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[Intervention Review]

Omega 3 fatty acids (fish oil) for maintenance of remission in Crohn's disease

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ABSTRACT

Background

The anti-inflammatory effects of n-3 (omega-3 fatty acids, fish oil) have been suggested to be beneficial in chronic inflammatory disorders such as inflammatory bowel disease. This review is an update of a previously published Cochrane review.

Objectives

To systematically review the efficacy and safety of n-3 for maintenance of remission in Crohn's disease (CD).

Search methods

The following databases were searched from inception to November 2013 without language restriction: CENTRAL, MEDLINE, EMBASE, HealthSTAR, PubMed, and ACP journal club.

Selection criteria

Randomized placebo-controlled trials (RCT) of n-3 for maintenance of remission in CD were included. Studies must have enrolled patients of any age group, who were in remission at the time of recruitment, and were followed for at least six months. The intervention must have been fish oil or n-3 given in pre-defined dosage. Co-interventions were allowed only if they were balanced between the study groups.

Data collection and analysis

The primary outcome was the relapse rate and secondary outcomes included change in disease activity scores, time to first relapse and adverse events. Two independent investigators reviewed studies for eligibility, extracted the data and assessed study quality using the Cochrane risk of bias tool. The overall quality of the evidence supporting the primary and selected secondary outcomes was reassessed for the current update using the GRADE system. We used the RevMan software for analyses. We calculated the risk ratio (RR) and corresponding 95% confidence interval (CI) for dichotomous outcomes and the hazard ratio and 95% CI for time-to-event outcomes. Random-effects or fixed-effect models were used according to degree of heterogeneity and sensitivity analyses were performed in an attempt to explore possible sources of heterogeneity.

Main results

Six studies with a total of 1039 patients were eligible for inclusion. The two largest studies were rated as low risk of bias for all assessed items. Four studies were rated as unclear risk of bias for randomization and allocation concealment. Two studies were rated as high risk of bias for incomplete outcome data and selective reporting. There was a marginal significant benefit of n-3 therapy for maintenance of remission. Thirty-nine per cent of patients in the n-3 group relapsed at 12 months compared to 47% of placebo patients (6 studies, 1039 patients; RR 0.77, 95% CI 0.61 to 0.98). A GRADE analysis rated the overall quality of the evidence for the primary outcome (i.e. relapse) as

very low due to unexplained heterogeneity ($I^2 = 58\%$), publication bias, and a high or unknown risk of bias in four studies in the pooled analysis. When two large studies at low risk of bias were considered the benefit was no longer statistically significant. Thirty-seven per cent of patients in the n-3 group relapsed at 12 months compared to 42% of placebo patients (2 studies, 738 patients; RR 0.88, 95% CI 0.74 to 1.05). No significant heterogeneity was identified for this pooled analysis ($I^2 = 0\%$). A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was moderate due to sparse data (294 events). No serious adverse events were recorded in any of the studies but in a pooled analyses there was a significantly higher rate of diarrhea (4 studies, 862 patients; RR 1.36 95% CI 1.01 to 1.84) and upper gastrointestinal tract symptoms (5 studies, 999 patients; RR 1.65, 95% CI 1.25 to 2.18) in the n-3 treatment group.

Authors' conclusions

Evidence from two large high quality studies suggests that omega 3 fatty acids are probably ineffective for maintenance of remission in CD. Omega 3 fatty acids appear to be safe although they may cause diarrhea and upper gastrointestinal tract symptoms.

PLAIN LANGUAGE SUMMARY

Omega 3 fatty acids (fish oil) for maintenance of remission in Crohn's disease

Fish oil contains omega 3 fatty acids that may be beneficial in reducing inflammation, such as seen in the bowel of Crohn's disease patients. Randomized placebo-controlled studies that evaluated the effect of daily intake of capsules containing omega-3 fatty acids to maintain remission in Crohn's disease were reviewed. Six studies including 1039 patients were included in the review. A pooled analysis of six studies suggests a marginal benefit for omega 3 fatty acids over placebo (i.e. fake medicine) in preventing relapse of disease at one year. However, these results need to be interpreted with caution due to differences across the studies in terms of induction of remission regimens (e.g. surgical remission versus drug therapy) patients (e.g. adult versus pediatric patients) and medication regimens (e.g. some studies used different placebos), the possibility of publication bias (i.e. only studies with positive results are published) and low methodological quality in four studies in the pooled analysis. When the two largest and highest quality studies were pooled the results showed no benefit to omega-3 treatment over placebo. There were no serious side effects in any of the studies. Common side effects included unpleasant taste, bad breath, heartburn, nausea and diarrhea. Evidence from two large high quality studies suggests that omega 3 fatty acids are probably ineffective for maintenance of remission in CD. Omega 3 fatty acids appear to be safe although they may cause diarrhea and upper gastrointestinal tract symptoms.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

n-3 therapy compared with placebo for maintaining remission in CD

Patient or population: Crohn's disease patients in remission

Settings: adult and pediatric outpatient gastroenterology and IBD centers, single-center and multicenter; not stated in one study (Belluzzi 1997).

Intervention: n-3 or fish oil capsules

Comparison: placebo capsules

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo	n-3 or fish oil capsules				
Relapse rate at one year (all studies)	Study population		RR 0.77 (0.61 to 0.98)	1039 (6 studies)	⊕⊕⊕⊕ very low 2,3,4	
	471 per 1000 ¹	363 per 1000 (287 to 462)				
Relapse rate at one year (sensitivity analysis of Belluzzi 1996)	Study population		RR 0.77 (0.64 to 0.93)	904 (5 studies)	⊕⊕⊕⊕ very low 3,4,5	
	459 per 1000	353 per 1000 (294 to 462)				
Relapse rate at one year (only EPIC studies)	Study population		RR 0.88 (0.74 to 1.05)	738 (2 studies)	⊕⊕⊕⊕ moderate 6	Well-designed and implemented studies, larger than all other studies combined
	424 per 1000	373 per 1000 (314 to 445)				
Adverse events rate-Diarrhea	Study population		RR 1.36 (1.01 to 1.84)	862 (4 studies)	⊕⊕⊕⊕ moderate 7	
	140 per 1000	190 per 1000 (141 to 258)				
Adverse events rate- Upper GI (nausea, vomiting, halitosis, heartburn, dyspepsia, dysgeusia and bloating)	Study population		RR 1.98 (1.38 to 2.85)	999 (5 studies)	⊕⊕⊕⊕ moderate 8	
	123 per 1000	244 per 1000				

(170 to 351)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk Ratio; **RD:** Risk Difference; **OR:** Odds Ratio; **HR:** Hazard Ratio.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

- 1 The control group risk estimate comes from the control arm of the included studies.
- 2 Significant unexplained heterogeneity.
- 3 Likely publication bias is indicated by the absence of negative small studies.
- 4 Two of the studies in the analysis were at high risk of bias due to incomplete outcome data and selective reporting.
- 5 Sparse data (374 events).
- 6 Sparse data (294 events).
- 7 Sparse data (144 events).
- 8 Sparse data (167 events).

BACKGROUND

Crohn's disease

Crohn's disease (CD) is characterized by chronic intestinal inflammation causing a varying spectrum of clinical symptoms. Some patients have chronically active disease, while others have a pattern of clear exacerbations and remissions. It is currently hypothesized that chronic inflammation develops in genetically susceptible hosts in response to as yet unidentified environmental triggers, likely microbial in origin. No maintenance medication has been shown to be completely effective in preventing relapse, and thus prolonging remission intervals while minimizing adverse reactions has been the aim of treatment. Adherence to a low residue diet may reduce symptoms in patients with intestinal stenosis and administration of formulated food as the sole source of nutrition is efficacious in alleviating mucosal inflammation (Zachos 2007). Otherwise, no dietary restrictions or interventions have been convincingly shown to treat active CD or to prevent clinical exacerbation.

Omega-3 poly-unsaturated fatty acids (n-3)

Randomized controlled trials have suggested a positive effect of n-3 in various disease states, including cardiovascular, inflammatory, immunological, psychological, and neurological disorders (Akabas 2006; Belluzzi 2002; Ergas 2002; Hooper 2004; Ruxton 2004; Simopoulos 2002). The beneficial effects of n-3 are thought to be secondary to anti-inflammatory, antithrombotic, antiarrhythmic, hypolipidemic and vasodilatory properties. Omega-3 polyunsaturated fatty acids (n-3) are incorporated into the wall of inflammatory cells and decrease the concentration of arachidonic acid (C20:4, n-6). Arachidonic acid is the key substrate of cyclooxygenase and 5-lipoxygenase enzymes which produce proinflammatory cytokines (Hillier 1991). In this way, n-3 fatty acids reduce the production of leukotriene B₄, thromboxane A₂, prostaglandin E₂, interleukin-1, interleukin-6 and tumor necrosis factor, and scavenge free radicals (Endres 1989; Fisher 1986; Kim 1996; Lee 1985; Simopoulos 2002).

Although n-3 can be obtained from various vegetables, the major source of n-3 is fish oil. The marine sources of n-3 include eicosapentanoic acid (EPA or 20:5), docosahexanoic acid (DHA, 22:6) and docosapentanoic acid (DPA, 22:5), which are the longer chain n-3 forms. Alpha linolenic acid (ALA, 18:3) is the shorter chain n-3 obtained from nuts and vegetable oils. Although an endogenous process exists whereby ALA can be partially converted to the effective longer chain n-3, there is debate about the effectiveness of this conversion (Arterburn 2006; Ruxton 2004).

n-3 and Crohn's disease

Studies on animal models and tissues of IBD patients have demonstrated the strong anti-inflammatory properties of n-3 (Nakazawa 2000; Vilaseca 1990). It has been proposed that a diet rich in fish oil protected the Japanese from IBD and now the rate of IBD is increasing due to dietary shift from n-3 to n-6 (Nakazawa 2000). Reports of n-3 use for maintaining remission in CD have been conflicting (MacLean 2005). Although n-3 has an excellent safety profile, when administered as raw fish oil it was shown to have troublesome adverse effects that reduced compliance. These adverse effects include unpleasant taste, halitosis, heartburn, nausea and diarrhea (Kim 1996; Lorenz 1989). Investigators have suggested the use of enteric coated capsules to improve compliance and absorption (Belluzzi 1994).

Importance of this review

Narrative reviews of fish oil in CD have reported conflicting conclusions, based on the same published studies (Belluzzi 2002; Endres 1999; Kim 1996; Nakazawa 2000; Simopoulos 2002). Our previous systematic review published in 2009 concluded that omega-3 fatty acids are probably ineffective for maintenance of remission in Crohn's disease (Turner 2009). In light of continued public interest in finding natural alternatives or adjuncts to current immunosuppressive therapies and the four years that have elapsed since the last literature search, we aimed to update our previous review.

OBJECTIVES

The primary objective of this study was to systematically review the effectiveness of fish oil or n-3 for maintaining remission in CD. A secondary objective was to evaluate the adverse events associated with fish oil or n-3 for maintaining remission in CD.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized placebo-controlled trials of fish oil or n-3 therapy administered for at least six months, reporting at least one of the primary or the secondary outcomes and published in any language, were included in this review. Studies published in an abstract form only were included if enough data were provided to assess the reported outcomes.

Types of participants

Crohn's disease patients (diagnosed using established criteria) who were in remission at the time of recruitment were included. We did not apply any age restrictions (both pediatric and adult patients were included). The following validated clinical indices could have been used to assess disease activity and remission: the Crohn's disease activity index (CDAI) (Best 1976), the pediatric Crohn's disease activity index (PCDAI) (Hyams 1991), the weighted pediatric Crohn's disease activity index (wPCDAI) and the other short versions (Turner 2012), and the Harvey-Bradshaw index (Harvey 1980). In practice, only the first two indices were used in the eligible studies.

Types of interventions

Trials were included if fish oil or n-3 supplementation was given in any form (capsule, enteric coated or liquid) but with a defined dose. Co-interventions were allowed only if they were balanced between the study groups. Studies in which the intervention group received diet enriched with fish products were excluded as the dose was not clear in these studies and other confounding variables could exist.

Types of outcome measures

Primary outcome

The primary outcome was the relapse rate during the observation time. Definitions of relapse were guided by the validated indices specified above.

Secondary outcome

The secondary outcomes were change in disease activity scores, time to first relapse and adverse events (diarrhea,

nausea, vomiting, halitosis, heartburn, alterations in low density lipoproteins, alterations in glucose level, increase in bleeding time and abdominal pain). Withdrawal rate of participants among the intervention and control groups was also recorded. Other outcomes were recorded, if available: admission rate, use of steroids, disease activity at the end of follow-up period and quality of life. However, most of these data were not available. Studies reporting only surrogate outcomes (e.g. serum or tissue levels of cytokines or inflammatory markers) were excluded.

Search methods for identification of studies

Search methods for identification of studies

Electronic databases

An on-line database literature search from inception to November 2013 was performed for human studies, without language restrictions, using the following databases: MEDLINE (NLM, National Library of Medicine, Bethesda), EMBASE (Elsevier, NY) and HealthSTAR on OVID, as well as PubMed (NLM), the Cochrane Central Register of Controlled Trials (CENTRAL) and ACP journal club. On-going trials were identified from the registry link: www.clinicaltrials.gov. The search strategies used for each database are documented in [Appendix 1](#). All abstracts found by the above search strategy underwent individual screening for eligibility by DT.

Other sources

Additional citations were identified by manually searching the references of articles retrieved from the computerized databases and relevant review articles. Unpublished studies were sought by contacting experts in the field, but none were identified.

Data collection and analysis

Selection of studies

Abstracts of all articles meeting the above search strategy were screened for eligibility. Full text studies were retrieved if they were potentially eligible for inclusion. The retrieved full text articles were then independently reviewed by DT and AMG for eligibility. Disagreements were to be resolved by consensus between the remaining investigators.

Data extraction and management

Two investigators (DT, AMG) independently completed a data extraction form for all eligible studies. The following data were retrieved:

1. General information: title, journal, year, published or unpublished.
2. Study information: design, ways used to ensure adequacy of randomization, concealment of allocation and blinding, power calculation (a priori and post hoc).
3. Intervention: form and dose of n-3, type of comparison group, special diet used.
4. Eligibility: inclusion and exclusion criteria, total number screened and randomized.
5. Baseline characteristics (in each group): age, sex, race, disease severity (and how evaluated), concurrent medications used.
6. Follow-up: length of follow-up, assessment of compliance, withdrawals and loss to follow-up.
7. Outcome: time to first relapse, disease activity at each evaluation time (and how was assessed) number of relapses during the follow-

up period, adverse events, use of steroid, number of hospital admissions and weight.

Assessment of methodological quality of included studies

Two authors (RL and OL) independently assessed the quality of included studies using the Cochrane risk of bias tool ([Higgins 2011](#)). Factors assessed included:

- random sequence generation;
- allocation concealment;
- blinding;
- incomplete outcome data;
- selective outcome reporting; and
- other potential sources of bias.

We rated each of these factors as 'low risk', 'high risk' or 'unclear risk'. Disagreements were resolved by consensus.

We used the GRADE approach to assess the overall quality of evidence for the primary outcome and selected secondary outcomes of interest. Outcomes from pooling of randomized trials start as high quality evidence, but may be downgraded due to: (1) risk of bias, (2) indirectness of evidence, (3) inconsistency (unexplained heterogeneity), (4) imprecision (sparse data), and (5) reporting bias (publication bias). The overall quality of evidence for each outcome was determined after considering each of these elements, and categorized as high quality (i.e. further research is very unlikely to change our confidence in the estimate of effect); moderate quality (i.e. further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate); low quality (i.e. further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate); or very low quality (i.e. we are very uncertain about the estimate) ([Guyatt 2008](#); [Guyatt 2011](#); [Schünemann 2011](#)).

Missing data

Primary authors were contacted for missing data, but none replied. A sensitivity analysis was planned in this case.

Statistical analysis

Categorical data (as relapsed or not during the follow-up period) for each study were transformed into two by two tables.

Measures of treatment effect

We calculated the risk ratio (RR) and corresponding 95% confidence interval (95% CI) for dichotomous outcomes. For the primary analysis the actual relapse rate was used rather than the estimated rate (controlling for censored data), since most studies did not report the estimated relapse rate. The number needed to treat to benefit (NNTB) and the absolute risk reduction (risk difference) and corresponding 95% CI were also calculated where appropriate. For time-to-event data we calculated the hazard ratio (HR) and corresponding 95% CI. No continuous variables (i.e. number of relapses) were reported in the studies.

Meta-analysis

Random-effects or fixed-effect models were used to pool studies depending on clinical and statistical heterogeneity. Weighting was assigned according to the Mantel-Haenszel method. For time-to-event analyses, the generic inverse variance function was used, inputting the lnHR (hazard ratio) with its lnSE (standard error)

derived from the reported 95% CI of the HR. The lnSE was obtained using the formula: $\ln SE = (\ln(\text{lower 95\% CI limit}) - \ln(\text{upper 95\% CI limit})) / 3.92$.

Assessment of Heterogeneity

First, studies were independently reviewed for any clinical and methodological heterogeneity and possible reasons for heterogeneity were sought. The decision of whether to pool studies was aided by calculating the I^2 measure, interpreted as 25% (low heterogeneity), 50% (moderate) and 75% (high) (Higgins 2003). Next, the Cochran χ^2 test for homogeneity (Q test) was calculated, and since the test has low sensitivity to detect heterogeneity, $P < 0.1$ was considered to be statistically significant.

Subgroup analysis

A priori subgroup analyses were planned, governed by the number of identified studies: different dosing of eicosapentaic acid (EPA), follow-up duration (< 9 months and > 9 months), pediatric versus adult population (≤ 18 years of age and > 18 years), different formulation of the fish oil (raw, encapsulated, or enteric coated).

Sensitivity analysis

In order to assess the robustness of the eligibility criteria, planned sensitivity analyses included excluding poor quality studies, small studies (< 50 patients) and studies published in abstract form. A funnel plot was constructed to assess the possibility of publication bias.

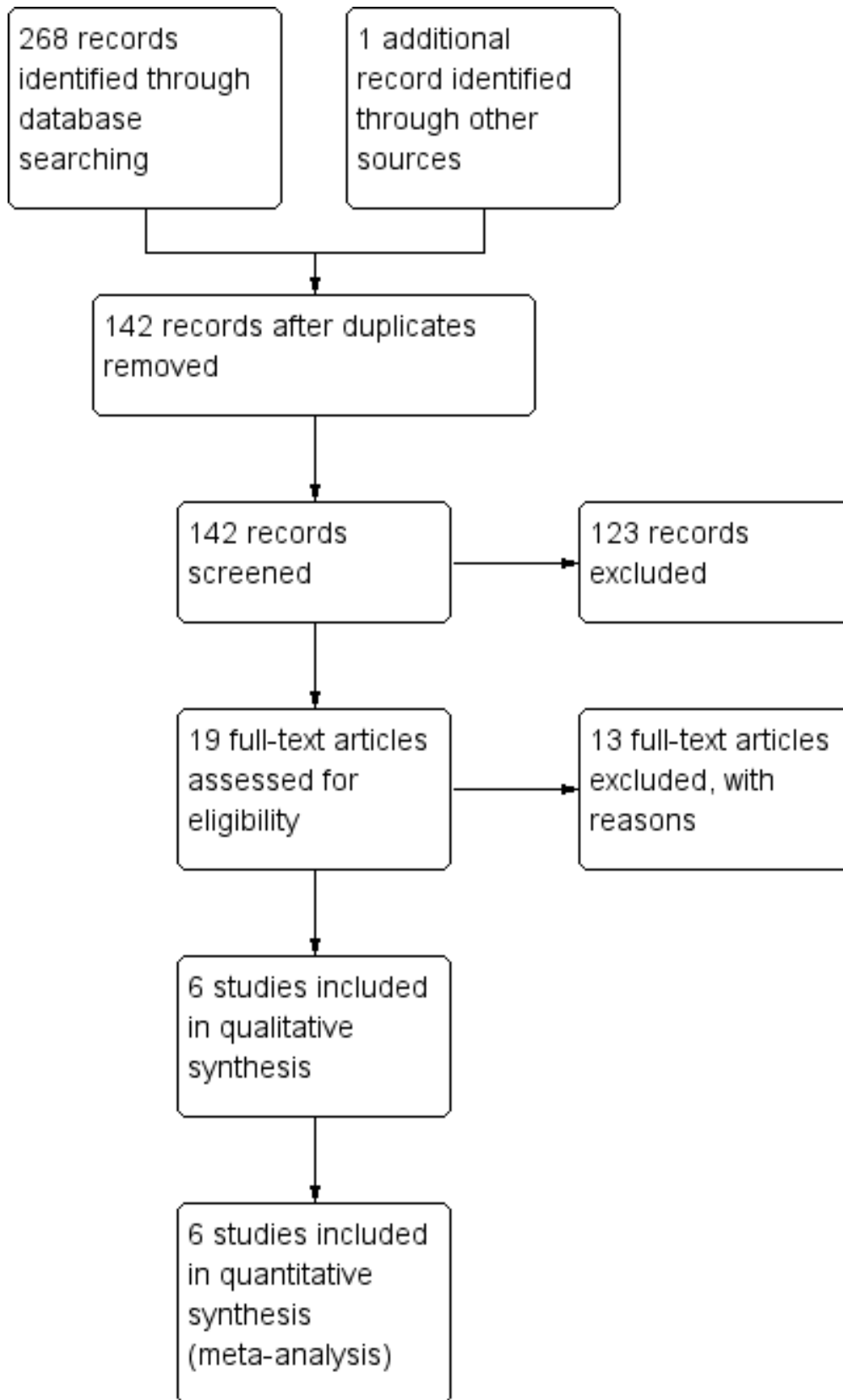
RESULTS

Description of studies

Results of the search

The initial search yielded 142 non-duplicated articles (See [Figure 1](#)). Based on abstract review, all potentially controlled trials and review articles for reference search were retrieved. Nineteen full text articles were assessed for eligibility. Two studies were excluded because they were not randomized controlled trials (Mate 1991; Tsujikawa 2000). Eight studies were excluded because they enrolled only active patients (i.e. focusing on whether n-3 can induce remission (Bamba 2003; Eivindson 2005; Nielsen 2005; Sakurai 2002; Seidman 2003; Socha 2002; Trebble 2004; Trebble 2005). One study was excluded because it enrolled patients with active and inactive Crohn's disease (Lorenz 1989). Two studies were excluded because n-3 treatment was for less than six months (Bjorkkjaer 2004; Geerling 2000). Six studies with a total of 1039 patients were included in this review (table of included studies). Two independent trials (EPIC-1 and EPIC-2) were reported in the same manuscript (Feagan 2008a) and were included in the last update (Turner 2009). No new studies were published since 2008, and thus no additional studies were included in the current review update. Agreement among reviewers regarding the eligibility of the included studies was 100%.

Figure 1. Study flow diagram.



Included studies:

1. Belluzzi 1996

- **Design:** A double blind, placebo-controlled trial of one year duration.
 - **Sample size:** A total of 78 adults (18 to 67 years of age, 50% men), 39 in each arm.
 - **Setting:** Outpatient clinics in Italy.
 - **Participants:** At baseline, participants were in remission (CDAI < 150 for at least 3 months, but less than 2 years) and high risk for relapse, judged by an increase in at least one of three serum inflammatory markers. No concurrent medications were allowed and there were no diet restrictions. Patients were followed every three months until one year.
 - **Interventions:** Enteric coated fish oil capsule with 60 minutes delay timed release (1.8 g/day of EPA and 0.9 g/day of DHA, as free fatty acids) versus identical placebo of 500 mg Miglyol 812 (a mixed-acid triglyceride of fractionated medium chain fatty acids made up of caprylic and capric acid). The enteric coated time released capsules were used to avoid troubling adverse reactions such as nausea and halitosis thereby improving compliance.
 - **Outcomes:** Relapse rates over one year of follow-up, as defined by CDAI > 150 or an increase of at least 100 points in CDAI from baseline for two weeks. Adverse events and time to first relapse were also monitored.
2. [Lorenz-Meyer 1996](#)
- **Design:** A double blind, placebo-controlled trial of one year duration with three groups: n-3, placebo and reduced carbohydrate intake. The data and discussion regarding this study will refer only to the n-3 intervention group in comparison with the placebo group (which was the primary aim of the trial).
 - **Sample size:** A total of 135 adults (17 to 65 years of age, 31% men), 70 in the n-3 arm and 65 in the placebo arm.
 - **Setting:** Multicenter study in Germany.
 - **Participants:** At baseline, participants were in remission (CDAI < 150), induced with a course of corticosteroids. Steroids were still administered during the first two months of the study, but no other co-interventions were allowed. Patients were instructed to consume a diet low in arachidonic acid and rich in fiber and were followed every three months until one year.
 - **Interventions:** Gelatin n-3 capsules (3.3 g/day of EPA and 1.8 g/day of DHA, as ethyl Esther) versus identical placebo of corn oil. A second intervention group was treated with a low carbohydrate diet but was ignored for the purpose of this review.
 - **Outcome:** Primary outcome was the relapse free time period after randomization as defined by CDAI > 200 and a change from baseline CDAI by at least 60 points, plus an increase of C-reactive protein serum level two standard deviations above normal mean. Relapse rate and adverse events were also monitored.
3. [Belluzzi 1997](#)
- This study was published in abstract form only. Additional information was supplied by the author by personal communication.
 - **Design:** A double blind, placebo-controlled trial of one year duration.
 - **Sample size:** A total of 50 adults (mean age 39 ± 13.8 years in the n-3 group, and 35.2 ± 7.9 in the control group, 58% male), 26 in the n-3 arm and 24 in the control arm.
- **Setting:** Outpatients at a single IBD center in Italy.
 - **Participants:** Crohn's disease patients in remission (CDAI < 150) one month following ileal resection. No co-interventions were administered and no specific diet was prescribed; participants were asked to continue their previous dietary habits.
 - **Interventions:** The n-3 group received the same regimen as [Belluzzi 1996](#) (enteric coated fish oil capsules with 60 minutes delay time release composed of 1.8 g/day of EPA and 0.9 g/day of DHA, as free fatty acids). Placebo capsules were Miglyol 812, as in [Belluzzi 1996](#).
 - **Outcome:** Relapse rates during a one year follow-up were recorded. Relapse was measured both clinically (CDAI > 150 with an increase of > 50 points from baseline) and by endoscopic or radiological appearance. For the meta-analysis, only clinical relapse rates were included, similar to the other three included trials.
4. [Romano 2005](#)
- **Design:** A double blind, placebo-controlled trial of one year duration.
 - **Sample size:** A total of 38 children (5 to 16 years of age, 53% male), 18 in the n-3 group and 20 in the comparison group.
 - **Setting:** Pediatric gastroenterology centers in Italy.
 - **Participants:** At baseline, participants were in remission (PCDAI < 20 for at least two months). Exclusion criteria included previous intestinal resection, previous immunomodulator therapy, and corticosteroid therapy in the last three months. No diet restrictions are reported.
 - **Interventions:** Time dependent 5-ASA (50 mg/kg/day) plus n-3 in gastro-resistant capsules (TRIOLIP-SOFAR, Italy; 1.2 g/day of EPA and 0.6 g/day of DHA, as triglycerides) versus time dependent 5-ASA (50 mg/kg/day) plus an olive oil placebo.
 - **Outcome:** Primary outcome was relapse rate within one year follow-up as defined by PCDAI > 20. Time to first relapse was also recorded but not thoroughly presented.
5. [Feagan 2008a](#) (EPIC-1)
- **Design:** A double blind, placebo-controlled trial of 52 weeks duration.
 - **Sample size:** A total of 383 adults randomized, but only 363 were eligible for the modified intention-to-treat (ITT) analysis, for which data were included only from patients who received at least 1 dose of the study drug and who provided any post randomization data (mean age 40.5 ± 15.2 years in the n-3 group and 38.2 ± 13.1 in the control group, 45% male), 183 in the n-3 group and 180 in the comparison group. Nine of the excluded patients were enrolled by a single site that violated the protocol in various cases.
 - **Setting:** Fifty-one IBD sites in Canada, Europe, Israel, and United States between January 2003 and February 2007. Patients were evaluated one week before randomization, at the time of randomization and at 4, 16, 30, 44, and 52 weeks thereafter.
 - **Participants:** At baseline, eligible participants were in remission (CDAI < 150) for at least three months and had at least one exacerbation within the previous year. Exclusion criteria included allergy or intolerance to n-3 or fish products; treatment with 5-aminosalicylates, immunosuppressives, tumor necrosis factor- α antagonists, or investigational drugs; existence of ostomy or short bowel syndrome; bowel resection or

obstruction in the preceding 3 months; malignancy (with the exception of resected basal or squamous cell skin cancer or carcinoma of the cervix in situ); substance abuse; and severe medical diseases other than CD.

- **Interventions:** Two time released 1 g gelatin capsules of n-3 twice daily (Epanova; Tillotts Pharma AG, Ziefen, Switzerland) consisted of approximately 2.2 g/day of EPA and 0.8 g/day of DHA as free fatty acids versus identical placebo of four 1 g of medium-chain triglyceride oil. To enhance tolerability, patients began with an initial dose of 1 g/day of the study drug for the first 7 days, increased to 2 g/day for 7 days and then further increased to the final dose. No new medications were allowed after randomization.
- **Outcome:** Primary outcome was time to relapse, defined by either an increase of the CDAI score to 150 points or greater and an increase of more than 70 points from the score calculated at the randomization visit, or the initiation of prohibited medical therapy or surgery for symptomatic active CD. Secondary outcomes were the change in mean scores on the CDAI and SF-36, the change in the mean serum triglyceride concentration, and the occurrence of adverse events.

6. Feagan 2008b (EPIC-2)

- **Design:** A double blind, placebo-controlled trial of 58 weeks duration.
- **Sample size:** A total of 379 adults randomized, but only 375 were eligible and received at least one dose of study medication and thus included in the analysis (mean age 38.5 ± 13.8 years in the n-3 group and 40 ± 13.6 in the control group, 43% male), 187 in the n-3 group and 188 in the comparison group.
- **Setting:** Forty-seven IBD sites in Canada, Europe, Israel, and United States between January 2003 and February 2007. Patients were evaluated at 8 weeks before randomization, at the time of randomization and at 2, 8, 16, 30, 44, and 58 weeks thereafter.
- **Participants:** Patients with active disease were treated with a standardized 16-week tapering course of either prednisone or budesonide at initial doses of 40 mg once daily and 9 mg once

daily, respectively. If the CDAI score was < 150 points 8 weeks after the initiation of corticosteroid, than the patient was eligible for randomization. At this time, patients were receiving either 20 mg/day of prednisone or 6 mg/day of budesonide. Exclusion criteria were similar to those described in EPIC-1.

- **Interventions:** Similar to the EPIC-1 trial. Corticosteroids were tapered off over 8 weeks.
- **Outcome:** Primary and secondary outcome measures were similar to those used in EPIC-1. In addition, an increase of the corticosteroid dose to control symptoms was considered a failure of treatment.

Risk of bias in included studies

None of the eligible articles were excluded based on poor quality. The results of the risk of bias analysis are summarized in [Figure 2](#). [Lorenz-Meyer 1996](#) did not describe methods used for randomization or allocation concealment and was rated as unclear for these items. Follow-up was adequate; however, the study had a drop-out rate of 8/70 (11%) in the intervention arm and 7/65 (11%) in the control arm. Another 7 and 8 patients, respectively, violated the protocol but the results represent an ITT analysis. [Belluzzi 1996](#) was a well designed study, but the report is lacking description on the methods used for randomization and allocation concealment. Blinding and follow-up were well described. The drop-out rate was 9%: 3% lost to follow-up and 6% withdrew because of diarrhea. These patients were not included in the relapse rate calculation and, thus, we performed sensitivity analysis to account for this potential bias. [Belluzzi 1997](#) was published as an abstract, with additional details supplied directly by the author. The drop-out rate was high (16%), and only 16/26 in the n-3 arm and 15/24 in the control arm were assessed for the primary outcome (endoscopic recurrence). Patients with clinical relapse were excluded from the analysis and this could be a source of attrition bias. [Romano 2005](#) was a small but well designed study. The report lacked a description of the methods used for randomization and allocation concealment. A concern was raised from the unexpectedly high rate of relapse among the control group. Follow-up was adequate and no patient dropped-out. The results of laboratory testing were not reported and this item was rated as high risk of bias.

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
Belluzzi 1996	?	?	+	-	+	+
Belluzzi 1997	?	+	+	?	+	+
Feagan 2008a	+	+	+	+	+	+
Feagan 2008b	+	+	+	+	+	+
Lorenz-Meyer 1996	?	?	+	+	+	+
Romano 2005	?	?	?	+	-	+

Feagan 2008a reports the results of the EPIC-1 and EPIC-2 studies. In these well designed, performed and reported studies, eligible patients were randomized in a 1:1 ratio using a central randomization number generator stratified by the induction therapy received prior to randomization or the duration of remission. Neither the investigators nor the patients were aware of the treatment assignment. Adherence to the study drug as assigned was evaluated at each clinic visit by interviewing the patient and by capsule counts. Lost to follow-up (not including patients that terminated the study early due to clinical relapse) was high but still in the acceptable range: 15.1% in EPIC-1 and 12.8% in EPIC-2. One critique of these studies is that the sample size calculation was performed for relapse rate while the primary outcome was based on survival analysis.

Effects of interventions

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

Relapse rate

All included studies reported the relapse rate at 1 year. Belluzzi 1996 found that significantly less patients from the intervention group relapsed (n = 11, 28%) compared to placebo (n = 27, 69%; P < 0.001) and concluded that enteric coated, timed release n-3 is highly effective in maintaining remission in Crohn's disease. This was not an ITT analysis as the outcome of patients who dropped out due to relocation (n = 2, 3%) or adverse events (n = 5, 6%) was not recorded. However, extrapolating from the survival curve, the estimated 1-year relapse rate was 39% in the intervention arm and 75% in the placebo arm. Lorenz-Meyer 1996 found no difference in the relapse rate of the intervention group (n = 40, 57%)

compared to placebo ($n = 36$, 55%; $P = 0.84$). Extrapolating from the survival curve, the estimated one year relapse rate was 69% in both groups. The authors concluded that gelatin capsules of ethyl ester fish oil capsules are not effective for maintenance of remission in Crohn's disease. [Belluzzi 1997](#) found no benefit for n-3 therapy for maintenance of remission after ileal resection. During the one year follow-up, less patients from the intervention group experienced clinical relapse ($n = 2$, 8% versus $n = 5$, 21%; $P = 0.24$) or histological relapse compared to placebo ($n = 9$, 34% versus $n = 15$, 62%; $P = 0.09$). The authors concluded that enteric coated, timed release fish oil seems to be effective for maintenance of remission after ileal resection in Crohn's disease. A very high relapse rate was found in the placebo group of the [Romano 2005](#) study ($n = 19/20$, 95% in the placebo group compared with $n = 11/18$, 61% in the intervention group; $P < 0.001$). [Romano 2005](#) concluded that enteric coated n-3 in addition to 5-ASA are effective for maintenance of remission in pediatric Crohn's disease. In this study compliance was optimal, no patients were lost to follow-up and all patients were analyzed.

In both EPIC-1 and EPIC-2 trials ([Feagan 2008a](#)), the largest of all existing studies, no significant difference in the relapse rate was found between the patients treated with n-3 or placebo. In EPIC-1, 54/183 (29.5%) treated with n-3 relapsed compared to 62/180 (34.4%) in the placebo group ($P = 0.31$). To control for 55 patients who discontinued the intervention prematurely but did not experience a relapse (26 in the n-3 group and 29 in the placebo group) a survival analysis was used, estimating the 1-year relapse rate of the n-3 group to be 31.6%, compared with 35.7% of the placebo group ($P = 0.30$). In EPIC-2, the relapse rate was 84/187 (44.9%) and 94/188 (50%) in the n-3 and placebo groups, respectively ($P = 0.38$). The 1-year relapse rate controlled for 48 patients who discontinued the intervention prematurely but did not experience a relapse (30 in the n-3 group and 18 in the placebo group) was estimated at 47.8% and 48.8% in the n-3 and placebo groups, respectively ($P = 0.48$).

Since all studies shared the primary outcome (relapse rate over 1 year in quiescent CD patients) the data were pooled in a meta-analysis (See [Analysis 1.1](#)). In the case of [Belluzzi 1997](#), clinical relapse was included (in contrast with endoscopic or radiographic relapse) to make it comparable with the other studies. The pooled risk ratio was statistically significant in favor of omega-3 fatty acids. Thirty-nine per cent of patients in the n-3 group relapsed at 12 months compared to 47% of placebo patients (6 studies, 1039 patients; RR 0.77, 95% CI 0.61 to 0.98). A GRADE analyses rated the overall quality of the evidence for the primary outcome (i.e. relapse) as very low due to unexplained heterogeneity ($I^2 = 58\%$), potential publication bias, and a high or unknown risk of bias in four studies in the pooled analysis. Although each study is somewhat different (i.e. one pediatric, one looked at post resection maintenance, one published in an abstract form, and some used a different placebo), the study by [Lorenz-Meyer 1996](#) differed the most having used a different formulation and dose of n-3. Thus, a subgroup analysis of the five studies that used enteric coated

capsules was performed (See [Analysis 1.2](#)). There was a reduction in the risk of relapse with the use of enteric coated n-3 compared with placebo with statistically significant heterogeneity ($P = 0.05$, $I^2 = 58\%$). The pooled effect was statistically significant (RR 0.71, 95% CI 0.54 to 0.93). This analysis was repeated after considering all drop-out patients in the intervention arm of [Belluzzi 1996](#) as failures and all drop-outs in the control arm as successes (See [Analysis 1.3](#)), but this did not alter the results (RR 0.77, 95% CI 0.64 to 0.93). As shown in [Analysis 1.4](#), the absolute risk reduction was 17% (95% CI 4% to 30%), and the calculated NNTB to prevent one relapse over a one year period was 5 (95% CI 3 to 25).

A sensitivity analysis excluding the abstract publication (See [Analysis 1.5](#)) did not change the results (RR 0.72; 95% CI 0.54 to 0.96). When the pediatric study by [Romano 2005](#) was excluded (See [Analysis 1.6](#)) the risk ratio was no longer statistically significant (RR 0.71; 95% CI 0.50 to 1.01). When including the *estimated* one year relapse rate ([Belluzzi 1996](#); [Feagan 2008a](#); [Lorenz-Meyer 1996](#)), rather than the actual relapse rate, the pooled risk ratio was no longer statistically significant ([Analysis 1.7](#); RR 0.61, 95% CI 0.37 to 1.02; $I^2 = 56\%$). When combining only the two largest and most rigorously performed studies, EPIC-1 and EPIC-2, the risk ratio was not statistically significant (See [Analysis 1.8](#)). Thirty-seven per cent of patients in the n-3 group relapsed at 12 months compared to 42% of placebo patients (2 studies, 738 patients; RR 0.88, 95% CI 0.74 to 1.05). No heterogeneity was detected for this comparison ($I^2 = 0\%$). A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was moderate due to sparse data (294 events).

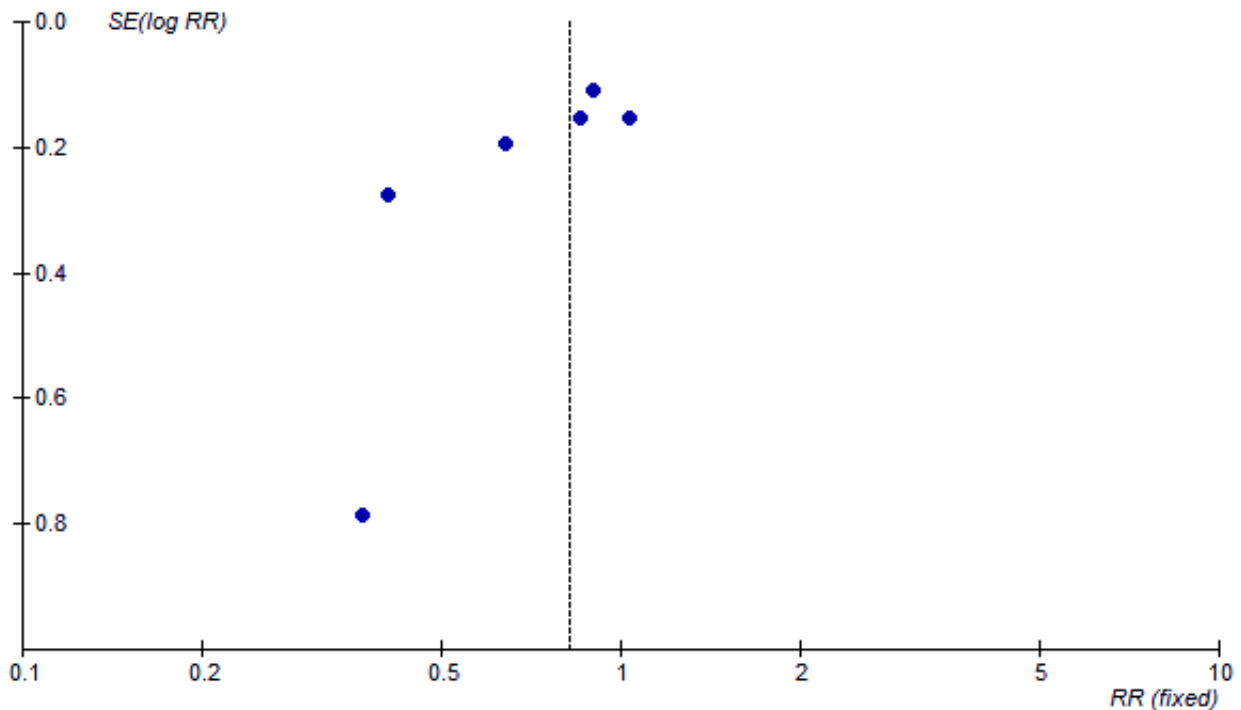
The small number of included studies limited the ability to construct a valid funnel plot. Nonetheless, the funnel plot ([Figure 3](#)) suggests the possibility of publication bias, with the representation of three positive but no negative low weighted studies.

Time to first relapse

Five studies reported on time to first relapse. [Romano 2005](#) reported the median time to first relapse which was eight months in the intervention group compared to one month in the placebo group. No survival analysis or formal comparisons were presented. [Belluzzi 1996](#) presented a survival curve; the median relapse free time was four months in the placebo group compared to greater than one year in the fish oil group (log rank test 0.006). At the end of the follow-up period, 23 of the 39 patients in the intervention arm (59%) and 10 of the 39 patients in the placebo group (26%) were still in remission ($P = 0.003$). In EPIC-1, EPIC-2 ([Feagan 2008a](#)) and [Lorenz-Meyer 1996](#) a survival analysis was the primary aim. In [Lorenz-Meyer 1996](#), extrapolating from the Kaplan Meier curve, the median relapse free periods of the placebo and the intervention arms were 133 and 159 days, respectively. This difference was not significant in both the ITT and per protocol analyses. Similarly, the proportion of relapse free patients after one year of follow-up was 31% in both groups.

Figure 3.

Review: Omega 3 fatty acids (fish oil) for maintenance of remission in Crohn's disease (For publication)
Comparison: 01 Omega-3 versus placebo
Outcome: 01 Relapse rate at one year (all studies)



Only EPIC-1 and EPIC-2 reported the Hazard Ratio (HR) with 95% CI (HR 0.82, 95% CI 0.57 to 1.18 for EPIC-1, and HR 0.90, 95% CI 0.67 to 1.21 for EPIC-2). The pooled log HR did not show any superiority for n-3 treatment relative to placebo (Analysis 1.9; HR 0.87, 95% CI 0.69 to 1.09). No heterogeneity was detected for this comparison ($I^2 = 0\%$).

Disease activity at the end of the year

Belluzzi 1996 reported on change of disease activity at the end of the follow-up period. The reduction in three inflammatory markers (erythrocytes sedimentation rate, serum alpha 2 globulins and alpha 1-acid glycoprotein) was significantly larger in the fish oil group compared to placebo. The EPIC-1 and EPIC-2 studies reported no significant differences between the study groups in CDAI scores, but data were not shown (Feagan 2008a).

Biological effect of n-3

Five studies reported the biological effect of treatment. Two studies evaluated the incorporation of n-3 into red blood cells (RBC) membranes and three studies evaluated the change in serum triglycerides. Belluzzi 1996 presented data on patients who remained in remission at the end of the follow-up period. Omega 3 fatty acids replaced 50% of the RBC arachidonic acid in the intervention arm and remained unchanged in the placebo arm. Romano 2005 showed that all subjects in the intervention arm had a statistically significant increase in the RBC concentration of EPA and DHA, and a decrease in arachidonic acid. Lorenz-Meyer 1996, and Feagan 2008a (EPIC-1 and EPIC-2) reported a significant decrease

in serum triglycerides among n-3 treated patients compared to placebo.

Quality of life

No significant difference in SF-36 scores was found between the study groups in the EPIC-1 and EPIC-2 studies (Feagan 2008a). These data were not shown.

Adverse events

Overall, no serious adverse events were reported in any of the trials. Belluzzi 1997 did not report on adverse events, but reported by personal communication that no serious adverse events occurred in either arm. Adverse events that were different between the treatment arms in at least one of the remaining five studies are summarized in Additional Table 1. Romano 2005 reported that there were no adverse events in either group, but no explicit list of items are presented. Belluzzi 1996 reported that 4/39 patients in the intervention arm withdrew due to adverse events compared to 1/39 patients in the placebo arm (due to diarrhea). Discontinuation rates secondary to adverse events in EPIC-1 and EPIC-2 (Feagan 2008a) were 9/183 versus 7/180 and 9/187 versus 5/188 in the n-3 and the placebo groups, respectively. In EPIC-1, 79.2% of patients who received n-3 had adhered to the study drug, compared with 75.6% of those who received placebo (P=0.40). The corresponding adherence rates for EPIC-2 were 75.4% and 81.4%, respectively (P=0.16).

Lorenz-Meyer 1996 was excluded from the meta-analysis of adverse events because the pathophysiology of the adverse events in that

study was very different than the others (upper gastrointestinal symptoms with regular gelatin capsules compared to more lower gastrointestinal symptoms with the timed release capsules used in all the other studies). In the pooled analyses, there was significantly more diarrhea and upper gastrointestinal symptoms with n-3 treatment compared to placebo. Nineteen per cent of n-3 patients had diarrhea compared to 14% of placebo patients (Analysis 1.10, 4 studies, 862 patients; RR 1.36, 95% CI 1.01 to 1.84). Twenty-one per cent of n-3 patients had upper gastrointestinal symptoms compared to 12% of the placebo group (Analysis 1.11, 5 studies, 999 patients; RR 1.65, 95% CI 1.25 to 2.18). No heterogeneity was detected for these comparisons ($I^2 = 0\%$ for both comparisons).

Other outcomes

Other planned outcomes (i.e. steroid use, admission rate, and number of exacerbations) were not reported in any of the studies.

DISCUSSION

Despite the fact that the EPIC studies did not show a clinical benefit to n-3, the pooled effect of the six included studies was marginally significant (RR 0.77, 95% CI 0.61 to 0.98). However, this presumed benefit is probably misleading for several reasons:

- 1) There was a large degree of heterogeneity in the pooled analysis that could not be explained on the basis of different methodology of the studies;
- 2) The statistically significant benefit did not hold when including the estimated, rather than the actual, one year relapse rate (calculated using survival estimates to account for censored data), nor did it hold when the small pediatric study (Romano 2005) was excluded; and
- 3) A funnel plot suggested publication bias, wherein small negative trials were under-represented.

Taken together, it is likely that the rigorously performed EPIC studies produced more precise estimates of the true treatment effect than the pooled analysis. It is important to emphasize that the sample size of each EPIC study was approximately double the sample size of all other included studies combined.

This conclusion is disappointing in view of indirect evidence that supports the effectiveness of n-3 in modulating inflammation of IBD. Orally administered n-3 is readily incorporated in IBD affected bowel mucosa (Hillier 1991), thereby reducing the production of local proinflammatory cytokines (Hillier 1991; Meister 2005). Fish oil also alters signaling pathways and has a direct effect on the expression of many genes (Bassaganya-Riera 2006; Deckelbaum 2006; Roy 2007). Fish oil proved to be protective in animal models with experimental IBD (Nieto 2002; Socha 2005; Vilaseca 1990). In a recent study, n-3 did not protect pigs from dextran sodium sulfate (DSS) induced IBD, but accelerated clinical remission (Bassaganya-Riera 2006). Finally, some reports indicated depleted serum n-3 in IBD patients (Kuroki 1997; Siguel 1996), but this was not replicated by others (Figler 2007; Socha 2005). An initial uncontrolled human study of fish oil supplementation, showed promising results for maintenance of remission in CD (Mate 1991).

It is difficult to explain the limited or absent clinical benefit of n-3 in Crohn's disease in view of the strong biologic rationale and the extensive supportive evidence from tissue samples and animal models. One explanation may lie in the delivery system of the drug. However, the n-3 fatty acids were being consumed and absorbed

in all studies, as reflected by decreased serum triglycerides and altered fatty acid composition of RBC. The dose might have been inadequate or the formulation not optimal. In a scientific study aimed to find the optimal chemical formulation in IBD, n-3 as enteric coated fatty acids with 60 minutes timed release had the highest serum and RBC incorporation rate and the lowest rate of adverse events, in comparison to different timed release and triglyceride compounds (Belluzzi 1994). The chemical formulation, thus, also seems to be important. It had been shown that the intestinal absorption of n-3 is higher with free fatty acids (e.g. Epanova™) compared with triacylglycerol (e.g. Max-EPA) or ester formulations (el Boustani 1987; Lawson 1988), probably due to enhanced absorption. Accordingly, the smaller effect size found in Romano 2005 could be attributed to the ethyl ester formulation that was used compared to the free fatty acids used in the other studies. In contrast, the EPIC studies failed to show benefit with Epanova™ tablets that contain timed release free fatty acids (albeit in a soft gelatin capsules; the authors claim that its bioavailability is similar to the hard capsules used by Belluzzi 1996). Notwithstanding the abovementioned data, it does appear that the biological effect of n-3 is more complex than once believed, and likely includes both anti-inflammatory and pro-inflammatory actions (Hokari 2013). This is also supported by a few animal studies that actually demonstrated a worsening of experimental colitis in mice receiving n-3 supplementation (Matsunaga 2008; Woodworth 2010). It has also been suggested that the administration of n-3 to established patients, as in the human interventional studies reviewed here, is fundamentally different from the animal studies in which n-3 was generally administered before the onset of disease (Marion-Letellier 2013).

Fish oil is considered very safe, but in the pooled analyses troublesome adverse events such as diarrhea and upper gastrointestinal symptoms were more frequent than in controls. Findings that n-3 may alter LDL level, bleeding time and glucose level have not been consistently reproduced (Oh 2005), and did not come up in any of the included studies. The non-serious but bothersome adverse events include unpleasant taste, halitosis, heartburn, nausea and diarrhea (Kim 1996; Lorenz 1989). It has been shown, that unlike raw fish, various over-the-counter n-3 preparations have at the most negligible amounts of mercury and organochlorines (Melanson 2005). Another concern relates to infants whose growth rate may be altered with high intake ratios of EPA to DHA (Akabas 2006).

A limitation of this review is the clinical heterogeneity among the included studies. The studies used different preparations of omega-3 fatty acids, with different compositions and different delivery systems. The placebo also varied among the trials, and it is possible that these placebos were not inert, with potentially either positive or negative effects. One of the studies was in the post-operative setting and another examined only pediatric patients. On the other hand, the studies were very similar in other aspects: all included only CD patients in remission, and used a similar end point of relapse rate over an identical follow-up period of one year. The use of any drug during a quiescent period is a tradeoff between the efficacy for maintaining remission and the associated adverse events. The current effective maintenance therapies for Crohn's disease, immunomodulators and infliximab, possess potentially concerning adverse reactions. Besides serious short term adverse events (e.g. infections, infusion reactions, pancreatitis, hepatitis and severe cytopenia), it has been shown that 6-mercaptopurine

and azathioprine (Kandiel 2005), and recently also infliximab (Thayu 2005), may increase the risk of developing lymphoma. The search for an effective yet safe drug to maintain remission in Crohn's disease continues.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence from two large high quality studies suggests that omega 3 fatty acids are probably ineffective for maintenance of remission in CD. Omega 3 fatty acids appear to be safe although they may cause diarrhea and upper gastrointestinal tract symptoms.

Implications for research

Further adequate sample-sized clinical trials are needed utilizing effective delivery methods of omega 3 fatty acids. Future studies should use different formulations of n-3 in the intervention arm,

inert placebo oil, and include long-term outcome data. However, before more large scale RCTs evaluating omega 3 products are conducted further basic research regarding the putative mechanism of action and the role of local drug delivery is needed.

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CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]

Belluzzi 1996

Methods	Double blind, placebo-controlled trial
Participants	N = 39 in each arm All patients had CDAI < 150 at baseline with an increase in inflammatory markers
Interventions	Enteric coated, n-3 as timed release fatty acids (1.8 g/day of EPA, 0.9 g/day of DHA) versus identical placebo of 500 mg Miglyol 812
Outcomes	Relapse rates over 1 year Adverse events Time to first relapse
Notes	
Risk of bias	
Bias	Authors' judgement Support for judgement

Belluzzi 1996 (Continued)

Random sequence generation (selection bias)	Unclear risk	Balanced block randomization scheme The method of randomization was not described
Allocation concealment (selection bias)	Unclear risk	The method of allocation concealment was not described
Blinding (performance bias and detection bias) All outcomes	Low risk	The study medications were packed identically and labelled with each patient's code number There was no difference in odor between the fish-oil and placebo preparations, provided the capsules were not broken
Incomplete outcome data (attrition bias) All outcomes	High risk	Participants who withdrew due to diarrrhea were not included in the relapse rate calculation and it is unclear whether they were included in lab results at the end of the study
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Belluzzi 1997

Methods	Double blind, placebo- controlled trial	
Participants	N = 26 in the intervention arm and 24 in the control arm Patients in remission one month following ileal resection	
Interventions	Enteric coated, n-3 as timed release fatty acids (1.8 g/day of EPA, 0.9 g/day of DHA) versus identical placebo of 500 mg Miglyol 812	
Outcomes	Clinical and endoscopic relapse rates over 1 year	
Notes	Published in abstract form	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The random list was prepared by the pharmacist of the company producing the product using a balanced block randomization scheme The method of randomization was not described
Allocation concealment (selection bias)	Low risk	Centrallized pharmacy randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	The study medications were packed identically and labelled with each patient's code number
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only 16/26 in the n-3 arm and 15/24 in the control arm were assessed for the primary outcome (endoscopic recurrence) This might be due to exclusion of patients with clinical relapse but no explanation was given

Belluzzi 1997 (Continued)

Selective reporting (reporting bias)	Low risk	Expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Feagan 2008a

Methods	Double blind, placebo-controlled trial (EPIC-1)	
Participants	n = 183 in the intervention arm and 180 in the control arm CDAI < 150 for at least three months and at least one exacerbation within the previous year	
Interventions	Enteric coated, n-3 as timed release fatty acids (2.2 g/day of EPA, 0.8 g/day of DHA) versus identical placebo of 4 g/day medium-chain triglyceride oil No new medications were allowed after randomization	
Outcomes	Time to relapse 1 year relapse rate Adverse events Change in CDAI Change in SF-36	
Notes	Both EPIC-1 and EPIC-2 were reported in one manuscript of Feagan 2008	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible patients were randomly assigned, in a 1:1 ratio using a random number generator
Allocation concealment (selection bias)	Low risk	Both studies used a central randomization procedure
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebo Neither the investigators nor the patients were aware of the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs balanced across intervention groups with similar reasons for withdrawal
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Feagan 2008b

Methods	Double blind, placebo- controlled trial (EPIC-2)
Participants	n = 187 in the intervention arm and 188 in the control arm Steroid induced remission with CDAI < 150 after 8 weeks of treatment
Interventions	Similar to the EPIC-1 trial; corticosteroids were tapered off over 8 weeks from randomization
Outcomes	Same as for EPIC-1 above
Notes	Both EPIC-1 and EPIC-2 were reported in one manuscript (Feagan 2008)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible patients were randomly assigned, in a 1:1 ratio using a random number generator
Allocation concealment (selection bias)	Low risk	Both studies used a central randomization procedure
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebo Neither the investigators nor the patients were aware of the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs balanced across intervention groups with similar reasons for withdrawal
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Lorenz-Meyer 1996

Methods	Double blind, placebo-controlled trial
Participants	N = 70 in the intervention arm and 65 in the control arm CDAI < 150 at baseline Patients on a diet low in arachidonic acid and rich in fiber
Interventions	Non-enteric coated, n-3 as ethylesther (3.3 g/day of EPA and 1.8 g/day of DHA) versus identical placebo of corn oil
Outcomes	Relapse rates over 1 year Adverse events
Notes	

Risk of bias

Lorenz-Meyer 1996 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebo of corn oil
Incomplete outcome data (attrition bias) All outcomes	Low risk	The study had a high drop-out rate, but the drop-out appeared to be balanced: 8/70 (11%) in the intervention arm and 7/65 (11%) in the control arm
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Romano 2005

Methods	Double blind, placebo-controlled trial
Participants	N = 18 in the intervention arm and 20 in the control arm PCDAI < 20 at baseline
Interventions	Enteric coated n-3 as triglycerides (1.2 g/day of EPA and 0.6 g/day of DHA) versus placebo of olive oil Both groups received 5-ASA (50 mg/kg/day)
Outcomes	Relapse rates over 1 year Time to first relapse
Notes	Pediatric study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-out rate not specifically reported, but there appear to have been no drop-outs

Romano 2005 (Continued)

Selective reporting (re-reporting bias)	High risk	Laboratory testing was performed as specified in the methods section, but no results are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Abbreviations: CDAI = Crohn's disease activity index; PCDAI = pediatric Crohn's disease activity index; 5-ASA = 5-amino salicylic acid; EPA = eicosapentanoic acid; DHA = docosahexanoic acid

Characteristics of excluded studies [ordered by study ID]

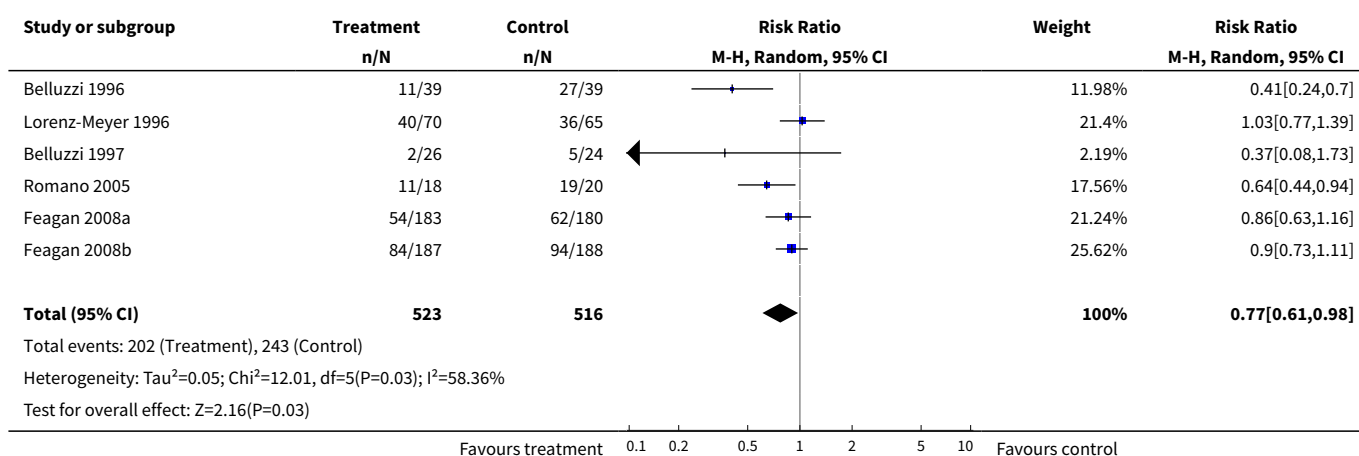
Study	Reason for exclusion
Bamba 2003	Study enrolled patients with active Crohn's disease
Bjorkkjaer 2004	N-3 treatment was for less than 6 months
Eivindson 2005	Study enrolled patients with active Crohn's disease
Geerling 2000	N-3 treatment was for less than 6 months
Lorenz 1989	Study enrolled both patients with active and non-active Crohn's disease Attempts to obtain data from the authors on the inactive patients only were unsuccessful
Mate 1991	Non-randomized study
Nielsen 2005	Study enrolled patients with active Crohn's disease
Sakurai 2002	Study enrolled patients with active Crohn's disease
Seidman 2003	Study enrolled patients with active Crohn's disease
Socha 2002	Study enrolled patients with active Crohn's disease
Trebble 2004	Study enrolled patients with active Crohn's disease
Trebble 2005	Study enrolled patients with active Crohn's disease
Tsujikawa 2000	Non-randomized study

DATA AND ANALYSES
Comparison 1. Omega-3 versus placebo

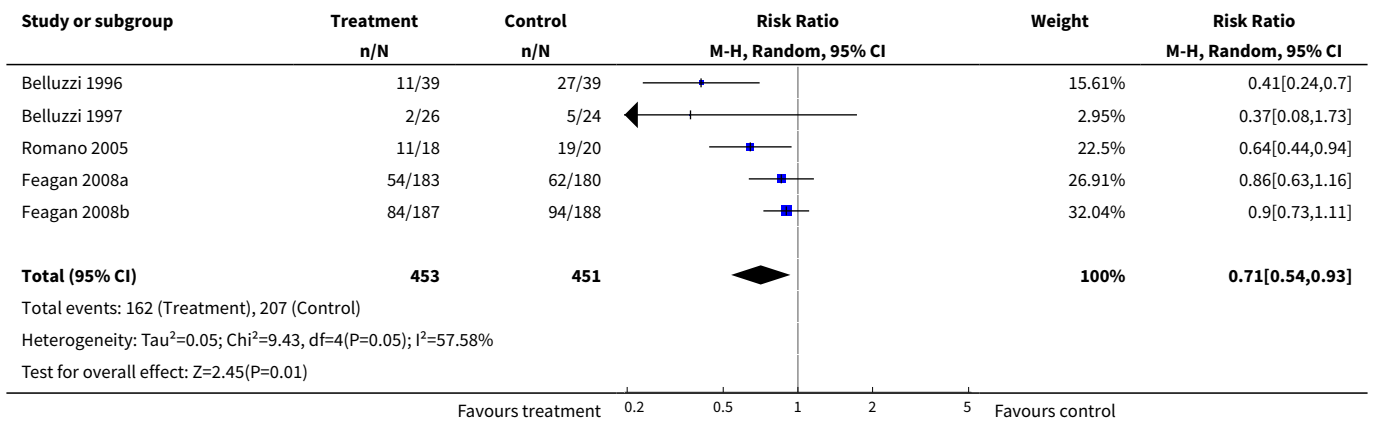
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relapse rate at one year (all studies)	6	1039	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.61, 0.98]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Relapse rate at one year (enteric coated studies)	5	904	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.54, 0.93]
3 Relapse rate at one year (sensitivity analysis of Belluzi 1996)	5	904	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.64, 0.93]
4 Relapse rate at one year (enteric coated - risk difference)	5	904	Risk Difference (M-H, Random, 95% CI)	-0.17 [-0.30, -0.04]
5 Relapse rate at one year (sensitivity analysis - excluding abstract study)	4	854	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.54, 0.96]
6 Relapse rate at one year (sensitivity analysis - excluding pediatric study)	4	866	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.50, 1.01]
7 Relapse rate at one year (all studies, rate in EPIC studies by survival estimates)	6	1039	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.66, 1.00]
8 Relapse rate at one year (only EPIC studies)	2	738	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.74, 1.05]
9 Relapse at one year, survival analysis (Hazard Ratios of the EPIC studies)	2		hazard ratio (Random, 95% CI)	0.87 [0.69, 1.09]
10 Adverse events rate: Diarrhea	4	862	Risk Ratio (M-H, Random, 95% CI)	1.36 [1.01, 1.84]
11 Adverse events rate: Upper GI symptoms (nausea, vomiting, halitosis, heartburn, dyspepsia, disgeusia and bloating)	5	999	Risk Ratio (M-H, Random, 95% CI)	1.65 [1.25, 2.18]

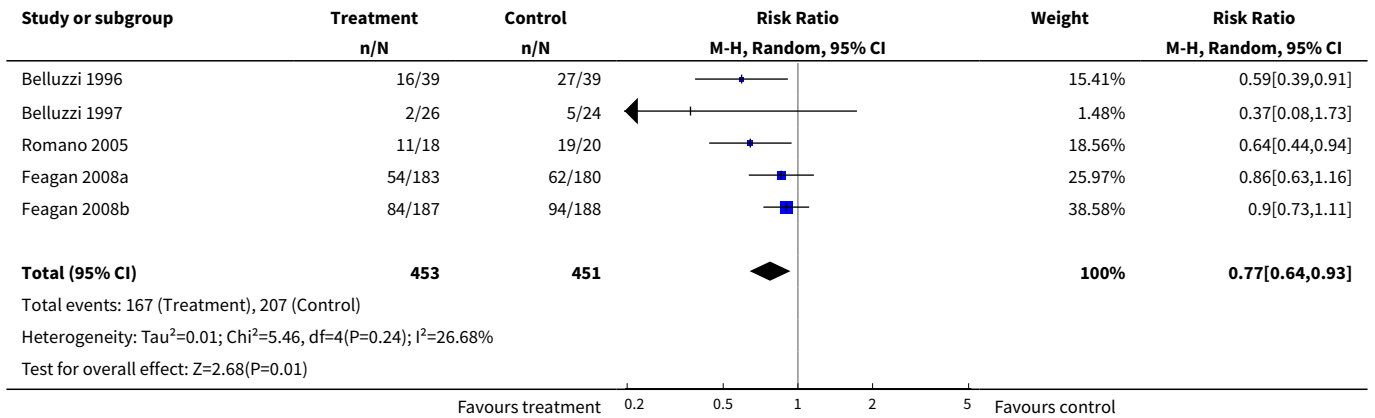
Analysis 1.1. Comparison 1 Omega-3 versus placebo, Outcome 1 Relapse rate at one year (all studies).



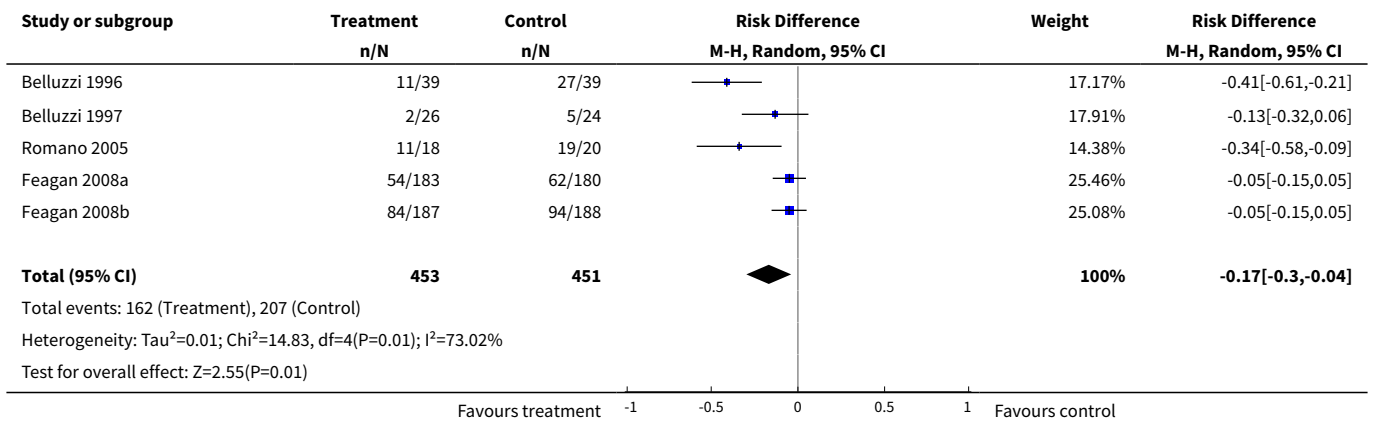
Analysis 1.2. Comparison 1 Omega-3 versus placebo, Outcome 2 Relapse rate at one year (enteric coated studies).



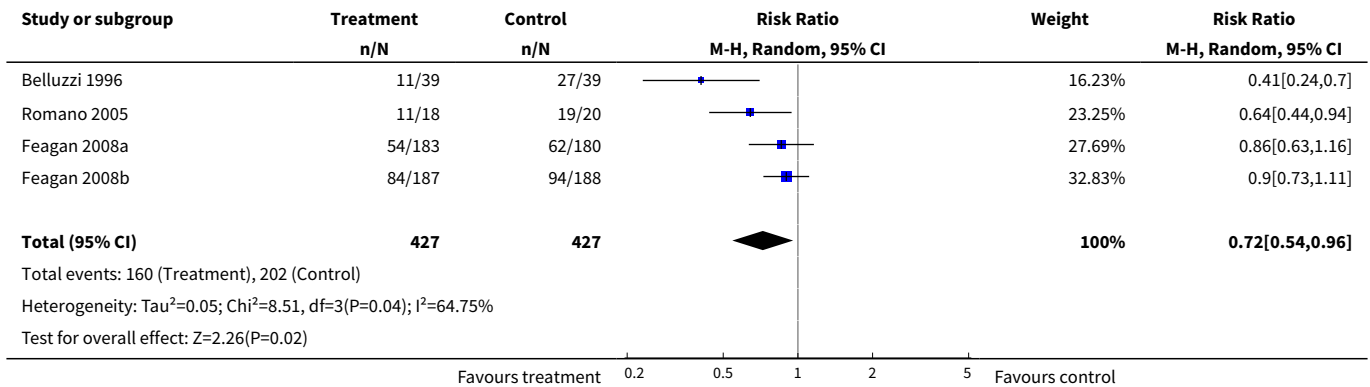
Analysis 1.3. Comparison 1 Omega-3 versus placebo, Outcome 3 Relapse rate at one year (sensitivity analysis of Belluzi 1996).



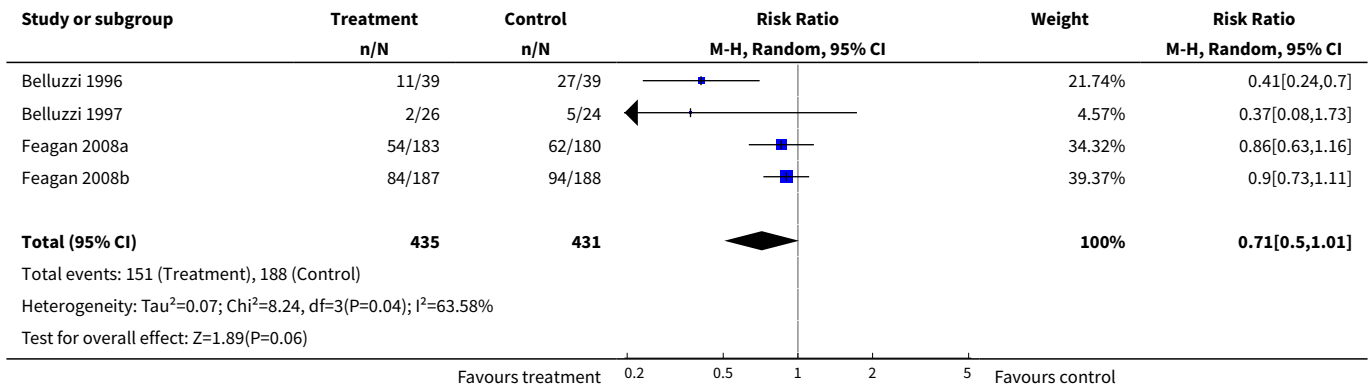
Analysis 1.4. Comparison 1 Omega-3 versus placebo, Outcome 4 Relapse rate at one year (enteric coated - risk difference).



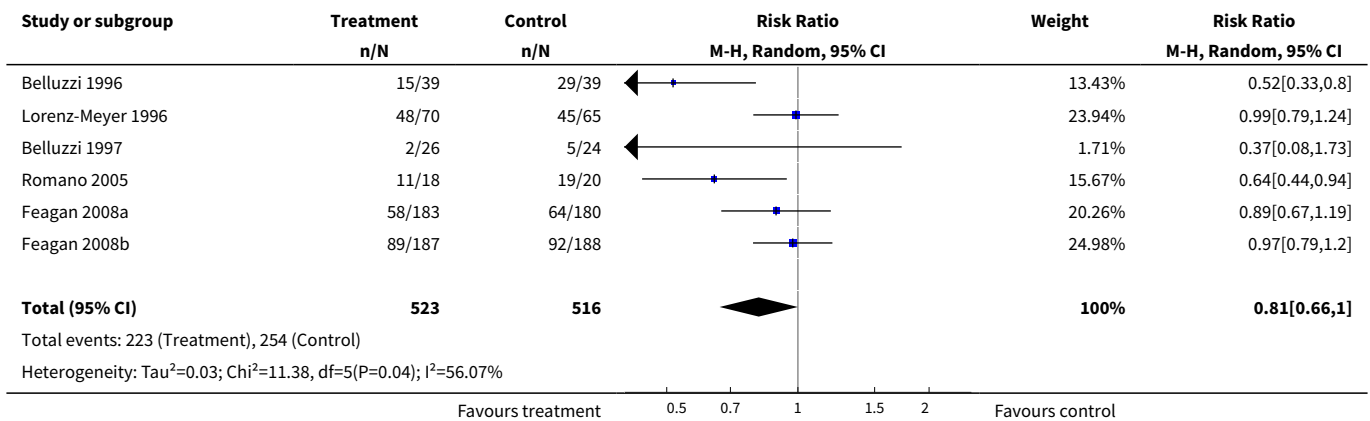
Analysis 1.5. Comparison 1 Omega-3 versus placebo, Outcome 5 Relapse rate at one year (sensitivity analysis - excluding abstract study).

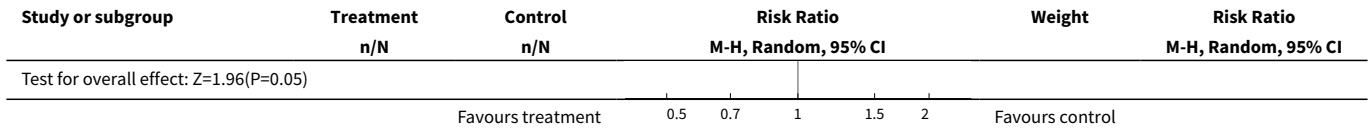


Analysis 1.6. Comparison 1 Omega-3 versus placebo, Outcome 6 Relapse rate at one year (sensitivity analysis - excluding pediatric study).

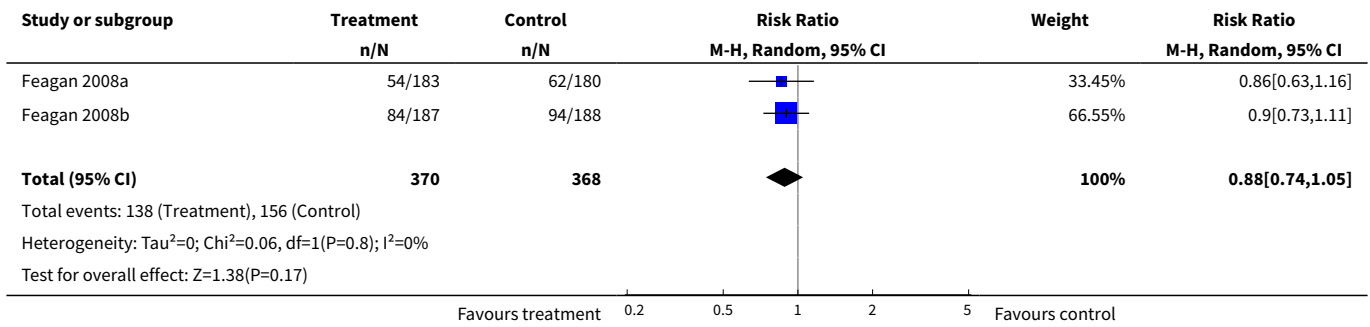


Analysis 1.7. Comparison 1 Omega-3 versus placebo, Outcome 7 Relapse rate at one year (all studies, rate in EPIC studies by survival estimates).

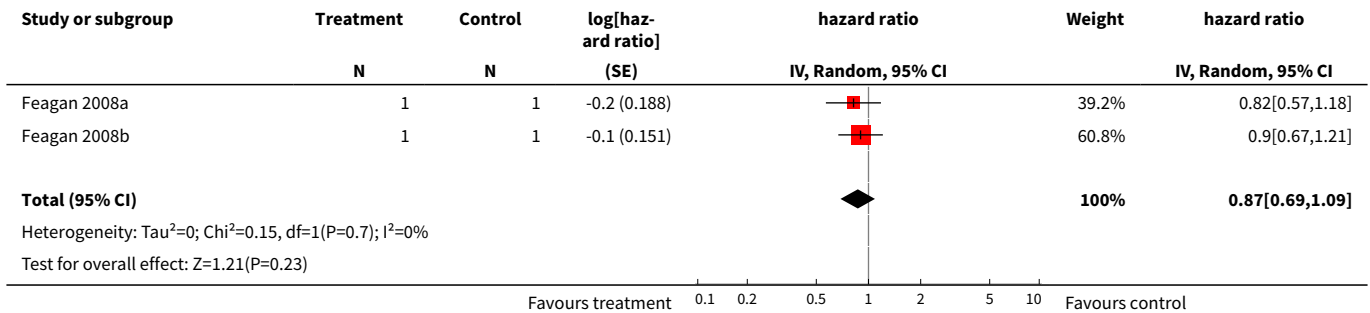




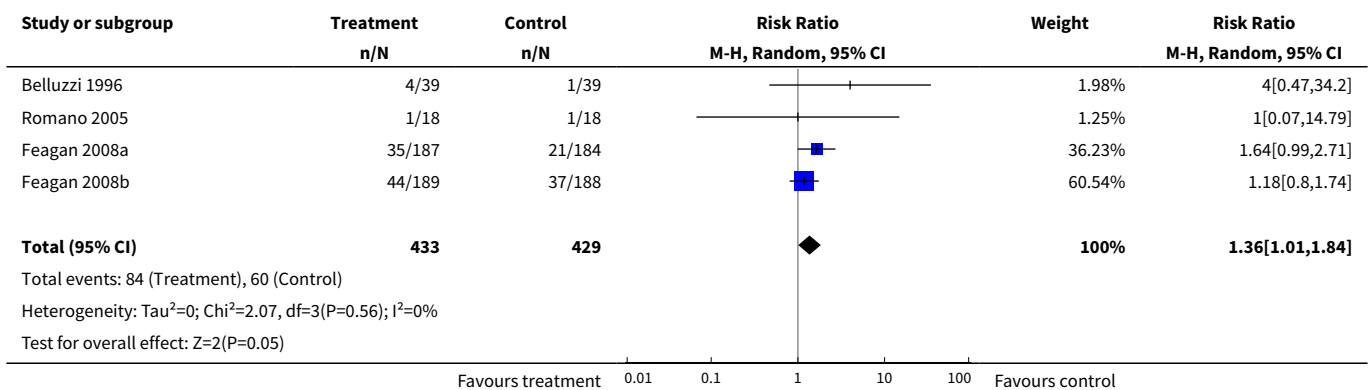
Analysis 1.8. Comparison 1 Omega-3 versus placebo, Outcome 8 Relapse rate at one year (only EPIC studies).



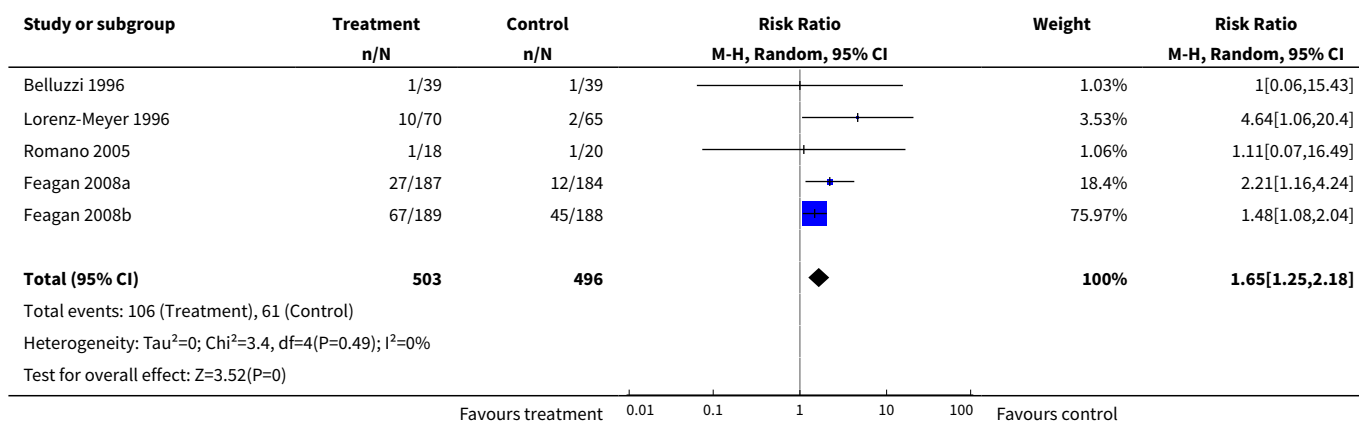
Analysis 1.9. Comparison 1 Omega-3 versus placebo, Outcome 9 Relapse at one year, survival analysis (Hazard Ratios of the EPIC studies).



Analysis 1.10. Comparison 1 Omega-3 versus placebo, Outcome 10 Adverse events rate: Diarrhea.



Analysis 1.11. Comparison 1 Omega-3 versus placebo, Outcome 11 Adverse events rate: Upper GI symptoms (nausea, vomiting, halitosis, heartburn, dyspepsia, dysgeusia and bloating).



ADDITIONAL TABLES

Table 1. Adverse events that were different between the intervention and control arms

Study	Belluzzi 1996	Lorenz-Meyer 1996	Romano 2005	Feagan 2008; EPIC 1	Feagan 2008; EPIC 2
Diarrhea -intervention vs control	4/39 (10%) vs. 1/39 (3%)	1/70 (1%) vs. 1/65 (2%)	0/18 (0%) vs. 0/20 (0%)	35/187 (19%) vs. 21/184 (11%)	44/189 (23%) vs 37/188 (20%)
Halitosis, or heartburn -intervention vs control	0/39 (0%) vs. 0/39 (0%)	10/70 (14%) vs. 2/65 (3%)	0/18 (0%) vs. 0/20 (0%)	not reported but dysgeusia: 2/187 (1%) vs 1/184 (0.5%)	not reported but dysgeusia: 10/189 (5%) vs. 2/188 (1%)
Nausea -intervention vs control	0/39 (0%) vs. 0/39 (0%)	0/70 (0%) vs. 0/65 (0%)	0/18 (0%) vs. 0/20 (0%)	17/187 (9%) vs. 4/184 (2%)	30/189 (16%) vs. 19/188 (10%)
All upper GI symptoms -intervention vs. controls (halitosis, nausea, vomiting, dyspepsia, dysgeusia and bloating)	0/39 (0%) vs. 0/39 (0%)	10/70 (14%) vs. 2/65 (3%)	0/18 (0%) vs. 0/20 (0%)	27/187 (14%) vs..12/184 (6.5%)	67/189 (35.5%) vs. 45/188 (24%)

APPENDICES

Appendix 1. Electronic Search Strategies

Appendix I – Electronic Search Strategies

Database	Search	Query	Results
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(Continued)

PUBMED run Nov. 22, 2013	1	(singl* OR doubl* OR tripl* OR trebl* OR blind* OR mask* OR placebo* OR single-blind* OR double-blind* OR triple-blind* OR random* OR (controlled clinical))	2,478,073
	2	(crohn* OR enteritis OR ileitis)	53,319
	3	(#1 AND #2)	6,478
	4	((fish oil) OR efamed OR (fish oils) OR promega OR (super epa) OR superepa OR (tuna oil) OR (tuna oils))	22,213
	5	(omega-3 OR (omega 3) OR (n-3 fatty acid) OR (n3 fatty acid) OR (n-3 PUFA) OR (n3 PUFA) OR (n-3 polyunsaturated) OR (n3 polyunsaturated) OR (n3 poly unsaturated) OR (n-3 poly unsaturated) OR (seal oil) OR (krill oil))	21,926
	6	(icosapentaenoic OR docosahexaenoic OR linolenic OR eicosapentaenoic OR alpha-linolenic OR EPA OR DHA)	30,125
	7	(#4 OR #5 OR #6)	45,886
	8	(#3 AND #7)	57
EMBASE + EMBASE Classic (1947 - 2013) run Nov. 22, 2013	1	random\$.tw.	882,607
	2	factorial\$.tw.	22,991
	3	(crossover\$ or cross over\$ or cross-over\$).tw.	72,085
	4	placebo\$.tw.	207,389
	5	single blind.mp.	24,794
	6	double blind.mp.	186,064
	7	triple blind.mp.	338
	8	(singl\$ adj blind\$).tw.	14,471
	9	(double\$ adj blind\$).tw.	151,927
	10	(tripl\$ adj blind\$).tw.	383
	11	assign\$.tw.	242,174
	12	allocat\$.tw.	83,271
	13	crossover procedure/	39,339
	14	double blind procedure/	123,454
	15	single blind procedure/	18,566

(Continued)

16	triple blind procedure/	60
17	randomized controlled trial/	362,954
18	or/1-17	1,298,268
19	(exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)	5,891,223
20	18 not 19	1,115,668
21	exp Crohn disease/ or crohn*.mp. or exp colon Crohn disease/	66,863
22	(enteritis or ileitis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	63,073
23	21 or 22	108,448
24	20 and 23	4,950
25	fish oil.mp. or exp fish oil/	14,247
26	(efamed or fish oils or promega or "super epa" or superepa or "tuna oil" or "tuna oils").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	3,778
27	omega-3.mp. or exp omega 3 fatty acid/	21,010
28	("omega 3" or "n-3 fatty acid" or "n3 fatty acid" or "n-3 PUFA" or "n3 PUFA" or "n-3 polyunsaturated" or "n3 polyunsaturated" or "n3 poly unsaturated" or "n-3 poly unsaturated" or "seal oil" or "krill oil").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	23,487
29	icosapentaenoic acid.mp. or exp icosapentaenoic acid/	10,769
30	docosahexaenoic acid.mp. or exp docosahexaenoic acid/	14,509
31	linolenic acid.mp. or exp linolenic acid/	11,370
32	("eicosapentaenoic acid" or "eicosapentaenoic acid*" or "icosapentaenoic acid*" or "docohexaenoic acid*" or "alpha-linolenic acid" or "linolenic acid*" or "alpha-linolenic acid*" or EPA or DHA).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	36,564
33	25 or 26 or 27 or 28 or 29 or 30 or 31 or 32	60,990
34	24 and 33	94
All OVID Medline (1946 - present)	1 random\$.tw.	73,9513

(Continued)

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2	factorial\$.tw.	18,494
3	(crossover\$ or cross over\$ or cross-over\$).tw.	64,433
4	placebo\$.tw.	169,408
5	single blind.mp.	24,116
6	double blind.mp.	160,664
7	triple blind.mp.	260
8	(singl\$ adj blind\$).tw.	11,808
9	(double\$ adj blind\$).tw.	121,299
10	(tripl\$ adj blind\$).tw.	320
11	assign\$.tw.	213,631
12	allocat\$.tw.	71,382
13	crossover procedure/	0
14	double blind procedure/	0
15	single blind procedure/	0
16	triple blind procedure/	0
17	randomized controlled trial/	390,954
18	or/1-17	1,106,670
19	(exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)	4,056,651
20	18 not 19	981,666
21	exp Crohn disease/ or crohn*.mp. or exp colon Crohn disease/	41,252
22	(enteritis or ileitis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	16,138
23	21 or 22	54,204
24	20 and 23	2,323
25	fish oil.mp. or exp fish oil/	20,955
26	(efamed or fish oils or promega or "super epa" or superepa or "tuna oil" or "tuna oils").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword head-	6,963

(Continued)

		ing word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	
27	omega-3.mp. or exp omega 3 fatty acid/		19,961
28	("omega 3" or "n-3 fatty acid" or "n3 fatty acid" or "n-3 PUFA" or "n3 PUFA" or "n-3 polyunsaturated" or "n3 polyunsaturated" or "n3 polyunsaturated" or "n-3 poly unsaturated" or "n-3 poly unsaturated" or "seal oil" or "krill oil").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]		15,620
29	icosapentaenoic acid.mp. or exp icosapentaenoic acid/		30
30	docosahexaenoic acid.mp. or exp docosahexaenoic acid/		7,754
31	linolenic acid.mp. or exp linolenic acid/		6,995
32	("eicosapentaenoic acid" or "eicosapentaenoic acid*" or "icosapentaenoic acid*" or "docohexaenoic acid*" or "alpha-linolenic acid" or "linolenic acid*" or "alpha-linolenic acid*" or EPA or DHA).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]		25,252
33	25 or 26 or 27 or 28 or 29 or 30 or 31 or 32		40,767
34	24 and 33		38
OVID HealthSTAR (1966 – Oct. 2013)			
1	random\$.tw.		506,378
2	factorial\$.tw.		9,199
3	(crossover\$ or cross over\$ or cross-over\$.tw.		46,972
4	placebo\$.tw.		137,186
5	single blind.mp.		23,308
6	double blind.mp.		160,326
7	triple blind.mp.		199
8	(singl\$ adj blind\$.tw.		9,666
9	(double\$ adj blind\$.tw.		110,768
10	(tripl\$ adj blind\$.tw.		246
11	assign\$.tw.		108,502
12	allocat\$.tw.		46,302

(Continued)

13	crossover procedure/	0
14	double blind procedure/	0
15	single blind procedure/	0
16	triple blind procedure/	0
17	randomized controlled trial/	174,967
18	or/1-17	742,216
19	(exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)	84,390
20	18 not 19	741,219
21	exp Crohn disease/ or crohn*.mp. or exp colon Crohn disease/	19,397
22	(enteritis or ileitis).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	4,406
23	21 or 22	23,010
24	20 and 23	1,651
25	fish oil.mp. or exp fish oil/	8,731
26	(efamed or fish oils or promega or "super epa" or superepa or "tuna oil" or "tuna oils").mp. [mp=title, original title, abstract, name of substance word, subject heading word]	2,663
27	omega-3.mp. or exp omega 3 fatty acid/	8,565
28	("omega 3" or "n-3 fatty acid" or "n3 fatty acid" or "n-3 PUFA" or "n3 PUFA" or "n-3 polyunsaturated" or "n3 polyunsaturated" or "n3 poly unsaturated" or "n-3 poly unsaturated" or "seal oil" or "krill oil").mp. [mp=title, original title, abstract, name of substance word, subject heading word]	7,187
29	icosapentaenoic acid.mp. or exp icosapentaenoic acid/	6
30	docosahexaenoic acid.mp. or exp docosahexaenoic acid/	2,341
31	linolenic acid.mp. or exp linolenic acid/	1,890
32	("eicosapentaenoic acid" or "eicosapentaenoic acid*" or "icosapentaenoic acid*" or "docohexaenoic acid*" or "alpha-linolenic acid" or "linolenic acid*" or "alpha-linolenic acid*" or EPA or DHA).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	9,522
33	25 or 26 or 27 or 28 or 29 or 30 or 31 or 32	16,205
34	24 and 33	28

(Continued)

Cochrane Library (CENTRAL) run Nov. 22, 2013	1	crohn* or enteritis or ileitis	1,797
	2	(fish oil) or efamed or (fish oils) or promega or (super epa) or superepa or (tuna oil) or (tuna oils)	1,535
	3	omega-3 or (omega 3) or (n-3 fatty acid) or (n3 fatty acid) or (n-3 PUFA) or (n3 PUFA) or (n-3 polyunsaturated) or (n3 polyunsaturated) or (n3 polyunsaturated) or (n-3 poly unsaturated) or (seal oil) or (krill oil)	2,930
	4	icosapentaenoic or docosahexaenoic or linolenic or eicosapentaenoic or alpha-linolenic or EPA or DHA	2,168
	5	#2 or #3 or #4	4,549
	6	#1 and #5	49*
ACP Journal Club run Nov. 22, 2013		“crohn*” OR “ileitis” OR “enteritis”	7 hits, none of which were related to fish oils
DDW abstracts (1981-2010; later abstracts are found in EMBASE)		(crohn* OR ileitis OR enteritis) AND (omega OR fish OR tuna OR seal OR krill OR polyunsaturated OR icosapentaenoic OR docosahexaenoic OR linolenic OR eicosapentaenoic OR PUFA OR DHA OR EPA OR fatty OR promega OR efamed)	24

* Of those 49 hits, only 27 were references to clinical trials and thus only those 27 hits were exported to Endnote.

WHAT'S NEW

Date	Event	Description
18 June 2014	Amended	Contains new information provided by author of included study

HISTORY

Protocol first published: Issue 1, 2007

Review first published: Issue 2, 2007

Date	Event	Description
30 May 2014	Amended	Correction regarding correspondence with author of included study
22 November 2013	New search has been performed	New search, no new studies identified

Date	Event	Description
22 November 2013	New citation required but conclusions have not changed	Updated review with two new authors

CONTRIBUTIONS OF AUTHORS

RL Responsible for search for new literature published since the previous review, reviewed and edited the updated manuscript.

OL Participated in review and editing of the updated manuscript.

AMG Formulated the research question, provided IBD expert opinion, selected and reviewed the eligible studies, involved in the analyses, and reviewed the manuscript.

DT Responsible for the literature search, selecting and reviewing the eligible studies, performing the analyses; wrote the previous versions of the manuscript and reviewed the current manuscript.

DECLARATIONS OF INTEREST

None known.

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- Hospital for Sick Children, Toronto, Canada.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Crohn Disease [*diet therapy]; Fatty Acids, Omega-3 [*therapeutic use]; Fish Oils [*therapeutic use]; Randomized Controlled Trials as Topic; Remission Induction; Secondary Prevention

MeSH check words

Adult; Child; Humans