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The effectiveness of omega-3 supplementation in reducing ADHD associated symptoms in children as measured by the Conners' rating scales: A systematic review of randomized controlled trials

Muhammad Abdullah*, Benjamin Jowett, Paula Jane Whittaker, Lesley Patterson

University of Manchester, Faculty of Biology, Medicine and Health, United Kingdom, England

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ABSTRACT

Omega-3 supplements are considered to have anti-inflammatory effects which may be beneficial as inflammation has been linked to ADHD. The aim of this review is to examine the effectiveness of omega-3 supplementation at reducing ADHD symptoms in children and adolescents. Medline, Cinahl+, PsycINFO, Cochrane and Embase were searched for trials investigating the effects of omega-3 supplementation in children and adolescents with ADHD. The primary outcome measure was a mean difference in Conners' rating scale (CRS) between the intervention and placebo group. Search terms used include ADHD, omega-3, fish oils, eicosapentaenoic acid, docosahexaenoic acids, alpha-linolenic acid and Conners' rating scale. Randomized controlled trials examining the efficacy of omega-3 supplementation in children and adolescents as measured by CRS were included. Studies using a combination of polyunsaturated fatty acids or any other rating scale were excluded. Seven trials were included in this review, totalling 926 participants. We found no evidence of publication bias or heterogeneity between trials. Overall, there was a slightly greater reduction in CRS score in favour of the experiment group. One study found a greater reduction in score in favour of the placebo group. Neither findings were statistically significant. There is little supportive evidence to validate the claim of omega-3 supplementation to reduce the degree of ADHD symptoms experienced by children and adolescents. Both experiment and control groups saw similar reductions in Conners rating scale score.

1. Introduction

1.1. Attention Deficit Hyperactivity Disorder

The National Institute of Mental Health (NIMH) defines Attention Deficit Hyperactivity Disorder (ADHD) as a brain disorder marked by an ongoing pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development (NIMH, 2016). Approximately 5% of the worldwide population is estimated to have ADHD with a higher prevalence in males (Cantwell, 1996; Faraone and Wilens, 2003; American Psychiatric Association, 2013). A diagnosis of ADHD should be based on validated criteria such as the DSM-IV for ADHD (Gillies et al., 2012; NICE, 2016). Assessment is observational and supported by behaviour rating scales (Barkley, 1998; NICE, 2016).

The exact aetiology of ADHD is unknown but there is a 3–5 times increased risk between first-degree relatives suggesting a genetic component (Stephen V Faraone and Biederman, 1994). For example, genetic studies have found associations with variations in genes for the dopamine transporter and dopamine receptors 4 and 5 (Curran et al., 2001; S V Faraone et al., 2001; Maher et al., 2002). However, each of these alleles only increases the relative risk for ADHD slightly (odds ratio: 1.2–1.9) which is consistent with the general consensus that ADHD is a complex disorder of multiple aetiological factors (Taylor et al., 2004). Evidence exists to suggest possible structural, functional and neurotransmitter alterations in various regions of the brain in ADHD sufferers (ADHD Institute, 2017).

Currently, there is no cure for ADHD, but treatments may aid the reduction of symptoms and improve function (NIMH, 2016). Many families prefer to avoid the use of traditional pharmacotherapies, often because of short-term side effects or doubts regarding long-term efficacy (Bloch and Qawasmi, 2011). For example, stimulants are associated with short-term side effects such as decreased appetite, weight loss and insomnia (Biederman, 2005; Cantwell, 1996). Longer term use may cause growth reduction and worsen comorbid symptoms such as tics (Daley, 2004). Non-stimulant pharmacotherapies include antidepressants, anti-anxiety agents, bupropion and atomoxetine (Gillies

* Corresponding author. Room 2.545 Stopford Building, University of Manchester, Oxford Road, Manchester M13 9PT, United Kingdom, England.
E-mail address: Muhammad.abdullah-3@student.manchester.ac.uk (M. Abdullah).

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et al., 2012). Instead of the aforementioned pharmacotherapies, alternative treatments such as omega-3 supplements are often used by families (Bloch and Qawasmi, 2011; Chan and Kemper, 2000).

Studies have found children with ADHD to have significantly lower plasma and blood concentrations of omega-3 PUFA's (Burgess et al., 2000; Chen et al., 2004; Mitchell et al., 1987; Stevens et al., 1995). A 2007 trial found improvements in blood composition and concentration of EPA, DHA and total PUFA after omega-3 supplementation (Metherel, 2007).

1.2. Polyunsaturated fatty acids

Omega-3 fatty acids belong to a group of polyunsaturated fatty acids (PUFAs), characterised by a carbon double bond in the 3rd position of their carbon chain from the methyl end (Angelo et al., 2014). The three types of omega-3 fatty acids relevant to human physiology are alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The former is found in plant oils (e.g. walnuts) and the latter two in fish oils (Angelo et al., 2014). These cannot be synthesized in the body and so are essential in one's diet (NIMH, 2018).

Omega-6 fatty acids are also a family of PUFA's, characterised by a carbon double bond in the 6th position of their carbon chain from the methyl end (Angelo et al., 2014). This group are known for their potentially pro-inflammatory effects in the body (National Institutes of Health, 2018). Whereas omega-3 fatty acids are considered anti-inflammatory (Artemis P Simopoulos, 2002a,b).

A western diet is typically considered to have an average omega-6:omega-3 of 15–16.7:1 but as low as a 5:1 ratio was needed to show a beneficial effect in asthma patients and a 10:1 ratio had adverse consequences (A P Simopoulos, 2002a,b). A higher proportion of omega-6: omega-3 fat in the diet shifts the physiological state in the tissues towards prothrombotic, proinflammatory and proconstrictive states (A.P. Simopoulos, 2003). Omega-6 fatty acids are considered to interfere with the health benefits of omega-3`s due to competition for the same rate-limiting enzymes (A.P. Simopoulos, 2003). A high ratio of omega-6: omega-3 fatty acids has been proposed to promote neuroinflammation which is linked to ADHD (D. Anand, Colpo, Zeni, Zeni and Teixeira, 2017; Freeman and Rapaport, 2011; Sears, 2011). A research review found a lower concentration of omega-3 fatty acids in subjects with ADHD showing increased behavioural symptoms with lower plasma concentrations. It was thereby suggested that a lack of fatty acids may exacerbate ADHD symptoms (Rojas and Chan, 2005).

1.3. Present research

Several randomized controlled trials (RCTs) have been published on the effectiveness of omega-3 supplementation to reduce ADHD symptoms, reporting mixed results. A systematic review supported the role of omega-3 supplementation as a clinically relevant intervention, especially if guided by a biomarker-based personalisation approach (Chang et al., 2017). However, the included studies used a variety of rating scales. Assessing different aspects of behavioural, emotional and social problems making comparisons between studies problematic.

A systematic review by Bloch and Qawasmi (2011) found a small benefit of omega-3 fatty acid supplementation and concluded that the results do not support using omega-3 fatty acids as a replacement for traditional pharmacological treatments in children with significant ADHD symptomology.

There are a variety of different scales for monitoring symptom control in ADHD. The Conners' Rating Scales (CRS) are well validated and widely used. To quantify the effectiveness of omega-3, this review will focus on the change achieved specifically with CRS. Currently, no systematic review or meta-analysis has been conducted to determine the effectiveness of omega-3 supplementation in reducing symptoms of ADHD in children and adolescences as measured by CRS only.

1.4. Conners' rating scales

Rating scales allow the observer to quantify the degree or frequency of behavioural characteristics of interest. The original CRS was published in 1970. The Conners' Parent Rating Scale (CPRS) was developed initially as a comprehensive checklist to obtain parental reports of the basic presenting problems for children referred to psychiatry (Conners, 1970). The scales include teacher or parent as well as long and short versions. CRS have become popular for screening and assessing behaviour problems including assessing psychosocial and drug treatment outcomes (Conners et al., 1998).

The first version was published in 1970 by Dr Keith Conner who derived the 73-item questionnaire from the systematic questioning of parents (Conner, 1970). Three years later the CPRS-93 was introduced to identify hyperkinetic children and evaluate the effectiveness of drug treatment in controlling their behaviour (Conners, 1973). It is a 93-item questionnaire intended to assess problematic behaviours in children across 25 different areas (Gianarris et al., 2001).

In 1978, a revised 48 item version was created from the 93-item version – the Conners' Parent Rating Scale-Revised (CPRS-48). The changes included slight rewording and substantial shortening to simplify administration and interpretation. To assess similarity, this newly revised scale was factor analysed and compared with previous scales (Goyette et al., 1978). Additionally, the CPRS-48 contains the hyperactivity index (HI) which includes 10 items that are considered to be most sensitive to treatment effects (Catale et al., 2014).

In 1997, Dr Conner released a new revision with both an 80-item long version (CPRS-R:L) and a 27-item short version (CPRS-R:S) (Connors, 1997). This revision is based on a larger sample of over 2400 children. The revision took place to address shortcomings in the original version including a small non-representative normative sample and content which was considered outdated (Connors, 1997). Although this revision doesn't differ drastically from the previous revisions, it does contain the ADHD index and DSM-IV symptoms as new additions (Gianarris et al., 2001).

The CPRS has been adapted into several languages including French (Dugas et al., 1987). Culturally adapted normative data is lacking, however, Catale et al. (2014) using confirmatory factor analysis showed that CPRS still retained high rates of sensitivity and specificity when ADHD and control group scores are compared using the French version.

CRS are quick and easy to use which makes them ideal for use by a wide range of outcome assessors. Minimal training is required to be able to administer the test with 20 min for the long and 10 min for the short version (Conners, 2008; Gianarris et al., 2001). The test considers both home and school settings, has a broad scope and standardized administration which reduces the likelihood of important areas being overlooked. This highly standardized nature allows for more relevant comparison of scores (Gianarris et al., 2001). Studies showed that the CPRS consistently distinguishes ADHD from controls (Ackerman et al., 1979; Plomin and Foch, 1981). Catale et al. (2014) confirmed that the CPRS, particularly the impulsive-hyperactive and HI subscales, were successful at discriminating between ADHD and control children with high levels of specificity and sensitivity. The psychometric properties of the CPRS have made this scale an attractive research and clinical instrument. Studies have shown good reliability as assessed by test-retest and interrater reliability (A Glow, H Glow, & E Rump, 1982; Conners, 1973). Furthermore, there is research demonstrating the CPRS ability to differentiate children with a behavioural disorder from unaffected children (Prior et al., 1983; Ross and Ross, 1982). The aim of this review is to assess the effectiveness with just the CRS to minimise heterogeneity between studies.

2. Materials and methods

A systematic review was conducted of omega-3 supplementation on children and adolescent participants with ADHD that used CRS to

measure outcome. The review was is reported in accordance with PRISMA guidelines (Moher et al., 2009).

2.1. Literature search

Searches was carried out in February 2018 in Medline, Embase, CINAHL Plus, the Cochrane Central Register of Controlled Trials and PsychINFO. Search terms included ADHD, omega-3, fish oils, eicosapentaenoic acid, docosahexaenoic acids, alpha-linolenic acid and Conners' scale. The search strategy used a combination of database-specific thesaurus terms and free text adapted to each database as shown in Appendix A Tables 2–6. No language restrictions were applied. Forward citation was performed from relevant systematic review articles. References of appropriate systematic reviews were hand searched for additional citations. Two authors (MA and BJ) independently screened titles and abstracts against the inclusion and exclusion criteria. Two authors (MA and BJ) independently reviewed the full texts of the remaining articles for inclusion. Any discrepancies were resolved by consensus discussion chaired by a third author (PW).

2.2. Inclusion criteria

Studies were included in this review if: (1) studies were randomized, double-blinded, placebo controlled trials of omega-3 supplementation including DHA or EPA alone or in combination; (2) the intervention was a supplement (i.e. not a fortified food); (3) vitamin and mineral additions were acceptable given that this was uniform across all groups (e.g. vitamin E to prevent oxidation of the fatty acids); (4) participants were aged between 3 and 18 years old and had a diagnosis of ADHD; (5) the study measured clinical symptoms of ADHD as reported by parents or teachers using one of Conners' rating scales (excluding Conners' abbreviated rating scale); (6) there was a minimum intervention period of 8 weeks.

2.3. Exclusion criteria

The exclusion criteria for this review were: (1) any study that did not report the change in score of Conners Rating Scale specifically; (2) studies carried out on non-humans or adult humans; (3) the intervention did not contain a mixture of different types of polyunsaturated fatty acids (i.e. omega-3 and omega-6 combinations). Appendix C, table 13 shows studies excluded.

2.4. Data collection and analysis

Two authors (MA and BJ) independently extracted data from the included studies using Microsoft Excel spreadsheets with predetermined headings to extract participants, intervention and outcome measurement information. Any discrepancies were resolved by consensus discussion chaired by a third author (PW). Any missing information was requested from the study investigators.

2.5. Statistical analysis

A quantitative synthesis of data was planned on the condition that the studies are sufficiently homogenous. Aggregate data was planned to be used for each intervention group.

If data were available, subgroup analyses were planned to assess the differential impact of gender, age group (under five years, five to 12 years and 13–18 years) and length of treatment.

RCTs that met the inclusion criteria were assessed for methodological and statistical heterogeneity. Only the outcomes of studies that displayed adequate methodological and statistical homogeneity (indicated by an I^2 of less than 50%) would qualify to be pooled using meta-analysis using Stats Direct software.

2.6. Risk of bias assessment

All of the included studies were assessed for methodological quality, using the Cochrane Collaboration tool for assessing the risk of bias of controlled trials (Higgins and Green, 2011). The following criteria were assessed as “low risk of bias”, “high risk of bias” or “unclear risk of bias”: the adequacy of sequence generation; allocation concealment; the blinding of participants and personnel; the blinding of outcome assessors; and whether outcome data was adequately addressed.

Two authors independently assessed the risk of bias of the included studies (MA and BJ). Any disagreements were resolved by consensus discussion chaired by a third author (PW). See Appendix B, Tables 7–14 for in-depth analysis of bias assessment.

3. Results

3.1. Selection of studies

606 articles were identified by the bibliographic database search and 31 from reference list searching (total N = 637). 284 duplicates were removed (N = 353). 317 were excluded by title and abstract screening (N = 36). A total of 36 studies were assessed using their full text against the inclusion and exclusion criteria. 7 RCTs met the inclusion criteria requirements (see Fig. 1). The results from these have been extracted and formatted into a data extraction table (see Table 1).

3.2. Included studies

All included studies were randomized double-blind placebo-controlled trials published between 2009 and 2017. Belanger et al. (2009) was a one-way cross over design with the cross over period excluded from the data extraction. Manor et al. (2012) had an open-label extension design of which the open-label extension period was excluded in the data extraction.

In two studies both the study and control groups were given standard pharmacological therapy alongside omega-3 supplementation or a placebo (Anand and Sachdeva, 2016; Salehi et al., 2016). Salehi et al. (2016) used methylphenidate as the pharmacological therapy and compared against a white sugar capsule the placebo. Anand and Sachdeva (2016) used atomoxetine and had nothing to imitate the placebo. Manor et al. (2012) did not specifically describe what the placebo was composed of. The remaining studies described a placebo that looked identical to the active intervention.

All studies took place after the revised CRS was published in 1997. Only three studies explicitly mentioned using the revised scale (Anand and Sachdeva, 2016; Cornu et al., 2017; Manor et al., 2012). Two studies mentioned using the short form of the scale (Anand and Sachdeva, 2016; Gustafsson et al., 2010). Two studies mentioned using the long version (Cornu et al., 2017; Manor et al., 2012). Cornu et al. (2017) used the revised long version (48 item). Manor et al. (2012) used the Long-Hebrew version and gave no indication to the number of items in the scale they used.

Two studies gave no detail on the scale used. Belanger et al. (2009) states the use of “parent and teacher Conners' questionnaires” and Salehi et al. (2016) states “The Conners' Parent and Teacher Rating Scales”.

3.3. Bias assessment of included studies

Overall the studies performed well on the bias assessment as shown in Figs. 2 and 3. Two out of the six studies were assessed as low risk for all domains (Cornu et al., 2017; Manor et al., 2012).

Belanger et al. (2009) received unclear for random allocation concealment as insufficient information was provided. The rest of the included studies were graded as low risk.

The most common domain that was unclear was blinding of

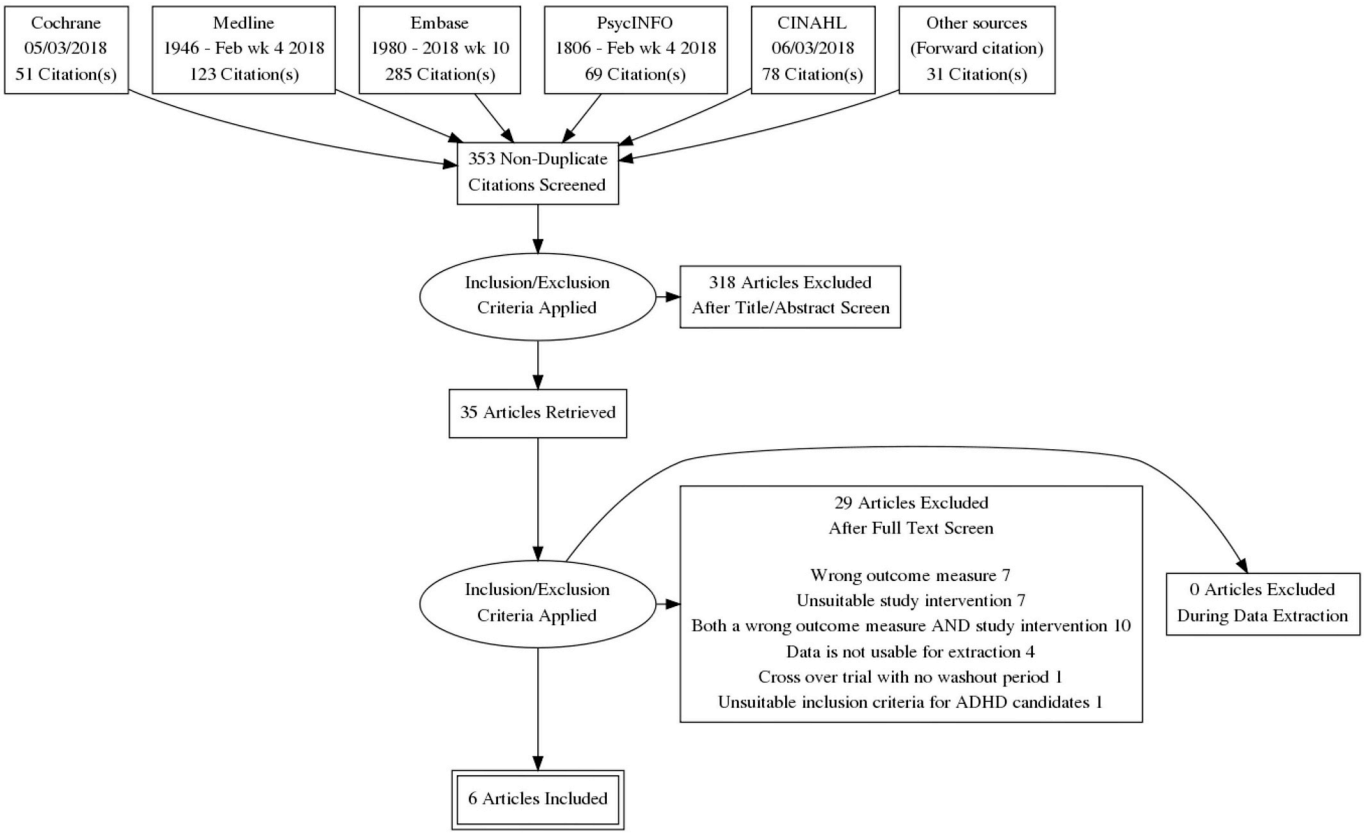

Fig. 1. PRISMA flow diagram.

outcome assessment which was inadequately described by three studies (Belanger et al., 2009; Gustafsson et al., 2010; Salehi et al., 2016). Anand and Sachdeva (2016) had an unequal number of tablets between the experiment and control group.

Four studies were assessed as low-risk of bias for blinding of participants and personnel (Belanger et al., 2009; Cornu et al., 2017; Gustafsson et al., 2010; Manor et al., 2012). These four studies provided a placebo which was a mimic of the true omega-3 supplement. There is a possibility of taste differentiation, but this was not considered to introduce a risk of bias. Salehi et al. (2016) received unclear risk of bias for providing a white sugar tablet as the placebo which did not mimic the omega-3 supplement. Anand and Sachdeva (2016) also received unclear risk of bias for providing no placebo pill.

Five studies provided complete information on outcome data, drop outs and/or use of intention to treat analysis (Anand and Sachdeva, 2016; Belanger et al., 2009; Cornu et al., 2017; Gustafsson et al., 2010; Manor et al., 2012). All these studies. Salehi et al. (2016) was assessed as unclear risk for providing insufficient information on the dropouts nor did it provide information on the use of intention to treat analysis.

All six studies received a low-risk assessment for selective reporting as all pre-specified outcomes were reported.

3.4. Effect of intervention

Four studies used CPRS alone of which three showed a greater reduction of the score in the experiment group compared to the control group, but these changes were not statistically significant. Altogether these studies included 176 participants (Anand and Sachdeva, 2016; Belanger et al., 2009; Salehi et al., 2016). Cornu et al. (2017) with 149 participants showed a greater reduction CPRS score in the control group compared to the experiment group, but still, this change did not reach statistical significance.

The remaining two studies looked at both CPRS and Conners teacher rating scale (CTRS). These combined included 239 participants and showed similar changes in scores to the other included studies (Gustafsson et al., 2010; Manor et al., 2012).

In Gustafsson et al. (2010) the largest change was seen on the CTRS in favour of the experiment group (6.6 vs 2.8) but this was not statistically significant. The CPRS changed similarly in both groups. In Manor et al. (2012), CPRS decreased greater in the study group, but this was not statistically significant. CTRS showed overall difference despite significant reductions in two subscales (the global: emotional lability and the DSM-IV: inattentive scales).

3.5. Augmentation trials

In both augmentation trials the greater reduction in score was in favour of the experiment group but this did not reach statistical significance in either of the studies (Anand and Sachdeva, 2016; Salehi et al., 2016).

3.6. Monotherapy trials

Belanger et al. (2009) had the fewest participants (N = 26). This monotherapy trial showed a greater (but not statistically significant) reduction in rating score in favour of the experiment group. Of the 26 participants, only eight subjects (four from each group) showed significant clinical improvement.

Gustaffson et al. (2010) included 92 participants and analysed CPRS and CTRS separately as well as combined (CPRS + CTRS). In all outcomes, both the experiment and control-treated children showed very similar changes after 15 weeks of treatment.

Manor et al. (2012) analysed CPRS and CTRS separately. There was a greater numerical score reduction in CPRS in favour of the experiment group but CTRS changed very similarly for both groups.

Cornu et al. (2017) included 149 participants, and showed a greater

Table 1
Data extraction table.

		Design and rating scale	Intervention	Experiment Participants, age (mean ± SD) and gender (%male)	Placebo	Comparison Participants and age (mean ± SD)	Results
1	(Salehi et al., 2016) Iran 2016	8 Week randomized, double-blind control trial using Conners' parent and teacher rating scales Children who were diagnosed as ADHD based on 18-question questionnaire of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revised (DSM-IV-TR)	Methylphenidate along with 100 mg Eicosapentaenoic fatty acid for children < 25 kg, 200 mg for 26–35 kg, and 400 mg for children > 35 kg/day, respectively	N = 50 8.6 ± 1.7 78% male	Methylphenidate along with a white sugar capsule	N = 50 9.12 ± 2.2 64%	Experiment group score changed from 56.1 ± 9.5 to 36.5 ± 8.9 (−19.6). The control group score changed from 55 ± 9.3 to 36.1 ± 4.3 (−18.9). The mean difference is in favour of the experiment group with a difference of 0.7 The change is greater in the experiment group, but this is not statistically significant
2	Anand & Sachdeva (2016) India 2016	4-Month prospective double blind randomized control trial using Conners parent rating scale – revised (CPRS-R). Children diagnosed by psychiatrist according to the DSM-IV TR criteria and Kiddie-Schedule for Affective Disorders and Schizophrenia - Present and lifetime version (KSADS-PL)	Atomoxetine along with180 mg of EPA and 120 mg of DHA	N = 25 6.1 68% male	Just Atomoxetine	N = 25 6.0 72% male	Experiment group score changed from 39.1 ± 2.1 to 36.6 ± 2.2 (−2.5). The control group score changed from 38.4 ± 2.3 to 37.4 ± 2.2 (−1). The mean difference is in favour of the experiment group with a difference of 1.5 The change is greater in the experiment group, but this is not statistically significant
3	Belanger et al. (2009) Canada 2009	8 Week randomized double-blind, one-way, crossover study using Conners Parent Rating Scale Children chosen with a Diagnostic and Statistical Manual of Mental Disorders, Fourth edition *(DSM-IV)* diagnosis of ADHD based on the results of the parent and teacher Conners' questionnaires and a clinical evaluation	Body weight dosage of 500 mg EPA and 200 mg of DHA for 16–25 kg, 750 mg EPA and 300 mg DHA for 26–35 kg and 1000 mg EPA and 400 mg DHA for 36–45 kg	N = 13 9.3 ± 0.4 69% male	500 mg of sunflower oil	N = 13 9.09 ± 0.50 69% male	The experiment group changed from 67.1 ± * to 60.1 ± *(-6.5). The control group changed from 63.8 ± * to 59.0 ± * (−4.8). The mean difference is in favour of the experiment group with a difference of 1.7 The change is greater in the experiment group, but this is not statistically significant
4	Cornu et al. (2017) France 2017	3 Month randomized double-blind, placebo-controlled clinical trial using a 48-Item Conners' parent rating scale-revised (CPRS-R: L) ADHD diagnosis was performed by child psychiatrists specialised in ADHD according to DSM-IV-TR criteria	For children aged 6–8 years, EPA 336 mg and DHA 84 mg; for children aged 9–11 years, EPA 504 mg and DHA 126 mg, and for children aged 12–15 years EPA: 672 mg and DHA 168 mg; capsules also contained 100 µg vitamin A, 1.25 µg vitamin D, and 3.5 mg vitamin E	N = 72 10.2 ± 2.8 76.3% male	Olive oil, the same amount of vitamin A, D, and E	N = 77 9.7 ± 2.5 80.5% male	The experiment group score changed from 57.7 ± * to 54.3 ± * (−2.6). The control group changed from 56.8 ± * to 48.6 ± * (−7.7). The mean difference is in favour of the control group with a difference of 5.1 The change is greater in the control group, but this is not statistically significant

(*continued on next page*)

Table 1 (*continued*)

		Design and rating scale	Intervention	Experiment Participants, age (mean ± SD) and gender (%male)	Placebo	Comparison Participants and age (mean ± SD)	Results
5	Gustafsson et al. (2010) Sweden 2010	15 Week Prospective randomized and double blinded study using Conners parent rating scale short form (CPRS-S) 27 items and Conners teacher rating scale short form (CTRS-S) 28 items. Children chosen with a clinical diagnosis of ADHD of combined type (fulfilling DSM-IV criteria A–E)	500 mg EPA + 2.7 mg DHA and 10 mg Vitamin E mixed tocopheroles	N = 46 7–12 years of age	Mixture of rape seed oil and medium-chain triglycerides	N = 46 7–12 years of age	The experiment group score changed from 51.0 ± 16.5 to 43.8 ± 18.6 (−7.2) for the CPRS and 49.7 ± 18.0 to 43.1 ± 18.8 (−6.6) for the CTRS scale. The control group score changed from 46.0 ± 15.5 to 39.4 ± 18.4 (-6.6) for the CPRS scale and 43.5 ± 14.9 to 40.7 ± 17.9 (−2.8) for the CTRS scale. The mean difference is in favour of the experiment group with a difference of 0.6 for the CPRS and 3.8 for the CTRS. Overall both the experiment and control groups were similar after 15 weeks of treatment. The biggest difference change was seen on the CTRS scale between the experiment group and control group (−6.6 vs −2.8) but this is not significant
6	Manor et al. (2012) Israel 2012	15-Week, double-blind, placebo-controlled phase (week 0 through week 15) that was subsequently followed by a 15-week open-label extension period (week 15 through week 30). This study used Conners teacher rating scale revised long-hebrew version (CRS-T) and Conners parent rating scale revised long-hebrew version (CRS-P). Children with 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	300 mg of PS and 120 mg of EPA + DHA (EPA/DHA ratio of 2:1)	N = 100 9.2 ± 2.0 72% male	Does not say specifically what the placebo is composed of	N = 47 9.2 ± 1.8 68% male	The experiment group score changed from 66.3 ± * to 61.8 ± * (−4.4) for CRS-P and 62.7 ± * to 61.5 ± * (−1.2) for CRS-T The control group score changed from CRS-P changed from 65.6 ± * to 62.5 ± * (−3.10) for the CRS-P and 63.4 ± * to 62.4 ± * (−1.2) for CRS-T. The mean difference is in favour of the experiment group with a difference of 1.3 for the CRS-P but the mean difference was 0.0 for the CRS-T The changes in score were very similar between the experiment and control group for both parent and teacher rating scales

*Standard deviation was not available.

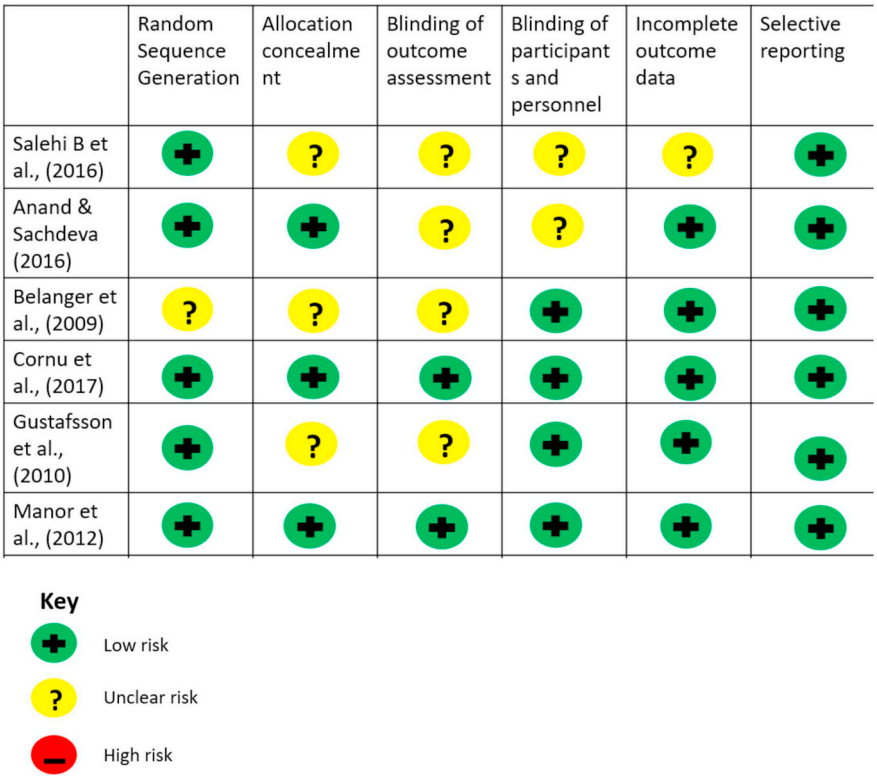

Fig. 2. Risk of bias for individual RCTs.

CPRS reduction in favour of the control group (7.7 vs 2.6). Overall there was no significant difference between the two groups.

3.7. Subgroup analysis

Two studies found a greater improvement in male participants (Anand and Sachdeva, 2016; Manor et al., 2012). Anand and Sachdeva (2016) found that males in the study group had a greater improvement in ADHD scores compared to males in the control group but this was not statistically significant. However, there was no difference in score change among female participants between experiment and control groups. Manor et al. (2012) similarly found that the subgroup of boys preferentially benefited from the treatment as compared to the placebo, whereas there was no significant effect observed in girls.

3.8. CPRS vs CTRS

CPRS tended to show a greater reduction compared to their teacher counterparts. This is seen consistently in both studies looking at both the teacher and parent-rated scale (Gustafsson et al., 2010; Manor et al., 2012).

4. Discussion

4.1. Summary of results

Overall there was little evidence to suggest that omega-3 supplementation provides any benefit for the symptoms of ADHD in children and adolescents. Although five out of six studies showed a greater numerical reduction in favour of omega-3 supplementation in CRS, none were statistically significant.

Belanger et al. (2009) found a statistically significant improvement in several of the CPRS subscales in both groups which may be a significant indication of the placebo effect on parent's judgement of their child's behaviour during treatment. Cornu et al. (2017) concluded that there is no biological explanation for a greater effect in the placebo group compared with the active group so the result could be incidental (Cornu et al., 2017).

Two studies found a greater improvement in male participants compared to their female counterparts (Anand and Sachdeva, 2016; Manor et al., 2012).

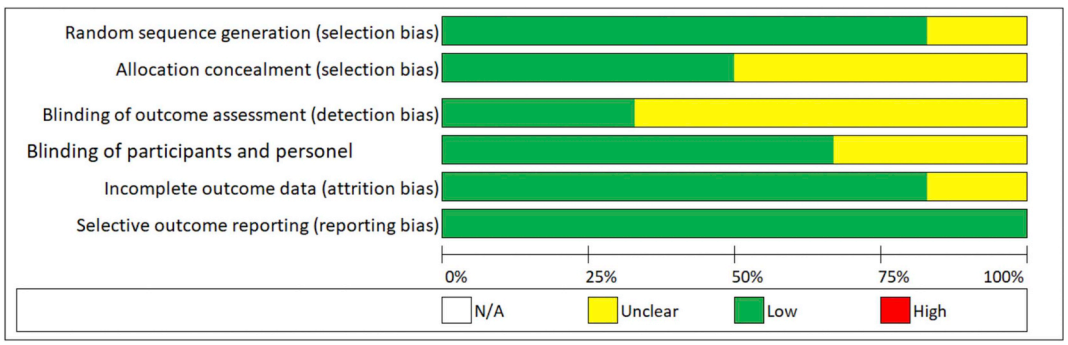

Fig. 3. Risk of bias summary.

4.2. Methodology

This is the first systematic review to analyse the efficacy of omega-3 supplementation in reducing ADHD symptoms as assessed solely by CRS in RCTs. Due to methodological differences and lack of data, meta-analysis was not possible. Despite limiting to just CRS, the different versions of the CRS sufficiently reduce the homogeneity of the studies.

Not all information, such as standard deviations, were present in the published articles of included studies. Every effort was made to retrieve information from authors. It had been proposed that a sensitivity analysis would be carried out to try and identify the source of heterogeneity; however, due to the low number of included trials, this was not possible. Random-effects model was planned for meta-analysis, but this was not possible due to inadequate standard deviation data from studies and the variety of CRS used.

4.3. Limitations of Conners Rating Scale

The original CPRS-93 was quickly accepted as a diagnostic aid and research tool despite the absence of empirical backing (Gianarris et al., 2001). Although studies such as Ackerman et al. (1979) and Plomin and Foch (1981) have shown that CRS distinguishes ADHD from controls, numerous studies have also shown that the CPRS is equally effective at distinguishing controls from other disorders such as conduct disorder and children with hydrocephalus as infants (Russell A. Barkley, 1984; Elisabeth et al., 2018), and between different types of behavioural disorders (Kuehne et al., 1987; Leon et al., 1980). However some authors have questioned the specificity of the CRS to ADHD as some studies have found the CPRS to be unable to differentiate ADHD from other disorders (Stein et al., 1995; Zelko, 1991).

Despite being broad in nature, the scales can be seen as narrow in scope as they only extract information from parents and teachers (Gianarris et al., 2001). Inter-reliability between parents (i.e. mother and father) has been found to be between 0.59 and 0.35 (Fitzgerald et al., 1994; Keith Conners, 1970). Concurrently, reliability between parents and teachers is even lower, ranging from 0.33 to 0.03 (R A Barkley, 1988; Chelune et al., 1986). Although this demonstrates its nature to be prone to outcome assessor bias, comparison of scoring between outcome assessors can provide great insight into the consistency of behaviours and perception by different observers across different situations (Gianarris et al., 2001). For this reason, it is important to always consider that the CRS reflect perception and are not a direct measure of the child's behaviour. This makes them subject to influence by external factors such as the outcome assessor's mood, time spent with the child and the behavioural characteristic of most concern to the assessor (Gianarris et al., 2001). Other factors that have been considered in research to affect results include: parents mental health, number of children in the household and marital discord. (Conger et al., 1984; Fitzgerald et al., 1994; Frick et al., 1989; Schaughency and Lahey, 1985; Smith and Jenkins, 1991). Outcome assessors may have a difficult time translating behaviour into classifications such as “just a little true” or “pretty much true”. Finally, scoring by parents may be elevated due to enhanced levels of concern with the need to justify a reason for unfavourable behaviour especially before the intervention period. Scores may be reduced with the desire for the child to be well or denial, especially post-intervention period (Gianarris et al., 2001).

In this review, only three out of the six studies explicitly mentioned the use of the revised scale (Anand and Sachdeva, 2016; Cornu et al., 2017; Manor et al., 2012). The original CRS was revised to address certain shortcomings such as small non-representative normative sample and content that was considered outdated (Connors, 1997). The included studies showed such a variety of scales in addition to uncertainty on the particular version which was used. This highlighted to us that not only would a meta-analysis be unsuitable but also continuous data comparison between studies is limited.

Across studies CPRS tended to show a higher reduction in score in the compared CTRS in trials using both as an outcome. Parents will inevitably tend to be more sensitive than teachers (or other professionals) to changes in their child's behaviour, especially over a short intervention period. This has been found in other trials too (Schab and Trinh, 2005; Sinn and Bryan, 2007). On the other hand, some studies have shown a higher change in teacher-rated scoring compared to parent-rated scoring (Kirby et al., 2010; Richardson and Montgomery, 2005). These differences could be co-incidental or due to missing data.

4.4. Other limitations

The data is limited in terms of its ability for comparison between trials. For example, all studies had parental, but only Gustafsson et al. (2010) and Manor et al. (2012) included teacher rating scales. As different versions of the CRS vary in format and scope, a meta-analysis was unsuitable.

Another limitation is that two of the studies: Belanger et al. (2009) and Salehi et al. (2016) were very short with an intervention period of eight weeks long. It may take up to 3months for the brain to recover from any chronic PUFA deficiency (Richardson and Puri, 2000). These two trials may have been too short to demonstrate any real benefit. Future trials should ensure that the intervention period lasts at least three months or preferably longer.

Ensuring adequate blinding is crucially important due to the nature of the outcome assessment. It is difficult to mask the distinctive taste of fish oil. This raises the possibility that parents were aware when their children were receiving an omega-3 supplement (especially if their child was formerly known to complain about the fishy taste for example).

By limiting the review to only CRS, this may have prevented the review from identifying significant effects seen by trials using other scales. This would increase the power of this systematic review as it would have allowed for more studies to be included.

4.5. Conclusion and future recommendations

Currently, there is insufficient evidence to conclude that omega-3 supplementation is of any benefit in improving the symptoms measured by the CRS in children and adolescents with ADHD. These behaviours include: 1) Inattention such as poor concentration/attention or difficulty keeping their mind on work; 2) hyperactivity/impulsivity, where there is high activity levels, restlessness and/or impulsive; 3) Learning problems such as academic struggles (particularly in reading, writing and/or maths); 4) Executive functioning (difficulty starting or finish projects); 5) Aggression and 6) Poor relations (the child may have difficulty with friendships). Given that there are no identified harms associated with omega-3 supplementation, families may wish to try supplementation on their own accord, bearing in mind that it is advised to trial for at least three months or longer (NIH, 2018). Nonetheless, overall, there is little supportive data on which an evidenced-based decision can be made. In the future, as more trials come to light, there may be better evidence to answer the question of whether omega-3 supplementation is effective or not for reducing the symptoms of ADHD in children and adolescents. It is important for future trials to have an adequate sample size and use the supplements for considerably longer periods, more than three months at least for the full effect to take place (Gillies et al., 2012). This is particularly important because small sample sizes may obscure medium or small treatment effects. A larger sample size should help negate this effect.

Salehi et al. (2016) found no significant difference between omega-3 group compared to the placebo group in the mean scores of CRS ($P = 0.89$). This study also looked at zinc supplementation as a third group of study. Regarding this group, it was concluded that patients who had taken zinc alongside methylphenidate, showed a significant difference in mean scores of CRS during the time of treatment. The supplementation of zinc may be something to observe in future studies

and systematic reviews. Likewise, as Anand and Sachdeva., (2016) and Manor et al. (2012) found that males responded better to the omega-3 supplementation compared to the females. It may be worthwhile to further analyse the response between males and females in future studies.

Two previous systematic reviews found a greater effect with higher dosages (Bloch and Qawasmi, 2011; Chang et al., 2017). Chang et al. (2017) found that only studies with an EPA dosage of 500 mg or greater showed a significant effect. Future studies are advised to be larger and longer whilst incorporating subgroup analysis particularly in gender, age and dosage of supplementation.

The ADHD institute states that rating scales vary in format and scope and recognise the need for multidisciplinary input on a patient's condition and symptomatology (ADHD Institute, 2017b). With these variabilities, rating scales can be chosen to best suit the type of study and available resources. The general consensus seems to agree that diagnosis should include assessment of symptoms with reference to DSM-5 criteria (Taylor et al., 2004; APA, 2013; NICE, 2016). NICE states that a diagnosis shouldn't be made based on a rating scale scores, however rating scales such as CRS are valuable adjuncts when there is doubt about symptoms (NICE, 2016). The ADHD institute mentions 13 different symptom rating scales for children and adolescents including the CPRS-Revised (ADHD Institute, 2017). These scales are recommended to be used for monitoring progression of symptoms and throughout the course of treatment for effectiveness (Taylor et al., 2004). But there seems to be no consensus of the best rating scale. For future research, it may be worthwhile to consider a single or at least fewer variations of rating scales for homogeneity and easier, more reliable data analysis.

Author disclosure

Conflict of interest

None.

4.6. Contributors

Two authors (MA and BJ) independently screened titles and abstracts against the inclusion and exclusion criteria below. Two authors (MA and BJ) independently reviewed the full texts of the remaining articles for inclusion. Any discrepancies were resolved by consensus discussion chaired by a third and fourth author (PW and LP). Two authors independently assessed the risk of bias of the included studies (MA and BJ). Any disagreements were resolved by consensus discussion chaired by a third and fourth author (PW and LP).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2018.12.002.

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