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Tan ML, Ho JJ, Teh KH.
Polyunsaturated fatty acids (PUFAs) for children with specific learning disorders.
Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.: CD009398.
DOI: [10.1002/14651858.CD009398.pub3](https://doi.org/10.1002/14651858.CD009398.pub3).

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[Intervention Review]

Polyunsaturated fatty acids (PUFAs) for children with specific learning disorders

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Editorial group: Cochrane Developmental, Psychosocial and Learning Problems Group.

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 9, 2016.

Citation: Tan ML, Ho JJ, Teh KH. Polyunsaturated fatty acids (PUFAs) for children with specific learning disorders. *Cochrane Database of Systematic Reviews* 2016, Issue 9. Art. No.: CD009398. DOI: [10.1002/14651858.CD009398.pub3](https://doi.org/10.1002/14651858.CD009398.pub3).

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ABSTRACT

Background

About 5% of school children have a specific learning disorder, defined as unexpected failure to acquire adequate abilities in reading, writing or mathematics that is not a result of reduced intellectual ability, inadequate teaching or social deprivation. Of these events, 80% are reading disorders. Polyunsaturated fatty acids (PUFAs), in particular, omega-3 and omega-6 fatty acids, which normally are abundant in the brain and in the retina, are important for learning. Some children with specific learning disorders have been found to be deficient in these PUFAs, and it is argued that supplementation of PUFAs may help these children improve their learning abilities.

Objectives

1. To assess effects on learning outcomes of supplementation of polyunsaturated fatty acids (PUFAs) for children with specific learning disorders.
2. To determine whether adverse effects of supplementation of PUFAs are reported in these children.

Search methods

In November 2015, we searched CENTRAL, Ovid MEDLINE, Embase, PsycINFO, 10 other databases and two trials registers. We also searched the reference lists of relevant articles.

Selection criteria

Randomised controlled trials (RCTs) or quasi-RCTs comparing PUFAs with placebo or no treatment in children younger than 18 years with specific learning disabilities, as diagnosed in accordance with the fifth (or earlier) edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), or the 10th (or earlier) revision of the *International Classification of Diseases* (ICD-10) or equivalent criteria. We included children with coexisting developmental disorders such as attention deficit hyperactivity disorder (ADHD) or autism.

Data collection and analysis

Two review authors (MLT and KHT) independently screened the titles and abstracts of articles identified by the search and eliminated all studies that did not meet the inclusion criteria. We contacted study authors to ask for missing information and clarification, when needed. We used the GRADE approach to assess the quality of evidence.

Main results

Two small studies involving 116 children, mainly boys between 10 and 18 years of age, met the inclusion criteria. One study was conducted in a school setting, the other at a specialised clinic. Both studies used three months of a combination of omega-3 and omega-6 supplements

as the intervention compared with placebo. Although both studies had generally low risk of bias, we judged the risk of reporting bias as unclear in one study, and as high in the other study. In addition, one of the studies was funded by industry and reported active company involvement in the study.

None of the studies reported data on the primary outcomes of reading, writing, spelling and mathematics scores, as assessed by standardised tests.

Evidence of low quality indicates that supplementation of PUFAs did not increase the risk of gastrointestinal disturbances (risk ratio 1.43, 95% confidence interval 0.25 to 8.15; two studies, 116 children). Investigators reported no other adverse effects.

Both studies reported attention deficit hyperactivity disorder (ADHD)-related behaviour outcomes. We were unable to combine the results in a meta-analysis because one study reported findings as a continuous outcome, and the other as a dichotomous outcome. No other secondary outcomes were reported.

We excluded one study because it used a cointervention (carnosine), and five other studies because they did not provide a robust diagnosis of a specific learning disorder. We identified one ongoing study and found three studies awaiting classification.

Authors' conclusions

Evidence is insufficient to permit any conclusions about the effect of PUFAs on the learning abilities of children with specific learning disorders. Well-designed RCTs with clearly defined populations of children with specific learning disorders who have been diagnosed by standardised diagnostic criteria are needed.

PLAIN LANGUAGE SUMMARY

Polyunsaturated fatty acids (PUFAs) for children with specific learning disorders

Review question

We reviewed the evidence on the effects of polyunsaturated fatty acids (PUFAs), compared with placebo or no treatment, on reading, writing or mathematical abilities of children up to 18 years of age who have specific learning disorders.

Background

Children with specific learning disorders are those whose abilities in reading, spelling, writing and mathematics are considerably below what is expected for their age, and whose problems are not a result of lower intelligence, inadequate teaching or social deprivation. A child may have a single disorder, such as a reading disorder, or a combined disorder, such as a reading and mathematics disorder. Children may have other problems too, such as attention deficit hyperactivity disorder (ADHD), along with a specific learning disorder.

Polyunsaturated fatty acids are known to be necessary for normal brain development and function. The best known PUFAs are the omega-3 fatty acids, which include docosahexaenoic acid (commonly known as DHA), but the omega-6 fatty acids are also well known. Polyunsaturated fatty acids must be obtained from foods or supplements, as the human body cannot make them from other types of fat. Because they are needed for normal brain growth and development, PUFAs might help children with specific learning disorders.

Study characteristics

The evidence is current to November 2015.

We found two small studies involving 116 children that met our inclusion criteria. Both studies gave children a combination of omega-3 and omega-6 capsules as the intervention for three months. Most of these studies involved boys between 10 and 18 years of age - one was conducted in a school setting, and the other at a specialised clinic. One of the studies was funded by the company that supplied the omega-3 and omega-6 supplements.

Another study could not be included in this review because investigators added carnosine (an amino acid that is highly concentrated in the brain) to the PUFAs. Carnosine and PUFAs might have similar effects, so it would not be possible to separate the effects of the two ingredients. Review authors excluded five studies because it was not confirmed that a specific learning disorder was diagnosed in these children.

Key results

None of the included studies reported effects of PUFAs on reading, writing, spelling or mathematical abilities of children.

Evidence of low quality (because studies included few participants and showed evidence of bias) suggests that using PUFAs did not increase the risk of minor disturbances to the digestive system. Included studies reported no other types of adverse effects.

Both studies reported on ADHD-related behaviour. However, the format of available data did not allow us to readily combine them or to reach any conclusions. Included studies reported no other secondary outcomes.

Conclusion

Evidence is not sufficient to support or refute the use of PUFAs in children with specific learning disorders.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Summary of findings table

PUFAs vs placebo

Patient or population: children with specific learning disorders
Setting: community
Intervention: PUFAs
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with PUFAs				
Standardised tests of reading, writing, spelling or mathematics skills (overall)	None of the included studies assessed effects on standardised tests of reading, writing, spelling or mathematics skills		Not estimable	-	-	-
Adverse effect (gastrointestinal disturbance) Follow-up: mean 3 months	Study population		RR 1.43 (0.25 to 8.15)	116 (2 RCTs)	⊕⊕⊕⊖ Low ^{a,b}	-
	35 per 1000	50 per 1000 (9 to 286)				

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
 CI: confidence interval; PUFAs: polyunsaturated fatty acids; RCTs: randomised controlled trials; RR: risk ratio

GRADE Working Group grades of evidence

High quality. We are very confident that the true effect lies close to that of the estimate of effect.

Moderate quality. We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of effect but may be substantially different.

Low quality. Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of effect.

Very low quality. We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

^aSmall sample size with few events. Extremely wide CIs.

^bSelective outcome reporting in one study.

BACKGROUND

Description of the condition

Specific learning disorders are a heterogeneous group of disorders that can be broadly defined as unexpected, specific and persistent failure to acquire adequate academic skills despite conventional teaching, adequate intelligence and ample sociocultural opportunities (Lagae 2008). These specific academic skills have been categorised as listening (receptive language), speaking (expressive language), basic reading, reading comprehension, written expression, mathematical calculation and mathematical reasoning (Lyons 1996). In general, about 5% of school children have a specific learning disorder (Lagae 2008), 80% of which are reading disorders (Shaywitz 1998).

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) (APA 2013) and the *International Classification of Diseases, 10th Revision* (ICD-10) (WHO 1992) classify and describe specific learning disorders similarly. They point out two important characteristics. First, learning disorders are developmental disorders that begin in early childhood and do not result from inadequate opportunities for learning nor from the presence of physical abnormalities. Second, researchers have noted a discrepancy between expected achievement for the level of intelligence and actual achievement on individually administered, standardised tests of reading, writing and mathematics.

Specific learning disorders present as a reading disorder (dyslexia), a writing disorder (dysgraphia), a mathematical skills disorder (dyscalculia) or a combination of any of the three. The specific learning disorder that occurs most often as an independent disorder is reading disorder, or dyslexia. Dyslexia affects between 5% and 17.5% of school-aged children (Shaywitz 1998). The next most common disorder is dyscalculia, which affects between 3% and 6.5% of school-aged children (Shalev 2004). Other types of specific learning disorders, such as difficulties with writing or spelling, are usually accompanied by a reading disorder (APA 2000; Dirks 2008). It is not unusual for individuals with a specific learning disorder to have other coexistent neurodevelopmental problems such as attention deficit hyperactivity disorder (ADHD), developmental co-ordination disorder, conduct disorder, oppositional defiant disorder, major depressive disorder and dysthymic disorder (APA 2000). A recent review found that up to 45% of children have a specific learning disorder coexisting with ADHD (DuPaul 2013). DSM-5 provides a more inclusive definition and states that it is no longer necessary to divide specific learning disorders into the categories above (APA 2013).

Researchers who assess learning outcomes or academic achievement in children with specific learning disorders should measure the component skills of reading, spelling and mathematics by administering various achievement tests (Beitchman 1997). Tests of reading should assess accuracy, fluency and comprehension (Beitchman 1997), and tests of mathematics should assess numerical concepts, number facts and arithmetic procedures (Shalev 2004). Writing is sometimes assessed as spelling (Angelelli 2004), but specific tests are also available to assess handwriting. These assessments are best done by means of standardised tests, namely, tests that can be conducted under exact and repeatable conditions and yield scores that can be interpreted uniformly (Domino 2006).

Children with specific learning disorders may have poor academic achievement, as well as problems with self-esteem (Terras 2009) and school failure (Lagae 2008). In the United States in 2006, about 25% of school-aged children and adolescents with specific learning disorders failed to complete school (USDE 2011).

Description of the intervention

Polyunsaturated fatty acids (PUFAs) are essential fatty acids that must be obtained through the diet because the human body is incapable of producing them (Innis 2008). Polyunsaturated fatty acids are classified according to the position of double bonds from the methyl end of the molecule. The main classes of PUFAs studied in children with neurodevelopmental problems are omega-3 and omega-6 fatty acids (Schuchardt 2010). Little is known about the use of other PUFAs, such as omega-9 (oleic acid), in these children.

The omega-3 fatty acids include alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Simopoulos 1991). Among these, DHA is most abundantly found in the human central nervous system and is concentrated in the membrane lipids of cerebral gray matter and in the retina (Innis 2008). Omega-6 fatty acids comprise linoleic acid (LA), gamma-linolenic acid (GLA) and arachidonic acid (AA) (Simopoulos 1991). Common dietary sources of omega-3 fatty acids are oily fish (Whelan 2009), and omega-6 fatty acids are commonly found in grains such as wheat, rice and maize (Simopoulos 1991). Alternative sources of omega-3 fatty acids include marine microbiota and transgenic oilseeds (Sayanova 2011).

Conversion of the omega-3 fatty acid precursor ALA to EPA and DHA requires the same enzyme as is required for conversion of the omega-6 fatty acid precursor LA to GLA and AA. Therefore, an increase in the supply of LA will lead to competitive reduction in production of EPA and DHA (Schuchardt 2010). The importance of this competition is that both AA (omega-6) and EPA (omega-3) are parent derivatives of eicosanoids, but they have different physiological functions (Simopoulos 2002). The ideal omega-6/omega-3 ratio is 1:1 to 4:1, but ratios in the modern diet may be as high as 20:1 (Simopoulos 2002). The ratio of omega-6 to omega-3 fatty acids is thus important, and abnormalities in this ratio are seen in adults with dyslexia (Cyhlarova 2007; Laasonen 2009) and in children with ADHD and learning disabilities (Milte 2011).

Polyunsaturated fatty acid supplements are given as omega-3 fatty acids alone (Richardson 2005), or as omega-3 fatty acids in combination with omega-6 fatty acids (Johnson 2009). Most PUFA supplements contain some vitamin E (usually 0.6 mg of alpha-tocopherol to 1 gram PUFA) to prevent oxidation of PUFAs in tissues (Valk 2000). The duration of PUFA supplementation is an important factor. Kinetic studies show that it takes about four to six months for DHA to achieve a steady state in red blood cell membranes (Arterburn 2006). Therefore, any duration of intervention less than three months is likely to be ineffective.

How the intervention might work

Polyunsaturated fatty acids have two major functions in the central nervous system: maintaining the fluidity of the cell membrane and sustaining the integrity of the myelin sheath (Yehuda 2005). Neuronal cell membrane fluidity is necessary for exchange of neuronal information. Both ALA (omega-3) and LA (omega-6) can directly increase the fluidity index of the cell membrane (Yehuda

2005). Deficiency in omega-3 fatty acids, especially during the early years of development, can result in delayed myelination of neurons and may manifest as learning, motor, visual and auditory abnormalities (Yehuda 2005). In an animal study model, the addition of an omega-6-rich diet reversed the learning disability of omega-3-deficient rats (Ikemoto 2001).

Children with neurodevelopmental disorders, such as dyslexia, dyspraxia, ADHD and autism, have a higher incidence of omega-3 fatty acid deficiency and imbalance of omega-3 and omega-6 fatty acids (Richardson 2000a). The earliest suggestion that children with a specific learning disorder may have an imbalance or deficiency in fatty acids came in a case report in 1985 (McDonald Baker 1985). Subsequently, two studies demonstrated that individuals with dyslexia were more likely to have fatty acid deficiency signs (FADS), which include excessive thirst, frequent urination, dry skin, dry hair, brittle nails, dandruff and follicular keratosis (Richardson 2000b; Stevens 1996). However, to date, no studies have specifically compared omega-3 fatty acid levels in children with a specific learning disorder versus those in the general population. One study measuring cheek cell omega-3 fatty acid levels in children attending mainstream school found no correlation of omega-3 fatty acid level with reading or spelling abilities (Kirby 2010). Another randomised controlled trial (RCT) showed a significant improvement in the reading ability of children with developmental co-ordination disorder whose diet was supplemented with omega-3 fatty acids (Richardson 2005).

The exact mechanism by which PUFAs may work in children with specific learning disorders remains unknown. Most available evidence pertains to reading disorders only. Below, we present three possible explanations of how supplementation of PUFAs may help children with a specific reading disorder.

Improving the visual magnocellular pathway

The visual neural pathway responsible for transmitting signals from the retina to the brain can be divided into large, heavily myelinated cells - the magnocellular pathway - and smaller cells - the parvocellular pathway (Stein 1997). The magnocellular pathway is responsible for visual motion sensitivity, which is strongly related to reading ability (Stein 2000). Dyslexic individuals have been found to have poor motion sensitivity and abnormalities in binocular stability, both of which are linked to the visual magnocellular pathway (Stein 2000). The role of PUFAs in specific reading disorders or dyslexia may be linked to both early development of the magnocellular pathway (Taylor 2000) and its dysfunction (Stein 2000).

Improving working memory

In animal studies, rats raised with a diet deficient in omega-3 fatty acids were found to have poorer reference and working memory (Chung 2008). Children with specific learning disorders - reading or mathematics disorder alone or in combination (Geary 2011; Schuchardt 2008) - also have impairments in their working memory. Therefore, PUFA supplementation could help to improve their learning abilities.

Improving dark adaptation

Vision in low light is regulated mainly by rod cells in the retina, which are rich in omega-3 fatty acids, in particular, DHA (Innis 2008). Poor dark adaptation or reduced scotopic sensitivity has

been associated with dyslexia, although not consistently (Carroll 1994; Greatrex 2000). If such an association is substantiated, this adds to the biological plausibility of why omega-3 might be involved in dyslexia. In a small study of a group of dyslexic individuals, supplementation with DHA-rich fish oil improved their dark adaptation (Stordy 2000).

Safety concerns of PUFA supplementation

Researchers have expressed two major concerns regarding PUFA supplements. The first arises from the sources of PUFAs, especially omega-3 fatty acids, which often are derived from oily fish. Concerns surround consumption of oily fish and toxic environmental contamination from mercury, polychlorinated biphenyls (PCBs) and dioxin (Bays 2007; USFDA 1995). Strict adherence to good manufacturing guidelines is the key factor in the production of omega-3 fatty acid supplements that are free from these contaminants (Bays 2007). The second concern involves adverse effects resulting directly from omega-3 fatty acids, specifically, increased risk of bleeding and reduced immunity (USFDA 2000). High doses of omega-3 fatty acids are thought to impair platelet aggregation and reduce the individual's immune response (Lien 2009). However, a review of preclinical toxicology studies and intervention studies showed that omega-3 fatty acid supplementation is generally safe (Lien 2009). A narrative review on the safety of PUFAs in high-risk individuals taking up to three grams of PUFAs per day did not show increased risk of bleeding (Hamazaki 2014). Other minor adverse effects include hypersensitivity to fish or seafood and gastrointestinal disturbances (Abramowicz 2014; Prester 2016).

Why it is important to do this review

The shift in the burden of health care for children from acute, life-threatening problems to chronic, non-communicable diseases has resulted in increased recognition of specific learning disorders (Liu 2012; Lopez 2006). At present, the mainstay of treatment for a child with a specific learning disorder is educational intervention because learning disorders are viewed essentially as language-based disorders (Handler 2011). To be effective, educational interventions require long-term commitment from the child and his or her family (Alexander 2004). During childhood, intervention is focused on remediation, but in adulthood, intervention is targeted at adjustment and compensation strategies (Lagae 2008). Therefore, it is not surprising that individuals with this disability and their families look for unconventional methods of treatment, such as visual training, optometric exercise, tinted glasses and cerebellar exercises (Lagae 2008). Most of these methods are costly and have not been scientifically proven (NPG 2007).

Nutritional supplementation is a popular alternative treatment because of its ease of administration, relative safety, availability and affordability. Two Cochrane systematic reviews recently examined the use of PUFAs in children with ADHD (Gillies 2012) and autism spectrum disorders (James 2011). Review authors concluded that little or no evidence indicates that PUFAs are beneficial for children with ADHD or autism. This review will add to our understanding of the potential therapeutic role of PUFAs.

OBJECTIVES

1. To assess effects on learning outcomes of supplementation of polyunsaturated fatty acids (PUFAs) for children with specific learning disorders.
2. To determine whether adverse effects of supplementation of PUFAs are reported in these children.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) or quasi-RCTs.

Types of participants

Children under 18 years of age with specific learning disorders, as diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) ([APA 2013](#)) or earlier editions; the *International Classification of Diseases, 10th Revision* (ICD-10) ([WHO 1992](#)) or earlier revisions; or similar criteria. Specific learning disorders may include:

1. reading disorder (developmental dyslexia);
2. mathematics disorder (developmental dyscalculia);
3. writing disorder (dysgraphia); and
4. spelling disorder.

The specific learning disorder may occur in conjunction with other neurodevelopmental disorders such as attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASDs).

Types of interventions

Polyunsaturated fatty acids (PUFAs) compared with placebo or no treatment. Any other nutritional supplements and educational interventions could have been used but must have been given to both intervention and control groups.

('Nutritional supplements' refers to interventions that may directly affect the outcome and does not include antioxidants, such as vitamin E, added to PUFA supplements for the purpose of preventing oxidation.)

Types of outcome measures

Primary outcomes

1. Reading, writing, spelling or mathematics scores measured by standardised tests such as:
 - a. Weschsler Objective Reading Dimensions ([Weschler 1993](#));
 - b. Woodcock Reading Mastery Tests ([Woodcock 2011](#));
 - c. Gray Oral Reading Test ([Bryant 2011](#));
 - d. Wide Range Achievement Test ([Robertson 2006](#));
 - e. Young's Group Mathematics Test ([Young 1996](#));
 - f. Neuropsychological Test Battery for Number Processing and Calculation in Children ([von Aster 2006](#));
 - g. British Ability Scales ([BAS3 2011](#));
 - h. Test of Handwriting Skills - Revised ([Milone 2007](#)); and
 - i. other similar tests, provided they are standardised for the population intended.

2. Reports of adverse effects, including:
 - a. bleeding manifestation such as prolonged bleeding time or haemorrhagic stroke;
 - b. reduction of immunity such as increased incidence of infection; and
 - c. other minor adverse effects such as hypersensitivity or gastrointestinal disturbances.

Secondary outcomes

Only results of validated scales (if used) were to be included.

1. Parent- or teacher-reported outcomes such as academic performance, school dropout or behaviour.
2. Self-reported outcomes such as self-esteem.

Search methods for identification of studies

We ran searches for this review update in October 2014 and November 2015 (see [Appendix 1](#)). When possible, we limited updated searches to the period following the previous search. Review authors conducted searches for the original review ([Tan 2012](#)) in July 2011 and April 2012 (see [Appendix 2](#)), with no restrictions on language or date.

Electronic searches

We searched the electronic databases and trials registers listed below.

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 10) in the Cochrane Library, which includes the Cochrane Developmental, Psychosocial and Learning Problems Group Specialised Register.
2. Ovid MEDLINE (1946 to November week 2 2015).
3. Embase Ovid (1980 to 2015 week 46).
4. PsycINFO Ovid (1967 to November week 2 2015).
5. ERIC ProQuest (Education Resources Information Center; 1966 to current).
6. Science Citation Index - Expanded Web of Science (1970 to 19 November 2015).
7. Social Science Citation Index Web of Science (1970 to 19 November 2015).
8. Conference Proceedings Citation Index - Science Web of Science (1990 to 19 November 2015).
9. Conference Proceedings Citation Index - Social Sciences & Humanities Web of Science (1990 to 19 November 2015).
10. *Cochrane Database of Systematic Reviews* (CDSR; 2015, Issue 11 of 12) in the Cochrane Library.
11. Database of Abstracts of Reviews of Effects (DARE; 2015, Issue 2 of 4) in the Cochrane Library.
12. ZETOC (all available years; zetoc.jisc.ac.uk/wzgw?db=etoc).
13. WorldCat (limited to theses and dissertations; all available years; worldcat.org).
14. Networked Digital Library of Theses and Dissertations (NDLTD; all available years; ndltd.org).
15. ClinicalTrials.gov (all available years; clinicaltrials.gov).
16. World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; all available years; apps.who.int/trialsearch).

Searching other resources

We also searched the references of relevant reports identified by the searches.

Data collection and analysis

Selection of studies

Two review authors (MLT and KHT) independently screened the titles and abstracts of articles identified by the search and eliminated all studies that clearly did not meet the inclusion criteria. We retrieved full-text reports for the remaining papers, and two review authors (MLT and KHT) screened them for inclusion. We resolved all disagreements by discussion and by including a third review author as arbitrator (JJH). Review authors were not blinded to the names of the study authors, nor to institutions or journals of publication. We documented all reasons for excluding studies assessed in full text (see [Characteristics of excluded studies](#)).

Data extraction and management

MLT and KHT independently extracted data from included studies onto a specially designed data extraction form. We extracted data on study setting and methods, participant characteristics, interventions and placebo, and on outcome measures. We contacted study authors by email to seek clarification of data or to request further information about the study, when required. We resolved disagreements by discussion and by including a third review author as arbitrator (JJH).

Assessment of risk of bias in included studies

We used the Cochrane risk of bias tool in assessing risk of bias in included studies ([Higgins 2011a](#)). Two review authors (MLT and KHT) independently assessed each study for risk of bias in sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other sources of bias. For each of these risk of bias elements, we rated studies as having low, unclear or high risk of bias. We resolved disagreements by discussion and by including a third review author as arbitrator (JJH).

Sequence generation

We rated studies as having low risk of bias if the method of sequence generation consisted of random allocating of participants by random number generator or table, toss of a coin, roll of a dice or drawing of lots. We considered studies that used non-random sequence generation, including methods such as alternation or date of birth, as having high risk of bias. When information was insufficient to permit a judgement, we rated the study as having unclear risk of bias.

Allocation concealment

We looked to see whether allocation to the intervention was concealed and could not be predicted by participants or investigator by methods such as central allocation, sequentially numbered identical drug containers or sequentially numbered sealed, opaque envelopes. We rated studies that used these methods of allocation concealment as having low risk of bias. We rated studies as having high risk of bias if investigators used open random allocation or unsealed or non-opaque envelopes. When

information was insufficient to permit a judgement, we rated the study as having unclear risk of bias.

Blinding of participants and personnel

All participants and personnel can be blinded in studies examined for this review. In addition to the identical appearance of pills or capsules of PUFAs, the smell and taste should be similar, as PUFAs derived from fish sources have a distinct taste and smell. This has been shown to be detectable even when provided in capsular form ([Makrides 2010](#)). We rated blinding of participants and personnel as introducing low risk of bias if blinding was described adequately and knowledge of the allocated intervention was prevented throughout the study. We rated the study as having high risk of performance bias if researchers reported no blinding or incomplete blinding. When information was insufficient to permit a judgement, we rated the study as having unclear risk of performance bias.

Blinding of outcome assessments

We first considered if the outcome was likely (such as self-reported or parent-reported outcomes) or not likely (such as results from standardised tests of learning abilities and some teacher-reported outcomes) to be influenced by blinding. We then rated the study as having low risk of detection bias if blinding was described adequately and knowledge of the allocated intervention was prevented throughout the study. We rated the study as having high risk of detection bias if researchers reported no blinding, or incomplete blinding, and the outcome was likely to be influenced by this. When information was insufficient to permit a judgement, we rated the study as having unclear risk of bias.

Incomplete outcome data

For each outcome of included studies, we looked for reports of attrition and exclusion, including reasons, for each intervention group. We rated studies that addressed incomplete outcome data adequately - all intervention groups had similar reasons for missing data (not related to the true outcome) and numbers in all groups were balanced - as having low risk of bias. We rated studies with imbalanced numbers or different reasons for missing data across groups, or that performed 'as treated' analysis with substantial departure of the intervention received from that assigned at randomisation, as having high risk of bias. When information was insufficient to permit a judgement, we rated the study as having unclear risk of bias.

Selective outcome reporting

We looked for selective outcome reporting by determining whether all prespecified outcomes from the study's protocol (if available) were reported or all expected outcomes from the study were reported; in such cases, we rated studies as having low risk of bias. We rated studies that did not report all of their prespecified outcomes or did not report an expected key outcome as having high risk of bias. When information was insufficient to permit a judgement, we rated the study as having unclear risk of bias.

Other sources of bias

We looked at studies to identify other sources of potential bias, such as inappropriate design, premature stopping of the study, extreme baseline imbalance or suspicion of fraud. We rated studies with such biases as having high risk of bias. We rated studies that were

free of these biases as having low risk of bias. If information on which to base our judgement was insufficient, we rated the study as having unclear risk of bias.

Measures of treatment effect

Continuous data

Treatment effects were likely to use a variety of standardised tests. For this review, as only one study provided continuous data (and therefore one test), we presented the mean difference (MD) with 95% confidence interval (CI). Our strategy for continuous data obtained through different tests or scales was set out in our protocol ([Tan 2011](#)) and is presented in [Table 1](#).

Dichotomous data

When dichotomous data were presented, we used the risk ratio (RR) with 95% CI.

Unit of analysis issues

Because we considered that a carry-over effect was likely, we treated the cross-over study included in this review as a parallel-group study and therefore used only data from the first period. We identified no cluster-randomised studies and no studies with multiple intervention groups for inclusion in this review. Our strategy for managing cross-over studies, cluster-randomised studies and studies with multiple intervention groups in future updates of this review was set out in our protocol ([Tan 2011](#)) and is presented in [Table 1](#).

Dealing with missing data

We described details of participant dropout for each of the included studies in 'Risk of bias' tables (beneath the [Characteristics of included studies](#) tables). We contacted the original authors of a particular study to request unreported summary data. We encountered no other missing data issues. Our strategy for dealing with missing data in future updates of this review was set out in our protocol ([Tan 2011](#)) and is presented in [Table 1](#).

Assessment of heterogeneity

Variation across selected studies may be a result of participant factors (e.g. different specific learning disorders) or study factors (e.g. study design, dropout rates, types and combinations of PUFAs used). We assessed heterogeneity across studies by visually inspecting the forest plots for overlapping CIs. We assessed for statistical heterogeneity by using the χ^2 test or the I^2 statistic. The I^2 statistic describes the percentage of variability that is due to heterogeneity rather than to chance. A rough estimate for interpretation of I^2 follows ([Deeks 2011](#)).

1. $I^2 = 0\%$ to 40% : might not be important.
2. $I^2 = 30\%$ to 60% : may represent moderate heterogeneity.
3. $I^2 = 50\%$ to 90% : may represent substantial heterogeneity.
4. $I^2 = 75\%$ to 100% : represents considerable heterogeneity.

The threshold for interpreting the I^2 value can be misleading. Therefore, we determined the importance of the observed I^2 by looking at the magnitude and direction of the effect, as well as the strength of evidence for clinical heterogeneity.

Assessment of reporting biases

We did not have enough studies to assess for reporting bias. Our strategy for assessing reporting biases in future updates of this review was set out in our protocol ([Tan 2011](#)) and is presented in [Table 1](#).

Data synthesis

When we identified two or more homogenous studies for each outcome, we performed a meta-analysis using Review Manager 5 (RevMan 5) ([RevMan 5 2014](#)) and the fixed-effect model. We did not combine for meta-analysis studies that were clinically distinct - different treatment combinations or different measurements of learning abilities - and instead presented a narrative description of study results. This narrative description included the general direction, size, consistency and strength of evidence of effect for each individual study but did not compare the effects of each study and did not present an overall conclusion.

Assessment of the quality of the evidence using the GRADE approach

For this update, we specified how we intended to use the GRADE approach, as outlined in the [GRADE Handbook](#), to assess the quality of the body of evidence related to the following outcomes.

1. Reading, writing, spelling or mathematics scores measured by standardised tests.
2. Reports of adverse effects.

We used [GRADEpro GDT](#) to import data from [RevMan 5 2014](#) when creating 'Summary of findings' tables. We produced a summary of the intervention effect and a measure of quality for each of the above outcomes using the GRADE approach. The GRADE approach considers five factors (study limitations, consistency of effect, imprecision, indirectness and publication bias) in assessing the quality of the body of evidence for each outcome. Evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

We downgraded the quality of evidence for adverse effects to low because of imprecision (small sample size and wide CIs) and study limitations (selective reporting in one study). Reading, writing, spelling and mathematics scores on standardised tests were not reported in the included studies.

Subgroup analysis and investigation of heterogeneity

We did not have enough studies to perform a subgroup analysis. Our strategies for subgroup analysis and investigation of heterogeneity in future updates of this review were set out in our protocol ([Tan 2011](#)) and are presented in [Table 1](#).

Sensitivity analysis

We did not have enough studies to perform a sensitivity analysis. Our strategy for sensitivity analysis in future updates of this review was set out in our protocol ([Tan 2011](#)) and is presented in [Table 1](#).

RESULTS

Description of studies

Results of the search

The original search for the previous version of this review identified 795 unique records (794 from the search of databases and one record from another source) (Tan 2012). This record (Anon 2004) was an unpublished study identified from a narrative review on the effects of PUFAs (Richardson 2004). It was not cited, and attempts to contact the author of the narrative review failed. In addition, one paper could not be obtained even after we attempted to contact the publisher and the study author (Richardson 2000).

Searches for this update yielded 302 unique records, including one record discovered in the reference list of a study (Soerensen 2013). We excluded 272 irrelevant records upon reviewing titles alone, and an additional 20 records after reading the abstracts. We retrieved eight full-text articles, which reported five studies, all of which we excluded with reasons (Milte 2012; Parletta 2013; Perera 2012; Soerensen 2013; Richardson 2012). We found no new studies for inclusion, but we identified one ongoing study (ISRCTN48803273) and one study awaiting classification (ISRCTN54901093), both of which may be relevant to this review.

To date, therefore, this review has two included studies, nine excluded studies, three studies awaiting classification and one ongoing study. See Figure 1.

Figure 1. Study selection flow chart.

Included studies

We have included in this update two studies ([Johnson 2009](#); [Richardson 2002](#)), which we identified in our original search and previously excluded. Neither study reports on the primary outcome for this review, but MECIR (Methodological Expectations of Cochrane Intervention Reviews) guidance ([Chandler 2013](#)) indicates that reported outcomes should not be considered among the inclusion criteria for a review. (See [Differences between protocol and review.](#))

Study population

[Johnson 2009](#) included 75 children, all with a diagnosis of ADHD, out of which 32 (43% of the entire study population: 12 out of 37 in the intervention group and 20 out of 38 in the control group) had a combination reading and writing disorder, which was diagnosed on the basis of criteria from the fourth edition of the DSM (DSM-IV) ([APA 2000](#)). [Richardson 2002](#) included 41 children with a specific reading disorder, which was diagnosed on the basis of "usual diagnostic criteria for specific developmental dyslexia". Although the criteria were not named, the description of the diagnostic criteria used would fit DSM-IV ([APA 2000](#)). These children had higher than normal

scores on the Conners' Parent Rating Scale (CPRS) (Conners 1997) but were given no formal diagnosis of ADHD. Most of the children in both studies were boys from 10 to 18 years of age.

Settings

Both studies were conducted in high-income countries - Richardson 2002 in a school setting, and Johnson 2009 in a clinic setting.

Intervention and comparators

Both studies used a combination of omega-3 and omega-6 supplements given as capsules, although the doses were slightly different; Richardson 2002 used a higher omega-6 dose compared with Johnson 2009. Investigators in both studies used olive oil as the placebo and provided no additional interventions.

Study design

Johnson 2009 was described as a cross-over study. The first period was an RCT, but the second period included no randomisation, and all participants received the intervention treatment. Therefore, we used first period data and treated this as a parallel-group study. Richardson 2002 was a parallel-group study.

Duration of intervention

Both studies gave the intervention for three months.

Outcomes

Neither study reported the results of standardised tests of reading, writing, spelling or mathematics skills.

Both studies reported adverse effects as the number of participants in each group who developed the effects. The main adverse effects reported were dyspepsia, diarrhoea, vomiting and "digestive upset".

Both studies measured behaviour by using validated scales; Richardson 2002 used Conners' Parent Rating Scale - Long (Conners 1997), and Johnson 2009 used the ADHD Rating Scale - Fourth Version (ADHD-RS-IV) (DuPaul 1998) and the Clinical Global Impression (CGI) - Severity scale (CGI-S) (Guy 1976). Johnson 2009 used several other outcome assessment tools but did not report this (see Characteristics of included studies). Richardson 2002 reported mean scores, but Johnson 2009 reported mean change in scores for all participants, irrespective of whether they had a learning disorder. Study authors also reported the number of participants who had a reduction in score of at least 25% on the

ADHD-RS-IV (called 'responders' in the study) and provided data for the subgroup of participants with specific learning disorders.

Both studies measured outcomes at three months.

Funding source

Johnson 2009 was funded by the company that produced the PUFA supplement used in the study. Richardson 2002 was funded by The Dyslexia Trust.

Excluded studies

We excluded nine studies (12 reports) after assessing the full text. One was an open-label study that included no comparison group (Lindmark 2007). One was a review that included reports of unpublished, non-randomised studies (Portwood 2006). One study involved normal children (Soerensen 2013). We excluded five studies because the children were not diagnosed with specific learning disorders (Milte 2012; Parletta 2013; Perera 2012; Richardson 2005; Richardson 2012), and another study because the intervention contained another active ingredient (carnosine) (Kairaluoma 2009). Study authors stated that carnosine had its own potential enhancing effects on cognition, and, although it can be used to provide an antioxidant effect for PUFAs, we judged the addition of carnosine as a cointervention, which was not given to the control group. See Characteristics of excluded studies.

Studies awaiting classification

We could not obtain one abstract even after we attempted to contact the publisher and the study author (Richardson 2000). In addition, in a narrative review on the effects of PUFAs (Richardson 2004), we found a reference to an anonymous, unpublished and uncited study (Anon 2004). It is not clear whether Anon 2004 refers to a completely unpublished study or is a duplicate of Richardson 2000. We also found a record of a completed study (ISRCTN54901093) on the WHO ICTRP. The contact author of this study has since retired, and our attempts to contact the author's institution have yielded no further information about the study.

Ongoing studies

We found one ongoing study (ISRCTN48803273), which was completed in 2015 but has not yet published study results.

Risk of bias in included studies

We present our assessment of risk of bias in included studies in the 'Risk of bias' tables found beneath the Characteristics of included studies tables and summarise this in Figure 2.

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

Allocation

Random sequence generation

[Richardson 2002](#) used a computer-generated sequence, and so we rated this study as having low risk of selection bias. We rated [Johnson 2009](#) as having unclear risk of selection bias, as it was not clear how the randomisation code was generated.

Allocation concealment

As both studies used sequentially numbered bottles for allocation, we rated both as having low risk of selection bias related to allocation concealment.

Blinding

Blinding of participants and personnel

Although both studies described their placebos as identical-looking, investigators did not mention the taste. Polyunsaturated fatty acids were derived from fish in [Johnson 2009](#), but the source is not clear in [Richardson 2002](#). Difficulty in masking the taste led to our judgement that both studies had unclear risk of performance bias.

Blinding of outcome assessment

We judged both studies to be at low risk of detection bias because it is unlikely that taste would have become known to the assessors.

Incomplete outcome data

Although both studies reported a substantial number of dropouts, the numbers and reasons for dropouts were similar in both groups, and in each study, analysis was based only on participants who had complete data. Consequently, we rated both studies as having low risk of attrition bias.

Selective reporting

The expected outcome in both studies was the result of reading tests. However, neither study reported this information. The study protocols of both studies were not available for review authors to

assess whether this outcome was predetermined. Consequently, we rated [Richardson 2002](#) as having unclear risk of reporting bias. [Johnson 2009](#) reported that the study administered other outcome measures (including reading-writing tests) to study participants, but some of these outcomes would be reported in a separate publication. We found no other publication of this study in our search. Therefore, we rated [Johnson 2009](#) as having high risk of reporting bias.

Other potential sources of bias

We detected no other potential sources of bias. Although [Johnson 2009](#) was funded by the manufacturer of the PUFAs, and the company was clearly involved in the randomisation and allocation concealment process, we did not consider funding to be an additional source of bias ([Higgins 2011a](#), section 8.15.15). We assessed independently the specific aspects of methods (sequence generation and allocation concealment) that might have been influenced by vested interests. Thus, we rated both studies as having low risk of other sources of bias.

Effects of interventions

See: [Summary of findings for the main comparison](#) [Summary of findings table](#)

Comparison: PUFAs versus placebo

The summary of effects of the intervention can be found in [Summary of findings for the main comparison](#).

Primary outcomes

Reading, writing, spelling and mathematics scores

No studies reported data on this outcome.

Reporting of adverse effects

The adverse effects reported in both studies were gastrointestinal disturbances. For [Johnson 2009](#), we used data from the first period for all participants, irrespective of the diagnosis, when analysing adverse effects because these effects would not be expected to

be specific only to those with specific learning disorders. There was no difference in the risk of gastrointestinal disturbances when comparing the PUFA group with the placebo group (RR 1.43, 95% CI

0.25 to 8.15; $I^2 = 0\%$; two studies, 116 children; low-quality evidence; see Figure 3). We downgraded the evidence to low quality because of imprecision and study limitations.

Figure 3. Forest plot of comparison: 1 PUFAs versus placebo, outcome: 1.1 Adverse effects (gastrointestinal disturbances).

Secondary outcomes

Parent- or teacher-reported outcomes

Both studies reported the results of ADHD symptom scores. Richardson 2002 used the CPRS - Long (Conners 1997), and Johnson 2009 used the ADHD-RS-IV, Parent Version (DuPaul 1998). Richardson 2002 reported mean ADHD symptom scores and revealed no differences in PUFA and placebo groups after 12 weeks of intervention (MD -5.20, 95% CI -12.26 to 1.86; 29 children). However, Johnson 2009 reported the number of responders (those with > 25% reduction in ADHD scores) for the subgroup with specific learning disorders, revealing more responders in the PUFA group than in the placebo group. We have contacted the authors of Johnson 2009 to request summary data for the subgroup with specific learning disorders but have not yet received a response. Therefore, for this outcome, no meta-analysis was possible because one study reported continuous data, and the other dichotomous data.

Self-reported outcomes

No studies reported data on this outcome.

DISCUSSION

Summary of main results

Two small studies met the eligibility criteria for this review, but neither measured the primary learning outcomes. Therefore, to date, no information is available to guide us in the use of polyunsaturated fatty acids (PUFAs) for children with specific learning disorders.

The little evidence that we have reveals that PUFAs did not increase the risk of developing gastrointestinal disturbance compared with placebo, when taken for three months. Included studies did not report other adverse effects.

Overall completeness and applicability of evidence

We were unable to find any studies that directly assessed the use of PUFAs and their effects on learning outcomes of children with specific learning disorders. The two included studies reported only attention deficit hyperactivity disorder (ADHD)-related behavioural outcomes. Given the extensive overlap of specific learning disorders and ADHD, it is important to know

whether PUFAs have any effects on learning outcomes - the core problem associated with specific learning disorders. Improvement in behaviour does not necessarily result in improvement in reading, spelling, writing or mathematics skills.

When other active elements are added to the PUFA supplement, such as carnosine in Kairaluoma 2009, and no comparative placebos are given, it is not possible to attribute any effects of the intervention to PUFAs. Our search found many studies of PUFAs given to help children with unspecified learning problems or to improve learning in normal children. Our review excluded studies that examined children without a diagnosis of specific learning disorders. Therefore, this review is unable to address the question of whether PUFAs have any effect on poorly performing or normal children in mainstream education.

Quality of the evidence

We used the GRADE approach to assess the quality of the evidence for adverse effects. We downgraded the evidence by two levels to low quality because of small sample size and few events (imprecision), as well as high risk of reporting bias (study limitations), in Johnson 2009.

Potential biases in the review process

For three studies, it remains unclear whether they meet our inclusion criteria (see Characteristics of studies awaiting classification). We were able to retrieve neither the abstract nor the full text for one study that might qualify for inclusion in this review (Richardson 2000). This article is no longer available from the publisher, and our attempts to contact the study author were unsuccessful. Our handsearch of the citations of other studies revealed that this study is often cited together with Richardson 2002; therefore, it is possible that the two citations may apply to the same study. Also, in a review of clinical studies on PUFAs in children with ADHD and dyslexia (Richardson 2004), we found one report of an unpublished randomised controlled trial (RCT) of 102 children eight to 12 years of age who had reading difficulties (Anon 2004). No citation is available for this unpublished report, and we could not contact the author of the review to request further information. We could not find the results of another completed study, retrospectively registered on the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (ISRCTN54901093), which may have met our inclusion

criteria. The contact author has retired, and we could obtain no further information about the study from the contact institution.

For this update, we reviewed our eligibility criteria and made a decision to leave as they were the prespecified strict criteria for the diagnosis of specific learning disorders. We avoided taking a pragmatic approach to the definition of learning disorders because children might not learn for a variety of other reasons, including other nutritional and environmental factors, such as socioeconomic status and access to school, and the presence of other neurodevelopmental disorders, especially ADHD (DuPaul 2013; Hamilton 2006). We believe our strict criteria strengthen this review.

Agreements and disagreements with other studies or reviews

One of the excluded studies that involved children with dyslexia reported that supplementation with PUFAs had a positive effect on speed of reading and decoding fluency (Lindmark 2007). However, this study was small (17 children) and was not randomised, controlled or blinded. Another excluded study, which was an RCT (Kairaluoma 2009), examined effects of PUFAs and carnosine on 61 children with specific learning disorders and found no evidence of benefit for reading, spelling or mathematics outcomes.

No systematic reviews have examined PUFAs and specific learning disorders, but two narrative reviews combined clinical studies on dyslexia, dyspraxia and ADHD (Richardson 2004; Schuchardt 2010). These reviews concluded that PUFAs may be beneficial for common neurodevelopmental conditions such as these.

AUTHORS' CONCLUSIONS

Implications for practice

To date, no RCTs have assessed the use of PUFAs alone for improvement in reading, writing or mathematics skills in children with specific learning disorders. At this time, evidence is insufficient to support or refute the use of PUFAs in children with specific learning disorders.

Implications for research

Adequately powered and well-designed RCTs are needed to study the effects of PUFAs in children with specific learning disorders. The definition of specific learning disorders should be consistent with

any well-published, standardised criteria such as the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) (APA 2013) and the *International Classification of Diseases* (ICD-10) (WHO 1992). As PUFA supplements may contain other active elements, it is important that these elements be given to both intervention and control groups. No optimal dosage of PUFAs can be recommended at the moment (Schuchardt 2010). Studies identified in Gillies 2012 and James 2011 reviews on the use of PUFAs in children with neurodevelopmental problems used doses of PUFAs, given as omega-3 alone or combined with omega-6, ranging from 200 mg/d to 1500 mg/d. Outcome measures should focus on standardised tests for measuring learning abilities, such as reading, writing and mathematics skills, as well as adverse effects. On the basis of evidence required to reach a steady state, the intervention period should be longer than three months (at least four months to six months), although we have no clear evidence to guide us on the duration of the intervention required to bring about a measurable change in learning outcomes.

When secondary outcomes (such as behaviour) are reported, we cannot be sure if they would directly affect learning ability, which is the main concern for children with specific learning disorders. If possible, care should be taken to hide the taste and smell of PUFAs, as the 'fishy' taste could potentially break the blinding process (Makrides 2010).

Further research is also needed to establish the most appropriate age for initiation of PUFAs. This is important because changes in the brain associated with specific learning disorders that might be modifiable by PUFAs may occur in very young children or even during foetal life (Taylor 2000). One of the challenges of conducting studies in younger children is the need for reliable early diagnostic tests. Hence, more studies are needed to develop such tests.

ACKNOWLEDGEMENTS

We would like to thank members of the CDPLPG editorial team - Geraldine Macdonald, Steve Milan, Joanne Wilson and Gemma O'Loughlin - for providing technical support, patience and guidance, as well as the Information Specialist, Margaret Anderson, for helping with the search strategies and running the searches. We would also like to thank the external referees and statistician who helped with this review. Not forgetting the past editorial team - Laura MacDonald and Elaine McKay - who were very much involved in the earlier version of this review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Johnson 2009

Methods	The study authors report that this is a cross-over study using combination omega-3 and omega-6 PUFAs versus placebo. The first period consisted of a randomised controlled study, but in the second period, all participants received the active intervention. Therefore, we considered the first period to be a parallel-group study, and the second period a non-random study. We excluded the second period from the analysis.
Participants	<p>Total number of participants: 75 (subgroup with a reading and writing disorder: 32)</p> <p>Mean age: 12 years (entire group)</p> <p>Male/female ratio: 64:11 (entire group)</p> <p>Setting: Child Neuropsychiatry Clinic, Sweden</p> <p>Inclusion criteria: children between 8 and 18 years of age with DSM-IV-diagnosed ADHD (APA 2000), using ADHD Rating Scale Fourth Version (ADHD-RS-IV (DuPaul 1998)). A subgroup of children with a reading and writing disorder were diagnosed on the basis of DSM-IV criteria.</p>

Johnson 2009 (Continued)

Exclusion criteria: autism (however, diagnosis of autistic symptoms in cases meeting three or more, but not full, symptom criteria for a diagnosis of autistic disorder, Asperger syndrome or any of the other autism spectrum disorders was not an exclusion criterion), psychosis, bipolar disorder, mental retardation, uncontrolled seizure disorder, hyperthyroidism or hypothyroidism, significant other medical conditions, weight < 20 kg, alcohol or drug abuse, the use of any psychoactive drugs or omega-3 preparations in the past 3 months

Interventions	Intervention: 3 capsules daily of omega-3 and omega-6 PUFAs corresponding to a daily dose of 558 mg EPA, 174 mg DHA, 60 mg gamma linoleic acid, and 10.8 mg vitamin E for 3 months Placebo: identical capsules containing olive oil	
Outcomes	Primary outcomes (reported) 1. ADHD-RS-IV, Parent Version (DuPaul 1998) 2. Clinician-rated Clinical Global Impressions - Severity scale (Guy 1976) Secondary outcomes (reported) 1. Number of responders (defined as those with reduction of ≥ 25% in ADHD-RS-IV scores) 2. Adverse effects Unreported outcomes 1. Global Assessment of Functioning Scale (Jones 1995) 2. Swanson, Nolan and Pelham (SNAP) IV (Swanson 1992) 3. Five to Fifteen (FTF) Parent Scale (Kadesjo 2004) 4. Brown's Attention Deficit Disorders Scale for Children and Adolescents (Brown 1996) 5. Brown's Self Report (Brown 2001) 6. Brown's Teacher Scale (Brown 1996) 7. Other "reading-writing tests by special education teacher"	
Notes	Funded by: Equazen UK Ltd (manufacturers of the PUFA supplements). Funders provided the sequence generation and allocation concealment for the study. We contacted the study authors for additional outcome data for the subgroup with a specific learning (reading and writing) disorder, but we have received no response at the time of publication of this review.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The manufacturer of omega 3/6 provided consecutively numbered identical bottles of which 50% contained active treatment and 50% placebo in random order according to a code list that was not accessible to the investigators." Investigators do not describe how the "code list" was generated.
Allocation concealment (selection bias)	Low risk	"The manufacturer of omega 3/6 provided consecutively numbered identical bottles of which 50% contained active treatment and 50% placebo in random order according to a code list that was not accessible to the investigators."
Blinding of participants and personnel (performance bias) Parent reported outcome	Unclear risk	"Identical capsules" were used as placebo, but it was not mentioned if the taste was similar.

Johnson 2009 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Identical capsules" were used as placebo. The "code list" was not accessible to the investigators.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Although researchers reported a larger number of dropouts in the placebo group (8 out of 38 vs 3 out of 37 in the intervention group), the reasons for dropping out were similar and were unrelated to the intervention - majority resulting from poor motivation and problems swallowing the capsules. Study authors did not mention intention-to-treat and excluded from the analysis all participants who dropped out.
Selective reporting (reporting bias)	High risk	Investigators stated in the methods of this study that children underwent several neuropsychological tests and reading-writing tests at the first and third visits. Other self-reported scales on behaviour were administered as well but were not reported. It was stated that results of some of the other examinations and instruments would be reported in another publication. We found no other publication of this trial during our searches. The study protocol was not available.
Other bias	Low risk	No other bias was detected.

Richardson 2002

Methods	Randomised controlled parallel-group study	
Participants	Total number of participants: 41 Mean age: 10.25 years Male/female ratio: 35:6 Setting: special education school, Northern Ireland Inclusion criteria: children between 8 and 12 years of age with a specific reading disorder (diagnosed on the basis of 'usual diagnostic criteria for specific developmental dyslexia') Exclusion criteria: use of fatty acid supplements within the previous 6 months, regular consumption of oily fish more than twice a week, history of any other neurological or major psychiatric disorder or other significant medical problems	
Interventions	Intervention: 8 capsules of omega-3 and omega-6 per day, corresponding to a daily dose of EPA 186 mg, DHA 480 mg, g-linolenic acid 96 mg, vitamin E (as DL-d tocopherol) 60 IU, cis-linoleic acid 864 mg, AA 42 mg and thyme oil 8 mg Placebo: olive oil	
Outcomes	Behaviour: Conners' Parent Rating Scale - Long	
Notes	Funded by: Dyslexia Research Trust	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated code was used.

Richardson 2002 (Continued)

Allocation concealment (selection bias)	Low risk	"Coded treatments were allocated sequentially to subjects in strict order of their registration for the trial. There was no direct contact at any stage between the generator and executors of the assignment."
Blinding of participants and personnel (performance bias) Parent reported outcome	Unclear risk	Identical-looking placebos were used. However, investigators did not mention if the taste was similar.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Identical-looking placebos were used. Treatment codes were kept by a third party not involved with the trial, and envelopes containing the treatment code were returned unbroken by the trial supervisor.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Both groups had similar numbers of dropouts (PUFAs = 5; placebo = 4), with similar reasons for withdrawing (most often, lack of interest). One from each group dropped out because of the adverse effect of gastrointestinal disturbance. Analysis included only participants with complete data.
Selective reporting (reporting bias)	Unclear risk	Study protocol was not available. At baseline, reading achievements (British Ability Scales (BAS), Word Reading) were included as screening criteria. As reading achievement is an expected outcome in this study, it is not known whether this outcome was prespecified in the protocol and was not reported.
Other bias	Low risk	No other bias was detected.

ADHD: attention deficit hyperactivity disorder.

DHA: docosahexaenoic acid.

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

EPA: eicosapentaenoic acid.

PUFAs: polyunsaturated fatty acids.

Characteristics of excluded studies [author-defined order]

Study	Reason for exclusion
Lindmark 2007	We excluded this study because it was not a randomised controlled trial, and it included no comparison group.
Richardson 2005	We excluded this study because it included only children with a developmental co-ordination disorder. Investigators made no attempt to separate out a subgroup with specific learning disorders. Although changes in reading and spelling abilities were assessed as an outcome, results cannot be applied to children with specific learning disorders.
Portwood 2006	We excluded this study because it is a review of the results of Richardson 2005 . Review authors reported results of 2 other unpublished non-randomised controlled studies, in which 1 study population did not have learning difficulties.
Kairaluoma 2009	In addition to PUFAs, carnosine was given as a cointervention and was not given to the control group. Study authors stated that carnosine had its own potential enhancing effects on cognition. Therefore, any effects of interventions cannot be attributed to PUFAs alone.
Milte 2012	This is a 3-way cross-over study. Two publications from separate times of the study were available. The study population included children with ADHD and parent-reported learning difficulties who had not been diagnosed with specific learning disorders. All 3 groups were given PUFAs in the form of EPA and DHA (omega-3) and LA (omega-6).

Study	Reason for exclusion
Parletta 2013	We excluded this study because the study population was not diagnosed with specific learning difficulties. Children were recruited from a school where most children had poorer academic performance (indigenous children) compared with a normal population. However, reasons for their learning difficulties were not reported and may have been related to background and culture, rather than to a higher incidence of specific learning disorders.
Perera 2012	Study population consisted of children with ADHD and poor academic performance. We excluded this study because the study population was not given a diagnosis of a specific learning disorder.
Soerensen 2013	Three published reports described this cluster-randomised study. We excluded the study because the study population consisted of normal children from a mainstream school. The intervention was not a specific PUFA supplement, but rather a meal with fish added twice a week.
Richardson 2012	The study population was recruited from a mainstream school and had reading scores < 33rd centile. Although much care was taken to exclude children who had other reasons for poor reading, such as visual/hearing impairment, low intellectual capacity and possible socioeconomic influence, study authors did not describe any attempt to formally diagnose a specific learning disorder on the basis of recognised criteria. Thus, we excluded the study.

ADHD: attention deficit hyperactivity disorder.

DHA: docosahexaenoic acid.

EPA: eicosapentaenoic acid.

LA: linoleic acid.

PUFAs: polyunsaturated fatty acids.

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

[Anon 2004](#)

Methods	From a review by Richardson 2004 : "The second RCT of fatty acid treatment in dyslexia involved 102 children aged 8 - 12 years referred to a research clinic for investigation of their reading difficulties. Results have not yet been fully analysed or submitted for peer-reviewed publication, hence only an outline can be given here. The treatments used were the same as for the pilot study just described, but the main aim of this study was to determine the effects of fatty acid treatment on reading progress, so children were treated in parallel groups for a full six months in order to allow time for any changes in their reading achievement to become apparent. The primary outcome measure was changes in reading age as assessed via standardised tests of single word reading. Blood samples were collected from a subset of participants, but unexpected changes at collaborating laboratories have unfortunately precluded proper analysis of these."
Participants	
Interventions	
Outcomes	
Notes	No reference was given, and we received no reply when we contacted the review author for additional details about this study.

[ISRCTN54901093](#)

Methods	Prospective randomised double-blinded placebo-controlled group study
---------	--

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ISRCTN54901093 (Continued)

Participants	Children 11 to 16 years of age who were attending Cambridge Park Special School in Grimsby, United Kingdom
Interventions	Concentrated fish oil, 500 mg daily
Outcomes	Young's Reading Test Young's Math Tests Schonell Group Spelling Test Nelson Insight Self-Esteem Test
Notes	This study was completed in 2007 and had a retrospective registration on WHO ICTRP in 2012. The contact author has since retired, and our correspondence with the author's institution yielded no further information about this study (Tan 2015 [pers comm]). Contact Address: Dr S Kumar, Diana Princess of Wales Hospital, Scartho Road, Grimsby DN33 2BA UK Tel: +44 (0) 1472 874111

Richardson 2000

Methods	
Participants	
Interventions	
Outcomes	
Notes	Details of the study are not available, and we could not obtain the abstract/full text even after we made several attempts to contact the study author. The journal is no longer available.

ISRCTN: International Standard Registered Clinical/sOCial sTudy Number.

LA: linoleic acid.

WHO ICTRP: World Health Organization International Clinical Trials Registry Platform.

Characteristics of ongoing studies [ordered by study ID]

ISRCTN48803273

Trial name or title	The DHA (docosahexaenoic acid) Oxford Learning and Behaviour Study (DOLAB II): a randomised double-blind controlled study measuring effects of DHA on children's reading ability, cognition and behaviour
Methods	Randomised double-blinded placebo-controlled trial (fixed dose, parallel groups)
Participants	Normal children 7 to 9 years of age in mainstream state schools who are underperforming in reading according to nationally standardised tests
Interventions	3 × 500 mg capsules per day, each capsule providing 200 mg of DHA omega-3 as a triglyceride
Outcomes	Children's age-standardised scores for learning (reading performance and working memory) and behaviour (parent ratings of ADHD-type symptoms), assessed both at baseline and post intervention. The following validated measures will be used: 1. British Ability Scale (BAS II): Word Reading

Polyunsaturated fatty acids (PUFAs) for children with specific learning disorders (Review)

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ISRCTN48803273 (Continued)

2. British Ability Scale (BAS II): Recall of Digits
3. Conners' Parent Rating Scale - Long (CPRS-L)
4. British Ability Scale: Third Edition (BAS3): Word Reading

Starting date	January 2013
Contact information	paul.montgomery@spi.ox.ac.uk
Notes	Study was completed in July 2015. We have found no publications. (See ISRCTN48803273 , last accessed 26 May 2016.)

ISRCTN: International Standard Registered Clinical/sociAl sTudy Number.

DATA AND ANALYSES

Comparison 1. PUFAs versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse effects (gastrointestinal disturbances)	2	116	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.25, 8.15]
2 Behavioural effects (ADHD symptoms score)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 PUFAs versus placebo, Outcome 1 Adverse effects (gastrointestinal disturbances).

Analysis 1.2. Comparison 1 PUFAs versus placebo, Outcome 2 Behavioural effects (ADHD symptoms score).

Study or subgroup	PUFAs		Placebo		Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)		
Richardson 2002	15	60.5 (9.2)	14	65.7 (10.2)		-5.2[-12.26,1.86]

Favours PUFAs -10 -5 0 5 10 Favours placebo

ADDITIONAL TABLES

Table 1. Additional methods

Measures of treatment effect
<p>Continuous data</p> <p>Treatment effects are likely to require a variety of standardised tests. If we encounter the use of different tests for the same outcome, and we judge these to be similar enough, we will calculate the standardised mean difference (SMD) and the 95% confidence interval (CI) for each.</p>
Unit of analysis Issues
<p>Cross-over studies</p> <p>In the analysis of studies with cross-over design, we will first consider the possibility of carry-over effect, whether only first period data are available, if any analysis is incorrect and if results are comparable with those of parallel-group studies. We will use the methods suggested in the <i>Cochrane Handbook for Systematic Reviews of Interventions</i> when analysing and incorporating the trials for meta-analysis (Higgins 2011b, section 16.4). As a carry-over effect is likely, given the persistence of PUFAs in tissues (Katan 1997), when data are available for the first period, we will use these in the analyses of learning and behavioural outcomes. However, as adverse effects are readily reversible outcomes, we could use data from both phases.</p> <p>Cluster-randomised studies</p> <p>We do not anticipate finding any cluster-randomised trials for this review. However, if we do find them, we will analyse them in the unit to which they were randomised and we will adjust the effective sample size using an intracluster correlation coefficient (ICC), which we will obtain from the studies themselves, if given, or will estimate from similar studies. If we use ICCs from other sources, we will report this and will conduct sensitivity analyses to investigate the effects of variation in the ICC, as suggested in the <i>Cochrane Handbook for Systematic Reviews of Interventions</i> (Higgins 2011b, section 16.3).</p> <p>Studies with multiple intervention groups</p> <p>For studies with more than 2 intervention groups, we will combine the intervention (if they are similar, e.g. different dose of PUFAs or different combination of PUFAs), and control groups to create a single pair-wise comparison. If any of the intervention groups is completely different (e.g. visual exercises, music therapy), we will exclude that particular intervention group from the analysis.</p>
Dealing with missing data
<p>If more studies are included in the future, we will explore by sensitivity analysis the impact of including studies with high levels of missing data in the overall assessment of treatment effect. We will exclude from the analysis studies with missing data that have a high impact on the final results. For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis (i.e. we will attempt to include in the analyses all participants randomised to each group). Missing standard deviations (SDs) may be imputed according to the methods provided in the <i>Cochrane Handbook for Systematic Reviews of Interventions</i> (Higgins 2011b).</p>
Assessment of reporting biases
<p>If we identify 10 or more studies, we will use funnel plots to assess the relationships of treatment effect size and standard error. Asymmetry in the funnel plot may be a result of reporting bias, but could also be a true reflection of heterogeneity among intervention effects. We will further examine clinical heterogeneity of the studies as a possible explanation. We will compare results obtained from published studies and results from other sources (e.g. correspondence) to detect publication bias.</p>
Subgroup analysis and investigation of heterogeneity
<p>We intend to perform subgroup analyses for the primary outcome only. We will investigate the following subgroups.</p> <ol style="list-style-type: none"> 1. Different combinations of PUFAs (e.g. using only DHA or DHA combined with EPA or ALA). 2. Type of specific learning disorder (e.g. specific reading disorder vs specific mathematical disorder). 3. Presence of comorbidity of ADHD or autism. 4. Age when supplementation is given (e.g. preschool or early primary school vs late primary school or secondary school).

Table 1. Additional methods (Continued)

5. Duration of intervention (< 3 months, 3 to 6 months, > 6 months).

Sensitivity analysis

If we identify enough studies, we will perform a sensitivity analysis to assess how much the quality of the studies affects meta-analysis results. We will conduct sensitivity analyses to find out if excluding studies with high risk of bias (as assessed by using the Cochrane tool for assessing risk of bias) has an impact on the final results. These will include studies with cross-over design, inadequate sequence allocation and concealment, missing data or use of any imputed values.

ADHD: attention deficit hyperactivity disorder.

ALA: alpha-lipoic acid.

DHA: docosahexaenoic acid.

EPA: eicosapentaenoic acid.

PUFAs: polyunsaturated fatty acids.

APPENDICES

Appendix 1. Search strategies 2012 onwards

Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, which includes the Cochrane Developmental, Psychosocial and Learning Problems Group Specialised Register

2014, issue 9. Searched 14 October 2014. Limited to publication year=2012-2014 [4 records]

2015, issue 10. Searched 19 November 2015. Limited to publication year=2014-2015 [1 record]

#1 MeSH descriptor Fatty Acids, this term only

#2 MeSH descriptor Fatty Acids, Omega-3 explode tree 1

#3 MeSH descriptor Fatty Acids, Omega-6, this term only

#4 (omega NEXT 3 or omega NEXT 6)

#5 ((eicosa* or icoso* or docosahex* or alpha-linol*) NEXT acid*)

#6 poly NEXT unsaturat* NEXT fatty NEXT acid*

#7 polyunsaturat* NEXT fatty NEXT acid*

#8 (fatty NEXT acid*) NEAR/3 (n NEXT 3 or n NEXT 6)

#9 essential NEXT fatty NEXT acid*

#10 PUFA*

#11 MeSH descriptor Fish Oils, this term only

#12 MeSH descriptor Linseed Oil, this term only

#13 (EFA or EPA or MaxEPA or DHA or ALA)

#14 (oil* NEAR/3 (fish* or flax or linseed))

#15 (#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)

#16 MeSH descriptor Learning Disorders, this term only

#17 MeSH descriptor Dyslexia, this term only

#18 (learn* NEAR/3 (difficult* or disorder* or disabilit* or deficien* or problem*))

#19 (academic skill* NEAR/3 disorder*)

#20 (scholastic skill* NEAR/3 disorder*)

#21 dyslexi*

#22 (reading* NEAR/3 (abilit* or accurac* or comprehension or disorder* or disabilit* or difficult* or deficien* or fluenc* or problem* or speed*))

#23 ((word or text) NEXT blind*)

#24 MeSH descriptor Mathematics, this term only

#25 dyscalcul*

#26 ((math* or arithmetic*) near/3 (abilit* or disorder* or disabilit* or problem* or difficult* or deficien* or fluenc* or skill*))

#27 MeSH descriptor Writing, this term only

#28 MeSH descriptor Agraphia, this term only

#29 agraphia* or dysgraphia*

#30 (spell* near/3 (abilit* or disorder or disabilit* or problem* or difficult* or deficien* or fluenc* or skill*))

#31 (writing NEAR/3 (abilit* or disorder or disabilit* or problem* or difficult* or deficien* or fluenc* or skill*))

#32 written NEXT expression NEXT disorder*

#33 (#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32)

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#34 (#15 AND #33)

Ovid MEDLINE

1946 to October Week 1 2014. Limited to date added=20120401-20141014 [6 records]

1946 to November Week 2 2015. Limited to date added=20141001-20151112 [No records]

1 Fatty Acids/
2 fatty acids, unsaturated/
3 exp fatty acids, omega-3/
4 exp fatty acids, omega-6/
5 alpha-linolenic acid/
6 docosahexaenoic acids/
7 eicosapentaenoic acid/
8 (omega 3 or omega 6).tw.
9 ((eicosa\$ or icos\$ or docosahex\$ or alpha-linol\$) adj acid\$).tw.
10 polyunsaturat\$ fatty acid\$.tw.
11 poly-unsaturat\$ fatty acid\$.tw.
12 (fatty acid\$ adj3 (n-3 or n-6)).tw.
13 essential fatty acid\$.tw.
14 PUFA.tw.
15 Fish Oils/
16 linseed oil/
17 (EFA or EPA or MaxEPA or DHA or ALA).tw.
18 (oil\$ adj3 (fish\$ or flax or linseed)).tw.
19 or/1-18
20 Learning Disorders/
21 (learn\$ adj3 (difficult\$ or disorder\$ or disabilit\$ or deficien\$ or problem\$)).tw.
22 (academic skill\$ adj3 disorder\$).tw.
23 (scholastic skill\$ adj3 disorder\$).tw.
24 Dyslexia/
25 dyslexi\$.tw.
26 (reading\$ adj3 (abilit\$ or accurac\$ or comprehension or disorder\$ or disabilit\$ or difficult\$ or deficien\$ or fluenc\$ or problem\$ or speed\$)).tw.
27 ((word or text) adj blind\$).tw.
28 Mathematics/
29 dyscalcul\$.tw.
30 ((math\$ or arithmetic\$) adj3 (abilit\$ or disorder\$ or disabilit\$ or problem\$ or difficult\$ or deficien\$ or fluenc\$ or skill\$)).tw.
31 Writing/
32 Agraphia/
33 (agraphia\$ or dysgraphia\$).tw.
34 (spell\$ adj3 (abilit\$ or disorder\$ or disabilit\$ or problem\$ or difficult\$ or deficien\$ or fluenc\$ or skill\$)).tw.
35 (writing adj3 (abilit\$ or disorder\$ or disabilit\$ or problem\$ or difficult\$ or deficien\$ or fluenc\$ or skill\$)).tw.
36 written expression disorder\$.tw.
37 or/20-36
38 19 and 37
39 randomized controlled trial.pt.
40 controlled clinical trial.pt.
41 randomi#ed.ab.
42 placebo\$.ab.
43 drug therapy.fs.
44 randomly.ab.
45 trial.ab.
46 groups.ab.
47 or/39-46
48 exp animals/ not humans.sh.
49 47 not 48
50 38 and 49

Embase Ovid

1980 to 2014 Week 41. Searched 14 October 2014. Limited to publication year= 2012-current [16 records]

1980 to 2015 Week 46. Searched 19 November 2015. Limited to EM=201441-201546 [5 records]

1 fatty acid/
 2 omega 3 fatty acid/ or omega 6 fatty acid/
 3 docosahexaenoic acid/
 4 linolenic acid/
 5 icosapentaenoic acid/
 6 (omega 3 or omega 6).tw.
 7 ((eicosa\$ or icosas\$ or docosahex\$ or alpha-linol\$) adj acid\$).tw.
 8 polyunsaturat\$ fatty acid\$.tw.
 9 poly-unsaturat\$ fatty acid\$.tw.
 10 (fatty acid\$ adj3 n-3).tw.
 11 essential fatty acid\$.tw.
 12 PUFA.tw.
 13 Fish Oils/
 14 linseed oil/
 15 (EFA or EPA or MaxEPA or DHA or ALA).tw.
 16 (oil\$ adj3 (fish\$ or flax or linseed)).tw.
 17 or/1-16
 18 learning disorder/
 19 (learn\$ adj3 (difficult\$ or disorder\$ or disabilit\$ or deficien\$ or problem\$)).tw.
 20 (academic skill\$ adj3 disorder\$).tw.
 21 (scholastic skill\$ adj3 disorder\$).tw.
 22 dyslexia/
 23 dyslexi\$.tw.
 24 (reading\$ adj3 (abilit\$ or accurac\$ or comprehension or disorder\$ or disabilit\$ or difficult\$ or deficien\$ or fluenc\$ or problem\$ or speed\$)).tw.
 25 ((word or text) adj blind\$).tw.
 26 Mathematics/
 27 dyscalcul\$.tw.
 28 ((math\$ or arithmetic\$) adj3 (abilit\$ or disorder\$ or disabilit\$ or problem\$ or difficult\$ or deficien\$ or fluenc\$ or skill\$)).tw.
 29 Writing/
 30 Agraphia/
 31 (agraphia\$ or dysgraphia\$).tw.
 32 (spell\$ adj3 (abilit\$ or disorder\$ or disabilit\$ or problem\$ or difficult\$ or deficien\$ or fluenc\$ or skill\$)).tw.
 33 (writing adj3 (abilit\$ or disorder\$ or disabilit\$ or problem\$ or difficult\$ or deficien\$ or fluenc\$ or skill\$)).tw.
 34 written expression disorder\$.tw.
 35 or/18-34
 36 exp Clinical trial/
 37 Randomized controlled trial/
 38 Randomization/
 39 Single blind procedure/
 40 Double blind procedure/
 41 Crossover procedure/
 42 Placebo/
 43 Randomi#ed.tw.
 44 RCT.tw.
 45 (random\$ adj3 (allocat\$ or assign\$)).tw.
 46 randomly.ab.
 47 groups.ab.
 48 trial.ab.
 49 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).tw.
 50 Placebo\$.tw.
 51 Prospective study/
 52 (crossover or cross-over).tw.
 53 prospective.tw.
 54 or/36-53
 55 17 and 35 and 54

PsycINFO Ovid

1967 to October Week 2 2014. Searched 14 October 2014. Limited to UP=20120401-20141014 [10 records]

1967 to November Week 2 2015. Searched 19 November 2015. Limited to UP=20141010-20151109 [3 records]

1 Fatty Acids/

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2 (omega 3 or omega 6).tw.
3 (eicosa\$ or icosahex\$ or docosahex\$ or alpha-linol\$).tw.
4 fatty acid\$.tw.
5 (PUFA or PUFAs).tw.
6 (EFA or EPA or MaxEPA or DHA or ALA).tw.
7 (fish\$ oil\$ or flax oil\$ or linseed oil\$).tw.
8 Learning Disabilities/ or Dyslexia/ or Reading/
9 (learn\$ adj3 (difficult\$ or disorder\$ or disabilit\$ or deficien\$ or problem\$)).tw.
10 (academic skill\$ adj3 disorder\$).tw.
11 (scholastic skill\$ adj3 disorder\$).tw.
12 dyslexi\$.tw.
13 (reading\$ adj3 (abilit\$ or accurac\$ or comprehension or disorder\$ or disabilit\$ or difficult\$ or deficien\$ or fluenc\$ or problem\$ or speed\$)).tw.
14 ((word or text) adj blind\$).tw.
15 Mathematics/
16 dyscalcul\$.tw.
17 ((math\$ or arithmetic\$) adj3 (abilit\$ or disorder\$ or disabilit\$ or problem\$ or difficult\$ or deficien\$ or fluenc\$ or skill\$)).tw.
18 Spelling/ or Handwriting/
19 written expression disorder\$.tw.
20 (agraphia\$ or dysgraphia\$).tw.
21 (spell\$ adj3 (abilit\$ or disorder\$ or disabilit\$ or problem\$ or difficult\$ or deficien\$ or fluenc\$ or skill\$)).tw.
22 (writing adj3 (abilit\$ or disorder\$ or disabilit\$ or problem\$ or difficult\$ or deficien\$ or fluenc\$ or skill\$)).tw.
23 or/1-7
24 or/8-22
25 23 and 24

ERIC EBSCO (Education Resources Information Center)

1966 to current. Searched 10 October 2014. Limited to publication year 2012 to 2014 [10 records]

1966 to current. Searched 19 November 2015. Limited to publication year 2014 to 2015 [18 records]

S23 S10 AND S22
S22 S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21
S21 (learn* N3 (difficult* OR disorder* OR disabilit* OR deficien* OR problem*))
S20 (reading* N3 (abilit* OR accurac* OR comprehension OR disorder* OR disabilit* OR difficult* OR deficien* OR fluenc* OR problem* OR speed*))
S19 ((math* OR arithmetic*) N3 (abilit* OR disorder* OR disabilit* OR problem* OR difficult* OR deficien* OR fluenc* OR skill*))
S18 (spell* N3 (abilit* OR disorder OR disabilit* OR problem* OR difficult* OR deficien* OR fluenc* OR skill*))
S17 (writing N3 (abilit* OR disorder OR disabilit* OR problem* OR difficult* OR deficien* OR fluenc* OR skill*))
S16 ("academic skill* disorder*" OR "scholastic skill* disorder*" OR "written expression disorder*")
S15 (dyslexi* OR dyscalcul* OR agraphia* OR dysgraphia*)
S14 DE "Reading Difficulties"
S13 DE "Learning Disabilities" OR DE "Learning Problems"
S12 DE "Writing Difficulties"
S11 DE "Dyslexia"
S10 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9
S9 (oil* N3 (fish* OR linseed* OR flax*))
S8 EFA OR EPA OR MaxEPA OR DHA OR ALA
S7 alpha-linol* OR alpha linol*
S6 eicosa* or icosahex* OR docosahex*
S5 PUFA OR PUFAS
S4 FATTY ACID*
S3 fatty acid*
S2 OMEGA 6
S1 OMEGA 3

Science Citation Index - Expanded Web of Science (SCI)

1970 to 10 October 2014. Searched 14 October 2014. Limited to publication year 2012 to 2014 [22 records]

1970 to 19 November 2015. Seached 20 November 2015. Limited to publication year 2014 to 2015 [5 records]

19 #18 AND #17

DocType=All document types; Language=All languages;

#18 TS=(random* or control* or trial* or groups* or effectiveness or evaluation or placebo*)

Polynsaturated fatty acids (PUFAs) for children with specific learning disorders (Review)

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DocType=All document types; Language=All languages;
#17 #16 AND #7
DocType=All document types; Language=All languages;
#16 #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8
DocType=All document types; Language=All languages;
#15 TS=(written expression disorder*)
DocType=All document types; Language=All languages;
#14 TS=(writing* abilit* or writing* accurac* or writing* comprehension or writing* disorder* or writing* disabilit* or writing* difficult* or writing* deficien* or writing* fluenc* or writing* problem* or writing* speed*)
DocType=All document types; Language=All languages;
#13 TS=(spell* abilit* or spell* accurac* or spell* comprehension or spell* disorder* or spell* disabilit* or spell* difficult* or spell* deficien* or spell* fluenc* or spell* problem* or spell* speed*)
DocType=All document types; Language=All languages;
#12 TS= (math* abilit* or math* accurac* or math* comprehension or math* disorder* or math* disabilit* or math* difficult* or math* deficien* or math* fluenc* or math* problem* or math* speed*)
DocType=All document types; Language=All languages;
#11 TS=(reading abilit* or reading accurac* or reading comprehension or reading disorder* or reading disabilit* or reading difficult* or reading deficien* or reading fluenc* or reading problem* or reading speed*)
DocType=All document types; Language=All languages;
#10 TS= (dyslexi* or dyscalcul* or agraphia* or dysgraphia*)
DocType=All document types; Language=All languages;
#9 TS= (academic skill* disorder* or scholastic skill* disorder*)
DocType=All document types; Language=All languages;
#8 Ts=(learn* difficult* or learn* disorder* or learn* disabilit* or learn* deficien* or learn* problem*)
DocType=All document types; Language=All languages;
#7 #6 OR #5 OR #4 OR #3 OR #2 OR #1
DocType=All document types; Language=All languages;
#6 TS=(EFA or EPA or MaxEPA or DHA or ALA)
DocType=All document types; Language=All languages;
#5 TS= (oil* SAME (fish* or flax or linseed))
DocType=All document types; Language=All languages;
#4 TS=(PUFA*)
DocType=All document types; Language=All languages;
#3 TS= ((eicosa* or icos* or docosa* or alpha-linol*) SAME acid*)
DocType=All document types; Language=All languages;
#2 TS=(omega 3 or omega 6)
DocType=All document types; Language=All languages;
#1 TS=(fatty acid*)
DocType=All document types; Language=All languages;

Social Sciences Citation Index Web of Science (SSCI)

1970 to 10 October 2014. Searched 14 October 2014. Limited to publication year 2012 to 2014 [73 records]
1970 to 19 November 2015. Searched 19 November 2015. Limited to publication year 2014 to 2015 [5 records]

19 #18 AND #17
DocType=All document types; Language=All languages;
#18 TS=(random* or control* or trial* or groups* or effectiveness or evaluation or placebo*)
DocType=All document types; Language=All languages;
#17 #16 AND #7
DocType=All document types; Language=All languages;
#16 #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8
DocType=All document types; Language=All languages;
#15 TS=(written expression disorder*)
DocType=All document types; Language=All languages;
#14 TS=(writing* abilit* or writing* accurac* or writing* comprehension or writing* disorder* or writing* disabilit* or writing* difficult* or writing* deficien* or writing* fluenc* or writing* problem* or writing* speed*)
DocType=All document types; Language=All languages;
#13 TS=(spell* abilit* or spell* accurac* or spell* comprehension or spell* disorder* or spell* disabilit* or spell* difficult* or spell* deficien* or spell* fluenc* or spell* problem* or spell* speed*)
DocType=All document types; Language=All languages;
#12 TS= (math* abilit* or math* accurac* or math* comprehension or math* disorder* or math* disabilit* or math* difficult* or math* deficien* or math* fluenc* or math* problem* or math* speed*)

Polyunsaturated fatty acids (PUFAs) for children with specific learning disorders (Review)

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DocType=All document types; Language=All languages;
#11 TS=(reading abilit* or reading accurac* or reading comprehension or reading disorder* or reading disabilit* or reading difficult* or reading deficient* or reading fluenc* or reading problem* or reading speed*)
DocType=All document types; Language=All languages;
#10 TS= (dyslexi* or dyscalcul* or agraphia* or dysgraphia*)
DocType=All document types; Language=All languages;
#9 TS= (academic skill* disorder* or scholastic skill* disorder*)
DocType=All document types; Language=All languages;
#8 Ts=(learn* difficult* or learn* disorder* or learn* disabilit* or learn* deficient* or learn* problem*)
DocType=All document types; Language=All languages;
#7 #6 OR #5 OR #4 OR #3 OR #2 OR #1
DocType=All document types; Language=All languages;
#6 TS=(EFA or EPA or MaxEPA or DHA or ALA)
DocType=All document types; Language=All languages;
#5 TS= (oil* SAME (fish* or flax or linseed))
DocType=All document types; Language=All languages;
#4 TS=(PUFA*)
DocType=All document types; Language=All languages;
#3 TS= ((eicosa* or icosa* or docosahex* or alpha-linol*) SAME acid*)
DocType=All document types; Language=All languages;
#2 TS=(omega 3 or omega 6)
DocType=All document types; Language=All languages;
#1 TS=(fatty acid*)
DocType=All document types; Language=All languages;

Conference Proceedings Citation Indexes Web of Science

Conference Proceedings Citation Index - Science (CPCI-S) and Conference Proceedings Citation Index - Social Science and Humanities (CPCI-SS&H)

1990 to 10 October 2014. Searched 14 October 2014. Limited to publication year 2012 to 2014 [5 records]

1990 to 19 November 2015. Searched 19 November 2015. Limited to publication year 2014 to 2015 [No records]

19 #18 AND #17

DocType=All document types; Language=All languages;

#18 TS=(random* or control* or trial* or groups* or effectiveness or evaluation or placebo*)

DocType=All document types; Language=All languages;

#17 #16 AND #7

DocType=All document types; Language=All languages;

#16 #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8

DocType=All document types; Language=All languages;

#15 TS=(written expression disorder*)

DocType=All document types; Language=All languages;

#14 TS=(writing* abilit* or writing* accurac* or writing* comprehension or writing* disorder* or writing* disabilit* or writing* difficult* or writing* deficient* or writing* fluenc* or writing* problem* or writing* speed*)

DocType=All document types; Language=All languages;

#13 TS=(spell* abilit* or spell* accurac* or spell* comprehension or spell* disorder* or spell* disabilit* or spell* difficult* or spell* deficient* or spell* fluenc* or spell* problem* or spell* speed*)

DocType=All document types; Language=All languages;

#12 TS= (math* abilit* or math* accurac* or math* comprehension or math* disorder* or math* disabilit* or math* difficult* or math* deficient* or math* fluenc* or math* problem* or math* speed*)

DocType=All document types; Language=All languages;

#11 TS=(reading abilit* or reading accurac* or reading comprehension or reading disorder* or reading disabilit* or reading difficult* or reading deficient* or reading fluenc* or reading problem* or reading speed*)

DocType=All document types; Language=All languages;

#10 TS= (dyslexi* or dyscalcul* or agraphia* or dysgraphia*)

DocType=All document types; Language=All languages;

#9 TS= (academic skill* disorder* or scholastic skill* disorder*)

DocType=All document types; Language=All languages;

#8 Ts=(learn* difficult* or learn* disorder* or learn* disabilit* or learn* deficient* or learn* problem*)

DocType=All document types; Language=All languages;

#7 #6 OR #5 OR #4 OR #3 OR #2 OR #1

DocType=All document types; Language=All languages;

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#6 TS=(EFA or EPA or MaxEPA or DHA or ALA)
DocType=All document types; Language=All languages;
#5 TS=(oil* SAME (fish* or flax or linseed))
DocType=All document types; Language=All languages;
#4 TS=(PUFA*)
DocType=All document types; Language=All languages;
#3 TS=((eicosa* or icos* or docosa* or alpha-linol*) SAME acid*)
DocType=All document types; Language=All languages;
#2 TS=(omega 3 or omega 6)
DocType=All document types; Language=All languages;
#1 TS=(fatty acid*)
DocType=All document types; Language=All languages;

Cochrane Database of Systematic Reviews (CDSR) and Database of Abstracts of Reviews of Effects (DARE) in the Cochrane Library

CDSR: 2014, issue 10. Searched 14 October 2014 [2 records]
CDSR: 2015, issue 11. Searched 19 November 2015 [No records]

DARE: 2014, issue 3. Searched 14 October 2014 [No records]
DARE: 2015, issue 2. Searched 19 November 2015 [No records]

#1 MeSH descriptor Fatty Acids, this term only
#2 MeSH descriptor Fatty Acids, Omega-3 explode tree 1
#3 MeSH descriptor Fatty Acids, Omega-6, this term only
#4 (omega NEXT 3 or omega NEXT 6)
#5 ((eicosa* or icos* or docosa* or alpha-linol*) NEXT acid*)
#6 poly NEXT unsaturat* NEXT fatty NEXT acid*
#7 polyunsaturat* NEXT fatty NEXT acid*
#8 (fatty NEXT acid*) NEAR/3 (n NEXT 3 or n NEXT 6)
#9 essential NEXT fatty NEXT acid*
#10 PUFA*
#11 MeSH descriptor Fish Oils, this term only
#12 MeSH descriptor Linseed Oil, this term only
#13 (EFA or EPA or MaxEPA or DHA or ALA)
#14 (oil* NEAR/3 (fish* or flax or linseed))
#15 (#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)
#16 MeSH descriptor Learning Disorders, this term only
#17 MeSH descriptor Dyslexia, this term only
#18 (learn* NEAR/3 (difficult* or disorder* or disabilit* or deficien* or problem*))
#19 (academic skill* NEAR/3 disorder*)
#20 (scholastic skill* NEAR/3 disorder*)
#21 dyslexi*
#22 (reading* NEAR/3 (abilit* or accurac* or comprehension or disorder* or disabilit* or difficult* or deficien* or fluenc* or problem* or speed*))
#23 ((word or text) NEXT blind*)
#24 MeSH descriptor Mathematics, this term only
#25 dyscalcul*
#26 ((math* or arithmetic*) near/3 (abilit* or disorder* or disabilit* or problem* or difficult* or deficien* or fluenc* or skill*))
#27 MeSH descriptor Writing, this term only
#28 MeSH descriptor Agraphia, this term only
#29 agraphia* or dysgraphia*
#30 (spell* near/3 (abilit* or disorder* or disabilit* or problem* or difficult* or deficien* or fluenc* or skill*))
#31 (writing NEAR/3 (abilit* or disorder* or disabilit* or problem* or difficult* or deficien* or fluenc* or skill*))
#32 written NEXT expression NEXT disorder*
#33 (#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32)
#34 (#15 AND #33)

ZETOC

(zetoc.jisc.ac.uk)

All available years. Searched 14 October 2014. Limited to conference proceedings [1 record]
All available years. Searched 19 November 2015. Limited to conference proceedings [No records]

9 0 conference: omega-6 learning
8 0 conference: omega-6 dyslexia
7 0 conference: omega-3 dyslexia
6 1 conference: omega-3 learning
5 0 conference: omega-6 dyscalculia
4 0 conference: omega-3 dyscalculia
3 0 conference: fatty acids dyscalculia
2 1 conference: fatty acids dyslexia
1 6 conference: fatty acids learning

WorldCat

(worldcat.org)

All available years. Searched 14 October 2014. Limited to theses [2 records]

All available years. Searched 19 November 2015. Limited to theses. Limited to 2014-2015 [No records]

KW: (learn* OR dyslexi* OR dyscalcul* OR reading OR spelling OR writing OR mathematic* OR arithmetic*) AND KW: (omega-3 OR omega-6 OR fatty acids OR PUFA* OR fish oil* OR oil* fish OR linseed OR flax OR PUFA* OR icos* OR docosahex* OR alpha-linol*)

Networked Digital Library of Theses and Dissertations (NDLTD)

(search.ndltd.org)

All available years. Searched 5 November 2015 [132 records]

Keywords: (polyunsaturated OR omega) AND children

ClinicalTrials.gov

(clinicaltrials.gov)

All available years. Searched 14 October 2014 [9 records]

All available years. Searched 19 November 2015 [12 records]

Keywords: omega-3 OR omega-6 AND limited to Age group: Child

World Health Organization International Clinical Trials Registry Platform (WHO ICTRP)

(who.int/ictRP/en)

All available years searched 14 October 2014 [35 records]

All available years searched 19 November 2015 [10 records]

Keywords: omega-3 OR omega-6 AND limited to Trials with children

Appendix 2. Search strategies up to 2012**CENTRAL, in the Cochrane Library**

2012, issue 4. Searched 23 April 2012.

2011, issue 2. Searched 21 July 2011.

- #1 MeSH descriptor Fatty Acids, this term only
- #2 MeSH descriptor Fatty Acids, Omega-3 explode tree 1
- #3 MeSH descriptor Fatty Acids, Omega-6, this term only
- #4 (omega NEXT 3 or omega NEXT 6)
- #5 ((eicosa* or icos* or docosahex* or alpha-linol*) NEXT acid*)
- #6 poly NEXT unsaturat* NEXT fatty NEXT acid*
- #7 polyunsaturat* NEXT fatty NEXT acid*
- #8 (fatty NEXT acid*) NEAR/3 (n NEXT 3 or n NEXT 6)
- #9 essential NEXT fatty NEXT acid*
- #10 PUFA*
- #11 MeSH descriptor Fish Oils, this term only
- #12 MeSH descriptor Linseed Oil, this term only
- #13 (EFA or EPA or MaxEPA or DHA or ALA)
- #14 (oil* NEAR/3 (fish* or flax or linseed))

#15 (#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)
 #16 MeSH descriptor Learning Disorders, this term only
 #17 MeSH descriptor Dyslexia, this term only
 #18 (learn* NEAR/3 (difficult* or disorder* or disabilit* or deficien* or problem*))
 #19 (academic skill* NEAR/3 disorder*)
 #20 (scholastic skill* NEAR/3 disorder*)
 #21 dyslexi*
 #22 (reading* NEAR/3 (abilit* or accurac* or comprehension or disorder* or disabilit* or difficult* or deficien* or fluenc* or problem* or speed*))
 #23 ((word or text) NEXT blind*)
 #24 MeSH descriptor Mathematics, this term only
 #25 dyscalcul*
 #26 ((math* or arithmetic*) NEAR/3 (abilit* or disorder* or disabilit* or problem* or difficult* or deficien* or fluenc* or skill*))
 #27 MeSH descriptor Writing, this term only
 #28 MeSH descriptor Agraphia, this term only
 #29 agraphia* or dysgraphia*
 #30 (spell* NEAR/3 (abilit* or disorder* or disabilit* or problem* or difficult* or deficien* or fluenc* or skill*))
 #31 (writing NEAR/3 (abilit* or disorder* or disabilit* or problem* or difficult* or deficien* or fluenc* or skill*))
 #32 written NEXT expression NEXT disorder*
 #33 (#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32)
 #34 (#15 AND #33)

Ovid MEDLINE

1948 to April Week 2 2012. Searched 23 April 2012.

1948 to July Week 2 2011. Searched 21 July 2011.

1 Fatty Acids/
 2 fatty acids, unsaturated/
 3 exp fatty acids, omega-3/
 4 exp fatty acids, omega-6/
 5 alpha-linolenic acid/
 6 docosahexaenoic acids/
 7 eicosapentaenoic acid/
 8 (omega 3 or omega 6).tw.
 9 ((eicosa\$ or icos\$ or docosahex\$ or alpha-linol\$) adj acid\$.tw.
 10 polyunsaturat\$ fatty acid\$.tw.
 11 poly-unsaturat\$ fatty acid\$.tw.
 12 (fatty acid\$ adj3 (n-3 or n-6)).tw.
 13 essential fatty acid\$.tw.
 14 PUFA.tw.
 15 Fish Oils/
 16 linseed oil/
 17 (EFA or EPA or MaxEPA or DHA or ALA).tw.
 18 (oil\$ adj3 (fish\$ or flax or linseed)).tw.
 19 or/1-18
 20 Learning Disorders/
 21 (learn\$ adj3 (difficult\$ or disorder\$ or disabilit\$ or deficien\$ or problem\$)).tw.
 22 (academic skill\$ adj3 disorder\$).tw.
 23 (scholastic skill\$ adj3 disorder\$).tw.
 24 Dyslexia/
 25 dyslexi\$.tw.
 26 (reading\$ adj3 (abilit\$ or accurac\$ or comprehension or disorder\$ or disabilit\$ or difficult\$ or deficien\$ or fluenc\$ or problem\$ or speed\$)).tw.
 27 ((word or text) adj blind\$).tw.
 28 Mathematics/
 29 dyscalcul\$.tw.
 30 ((math\$ or arithmetic\$) adj3 (abilit\$ or disorder\$ or disabilit\$ or problem\$ or difficult\$ or deficien\$ or fluenc\$ or skill\$)).tw.
 31 Writing/
 32 Agraphia/
 33 (agraphia\$ or dysgraphia\$).tw.
 34 (spell\$ adj3 (abilit\$ or disorder\$ or disabilit\$ or problem\$ or difficult\$ or deficien\$ or fluenc\$ or skill\$)).tw.
 35 (writing adj3 (abilit\$ or disorder\$ or disabilit\$ or problem\$ or difficult\$ or deficien\$ or fluenc\$ or skill\$)).tw.

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36 written expression disorder\$.tw.
37 or/20-36
38 19 and 37
39 randomized controlled trial.pt.
40 controlled clinical trial.pt.
41 randomi#ed.ab.
42 placebo\$.ab.
43 drug therapy.fs.
44 randomly.ab.
45 trial.ab.
46 groups.ab.
47 or/39-46
48 exp animals/ not humans.sh.
49 47 not 48
50 38 and 49

Embase Ovid

1980 to 2012 Week 16. Searched 23 April 2012.
1980 to 2011 Week 28. Searched 21 July 2011.

1 fatty acid/
2 omega 3 fatty acid/ or omega 6 fatty acid/
3 docosahexaenoic acid/
4 linolenic acid/
5 icosapentaenoic acid/
6 (omega 3 or omega 6).tw.
7 ((eicosa\$ or icoso\$ or docosahex\$ or alpha-linol\$) adj acid\$.tw.
8 polyunsaturat\$ fatty acid\$.tw.
9 poly-unsaturat\$ fatty acid\$.tw.
10 (fatty acid\$ adj3 n-3).tw.
11 essential fatty acid\$.tw.
12 PUFA.tw.
13 Fish Oils/
14 linseed oil/
15 (EFA or EPA or MaxEPA or DHA or ALA).tw.
16 (oil\$ adj3 (fish\$ or flax or linseed)).tw.
17 or/1-16
18 learning disorder/
19 (learn\$ adj3 (difficult\$ or disorder\$ or disabilit\$ or deficien\$ or problem\$)).tw.
20 (academic skill\$ adj3 disorder\$.tw.
21 (scholastic skill\$ adj3 disorder\$.tw.
22 dyslexia/
23 dyslexi\$.tw.
24 (reading\$ adj3 (abilit\$ or accurac\$ or comprehension or disorder\$ or disabilit\$ or difficult\$ or deficien\$ or fluenc\$ or problem\$ or speed \$)).tw.
25 ((word or text) adj blind\$.tw.
26 Mathematics/
27 dyscalcul\$.tw.
28 ((math\$ or arithmetic\$) adj3 (abilit\$ or disorder\$ or disabilit\$ or problem\$ or difficult\$ or deficien\$ or fluenc\$ or skill\$)).tw.
29 Writing/
30 Agraphia/
31 (agraphia\$ or dysgraphia\$.tw.
32 (spell\$ adj3 (abilit\$ or disorder\$ or disabilit\$ or problem\$ or difficult\$ or deficien\$ or fluenc\$ or skill\$)).tw.
33 (writing adj3 (abilit\$ or disorder\$ or disabilit\$ or problem\$ or difficult\$ or deficien\$ or fluenc\$ or skill\$)).tw.
34 written expression disorder\$.tw.
35 or/18-34
36 exp Clinical trial/
37 Randomized controlled trial/
38 Randomization/
39 Single blind procedure/
40 Double blind procedure/
41 Crossover procedure/

42 Placebo/
43 Randomised.tw.
44 RCT.tw.
45 (random\$ adj3 (allocat\$ or assign\$)).tw.
46 randomly.ab.
47 groups.ab.
48 trial.ab.
49 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).tw.
50 Placebo\$.tw.
51 Prospective study/
52 (crossover or cross-over).tw.
53 prospective.tw.
54 or/36-53
55 17 and 35 and 54

PsycINFO Ovid

1806 to April Week 3 2012. Searched 23 April 2012.

1 Fatty Acids/
2 (omega 3 or omega 6).tw.
3 (eicosa\$ or icosahex\$ or docosahex\$ or alpha-linol\$).tw.
4 fatty acid\$.tw.
5 (PUFA or PUFAs).tw.
6 (EFA or EPA or MaxEPA or DHA or ALA).tw.
7 (fish\$ oil\$ or flax oil\$ or linseed oil\$).tw.
8 Learning Disabilities/ or Dyslexia/ or Reading/
9 (learn\$ adj3 (difficult\$ or disorder\$ or disabilit\$ or deficien\$ or problem\$)).tw.
10 (academic skill\$ adj3 disorder\$).tw.
11 (scholastic skill\$ adj3 disorder\$).tw.
12 dyslexi\$.tw.
13 (reading\$ adj3 (abilit\$ or accurac\$ or comprehension or disorder\$ or disabilit\$ or difficult\$ or deficien\$ or fluenc\$ or problem\$ or speed\$)).tw.
14 ((word or text) adj blind\$).tw.
15 Mathematics/
16 dyscalcul\$.tw.
17 ((math\$ or arithmetic\$) adj3 (abilit\$ or disorder\$ or disabilit\$ or problem\$ or difficult\$ or deficien\$ or fluenc\$ or skill\$)).tw.
18 Spelling/ or Handwriting/
19 written expression disorder\$.tw.
20 (agraphia\$ or dysgraphia\$).tw.
21 (spell\$ adj3 (abilit\$ or disorder\$ or disabilit\$ or problem\$ or difficult\$ or deficien\$ or fluenc\$ or skill\$)).tw.
22 (writing adj3 (abilit\$ or disorder\$ or disabilit\$ or problem\$ or difficult\$ or deficien\$ or fluenc\$ or skill\$)).tw.
23 or/1-7
24 or/8-22
25 23 and 24

PsycINFO EBSCO

1887 to current. Searched 22 July 2011.

S24 S8 and S23
S23 S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22
S22 agraphia* or dysgraphia*
S21 (writing N3 abilit*) or (writing N3 disorder*) or (writing N3 disabilit*) or (writing N3 difficult*) or (writing N3 deficien*) or (writing N3 problem*) or (writing N3 fluenc*) or (writing N3 skill*)
S20 (spell* N3 abilit*) or (spell* N3 disorder*) or (spell* N3 disabilit*) or (spell* N3 difficult*) or (spell* N3 deficien*) or (spell* N3 problem*) or (spell* N3 fluenc*) or (spell* N3 skill*)
S19 written expression disorder*
S18 DE "Handwriting"
S17 DE "Spelling"
S16 (math* N3 abilit*) or (math* N3 disorder*) or (math* N3 disabilit*) or (math* N3 difficult*) or (math* N3 deficien*) or (math* N3 problem*) or (math* N3 fluenc*) or (math* N3 skill*)
S15 dyscalcul*
S14 DE "Mathematics"

S13 academic skill* or scholastic skill*
S12 (learning* N3 disorder*) or (learning* N3 disabilit*) or (learning* N3 difficult*) or (learning* N3 deficien*) or (learning* N3 problem*)
S11 dyslex* or word* blind* or text* blind*
S10 (reading* N3 abilit*) or (reading* N3 accurac*) or (reading* N3 comprehension) or (reading* N3 disorder*) or (reading* N3 disabilit*)
or (reading* N3 difficult*) or (reading* N3 deficien*) or (reading* N3 problem*)
S9 DE "Learning Disabilities" OR DE "Dyslexia" OR DE "Reading Disabilities"
S8 S1 or S2 or S3 or S4 or S5 or S6 or S7
S7 fish* oil* or flax oil* or linseed oil*
S6 (EFA or EPA or MaxEPA or DHA or ALA)
S5 PUFA*
S4 fatty acid* Search modes
S3 eicosa* or icos* or docosahex* or alpha-linol*
S2 omega 3 or omega 6
S1 DE "Fatty Acids"

ERIC ProQuest

1966 to current. Searched 22 July 2011 and 24 April 2012.

Searched for:(((("omega 3" OR "omega 6" OR fatty acid* OR PUFA OR PUFAs OR eicosa* or icos* OR docosahex* OR alpha-linol* OR "alpha limol*" OR EFA OR EPA OR MaxEPA OR DHA OR ALA) OR (oil* NEAR/3 (fish* OR linseed* OR flax*)) AND (SU.EXACT ("Dyslexia") OR SU.EXACT("Writing Difficulties") OR SU.EXACT("Learning Disabilities") OR SU.EXACT("Reading Difficulties") OR (dyslexi* OR dyscalcul* OR agraphia* OR dysgraphia*) OR ("academic skill* disorder*" OR "scholastic skill* disorder*" OR "written expression disorder*") OR (writing NEAR/3 (abilit* OR disorder OR disabilit* OR problem* OR difficult* OR deficien* OR fluenc* OR skill*)) OR (spell* NEAR/3 (abilit* OR disorder OR disorder OR disabilit* OR problem* OR difficult* OR deficien* OR fluenc* OR skill*)) OR ((math* OR arithmetic*) NEAR/3 (abilit* OR disorder* OR disabilit* OR problem* OR difficult* OR deficien* OR fluenc* OR skill*)) OR (reading* NEAR/3 (abilit* OR accurac* OR comprehension OR disorder* OR disabilit* OR difficult* OR deficien* OR fluenc* OR problem* OR speed*)) OR (learn* NEAR/3 (difficult* OR disorder* OR disabilit* OR deficien* OR problem*)))))

Web of Science databases

SCI, SSCI, CPCI-S, CPCI-SS&H

SCI and SSCI: 1970 to current. Searched 22 July 2011 and 24 April 2012.

CPCI-S and CPCI-SS&H: 1990 to current. Searched 22 July 2011 and 24 April 2012.

19 #18 AND #17

DocType=All document types; Language=All languages;

#18 TS=(random* or control* or trial* or groups* or effectiveness or evaluation or placebo*)

DocType=All document types; Language=All languages;

#17 #16 AND #7

DocType=All document types; Language=All languages;

#16 #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8

DocType=All document types; Language=All languages;

#15 TS=(written expression disorder*)

DocType=All document types; Language=All languages;

#14 TS=(writing* abilit* or writing* accurac* or writing* comprehension or writing* disorder* or writing* disabilit* or writing* difficult* or writing* deficien* or writing* fluenc* or writing* problem* or writing* speed*)

DocType=All document types; Language=All languages;

#13 TS=(spell* abilit* or spell* accurac* or spell* comprehension or spell* disorder* or spell* disabilit* or spell* difficult* or spell* deficien* or spell* fluenc* or spell* problem* or spell* speed*)

DocType=All document types; Language=All languages;

#12 TS=(math* abilit* or math* accurac* or math* comprehension or math* disorder* or math* disabilit* or math* difficult* or math* deficien* or math* fluenc* or math* problem* or math* speed*)

DocType=All document types; Language=All languages;

#11 TS=(reading abilit* or reading accurac* or reading comprehension or reading disorder* or reading disabilit* or reading difficult* or reading deficien* or reading fluenc* or reading problem* or reading speed*)

DocType=All document types; Language=All languages;

#10 TS= (dyslexi* or dyscalcul* or agraphia* or dysgraphia*)

DocType=All document types; Language=All languages;

#9 TS=(academic skill* disorder* or scholastic skill* disorder*)

DocType=All document types; Language=All languages;

#8 Ts=(learn* difficult* or learn* disorder* or learn* disabilit* or learn* deficien* or learn* problem*)

DocType=All document types; Language=All languages;

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#7 #6 OR #5 OR #4 OR #3 OR #2 OR #1
DocType=All document types; Language=All languages;
#6 TS=(EFA or EPA or MaxEPA or DHA or ALA)
DocType=All document types; Language=All languages;
#5 TS=(oil* SAME (fish* or flax or linseed))
DocType=All document types; Language=All languages;
#4 TS=(PUFA*)
DocType=All document types; Language=All languages;
#3 TS=((eicosa* or icos* or docosahex* or alpha-linol*) SAME acid*)
DocType=All document types; Language=All languages;
#2 TS=(omega 3 or omega 6)
DocType=All document types; Language=All languages;
#1 TS=(fatty acid*)
DocType=All document types; Language=All languages;

CDSR and DARE in the Cochrane Library

CDSR: 2011, Issue 2. Searched 25 July 2011.

CDSR: 2012, Issue 4. Searched 24 April 2012.

DARE: 2011, Issue 2. Searched 25 July 2011.

DARE: 2012, Issue 2. Searched 24 April 2012.

#1 MeSH descriptor Fatty Acids, this term only
#2 MeSH descriptor Fatty Acids, Omega-3 explode tree 1
#3 MeSH descriptor Fatty Acids, Omega-6, this term only
#4 (omega NEXT 3 or omega NEXT 6)
#5 ((eicosa* or icos* or docosahex* or alpha-linol*) NEXT acid*)
#6 poly NEXT unsaturat* NEXT fatty NEXT acid*
#7 polyunsaturat* NEXT fatty NEXT acid*
#8 (fatty NEXT acid*) NEAR/3 (n NEXT 3 or n NEXT 6)
#9 essential NEXT fatty NEXT acid*
#10 PUFA*
#11 MeSH descriptor Fish Oils, this term only
#12 MeSH descriptor Linseed Oil, this term only
#13 (EFA or EPA or MaxEPA or DHA or ALA)
#14 (oil* NEAR/3 (fish* or flax or linseed))
#15 (#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)
#16 MeSH descriptor Learning Disorders, this term only
#17 MeSH descriptor Dyslexia, this term only
#18 (learn* NEAR/3 (difficult* or disorder* or disabilit* or deficien* or problem*))
#19 (academic skill* NEAR/3 disorder*)
#20 (scholastic skill* NEAR/3 disorder*)
#21 dyslexi*
#22 (reading* NEAR/3 (abilit* or accurac* or comprehension or disorder* or disabilit* or difficult* or deficien* or fluenc* or problem* or speed*))
#23 ((word or text) NEXT blind*)
#24 MeSH descriptor Mathematics, this term only
#25 dyscalcul*
#26 ((math* or arithmetic*) NEAR/3 (abilit* or disorder* or disabilit* or problem* or difficult* or deficien* or fluenc* or skill*))
#27 MeSH descriptor Writing, this term only
#28 MeSH descriptor Agraphia, this term only
#29 agraphia* or dysgraphia*
#30 (spell* NEAR/3 (abilit* or disorder* or disabilit* or problem* or difficult* or deficien* or fluenc* or skill*))
#31 (writing NEAR/3 (abilit* or disorder* or disabilit* or problem* or difficult* or deficien* or fluenc* or skill*))
#32 written NEXT expression NEXT disorder*
#33 (#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32)
#34 (#15 AND #33)

ZETOC

(zetoc.jisc.ac.uk)

All available years. Searched 25 July 2011 and 24 April 2012. Limited to conference proceedings.

Polyunsaturated fatty acids (PUFAs) for children with specific learning disorders (Review)

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9 0 conference: omega-6 learning
8 0 conference: omega-6 dyslexia
7 0 conference: omega-3 dyslexia
6 1 conference: omega-3 learning
5 0 conference: omega-6 dyscalculia
4 0 conference: omega-3 dyscalculia
3 0 conference: fatty acids dyscalculia
2 1 conference: fatty acids dyslexia
1 6 conference: fatty acids learning

WorldCat

(worldcat.org)

All available years. Searched 22 July 2011 and 24 April 2012. Limited to dissertation and theses.

KW: (learn* OR dyslexi* OR dyscalcul* OR reading OR spelling OR writing OR mathematic* OR arithmetic*) AND KW: (omega-3 OR omega-6 OR fatty acids OR PUFA* OR fish oil* OR oil* fish OR linseed OR flax OR PUFA* OR icos* OR docosahex* OR alpha-linol*)

NDLTD

(search.ndltd.org)

All available years. Search 8 December 2011.

(polyunsaturate\$ fatty acid\$ OR (omega 3)) AND (+ (learning disabilit\$ OR disorder\$) OR dyslexia OR dyscalculia) ("docosahexaenoic acid")

ClinicalTrials.gov

(clinicaltrials.gov)

All available years. Searched 25 July 2011 and 24 April 2012.

Keywords: omega-3 OR omega-6 AND limited to Age group: Child

WHO ICTRP

(who.int/ictcp/en)

All available years. Searched 25 July 2011 and 24 April 2012.

Keywords: omega-3 OR omega-6 AND limited to Trials with children

WHAT'S NEW

Date	Event	Description
15 April 2016	New citation required but conclusions have not changed	Two new studies are included in this review.
19 November 2015	New search has been performed	This review was updated after new searches were conducted in October 2014 and November 2015.

CONTRIBUTIONS OF AUTHORS

MLT and KHT screened the search records, selected the studies and extracted data from the studies.
MLT wrote the review with comments from JJH.

MLT is the guarantor for this review.

DECLARATIONS OF INTEREST

- May Loong Tan - none known.

- Jacqueline J Ho - has a family member who works for a pharmaceutical company that produces omega-3 supplements.
- Keng Hwang Teh - none known.

SOURCES OF SUPPORT

Internal sources

- Penang Medical College, Malaysia.

Penang Medical College is the employer of ML Tan and JJ Ho, and provided research time, as well as use of IT and library resources.

- The Sultanah Bahiyah Hospital, Alor Setar, Malaysia.

Research time for KH Teh

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Section	Review (update 2016)
Background	We updated information and references.
Methods	<p>We added "or earlier editions/revisions" for the diagnostic criteria provided in the subsection on Types of participants.</p> <p>We added "other minor adverse effects such as hypersensitivity and gastrointestinal disturbances" to the subsection on Primary outcomes</p> <p>We removed from the subsection on Types of outcome measures the criterion that studies must report our primary learning outcomes to be included.</p> <p>We revised the subsection on Dealing with missing data, to give it more clarity.</p> <p>We added a section on assessment of quality of included studies and selected outcomes for inclusion in a 'Summary of findings' table. (See section on GRADE, beneath the section on Data synthesis.)</p>
Section	Review (2012)
Methods	<p>Types of interventions</p> <p>We added a caveat that "other nutritional supplements" does not include antioxidants added to PUFA supplements, because they are unlikely to affect the results (see Types of interventions above, and in Tan 2012).</p> <hr/> <p>Primary outcomes</p> <p>We added that only studies with our primary learning outcomes will be included because we consider this to be crucial in the evaluation of effects of PUFAs in children with specific learning disorders (see subsection on 'Types of outcome measures' in Tan 2012). PUFAs are also given to children with similar neurodevelopmental disorders (such as ADHD), and their effects on behaviour have already been evaluated by another review (Gillies 2012).</p>
Subgroup analysis	We added 'duration of intervention' to our list of subgroup analyses because this may have an effect on the efficacy of PUFAs (see Subgroup analysis and investigation of heterogeneity above, and in Tan 2012).

Footnotes

ADHD: attention deficit hyperactivity disorder.
PUFAs: polyunsaturated fatty acids.

INDEX TERMS

Medical Subject Headings (MeSH)

Fatty Acids, Omega-3 [therapeutic use]; Fatty Acids, Omega-6 [therapeutic use]; Fatty Acids, Unsaturated [*therapeutic use]; Learning Disabilities [*drug therapy]

MeSH check words

Child; Humans