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Omega-3 fatty acids for cystic fibrosis (Review)

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[Intervention Review]

Omega-3 fatty acids for cystic fibrosis

Colleen Oliver¹, Helen Watson²¹Brunswick West, Australia. ²Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK**Contact address:** Helen Watson, Cambridge University Hospitals NHS Foundation Trust, Addenbrookes Hospital, Cambridge Biomedical Campus, Hills Road, Cambridge, CB2 0QQ, UK. Helen.watson@addenbrookes.nhs.uk, drhelenwatson@gmail.com.**Editorial group:** Cochrane Cystic Fibrosis and Genetic Disorders Group**Publication status and date:** Edited (no change to conclusions), published in Issue 2, 2020.**Citation:** Oliver C, Watson H. Omega-3 fatty acids for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2016, Issue 1. Art. No.: CD002201. DOI: [10.1002/14651858.CD002201.pub5](https://doi.org/10.1002/14651858.CD002201.pub5).

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ABSTRACT

Background

Studies suggest that a diet rich in omega-3 essential fatty acids may have beneficial anti-inflammatory effects for chronic conditions such as cystic fibrosis. This is an updated version of a previously published review.

Objectives

To determine whether there is evidence that omega-3 polyunsaturated fatty acid supplementation reduces morbidity and mortality and to identify any adverse events associated with supplementation.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Trials Register comprising references identified from comprehensive electronic database searches and handsearches of relevant journals and abstract books of conference proceedings. Authors and persons interested in the subject of the review were contacted.

Date of last search: 13 August 2013.

Selection criteria

Randomised controlled trials in people with cystic fibrosis comparing omega-3 fatty acid supplements with placebo.

Data collection and analysis

Two authors independently selected studies for inclusion, extracted data and assessed the risk of bias of the studies.

Main results

The searches identified 15 studies; four studies with 91 participants (children and adults) were included; duration of studies ranged from six weeks to six months. Two studies were judged to be at low risk of bias based on adequate randomisation but this was unclear in the other two studies. Three of the studies adequately blinded patients, however, the risk of bias was unclear in all studies with regards to allocation concealment and selective reporting.

Two studies compared omega-3 fatty acids to olive oil for six weeks. One study compared a liquid dietary supplement containing omega-3 fatty acids to one without for six months. One study compared omega-3 fatty acids and omega-6 fatty acids to a control (capsules with customised fatty acid blends) for three months. Only one short-term study (19 participants) comparing omega-3 to placebo reported a significant improvement in lung function and Shwachman score and a reduction in sputum volume in the omega-3 group. Another study (43 participants) demonstrated a significant increase in serum phospholipid essential fatty acid content and a significant drop in the n-6/n-3 fatty acid ratio following omega-3 fatty acid supplementation compared to control. The longer-term study (17 participants) demonstrated

a significant increase in essential fatty acid content in neutrophil membranes and a significant decrease in the leukotriene B4 to leukotriene B5 ratio in participants taking omega-3 supplements compared to placebo.

Authors' conclusions

This review found that regular omega-3 supplements may provide some benefits for people with cystic fibrosis with relatively few adverse effects, although evidence is insufficient to draw firm conclusions or recommend routine use of these supplements in people with cystic fibrosis. This review has highlighted the lack of data for many outcomes meaningful to people with or making treatment decisions about cystic fibrosis. A large, long-term, multicentre, randomised controlled study is needed to determine any significant therapeutic effect and to assess the influence of disease severity, dosage and duration of treatment. Future researchers should note the need for additional pancreatic enzymes.

PLAIN LANGUAGE SUMMARY

The use of omega-3 supplements in people with cystic fibrosis

Review question

We reviewed the evidence about the effect of giving omega-3 supplements to people with cystic fibrosis.

Background

In people with cystic fibrosis recurring cycles of infection and inflammation are thought to worsen lung function. Studies suggest that omega-3 fatty acids, such as those derived from fish oils, may work to counter the inflammation and may be of benefit in chronic inflammatory diseases including cystic fibrosis. This is an updated version of the review.

Search date

The evidence is current to: 13 August 2015.

Study characteristics

This review includes four small studies which compare omega-3 supplements to placebo. In total there were 91 participants, including both children and adults. The studies lasted between six weeks and six months.

Key results

One six-week study reported that lung function and clinical status improved when taking omega-3 supplements. Volunteers also produced less sputum when taking omega-3 supplements. Two longer studies found that people taking omega-3 supplements showed definite increases in levels of essential fatty acids in their white blood cell membranes and also in levels of phospholipids (molecules that provide structure and protection to cells) measured in blood samples. Few side effects were reported in any of the studies. We conclude that regular omega-3 supplements may benefit people with cystic fibrosis with few side effects. However, there is not enough evidence from the four small studies included in this review to draw firm conclusions or recommend the routine use of these supplements in people with cystic fibrosis. Larger and longer trials are needed to assess the clinical benefit of omega-3 supplementation and to determine the appropriate dosage.

Quality of the evidence

We do not think there are any factors in the way the studies were run which will influence the results in a negative way. It was not clear if these studies had any other risk of bias which might affect the results.

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is the most common life-threatening genetically inherited disease in the Caucasian population, affecting approximately one in 2500 births (CF Trust 2006). Pulmonary inflammation is believed responsible for the progressive loss of lung function that is the major cause of morbidity and mortality in CF (Konstan 1996). In response to lung infections, with organisms such as *Pseudomonas aeruginosa*, neutrophils (white blood cells) accumulate within the airways, producing proteolytic enzymes and oxidants which mediate the inflammatory response (Wilmott 2000). These neutrophils contribute to the thick and viscous secretions characteristic of CF, leading to mucus plugging of the smaller airways and further cycles of infection and inflammation. Treatment with anti-inflammatory drugs, including corticosteroids (Cheng 1999) and non-steroidal anti-inflammatory agents (Lands 2007) have been shown to have some benefit.

Description of the intervention

Mucus may also prevent pancreatic enzymes reaching the intestine and lead to malabsorption (especially fat malabsorption), diarrhoea and failure to thrive (Hunt 1985; Imrie 1975). The importance of growth and nutrition on survival in CF is well established (Corey 1998; Dodge 1988; Gaskin 1982). Dietary strategies concentrate upon providing a high energy and high protein diet, together with pancreatic enzyme replacement therapy. Despite this, however, there are many people with CF with sub-optimal nutritional absorption who continue to require fat soluble vitamins on a daily basis (Benabdeslam 1998).

How the intervention might work

It has been hypothesised that essential fatty acid deficiency may contribute to the development of respiratory disease in infants, even before clinical signs become apparent (Lloyd-Still 1996). Furthermore, animal models suggest that phenotypic changes in the CF-affected organs of lung, pancreas and intestine may be due to a defect in essential polyunsaturated fatty acid metabolism (Freedman 1999).

In humans, the polyunsaturated fatty acids (PUFA) linoleic acid (18:2 omega-6, or n-6) and alpha-linolenic (18:3 omega-3, or n-3) are 'essential' for normal growth and function; the only source is dietary. The nomenclature refers to their chemical structure.

Research into the omega-3 series of essential polyunsaturated fatty acids stems from the observation that the native Inuit (Eskimo) of Greenland (who consume a traditional diet rich in fish oils) have a very low incidence of some of the chronic inflammatory immune-based disorders commonly found in Europe and North America (Corcoran 1937; Osterud 1995). Fish oils are the richest dietary source of the metabolically active omega-3 fatty acid derivatives eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA); however alternative and novel sources are currently being researched. Omega-3 fatty acids have been shown to play an important role in the integrity of cellular membranes, where they exert a profoundly anti-inflammatory response. Some of the beneficial effects of omega-3 fatty acids on inflammatory disease can be explained by a decrease in the production of pro-inflammatory metabolites from the omega-6 fatty acid family and an increase in the biologically less-active omega-3 end products

(Gaszo 1989). Studies suggest that these fatty acids can exert anti-inflammatory effects which may benefit a range of chronic inflammatory diseases, including CF.

Why it is important to do this review

As has been discussed above, the absorption of fatty acids may be impaired in people with CF for a number of reasons and it is therefore possible that supplementation with omega-3 fatty acids may prove to be an effective treatment although details of dosage and administration remain to be elucidated. This is an update of previous versions of the review (Beckles-Willson 2002; Oliver 2010; Oliver 2011; Oliver 2013).

OBJECTIVES

To determine whether there is evidence that omega-3 polyunsaturated fatty acid supplementation reduces morbidity and mortality. To identify any adverse events associated with omega-3 polyunsaturated fatty acid supplementation.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), quasi-randomised trials, and cross-over trials.

Types of participants

People with CF, of any age and severity, diagnosed clinically and by sweat or genetic testing.

Types of interventions

Dietary supplementation of omega-3 essential fatty acids of any dosage, frequency and duration compared with placebo in people with CF. The supplements contain omega-3 fatty acids in the form of eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA), or both. Studies were included if they compared the effect of this intervention with a placebo with low omega-3 or omega-6 fatty acid content, such as olive oil.

Types of outcome measures

Primary outcomes

1. Number of respiratory exacerbations including:
 - a. hospitalisations
 - b. number of courses of antibiotics given (oral and intravenous) (moved from secondary outcomes in a *post hoc* change)
2. Adverse events and dropouts
3. Lung function including
 - a. per cent predicted forced expiratory volume in one second (FEV₁)
 - b. forced vital capacity (FVC)

Secondary outcomes

1. Quality of life
2. Number of deaths
3. Clinical variables including indices of growth or nutrition
4. Bronchial responsiveness as measured by any provocation testing

5. Biochemical markers of essential fatty acid status including plasma, platelet and erythrocyte (red blood cell) levels of EPA or DHA or both, plus omega-3 to omega-6 fatty acid ratio

Search methods for identification of studies

Electronic searches

Relevant studies were identified from the Group's cystic fibrosis trials register using the terms: omega-3 fatty acids.

The Group's Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of *The Cochrane Library*), weekly searches of MEDLINE, a search of Embase to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching through the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant sections of the [Cystic Fibrosis and Genetic Disorders Group Module](#).

In addition, the original review team performed electronic searches of CINAHL and EMBASE (from 1995 to April 2007) ([Appendix 1](#)). When the current review team took on this review, these searches were no longer run.

Date of the most recent search of the Group's Cystic Fibrosis Trials Register: 13 August 2013.

Searching other resources

The reference lists of all studies identified have also been checked. The first author of each paper, and others with a known interest in the subject of the review, were contacted and invited to identify any other published or unpublished studies that might be relevant.

Data collection and analysis

Selection of studies

For the current version of the review, two authors (CO, HW) independently selected studies to be included in the review. If there had been any disagreement, they would have resolved this by discussion.

Data extraction and management

The two authors (CO, HW - originally TN'D and for the 2011 update NJ) independently extracted data onto data acquisition forms. Authors discussed all stages of data extraction and interpretation and there were no disagreements to resolve.

They grouped outcome data into those measured at six and twelve weeks and at six months from baseline. For future updates of this review, if data are reported at any other time periods, they will consider reporting these as well.

Since hospitalisations are often used as a marker for respiratory exacerbations, if the authors include a study which reports hospitalisations in addition to or instead of exacerbations, they will include this information in the review under the first primary outcome 'Number of respiratory exacerbations'.

Assessment of risk of bias in included studies

Two authors (CO, HW) assessed each trial using the domain-based evaluation as described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

The authors assessed the following domains as low risk of bias, unclear risk of bias or high risk of bias:

1. randomisation (low risk - random number table, computer-generated lists or similar methods; unclear risk - described as randomised, but no details given; high risk - e.g. alternation, the use of case record numbers, and dates of birth or day of the week).
2. concealment of allocation (low risk - e.g. list from a central independent unit, on-site locked computer, identically appearing numbered drug bottles or containers prepared by an independent pharmacist or investigator, or sealed opaque envelopes; unclear risk - not described; high risk - if allocation sequence was known to, or could be deciphered by the investigators who assigned participants or if the trial was quasi-randomised).
3. blinding (of participants, personnel and outcome assessors) (low risk - e.g. there was no blinding, but we judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding, or at least outcome assessors were blinded; unclear risk - not described; high risk - e.g. no or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding, or blinding was attempted, but likely to have been broken).
4. incomplete outcome data (Whether investigators used an intention-to-treat analysis) (low risk - e.g. no missing data, or missing data have been imputed using appropriate methods; unclear risk - e.g. insufficient reporting of attrition/exclusions; high risk - e.g. reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups).
5. selective outcome reporting (low risk - e.g. the study protocol is available and all of the studies pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; unclear risk - e.g. insufficient information to permit judgement; high risk - e.g. not all of the study's pre-specified primary outcomes have been reported).
6. other potential sources of bias (low risk - the study appears to be free of other sources of bias; unclear risk - e.g. insufficient information to assess whether an important risk of bias exists; high risk - e.g. had a potential source of bias related to the specific study design used, or had extreme baseline imbalance).

The authors compared assessments and resolved any inconsistencies by discussion.

Measures of treatment effect

For binary outcomes, the authors have calculated a pooled estimate of the treatment effect for each outcome across studies using the odds ratio (OR) (the odds of an outcome among treatment allocated participants to the corresponding odds among controls) and 95% confidence intervals (CIs). For continuous outcomes, they recorded either mean change from baseline for each group or mean post-treatment or intervention values and standard deviations for each group. Then, where appropriate, they have calculated

a pooled estimate of treatment effect by calculating the mean difference (MD) and 95% CIs.

Unit of analysis issues

When conducting a meta-analysis combining results from cross-over studies the authors planned to use the methods recommended by Elbourne (Elbourne 2002). Limited availability of data would mean, we would only able to either use only the first-arm data or to treat the cross-over studies as if they are parallel studies. Elbourne states that this approach will produce conservative results as it does not take into account within-patient correlation (Elbourne 2002). Also each participant will appear in both the treatment and control group, so the two groups will not be independent. For the cross-over study included in the review, the authors were not able to access the first-arm data, and so they have treated the study as if it were parallel. If they are able to obtain a correlation co-efficient for future updates of this review, they will analyse the data more appropriately.

Dealing with missing data

For future updates of the review, in order to allow an intention-to-treat analysis, the authors will seek data on the number of participants by allocated treatment group, irrespective of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded from treatment or follow up.

The review authors have requested missing data from the primary investigators of two studies on several occasions (Koletzko 2000; Romano 1997); however, up until 2007 there was no response. They have therefore excluded these studies and do not plan to contact the authors of them again in the future.

Assessment of heterogeneity

For future updates of the review, if the authors are able to present combined data from a sufficient number of studies (at least four), they will test for heterogeneity between study results using the I^2 statistic (Higgins 2003). For this measure of consistency of results across studies values range from 0% to 100%. They plan to categorise heterogeneity in a simple way such that if the I^2 value is around 25% or below, they consider heterogeneity to be low; if the value is around 50%, they will consider it moderate; if the value is around 75% or above, they will consider it high.

Assessment of reporting biases

The review authors checked that the study investigators reported on all the outcomes they stated they planned to measure in the full publications of their studies. When the authors include a sufficient number of studies, they will attempt to assess whether this review is subject to publication bias by using a funnel plot. If they detect asymmetry, they will explore causes other than publication bias.

The review authors also checked for selective outcome reporting by comparing the protocols of the included studies (where available) to the final paper to ensure that the investigators reported all outcomes measured. If the study protocols were not available, the review authors compared the 'Methods' section to the 'Results' section in the final published paper.

Data synthesis

The review authors have analysed their data using a fixed-effect model. However, if for future updates they identify moderate or high degrees of heterogeneity, they will analyse the data using a random-effects model.

Subgroup analysis and investigation of heterogeneity

If the authors identify moderate or high degrees of heterogeneity and they are able to included sufficient studies in the review (at least four), they plan to investigate this by performing subgroup analyses (e.g. children versus adults and severity of existing lung disease).

Sensitivity analysis

If the authors identify moderate or high degrees of heterogeneity and they are able to include sufficient studies in the review, they also plan a sensitivity analysis comparing trials with or without cross-over design.

RESULTS

Description of studies

Results of the search

The literature searches identified 15 studies. Four studies involving 91 participants with CF met the inclusion criteria (Henderson 1994; Keen 2010; Lawrence 1993; Panchaud 2006). Two further papers have been published in abstract form at a conference and appear to meet our inclusion criteria (O'Sullivan 2011; Hanssens 2015). The authors will be contacted for further information and for now the studies have been listed under [Studies awaiting classification](#). One study previously listed as ongoing has been completed and published; however, on closer consideration this study was not eligible for inclusion in the review (Alicandro 2013). For one study, we did not have sufficient information to include it in past reviews and had contacted the authors for further information; no response was received therefore the study has been excluded (Starling 1988). Thus, a total of nine studies were excluded in this version of the review (Alicandro 2013; Christophe 1992; Katz 1996; Koletzko 2000; Kurlandsky 1994; Lloyd-Still 2006; Romano 1997; Starling 1988; van Biervliet 2008). Please also see the PRISMA diagram generated for this process (Figure 1).

Figure 1. Study flow diagram.

Figure 1. (Continued)

Included studies

Trial characteristics

All four included trials were randomised controlled trials (Henderson 1994; Keen 2010; Lawrence 1993; Panchaud 2006). Trial duration varied from six weeks (Henderson 1994) to six months (Panchaud 2006). Likewise the number of participants varied from 12 (Henderson 1994) to 43 (Keen 2010).

Two studies were of parallel design (Henderson 1994; Keen 2010). Henderson split participants into four groups, two of which were in people without CF, we did not consider information from the groups without CF, as this was not an objective of the review. The two groups of participants with CF received either active supplement or placebo. We required additional data to analyse comparisons between the two CF groups; however, a reply from the author has not been received (Henderson 1994). Keen randomised participants to three groups: one group received a high omega-3 fatty acid blend (EPA and DHA); one group received a fatty acid blend containing predominantly omega-6 fatty acids (linoleic acid (LA), arachidonic acid (AA)); the control group received a high saturated fatty acid (SFA) blend. Only results of 35 participants who completed the study were used. We did not consider results from the group receiving the omega-6 fatty acid intervention as this was not an objective of the review (Keen 2010).

Two studies were of cross-over design (Lawrence 1993; Panchaud 2006). Lawrence found a carry-over effect despite a 12-week washout period, therefore, only the results from the 16 participants who completed the first six-week period of the study were used (Lawrence 1993). Panchaud did not include a washout period (Panchaud 2006).

Participants

All four studies included both children and adults (Henderson 1994; Keen 2010; Lawrence 1993; Panchaud 2006), although only one study included older adults, where the age range was stated as up to 41 years (Keen 2010). None of the studies were very large; the number of participants in each trial ranged from 12 (Henderson 1994) to 43 (Keen 2010). There were more males in three of the studies (Henderson 1994; Lawrence 1993; Panchaud 2006), but one more female than males in the Keen study (Keen 2010).

Three studies described participants as having pancreatic insufficiency (Henderson 1994; Keen 2010; Panchaud 2006). Two studies stated that participants were chronically infected with *Pseudomonas aeruginosa* (Keen 2010; Lawrence 1993). Keen additionally described participants as having severe mutations (Keen 2010).

Interventions

Two studies compared omega-3 fatty acids to olive oil control for a six-week treatment period (Henderson 1994; Lawrence 1993). One study compared omega-3 fatty acids to placebo control for a six-month treatment period (Panchaud 2006). Another study compared essential fatty acid supplementation to a placebo for a three-month treatment period (Keen 2010).

The dose and form of omega-3 fatty acids differed between the studies. Henderson used four 1 g capsules of fish oil, twice daily (containing a daily dose of 3.2 g eicosapentaenoic acid (EPA) and 2.2 g docosahexaenoic acid (DHA)) (Henderson 1994). Lawrence used fish oil capsules containing a daily total of 2.7 g EPA (Lawrence 1993). Panchaud used a liquid PUFA mixture containing 0.2 g EPA and 0.1 g DHA per 200 ml (Panchaud 2006). The volume of supplementation was determined according to participant's weight; intake ranged from 200 mg to 600 mg EPA and 100 mg to 300 mg DHA per day. Keen used a customised fatty acid

blend containing 21.27 % mmol EPA and 6.99 % mmol DHA and participants received 50 mg per kg body weight per day (Keen 2010).

Outcomes

All four studies reported on adverse events (Henderson 1994; Keen 2010; Lawrence 1993; Panchaud 2006) and three on deaths (Henderson 1994; Lawrence 1993; Panchaud 2006). Two studies reported on changes in haematological indices (Henderson 1994; Lawrence 1993). Two studies presented data on serum fatty acid content (Henderson 1994; Keen 2010) and two on changes in in-vitro neutrophil chemotaxis (Lawrence 1993; Panchaud 2006). Two studies reported responses to inflammatory markers and nutritional indices (Keen 2010; Panchaud 2006); both Keen and Lawrence reported on lung function (Keen 2010; Lawrence 1993).

Excluded studies

Seven studies were excluded in the previous version of the review (Christophe 1992; Lloyd-Still 2006; Katz 1996; Kurlandsky 1994; Koletzko 2000; Romano 1997; van Biervliet 2008). One study used parenteral (via blood stream), not enteral (oral) supplementation with omega-3 fatty acids (Katz 1996). Four studies compared

omega-3 supplementation with a large omega-6 fatty acid source, rather than a neutral placebo that contains relatively little omega-3 or omega-6 fatty acid such as olive oil. One study compared omega-3 supplementation with borache oil (Christophe 1992), two studies with sunflower oil (Kurlandsky 1994; van Biervliet 2008) and one study with corn/soy oil as placebo (Lloyd-Still 2006). Two studies were excluded on the basis of insufficient information and a lack of response from the studies' authors (Koletzko 2000; Romano 1997).

For this updated review, a further two studies have been excluded (Alicandro 2013; Starling 1988). One study compared omega-3 supplementation with a large omega-6 fatty acid source (germ oil) rather than a neutral placebo containing relatively little omega-3 or omega-6 (Alicandro 2013). One study was excluded due to insufficient information and a lack of response from the author (Starling 1988).

Risk of bias in included studies

Please see the risk of bias summary presented in the figures (Figure 2).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Henderson 1994	+	?	+	+	?	+
Keen 2010	+	?	?	?	?	-
Lawrence 1993	?	?	+	+	?	+
Panchaud 2006	?	?	+	?	?	+

Allocation

Generation of randomisation sequence

All four studies were described as randomised but only two of them gave any details of the randomisation process. The Henderson study was randomised using a stratified randomised block design, whilst the Keen study was randomised using a random number generator (Henderson 1994; Keen 2010). We graded these studies as having a low risk of bias. The other two studies did not state the randomisation technique, so were graded as having an unclear risk of bias (Lawrence 1993; Panchaud 2006).

Concealment of allocation

Allocation concealment was graded as having an unclear risk of bias for all four studies as no details were provided in the primary papers (Henderson 1994; Keen 2010; Lawrence 1993; Panchaud 2006).

Blinding

All four studies were described as double blind, details were provided as follows. While the capsules in the Henderson study were also not described as identical, it was stated that the placebo olive oil capsules were flavoured to obtain a slight fish taste which the review authors agreed would be sufficient to blind participants (Henderson 1994). In the Lawrence study the treatment was administered as "identical olive oil capsules" (Lawrence 1993). In the third study the placebo treatment was not stated to be identical but it was described as the same liquid dietary supplement as the intervention but without the PUFA mixture (Panchaud 2006). We therefore attributed a low risk of bias to each of these three studies. In the Keen study, the appearance of the capsules was not described and 2 of 12 participants complained of a fish smell in the omega-3 treatment group, therefore the risk of bias in this study is unclear (Keen 2010).

Incomplete outcome data

In all four studies, withdrawals from the study were discussed with explanations (Henderson 1994; Keen 2010; Lawrence 1993; Panchaud 2006). Further details of these withdrawals are given in the [Characteristics of included studies](#) tables. Only one study included all participants in the data analysis, which was performed according to the intention-to-treat principle (Henderson 1994). This study was judged to have a low risk of bias. The other three studies did not employ this approach, but did describe withdrawals from the study (Lawrence 1993; Panchaud 2006; Keen 2010). In one study, some of the data from baseline and end of treatment in the placebo and treatment groups were excluded from analysis due to "technical reasons" which were not defined (Panchaud 2006). More than 15% of participants entering the trial were excluded from data analysis in one study (Keen 2010). We therefore assessed the Lawrence study as having a low risk of bias, but the Panchaud and Keen studies as having an unclear risk of bias.

Selective reporting

We have not been able to determine any selective reporting from the final publication of any of the included studies; however, we have not been able to compare the full study reports to the original study protocols (Henderson 1994; Keen 2010; Lawrence 1993; Panchaud 2006).

Other potential sources of bias

We have not been able to determine any other potential sources of bias in three of the included studies and judge there to be a low risk of bias (Henderson 1994; Lawrence 1993; Panchaud 2006). There is a potential source of bias in one of the studies that did not describe the actual dose of EPA and DHA given (Keen 2010).

Effects of interventions

Many of the protocol-defined outcomes in our review were not reported in any of the studies (Henderson 1994; Keen 2010; Lawrence 1993; Panchaud 2006); those clinical outcomes that were reported in one trial, published medians and ranges, which cannot be entered into the data tables and therefore these outcomes were not formally analysed within our review (Lawrence 1993).

Primary outcomes

1. Number of respiratory exacerbations

One study reported no difference in antibiotic use during the study compared with a similar time period in the previous year (Keen 2010). This outcome was not measured in three of the studies (Henderson 1994; Lawrence 1993; Panchaud 2006).

2. Adverse events and dropouts

a. Steatorrhoea

Two studies reported the need for participants in both the study and placebo groups, to increase their daily dose of pancreatic enzymes to prevent steatorrhoea (Henderson 1994; Lawrence 1993). This was not reported in the other two studies (Keen 2010; Panchaud 2006).

b. Diarrhoea

Two out of seven participants in the Henderson study stopped fish oil supplements because of diarrhoea; the same symptoms caused two out of five participants in the placebo group with CF to withdraw. There was no significant difference between the groups, odds ratio (OR) 0.60 (95% confidence interval (CI) 0.05 to 6.80) (Henderson 1994). Diarrhoea was not reported in the remaining three studies (Lawrence 1993; Panchaud 2006; Keen 2010).

c. Asthma

Only Lawrence reported this event; 3 out of 19 participants had an asthma exacerbation requiring corticosteroid therapy. These were excluded from analysis. The authors argued that corticosteroids affect essential fatty acid metabolism. One of the three participants was taking the active treatment (Lawrence 1993).

d. Stomach pains

Only Keen reported the incidence of stomach pains; five participants (treatment group not specified) of the 35 who completed the study complained of stomach pains (Keen 2010).

3. Lung function

Lawrence reported a significant increase in FEV₁ in the EPA group (median 0.25 L, range 0.1 L to 0.85 L) compared with the placebo group (median -0.1 L, range -1.15 L to 0.24 L), *P* = 0.006. There was also a significant rise in FVC in the EPA group (median 0.6 L, range -0.1 L to 0.75 L) as compared with placebo (median 0 L,

range -0.15 L to 0.35 L), $P = 0.011$ (Lawrence 1993). There were no significant differences in lung function reported in the Panchaud study, mean difference (MD) 2.00 (95% CI -19.11 to 23.11) (Analysis 1.2) (Panchaud 2006). No change in lung function was reported in the Keen study (Keen 2010); lung function was not measured in the Henderson study (Henderson 1994).

Secondary outcomes

1. Quality of life

This outcome was not measured in any of the studies.

2. Number of deaths

None occurred in any of the studies (Henderson 1994; Keen 2010; Lawrence 1993; Panchaud 2006)..

3. Clinical variables

Lawrence reported a significant fall in daily sputum volumes in the EPA group (median fall -10 ml, range -50 ml to 5 ml) compared with the placebo group (median fall 0 ml, range 0 ml to 10 ml), $P = 0.015$ (Lawrence 1993).

The Shwachman score is an overall clinical scoring system in CF, when an increase in the score indicates improvement in clinical conditions (Shwachman 1958). A significant increase in Shwachman score was also reported in the EPA group (median rise 5%, range -10% to 20%) compared with the placebo group (median rise 0%, range -10% to 0%), $P = 0.034$ (Lawrence 1993).

Clinical parameters were recorded in two studies as exploratory outcomes. No significant differences were found in anthropometric parameters in one study (Panchaud 2006). Panchaud reported a body mass index (BMI) SD score using the nine centiles for BMI in British girls and boys as normal value, and their associated coefficient of variation. There was no significant difference between the PUFA group and the placebo group, MD 0.00 (95% CI -0.64 to 0.64) (Panchaud 2006). Significant weight gain was reported in the omega-3 fatty acid group and placebo group from baseline (Keen 2010). Only medians and ranges were reported which did not allow us to include the data in a meta-analysis; median difference (range) 1.75 kg (0.0 to 3.5, $P = 0.001$) and 1.0 kg (-2.0 to 5.5, $P = 0.004$) in the omega-3 fatty acid group and placebo group respectively (Keen 2010).

4. Bronchial responsiveness

This outcome was not measured in any of the studies.

5. Biochemical markers of essential fatty acid status

Panchaud reported a significant increase in EPA content of the neutrophil membrane in the omega-3 PUFA-supplemented group compared to the placebo group (mean (SD) 0.7 (0.6) compared to 1.6 (0.6) $\mu\text{mol } \%$, $P < 0.01$) (Panchaud 2006). This is also significant in our analysis, MD 0.90 (95% CI 0.46 to 1.34). However, no significant differences were observed in DHA membrane concentration between the study groups, MD 0.10 (95% CI -0.45 to 0.65) (Panchaud 2006) (Analysis 1.4). The leukotriene B_4 to leukotriene B_5 ratio decreased significantly more in the omega-3 PUFA-supplemented group compared to placebo, MD -48.00 (95% CI -61.06 to -34.94) (Panchaud 2006) (Analysis 1.5).

Keen reported means and standard errors (which we converted to SDs to allow analysis in RevMan) on the EPA and DHA content of serum phospholipids and the n6 to n3 ratio (Keen 2010). There was a significant increase from baseline in EPA content of serum phospholipids in the omega-3 supplemented group compared to placebo, MD 0.70 (95% CI 0.42 to 0.98) (Keen 2010) (Analysis 1.5). Similarly, there was a significant increase in DHA content of serum phospholipids in the treatment group compared to placebo, MD 1.10 (95% CI 0.39 to 1.81) (Keen 2010) (Analysis 1.5). There was also a significant decrease in n-6/n-3 ratio in the omega-3 group compared to placebo MD -1.42 (95% CI -2.30 to -0.54) (Keen 2010) (Analysis 1.6). Further biochemical marker data were reported by Keen, but these were reported as medians and ranges which we were not able to analyse in RevMan. A significant decrease in the inflammatory markers, ESR and IL-8 was reported in the omega-3 fatty acid supplemented group. In the omega-3 fatty acid supplemented group, ESR decreased from a median (range) of 7 mm/h (3 to 26) at baseline to 6 mm/h (3 to 25) after three months ($P=0.05$). After supplementation with omega-3 fatty acids, IL-8 decreased significantly from a median of 17.5 pg/ml (<0.8 to 35) to 9.3 pg/ml (0.8 to 22) ($P = 0.0017$) after three months (Keen 2010).

DISCUSSION

The most notable feature highlighted by this review was the lack of data for many of the outcomes likely to be meaningful to people with or making treatment decisions about CF. Information was limited on a number of the primary outcomes that we would have expected to find in a randomised controlled trial. One short-term study with 16 participants reported benefits from omega-3 supplementation with improved FEV₁, FVC and Schwachman score (Lawrence 1993). Another, longer-term study with 17 participants found omega-3 supplementation improved fatty acid status within cellular membranes, which may exert anti-inflammatory effects (Panchaud 2006). The Lawrence study also indicated an improvement in sputum volumes with omega-3 supplements, although it should be noted that the treatment group had a higher median sputum volume at baseline and therefore had more scope for improvement (Lawrence 1993). The Keen study also showed that short-term supplementation with omega-3 fatty acids favourably influences serum phospholipid fatty acid pattern and inflammatory markers in people with CF (Keen 2010).

The risks of bias varied across studies and domains. Two of the four included studies had a low risk of bias from sequence generation, but for the remaining two this was unclear; all of the studies had an unclear risk of bias due to allocation concealment. The authors judged all but one of the studies to have adequately blinded patients by giving control oils that were sufficiently similar to the active fish oils that no difference could be observed. Two of the four studies had a low risk of bias from incomplete outcome data as either all patients were included in the analysis or withdrawals clearly accounted for; the remaining two studies had an unclear risk of bias for this domain. All studies were judged to have an unclear risk of bias due to selective reporting as the original study protocols were not accessible. Finally, one study was judged to be at high risk of bias as it did not report the actual doses of treatment or control oils given.

On a practical point, two of the studies reported that people with CF needed to increase their intake of pancreatic enzymes in order to control symptoms of steatorrhoea (Henderson 1994; Lawrence

1993). The authors attributed this to the increased fat intake of both the fish oil and the placebo, olive oil (Henderson 1994; Lawrence 1993). Future researchers should note the need for additional pancreatic enzymes. Panchaud reported that participants did not increase pancreatic enzyme dose, which was most likely due to the lower level of omega-3 supplementation relative to the other two studies (200 mg to 600 mg EPA compared to 2.7 g and 3.2 g EPA in the Lawrence and Henderson studies respectively) (Panchaud 2006). Participants in the Keen study did increase their pancreatic enzyme supplements for the trial period. No side effects of diarrhoea or steatorrhoea were reported, although stomach pains were reported (Keen 2010).

There is no information available about the distribution of the data in any of the studies. These data may be highly skewed because of the small number of participants and so the results are not generalisable to other people with CF.

At present, we are unaware of any published data available about the effects of long-term supplementation or appropriate dosage of omega-3 fatty acids.

AUTHORS' CONCLUSIONS

Implications for practice

We conclude that the limited evidence from these four small studies is not adequate to support any change in clinical practice. The reported benefits, from the use of omega-3 fatty acid supplements,

are from small studies in which the risk of bias is unclear and hence cannot be used to make recommendations for practice (Henderson 1994; Lawrence 1993; Panchaud 2006; Keen 2010).

There is little evidence to recommend that people with CF supplement or modify their dietary intake of fish oil in order to improve their CF control. Equally, there is an absence of evidence that they are at risk if they do so. Although the data are sparse, it would seem prudent for people with CF taking fish oil supplements to take no more than the recommended dose and to increase their pancreatic enzymes.

Implications for research

Further large, long-term, multicentre, randomised, controlled studies are needed in order to determine if there is a significant therapeutic effect and to assess the influence of disease severity, dosage and duration of treatment. Future researchers should note the need for additional pancreatic enzymes.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Henderson 1994

Methods	6-week, parallel design trial with 4 arms. Randomised using stratified randomised block design.
Participants	12 children and young adults diagnosed with CF and pancreatic insufficiency (mean (SD) age 12.2 (5.4) years) on genotype or sweat test and able to complete the spirometric tests. Also pancreatic insufficient and plasma vitamin A and E levels within the normal range. 13 gender and age-matched people, without CF (mean (SD) age 13.4 (6.3) years), 7 male, 6 female.
Interventions	8 x 1 g capsules fish oil (4 capsules twice daily) (3.19 g EPA and 2.21 g DHA) compared with olive oil placebo capsules flavoured to obtain a slight fish taste, over 6 weeks.
Outcomes	Outcomes included in this review: number of people experiencing adverse events;

Omega-3 fatty acids for cystic fibrosis (Review)

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Henderson 1994 (Continued)

number of deaths;
changes in haematological indices;
changes in plasma and erythrocyte levels of EPA and DHA and EPA/AA ratio.

Notes Significantly lower plasma n-6 fatty acids (linoleic acid and arachidonic acid) noted at baseline in participants with CF compared with the group who did not have CF.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using a stratified randomised block design.
Allocation concealment (selection bias)	Unclear risk	Not discussed in paper.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double blind - while the capsules were not described as identical, it was stated that the placebo olive oil capsules were flavoured to obtain a slight fish taste which we agreed would be sufficient to blind participants.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals from the study were discussed with explanations (20 out of 25 randomised participants completed the study). Study included all participants in the data analysis, which was performed according to the intention-to-treat principle.
Selective reporting (reporting bias)	Unclear risk	Protocol not available for comparison, so unable to definitely eliminate selective reporting.
Other bias	Low risk	No additional bias identified.

Keen 2010

Methods	3-month, parallel design trial. Randomised using random number generator.
Participants	43 children and adults with "severe" CF mutations (age range 7 to 41 years); 35 participants completed the study; 18 female, 17 males. 20 participants were chronically infected with <i>Pseudomonas aeruginosa</i> . 8 participants discontinued the study and the inclusion parameters of these patients did not differ from those who completed the study.
Interventions	50 mg/kg per day of 1 of 3 fatty acid blend capsules over 3 months; group A capsules contained predominantly EPA and DHA, group C contained high proportion of linoleic acid and arachidonic acid and group B (placebo) contained predominantly saturated fatty acids. Participants increased their pancreatic enzymes by 10% to 20% to maintain normal stools.
Outcomes	Outcomes included in this review: changes in serum phospholipid essential fatty acid content; changes in inflammatory markers; adverse effects; BMI and weight; lung function; medical treatment.
Notes	Actual dose of EPA and DHA administered not described.

Risk of bias
Omega-3 fatty acids for cystic fibrosis (Review)

Keen 2010 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using random number generator.
Allocation concealment (selection bias)	Unclear risk	Not discussed in paper.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind; treatment was assumed to be administered as identical capsules; however, 2 participants complained of fish smell in group A.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	45 participants were initially randomised, but 2 were excluded due to acute exacerbations and therefore did not enter the study. Withdrawals from study were described: 35 participants completed the study; 8 discontinued because of low compliance (n = 4), stomach pains (n = 2) and weight gain (n = 2). Study did not include all participants in the data analysis, therefore data was not analysed as 'intention to treat'.
Selective reporting (reporting bias)	Unclear risk	Protocol not available for comparison, so unable to definitely eliminate selective reporting.
Other bias	High risk	The lack of information on dosage is a potential risk of bias.

Lawrence 1993

Methods	6-week cross-over study planned. However, significant carry-over effect of treatment noted at end of study, therefore analysis restricted to the first 6-week treatment period.	
Participants	19 adolescents and adults diagnosed with CF on genotype, sweat test, or clinically (median age 17 years, age range 12 years to 26 years), 11 male, 5 female. 3 participants excluded due to requiring a course of corticosteroids for asthma attacks. All were recruited within 4 weeks of hospitalisation for acute respiratory infection and judged to be in optimum condition for disease stage. All were <i>Pseudomonas aeruginosa</i> colonised and produced at least 5 ml sputum daily. Initial randomisation gave groups with comparable baseline characteristics except for age. The treatment group also had significantly greater weight, peripheral blood leucocyte and neutrophil counts.	
Interventions	2.7 g EPA daily compared with identical olive oil placebo capsules, over 6 weeks.	
Outcomes	Outcomes included in this review: number of people experiencing adverse events; number of deaths; changes in haematological and growth indices; changes in lung function; changes in in-vitro neutrophil chemotaxis.	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Did not state the randomisation technique.

Omega-3 fatty acids for cystic fibrosis (Review)

Lawrence 1993 (Continued)

Allocation concealment (selection bias)	Unclear risk	No details were provided in the primary paper.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double blind, treatment was administered as 'identical olive oil capsules'.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of the 19 participants recruited, 3 participants were excluded from the study before analysis due to corticosteroid treatment during the first treatment period.
Selective reporting (reporting bias)	Unclear risk	Protocol not available for comparison, so unable to definitely eliminate selective reporting.
Other bias	Low risk	No additional bias identified.

Panchaud 2006

Methods	2 x 6-month period, cross-over trial with no washout period.
Participants	17 children and young adults with CF and pancreatic insufficiency (mean (SD) age 18 (9) years), 10 male and 7 female. 1 participant discontinued study after 8 months for personal convenience.
Interventions	Liquid dietary supplement containing PUFA mixture (EPA, DHA, GLA and STA) compared with liquid dietary supplement without PUFA mixture over 6 months. Volume of supplementation was determined according to participant's weight; intake ranged from 100 mg - 300 mg DHA and 200 mg - 600 mg EPA per day.
Outcomes	Outcomes included in this review: number of people experiencing adverse events; number of deaths; changes in peripheral blood neutrophil membrane composition; in vitro neutrophilic response to inflammatory stimuli; changes in in-vitro neutrophil chemotaxis.
Notes	Relatively low daily dose EPA and DHA compared to previous clinical trials.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Did not state the randomisation technique.
Allocation concealment (selection bias)	Unclear risk	No details were provided in the primary paper.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double blind, placebo treatment was not stated to be identical but it was described as the same liquid dietary supplement as the intervention but without the PUFA mixture.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	17 participants were randomised; 16 completed the study and one discontinued after 8 months for personal convenience. Due to technical reasons, data could not be analysed for several participants' samples at baseline (4 participants), after treatment with omega-3 supplements (1) and after placebo (2).

Omega-3 fatty acids for cystic fibrosis (Review)

Panchaud 2006 (Continued)

High possibility of attrition bias since the analysis of the final cohort differed from the original cohort.

Selective reporting (reporting bias)	Unclear risk	Protocol not available for comparison, so unable to definitely eliminate selective reporting.
Other bias	Low risk	No additional bias identified.

AA: arachidonic acid
CF: cystic fibrosis
DHA: docosahexaenoic acid
EPA: eicosapentaenoic acid
GLA: gamma-linolenic acid
PUFA: polyunsaturated fatty acids
SD: standard deviation
STA: stearidonic acid

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Alicandro 2013	Omega 3 supplementation compared with large omega-6 fatty acid source (germ oil) rather than a neutral placebo that contains relatively little omega-3 or omega-6 fatty acid (olive oil).
Christophe 1992	Omega-3 supplementation compared with large omega-6 fatty acid source (borache oil) rather than a neutral placebo that contains relatively little omega-3 or omega-6 fatty acid (olive oil).
Katz 1996	Parenteral (via blood stream), not enteral (oral) supplementation with omega-3 fatty acids.
Koletzko 2000	Eligibility unclear, attempts made to contact author for further information, but no response received.
Kurlandsky 1994	Omega-3 supplementation compared with large omega-6 fatty acid source (sunflower oil) rather than a neutral placebo that contains relatively little omega-3 or omega-6 fatty acid (olive oil).
Lloyd-Still 2006	Omega-3 supplementation compared with large omega-6 fatty acid source (corn/soy) rather than a neutral placebo that contains relatively little omega-3 or omega-6 fatty acid (olive oil).
Romano 1997	Eligibility unclear, attempts made to contact author for further information, but no response received.
Starling 1988	Eligibility unclear, attempts made to contact author for further information, but no response received.
van Biervliet 2008	Omega-3 supplementation compared with large omega-6 fatty acid source (sunflower oil) rather than a neutral placebo that contains relatively little omega-3 or omega-6 fatty acid (olive oil).

Characteristics of studies awaiting assessment [ordered by study ID]

Hanssens 2015

Methods	12-month longitudinal randomised double-blind placebo-controlled trial.
Participants	16 people with CF, homozygous D508, over 5 years of age.

Omega-3 fatty acids for cystic fibrosis (Review)

Hanssens 2015 (Continued)

Interventions	Randomised to placebo or oral supplement of omega 3, 60 mg/kg.
Outcomes	Clinical and nutritional status; lung function; exercise tolerance.
Notes	N = 13 completed, 6 intervention, 7 placebo. Supplement well-tolerated.

O'Sullivan 2011

Methods	12-month parallel trial.
Participants	83 infants diagnosed with CF in the first 2 months of life who were exclusively bottle fed.
Interventions	Infant formula containing DHA and AA compared to standard infant formula containing no DHA or AA over 12 months.
Outcomes	Weight and height at 1 year of age; serum DHA and AA levels, IRT and alpha feto-protein levels; Brasfield CXR score.
Notes	Fecal elastase measured at screening and then monthly for the study duration.

AA: arachidonic acid
CF: cystic fibrosis
CXR: chest x-ray
DHA: docosahexaenoic acid
IRT: immunoreactive trypsin

DATA AND ANALYSES
Comparison 1. Omega-3 fatty acids versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Diarrhoea and eructation	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Lung function	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 FEV1 % predicted	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 FVC % predicted	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Clinical variables	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Change in body mass index	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Biochemical markers of essential fatty acid status (EPA & DHA content)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Change in EPA % content of neutrophil membrane	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Change in DHA % content of neutrophil membrane	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Biochemical markers of essential fatty acid status (B4/B5 ratio)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 Leukotriene B4 to leukotriene B5 ratio	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Biochemical markers of essential fatty acid status (EPA & DHA content)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 Change in EPA content of serum phospholipids	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Change in DHA content of serum phospholipids	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Biochemical markers of essential fatty acid status (n6/n3)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 Change in n6/n3 ratio content of serum phospholipids	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Omega-3 fatty acids versus placebo, Outcome 1 Adverse events.

Study or subgroup	Fish oil n/N	Olive oil n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.1.1 Diarrhoea and eructation				
Henderson 1994	2/7	2/5		0.6[0.05,6.79]
			Favours fish oil 0.01 0.1 1 10 100 Favours olive oil	

Analysis 1.2. Comparison 1 Omega-3 fatty acids versus placebo, Outcome 2 Lung function.

Study or subgroup	Omega-3		Placebo		Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)		
1.2.1 FEV1 % predicted						
Panchaud 2006	15	66 (30)	14	64 (28)		2[-19.11,23.11]
1.2.2 FVC % predicted						
Panchaud 2006	15	80 (22)	14	81 (21)		-1[-16.65,14.65]
					Favours placebo -20 -10 0 10 20 Favours omega-3	

Analysis 1.3. Comparison 1 Omega-3 fatty acids versus placebo, Outcome 3 Clinical variables.

Study or subgroup	Omega-3		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
1.3.1 Change in body mass index						
Panchaud 2006	15	-0.9 (0.8)	14	-0.9 (1)		0 [-0.64, 0.64]

Analysis 1.4. Comparison 1 Omega-3 fatty acids versus placebo, Outcome 4 Biochemical markers of essential fatty acid status (EPA & DHA content).

Study or subgroup	Omega-3		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
1.4.1 Change in EPA % content of neutrophil membrane						
Panchaud 2006	15	1.6 (0.6)	14	0.7 (0.6)		0.9 [0.46, 1.34]
1.4.2 Change in DHA % content of neutrophil membrane						
Panchaud 2006	15	2.1 (0.7)	14	2 (0.8)		0.1 [-0.45, 0.65]

Analysis 1.5. Comparison 1 Omega-3 fatty acids versus placebo, Outcome 5 Biochemical markers of essential fatty acid status (B4/B5 ratio).

Study or subgroup	Omega-3		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
1.5.1 Leukotriene B4 to leukotriene B5 ratio						
Panchaud 2006	15	24 (7)	14	72 (24)		-48 [-61.06, -34.94]

Analysis 1.6. Comparison 1 Omega-3 fatty acids versus placebo, Outcome 6 Biochemical markers of essential fatty acid status (EPA & DHA content).

Study or subgroup	Omega-3		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
1.6.1 Change in EPA content of serum phospholipids						
Keen 2010	12	0.8 (0.3)	10	0.1 (0.3)		0.7 [0.42, 0.98]
1.6.2 Change in DHA content of serum phospholipids						
Keen 2010	12	0.8 (1)	10	-0.3 (0.6)		1.1 [0.39, 1.81]

Analysis 1.7. Comparison 1 Omega-3 fatty acids versus placebo, Outcome 7 Biochemical markers of essential fatty acid status (n6/n3).

Study or subgroup	Omega-3		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
1.7.1 Change in n6/n3 ratio content of serum phospholipids						
Keen 2010	12	-1.4 (1.4)	10	0 (0.6)		-1.42[-2.3,-0.54]
					Favours omega-3	Favours placebo

APPENDICES

Appendix 1. Search strategies: Embase and CINAHL (1995 to April 2007)

Search terms

1. cystic fibrosis
2. essential fatty acids
3. diet
4. nutrition
5. fish oil
6. omega-3 fatty acid
7. n-3 fatty acid
8. eicosapentaenoic acid
9. epa
10. docosahexaenoic acid
11. dha

WHAT'S NEW

Date	Event	Description
27 February 2020	Amended	<p>Clarification statement added from Alan Smyth, Co-ordinating Editor on 27 February 2020: This review was found by the Cochrane Funding Arbiters, post-publication, to be noncompliant with the Cochrane conflict of interest policy, which includes the relevant parts of the Cochrane Commercial Sponsorship Policy. The review will be updated by August 2020; both authors of the future update will be free of conflicts.</p> <p>Current version (post-publication): Colleen Oliver: no conflicts of interest. Helen Watson received funding for travel from Abbott Nutrition (manufacturer of ENSURE® ORIGINAL THERAPEUTIC NUTRITION with omega-3 fatty acid ALA) (June 2013).</p>

HISTORY

Protocol first published: Issue 3, 2000
Review first published: Issue 3, 2002

Date	Event	Description
5 January 2016	New citation required but conclusions have not changed	<p>The previous lead author (CO) has stepped down and is now the co-author; the former co-author (HW) is now the lead author.</p> <p>No new information has been included in this updated review, hence our conclusions remain the same.</p>
5 January 2016	New search has been performed	<p>A search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register identified a single new reference which has been listed as 'Awaiting assessment' until further information is available (Hanssens 2015).</p> <p>One study previously listed as ongoing has been completed and published; however, on closer consideration this study was not eligible for inclusion in the review (Alicandro 2013). A further study previously listed as 'Awaiting assessment' was excluded due to insufficient information and a lack of response from the author (Starling 1988).</p>
26 November 2013	New search has been performed	<p>A search of the Cystic Fibrosis & Genetic Disorders Group's Cystic Fibrosis Trials Register identified four new references. Three of these related to a study previously listed as ongoing, including the full paper (Alicandro 2013); and the fourth was a reference to an abstract of a new study. We have excluded the Alicandro study and the new abstract by O'Sullivan is listed as awaiting classification until we can obtain further information to allow us to include or exclude the study (O'Sullivan 2011).</p>
26 November 2013	New citation required but conclusions have not changed	<p>Nikki Jahnke has stepped down as co-author and Helen Watson is the new co-author on this review.</p> <p>No new studies were included in this update of the review, therefore our conclusions remain the same.</p>
10 March 2011	New citation required but conclusions have not changed	<p>The title of the review has been amended removing 'from fish oils' and hence expanding the different potential sources of omega-3 fatty acids to be considered for this review.</p> <p>One of the authors, Dr Mark Everard, has stepped down from the review team. A new author, Nikki Jahnke, joined the team for this update. Another author, Tracy N'Diaye, has not been actively involved in this update of the review and is currently not listed on the citation.</p>
10 March 2011	New search has been performed	<p>A search of the Cystic Fibrosis Trials Register identified eleven new references to six trials which were potentially eligible for inclusion in the review. Three of these studies were excluded (Christophe 1992; Lloyd-Still 2006; van Biervliet 2008). One study was listed as awaiting assessment (Starling 1988). One study was listed as ongoing (Alicandro 2013). One study was included in the review (Keen 2010).</p>
11 November 2009	Amended	Contact details updated.
12 August 2009	Amended	Contact details updated.
13 June 2008	New search has been performed	<p>A search of the Group's Cystic Fibrosis Trials Register did not identify any studies potentially eligible for inclusion in the review.</p>

Date	Event	Description
2 June 2008	Amended	Converted to new review format.
22 August 2007	New search has been performed	One new study has been included in the review (Panchaud 2006) and the methodological quality of the study was assessed using the criteria suggested by Jüni (Jüni 2001).
22 August 2007	Amended	<p>The methodological quality of the two previously included studies were also re-assessed using the criteria described by Jüni (Jüni 2001).</p> <p>Two studies previously listed as 'Awaiting assessment' have been excluded from the review on the basis of insufficient information and lack of response from the primary investigators.</p> <p>The previous 'Synopsis' has been replaced by a 'Plain Language Summary'.</p> <p>The outcome measures have been re-ordered, a number of these have been moved from primary outcomes to secondary outcomes.</p> <p>Given that the review has been substantively updated and following the death of the previous lead author, Naomi Beckles-Wilson, her name has been removed from the byline of this review and her contribution recognised in the 'Acknowledgements' section.</p>
22 August 2007	New citation required and conclusions have changed	Substantive amendment
10 November 2004	New search has been performed	No new references were found in the latest search of the Group's trials register.
26 November 2003	New search has been performed	No new references were found in the latest search of the Group's trials register.
1 March 2002	New search has been performed	Handsearching of several ASPEN/ESPEN and BAPEN conference proceedings were carried out by a contributor to the Group for another review. This search was not thorough. However, some RCTs were identified, including one of the references included in this review (Manner 1993), identified from the ASPEN proceedings.

CONTRIBUTIONS OF AUTHORS

Original review

NBW formulated the question, was primarily responsible for development of the protocol and writing the original review. NBW and TN'D selected the studies, graded the quality and extracted the data.

ME was consulted at all stages of the review, providing advice and support when needed.

Updates from 2007

Following the death of the lead author NBW, CO has taken on the lead and acts as guarantor of the review from 2007. The methodological quality of the included studies was re-assessed by CO using the criteria described by Jüni (Jüni 2001) and then again to reflect the current Cochrane guidelines with regards to risk of bias.

At the update in 2011, ME stepped down from the review team and a new author, NJ joined the team. For this update also, TN'D has not been actively involved and her name does not currently appear on the citation.

At the update in 2013, NJ stepped down from the review team and a new author, HW, joined the team.

At the update in 2016, CO stepped down as lead author, but remained as a co-author. HW became lead author.

DECLARATIONS OF INTEREST

None known.

Clarification statement added from Alan Smyth, Co-ordinating Editor on 27 February 2020: This review was found by the Cochrane Funding Arbiters, post-publication, to be noncompliant with the [Cochrane conflict of interest policy](#), which includes the relevant parts of the [Cochrane Commercial Sponsorship Policy](#). The review will be updated by August 2020; both authors of the future update will be free of conflicts.

Current version (post-publication): Colleen Oliver: no conflicts of interest. Helen Watson received funding for travel from Abbott Nutrition (manufacturer of ENSURE® ORIGINAL THERAPEUTIC NUTRITION with omega-3 fatty acid ALA) (June 2013).

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External sources

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The former secondary outcome "number of courses of antibiotics given (oral and intravenous)" has been moved to a sub-outcome of the primary outcome "Number of respiratory exacerbations" as often respiratory exacerbations are defined by the courses of antibiotics prescribed.

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; Cystic Fibrosis [*diet therapy]; Fatty Acids, Omega-3 [*administration & dosage]; Fatty Acids, Omega-6 [administration & dosage]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans