University of York
Centre for Reviews and Dissemination
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PROSPERO International prospective register of systematic reviews

Dietary polyunsaturated fat for prevention and treatment of inflammatory bowel disease

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Review question(s)

To assess the effect of altering omega-3, omega-6 and total PUFA intake in adults on inflammatory bowel disease and broader markers of inflammation.

Searches

Electronic searches

We will identify trials through systematic searches of the following bibliographic databases:

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

2. MEDLINE (Ovid)

3. Embase (Ovid)

We will also conduct a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch/). We will search all databases from their inception to the present, and we will impose no restriction on language of publication or time.

Types of study to be included

We will include randomised controlled trials of any number of participants, comparing higher omega-3, omega-6 or PUFA intake with lower omega-3, omega-6 or PUFA intake, or omega-3 vs omega-6, with follow-up for 6 months or longer, and having assessed a primary outcome.

Condition or domain being studied

Inflammatory bowel disease (Crohn's Disease & ulcerative colitis)

Participants/ population

Men and women aged 18 or over with or without a diagnosis of inflammatory bowel disease. Studies will be excluded where participants are pregnant or acutely ill (diagnosed with current cancer, undergoing heart or renal transplantation, with AIDS or HIV, on haemodialysis, with IgA glomerulonephritis or any other renal problem).

Intervention(s), exposure(s)

Eligible studies will compare higher with lower total polyunsaturated fat (PUFA) intakes. The intervention must be either dietary supplementation, or a provided diet, or advice on diet. The advice, foodstuffs or supplements must aim to increase or decrease total PUFA intake, or, if no clear aim is stated (but implied, such as aiming to provide a ‘hearthealth’ or ‘Mediterranean’ diet), then the intervention must achieve an increase or decrease of at least 10% of the baseline total PUFA level.

Supplementation may be in oil or capsule form, or as foodstuffs provided, to be consumed by mouth (we will exclude enteral and parenteral feeds and enemas). Studies will not be included if they include a multiple risk factor

intervention on lifestyle factors other than diet and supplementation (unless the effect of diet or supplementation could be separated out from the other interventions). Where the alteration of PUFA intake is only part of a dietary intervention (such as a combined intervention to increase PUFA and fruit and vegetable intake) the study will be excluded.

Comparator(s)/ control

Studies will be included if they compared the effect of this intervention with usual diet, no advice, no supplementation or placebo (as appropriate) or with the opposite intervention (raised versus lower PUFA intake).

Outcome(s)

Primary outcomes

1. Rates of remission and/or relapse

2. Measures of disease severity

3. New diagnosis of IBD

4. Changes in inflammatory markers: hsCRP, CRP, ESR, IL-6, faecal calprotectin

Secondary outcomes

1. Corticosteroid, immunosuppressant, immunomodulator use

2. Quality of life

3. Body weight and measures of adiposity

4. Changes in inflammatory markers (excluding those extracted as a primary outcome)

5. Side effects

6. Drop outs

Data extraction, (selection and coding)

Review authors will independently screen titles and abstracts for inclusion of all the potential studies we identify as a result of the search and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'.

If there are any disagreements, a third author will be asked to arbitrate. We will retrieve the full text study reports/publication and two review authors will independently screen the full-text, identify studies for inclusion, and identify and record reasons for exclusion of ineligible studies. We will resolve any disagreement through discussion.

Risk of bias (quality) assessment

Two reviewers will independently assess risk of bias for each study, alongside data extraction, using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. We will resolve any disagreements by discussion or by involving another reviewer.

Additional review-specific criteria will include similarity or not of type and intensity of intervention in both arms (attention) and compliance. A study will be considered at low risk of attention bias when participants were given the same amount of time and attention from study staff and health professionals whether they were in the intervention or control arms, and at low risk of compliance bias when compliance was assessed, results of that assessment clearly reported for both intervention and control arms, and where most participants appeared to have taken at least 75% of the intended PUFA dose. A trial will be considered to be at low risk of bias if allocation concealment was adequate, and participant, provider and outcome assessor blinding were all coded at low risk of bias. All other trials were considered at moderate or high risk of bias

Strategy for data synthesis

Primary measures of interest will be effects of dietary advice or supplementation of omega 3 fats, omega 6 fats, and

total PUFA, on primary outcomes. We will separate out effects of omega 3, omega 6 and total PUFA in all analyses (giving 3 separate sets of results, one for omega 3 fats, one for omega 6 and one for total PUFA).

We will undertake meta-analyses if there is sufficient similarity in treatments, participants and underlying clinical questions for pooling to make sense. Our primary analyses will assess effects of dietary or supplemental sources of omega-3 fatty acids, omega-6 fatty acids or total PUFA separately.

We will use a random effects model, as dietary interventions are complex and tend to be heterogeneous, but we will compare the results of random-effects and fixed-effect meta-analysis in sensitivity analyses. We will also undertake sensitivity analyses to assess the effects of methodological rigour as well as study size.

Analysis of subgroups or subsets

We will examine the effects of altering omega-3, omega-6 and total polyunsaturated fatty acid (PUFA) intake on primary outcomes by performing subgroup analyses on:

1. Diagnosis of ulcerative colitis (UC) or Crohn's Disease (CD) if combined IBD outcomes and data available;

2. Baseline IBD severity;

3. Replacement of saturated fatty acid (SFA) with PUFA;

4. Replacement of monounsaturated fatty acid (MUFA) with PUFA;

5. For long chain omega 3 fats: At least 150, 250, 400 mg/ daily from all sources including supplements (above or below each threshold) fish omega 3 dose - low dose 0.4 to 2.4g/day, medium dose 2.5 to 4.4 g/day, and high dose =4.5g/day of combined long chain omega 3 fats;

6. For a-linolenic acid (ALA), omega 6 and total PUFA: higher vs lower levels of intake;

7. Number of participants: studies with less than 60 participants, between 61 and 99 participants, over 100 participants;

8. Dietary supplemental source: dietary advice, supplemental foods (for example margarine fortified with rapeseed, tins of sardines or oils to use in cooking) provided by the study, or supplements (capsules or oils) provided to take as medicine;

9. Trial duration: studies with short-term follow-up (6 to 12 months), medium-term follow up (12 to 23 months), long-term follow up (24 to 48 months);

10. Baseline omega 3, omega 6 or total PUFA intake;

11. Level of baseline medication use: corticosteroid, immunosuppressant, immuno-modulatory therapies;

12. For the total PUFA analyses we will assess and analyse by n3/n6 ratio (for whole diet in intervention and control groups) where possible;

13. Pre-diagnostic inflammatory markers, such as CRP level, in IBD and non-IBD patients;

14. Age;

15. Gender;

16. Weight.

Sensitivity analysis:

Sensitivity analyses will be used to assess robustness of results to trial quality:

• meta-analysis using fixed, rather than random, effects

• excluding high risk of bias studies

Funnel plots will be used to assess for evidence of small study bias (Egger 1997). Type and frequency of side effects and adverse effects were tabulated (with the other extracted data on adverse effects) and compared between different studies and designs.

The quality of evidence will be rated using GRADE (Grading of Recommendations Assessment, Development and Evaluation, which provides an explicit and comprehensive method to rate quality of evidence in health, GRADE Working Group 2004) using GRADEpro software, and reported in the Summary of Findings table.

Dissemination plans
We will publish in appropriate peer-reviewed journals

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Conflicts of interest
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Stage of review at time of this submission	Started	Completed
Preliminary searches	No	Yes
Piloting of the study selection process	No	Yes
Formal screening of search results against eligibility criteria	No	Yes
Data extraction	Yes	No
Risk of bias (quality) assessment	Yes	No
Data analysis	Yes	No