netherlands, year/s not stated **Funding:** this study was financially supported by Unilever Research & Development
Interventions	**Intervention (19 participants):** omega-3 PUFA nutritional supplement; daily dose of 10 g of omega-3-fortified margarine for 16 weeks. It was a full-fat (80%) margarine, containing 650 mg of DHA and 650 mg of EPA per 10-gram serving. **Control (19 participants):** placebo; daily dose of 10 g of normal margarine for 16 weeks
Outcomes	1. ADHD diagnosis at 16 weeks a. DSM-IV diagnosis of ADHD confirmed by trained researcher with Diagnostic Interview Schedule for Children-Parent Version (DISC-P) 2. ADHD symptoms at 16 weeks a. Child Behavior Checklist (CBCL) b. Teacher Report Form (TRF) c. Strengths and Weaknesses of ADHD symptoms and Normal behavior scale (SWAN) 3. Behaviour at 16 weeks a. Parent-rated CBCL: aggression
Notes	Values are percentage counts, mean, median, range, SE/SEM, SD, and 95% CI.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	**Comment:** Participants were randomly assigned --- by a member of the Unilever Center for Nutritional Intervention Trials.
Allocation concealment (selection bias)	Unclear risk	**Comment:** allocation not described but stated study was double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "Double-blind randomised placebo-controlled dosing, where investigators, parents, and participants were all blind to the treatment conditions." (p2300)
Blinding of outcome assessment (detection bias)	Low risk	**Quote:** "investigators, parents, and participants were all blind to the treatment conditions." (p2300)

Bos 2015 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** ITT analysis used for 76/79 who completed
Selective reporting (reporting bias)	Unclear risk	**Comment:** Teacher Report Form was excluded because of low response rate. The SWAN was collected five times to measure change over time but was not reported.
Other bias	High risk	**Comment:** This study was financially supported by Unilever Research & Development.

Brue 2001

Study characteristics	
Methods	**Design:** parallel trial **Comparison:** omega-3 PUFA + dietary supplement vs dietary supplement
Participants	**Inclusion criteria:** 1. children diagnosed with DSM-IV ADHD-combined type by a physician or psychologist **Exclusion criteria:** 1. serious pre-existing medical or psychological condition; 2. stimulant medication other than methylphenidate (Ritalin) **Number of participants:** 51 **Mean age:** 8.4 years **Gender:** 44 boys and 7 girls at follow-up (number of participants at enrolment was not reported) **Using ADHD drugs at baseline:** % **ADHD subtypes:** combined; inattentive; hyperactive **Baseline scores:** not stated **Setting:** USA, year/s not stated **Funding:** not stated
Interventions	**Intervention (no. of participants not stated):** omega-3 PUFA for 12 weeks; 100 mg of flax seed (rich in omega-3 PUFA) plus double dietary supplement; 20 mg of Ginkgo biloba, 400 mg of Melissa officinalis, 60 mg of Grapine, 70 mg of dimethylaminoethanol, and 200 mg of l-glutamine **Control (no. of participants not stated):** double dietary supplement for 12 weeks; 20 mg of Ginkgo biloba, 400 mg of Melissa officinalis, 60 mg of Grapine, 70 mg of dimethylaminoethanol, and 200 mg of l-glutamine Note: this was the second of two 12-week trials. In this second trial, an omega-3 PUFA in combination with a dietary supplement (given to the group who received a single dietary supplement in trial 1) was compared to a double dose of the dietary supplement (placebo group in trial 1). Both were given twice a day for 12 weeks.
Outcomes	1. ADHD symptoms at 12 weeks

Brue 2001 *(Continued)*

a. Parent- and teacher-rated Conners Rating Scales (revised: long form): inattentive and hyperactive-impulsive subscales

Notes	Outcome data could not be used in meta-analysis as variances were not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** not stated
Allocation concealment (selection bias)	Unclear risk	**Comment:** not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment:** Parents and teachers did not know which group the participant was allocated to until the trial was completed. Only the trial physician had access to this information.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** Data collectors did not know which group the participants were allocated to until the trial was completed.
Incomplete outcome data (attrition bias) All outcomes	High risk	**Comment:** 9/60 children lost to follow-up but not clear what sample numbers were used in the analysis
Selective reporting (reporting bias)	Low risk	**Comment:** all outcomes listed in paper were reported
Other bias	Unclear risk	**Comment:** baseline characteristics of each group not reported. The PUFA group had received an additional 12 weeks of dietary supplement before this second trial was started.

Bélanger 2009

Study characteristics

Methods	**Design:** cross-over trial **Comparison:** omega-3 vs omega-6 PUFA
Participants	**Inclusion criteria:** 1. children aged 6 years 11 months to 11 years 11 months; 2. with DSM-IV diagnosis based on parent and teacher questionnaires and clinical evaluation; 3. an IQ above 85 on the Wechsler Intelligence Scale for Children **Exclusion criteria:** 1. children with mental health disorders (except ADHD comorbidity); 2. taking ADHD medication, sedatives, anxiolytics, or antipsychotics; 3. with a medical condition requiring long-term treatment; 4. allergy to sunflower or fish oil; 5. coagulation disorders. Children who consumed natural medicine products, fish, flaxseed oil, and omega-3-enriched food during the trial were also excluded. **Number of participants:** 36 (26 completed) **Mean age:** 9.2 years

Bélanger 2009 *(Continued)*

	Gender: 18 boys and 8 girls at completion of both phases **ADHD subtypes:** inattentive = 20; other = 17 **Using ADHD drugs at baseline:** 0% **Baseline scores:** DSM-IV symptoms: omega-3 = 74.2, omega-6 = 71.1; hyperactive-impulsive: omega-3 = 67.7, omega-6 = 66.9; inattentive: omega-3 = 76.4, omega-6 = 71.3 **Setting:** ADHD clinic, Montreal, Canada, year/s not stated **Funding:** JA DeSève Research Chair in Nutrition (EL) and NutriSanté Inc (Canada) - financial support and gift of n-3 and n-6 capsules.
Interventions	**Intervention (13 participants):** omega-3 PUFA for 8 weeks; children received between 2 and 4 capsules daily based on body weight; each capsule (Nutri-Santé, Canada) contained 25 mg of phospholipids, 250 mg of EPA, 100 mg of DHA, and 3.75 units of vitamin E **Control (13 participants):** omega-6 PUFA for 8 weeks (described as placebo, Nutri-Santé, Canada); each capsule contained 500 mg of sunflower oil, which included 70% of linoleic acid, 20% of oleic acid, 5% of palmitic and stearic acid, and 3.75 units of vitamin E. It is unclear how many of these capsules were given.
Outcomes	1. ADHD symptoms at 8 weeks a. Parent- and teacher-rated Strengths and Weaknesses of ADHD symptoms and Normal behavior scale (SWAN) b. Parent- and teacher-rated Conners questionnaires. All were measured. 2. Side effects at 8 weeks
Notes	First-phase data were collected for this review. Variances were not reported, therefore data could not be included in a meta-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** not stated
Allocation concealment (selection bias)	Unclear risk	**Comment:** not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** The authors stated that this was a double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** described as a double-blind trial but no further detail given
Incomplete outcome data (attrition bias) All outcomes	High risk	**Comment:** data reported for 26/37 enroled participants at the end of both 8-week phases
Selective reporting (reporting bias)	High risk	**Comment:** data from the teacher-rated Conners and SWAN questionnaires were not reported
Other bias	High risk	**Comment:** The trial was funded by Nutri-Santé.

Chang 2019

Study characteristics	
Methods	**Design:** parallel trial **Comparison:** omega-3 PUFA vs placebo
Participants	**Inclusion criteria:** 1. children and adolescents aged 6 to 18 years; 2. DSM-5 diagnosis of ADHD with either inattention, hyperactivity, or combined presentation; 3. drug naïve or had no medication for the past 6 months **Exclusion criteria:** 1. IQ < 70, based on a documented history of mental retardation; 2. for those ages 6 to 12 years old, a Peabody Picture Vocabulary Test-Revised (PPVT-R) percentile scores less than 5% (indicating speech delay or intellectual disability); 3. other comorbid psychiatric disorders, such as autism spectrum disorder, anxiety disorder, conduct disorder, and other major psychiatric disorders; 4. comorbid physical disorders, such as thyroid dysfunction and cerebral palsy; 5. currently using omega-3 PUFAs supplements; 6. allergy to omega-3 PUFAs **Number of participants:** 103 (92 completed) **Mean age:** 9.49 years **Gender:** 79 boys and 13 girls **ADHD subtypes:** not stated **Using ADHD drugs at baseline:** drug naïve or no medication in the previous 6 months **Baseline scores:** SNAP-IV total scores: omega-3 = 31.25, placebo = 32.41 **Setting:** Department of Psychiatry, Taiwan, 2016 to 2017 **Funding:** not stated
Interventions	**Intervention (48 participants):** omega-3 PUFA for 12 weeks; EPA as 1.2 g/day soybean oil **Control (44 participants):** placebo for 12 weeks
Outcomes	1. ADHD symptom scores at 1, 2, 4, 8, and 12 weeks a. SNAP-IV rated by parents, teachers, and youth (ages 12 years or older) 2. Behaviour at 12 weeks a. SNAP-IV rated by parents: oppositional behaviour b. Parent-rated Strengths and Difficulties Questionnaires: conduct, internalising, externalising behaviour
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	“The randomisation numbers were generated from the computer”
Allocation concealment (selection bias)	Unclear risk	“The investigators were blinded to both the group allocation during the study and when assessing the outcome measurements.”
Blinding of participants and personnel (performance bias)	Unclear risk	“double-blind”

Chang 2019 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated "Investigators were blinded to both the group allocation during the study and when assessing the outcome measurements."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	11/103 participants lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Did not report SDQ or WISC-IV scores
Other bias	Unclear risk	No comparison of characteristics of intervention and placebo groups although baseline scores were reported

Cornu 2018

Study characteristics	
Methods	**Design:** parallel trial **Comparison:** omega-3 PUFA vs placebo
Participants	**Inclusion criteria:** 1. children and adolescents aged 6 to 15 years; 2. referred for hyperactivity symptoms; 3. diagnosed with ADHD by child psychiatrists according to DSM-IV-TR criteria **Exclusion criteria:** 1. known intolerance to omega-3 fatty acids; 2. intake of fatty acid or fish oil dietary supplements for more than 1 week during the previous 3 months; 3. MPH or other ADHD drug during the previous month or required MPH treatment **Number of participants:** 160 (145 completed) **Mean age:** 9.9 years **Gender:** 118 boys and 42 girls **ADHD subtypes:** not stated **Using ADHD drugs at baseline:** 0% in previous month **Baseline scores:** ADHD-RS-IV scores: omega-3 = 36.5, placebo = 38.1 **Setting:** 5 child psychiatry centres, France, 2009 to 2011 **Funding:** study was sponsored by the URGO laboratories
Interventions	**Intervention (71 participants):** omega-3 PUFA for 3 months; daily dosage for children aged 6 to 8 years = 336 mg of EPA and 84 mg of DHA; for children aged 9 to 11 years = 504 mg of EPA and 126 mg of DHA; and for children aged 12 to 15 years = 672 mg EPA and 168 mg of DHA; capsules also contained 100 µg of vitamin A, 1.25 µg of vitamin D, and 3.5 mg of vitamin E. Other hyperactivity treatments and other omega-3 supplements or psychotropic drugs were not allowed. **Control (74 participants):** placebo for 3 months; capsules composed of olive oil, the same amount of vitamin A, D, and E, with traces of marine lipid concentrate: EPA (18%), DHA (12%), totalling 4.83 mg, to give the capsules a similar taste and smell. The placebo capsules were indistinguishable from the active capsule.
Outcomes	1. ADHD symptoms at 1, 2, 3 months

Cornu 2018 *(Continued)*

a. ADHD Rating Scale-IV
2. Behaviour at 3 months
   a. Conners Parent Rating Scale Revised
3. Depression 3 months
   a. Children's Depression Inventory

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** randomisation list was generated by the study statistician
Allocation concealment (selection bias)	Low risk	**Comment:** To ensure concealment, all participating centres called the coordinating centre for group allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment:** Patients, investigators, and the coordination centre were blinded to group allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** Patients, investigators, and the coordination centre were blinded to group allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** ITT analysis used for 157/162 though 14/162 were lost to follow-up
Selective reporting (reporting bias)	Unclear risk	**Comment:** ADHD-RS IV not reported at 1 and 2 months; Conners subscores (including anxiety) not reported at 3 months
Other bias	High risk	**Comment:** The study was sponsored by the URGO laboratories.

Crippa 2019

Study characteristics

Methods	**Design:** parallel trial **Comparison:** omega-3 PUFA vs placebo
Participants	**Inclusion criteria:** 1. children aged 7 to 14 years; 2. diagnosed with ADHD using DSM-IV-TR criteria; 3. with an IQ of more than 80; 4. ADHD drug naïve **Exclusion criteria:** 1. history of seizures or other neurological disorders; 2. diagnosed genetic disorders; 3. consumption of omega-3 or omega-6 supplements in the previous 3 months **Number of participants:** 50 (48 completed) **Mean age:** PUFA = 11.06 (SD 1.65) years, placebo = 10.91 (SD 1.42) years **Gender:** female/male ratio reported: PUFA = 2/23, placebo = 2/23 **ADHD subtype:** inattentive subtype = 16%; hyperactive-impulsive = 33%; and combined = 51%

Crippa 2019 *(Continued)*

	Using ADHD drugs at baseline: 0% **Baseline scores:** ADHD Rating Scale-IV, inattention: PUFA = 14.20 (SD 5.11), placebo = 17.28 (SD 5.98); ADHD Rating Scale, hyperactivity/impulsivity: PUFA = 15.36 (SD 5.45), placebo = 14.48 (SD 5.23) **Setting:** child psychopathology unit, Lecco, Italy, 2012 to 2014 **Funding:** supported by unrestricted research grant from Dietetic Metabolic Food srl., which provided the investigational product and the respective placebo
Interventions	**Intervention (25 participants):** omega-3 PUFA for 6 months; 2 soft gelatin pearls per day providing a dose of 500 mg algal DHA **Control (23 participants):** placebo for 6 months; 2 pearls per day containing 500 mg of wheat germ oil. The placebo was stabilised with a low concentration of vitamin E. The placebo pearls matched the DHA ones in touch, smell, and size. Note that a 6-month period was chosen, as long-chain PUFA levels in the brain can take up to 3 months to recover from a deficiency state.
Outcomes	1. ADHD symptoms at 4 and 6 months a. ADHD Rating Scale-IV: Parent Version-Investigator b. Conners Parent Rating Scale - Revised 2. Behaviour at 4 and 6 months a. Parent-rated Strengths and Difficulties Questionnaires: conduct
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "Participants were assigned a study number and randomly allocated by an independent third person to either the supplement or the placebo group using a computer-generated randomization scheme." (p572)
Allocation concealment (selection bias)	Low risk	**Comment:** Participants were assigned a study number and randomly allocated by an independent third person to either the supplement or the placebo group using a computer-generated randomization scheme. The Placebo matched the DHA capsules in touch, smell, and size. The supplement or placebo was provided in six identical boxes labelled with an identifying code.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment:** Children, parents, and study investigators were blinded to the randomization until completion of data collection and analysis.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** Children, parents, and study investigators were blinded to the randomization until completion of data collection and analysis.
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** ITT analyses used to estimate missing data. There were no missing data in the PUFA group and 2/25 in the placebo group.
Selective reporting (reporting bias)	High risk	**Comment:** SDQ not reported

Crippa 2019 *(Continued)*

Other bias	High risk	**Comment:** Funded by Dietetic Metabolic Food srl., which produced the PUFA supplement.

Dashti 2014

Study characteristics	
Methods	**Design:** parallel trial **Comparison:** omega-3 PUFA vs MPH vs placebo
Participants	**Inclusion criteria:** 1. children aged 6 to 12 years; 2. with a score of more than 65 on the Conners Parent and Teacher Rating Scales; 3. an IQ higher than 70 (using the Kaufman Brief Intelligence Test) **Exclusion criteria:** 1. side effects of MPH; 2. previous ADHD treatment; 3. omega-3 supplementation in the previous 3 months; 4. severe psychiatric disorders **Number of participants:** 85 **Mean age:** 8.2 years **Gender:** 48 boys and 37 girls **ADHD subtypes:** combined = 44; hyperactivity/impulsivity = 21; and ADD = 20 **Using ADHD drugs at baseline:** 0% **Baseline scores:** Conners - Parent rating: omega-3 = 25.89, placebo = 22.58, MPH = 24.20 **Setting:** Tamin Ejtemaei Central Hospital, Iran, 2010 to 2012 **Funding:** not stated
Interventions	**Intervention:** 1. Omega-3 PUFA **(28 participants)** for 3 days; 1 g in 1 capsule per day 2. Methylphenidate **(29 participants)** for 4 weeks; 0.3 to 1 mg/kg of Ritalin, 3 times per day **Control:** placebo **(28 participants)** for 4 weeks; not described
Outcomes	1. ADHD symptoms at 2 and 4 weeks a. Conners - Parent rating b. Conners - Teacher rating
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Comment:** not described
Allocation concealment (selection bias)	Unclear risk	**Comment:** not described
Blinding of participants and personnel (performance bias)	Unclear risk	**Comment:** not described

Dashti 2014 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** LTFU and analysis not described
Selective reporting (reporting bias)	Unclear risk	**Comment:** outcomes at 2 weeks not reported
Other bias	Low risk	**Comment:** no differences in a range of symptom scores

Dubnov-Raz 2014

Study characteristics	
Methods	**Design:** parallel trial **Comparison:** omega-3/omega-6 PUFA vs placebo
Participants	**Inclusion criteria:** 1. children and adolescents aged 6 to 16 years; 2. recently diagnosed with ADHD; 3. who were drug naïve and untreated **Exclusion criteria:** 1. refusal to undergo any or all of the testing procedures or to take the designated supplement; 2. a history of chronic health conditions other than ADHD; 3. use of any chronic medications or dietary supplements, specifically methylphenidate or fatty acid/fish oil supplements **Number of participants:** 17 **Mean age:** 11.0 years **Gender:** 10 boys and 7 girls **ADHD subtypes:** not stated **Using ADHD drugs at baseline:** 0% **Baseline scores:** Conners parent scores: omega-3 = 76, placebo = 62; Conners teacher scores: omega-3 = 69, placebo = 59 **Setting:** 2 ambulatory ADHD specialty clinics, Israel, year/s not stated **Funding:** study was funded by the Israel Association of Ambulatory Pediatrics
Interventions	**Intervention (8 participants):** omega-3/omega-6 PUFA for 8 weeks; children received 2 g/day of sage oil (50% to 54% of alpha-linolenic acid, 20% to 23% of oleic acid, 16% to 18% of linoleic acid, 6% to 7% of palmitic acid, and 2% to 3% of stearic acid), in 2 gel capsules daily, for 8 weeks. This corresponds to a supplementation of approximately 1 g/day of alpha-linolenic acid. **Control (9 participants):** placebo (lactose) for 8 weeks; given in 2 gel capsules daily
Outcomes	1. ADHD symptoms measured at 8 weeks a. Parent and teacher Conners rating scales
Notes	

Dubnov-Raz 2014 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** Bottles of capsules were coded by a person uninvolved in the study.
Allocation concealment (selection bias)	Low risk	**Comment:** Both types of capsules were supplied in identical amounts in solid plastic bottles, which were numbered consecutively.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** All study participants, parents, teachers, and study personnel were blinded to the allocation until completion of all data collection.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** All study personnel were blinded to the allocation until completion of all data collection.
Incomplete outcome data (attrition bias) All outcomes	High risk	**Comment:** analysis done on final sample of 17/40 participants; loss to follow-up: 23/40
Selective reporting (reporting bias)	Low risk	**Comment:** all relevant outcomes listed in paper and protocol NCT00874536 were reported
Other bias	High risk	**Comment:** Conners Parent rating was 27% higher at baseline in omega-3 group

Gow 2012

Study characteristics

Methods	**Design:** parallel trial **Comparison:** omega-3 PUFA vs placebo
Participants	**Inclusion criteria:** 1. male adolescents; 2. aged 12 to 17 years; 3. with Conners Parent and Teachers Rating scores of 65 or more; 4. meeting DSM-IV criteria for ADHD (using Children's Interview of Psychiatric Symptoms (ChIPS)) **Exclusion criteria:** 1. IQ of 70 or less; 2. diagnosis of autism; 3. learning disorders; 4. serious mental health conditions; 5. taken omega-3 supplements in the previous 6 months; 6. history of diabetes or other metabolic disorder influencing fatty acid metabolism; 7. not living in a family home or residential school; 8. under special diets; 9. not in school during the intervention; 10. serious or chronic disease; 11. low coagulation function; 12. abnormal blood tests; 13. using medications: alpha tocopherol, selected anticoagulants (aspirin, warfarin, heparin), cyclosporine, clopidogrel, etretinate and topical steroids, cholesterol-lowering medications (atorvastatin, lovastatin, and simvastatin), NSAIDs, dalteparin, dipyrdamole, enoxaparin, ticlopedine; 14. known allergy for fish product derivatives, vitamin E derivatives, and gelatine **Number of participants:** 29 **Mean age:** not stated **Gender:** 29 boys and 0 girls **ADHD subtypes:** not stated

Gow 2012 *(Continued)*

	Using ADHD drugs at baseline: 21 were medication naïve **Baseline scores:** SDQ hyperactivity/concentration (ADHD) scores: 1.41 **Setting:** special schools in London and Kent, UK, 2004 to 2008 **Funding:** sponsored by Vifor Pharma, for approving a grant to King's College London; also part funding and support from the Mother and Child and Letten Foundations
Interventions	**Intervention (no. of participants not stated):** omega-3 PUFA for 12 weeks; Equazen eye q (dose of active: x 6 daily; each containing 400 mg of fish oil and 100 mg of evening primrose oil with the following active ingredients: EPA (93 mg), DHA (29 mg), gamma-linolenic acid (10 mg), and vitamin E (1.8 mg)). The 7 participants on medication had a washout of 48 hours. **Control (no. of participants not stated):** placebo for 12 weeks; identical placebo containing medium-chain triglycerides
Outcomes	1. ADHD symptoms measured at 12 weeks a. ADHD Behaviour (Strengths and Difficulties Questionnaire) b. Barrat's Impulsivity Scale 2. Behaviour measured at 12 weeks a. Conners Teacher and Parent Rating Scales - Oppositional b. Strengths and Difficulties Questionnaire - Conduct c. Buss-Perry Aggression Questionnaire 3. Depression measured at 12 weeks a. Depression Anxiety Stress Scale 4. Anxiety measured at 12 weeks a. Depression Anxiety Stress Scale
Notes	Outcome data were not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** Randomisation into groups was carried out by the Mental Health & Neuroscience Clinical Trials Unit based at the Institute of Psychiatry, KCL.
Allocation concealment (selection bias)	Unclear risk	**Comment:** not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** number of participants lost to follow up was unclear
Selective reporting (reporting bias)	Unclear risk	**Comment:** no outcome data reported

Gow 2012 *(Continued)*

Other bias	High risk	**Comment:** Sponsored in part by sponsored by Vifor Pharma, which produced PUFA supplements.

Gustafsson 2010

Study characteristics	
Methods	**Design:** parallel trial **Comparison:** omega-3 PUFA vs placebo
Participants	**Inclusion criteria:** 1. children aged between 7 and 12 years; 2. with a diagnosis of ADHD combined type meeting DSM-IV criteria; 3. inclusive of any neuropsychiatric comorbidity; 5. had been evaluated for pharmacological treatment **Exclusion criteria:** 1. mental retardation (IQ < 70); 2. autism; 3. major depression; 4. epileptic seizure during the preceding 2 years; 5. other neurological or endocrine disorders; 6. fish allergy; 7. severely impaired hearing or vision; 8. severe sleeping disorder; 9. psychotic symptoms or ongoing psychoactive, anticonvulsant, or stimulant medication. Also, if the child had taken a PUFA, a washout period of 10 weeks was required. **Number of participants:** 92 **Mean age:** not reported; range = 7 to 12 years **Gender:** not stated **ADHD subtypes:** all combined **Using ADHD drugs at baseline:** 0% **Baseline scores:** parent-rated Conners score: placebo = 46.0, PUFA = 51.0; teacher-rated Conners score: placebo = 43.5, PUFA = 49.7 **Setting:** 8 child and adolescent psychiatric and paediatric clinics, Sweden, 2005 to 2007 **Funding:** not stated
Interventions	**Intervention (46 participants):** omega-3 PUFA for 15 weeks; 1 capsule daily containing 500 mg of EPA, 2.7 mg of DHA, 10 mg of vitamin E (PlusEPA; Minami Nutrition, Belgium); all took the supplement for at least 70 days **Control (46 participants):** placebo for 15 weeks; 1 placebo capsule (rapeseed oil and medium-chain triglycerides) daily
Outcomes	1. ADHD symptoms at 15 weeks a. Parent and Teacher Conners Rating Scale: total score, and inattentive and hyperactive-impulsive subscales 2. Behaviour at 15 weeks a. Parent and Teacher Conners Rating Scale: oppositionality subscales 3. Side effects a. Nausea b. Diarrhoea c. Nose bleed
Notes	
Risk of bias	

Gustafsson 2010 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** Participants were assigned a study number and randomised in blocks of 4 according to a computer-generated code.
Allocation concealment (selection bias)	Unclear risk	**Comment:** not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment:** placebo and PUFA were in "identical" (p1542) capsules
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** capsules "identical" (quote) and parent and teacher-rated scales used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** The authors reported that ITT analysis was done on 92 participants but this did not include "17 drop-outs" (quote) of the 109 participants
Selective reporting (reporting bias)	Low risk	**Comment:** all outcomes listed in paper and protocol EUCTR2004-003853-13-SE were reported
Other bias	Unclear risk	**Comment:** Minami Nutrition sponsored the study.

Hariri 2012

Study characteristics	
Methods	**Design:** parallel trial **Comparison:** omega-3 PUFA vs placebo
Participants	**Inclusion criteria:** 1. children aged 6 to 11 years; 2. on MPH (Ritalin); 3. Conners Abbreviated Questionnaire score (ASQ-P) > 14 **Exclusion criteria:** 1. infectious diseases; 2. diabetes; 3. hyperthyroidism; 4. convulsion; 5. epilepsy; 6. taking omega-3 supplements **Number of participants:** 120 (86 completed) **Mean age:** 7.90 years **Gender:** 74 boys and 46 girls **ADHD subtypes:** not stated **Using ADHD drugs at baseline:** 100% **Baseline scores:** Conners abbreviated scores: omega-3 = 24.45, placebo = 24.12 **Setting:** EbneSina Hospital, Mashhad, Iran, year/s not stated **Funding:** not stated
Interventions	**Intervention (46 participants):** omega-3 PUFA for 8 weeks; soft gel capsules containing a daily dose of 900 mg of omega-3 PUFA containing 635 mg of EPA, 165 mg of DHA, and 100 mg of other n-3 fatty acids (Minami Nutrition, Belgium)

Hariri 2012 *(Continued)*

	Control (40 participants): placebo for 8 weeks; soft gel capsules, visually similar to n-3 capsules and containing 900 mg of olive oil
Outcomes	1. ADHD symptoms measured at 8 weeks a. Conners Abbreviated Questionnaire score (ASQ-P)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "balanced block randomisation" (p331)
Allocation concealment (selection bias)	Unclear risk	**Comment:** not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** described as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** described as double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** loss to follow-up: 7/120
Selective reporting (reporting bias)	Low risk	**Comment:** primary outcome reported
Other bias	Low risk	**Comment:** no differences between groups on a range of variables

Hirayama 2004

Study characteristics

Methods	**Design:** parallel trial **Comparison:** omega-3 PUFA supplemented foods vs placebo supplemented foods
Participants	**Inclusion criteria:** 1. children aged 6 to 12 years; 2. attending summer camp for psychiatric disorders; 3. diagnosed or suspected to have ADHD according to DSM-IV criteria, diagnostic interviews, and behavioural observation by psychiatrists **Exclusion criteria:** not stated **Number of participants:** 40 **Median age:** 9 years **Gender:** 32 boys and 8 girls **ADHD subtypes:** combined = 13; inattentive = 16; hyperactive-impulsive = 3; unclear = 8

Hirayama 2004 *(Continued)*

	Using ADHD drugs at baseline: 10% **Baseline scores:** number of DSM-IV-defined attention deficit symptoms: PUFA = 11, placebo = 8; hyperactivity symptoms: PUFA = 2, placebo = 2; and impulsivity symptoms: PUFA = 0, placebo = 2 **Setting:** summer camp for children with psychiatric disorders, Japan, year/s not stated **Funding:** not stated
Interventions	**Intervention (20 participants):** omega-3 PUFA for 2 months; fish oil-supplemented diet provided a total 3.6 g of DHA and 0.7 g of EPA per week. Fish oil-enriched food included fermented soybean milk (600 mg of DHA or 125 mL, 3 times per week), bread rolls (300 mg of DHA or 45 g, 2 times per week), and steamed bread (600 mg of DHA or 60 g, 2 times per week). **Control (20 participants):** placebo for 2 months; indistinguishable foods containing olive oil
Outcomes	1. ADHD symptoms measured at 8 weeks a. Parent- and teacher-rated number of DSM-IV-defined attention deficit, hyperactivity and impulsivity symptoms
Notes	Median number of symptoms (and range) reported, therefore data could not be included in a meta-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** Treatment was randomly assigned using a telephone book as a table of random numbers.
Allocation concealment (selection bias)	Low risk	**Comment:** Treatment allocation was conducted by a third party in a double-blind manner.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment:** The authors described the trial as double-blind. The fish oil taste in supplemented foods was masked.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** Interventions were "masked" (p469), and parent and teacher-rated scales used
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** all participants enroled in the trial included in data analysis; loss to follow-up: 0/40
Selective reporting (reporting bias)	Low risk	**Comment:** all outcomes listed in paper appear to have been reported
Other bias	Unclear risk	**Comment:** The number of symptoms were different at baseline though this was not significant. The number of children with Asperger's syndrome was lower (2 versus 7) and learning disorder was higher (10 versus 5) in the PUFA group.

Ivity 2015

Study characteristics

Ivity 2015 *(Continued)*

Methods	**Design:** parallel trial **Comparison:** omega-3 PUFA supplement vs placebo
Participants	**Inclusion criteria:** 1. children aged between 5 and 12 years; 2. diagnosed by a qualified healthcare professional (paediatrician, psychiatrist, or psychologist) as having any of the subtypes of ADHD, according to DSM-IV criteria; 3. of normal intelligence according to parent report or an IQ of at least 70 on a standardised test. Participants could present with comorbid conditions, including oppositional defiant disorder, conduct disorder, anxiety disorders, mood disorders, and learning disorders. **Exclusion criteria:** 1. taking medication to treat ADHD or other prescription medication, or both; 2. consuming any special diets or supplements that contained DHA; 3. diagnosed with foetal alcohol syndrome or autism **Number of participants:** not stated **Median age:** not stated **Gender:** not stated **ADHD subtypes:** not stated **Using ADHD drugs at baseline:** 0% **Baseline scores:** not stated **Setting:** mental health organisation, Canada, year/s not stated **Funding:** not stated
Interventions	**Intervention (13 participants):** omega-3 PUFA for 4 months; 2 capsules (children weighing 40 to 79 pounds) or 3 capsules (children weighing 80 to 140 pounds) of Omega-3 Think (Genuine Health, Toronto, Canada) capsules (250 mg of DHA and 100 mg of EPA) **Control (13 participants):** placebo for 4 months; capsules containing olive oil
Outcomes	1. ADHD symptoms measured at 8 and 16 weeks a. Teacher-rated Conners 3 Rating Scale
Notes	Only inattention at 8 weeks was reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Both the supplement and placebo capsules were counted and put into identical opaque Nalgene pill bottles by the assistant and numerically coded
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Method of blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method of blinding not described

Ivity 2015 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	30/56 LTFU
Selective reporting (reporting bias)	High risk	Only inattention at 8 weeks was reported
Other bias	High risk	Demographic characteristics of participants, and reasons for withdrawal/drop-out were not reported

Johnson 2009

Study characteristics	
Methods	**Design:** cross-over trial **Comparison:** omega-3/omega-6 PUFA vs placebo
Participants	**Inclusion criteria:** 1. children and adolescents aged 8 to 18 years; 2. diagnosed with ADHD of any type (according to DSM-IV criteria); 3. scoring at least 1.5 SD above the age norm for their diagnostic subtype using the parent ADHD-RS-IV **Exclusion criteria:** 1. autism; 2. psychosis; 3. bipolar disorder; 4. mental retardation; 5. uncontrolled seizure disorder; 6. hyper- or hypothyroidism; 7. significant other medical conditions; 8. weight below 20 kg; 9. alcohol or drug abuse; 10. use of psychoactive drugs; 11. omega-3 preparations in the last 3 months **Number of participants:** 65 (64 completed) **Mean age:** 12 years **Gender:** 54 boys and 11 girls **ADHD subtypes:** combined = 35; inattentive = 40; hyperactive-impulsive = 0 **Using ADHD drugs at baseline:** 0% **Baseline scores:** ADHD-RS-IV, total: PUFA = 33.5, placebo = 32.4; ADHD-RS-IV, inattention: PUFA = 19.8, placebo = 19.5; ADHD-RS-IV hyperactivity/impulsivity: PUFA = 14.2, placebo = 12.5 **Setting:** 3 child neurology/psychiatry clinics in Southwest Sweden, year/s not stated **Funding:** the study was funded by Equazen UK Ltd
Interventions	**Intervention (34 participants):** omega-3/omega-6 PUFA (Equazen eye q) for 3 months; 3 capsules twice daily corresponding to 558 mg of EPA, 174 mg of DHA, 60 mg of gamma-linolenic acid, and 10.8 mg of vitamin E **Control (30 participants):** placebo (olive oil) for 3 months; 3 capsules twice daily
Outcomes	1. Improvement in ADHD symptoms measured at 12 weeks a. Defined as more than a 25% improvement in ADHD symptoms 2. ADHD symptoms measured at 12 weeks a. Clinician-rated ADHD Rating Scale scores: total scores, and inattention and hyperactive/impulsive subscale scores
Notes	The authors described the study as cross-over because the supplement was given to all children in the 2nd phase. We used first-phase data in the meta-analysis.

Johnson 2009 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** Participants were assigned to treatment in random order using a code list but it is not clear how the code list sequence was generated.
Allocation concealment (selection bias)	Low risk	**Comment:** Treatment assignment was determined using a code list, which was not accessible to investigators and was not broken until all patients had completed the study.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment:** The authors described this trial as double-blind. Also, "identical capsules" (p395) were used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** described as double-blinded but no further details given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** not stated; loss to follow-up: 11/75
Selective reporting (reporting bias)	Unclear risk	**Comment:** The authors state that several outcomes will be reported in future publications.
Other bias	High risk	**Comment:** study funded by Equazen, UK that produced PUFA supplement.

Kean 2017

Study characteristics	
Methods	**Design:** parallel trial **Comparison:** omega-3 PUFA vs placebo
Participants	**Inclusion criteria:** children and adolescents aged 6 to 14 years, with a score of 15 or more on the DSM-IV ADHD rating scale (73 with ADHD diagnosis), fluent in English, and non-smoking **Exclusion criteria:** primary medical diagnosis other than ADHD, oppositional defiant disorder or similar, behavioural disorders; currently taking any medication (other than stimulants if a formal diagnosis of ADHD or other behavioural disorder has been made); current or history of heart disease, or high blood pressure, or diabetes; health conditions that would affect food metabolism, including the following: food allergies, kidney disease, liver disease, and/or gastrointestinal diseases (e.g. irritable bowel syndrome, coeliac disease, peptic ulcers); pregnant or breastfeeding; unable to participate in all scheduled visits, treatment plan, tests, and other trial procedures according to the protocol; allergy to shellfish; epilepsy or photosensitivity **Number of participants:** 144 (73 with ADHD; 65 completed) **Mean age:** 8.82 years **Gender:** 123 boys and 21 girls **ADHD subtypes:** subsample analysis of combined high hyperactivity and inattention - combined type (n = 65, 29 received omega-3)

Kean 2017 *(Continued)*

	Using ADHD drugs at baseline: 52/144 taking pharmaceutical medications **Baseline scores:** Conners Parent Rating Scale, inattention = 78.84 boys, 83.25 girls; hyperactivity = 80.85 boys, 80.75 girls **Setting:** university, New Zealand, year/s not stated **Funding:** study was funded by a grant from Pharmalink Pty Ltd
Interventions	**Intervention (29 participants):** marine oil extract (PCSO-524) under the brand names Lyprinol and Omega XL. The principal ingredients per 260-milligram capsule were 50 mg eicosatetraenoic acid including EPA and 5.5 mg DHA; 3 capsules for participants ≤ 45 kg, 4 capsules for participants > 45 kg for 14 weeks **Control (36 participants):** placebo, 3 to 4 capsules daily for 14 weeks
Outcomes	1. ADHD symptoms measured at 14 weeks a. Conners Parent Rating Scale - hyperactivity, inattention 2. Behaviour at 14 weeks a. Conners Parent Rating Scale - aggression, conduct; oppositional
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Use of a computer-generated randomisation which was done by a neutral third party
Allocation concealment (selection bias)	Low risk	Blinding was achieved by enlisting a person outside of the project to code the treatments and maintain the key to this code until data collection was completed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding was achieved by enlisting a person outside of the project to code the treatments and maintain the key to this code until data collection was completed, "the placebo capsule matched the PCSO-524® capsule in touch, taste, smell and size" (p406)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding was achieved by enlisting a person outside of the project to code the treatments and maintain the key to this code until data collection was completed
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analyses was used for 112/144 but the data reported data were only for 65 participants with combined ADHD
Selective reporting (reporting bias)	High risk	Conners Parent Rating scores at 4, 8, 10 and 18 weeks and mood scores were not reported
Other bias	High risk	The study was funded by a grant from Pharmalink Pty Ltd.

Lim-Ashworth 2013

Study characteristics

Methods	**Design:** parallel trial

Lim-Ashworth 2013 *(Continued)*

	Comparison: omega-3 PUFA vs placebo vs omega-3 PUFA plus social skills vs placebo plus social skills
Participants	**Inclusion criteria:** 1. children and adolescents aged 9 to 16 years; 2. who had been diagnosed with ADHD **Exclusion criteria:** not stated **Number of participants:** 39 **Mean age:** not stated **Gender:** not stated **ADHD subtypes:** not stated **Using ADHD drugs at baseline:** not stated **Baseline scores:** not stated **Setting:** Singapore, year/s not stated **Funding:** not stated
Interventions	**Intervention** 1. **Omega-3 PUFA (no. of participants not stated):** not described, and duration unclear, although it appears to be 6 months 2. **Omega-3 PUFA + social skills (no. of participants not stated):** not described, and duration unclear, although it appears to be 6 months **Control** 1. **Placebo (no. of participants not stated):** not described, and duration unclear, although it appears to be 6 months 2. **Placebo + social skills (no. of participants not stated):** not described, and duration unclear, although it appears to be 6 months
Outcomes	1. ADHD symptoms measured at 3 and 6 months a. Child Behavior Checklist (CBCL) - parent b. Conners Parent Rating Scale - parent 2. Behaviour at 3 and 6 months a. CBCL - parent b. Conners Parent Rating Scale - parent
Notes	Outcome data were not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** not described
Allocation concealment (selection bias)	Unclear risk	**Comment:** not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** not described

Lim-Ashworth 2013 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** not described; loss to follow-up: not stated (39 enroled)
Selective reporting (reporting bias)	Unclear risk	**Comment:** Outcome data were not reported
Other bias	Unclear risk	**Comment:** inadequate information

Manor 2012

Study characteristics	
Methods	**Design:** parallel trial **Comparison:** omega-3 PUFA vs placebo
Participants	**Inclusion criteria:** 1. children aged between 6 and 13 years, of normal weight and height, regularly attended school and had a confirmed DSM-IV ADHD diagnosis following assessment by the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime (K-SADS-PL) Version 1 assessed by qualified and experienced psychiatrist (K-SADS-PL or CGI-S) or psychiatric social worker (K-SADS-PL); 2. a score of at least 1.5 SD above the normal for the patient's age and gender in the Teacher-rated ADHD Rating Scale-IV (RS-IV) School Version; 3. a score of 4 or higher (moderately ill or worse) in the CGI-S test; 4. willingness of the parent and a teacher who is familiar with the child to participate **Exclusion criteria:** 1. girls with 3 previous regular menstrual cycles; 2. history or diagnosis of serious systemic or neurological condition; 3. failure to respond to 2 or more adequate courses of stimulant therapy; 4. pervasive developmental disorder; 5. diagnosed psychotic disorders; 6. suicidal risk or current psychiatric comorbidity requiring pharmacotherapy; 7. use of potent psychotropics, including ADHD treatments and dietary supplements, 4 weeks prior to study; 8. history of DSM-IV alcohol or substance abuse; 9. more than 250 mg/day of caffeine; allergic reactions or sensitivity to marine products, soy, or corn; 10. any illness that could jeopardise the patient's health or prevent them from completing the trial **Number of participants:** 200 (147 completed) **Mean age:** 9.2 years **Gender:** 104 boys and 43 girls at follow-up **ADHD subtypes:** combined = 97; inattentive = 47; hyperactive = 3 **Using ADHD drugs at baseline:** 0% within previous 4 weeks **Baseline scores:** DSM-IV, total: PUFA = 63.65, placebo = 64.43; DSM-IV, inattention: PUFA = 63.66, placebo = 64.80; DSM-IV, hyperactivity/impulsivity: PUFA = 61.15, placebo = 60.9 **Setting:** community recruitment, Israel, year/s not stated **Funding:** study was funded by Enzymotec Ltd, Israel
Interventions	**Intervention (100 participants):** omega-3 PUFA for 15 weeks; 4 capsules (2 capsules twice a day) provided 300 mg of phosphatidylserine, 80 mg of EPA, 40 mg of DHA (Vayarin). For treatment adherence

Manor 2012 *(Continued)*

	monitoring, participants returned all treatment packs at each visit, and adherence was calculated using the number of remaining capsules. **Control (47 participants):** placebo for 15 weeks; 4 capsules (2 capsules twice a day) of an identical-looking capsule filled with cellulose
Outcomes	1. ADHD symptoms at 15 weeks a. Change in parent- and teacher-rated Conners DSM-IV total, inattentive and hyperactivity/impulsivity symptoms 2. Behaviour at 15 weeks a. Change in parent- and teacher-rated Conners oppositional behaviour 3. Quality of life at 15 weeks a. Change in Child Health Questionnaire Psychosocial summary score
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** web-based random allocation procedure used
Allocation concealment (selection bias)	Low risk	**Comment:** web-based random allocation procedure used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment:** placebo and PUFA capsules described as identical
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** capsules "identical" (p336), and parent and teacher-rated scales used
Incomplete outcome data (attrition bias) All outcomes	High risk	**Comment:** per protocol analysis used on 147/200 participants; loss to follow-up: 53/200
Selective reporting (reporting bias)	High risk	**Comment:** The SDQ was described as an assessment that was used but the results were not reported.
Other bias	High risk	**Comment:** Four of the ten authors were employed by the company which produced the omega-3 supplement which also funded the study.

Matsudaira 2015

Study characteristics

Methods	**Design:** parallel trial **Comparison:** omega-3 PUFA vs placebo
Participants	**Inclusion criteria:** 1. male adolescents recruited form schools and parent groups; 2. aged 12 to 17 years (thesis says 12 to 16) recruited meeting DSM-IV criteria through clinical interview; 3. mean standardised score > 65 (> 95th percentile) on both Conners Teacher Rating Scale and Conners Parent Rating Scale; 4. IQ > 70 (Kaufman Brief Intelligence Test Second Edition)

Matsudaira 2015 *(Continued)*

	Exclusion criteria: 1. female adolescent; 2. omega-3 use within past 3 months; 3. diabetes or other metabolic disorder influencing fatty acid metabolism; 4. non-English speaker; 5. not living in the family home or residential school; 6. serious or chronic disease; 7. low blood coagulation function; 8. medications that could affect coagulation; 9. cholesterol-lowering medications; 10. NSAIDs; 11. other nutritional supplements; 12. allergy to fish product derivatives; 13. pancreatic insufficiency 14. abnormal blood triglycerides **Number of participants:** 76 (69 completed) **Mean age:** 13.7 years **Gender:** all 76 participants were male **ADHD subtypes:** combined = 65.8%; inattentive = 23.7%; hyperactive/impulsive = 10.5% **Using ADHD drugs at baseline:** 48-hour washout **Baseline scores:** Conners Parent Rating Scale (CPRS-L) scores: omega-3 = 74.7, placebo = 74.8 **Setting:** Mental Health and Neuroscience Clinical Trials Unit, Institute of Psychiatry, King's College London, UK, 2004 to 2008 **Funding:** The Mother and Child Foundation will fund this trial. Equazen Nutraceutical Ltd will provide EFA capsules.
Interventions	**Intervention (33 participants):** omega-3 PUFA for 12 weeks; 6 Equazen eye q capsules daily (3000 mg daily containing omega-3 PUFAs: 558 mg of EPA, 174 mg of DHA, 60 mg of gamma-linolenic acid, and 9.6 mg of vitamin E) **Control (36 participants):** placebo for 12 weeks; 6 capsules containing medium-chain triglycerides daily
Outcomes	1. ADHD symptoms at 12 weeks a. Conners Teacher Rating Scale (CTRS-L) b. Conners Parent Rating Scale (CPRS-L) c. Strengths and Difficulties Questionnaire
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** allocation done by Clinical Trials Unit
Allocation concealment (selection bias)	Low risk	**Comment:** allocated a treatment box number, kept and dispensed from hospital pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** not described

Matsudaira 2015 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** The linear regression of the CTRS ADHD index was reported as both ITT and PP analyses. However, only 69/76 randomised participants were included in the linear regression.
Selective reporting (reporting bias)	Low risk	**Comment:** all outcomes listed in paper and protocol were reported
Other bias	Low risk	**Comment:** groups were comparable at baseline in terms of age, sex, IQ, type of ADHD and ADHD symptoms

Milte 2012

Study characteristics	
Methods	**Design:** parallel trial **Comparison:** EPA-rich fish oil vs DHA-rich fish oil vs placebo
Participants	**Inclusion criteria:** 1. diagnosis of ADHD, or parent-rated symptoms higher than the 90th percentile on the Conners Parent Rating Scale and parent-reported learning difficulties (described as literacy performance behind their year level at school); 2. aged 7 to 12 years **Exclusion criteria:** 1. had consumed omega-3 PUFA supplements during the 3 months before the study; 2. were taking any ADHD medication **Number of participants:** 90 (70 completed) **Mean age:** EPA = 8.8 years, DHA = 8.9 years, placebo = 9.1 years **Gender:** EPA = 80% boys, DHA = 75% boys, placebo = 83% boys **ADHD subtypes:** not stated **Using ADHD drugs at baseline:** 0% **Baseline scores:** Conners Parent Rating Scale: EPA = 75.70, DHA = 75.96, placebo = 77.62 **Setting:** Nutritional Physiology Research Centre and Institute of Health and Biomedical Innovation, Australia, 2007 to 2009 **Funding:** Australian Research Council Linkage Project grant (LP0776922) in partnership with Novasel Australia
Interventions	**Intervention** 1. Omega-3 PUFA **(25 participants)** (EPA-rich fish oil) for 4 months; EPA-rich fish oil (providing 1109 mg of EPA and 108 mg of DHA daily, and stabilised with a low concentration of vitamin E), 4 x 500-milligram capsules per day for 4 months 2. Omega-3 PUFA **(20 participants)** (DHA-rich fish oil) for 4 months; DHA-rich fish oil (providing 264 mg of EPA and 1032 mg of DHA daily, and stabilised with a low concentration of vitamin E), 4 x 500-milligram capsules per day for 4 months **Control (25 participants):** placebo for 4 months; safflower oil control (providing 1467 mg of linoleic acid daily, and stabilised with a low concentration of vitamin E), 4 x 500-milligram capsules per day for 4 months
Outcomes	1. ADHD symptoms at 16 weeks a. Conners Parent Rating Scale (long version) 2. Side effects at 16 weeks

Milte 2012 *(Continued)*

a. Number and type of adverse events
3. Behaviour at 16 weeks
a. Conners Parent Rating Scale: oppositional

Notes	ADHD symptoms were reported as linear mixed-model effect sizes and 95% CI, and therefore could not be used in meta-analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quotes:** "randomised"; "using the process of randomization by minimization…based on age and gender" (p671) **Comment:** method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	**Comment:** not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "Study investigators involved in the data collection, parents, and children were blinded to the randomization until completion of the data collection and analysis." (p671)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "Study investigators involved in the data collection, parents, and children were blinded to the randomization until completion of the data collection and analysis." (p671)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** 90 participants randomised, and 87 evaluated
Selective reporting (reporting bias)	Unclear risk	**Comment:** week-16 data not reported for any outcome
Other bias	Low risk	**Quote:** "There were no significant differences between the groups". (p673)

Moghaddam 2017

Study characteristics

Methods	**Design:** parallel trial **Comparison:** omega-3 PUFA + MPH vs placebo + MPH
Participants	**Inclusion criteria:** 1. ADHD based on ADHD Rating Scale cut-off; 2. at least a 25% reduction of symptoms on treatment **Exclusion criteria:** 1. major psychological disease, except ODD and learning disorder; 2. IQ < 70; 3. taking psychoactive drugs within 2 weeks; 4. major neurological disease; 5. taking any drug affecting the nervous system at least 2 weeks before the study **Number of participants:** 40 (30 completed) **Mean age:** PUFA = 9.5 (SD 2.0) years, placebo = 8.9 (SD 1.6) years **Gender:** 33 boys, 7 girls

Moghaddam 2017 *(Continued)*

	ADHD subtypes: not stated **Using ADHD drugs at baseline:** 0% **Baseline scores:** ADHD Rating Scale: PUFA = 39.9 (SD 4.9), placebo = 41.2 (SD 2.7) **Setting:** state and private outpatient clinics, Iran, 2014 **Funding:** not stated
Interventions	**Intervention (18 participants):** omega-3 PUFA + MPH for 8 weeks; omega-3 capsules containing 180 mg of EPA and 120 mg of DHA + MPH (titrated from 0.6 mg/kg to 1 mg/kg over 2 weeks) **Control (12 participants):** placebo + MPH for 8 weeks; 1 mg/kg of MPH (titrated from 0.6 mg/kg over 2 weeks)
Outcomes	1. Improvement in ADHD symptoms at 8 weeks a. Improvement of at least 25% (measure unclear) 2. ADHD symptoms at 8 weeks a. Mean symptom severity - ADHD Rating Scale
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "Random numbers table" (p4413)
Allocation concealment (selection bias)	Unclear risk	**Comment:** not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** rated by psychiatrist but blinding not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** number randomised unclear; loss to follow-up: unclear
Selective reporting (reporting bias)	Unclear risk	**Comment:** prespecified outcomes not clear
Other bias	High risk	**Comment:** inattention and hyperactivity-impulsivity subscores were very different between intervention groups at baseline

Mohammadzadeh 2019

Study characteristics

Methods	**Design:** parallel trial

Mohammadzadeh 2019 *(Continued)*

	Comparison: omega-3 PUFA + MPH vs placebo + MPH
Participants	**Inclusion criteria:** 1. children aged 6 to 12 years; 2. with diagnosed DSM-IV-TR ADHD **Exclusion criteria:** 1. supplementation with omega-3 in at least the last 6 months; 2. the presence of any known physical illness, mental disability, or known psychiatric disorders (autism spectrum disorders, schizophrenia, intellectual impairment, and other psychiatric disorders); 3. seizure; 4. any psychiatric comorbidity that needs treatment or suicide ideation **Number of participants:** 66 (60 completed) **Mean age:** omega-3 + MPH = 7.7 (SD 1.65) years, placebo + MPH = 8.20 (SD 1.72) years **Gender:** 49/66 boys and 17/66 girls **ADHD subtypes:** not stated **Using ADHD drugs at baseline:** not stated **Baseline** ADHD Rating Scale scores: omega-3 = 42.61 (SD 7.18), placebo = 42.61 (SD 6.86) **Setting:** child and adolescent psychiatric clinic of Besat Hospital in Sanandaj, Iran, 2016 **Funding:** not stated
Interventions	**Intervention (31 participants):** omega-3 PUFA + MPH for 8 weeks; 180 mg of EPA capsules and 120 mg of DHA twice a day (once a day first week), plus MPH (up to 30 mg/day for children above 30 kg and 20 mg/day for children up to 30 kg, starting at 10 mg/day in the first week) **Control (29 participants):** placebo (olive oil) + MPH for 8 weeks; up to 30 mg/day of MPH for children above 30 kg and 20 mg/day of MPH for children up to 30 kg, starting at 10 mg/day in the first week
Outcomes	1. ADHD symptoms at 2, 4, 8 weeks a. ADHD Parent Rating Scale
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** The randomisation list was made using a computerised random-number generator based on a random-number table.
Allocation concealment (selection bias)	Low risk	**Comment:** Participants were referred with a code to the pharmacist. In addition, the patient, parents and the person who administrated the medications, were blinded. Omega-3 and placebo were given to patients as pockets (1 and 2) as the same gel-shaped capsules.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment:** allocation was blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** parents were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** analysis conducted on 60/66 who were not lost to follow-up; loss to follow-up by group: PUFA = 2/33, placebo = 4/33

Mohammadzadeh 2019 *(Continued)*

Selective reporting (reporting bias)	High risk	**Comment:** Conner's and ADHD Rating Scales - self-report was listed as outcome in protocol IRCT2016060128182N2 but not reported
Other bias	Low risk	**Comment:** no differences in age, gender, demographic

NCT01807299

Study characteristics	
Methods	**Design:** parallel trial **Comparison:** omega-3 PUFA + physical training vs placebo + physical training
Participants	**Inclusion criteria:** 1. children aged 7 to 14 years with ADHD; 2. boys; 3. sedentary; 4. studying in a regular school **Exclusion criteria:** 1. taking psychoactive medications; 2. taking omega supplement **Number of participants:** 53 (47 completed) **Mean age:** 10.51 years **Gender:** all 53 participants were male **ADHD subtypes:** not stated **Using ADHD drugs at baseline:** 0% **Baseline Conners scores:** omega-3 = 36.64; omega-3 + physical training = 36.82; control = 42.31; control + physical training = 40.08 **Setting:** school, Brazil, year/s not stated **Funding:** not stated
Interventions	**Intervention (22 participants):** capsules of omega-3, 2 g per day of fish oil for 90 days +/- physical training **Control (25 participants):** 2 g per day of mineral oil +/- physical training for 90 days
Outcomes	1. ADHD symptoms at 3 months (rater not stated) a. Conners Rating Scale
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	Unclear risk	Not stated

NCT01807299 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported
Other bias	Unclear risk	PUFA and control groups were similar for age, gender ethnicity and baseline scores

Perera 2012

Study characteristics	
Methods	**Design:** parallel trial **Comparison:** omega-3/omega-6 PUFA vs placebo
Participants	**Inclusion criteria:** 1. children aged 6 to 12 years; 2. treated with MPH and behaviour therapy for more than 6 months for ADHD; 3. refractory to treatment confirmed using the parent version of the SNAP-IV, clinical interview, and clinical records for the previous 3 months **Exclusion criteria:** 1. “being registered for less than 6 months”; 2. "hyperactivity was primarily related to intellectual impairment, brain injury, and insult”; 3. “satisfactory outcome in ADHD symptoms, behavior, and school-based learning”; 4. “missed follow-up appointments and medication refills” **Number of participants:** 94 **Mean age:** 9.3 years **Gender:** 69 boys and 25 girls **ADHD subtypes:** not stated **Using ADHD drugs at baseline:** 100% **Baseline scores:** not reported **Setting:** “outpatient treatment program for ADHD” (p748), Sri Lanka, year/s not stated **Funding:** the preparation of study material was sponsored by Igennus Ltd, Cambridge, UK/Gpristine Pvt Ltd, Sri Lanka
Interventions	**Intervention (48 participants):** omega-3/omega-6 PUFA for 6 months; 1 capsule twice daily of omega-3 and omega-6 (Vegepa capsule - fish oil and evening primrose oil, 296.37 mg of omega-3 and 180.75 mg of omega-6) **Control (46 participants):** placebo (sunflower oil) for 6 months; 1 capsule twice daily
Outcomes	1. Improvement at 3 and 6 months a. Improvement - score less than total score of 22 on parent-rated “11-item checklist” which “assessed symptoms of ADHD and associated behavioral problems and learning difficulties" 2. ADHD symptoms at 3 and 6 months

Perera 2012 *(Continued)*

a. Parent-rated “11-item checklist” which “assessed symptoms of ADHD and associated behavioral problems and learning difficulties”

Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** not described
Allocation concealment (selection bias)	Low risk	**Quote:** ”The researchers and the patients were masked to group allocation, carried out by an independent third person" (p749)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quotes:** "Active treatment or placebo --- were labeled in code”; "A capsule of identical appearance containing sunflower oil was used as the placebo" (p749)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quotes:** Parent-reported outcomes "Active treatment or placebo --- were labeled in code”; "A capsule of identical appearance containing sunflower oil was used as the placebo" (p749)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** analysis conducted on 48/49 in PUFA group and 46/49 in placebo group
Selective reporting (reporting bias)	Low risk	**Comment:** The trial registration, SLCTR/2009/006, listed the following measures: the "1.Diagnosis of behaviour disorder will be made using DSM IV TR criteria. Comorbid disorders will be similarly diagnosed. 2. SNAP IV completed by parent and teacher will be used to further validate the diagnosis and assess the severity of the symptoms. SDQ will be used to assess the specific symptoms of ADHD and its impact. 3. SNAP IV and SDQ will be used to objectively assess the outcome in 1 month, 3 months and 6 months in addition to the clinical assessment" (quote), at 1 month, 3 months and 6 months. In addition, monthly recording of side-effects were referred to in the paper but were not reported.
Other bias	High risk	**Comment:** The preparation of study material was sponsored by Igennus Ltd which produced PUFA supplements. The parent-rated “11-item checklist” (p749) was not reported as valid or reliable, or both.

Raz 2009a

Study characteristics

Methods	**Design:** parallel trial **Comparison:** omega-3/omega-6 PUFA vs placebo
Participants	**Inclusion criteria:** 1. children aged 7 to 13 years; 2. with a written diagnosis of ADHD from a child psychiatrist, neurologist, paediatrician, or clinical psychologist

Raz 2009a *(Continued)*

	Exclusion criteria: 1. use of ADHD medication in the past month; 2. use of EFA supplements in the past 3 months; 3. presence of pervasive developmental disorder, seizure disorder, schizophrenia, major depression, or bipolar disorder **Number of participants:** 63 **Mean age:** 10.5 years **Gender:** 38 boys and 25 girls at follow-up **ADHD subtypes:** combined = 44; inattentive = 29; hyperactive = 27 **Using ADHD drugs at baseline:** 0% **Baseline scores:** parent-rated DSM-IV attention subscale: PUFA = 4.05, placebo = 4.43; parent-rated DSM-IV hyperactivity-impulsivity subscale: PUFA = 3.29, placebo = 3.14; teacher-rated Conners ADHD: PUFA = 3.85, placebo = 3.71 **Setting:** Bar-Ilan University, Tel-Hashomer Israel and Hillel-Yaffe Medical Center, Hadera, Israel, 2007 **Funding:** not stated
Interventions	**Intervention (32 participants):** omega-3/omega-6 PUFA for 7 weeks; an oral soft gel capsule containing 240 mg of linoleic acid, 60 mg of alpha-linolenic acid, 95 mg of mineral oil, and 5 mg of alpha-tocopherol, given twice daily **Control (31 participants):** placebo for 7 weeks; 500 mg of ascorbic acid as an oral tablet twice daily
Outcomes	1. ADHD symptoms at 7 weeks a. Parent-rated DSM-IV attention and hyperactivity-impulsivity subscales b. Teacher-rated Conners scale 2. Side effects: nausea
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** The method of randomisation was not described except that participants were matched for gender and age and then randomised within each pair.
Allocation concealment (selection bias)	Unclear risk	**Comment:** assignment of treatments was based on study number
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** The authors described the trial as double-blind. However, active and control interventions were different i.e. soft gel capsules and tablets respectively.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** The researchers, teachers, parents and children were all directly involved in data collection, and all were blinded to treatment allocation until the end of the study.
Incomplete outcome data (attrition bias) All outcomes	High risk	**Comment:** data reported for 63/78 enrolled participants who remained in the trial at 7 weeks, loss to follow-up: 15/78

Raz 2009a *(Continued)*

Selective reporting (reporting bias)	High risk	**Comment:** The authors stated that the Conners subscales were "found to be unreliable" (p169), but not how this was demonstrated. These data were not reported.
Other bias	Low risk	**Comment:** There were no statistically significant differences between groups in stimulant use, co-morbidities, inattention, hyperactivity/impulsivity, EFA deficiency score or blood biochemistry.

Rodriguez 2019

Study characteristics	
Methods	**Design:** parallel trial **Comparison:** omega-3 PUFA vs placebo
Participants	**Inclusion criteria:** 1. boys and girls between 6 and 18 years of age; 2. DSM-5 diagnosis of ADHD confirmed by a trained researcher using the Diagnostic Interview Schedule for Children-Parent Version (DISC-P) with any subtype of ADHD (hyperactive-impulsive, inattentive, combined hyperactive-inattentive) **Exclusion criteria:** 1. total IQ scores lower than 70 and greater than 130; 2. blood coagulation disorders, cognitive impairment, or autism spectrum disorder; 3. intolerance to fish proteins, and treatment with dietary supplements containing omega-6 or omega-3 PUFAs during the preceding month **Number of participants:** not stated **Mean age:** 11.7 years **Gender:** not stated **ADHD subtypes:** not stated **Using ADHD drugs at baseline:** more than 70% were using psychostimulant medication **Baseline:** not stated **Comorbid conditions:** present in 12 and 4 participants in the DHA and placebo groups, respectively **Setting:** faculty of psychology, Spain, year/s not stated **Funding:** not stated
Interventions	**Intervention (32 participants):** each sachet of omega-3 fatty acids contained: 1000 mg DHA, 90 mg EPA, and 150 mg docosapentaenoic acid. Doses were 1 sachet/day in children weighing ≤ 32 kg and 2 sachets/day in those weighing > 32 kg for 6 months **Control (34 participants):** placebo sachets were composed of the same amount of olive oil with banana flavour to give a similar taste and smell
Outcomes	1. ADHD symptoms at 3, 6 months a. Scale for the Assessment of Attention Deficit Hyperactivity Disorder (EDAH) for families b. Abbreviated Conners Rating Scale - Parent
Notes	
Risk of bias	

Rodriguez 2019 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization (1:1) was performed according to a computer-generated random sequence
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, parents, and investigators assessing outcome measures were blind to the intervention condition
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, parents, and investigators assessing outcome measures were blind to the intervention condition
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analyses were referred to in paper but were not reported, 19/85 lost to follow-up
Selective reporting (reporting bias)	Low risk	All relevant outcomes listed in paper were reported
Other bias	Unclear risk	Baseline scores were similar for PUFA and placeo but other comparisons between groups were not reported

Salehi 2016

Study characteristics	
Methods	**Design:** parallel trial **Comparison:** omega-3 PUFA + MPH vs placebo + MPH
Participants	**Inclusion criteria:** 1. primary and middle school students; 2. aged 6 to 15 years; 3. diagnosed as new cases of ADHD based on DSM-IV-TR questionnaire **Exclusion criteria:** 1. psychiatric drug usage; 2. other psychiatric disorders; 3. sensitivity to zinc sulfate or omega-3; 4. mental retardation; 5. acute systemic disease; 6. unable to use oral medication; 7. refusing medication because of side effects; 8. change of treatment **Number of participants:** 100 **Mean age:** PUFA = 8.6 years, placebo = 9.1 years **Gender:** 71 boys and 29 girls **ADHD subtypes:** combined = 44; inattentive = 29; hyperactive = 27 **Using ADHD drugs at baseline:** 100% **Baseline scores:** Conners: omega-3 = 56.1, placebo = 55.0 **Setting:** Amirkabir Hospital of Arak, Iran, 2012 **Funding:** stated that no funding was received

Salehi 2016 *(Continued)*

Interventions	**Intervention (50 participants):** omega-3 PUFA for 8 weeks (100 mg/day of EPA for children < 25 kg, 200 mg/day for children 26 to 35 kg, and 400 mg/day for children > 35 kg) plus MPH (Ritalin) (10 mg daily for children under 20 kg, 10 mg twice a day for children over 20 kg) **Control (50 participants):** placebo (sugar) for 8 weeks plus MPH (Ritalin) (10 mg daily for children under 20 kg, 10 mg twice a day for children over 20 kg)
Outcomes	1. ADHD symptoms measured at 2, 4, 8 weeks a. Conners Parent Rating Scale b. Conners Teacher Rating Scale
Notes	Study has a clinical trial registry ID of IRCT20110416201N1, but we could not find the protocol.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** Selection of patients in all groups was done based on block of 6 randomisation but not further described
Allocation concealment (selection bias)	Unclear risk	**Comment:** not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** states that it was double-blind but not further described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** states that it was double-blind but not further described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** appears that 100% followed up but there may have been more randomised; loss to follow-up: unclear
Selective reporting (reporting bias)	Unclear risk	**Comment:** protocol (IRCT20110416201N1) could not be found
Other bias	Unclear risk	**Comment:** much lower proportion diagnosed with hyperactivity subtype in PUFA group (12% vs 42%)

Sinn 2007

Study characteristics

Methods	**Design:** cross-over trial **Comparison:** omega-3 or omega-6 PUFA ± multivitamins vs placebo followed by PUFA ± multivitamin supplement
Participants	**Inclusion criteria:** 1. children aged 7 to 12 years; 2. with scores of 2 SD or more above the population average on the parent-rated Conners Abbreviated ADHD Index **Exclusion criteria:** 1. children who had taken stimulant medication and any form of omega-3 supplementation in the previous 3 months

Sinn 2007 *(Continued)*

	Number of participants: 167 (104 completed) **Mean age:** 9.4 years **Gender:** 77 boys and 27 girls at follow-up **ADHD subtypes:** not stated **Using ADHD drugs at baseline:** 0% **Baseline scores:** Conners ADHD Index, parent rated, mean: PUFA = 26.68, placebo = 26.67 **Setting:** South Australia, 2004 **Funding**: study was supported by a Ph.D. scholarship from the University of South Australia and the Commonwealth Scientific and Industrial Research Organisation (CSIRO), Division of Human Nutrition. Supplements were supplied by Equazen Neutraceuticals, Novasel Australia, and Blackmores Australia.
Interventions	**Intervention (76 participants):** 1. Omega-3/omega-6 PUFA for 15 weeks: 6 capsules daily PUFA (eye q Equazen, UK and Novasel, Australia); each capsule contained 400 mg of fish oil, 100 mg of primrose oil containing 93 mg of EPA, 29 mg of DHA, and 10 mg of gamma-linolenic acid, and 1.8 mg of vitamin E 2. PUFA plus multivitamin for 15 weeks: 1 tablet per day of multivitamin containing vitamin A, thiamine, vitamin B_2, B_6, C, D, B_{12}, E, biotin, B_5, calcium hydrogen phosphate, iron fumarate, magnesium oxide, manganese sulphate, zinc oxide, copper gluconate, potassium iodide (Blackmores, Australia) plus PUFA as above **Control (28 participants):** placebo for 15 weeks; 6 capsules daily of palm oil. There was no placebo for the multivitamin, but the contents of the intervention packaging were blinded.
Outcomes	1. Symptoms at 15 weeks a. Parent-rated Revised Conners Rating Scales b. Teacher-rated Revised Conners Rating Scales 2. Behaviour at 15 weeks a. Conners Parent Rating Scale: oppositional behaviour
Notes	We collected first-phase data for this review. Although adjusted mean data were available for 104 participants at the end of this phase, the unadjusted data, which were available for 87 participants, were used.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** participants were randomised within age and gender
Allocation concealment (selection bias)	Low risk	**Comment:** Independently held code numbers were used to conceal allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment:** The authors described phase 1 as double-blind. Packaging was designed to maintain blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** packaging designed to maintain blinding and parent-rated scales used

Sinn 2007 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	**Comment:** Missing data were replaced with the variable mean value for 1 or 2 missing responses. Cases with 3 or more missing responses were deleted from the data set, loss to follow-up: 63/167
Selective reporting (reporting bias)	High risk	**Comment:** Teacher-rated outcomes, which were not significantly different, were not reported.
Other bias	Unclear risk	**Comment:** Children who withdrew had significantly higher baseline scores on the Conners Index (withdrew before starting: 28.92, withdrew during phase 1: 28.74, completed phase 1: 26.27).

Stevens 2003

Study characteristics	
Methods	**Design:** parallel trial **Comparison:** omega-3/omega-6 PUFA vs placebo
Participants	**Inclusion criteria:** 1. children aged 6 to 13 years; 2. diagnosed with ADHD by a clinical psychologist, psychiatrist, or paediatrician; 3. with thirst or skin symptoms, or both **Exclusion criteria:** 1. chronic health problems; 2. distance from the test site; 3. inability to swallow capsules; 4. lack of interest **Number of participants:** 47 (33 completed) **Mean age:** 9.8 years **Gender:** 41 boys and 6 girls at baseline **ADHD subtypes:** not stated **Using ADHD drugs at baseline:** 66% **Baseline scores:** Conners Abbreviated Questionnaire, parent-rated: PUFA = 16.5, placebo = 19.9; Conners Abbreviated Questionnaire, teacher-rated: PUFA = 10.5, placebo = 13.1 **Setting:** central Indiana, USA, year/s not stated **Funding:** study was funded by grants from the National Institute of Mental Health (# RO3 MH56414) and Scotia Pharmaceuticals Ltd
Interventions	**Intervention (18 participants):** omega-3/omega-6 PUFA for 4 months; 8 capsules daily, which contained 60 mg of DHA, 10 mg of EPA, 5 mg of arachidonic acid, 12 mg of gamma-linolenic acid, and 3 mg of vitamin E (Efalex; Efamol Ltd, UK) **Control (15 participants):** placebo for 4 months; 8 capsules daily, which contained 0.8 g of olive oil
Outcomes	1. Improvement at 4 months a. Defined as no longer meeting the parent criteria for hyperactivity 2. ADHD symptoms at 4 months a. Parent- and teacher-rated Conners questionnaire b. Parent- and teacher-rated Disrupted Behavior Disorders Rating Scale: hyperactivity, attention 3. Behaviour at 4 months a. Parent- and teacher-rated Disrupted Behavior Disorders Rating Scale: conduct, oppositional defiant behaviour

Stevens 2003 *(Continued)*

Notes	SDs calculated from range.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** randomisation was balanced for age and gender
Allocation concealment (selection bias)	Unclear risk	**Comment:** not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment:** The authors described the trial as double-blind. The odour and appearance of the placebo capsules were described as comparable to the PUFA capsules.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** The capsules were "comparable" (p1009), and parent and teacher-rated were scales used.
Incomplete outcome data (attrition bias) All outcomes	High risk	**Comment:** The authors reported that ITT analysis was done but reported data from the 33 of 50 participants who completed the trial.
Selective reporting (reporting bias)	Low risk	**Comment:** all outcomes listed in paper were reported
Other bias	High risk	**Comment:** Sponsored in part by sponsored by Scotia Pharmaceuticals Ltd, which produced PUFA supplements.

Vaisman 2008

Study characteristics

Methods	**Design:** parallel trial **Comparator:** omega-3 PUFA vs placebo
Participants	**Inclusion criteria:** 1. aged 8 to 13 years; 2. had received a previous diagnosis of ADHD by a clinical psychiatrist, neurologist, or paediatrician **Exclusion criteria:** 1. significant sensory or neurological limitations; 2. epilepsy; 3. mental retardation; 4. psychosis; 5. pervasive developmental disorder; 6. taking medications with known central nervous system effects (including stimulants or dietary supplements other than vitamins); 7. a total Test of Variables of Attention Score more than 1.8 SD lower than age and gender means **Number of participants:** 60 **Mean age:** 9.3 years **Gender:** 45 boys and 15 girls at follow-up **ADHD subtypes:** not stated **Using ADHD drugs at baseline:** 0% **Baseline scores:** Conners Rating Scale: PUFA = 15.8; placebo = 15.1

Vaisman 2008 *(Continued)*

	Setting: medical centre in Tel Aviv, Israel, 2004 to 2005 **Funding:** not stated
Interventions	**Intervention (39 participants):** PUFA for 3 months 1. Phospholipid supplement enriched with n-3 fatty acids (Enzymotec Ltd, Israel) containing 95 mg of DHA, 156 mg of EPA, 300 mg of phosphatidylserine, rosemary extract, ascorbyl palmitate, and mixed natural tocopherols (0.8% by weight), emulsified to a dairy chocolate-flavoured spread containing 4 to 7 mg of citrus oil extract (to disguise taste) administered daily as 25 g of spread 2. Fish oil supplement (Ocean Nutrition) containing 96 mg of DHA, 153 mg of EPA and tocopherol mixture (0.2% by weight) daily, emulsified to a dairy chocolate-flavoured spread containing 4 to 7 mg of citrus oil extract (to disguise taste) administered daily as 25 g of spread for 3 months **Control (21 participants):** placebo for 3 months; rapeseed oil supplement emulsified to a dairy chocolate-flavoured spread containing 4 to 7 mg of citrus oil extract, administered as 25 g of spread per day for 3 months
Outcomes	1. Symptoms at 3 months a. Change in parent-rated abbreviated Conners Rating Scale
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** A block randomisation with a block size of 3 was used.
Allocation concealment (selection bias)	Unclear risk	**Comment:** Allocation concealment was not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment:** The supplements appeared "identically appearing" (p1172); therefore, participants were probably blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** The supplements appeared identical and a parent-rated scale was used.
Incomplete outcome data (attrition bias) All outcomes	High risk	**Comment:** A per protocol analysis was used for 60 of 83 participants.
Selective reporting (reporting bias)	Low risk	**Comment:** all outcomes listed in paper and protocol appear to have been reported
Other bias	Unclear risk	**Comment:** The principal author was a consultant to Enzymotec Pty Ltd and the Director was another author.

Voigt 2001

Study characteristics

Methods	**Design:** parallel trial

Voigt 2001 *(Continued)*

	Comparator: omega-3 PUFA vs placebo
Participants	**Inclusion criteria:** 1. children aged 6 to 12 years; 2. previously diagnosed with ADHD by a physician and confirmed by a neurodevelopmental physician; 3. with significant social or academic impairment; 4. receiving effective stimulant maintenance therapy **Exclusion criteria:** 1. ineffective treatment; 2. treatment with other psychotropics; 3. diagnosis of other psychiatric disorders; 4. use of dietary supplements other than vitamins; 5. a significant life event within 6 months; 6. head injury or seizure; 7. mental retardation or pervasive developmental disorder; 8. premature birth; 9. exposure to tobacco or other drugs in utero; 10. lipid metabolism disorder **Number of participants:** 54 (53 completed) **Mean age:** 9.3 years **Gender:** 42 boys and 12 girls **ADHD subtypes:** combined = 48; inattentive = 5 **Using ADHD drugs at baseline:** 100% **Baseline scores:** mean response time (TOVA): PUFA = 1.43, placebo = 1.56 **Setting:** USA, year/s not stated **Funding:** study was also funded in part by a grant from the Martek Biosciences Corp, Columbia, Maryland, which also provided the DHA and placebo capsules used in the study
Interventions	**Intervention (27 participants):** omega-3 PUFA for 4 months; 3 capsules daily of an algae-derived triglyceride capsule providing 345 mg of DHA (DHASCO, Martek Biosciences Corp) **Control (26 participants):** placebo for 4 months; 3 capsules daily - not described further
Outcomes	1. ADHD symptoms for 4 months a. Parent-rated Child Behavior Checklist: attention 2. Behaviour for 4 months a. Parent-rated Child Behavior Checklist: internalising, externalising
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** computer-generated randomisation scheme
Allocation concealment (selection bias)	Unclear risk	**Comment:** not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment:** The authors described the trial as double-blind. Placebo described as "identical in appearance" (p190) to PUFA capsule
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** The capsules appeared "identical" (p190) and parent-rated scales were used.
Incomplete outcome data (attrition bias)	High risk	**Comment:** data reported for 53/63 enroled participants who completed the trial

Voigt 2001 *(Continued)*
All outcomes

Selective reporting (reporting bias)	High risk	**Comment:** The authors stated there were no differences in the Conners Rating Scales but these data were not reported.
Other bias	High risk	**Comment:** Study funded by Martek Biosciences Corporation that produced PUFA supplement.

Widenhorn-Müller 2014

Study characteristics

Methods	**Design:** parallel trial **Comparison:** omega-3 PUFA vs placebo
Participants	**Inclusion criteria:** 1. children aged 6 to 12 years; 2. with ADHD meeting DSM-IV criteria **Exclusion criteria:** 1. IQ < 70; 2. use of stimulants, other psychoactive medication, or fatty acid supplements in the previous 6 months; 3. allergies to fish or fish products **Number of participants:** 97 (92 completed) **Mean age:** 8.9 years **Gender:** 74 boys and 21 girls **ADHD subtypes:** combined = 41; inattentive = 52; hyperactive-impulsive = 2 **Using ADHD drugs at baseline:** 0% **Baseline scores:** Diagnostik-System für Psychische Störungen (DISYPS-II) scores: omega-3 = 1.68, placebo = 1.64 **Setting:** Division of Social Pediatrics and Child Neurology University Children's Hospital, Ulm, Germany, year/s not stated **Funding:** study was funded by the German Federal Ministry of Education and Research Grant 01EA1312
Interventions	**Intervention (45 participants):** omega-3 PUFA for 16 weeks; 720 mg of omega-3 fatty acids in 2 capsules (600 mg of EPA or 120 mg of DHA) **Control (47 participants)::** placebo (olive oil) for 16 weeks
Outcomes	1. ADHD symptoms at 16 weeks a. Parent- and teacher-rated DISYPS-II 2. Behaviour at 16 weeks a. Parent-rated Child Behavior Checklist: internalising, externalising
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** computer-generated random sequence

Widenhorn-Müller 2014 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	**Comment:** not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "Participants, parents and those assessing outcome measures were blind to the intervention condition. Blinding was maintained until data analysis was completed." (p50)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "Participants, parents and those assessing outcome measures were blind to the intervention condition. Blinding was maintained until data analysis was completed." (p50)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** "Data were analysed per protocol" (p 53) for 95/110 participants who completed the trial. Multiple imputation was used as a sensitivity analysis; loss to follow-up: 15/100
Selective reporting (reporting bias)	Low risk	**Comment:** all registered outcomes were reported; trial registration: ClinicalTrials.gov; NCT01055119
Other bias	Unclear risk	**Comment:** no differences in age, gender, IQ or ADHD subtype

ADD: attention deficit disorder; **ADHD:** attention deficit hyperactivity disorder; **ADHD-RS-IV:** Attention Deficit Hyperactivity Rating Scale, fourth version; **CGI-S:** Clinical Global Impression-Severity; **CI:** confidence intervals; **CNS:** central nervous system; **DHA:** docosahexanoic acid; **DSM-III:** Diagnostic and Statistical Manual of Mental Disorders, third edition; **DSM-IV:** Diagnostic and Statistical Manual of Mental Disorders, fourth edition; **DSM-IV-TR:** Diagnostic and Statistical Manual of Mental Disorders, fourth edition Text Revision; **DSM-5:** Diagnostic and Statistical Manual of Mental Disorders, fifth edition; **EFA:** essential fatty acids; **EPA:** eicosapentaenoic acid;**IQ**: intelligence quotient; **ITT:** intention-to-treat; **IU:** international units; **MPH**: methylphenidate; **NSAIDs:** non-steroidal anti-inflammatory drugs; **ODD:** oppositional defiant disorder; **PUFA:** polyunsaturated fatty acids; **SD:** standard deviation; **SDQ**: Strengths and Difficulties Questionnaire;**SE:** standard error; **SEM:** standard error of the mean; **SNAP-IV:** Swanson, Nolan, and Pelham, fourth revision; **TOVA:** Test of Variables of Attention

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Anonymous 2009	Review of Johnson 2009
Doebel 2005	Overview of articles and trials of nutrients in children with ADHD
Döpfner 2021	Children were not diagnosed with ADHD.
Greeff 2011	Children were not diagnosed with ADHD.
Harding 2003	Not a randomised or quasi-randomised controlled trial
Johnson 2017	Children were not diagnosed with ADHD.
Joshi 2006	Pre-post study
Meguid 2016	Case-control study followed by open-label interventional phase
NCT01777048	Study terminated.
NCT01778647	Study terminated.

Study	Reason for exclusion
Richardson 2002	The Conners cut-off score used as an inclusion criterion was not stated.
San Mauro Martin 2019	Not a randomised or quasi-randomised controlled trial
Tan 2014	Participants were a subgroup with ADHD from a larger randomised controlled trial of supplementation and social skills training in children with disruptive behaviour disorders.
Wilens 2017	Open-label pilot study of omega-3 PUFAs in 10 children aged 6 to 17 years with ADHD

ADHD: attention deficit hyperactivity disorder; **PUFAs:** polyunsaturated fatty acids

Characteristics of studies awaiting classification *[ordered by study ID]*

Carucci 2017

Methods	**Design:** multicentre parallel randomised trial **Comparison:** omega-3/omega-6 vs placebo
Participants	**Inclusion criteria:** 1. mild to moderate inattentive ADHD according to DSM-IV criteria; 2. aged 6 to 12 years old **Exclusion criteria:** not stated **Sample size:** 160
Interventions	**Intervention:** omega-3/omega-6 PUFA **Control:** placebo
Outcomes	**ADHD symptoms,** assessed with ADHD Rating Scale (ADHD-RS-IV) score **Depression,** assessed with CDRS-R (Children's Depression Rating Scale-Revised) **Anxiety**, assessed with MASC (Multidimensional Anxiety Scale for Children) **Timing of outcome assessment:** 6 and 12 months
Notes	**Country:** Italy **Clinical trial register:** not stated **Start date:** not stated **Funding:** study was supported by an unrestricted grant from Vifor Pharma

IRCT201104166201N1

Methods	**Design:** parallel randomised trial **Comparison:** omega-3 supplement + MPH (Ritalin) vs placebo + MPH (Ritalin)
Participants	**Inclusion criteria:** 1. aged 6 to 15 years; 2. newly diagnosed patient; 3. no history of taking any psychiatric drug; 4. no other psychiatric disorders; 5. no contraindication for the use of zinc and omega-3; 6. diagnosis of ADHD based on DSM-IV criteria and diagnostic interview of psychiatrist

IRCT201104166201N1 *(Continued)*

	Exclusion criteria: 1. parents or children withdrew from the study for any reason; 2. child is suffering from acute physical illness; 3. children cannot use oral drugs; 4. complications of drugs such that they must be stopped; 5. alter treatment; 6. drug is not used; 7. any previous psychiatric disorders; 8. mental retardation; 9. patient cannot use drugs **Sample size:** 150
Interventions	**Intervention:** dose of omega-3 supplement based on child's weight: 100 mg of EPA for children less than 25 kg, 200 mg of EPA for children between 26 and 35 kg, 400 mg for children above 36 kg, plus MPH (Ritalin) **Control:** MPH (Ritalin)
Outcomes	**ADHD symptoms,** assessed with Conners Rating Scale **Timing of outcome assessment:** 2, 4, 8 weeks
Notes	**Clinical trial register:** Iranian Clinical Trial Registry (IRCT201104166201N1) **Start date:** 2011 **Country:** Iran **Contact:** Hamid Sheykholeslami, email: hamid.sh@arakmu.ac.ir **Status:** no updates posted

IRCT201304035393N3

Methods	**Design:** parallel randomised trial **Comparison:** omega-3 + MPH (Ritalin) vs MPH (Ritalin)
Participants	**Inclusion criteria:** 1. children aged 6 to 12 years old with score > 65 on both parent and teacher versions of Conners Rating Scale; 2. IQ > 70 using Kaufman Brief Intelligence Test; 3. informed consent **Exclusion criteria:** 1. occurrence of unintended side effects; 2. previous treatment of ADHD; 3. omega-3 supplement consumption during past 3 months; 4. severe psychiatric disorders **Sample size:** 85
Interventions	**Intervention:** omega-3 (1 g), 3 capsules divided in 3 days with MPH (Ritalin), 0.3 to 1 mg/kg 3 times a day **Control:** MPH (Ritalin), 0.3 to 1 mg/kg 3 times a day
Outcomes	**ADHD symptoms,** assessed with Connors test for ADHD **Timing of outcome asssessment:** 4 weeks
Notes	**Clinical trial register:** Iranian Clinical Trial Registry (IRCT201304035393N3) **Start date:** 2009 **Country:** Iran **Contact:** Hamid Reza Soltani.G, email: hrsgmed@yahoo.com **Status:** recruitment completed, no results posted

IRCT2016050918927N2

Methods	**Design:** parallel randomised trial **Comparison:** omega-3 + MPH vs MPH
Participants	**Inclusion criteria:** 1. children aged between 7 and 12 years; 2. ADHD diagnosis by expert paediatric psychology physician using DSM diagnosis index; 3. no prevention for omega-3 supplements; 4. IQ index above 70; 5. without other psychological disorders; 6. no intake of omega-3 supplements since 2 months ago; and 7. intake of MPH tablet with a dose of 0.5 to 1 mg/kg/day as a medical treatment **Exclusion criteria:** 1. treatment stopped by the child or parents; 2. incorrect intake of the drug by the child; 3. change the treatment method; 4. stop the treatment due to the side effects of the drug; 5. acute physical disease **Sample size:** 80
Interventions	**Intervention:** 300 mg omega-3 capsule with 0.5 to 1 mg/kg/day MPH for 6 weeks **Control:** 0.5 to 1 mg/kg/day MPH for 6 weeks
Outcomes	**ADHD symptoms,** assessed with Conners questionnaire **Timing of outcome assessment:** 6 weeks
Notes	**Clinical trial register:** Iranian Clinical Trial Registry (IRCT2016050918927N2) **Start date:** not stated **Country:** Iran **Contact:** Seyed Gholamreza Noorazar, email: noorazars@tbzmed.ac.ir **Status:** no updates posted

NCT00770627

Methods	**Design:** parallel randomised trial **Comparison:** omega-3 vs placebo
Participants	**Inclusion criteria:** 1. children aged 6 to 15 years and 11 months, with hyperactivity confirmed by DSM-IV criteria; 2. children and parents' consent **Exclusion criteria:** 1. without MPH treatment; 2. fish or other sea products allergy; 3. intake of sea omega-3 fatty acids supplements more 1 week during 3 months before the trial; 4. children need quickly to take MPH: social, family, or school risk; 5. intake methylphenidate 30 days before the trial or/and intake it during 1 consecutive week **Sample size:** 160
Interventions	**Intervention:** children between 6 and 8 years of age, 2 caps/day; children between 9 and 11 years, 3 caps/day; children between 12 and 15 years, 4 caps/day **Control:** placebo
Outcomes	**ADHD symptoms,** assessed with ADHD Rating Scale

NCT00770627 *(Continued)*

	Timing of outcome assessment: 12 weeks
Notes	**Clinical trial register:** ClinicalTrials.gov (NCT00770627) **Start date:** 2008 **Country:** France **Contact:** Doctor Olivier Revol, Pierre Wertheimer Hospital **Status:** no updates posted

NCT02114632

Methods	**Design:** parallel randomised trial **Comparison:** omega-3/omega-6 PUFA vs placebo
Participants	**Inclusion criteria:** 1. patients will be boys between the ages of 8 and 16 years; 2. patients must meet DSM-IV diagnostic criteria for ADHD confirmed by Schedule for Affective Disorders and Schizophrenia - Present and Lifetime Version (K-SADS-PL); 3. patients must be of normal intelligence as assessed by the Wechsler Intelligence Scale for Children - Revised Edition (WISC-R); 4. treatment of ADHD by such drugs as: atomoxetine, reboxetine, clonidine, desipramine, or clomipramine or children with ADHD without pharmacological treatment **Exclusion criteria:** 1. patients who have a documented history of bipolar I or II disorder, psychosis, or autism; 2. patients with a history of epilepsy; 3. patients with a history of asthma treated with corticosteroids; 4. patients with diabetes, haemorrhagic problem, hyperlipidaemia, hypertension, hyperthyroidism, or hypothyroidism; 5. patients taking any psychotropic medication other than above-mentioned on a regular basis, including health food supplements that the investigator feels have central nervous system activity, must have a washout of at least 3 months before study entry, and such medications are not allowed during the study; 6. patients with a history of alcohol or drug abuse within the past 3 months (excessive or compulsive use as judged by the investigator) **Sample size:** 89
Interventions	**Intervention:** 6 capsules of food supplement "Eye q" per day divided in 2 daily doses (558 mg EPA, 174 mg DHA, 60 mg GLA per day) **Control:** placebo - olive oil
Outcomes	**ADHD symptoms,** assessed with neuropsychological tests and parents and teacher questionnaires **Timing of outcome assessment:** 3 months
Notes	**Clinical trial register:** ClinicalTrials.gov (NCT02114632) **Start date:** 2007 **Country:** Poland **Contact:** Magdalena Grygo, MD, Medical University of Warsaw **Status:** completed, no results posted

NCT02248948

Methods	**Design:** parallel randomised trial

NCT02248948 *(Continued)*

	Comparison: omega-3/omega-6 PUFA vs placebo
Participants	**Inclusion criteria:** 1. aged between 6 and 11 years 11 months; 2. ADHD diagnosis according to DSM-IV-TR criteria; 3. children whose parents are able to reliably meet all visits and all the tests required for this study based on researcher judgment; 4. patient representative (either parents or legal guardians) must understand the conditions of the study and sign the informed consent **Exclusion criteria:** 1. patients who do not meet diagnostic criteria for ADHD; 2. patients with a previously known allergy or intolerance to the components of omega-3 supplement; 3. patients with underlying diseases that, according to medical criteria, are not eligible for supplementation with omega-3 fatty acids: fatty liver disease (or other liver disease), bleeding disorders, and cardiovascular disease; 4. patients with allergies to fish or shellfish (or both); 5. patients who have received ADHD pharmacological treatment or fatty acid supplements at any dose for more than 7 consecutive days within the last 3 months; 6. patients who have received psychological or psycho-educational treatment in the past 3 months; 7. patients who have had some kind of psychometric diagnostic tests in the last year; 8. patients with scores corresponding to a lower mental age (more than 1 year less) according to the Wechsler Intelligence Cubes Scale for Children (WISC-IV); 9. patients with severe emotional problems according to the CAS or STAIC tests; 10. patients participating in another clinical trial **Sample size:** 231
Interventions	**Intervention:** omega-3 fatty acid: 540 mg EPA, 340 mg DHA, 60 mg GLA/omega-6, 5 mg of vitamin D, and 6 mg of vitamin E in 4 mL as a daily dose, calculated based on child weight (≤ 28 kg = 4 mL; 29 to 40 kg = 6 mL, and ≥ 41 kg = 8 mL), once a day for 6 months **Control:** medium-chain triglycerides oil, with 5 mg of vitamin D and 6 mg of vitamin E in 4 mL as a daily dose calculated based on child weight (≤ 28 kg = 4 mL; 29 to 40 kg = 6 mL, and ≥ 41 kg = 8 mL), once a day for 6 months
Outcomes	**ADHD symptoms,** assessed with ADHD-Scale-IV rated by parents and teachers **Timing of outcome assessment:** 2, 4, 6 months
Notes	**Clinical trial register:** ClinicalTrials.gov (NCT02248948) **Start date:** 2014 **Country:** Spain **Contact:** Jordi Sasot Llevadot, MD, Centro Médico Teknon **Status:** completed, no results posted

NCT02348073

Methods	**Design:** parallel randomised trial **Comparison:** omega-3 vs placebo
Participants	**Inclusion criteria:** 1. children aged 6 to 15 years and 11 months; 2. children of either sex (male/female) suffering from epilepsy regardless of syndrome classification; 3. children on a stable dose of antiepileptic drugs (AED) for at least 1 month prior to inclusion and for whom no change is considered a priori for the 3 months following inclusion; 4. diagnosis of ADHD inattention or mixed type according to DSM-5 criteria; 5. children must agree to study participation, and their parents/legal guardian must provide written inform consent prior to participation in the study **Exclusion criteria:** 1. individuals less than 6 years or older than 16 years; 2. AED not stable for at least 1 month and/or a change in AED is expected in the 3 months following inclusion; 3. diagnosis of ADHD hyperactivity type exclusive according to DSM-5 criteria; 4. mental retardation defined

NCT02348073 *(Continued)*

	by a score < 70 on the verbal comprehension and perceptual reasoning Wechsler Intelligence Scale for Children - Fourth Edition (WISC-IV), performed within 18 months prior to inclusion or at V1; 5. diagnosis of a psychiatric comorbidity other than ADHD according to DSM-5 criteria, including: pervasive developmental disorders including autism disorders; bipolar disorders and psychotic disorders; 6. children suffering from diabetes, any type; 7. use of psychoactive drugs in ADHD within the previous month: methylphenidate, amphetamine, atomoxetine, modafinil, and antidepressants whatever the class; 8. use of dietary supplementation other than vitamins within the last 3 months; 9. use of ketogenic diet within the last 3 months; 10. allergy to fish or other sea products; 11. soy allergy; 12. absence of coverage by social security **Sample size:** 77
Interventions	**Intervention:** omega-3; 2 capsules Vayarin twice daily, containing 8.5 mg of DHA, 21.5 mg of EPA, and 75 mg of phosphatidylserine. 2 capsules twice daily, 20 to 30 minutes prior to breakfast and dinner, for 12 weeks **Control:** placebo; 2 capsules twice daily, identical to the active product, which contained cellulose and a small amount of fish powder to maintain the double-blind in odour and taste, for 12 weeks
Outcomes	**ADHD symptoms,** assessed with ADHD Rating Scale-IV **Timing of outcome assessment:** 12 weeks
Notes	**Clinical trial register:** ClinicalTrials.gov (NCT02348073) **Start date:** 2015 **Country:** France **Contact:** Sylvain Rheims, MD, Hospices Civils de Lyon **Status:** completed, no results posted

NCT02986672

Methods	**Design:** parallel randomised trial **Comparison:** omega-3 vs placebo
Participants	**Inclusion criteria:** 1. ADHD or attention deficit disorder according to DSM-IV criteria **Exclusion criteria:** 1. IQ below 70; 2. infantile autism, psychosis, bipolar disorders, and serious somatic disease; 3. any abnormal or pathological blood test during trial; 4. omega-3 supplement taken until 3 months before inclusion **Sample size:** 330
Interventions	**Intervention:** omega-3 as calanus oil in capsule form **Control:** placebo - medical paraffin in capsule form (2 mL volume per day)
Outcomes	**ADHD symptoms,** assessed with ADHD Rating Scale **Timing of outcome assessment:** 6 months
Notes	**Clinical trial register:** ClinicalTrials.gov (NCT02986672) **Start date:** 2017 **Country:** Norway

NCT02986672 *(Continued)*

	Contacts: Judeson R Joseph, MD, email: judeson.joseph@unn.no; Professor Siv Kvernmo, MD, email: siv.kvernmo@uit.no **Status:** recruiting

NCT03542643

Methods	**Design:** parallel randomised trial **Comparison:** omega-3 vs placebo
Participants	**Inclusion criteria:** 1. DSM-5-diagnosed ADHD; 2. aged 6 to 18 years old at time of enrolment; 3. Conners rating scales (CPRS) with scores ≥ 2 standard deviations; 4 drug native or no medication use for past 6 months; 5. signed informed consent **Exclusion criteria:** 1. IQ < 70; 2. comorbid other psychiatric disorders, such as autism spectrum disorders, anxiety disorders, conduct disorders, schizophrenia, major depressive disorders, and bipolar spectrum disorders; 3. comorbid physical disorders, such as thyroid dysfunction or cerebral palsy; 4. current use of omega-3 supplements; 5. allergy to omega-3 **Sample size:** 105
Interventions	**Intervention:** omega-3, 1 g of EPA **Control:** placebo - olive oil ethyl esters
Outcomes	**ADHD symptoms,** assessed with SNAP-IV scores **Timing of outcome assessment:** 2, 4, 8, 12 weeks
Notes	**Clinical trial register:** ClinicalTrials.gov (NCT03542643) **Start date:** 2016 **Country:** Taiwan **Contacts:** not stated **Status:** completed, no results posted

ADHD: attention deficit hyperactivity disorder; **CAS:** Cognitive Assessment System; **DHA:** docosahexanoic acid; **DSM:** Diagnostic and Statistical Manual of Mental Disorders; **DSM-IV:** Diagnostic and Statistical Manual of Mental Disorders, fourth edition; **DSM-IV-TR:** Diagnostic and Statistical Manual of Mental Disorders, fourth edition Text Revision; **DSM-5:** Diagnostic and Statistical Manual of Mental Disorders, fifth edition; **EPA:** eicosapentanoic acid; **GLA:** gamma-linolenic acid;**IQ**: intelligence quotient; **MPH:** methylphenidate; **PUFA:** polyunsaturated fatty acids; **SNAP-IV:** Swanson, Nolan, and Pelham, fourth revision; **STAIC:** State-Trait Anxiety Inventory for Children

Characteristics of ongoing studies *[ordered by study ID]*

CTRI/2020/05/025267

Study name	Efficacy of omega-3 fatty acids as an adjuvant therapy to methylphenidate in ADHD
Methods	Cluster-randomised trial
Participants	**Inclusion criteria:** 1. aged 6 to 12 years; 2. attending school; 3. IQ > 85; 4. have not received methylphenidate in the past

CTRI/2020/05/025267 *(Continued)*	**Exclusion criteria:** 1. children with autism spectrum disorder; 2. pre-existing structural brain damage and seizures; 3. presence of comorbid conduct disorder, anxiety disorder, or depressive disorder
Interventions	**Intervention 1:** methylphenidate: 0.3 mg/kg twice a day administered orally in the form of tablets for 12 weeks **Control intervention 1**: omega-3 fatty acids: 1000 mg per day including 180 mg EPA and 120 mg DHA **Control intervention 2:** methylphenidate versus methylphenidate plus omega-3 fatty acids: methylphenidate (0.3 mg/kg twice a day) verus methylphenidate plus omega-3 fatty acids (1000 mg per day) **Control intervention 3:** omega-3 fatty acids: omega-3 fatty acids (DHA + EPA) (1000 mg per day) administered orally in the form of capsules for 12 weeks
Outcomes	Unclear, ADHD symptoms?
Starting date	20 May 2020
Contact information	Dr Priti Arun, email: drpritiarun@gmail.com
Notes	No updates posted.

ADHD: attention deficit hyperactivity disorder; **ALA:** alpha-linolenic acid; **DHA:** docosahexanoic acid; **EPA:** eicosapentanoic acid; **IQ**: intelligence quotient; **LA:** linolenic acid; **PUFA:** polyunsaturated fatty acids

DATA AND ANALYSES

Comparison 1. PUFA versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 ADHD symptoms - improvement	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1.1 Short term	2	80	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.85, 1.76]
1.1.2 Medium term	3	191	Risk Ratio (M-H, Random, 95% CI)	1.95 [1.47, 2.60]
1.1.3 Long term	2	141	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.70, 3.95]
1.2 ADHD symptoms - total, parent rated	23		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.2.1 Short term	8	442	Std. Mean Difference (IV, Random, 95% CI)	0.17 [-0.25, 0.59]
1.2.2 Medium term	16	1166	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.24, 0.07]
1.2.3 Long term	1	60	Std. Mean Difference (IV, Random, 95% CI)	-0.30 [-0.81, 0.21]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 ADHD symptoms - inattention, parent rated	16		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.3.1 Short term	5	283	Std. Mean Difference (IV, Random, 95% CI)	0.01 [-0.31, 0.33]
1.3.2 Medium term	12	960	Std. Mean Difference (IV, Random, 95% CI)	-0.01 [-0.20, 0.17]
1.3.3 Long term	1	60	Std. Mean Difference (IV, Random, 95% CI)	-0.39 [-0.90, 0.12]
1.4 ADHD symptoms - hyperactivity/impulsivity, parent rated	14		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.4.1 Short term	5	283	Std. Mean Difference (IV, Random, 95% CI)	0.15 [-0.20, 0.50]
1.4.2 Medium term	10	869	Std. Mean Difference (IV, Random, 95% CI)	0.09 [-0.04, 0.23]
1.4.3 Long term	1	60	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.72, 0.29]
1.5 ADHD symptoms - total, teacher rated	10		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.5.1 Short term	4	185	Std. Mean Difference (IV, Random, 95% CI)	0.35 [-0.30, 1.00]
1.5.2 Medium term	6	498	Std. Mean Difference (IV, Random, 95% CI)	0.06 [-0.12, 0.24]
1.6 ADHD symptoms - inattention: teacher	7		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.6.1 Short-term	2	86	Std. Mean Difference (IV, Random, 95% CI)	0.02 [-0.40, 0.44]
1.6.2 Medium-term	5	428	Std. Mean Difference (IV, Random, 95% CI)	0.17 [-0.14, 0.49]
1.7 ADHD symptoms - hyperactivity/impulsivity, teacher rated	7		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.7.1 Short term	1	60	Std. Mean Difference (IV, Random, 95% CI)	0.00 [-0.51, 0.51]
1.7.2 Medium term	6	462	Std. Mean Difference (IV, Random, 95% CI)	0.15 [-0.03, 0.34]
1.8 ADHD symptoms - total, clinician rated	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only

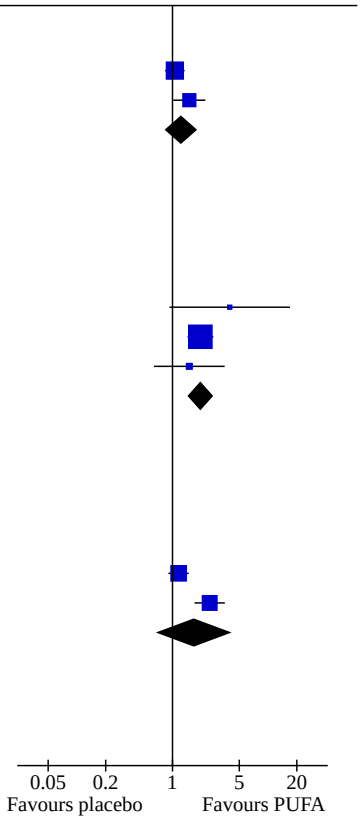
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.8.1 Short term	2	143	Std. Mean Difference (IV, Random, 95% CI)	-0.74 [-1.08, -0.40]
1.8.2 Medium term	1	64	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-0.84, 0.15]
1.9 ADHD symptoms - inattention, clinician rated	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.9.1 Short term	1	17	Std. Mean Difference (IV, Random, 95% CI)	-0.05 [-1.00, 0.90]
1.9.2 Medium term	2	124	Std. Mean Difference (IV, Random, 95% CI)	-0.29 [-0.65, 0.07]
1.10 ADHD symptoms - hyperactivity/impulsivity, clinician rated	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.10.1 Short term	2	53	Std. Mean Difference (IV, Random, 95% CI)	0.36 [-0.18, 0.91]
1.10.2 Medium term	1	64	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.77, 0.21]
1.11 Behaviour - internalising, parent rated	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.11.1 Medium term	3	237	Std. Mean Difference (IV, Random, 95% CI)	0.16 [-0.09, 0.42]
1.12 Behaviour - externalising, parent rated	6		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.12.1 Short term	1	60	Std. Mean Difference (IV, Random, 95% CI)	0.02 [-0.49, 0.52]
1.12.2 Medium term	5	340	Std. Mean Difference (IV, Random, 95% CI)	0.07 [-0.26, 0.41]
1.13 Behaviour - conduct, parent rated	6		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.13.1 Short term	1	60	Std. Mean Difference (IV, Random, 95% CI)	-0.10 [-0.60, 0.41]
1.13.2 Medium term	5	332	Std. Mean Difference (IV, Random, 95% CI)	0.16 [-0.05, 0.38]
1.14 Behaviour - oppositional, parent rated	6		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.14.1 Medium term	6	527	Std. Mean Difference (IV, Random, 95% CI)	0.02 [-0.17, 0.21]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.15 Behaviour - socialisation, parent rated	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.15.1 Medium term	2	145	Std. Mean Difference (IV, Random, 95% CI)	0.27 [-0.06, 0.60]
1.16 Behaviour - conduct, teacher rated	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.16.1 Short term	1	60	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.54, 0.48]
1.16.2 Medium term	2	118	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.39, 0.34]
1.17 Behaviour - oppositional, teacher rated	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.17.1 Medium term	2	224	Std. Mean Difference (IV, Random, 95% CI)	0.10 [-0.18, 0.37]
1.18 Behaviour - socialisation, teacher rated	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.18.1 Medium term	1	85	Std. Mean Difference (IV, Random, 95% CI)	-0.16 [-0.58, 0.27]
1.19 Quality of life: medium term	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
1.20 Side effects	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.20.1 Overall	8	591	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.69, 1.52]
1.20.2 Appetite loss	1	60	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.27, 0.83]
1.20.3 Anxiety	1	60	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.11, 1.28]
1.20.4 Dermatitis	1	147	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.06, 34.36]
1.20.5 Diarrhoea	3	207	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.36, 1.41]
1.20.6 Gastrointestinal discomfort	3	269	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.24, 2.22]
1.20.7 Headache	2	207	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.31, 1.01]
1.20.8 Hyperactivity	1	147	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.06, 34.36]
1.20.9 Insomnia	2	122	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.03, 3.91]
1.20.10 Irritability	1	60	Risk Ratio (M-H, Random, 95% CI)	0.07 [0.00, 1.12]
1.20.11 Nausea	5	428	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.41, 2.34]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.20.12 Nose bleed	2	158	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.09, 6.06]
1.20.13 Palpitations	1	60	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.25, 2.00]
1.20.14 Tics	2	207	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.06, 4.46]
1.20.15 Tremor	1	60	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.87]
1.21 Loss to follow-up	21		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.21.1 Short term	10	785	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.78, 1.41]
1.21.2 Medium term	13	1121	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.77, 1.37]
1.21.3 Long term	1	60	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.09, 0.98]

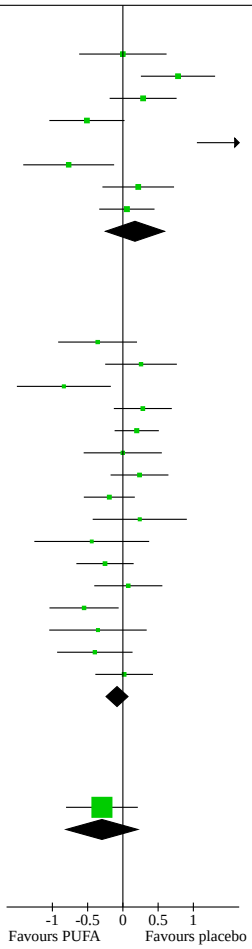
Analysis 1.1. Comparison 1: PUFA versus placebo, Outcome 1: ADHD symptoms - improvement

Study or Subgroup	PUFA Events	PUFA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Short term						
Assareh 2017	18	20	17	20	58.6%	1.06 [0.84 , 1.34]
Moghaddam 2017	18	20	12	20	41.4%	1.50 [1.02 , 2.21]
Subtotal (95% CI)		**40**		**40**	**100.0%**	**1.22 [0.85 , 1.76]**
Total events:	36		29			
Heterogeneity: Tau² = 0.04; Chi² = 2.68, df = 1 (P = 0.10); I² = 63%						
Test for overall effect: Z = 1.08 (P = 0.28)						
1.1.2 Medium term						
Johnson 2009	9	34	2	30	3.9%	3.97 [0.93 , 16.95]
Perera 2012	45	48	22	46	84.8%	1.96 [1.44 , 2.67]
Stevens 2003	9	18	5	15	11.3%	1.50 [0.64 , 3.52]
Subtotal (95% CI)		**100**		**91**	**100.0%**	**1.95 [1.47 , 2.60]**
Total events:	63		29			
Heterogeneity: Tau² = 0.00; Chi² = 1.34, df = 2 (P = 0.51); I² = 0%						
Test for overall effect: Z = 4.59 (P < 0.00001)						
1.1.3 Long term						
Barragán 2017	25	27	16	20	51.2%	1.16 [0.91 , 1.48]
Perera 2012	46	48	18	46	48.8%	2.45 [1.70 , 3.53]
Subtotal (95% CI)		**75**		**66**	**100.0%**	**1.67 [0.70 , 3.95]**
Total events:	71		34			
Heterogeneity: Tau² = 0.36; Chi² = 15.41, df = 1 (P < 0.0001); I² = 94%						
Test for overall effect: Z = 1.16 (P = 0.24)						



Analysis 1.2. Comparison 1: PUFA versus placebo, Outcome 2: ADHD symptoms - total, parent rated

Study or Subgroup	PUFA Mean	PUFA SD	PUFA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.2.1 Short term								
Assareh 2017	13	9	20	13	7	20	12.4%	0.00 [-0.62 , 0.62]
Barragán 2017	31.87	5.77	30	27.6	4.98	30	13.4%	0.78 [0.26 , 1.31]
Behdani 2013	-12.44	5.34	36	-14	5.4	33	14.0%	0.29 [-0.19 , 0.76]
Dashti 2014	18.44	8.31	28	22.66	8.01	28	13.3%	-0.51 [-1.04 , 0.02]
Dubnov-Raz 2014	79	8.75	8	62	4.5	9	6.3%	2.37 [1.05 , 3.68]
Moghaddam 2017	20.1	6	20	26.1	9	20	12.1%	-0.77 [-1.41 , -0.12]
Mohammadzadeh 2019	17.75	9.62	31	15.77	8.21	29	13.6%	0.22 [-0.29 , 0.73]
Salehi 2016	36.5	8.9	50	36.1	4.3	50	14.8%	0.06 [-0.34 , 0.45]
Subtotal (95% CI)			**223**			**219**	**100.0%**	**0.17 [-0.25 , 0.59]**
Heterogeneity: Tau² = 0.27; Chi² = 30.80, df = 7 (P < 0.0001); I² = 77%								
Test for overall effect: Z = 0.81 (P = 0.42)								
1.2.2 Medium term								
Anand 2016	36.6	2.21	25	37.4	2.18	25	5.3%	-0.36 [-0.92 , 0.20]
Barragán 2017	27.57	5.54	30	26.23	4.7	30	6.0%	0.26 [-0.25 , 0.77]
Bos 2015	7.6	3.5	19	10.1	2.2	19	4.1%	-0.84 [-1.50 , -0.17]
Chang 2019	26.88	10.02	48	24	10.17	44	7.7%	0.28 [-0.13 , 0.69]
Cornu 2018	32.8	11.4	77	30.6	10.9	80	10.0%	0.20 [-0.12 , 0.51]
Crippa 2019	25.79	8.67	25	25.81	11.89	25	5.4%	-0.00 [-0.56 , 0.55]
Gustafsson 2010	43.8	18.6	46	39.4	18.4	46	7.7%	0.24 [-0.17 , 0.65]
Manor 2012	-4.86	10.06	99	-2.95	9.44	42	8.8%	-0.19 [-0.55 , 0.17]
Matsudaira 2015	32.79	4.71	19	31.38	6.79	16	4.1%	0.24 [-0.43 , 0.91]
NCT01807299	36.64	12.75	11	42.31	12.1	13	3.0%	-0.44 [-1.26 , 0.37]
Perera 2012	15.46	3.65	48	20.74	29.3	46	7.8%	-0.25 [-0.66 , 0.15]
Rodriguez 2019	23.9	3.9	32	23.6	3.8	34	6.4%	0.08 [-0.41 , 0.56]
Sinn 2007	21.9	7.44	65	25.76	5.17	22	6.3%	-0.55 [-1.04 , -0.06]
Stevens 2003	-4.3	3.75	18	-2.9	4	15	3.9%	-0.35 [-1.04 , 0.34]
Vaisman 2008	-5	8.32	29	-2.35	3.73	26	5.6%	-0.40 [-0.93 , 0.14]
Widenhorn-Müller 2014	1.35	0.54	45	1.34	0.55	47	7.8%	0.02 [-0.39 , 0.43]
Subtotal (95% CI)			**636**			**530**	**100.0%**	**-0.08 [-0.24 , 0.07]**
Heterogeneity: Tau² = 0.04; Chi² = 24.62, df = 15 (P = 0.06); I² = 39%								
Test for overall effect: Z = 1.04 (P = 0.30)								
1.2.3 Long term								
Barragán 2017	24.33	5.09	30	25.83	4.87	30	100.0%	-0.30 [-0.81 , 0.21]
Subtotal (95% CI)			**30**			**30**	**100.0%**	**-0.30 [-0.81 , 0.21]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.14 (P = 0.25)								

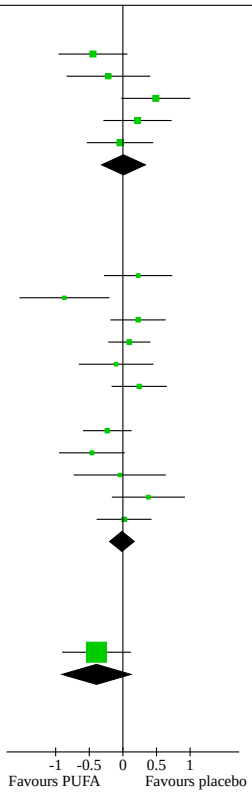


Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.3. Comparison 1: PUFA versus placebo, Outcome 3: ADHD symptoms - inattention, parent rated

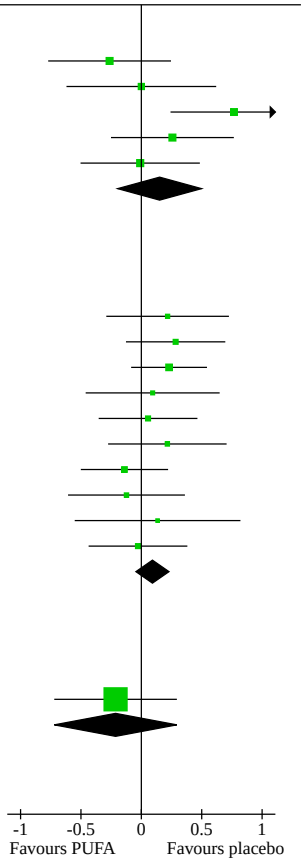
Study or Subgroup	PUFA Mean	PUFA SD	PUFA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
1.3.1 Short term									
Aman 1987	14.97	5.32	30	17.37	5.32	30	20.6%	-0.45 [-0.96 , 0.07]	? ? + + ? + −
Assareh 2017	6	5	20	7	4	20	16.6%	-0.22 [-0.84 , 0.41]	? ? ? ? ? + ?
Barragán 2017	14.13	2.52	30	12.97	2.14	30	20.6%	0.49 [-0.02 , 1.00]	+ − − − ? + −
Mohammadzadeh 2019	17.75	9.62	31	15.77	8.21	29	20.8%	0.22 [-0.29 , 0.73]	+ + + + ? − +
Raz 2009a	3.8	0.9	32	3.84	0.98	31	21.4%	-0.04 [-0.54 , 0.45]	? ? ? + − − +
Subtotal (95% CI)			**143**			**140**	**100.0%**	**0.01 [-0.31 , 0.33]**	
Heterogeneity: Tau² = 0.06; Chi² = 7.57, df = 4 (P = 0.11); I² = 47%									
Test for overall effect: Z = 0.06 (P = 0.95)									
1.3.2 Medium term									
Barragán 2017	12.57	2.08	30	12.13	1.72	30	8.2%	0.23 [-0.28 , 0.74]	+ − − − ? + −
Bos 2015	7.7	3	19	10.5	3.3	19	5.6%	-0.87 [-1.54 , -0.20]	− ? + + + ? −
Chang 2019	14.75	5.34	48	13.5	5.63	44	10.6%	0.23 [-0.18 , 0.64]	? ? ? + ? ? ?
Cornu 2018	16.7	6.1	77	16.1	6.3	80	13.6%	0.10 [-0.22 , 0.41]	+ + + + + ? −
Crippa 2019	14.38	4.51	25	14.95	6.55	25	7.3%	-0.10 [-0.65 , 0.45]	+ + + + + − −
Gustafsson 2010	10.9	4.7	46	9.7	5.1	46	10.6%	0.24 [-0.17 , 0.65]	+ ? + + ? + ?
Kean 2017	77.34	13.23	29	71.03	0	36		Not estimable	+ + + + − − −
Manor 2012	-4.97	9.79	99	-2.74	9.05	42	12.0%	-0.23 [-0.59 , 0.13]	+ + + + − − −
Sinn 2007	21.04	7.62	65	24.49	6.78	22	8.6%	-0.46 [-0.95 , 0.03]	? + + + − − ?
Stevens 2003	-6.8	3.75	18	-6.6	4.5	15	5.4%	-0.05 [-0.73 , 0.64]	? ? + + − + −
Voigt 2001	64.4	9.87	27	60.9	8.16	26	7.5%	0.38 [-0.16 , 0.92]	+ ? + + − − −
Widenhorn-Müller 2014	1.72	0.54	45	1.71	0.55	47	10.6%	0.02 [-0.39 , 0.43]	+ ? + + ? + ?
Subtotal (95% CI)			**528**			**432**	**100.0%**	**-0.01 [-0.20 , 0.17]**	
Heterogeneity: Tau² = 0.04; Chi² = 17.16, df = 10 (P = 0.07); I² = 42%									
Test for overall effect: Z = 0.15 (P = 0.88)									
1.3.3 Long term									
Barragán 2017	11.3	1.95	30	12.03	1.71	30	100.0%	-0.39 [-0.90 , 0.12]	+ − − − ? + −
Subtotal (95% CI)			**30**			**30**	**100.0%**	**-0.39 [-0.90 , 0.12]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.51 (P = 0.13)									



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

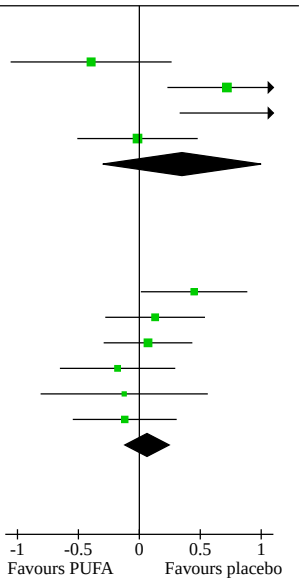
Analysis 1.4. Comparison 1: PUFA versus placebo, Outcome 4: ADHD symptoms - hyperactivity/impulsivity, parent rated

Study or Subgroup	PUFA Mean	PUFA SD	PUFA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.4.1 Short term								
Aman 1987	4.48	2.14	30	5.05	2.14	30	20.8%	-0.26 [-0.77 , 0.25]
Assareh 2017	4	3	20	4	3	20	17.1%	0.00 [-0.62 , 0.62]
Barragán 2017	17.73	4.32	30	14.6	3.71	30	20.1%	0.77 [0.24 , 1.29]
Mohammadzadeh 2019	7.96	4.92	31	6.77	4.15	29	20.8%	0.26 [-0.25 , 0.77]
Raz 2009a	2.86	1.12	32	2.87	0.96	31	21.3%	-0.01 [-0.50 , 0.48]
Subtotal (95% CI)			**143**			**140**	**100.0%**	**0.15 [-0.20 , 0.50]**
Heterogeneity: Tau² = 0.08; Chi² = 8.63, df = 4 (P = 0.07); I² = 54%								
Test for overall effect: Z = 0.85 (P = 0.39)								
1.4.2 Medium term								
Barragán 2017	14.93	3.79	30	14.1	3.74	30	7.3%	0.22 [-0.29 , 0.73]
Chang 2019	12.13	5.86	48	10.5	5.5	44	11.1%	0.28 [-0.13 , 0.70]
Cornu 2018	15.9	6.8	77	14.4	6.2	80	19.0%	0.23 [-0.08 , 0.54]
Crippa 2019	11.42	5.02	25	10.86	6.63	25	6.1%	0.09 [-0.46 , 0.65]
Gustafsson 2010	8.4	5.2	46	8.1	5.5	46	11.2%	0.06 [-0.35 , 0.46]
Kean 2017	78.1	14.23	29	74.97	14.45	36	7.8%	0.22 [-0.28 , 0.71]
Manor 2012	-4.23	11.44	99	-2.62	11.5	42	14.4%	-0.14 [-0.50 , 0.22]
Sinn 2007	11.07	12.45	65	12.45	5.29	22	8.0%	-0.12 [-0.61 , 0.36]
Stevens 2003	-7.9	4	18	-8.5	4.75	15	4.0%	0.13 [-0.55 , 0.82]
Widenhorn-Müller 2014	1.05	0.74	45	1.07	0.69	47	11.2%	-0.03 [-0.44 , 0.38]
Subtotal (95% CI)			**482**			**387**	**100.0%**	**0.09 [-0.04 , 0.23]**
Heterogeneity: Tau² = 0.00; Chi² = 4.77, df = 9 (P = 0.85); I² = 0%								
Test for overall effect: Z = 1.32 (P = 0.19)								
1.4.3 Long term								
Barragán 2017	13.03	3.44	30	13.8	3.68	30	100.0%	-0.21 [-0.72 , 0.29]
Subtotal (95% CI)			**30**			**30**	**100.0%**	**-0.21 [-0.72 , 0.29]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.82 (P = 0.41)								



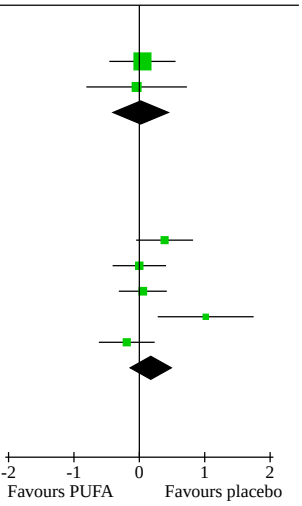
Analysis 1.5. Comparison 1: PUFA versus placebo, Outcome 5: ADHD symptoms - total, teacher rated

Study or Subgroup	PUFA Mean	PUFA SD	PUFA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.5.1 Short term								
Arnold 1989	1.39	0.58	18	1.59	0.39	18	25.3%	-0.40 [-1.06 , 0.26]
Behdani 2013	-6.75	2.75	36	-11.76	9.55	33	28.7%	0.72 [0.23 , 1.21]
Dubnov-Raz 2014	69	7.3	8	61	2.5	9	17.3%	1.43 [0.33 , 2.53]
Raz 2009a	3.64	1.48	32	3.66	1.12	31	28.6%	-0.02 [-0.51 , 0.48]
Subtotal (95% CI)			**94**			**91**	**100.0%**	**0.35 [-0.30 , 1.00]**
Heterogeneity: Tau² = 0.32; Chi² = 12.70, df = 3 (P = 0.005); I² = 76%								
Test for overall effect: Z = 1.05 (P = 0.29)								
1.5.2 Medium term								
Chang 2019	28.95	13.32	44	23.65	9.5	39	17.0%	0.45 [0.01 , 0.89]
Gustafsson 2010	43.1	18.8	46	40.7	17.9	46	19.3%	0.13 [-0.28 , 0.54]
Manor 2012	-1	8.57	94	-1.62	8.87	42	24.3%	0.07 [-0.29 , 0.44]
Matsudaira 2015	71.4	10.6	33	73.4	11.5	36	14.5%	-0.18 [-0.65 , 0.29]
Stevens 2003	-1.9	2.75	18	-1.4	5	15	7.0%	-0.12 [-0.81 , 0.56]
Widenhorn-Müller 2014	1.04	0.62	40	1.11	0.54	45	17.8%	-0.12 [-0.55 , 0.31]
Subtotal (95% CI)			**275**			**223**	**100.0%**	**0.06 [-0.12 , 0.24]**
Heterogeneity: Tau² = 0.00; Chi² = 5.10, df = 5 (P = 0.40); I² = 2%								
Test for overall effect: Z = 0.68 (P = 0.50)								



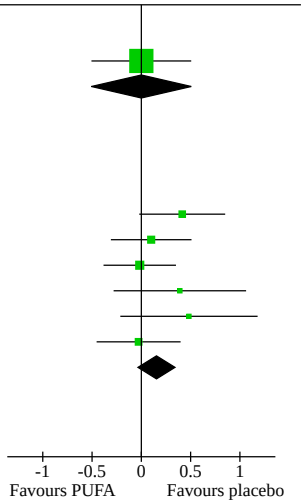
Analysis 1.6. Comparison 1: PUFA versus placebo, Outcome 6: ADHD symptoms - inattention: teacher

Study or Subgroup	PUFA Mean	PUFA SD	PUFA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.6.1 Short-term								
Aman 1987	2.69	0.62	30	2.66	0.62	30	69.8%	0.05 [-0.46 , 0.55]
Ivity 2015	2	3	13	2.1	1.4	13	30.2%	-0.04 [-0.81 , 0.73]
Subtotal (95% CI)			**43**			**43**	**100.0%**	**0.02 [-0.40 , 0.44]**
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%								
Test for overall effect: Z = 0.10 (P = 0.92)								
1.6.2 Medium-term								
Chang 2019	16.09	7.06	44	13.7	4.86	39	21.0%	0.39 [-0.05 , 0.82]
Gustafsson 2010	6.9	4.4	46	6.9	4.4	46	22.0%	0.00 [-0.41 , 0.41]
Manor 2012	-1.7	8.07	94	-2.17	10.23	41	23.7%	0.05 [-0.31 , 0.42]
Stevens 2003	-0.2	3.75	18	-4.6	4.75	15	12.0%	1.01 [0.28 , 1.75]
Widenhorn-Müller 2014	1.45	0.7	40	1.59	0.74	45	21.3%	-0.19 [-0.62 , 0.23]
Subtotal (95% CI)			**242**			**186**	**100.0%**	**0.17 [-0.14 , 0.49]**
Heterogeneity: Tau² = 0.07; Chi² = 9.67, df = 4 (P = 0.05); I² = 59%								
Test for overall effect: Z = 1.09 (P = 0.27)								



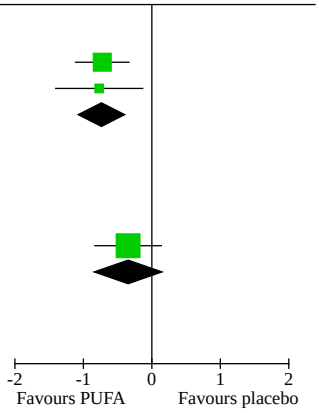
Analysis 1.7. Comparison 1: PUFA versus placebo, Outcome 7: ADHD symptoms - hyperactivity/impulsivity, teacher rated

Study or Subgroup	PUFA Mean	PUFA SD	PUFA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.7.1 Short term								
Aman 1987	2.58	0.8	30	2.58	0.8	30	100.0%	0.00 [-0.51 , 0.51]
Subtotal (95% CI)			**30**			**30**	**100.0%**	**0.00 [-0.51 , 0.51]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
1.7.2 Medium term								
Chang 2019	12.86	7.55	44	9.95	6.2	39	18.5%	0.41 [-0.02 , 0.85]
Gustafsson 2010	10.8	5.7	46	10.2	6.2	46	21.0%	0.10 [-0.31 , 0.51]
Manor 2012	-0.62	10.52	93	-0.46	7.99	41	26.0%	-0.02 [-0.38 , 0.35]
Matsudaira 2015	81.42	11	19	76.75	12.44	16	7.8%	0.39 [-0.28 , 1.06]
Stevens 2003	0.4	5	18	-2.5	6.75	15	7.3%	0.48 [-0.21 , 1.18]
Widenhorn-Müller 2014	0.68	0.76	40	0.7	0.67	45	19.4%	-0.03 [-0.45 , 0.40]
Subtotal (95% CI)			**260**			**202**	**100.0%**	**0.15 [-0.03 , 0.34]**
Heterogeneity: Tau² = 0.00; Chi² = 4.30, df = 5 (P = 0.51); I² = 0%								
Test for overall effect: Z = 1.61 (P = 0.11)								



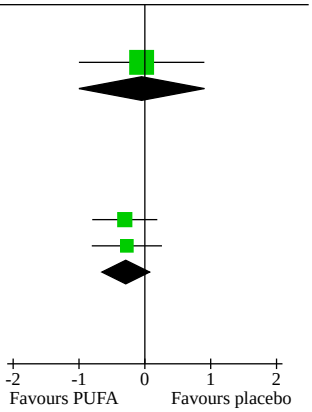
Analysis 1.8. Comparison 1: PUFA versus placebo, Outcome 8: ADHD symptoms - total, clinician rated

Study or Subgroup	PUFA Mean	PUFA SD	PUFA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.8.1 Short term								
Hariri 2012	21.03	3.98	53	24.02	4.22	50	72.3%	-0.72 [-1.12 , -0.32]
Moghaddam 2017	20.1	6	20	26.1	9	20	27.7%	-0.77 [-1.41 , -0.12]
Subtotal (95% CI)			**73**			**70**	**100.0%**	**-0.74 [-1.08 , -0.40]**
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%								
Test for overall effect: Z = 4.25 (P < 0.0001)								
1.8.2 Medium term								
Johnson 2009	-3.78	7.14	34	-1.65	4.54	30	100.0%	-0.35 [-0.84 , 0.15]
Subtotal (95% CI)			**34**			**30**	**100.0%**	**-0.35 [-0.84 , 0.15]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.37 (P = 0.17)								



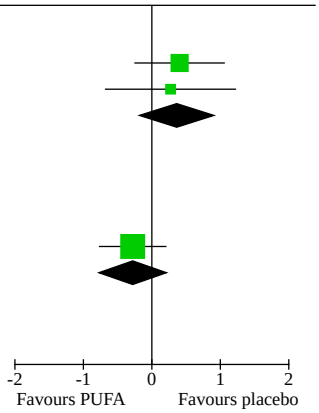
Analysis 1.9. Comparison 1: PUFA versus placebo, Outcome 9: ADHD symptoms - inattention, clinician rated

Study or Subgroup	PUFA Mean	PUFA SD	PUFA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.9.1 Short term								
Dubnov-Raz 2014	242	15	8	244	51.3	9	100.0%	-0.05 [-1.00 , 0.90]
Subtotal (95% CI)			**8**			**9**	**100.0%**	**-0.05 [-1.00 , 0.90]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.10 (P = 0.92)								
1.9.2 Medium term								
Johnson 2009	-2.69	3.59	34	-1.68	2.87	30	53.8%	-0.30 [-0.80 , 0.19]
Vaisman 2008	-4.03	7	39	-2.35	3.73	21	46.2%	-0.27 [-0.81 , 0.26]
Subtotal (95% CI)			**73**			**51**	**100.0%**	**-0.29 [-0.65 , 0.07]**
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%								
Test for overall effect: Z = 1.57 (P = 0.12)								



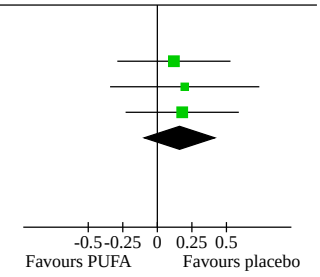
Analysis 1.10. Comparison 1: PUFA versus placebo, Outcome 10: ADHD symptoms - hyperactivity/impulsivity, clinician rated

Study or Subgroup	PUFA Mean	PUFA SD	PUFA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.10.1 Short term								
Arnold 1989	2.1	0.47	18	1.81	0.87	18	67.8%	0.41 [-0.26 , 1.07]
Dubnov-Raz 2014	61	115	8	29	108	9	32.2%	0.27 [-0.69 , 1.23]
Subtotal (95% CI)			**26**			**27**	**100.0%**	**0.36 [-0.18 , 0.91]**
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%								
Test for overall effect: Z = 1.31 (P = 0.19)								
1.10.2 Medium term								
Johnson 2009	-1.28	5.1	34	-0.13	2.38	30	100.0%	-0.28 [-0.77 , 0.21]
Subtotal (95% CI)			**34**			**30**	**100.0%**	**-0.28 [-0.77 , 0.21]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.11 (P = 0.27)								



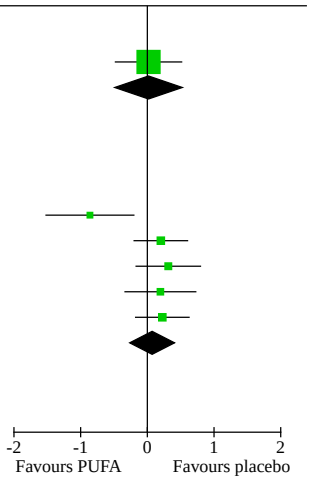
Analysis 1.11. Comparison 1: PUFA versus placebo, Outcome 11: Behaviour - internalising, parent rated

Study or Subgroup	PUFA Mean	PUFA SD	PUFA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.11.1 Medium term								
Chang 2019	6.85	3.3	48	6.45	3.32	44	38.8%	0.12 [-0.29 , 0.53]
Voigt 2001	53.1	10.91	27	51.2	7.65	26	22.3%	0.20 [-0.34 , 0.74]
Widenhorn-Müller 2014	58.69	11.14	45	56.77	10.01	47	38.8%	0.18 [-0.23 , 0.59]
Subtotal (95% CI)			**120**			**117**	**100.0%**	**0.16 [-0.09 , 0.42]**
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 2 (P = 0.97); I² = 0%								
Test for overall effect: Z = 1.23 (P = 0.22)								



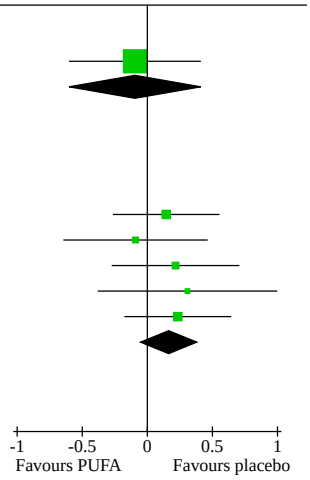
Analysis 1.12. Comparison 1: PUFA versus placebo, Outcome 12: Behaviour - externalising, parent rated

Study or Subgroup	PUFA Mean	PUFA SD	PUFA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.12.1 Short term								
Aman 1987	1.26	4.41	30	1.18	4.41	30	100.0%	0.02 [-0.49 , 0.52]
Subtotal (95% CI)			**30**			**30**	**100.0%**	**0.02 [-0.49 , 0.52]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.07 (P = 0.94)								
1.12.2 Medium term								
Bos 2015	7.8	3.5	19	11.8	5.4	19	14.8%	-0.86 [-1.53 , -0.19]
Chang 2019	10.75	3.44	48	10.09	2.99	44	23.2%	0.20 [-0.21 , 0.61]
Kean 2017	73.66	15.18	29	68.39	17.6	36	20.2%	0.31 [-0.18 , 0.81]
Voigt 2001	58.5	10.91	27	56.3	11.22	26	18.5%	0.20 [-0.34 , 0.74]
Widenhorn-Müller 2014	60.27	11.61	45	57.68	11.24	47	23.2%	0.22 [-0.19 , 0.63]
Subtotal (95% CI)			**168**			**172**	**100.0%**	**0.07 [-0.26 , 0.41]**
Heterogeneity: Tau² = 0.08; Chi² = 9.36, df = 4 (P = 0.05); I² = 57%								
Test for overall effect: Z = 0.42 (P = 0.68)								



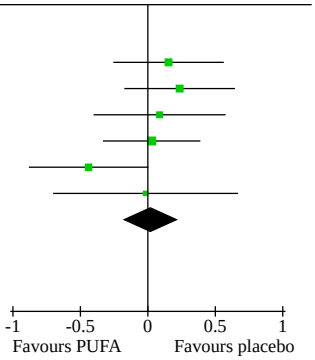
Analysis 1.13. Comparison 1: PUFA versus placebo, Outcome 13: Behaviour - conduct, parent rated

Study or Subgroup	PUFA Mean	PUFA SD	PUFA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.13.1 Short term								
Aman 1987	16.3	10.48	30	17.31	10.48	30	100.0%	-0.10 [-0.60 , 0.41]
Subtotal (95% CI)			**30**			**30**	**100.0%**	**-0.10 [-0.60 , 0.41]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.37 (P = 0.71)								
1.13.2 Medium term								
Chang 2019	3.63	2.04	48	3.34	1.92	44	27.8%	0.14 [-0.26 , 0.55]
Crippa 2019	3.25	1.7	25	3.43	2.18	25	15.2%	-0.09 [-0.65 , 0.46]
Kean 2017	66.07	14.43	29	62.56	17.16	36	19.4%	0.22 [-0.27 , 0.71]
Stevens 2003	-2.1	4	18	-3.4	4.25	15	9.8%	0.31 [-0.38 , 1.00]
Widenhorn-Müller 2014	58.93	7.11	45	57.19	7.61	47	27.8%	0.23 [-0.18 , 0.64]
Subtotal (95% CI)			**165**			**167**	**100.0%**	**0.16 [-0.05 , 0.38]**
Heterogeneity: Tau² = 0.00; Chi² = 1.14, df = 4 (P = 0.89); I² = 0%								
Test for overall effect: Z = 1.49 (P = 0.14)								



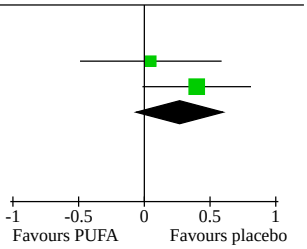
Analysis 1.14. Comparison 1: PUFA versus placebo, Outcome 14: Behaviour - oppositional, parent rated

Study or Subgroup	PUFA Mean	PUFA SD	PUFA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.14.1 Medium term								
Chang 2019	10.44	6.03	48	9.55	5.44	44	19.1%	0.15 [-0.26 , 0.56]
Gustafsson 2010	43.8	18.6	46	39.4	18.4	46	19.1%	0.24 [-0.17 , 0.65]
Kean 2017	69.41	18.67	29	67.92	15.51	36	14.0%	0.09 [-0.40 , 0.58]
Manor 2012	-3.12	10.25	99	-3.43	12.26	42	23.7%	0.03 [-0.33 , 0.39]
Sinn 2007	12.45	6.94	77	15.66	8.1	27	16.7%	-0.44 [-0.88 , 0.00]
Stevens 2003	-4.5	5.25	18	-4.4	6	15	7.5%	-0.02 [-0.70 , 0.67]
Subtotal (95% CI)			**317**			**210**	**100.0%**	**0.02 [-0.17 , 0.21]**
Heterogeneity: Tau² = 0.01; Chi² = 5.69, df = 5 (P = 0.34); I² = 12%								
Test for overall effect: Z = 0.19 (P = 0.85)								



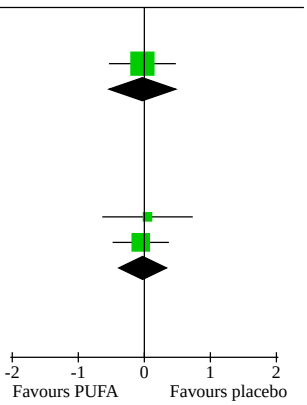
Analysis 1.15. Comparison 1: PUFA versus placebo, Outcome 15: Behaviour - socialisation, parent rated

Study or Subgroup	PUFA Mean	PUFA SD	PUFA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.15.1 Medium term								
Voigt 2001	56.7	8.31	27	56.3	7.65	26	37.2%	0.05 [-0.49 , 0.59]
Widenhorn-Müller 2014	61.89	10.13	45	58.3	7.61	47	62.8%	0.40 [-0.01 , 0.81]
Subtotal (95% CI)			**72**			**73**	**100.0%**	**0.27 [-0.06 , 0.60]**
Heterogeneity: Tau² = 0.00; Chi² = 1.02, df = 1 (P = 0.31); I² = 2%								
Test for overall effect: Z = 1.59 (P = 0.11)								



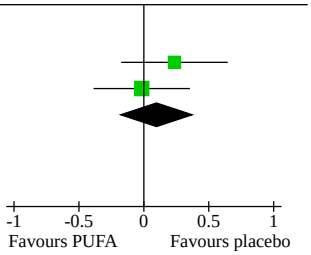
Analysis 1.16. Comparison 1: PUFA versus placebo, Outcome 16: Behaviour - conduct, teacher rated

Study or Subgroup	PUFA Mean	PUFA SD	PUFA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.16.1 Short term								
Aman 1987	16.3	10.48	30	16.61	10.48	30	100.0%	-0.03 [-0.54 , 0.48]
Subtotal (95% CI)			**30**			**30**	**100.0%**	**-0.03 [-0.54 , 0.48]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.11 (P = 0.91)								
1.16.2 Medium term								
Stevens 2003	0	5	18	-0.2	2.5	15	27.9%	0.05 [-0.64 , 0.73]
Widenhorn-Müller 2014	54.08	5.12	40	54.36	5.1	45	72.1%	-0.05 [-0.48 , 0.37]
Subtotal (95% CI)			**58**			**60**	**100.0%**	**-0.03 [-0.39 , 0.34]**
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.80); I² = 0%								
Test for overall effect: Z = 0.14 (P = 0.89)								



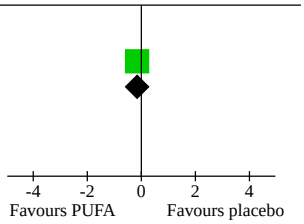
Analysis 1.17. Comparison 1: PUFA versus placebo, Outcome 17: Behaviour - oppositional, teacher rated

Study or Subgroup	PUFA Mean	PUFA SD	PUFA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.17.1 Medium term								
Gustafsson 2010	43.8	18.6	46	39.4	18.4	46	45.0%	0.24 [-0.17 , 0.65]
Manor 2012	-0.02	11.98	92	0.18	12.32	40	55.0%	-0.02 [-0.39 , 0.35]
Subtotal (95% CI)			**138**			**86**	**100.0%**	**0.10 [-0.18 , 0.37]**
Heterogeneity: Tau² = 0.00; Chi² = 0.80, df = 1 (P = 0.37); I² = 0%								
Test for overall effect: Z = 0.69 (P = 0.49)								



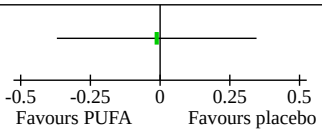
Analysis 1.18. Comparison 1: PUFA versus placebo, Outcome 18: Behaviour - socialisation, teacher rated

Study or Subgroup	PUFA Mean	PUFA SD	PUFA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.18.1 Medium term								
Widenhorn-Müller 2014	55.88	5.31	40	56.82	6.44	45	100.0%	-0.16 [-0.58 , 0.27]
Subtotal (95% CI)			**40**			**45**	**100.0%**	**-0.16 [-0.58 , 0.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.72 (P = 0.47)								



Analysis 1.19. Comparison 1: PUFA versus placebo, Outcome 19: Quality of life: medium term

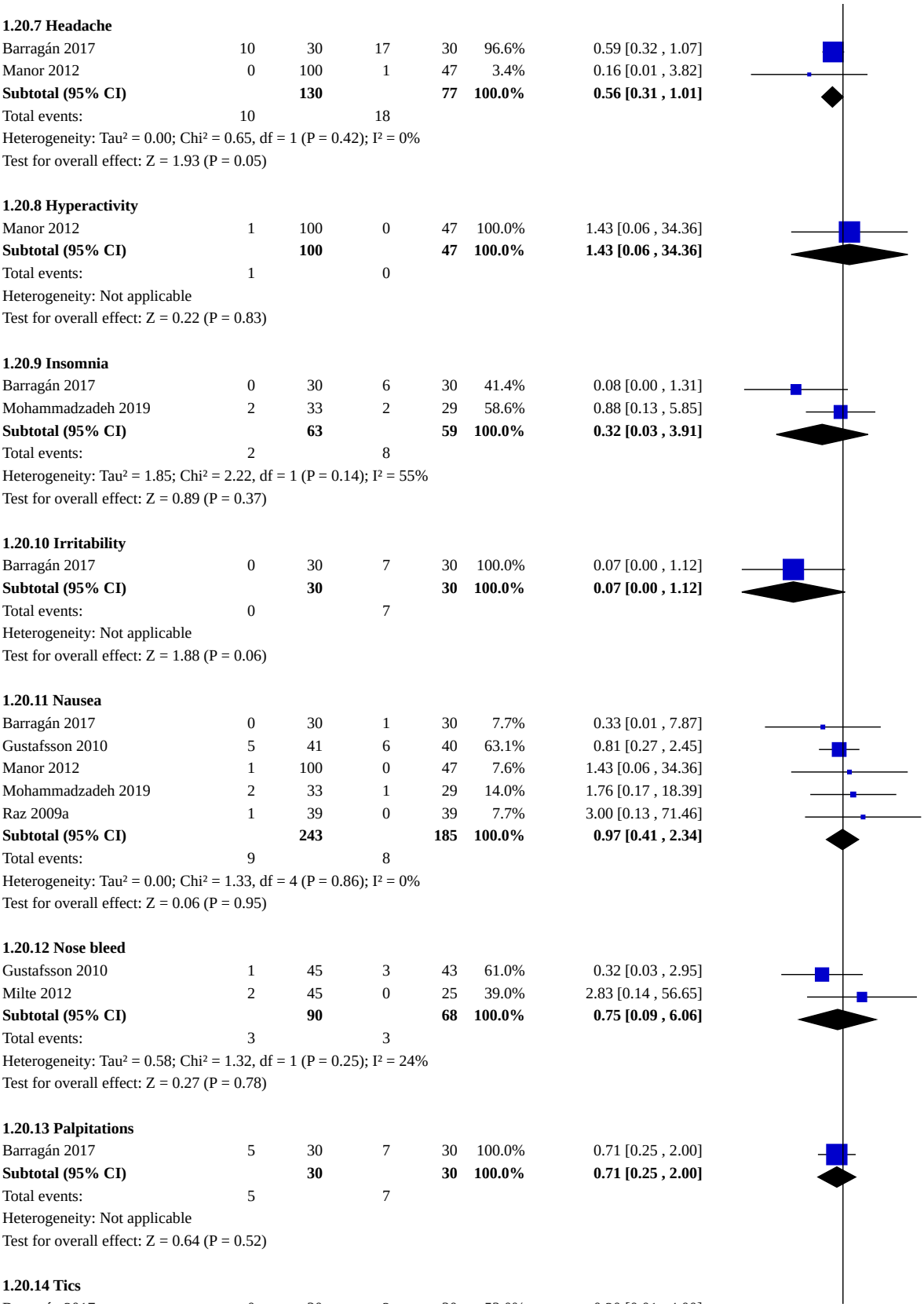
Study or Subgroup	PUFA Mean	PUFA SD	PUFA Total	Placebo Mean	Placebo SD	Placebo Total	Std. Mean Difference IV, Random, 95% CI
Manor 2012	1.25	9.55	94	1.37	10.26	44	-0.01 [-0.37 , 0.35]



Analysis 1.20. Comparison 1: PUFA versus placebo, Outcome 20: Side effects

Study or Subgroup	PUFA Events	PUFA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.20.1 Overall						
Barragán 2017	19	30	18	30	39.3%	1.06 [0.71 , 1.57]
Cornu 2018	2	80	8	82	6.2%	0.26 [0.06 , 1.17]
Crippa 2019	0	25	0	25		Not estimable
Gustafsson 2010	21	46	24	46	37.8%	0.88 [0.58 , 1.33]
Johnson 2009	2	34	1	30	2.7%	1.76 [0.17 , 18.50]
Matsudaira 2015	3	38	2	38	4.8%	1.50 [0.27 , 8.48]
NCT01807299	0	11	0	13		Not estimable
Raz 2009a	9	32	3	31	9.2%	2.91 [0.87 , 9.74]
Subtotal (95% CI)		**296**		**295**	**100.0%**	**1.02 [0.69 , 1.52]**
Total events:	56		56			
Heterogeneity: Tau² = 0.06; Chi² = 6.97, df = 5 (P = 0.22); I² = 28%						
Test for overall effect: Z = 0.10 (P = 0.92)						
1.20.2 Appetite loss						
Barragán 2017	10	30	21	30	100.0%	0.48 [0.27 , 0.83]
Subtotal (95% CI)		**30**		**30**	**100.0%**	**0.48 [0.27 , 0.83]**
Total events:	10		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.61 (P = 0.009)						
1.20.3 Anxiety						
Barragán 2017	3	30	8	30	100.0%	0.38 [0.11 , 1.28]
Subtotal (95% CI)		**30**		**30**	**100.0%**	**0.38 [0.11 , 1.28]**
Total events:	3		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.57 (P = 0.12)						
1.20.4 Dermatitis						
Manor 2012	1	100	0	47	100.0%	1.43 [0.06 , 34.36]
Subtotal (95% CI)		**100**		**47**	**100.0%**	**1.43 [0.06 , 34.36]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.22 (P = 0.83)						
1.20.5 Diarrhoea						
Barragán 2017	0	30	0	30		Not estimable
Gustafsson 2010	3	43	4	42	23.0%	0.73 [0.17 , 3.08]
Mohammadzadeh 2019	8	33	10	29	77.0%	0.70 [0.32 , 1.54]
Subtotal (95% CI)		**106**		**101**	**100.0%**	**0.71 [0.36 , 1.41]**
Total events:	11		14			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0%						
Test for overall effect: Z = 0.98 (P = 0.33)						
1.20.6 Gastrointestinal discomfort						
Barragán 2017	0	30	0	30		Not estimable
Manor 2012	6	100	4	47	83.4%	0.70 [0.21 , 2.38]
Mohammadzadeh 2019	1	33	1	29	16.6%	0.88 [0.06 , 13.43]
Subtotal (95% CI)		**163**		**106**	**100.0%**	**0.73 [0.24 , 2.22]**
Total events:	7		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%						
Test for overall effect: Z = 0.55 (P = 0.58)						
1.20.7 Headache						

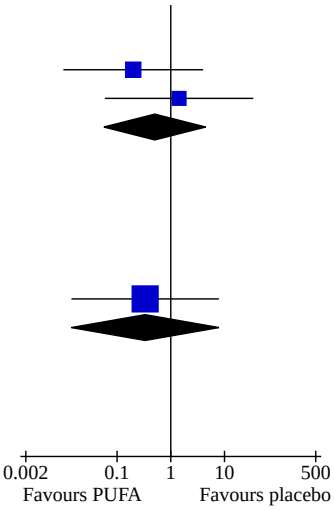
Analysis 1.20. (Continued)



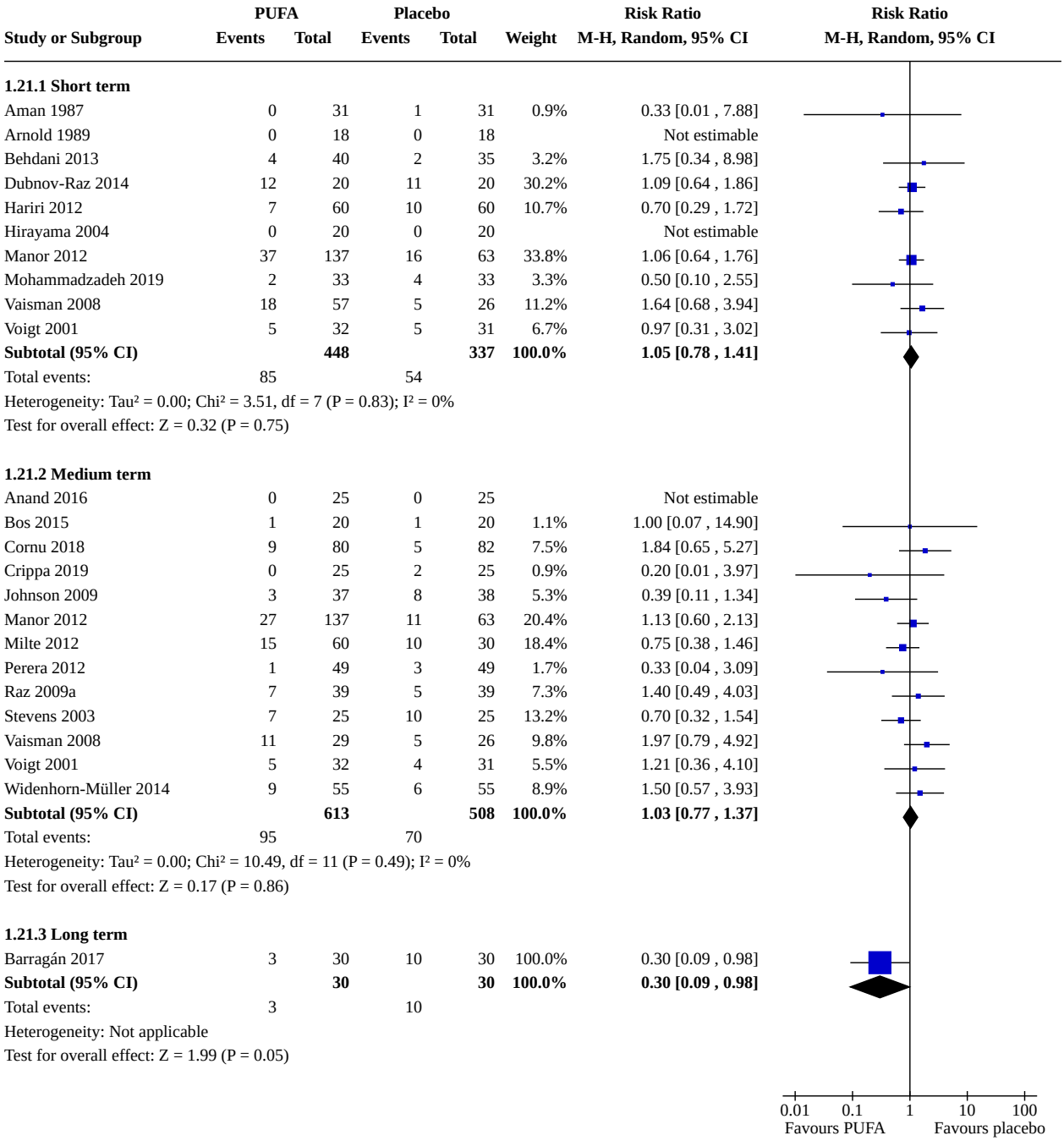
1.20.7 Headache						
Barragán 2017	10	30	17	30	96.6%	0.59 [0.32 , 1.07]
Manor 2012	0	100	1	47	3.4%	0.16 [0.01 , 3.82]
Subtotal (95% CI)		**130**		**77**	**100.0%**	**0.56 [0.31 , 1.01]**
Total events:	10		18			
Heterogeneity: Tau² = 0.00; Chi² = 0.65, df = 1 (P = 0.42); I² = 0%						
Test for overall effect: Z = 1.93 (P = 0.05)						
1.20.8 Hyperactivity						
Manor 2012	1	100	0	47	100.0%	1.43 [0.06 , 34.36]
Subtotal (95% CI)		**100**		**47**	**100.0%**	**1.43 [0.06 , 34.36]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.22 (P = 0.83)						
1.20.9 Insomnia						
Barragán 2017	0	30	6	30	41.4%	0.08 [0.00 , 1.31]
Mohammadzadeh 2019	2	33	2	29	58.6%	0.88 [0.13 , 5.85]
Subtotal (95% CI)		**63**		**59**	**100.0%**	**0.32 [0.03 , 3.91]**
Total events:	2		8			
Heterogeneity: Tau² = 1.85; Chi² = 2.22, df = 1 (P = 0.14); I² = 55%						
Test for overall effect: Z = 0.89 (P = 0.37)						
1.20.10 Irritability						
Barragán 2017	0	30	7	30	100.0%	0.07 [0.00 , 1.12]
Subtotal (95% CI)		**30**		**30**	**100.0%**	**0.07 [0.00 , 1.12]**
Total events:	0		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.88 (P = 0.06)						
1.20.11 Nausea						
Barragán 2017	0	30	1	30	7.7%	0.33 [0.01 , 7.87]
Gustafsson 2010	5	41	6	40	63.1%	0.81 [0.27 , 2.45]
Manor 2012	1	100	0	47	7.6%	1.43 [0.06 , 34.36]
Mohammadzadeh 2019	2	33	1	29	14.0%	1.76 [0.17 , 18.39]
Raz 2009a	1	39	0	39	7.7%	3.00 [0.13 , 71.46]
Subtotal (95% CI)		**243**		**185**	**100.0%**	**0.97 [0.41 , 2.34]**
Total events:	9		8			
Heterogeneity: Tau² = 0.00; Chi² = 1.33, df = 4 (P = 0.86); I² = 0%						
Test for overall effect: Z = 0.06 (P = 0.95)						
1.20.12 Nose bleed						
Gustafsson 2010	1	45	3	43	61.0%	0.32 [0.03 , 2.95]
Milte 2012	2	45	0	25	39.0%	2.83 [0.14 , 56.65]
Subtotal (95% CI)		**90**		**68**	**100.0%**	**0.75 [0.09 , 6.06]**
Total events:	3		3			
Heterogeneity: Tau² = 0.58; Chi² = 1.32, df = 1 (P = 0.25); I² = 24%						
Test for overall effect: Z = 0.27 (P = 0.78)						
1.20.13 Palpitations						
Barragán 2017	5	30	7	30	100.0%	0.71 [0.25 , 2.00]
Subtotal (95% CI)		**30**		**30**	**100.0%**	**0.71 [0.25 , 2.00]**
Total events:	5		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
1.20.14 Tics						

Analysis 1.20. (Continued)

1.20.14 Tics						
Barragán 2017	0	30	2	30	53.0%	0.20 [0.01 , 4.00]
Manor 2012	1	100	0	47	47.0%	1.43 [0.06 , 34.36]
Subtotal (95% CI)		**130**		**77**	**100.0%**	**0.50 [0.06 , 4.46]**
Total events:	1		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.78, df = 1 (P = 0.38); I² = 0%						
Test for overall effect: Z = 0.62 (P = 0.54)						
1.20.15 Tremor						
Barragán 2017	0	30	1	30	100.0%	0.33 [0.01 , 7.87]
Subtotal (95% CI)		**30**		**30**	**100.0%**	**0.33 [0.01 , 7.87]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						



Analysis 1.21. Comparison 1: PUFA versus placebo, Outcome 21: Loss to follow-up



Study or Subgroup	PUFA Events	PUFA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.21.1 Short term						
Aman 1987	0	31	1	31	0.9%	0.33 [0.01 , 7.88]
Arnold 1989	0	18	0	18		Not estimable
Behdani 2013	4	40	2	35	3.2%	1.75 [0.34 , 8.98]
Dubnov-Raz 2014	12	20	11	20	30.2%	1.09 [0.64 , 1.86]
Hariri 2012	7	60	10	60	10.7%	0.70 [0.29 , 1.72]
Hirayama 2004	0	20	0	20		Not estimable
Manor 2012	37	137	16	63	33.8%	1.06 [0.64 , 1.76]
Mohammadzadeh 2019	2	33	4	33	3.3%	0.50 [0.10 , 2.55]
Vaisman 2008	18	57	5	26	11.2%	1.64 [0.68 , 3.94]
Voigt 2001	5	32	5	31	6.7%	0.97 [0.31 , 3.02]
Subtotal (95% CI)		**448**		**337**	**100.0%**	**1.05 [0.78 , 1.41]**
Total events:	85		54			
Heterogeneity: Tau² = 0.00; Chi² = 3.51, df = 7 (P = 0.83); I² = 0%						
Test for overall effect: Z = 0.32 (P = 0.75)						
1.21.2 Medium term						
Anand 2016	0	25	0	25		Not estimable
Bos 2015	1	20	1	20	1.1%	1.00 [0.07 , 14.90]
Cornu 2018	9	80	5	82	7.5%	1.84 [0.65 , 5.27]
Crippa 2019	0	25	2	25	0.9%	0.20 [0.01 , 3.97]
Johnson 2009	3	37	8	38	5.3%	0.39 [0.11 , 1.34]
Manor 2012	27	137	11	63	20.4%	1.13 [0.60 , 2.13]
Milte 2012	15	60	10	30	18.4%	0.75 [0.38 , 1.46]
Perera 2012	1	49	3	49	1.7%	0.33 [0.04 , 3.09]
Raz 2009a	7	39	5	39	7.3%	1.40 [0.49 , 4.03]
Stevens 2003	7	25	10	25	13.2%	0.70 [0.32 , 1.54]
Vaisman 2008	11	29	5	26	9.8%	1.97 [0.79 , 4.92]
Voigt 2001	5	32	4	31	5.5%	1.21 [0.36 , 4.10]
Widenhorn-Müller 2014	9	55	6	55	8.9%	1.50 [0.57 , 3.93]
Subtotal (95% CI)		**613**		**508**	**100.0%**	**1.03 [0.77 , 1.37]**
Total events:	95		70			
Heterogeneity: Tau² = 0.00; Chi² = 10.49, df = 11 (P = 0.49); I² = 0%						
Test for overall effect: Z = 0.17 (P = 0.86)						
1.21.3 Long term						
Barragán 2017	3	30	10	30	100.0%	0.30 [0.09 , 0.98]
Subtotal (95% CI)		**30**		**30**	**100.0%**	**0.30 [0.09 , 0.98]**
Total events:	3		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.99 (P = 0.05)						

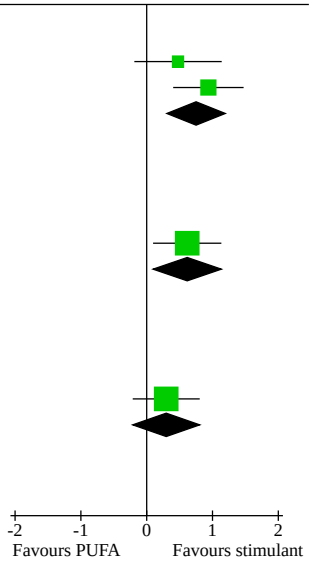
Comparison 2. PUFA versus stimulants

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 ADHD symptoms - total	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1.1 Short term	2	96	Std. Mean Difference (IV, Random, 95% CI)	0.75 [0.31, 1.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1.2 Medium term	1	60	Std. Mean Difference (IV, Random, 95% CI)	0.62 [0.10, 1.13]
2.1.3 Long term	1	60	Std. Mean Difference (IV, Random, 95% CI)	0.30 [-0.21, 0.81]
2.2 ADHD symptoms - inattention	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.2.1 Short term	1	60	Std. Mean Difference (IV, Random, 95% CI)	0.88 [0.35, 1.41]
2.2.2 Medium term	1	60	Std. Mean Difference (IV, Random, 95% CI)	0.47 [-0.04, 0.98]
2.2.3 Long term	1	60	Std. Mean Difference (IV, Random, 95% CI)	0.06 [-0.45, 0.57]
2.3 ADHD symptoms - hyperactivity/impulsivity	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.3.1 Short term	2	96	Std. Mean Difference (IV, Random, 95% CI)	0.66 [0.25, 1.07]
2.3.2 Medium term	1	60	Std. Mean Difference (IV, Random, 95% CI)	0.58 [0.07, 1.10]
2.3.3 Long term	1	0	Std. Mean Difference (IV, Random, 95% CI)	Not estimable

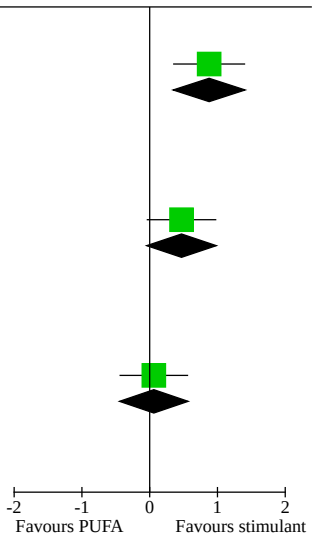
Analysis 2.1. Comparison 2: PUFA versus stimulants, Outcome 1: ADHD symptoms - total

Study or Subgroup	PUFA Mean	PUFA SD	PUFA Total	Stimulant Mean	Stimulant SD	Stimulant Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.1.1 Short term								
Arnold 1989	1.39	0.58	18	1.11	0.57	18	40.6%	0.48 [-0.19 , 1.14]
Barragán 2017	33.63	7.47	30	27.6	4.98	30	59.4%	0.94 [0.40 , 1.47]
Subtotal (95% CI)			**48**			**48**	**100.0%**	**0.75 [0.31 , 1.19]**
Heterogeneity: Tau² = 0.01; Chi² = 1.13, df = 1 (P = 0.29); I² = 11%								
Test for overall effect: Z = 3.31 (P = 0.0009)								
2.1.2 Medium term								
Barragán 2017	30.27	7.86	30	26.23	4.7	30	100.0%	0.62 [0.10 , 1.13]
Subtotal (95% CI)			**30**			**30**	**100.0%**	**0.62 [0.10 , 1.13]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.33 (P = 0.02)								
2.1.3 Long term								
Barragán 2017	27.77	7.84	30	25.83	4.67	30	100.0%	0.30 [-0.21 , 0.81]
Subtotal (95% CI)			**30**			**30**	**100.0%**	**0.30 [-0.21 , 0.81]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.14 (P = 0.25)								



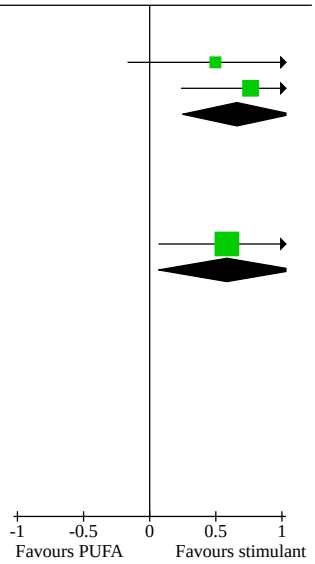
Analysis 2.2. Comparison 2: PUFA versus stimulants, Outcome 2: ADHD symptoms - inattention

Study or Subgroup	PUFA Mean	PUFA SD	PUFA Total	Stimulant Mean	Stimulant SD	Stimulant Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.2.1 Short term								
Barragán 2017	15.5	3.41	30	12.97	2.14	30	100.0%	0.88 [0.35 , 1.41]
Subtotal (95% CI)			**30**			**30**	**100.0%**	**0.88 [0.35 , 1.41]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.23 (P = 0.001)								
2.2.2 Medium term								
Barragán 2017	13.27	2.92	30	12.13	1.72	30	100.0%	0.47 [-0.04 , 0.98]
Subtotal (95% CI)			**30**			**30**	**100.0%**	**0.47 [-0.04 , 0.98]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.79 (P = 0.07)								
2.2.3 Long term								
Barragán 2017	12.17	2.7	30	12.03	1.71	30	100.0%	0.06 [-0.45 , 0.57]
Subtotal (95% CI)			**30**			**30**	**100.0%**	**0.06 [-0.45 , 0.57]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.24 (P = 0.81)								



Analysis 2.3. Comparison 2: PUFA versus stimulants, Outcome 3: ADHD symptoms - hyperactivity/impulsivity

Study or Subgroup	PUFA Mean	PUFA SD	PUFA Total	Stimulant Mean	Stimulant SD	Stimulant Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.3.1 Short term								
Arnold 1989	1.81	0.87	18	1.39	0.78	18	38.5%	0.50 [-0.17 , 1.16]
Barragán 2017	18.37	5.82	30	14.6	3.71	30	61.5%	0.76 [0.24 , 1.29]
Subtotal (95% CI)			**48**			**48**	**100.0%**	**0.66 [0.25 , 1.07]**
Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 1 (P = 0.54); I² = 0%								
Test for overall effect: Z = 3.14 (P = 0.002)								
2.3.2 Medium term								
Barragán 2017	17	5.84	30	14.1	3.74	30	100.0%	0.58 [0.07 , 1.10]
Subtotal (95% CI)			**30**			**30**	**100.0%**	**0.58 [0.07 , 1.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.21 (P = 0.03)								
2.3.3 Long term								
Barragán 2017	15.6	5.68	30	13.8	0	30		Not estimable
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								

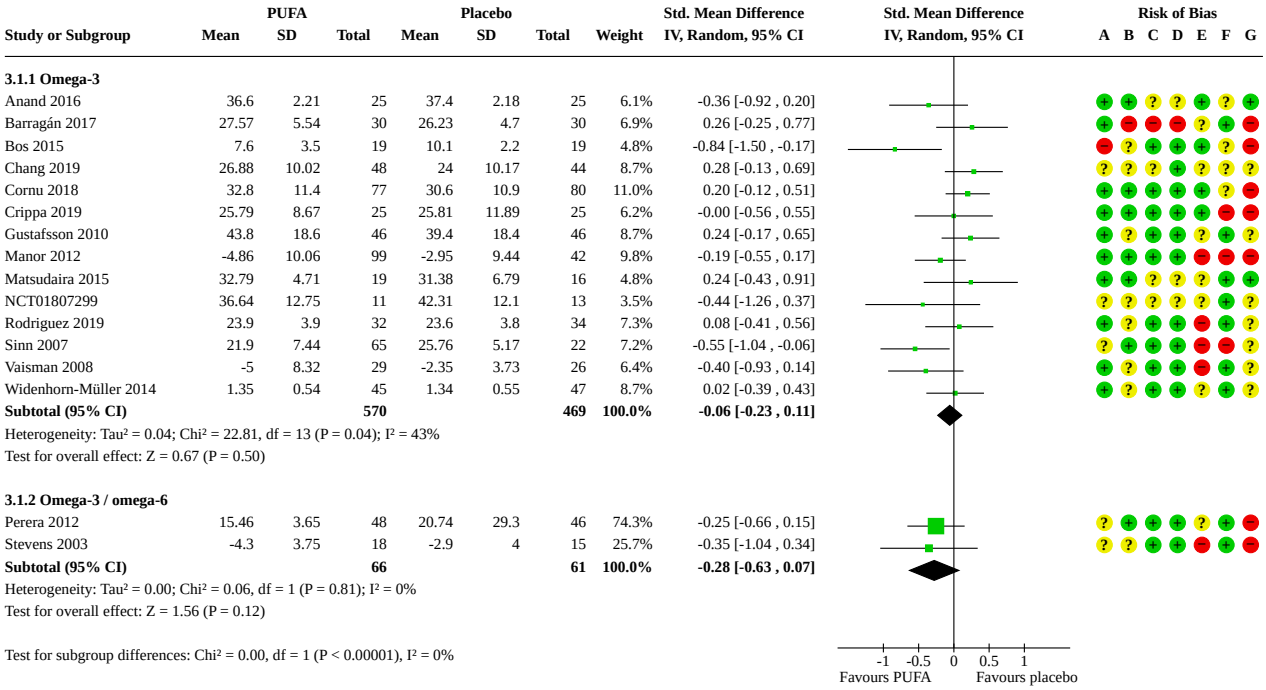


Comparison 3. Subgroup analysis by PUFA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 ADHD symptoms - total, parent rated	16		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1.1 Omega-3	14	1039	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.23, 0.11]
3.1.2 Omega-3 / omega-6	2	127	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.63, 0.07]

Analysis 3.1. Comparison 3: Subgroup analysis by PUFA, Outcome 1: ADHD symptoms - total, parent rated



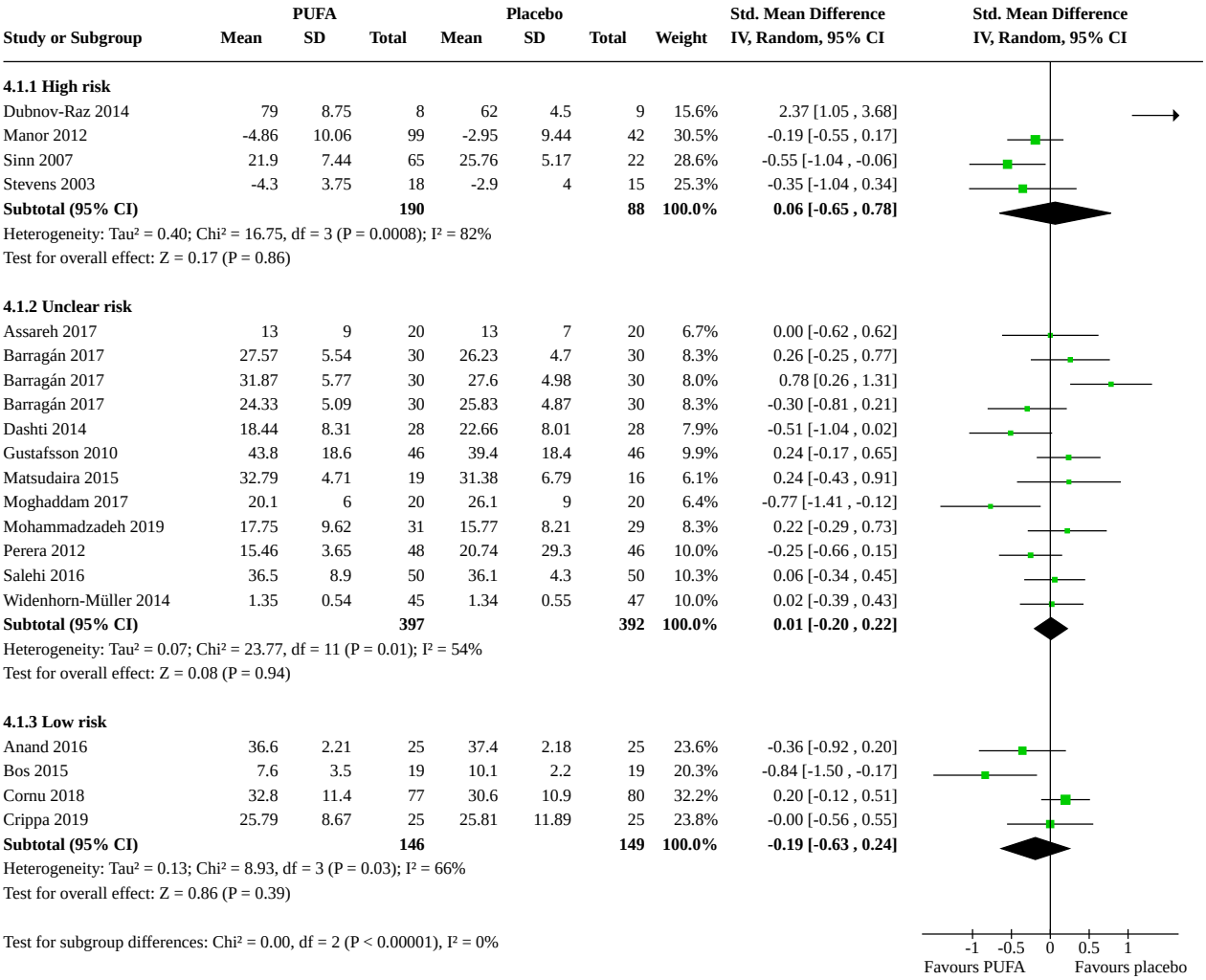
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 4. Sensitivity analyses

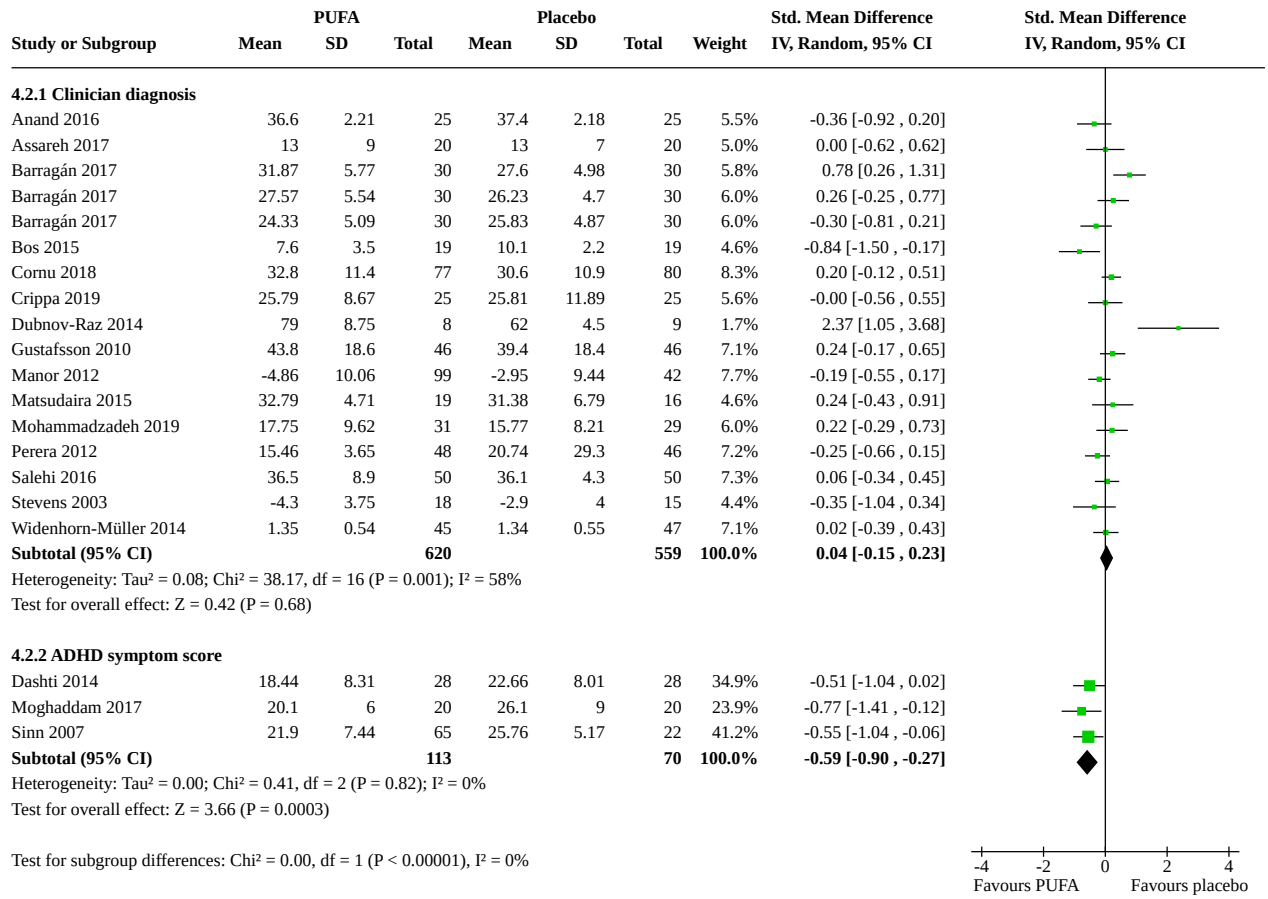
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Risk of attrition bias	18		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1.1 High risk	4	278	Std. Mean Difference (IV, Random, 95% CI)	0.06 [-0.65, 0.78]
4.1.2 Unclear risk	10	789	Std. Mean Difference (IV, Random, 95% CI)	0.01 [-0.20, 0.22]
4.1.3 Low risk	4	295	Std. Mean Difference (IV, Random, 95% CI)	-0.19 [-0.63, 0.24]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 Inclusion criteria	18		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
4.2.1 Clinician diagnosis	15	1179	Std. Mean Difference (IV, Random, 95% CI)	0.04 [-0.15, 0.23]
4.2.2 ADHD symptom score	3	183	Std. Mean Difference (IV, Random, 95% CI)	-0.59 [-0.90, -0.27]

Analysis 4.1. Comparison 4: Sensitivity analyses, Outcome 1: Risk of attrition bias



Analysis 4.2. Comparison 4: Sensitivity analyses, Outcome 2: Inclusion criteria



ADDITIONAL TABLES

Table 1. Other data

Study	Comparison	ADHD symptoms - total	ADHD - inattention[a]	ADHD - hyperactivity[a]
Bélanger 2009	Cross-over trial of omega-3 PUFA vs omega-6 PUFA - first phase *SD not reported and could not be calculated.*	**Conners Parent - mean change** omega-3: −8.8 omega-6: −5.4	**Conners Parent - mean change** omega-3: −9.1 omega-6: −7.3	**Conners Parent - mean change** omega-3: −7.2 omega-6: −3.1
Brue 2001	Parallel trial of omega-3 PUFA vs dietary supplement	-	**Conners Parent – non-MPH (Ritalin)** omega-3: 12.0 supplement: 13.7	**Conners Parent – non-MPH (Ritalin)** omega-3: 9.4 supplement: 13.1 P = 0.03

Table 1. Other data *(Continued)*

		SD not reported and could not be calculated.	**Conners Teacher – non-MPH (Ritalin)** omega-3: 19.1 supplement: 15.3	**Conners Teacher – non-MPH (Ritalin)** omega-3: 17.9 supplement: 13.4 P = 0.04
			Conners Parent – MPH (Ritalin) omega-3: 15.6 supplement: 14.6	**Conners Parent – MPH (Ritalin)** omega-3: 13.7 supplement: 13.5
			Conners Teacher – MPH (Ritalin) omega-3: 16.3 supplement: 12.2 P = 0.04	**Conners Teacher – MPH (Ritalin)** omega-3: 10.8 supplement: 12.3
Milte 2012	Parallel trial of EPA-rich fish oil vs DHA-rich fish oil vs placebo	-	-	**Correlation of PUFA Conners Parent hyperactivity score vs placebo over 4 months (95% CI)** EPA: 0.98 (−1.27 to 3.23) DHA: 1.12 (−1.30 to 3.53) **Correlation of PUFA Conners Parent ADHD index vs placebo over 4 months (95% CI)** EPA: 1.56 (−1.96 to 5.09) DHA: 1.64 (−2.15 to 5.43)

ADHD: attention deficit hyperactivity disorder; **CI:** confidence intervals; **EPA:** eicosapentanoic acid; **DHA:** docosahexanoic acid; **MPH:** methylphenidate; **PUFA:** polyunsaturated fatty acids; **SD:** standard deviation

[a]Where there were statistical differences between groups, P values are shown.

Table 2. Compliance with recommended dose of PUFA supplements

Study	Comparison	PUFA group	Control group
Manor 2012	Parallel trial of omega-3 vs placebo	92%	90%
Raz 2009a	Parallel trial of omega-3 or omega-6 vs placebo	92%	86%
Richardson 2002	Parallel trial of omega-3 or omega-6 vs placebo	90%	87%
Sinn 2007	Parallel trial of omega-3 or omega-6 vs placebo	88% across all groups	
Voigt 2001	Parallel trial of omega-3 vs placebo	97%	100%

PUFA: polyunsaturated fatty acids

APPENDICES

Appendix 1. Search strategies for review update

Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library

#1 [mh ^"attention deficit and disruptive behavior disorders"]
#2 [mh "attention deficit disorder with hyperactivity"]
#3 [mh "conduct disorder"]
#4 (ADHD or ADDH or ADHS or AD NEXT HD or HKD or TDAH)
#5 ((attention* or behav*) near/3 (defic* or dysfunc* or disorder*))
#6 ((disrupt* near/3 disorder*) or (disrupt* near/3 behav*) or (defian* near/3 disorder*) or (defian* near/3 behav*))
#7 (impulsiv* or inattentiv* or inattention*)
#8 [mh hyperkinesis]
#9 (hyperkin* or hyper next kin*)
#10 (minimal* near/3 brain near/3 (disorder* or dysfunct* or damage*))
#11 (hyperactiv* or hyper next activ*)
#12 {or #1-#11}
#13 [mh "fatty acids, unsaturated"]
#14 [mh "Fish Oils"]
#15 (omega next 3 or omega next 6)
#16 polyunsaturat* next fatty next acid*
#17 (poly next unsaturat* next fatty next acid*)
#18 (fatty next acid* near/3 (n next 3 or n next 6 or N3 or N6))
#19 (essential next fatty next acid*)
#20 PUFA*
#21 (oil* near/3 (fish* or flax* or linseed))
#22 ((eicosa* or icosa* or docosahex* or alpha-linol*) next acid*)
#23 (EFA or EFAs or EPA or EPAs or MaxEPA or MaxEPAs or DHA or DHAs or ALA or ALAs)
#24 {or #13-#23}
#25 #12 and #24
#26 [mh Adolescent]
#27 [mh Child]
#28 child* or adolescen* or teen* or pupil* or student* or girl* or boy* or schoolchild* or preschool* or pre next school* or toddler*
#29 {or #26-#28}
#30 #25 and #29 in Trials

MEDLINE Ovid

1 "attention deficit and disruptive behavior disorders"/
2 attention deficit disorder with hyperactivity/
3 conduct disorder/
4 ADHD.tw,kf.
5 ADDH.tw,kf.
6 ADHS.tw,kf.
7 ("AD/HD" or HKD).tw,kf.
8 TDAH.tw,kf.
9 ((attention$ or behav$) adj3 (defic$ or dysfunc$ or disorder$)).tw,kf.
10 ((disrupt$ adj3 disorder$) or (disrupt$ adj3 behav$) or (defian$ adj3 disorder$) or (defian$ adj3 behav$)).tw,kf.
11 (impulsiv$ or inattentiv$ or inattention$).tw,kf.
12 hyperkinesis/
13 (hyperkin$ or hyper-kin$).tw,kf.
14 (minimal adj3 brain adj3 (disorder$ or dysfunct$ or damage$)).tw,kf.
15 (hyperactiv$ or hyper-activ$).tw,kf.
16 or/1-15
17 exp fatty acids, unsaturated/
18 exp Fish Oils/
19 (omega 3$ or omega 6$).tw,kf.
20 polyunsaturat$ fatty acid$.tw,kf.
21 poly-unsaturat$ fatty acid$.tw,kf.

22 (fatty acid$ adj3 (n-3 or n3 or n-6 or n6)).tw,kf.
23 essential fatty acid$.tw,kf.
24 PUFA$.tw,kf.
25 (oil$ adj3 (fish$ or flax$ or linseed)).tw,kf.
26 ((eicosa$ or icosa$ or docosahex$ or alphalinol$ or alpha-linol$) adj acid$).tw,kf.
27 (EFA or EFAs or EPA or EPAs or MaxEPA or MaxEPAs or DHA or DHAs or ALA or ALAs).tw,kf.
28 or/17-27
29 16 and 28
30 Child/
31 child, preschool/
32 adolescent/
33 (child$ or adolescen$ or teen$ or pupil$ or student$ or girl$ or boy$ or schoolchild$ or preschool$ or pre-school$ or toddler$).tw,kf. (1733610)
34 or/30-33
35 randomized controlled trial.pt.
36 controlled clinical trial.pt.
37 randomi#ed.ab.
38 placebo$.ab.
39 drug therapy.fs.
40 randomly.ab.
41 trial.ab.
42 groups.ab.
43 or/35-42
44 exp animals/ not humans.sh.
45 43 not 44
46 29 and 34 and 45

MEDLINE Epub Ahead of Print Ovid

1 ADHD.tw,kf.
2 ADDH.tw,kf.
3 ADHS.tw,kf.
4 ("AD/HD" or HKD).tw,kf.
5 TDAH.tw,kf.
6 ((attention$ or behav$) adj3 (defic$ or dysfunc$ or disorder$)).tw,kf.
7 ((disrupt$ adj3 disorder$) or (disrupt$ adj3 behav$) or (defian$ adj3 disorder$) or (defian$ adj3 behav$)).tw,kf.
8 (impulsiv$ or inattentiv$ or inattention$).tw,kf.
9 (hyperkin$ or hyper-kin$).tw,kf.
10 (minimal adj3 brain adj3 (disorder$ or dysfunct$ or damage$)).tw,kf.
11 (hyperactiv$ or hyper-activ$).tw,kf.
12 or/1-11
13 (omega 3$ or omega 6$).tw,kf.
14 polyunsaturat$ fatty acid$.tw,kf.
15 poly-unsaturat$ fatty acid$.tw,kf.
16 (fatty acid$ adj3 (n-3 or n3 or n-6 or n6)).tw,kf.
17 essential fatty acid$.tw,kf.
18 PUFA$.tw,kf.
19 (oil$ adj3 (fish$ or flax$ or linseed)).tw,kf.
20 ((eicosa$ or icosa$ or docosahex$ or alphalinol$ or alpha-linol$) adj acid$).tw,kf.
21 (EFA or EFAs or EPA or EPAs or MaxEPA or MaxEPAs or DHA or DHAs or ALA or ALAs).tw,kf.
22 or/13-21
23 (child$ or adolescen$ or teen$ or pupil$ or student$ or girl$ or boy$ or schoolchild$ or preschool$ or pre-school$ or toddler$).tw,kf.
24 12 and 22 and 23
25 (random$ or trial$ or control$ or group$ or placebo$ or blind$ or prospectiv$ or longitudinal$ or meta-analys$ or systematic review $).tw.
26 24 and 25

MEDLINE In-Process and Other Non-indexed Citations Ovid

1 ADHD.tw,kf.
2 ADDH.tw,kf.
3 ADHS.tw,kf.
4 ("AD/HD" or HKD).tw,kf.

5 TDAH.tw,kf.
6 ((attention$ or behav$) adj3 (defic$ or dysfunc$ or disorder$)).tw,kf.
7 ((disrupt$ adj3 disorder$) or (disrupt$ adj3 behav$) or (defian$ adj3 disorder$) or (defian$ adj3 behav$)).tw,kf.
8 (impulsiv$ or inattentiv$ or inattention$).tw,kf.
9 (hyperkin$ or hyper-kin$).tw,kf.
10 (minimal adj3 brain adj3 (disorder$ or dysfunct$ or damage$)).tw,kf.
11 (hyperactiv$ or hyper-activ$).tw,kf.
12 or/1-11
13 (omega 3$ or omega 6$).tw,kf.
14 polyunsaturat$ fatty acid$.tw,kf.
15 poly-unsaturat$ fatty acid$.tw,kf.
16 (fatty acid$ adj3 (n-3 or n3 or n-6 or n6)).tw,kf.
17 essential fatty acid$.tw,kf.
18 PUFA$.tw,kf.
19 (oil$ adj3 (fish$ or flax$ or linseed)).tw,kf.
20 ((eicosa$ or icosa$ or docosahex$ or alphalinol$ or alpha-linol$) adj acid$).tw,kf.
21 (EFA or EFAs or EPA or EPAs or MaxEPA or MaxEPAs or DHA or DHAs or ALA or ALAs).tw,kf.
22 or/13-21
23 (child$ or adolescen$ or teen$ or pupil$ or student$ or girl$ or boy$ or schoolchild$ or preschool$ or pre-school$ or toddler$).tw,kf.
24 12 and 22 and 23
25 (random$ or trial$ or control$ or group$ or placebo$ or blind$ or prospectiv$ or longitudinal$ or meta-analys$ or systematic review $).tw.
26 24 and 25

Embase Ovid

1 attention deficit disorder/
2 hyperactivity/
3 conduct disorder/
4 ADHD.tw,kw.
5 ADDH.tw,kw.
6 ADHS.tw,kw.
7 ("AD/HD" or HKD).tw,kw.
8 TDAH.tw,kw.
9 ((attention$ or behav$) adj3 (defic$ or dysfunc$ or disorder$)).tw,kw.
10 ((disrupt$ adj3 disorder$) or (disrupt$ adj3 behav$) or (defian$ adj3 disorder$) or (defian$ adj3 behav$)).tw,kw.
11 (impulsiv$ or inattentiv$ or inattention$).tw,kw.
12 (hyperkin$ or hyper-kin$).tw,kw.
13 (minimal$ adj3 brain adj3 (disorder$ or dysfunct$ or damage$)).tw,kw.
14 (hyperactiv$ or hyper-activ$).tw,kw.
15 or/1-14
16 exp Fish Oils/
17 exp Fatty Acids, Unsaturated/
18 (omega 3$ or omega 6$).tw,kw.
19 polyunsaturat$ fatty acid$.tw,kw.
20 poly-unsaturat$ fatty acid$.tw,kw.
21 (fatty acid$ adj3 (n-3 or n3 or n-6 or n6)).tw,kw.
22 essential fatty acid$.tw,kw.
23 PUFA$.tw,kw.
24 (oil$ adj3 (fish$ or flax$ or linseed)).tw,kw.
25 ((eicosa$ or icosa$ or docosahex$ or alphalinol$ or alpha-linol$) adj acid$).tw,kw.
26 (EFA or EFAs or EPA or EPAs or MaxEPA or MaxEPAs or DHA or DHAs or ALA or ALAs).tw,kw.
27 or/16-26
28 exp child/
29 exp adolescent/
30 (child$ or adolescen$ or teen$ or pupil$ or student$ or girl$ or boy$ or schoolchild$ or preschool$ or pre-school$ or toddler$).tw,kw. (2478446)
31 or/28-30
32 Randomized controlled trial/
33 Controlled clinical study/
34 random$.ti,ab.
35 randomization/

36 intermethod comparison/
37 placebo.ti,ab.
38 (compare or compared or comparison).ti.
39 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. (2197245)
40 (open adj label).ti,ab.
41 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
42 double blind procedure/
43 parallel group$1.ti,ab.
44 (crossover or cross over).ti,ab.
45 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant $1)).ti,ab. (340958)
46 (assigned or allocated).ti,ab.
47 (controlled adj7 (study or design or trial)).ti,ab.
48 (volunteer or volunteers).ti,ab.
49 human experiment/
50 trial.ti.
51 or/32-50
52 (random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)
53 Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)
54 (((case adj control$) and random$) not randomi?ed controlled).ti,ab.
55 (Systematic review not (trial or study)).ti.
56 (nonrandom$ not random$).ti,ab.
57 "Random field$".ti,ab.
58 (random cluster adj3 sampl$).ti,ab.
59 (review.ab. and review.pt.) not trial.ti.
60 "we searched".ab. and (review.ti. or review.pt.)
61 "update review".ab.
62 (databases adj4 searched).ab.
63 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ (1086863)
64 Animal experiment/ not (human experiment/ or human/)
65 or/52-64
66 51 not 65
67 15 and 27 and 31 and 66

APA PsycInfo Ovid

1 exp attention deficit disorder/
2 hyperkinesis/
3 Conduct Disorder/
4 ADHD.tw.
5 ADDH.tw.
6 ADHS.tw.
7 ("AD/HD" or HKD).tw.
8 TDAH.tw.
9 ((attention$ or behav$) adj3 (defic$ or dysfunc$ or disorder$)).tw.
10 ((disrupt$ adj3 disorder$) or (disrupt$ adj3 behav$) or (defian$ adj3 disorder$) or (defian$ adj3 behav$)).tw.
11 (impulsiv$ or inattentiv$ or inattention$).tw.
12 (hyperkin$ or hyper-kin$).tw.
13 (minimal$ adj3 brain adj3 (disorder$ or dysfunct$ or damage$)).tw.
14 (hyperactiv$ or hyper-activ$).tw.
15 or/1-14
16 fatty acids/
17 (omega 3$ or omega 6$).tw.
18 polyunsaturat$ fatty acid$.tw.
19 poly-unsaturat$ fatty acid$.tw. (20)
20 (fatty acid$ adj3 (n-3 or n3 or n-6 or n6)).tw.
21 essential fatty acid$.tw.
22 PUFA$.tw.
23 (oil$ adj3 (fish$ or flax$ or linseed)).tw.

24 ((eicosa$ or icosa$ or docosahex$ or alphalinol$ or alpha-linol$) adj acid$).tw.
25 (EFA or EFAs or EPA or EPAs or MaxEPA or MaxEPAs or DHA or DHAs or ALA or ALAs).tw.
26 or/16-25
27 (adolescence 13 17 yrs or childhood birth 12 yrs or preschool age 2 5 yrs or school age 6 12 yrs or young adulthood 18 29 yrs).ag.
28 (child$ or adolescen$ or teen$ or pupil$ or student$ or girl$ or boy$ or schoolchild$ or preschool$ or pre-school$ or toddler$).tw.
29 or/27-28
30 clinical trials/
31 random$.tw.
32 (allocat$ or assign$).tw.
33 ((clinic$ or control$) adj trial$).tw.
34 ((control$ or experiment$ or intervention$) adj3 group$).tw.
35 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
36 (crossover$ or "cross over$").tw.
37 random sampling/
38 Experiment Controls/
39 Placebo/
40 placebo$.tw.
41 exp program evaluation/
42 treatment effectiveness evaluation/
43 ((effectiveness or evaluat$) adj3 (stud$ or research$)).tw.
44 or/30-43
45 15 and 26 and 29 and 44

CINAHL Plus EBSCOhost 2019 onwards

The study methods filter (lines S1 to S23) was developed by Glanville 2019.

S1 MH ("Randomized Controlled Trials")
S2 (MH "Double-Blind Studies")
S3 (MH "Single-Blind Studies")
S4 (MH "Random Assignment")
S5 (MH "Pretest-Posttest Design")
S6 MH ("Cluster Sample")
S7 TI (randomised OR randomized)
S8 AB (random*)
S9 TI (trial)
S10 (MH "Sample Size") AND AB (assigned OR allocated OR control)
S11 MH (Placebos)
S12 PT (Randomized Controlled Trial)
S13 AB (control W5 group)
S14 MH ("Crossover Design") OR MH ("Comparative Studies")
S15 AB (cluster W3 RCT)
S16 (MH "Animals+")
S17 MH ("Animal Studies")
S18 TI (animal model*)
S19 S16 OR S17 OR S18
S20 MH ("Human")
S21 S19 NOT S20
S22 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15
S23 S22 NOT S21
S24 (MH "Fish Oils+")
S25 (MH "Fatty Acids, Unsaturated+")
S26 essential fatty acid*
S27 PUFA*
S28 (fatty acid* N3 (n-3 or "n3" or n-6 or "n6"))
S29 (oil* N3 (fish* or flax* or linseed*))
S30 ((eicosa* or icosa*or docosahex* or alpha-linol*) N1 acid*)
S31 (EFA or EFAs or EPA or EPAs or MaxEPA or MaxEPAs or DHA or DHAs or ALA or ALAs)
S32 (omega-3 or omega 3 or omega3 or omega-6 or omega 6 or omega6)
S33 poly-unsaturat* fatty acid*
S34 polyunsaturat* fatty acid*
S35 S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34
S36 (MH "Child Behavior Disorders") or (MH "Attention Deficit Hyperactivity Disorder")

S37 adhd or addh or adhs or "AD/HD" or HKD or TDAH
S38 hyperactiv* or hyper-activ* or hyper activ*
S39 (minimal* N3 brain N3 (disorder* or dysfunct* or damage*))
S40 ((attention* or behav*) N3 (defic* or dysfunc* or disorder*))
S41 ((disrupt* N3 disorder*) or (disrupt* N3 behav*) or (defian* N3 disorder*) or (defian* N3 behav*))
S42 (impulsiv* or inattentiv* or inattention*)
S43 hyperkin* or hyper-kin* or hyper kin*
S44 S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43
S45 S23 AND S35 AND S44

CINAHLPlus EBSCOhost (2012 to 2018)

S30 S29 and S24 and S17
S29 S28 or S27 or S26 or S25
S28 (child* or adolescen* or teen* or pupil* or student* or girl* or boy* or schoolchild* or preschool* or pre-school* or toddler*)
S27 (MH "Child, Preschool")
S26 (MH "Child")
S25 (MH "Adolescence")
S24 S23 or S22 or S21 or S20 or S19 or S18
S23 attention deficit*
S22 brain dysfunction
S21 hyperkin*
S20 hyperactiv*
S19 adhd or addh or adhs
S18 (MH "Attention Deficit Hyperactivity Disorder")
S17 S16 or S15 or S14 or S13 or S12 or S11 or S10 or S9 or S8 or S7 or S6 or S5 or S4 or S3 or S2 or S1
S16 epa or epas
S15 eicosapentaenoic acid*
S14 omega-6*
S13 omega-3*
S12 ALA or ALAS
S11 alphalinolenic acid*
S10 alpha-linolenic acid*
S9 dha or dhas
S8 docosahexaenoic acid*
S7 fish oil*
S6 efa or efas
S5 essential fatty acid*
S4 pufa*
S3 polyunsaturated fatty acid*
S2 (MH "Fatty Acids, Unsaturated+")
S1 (MH "Fish Oils+")

Web of Science Core Collection Clarivate (Science Citation Index; Social Science Citation Index; Conference Proceedings Citation Index - Science; Conference Proceedings Citation Index - Social Sciences & Humanities)

# 20 #19 AND #18 AND #17 Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years
# 19 TS=(random* or placebo* or group* or assign* or control* or trial* or crossover or cross-over* or blind*)
Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years
# 18 TS=(child* or adolescen* or teen* or pupil* or student* or girl* or boy* or schoolchild* or preschool* or pre-school* or toddler*)
Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years
# 17 #16 AND #9
Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years
# 16 #15 OR #14 OR #13 OR #12 OR #11 OR #10
Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years
# 15 TS=(minimal* near/3 brain near/3 (disorder* or dysfunct* or damage*)
Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years
# 14 TS= (hyperactiv* or "hyper activ*" or hyperkin* or " hyper kin*")
Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years
# 13 TS=(impulsiv* or inattentiv* or inattention*)
Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years
# 12 TS= ((disrupt* near/3 disorder*) or (disrupt* near/3 behav*) or (defian* near/3 disorder*) or (defian* near/3 behav*))
Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years

# 11TS= ((attention* or behav*) near/3 (defic* or dysfunc* or disorder*))
Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years
# 10 TS= (ADHD or ADDH or ADHS or "AD/HD" or HKD or TDAH)
Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years
# 9 #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years
# 8 TS= (EFA or EFAs or EPA or EPAs or MaxEPA or MaxEPAs or DHA or DHAs or ALA or ALAs)
Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years
# 7 TS= ((eicosa* or icosa* or docosahex* or alphalinol* or alpha-linol*)
near/1 acid*)
Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years
# 6 TS= ("fatty acid*" near/3 (n-3 or n-6 or N3 or N6))
Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years
# 5 TS=(PUFA*) Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years
# 4 TS= ("essential fatty acid*")
Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years
# 3 TS= ("omega 3" or "omega 6")
Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years
# 2 TS=(oil* near/3 (fish* or flax* or linseed))
Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years
1 #TS= ("polyunsaturat* fatty acid*" OR "poly-unsaturat* fatty acid*") Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years

TROVE limited to theses (2012 to 2019)

title:((acids OR pufas OR omega) AND (adhd OR hyperactiv*))

WorldCat limited to theses (2012 to 2019)

kw:adhd OR attention deficit OR Hyperactiv* OR ADDH OR adhs OR TDAH or HKD AND kw:omega 3* OR omega 6* OR "fatty acid*" OR PUFA* OR eicosa* OR icosa* OR docosahex* OR alphalinol* OR "alpha linol*" OR EFA OR EFAs OR EPA OR EPAs OR MaxEPA OR MaxEPAs OR DHA OR DHAs OR ALA OR ALAs

Cochrane Database of Systematic Reviews (CDSR) in the Cochrane Library

#1 [mh ^"attention deficit and disruptive behavior disorders"]
#2 [mh " attention deficit disorder with hyperactivity"]
#3 [mh "conduct disorder"]
#4 (ADHD or ADDH or ADHS or "AD/HD" or HKD or TDAH):ti,ab,kw
#5 ((attention* or behav*) near/3 (defic* or dysfunc* or disorder*)):ti,ab,kw
#6 ((disrupt* near/3 disorder*) or (disrupt* near/3 behav*) or (defian* near/3 disorder*) or (defian* near/3 behav*)):ti,ab,kw
#7 (impulsiv* or inattentiv* or inattention*):ti,ab,kw
#8 [mh hyperkinesis]
#9 (hyperkin* or hyper next kin*):ti,ab,kw
#10 (minimal* near/3 brain near/3 (disorder* or dysfunct* or damage*)):ti,ab,kw
#11 (hyperactiv* or hyper next activ*):ti,ab,kw
#12 {or #1-#11}
#13 [mh "fatty acids, unsaturated"]
#14 [mh "Fish Oils"]
#15 (omega next 3* or omega next 6*):ti,ab,kw
#16 polyunsaturat* next fatty next acid*
#17 (poly next unsaturat* next fatty next acid*):ti,ab,kw
#18 (fatty next acid* near/3 (n next 3 or n next 6 or N3 or N6)):ti,ab,kw
#19 (essential next fatty next acid*):ti,ab,kw
#20 PUFA*:ti,ab,kw
#21 (oil* near/3 (fish* or flax* or linseed)):ti,ab,kw
#22 ((eicosa* or icosa* or docosahex* or alpha-linol*) next acid*):ti,ab,kw
#23 (EFA or EFAs or EPA or EPAs or MaxEPA or MaxEPAs or DHA or DHAs or ALA or ALAs):ti,ab,kw
#24 {or #13-#23}
#25 #12 and #24 in Cochrane Reviews, Cochrane Protocols

Epistemonikos

Publication type: Systematic review

Systematic review question: Intervention

(title:((title:(ADHD OR ATTENTION DEFICIT OR HYPERACTIV* OR INATTENT*) OR abstract:(ADHD OR ATTENTION DEFICIT OR HYPERACTIV* OR INATTENT*)) AND (title:(OMEGA OR FATTY ACID OR POLYUNSATURAT* OR UNSATURATE* OR OIL*) OR abstract:(OMEGA OR FATTY ACID OR POLYUNSATURAT* OR UNSATURATE* OR OIL*))) OR abstract:((title:(ADHD OR ATTENTION DEFICIT OR HYPERACTIV* OR INATTENT*) OR abstract:(ADHD OR ATTENTION DEFICIT OR HYPERACTIV* OR INATTENT*)) AND (title:(OMEGA OR FATTY ACID OR POLYUNSATURAT* OR UNSATURATE* OR OIL*) OR abstract:(OMEGA OR FATTY ACID OR POLYUNSATURAT* OR UNSATURATE* OR OIL*))))

Proquest Dissertations & Theses

ti(adhd OR attention deficit OR hyperactiv* OR ADDH OR adhs OR TDAH or HKD) AND noft((omega 3* OR omega 6* OR "fatty acid*" OR PUFA* OR eicosa* OR icosa* OR docosahex* OR alphalinol* OR "alpha linol*" OR EFA OR EFAs OR EPA OR EPAs OR MaxEPA OR MaxEPAs ORr DHA OR DHAs OR ALA OR ALAs))

ClinicalTrials.gov

CONDITION | ADHD OR HYPERACTIVITY OR ATTENTION DEFICIT AND INTERVENTION |PUFA OR OMEGA OR POLYUNSATURATED OR FATTY ACID

WHO International Clinical Trials Registry Platform

Basic search ADHD AND PUFA OR ADHD AND FATTY ACID OR ADHD AND OMEGA OR ADHD AND POLYUNSATURATED

Appendix 2. Search strategies for previous version of review

Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library

#1MeSH descriptor Fish Oils explode all trees
#2MeSH descriptor Fatty Acids, Unsaturated explode all trees
#3(polyunsaturated next fatty next acid*)
#4(pufa*)
#5(essential next fatty next acid*)
#6(efa or efas)
#7(fish oil*)
#8(docosahexaenoic acid*)
#9(dha or dhas)
#10(alpha-linolenic acid* or alphalinolenic acid*)
#11(ala or alas)
#12(omega NEXT 3*)
#13(omega NEXT 6*)
#14(eicosapentaenoic acid*)
#15(epa or epas)
#16(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)
#17MeSH descriptor Attention Deficit Disorder with Hyperactivity explode all trees
#18adhd
#19addh or adhs or "ad/hd"
#20hyperactiv* or hyper NEXT activ*
#21addh or adhs
#22hyperkin*
#23(minimal NEAR/3 brain NEAR/3 (disorder* or dysfunc* or damage*))
#24((attention* or behav*) NEAR/3 (defic* or dysfunc* or disorder*))
#25 ((disrupt*) NEAR/3 (disorder* or behav*)) or ((defian*) NEAR/3 (disorder* or behav*))
#26(#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25)
#27MeSH descriptor Adolescent, this term only
#28child* NEAR check word
#29child* or adolescen* or teen* or pupil* or student* or girl* or boy* or schoolchild* or preschool* or pre-school* or toddler*
#30(#27 OR #28 OR #29)
#31(#16 AND #26 AND #30)

MEDLINE (R) Ovid

1 exp Fish Oils/
2 exp Fatty Acids, Unsaturated/
3 polyunsaturated fatty acid$.tw.
4 pufa$.tw.
5 essential fatty acid$.tw.

6 efa.tw.
7 fish oil$.tw.
8 efas.tw.
9 docosahexaenoic acid$.tw.
10 (dha or dhas).tw.
11 alpha-linolenic acid$.tw.
12 alphalinolenic acid$.tw.
13 (ala or alas).tw.
14 omega-6$.tw.
15 omega-3$.tw.
16 eicosapentaenoic acid$.tw.
17 (epa or epas).tw.
18 or/1-17
19 "attention deficit and disruptive behavior disorders"/ or attention deficit disorder with hyperactivity/ or conduct disorder/
20 ADHD.tw.
21 ADDH.tw.
22 ADHS.tw.
23 "AD/HD".tw.
24 ((attention$ or behav$) adj3 (defic$ or dysfunc$ or disorder$)).tw. (28693)
25 ((disrupt$ adj3 disorder$) or (disrupt$ adj3 behav$) or (defian$ adj3 disorder$) or (defian$ adj3 behav$)).tw.
26 (impulsiv$ or inattentiv$ or inattention$).tw.
27 hyperkinesis/
28 hyperkine$.tw.
29 (minimal adj3 brain adj3 (disorder$ or dysfunct$ or damage$)).tw.
30 (hyperactiv$ or hyper-activ$).tw.
31 or/19-30
32 adolescent/ or child/ or child, preschool/
33 (child$ or adolescen$ or teen$ or pupil$ or student$ or girl$ or boy$ or schoolchild$ or preschool$ or pre-school$ or toddler$).tw.
34 32 or 33
35 randomized controlled trial.pt.
36 controlled clinical trial.pt.
37 randomi#ed.ab.
38 placebo$.ab.
39 drug therapy.fs.
40 randomly.ab.
41 trial.ab.
42 groups.ab.
43 or/35-42
44 exp animals/ not humans.sh.
45 43 not 44
46 18 and 31 and 34 and 45

Embase Ovid

1 exp Fish Oils/
2 exp Fatty Acids, Unsaturated/
3 polyunsaturated fatty acid$.tw.
4 pufa$.tw.
5 essential fatty acid$.tw.
6 efa.tw.
7 fish oil$.tw.
8 efas.tw.
9 docosahexaenoic acid$.tw.
10 (dha or dhas).tw.
11 alpha-linolenic acid$.tw.
12 alphalinolenic acid$.tw.
13 (ala or alas).tw.
14 omega-3$.tw.
15 eicosapentaenoic acid$.tw.
16 (epa or epas).tw.
17 omega-6$.tw.
18 or/1-17

19 attention deficit disorder/
20 hyperactivity/
21 conduct disorder/
22 ADHD.tw.
23 ADDH.tw.
24 ADHS.tw.
25 "AD/HD".tw.
26 ((attention$ or behav$) adj3 (defic$ or dysfunc$ or disorder$)).tw.
27 ((disrupt$ adj3 disorder$) or (disrupt$ adj3 behav$) or (defian$ adj3 disorder$) or (defian$ adj3 behav$)).tw.
28 (impulsiv$ or inattentiv$ or inattention$).tw.
29 hyperkine$.tw.
30 (minimal adj3 brain adj3 (disorder$ or dysfunct$ or damage$)).tw.
31 (hyperactiv$ or hyper-activ$).tw.
32 or/19-31
33 exp Clinical trial/
34 Randomized controlled trial/
35 Randomization/
36 Single blind procedure/
37 Double blind procedure/
38 Crossover procedure/
39 Placebo/
40 Randomi#ed.tw.
41 RCT.tw.
42 (random$ adj3 (allocat$ or assign$)).tw.
43 randomly.ab.
44 groups.ab.
45 trial.ab.
46 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
47 Placebo$.tw.
48 Prospective study/
49 (crossover or cross-over).tw.
50 prospective.tw.
51 or/33-50
52 18 and 32 and 51

PsycINFO EBSCOhost (2011 searches)

S30 S24 and S29
S29 S25 or S26 or S27 or S28
S28 AG preschool or AG school age
S27 AG adolescence
S26 AG childhood
S25 child* or adolescen* or teen* or pupil* or student* or girl* or boy* or schoolchild* or preschool* or pre-school* or toddler*
S24 S14 and S23
S23 S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22
S22 ((disrupt* N3 disorder*) or (disrupt* N3 behav*) or (defian* N3 disorder*) or (defian* N3 behav*))
S21 impulsiv* or inattentiv* or inattention*
S20 (attention* N3 deficit*) or (attention* N3 dysfunc*) or (attention* N3 disord*) or (behav* N3 deficit*) or (behav* N3 dysfunc*) or (behav* N3 disord*)
S19 (minimal N3 brain N3 dysfunct*) or (minimal N3 brain N3 disord*) or (minimal N3 brain N3 damage*)
S18 hyperkin*
S17 hyperactiv* or hyper-activ*
S16 adhd or addh or adhs or "ad/hd"
S15 DE "Attention Deficit Disorder with Hyperactivity"
S14 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13
S13 (epa or epas)
S12 eicosapentaenoic acid*
S11 omega-3* or omega-6*
S10 (ala or alas)
S9 alphalinolenic acid*
S8 alpha-linolenic acid*
S7 (dha or dhas)

S6 docosahexaenoic acid*
S5 fish oil*
S4 efa or efas
S3 essential fatty acid*
S2 pufa*
S1 polyunsaturated fatty acid*

PsycINFO Ovid (2008 and 2009 searches)

1 polyunsaturated fatty acid$.tw.
2 pufa$.tw.
3 essential fatty acid$.tw.
4 efa.tw.
5 fish oil$.tw.
6 efas.tw.
7 docosahexaenoic acid$.tw.
8 (dha or dhas).tw.
9 alpha-linolenic acid$.tw.
10 alphalinolenic acid$.tw.
11 (ala or alas).tw.
12 omega-3$.tw.
13 omega-6$.tw.
14 eicosapentaenoic acid$.tw.
15 (epa or epas).tw.
16 Attention Deficit Disorder with Hyperactivity/
17 adhd.tw.
18 addh.tw.
19 adhs.tw.
20 hyperactiv$.tw.
21 hyperkin$.tw.
22 brain dysfunction.tw.
23 attention deficit$.tw.
24 22 or 18 or 23 or 17 or 19 or 21 or 16 or 20
25 (child$ or adolescen$ or teen$ or pupil$ or student$ or girl$ or boy$ or schoolchild$ or preschool$ or pre-school$ or toddler$).tw.
26 or/1-15
27 25 and 24 and 26

CINAHL Plus EBSCOhost

S33 S27 and S32
S32 S28 or S29 or S30 or S31
S31 (child* or adolescen* or teen* or pupil* or student* or girl* or boy* or schoolchild* or preschool* or pre-school* or toddler*)
S30 (MH "Child, Preschool")
S29 (MH "Child")
S28 (MH "Adolescence")
S27 S17 and S26
S26 S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25
S25 (disrupt* N3 disorder*) or (disrupt* N3 behav*) or (defian* N3 disorder*) or (defian* N3 behav*)
S24 impulsiv* or inattentiv* or inattention*
S23 (attention* N3 deficit*) or (attention* N3 dysfunc*) or (attention* N3 disord*) or (behav* N3 deficit*) or (behav* N3 dysfunc*) or (behav* N3 disord*)
S22 (minimal N3 brain N3 dysfunct*) or (minimal N3 brain N3 disord*) or (minimal N3 brain N3 damage*)
S21 hyperkin*
S20 hyperactiv* or hyper-activ*
S19 adhd or addh or adhs or "ad/hd"
S18 (MH "Attention Deficit Hyperactivity Disorder")
S17 S16 or S15 or S14 or S13 or S12 or S11 or S10 or S9 or S8 or S7 or S6 or S5 or S4 or S3 or S2 or S1
S16 epa or epas
S15 eicosapentaenoic acid*
S14 omega-6* or omega 6*
S13 omega-3* or omega 3*
S12 ala or alas
S11 alphalinolenic acid*

S10 alpha-linolenic acid*
S9 dha or dhas
S8 docosahexaenoic acid*
S7 fish oil*
S6 efa or efas
S5 essential fatty acid*
S4 pufa*
S3 polyunsaturated fatty acid*
S2 (MH "Fatty Acids, Unsaturated+")
S1 (MH "Fish Oils+")

BIOSIS Web of Science

24 #23 AND #22
23 TS=(random* or crossover* or placebo* or assign* or control* or trial* or blind*)
22 #21 AND #20 AND #15
21 TS=(child* or adolescen* or teen* or pupil* or student* or girl* or boy* or schoolchild* or preschool* or pre-school* or toddler*)
20 #19 OR #18 OR #17 OR #16
19 Ts=attention deficit*
18 TS=brain dysfunction
17 TS=(hyperactiv* or hyperkin*)
16 TS=(adhd or addh or adhs)
15 #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
14 Ts=(epa or epas)
13 TS=eicosapentaenoic acid*
12 TS=omega-6*
11 TS=omega-3*
10 TS=(ala or alas)
9 Ts=alphalinolenic acid*
8 TS=alpha-linolenic acid*
7 TS=(dha or dhas)
6 Ts=docosahexaenoic acid*
5 Ts=fish oil*
4 TS=(efa or efas)
3 TS=essential fatty acid*
2 TS=pufa*
1 TS=(polyunsaturated fatty acid*)

Science Citation Index Web of Science

24 #23 AND #22
23 TS=(random* or crossover* or placebo* or assign* or control* or trial* or blind*)
22 #21 AND #20 AND #15
21 TS=(child* or adolescen* or teen* or pupil* or student* or girl* or boy* or schoolchild* or preschool* or pre-school* or toddler*)
20 #19 OR #18 OR #17 OR #16
19 Ts=attention deficit*
18 TS=brain dysfunction
17 TS=(hyperactiv* or hyperkin*)
16 TS=(adhd or addh or adhs)
15 #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
14 Ts=(epa or epas)
13 TS=eicosapentaenoic acid*
12 TS=omega-6*
11 TS=omega-3*
10 TS=(ala or alas)
9 Ts=alphalinolenic acid*
8 TS=alpha-linolenic acid*
7 TS=(dha or dhas)
6 Ts=docosahexaenoic acid*
5 Ts=fish oil*
4 TS=(efa or efas)
3 TS=essential fatty acid*
2 TS=pufa*

1 TS=(polyunsaturated fatty acid*)

Social Science Citation Index Web of Science

24 #23 AND #22
23 TS=(random* or crossover* or placebo* or assign* or control* or trial* or blind*)
22 #21 AND #20 AND #15
21 TS=(child* or adolescen* or teen* or pupil* or student* or girl* or boy* or schoolchild* or preschool* or pre-school* or toddler*)
20 #19 OR #18 OR #17 OR #16
19 Ts=attention deficit*
18 TS=brain dysfunction
17 TS=(hyperactiv* or hyperkin*)
16 TS=(adhd or addh or adhs)
15 #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
14 Ts=(epa or epas)
13 TS=eicosapentaenoic acid*
12 TS=omega-6*
11 TS=omega-3*
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9 Ts=alphalinolenic acid*
8 TS=alpha-linolenic acid*
7 TS=(dha or dhas)
6 Ts=docosahexaenoic acid*
5 Ts=fish oil*
4 TS=(efa or efas)
3 TS=essential fatty acid*
2 TS=pufa*
1 TS=(polyunsaturated fatty acid*)

Dissertation Abstracts via Dissertation Express

Search terms used:

polyunsaturated fatty acid
pufa
essential fatty acid
efa
docosahexaenoic acid
dha
alpha-linolenic acid
alphalinolenic acid
ala
omega-3
omega-6
eicosapentaenoic acid
epa

metaRegister of Controlled Trials (www.controlled-trials.com/mrct)

Search terms used:

fatty acid* AND ADHD

TROVE (trove.nla.gov.au), DART-Europe e-theses portal (www.dart-europe.eu/basic-search.php), Networked Digitial Library of Theses and Dissertations (NDLTD) (www.ndltd.org)

acids OR pufas OR omega AND adhd OR hyperactiv*

Appendix 3. Unused methods

We planned to conduct the following analyses in the case of sufficient data.

Issue	Method
Cluster-randomised trials	Had we identified any cluster-randomised trials that met our inclusion criteria, we would not have included them in meta-analyses, because this design for trials of essential fatty acid supplementation may have resulted in biased data.
Subgroup analysis and investigation of heterogeneity	Had sufficient data been available, we would have conducted subgroup analyses to assess the differential impact of gender, age group (0 to 5 years, 5 to 2 years, and 13 to 18 years), length of treatment, and omega-6 PUFA supplement. However, the low number of identified trials precluded these analyses.
Sensitivity analysis to identify source of heterogeneity	We had proposed conducting sensitivity analyses to attempt to identify the source of heterogeneity; however, due to the low number of included trials, this was not possible. We had also proposed sensitivity analyses based on the risk of selection bias (random sequence generation) and detection bias (outcome assessment), as these are associated with biased estimates of effect size (Moher 2009). However, all studies were rated as at high risk of selection and detection bias, so we were not able to conduct these analyses. Lastly, we aimed to conduct sensitivity analysis based on intention-to-treat data, but this analysis was precluded by inadequate data.

Appendix 4. Risk of bias assessment

We assessed random sequence generation (selection bias) as low risk of bias when allocations were generated independently, such as by the use of computer-generated random numbers tables generated by a study statistician or at a clinical trials unit. We considered studies that referred to unblinding to be at high risk of bias. We rated studies as at unclear risk of bias if there was insufficient information to reach a judgement of low or high risk of bias.

We assessed allocation concealment (selection bias) as low risk of bias if PUFA, placebo, or medications allocations were made off site by someone such as an independent pharmacist or trial co-ordinating centre, also if study authors stated that participants, their parents, teachers, or study investigators did not know to which group the participant had been allocated until the trial had been completed. We rated this domain as high risk of bias if it was apparent that allocation may have been unblind. We rated studies as at unclear risk of bias if there was insufficient information to reach a judgement of low or high risk of bias.

We assessed blinding of participants and personnel (performance bias) as low risk of bias if study authors stated that the trial was double-blind and there was no difference in the appearance of intervention and control supplements. We rated this domain as high risk of bias if it was apparent that allocation was not blinded. We rated studies as at unclear risk of bias if there was insufficient information to reach a judgement of low or high risk of bias.

We assessed blinding of outcome assessment (detection bias) as low risk of bias if the authors stated that raters or the rating was blinded, for example when the most commonly used parent- or teacher-rated scales were employed, the authors stated that parents or teachers were blind to the treatment condition or that ratings were blinded. We rated this domain as high risk of bias if there was evidence that ratings were unblinded or not blinded. We rated studies as at unclear risk of bias if there was insufficient information to reach a judgement of low or high risk of bias.

Participants, investigators, and the co-ordination centre were blinded to group allocation.

We assessed incomplete outcome data (attrition bias) as low risk of bias if follow-up was reported to be 100%, or ITT analysis was used for over 90% of those remaining at follow-up. We rated this domain as high risk of bias if there was more than 30% loss to follow-up, or the numbers used in the analysis were not clear, or if data were only reported for a subset of data. We rated this domain as unclear risk of bias if ITT analysis was used, but more than 30% were lost to follow-up.

We assessed selective reporting (reporting bias) as low risk of bias if all outcome data that were mentioned in the published paper and the protocol (if one could be identified) were reported. We rated studies as at high risk of bias if it was unclear what other outcomes were used, or data from specifically mentioned tools for primary outcomes such as the Conners and SWAN were not reported or only selectively reported. We rated studies as at unclear risk of bias if there was insufficient information to reach a judgement of low or high risk of bias.

We assessed other bias as low risk of bias if there were no apparent differences between PUFA and comparison groups at randomisation such as in age, gender, type of ADHD or baseline ADHD or behaviour scores. We rated studies as at high risk of other bias if there were important differences from the study protocol, such as inclusion of children that that did not appear to meet the original inclusion criteria. We also rated studies as high risk if there were important differences between groups in characteristics or baseline scores, such as markedly higher Conners scores. We rated studies as at unclear risk of bias if there were no data comparing PUFA and comparison groups for important variables or baseline scores.

Abbreviations:ADHD: attention deficit hyperactivity disorder; **ITT:** intention to treat; **SWAN:** Strengths and Weaknesses of ADHD symptoms and Normal behavior scale; **PUFA:** polyunsaturated fatty acids

Appendix 5. Studies by comparison

Comparison	Co-intervention	PUFA	Comparator	Number of studies	Studies
1. PUFA vs placebo	Nil	Omega-3 PUFA	Placebo	19	Bos 2015; Chang 2019; Cornu 2018; Crippa 2019; Dashti 2014 ; Gow 2012; Gustafsson 2010; Hariri 2012; Hirayama 2004; Ivity 2015; Kean 2017; Lim-Ashworth 2013; Manor 2012; Matsudaira 2015; Milte 2012; Rodriguez 2019; Vaisman 2008; Voigt 2001; Widenhorn-Müller 2014
1. PUFA vs placebo	Nil	Omega-6 PUFA	Placebo	2	Aman 1987; Arnold 1989
1. PUFA vs placebo	Nil	Omega-3/ omega-6 combined	Placebo	6	Assareh 2017; Dubnov-Raz 2014; Johnson 2009; Perera 2012; Raz 2009a; Stevens 2003
1. PUFA vs placebo	Atomoxetine	Omega-3 PUFA	Placebo	1	Anand 2016
1. PUFA vs placebo	Methylphenidate	Omega-3 PUFA	Placebo	4	Behdani 2013; Moghaddam 2017; Mohammadzadeh 2019; Salehi 2016
1. PUFA vs placebo	Multivitamin	Omega-3 PUFA	Placebo	1	Sinn 2007
1. PUFA vs placebo	Physical training	Omega-3 PUFA	Placebo	1	NCT01807299
1. PUFA vs placebo	Dietary supplement	Omega-3 PUFA	Placebo	1	Brue 2001
1. PUFA vs placebo	Methylphenidate	Omega-3/ omega-6 combined	Placebo	1	Barragán 2017
2. PUFA vs stimulant	Nil	Omega-3 PUFA	Methylphenidate	1	Dashti 2014
2. PUFA vs stimulant	Nil	Omega-3/ omega-6 combined	Methylphenidate	1	Barragán 2017
2. PUFA vs stimulant	Nil	Omega-3 PUFA	Dexamfetamine	1	Arnold 1989

(Continued)

3. PUFA vs PUFA	Nil	Omega-3 PUFA	Omega-6 PUFA	1	Bélanger 2009

PUFA: polyunsaturated fatty acids

WHAT'S NEW

Date	Event	Description
14 April 2023	New citation required but conclusions have not changed	24 new studies included in review following updated searches. No change to conclusions
14 April 2023	New search has been performed	Review updated following a new search in October 2019 and top-up searches in October 2020 and October 2021. GRADE certainty of the evidence ratings now added.

HISTORY

Protocol first published: Issue 3, 2009
Review first published: Issue 7, 2012

Date	Event	Description
5 October 2021	Amended	Top-up search
19 May 2021	Amended	Six additional trials included in review following updated searches. GRADE certainty of evidence now added.
26 October 2020	New search has been performed	Review updated following a updated searches.
19 October 2020	New search has been performed	Search update
10 September 2012	Amended	Reference amended
11 August 2009	Amended	Correction to spelling in the author line
28 June 2008	Amended	Substantive amendment
24 March 2008	Amended	Converted to new review format

CONTRIBUTIONS OF AUTHORS

- Conceptualised and designed the review: Donna Gillies (John Sinn, Sagar Ladd, and Melissa Ross on the original version)
- Co-ordinated the review: Donna Gillies
- Selection of studies for review: Donna Gillies, Matthew Leach, and Guillermo Perez Algorta
- Data extraction: Donna Gillies, Matthew Leach, and Guillermo Perez Algorta
- Data entry: Donna Gillies
- Assessed risk of bias in the included studies: Donna Gillies, Matthew Leach, and Guillermo Perez Algorta
- Assessed the certainty of the evidence: Donna Gillies, Matthew Leach, and Guillermo Perez Algorta

- Analysed the data: Donna Gillies
- Interpretation of data: Donna Gillies, Matthew Leach, and Guillermo Perez Algorta
- Writing the review: Donna Gillies
- Revising the review: Matthew Leach and Guillermo Perez Algorta
- Guarantor for review: Donna Gillies

DECLARATIONS OF INTEREST

Donna Gillies is a former Editor of Cochrane Developmental, Psychosocial and Learning Problems. She was not involved in the editorial process for this review.

Matthew Leach: has declared that he has no conflicts of interest.

Guillermo Perez Algorta: has declared that he has no conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Criteria for considering studies for this review > Types of outcomes > Secondary outcomes

We removed the outcomes of 'suicide' and 'self-harm' stated in the protocol for this review (Gillies 2009), as these data were considered inappropriate by the editors and authors when the original review was submitted (Gillies 2012). No data were collected on these outcomes as they had not been reported in any included study.

The need for the inclusion of learning-related outcomes was identified by one of the editors after submission of the original review (Gillies 2012). It is our intention to include these outcomes in any subsequent updates of this review.

Search methods

In 2020, we replaced the free theses sources (DART - Europe E-theses portal, TROVE, and WorldCat) with the subscription database ProQuest Dissertations & Theses because of its comprehensive coverage and flexible search interface.

*The meta*Register of Controlled Trials (*m*RCT) service ceased to function in 2016 and could not be searched.

Data collection and analysis

Subgroup analysis and investigation of heterogeneity

We carried out subgroup analyses for the type of PUFA supplement (i.e. omega-3 only, omega-6 only, or a combination of omega-3 and omega-6) because, as stated in the Background, they are thought to have differing actions, and the ratio of omega-3 to omega-6 PUFA may also have a role.

Sensitivity analysis

Because the inclusion criteria of some studies were based on scale cut-off scores, we conducted an additional sensitivity analysis in this update to evaluate whether there was any difference between these studies and studies that used a clinician diagnosis of ADHD.

In addition, we used only first-phase data of any cross-over trials, if available, because of the potential for carry-over of effects (Higgins 2022, Section 23.3.2). If first-phase data were not available, we used data for both phases where these were reported, but conducted a sensitivity analysis by excluding any such studies from the analysis.

Differences between protocol and this version of the review > Methods

We were not able to use all of our preplanned methods and have archived these for use in future updates of this review (Appendix 3).

We also conducted a meta-analysis of trials that compared omega-3 PUFA to omega-6 PUFA, although we had not considered this comparison in the protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

Amphetamine [therapeutic use]; Atomoxetine Hydrochloride [therapeutic use]; *Attention Deficit Disorder with Hyperactivity [drug therapy]; *Fatty Acids, Omega-3 [therapeutic use]; Fatty Acids, Unsaturated [therapeutic use]; *Methylphenidate [therapeutic use]; Quality of Life

MeSH check words

Adolescent; Child; Humans