World Health Organization

Set of systematic reviews of RCTs on the health effects of omega 3 polyunsaturated fats in adults

[ABRIDGED VERSION CONTAINING RESULTS FOR SELECTED OUTCOMES ONLY]

Prepared by:

Lee Hooper, Asmaa Abdelhamid, Sarah Ajabnoor, Julii Brainard, Tracey Brown, Sarah Hanson, Gabrielle Thorpe, Oluseyi F Jimoh, Priti Biswas, Xia Wang, Alex O'Brien, Daisy Donaldson, Lauren Winstanley, Zoya Ahmed, Faye Alabdulghafoor, Nicole Martin, Charlene Bridges, Katherine Deane and Fujian Song, for WHO NUGAG

This document reports on 4 systematic reviews of RCTs in adults:

1. **effects of omega 3 fats on all-cause mortality**
2. **effects of omega 3 fats on cardiovascular outcomes, including cardiovascular mortality, cardiovascular events, coronary heart disease and stroke**
3. **effects of omega 3 fats on lipids and other CVD risk factors**
4. **effects of omega 3 fats on atrial fibrillation**

Other reviews have been omitted:

5. **effects of omega 3 fats on neurocognitive outcomes, including dementia**
6. **effects of omega 3 fats on type 2 diabetes**
7. **effects of omega 3 fats on depression**
8. **effects of omega 3 fats on breast cancer**
9. **effects of omega 3 fats on inflammatory bowel disease**
10. **effects of omega 3 fats on measures of adiposity**

Index

Contents

Index ... 3

Chapter 1. Background and Objectives ... 5

Objectives ... 6

Chapter 2. Methods ... 7

Criteria for considering studies for this review ... 7

Search methods for identification of studies ... 8

Data collection and analysis ... 9

Results ... 19

Description of studies ... 19

Chapter 3. Do dietary or supplemental omega 3 fatty acids alter all-cause mortality? ... 22

Chapter 4. Do dietary or supplemental omega 3 fatty acids alter risk of cardiovascular events, coronary heart disease or stroke (in people with or without existing cardiovascular disease)? ... 33

Chapter 5. What are the effects of dietary or supplemental omega 3 fatty acids on CVD risk factors such as serum total cholesterol, HDL or LDL cholesterol or triglycerides? ... 80

Chapter 6. Do dietary or supplemental omega 3 fatty acids alter risk of atrial fibrillation (in people with or without existing atrial fibrillation)? ... 98

Chapter 7. Do dietary or supplemental omega 3 fatty acids alter risk of type 2 diabetes or treatment outcome in type 2 diabetes? ... 105

Chapter 8. Do dietary or supplemental omega 3 fatty acids alter risk of neurocognitive outcomes including dementia, or the course of dementia? ... 105

Chapter 9. Do dietary or supplemental omega 3 fatty acids alter risk of depression in people with or without an existing diagnosis of depression? ... 105

Chapter 10. Do dietary or supplemental omega 3 fatty acids alter risk of breast cancer (in primary or secondary prevention)? ... 105

Chapter 11. Do dietary or supplemental omega 3 fatty acids have a role in primary or secondary prevention of inflammatory bowel disease? ... 106

Chapter 12. Do dietary or supplemental omega 3 fatty acids alter the risk of increased adiposity or long term weight control? ... 106

Chapter 13. Discussion ... 107

Chapter 14. GRADE and summary ... 108

Appendix 1. Electronic searches ... 118

1a. Medline (Ovid) search strategy run in 2002 (for the previous version of the omega 3 review on the Cochrane Library) ... 118

1b Searches run in July 2016 and April 2017 ... 119

1c. Searches run in July and September 2016, and April 2017 for allied reviews ... 122

Appendix 2. Characteristics of included studies 125
Appendix 3. Baseline dietary intake data (before intervention starts) 206
Appendix 4. Dietary intake during the study intervention period 206
Appendix 5. Fatty acid status measures 206
Appendix 6. Dosage table for omega 3 interventions 206
Appendix 7. References to included studies 207

Appendix 8. Characteristics of ongoing studies 253
Appendix 9. Other references 254
Appendix 10. Other published versions of this review 261

Chapter 1. Background and Objectives

Since the suggestion by Bang (Bang 1972; Bang 1976), that the abundance of omega 3 fatty acids in the diet of the Greenland Eskimos was responsible for their low mortality from ischaemic heart disease, there has been considerable interest in the protective role and possible mechanism of action of marine unsaturated fats. This interest has spread to encompass plant seeds and oils rich in omega 3 fatty acids, including chia seed, flax (linseed) and rapeseed (canola) oils (Nettleton 1991), their derivatives (e.g. margarines), purslane leaves (Simopoulos 1992), and nuts (especially walnuts).

Omega 3 fats (also called Ω3 or n-3 fats) from fish sources include eicosapentaenoic acid (EPA or 20:5), docosahexaenoic acid (DHA, 22:6) and docosapentaenoic acid (DPA, 22:5), and are the longer chain omega 3 fats. Alpha-linolenic acid (ALA or α-linolenic, 18:3) is the shorter chain omega 3 fat from plants (also found in grass fed meats), which is partially converted to longer chain omega 3 fatty acids within our bodies. There is some debate about the effectiveness of this conversion, which may differ depending on other dietary factors (Li 1999; Pawlosky 2001) and whether assessed over short or long term. For this reason, the effectiveness of ALA may differ from that of the longer chain omega 3 fats (LCn3).

Proposed mechanisms for the protective role of omega 3 fats against cardiovascular diseases include: lowering of blood pressure; altered lipid profile, especially reduced serum triglyceride concentration; reduced thrombotic tendency; anti-inflammatory effects; anti-arrhythmic effects including reduction in heart rate; improved vascular endothelial function; increased plaque stability; increased paraoxonase levels and improved insulin sensitivity (Calabresi 2004; Bhatnagar 2003; BNF 1999; Geelen 2004; Thies 2003). This wide range of proposed mechanisms have also lead people to consider the potential efficacy of omega 3 fats in preventing or treating inflammatory conditions such as inflammatory bowel disease and arthritis, as well as conditions as diverse as obesity and depression.

Given that most LCn3 fats are ingested in the form of oily fish or fish oil (often fish liver) capsules, reports of high levels of various toxic compounds such as mercury, dioxins, polychlorinated biphenyls (PCBs) in oily fish (FSA 2000; MAFF 1998A; USFDA 1995) and fish oils (Liem 1997) are concerning. These are all fat soluble and accumulate over time in the body, so harms may be exhibited only after long term fish consumption or supplementation with fish oils. Animal intervention studies and human cohorts who have suffered accidental exposure to dioxins and PCBs suggest that pre-natal exposure may cause sub-fertility problems and adult exposures may lead to an excess of total cancers (JECFA 2001). Human cohorts exposed to high levels of mercury exhibit neurological problems, starting with paraesthesia, followed by stumbling and difficulty in articulating words, tunnel vision, impaired hearing, headaches, general muscle weakness, fatigue and irritability. In severe cases tremors or jerks can occur, and may lead on to coma and death (USFDA 1995). As many people eat oily fish once or twice a week or take fish oil supplements (oily fish intakes rose 44% between 1992 and 1997 in the UK, FSA 2000) it is important to explore the potentially harmful effects of fish-associated omega 3 intake. Omega 3 fats themselves may exhibit harm, for example through extension of bleeding times, increased risk of haemorrhagic stroke or suppression of normal immune responses (USFDA 2000).

The summation of many small protective risk factor effects of omega 3 fatty acids may add up to a large protective effect on mortality and/or cardiovascular events. Conversely, the protective effects may be small, dwarfed by toxic effects, or only exhibited in people at high risk of cardiovascular disease.

This set of systematic reviews and meta-analyses aimed to draw the evidence of benefits and harms together.

Objectives

The aim of this set of systematic reviews was to assess the effect of dietary or supplemental omega 3 fatty acids on total mortality, on cardiovascular events including cardiovascular mortality, cardiovascular events, coronary heart disease and stroke, atrial fibrillation, neurocognitive outcomes including dementia, type 2 diabetes, depression, breast cancer, inflammatory bowel disease and adiposity, using all available randomised clinical trials and meta-analytic techniques where appropriate.

The primary questions to be answered by the reviews, using all available randomised controlled trials in adults that provided omega 3 fats for at least 1 year, were:

- Do dietary or supplemental omega 3 fatty acids alter all-cause mortality?
- Do dietary or supplemental omega 3 fatty acids alter risk of cardiovascular events, coronary heart disease or stroke (in people with or without existing cardiovascular disease)?
- What are the effects of dietary or supplemental omega 3 fatty acids on serum total cholesterol, HDL or LDL cholesterol or triglycerides?
- Do dietary or supplemental omega 3 fatty acids alter risk of atrial fibrillation (in people with or without existing atrial fibrillation)?
- Do dietary or supplemental omega 3 fatty acids alter risk of type 2 diabetes or treatment outcome in type 2 diabetes?
- Do dietary or supplemental omega 3 fatty acids alter risk of neurocognitive outcomes including dementia, or the course of dementia?
- Do dietary or supplemental omega 3 fatty acids alter risk of depression in people with or without an existing diagnosis of depression?
- Do dietary or supplemental omega 3 fatty acids alter risk of breast cancer (in primary or secondary prevention)?
- Do dietary or supplemental omega 3 fatty acids have a role in primary or secondary prevention of inflammatory bowel disease?
- Do dietary or supplemental omega 3 fatty acids alter the risk of increased adiposity or long-term weight control?

Secondary questions include:

- Does any effect differ between fish (LCn3) and plant (ALA) omega 3 sources?
- If there are any effects, do they differ between dietary and supplemental omega 3 sources?
- Does any effect depend on what energy source the omega 3 is replacing in the diet (saturated fats, monounsaturated fats, omega 6 polyunsaturates, carbohydrates or other non-fat placebo, or undefined)?
- Does any effect differ between those with and without existing cardiovascular disease?
- Does the size of any effect depend on the dose of omega 3 fats taken per day?

- Does any effect depend on baseline intake of omega 3 fats?
- Does any effect depend on use of other medications at baseline?
- Does any protection depend on the n3 to n6 ratio for whole dietary intake (including any supplements) during the intervention period?
- Is any effect stronger with longer trial duration?
- Does any apparent effect differ by risk of bias of included RCTs?
- Is any apparent effect sensitive to running fixed rather than random effects meta-analyses?

Chapter 2. Methods

Criteria for considering studies for this review

Types of studies

All randomised controlled clinical trials that included diet advice or dietary supplementation to promote omega 3 fatty acid intake, versus placebo, no supplementation, usual diet or lower dose omega 3 where at least one of our outcomes was measured.

For cardiovascular (including lipids) , atrial fibrillation, adiposity, mortality and cancer outcomes minimum duration was 12 months (52 weeks or 360 days, for advice trials follow up must have been at least twelve months following advice, for trials where food or supplementation is provided then the provision must have continued for at least twelve months).

For neurocognitive outcomes, type 2 diabetes, depression and inflammatory bowel disease we accepted RCTs with follow up of at least 6 months (24 weeks, 168 days). In deciding the minimum duration of interventions, we were interested in how long omega 3 or omega 6 fats would take to equilibrate in various tissues of the body. Careful work by Browning (FISH - Browning 2012a) suggests that supplements of EPA and DHA equivalent to 1 portion of oily fish per week reach 95% of maximal incorporation by 5 days for EPA in plasma phosphatidylcholine (95% CI 0 to 18 days) to 273 days for DHA into blood mononuclear cells (95% CI 0 to 670 days). While this suggests individual variability, on average all compartments except blood mononuclear cells had equilibrated by 117 days (both EPA and DHA into plasma phosphatidylcholine, plasma cholesteryl esters, plasma nonesterified fatty acids, plasma triglycerides, erythrocytes and platelets). The authors stated “EPA and DHA reached a maximum in platelets in 3–4 weeks and 1–2 months, respectively, and in blood mononuclear cells in 6–9 months”. For this reason, we chose 6 months as the minimum duration of intervention to allow equilibration of most body compartments with EPA and DHA as well as time for this change in body composition to have some health effect.

Randomisation of individuals was accepted, or of clusters, as long as there were at least six clusters randomised.

Types of participants

Studies of adults (18 years or older, men and/or women) at any risk of cardiovascular disease (with or without existing cardiovascular disease) were accepted. This included people with increased risk of cancer, those undergoing or who have undergone coronary artery bypass grafting or angioplasty, and those with current or previous cardiovascular disease, breast cysts, diabetes mellitus, rheumatoid arthritis, multiple sclerosis, psoriasis, hay fever, asthma or ulcerative colitis (for example). We excluded studies who chose participants based on their being pregnant or acutely ill (with acute-stage cancer, undergoing heart or renal transplantation, with HIV or AIDS, on haemodialysis, with IgA glomerulonephritis, or any other renal problem except in diabetes).

Types of interventions

The intervention must have been supplementation (in the form of rich food sources, enriched foods or supplemental capsules), a provided diet or advice on diet. The foodstuffs or supplements must have been: oily fish (including mackerel, dogfish, salmon, herring, trout, tuna, sturgeon, stablefish, anchovy, sprat, coho, capelin, sardines, swordfish, sild, pilchard, brisling, menhaden, bloater, whitebait, crab and conger eel); fish oils (made from any of the above or a mixture of fish, or cod liver oil); linseed (flax), canola (rapeseed), perilla, purslane, mustard seed, candlenut, stillingia or walnut as a food, oil, made into a spreading fat or supplementing another food (such as bread, sausages or eggs). For ALA sources the product consumed had to have an omega 3 fat content of at least 10% of the total fat content. Refined eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) or alpha-linolenic acids, or concentrated fish or algal oils, were also accepted. Supplementation may have been in oil or capsule form or as food stuffs provided, to be consumed by mouth (excluding enteral and parenteral feeds and enemas).

Studies were not included if they included multiple risk factor intervention on lifestyle factors such as weight reduction, smoking or physical activity goals, or differential dietary interventions not involving dietary fats, except where that other intervention was a direct replacement for polyunsaturated fats or the effect of diet or supplementation could be separated out from the other interventions. The aim was that any health effects could be assigned to the omega 3 intervention.

Studies were included if they compared the effect of this dietary advice with the usual diet, no advice, no supplementation, placebo or lower dose omega 3. Trials were only included if outcome data could be collected (by communication with authors where necessary).

Outcome measures - see specific review chapters for outcomes

Search methods for identification of studies

We ran searches on CENTRAL, MEDLINE, EMBASE to 27th April 2017, ClinicalTrials.com, and the World Health Organization International Clinical Trials Registry Platform to September 2016. We also checked the included trials of relevant systematic reviews, and wrote to authors of included studies for additional studies and trial data (including unpublished outcome data).

Electronic searches

The search strategies for this review were updated and re-run on CENTRAL, MEDLINE (Ovid) and EMBASE (Ovid) to 27th April 2017 to identify any records added to the databases until this date. As this was an update of a 2002 search, date limits were applied to the terms from the original strategies so that only new records were found, but no date limits were applied to newly added terms. The MEDLINE search strategy for the original version of this review is shown in Appendix 1, and the updated searches are shown in Appendix 2. The results were de-duplicated against each other. The RCT filter for MEDLINE was the Cochrane sensitivity and precision-maximising RCT filter, and for EMBASE, terms as recommended in the Cochrane Handbook have been applied (Lefebvre 2011).

As we were also running searches for a new systematic review of the effects of polyunsaturated fats on cardiovascular disease (Abdelhamid 2016), and updating and extending a Cochrane review of the effects of omega 6 polyunsaturated fats on health outcomes (Al-khudhairy 2015) these searches were also run to 27th April 2017, using the same RCT filters. The results of these searches were downloaded, de-duplicated against the omega-3 searches, and all the titles and abstracts assessed as a single set for all three reviews.

We searched two trials registers, ClinicalTrials.gov (https://clinicaltrials.gov/) and the WHO International Clinical Trials Registry Platform (ICTRP, http://www.who.int/ictrp/en/) during September 2016 for registry entries for relevant completed and ongoing studies.

Searching other resources

Titles and abstracts retrieved during these electronic searches were assessed for relevant RCTs and relevant systematic reviews - the included studies in all relevant systematic reviews were checked for new trials and additional publications of included trials.

Authors of all large and long duration (and most authors of RCTs of less than 100 participants) included studies were contacted for references to studies not yet identified, including published, unpublished or ongoing studies. Published systematic reviews addressing diet and heart health were sought as a source of RCTs. Attempts were made to obtain full-text translations and/or evaluations of all relevant non-English articles.

Data collection and analysis

Selection of studies

Titles and abstracts resulting from the electronic and bibliographic searches were each assessed by at least two reviewers. The search results for this review, and two others, Abdelhamid 2016; Al-khudhairy 2015, were combined, de-duplicated and assessed at the same time. Titles and abstracts were only rejected on initial screen if the reviewer could determine from the title and abstract that the article was not a report of a randomised controlled trial; did not address omega 3 intake (or total polyunsaturated fat or omega 6 fat for the other two reviews); was exclusively in children or young adults (less than 18 years old), pregnant women or the critically ill; or was of less than twelve months duration; randomised fewer than 100 participants; or the intervention was multi-factorial and the effect of dietary fat could not be separated out. Studies were not rejected based on absence of outcome data. When a title/abstract could not be rejected with certainty, the full text of the article was obtained for further evaluation. If the reviewer was uncertain about the appropriateness of rejecting the article, the full text article was retrieved.

An in/out form was used to assess full text papers and studies for inclusion (or otherwise) into the review. The authors of all potentially included RCTs were contacted for further information on trial methodology and outcomes. Inclusion of full text RCTs was assessed independently by two assessors and any differences between reviewers' results were resolved by discussion and, when necessary, in consultation with the review team.

We included relevant studies regardless of their publication type or publication status (only available as trials registry entry and/or protocol, available only as a conference abstract, PhD thesis, report, or available as published paper). We also included studies published in languages other than English where we could obtain good enough translations to interpret them accurately.

Trials were included in a review where the inclusion criteria were fulfilled and we were aware that relevant outcome data had been collected, even when the outcome was not reported in any publication we could access or in a way we could use in analysis. We aimed to write to every author where this was the case to ask for outcome data we could include in the review (whether in meta-analysis or narratively). We also wrote to authors of all the studies of at least one year duration that had randomised at least 100 participants to ask whether they had collected data relevant to any of our reviews, even where we had no reason to believe that those data had been collected. We gathered extensive amounts of additional outcome data, as well as methodological information, this way, and these are incorporated into the reviews.

Data extraction and management

A data extraction form was designed for this review, tested by each of the reviewers on a common "training" study (SCIMO - von Schacky 1999) and adapted as appropriate. Data concerning participants, interventions, and outcomes, as described above in the selection criteria section, were extracted. Dichotomous data from dietary advice studies were extracted at the latest point available in the trial (regardless of the amount of reinforcement of the original dietary message), while dichotomous data from supplemental studies were extracted to the point that supplementation ended, or the trial ended, whichever was earlier. Continuous data were extracted at the nearest time point to 12 months, and also the latest point available in fixed term trials, but in studies where participants were followed up for varying durations (aside from dropouts) the participants data were extracted from the first time point following the mean trial duration. Data from periods following the end of a trial were not used in meta-analysis.

Risk of bias assessed using the Cochrane risk of bias tool were also extracted onto this form. In addition data were collected on potential effect modifiers including participants baseline risk of cardiovascular disease, trial duration, intensity of intervention (dietary advice, diet provided, dietary advice plus supplementation, supplementation alone), source of omega 3 fats (plant sources, fish oil supplements, fish consumption), medications used (including antihypertensive, antiarrhythmic or antithrombotic medication) and smoking status. Baseline risk of cardiovascular disease was defined as follows: high risk were participants with existing vascular disease including a history of myocardial infarction, stroke, peripheral vascular disease, angina, heart failure or previous coronary artery bypass grafting or angioplasty; moderate risk were participants with a familial risk, dyslipidaemia, diabetes mellitus, hypertension, chronic renal failure; low risk were other participants. For each study in which adverse effects were noted, the type of effect, how and at what time points in the study the information or data on these effects was elicited or collected and recorded, omega 3 dose, duration of intake, type of omega 3 (from fish or plant sources, as food, supplement or supplemented food) and the frequency of adverse effects (number of cases divided by the number of people exposed to the treatment) were noted.

For primary and secondary dichotomous outcomes we extracted numbers of participants experiencing an outcome, and total numbers of participants randomised (or in whom the outcome

was assessed where known), for each study arm. For continuous outcomes number of participants assessed, means and standard deviations of the final readings in each treatment arm was extracted, and for change in reading from baseline for each arm where available (standard deviations were calculated from other variance data where appropriate in RevMan software). Where data were available on both change and final readings (with relevant variance information), the data on change were used.

Where final reading data only were available, and the difference in that measure at baseline between the two arms was greater than the change over the trial in either arm, we did not include those data in meta-analysis as they were likely to mislead. (These data are noted in the Table of Characteristics of Included Studies as being too different at baseline to use).

Original reports of trial results were extracted by two reviewers independently. Differences between reviewers' results were resolved by discussion and, when necessary, in consultation with a third reviewer or the review team.

Assessment of risk of bias in included studies

All quality assessment was performed independently and in duplicate for each included study. The Cochrane criteria to examine study validity were used (Higgins 2011), including sequence generation; allocation concealment; blinding of participants, staff, and outcome assessors; incomplete outcome data; and selective outcome reporting. Additional review specific criteria included similarity or not of type and intensity of intervention in both arms (attention) and compliance. A study was 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. As the validity criteria had altered since the published version of this review, RCTs that were previously included were re-assessed for validity using these updated criteria.

Summary risk of bias

A trial was considered to be at low summary 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 summary risk of bias. This is because allocation concealment and blinding are core elements of ensuring that randomisation is successful in creating equivalent groups of participants and that these groups are treated and assessed equivalently during the studies, ensuring that any differences in outcomes are truly due to the intervention of interest. Other elements of risk of bias, such as incomplete outcome reporting, selective reporting, attention and compliance were not included in assessment of summary risk of bias, but were noted in the full tables on risk of bias.

Selection bias: Random sequence generation

For a low risk assessment the study authors needed to have described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. For example, the authors should have stated “the randomisation sequence was computer generated”. We allowed that a good method of randomisation was strongly implied if the authors discussed stratification and/or blocking. Therefore, if the authors

were not explicit about their randomisation method but did describe stratification or blocking we assessed this as low risk.

For a high risk assessment, the randomisation method was assessed as not truly random, and may not produce comparable groups.

For an unclear assessment, the study authors have not described their method in sufficient detail for the assessment of whether it would produce comparable groups. For example, the authors state “the trial was randomised” and provide no further information.

Selection bias: Allocation concealment

For a low risk assessment the study authors needed to have described the method used to conceal the allocation sequence in sufficient detail to determine whether the intervention allocations could have been foreseen in advance of, or during, enrolment. Good methods include putting the allocation codes in opaque sealed envelopes (ideally prepared by someone outside the treatment or assessment teams and sequentially numbered), using a telephone allocation system after the participants have consented to participant in the study or providing a random number that links to a specific set of capsules prepared and distributed centrally or by an arms-length pharmacist.

A high risk assessment was given where the allocation was known in advance of participants consenting to take part in the study.

An unclear assessment was given where the authors gave insufficient detail as to method.

Performance bias: Blinding of participants and personnel

For a low risk assessment, the study authors needed to have described all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Ideally, they should also have provided information relating to whether the intended blinding was effective. For example, the authors could say “both the intervention and placebo capsules looked and tasted the same.” However if the study authors did not provide information on whether the blinding was effective, but sufficient detail was given on a good method of blinding, then it was assumed that the blinding was effective and the risk of bias was low.

A high risk assessment was given where the study was unblinded or where blinding was broken, e.g. “the capsules were visually identical but the participants reported a strong fishy flavour in the intervention group only.”

An unclear assessment was given where insufficient methodological details were provided e.g. “the study was blinded.”

Detection bias: Blinding of outcome assessment

For a low risk assessment, the study authors needed to have described all measures used, if any, to blind the outcome assessors from knowledge of which intervention a participant received. Ideally, they should also have provided information relating to whether the intended blinding was effective. For example, the authors could say “the outcome assessors had no knowledge of the group allocation, and both the intervention and placebo capsules looked and tasted the same so the self-assessment scales were also blinded.” However if the study authors did not provide information on whether the blinding was effective, but sufficient detail was given on a good method of blinding of the assessors, then it was assumed that the blinding was effective and the risk of

bias is low. All biochemical assessment (lipids, glucose, CRP, insulin, PSA etc.) were considered at low risk of detection bias if outcome assessor blinding or double blinding was stated.

A high risk assessment was given where the study is unblinded or where blinding was broken, e.g. for a self-assessment measure "the capsules were visually identical but the participants reported a strong fishy flavour in the intervention group only."

An unclear assessment was given where insufficient methodological details were provided e.g. "the study was blinded."

Because the level of blinding could vary depending on the outcome e.g. if the assessor did not know the group allocation their assessments would be blinded, but the patient could taste which capsule they had been give then their self-assessments would not be blinded. In this case, the assessment of risk of bias was based on the blinding of the primary outcome(s) of the review. Where different primary outcomes have different assessments then we opted for the higher risk of bias (unclear rather than low, high rather than unclear) but noted in the text that that risk of bias was lower for other outcomes.

Attrition bias: Incomplete outcome data

For a low risk assessment, the study authors needed to describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. They needed to report the number of attritions and exclusions, the numbers in each group at each time point, the reasons for attrition/exclusion and any re-inclusions in analyses. Ideally, they would report how they imputed any missing data e.g. last observation carried forward. There needed to be a reasonable balance of attritions/exclusions between the arms of the study and no greater than 20% of the sample should be lost over a year.

For a high risk assessment the authors needed to have stated there was a substantial difference in the rates of attritions/exclusions between the study arms and/or greater than 20% of the baseline sample was lost over a year (>10% over 6 months).

For an unclear risk assessment, the authors would not have stated the reasons for attrition/ exclusion, or have been unclear about the numbers lost to attrition/exclusion in each study arm.

Reporting bias: Selective outcome reporting

For a low risk assessment, the study authors needed to have published their trial protocol or trials registry entry before the end of the study's recruitment period i.e. prospectively. They needed to have reported on all of the primary and secondary outcomes listed in the protocol/ registry entry. However reporting additional secondary outcomes in the results paper(s), although not ideal, was deemed to still be low risk.

For a high-risk assessment, the study authors must not have reported at least one primary or secondary outcome measure listed in the protocol/registry entry. It would also be deemed high risk if the results paper(s) reported a primary outcome that was not listed at all in the protocol or not listed as the primary outcome in the protocol.

For an unclear risk assessment no trial protocol or trials registry entry was found, it was registered retrospectively, or the dates of registration and participant recruitment were unclear.

Other sources of bias: Attention bias

For a low risk assessment, the study authors needed to have reported that the participants in the various arms of the study received the same amount of attention and time with the researchers and clinical teams. For example, “All participants attended the clinic for a baseline assessment which took 2 hours. They were then followed with monthly telephone calls, and finally attended for a 6 month assessment at the clinic which took 1 hour.” If the study only differed by the content of the capsules, and the assessment schedule was not stated to differ between the two arms, it was assumed this was low risk.

For a high risk assessment, the participants in different arms needed to receive different amounts of attention. For example “The intervention group only attended for additional assessments at months 2, 4, and 6” or “the rates of relapse differed substantially between the groups which led to differing amounts of treatment time and attention,” or “the intervention group received a 40 minute dietary education session.”

For an unclear assessment, the authors did not state the attention each arm received.

Other sources of bias: Limited compliance

The study authors needed to have reported on the level of compliance in all arms in sufficient detail to determine whether the study results are robust. We followed a flow chart to make this determination (Figure 1). The authors needed to have provided EPA numbers or at least a P value of the difference in fatty acids between the arms to justify their claims of compliance.

Other sources of bias: Other

If fraud concerns had been raised and the paper has been withdrawn, or the author had been found guilty of fraud by a legal or medical entity the paper was excluded from the review. However if fraud concerns have been raised, but the journal had not withdrawn the paper, or the author has not been formally sanctioned; then the study was included in the review, but concerns were raised here, and the risk of bias for this item was high.

Measures of treatment effect

Dichotomous data were combined using risk ratios (RR) to describe effect sizes, while continuous data were combined using mean differences (MD). Where effects were described by different but comparable measures or scales in different studies they were combined using standardised mean difference.

Unit of analysis issues

It was intended that if trials randomised by cluster were identified the patient numbers would be reduced to an effective sample size as described by Hauck 1991; however no such trials were identified. For combined outcomes (e.g. combined cardiovascular events) attempts were made to add numbers of individuals experiencing specific outcomes within studies, but only where we could be certain that we were not counting individual participants more than once within any one of our review outcome categories. However, individuals may have been counted for more than one of the review outcomes.

Deciding compliance risk of bias (C-RoB).

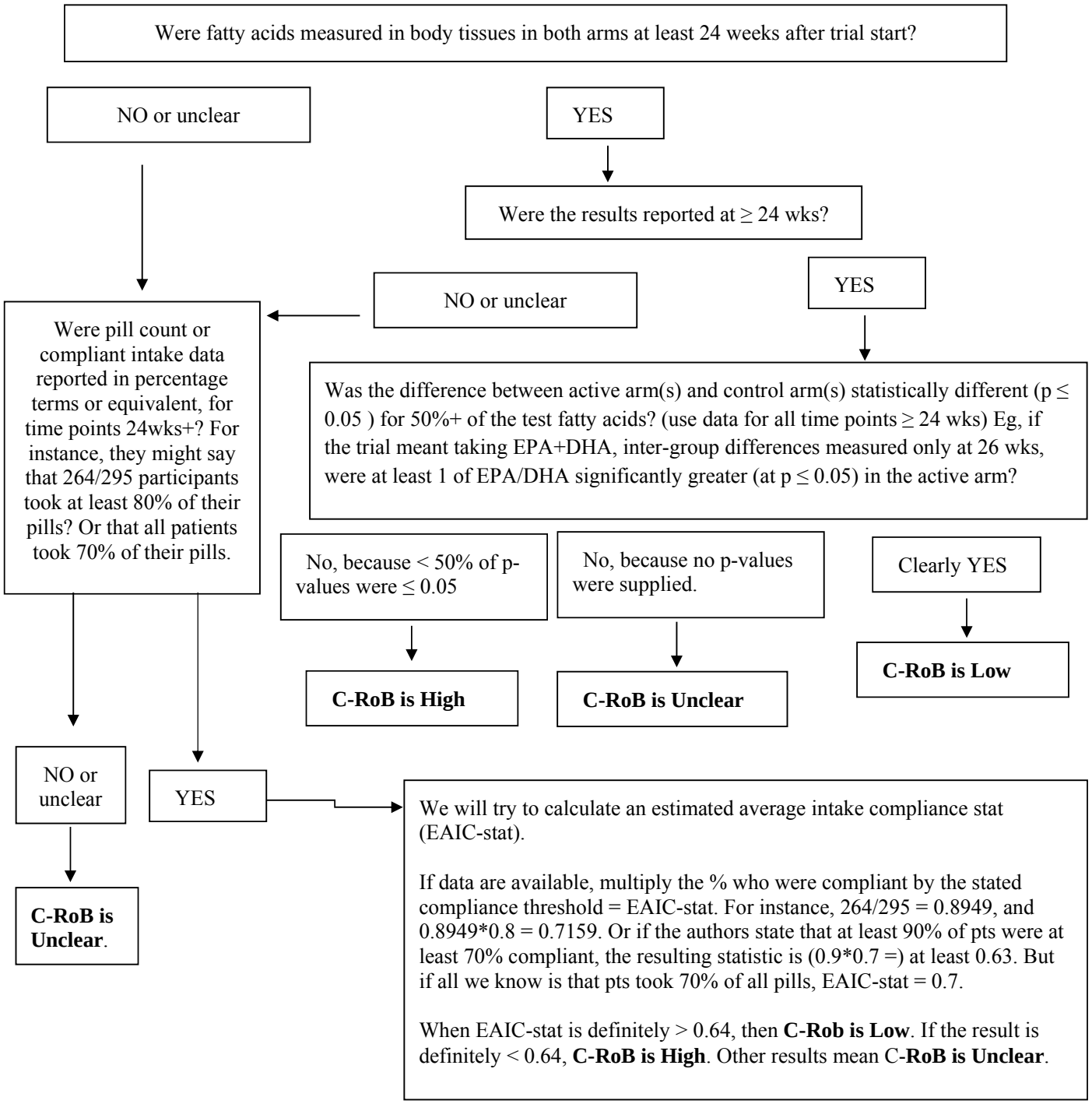


Figure 2.1. Schema for use in assessing compliance (part of risk of bias).

Dealing with missing data

We sought trials registry entries and study protocols to help us assess what outcomes were measured in each study. Where data appeared to have been collected, but were not found in published reports of the study we wrote to study authors to ask for information. For studies where we found no trials registry entries or protocols we wrote to study authors to ask whether they had collected information on any outcomes of interest that we had not yet located. Where it was clear that data existed, but could not be located to use within the review, this lack of data was noted and the potential effect of this missing data on effect sizes was assessed narratively.

Assessment of heterogeneity

Heterogeneity was assessed using Cochran's test (assumed to be present when $p<0.1$) and the I^2 test (Higgins 2003, assumed to be important when I^2 >60%.

We planned to use meta-regression to explore effects of omega 3 dose and duration of trial on mortality and cardiovascular events. Planned methods included random effects meta-regression (Berkley 1995) performed using the STATA command metareg (Sharp 1998): log(e) relative risk vs dose or duration, weighted by the standard error of the log(e) relative risk.

Assessment of reporting biases

Funnel plots were used to assess for evidence of small study bias (Egger 1997).

Data synthesis

Primary measures of interest were effects of dietary advice or supplementation of fish-based (long chain) omega 3 fats, and alpha linolenic acid (ALA), on primary outcomes. We separated out effects of long chain omega 3 fats and ALA in all analyses.

Treatment/control differences in the outcomes were combined across studies using relative risks (RR) or mean differences (MD) in random effects meta-analysis. If trials randomised by cluster are identified the patient numbers would be reduced to an effective sample size as described by Hauck 1991. For combined outcomes (e.g. combined cardiovascular events) attempts were made to add numbers of individuals experiencing specific outcomes within studies, but only where we were certain that we were not counting individual participants more than once within any one of our review outcome categories. However, individuals may have been counted for more than one of the review outcomes (in separate forest plots).

We chose random-effects meta-analysis as our primary method of pooling as these dietary trials, while all assessing effects of higher vs lower doses of omega 3 fats included dietary and supplemental interventions at a range of doses and over a range of durations and baseline intakes. Under these conditions a biologically active omega 3 would be likely to manifest slightly different true effects in different trials, so that the assumptions underlying random effects meta-analysis would be more appropriate than those underlying fixed effects analysis.

Subgroup analysis and investigation of heterogeneity

For long chain omega 3 studies, and for ALA studies separately, we planned to use subgrouping on primary outcomes for each review to explore effects of increased intake by:

1. Subgroup by intervention type (Dietary advice/ supplemental foods / supplements (capsules or pills) / any combination)

2. Replacement (what is the intervention compared with – EPA vs olive oil is MUFA replaced by EPA, options included omega 3 replacing SFA, MUFA, omega 6, carbohydrates, fat mixture, non-fat placebo or nil)
3. By dose of n3 (LCn3 ≤150mg/d, >150 to 250mg/d, >250 to 400mg/d, >400 to 2400mg/d, >2.4 to 4.4g/d, >4.4g/d, ALA low <5g/d, ALA high ≥5g/d, unknown dose)
4. By baseline intake of long chain omega 3,
    - Low intake: <100mg/d EPA+DHA or <1100mg/d total n3 or <0.5%E from total n3 or <50mg/d DHA or <50mg/d EPA or ≤1g/d ALA
    - Moderate intake: 100-250mg/d EPA+DHA or 1100-2250mg/d total n3 or 0.5- 1.5%E from total n3 or 50-150mg/d DHA or 50-150mg/d EPA or >1-2g/d ALA
    - High intake: >250mg/d EPA+DHA or >2250mg/d total n3 or >1.5%E from total n3 or >150mg/d DHA or >150mg/d EPA or >2g/d ALA
5. By baseline risk of CVD (low or moderate CVD risk or primary prevention, high CVD risk or secondary prevention)
6. Assess and analyse by medication used in control group.
7. By duration
    - Short duration: 6 months to <1year in study
    - Medium duration: 1 to <2 years in study
    - Medium-long duration: 2 to <4 years in study
    - Long duration: ≥4 years in study
8. By n3/n6 ratio (for whole diet in intervention and control groups)

There were insufficient data on underlying dietary omega 3 or omega 6 intake (Appendix 4) to carry out the last of these subgroupings, and insufficient data on baseline dietary intakes or body status (Appendices 3 and 5) to subgroup by baseline status.

We planned to use meta-regression to explore effects of long chain omega 3 dose, ALA dose (looking for evidence of dose response for each) and duration of trial on primary outcomes. We used random effects meta-regression (Berkley 1995) using the STATA command metareg (Sharp 1998): log(e) relative risk vs dose or duration, weighted by the standard error of the log(e) relative risk.

Sensitivity analysis

Sensitivity analyses were used to assess robustness of results to inclusion criteria and analysis type. Planned sensitivity analyses were to run meta-analyses of primary outcomes again:

- Using fixed effects analyses, and
- Including only studies at low summary risk of bias.

Sensitivity analyses limiting studies to those judged at low summary risk of bias are sometimes shown as subgroupings (separating out studies at low summary risk of bias, and moderate to high summary risk of bias into separate subgroups, which allows readers to see the contrast or otherwise between these groups). However, their interpretation is as sensitivity analyses.

Funnel plots were 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.

GRADE assessment

The quality of evidence was 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.

Specific WHO requirements

During the WHO NUGAG meeting in November 2016 WHO requested that we make the following changes in this set of reviews:

- Omit studies by RB Singh (as there have been serious concerns about their veracity)
  - Completed
- Omit studies confounded by dietary aims other than those around dietary fat (eg with fruit and veg aims or weight reduction aims)
  - Completed
- Assess and analyse by baseline intakes
  - Baseline intakes are have been collated and data extracted, see Appendix 3,
  - Analysis by baseline intakes has not been possible due to very limited baseline intake data
- Assess and analyse by foods vs supplements
  - Each intervention has been classified as dietary advice, rich foods provided, enriched foods provided or supplements (capsules), and is collated in the Table of Characteristics in Appendix 2, under Interventions
  - We have subgrouped primary outcomes by intervention type.
- Assess and analyse by medication used in control group
  - Medication use has been data extracted and collated, and collated in the Table of Characteristics in Appendix 2, under Participants.
  - We have subgrouped primary outcomes by medication use (exact categorisation varies for each outcome)
- Include studies of at least 1 year (continuous) duration for cardiovascular outcomes and mortality in SRs and subgroup according to study duration
  - These inclusion criteria have been used
  - Subgrouping by duration has been carried out for primary outcomes
- Assess and analyse by n3/n6 ratio (for whole diet in intervention and control groups) where possible
  - We planned to use dietary intake during the study intervention period (collated and displayed in Appendix 4) to enable this analysis, but unfortunately there are few data available so this analysis was not possible.
- Risk of bias: we removed the RoB categories of funding and causality
  - Funding information has been removed from risk of bias assessment and appears in the table of characteristics instead.
  - Causality has been removed from risk of bias assessment as it is no longer necessary (as mixed dietary interventions have been excluded).
- Risk of bias: Consider adding compliance – consider how compliance assessed and how compliant the population appear to be
  - Schema for assessment of compliance has been developed, see methodology section
  - Body measures of fatty acids are collated in Appendix 5.
  - Compliance schema was used during assessment of risk of bias (in duplicate)

Results

Description of studies

Results of the search

We identified a set of RCTs which had randomised participants to some type of omega 3 intervention compared to a relevant control for at least 6 months, and noted what outcomes had been measured (using protocols, trial registry entries, abstracts and methodology text). Relevant studies within this pool of trials were then allocated to each review, regardless of whether important outcomes were reported. Author replies often added data on new outcomes, so trials were added to different reviews as we discovered more about them. Studies with no available data were generally included only as ongoing studies (although the period of non-publication can be decades), but studies with only a published abstract were treated as published trials.

The electronic searches generated 37810 titles and abstracts, which were de-duplicated to 19772 hits. These were assessed along with 53 previously included studies (to reassess for inclusion), 986 potentially relevant trials registry entries and 35 new references gained from systematic review reference lists, so that 20846 titles and abstracts were assessed in duplicate for collection of full texts. 2155 were collected as full text, of which 226 were systematic reviews, and the remaining 1929 papers were assessed in duplicate for inclusion, and grouped into studies. Of these, we included 186 RCTs of omega 3, omega 6 or total PUFA interventions assessing effects on at least one of our outcomes, of which 162 assessed effects of omega 3 fats. Details of the flow of studies are in Figure 2.2.

Of these 162 RCTs, 95 were of at least 12 months duration, while the remaining 67 were between 6 and 12 months in duration. See Appendix 2, “Characteristics of Studies” for details of included trials, including participants, intervention, methods and outcomes. This table also details risk of bias assessments for each included study.

Details of baseline dietary intake (before the intervention began) are found in Appendix 3. Details of dietary intake during the interventions (including food and supplemental or trial intake) are shown in Appendix 4, and Appendix 5 provides details of trial dosage (the planned dose of omega 3 fats to be added onto baseline dietary intake in the form of supplements, supplementary foods or additional dietary advice).

Risk of bias

Summary risk of bias for all included studies is shown in Figure 2.3, while Figure 2.4 provides details of risk of bias for each trial by risk of bias domain, and appendix 1 provides reasoning for the assessments trial by trial. Overall, 26 RCTs were found to be at low summary risk of bias, while the remaining 136 were at moderate or high risk.

Risk of bias will be discussed in more detail within each review.

Excluded studies

We read full texts of over 2000 papers (Figure 2.2), so the full list of excluded studies is too extensive to add to this review. The main reasons for exclusion of full text papers was that they had a duration of less than 12 months (this was often unclear in abstracts, so full text papers were collected to check), or less than 6 months for studies assessing effects of depression and anxiety, cognition, diabetes, or irritable bowel disease.

We located several studies that were excluded after concerns were raised over fraud, but all assessed effects of omega 6 rather than omega 3 interventions so are not detailed here.

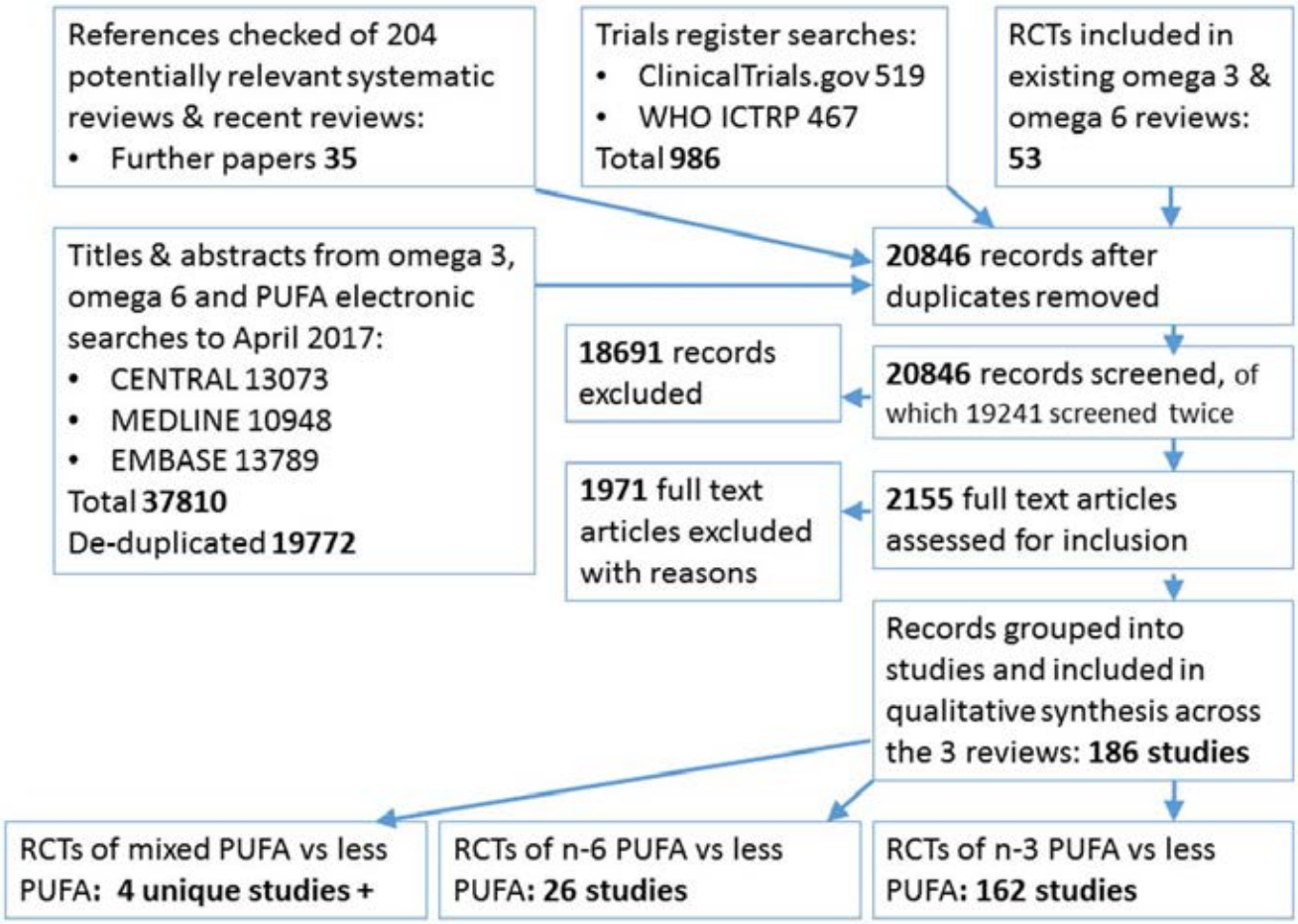


Figure 2.2. Flow diagram for this set of reviews. *Please note that some of the n3 PUFA trials mentioned in this flowchart no longer appear in this version of the report as they relate to outcomes not mentioned here.*

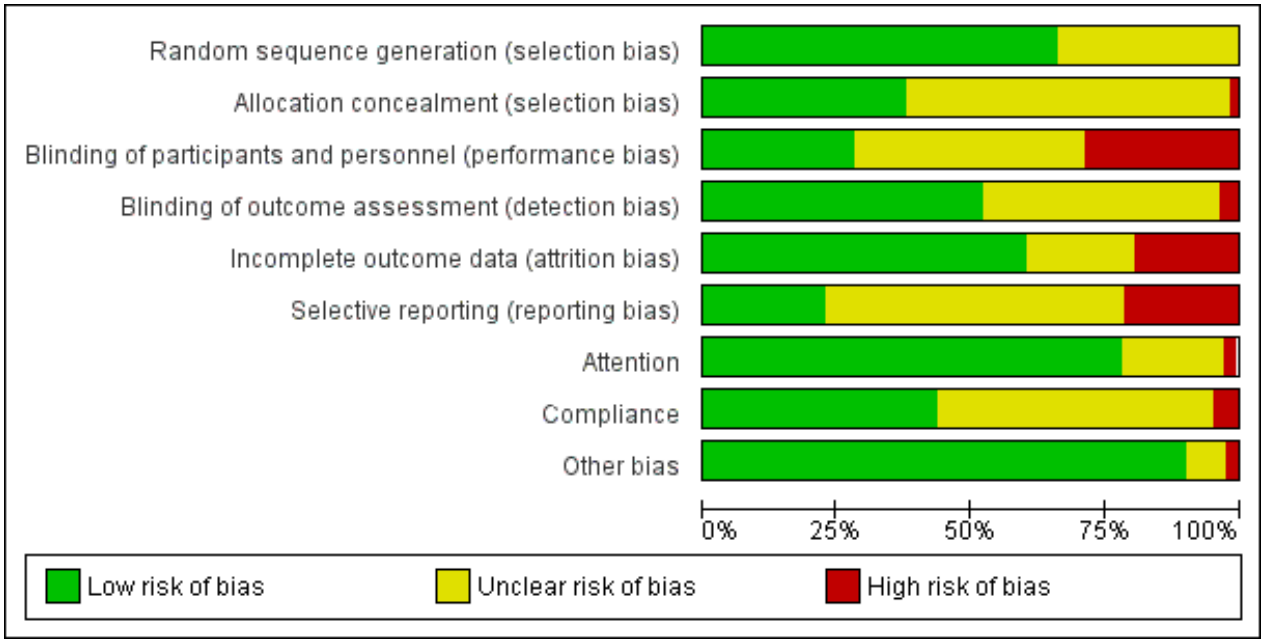


Figure 2.3. Risk of bias summary for all the RCTs in the sets of reviews

Figure 2.4. Risk of bias assessment study by study *(omitted for this report)*

Chapter 3. Do dietary or supplemental omega 3 fatty acids alter all-cause mortality?

We included only RCTs of at least one year duration in this review, and included mortality events from all studies where mortality was reported as an outcome or as a reason for study attrition. Deaths from any cause were included. For studies where deaths were not reported, but where at least 100 participants had been randomised, we wrote to the contact author to request information on deaths. Where we were clear that no deaths had occurred we excluded the study from this review.

We included 39 RCTs of LCn3 fatty acid interventions and 4 of ALA interventions, Figure 3.1. Trials of LCn3 fats included over 92,000 participants (in trials of at least 1 year), and documented 8189 deaths. There was no clear effect on all-cause mortality in random effects meta-analysis (RR 0.98, 95%CI 0.93 to 1.03), without important heterogeneity (I^2 12%).

Trials of ALA included over 18,000 participants and documented 458 deaths, without important heterogeneity and with no suggestion of any protective effect (RR 1.00, 95% CI 0.84 to 1.20, I^2 0%).

The funnel plot suggested that there may be some trials missing showing higher RR of death in the omega 3 arms (Figure 3.2). If this were the case then the real RR of all-cause mortality associated with increased omega 3 fats would be higher than the RRs shown above.

Sensitivity analysis, using fixed effects analysis instead of random effects suggested no significant effects for either LCn3 or ALA subgroups (not shown). Sensitivity analysis also suggested no statistically significant harm or benefit in studies at low summary risk of bias (this is shown as a subgrouping, allowing readers to assess effects in studies at low summary risk of bias, and any contrasting or similar effects in studies at moderate to high summary risk of bias, here suggesting no important differences between subgroups, Figure 3.3).

Subgrouping by dose did not suggest important differences between subgroups, though there was a suggestion of benefit in two trials with lower omega 3 dose (both trials supplementing with less than 400mg/d of EPA+DHA), Figure 3.4. There were no clear differences by primary or secondary CVD prevention (Figure 3.5), statin use during the study (Figure 3.7), compound replaced by omega 3 in the intervention group compared to control (Figure 3.8) or type of intervention (dietary advice, supplements, supplemented food or a combination, Figure 3.9).

One of the duration subgroups suggested statistically significant reduction in risk – not in trials of less than 2 years or over 4 years, but in trials of 2-4 years duration only (between subgroup I^2 80%), Figure 3.6. Within the 14 trials there were 3709 deaths, RR 0.91, 95% CI 0.86 to 0.96, I^2 0%. We assessed duration effects in this set of reviews for signs that there may be greater effects in longer trials (which could suggest that we may be missing true effects in shorter trials, and that there may be important health effects over longer duration). In this analysis we note that most deaths occurred in trials of at least 4 years duration (there were 4164 deaths in trials of at least 4 years duration). In this long duration grouping there was no relationship between omega 3 intervention arm and risk of all-cause mortality, RR 1.03, 95% CI 0.98 to 1.09, I^2 0%, with large numbers of events, tight confidence intervals and little heterogeneity. Similarly, there is no suggested effect of omega 3 fats in the shorter term trials (of 12 months to less than 24 months duration, 301 deaths, RR 1.03, 95% CI 0.82 to 1.30, I^2 0%) although there were fewer events and

the confidence intervals were wider. Because there were no suggested effects of omega 3 fats in trials of shorter or longer duration we do not take the statistically significant effect in the trials of 24 to <48 months duration to be highly meaningful. Given that we have conducted a large number of subgroup analyses it is likely that some will provide spuriously statistically significant results. Here the data do not appear to be suggesting that we may be missing important effects by including studies of too short a duration, or that waiting for longer is likely to provide important effects not visible in shorter duration trials.

There were insufficient data to run subgrouping based on baseline omega 3 intake (Appendix 2) or omega 3/omega 6 ratio.

Summary

We have data from large numbers of adults enrolled in RCTs over long durations. The data do not suggest any benefits or harms of omega 3 fats on all-cause mortality. This is robust to sensitivity analyses removing studies at moderate to high risk of bias, and running fixed-effects meta-analysis. Correcting any slight small study bias would tend to raise the risk ratio.

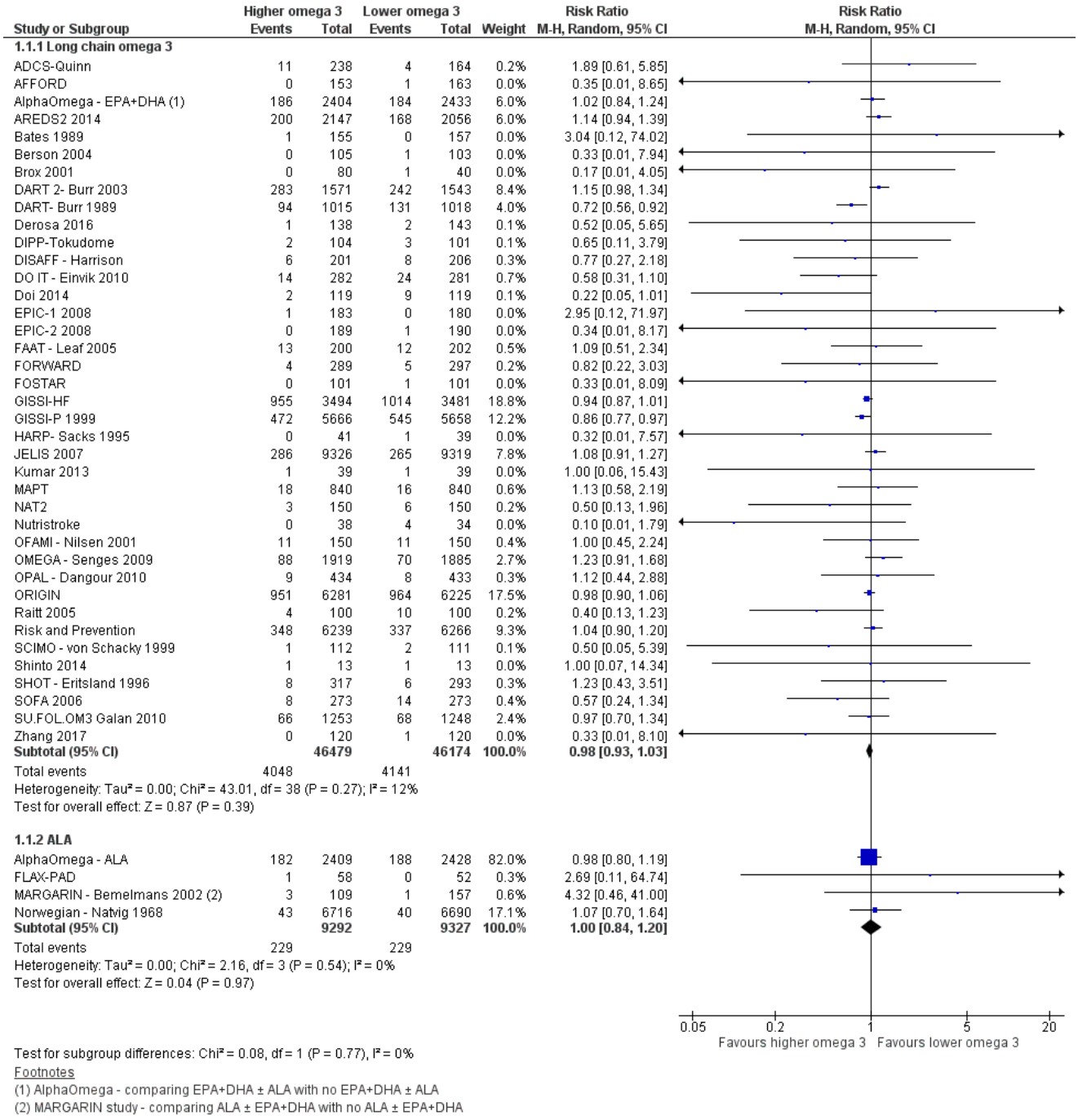


Figure 3.1. Forest plot including all studies with data on mortality from any cause, where at least one death occurred, subgrouped by long-chain omega-3 fats (LCn3, including fish oils, EPA and DHA) and ALA (from plant sources), and including risk of bias assessment.

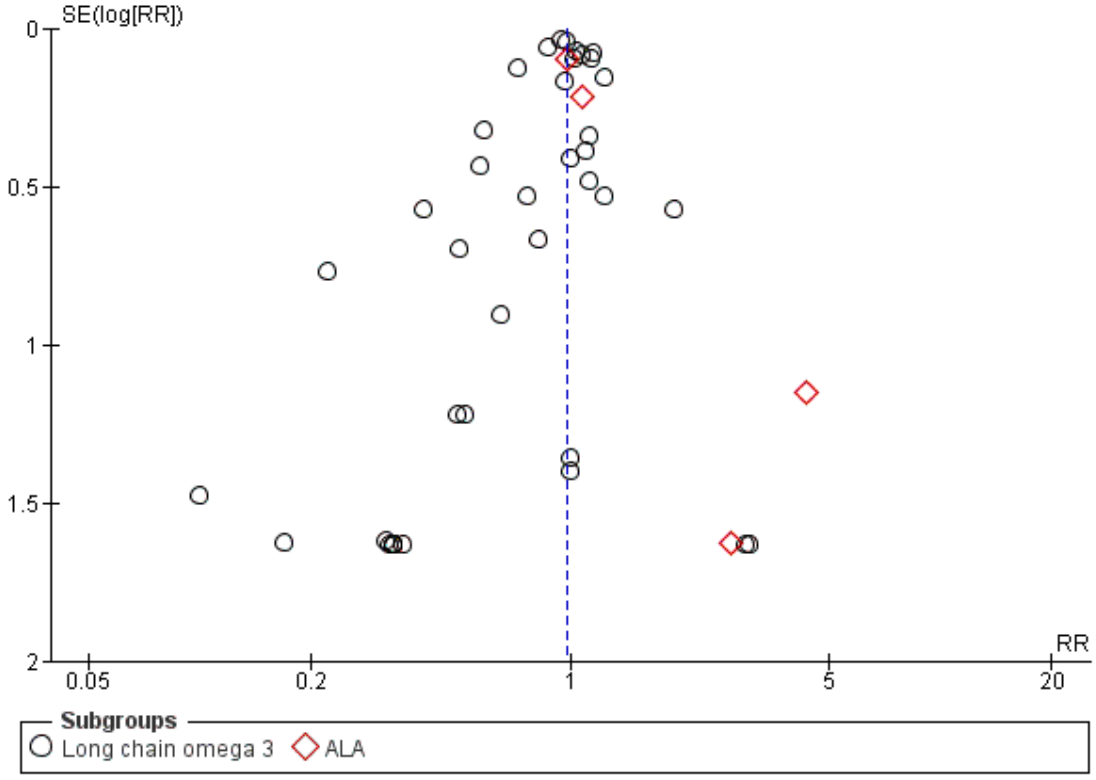


Figure 3.2. Funnel plot of all-cause mortality data.

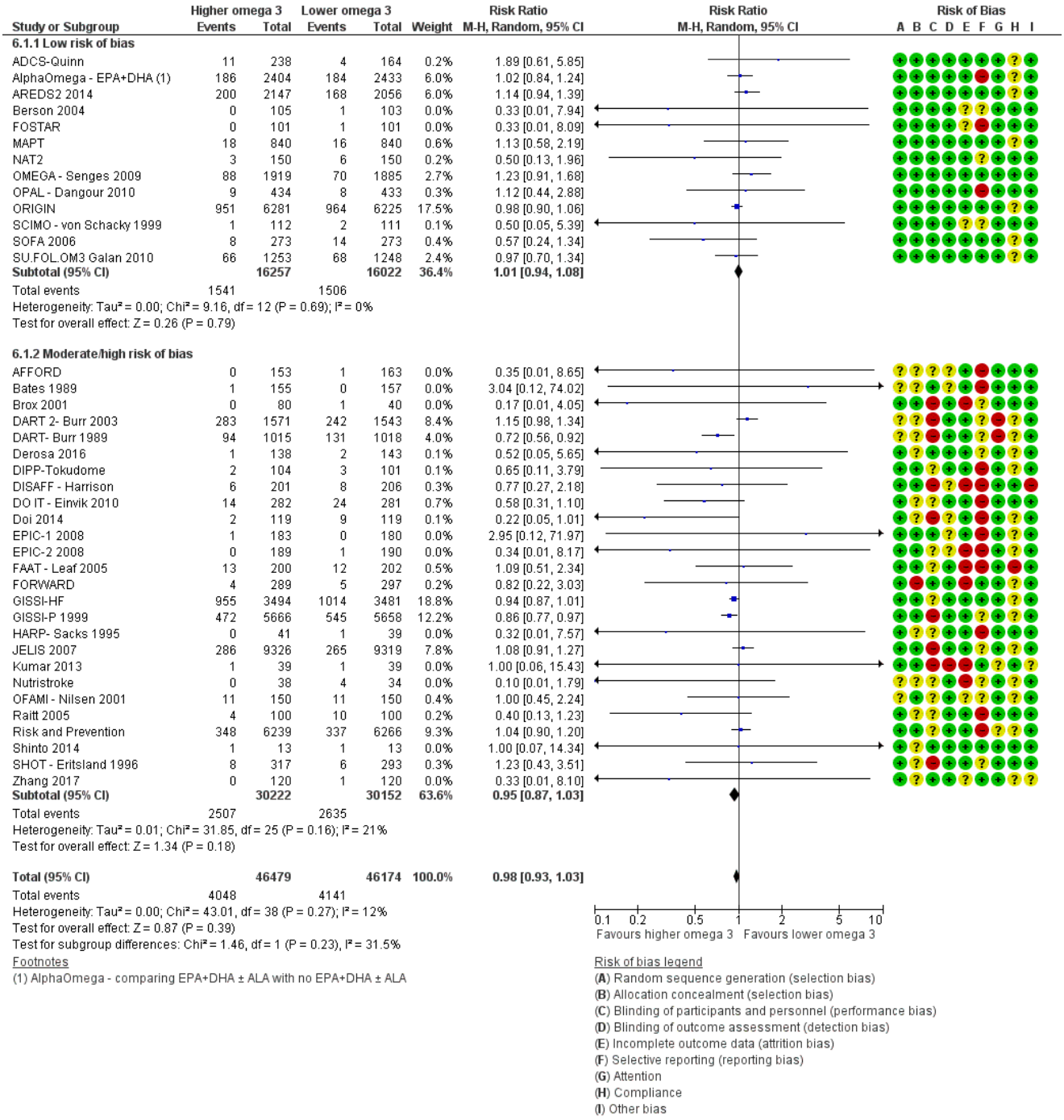


Figure 3.3. Forest plot of all-cause mortality, sensitivity analysis limiting to studies at low summary risk of bias (shown as subgrouped by risk of bias).

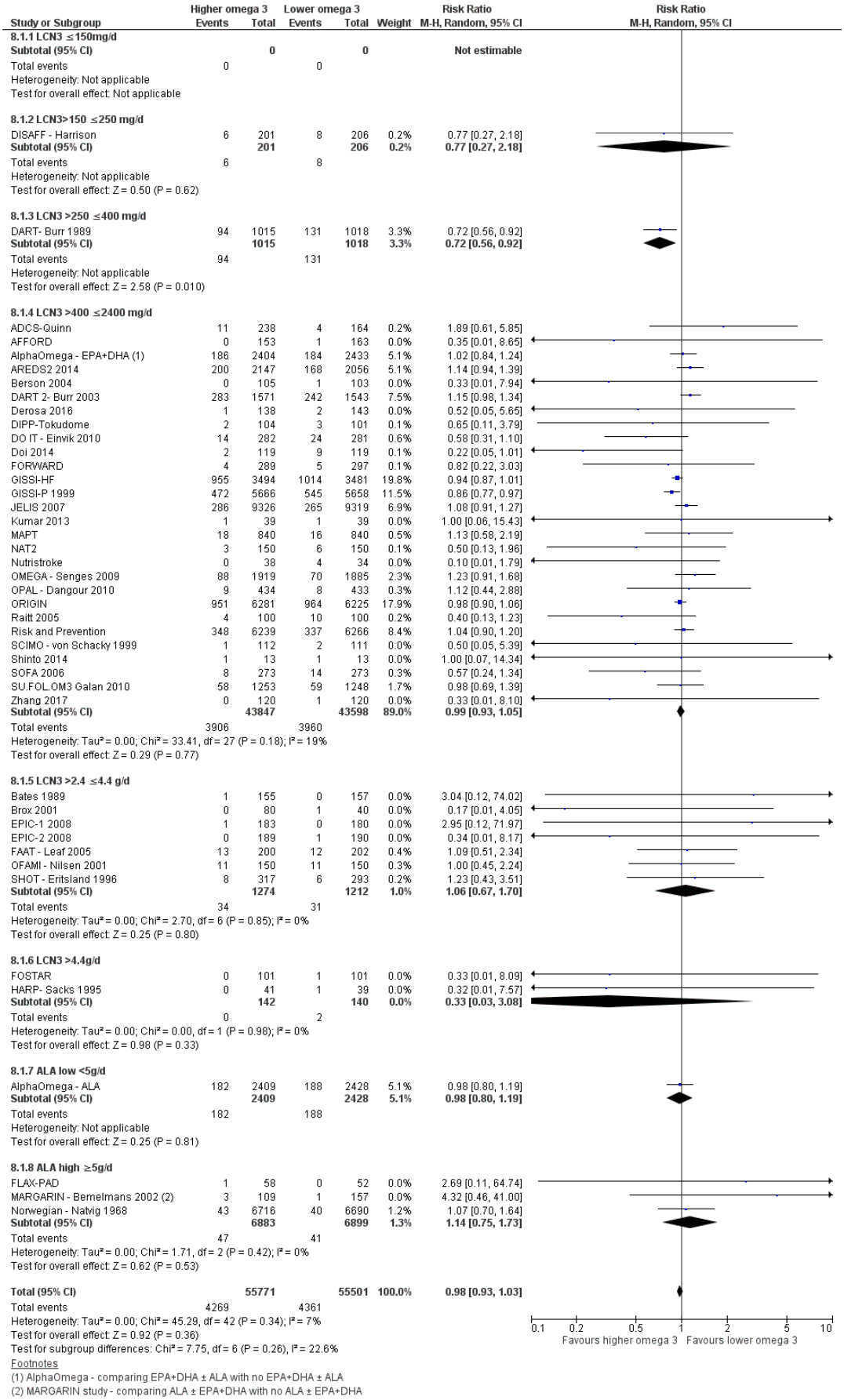


Figure 3.4. Forest plot of all-cause mortality, subgrouped by dose.

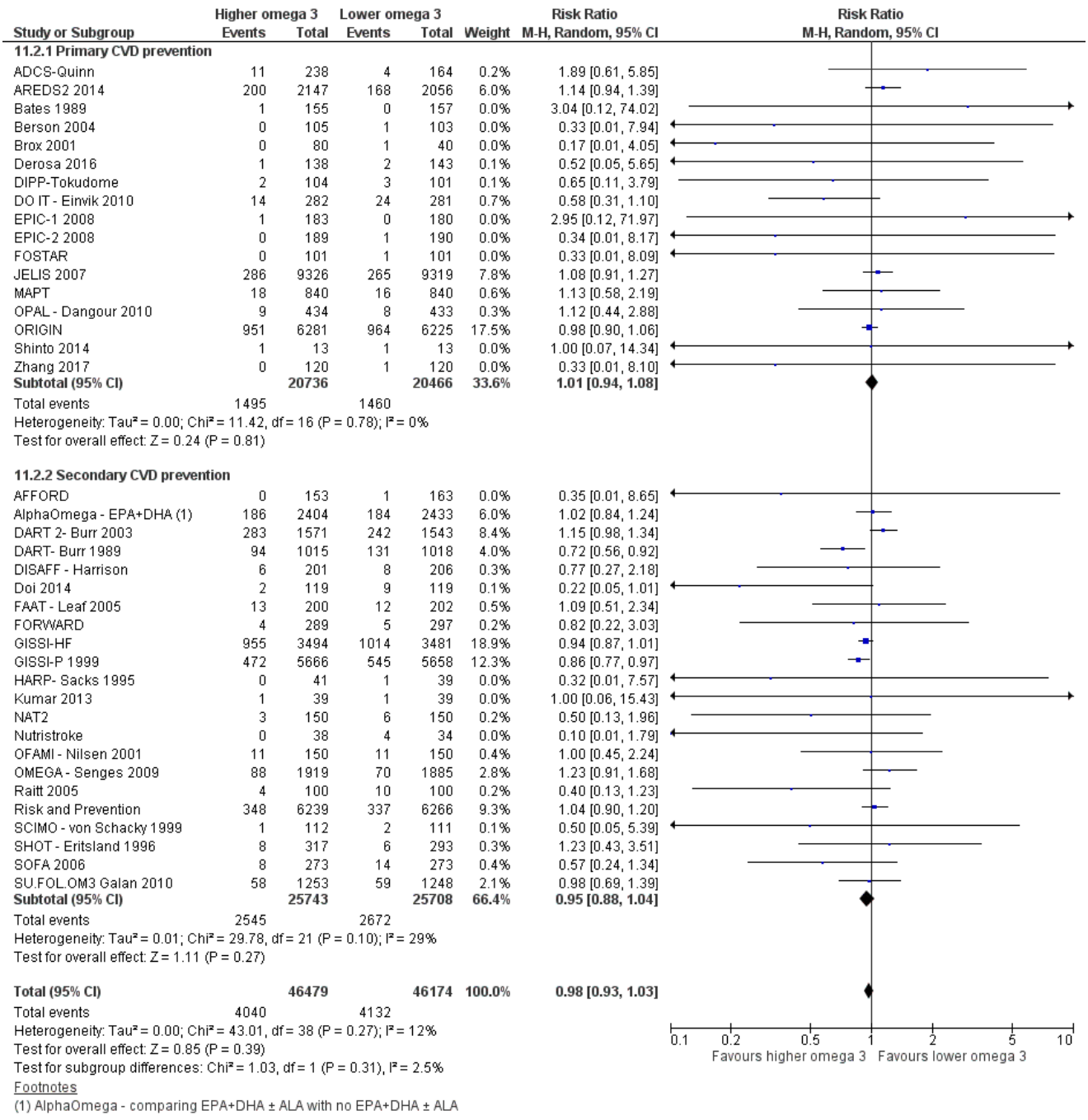


Figure 3.5. Forest plot of all-cause mortality, subgrouped by primary or secondary prevention of CVD.

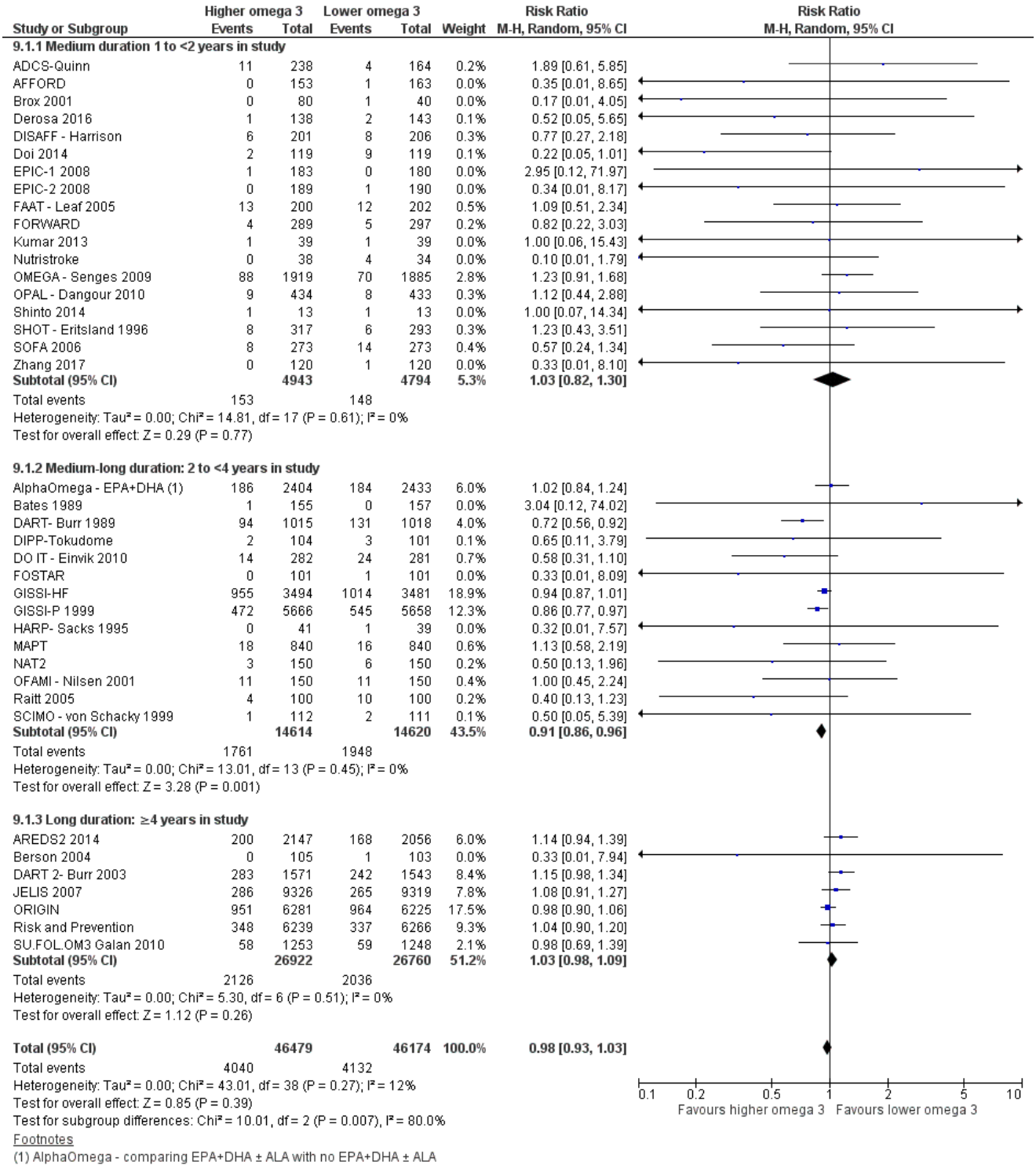


Figure 3.6. Forest plot of all-cause mortality, subgrouped by duration of intake.

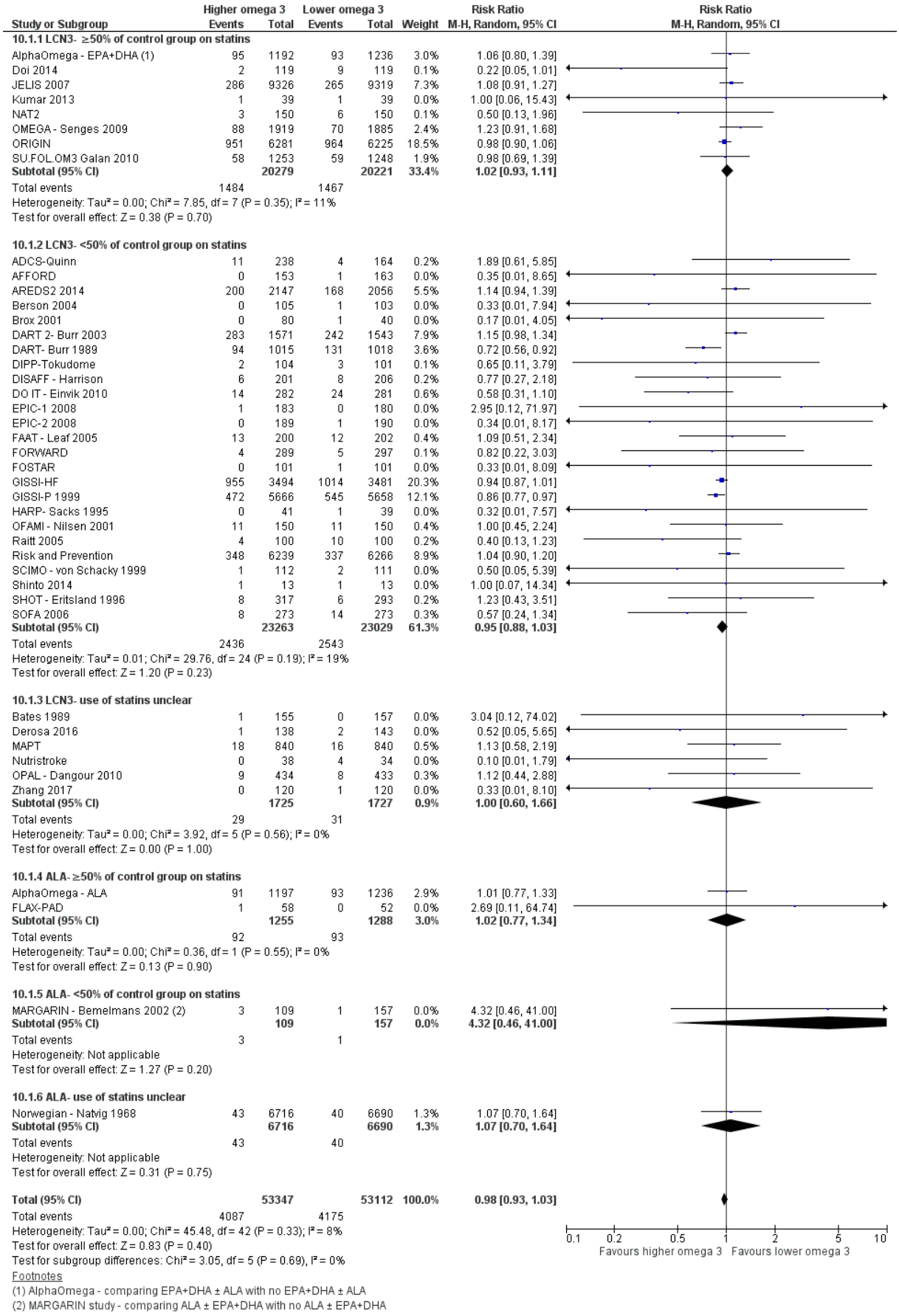


Figure 3.7. Forest plot of all-cause mortality, subgrouped by statin use through the trial

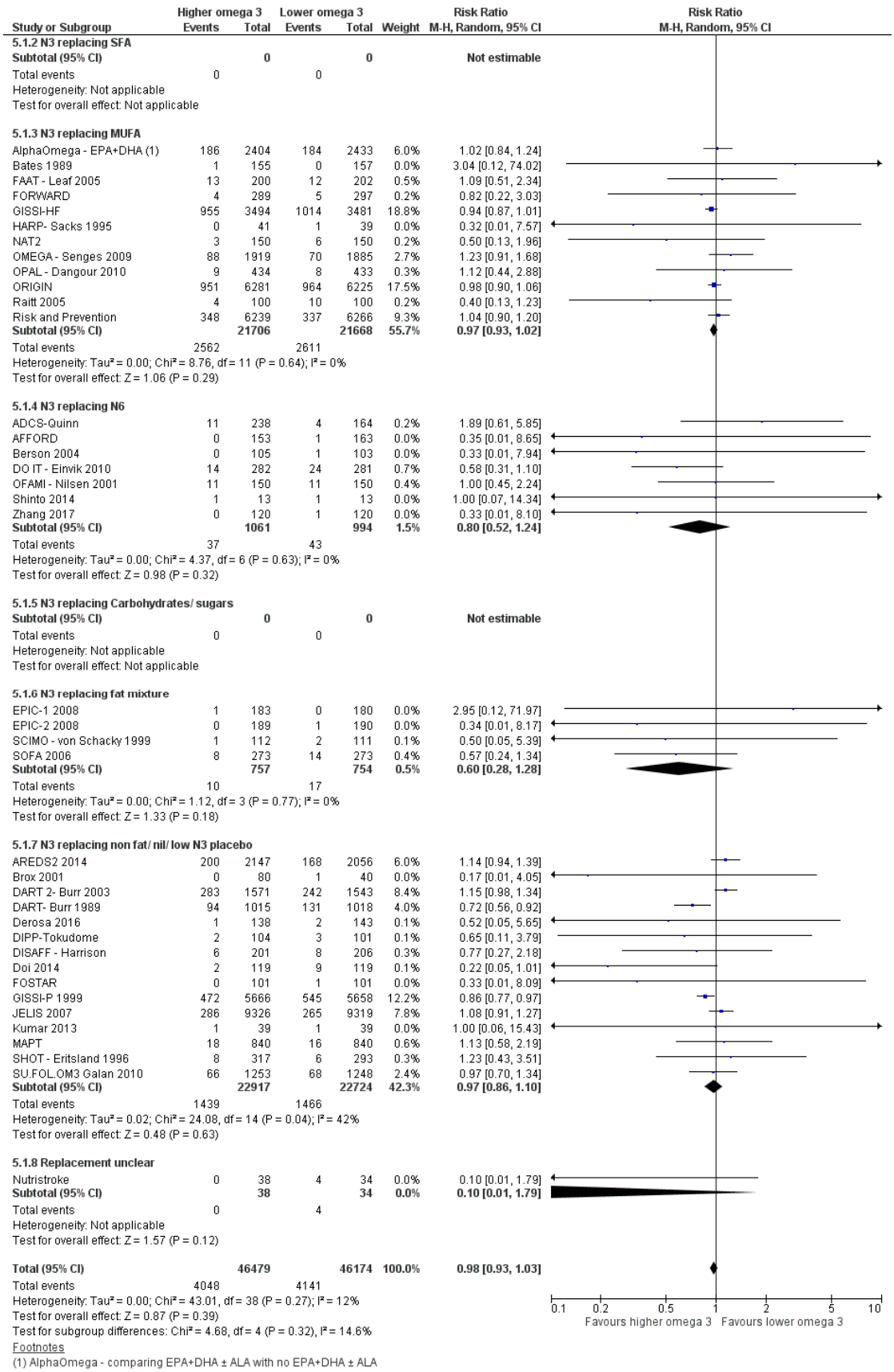


Figure 3.8. Forest plot of all-cause mortality, subgrouped by what omega 3 is replacing

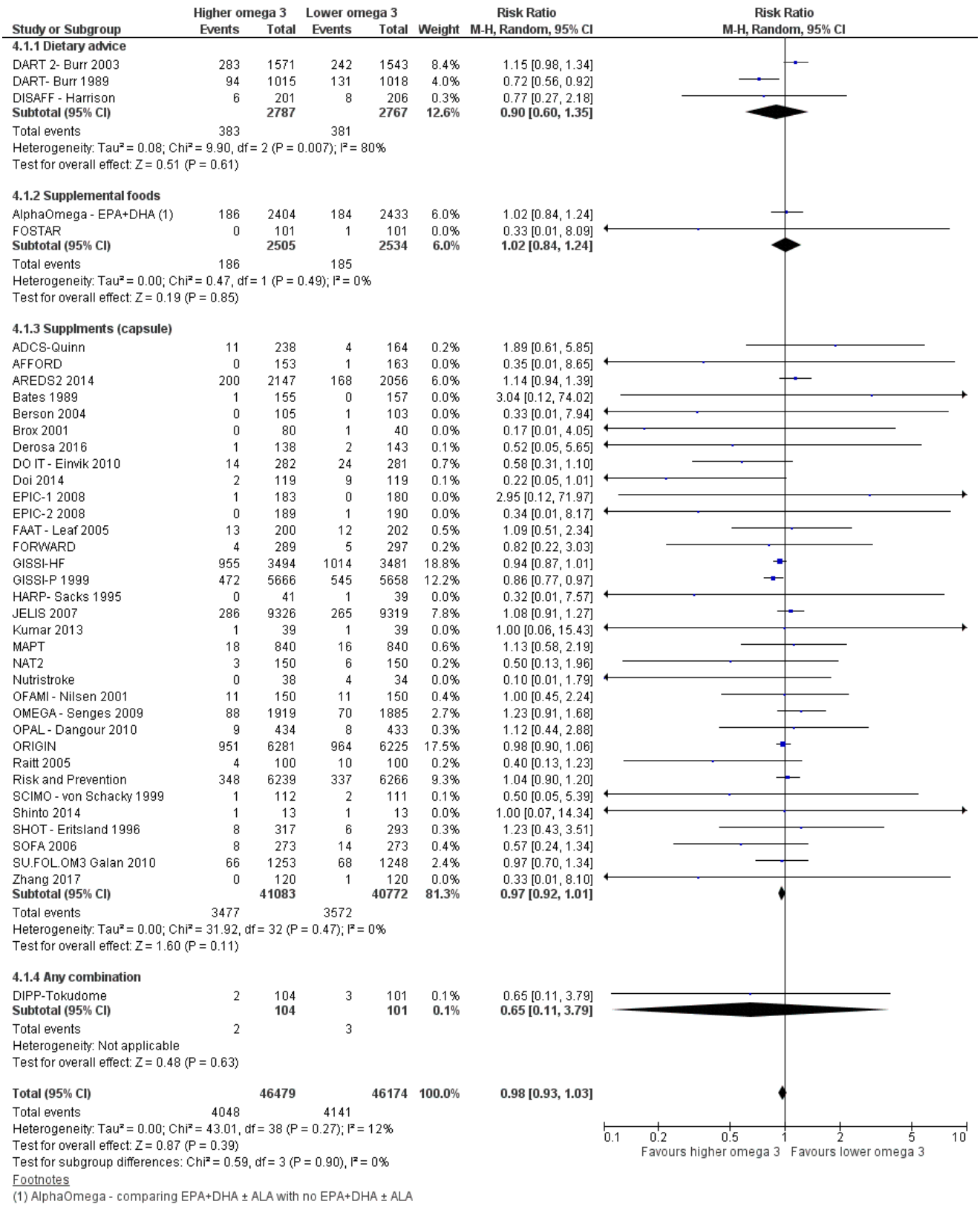


Figure 3.9. Forest plot of all-cause mortality, subgrouped by type of intervention

Chapter 4. Do dietary or supplemental omega 3 fatty acids alter risk of cardiovascular events, coronary heart disease or stroke (in people with or without existing cardiovascular disease)?

We included only RCTs of at least one year duration in this review, and included cardiovascular events from all studies where such events were reported as outcomes or as reasons for study attrition. For studies where cardiovascular events were not reported, or only some were reported, but where at least 100 participants had been randomised, we wrote to the contact author to request information on any available cardiovascular outcomes. Where we were clear that no cardiovascular outcomes had occurred we excluded the study from this review.

Primary outcomes – Cardiovascular deaths

Data for cardiovascular deaths included deaths from any cardiovascular cause. Where a trial did not report cardiovascular death, but deaths from individual cardiovascular causes these were summed. Where these were not available, but cardiac death was available this was used in place of cardiovascular death.

Twenty five RCTs assessed effects of LCn3 fats on cardiovascular deaths, including over 67,000 participants and registering 4544 cardiovascular deaths. Four RCTs assessed effects of ALA on cardiovascular deaths, 219 cardiovascular deaths in over 18000 participants. Meta-analysis did not suggest any effect of LCn3 fats (RR 0.95, 95%CI 0.87 to 1.03, I^2 24%) or ALA (RR 0.96, 95%CI 0.74 to 1.25, I^2 0%) on cardiovascular deaths, Figure 4.1.

The funnel plot suggested some small study bias (Figure 4.2) – suggesting that studies showing more cardiovascular deaths in the intervention arms are missing. If such studies are missing this will tend to bias the results towards suggesting protection from omega 3 fats, and if we “filled in” missing studies the RR would rise by a small amount.

Sensitivity analysis, using fixed effects, suggested a statistically significant reduction in cardiovascular deaths in studies of LCn3 fats (RR 0.94, 95% CI 0.89 to 1.00, p=0.04, I^2 24%). Sensitivity analyses limiting studies to those at low summary risk of bias suggested no effect of LCn3 fats on cardiovascular deaths RR 0.99 (95% CI 0.90 to 1.09, I^2 0%, Figure 4.3).

Subgrouping by dose did suggest one subgroup with statistically significant protection against CV death, 250-400mg/d EPA+DHA, though this group contained only one trial, and there was no important heterogeneity between subgroups (Figure 4.4). Subgrouping by duration suggested heterogeneity between subgroups, with statistically significant reductions in CV deaths in the 2-4 year duration subgroup, but not those of 1-2 years, or over 4 years (Figure 4.5). There was no suggestion that there is an important effect in longer duration trials that we are missing by including studies of shorter duration.

There was no important heterogeneity between subgroups when grouping by primary or secondary prevention, Figure 4.6, replacement or statin use. One of the dietary type subgroupings, supplements (capsules), was statistically significant, Figure 4.7.

There were insufficient data to run subgroups based on ALA intake or LCn3 interventions based on baseline omega 3 intake or omega 3/omega 6 ratio.

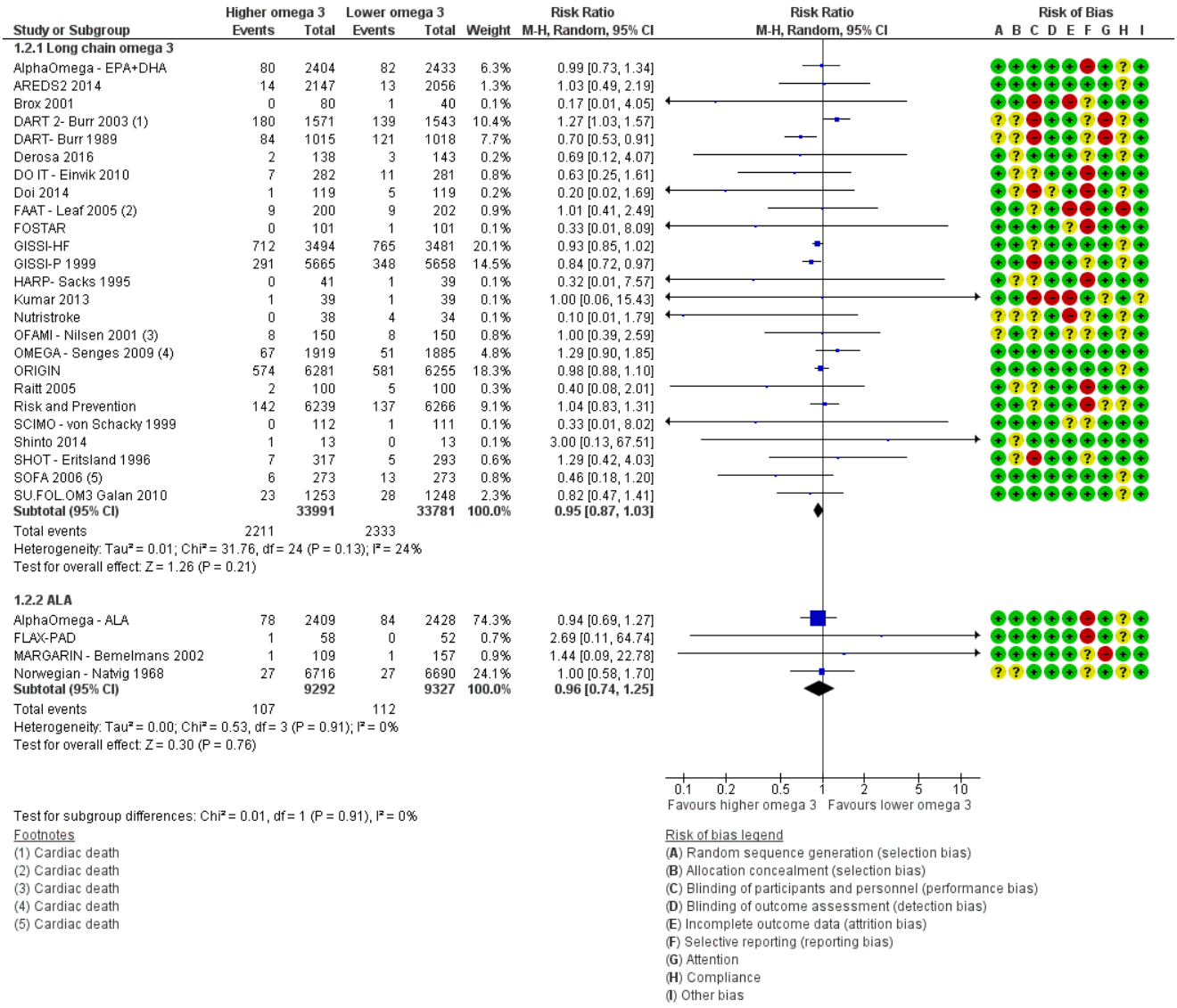


Figure 4.1. Meta-analysis of the effect of omega 3 fats on cardiovascular deaths, subgrouped by LCn3 or ALA intervention.

Summary

There is no evidence that omega 3 fats alter risk of cardiovascular deaths in either primary or secondary prevention of CVD, and there is no suggestion that longer duration or higher doses would be more effective.

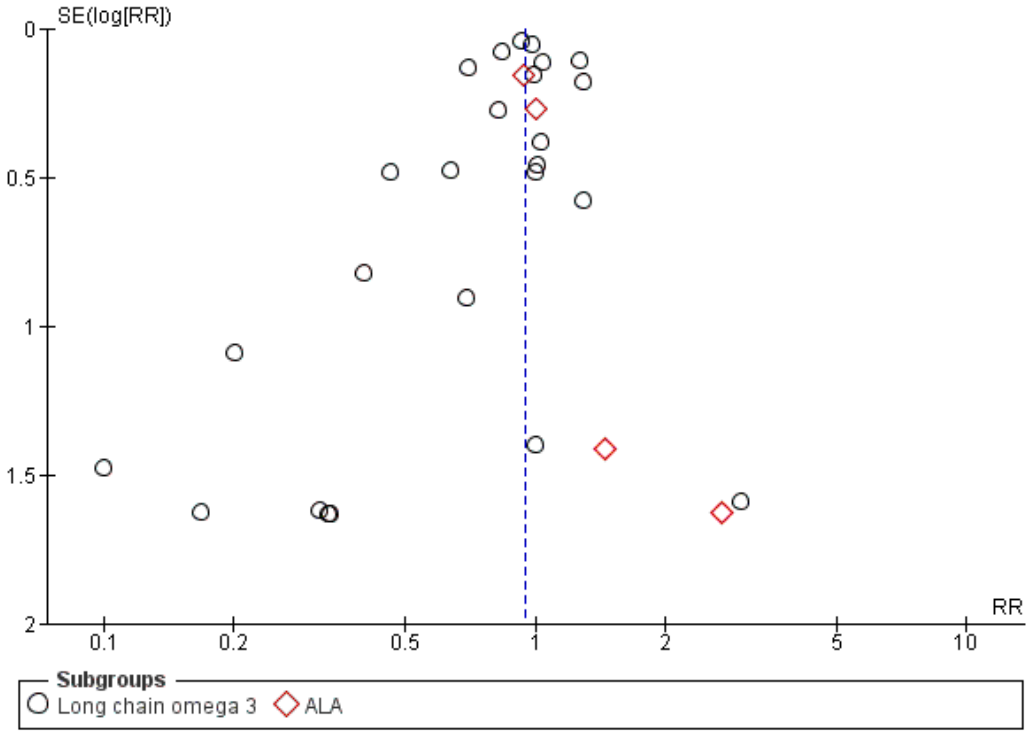


Figure 4.2. Funnel plot of the effect of omega 3 fats on cardiovascular deaths.

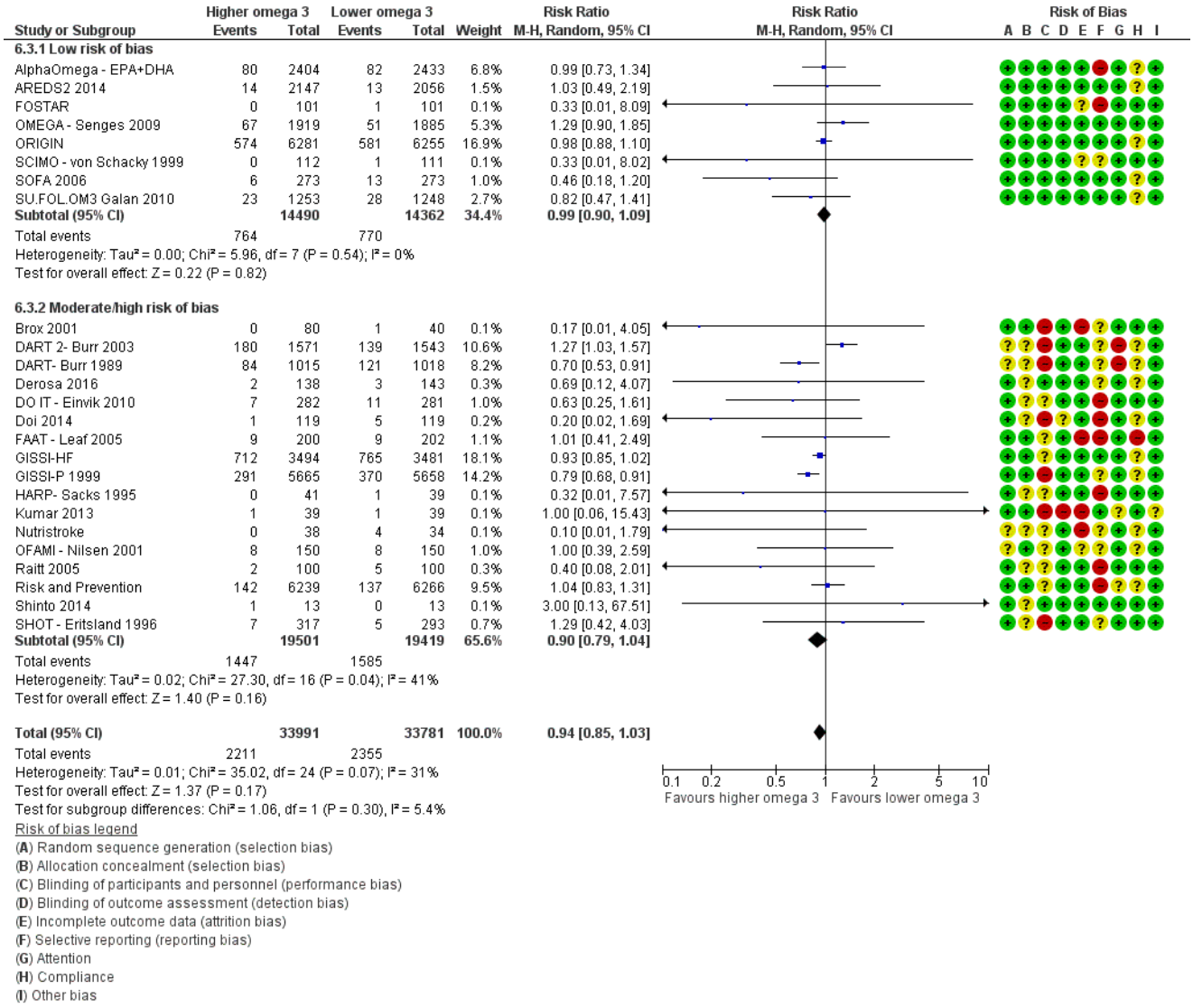


Figure 4.3. Meta-analysis of the effect of LCn3 fats on cardiovascular deaths, sensitivity analysis limiting to studies at low summary risk of bias (shown as subgrouped by risk of bias).

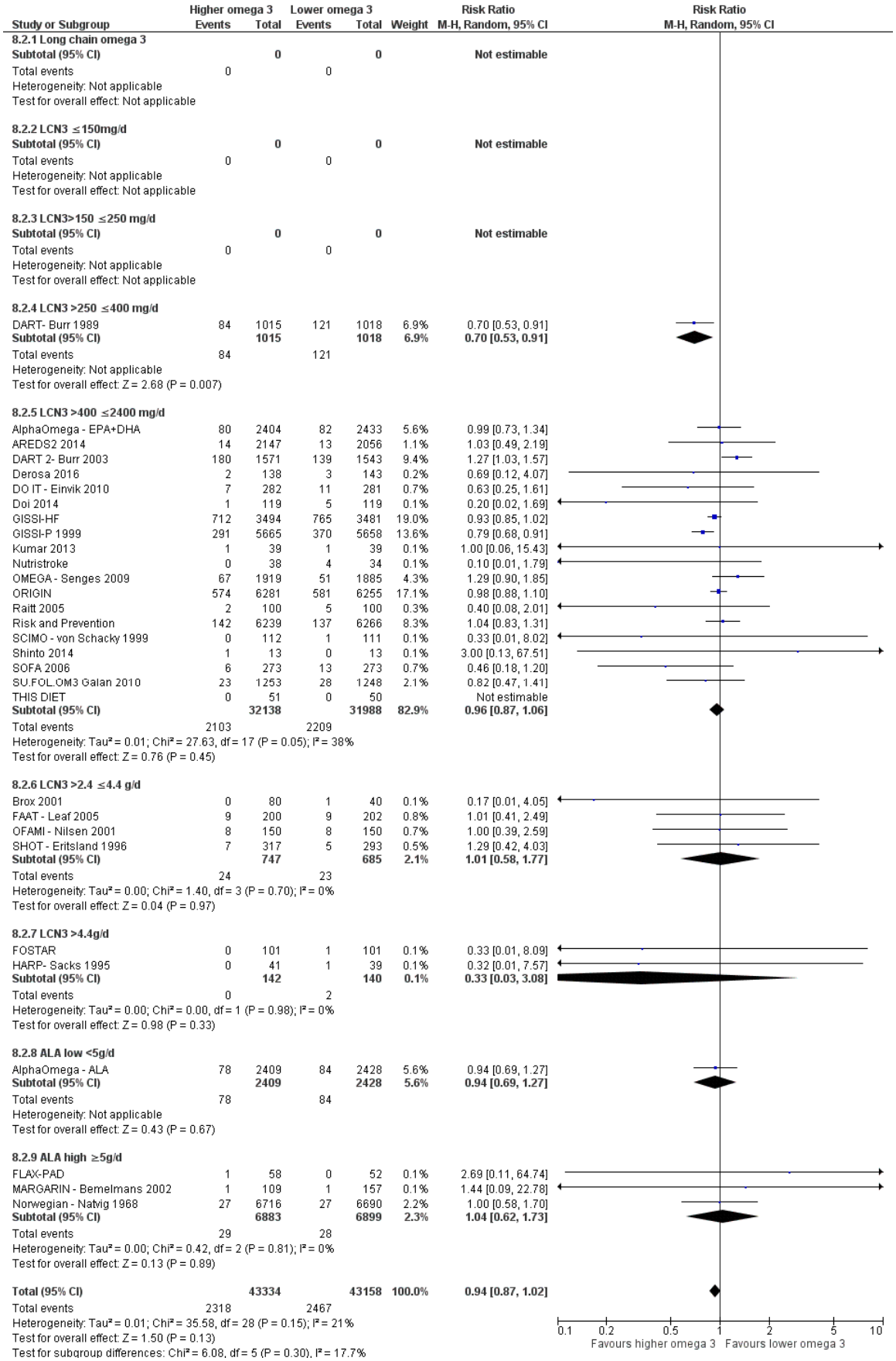


Figure 4.4. Meta-analysis of the effect of omega 3 fats on cardiovascular deaths, subgrouped by dose.

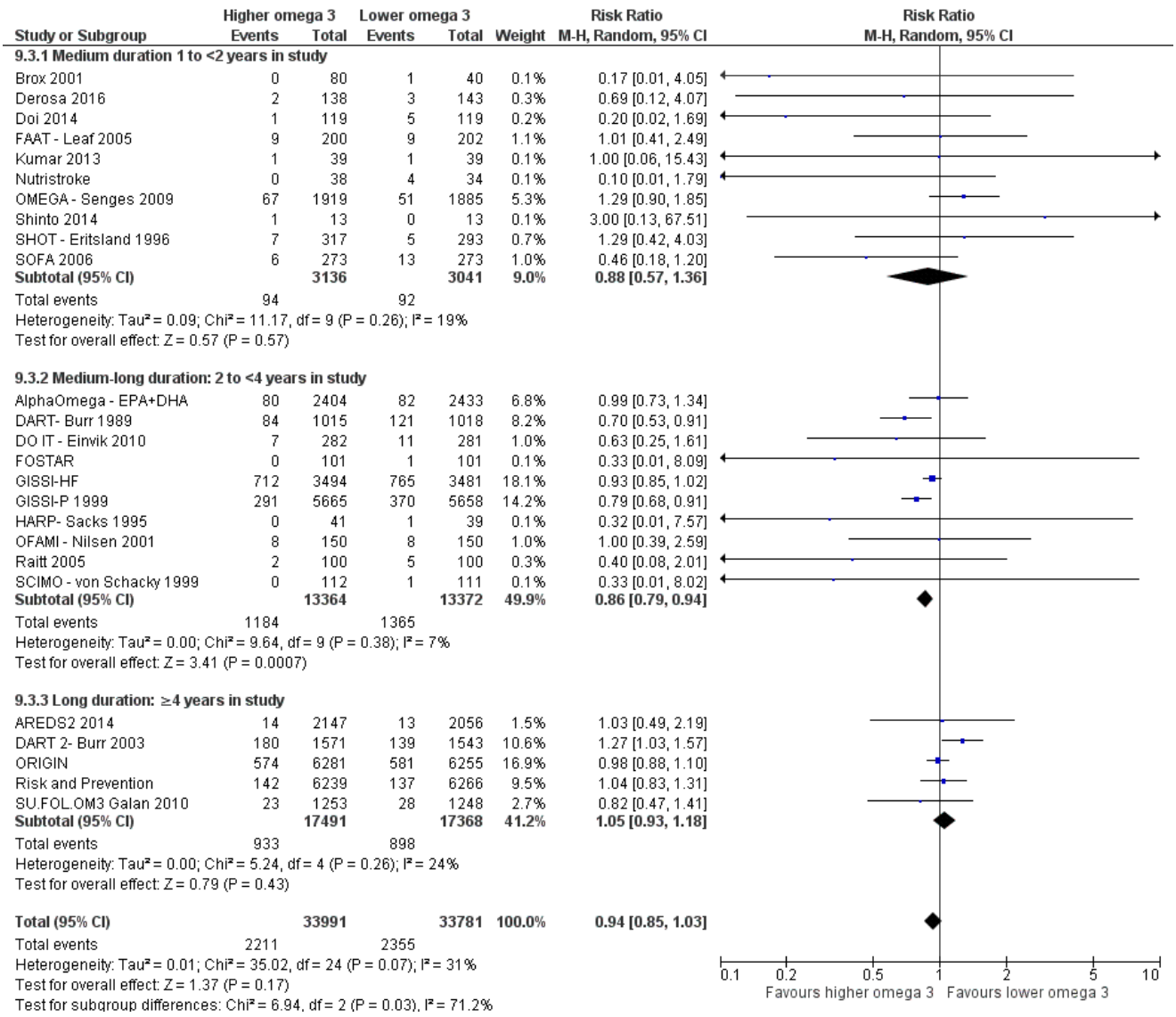


Figure 4.5. Meta-analysis of the effect of LCn3 fats on cardiovascular deaths, subgrouped by duration.

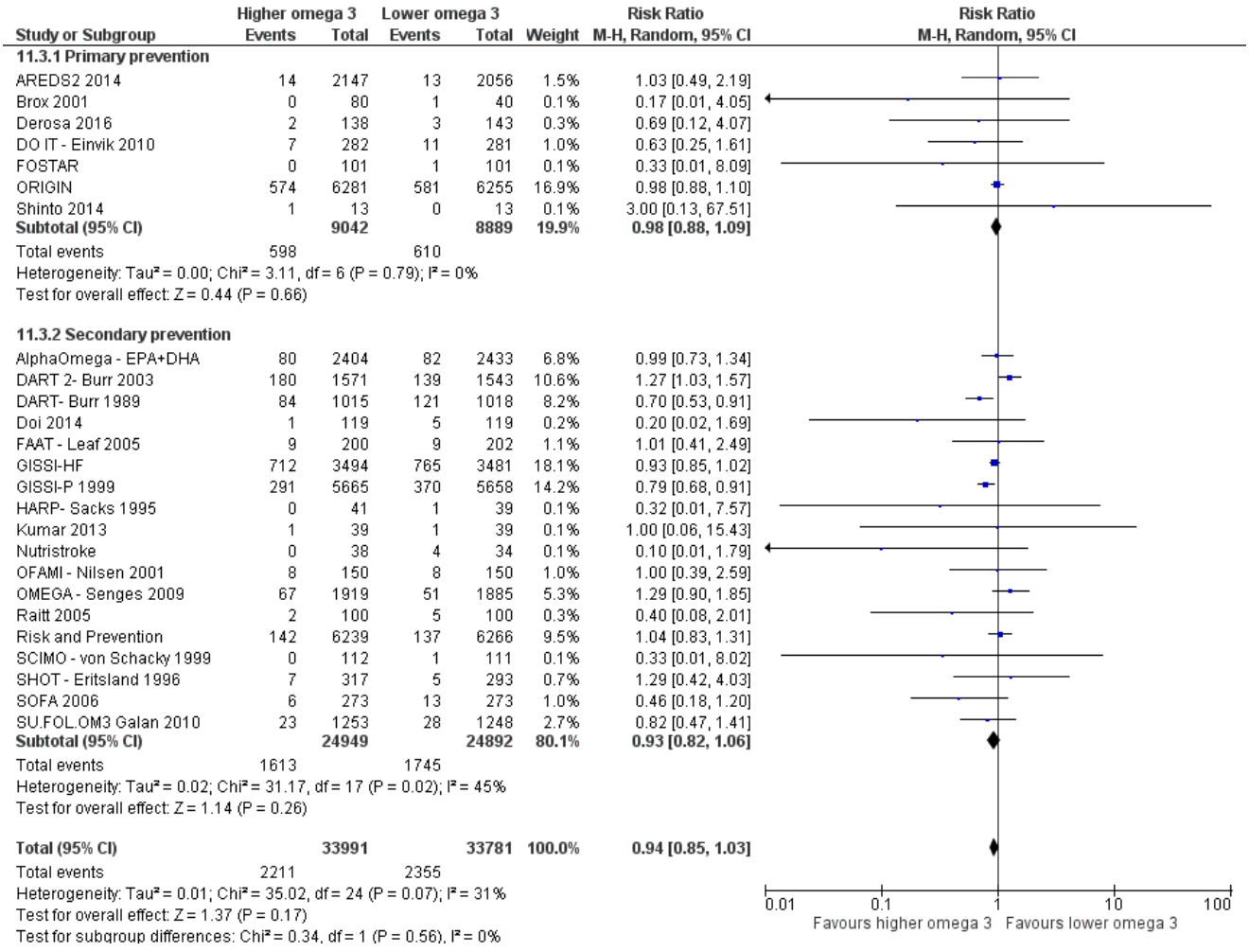


Figure 4.6. Meta-analysis of the effect of LCn3 fats on cardiovascular deaths, subgrouped by primary or secondary CVD prevention.

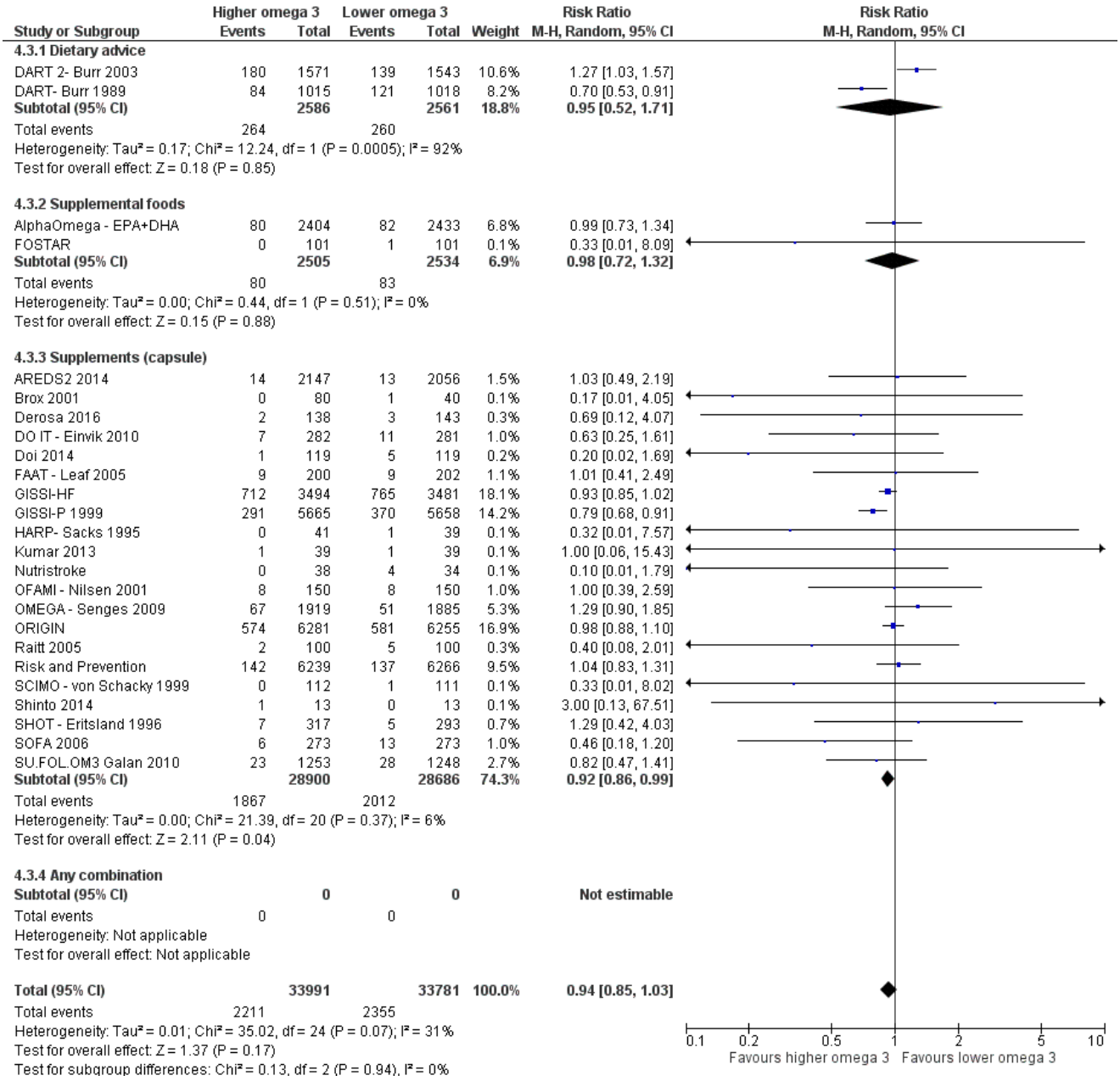


Figure 4.7. Meta-analysis of the effect of LCn3 fats on cardiovascular deaths, subgrouped by type of intervention.

Primary outcomes – Cardiovascular events

We included 32 RCTs of LCn3 fats assessing effects on people experiencing at least one cardiovascular event. These studies included over 89,000 participants and documented 14636 people with events, finding no effect of omega 3 fats on cardiovascular events (RR 0.99, 95% CI 0.94 to 1.04, I^2 36%), Figure 4.8. There were fewer trials of ALA intervention, three, including over 18000 participants and 868 people with cardiovascular events, finding no effect of ALA (RR 0.96, 95% CI 0.75 to 1.24, I^2 47%).

The funnel plot is not perfectly balanced, and if anything would suggest we may be missing one or two small studies which suggest increased risk of CVD events in the intervention group, but the bias does not appear severe, Figure 4.9.

Sensitivity analyses did not suggest any significant effects when we used fixed in place of random effects meta-analysis. Sensitivity analyses limiting to studies at low summary risk of bias did not suggest any effect of LCn3 fats on cardiovascular events (RR 1.01, 95% CI 0.96 to 1.05, I^2 2%, Figure 4.10).

No subgroup suggested a statistically significant effect, including subgrouping by primary or secondary prevention, Figure 4.11, by type of intervention, Figure 4.12, or by duration, Figure 4.13.

There were insufficient data to run subgrouping on ALA intervention studies, or LCn3 studies based on baseline omega 3 intake or omega 3/omega 6 ratio.

Summary

There is no evidence that omega 3 fats alter risk of cardiovascular events in either primary or secondary prevention of CVD.

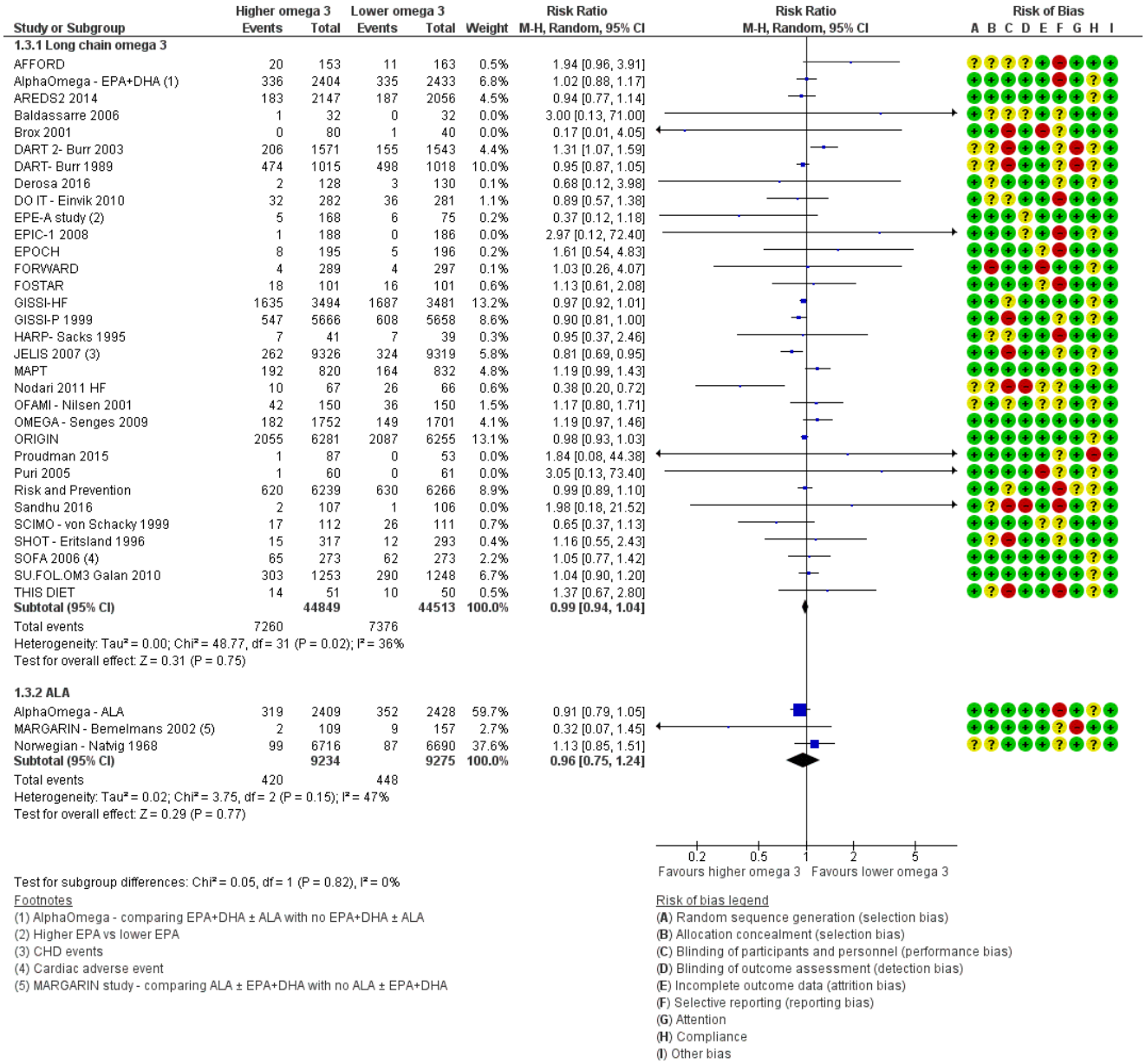


Figure 4.8. Meta-analysis of effects of omega 3 fats on cardiovascular events, subgrouped by LCn3 or ALA interventions.

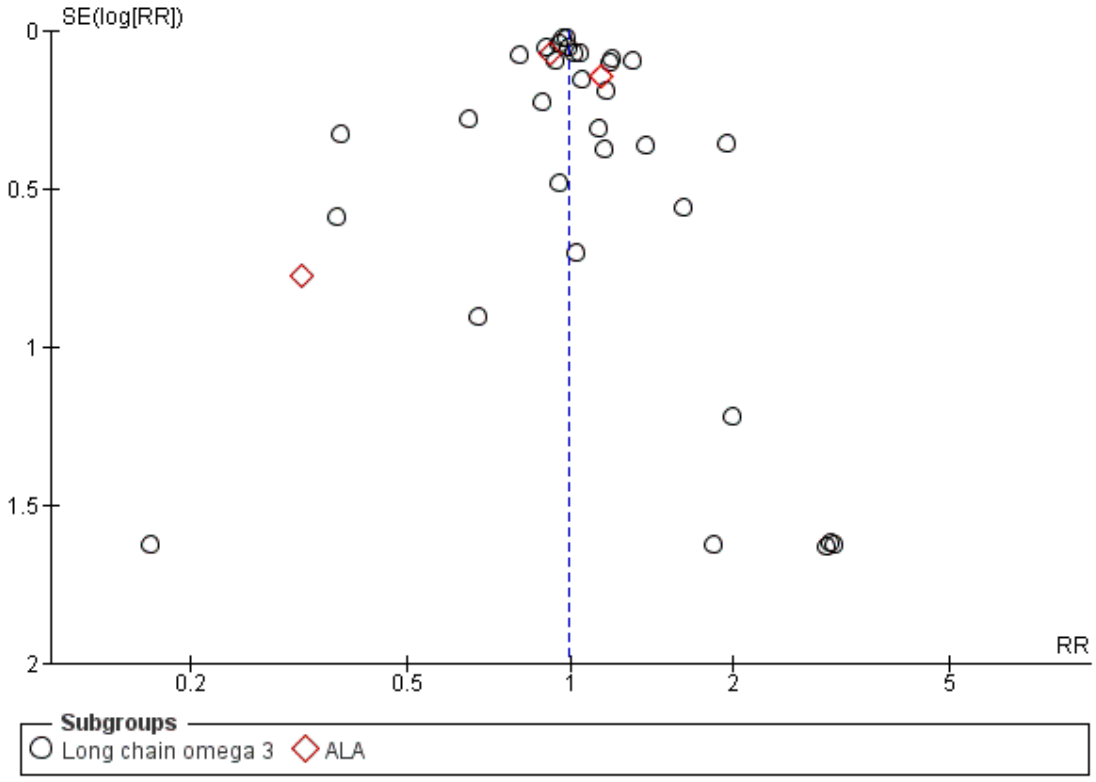


Figure 4.9. Funnel plot of effects of omega 3 fats on cardiovascular events

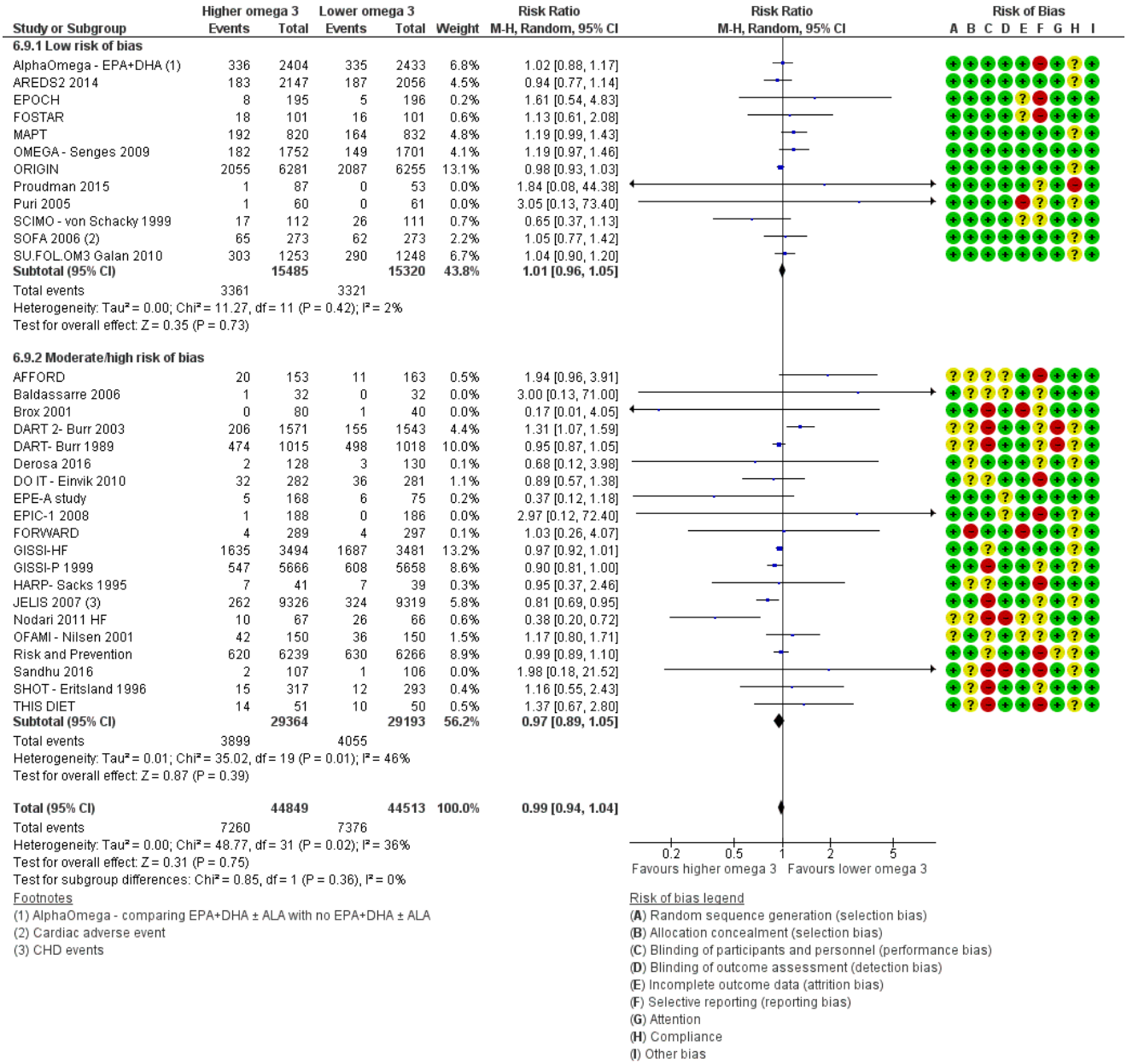


Figure 4.10. Meta-analysis of effects of long chain omega 3 fats on cardiovascular events, sensitivity analysis limiting to studies at low summary risk of bias (shown as subgrouped by risk of bias).

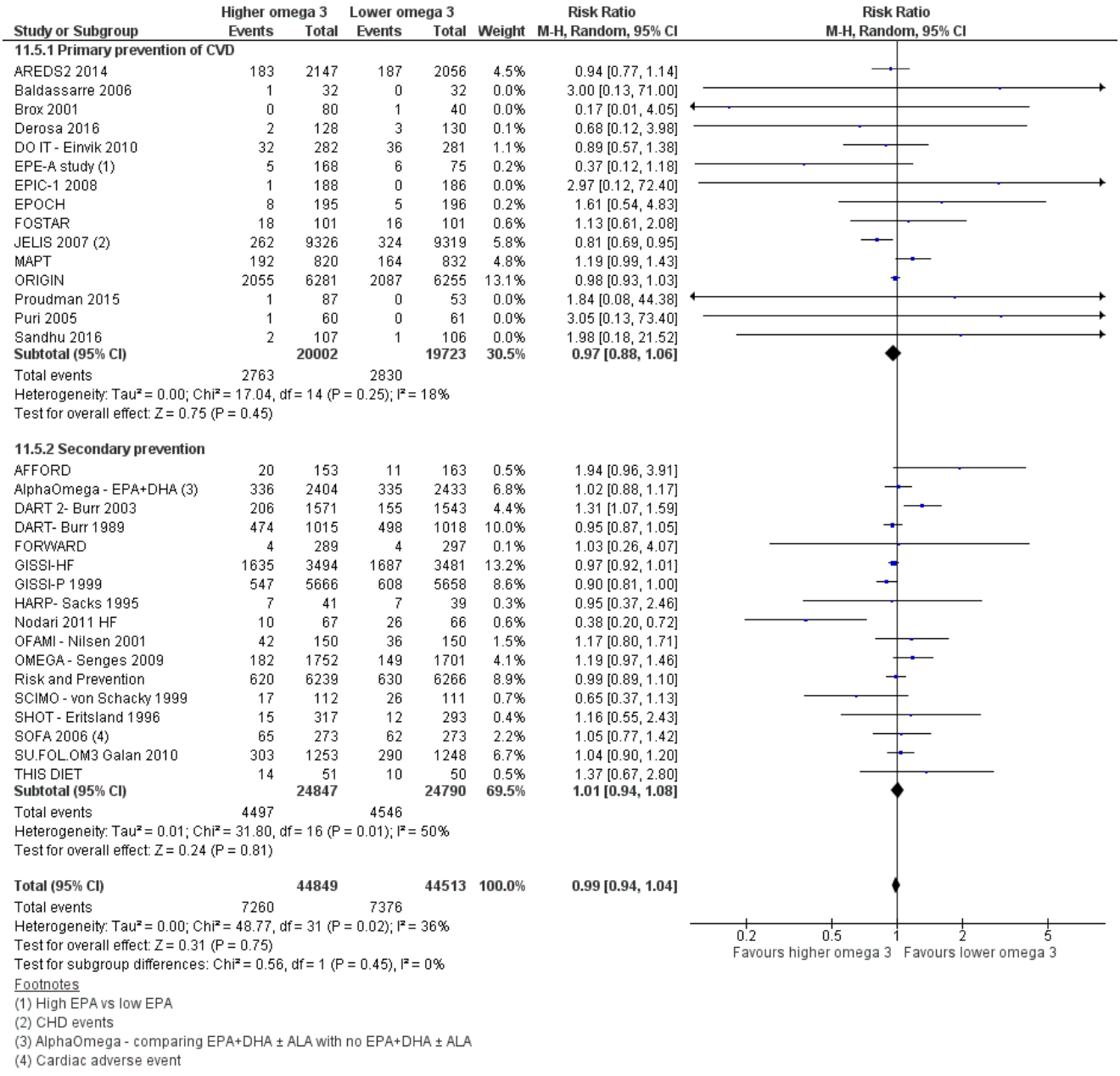


Figure 4.11. Meta-analysis of effects of long chain omega 3 fats on cardiovascular events, subgrouped by primary and secondary prevention.

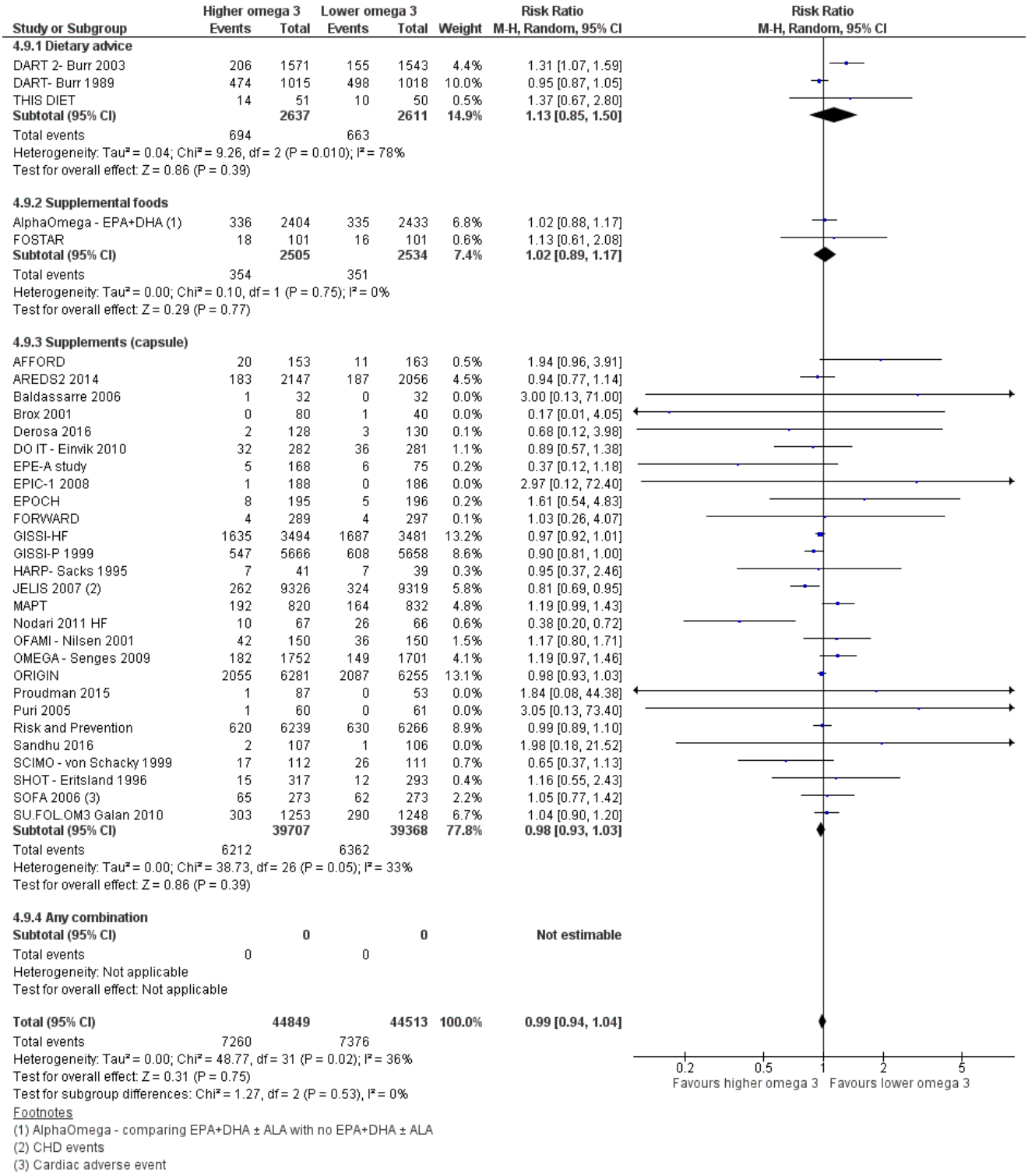


Figure 4.12. Meta-analysis of effects of long chain omega 3 fats on cardiovascular events, subgrouped by intervention type (dietary advice, supplement etc.).

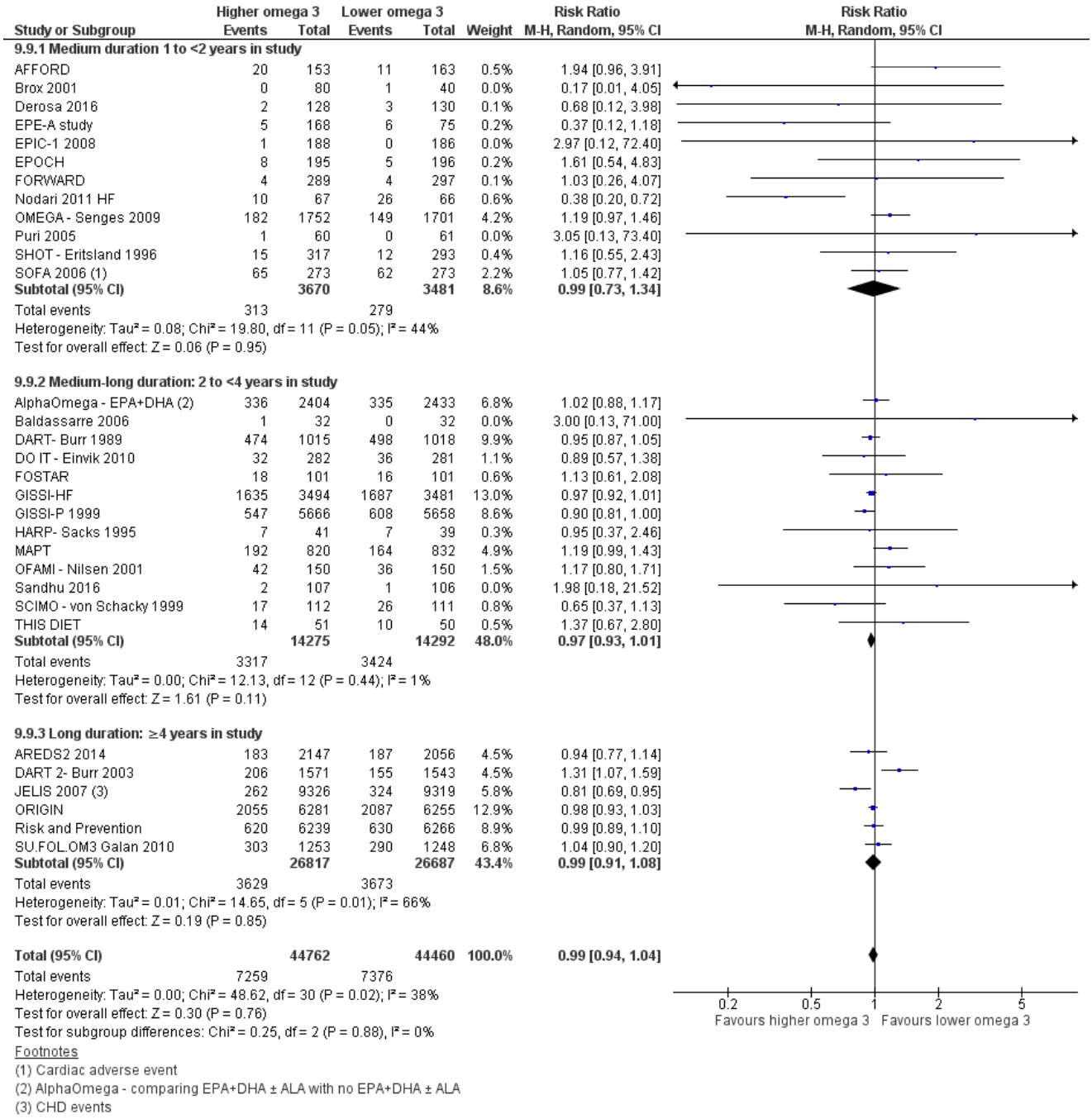


Figure 4.13. Meta-analysis of effects of long chain omega 3 fats on cardiovascular events, subgrouped by duration of intervention.

Additional outcome – Coronary Heart Disease deaths

This outcome was not requested by WHO NUGAG, but added later as there was some controversy about it. As we have collected the full set of trials of at least 1 year duration that randomised to higher or lower omega 3 fats, this is a truly systematic review of effects of omega 3 fats on CHD deaths, despite the outcome being added later in the systematic reviewing process.

We included data reported as coronary deaths, or where these were not reported, IHD death, fatal MI or cardiac death (using the first of these available in any study). We also decided to run a sensitivity analysis excluding studies with cardiac death data only.

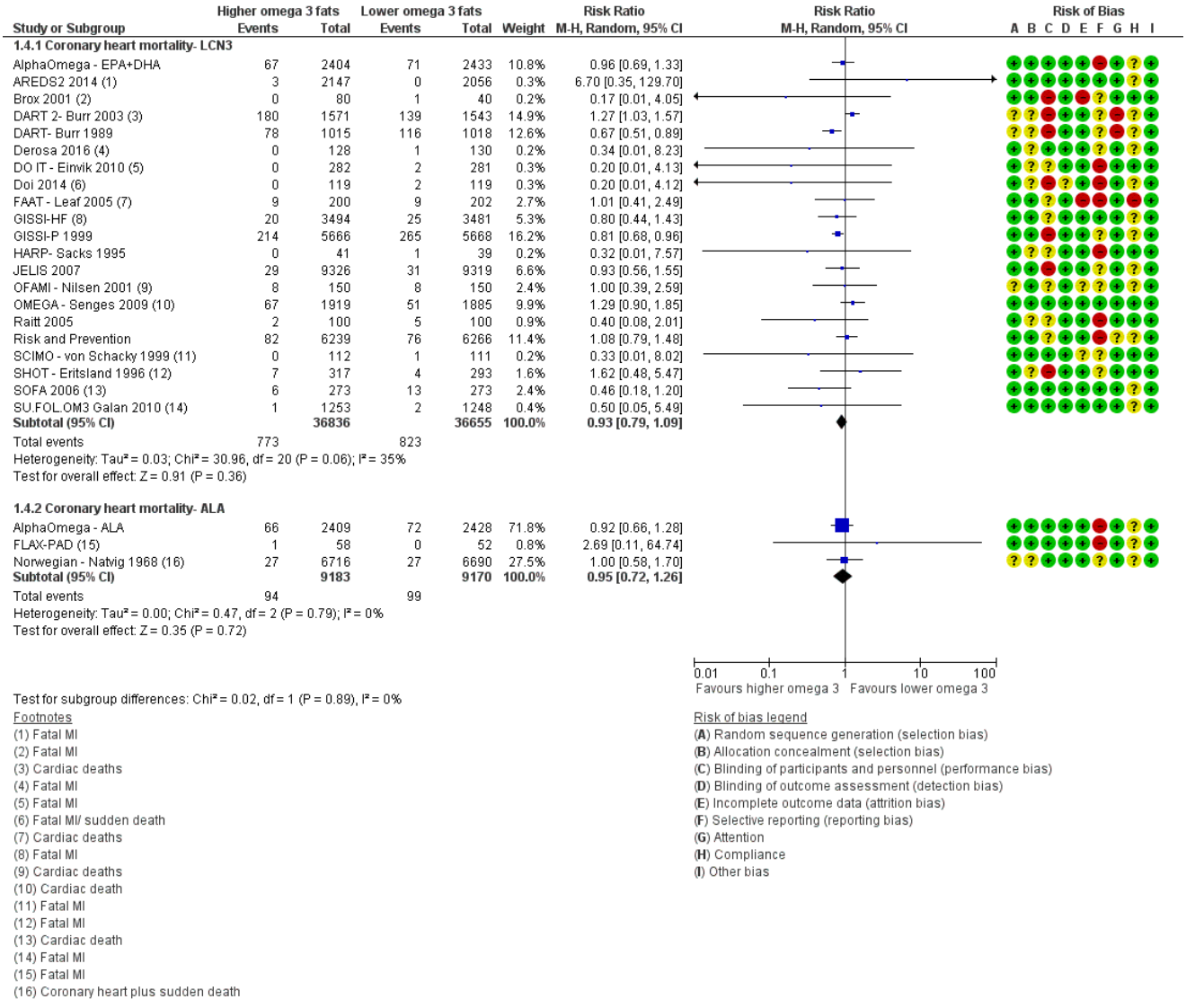


Figure 4.14. Meta-analysis of the effect of LCn3 fats on coronary heart disease deaths, subgrouped by LCn3 and ALA.

Twenty one trials assessed effects of long chain omega 3 fats (LCn3) on coronary heart disease deaths, including over 73,000 people and noting 1596 CHD deaths. Random effects meta-analysis suggested no effect of LCn3 on CHD deaths (RR 0.93, 95% CI 0.79 to 1.09, I^2 35%), Figure 4.14.

The funnel plot suggested a slight imbalance, suggesting missing studies with higher risk of CHD death with LCn3, Figure 4.17. If we "filled in" potentially missing studies to redress the imbalance, the RR would rise.

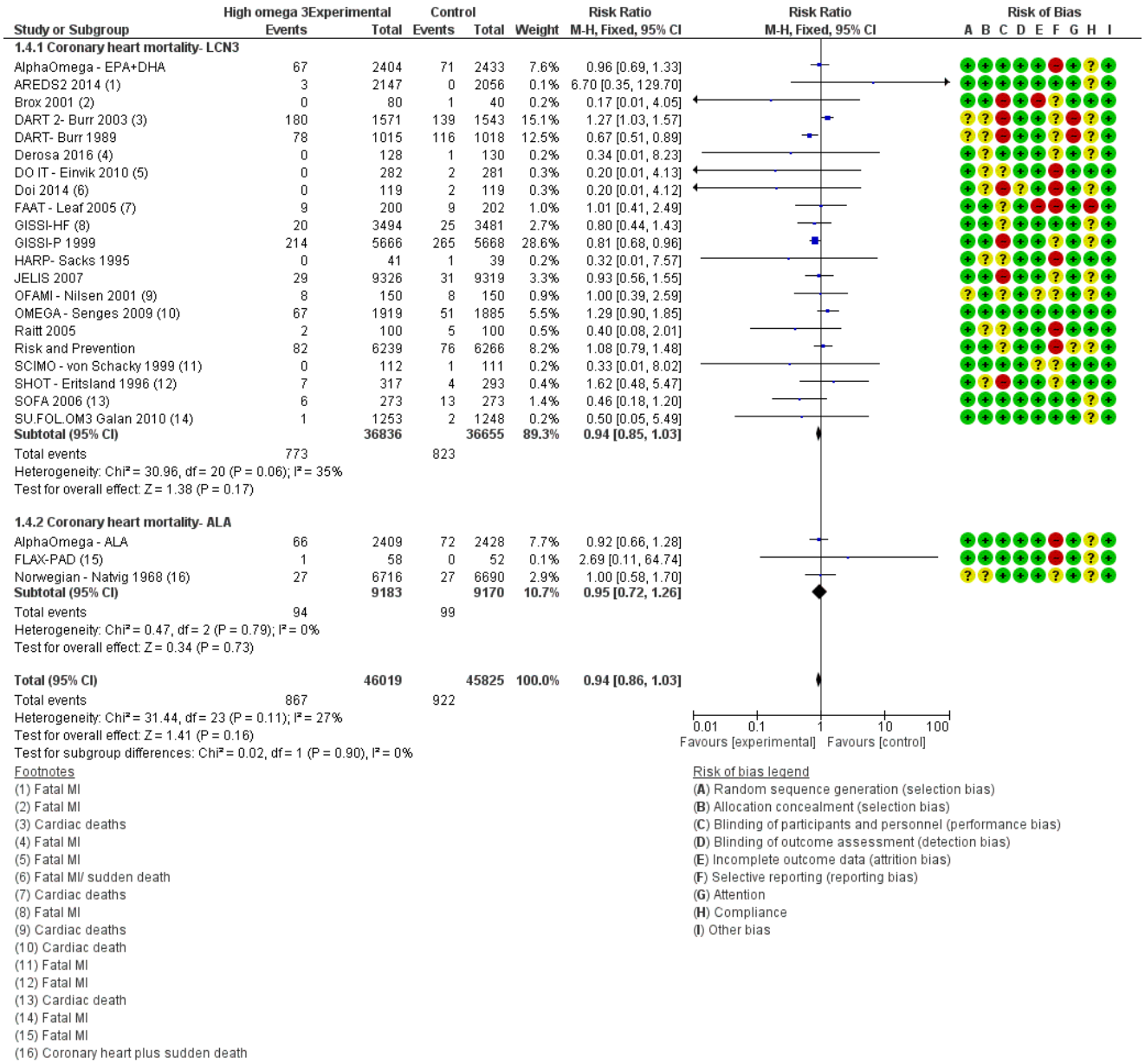
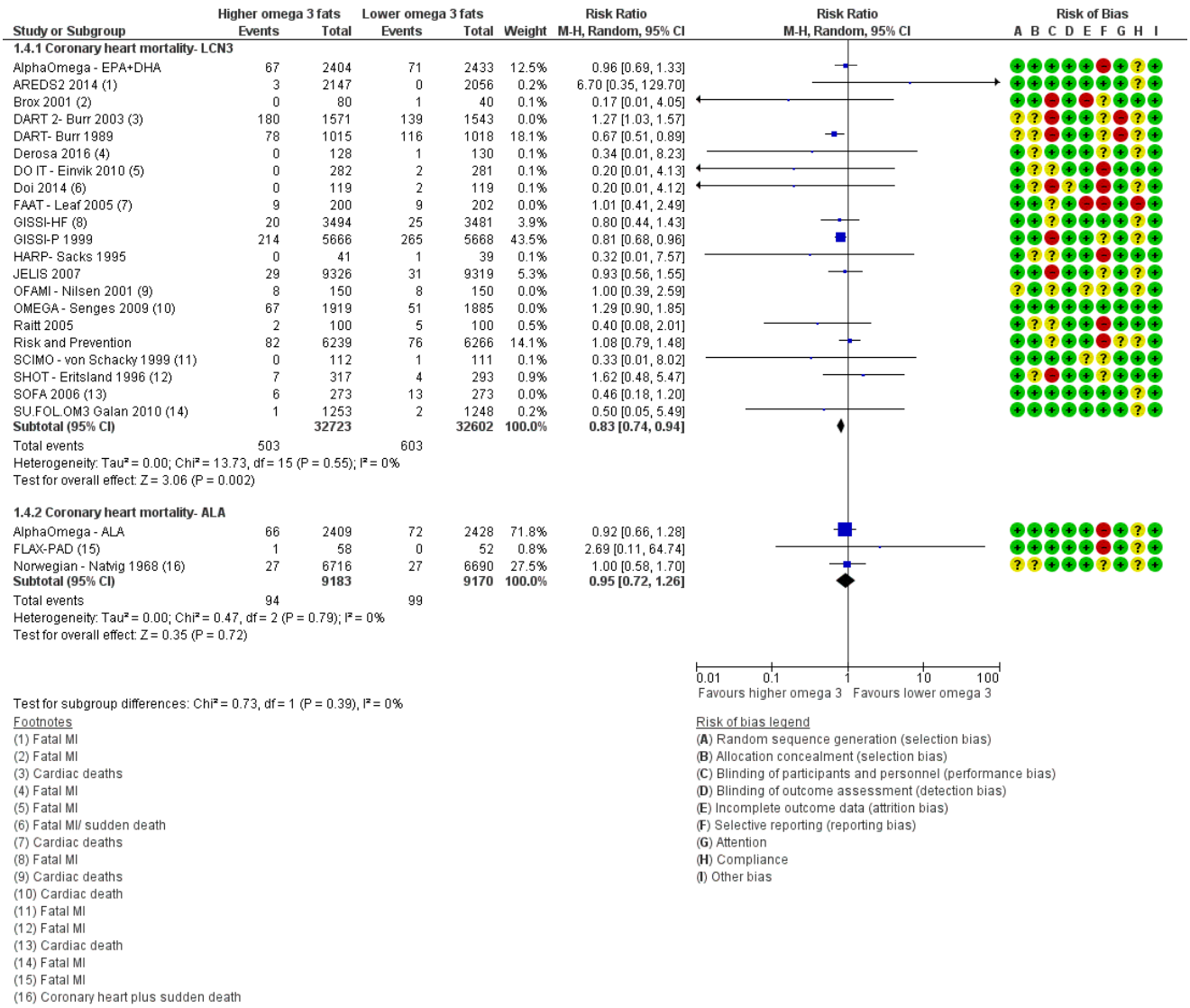


Figure 4.15. Sensitivity analysis. Forest plot of the effect of LCn3 fats on coronary heart disease deaths, using fixed effects meta-analysis.

Sensitivity analyses using fixed effects did not alter the suggested lack of statistical significance (RR 0.94, 95% CI 0.85 to 1.03, I^2 35%, Figure 4.15), while excluding studies only reporting cardiac deaths omits several studies at low risk of bias and suggests reduction of CHD death with LCn3 (RR 0.83, 95% CI 0.74 to 0.94, I^2 05, Figure 4.16). Sensitivity analysis, omitting studies at moderate to high risk of bias removed any suggested effect of LCn3 on CHD deaths (RR 0.99, 95% CI 0.70 to 1.41, I^2 27%, Figure 4.18).



Test for subgroup differences: Chi² = 0.73, df = 1 (P = 0.39), I² = 0%

Footnotes

(1) Fatal MI
(2) Fatal MI
(3) Cardiac deaths
(4) Fatal MI
(5) Fatal MI
(6) Fatal MI/ sudden death
(7) Cardiac deaths
(8) Fatal MI
(9) Cardiac deaths
(10) Cardiac death
(11) Fatal MI
(12) Fatal MI
(13) Cardiac death
(14) Fatal MI
(15) Fatal MI
(16) Coronary heart plus sudden death

Risk of bias legend

(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Attention
(**H**) Compliance
(**I**) Other bias

Figure 4.16. Sensitivity analysis. Forest plot of the effect of LCn3 fats on coronary heart disease deaths, omitting studies only reporting cardiac death.

The three trials, including over 18,000 participants with 193 CHD deaths, that assessed risk of CHD death with ALA intake suggested no effect (RR 0.95, 95% CI 0.72 to 1.26, I^2 0%), Figure 4.14.

Subgrouping was not possible for ALA studies, as there were too few trials included. There were insufficient data to run subgrouping for LCn3 trials based on baseline omega 3 intake or omega 3/omega 6 ratio.

Subgrouping the LCn3 trials by history of CAD, primary or secondary prevention of CVD, omega 3 dose, intervention type, replacement, and statin use did not suggest any statistically significant subgroups or important differences between subgroups. However, subgrouping by duration suggested no effect in studies of one to less than 2 years, a protective effect in studies of two to less than 4 year, and a marginally harmful effect in studies of at least 4 years duration, Figure 4.20.

Summary

Any effect of LCn3 on CHD deaths appears to depend on assumptions made in analyses. There was no statistically significant effect of LCn3 on CHD deaths in the main analysis, or in sensitivity analyses using fixed-effects meta-analysis or omitting studies at moderate to high summary risk of bias (whether or not we included studies reporting cardiac deaths). However, excluding studies only reporting cardiac deaths omitted several studies at low risk of bias and suggested reduction of CHD death with LCn3. Correcting the funnel plot by filling in possible missing studies would tend to raise the RR of all analyses. We suggest that any apparent effect is partly driven by reporting bias and partly by studies at moderate to high risk of bias.

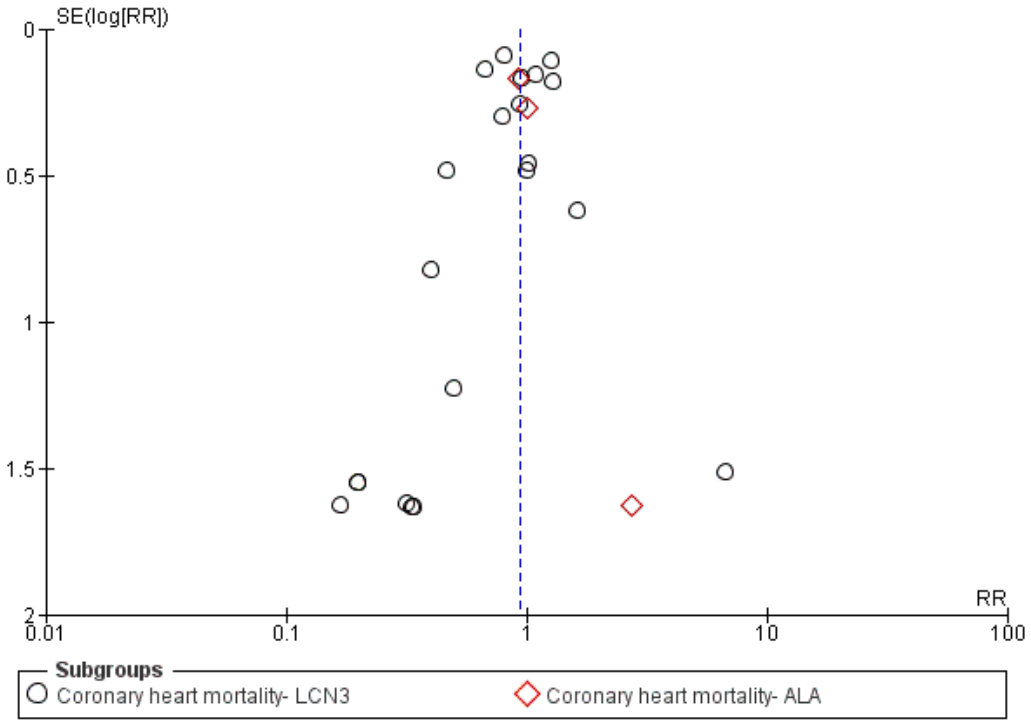


Figure 4.17. Funnel plot for meta-analysis of the effect of LCn3 fats on coronary heart disease deaths.

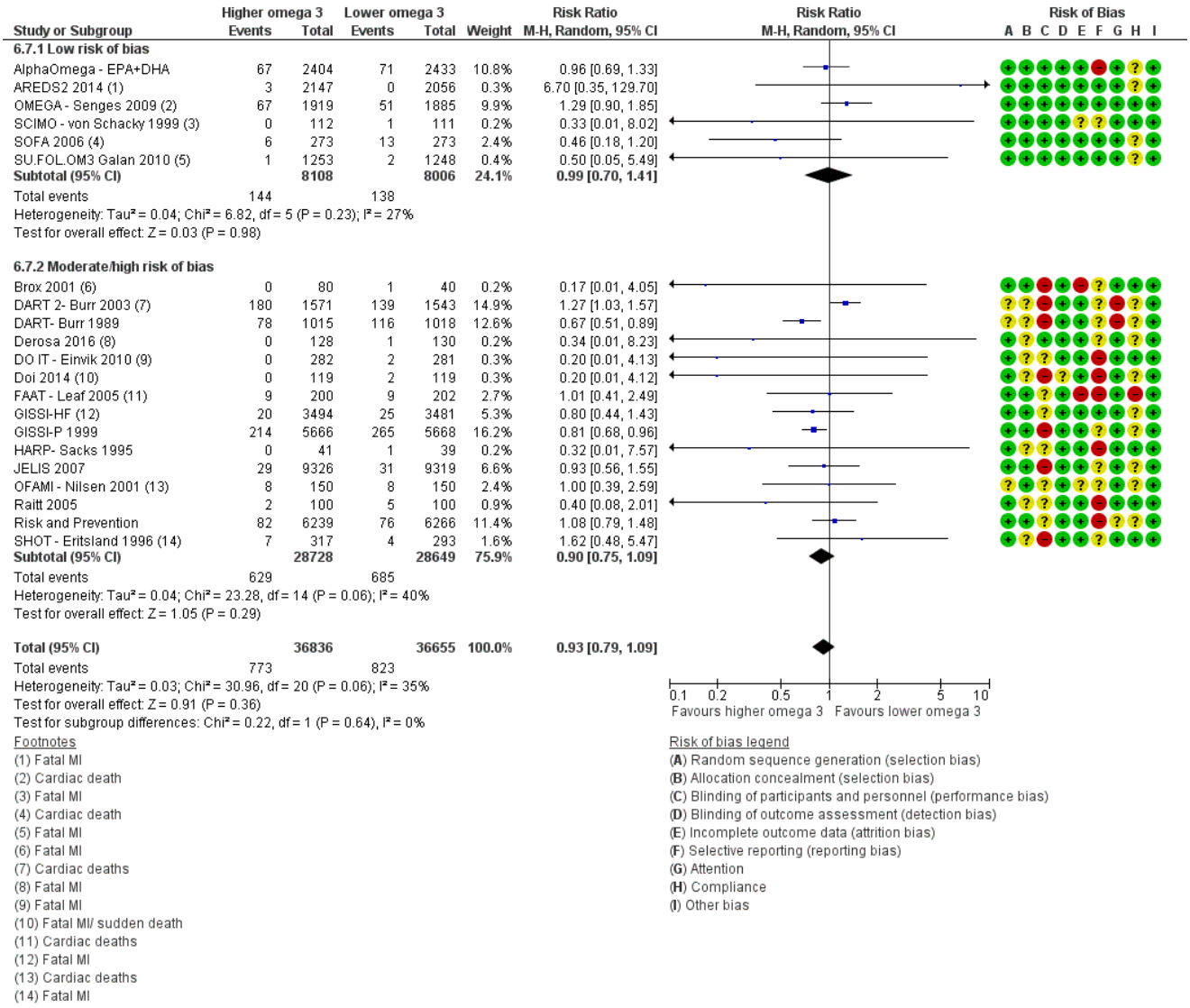


Figure 4.18. Meta-analysis of the effect of LCn3 fats on coronary heart disease deaths, sensitivity analysis limiting to studies at low summary risk of bias (shown as subgrouped by risk of bias to allow analysis of the contrast between the two sets of trials).

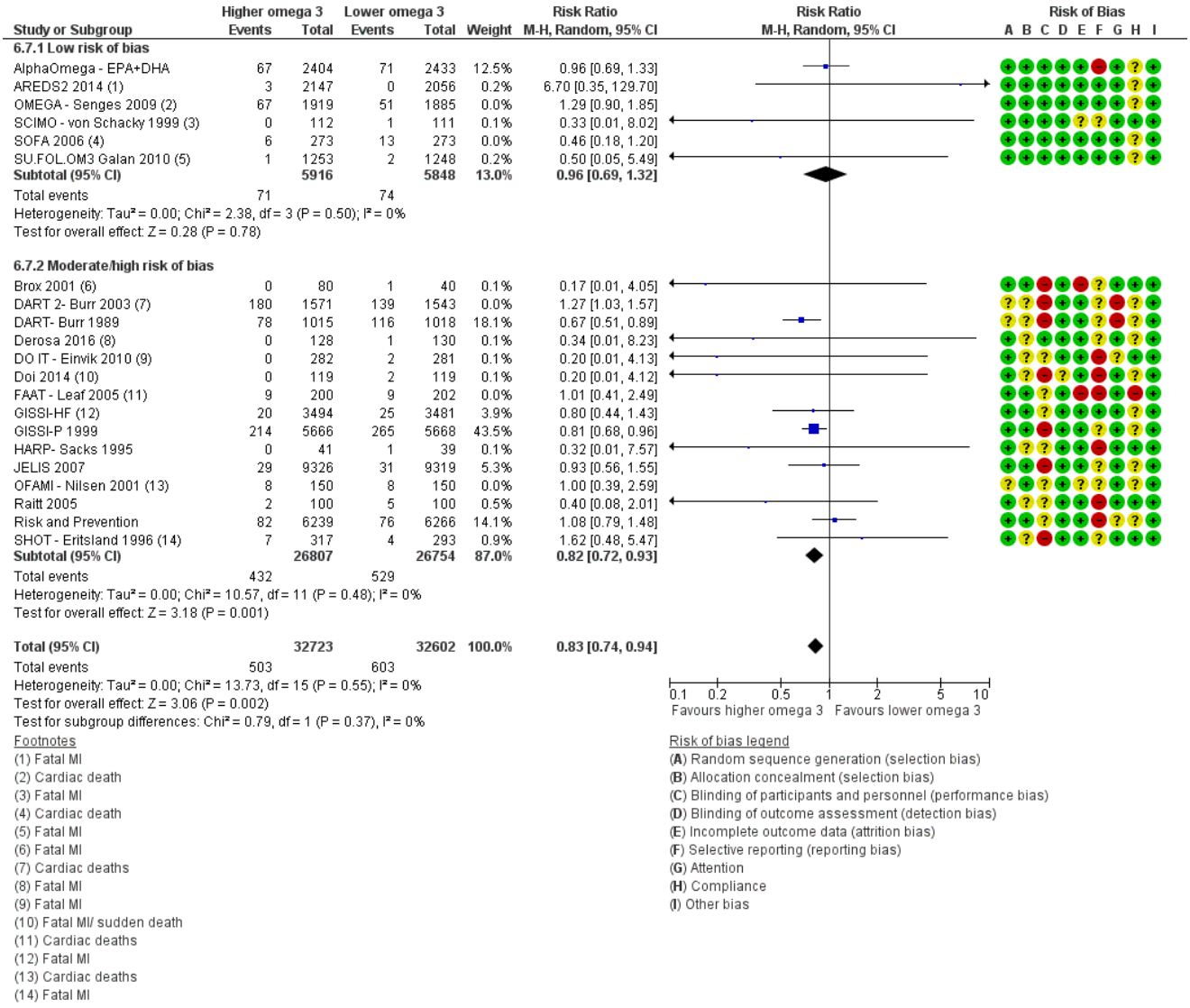


Figure 4.19. Sensitivity analysis. Forest plot of the effect of LCn3 fats on coronary heart disease deaths, subgrouped by risk of bias, omitting studies only reporting cardiac death.

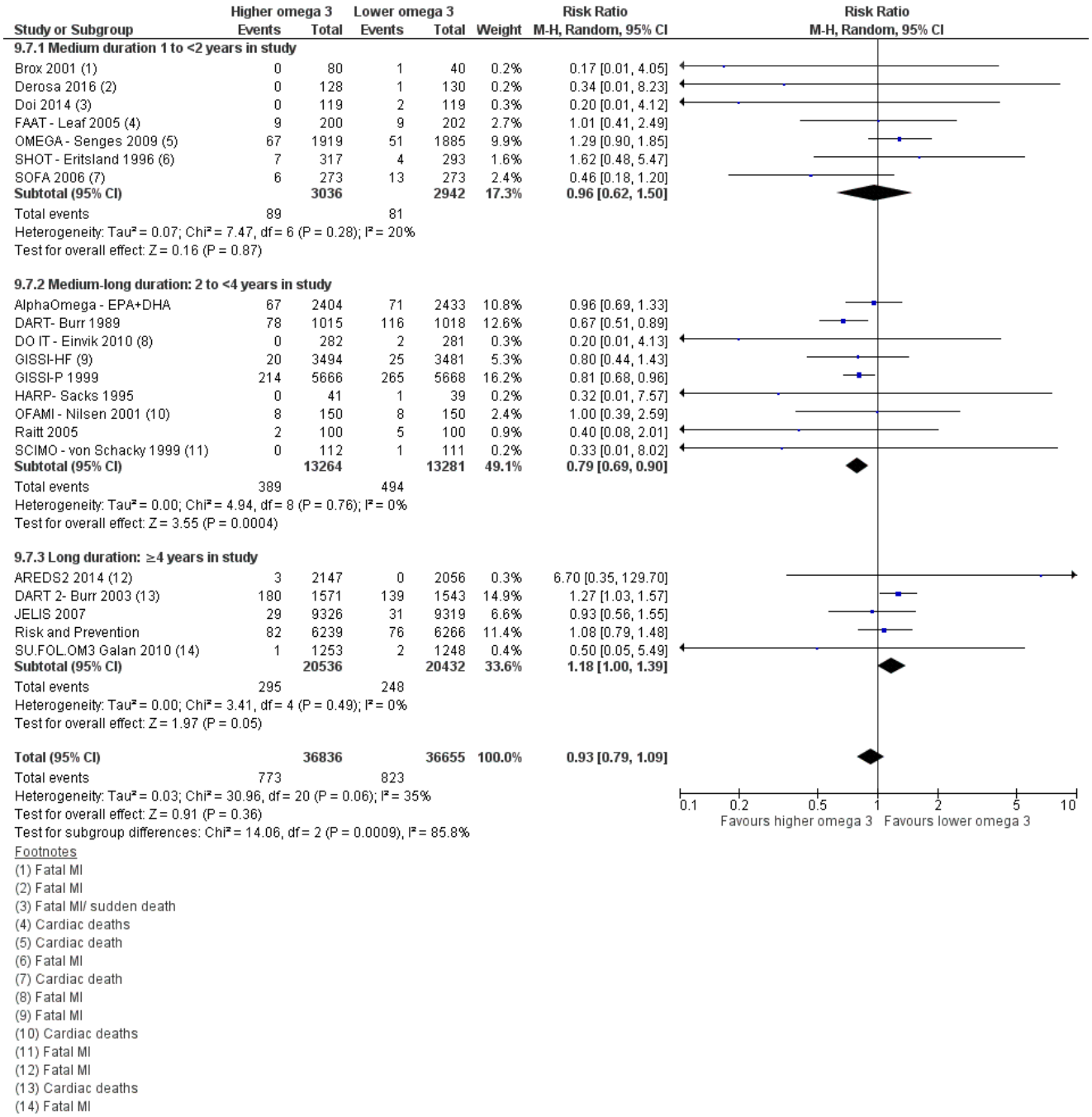


Figure 4.20. Meta-analysis of the effect of LCn3 fats on coronary heart disease deaths, subgrouped by duration of intervention.

Primary outcomes – Coronary Heart Disease events

Coronary heart event data were collated (as with all event data) based on how many people experienced at least one event (not how many events occurred). In order to maximise available data we used the first outcome in this list reported for each trial: CHD or coronary events; total MI; acute coronary syndrome; or angina (stable and unstable).

Twenty eight RCTs assessing effects of LCn3, including over 84,000 participants, reported 5469 participants as having coronary heart disease events. Meta-analysis suggested a 7% reduction in coronary heart disease with higher LCn3 intake (RR 0.93, 95% CI 0.88 to 0.97, I^2 0%), Figure 4.21.

The funnel plot suggested no great bias, but perhaps a few studies showing harm with omega 3 fats were missing, Figure 4.22.

Sensitivity analyses using fixed effects meta-analysis suggested a significant positive effect on CHD events of LCn3 (RR 0.92, 95% CI 0.88 to 0.97, I^2 0%), while limiting studies to those at low summary risk of bias suggested no effects of LCn3 fats on CHD events (RR 0.98, 95% CI 0.91 to 1.05, I^2 0%, 2222 people experienced a CHD event). There were important differences between subgroups of studies at low risk of bias and those at moderate to high risk of bias (p=0.08, I^2 67.4%), with statistically significant effects in studies of moderate to high risk of bias, Figure 4.23.

Subgrouping LCn3 studies by history of previous CAD, or not, suggested a statistically significant effect in the previous CAD group only (though no important differences between subgroups, Figure 4.24). Similarly, subgrouping by primary or secondary prevention (people with CVD or not at baseline) suggested a statistically significant effect in the secondary prevention group only, though with no important differences between subgroups. Subgrouping by dose suggested an effect only in the 0.4 to 2.4g/d LCn3 subgroup (Figure 4.26), by duration an effect only in the 2 to <4 years category (Figure 4.27), by intervention type only in the supplements (capsules) subgroup (Figure 4.25), and none of these subgroupings suggested important differences between subgroups. Subgrouping by replacement suggested reduction in CHD events in the group where LCn3 was compared to nil or a non-fat or lower n3 comparator, and subgrouping by statin use suggested a benefit only in the subgroup where fewer than 50% were using statins, but with no important differences between subgroups. There was no suggestion that longer duration or higher dose LCn3 had greater benefits.

Three RCTs assessed effects of ALA on CHD events, including over 18,000 participants, and 396 people experienced CHD events. There was no suggestion of any effect of ALA on CHD events (RR 1.00, 95% CI 0.78 to 1.29, I^2 24%).

Subgrouping was not possible for ALA studies, as there were too few trials included. There were insufficient data to run subgrouping for LCn3 trials based on baseline omega 3 intake or omega 3/omega 6 ratio.

Summary

Although the analysis included over 84,000 participants, 5469 of whom experienced coronary heart disease, the evidence suggesting a small reduction in risk of coronary heart disease with LCn3 intake is not convincing. When we omit studies at moderate to high risk of bias the effect appears negligible and no longer statistically significant. The overall effect size of all 28 RCTs suggested a 7% reduction in coronary heart disease (RR 0.93, 95% CI 0.88 to 0.97, I^2 0%), but in

the 11 studies at low risk of bias, which included 2222 people experiencing at least one CHD event, there was no clear effect (RR 0.97, 95% CI 0.90 to 1.05, I^2 0%, p=0.51). We suggest that the apparent effect of LCn3 fats in reducing CHD is due to studies at moderate to high risk of bias only, and is not seen in less biased studies.

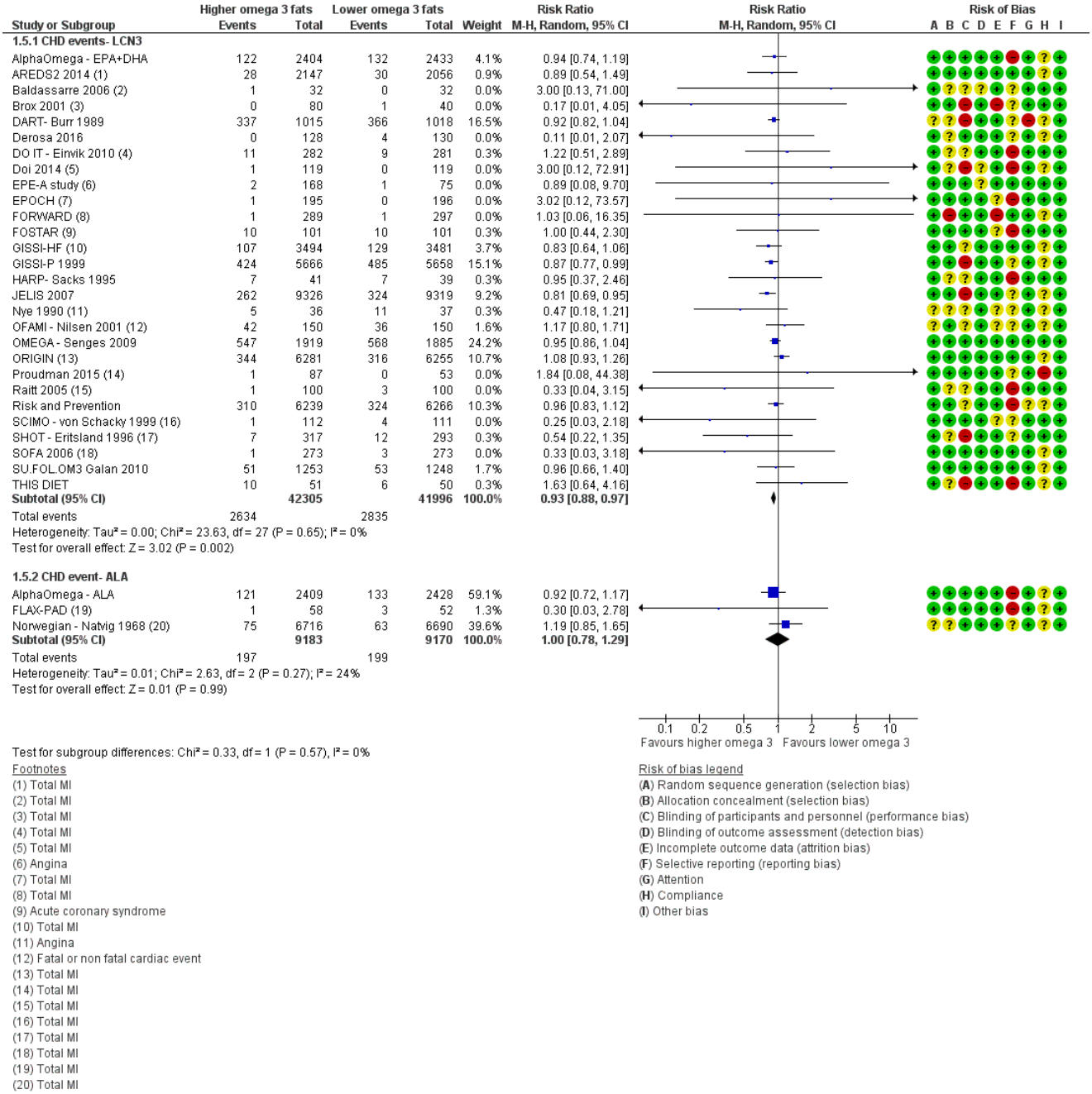


Figure 4.21. Meta-analysis of the effect of LCn3 fats on coronary heart disease, subgrouped by LCn3 and ALA.

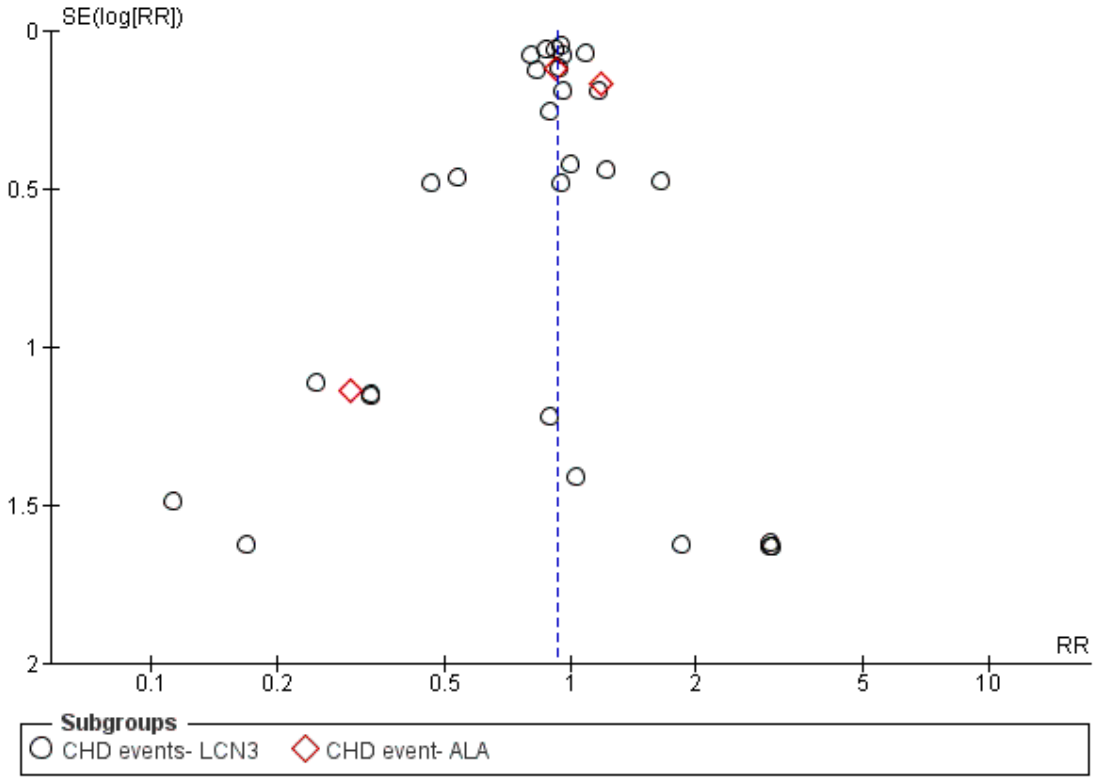


Figure 4.22. Funnel plot for meta-analysis of the effect of LCn3 fats on coronary heart disease.

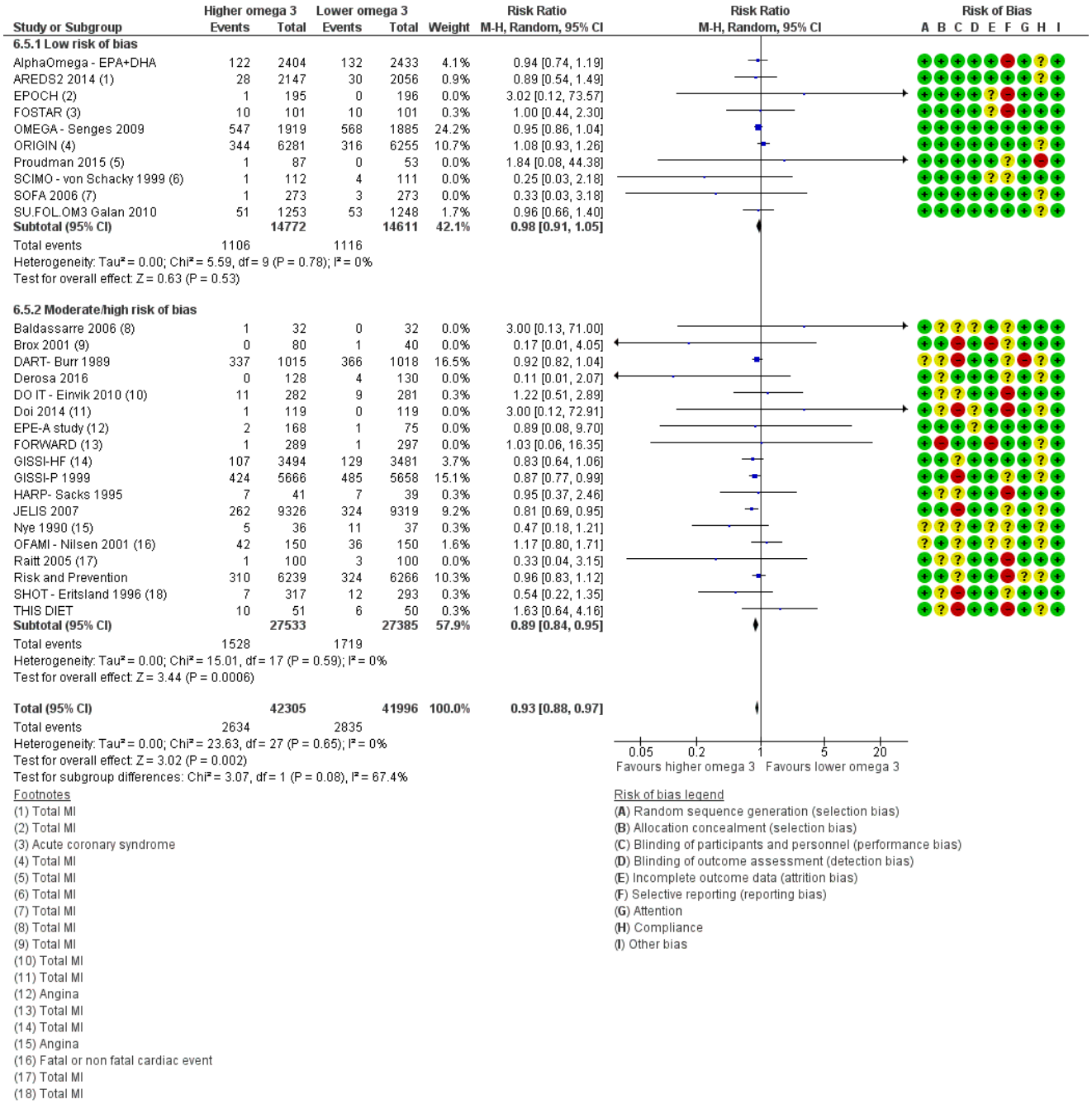


Figure 4.23. Meta-analysis of the effect of LCn3 fats on coronary heart disease, sensitivity analysis omitting trials at moderate to high summary risk of bias (shown subgrouped by summary risk of bias to allow readers to contrast effects in the two sets of studies).

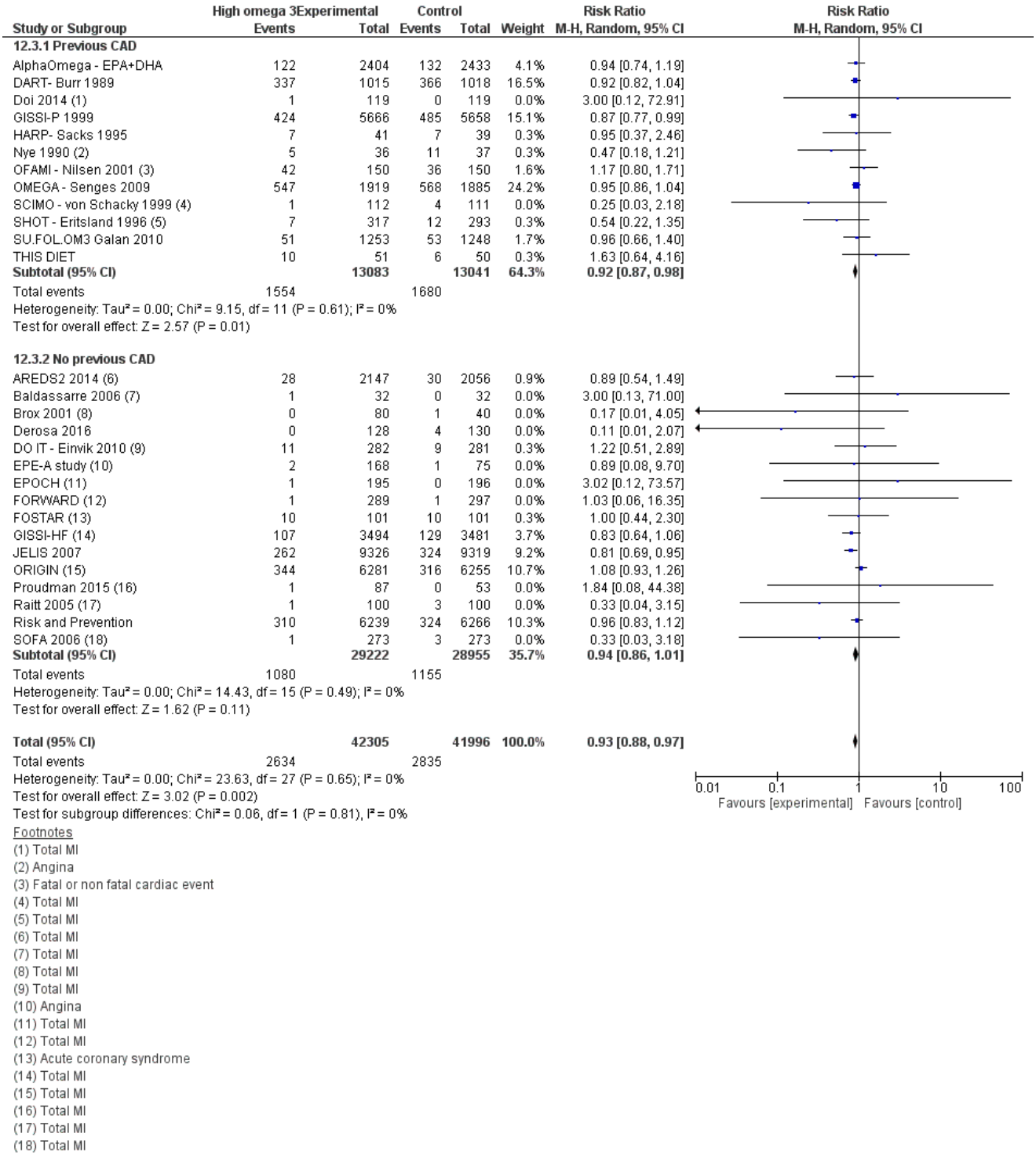


Figure 4.24. Meta-analysis of the effect of LCn3 fats on coronary heart disease, subgrouped by previous CAD history.

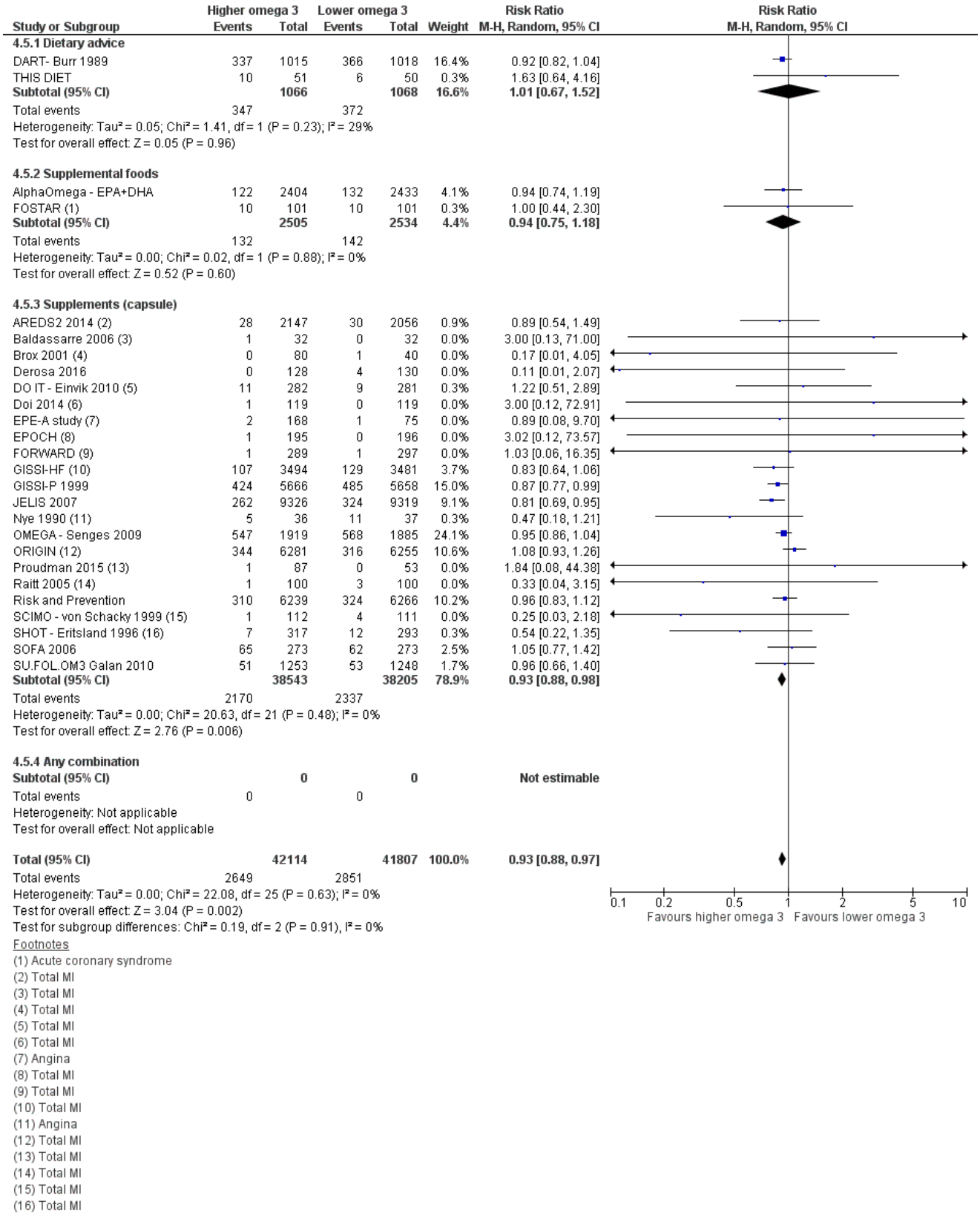


Figure 4.25. Meta-analysis of the effect of LCn3 fats on coronary heart disease, subgrouped by type of intervention.

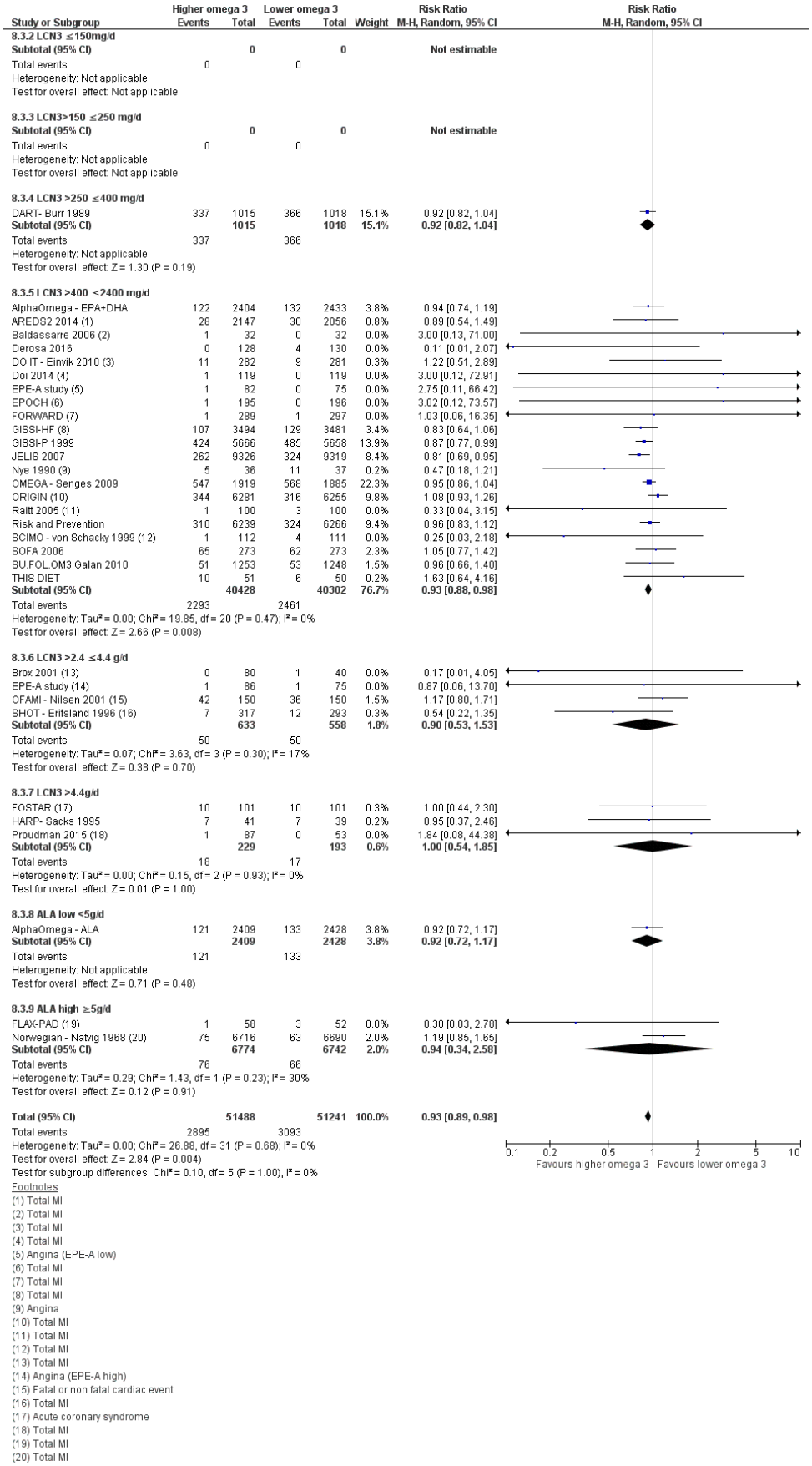


Figure 4.26. Meta-analysis of the effect of LCn3 fats on coronary heart disease, subgrouped by dose.

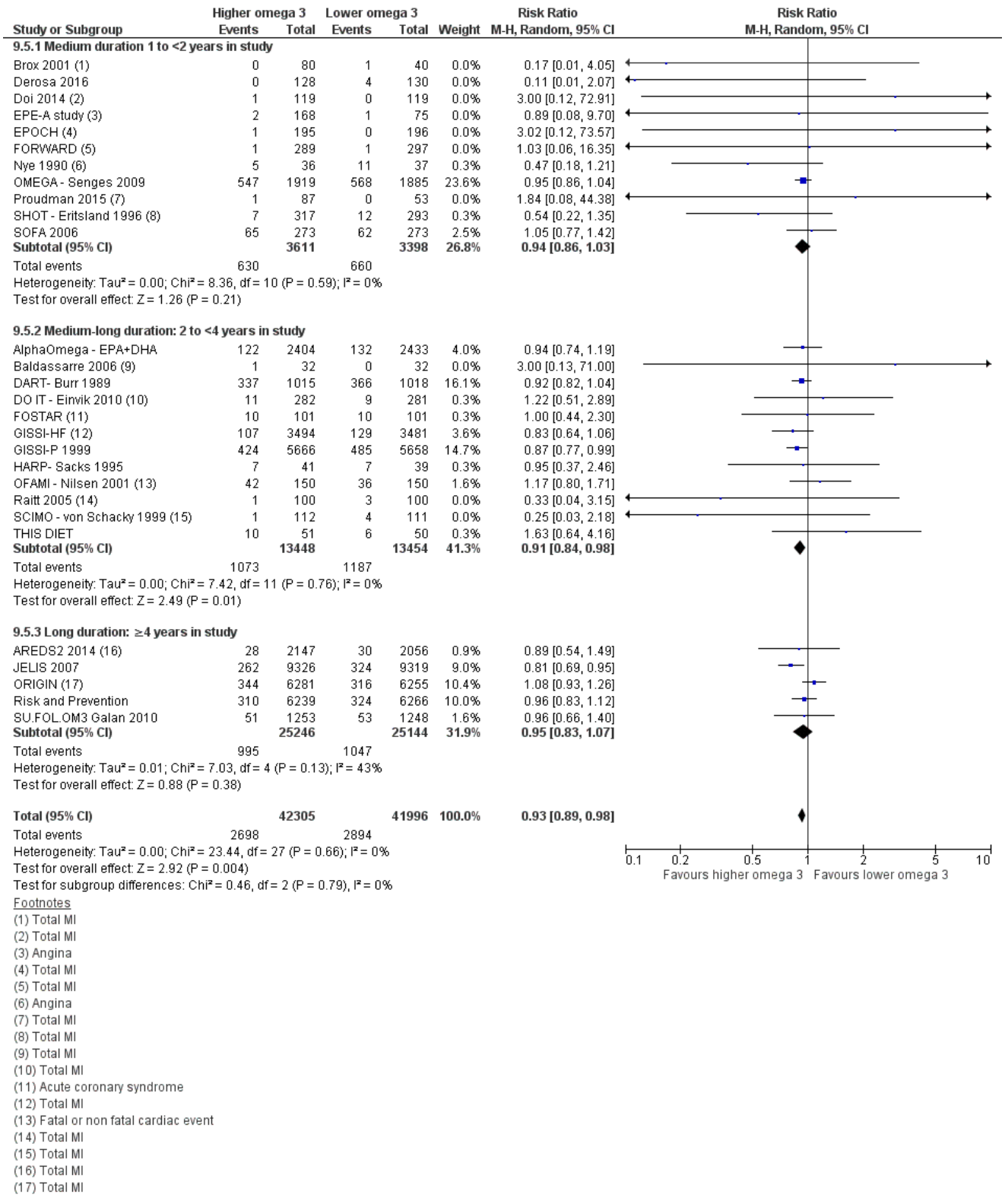


Figure 4.27. Meta-analysis of effects of omega 3 fats on CHD, subgrouped by duration.

Primary outcomes – Stroke

We included 28 RCTs of LCn3 fats assessing effects on risk of stroke (including fatal and non-fatal stroke, haemorrhagic and ischaemic). These studies included over 89,000 participants and documented 1822 people having a stroke, finding no effect of omega 3 fats on stroke (RR 1.06, 95% CI 0.96 to 1.16, I^2 0%), Figure 4.28. There were four trials of ALA intervention, including over 18000 participants and 49 strokes, finding no effect of ALA (RR 1.16, 95% CI 0.65 to 2.05, I^2 0%).

The funnel plot did not suggest any small study bias, Figure 4.29.

Fixed effects meta-analyses do not alter the lack of effect. LCn3 effects did not appear to differ by summary risk of bias. Omitting studies at moderate to high summary risk of bias suggested no effect of omega 3 fats on stroke (RR 1.00, 95% CI 0.86 to 1.17, I2 3%), while the studies at moderate to high risk of bias were also statistically non-significant but tended to suggest some increase in stroke risk (RR 1.13, 95% CI 0.98 to 1.28, I^2 0%, Figure 4.30).

Subgrouping by primary or secondary prevention suggested harm in those with a previous history of CVD (RR 1.21, 95% CI 1.05 to 1.40, I^2 0%), but no effect in primary prevention (Figure 4.31). Subgrouping by statins, where fewer than 50% of participants appeared to be using statins during the trial suggested that omega 3 fats were associated with increased stroke risk (RR 1.18 95% CI 1.02 to 1.37), but there were not clear differences between subgroups (I^2 0%), Figure 4.32.

Subgrouping by type of intervention, dose and duration suggested no statistically significant effect in any subgroup (Figures 4.33 to 4.35). There were insufficient data to run subgrouping for ALA interventions or for LCn3 interventions based on baseline omega 3 intake or omega 3/omega 6 ratio.

Summary

There is no evidence that omega 3 fats reduce the risk of stroke.While there is a suggestion that LCn3 fats may increase stroke risk in secondary prevention of CVD, no increased risk of stroke is apparent in studies at low risk of bias.

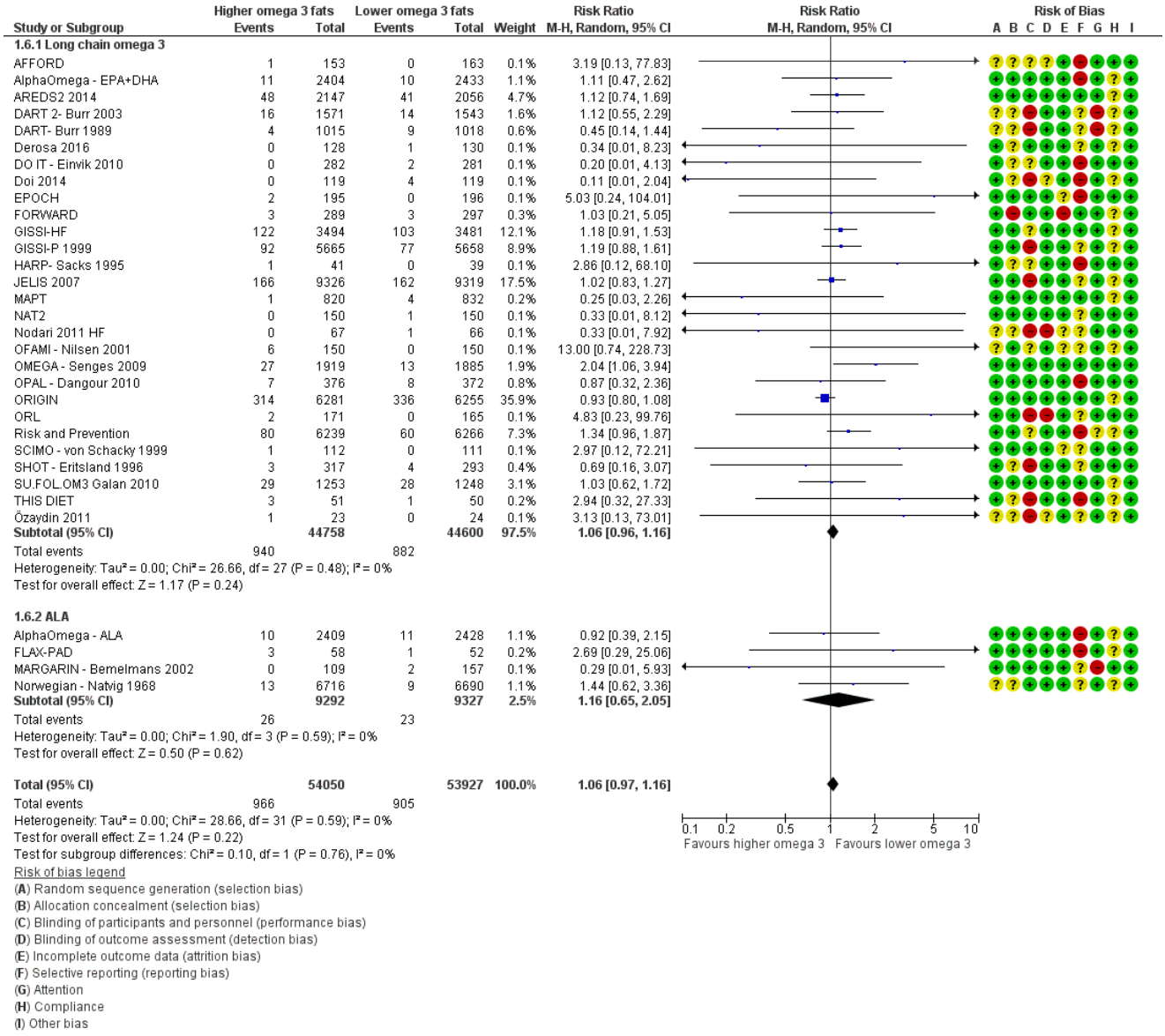


Figure 4.28. Meta-analysis of effects of omega 3 fats on stroke, subgrouped by LCn3 or ALA.

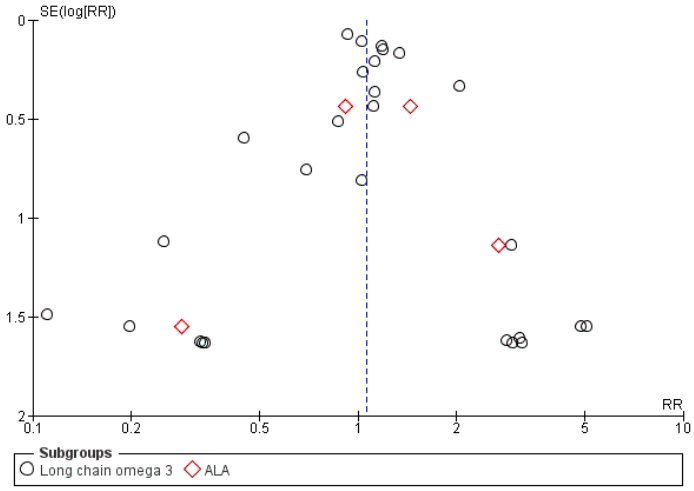


Figure 4.29. Funnel plot for effect of omega 3 fats on stroke.

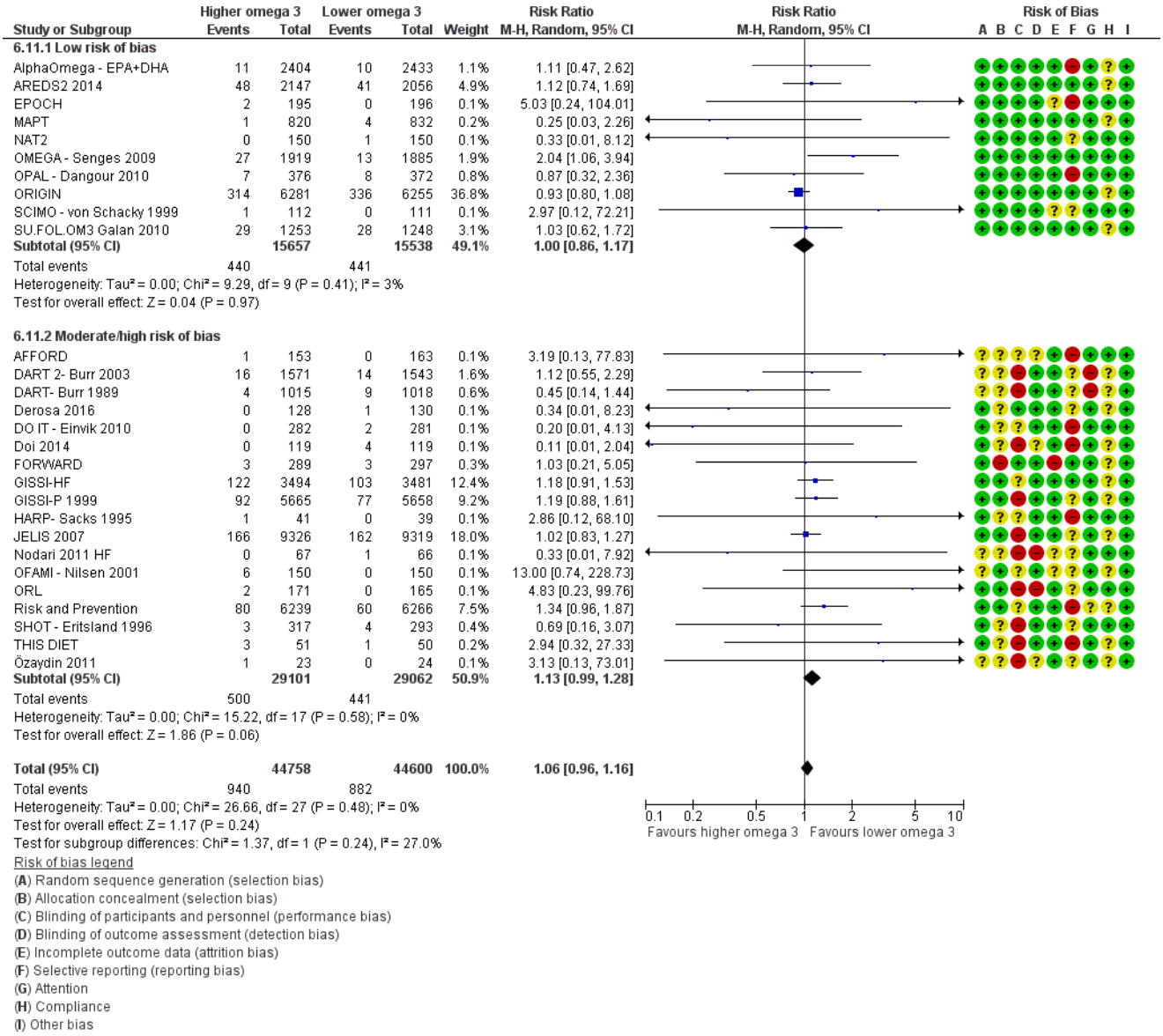


Figure 4.30. Meta-analysis of effects of omega 3 fats on stroke, sensitivity analysis omitting studies at moderate to high summary risk of bias (shown as a subgrouping to allow comparison of studies at different summary risk of bias).

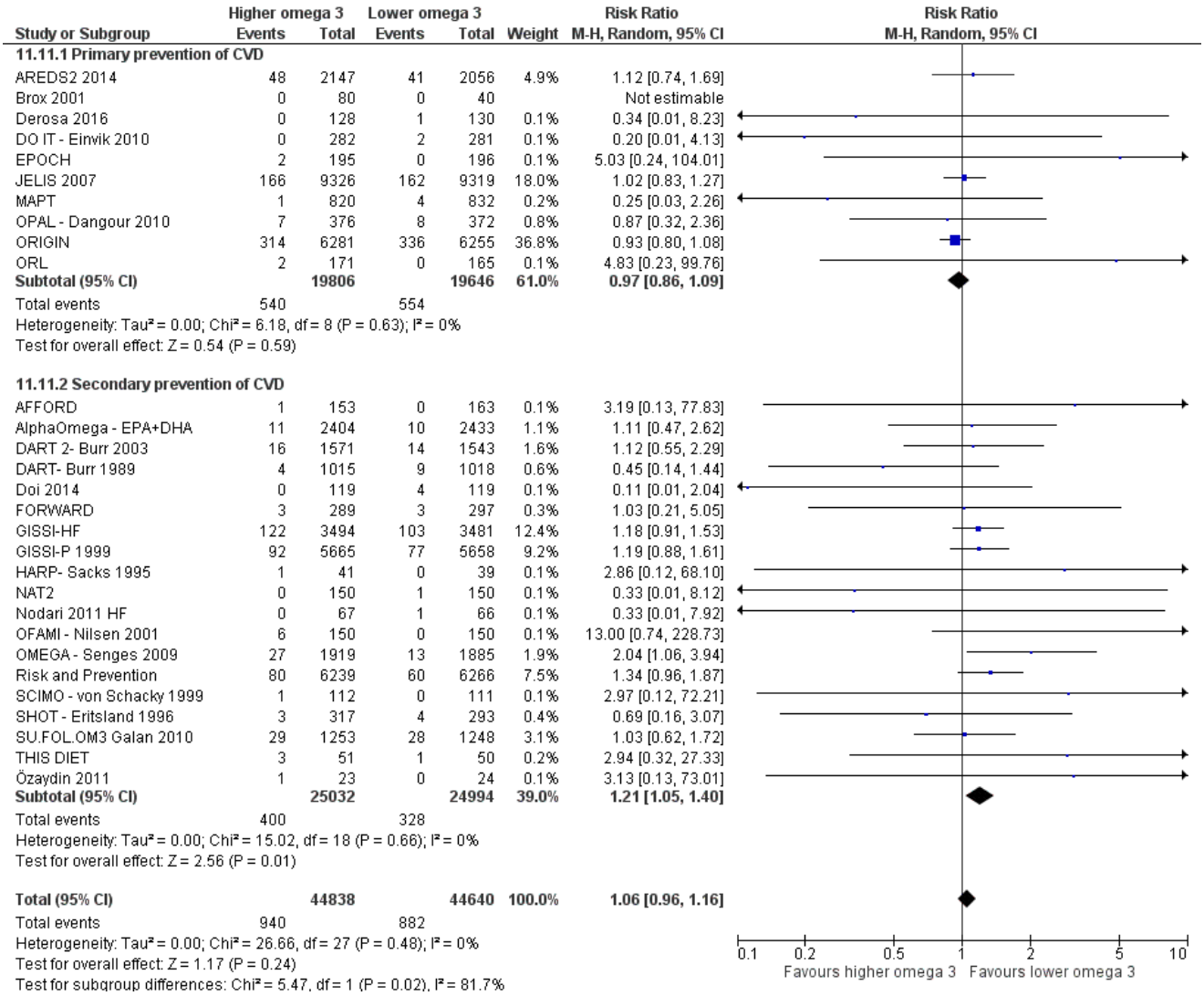


Figure 4.31. Meta-analysis of effects of omega 3 fats on stroke, subgrouped by primary (no existing CVD at baseline) or secondary prevention of CVD.

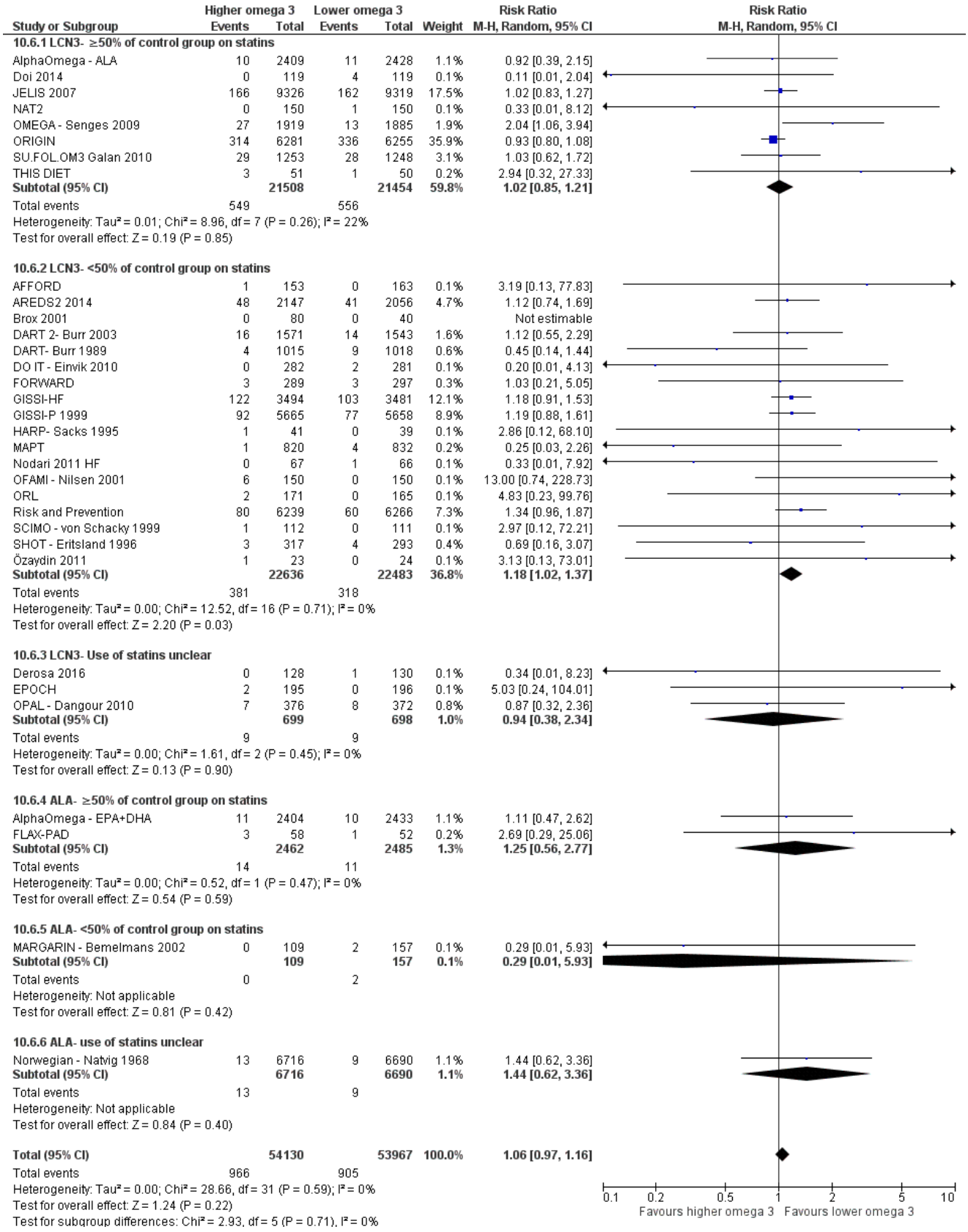


Figure 4.32. Meta-analysis of effects of omega 3 fats on stroke, subgrouped by use of statins.

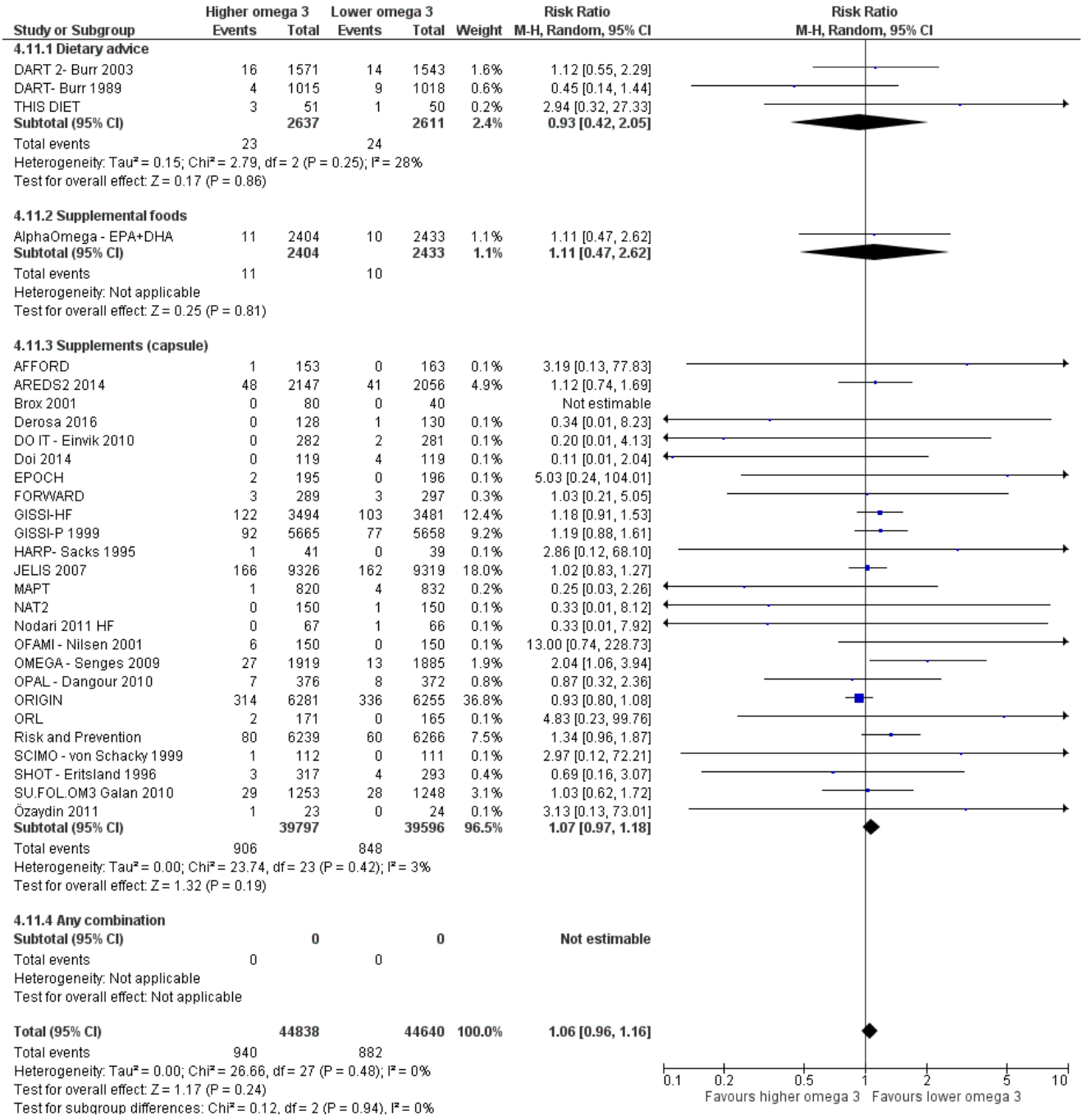


Figure 4.33. Meta-analysis of effects of omega 3 fats on stroke, subgrouped by type of intervention.

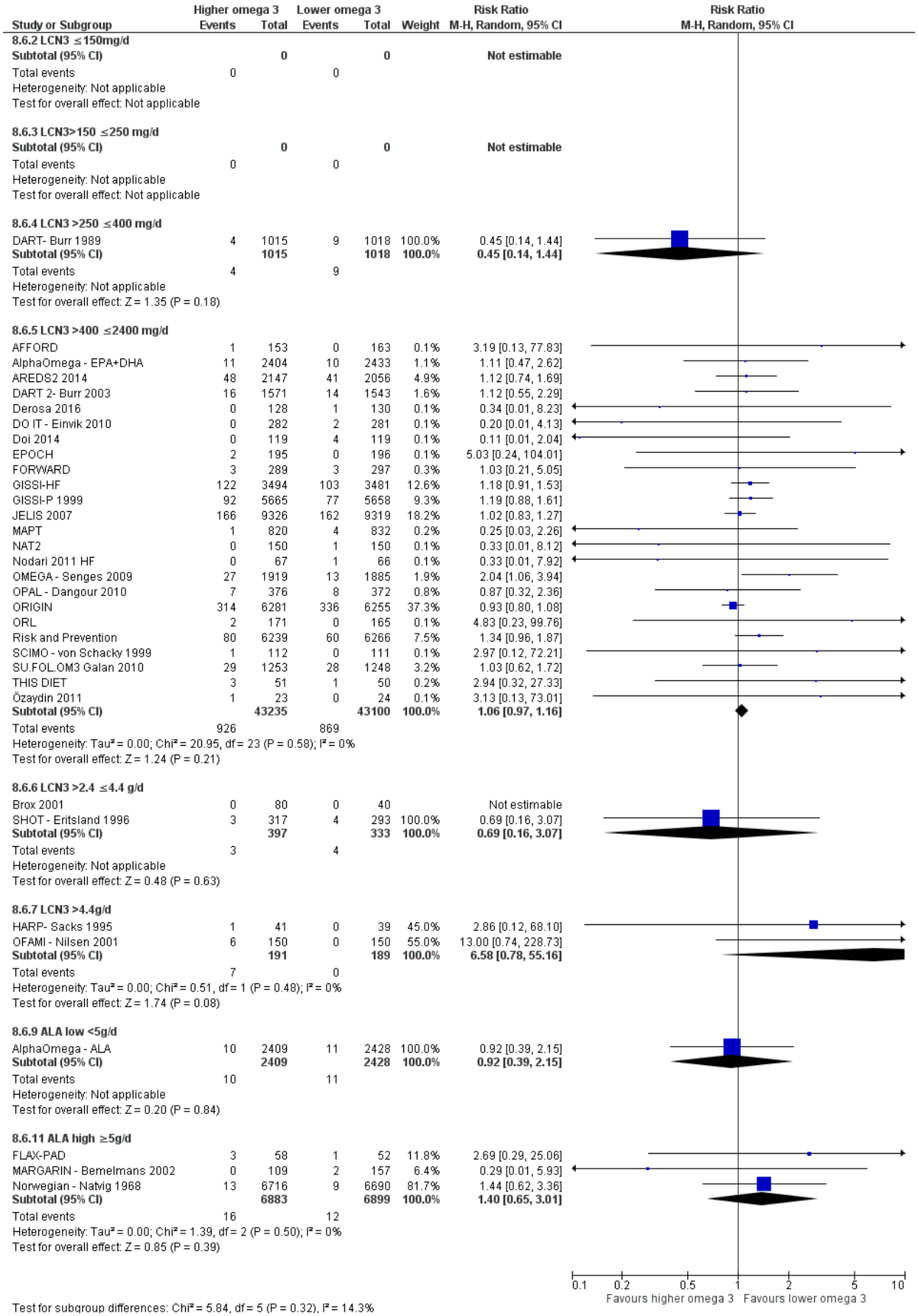


Figure 4.34. Meta-analysis of effects of omega 3 fats on stroke, subgrouped by omega 3 dose.

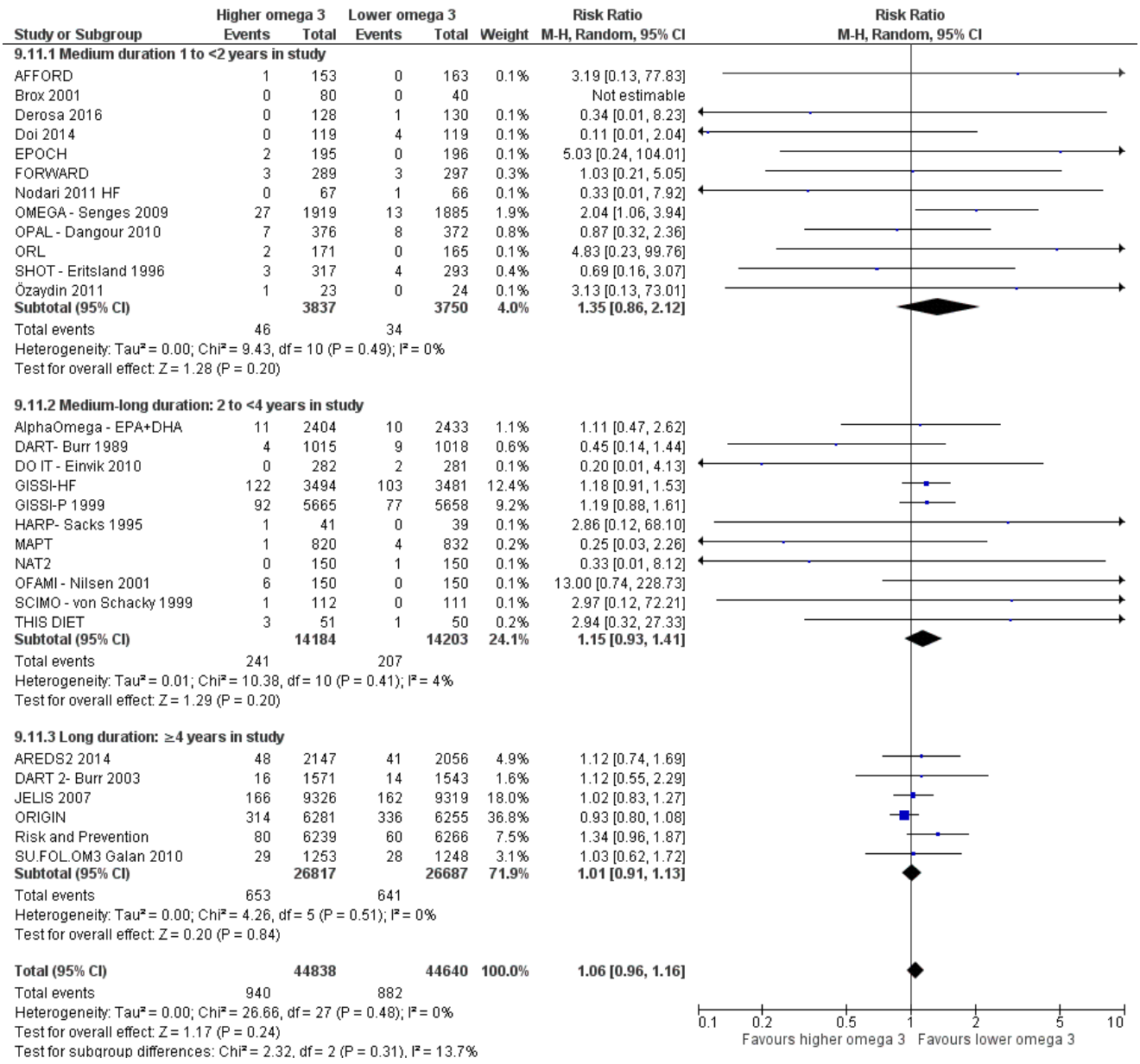


Figure 4.35. Meta-analysis of effects of omega 3 fats on stroke, subgrouped by duration.

Secondary outcomes – Myocardial Infarction (MI)

Twenty three trials randomising >72,000 participants to LCn3 or control reported on 2200 people experiencing MI. There were no clear effects of LCn3 fats on myocardial infarction, whether combined fatal and nonfatal (RR 0.95, 95% CI 0.88 to 1.03, I^2 0%, Figure 4.36), fatal alone or non-fatal alone (Figures 4.38 and 4.39).

The funnel plot for omega 3 fats suggested that there might be some small studies that suggested increased numbers of MI with omega 3 fats missing from the data set, Figure 4.37.

Sensitivity analyses using fixed effects analysis (RR 0.95, 95% CI 0.87 to 1.03), and omitting trials at moderate to high summary risk of bias (RR 1.02, 95% CI 0.91 to 1.14) suggested no statistically significant effects on MI (fatal and non-fatal combined).

We did not conduct subgrouping with secondary outcomes.

Three trials reported effects of ALA with no suggestion that ALA intake alters risk of MI (fatal and non-fatal, RR 1.00, 95% CI 0.76 to 1.32, I^2 26%).

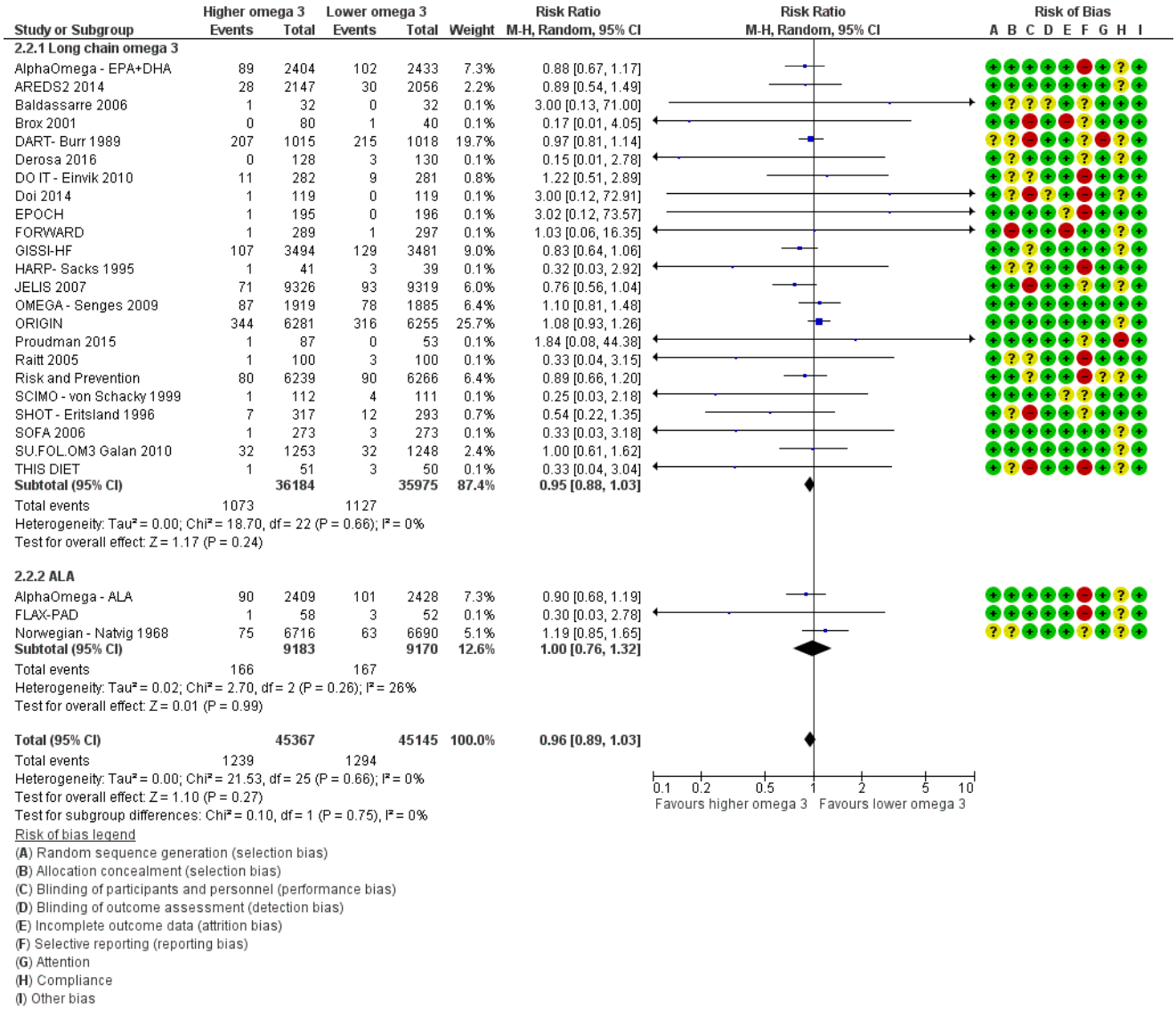


Figure 4.36. Meta-analysis of effects of omega 3 fats on MI (fatal or non-fatal combined), subgrouped by LCn3 or ALA intervention.

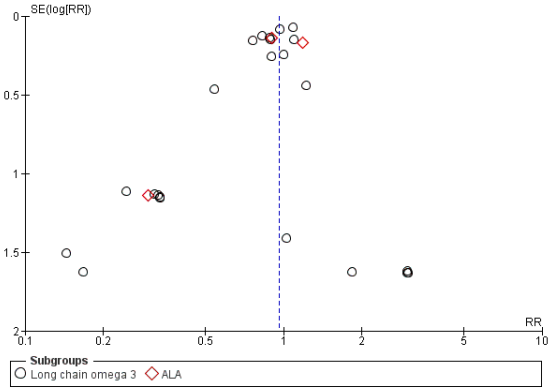


Figure 4.37. Funnel plot of effects of omega 3 fats on MI (fatal or non-fatal combined), subgrouped by LCn3 or ALA intervention.

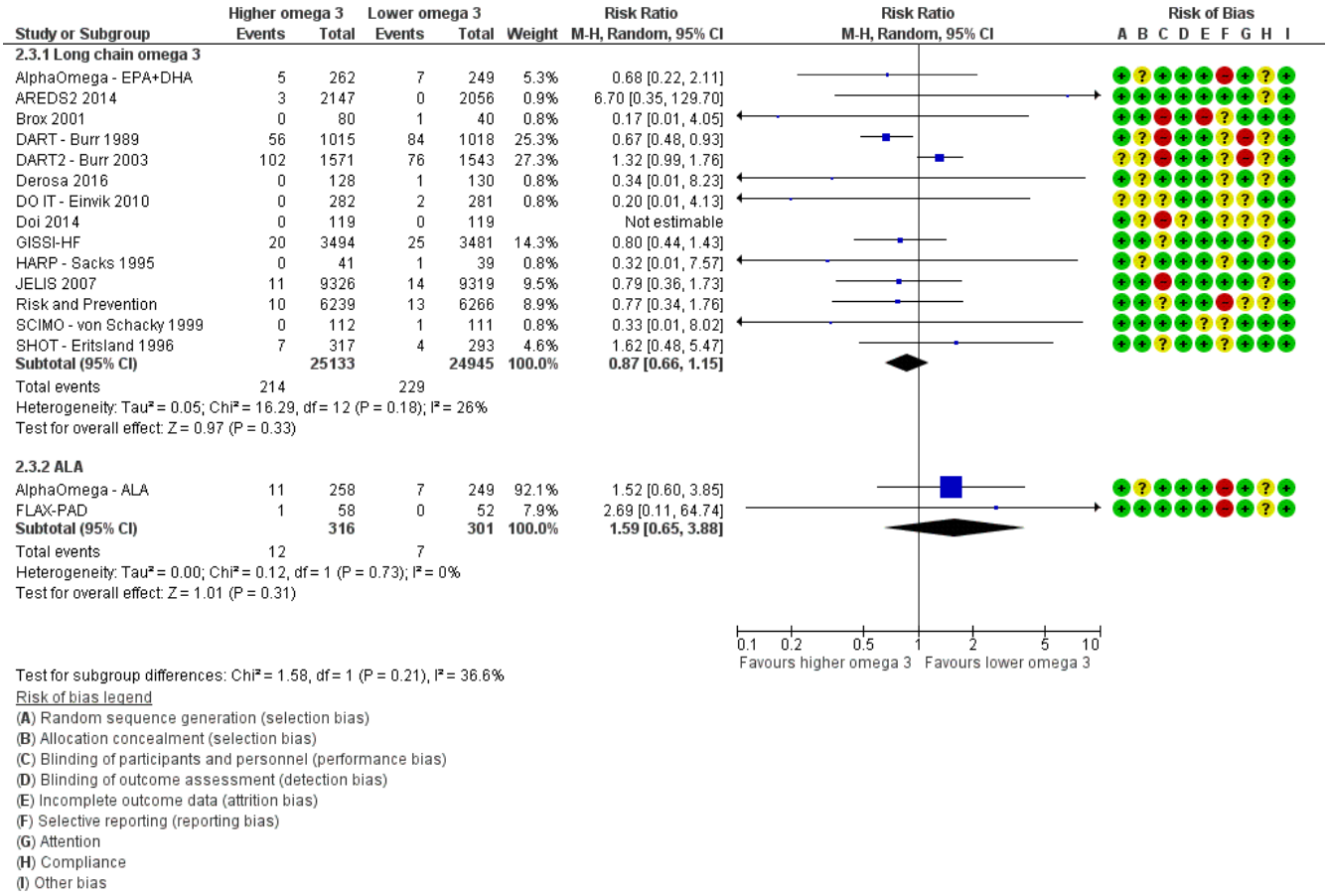


Figure 4.38. Meta-analysis of effects of omega 3 fats on fatal MI, subgrouped by LCn3 or ALA intervention.

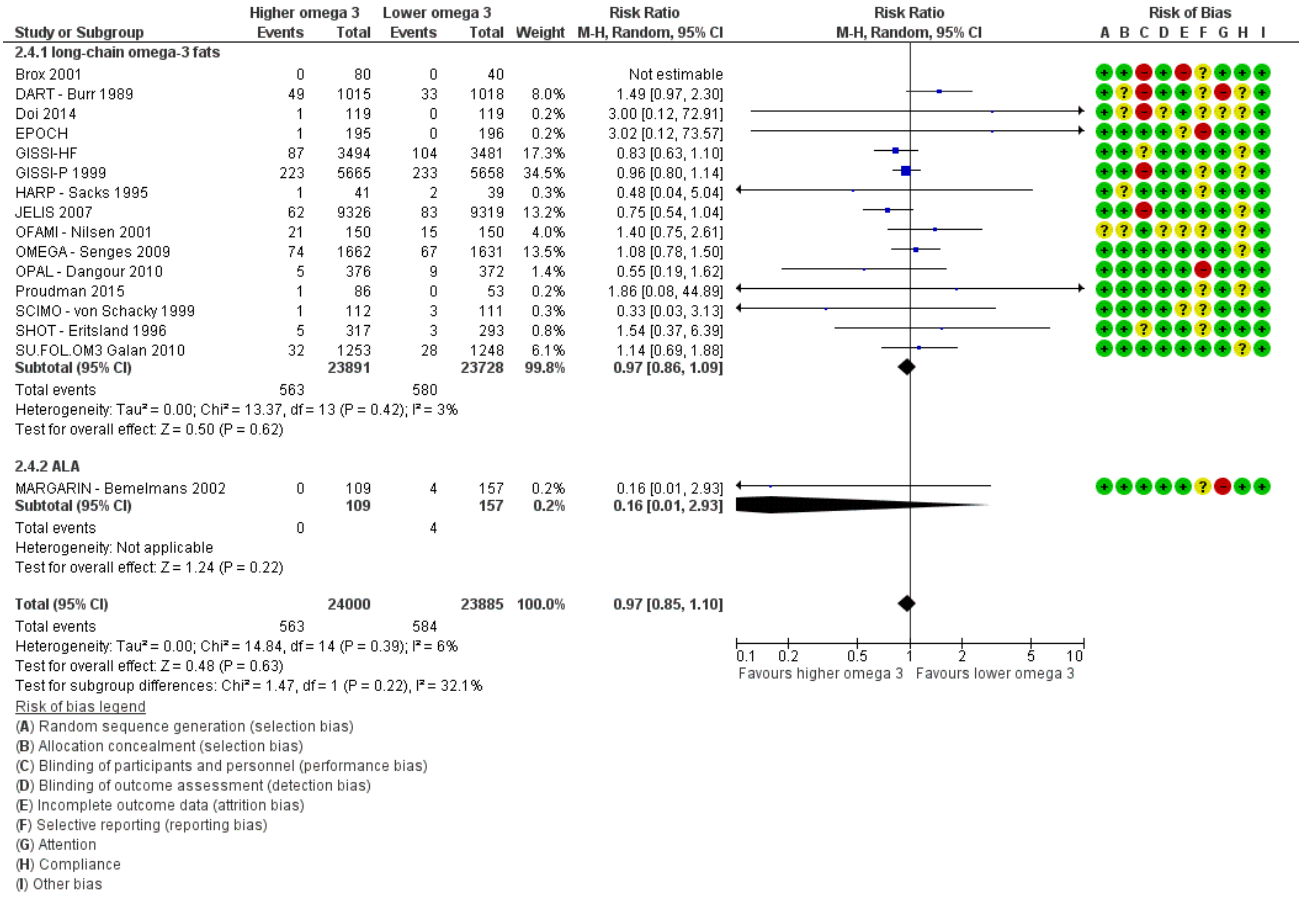


Figure 4.39. Meta-analysis of effects of omega 3 fats on non-fatal MI, subgrouped by LCn3 or ALA intervention.

Secondary outcomes – ischaemic and haemorrhagic stroke

Few strokes were presented classified as ischaemic or haemorrhagic, and meta-analysis suggests no relationships between omega 3 intake and any of these subtypes, or transient ischaemic attack (Figures 4.33 to 4.35).

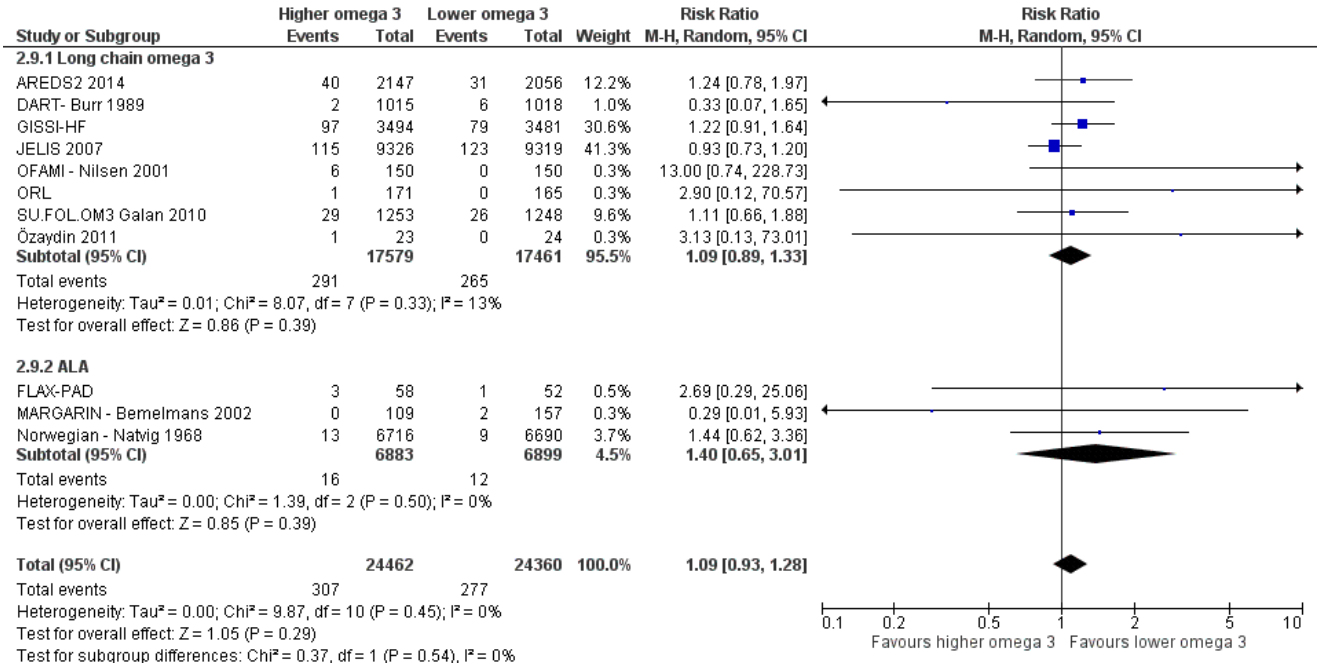


Figure 4.40. Meta-analysis of effects of omega 3 fats on ischaemic stroke, subgrouped by LCn3 or ALA intervention.

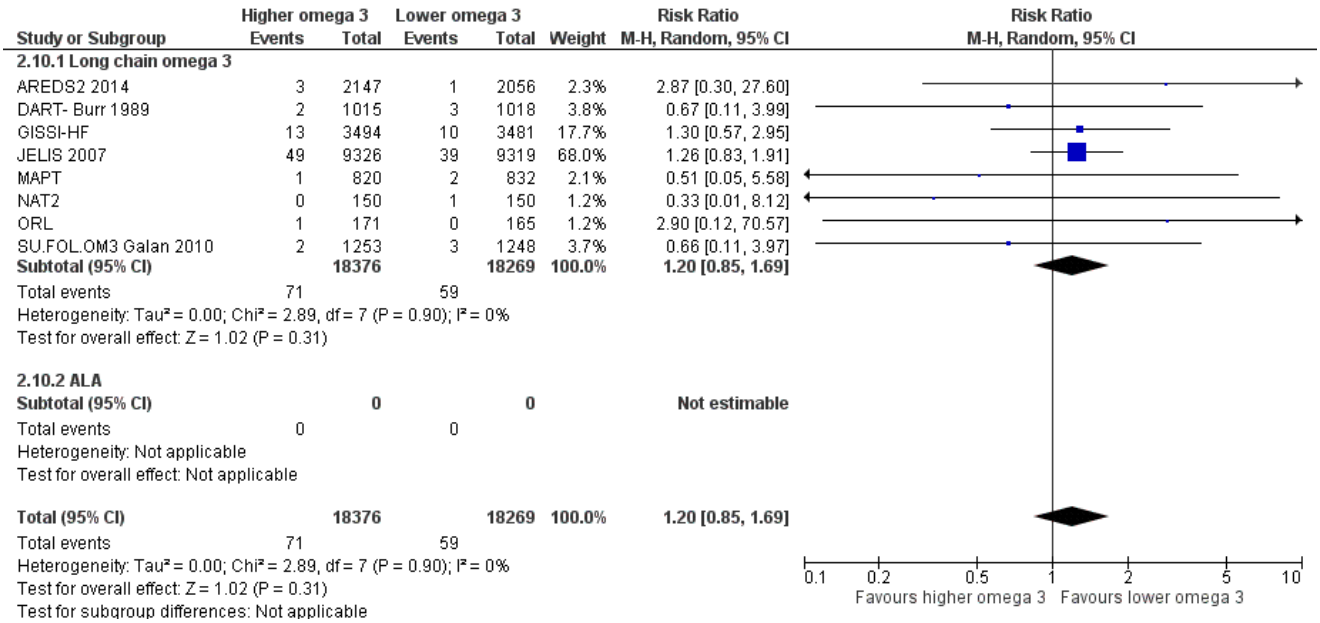


Figure 4.41. Meta-analysis of effects of omega 3 fats on haemorrhagic stroke, subgrouped by LCn3 or ALA intervention.

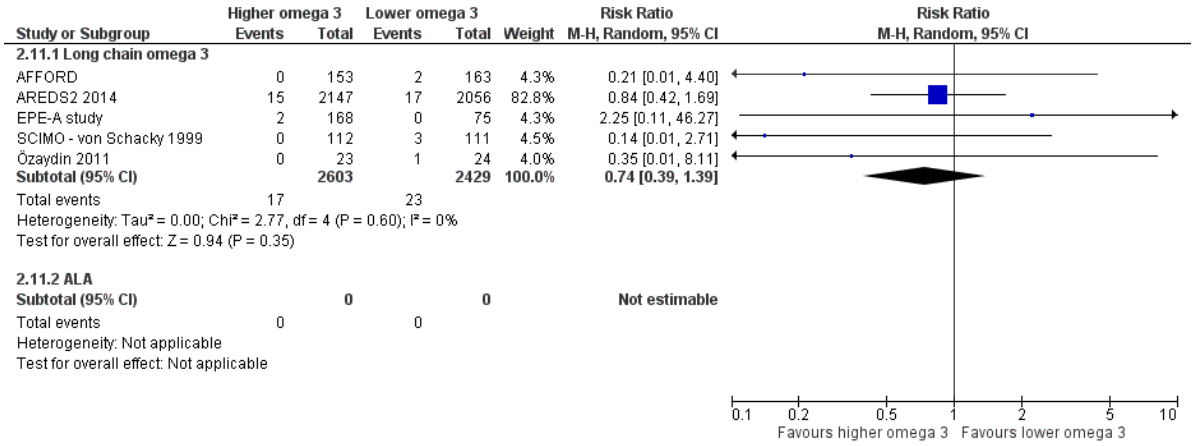


Figure 4.42. Meta-analysis of effects of omega 3 fats on transient ischaemic events (TIA), subgrouped by LCn3 or ALA intervention.

Secondary outcomes – other cardiovascular outcomes

Within studies that had data on mortality, primary cardiovascular outcomes, lipids or adiposity we also collated data on MACCEs (Figure 4.36), sudden cardiac death (Figure 4.37), heart failure diagnosis (Figure 4.38), angina (Figure 4.39), peripheral vascular events (Figure 4.40) and revascularisations (Figure 4.41).

There was no suggestion that omega 3 fats (either LCn3 or ALA) had any effect on any of these outcomes, although data were limited for some outcomes.

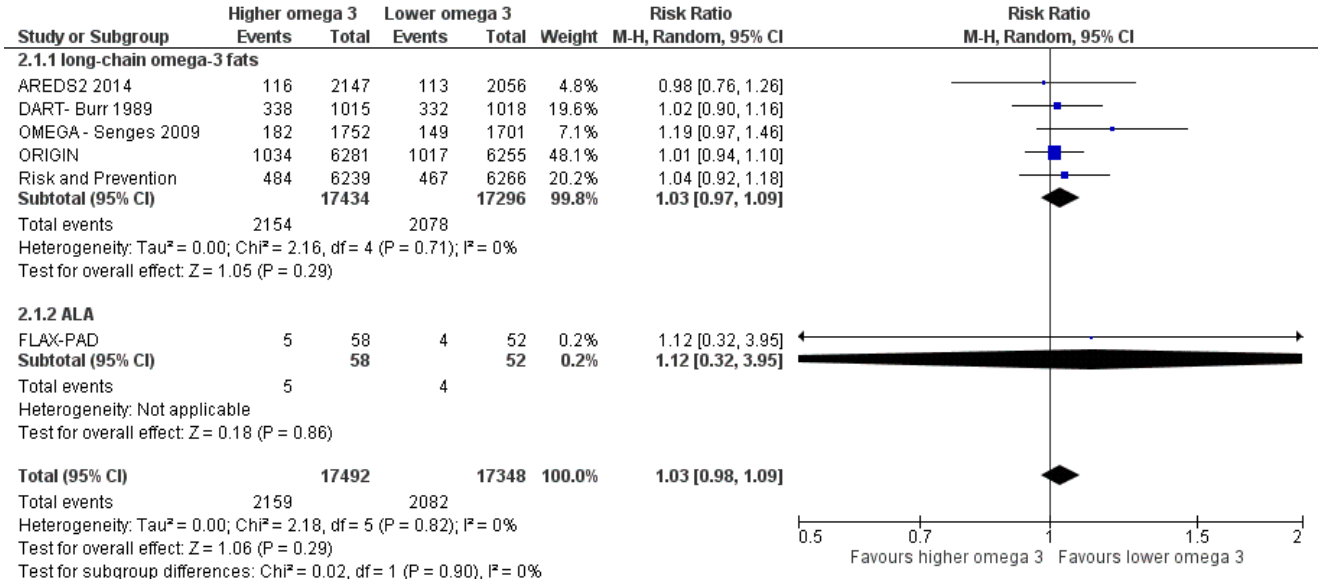


Figure 4.43. Meta-analysis of effects of omega 3 fats on MACCEs, subgrouped by LCn3 or ALA intervention.

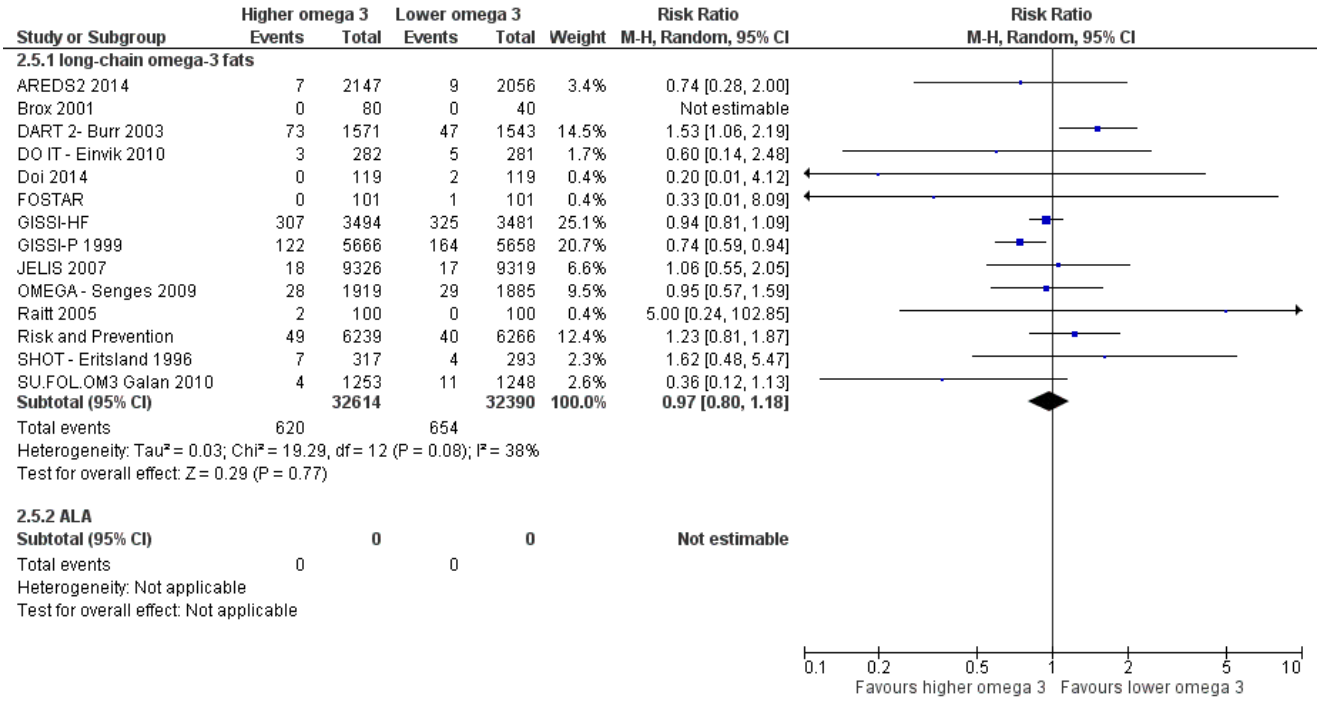


Figure 4.44. Meta-analysis of effects of omega 3 fats on sudden cardiac death, subgrouped by LCn3 or ALA intervention.

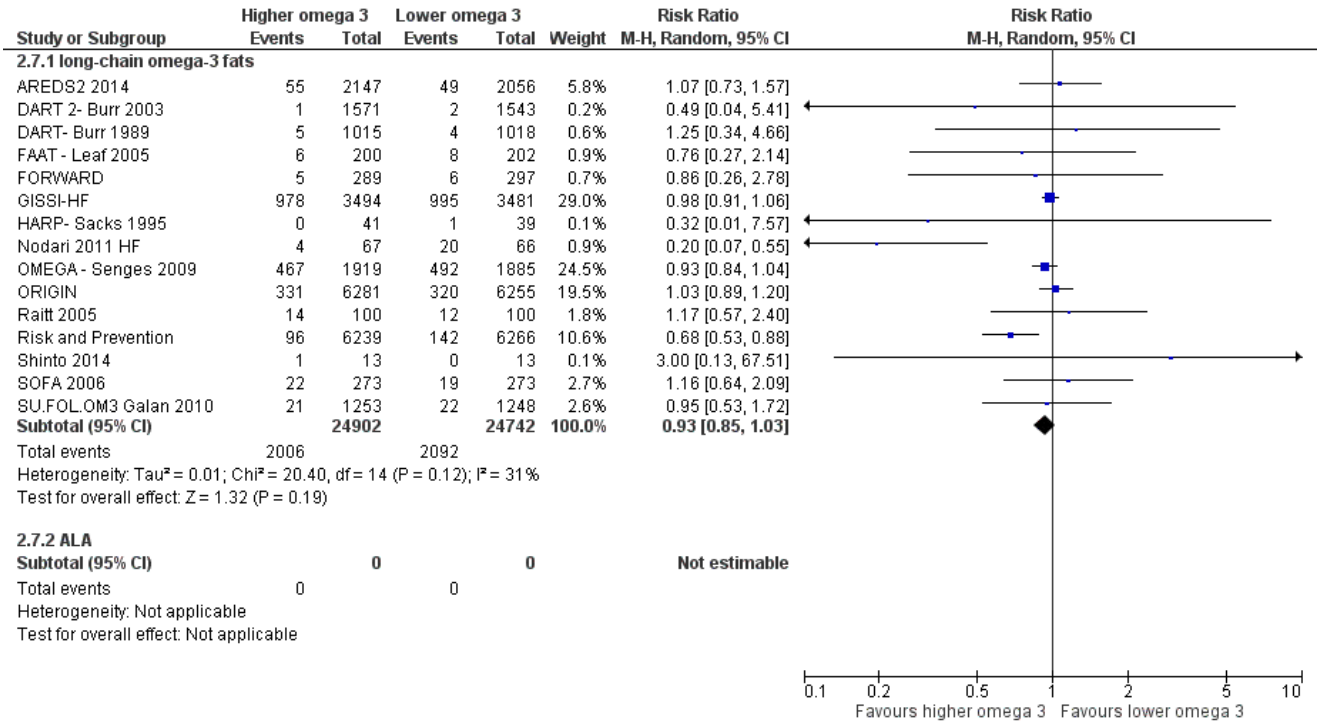


Figure 4.45. Meta-analysis of effects of omega 3 fats on heart failure diagnosis, subgrouped by LCn3 or ALA intervention.

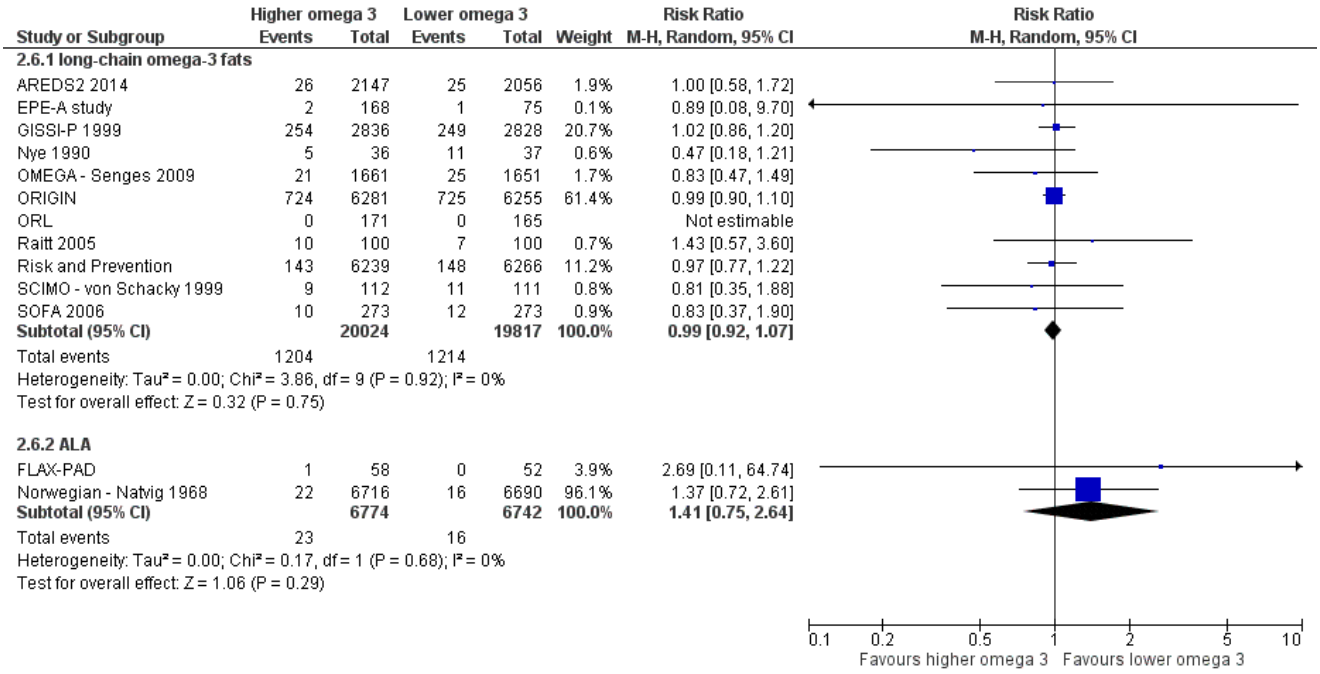


Figure 4.46. Meta-analysis of effects of omega 3 fats on angina, subgrouped by LCn3 or ALA intervention.

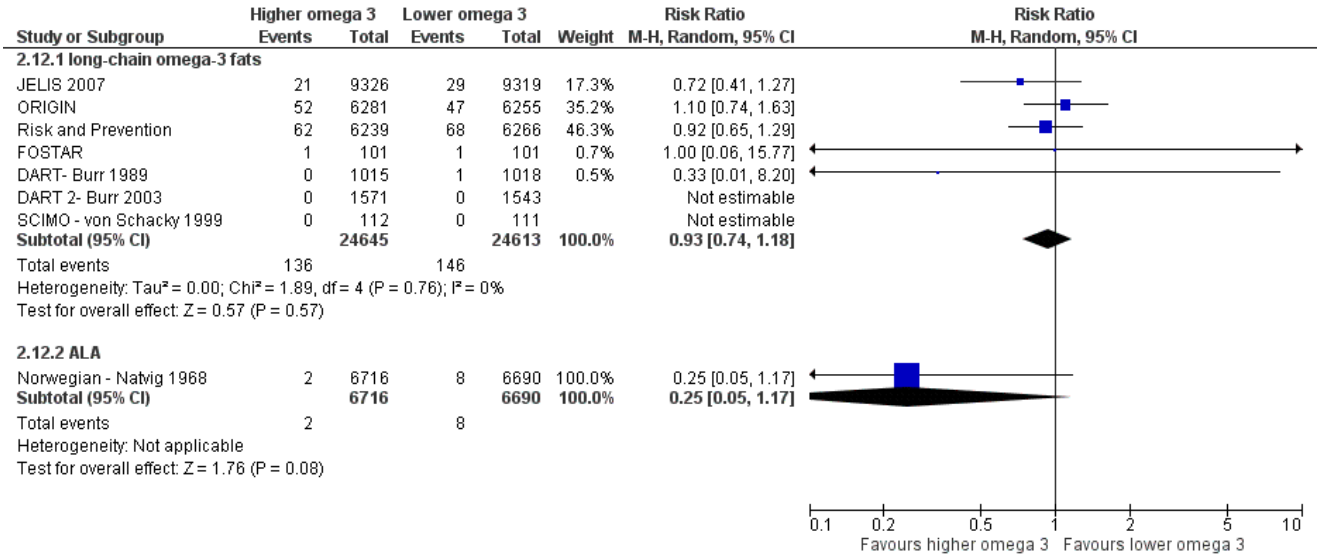


Figure 4.47. Meta-analysis of effects of omega 3 fats on peripheral vascular events, subgrouped by LCn3 or ALA intervention.

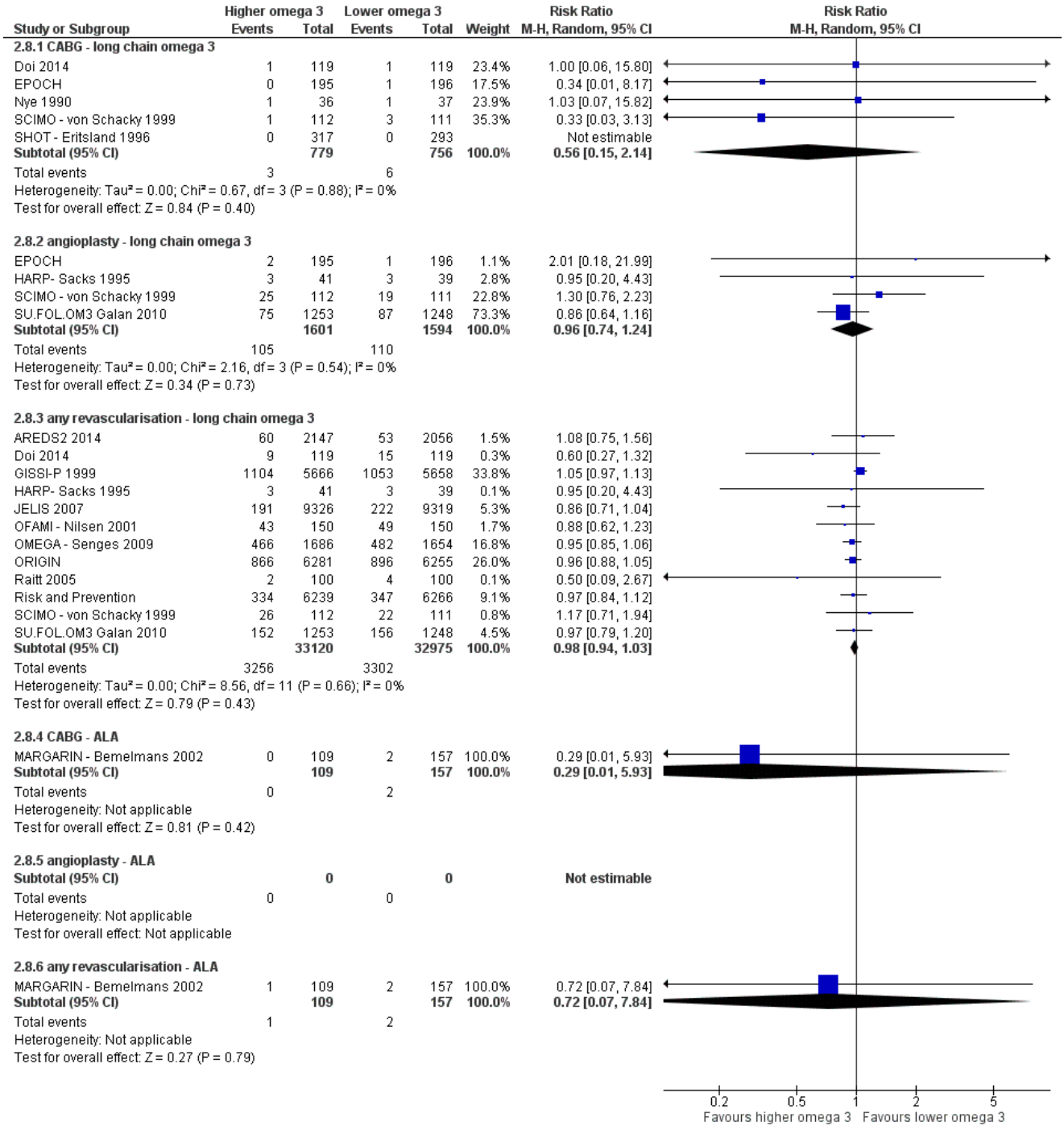


Figure 4.48. Meta-analysis of effects of omega 3 fats on revascularisation, subgrouped by LCn3 or ALA intervention.

Chapter 5. What are the effects of dietary or supplemental omega 3 fatty acids on CVD risk factors such as serum total cholesterol, HDL or LDL cholesterol or triglycerides?

We collected and included all RCTs of omega 3 interventions with a duration of at least 12 months, and which measured serum lipids, to help assess longer-term effects of omega 3 fats on cardiovascular risk factors. Forest plots present the data on effects on serum total cholesterol, triglycerides, low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol (all converted to mmol/L).

Primary outcomes – serum total cholesterol

Meta-analysis included 27 RCTs of LCn3 fats (over 37,000 participants) which suggested no clear effect of omega 3 fats on serum total cholesterol (MD -0.01mmol/L, 95% CI -0.05 to 0.04, I^2 19%). Fixed effects sensitivity analysis suggested that LCn3 fats cause a small reduction in total cholesterol (MD-0.04mmol/L, 95% CI -0.06 to -0.02), while sensitivity analysis removing trials at moderate to high summary risk of bias suggested no effect of LCn3 on total serum cholesterol (RR 0.02 mmol/L, 95% CI -0.05 to 0.08, I^2 10%, Figure 5.3).

We included six RCTs of ALA (2164 participants) which suggested no clear effect of ALA on serum total cholesterol (MD -0.09mmol/L, 95% CI -0.23 to 0.05, I^2 63%), Figure 5.1. Fixed effects sensitivity analysis did suggest that ALA reduced total cholesterol (MD -0.10mmol/L, 95% CI -0.17 to -0.03). Sensitivity analysis removing trials at moderate to high risk of bias suggested no effect of ALA on serum total cholesterol (RR 0.00mmol/L, 95% -0.13 to 0.14, I^2 21%).

The funnel plot did not suggest problems with small study or publication bias, Figure 5.2.

No subgroups suggested any effect when subgrouping by duration or replacement, but single subgroups in other subgroupings suggested small reductions of total cholesterol with omega 3 fats (supplements in type of intervention, the 2.4 to 4.4g/d dose group (Figure 5.4), primary prevention (not secondary), and the group of ALA studies where statin use was unclear.

Summary

Studies at low summary risk of bias suggest no effect of omega 3 fats on serum total cholesterol.

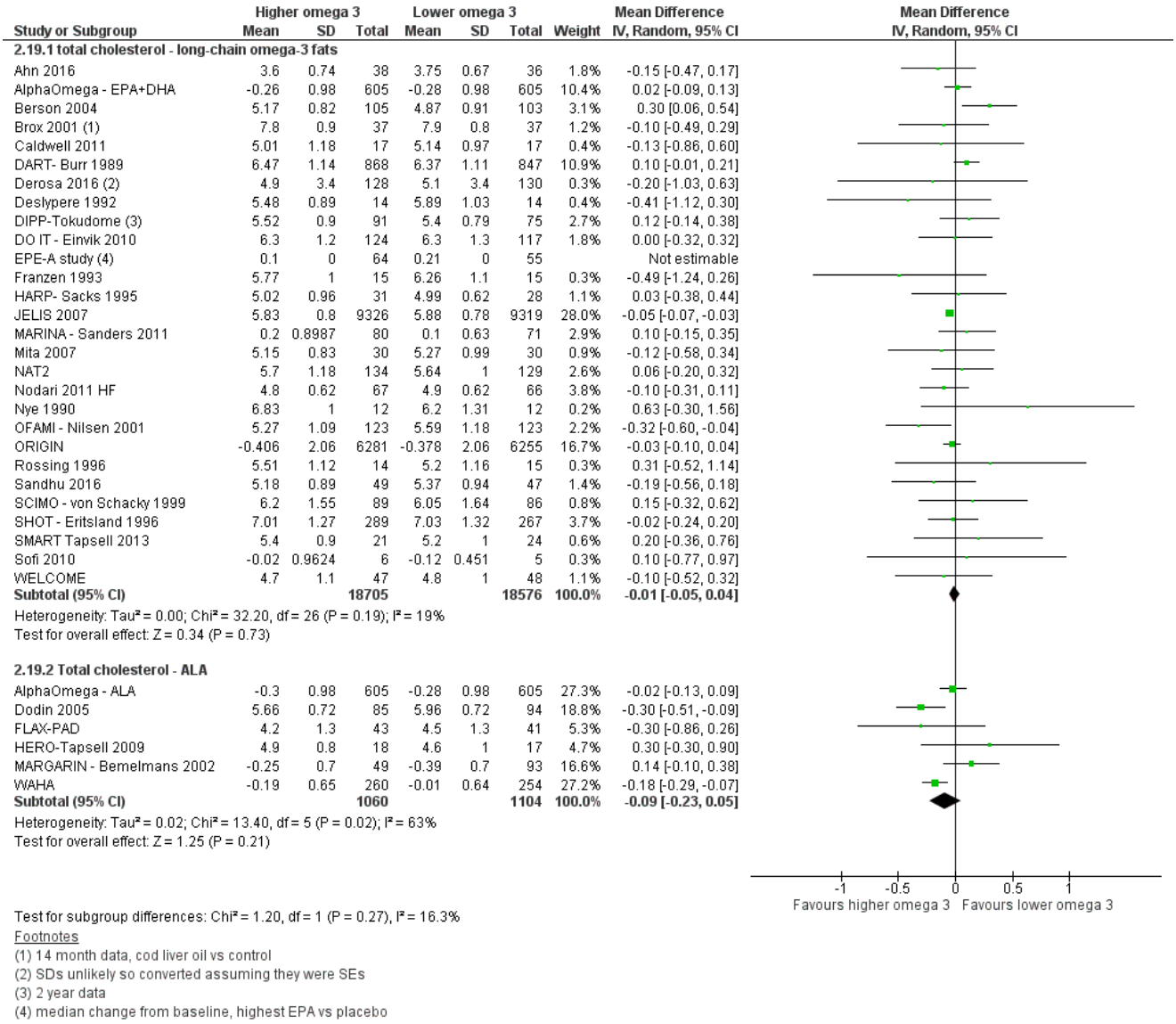


Figure 5.1. Meta-analysis of effects of omega 3 fats on serum total cholesterol, subgrouped by LCn3 or ALA intervention.

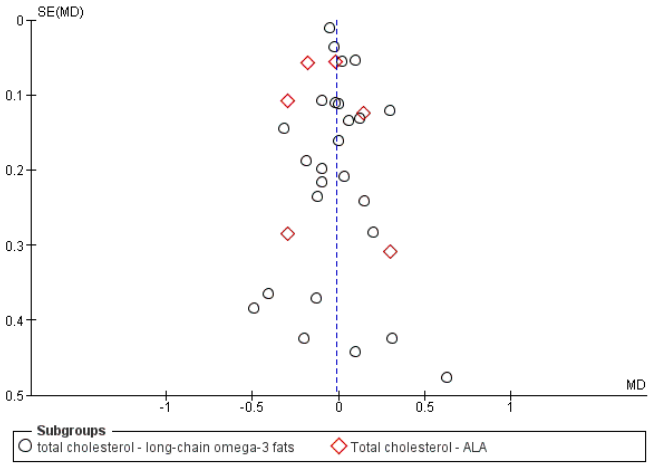


Figure 5.2. Funnel plot of effects of omega 3 fats on serum total cholesterol.

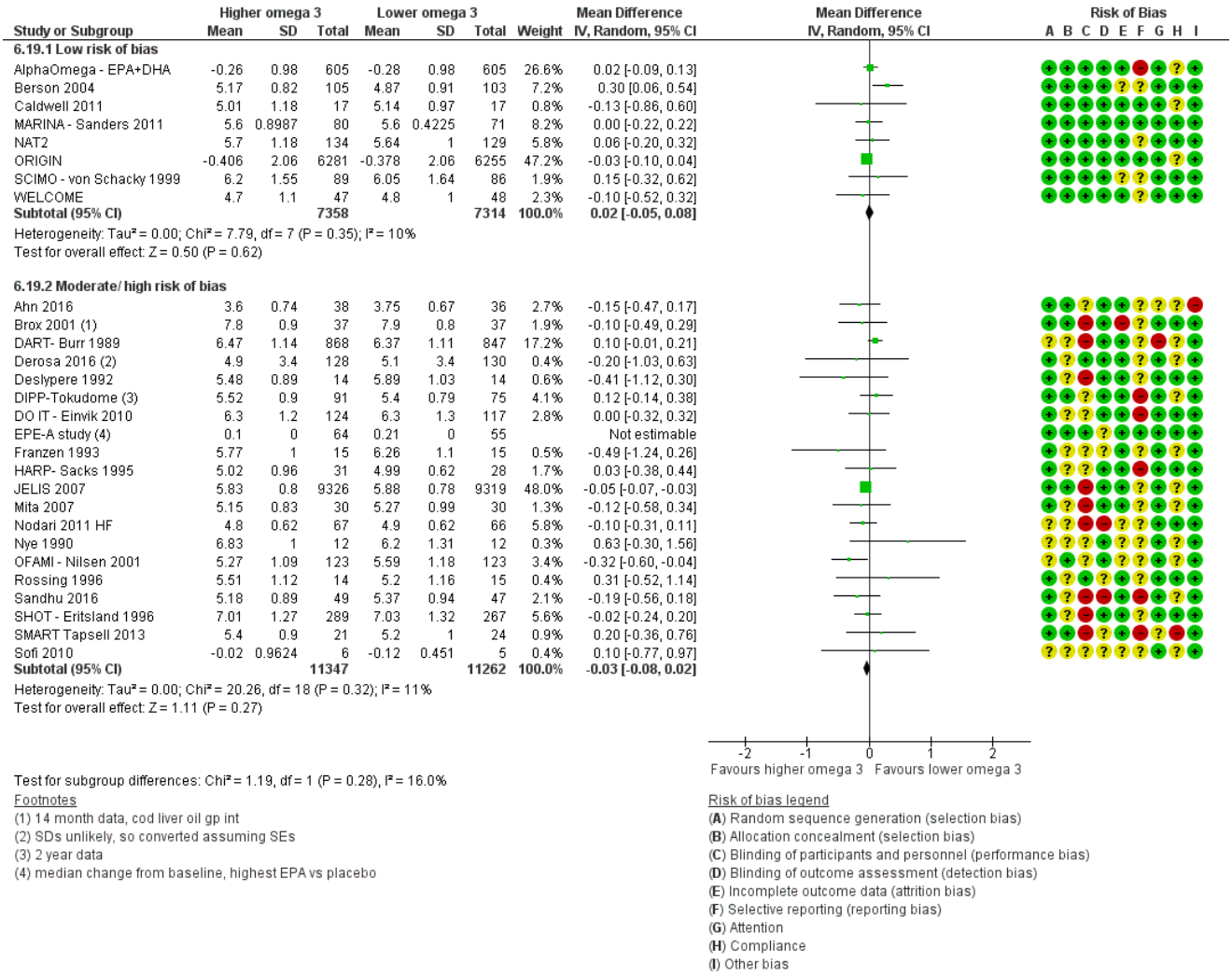


Figure 5.3. Meta-analysis of effects of LCn3 fats on serum total cholesterol, subgrouped by summary risk of bias.

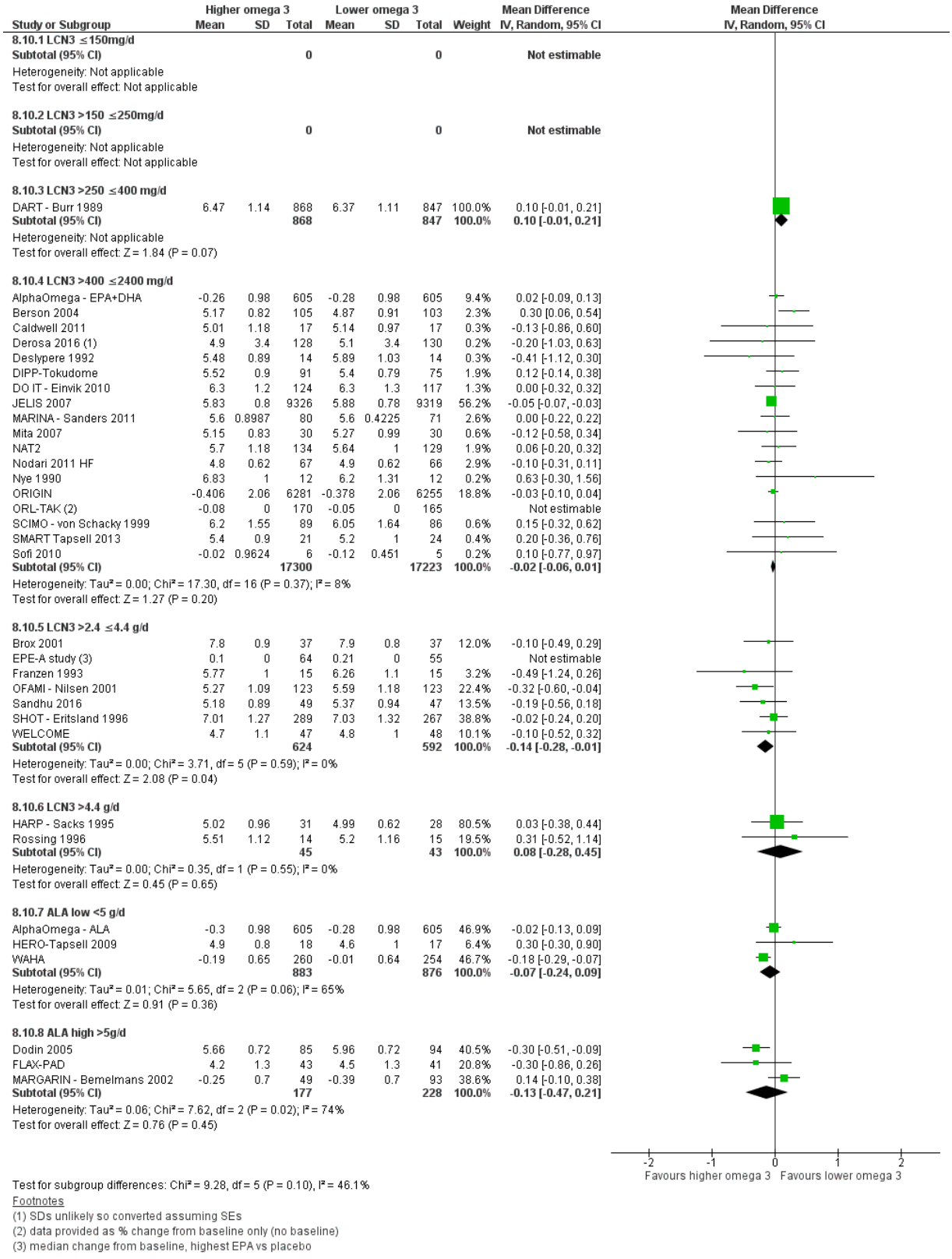


Figure 5.4. Meta-analysis of effects of omega 3 fats on serum total cholesterol, subgrouped by LCn3 or ALA dose.

Primary outcomes – serum triglycerides or triacylglycerols (TG)

Meta-analysis included 24 RCTs of LCn3 fats (over 35,000 participants) which suggested that omega 3 fats reduce serum triglycerides (MD -0.23mmol/L, 95% CI -0.30 to -0.15, I^2 46%), Figure 5.5. The statistical significance of this effect was not altered when we used fixed rather than random effects analysis. Sensitivity analysis removing trials at moderate to high risk of bias still suggested reductions in triglycerides (MD -0.17mmol/L, 95% CI -0.25 to -0.09, I^2 24%), Figure 5.7.

We included six RCTs of ALA (1776 participants) which suggested no clear effect of ALA on serum triglyceride (MD -0.03mmol/L, 95% CI -0.11 to 0.05, I^2 0%), Figure 5.5. The statistical significance of this effect was not altered when we used fixed rather than random effects analysis.

The funnel plot suggested different effects of LCn3 and ALA on triglycerides, Figure 5.6.

Most subgroups with more than two or three LCn3 trials suggested statistically significant reductions in serum triglycerides, while subgroups of ALA studies did not. Triglyceride reductions were clearly apparent in primary and secondary prevention, at all durations, and at all doses of LCn3, suggesting greater effects with greater doses of LCn3, Figure 5.8.

Summary

Studies at low summary risk of bias suggest that LCn3 fats reduce serum triglycerides, while ALA does not.

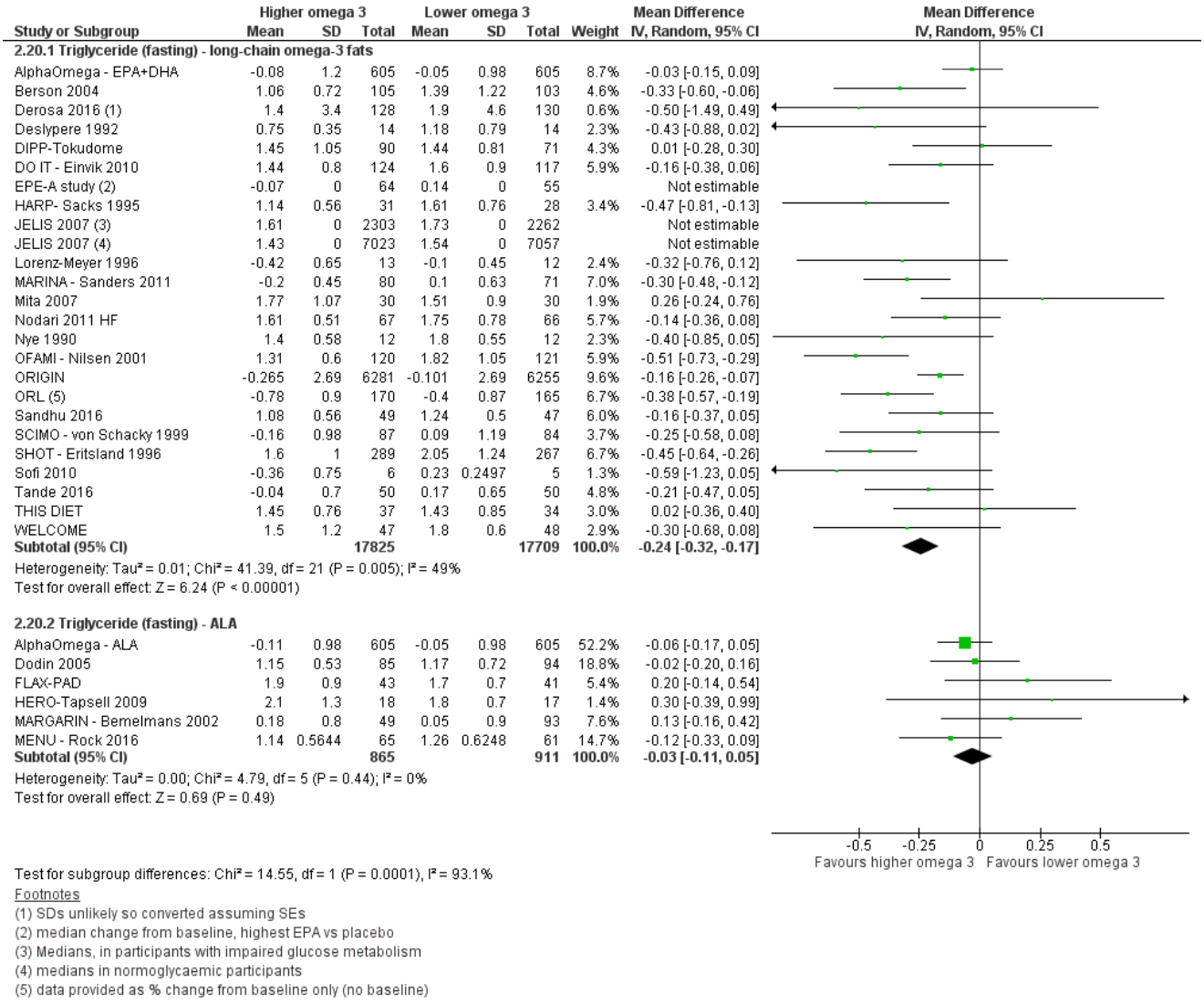


Figure 5.5. Meta-analysis of the effects of omega 3 fats on serum triglycerides, subgrouped by LCn3 or ALA.

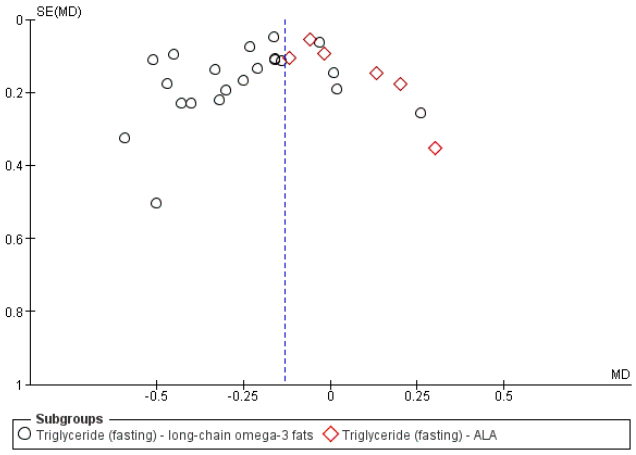


Figure 5.6. Funnel plot of the effects of omega 3 fats on serum triglycerides, subgrouped by LCn3 or ALA.

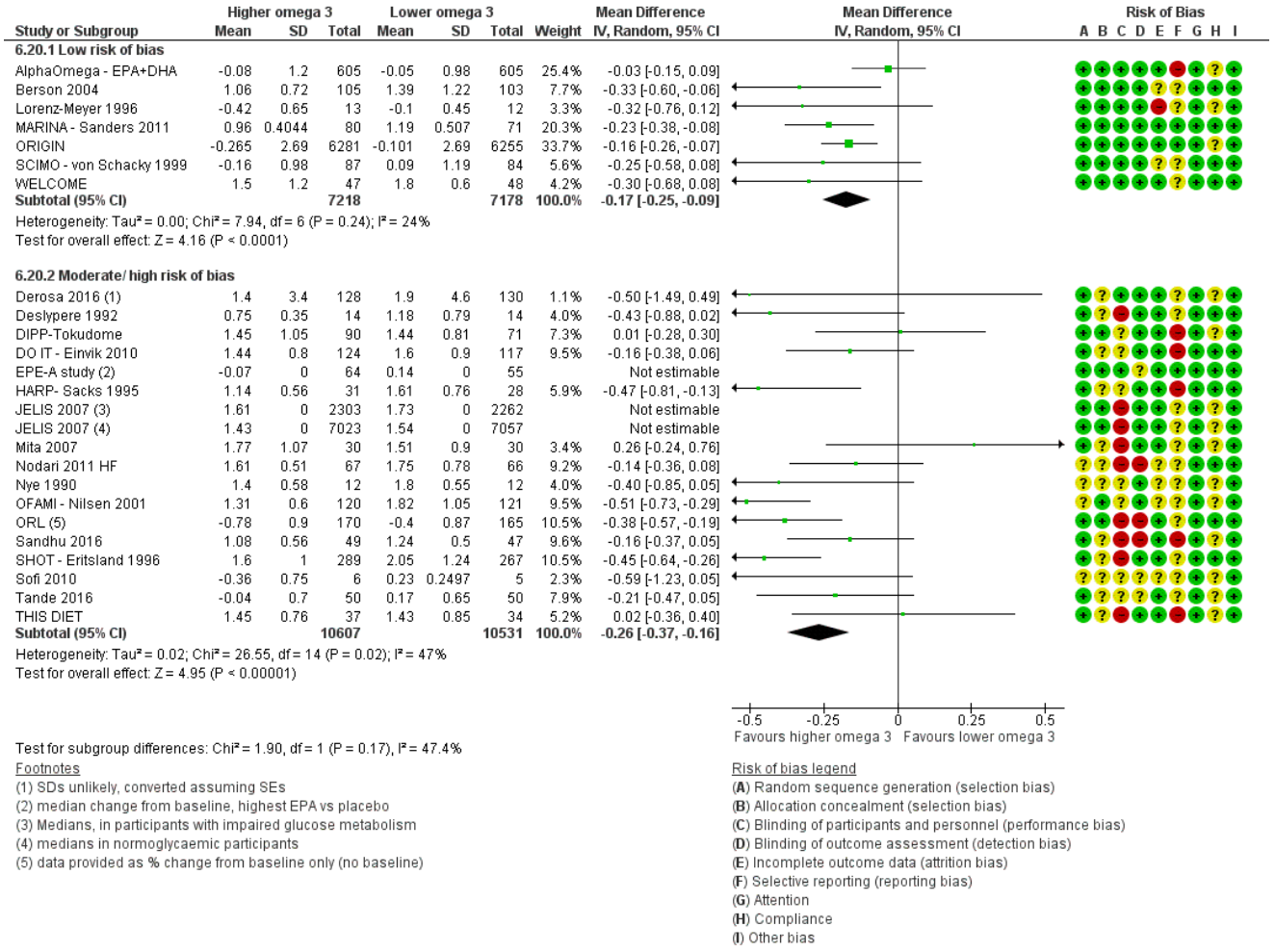


Figure 5.7. Meta-analysis of the effects of omega 3 fats on serum triglycerides, sensitivity analysis removing trials of moderate to high risk of bias (though shown as a subgrouping by summary risk of bias).

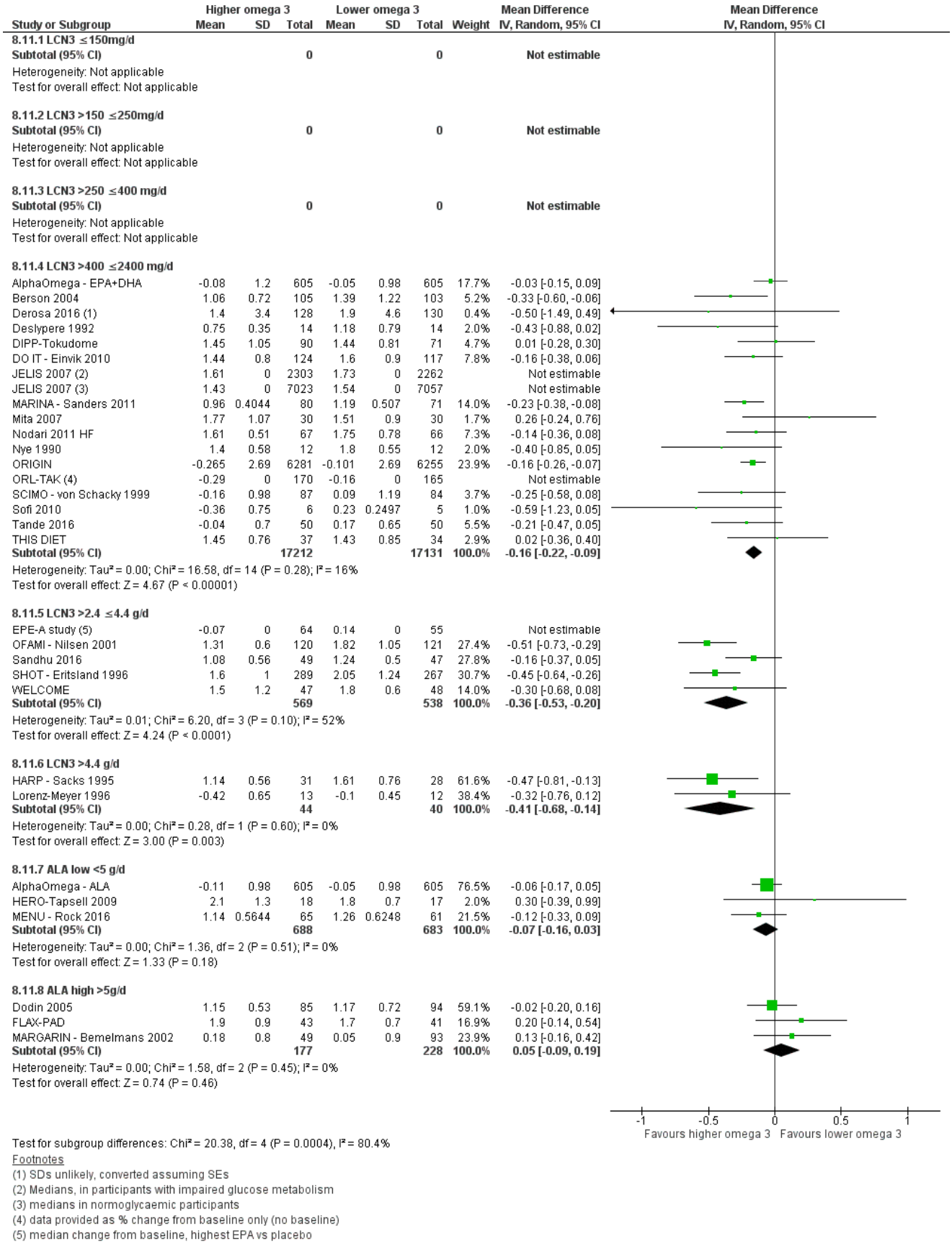


Figure 5.8. Meta-analysis of the effects of omega 3 fats on serum triglycerides (mmol/L), subgrouped by LCn3 and ALA dose.

Primary outcomes – serum low density lipoprotein (LDL)

Meta-analysis included 22 RCTs of LCn3 fats (over 34,000 participants) which suggested no effect of omega 3 fats on serum LDL (MD 0.01mmol/L, 95% CI -0.01 to 0.03, I^2 0%), Figure 5.9. The lack of statistical significance of this effect was not altered when we used fixed rather than random effects analysis, or removed trials at moderate to high risk of bias (Figure 5.11).

We included seven RCTs of ALA (2201 participants) which suggested no effect of ALA on serum LDL (MD -0.05mmol/L, 95% CI -0.15 to 0.04, I^2 46%), Figure 5.9. The statistical significance of this effect was not altered when we used fixed rather than random effects analysis.

The funnel plot did not suggest any small study or publication bias, Figure 5.10.

This lack of effect did not differ by omega 3 dose, duration, type of intervention, primary or secondary prevention or type of replacement. There was a suggestion that in populations with low statin use that omega 3 fats may increase LDL, Figure 5.12.

Summary

Studies at low summary risk of bias suggest no effect of omega 3 fats on LDL cholesterol.

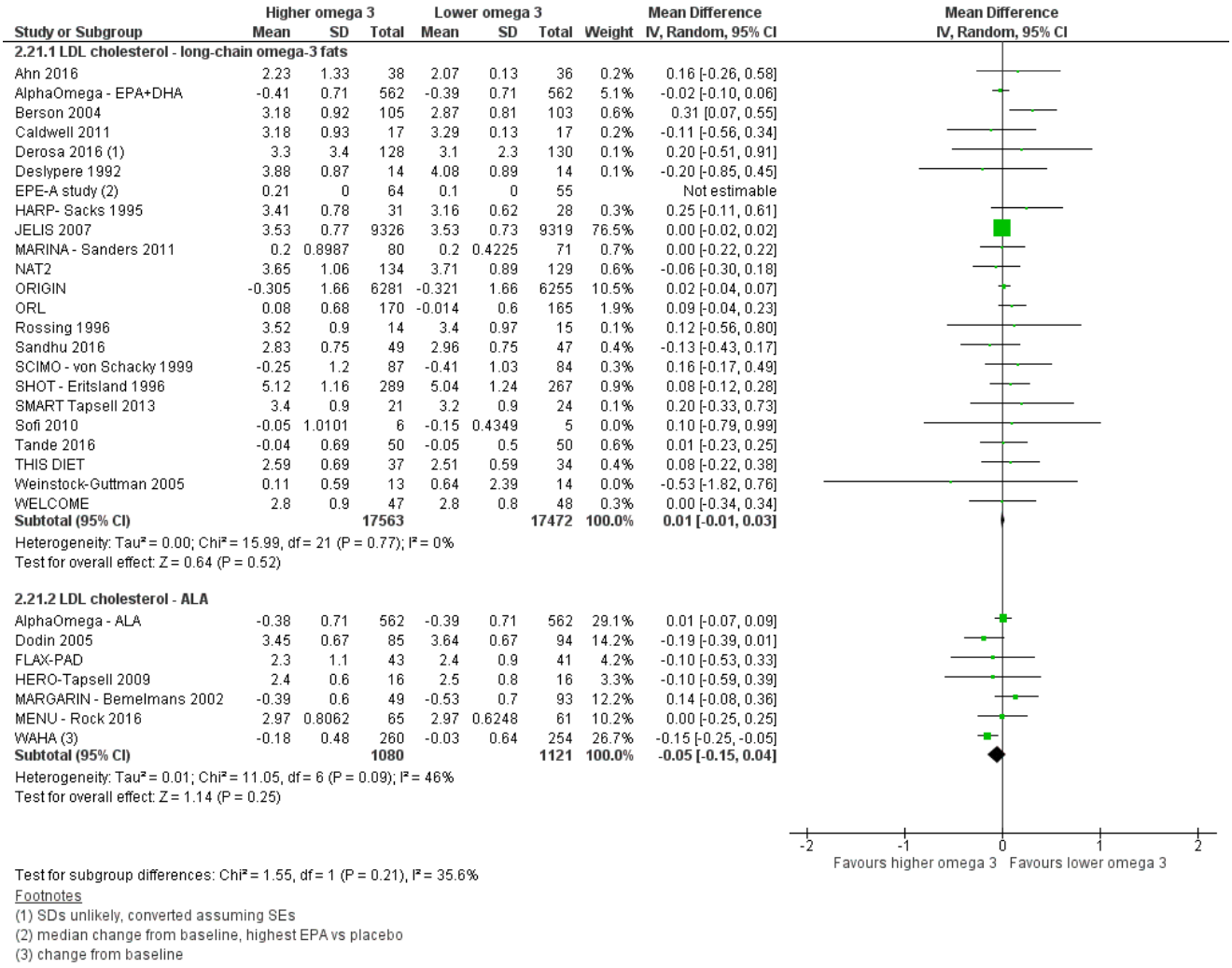


Figure 5.9. Meta-analysis of the effects of omega 3 fats on serum LDL (mmol/L), subgrouped by LCn3 and ALA.

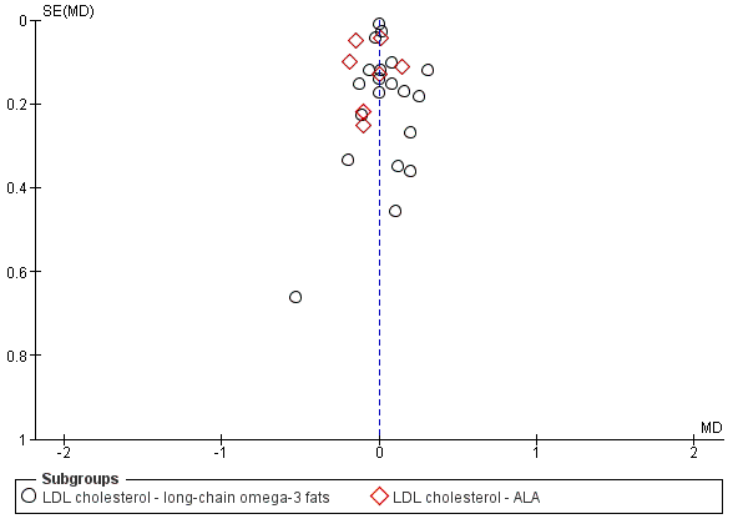


Figure 5.10. Funnel plot of the effects of omega 3 fats on LDL cholesterol.

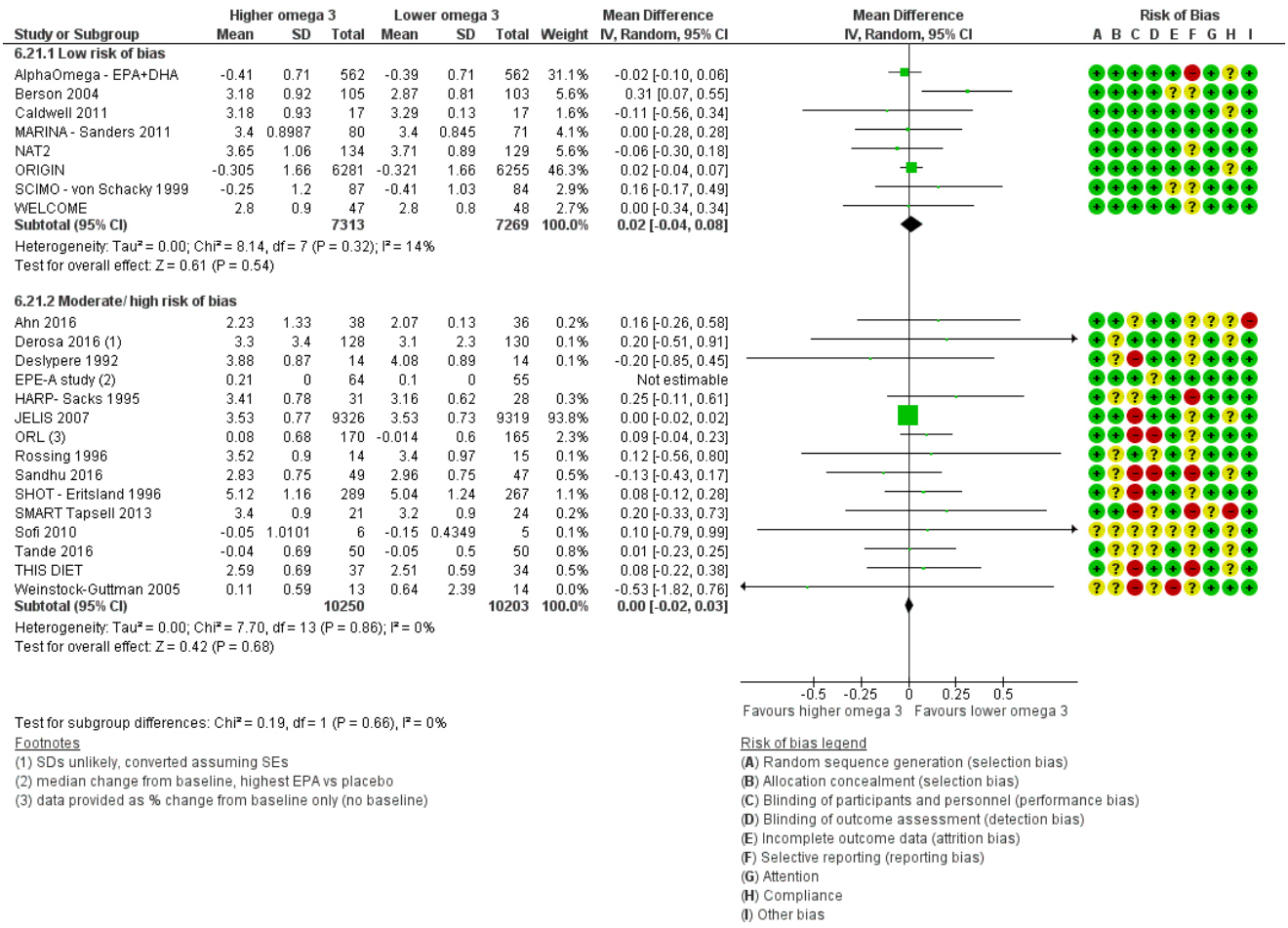


Figure 5.11. Meta-analysis of effects of omega 3 fats on serum LDL (in mmol/L), sensitivity analysis, removing trials at moderate to high risk of bias (shown in a separate subgroup).

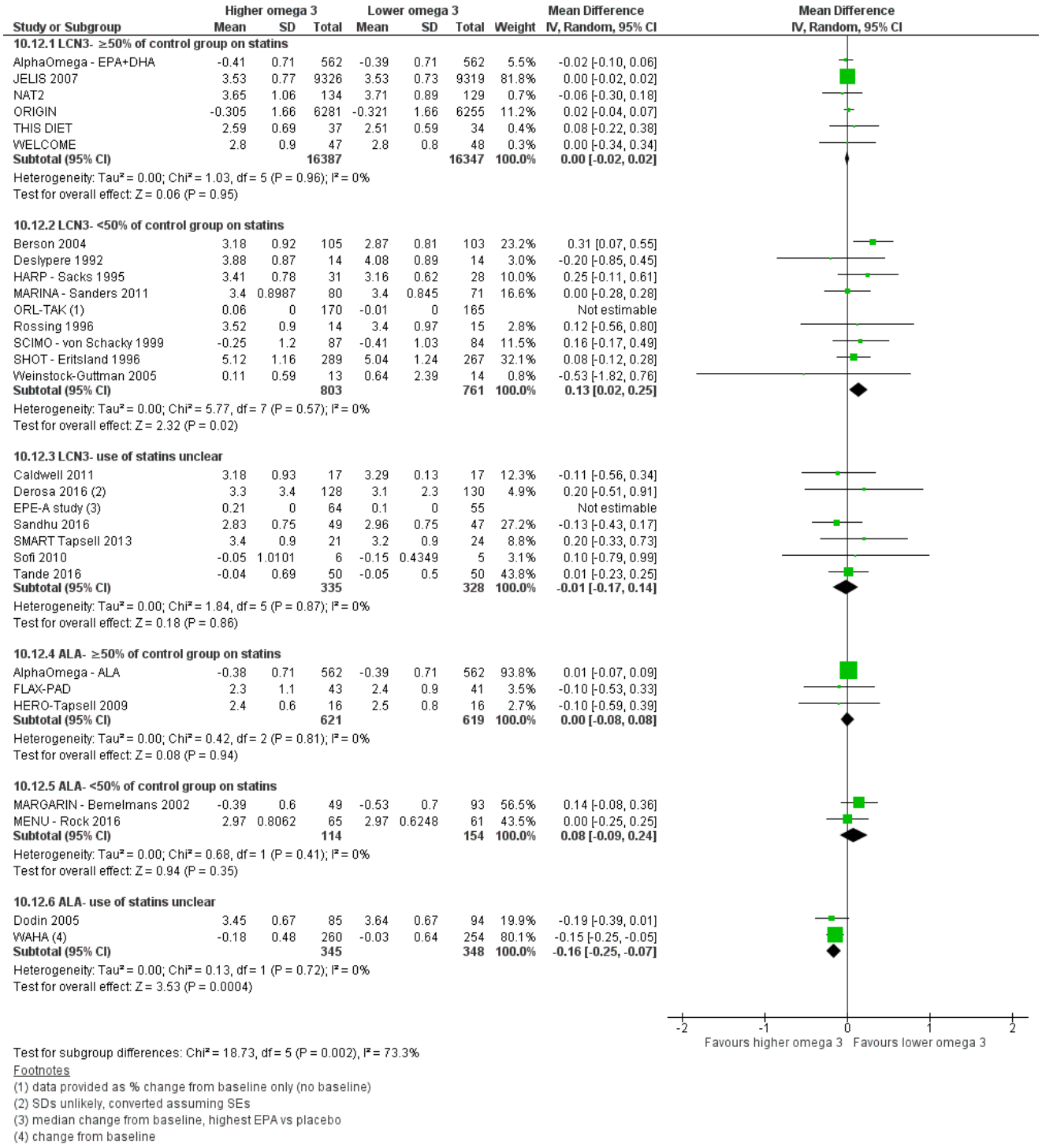


Figure 5.12. Meta-analysis of effects of omega 3 fats on serum LDL (in mmol/L), subgrouped by statin use.

Primary outcomes – serum high density lipoprotein (HDL)

Meta-analysis included 26 RCTs of LCn3 fats (over 37,000 participants) which suggested that long chain omega 3 fats increase serum HDL by a small amount in the long term (MD 0.02mmol/L, 95% CI 0.00 to 0.04, I^2 48%, p=0.03), Figure 5.13. The statistical significance of this effect was not altered when we used fixed rather than random effects analysis. Sensitivity analysis, removing trials at moderate to high risk of bias suggested no effect of omega 3 fats on HDL in studies at low risk of bias, though there was no suggestion of a differential effect in studies at low risk of bias, compared to those at moderate to high risk of bias, Figure 5.15.

The funnel plot did not suggest any small study or publication bias, Figure 5.14.

We included six RCTs of ALA (1776 participants) which suggested no effect of ALA on serum HDL (MD -0.02mmol/L, 95% CI -0.08 to 0.03, I^2 53%), Figure 5.13. Fixed effects analysis suggested almost statistically significant reduction of serum HDL with ALA, but by a very small amount (MD -0.02mmol/L, 95% CI -0.05 to 0, p=0.05), however, given the I^2 of 53% random effects meta-analysis appears the appropriate approach.

Dose effects were unclear, with 2.2 to 4.4g/d LCn3 appearing to increase HDL while higher and lower doses did not, and higher doses of ALA appearing to reduce HDL, Figure 5.16. Only studies of 1-2 years duration increased HDL, longer trials did not. Omega 3 replacing omega 6 fats increased HDL, but not other replacements. Supplements and supplementary foods increased HDL while diet advice and combined interventions did not.

Summary

Given that there were no clear dose effects, and studies at low summary risk of bias suggest no effect of omega 3 fats on serum HDL cholesterol, we suggest that there is no effect or a very small effect only of LCn3 on serum HDL.

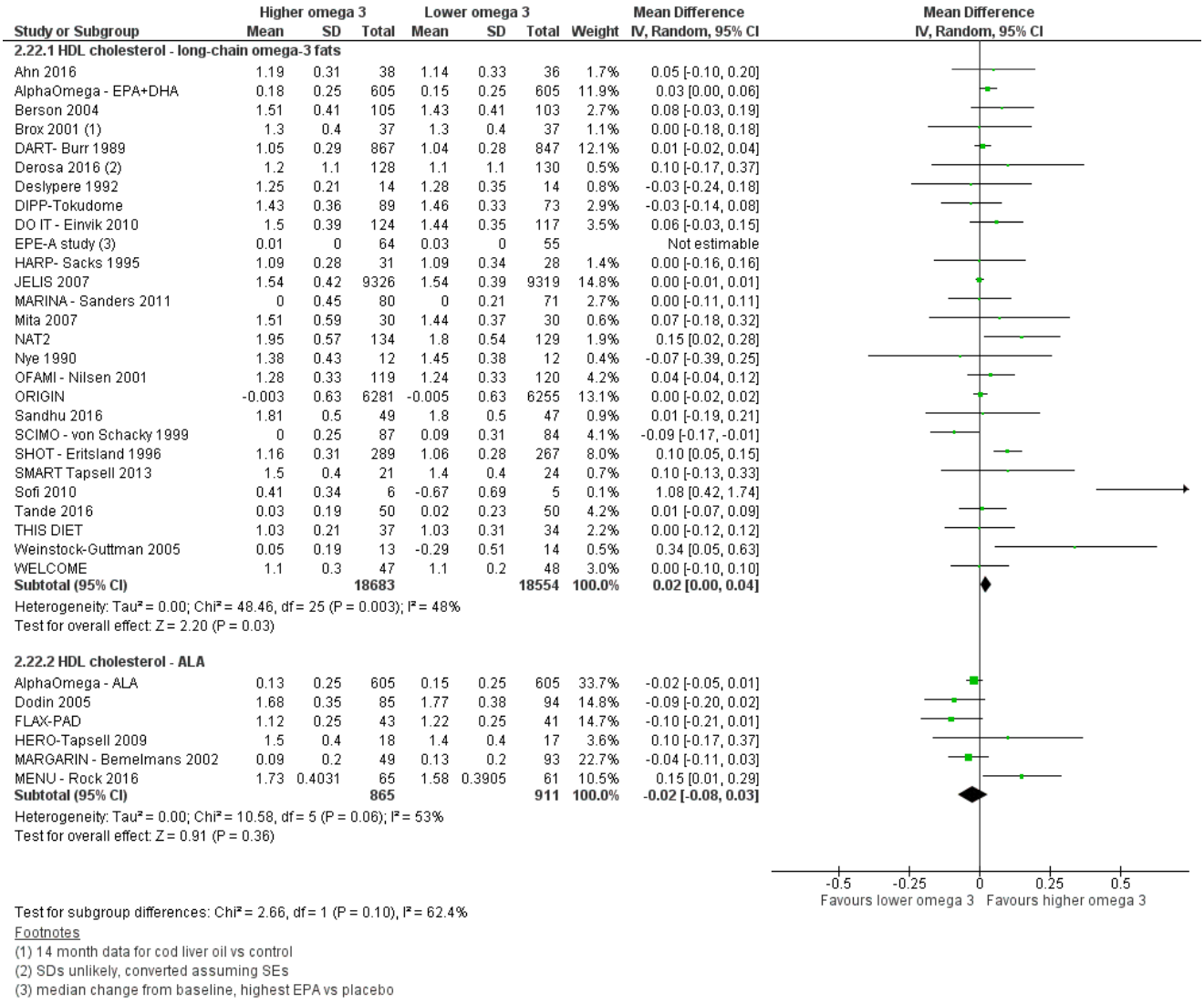


Figure 5.13. Meta-analysis of effects of omega 3 fats on serum HDL (in mmol/L), subgrouped by LCn3 or ALA intervention.

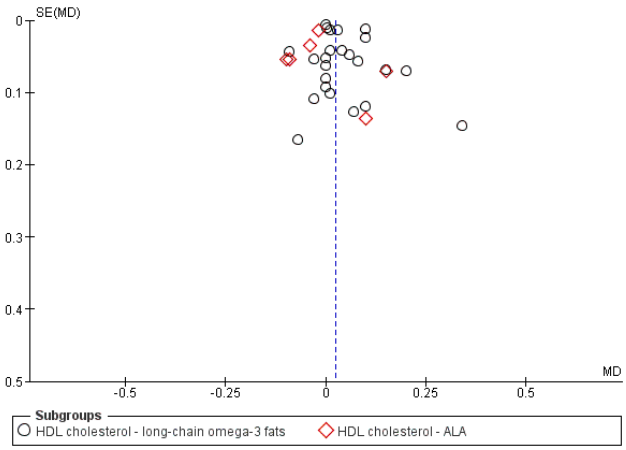


Figure 5.14. Funnel plot of effects of omega 3 fats on serum HDL (in mmol/L).

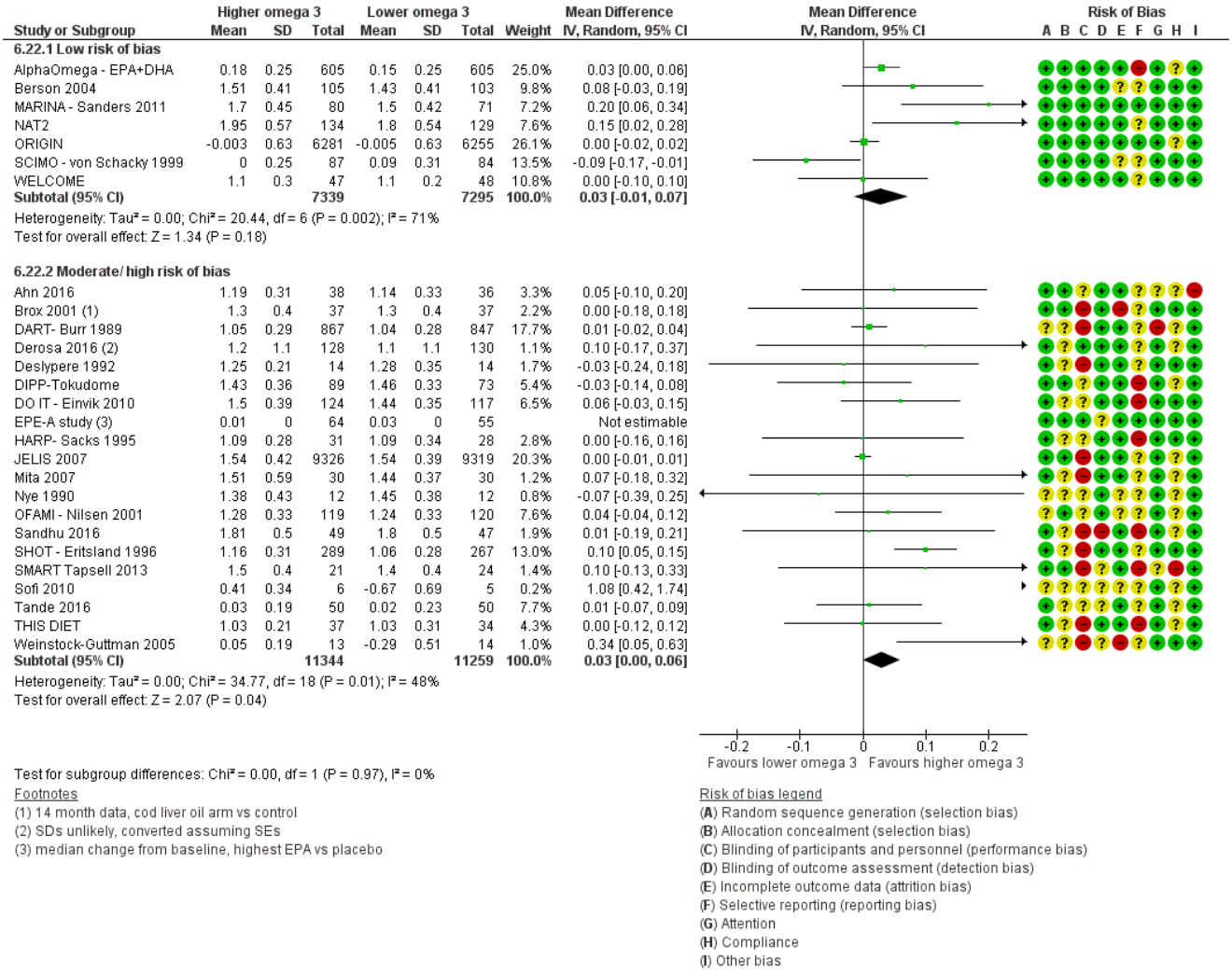


Figure 5.15. Meta-analysis of effects of omega 3 fats on serum HDL (in mmol/L), subgrouped by summary risk of bias.

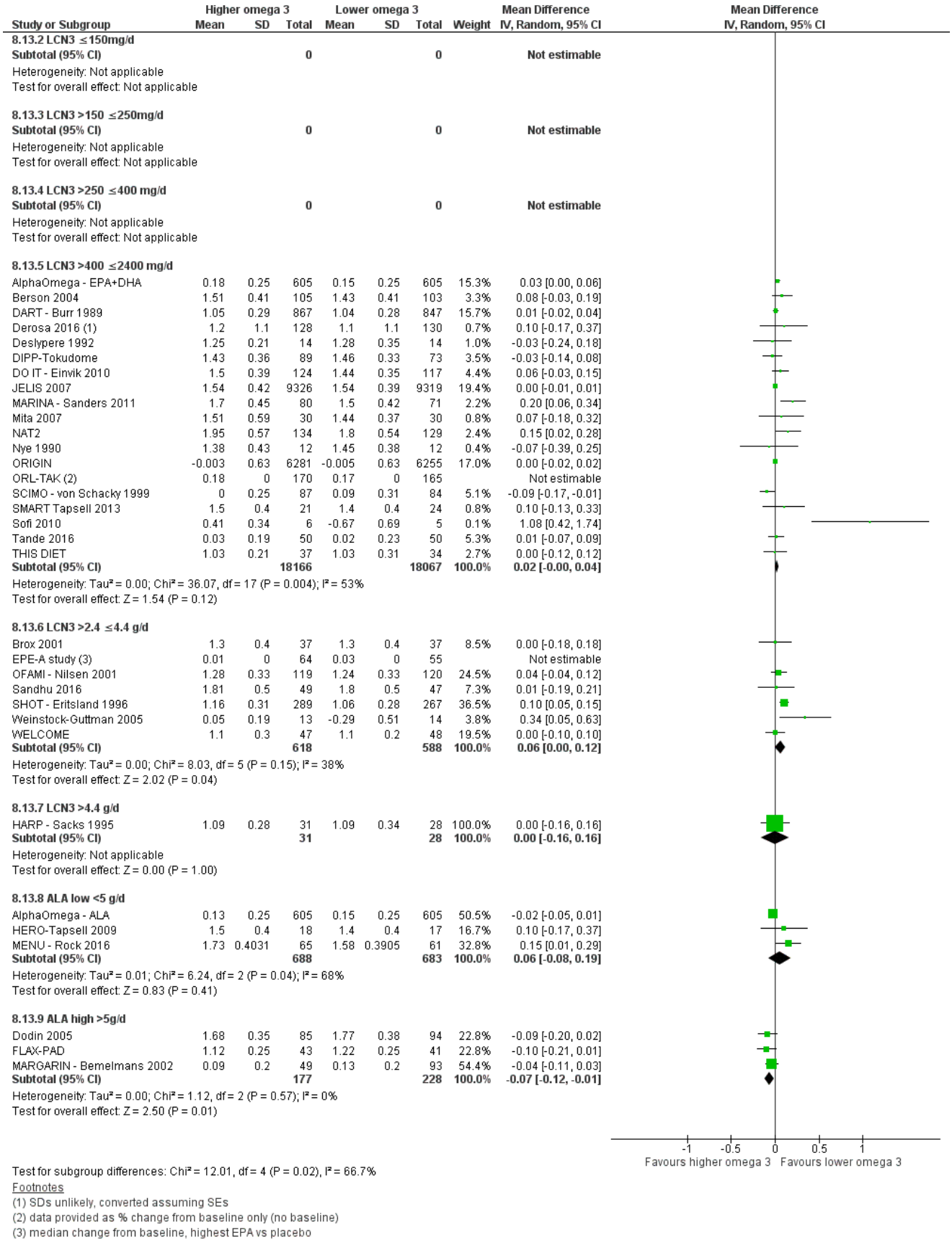


Figure 5.16. Meta-analysis of effects of omega 3 fats on serum HDL (in mmol/L), subgrouped by LCn3 or ALA dose.

Secondary outcomes – blood pressure (BP)

We collected BP data only from RCTs of omega 3 fatty acids with at least 1 year duration that were included as they had collected mortality, CVD, lipid or adiposity data. For this reason, it is likely that some studies that collected BP data over at least 1 year will be missing from our analysis. On the other hand, we have accumulated data from over 36,000 participants in trials for at least 1 year on the effects of LCn3 fats on BP, and 1671 participants on effects of ALA and there is no particular reason to feel that this should be a biased set of data.

Meta-analysis clearly suggested that long-term omega 3 fats, from either fish or plant sources, had no important effects on blood pressure, Figure 5.17.

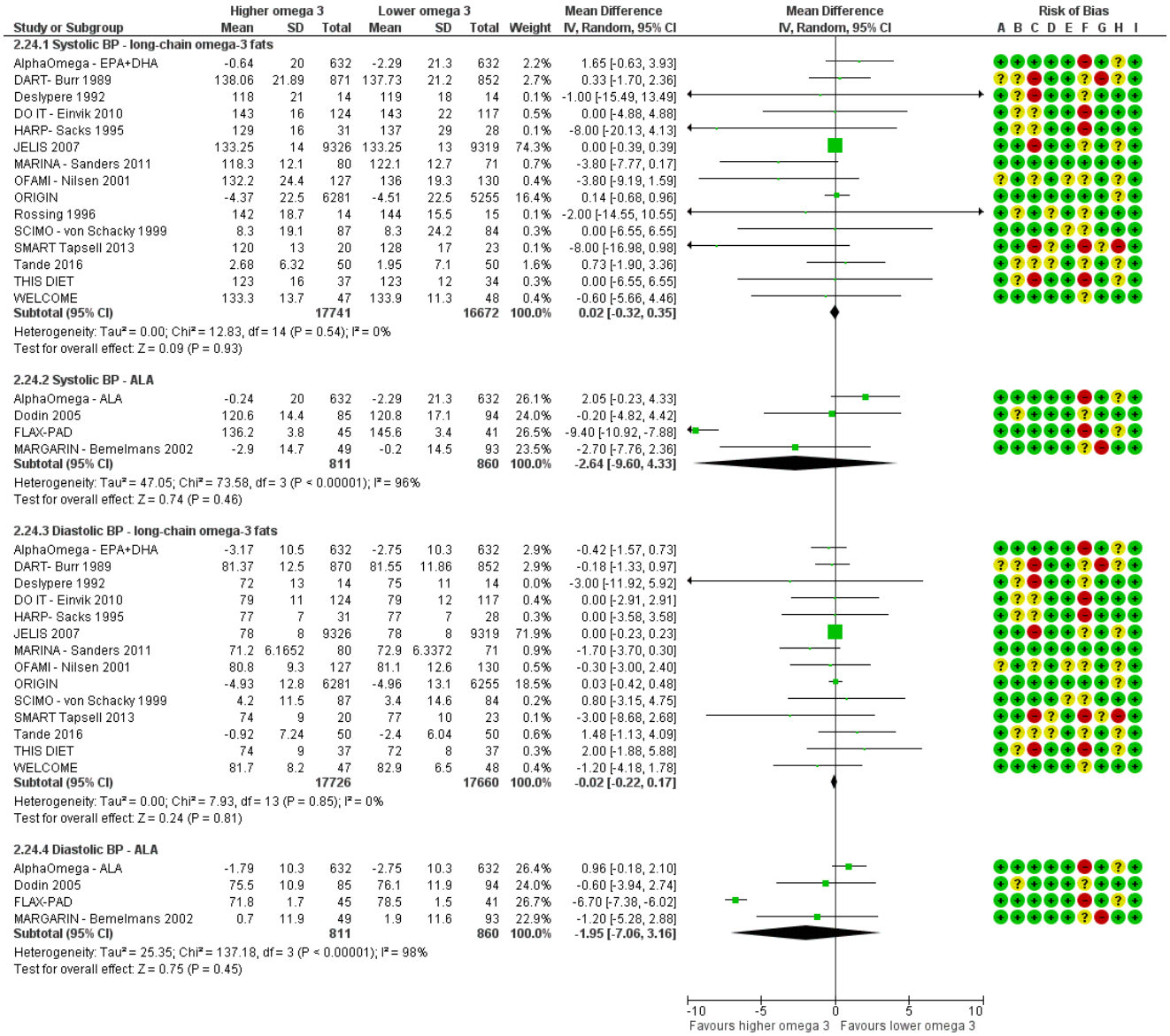


Figure 5.17. Meta-analysis of effects of long-chain and ALA omega 3 fats on systolic and diastolic blood pressure.

Chapter 6. Do dietary or supplemental omega 3 fatty acids alter risk of atrial fibrillation (in people with or without existing atrial fibrillation)?

We included all relevant RCTs of at least 1 year duration that assessed effects of omega 3 fats (LCn3 or ALA) on recurrent or new atrial fibrillation.

Primary outcomes – new atrial fibrillation (AF), ventricular fibrillation (VF) and ventricular tachycardia (VT)

In people without atrial fibrillation at baseline we included 16 RCTs of over 49,000 participants with 2132 new cases of AF, VF or VT. The data suggested no effect of LCn3 fats on new atrial or ventricular fibrillation or ventricular tachycardia (RR 1.07, 95% CI 0.99 to 1.16, I^2 0%), Figure 6.1. This did not alter when fixed effects analysis were used, or when we omitted trials at moderate to high risk of bias (RR 1.08, 95% CI 0.96 to 1.23, I^2 0%).

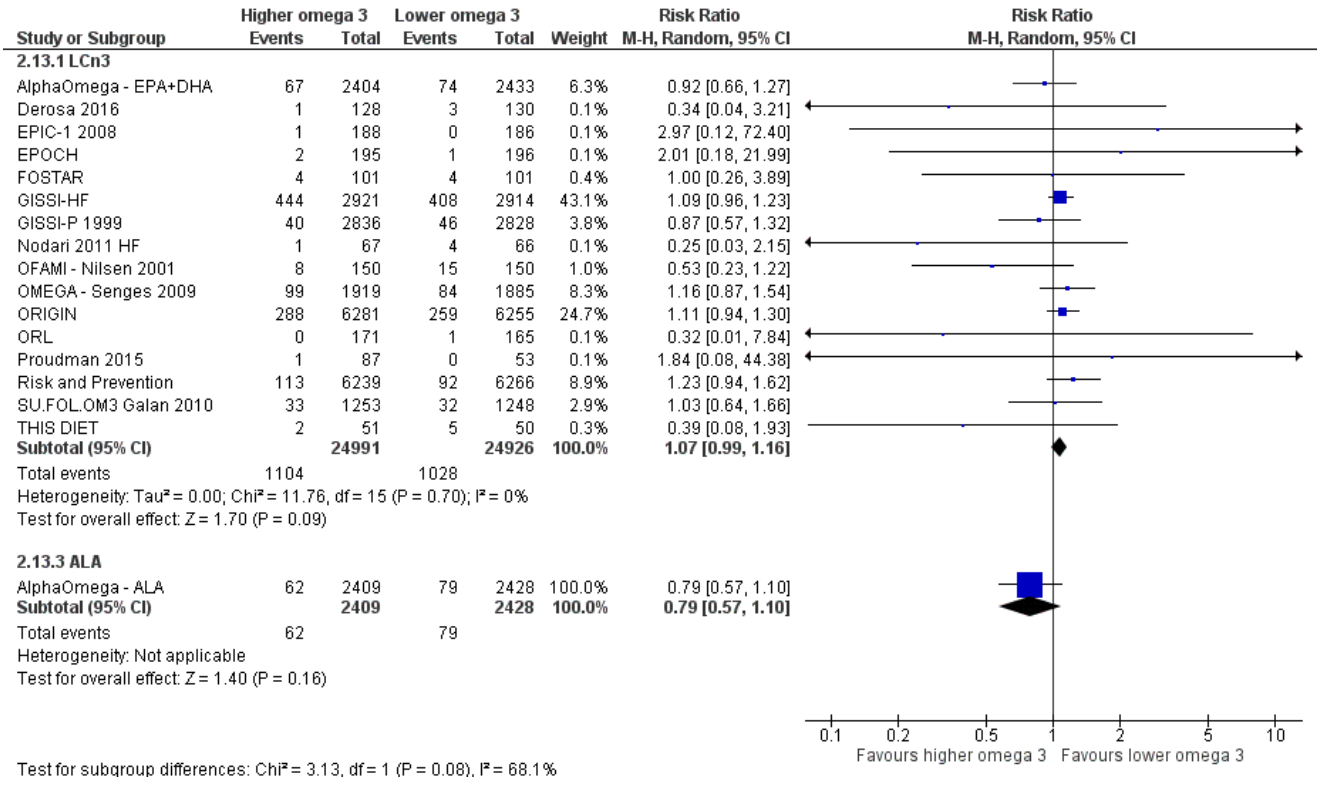


Figure 6.1. Meta-analysis of effects of LCn3 fats on new atrial or ventricular fibrillation or ventricular arrhythmia.

The funnel plot of LCn3 intervention trials suggested little small study bias, Figure 6.2, but any bias here will be suggesting protection rather than harm (so that the real effects may be slightly more

harmful than suggested above, potentially making the effects of omega 3 harmful in terms of first atrial or ventricular fibrillation event).

Effects remained non-significant in all LCn3 subgroups when assessed by duration, statin use, and primary or secondary prevention. When we subgrouped by dose the 400-2400mg/d category was significantly harmful, as was the supplements subgroup (when assessing intervention type), and replacement of MUFA, but not other replacements, Figure 6.4.

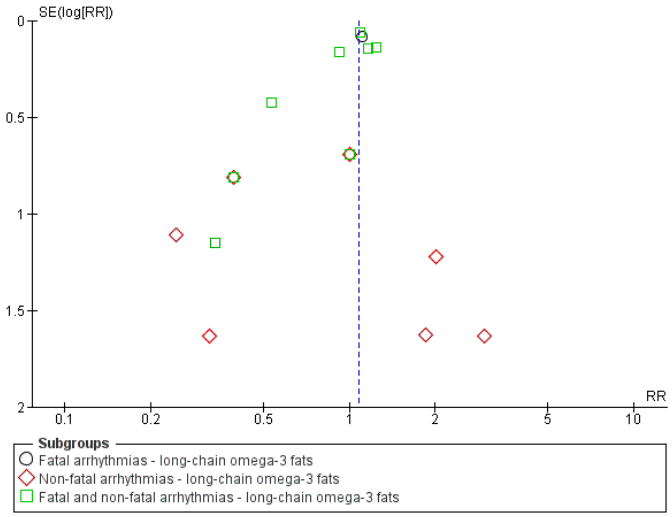


Figure 6.2. Funnel plot of LCn3 fats on new atrial fibrillation.

Only one RCT including almost 5000 participants was available to assess effects of ALA on new atrial fibrillation, suggesting no clear effect, Figure 6.4.

Summary

Studies at low risk of bias suggest no clear effect of omega 3 fats on new atrial or ventricular fibrillation, or ventricular arrhythmia, but if any effect exists, it is likely that LCn3 fats increase the risk of new atrial fibrillation.

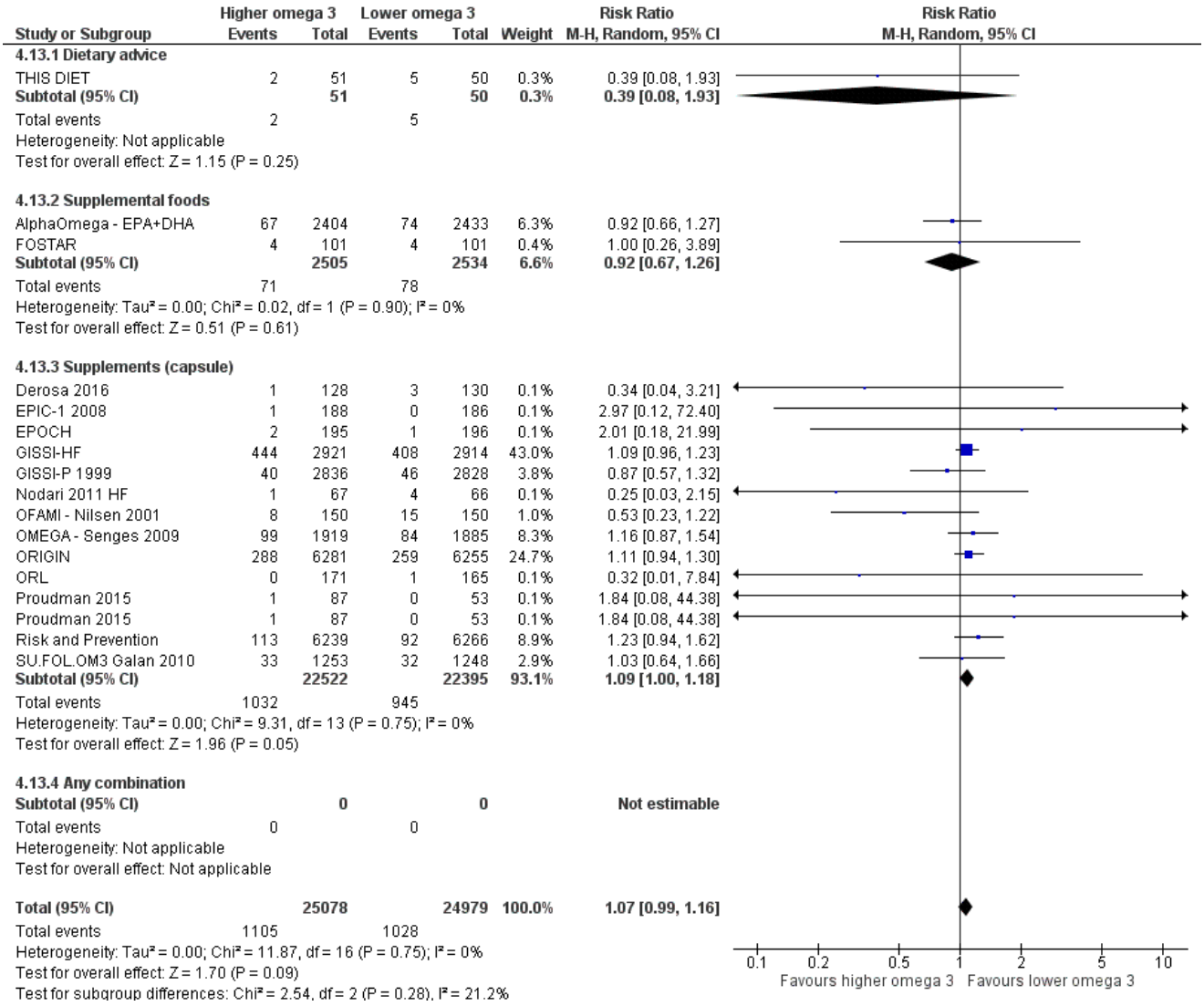


Figure 6.3. Meta-analysis of LCn3 fats on new atrial fibrillation, subgrouping by type of intervention.

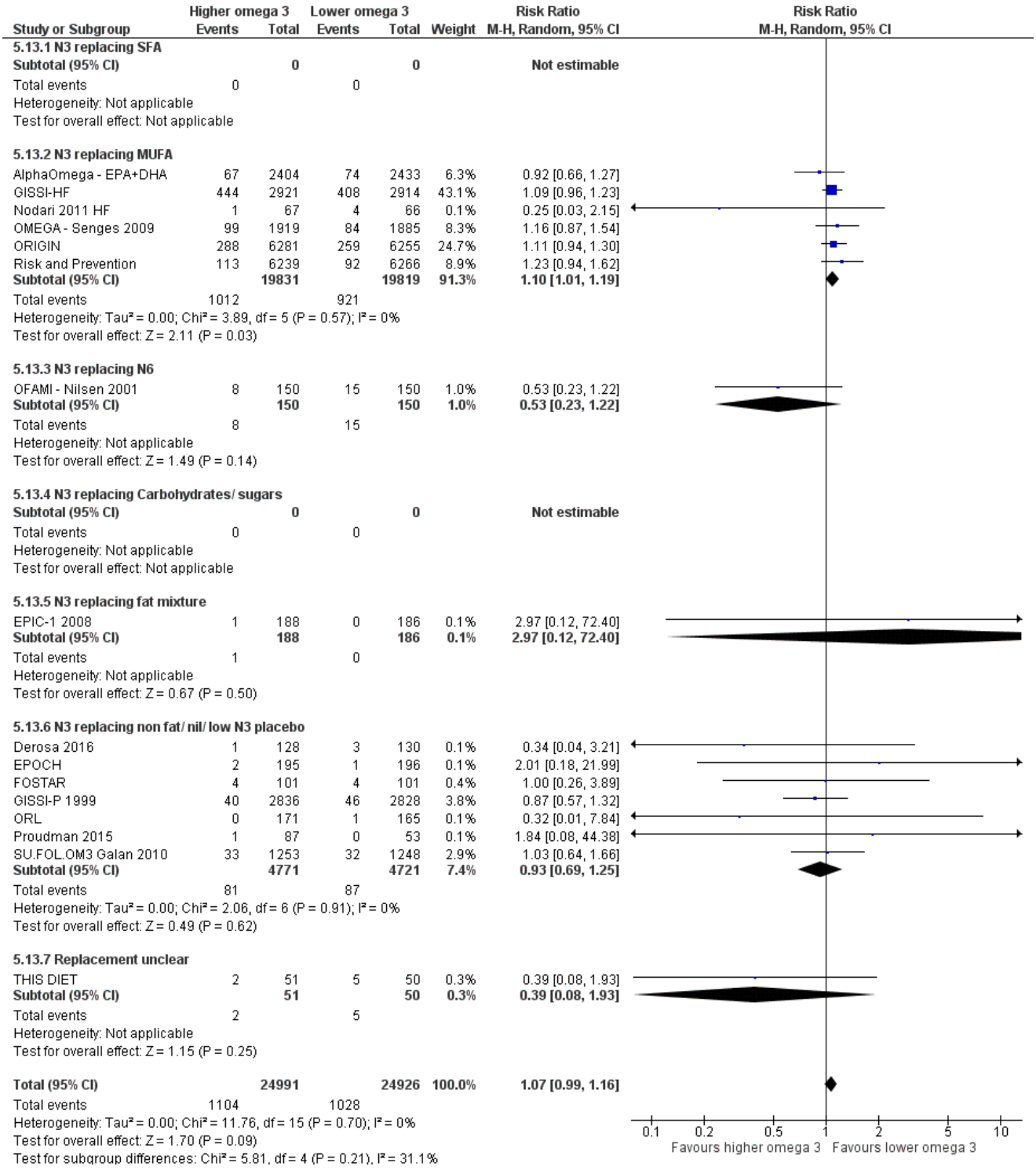


Figure 6.4. Meta-analysis of effects of omega 3 fats on new atrial fibrillation, subgrouping by replacement.

Primary outcomes – recurrent atrial fibrillation (AF), ventricular fibrillation (VF) and ventricular tachycardia (VT)

We included 11 RCTs of over 3,000 people with atrial fibrillation, ventricular fibrillation or ventricular tachycardia at baseline and the data suggested no effect of LCn3 fats on recurrence by study end (1569 participants had recurrence of fibrillation by study end, RR 0.93, 95% CI 0.83 to 1.05, I^2 62%), Figure 6.5. This lack of effect did not alter when fixed effects analysis were used, or when trials at moderate to high risk of bias were omitted (though data were very limited, Figure 6.7). There was no suggestion of small study bias, Figure 6.6. No studies assessed effects of ALA on recurrent arrhythmia.

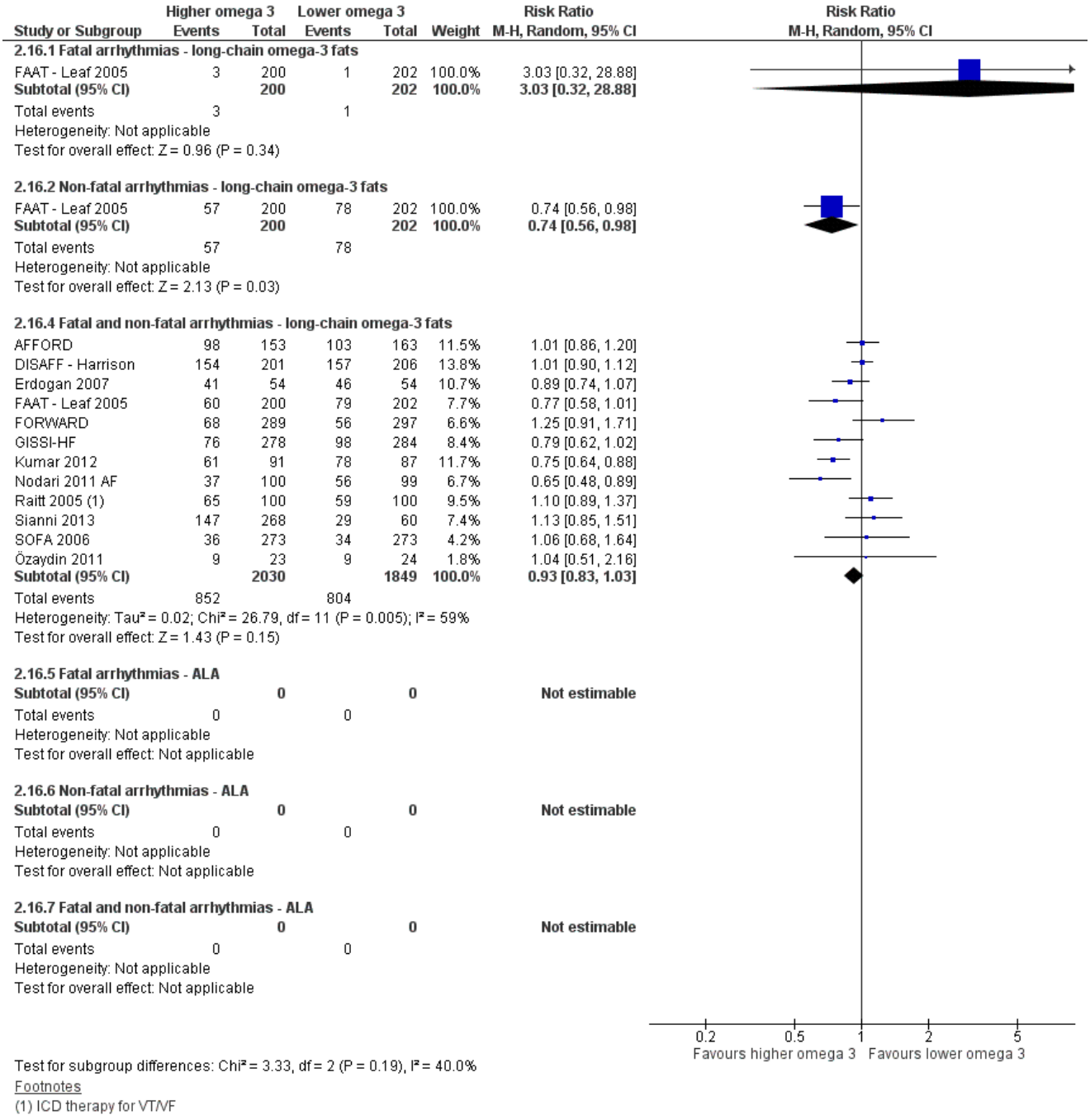


Figure 6.5. Meta-analysis of effects of omega 3 fats on recurrent atrial fibrillation.

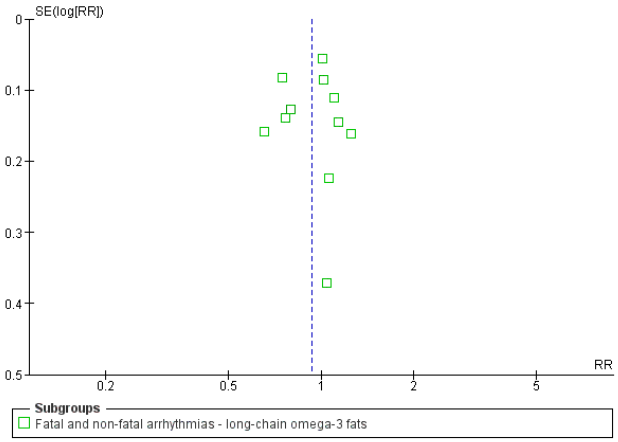


Figure 6.6. Funnel plot of effects of LCn3 fats on recurrence of arrhythmias

Subgrouping by dose, duration, primary or secondary prevention, replacement, statins and intervention type did not produce any statistically significant subgroups or clearly reduce heterogeneity.

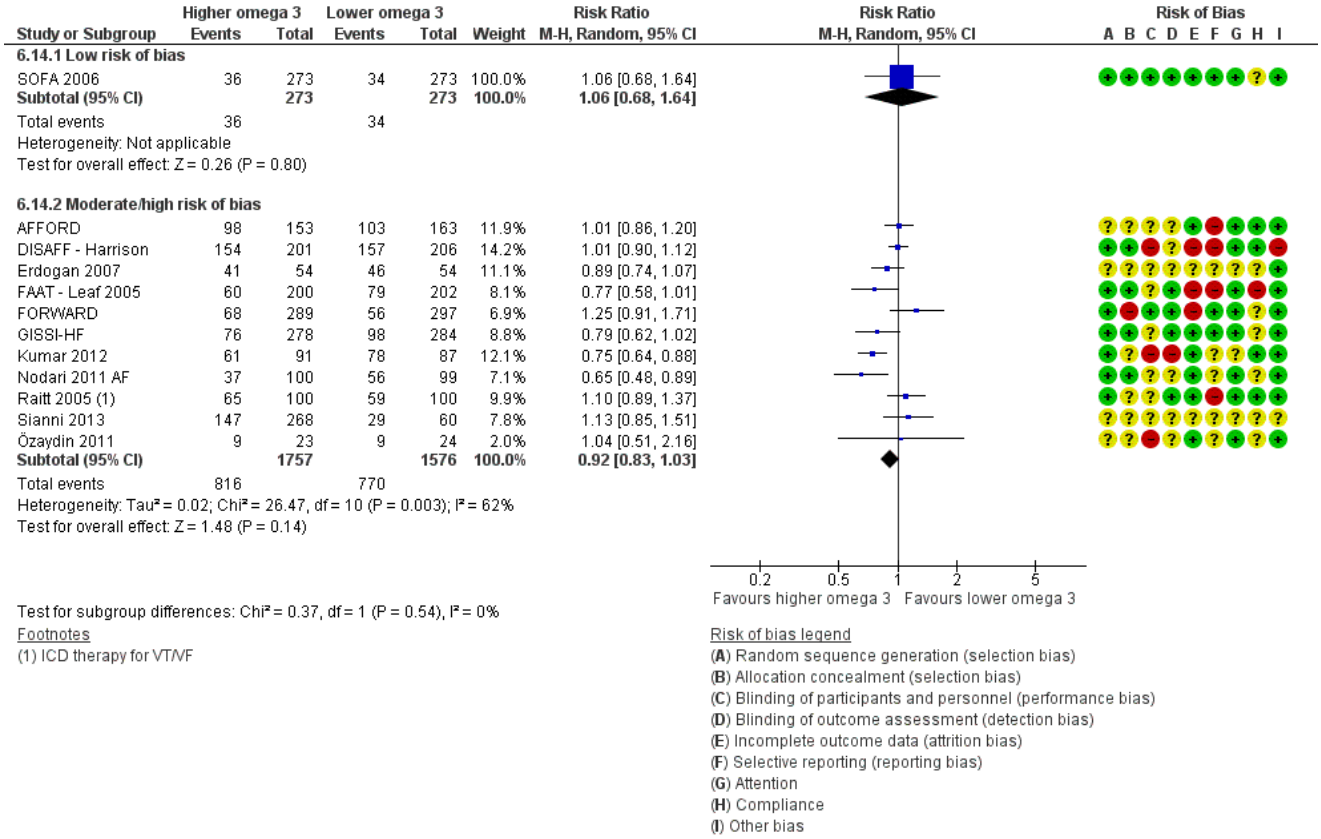


Figure 6.7. Meta-analysis of the effects of LCn3 fatty acids on recurrent arrhythmia, sensitivity analysis removing trials of moderate to high summary risk of bias (shown as subgrouping by summary risk of bias).

Summary

LCn3 fats do not appear to reduce new or recurrent arrhythmias.

Chapter 7. Do dietary or supplemental omega 3 fatty acids alter risk of type 2 diabetes or treatment outcome in type 2 diabetes?

This chapter has been omitted from this version of the report.

Chapter 8. Do dietary or supplemental omega 3 fatty acids alter risk of neurocognitive outcomes including dementia, or the course of dementia?

This chapter has been omitted from this version of the report.

Chapter 9. Do dietary or supplemental omega 3 fatty acids alter risk of depression in people with or without an existing diagnosis of depression?

This chapter has been omitted from this version of the report.

Chapter 10. Do dietary or supplemental omega 3 fatty acids alter risk of breast cancer (in primary or secondary prevention)?

This chapter has been omitted from this version of the report.

Chapter 11. Do dietary or supplemental omega 3 fatty acids have a role in primary or secondary prevention of inflammatory bowel disease?

This chapter has been omitted from this version of the report.

Chapter 12. Do dietary or supplemental omega 3 fatty acids alter the risk of increased adiposity or long term weight control?

This chapter has been omitted from this version of the report.

Chapter 13. Discussion

Summary of the findings of this set of systematic reviews is found in the next chapter. *This section has been shortened to include only comments relevant to the remaining systematic reviews in this report.*

The notable finding overall is the suggestion of so few health effects of omega 3 fats on health outcomes. Nowhere do we see strong suggestions of health benefits (or harms) from increasing ALA, any potential effects spring from the long-chain omega 3 fats.

Where there are suggestions of health effects of long-chain omega 3 fats, for example in protecting against coronary heart disease events, or in increasing stroke rates, these effects are only seen in studies at moderate to high risk of bias, not when we limit analyses to studies judged at low summary risk of bias.

For several outcomes (including all-cause mortality, CVD mortality and CHD mortality) there were statistically significant effects seen in the studies of 2 to <4 years, but no effects seen in shorter or longer duration trials. Given that these outcomes all had high numbers of events in the longer duration trials (so that lack of statistical significance in these subgroups did not appear to be due to a lack of power) we did not interpret them as suggesting greater effectiveness at longer duration. It is more likely that, in the absence of any rationale for a 2-4 year effect in the absence of an effect at shorter and longer durations, and given the large number of subgroup analyses we performed, these appear spuriously statistically significant.

Chapter 14. GRADE and summary

The primary questions to be answered, and the answers suggested by these reviews, using all available randomised controlled trials in adults, which provided omega 3 fats for at least 1 year, are as follows:

All-cause mortality

Do dietary or supplemental omega 3 fatty acids alter **all-cause mortality**?

There is no suggestion that either dietary or supplemental omega 3 fats have any effect on all-cause mortality (Figure 3.9).

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High	Low omega-3 fats (primary outcomes)	Relative (95% CI)	Absolute		
All-cause (total) mortality - Long chain omega 3 (assessed with: deaths), minimum duration 1 year												
39	randomised trials	no serious risk of bias[1]	no serious inconsistency[2,3]	no serious indirectness[4]	no serious imprecision[5]	none[6]	4048/46479 (8.7%)	4141/46174 (9%)	RR 0.98 (0.93 to 1.03)	2 fewer per 1000 (from 6 fewer to 3 more)	⊕⊕⊕⊕ HIGH of no effect	CRITICAL
								3.7%		1 fewer per 1000 (from 3 fewer to 1 more)		
All-cause (total) mortality - ALA (assessed with: deaths), minimum duration 1 year												
4	randomised trials	no serious risk of bias[1]	no serious inconsistency[2,3]	no serious indirectness	serious[7]	none[8]	229/9292 (2.5%)	229/9327 (2.5%)	RR 1 (0.84 to 1.2)	0 fewer per 1000 (from 4 fewer to 5 more)	⊕⊕⊕O MODERATE of	CRITICAL

								0.6%		0 fewer per 1000 (from 1 fewer to 1 more)	no effect	

[1] There was no effect when data were limited to RCTs at low summary risk of bias.
[2] I^2 was <60%
[3] Effects did not differ in fixed effects meta-analysis.
[4] Varied adult population including men and women, those with existing CVD, healthy adults, adults with some CVD risk factors, and adults with other health problems but no previous CVD.
[5] This analysis included a large number of long term studies with consistent results. There is a clear and precise suggestion that omega 3 fats do not influence mortality in an important way.
[6] Funnel plot showed a slight suggestion of some missing data - if such studies were added into the analysis they would move the RR closer to 1.
[7] While the RR does not suggest any effect, the confidence intervals do not rule out important benefits or harms.
[8] Fewer than 8 RCTs, so funnel plot not interpretable.

Cardiovascular outcomes

Do dietary or supplemental omega 3 fatty acids alter risk of cardiovascular death, cardiovascular events, *coronary heart disease deaths,* coronary heart disease or stroke (in people with or without existing cardiovascular disease)?

Cardiovascular death. There is no evidence that LCn3 fats or ALA alter risk of cardiovascular deaths in either primary or secondary prevention of CVD (Figures 4.1 and 4.6), and there is no suggestion that studies at lower risk of bias (Figure 4.3), those with longer duration (figure 4.5) or using higher doses (Figure 4.4) offer more benefit.

Cardiovascular events. There is no suggestion that either dietary or supplemental omega 3 fats, or studies of LCn3 fats at low risk of bias, have any effect on cardiovascular events (Figure 4.10 and 4.12).

There is no suggestion that LCn3 fats or ALA have any effect on cardiovascular events in people with or without existing cardiovascular disease (Figure 4.11).

CHD deaths. Any effect of LCn3 on CHD deaths appears to depend on assumptions made in analyses. Studies at low risk of bias suggest no effect of LCn3 on CHD deaths (whether or not we include studies reporting cardiac deaths, Figures 4.18 and 4.19). There are no clear effects of dose or duration. We suggest that any apparent effect is partly driven by reporting bias and partly by studies at moderate to high risk of bias.

CHD events. Despite 5469 participants in long term omega 3 trials experiencing coronary heart disease, the evidence of protection by LCn3 is not convincing. This is because when we omit studies at moderate to high risk of bias the effect appears negligible and no longer statistically significant. The overall effect size of all 28 RCTs suggested a 7% reduction in coronary heart disease (RR 0.93, 95% CI 0.88 to 0.97, I^2 0%, Figure 4.23), but in the 10 studies at low risk of bias there was no clear effect (RR 0.98, 95% CI 0.91 to 1.05, I^2 0%, p=0.53). There was no suggestion of dose effects (Figure 4.26) or greater effects at longer duration (Figure 4.27).

There is no suggestion that either dietary or supplemental omega 3 fats have any effect on stroke (Figure 4.33). The suggestion of harm from omega 3 fats on secondary prevention of stroke appears to be driven by studies at moderate to high risk of bias (Figure 4.30, 4.31)

There is some evidence of protective effects against CHD events of LCn3 fats and some suggestion of harmful effects from LCn3 fats on stroke in those with existing CVD. However, neither effect is present in studies at low risk of bias.

Stroke. There is no evidence that omega 3 fats reduce the risk of stroke. While there is a suggestion that LCn3 fats may increase stroke risk in secondary prevention of CVD, no increased risk of stroke is apparent in studies at low risk of bias.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High	Low omega-3 fats (primary outcomes)	Relative (95% CI)	Absolute		
Cardiovascular deaths - Long chain omega 3 (assessed with: deaths from any cardiovascular cause (deaths from individual cardiovascular causes were summed, where these were not available, but cardiac death was available this was used in place of cardiovascular death))												
25	randomised trials	no serious risk of bias[1]	no serious inconsistency[2]	no serious indirectness[4]	serious[7]	none[6]	2211/33991 (6.5%)	2333/33781 (6.9%)	RR 0.95 (0.87 to 1.03)	3 fewer per 1000 (from 9 fewer to 2 more)	⊕⊕⊕O MODERATE of no effect	
								3.4%		2 fewer per 1000 (from 4 fewer to 1 more)		
Cardiovascular deaths - ALA (assessed with: deaths from any cardiovascular cause (deaths from individual cardiovascular causes were summed, where these were not available, but cardiac death was available this was used in place of cardiovascular death))												
4	randomised trials	no serious risk of bias[1]	no serious inconsistency[2,3]	no serious indirectness[4]	serious[7]	none[8]	107/9292 (1.2%)	112/9327 (1.2%)	RR 0.96 (0.74 to 1.25)	0 fewer per 1000 (from 3 fewer to 3 more)	⊕⊕⊕O MODERATE of no effect	
								0.5%		0 fewer per 1000 (from 1 fewer to 1 more)		
Coronary Heart Disease - CHD events- LCN3 (assessed with: First outcome in this list reported for each trial: CHD or coronary events; total MI; acute coronary syndrome; or angina (stable and unstable))												
28	randomised trials	serious[9]	no serious inconsistency[2,3]	no serious indirectness[4]	no serious imprecision	none	2634/42305 (6.2%)	2835/41996 (6.8%)	RR 0.93 (0.88 to 0.97)	5 fewer per 1000 (from 2 fewer to 8 fewer)	⊕⊕⊕O MODERATE of no effect	CRITICAL
								3.7%		3 fewer per 1000 (from 1 fewer to 4 fewer)		
Coronary Heart Disease - CHD event- ALA (assessed with: First outcome in this list reported for each trial: CHD or coronary events; total MI; acute coronary syndrome; or angina (stable and unstable))												
3	randomised trials	no serious risk of bias[1]	no serious inconsistency[2,3]	no serious indirectness	serious[7]	none[8]	197/9183 (2.1%)	199/9170 (2.2%)	RR 1 (0.78 to 1.29)	0 fewer per 1000 (from 5 fewer to 6 more)	⊕⊕⊕O MODERATE of no effect	CRITICAL
								5.5%		0 fewer per 1000 (from 12 fewer to 16 more)		

Coronary heart mortality - Coronary heart mortality- LCN3 (assessed with: Coronary deaths, or where these were not reported, IHD death, fatal MI or cardiac death (in that order))												
21	randomised trials	no serious risk of bias[1]	no serious inconsistency[2,10]	no serious indirectness[4]	serious[7]	none[6]	773/36836 (2.1%)	823/36655 (2.2%)	RR 0.93 (0.79 to 1.09)	2 fewer per 1000 (from 5 fewer to 2 more)	⊕⊕⊕O MODERATE of no effect	IMPORTANT
								2.5%		2 fewer per 1000 (from 5 fewer to 2 more)		
Coronary heart mortality - Coronary heart mortality- ALA (assessed with: Coronary deaths, or where these were not reported, IHD death, fatal MI or cardiac death (in that order))												
3	randomised trials	no serious risk of bias[1]	no serious inconsistency[2,10]	no serious indirectness	serious[7]	none[8]	94/9183 (1%)	99/9170 (1.1%)	RR 0.95 (0.72 to 1.26)	1 fewer per 1000 (from 3 fewer to 3 more)	⊕⊕⊕O MODERATE of no effect	IMPORTANT
								0.4%		0 fewer per 1000 (from 1 fewer to 1 more)		
Combined cardiovascular events - Long chain omega 3 (assessed with: Summed available cardiovascular events where we were sure we were not including any participant twice)												
32	randomised trials	no serious risk of bias[1]	no serious inconsistency[2,3]	no serious indirectness[4]	no serious imprecision	none[6]	7260/44849 (16.2%)	7376/44513 (16.6%)	RR 0.98 (0.95 to 1.01)	3 fewer per 1000 (from 8 fewer to 2 more)	⊕⊕⊕⊕ HIGH of no effect	CRITICAL
								10.1%		2 fewer per 1000 (from 5 fewer to 1 more)		
Combined cardiovascular events - ALA (assessed with: Summed available cardiovascular events where we were sure we were not including any participant twice)												
3	randomised trials	no serious risk of bias[1]	no serious inconsistency[2]	no serious indirectness	serious[7]	none[8]	420/9234 (4.5%)	448/9275 (4.8%)	RR 0.95 (0.83 to 1.07)	2 fewer per 1000 (from 8 fewer to 3 more)	⊕⊕⊕O MODERATE of no effect	CRITICAL
								5.7%		3 fewer per 1000 (from 10 fewer to 4 more)		
Stroke - Long chain omega 3 (assessed with: Fatal or non-fatal, ischaemic or haemorrhagic stroke combined)												
28	randomised trials	no serious risk of bias[1]	no serious inconsistency[2,3]	no serious indirectness[4]	serious[7,11]	none	940/44758 (2.1%)	882/44600 (2%)	RR 1.06 (0.97 to 1.16)	1 more per 1000 (from 1 fewer to 3 more)	⊕⊕⊕O MODERATE of no effect	CRITICAL
								0.9%		1 more per 1000 (from 0 fewer to 1 more)		
Stroke - ALA (assessed with: Fatal or non-fatal, ischaemic or haemorrhagic stroke combined)												
4	randomised trials	no serious risk of bias[1]	no serious inconsistency[2]	no serious indirectness	serious[7]	none[8]	26/9292 (0.3%)	23/9327 (0.2%)	RR 1.15 (0.66 to 2)	0 more per 1000 (from 1 fewer to 2 more)	⊕⊕⊕O MODERATE of no effect	CRITICAL
								0.9%		1 more per 1000 (from 3 fewer to 9 more)		

[1] There was no effect when data were limited to RCTs at low summary risk of bias.

[2] I^2 was <60%

[3] Effects did not differ in fixed effects meta-analysis.

[4] Varied adult population including men and women, those with existing CVD, healthy adults, adults with some CVD risk factors, and adults with other health problems but no previous CVD.
[5] This analysis included a large number of long term studies with consistent results. There is a clear and precise suggestion that omega 3 fats do not influence mortality in an important way.
[6] Funnel plot showed a slight suggestion of some missing data - if such studies were added into the analysis they would move the RR closer to 1.
[7] While the RR does not suggest any effect, the confidence intervals do not rule out important benefits or harms.
[8] Fewer than 8 RCTs, so funnel plot not interpretable.
[9] Subgrouping by risk of bias suggests no effect in studies at low risk of bias, and significant effects only in studies of moderate to high risk of bias
[10] When we ran fixed effects meta-analysis the data changed, suggested that omega 3 fats reduced risk of this outcome.
[11] While there were no clear effects of omega 3 on stroke overall, data suggested that omega 3 fats might increase risk of stroke in people with existing CVD (secondary prevention).

Serum lipids

What are the effects of dietary or supplemental omega 3 fatty acids on serum total cholesterol, HDL or LDL cholesterol or triglycerides?

Any effects on serum total cholesterol HDL and LDL of omega 3 fats are small, but there does appear to be a dose-related reduction in TG associated with an increase on LCn3 fats. This effect is not clear in the few studies of dietary advice or supplemental foods, or of ALA, but is clear with supplemental LCn3.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GRADE outcomes	Control	Relative (95% CI)	Absolute		
Serum total cholesterol - LCn3 (measured with: mmol/L; Better indicated by lower values)												
28	randomised trials	serious[1,10,13]	no serious inconsistency[2]	no serious indirectness	no serious imprecision[11]	none	18705	18576	-	MD 0.01 lower (0.05 lower to 0.04 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Serum total cholesterol - ALA (measured with: mmol/L; Better indicated by lower values)												
6	randomised trials	no serious risk of bias[1]	serious[8]	no serious indirectness	no serious imprecision	none[7]	1060	1104	-	MD 0.09 lower (0.23 lower to 0.05 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Serum triglyceride - LCn3 (measured with: mmol/L; Better indicated by lower values)												
24	randomised trials	no serious risk of bias[1,3]	no serious inconsistency[2]	no serious indirectness	no serious imprecision[14]	dose response gradient[15]	17825	17709	-	MD 0.23 lower (0.30 to 0.15 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT
Serum triglyceride - ALA (measured with: mmol/L; Better indicated by lower values)												
6	randomised trials	no serious risk of bias[1]	no serious inconsistency[2]	no serious indirectness	serious[11]	none[7]	865	911	-	MD 0.03 lower (0.11 lower to 0.05 higher)	⊕⊕⊕O MODERATE	IMPORTANT

Serum low density lipoprotein LCn3 (measured with: mmol/L; Better indicated by lower values)												
23	randomised trials	no serious risk of bias[1,3]	no serious inconsistency[2]	no serious indirectness	no serious imprecision[11]	none	17525	17436	-	MD 0.00 higher (0.01 lower to 0.02 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Serum low density lipoprotein - ALA (measured with: mmol/L; Better indicated by lower values)												
7	randomised trials	no serious risk of bias[1,3]	no serious inconsistency[2]	no serious indirectness	serious[9]	none[7]	1080	1121	-	MD 0.05 lower (0.15 lower to 0.04 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Serum high density lipoprotein - LCn3 (measured with: mmol/L; Better indicated by lower values)												
27	randomised trials	serious[3,16]	no serious inconsistency[2]	no serious indirectness	no serious imprecision[14]	none	18815	18683	-	MD 0.03 higher (0.01 higher to 0.05 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Serum high density lipoprotein - ALA (measured with: mmol/L; Better indicated by lower values)												
6	randomised trials	serious[1,17]	no serious inconsistency[2]	no serious indirectness	serious[11]	none[7]	865	911	-	MD 0.02 lower (0.08 lower to 0.03 higher)	⊕⊕OO LOW	IMPORTANT

[1] Effect did not alter when analysis was limited to studies at low summary risk of bias.
[2] I^2 was less than 60%
[3] Effect did not alter when fixed effects meta-analysis was run.
[4] The suggested effect of omega 3 fats was to increase the risk of new AF, VF and/or VT, however possible effects ranged from a small amount of benefit to harm.
[5] A small amount of publication bias is suggested. If we added in potentially missing studies then this would increase the suggestion of harm by omega 3 fats.
[6] 95% confidence intervals include serious benefit and serious harm
[7] Not possible to assess as fewer than 8 studies included.
[8] I^2 was greater than 60%
[9] Effect, as assessed by 95% confidence intervals, includes benefit and serious harm.
[10] There is a specific danger of missing data for this outcome.
[11] Overall the data suggest no effect of these fats on this outcome, but 95% confidence intervals include modest benefit and modest harm.
[12] No studies were at low summary risk of bias
[13] Running fixed effects meta-analysis suggested an effect of omega 3 fats on this outcome.
[14] This is a clearly statistically significant effect
[15] Subgrouping suggested that higher doses of LCn3 fats resulted in greater TG lowering.
[16] Studies at low risk of bias suggested no statistically significant effect.
[17] Studies at low risk of bias suggested a borderline statistically significant reduction in HDL with increased omega-3 fats (p=0.05).

Atrial and ventricular fibrillation, or ventricular arrhythmia

Do dietary or supplemental omega 3 fatty acids alter risk of atrial fibrillation (in people with or without existing atrial fibrillation)?

There is no evidence of a protective effect of LCn3 fats against new arrhythmias and the potential of a small amount of harm associated with supplements (but not dietary or supplemental food sources, Figure 6.3). There is no suggestion of any effect of omega 3 fats on recurrent arrhythmias (Figure 6.7).

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GRADE outcomes	Control	Relative (95% CI)	Absolute		
New arrhythmias - LCn3 (assessed with: AF, VT and/or VF, fatal or nonfatal)												
16	randomised trials	no serious risk of bias[1]	no serious inconsistency[2,3]	no serious indirectness	serious[4]	none[5]	1104/24991 (4.4%)	1028/24926 (4.1%)	RR 1.07 (0.99 to 1.16)	3 more per 1000 (from 0 fewer to 7 more)	⊕⊕⊕O MODERATE	IMPORTANT
								2.8%		2 more per 1000 (from 0 fewer to 4 more)		
New arrhythmias - ALA (follow-up mean 40 months; assessed with: AF, VT and/or VF, fatal or nonfatal)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none[7]	62/2409 (2.6%)	79/2428 (3.3%)	RR 0.79 (0.57 to 1.1)	7 fewer per 1000 (from 14 fewer to 3 more)	⊕⊕⊕O MODERATE	IMPORTANT
								3.3%		7 fewer per 1000 (from 14 fewer to 3 more)		

Recurrent arrhythmias - LCn3 fats (assessed with: AF, VT and/or VF, fatal or nonfatal in people with a history of AF, VT or VF)												
11	randomised trials	no serious risk of bias[1]	serious[8]	no serious indirectness	serious[9]	none	811/1976 (42%)	758/1795 (43.5%)	RR 0.93 (0.83 to 1.05)	30 fewer per 1000 (from 74 fewer to 13 more)	⊕⊕OO LOW	IMPORTANT
								52.5%		37 fewer per 1000 (from 89 fewer to 16 more)		
Recurrent arrhythmias - ALA (assessed with: AF, VT and/or VF, fatal or nonfatal in people with a history of AF, VT or VF)												
0	no evidence available					none	-	-	not pooled	not pooled		IMPORTANT
								0%		not pooled		

[1] Effect did not alter when analysis was limited to studies at low summary risk of bias.
[2] I^2 was less than 60%
[3] Effect did not alter when fixed effects meta-analysis was run.
[4] The suggested effect of omega 3 fats was to increase the risk of new AF, VF and/or VT, however possible effects ranged from a small amount of benefit to harm.
[5] A small amount of publication bias is suggested. If we added in potentially missing studies then this would increase the suggestion of harm by omega 3 fats.
[6] 95% confidence intervals include serious benefit and serious harm
[7] Not possible to assess as fewer than 8 studies included.
[8] I^2 was greater than 60%
[9] Effect, as assessed by 95% confidence intervals, includes benefit and serious harm.

This remainder of this chapter has been omitted from this version of the report.

Appendix 1. Electronic searches

1a. Medline (Ovid) search strategy run in 2002 (for the previous version of the omega 3 review on the Cochrane Library)

MEDLINE search run in 2002 for the previous version of this review.
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1950 to Present>
Search Strategy:
---
1 exp Fish Oils/
2 exp Linseed Oil/
3 linolenic acids/ or exp alpha-linolenic acid/
4 exp Fatty Acids, Omega-3/
5 (fish adj5 (diet$ or nutrit$ or oil$ or supplement$)).tw.
6 (oil$ adj3 (cod$ or marin$ or rapeseed$ or canola$)).tw.
7 (omega-3 or omega3).tw.
8 (eicosapentaen$ or icosapentaen$).tw.
9 docosahexaen$.tw.
10 (Linolen$ or alpha-linolen$ or alphalinolen$).tw.
11 (maxepa$ or omacor$).tw.
12 (trout or kipper$ or salmon or mackerel$ or tuna or tunafish or sardine$ or pilchard$ or herring$).tw.
13 flax$.tw.
14 rapeseed$.tw.
15 canola$.tw.
16 alphalinolen$.tw.
17 perilla$.tw.
18 linolen$.tw.
19 linseed$.tw.
20 maxepa$.tw.
21 (oil$ adj3 colza).tw.
22 (marin$ adj3 (lipid$ or oil$)).tw.
23 naudicelle$.tw.
24 sild.tw.
25 (clupe$ adj3 hareng$).tw.
26 whitebait$.tw.
27 sprat$.tw.
28 brisling$.tw.
29 (salmo adj3 trut$).tw.
30 bloater.tw.
31 scomb$.tw.
32 conger$.tw.
33 tunny.tw.
34 tuna-fish.tw.
35 thunnus$.tw.
36 swordfish$.tw.

37 xiphias$.tw.
38 dogfish.tw.
39 scyliorhinus$.tw.
40 (crab or crabs).tw.
41 (cancer adj3 pagurus).tw.
42 (laks or lax).tw.
43 exp Flax/
44 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
45 randomized controlled trial.pt.
46 controlled clinical trial.pt.
47 randomized.ab.
48 placebo.ab.
49 clinical trials as topic.sh.
50 randomly.ab.
51 trial.ti.
52 50 or 47 or 51 or 46 or 45 or 48 or 49
53 (animals not (human and animals)).sh.
54 52 not 53
55 44 and 54
56 (20$ not (2000$ or 2001$)).ed.
57 55 and 56
This search strategy updated the previous searches run in 2002.

1b Searches run in July 2016 and April 2017

The searches in 1a have been updated and re-run to identify any records added to the databases since the last search. Date limits have been applied to the terms from the original strategies so that only new records will be found, but no date limits have been applied to the newly added terms. The RCT filter for MEDLINE is the Cochrane sensitivity and precision-maximising RCT filter, and for Embase, terms as recommended in the Cochrane Handbook have been applied (Lefebvre 2011).

CENTRAL
#1 MeSH descriptor: [Fish Oils] explode all trees
#2 MeSH descriptor: [Linseed Oil] this term only
#3 MeSH descriptor: [Linolenic Acids] this term only
#4 MeSH descriptor: [Fatty Acids, Omega-3] explode all trees
#5 (fish near/3 oil*)
#6 (oil* near/3 (cod* or marin*))
#7 (omega-3 or omega3 or (omega* near/5 fat*))
#8 eicosapentaen*
#9 docosahexaen*
#10 (oil* near/3 (flax* or rapeseed* or canola*))
#11 (Linolen* or alpha-linolen* or alphalinolen*)
#12 (perilla* or linseed* or maxepa*)

#13 (oil* near/3 (rape or colza))
#14 (marin* near/3 lipid*)
#15 (naudicelle* or herring* or sild)
#16 (clupe* near/3 hareng*)
#17 (whitebait or sardine* or sardina* or pilchard* or sprat* or brisling*)
#18 (salmo* near/3 trut*)
#19 (trout or bloater or kipper* or salmon or mackerel* or scomb* or conger* or tuna or tunny or tunafish or tuna-fish)
#20 (thunnus* or swordfish* or xiphias* or dogfish or scyliorrhinus*)
#21 (crab or crabs or (cancer pagarus))
#22 (DHA or EPA)
#23 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 Publication Year from 2002 to 2016
#24 MeSH descriptor: [Salmoniformes] explode all trees
#25 MeSH descriptor: [Tuna] this term only
#26 MeSH descriptor: [alpha-Linolenic Acid] this term only
#27 MeSH descriptor: [Flax] this term only
#28 (fish near/3 (diet* or capsul* or nutrit* or supplement*))
#29 (icosapentaen* or docosapentaen*)
#30 (oil* near/3 (purslane or mustard* or candlenut* or stillingia or walnut*))
#31 (laks or lax)
#32 (ALA or DPA)
#33 (algal near oil*)
#34 #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33
#35 #23 or #34

MEDLINE Ovid
1. exp Fish Oils/
2. Linseed Oil/
3. linolenic acids/ or alpha-linolenic acid/
4. Flax/
5. exp Fatty Acids, Omega-3/
6. (fish adj3 (diet* or nutrit* or oil* or supplement*)).ti,ab.
7. (oil* adj3 (cod* or marin*)).ti,ab.
8. (omega-3 or omega3 or (omega* adj5 fat*)).ti,ab.
9. eicosapentaen*.ti,ab.
10. docosahexaen*.ti,ab.
11. (oil* adj3 (flax* or rapeseed* or canola*)).ti,ab.
12. (Linolen* or alpha-linolen* or alphalinolen*).ti,ab.
13. (perilla* or linseed* or maxepa*).ti,ab.
14. (oil* adj3 (rape or colza)).ti,ab.
15. (marin* adj3 lipid*).ti,ab.
16. (naudicelle* or herring* or sild).ti,ab.
17. (clupe* adj3 hareng*).ti,ab.
18. (whitebait or sardine* or sardina* or pilchard* or sprat* or brisling*).ti,ab.
19. (salmo* adj3 trut*).ti,ab.
20. (trout or bloater or kipper* or salmon or mackerel* or scomb* or conger* or tuna or tunny or tunafish or tuna-fish).ti,ab.
21. (thunnus* or swordfish* or xiphias* or dogfish or scyliorrhinus* or laks or lax).ti,ab.
22. (crab or crabs or cancer pagarus).ti,ab.
23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24. randomized controlled trial.pt.

25. controlled clinical trial.pt.
26. randomized.ab.
27. placebo.ab.
28. clinical trials as topic.sh.
29. randomly.ab.
30. trial.ti.
31. 24 or 25 or 26 or 27 or 28 or 29 or 30
32. exp animals/ not humans.sh.
33. 31 not 32
34. 23 and 33
35. limit 34 to ed=20020201-20160721
36. exp salmoniformes/ or tuna/
37. (fish adj3 capsul*).ti,ab.
38. icosapentaen*.ti,ab.
39. docosapentaen*.ti,ab.
40. (oil* adj3 (purslane or mustard* or candlenut* or stillingia or walnut*)).ti,ab.
41. 36 or 37 or 38 or 39 or 40
42. 33 and 41
43. 35 or 42

Embase Ovid

1. exp salmoniformes/ or tuna/
2. fish oil/
3. linseed oil/
4. linolenic acid/
5. Flax/
6. omega 3 fatty acid/
7. (fish adj3 (diet* or nutrit* or oil* or supplement*)).ti,ab.
8. (oil* adj3 (cod* or marin*)).ti,ab.
9. (omega-3 or omega3 or (omega* adj5 fat*)).ti,ab.
10. (eicosapentaen* or icosapentaen*).ti,ab.
11. docosahexaen*.ti,ab.
12. (oil* adj3 (flax* or rapeseed* or canola*)).ti,ab.
13. (Linolen* or alpha-linolen* or alphalinolen*).ti,ab.
14. (perilla* or linseed* or maxepa*).ti,ab.
15. (marin* adj3 lipid*).ti,ab.
16. (naudicelle* or herring* or sild).ti,ab.
17. (clupe* adj3 hareng*).ti,ab.
18. (whitebait or sardine* or sardina* or pilchard* or sprat* or brisling*).ti,ab.
19. (salmo* adj3 trut*).ti,ab.
20. (trout or bloater or kipper* or salmon or mackerel* or scomb* or conger* or tuna or tunny or tunafish or tuna-fish).ti,ab.
21. (thunnus* or swordfish* or xiphias* or dogfish or scyliorrhinus* or laks or lax).ti,ab.
22. (crab or crabs or (cancer adj3 pagarus)).ti,ab.
23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24. random$.tw.
25. placebo$.tw.
26. (doubl$ adj blind$).tw.
27. (singl$ adj blind$).tw.
28. double blind procedure/
29. randomized controlled trial/
30. single blind procedure/

31. 24 or 25 or 26 or 27 or 28 or 29 or 30
32. (animal/ or nonhuman/) not human/
33. 31 not 32
34. 23 and 33
35. (2002* or 2003* or 2004* or 2005* or 2006* or 2007* or 2008* or 2009* or 2010* or 2011* or 2012* or 2013* or 2014* or 2015* or 2016*).dd,em.
36. 34 and 35
37. exp salmonine/
38. (fish adj3 capsul*).ti,ab.
39. docosapentaen*.ti,ab.
40. (ALA or DHA or DPA or EPA).ti,ab.
41. (algal adj oil*).ti,ab.
42. 37 or 38 or 39 or 40 or 41
43. 33 and 42
44. 36 or 43

1c. Searches run in July and September 2016, and April 2017 for allied reviews

These searches have each been run from database inception, due to the widening of the inclusion criteria, then de-duplicated with each other. The RCT filter for MEDLINE is the Cochrane sensitivity and precision-maximising RCT filter, and for EMBASE, terms as recommended in the Cochrane Handbook have been applied (Lefebvre 2011).

CENTRAL
#1 MeSH descriptor: [Fatty Acids, Essential] explode all trees
#2 MeSH descriptor: [Fatty Acids, Unsaturated] this term only
#3 ((polyunsaturat* or poly-unsaturat*) near/3 fat*)
#4 (poly* adj4 unsat* near/4 fatty acid*)
#5 PUFA
#6 MeSH descriptor: [Fatty Acids, Omega-6] explode all trees
#7 omega-6
#8 (n-6 near/4 acid*) or ("n 6" near/4 acid*)
#9 linoleic acid*
#10 MeSH descriptor: [Corn Oil] this term only
#11 MeSH descriptor: [Cottonseed Oil] this term only
#12 MeSH descriptor: [Olive Oil] this term only
#13 MeSH descriptor: [Safflower Oil] this term only
#14 MeSH descriptor: [Sesame Oil] this term only
#15 MeSH descriptor: [Soybean Oil] this term only
#16 ((corn or maize or mazola) near/4 oil*)
#17 (cottonseed* or (cotton next seed*))
#18 (olive near/4 oil*)
#19 (safflower near/4 oil*)
#20 (sesame near/4 oil*)
#21 ((soy bean or soybean) near/4 (oil* or fat*))
#22 (so?a near/4 oil*)
#23 so?aoil*
#24 (soy near/4 oil*)
#25 (sunflower near/4 oil*)
#26 helianth*
#27 (grapeseed near/4 oil*)
#28 (canola near/4 oil*)

#29 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28

MEDLINE Ovid

1. exp fatty acids, essential/
2. fatty acids, unsaturated/
3. ((polyunsaturat* or poly-unsaturat*) adj3 fat*).ti,ab.
4. (poly* adj4 unsat* adj4 fatty acid*).ti,ab.
5. PUFA.ti,ab.
6. exp fatty acids, omega-6/
7. omega-6.ti,ab.
8. (n-6 adj4 acid*).ti,ab.
9. linoleic acid*.ti,ab.
10. corn oil/ or cottonseed oil/ or olive oil/ or safflower oil/ or sesame oil/ or soybean oil/
11. ((corn or maize or mazola) adj4 oil*).ti,ab.
12. (cottonseed* or (cotton adj seed*)).ti,ab.
13. (olive adj4 oil*).ti,ab.
14. (safflower adj4 oil*).ti,ab.
15. (sesame adj4 oil*).ti,ab.
16. ((soy bean or soybean) adj4 (oil* or fat*)).ti,ab.
17. (so?a adj4 oil*).ti,ab.
18. so?aoil*.ti,ab.
19. (soy adj4 oil*).ti,ab.
20. (sunflower adj4 oil*).ti,ab.
21. helianth*.ti,ab.
22. (grapeseed adj4 oil*).ti,ab.
23. (canola adj4 oil*).ti,ab.
24. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. randomized controlled trial.pt.
26. controlled clinical trial.pt.
27. randomized.ab.
28. placebo.ab.
29. clinical trials as topic.sh.
30. randomly.ab.
31. trial.ti.
32. 25 or 26 or 27 or 28 or 29 or 30 or 31
33. exp animals/ not humans.sh.
34. 32 not 33
35. 24 and 34

Embase Ovid

1. exp essential fatty acid/
2. unsaturated fatty acid/ or docosapentaenoic acid/ or omega 6 fatty acid/ or polyunsaturated fatty acid/
3. ((polyunsaturat* or poly-unsaturat*) adj3 fat*).ti,ab.
4. (poly* adj4 unsat* adj4 fatty acid*).ti,ab.
5. PUFA.ti,ab.
6. omega-6.ti,ab.
7. (n-6 adj4 acid*).ti,ab.
8. linoleic acid*.ti,ab.
9. edible oil/ or canola oil/ or corn oil/ or cotton seed oil/ or olive oil/ or safflower oil/ or safflower oil plus soybean oil/ or sesame seed oil/ or soybean oil/ or sunflower oil/

10. ((corn or maize or mazola) adj4 oil*).ti,ab.
11. (cottonseed* or (cotton adj seed*)).ti,ab.
12. (olive adj4 oil*).ti,ab.
13. (safflower adj4 oil*).ti,ab.
14. (sesame adj4 oil*).ti,ab.
15. ((soy bean or soybean) adj4 (oil* or fat*)).ti,ab.
16. (so?a adj4 oil*).ti,ab.
17. so?aoil*.ti,ab.
18. (soy adj4 oil*).ti,ab.
19. (sunflower adj4 oil*).ti,ab.
20. helianth*.ti,ab.
21. (grapeseed adj4 oil*).ti,ab.
22. (canola adj4 oil*).ti,ab.
23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24. double blind procedure/
25. single blind procedure/
26. randomized controlled trial/
27. ((double* or single*) adj blind*).ti,ab.
28. (random* or placebo*).ti,ab.
29. 24 or 25 or 26 or 27 or 28
30. (animal/ or nonhuman/) not human/
31. 29 not 30
32. 23 and 31

Appendix 2. Characteristics of included studies

This table has been shortened for this version of the review, omitting details of outcomes, funding and risk of bias assessment. Not all of these studies are relevant to the remaining chapters – they may have been included for use in chapters not included in this version of the report.

ADCS-Quinn 2010

Methods	Alzheimer's Disease Cooperative Study (ADCS) RCT, parallel, (n3 DHA vs n6 LA), 18 months Summary risk of bias: Low
Participants	Individuals with mild to moderate Alzheimer disease. N: 238 int., 164 control. Level of risk for CVD: Low Male: 52.9% int., 40.2% control. Mean age (SD): 76 (9.3) int., 76 (7.8) control Age range: unclear Smokers: 24.4% int., 21.9% control Hypertension: NR Medications taken by at least 50% of those in the control group: Cholinesterase inhibitor, Memantine Medications taken by 20-49% of those in the control group: None Medications taken by some, but less than 20% of the control group: None Location: USA Ethnicity: NR
Interventions	Type: supplement (capsule) Comparison: DHA vs omega 6 Intervention: 2x 1g algal-derived DHA capsules (Neuromins) per day for a total daily dose of 2g, each capsule contain 45% to 55% of DHA and does not contain EPA (950 mg soft-gel capsules that contain approximately 510 mg DHA): DHA 1.02g/d. Control: 2x 1g Placebo capsules per day (made up of corn or soy oil). Compliance: measured by pill counts at every visit. Length of intervention: 18 months

AFFORD 2014

Methods	Multi-centre Study to Evaluate the Effect of N-3 Fatty Acids on Arrhythmia Recurrence in Atrial Fibrillation (AFFORD) RCT, parallel, (n3 EPA+DHA vs n6), 12 months Summary risk of bias: Moderate or high
Participants	People with symptomatic paroxysmal or persistent AF N: 165 int., 172 control. (analysed, int: 153 cont: 163) Level of risk for CVD: High Male: 69% int., 65% control. Mean age (SD): 60 (12) int., 62 (13) control Age range: NR Smokers: NR Hypertension: 45% int, 42% cont Medications taken by at least 50% of those in the control group: oral anticoagulant Medications taken by 20-49%: beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers Medications taken by some, but <20%: None Location: Canada Ethnicity: NS

Interventions	Type: supplement (fish oil) Comparison: EPA & DHA vs omega 6 safflower oil Intervention: 4x 1g enteric-coated fish oil capsules/d (1.6g/d EPA + 0.8g/d DHA, Genuine Health, Toronto, Ontario, Canada): EPA+DHA 2.4g/d Control: 4x1g matching placebo capsules, 4g/d safflower oil. Compliance: Omega 3 index increased in intervention group, but not control, over the study Duration of intervention: 6 to 16 months

Ahn 2016

Methods	RCT, parallel, (EPA+ DHA + statins vs statins), 12 months Summary risk of bias:
Participants	Statin treated CAD patients undergoing PCI N: 38 int., 36 control. Level of risk for CVD: High Male: 63.2% int., 72.2% control. Mean age (SD): 59.6(9.1) int., 60.7 (0.8) sic control Age range: unclear Smokers: 36.8% int., 58.3% control Hypertension: 50% in both groups Medications taken by at least 50% of those in the control group: Aspirin, Clopidogrel, ACEi/ARB, Beta blockers, atorvastatin Medications taken by 20-49% of those in the control group: Cilostazol Medications taken by some, but less than 20% of the control group: rosuvastatin, Nitrates, Calcium antagonists. Location: South Korea Ethnicity: NR
Interventions	Type: supplement (capsule) Comparison: EPA+DHA vs unclear (nil) Intervention: 3 g of ω-3 PUFA containing 1395 mg of EPA and 1125 mg of DHA per day. No further details. Control: unclear whether control group were given placebo or only statins. Compliance: unclear how it was measured but reported good compliance with no numbers. Length of intervention: 12 months

Almallah 1998

Methods	Pilot 2 arm double-blind RCT, placebo controlled (n3 EPA+DHA vs n6 LA), 6 months Summary risk of bias: Moderate to high
Participants	Individuals with ulcerative colitis with only distal disease (to enable assessment via sigmoidoscopy) attending the outpatients clinic. No participant was on steroids before starting supplementation. All were taking a standard western diet and were identified as having UC via rectal biopsy. N: 9 int., 9 control (analysed – int: 9 cont: 9) Level of risk for CVD: Low Male: 44.4% int., 55.6% control. Mean age (SD): 54 int.; 41 cont. (SD not reported) Age range: 29-64 int., 32-74 cont. Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: Sulphasalazine, mesalazine (for ethical reasons patients were maintained on their existing long-term medication with either preparation) Medications taken by 20-49% of those in the control group: Medications taken by some, but less than 20% of the control group Location: Scotland Ethnicity: NR
Interventions	Type: supplement (food: fish oil or sunflower oil) Comparison: EPA+DHA vs MUFA/n6 FA Intervention: 15mls/day fish oil (including 3.2g/d EPA + 2.4g/d DHA; supplied by Callanish Ltd, Isle of Lewis, Scotland): EPA+DHA 5.6g/d

Control: 15mls/day sunflower oil (including 2.6g oleic acid and 7.9g linoleic acid; supplied by Callanish Ltd, Isle of Lewis, Scotland)
Compliance: used bottles of oil counted but data not provided; no FA status data.
Duration of intervention: 6 months

AlphaOmega - ALA

Methods

RCT, (n3 ALA vs MUFA), 40 months
Summary risk of bias: Low

Participants

60-80 year olds with previous MI
N: 1197 ALA int., 1236 control (1212 ALA + EPA/DHA intervention group)
Level of risk for CVD: High.
Male: 77.9% int., 78.7% control
Mean age (SD): 69.0 (5.6) int., 68.9 (5.6) control.
Age range: 60-80 years
Smokers: 17.4% int., 18% control.
Hypertension: Unclear
Medications taken by at least 50% of those in the control group: lipid lowering medication, antihypertensives, antithrombotics.
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: antiarrhythmic drugs, antidiabetic drugs.
Location: The Netherlands
Ethnicity: NR

Interventions

Type: Supplementary margarine
Comparison: ALA vs MUFA
Intervention 20g of enriched margarine per day incorporating: 2g ALA.
8x250g margarine tubs delivered every 12 weeks: ALA 2g/d
Control: 20g of margarine per day. No additional n-3 PUFAs. Identical margarine (oleic acid) placebo.
Compliance: Unused margarine tubs were returned- daily intakes of margarine and n-3 fatty acids were calculated based on the amount unused. Adherence was measured by levels of fatty acids in plasma cholesteryl esters, margarine and questionnaires. 90.5% of patients adhered to the protocol and consumed 20.6 (2.8) g of margarine/d.
Length of intervention: 40 months.

AlphaOmega - EPA+DHA

Methods

RCT, (n3 EPA+DHA vs MUFA), 40 months
Summary risk of bias: Low

Participants

60-80 year olds with previous MI.
N: 1192 EPA/DHA int., 1236 control (1212 ALA + EPA/DHA intervention group)
Level of risk for CVD: High
Male: 78.1% int., 78.7% control.
Mean age (SD): 69.1 (5.6) int., 68.9 (5.6) control
Age range: 60-80 years
Smokers: 16.8%, int., 18% control.
Hypertension: Unclear
Medications taken by at least 50% of those in the control group: lipid lowering medication, antihypertensives, antithrombotics.
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: antiarrhythmic drugs, antidiabetic drugs.
Location: The Netherlands
Ethnicity: NR

Interventions

Type: Supplementary Margarine
Comparison 1: EPA & DHA vs MUFA
Intervention 20g of enriched margarine per day incorporating 400mg EPA-DHA (240mg/d EPA and 160mg/d DHA): EPA+DHA 0.4g/d
Control: 20g of margarine per day. No additional n-3 PUFAs. Identical margarine (oleic acid) placebo.

Compliance: Unused margarine tubs were returned- daily intakes of margarine and n-3 fatty acids were calculated on the basis of the amount unused. Adherence was measured by levels of fatty acids in plasma cholesteryl esters, margarine and questionnaires. 90.5% of patients adhered to the protocol.
Length of intervention: 40 months.

AREDS2 2014

Methods

Age-Related Eye Disease Study 2 (AREDS2)
RCT, parallel, 2x2 factorial (n3 EPA+DHA vs nil) also randomised to lutein and zeaxanthin vs nil, 5 years
Summary risk of bias: Moderate or high

Participants

People aged 50-85 at high risk of progression to advanced age-related macular degeneration (AMD).
N: 2147 Int (1068 DHA/EPA, 1079 DHA/EPA + Lutein/Zeaxanthin), 2056 control (1012 placebo, 1044 Lutein/Zeaxan)
Level of risk for CVD: Low (however ~20% had previous CV event)
Male: Int 42.1%, Cont 44.4%
Age: Int median 74.6 (IQR 11.1), Cont median 74 (IQR 11.1) years
Age range: 68-79 years
Smokers: Int 6.3%, Cont 7.2%
Hypertension: Unclear
Medications taken by at least 50% of those in the control group: Multivitamins
Medications taken by 20-49% of those in the control group: Cholesterol lowering drugs, aspirin
Medications taken by some, but less than 20% of the control group: NSAID, paracetamol
Location: USA
Ethnicity: White 96.5% int., 96.6% cont., Hispanic 2.6 int., 1.3 cont.

Interventions

Type: supplement (capsule)
Comparison: EPA & DHA vs nil
Intervention 350 mg/d DHA plus 650 mg/d EPA added to the standard AREDS supplement of Vitamin C (500mg/d), Vitamin E (440IU/d), beta-carotene (15mg/d), zinc oxide (80mg/d) and cupric oxide (2mg/d): EPA+DHA 1.0g/d
Control: standard AREDS supplement of Vitamin C (500mg/d), Vitamin E (400IU/d), beta-carotene (15mg/d), zinc oxide (80mg/d) & cupric oxide (2mg/d).
Compliance: Assessed by pill count - 84% of participants in each group took at least 75% of study medications
Length of intervention: 60 months.

Baldassarre 2006

Methods

RCT, (n3 EPA+DHA vs MUFA), 24 months
Summary risk of bias: Moderate or high

Participants

45-70 year olds with combined hypolipoproteinaemia
N: 32 int., 32 control
Level of risk for CVD: Moderate.
Male: 29% int., 29% control
Mean age (SD): 53.7 (7.2) int., 53.7 (6.9) control.
Age range: 45-70 years (inclusion)
Smokers: 28.1% int., 28.1% control.
Hypertension: None (exclusion criteria)
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR. (Patients on HRT, anti-hypertensive drugs, lipid lowering drugs, or who smoked > 10 cigarettes were excluded)
Location: Italy
Ethnicity: NR

Interventions

Type: Capsules

Comparison: LCN3 vs MUFA
Intervention 1g x 6 soft gelatine capsules/ day of fatty acid mixture (19% EPA), 13% DHA, 19% palmitic acid, 18% oleic acid, 2% LA and 29% other minor components) providing 1.08g/d EPA, 0.72g/d DHA, 0.01g/d tocopherol acetate, divided to three doses: EPA+DHA 1.8g/d
Control: 1g x 6 opaque identical soft gelatine capsules/ day of olive oil divided to three doses.
Compliance: assessed by counting returned capsules at each visit and by measuring EPA and DHA levels at month 24
Length of intervention: 24 months.

Baleztena 2015

Methods

RCT, parallel, (n3 EPA+DHA assumed vs nil), 12 months
Summary risk of bias: Moderate to high

Participants

Population:
N: NR int., NR control. (analysed, int: NR cont: NR), total given as 99
Level of risk for CVD: NR
Male: NR% int., NR% control. Overall given as 68%
Mean age (SD): NR int., NR control, overall given as 89.9(6.2)
Age range: 75 and above
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Spain
Ethnicity: NR

Interventions

Type: omega-3 supplement (capsule)
Comparison: Omega-3 vs placebo (empty gelatine capsule)
Intervention: omega-3 supplement (0.35g n-3 capsule, 3 times daily): EPA+DHA 1.05g/d (probably)
Control: placebo (empty gelatine capsule)
Compliance: NR
Duration of intervention: 12 months

Balfego 2016

Methods

RCT, parallel, (n3 fish vs mixed fats), 6 months
Summary risk of bias: Moderate or high

Participants

Drug-naive patients with type 2 diabetes
N: 19 int., 16 control. (analysed, int: 17 cont: 15)
Level of risk for CVD: Moderate
Male: 42.1% int., 50.0% control.
Mean age (SD): 60 (7.41) int., 61.2 (9.6) control
Age range: Inclusion 40-70 years
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: Statins, beta blockers
Location: Spain
Ethnicity: NR

Interventions

Type: supplemented food (sardine-enriched or not)
Comparison: omega-3 vs lower omega-3
Intervention: Standard diet for type 2 diabetes enriched with sardines plus dietary advice
Control: Standard diet for type 2 diabetes plus dietary advice
Compliance: Erythrocyte omega-3 index; and 3-d food record and food frequency questionnaire
Duration of intervention: 6 months

Bates 1989

Methods	RCT, parallel, (n3 EPA+DHA vs MUFA), 24 months Summary risk of bias: Moderate or high
Participants	People with multiple sclerosis N: 155 int., 157 control. (analysed, int: 145 cont: 147) Level of risk for CVD: Low Male: 34.2% int., 30.6% control. Mean age (SD): 34.0 (6.6) int., 33.7 (6.3) control Age range: NR but 16-45 years inclusion criteria Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49%: NR Medications taken by some, but <20%: NR Location: UK Ethnicity: NR
Interventions	Type: supplement (fish oil capsule) Comparison: EPA & DHA vs MUFA Intervention: 20x0.5g/d capsules MaxEPA fish body oil (10g/d fish oil providing 1.71g/d EPA +1.14g/d DHA +10IU/d vitamin E), plus all advised to reduce animal fat and ensure plentiful omega 6 fats: EPA+DHA 2.85g/d Control: 20x0.5g/d capsules olive oil (10g/d olive oil), plus all advised to reduce animal fat and ensure plentiful omega 6 fats. All capsules contained 0.5IU vitamin E & 100 ppm dodecylgallate to minimise peroxide formation. Compliance: serum EPA and DHA rose in intervention group but fell in controls Duration of intervention: 24 months (5 years mentioned but outcomes not reported)

Baxheinrich 2012

Methods	RCT, parallel, (n3 ALA vs MUFA), 6 months Summary risk of bias: Moderate or high
Participants	Participants with metabolic syndrome N: 47 int., 48 control. (analysed, int: 40 cont: 41) Level of risk for CVD: Moderate Male: 32.10% in both groups combined Mean age (SD): 52.3 (10.6) int., 50.3 (9.8) control Age range: NR Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: Germany Ethnicity: NR
Interventions	Type: supplement (advice to consume hypoenergetic diet with rapeseed oil or olive oil) Comparison: ALA vs MUFA Intervention: Rapeseed oil (Brokelmann) and a rapeseed-based margarine (Othuna): ALA 3.5g/d Control: Olive oil (including <1g/d ALA, Lamotte Oils) Compliance: Dietary record Duration of intervention: 6 months

Belch 1988

Methods	3 parallel arm placebo-controlled RCT (n6 GLA vs n6 GLA + n3 EPA vs nil), 12 months Summary risk of bias: Moderate to high
Participants	People with classical or definite RA as defined by the American Rheumatism Association criteria.

N: 16 int.1 (EPO), 15 int.2 (EPO+ fish oil), 18 cont. (analysed: int.1:16; int.2:15; cont: 18)
Level of risk for CVD: Low
Male: 6.25% int.1, 26.6% int.2, 5.5% control.
Median age: 46 int.1, 53 int.2, 48 control
Age range: 35-68 int.1, 28-73 int.2, 30-74 cont.
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NSAIDs (All patients required first-line NSAID therapy for symptom control but none were severe enough to warrant second line therapy)
Location: UK
Ethnicity: NR

Interventions

Type: supplement (capsules with evening primrose oil, evening primrose oil + fish oil or liquid paraffin)
Comparison: more GLA or GLA+EPA vs mineral oil
Intervention 1: 12 capsules containing EPO (540mg/d GLA + 120mg/d vitamin E) :GLA 0.54g/d
Intervention 2: 12 capsules containing EPO+EPA (450mg/d GLA + 240mg/d EPA + 120mg/d vitamin E): EPA 0.24g/d plus GLA 0.45g/d
Control: 12 capsules/d containing liquid paraffin + 120mg/d vitamin E
Compliance: erythrocyte fatty acid levels checked at 0, 6 & 12m but not published
Duration of intervention: 12 months

Belluzzi 1996

Methods

RCT, double blind, parallel, placebo controlled (fn3 EPA+DHA vs mixed fat MCT), 12 months
Summary risk of bias: Low

Participants

Individuals with established diagnosis of Crohn's Disease in clinical remission
N: 39 int., 39 control. (analysed – primary outcome, int: 34 cont: 37)
Level of risk for CVD: Low
Male: 51.3% int., 48.7% control.
Mean age (SD): NR. Median age: 34 int., 39 control
Age range: 18-67 int., 20-65 control
Smokers: 35.9% int., 33.33% control
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Italy
Ethnicity: NR
% with diseased small bowel: 51.3% int., 51.3% control
% with diseased colon: 12.8% int., 10.3% control
% with small and large bowel disease: 35.9% int., 38.5% control

Interventions

Type: supplement (capsules with EPA+DHA or capric/caprylic acid)
Comparison: EPA+DHA vs SFA
Intervention: 9x500mg capsules per day (including 1.8g/d EPA + 0.9g/d DHA; Purepa, Tillotts Pharma, Switzerland): EPA+DHA 2.7g/d
Control: 9x500mg capsules per day (including 1.8g/d capric acid + 2.7g/d caprylic acid, types of MCT; Myglyol 812, Dynamit Nobel Chemicals, Germany)
Compliance: capsule count, adiposity (RBCs)
Duration of intervention: 12 months

Berbert 2005

Methods

3x parallel arm, placebo-controlled RCT (n3 EPA+DHA vs n6 LA), 24 weeks/6 months
Summary risk of bias: moderate-high

Participants

People with rheumatoid arthritis according to the American College of Rheumatology criteria.

	N: 18 int., 17 control. (analysed: 13 int., 13 cont.) Level of risk for CVD: Low Male: 30.8% int., 15.4% control. Mean age (SD): 51 (13) int., 48 (10) control Age range: NR Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: One SAARD (slow-acting anti-rheumatic drug) Medications taken by 20-49% of those in the control group: NSAID & 2xSAARD Medications taken by some, but less than 20% of the control group: 3xSAARD Location: Brazil Ethnicity: NR
Interventions	Type: supplement (capsules containing EPA+DHA or soy oil) Comparison: EPA + DHA vs MUFA/n6 Intervention: 3g/d (20 capsules) containing 1.8g EPA & 1.2g DHA (total n3 PUFA 3g/d) manufactured by R>P Scherer do Brasil Encapsulacoes, Sao Paulo, Brazil: EPA+DHA 3.0g/d Control: soy oil (amount & encapsulation unspecified). Compliance: capsule count Duration of intervention: 24 weeks/6 months

Berson 2004

Methods	RCT, parallel, (n3 DHA vs n6 LA), 48 months Summary risk of bias: Moderate or high
Participants	People with retinitis pigmentosa aged 18-55. N: 221 randomised overall, analysed 105 int., 103 control Level of risk for CVD: Low Male: 48% int., 54% control. Mean age (SD): 37.8 (6.5) int., 36.0 (7.2) control Age range: unclear (18-55 inclusion criterion) Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: vitamin A Medications taken by 20-49% of those in the control group: multivitamins Medications taken by some, but less than 20% of the control group: NR Location: USA Ethnicity: unclear (6% of the study population were minorities).
Interventions	Type: supplement (DHA capsules) Comparison: DHA vs omega 6 Intervention: 6x500mg capsules/d of DHA (1.2g/d DHA plus 1.8g vegetable oil) plus <0.0006mg/d tocopherols plus 15000IU retinyl palmitate (vitamin A): DHA 1.2g/d Control: 6x500mg capsules/d of soy and corn oils (half each) with 120mg/d ALA, plus <0.0006mg/d tocopherols plus 15000IU retinyl palmitate (vitamin A) Compliance: 92% of capsules taken by both intervention and control groups (assessed by monthly calendars), Plasma DHA much higher in intervention than control Length of intervention: 48 months

Bo 2017

Methods	RCT, parallel, (n3 EPA+DHA vs MUFA), 6 months Summary risk of bias: Moderate or high
Participants	Older adults with mild cognitive impairment N: 44 int., 42 control. (analysed, int: 44 cont: 42) Level of risk for CVD: low Male: 59% int., 60% control. Mean age (SD) y: 71.8 (5.7) int., 70.5 (6.8) control Age range: NR but inclusion criteria were ≥60 years

Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: China
Ethnicity: NR

Interventions

Type: supplement
Comparison: EPA+DHA vs MUFA
Intervention: 4x1g capsules every nine days (each capsule contained 120 mg DHA & 180 mg EPA, Royal DSM Company of Holland, Shanghai, 480 mg/d DHA and 720 mg/d EPA): EPA+DHA 1.2g/d
Control: 4x1g isocaloric placebo olive oil capsules every nine days (each containing 550 mg of oleic acid)
Compliance: NR
Duration of intervention: 6 months

Boespflug 2016

Methods

RCT, parallel (n3 EPA+DHA vs n6 LA), 6 months
Summary risk of bias: moderate to high

Participants

Population: older adults with subjective memory impairment
N: 15 int., 12 control. (analysed, int: 11 cont: 10)
Level of risk for CVD: Low
Male: 45.5% int., 30.0% control.
Mean age (SD): 70.1 (6.12) int., 66.4 (3.75) control
Age range:62-80
Smokers: NR
Hypertension: 36.4% int., 40.0% control
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: USA
Ethnicity: NR

Interventions

Type: food supplement (fish oil with DHA +EPA)
Comparison: DHA + EPA vs n-6
Intervention: fish oil capsule (1.6g/d EPA + 0.8g/d DHA; 4 capsules/d): EPA+DHA 2.4g/d
Control: placebo (corn oil, no other information)
Compliance: NR but erythrocyte fatty acid composition was determined)
Duration of intervention: 6 months

Bonnema 1995

Methods

RCT, parallel, (n3 EPA+DHA vs MUFA), 6 months
Summary risk of bias: Moderate or high

Participants

Adults with insulin-treated diabetes and microalbuminuria
N: 14 int., 14 control. (analysed, int: 14 cont: 13)
Level of risk for CVD: moderate (diabetes)
Male: 57% int., 50% control.
Mean age (SD) years: 47 (16) int., 41 (12) control
Age range: NR
Smokers: 71% int., 57% control
Hypertension: 0% int., 0% control
Medications taken by at least 50% of those in the control group: insulin
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
(Diuretics allowed, and vasoactive and lipid lowering drugs prohibited)
Location: Denmark
Ethnicity: NR

Interventions

Type: supplement
Comparison: fish oil capsules vs olive oil capsules
Intervention: 6x1g fish oil capsules (Pikasol) daily (with conventional

diabetic diet) including 2g/d EPA plus 1.32g/d DHA: EPA+DHA 3.32g/d
Control: 6x1g olive oil capsules daily (with conventional diabetic diet)
Compliance: Capsule count, average daily consumption was >95% expected amount
Duration of intervention: 6 months

Brox 2001

Methods

RCT, parallel, 3 arms (n3 EPA+DHA from cod liver vs n3 EPA+DHA from seal oil vs nil), 14mo
Summary risk of bias: moderate or high

Participants

Subjects with moderate hypercholesterolemia
N: 40 seal oil (SO), 40 cod liver oil (CLO), 40 control (numbers analysed vary by outcome)
Level of risk for CVD: Moderate (dyslipidaemia)
Male: 53% seal oil, 50% cod liver oil, 48% control
Mean age, SD: 53.2 seal oil, 55.0 cod liver oil, 55.8 control
Age range: 43-66
Smokers: Unclear
Hypertension: Unclear
Medications taken by at least 50% of those in the control group: None allowed
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Norway
Ethnicity: NR

Interventions

Type: supplement (oil)
Comparison: EPA & DHA vs nil
Intervention: seal oil - 15 ml/d (2.6g, 1.1g/d EPA + 1.5/d DHA) (total n-3 3.9g/d, total PUFA 4.2g/d): EPA+DHA 2.6g/d
Cod liver oil - 15 ml/d (3.3g, 1.5g/d EPA + 1.8g/d DHA) (total n-3 4.1g/d, total PUFA 4.35g/d): EPA+DHA 3.3g/d
Control: nil, no supplement
Compliance: serum omega-3 fatty acids, rose from around 1 mmol/L to 2.4 (seal oil), 2.1 (cod liver oil) and 1.2 mmol/L (control)
Length of intervention: 14 months

Caldwell 2011

Methods

RCT, parallel, (n3 EPA+DHA or n6 LA), 12 months
Summary risk of bias: Moderate or high

Participants

Participants with non-cirrhotic NASH (non-alcoholic steatohepatitis)
N: 20 int., 21 control (analysed 17 int., 17 control).
Level of risk for CVD: Moderate
Male: 35.3% int., 41.2% control.
Mean age (SD): 46.4 (12.1) int., 47.2 (12) control
Age range: 25-72
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: USA
Ethnicity: Int.,100% Caucasian, Control 94.% Caucasian, 5.9% other.

Interventions

Type: supplement (capsule)
Comparison: EPA+DHA vs omega 6
Intervention: 3x 1g fish oil capsules/d (Nordic Natural) for a total 2.1g/d n3, each capsule contained 70% of n-3 (1050 mg EPA, 750 mg DHA & 300 mg other n-3): EPA+DHA 1.8g/d
Control: 3x 1g Identical placebo (soybean) capsules per day containing 8% fish oils.
Both groups had dietary counselling on caloric intake and physical activity
Compliance: unclear (measured n6-n3 ratio due to its link to hepatic lipid composition)

Length of intervention: 12 months

Chiu 2008

Methods

RCT, parallel, omega 3 supplements (n3 EPA+DHA vs MUFA), 6 months
Summary risk of bias: Moderate to high

Participants

pop: Older adults with Alzheimer's Disease or Mild Cognitive Impairment
N: 24 int., 22 control. (analysed, int: 17 cont: 12)
Level of risk for CVD: Low
Male: 35% int., 53.3% control.
Mean age (SD): 74 (NR) int., 76.5 (NR) control
Age range: 70.1-77.8 (int), 71.8-81.1 (control)
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Taiwan (Taipei City Psychiatric Center, Taipei City Hospital, Taipei)
Ethnicity: NR

Interventions

Type: Dietary supplement (capsule DHA + EPA)
Comparison: DHA & EPA vs olive oil
Intervention: Dietary supplement (180mg EPA + 120mg DHA/capsule), 3 capsules twice daily, total dosage of 1.08g/d EPA + 0.72g/d DHA: EPA+DHA 1.8g/d
Control: Olive oil (placebo), 3 capsules twice daily containing olive oil esters.
Compliance: 92.4%, intervention; 81.8%, control
Duration of intervention: 6 months

Chiu 2010

Methods

RCT, parallel, (n3 DHA+EPA vs MUFA), 11 months (48 weeks)
Summary risk of bias: Moderate or high

Participants

pop: older people with Late-Life Depression
N: NR int., NR control. (analysed, int: NR cont: NR), total number reported to be recruited on the trial register is 89
Level of risk for CVD: low
Male: NR int., NR control.
Mean age (SD): x (y) int., z (a) control
Age range: 60 years old or over;
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Taiwan
Ethnicity: NR

Interventions

Type: omega-3 dietary supplement
Comparison: omega-3 vs placebo olive oil)
Intervention: Three capsules per day. Each capsule included 600mg EPA (20:5n-3), 400 mg of DHA (22:6n-3), tertiary-butylhydroquinone 0.2 mg/g and tocopherols 2 mg/g, totalling 1.8g/d EPA plus 1.2g/d DHA: EPA+DHA 3.0g/d
Control: placebo capsules containing olive oil.
Compliance: NR
Duration of intervention: 11 months (48 weeks)

Clark 2016

Methods

RCT, parallel, (n3 EPA+DHA vs n6 LA), 9 months
Summary risk of bias: Moderate or high

Participants

Adults with impaired glucose metabolism or type 2 diabetes mellitus
N: 36 randomised (not specified by arm) (analysed, int: 16 cont: 17)

Level of risk for CVD: Low
Male: 63% int., 59% control.
Mean age (SD): 61.8 (NR) int., 58.1 (NR) control
Age range: 52-67 int, 51-68 cont, years
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Non-steroidal anti-inflammatory medication and diabetic medications were not allowed, statins were allowed (but unclear how many used them)
Location: Scotland, UK
Ethnicity: NR

Interventions

Type: supplement (capsule)
Comparison: fish oil vs maize oil
Intervention: 6g/d fish oil from menhaden & pacific herring as 6x1g EPAX 6000 TG (EPAX AS), 3.9g/d omega 3: EPA+DHA 3.9g/d
Control: 6g/d as 6x1g maize oil (<2% EPA+DHA)
Compliance: monthly capsule count plus phospholipid composition of erythrocyte membranes
Duration of intervention: 9 months

Connor 1993

Methods

RCT, cross-over, (n3 EPA+DHA vs MUFA), 12 months
Summary risk of bias: Moderate or high

Participants

Participants with non-insulin dependent diabetes and hypertriglyceridemia
N: 16 int., 16 control. (analysed, int: 16 cont: 16)
Level of risk for CVD: Moderate
Male: NR
Mean age (SD): 58.7 (7.8) in both groups combined
Age range: 46-72 years overall
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: USA
Ethnicity: NR

Interventions

Type: supplement (fish oil or olive oil)
Comparison: EPA+DHA vs MUFA
Intervention: 15g fish oil/d (including 4.1g/d EPA and 1.9g/d DHA, Promegae, Parke David Warner Lambert): EPA+DHA 6.0g/d
Control: 15g olive oil/d (Perke David Warner Lambert)
Compliance: Plasma fatty acids
Duration of intervention: 2 consecutive 6 month periods of intervention or control

Darghosian 2015

Methods

RCT, double blind, parallel, placebo-controlled (n3 EPA+DHA vs n6 LA), 6 months
Summary risk of bias: medium-high

Participants

People with paroxysmal or persistent AF
N: 126 int., 64 control. (analysed, int: 126 cont: 64)
Level of risk for CVD: High
Male: 53% int., 66% control.
Mean age (SD): 62 (12) int., 61 (11) control
Age range: NR
Smokers: NR
Hypertension: 62% int., 69% control
Medications taken by at least 50% of those in the control group: beta-blocker (64%)
Medications taken by 20-49% of those in the control group: Class I agent

(23%), Solatol/ dofetilide (31%), Statin (44%), ACE inhibitor (25%), Warfarin (44%)
Medications taken by some, but less than 20% of the control group: Angiotensin receptor blocker (9%), Amiodarone (12%)
Location: USA
Ethnicity: int. 94% white, control 95% white

Interventions

Type: supplement (capsules containing EPA+DHA or corn oil)
Comparison: EPA + DHA vs SFA/MUFA
Intervention: 4g/d capsules containing 1.86g/d EPA & 1.5g/d DHA (total n3 PUFA 3.36g/d) manufactured as Lovaza by GlaxoSmithKline: EPA+DHA 3.36g/d
Control: 4g/day capsules containing corn oil, manufactured by GlaxoSmithKline. Identical in appearance to intervention.
Compliance: capsule count
Duration of intervention: 6 months

DART - Burr 1989

Methods

Diet And Reinfarction Trial (DART)
RCT - parallel, 2x2x2 factorial (n3 EPA+DHA vs nil or fat advice vs not, dietary fibre advice vs not), 2 years
Summary risk of bias: medium or high

Participants

Men recovering from myocardial infarction
N: 1015 int., 1018
Level of risk for CVD: High (post-MI)
Male: 100%
Mean age, SD: 56.7 int, 56.4 control (SDs not stated)
Age range: Unclear
Smokers: 61.7% int., 62.2% control
Hypertension: 22.7% int., 24.6% control
Medications taken by at least 50% of those in the control group: None reported
Medications taken by 20-49% : beta-blockers, other antihypertensives, antianginals
Medications taken by some, but <20%: anticoagulant, Asprin/antiplatelet, digoxin/antiarrhythmic
Location: UK
Ethnicity: not stated

Interventions

Type: dietary advice (to eat more oily fish)
Comparison: EPA & DHA vs nil
Intervention: Advised to eat at least 2 weekly portions of 200-400g fatty fish (mackerel, herring, kipper, pilchard, sardine, salmon, trout). If this was not possible, given MaxEPA capsules, 3/d (0.5g EPA/d). 191 of 883 participants were taking MaxEPA at 2 years. Advice was reinforced 3-monthly: EPA 0.5g/d
Control: No such dietary advice or capsules.
Compliance: 7 day weighed food diary of a random sub-sample indicated intake of 2.5g/week EPA int., 0.8g/week EPA control.
Length of intervention: 24 months

DART2 - Burr 2003

Methods

DART2
RCT, 2x2 (n3 EPA+DHA vs nil, also fruit, veg & oats vs no specific advice), 3-9 years
Summary risk of bias: Moderate or high

Participants

Men treated for angina
N: 1571 int., 1543 cont (all analysed for events)
Control Level of risk for CVD: High
Male: 100%
Mean age (SD): 61.1 (NR) int., 61.1 (NR) control
Age range: Unclear
Smokers: 25% int., 23% control
Hypertension: 49% int., 47% control

Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% : lipid lowering, beta-blockers
Medications taken by some, but less than 20% of the control group: NR
Location: UK
Ethnicity: NR

Interventions

Type: dietary advice (to eat more oily fish or take fish oil capsules)
Comparison: EPA & DHA vs nil
Intervention: Most (1109) advised to eat at least 2 weekly portions of fatty fish OR take MaxEPA capsules, 3/d (0.5g EPA/d). But 462 participants were sub-randomised to receive only fish oil capsules, not dietary fish advice: EPA 0.5g/d
Control: None specific sensible eating advice that did not include either of the interventions.
Compliance: Postal dietary questionnaire suggested dietary EPA intake increased by 2.4g /week int., 0.2g /week control
Duration of intervention: 36 to 108 months

Dasarathy 2015

Methods

RCT, parallel, (n3 EPA & DHA vs n6 LA), 11 months
Summary risk of bias: Moderate or high

Participants

NASH patients with type 2 diabetes
N: 18 int., 19 control. (analysed, int: 18 cont: 19)
Level of risk for CVD: Moderate
Male: 33.3% int., 10.5% control
Mean age (SD): 51.5 (6.9) int., 49.8 (12.1) control
Age range: NR
Smokers: NR
Hypertension: 94.4% int., 68.4% control
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: USA
Ethnicity: 94.4% Caucasian & 5.6% Black int., 89.5% Caucasian & 10.5% Hispanic in control

Interventions

Type: supplement (capsules with EPA+DHA or corn oil)
Comparison: EPA & DHA vs n6 LA
Intervention: 6 capsules/d “Opti-EPA” fish oil concentrate (including 2.16g/d EPA + 3.6g/d DHA, Douglas Laboratories): EPA+DHA 5.76g/d
Control: 6 capsules/d corn oil
Compliance: Pill counts and patient self-report
Duration of intervention: 48 weeks

Delamaire 1991

Methods

RCT, parallel, (n3 EPA+DHA vs n6 LA), 6 months
Summary risk of bias: Moderate or high

Participants

People with well-controlled insulin-dependent diabetes mellitus (DM)
N: 11 int., 17 control. (analysed, int: NR cont: NR)
Level of risk for CVD: Moderate
Male: NR
Mean age (SD): NR
Age range: NR
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: France
Ethnicity: NR

Interventions

Type: supplement
Comparison: MaxEPA vs peanut oil
Intervention: 4 capsules/d of MaxEPA (0.7g/d EPA + 0.5g/d DHA):

EPA+DHA 1.2g/d
Control: 4 capsules/d peanut oil
Compliance: NR
Duration of intervention: 6 months

Derosa 2009

Methods

RCT, parallel, (n3 EPA+DHA vs non-fat placebo), 6 months
Summary risk of bias: Moderate or high

Participants

Italian Caucasian adults with combined dyslipidaemia
N: 168 int., 164 control. (analysed, int: 165 cont: 162)
Level of risk for CVD: moderate
Male: 49% int., 50% control
Mean age (SD): 51.3 (7.2) int., 50.7 (6.8) control
Age range: unclear, but inclusion criteria were aged ≥18 years
Smokers: 22% int, 25% cont
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR (no participants were allowed to have taken or be taking medication that would influence lipid metabolism)
Location: Pravia & Bologna areas of Italy
Ethnicity: Caucasian

Interventions

Type: supplement
Comparison: omega 3 capsules vs sugar pills
Intervention: 1.125g/d EPA plus 1.875g/d DHA as ethylic esters, split over 3 meals (SPA Societa Produtti Antibiotici): EPA+DHA 3.0g/d
Control: pills of sucrose, mannitol and mineral salts, 3g/d split over 3 meals
Compliance: assessed by pill count returned at clinic visits, but compliance data not reported
Duration of intervention: 6 months

Derosa 2011

Methods

RCT, parallel, (n3 EPA+DHA vs non-fat placebo), 6 months
Summary risk of bias: Moderate or high

Participants

White adults with combined lipidaemia (raised total cholesterol and TG)
N: 84 int., 83 control (analysed 78 int., 79 control).
Level of risk for CVD: Moderate
Male: 49% int., 49% control.
Mean age (SD): 54.5 (7.0) overall, not given by arm
Age range: NR but inclusion criteria were 18-75 years
Smokers: 27% int., 31% control
Hypertension: 51.5% with history of hypertension (not given by arm)
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: ACE inhibitors, ARBs, calcium antagonists, beta-blockers, diuretics, alpha-blockers
Location: Italy
Ethnicity: White

Interventions

Type: Capsule (n-3 PUFA)
Comparison: EPA & DHA vs filler (non-fat)
Intervention: 3x1g capsule/ day n-3 PUFAs (ethyl esters, each 1-g capsule of n-3 PUFAs contains 85% n3 ethyl esters), total 1.2g/d EPA + 1.35g/d DHA plus controlled diet with 600kcal deficit, 50% CHO, 30% fat, 6% SFA, 20% protein, increased physical activity: EPA+DHA 2.55g/d
Control: placebo (capsule containing sucrose, mannitol and mineral salts magnesium stearate and silicon dioxide, used as anti-caking agents) plus controlled diet with 600kcal deficit, 50% CHO, 30% fat, 6% SFA, 20% protein, increased physical activity
Compliance: measured by counting the number of pills returned at the time of specified clinic visits, no data found

Length of intervention: 6 months

Derosa 2016

Methods
RCT, parallel, (n3 EPA+DHA vs non-fat placebo), 18 months
Summary risk of bias: Moderate or high

Participants
Caucasian overweight/obese patients with impaired fasting glucose or impaired glucose tolerance (IGT)
N: 138 int., 143 control (analysed 128 int., 130 control).
Level of risk for CVD: Low
Male: 50.72% int., 48.95% control.
Mean age (SD): 53.4 (11.2) int., 54.8 (12.1) control
Age range: unclear
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Italy
Ethnicity: Caucasian

Interventions
Type: Capsule (n-3 PUFA)
Comparison: EPA & DHA vs filler (non-fat)
Intervention: 3x1g capsule/ day n-3 PUFAs (ethylic esters, each 1-g capsule of n-3 PUFAs contains highly concentrated ethyl esters of omega-3 fatty acids, primarily eicosapentaenoic acid [EPA], and docosahexaenoic acid [DHA] in the proportion of 0.9–1.5), exact daily contents unclear, assume approx. 2.55g/d EPA+DHA
Control: placebo (a capsule containing sucrose, mannitol and mineral salts magnesium stearate and silicon dioxide, used as anti-caking agents)
Both groups were given diet advice to follow a controlled-energy diet based on (AHA) recommendations (50% of calories from carbohydrates, 30% from fat (6% saturated), and 20% from proteins, with a maximum cholesterol content of 300 mg/day and 35 g/day of fibre). Individuals were also encouraged to increase their physical activity by walking briskly for 20 to 30 Min, 3 to 5 times per week, or by cycling.
Compliance: measured by counting the number of pills returned at the time of specified clinic visits
Length of intervention: 18 months

Deslypere 1992

Methods
RCT 4 arms, (n3 EPA+DHA (3 different doses) vs MUFA), 12 months
Summary risk of bias: Moderate or high

Participants
Healthy monks
N: 14 high, 15 medium, 15 low dose int., 14 control
Level of risk for CVD: Low
Male: 100%
Mean age (SD): 56.2 (16.5) (not reported by arm).
Age range: 21-87
Smokers: None.
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR. (No medications influencing lipid metabolism or non-steroidal anti-inflammatory drugs were allowed)
Location: The Netherlands
Ethnicity: NR

Interventions
Type: Capsules
Comparison: LCN3 vs MUFA
Intervention 9 capsules (9g vol.) per day, of which 3, 6 or 9 were fish oil (Labaz, Brussels, Belgium) & any remainder were placebo (providing respectively 1.12g/d; 2.24g/d or 3.37g/d EPA+DHA)
Control: 9 placebo capsules made up of olive oil (Puget Marseille, France)

	and Palmoil (Loders-Kroklaan Wormerveen, the Netherlands) with the same SFA, cholesterol and vitamin E as the fish oil capsules. Compliance: assessed by counting remaining capsules every 2 months and by measuring EPA concentration. Excellent compliance reported and shown by the EPA concentration results. Length of intervention: 12 months.
DIPP-Tokudome 2015	
Methods	Dietary Intervention for Patients Polypectomised for tumours of the colorectum (DIPP) RCT, parallel, 4 arms (n3 EPA+DHA vs n3 ALA vs nil), 24 months Summary risk of bias: Moderate or high
Participants	Patients previously polypectomised for colorectal tumours N: 104 int., 101 control. Level of risk for CVD: Low Male: 73.1% int., 74.3% control. Mean age (SD): 58.3 (9.5) int., 59.7 (8.9) control Age range: 35-75 Smokers: 65.4% int., 61.4% control Hypertension: NR. Medications taken by at least 50% of those in the control group: Supplements Medications taken by 20-49% of those in the control group: None Medications taken by some, but less than 20% of the control group: Oral contraceptive pills Location: Japan Ethnicity: NR
Interventions	Type: advice plus supplement (fish oil capsules) Comparison: EPA & DHA vs ALA vs nil Intervention 1: advice to reduce total fat intake, decrease consumption of n-6 PUFAs, increase intake of n-3 PUFAs from fish/marine foods Intervention 2: advice to reduce total fat intake, decrease consumption of n-6 PUFAs, increase intake of n-3 PUFAs from perilla oil rich in ALA Intervention 3: advice to reduce total fat intake, decrease consumption of n-6 PUFAs, increase intake of n-3 PUFAs from eight capsules of fish oil/day (equivalent to 96 mg/day of EPA and 360 mg/day of DHA) Control: advice to decrease intake of fats/oils as a whole Compliance: measured via semi-quantitative food frequency questionnaire, plasma fatty acid concentrations, fatty acid compositions in the membranes of red blood cells and the sigmoid colon. Reported satisfactorily high compliance with protocol was noted in both groups but no figures. Length of intervention: 24 months
DISAFF - Harrison 2003	
Methods	Dietary Intervention Study for AF (DISAFF) RCT, parallel, 2 arms (n3 EPA+DHA vs nil), 12 months Summary risk of bias: Moderate or high
Participants	People presenting for first treatment of acute/persistent atrial fibrillation or flutter, confirmed by ECG N: Int 201, control 206 Level of risk for CVD: High (patients with atrial fibrillation) Male: Int 64.7%, Cont 63.6% Mean age (SD): Int 67.7 (9.4), Cont 68.7 (9.5) years Age range: unclear Smokers: Int 10.9%, Cont 12.1% Hypertension: Int 48.2%, Cont 40.8% Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: Antiarrythmics, antithrombotics Medications taken by some, but less than 20% of the control group: NR Location: UK Ethnicity: White British

Interventions	Type: Dietary advice Comparison: EPA & DHA vs nil Intervention: Dietary assistants gave advice and support to eat 2 to 3 portions of oily fish per week (providing up to 10g LCn3/ week), plus 2 to 3 portions of fruit & vegetables per day: EPA+DHA 1.4g/d Control: Dietary assistants gave advice and support to eat 2 to 3 portions of fruit & vegetables per day. No other health/lifestyle given as part of the trial. Compliance: Assessed red blood cell fatty acids and found some increases in EPA and DHA in intervention compared to control Length of intervention: 12 months.

DO IT - Einvik 2010

Methods	Diet and Omega 3 Intervention Trial on Atherosclerosis (DO IT) RCT, parallel, 2x2 factorial (n3 DHA+EPA vs n6 LA also dietary advice intervention), 36 months Summary risk of bias: Moderate or high
Participants	Elderly men with long standing dyslipidaemia or hypertension (a subset of Oslo Diet heart study) N: Int 282 (140 n-3 capsules + 142 n-3 capsules & dietary advice), Control 281 (142 placebo capsules + 139 placebo capsules & dietary advice) Level of risk for CVD: Moderate Male: Int 100%, Control 100% Mean age (SD): Int 70.4 (2.9), Control 69.7 (3.0) years Age range: 64-76 years Smokers: Int 35%, Control 33% Hypertension: Int 29%, Control 27% Medications taken by at least 50% of those in the control group: None Medications taken by 20-49% of those in the control group: statins and Acetylsalicylic acid. Medications taken by some, but less than 20% of the control group: βeta-blockers, ACE-inhibitors, and Nitrates. Location: Norway Ethnicity: NR
Interventions	Type: supplement/ capsule (also dietary advice as the factorial intervention) Comparison: EPA & DHA vs omega 6 Intervention: 2x2 capsules/d including 2.4g/d of omega 3 PUFA (Pikasol, 0.84g/d EPA plus 0.48g/d DHA plus 8.4mg/d tocopherols): EPA+DHA 1.32g/d Control: 2x2 capsules/d including 4g/d corn oil (2.24 g/d linoleic, 1.28g/d oleic acid, 16mg/d tocopherols) Compliance: pharmacy records suggested that >90% of supplements were taken, and plasma EPA and DHA were raised in intervention compared to control participants. Duration of intervention: 36 months.

Dodin 2005

Methods	RCT, parallel, (n3 ALA vs n6 LA), 12 months Summary risk of bias: Moderate or high
Participants	Healthy menopausal women N: 101 int., 98 control. (analysed, int: 85 cont: 94) Level of risk for CVD: Low Male: 0% int., 0% control. Mean age (SD): 54.0 (4.0) int., 55.4 (4.5) control Age range: 49-65 Smokers: 8% int., 6% control Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: Canada Ethnicity: French Canadian
Interventions	Type: food supplement (flaxseed)

Comparison: more ALA vs less ALA
Intervention: 40g/d flaxseed incorporated into diets (providing 21,071g total lignans, 180 calories, 16g lipids (57% ALA), and 11g total dietary fibre), 9.1g/d ALA
Control: 40g/d wheat germ incorporated into diets (providing 196g total lignans, 144 calories, 4g lipids (6.9% ALA), and 6g total dietary fibre
Compliance: first morning urine collection was performed at randomisation and at month 12 to measure urinary lignin levels. In addition, study participants recorded their daily intake of seeds on diary cards and were asked to return unused bread and packages of seeds at each visit. Good compliance reported
Duration of intervention: 12 months

Doi 2014

Methods

RCT, parallel, (n3 EPA vs nil), 12 months
Summary risk of bias: Moderate or high

Participants

Patients having PCI after acute MI
N: 119 int., 119 control analysed.
Level of risk for CVD: High
Male: 77% int., 76% control.
Mean age (SD): 70 (11) int., 71 (12) control
Age range: unclear
Smokers:28% int., 32% control
Hypertension: 71% int., 69% control.
Medications taken by at least 50% of those in the control group: Aspirin, Ticlopidine, b-blockers, statins (as part of treatment)
Medications taken by 20-49% of those in the control group: ARB/ ACE inhibitors
Medications taken by some, but less than 20% of the control group: None
Location: Japan
Ethnicity: NR

Interventions

Type: supplement (EPA)
Comparison: EPA vs nil
Intervention: Purified EPA ethyl esters (>98%) 1800mg EPA/day within 24 hours after PCI plus statins: EPA 1.8g/d
Control: statins with no EPA
Compliance: not reported.
Length of intervention: 12 months

Ebrahimi 2009

Methods

RCT, parallel, (n3 EPA+DHA vs nil), 6 months
Summary risk of bias: Moderate or high

Participants

People with metabolic syndrome
N: 60 int., 60 control. (analysed, int: 47 cont: 43)
Level of risk for CVD: moderate
Male: 15% int., 9% control.
Mean age (SD): 53.5 (12.7) int., 52.3 (11.1) control
Age range: NR but 40-70yrs inclusion criteria
Smokers: 4% int., 2% control
Hypertension: 32% int., 32% control
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: antihypertensives (14.3%), antidiabetic medication (16.7%)
Location: Iran
Ethnicity: NR

Interventions

Type: supplement
Comparison: EPA+DHA vs nil (no placebo)
Intervention: 1x1g capsule of fish oil/d (180mg/d EPA, 120mg/d DHA): EPA+DHA 3.0g/d
Control: nil, no placebo
Compliance: assessed by counting tablets at weekly visits and those who

did not take their capsules were excluded but unclear how many this was (and not feasible in control group)
Duration of intervention: 6 months

ELIA - Takaki 2011

Methods

RCT, parallel, (n3 EPA vs nil), 11 months
Summary risk of bias: Moderate or high

Participants

People with CAD and dyslipidaemia on statins
N: 25 int., 25 control. (analysed, int: 23 or 24 cont: 23 or 24)
Level of risk for CVD: high
Male: 84% int., 80% control.
Mean age (SD) y: 61.6 (5.6) int., 60.9 (7.0) control
Age range: NR but 20-70 years inclusion criteria
Smokers: 20% int., 24% control.
Hypertension: 56% int., 64% control.
Medications taken by at least 50% of those in the control group: statins (100%, inclusion criterion), antihypertensive agents (80%), antiplatelet agents (88%)
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: antidiabetic agents (16%)
Location: Japan
Ethnicity: NR

Interventions

Type: supplement
Comparison: EPA vs nil
Intervention: 1.8g/d EPA (no further details) plus statin treatment (from before trial) plus dietary advice (not specified): EPA 1.8g/d
Control: no placebo, only statin treatment (from before trial) plus dietary advice (not specified)
Compliance: assessed by questionnaire on adherence at each clinic appointment and blood EPA/AA ratio. Reports good adherence (receipt of at least 80% of meds) was seen in both (sic) groups, and blood EPA/AA was significantly higher in intervention than control group.
Duration of intervention: x months

EPE-A study 2014

Methods

EPE-A
RCT, parallel, 3 arms (n3 EPA, low dose vs high dose vs unclear placebo), 12 months
Summary risk of bias: Moderate or high

Participants

People with non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD)
N: 86 int_high, 82 int_low, 75 control. (analysed 64, 55, 55 respectively, ITT analysis for primary outcomes)
Level of risk for CVD: Low (although 35% had type II diabetes)
Male: 33.7% int_high, 41.5% int_low , 42.7% control.
Mean age (SD): 47.8 (11.1) int_high, 47.8 (12.5) int_low, 50.5 (12.5) control
Age range: NR
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: USA
Ethnicity:
white int_low: 94% int_high: 87% cont: 90.7%
African American Int_low: 3.7% Int_high: 2.3% cont: 4.0%
Others int_low: 2.4% int_high: 10.5% cont: 5.3%

Interventions

Type: Supplement (Omega 3 capsule)
Comparison 1: high EPA vs low EPA
Comparison 2: EPA vs placebo (placebo contents not reported)
Intervention: High: EPA-E 2.7g/d, 3x EPA-E 300 mg capsules: EPA+DHA

	2.7g/d Low: EPA-E 1.8g/d, 2x EPA-E 300 mg capsules + 1placebo capsule: EPA+DHA 1.8g/d Control: 3x placebo capsules - The pills were identical with respect to size, colour and gross smell. Compliance: was estimated by pill count and measuring the ratio of serum EPA to arachidonic acid. Compliance rates for the 3 groups (placebo vs EPA-E 1800 mg/d vs EPA-E 2700 mg/d) were 89.5% (6.8%), 90.3% (5.7%) and 89.5% (5.3%) respectively. Length of intervention: 12 months

EPIC-1 2008

Methods	EPANOVA in Crohn's Disease, Study 1 (EPIC-1) RCT, parallel, 2arm (omega 3 vs MCT), 52 weeks Summary risk of bias: Moderate or high
Participants	Adults with quiescent Crohn's disease (CDAI) score <150 N: 188 int., 186 control Level of risk for CVD: Low Male: 48.1% int., 41.1% control Mean age (SD): 40.5 (15.2) int., 38.2 (13.1) control Age range: 18-70 y Smokers: 30.6% int., 34.4% control Hypertension: Unclear Medications taken by at least 50% of those in the control group: Oral 5-ASA therapy, Systemic corticosteroids – prednisolone, budesonide Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: Antibiotic therapy, Topical rectal therapy, Immune-modifying agents, Immune modifiers/biologics Location: Canada, Europe, Israel, United States Ethnicity: NR
Interventions	Type: supplement (capsule) Comparison: EPA & DHA vs MCT Intervention: 2x2 1g gelatine capsules omega-3 free fatty acids (Epanova-2.2g/d EPA, 0.8g/d DHA): EPA 3.0g/d Control: 4 x1g capsules medium chain triglycerides Compliance: pill counts, 79.2% adhered int., 75.6% adhered control Length of intervention: mean 52 weeks

EPIC-2 2008

Methods	EPANOVA in Crohn's Disease, Study 2 (EPIC-2) RCT, parallel, 2 arms (omega 3 vs MCT), 58 weeks Summary risk of bias: Moderate or high
Participants	Adults with a confirmed diagnosis of Crohn's Disease and a Crohn's Disease Activity Index (CDAI) score <150 who are responding to steroid induction therapy N: int., 189, control 190 (187 int., 188 control analysed) Level of risk for CVD: Low (People with quiescent Crohn's disease) Male: 48.1% int., 41.1% control Mean age (SD): 38.5 (13.8) int., 40.0 (13.6) years control Age range: >16 yrs. Smokers: 25.1% int., 37.2% control Hypertension: Unclear Medications taken by at least 50% of those in the control group: Systemic corticosteroids – prednisolone, budesonide (but tapered and discontinued during the study) Medications taken by 20-49% of those in the control group: only reported for prior 12 mo. Medications taken by some, but less than 20% of the control group: only reported for prior 12 mo. Location: Canada, Europe, Israel, United States Ethnicity: NR

Interventions

Type: supplement (capsule)
Comparison: EPA & DHA vs MCT
Intervention: 2x2 1g gelatine capsules omega-3 free fatty acids (Epanova) providing total dose ~2.2g/d EPA, 0.8g/d DHA: EPA+DHA ~3.0g/d
Control: 2x2 1g capsules medium chain triglyceride oil
Compliance: measured by patient interviews and pill counts, 75.4% adhered int., 81.4% adhered control
Length of intervention: mean 58 weeks

EPOCH 2014

Methods

Older People, Omega-3 and Cognitive Health (EPOCH)
RCT, parallel (n3 EPA+DHA vs MUFA), 18 months
Summary risk of bias: Low

Participants

Healthy older adults with no cognitive impairment.
N: 195 int, 196 control (reported by author)
Level of risk for CVD: Low
Male: NR
Mean age (SD): NR
Age range: NR, but 65-90 recruited
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Australia
Ethnicity: NR

Interventions

Type: supplement (fish oil capsules)
Comparison: high EPA & DHA vs MUFA and low EPA & DHA
Intervention: 4 capsules/d (1.72g/d DHA and 0.60g/d EPA): EPA+DHA 2.32g/d
Control: 4 capsules/d (3.960g/d olive oil and 40 mg/d fish oil)
Compliance: count of all unused supplements returned at three-monthly intervals, plus self-report calendars, mailed back on a monthly basis. If compliance fell below 85% (re calendars), they were contacted by a researcher who noted the reasons. Compliance also assessed by erythrocyte membrane n-3 LC PUFA status
Length of intervention: 18 months

Erdogan 2007

Methods

RCT, parallel (n3 EPA+DHA vs unclear), 12 months
Summary risk of bias: Moderate to high

Participants

People with successful external cardioversion
N: unclear int, unclear control (54 analysed int, 54 cont)
Level of risk for CVD: High
Male: 70% int, 74% cont
Mean age (SD): 65.0 (mean for whole group, SD not reported)
Age range: NR
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Germany
Ethnicity: NR

Interventions

Type: supplement (probably, not described)
Comparison: high EPA & DHA vs unclear placebo
Intervention: described only as "PUFA" but included in SR by Erdogan et al on effects of n3 PUFA
Control: described only as "placebo"
Compliance: NR
Length of intervention: 12 months

Eschen 2010

Methods	RCT, parallel, (n3 EPA+DHA vs MUFA), 6 months Summary risk of bias: Moderate or high
Participants	People with congestive heart failure N: 69 int., 69 control. (analysed, int: NR cont: NR) Level of risk for CVD: High Male: 83% int., 88% control. Mean age (SD) yrs.: 58 (10) int., 61 (8) control Age range: NR but inclusion criteria were 19-80 years Smokers: 13% int., 17% control. Hypertension: 46% int., 39% control. Medications taken by at least 50% of those in the control group: beta blockers (84%), RAS inhibitors (angiotensin converting enzyme inhibitor or angiotensin II receptor blocker, 97%), Aspirin (53%), statins (52%) Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: Italy Ethnicity: NR
Interventions	Type: supplement Comparison: EPA+DHA vs MUFA Intervention: 1 capsule/d of EPA and DHA as ethyl esters (including 0.9g/d EPA+DHA, Società Prodotti Antibiotici S.p.A., Milano): EPA+DHA 0.9g/d Control: 1 capsule/d of olive oil (including 1g/d olive oil, Società Prodotti Antibiotici S.p.A., Milano) Compliance: assessed by analysis of plasma EPA and DHA, both were significantly greater at 24 weeks in the intervention than control groups ($p<0.001$). Duration of intervention: 6 months (24 weeks)

FAAT - Leaf 2005

Methods	Fatty Acid Antiarrhythmia Trial - FAAT RCT, parallel, 2 arms (n3 EPA+DHA vs MUFA) 12 months Summary risk of bias: Moderate or high
Participants	People with implanted cardioverter defibrillators (ICDs) N: Int 200, Cont 202 Level of risk for CVD: High (patients with ICDs). Male: Int 84.5%, Cont 81.7% Mean age (SD): Int 65.7 (11.6), Cont 65.3 (11.7) years Age range: unclear Smokers: Int 15%, Cont 11.4% Hypertension: Unclear Medications taken by at least 50% of those in the control group: ACE inhibitors, beta-blockers Medications taken by 20-49%: diuretics Medications taken by some, but <20%: calcium channel blockers, amiodarone, sotalol, type 1 antiarrhythmics Location: USA Ethnicity: int 95.5% white, control 96.5% white
Interventions	Type: Supplement/ capsule Comparison: EPA & DHA vs MUFA Intervention: 4x1g/d fish oil gelatine capsules, 2.6g EPA + DHA per day (Pronova Biocare, quantities of EPA & DHA unclear): EPA+DHA 2.6g/d Control: 4x1g/d olive oil capsules, 4g/d (in identical gelatine capsules, <0.06g/d EPA +<0.06g/d DHA) All were advised to use olive oil rather than the common plant seed oils for cooking, dressings, and sauces Compliance: Pill counts and platelet phospholipid data suggested greater omega 3 intake in intervention participants. 35% were non-compliers (36.5% int., 34.2% control) Duration of intervention: 12 months.

Fakhrzadeh 2010

Methods	RCT, parallel, (n3 EPA+DHA vs mixed fat MCT), 6 months Summary risk of bias: Moderate or high
Participants	Elderly residents (65 yrs. or over) N: 134 in both groups combined. (analysed, int: 62 cont: 62) Level of risk for CVD: Low Male: 43.5% int., 38.7% control Mean age (SD): 74.7 (10.1) int., 74.9 (8.8) control Age range: NR Smokers: 21.0% int., 14.8% control Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: Statins Location: Iran Ethnicity: NR
Interventions	Type: supplement (fish oil capsule vs placebo) Comparison: n-3 vs nil Intervention: 1g/d fish oil capsule (180mg EPA, 120mg DHA, Zahravi Pharmacy Company, Iran): EPA+DHA 0.3g/d Control: 1g/d placebo capsule (medium-chain triglycerides, Zahravi Pharmacy Company, Iran) Compliance: Capsule consumption observed by two nurses Duration of intervention: 6 months

Ferreira 2015

Methods	RCT, parallel, (n3 EPA vs unclear), 6 months Summary risk of bias: Low
Participants	Population: Adults with Huntington's disease N: 147 int., 143 control. (analysed, int: 97 cont: 87) Level of risk for CVD: Low Male: 54.4% int., 51% control. Mean age (SD): 52.9 (10.28) int., 52.2 (10.70) control Age range: NR Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: UK, Germany, Portugal, Spain, Italy, and Austria Ethnicity: int: Caucasian 145, Asian 1 other 1; cont: Caucasian 141, Oriental, other 1 Depression: Long term condition (high risk) Anxiety: Long term condition (high risk)
Interventions	Type: supplement Comparison: EPA vs placebo Intervention: 4x500mg/d capsules of ethyl-EPA (2 g/d EPA): EPA 2.0g/d Control: placebo (identical in appearance to the test product, but not clear what it constitutes) Compliance: NR Duration of intervention: 6 months

Finnegan 2003

Methods	RCT, parallel, 5 arms (n3 EPA+DHA vs n3 ALA vs n6 LA), 6 months Summary risk of bias: Moderate or high
Participants	People with hyperlipidaemia N: 200 randomised into study (NR by arm), (analysed, high EPA+DHA 31, low EPA+DHA 30, high ALA 29, low ALA 30, cont 30) Level of risk for CVD: moderate Male: high EPA+DHA 58%, low EPA+DHA 57%, high ALA 59%, low ALA

	57%, cont 60% Mean age (SD): high EPA+DHA 54(11), low EPA+DHA 53(11), high ALA 54(11), low ALA 52(11), cont 55(11) Age range: NR Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: UK Ethnicity: NR
Interventions	Type: supplement / supplemented food Comparison: high EPA+DHA vs low EPA+DHA vs high ALA vs low ALA 30 vs n6 PUFA Intervention: **high EPA+DHA** 1.7g/d EPA+DHA including 25g of margarine containing 0.5g/d EPA+DHA (Unilever) plus 3 fish oil capsules including 0.8g/d EPA+DHA (Roche): EPA+DHA 1.7g/d **low EPA+DHA** 0.8g/d EPA+DHA including 25g of margarine containing 0.5g/d EPA+DHA (Unilever) plus control capsules (Roche): EPA+DHA 0.8g/d **high ALA** 9.5g/d ALA including 25g/d of margarine containing rapeseed & linseed oils plus control capsules (Roche): ALA 9.5g/d **low ALA** 4.5g/d ALA including 25g/d margarine containing rapeseed & linseed oils plus control capsules (Roche): ALA 4.5g/d **Control:** 25g/d linoleic-acid rich margarine plus control capsules (Roche) Compliance: assessed through return of margarine pots and capsule packs, plus through measurement of plasma phospholipid fatty acid composition, compliance with margarine was >92% across groups, with capsules was >88% across groups and not significantly different between groups Duration of intervention: 6 months

FISHGASTRO - Pot 2009

Methods	Fish Consumption and Gastro-Intestinal Health (FishGastro) RCT, parallel, multicentre (n3 EPA+DHA rich fish vs low n3 EPA+DHA fish), both arms included dietary advice, and the third arm is dietary advice only, 6 months Summary risk of bias: Moderate to high
Participants	Attendees visiting the hospital for colonoscopy as part of their regular medical care, subdivided into 3 groups: 1. People with colorectal polyps; 2. People with inactive ulcerative colitis; 3. People with no macroscopic signs of disease. N: 82 int.1 (advice & salmon), 78 int.2 (advice & cod), 82 control (advice only). (analysed: 74 int.1, 70 int.2, 69 cont.) Level of risk for CVD: Low Male: 49% int.1, 59% int.2, 46% control. Mean age (SEM): 55.1(11.5) int.1, 57.4(10.3) int.2, 55.3(9.5) control Age range: NR Smokers: 26% int.1, 11.4% int.2, 15.9% cont. Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR (Excluded if taking ASAs or NSAIDs) Location: UK & Netherlands Ethnicity: NR
Interventions	Type: dietary advice and supplement (supplement containing either higher EPA+DHA or lower EPA/DHA) or dietary advice only Comparison: high n3 fish diet vs low n3 fish diet vs low fish diet Intervention 1: 300g/wk. salmon containing 2.1g/wk. EPA & 4.2g/wk. DHA (total n3 PUFA 9.9g/wk. PLUS 3.9g/wk. n6 PUFA): EPA+DHA 1.4g/d Intervention 2: 300g/wk. cod containing 1.8g/wk. total n3 PUFA: EPA+DHA

	0.26g/d Control: dietary advice only Fish provider: salmon provided by Marine Harvest, Norway; cod provided by Pescanova, Spain Compliance: post-intervention serum FA composition & food diaries Duration of intervention: 24 wks./6 months
FLAX-PAD 2013	
Methods	Effects of Dietary Flaxseed on Symptoms of Cardiovascular Disease in Patients With Peripheral Arterial Disease (FLAX PAD) RCT, parallel, (n3 ALA vs mixed fat), 12 months Summary risk of bias: Low
Participants	Patients with peripheral artery disease, over 40 years old. N: 58 int., 52 control. Level of risk for CVD: High (all had peripheral artery disease, 80% had hyperlipidaemia) Male: 74.1% int., 73.1% control. Mean age (SD): 67.4 (8.06) int., 65.3 (9.4) control Age range: unclear Smokers: 19.2% int., 34.6% control Hypertension: 81% int., 69.2% control. Medications taken by at least 50% of those in the control group: lipid lowering medication, antihypertensives, antithrombotics Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: Insulin or blood sugar lowering drugs Location: Canada Ethnicity: Unclear
Interventions	Type: food supplement (milled flaxseed) Comparison: ALA vs mixed dietary oils Intervention: food products (i.e. bagels, muffins, bars, pasta, buns, and milled seeds) containing 30 g of milled flaxseed daily: ALA dose unclear Control: placebo food products (i.e. bagels, muffins, bars, pasta, buns, and milled seeds) containing a mixture of wheat, wheat bran, and mixed dietary oils to replace the flaxseed daily Compliance: plasma levels of enterolignans and the n3 fatty acid ALA were used as markers of dietary compliancy. Length of intervention: 12 months
FORWARD 2013	
Methods	Randomized Trial to Assess Efficacy of PUFA for the Maintenance of Sinus Rhythm in Persistent Atrial Fibrillation (FORWARD) RCT, parallel, (n3 EPA+DHA vs MUFA), 12 months Summary risk of bias: Moderate or high
Participants	Patients with paroxysmal atrial fibrillation N: 289 int., 297 control. Level of risk for CVD: High Male: 57.8% int., 51.9% control. Mean age (SD): 66.3 (12) int., 65.9 (10.5) control Age range: >21 Smokers: 9% int., 6.2% control Hypertension: 92.2% int., 90.8% control. Medications taken by at least 50% of those in the control group: Aspirin, Amiodarone, ‘any antithrombotic treatment’, beta-blockers Medications taken by 20-49% of those in the control group: Anticoagulants Medications taken by some, but less than 20% of the control group: None reported Location: Argentina Ethnicity: NR
Interventions	Type: supplement (capsule) Comparison: EPA & DHA vs MUFA

Intervention: one capsule/ day containing 1g of n-3 PUFA (Societá Prodotti Antibiotici and SigmaTau, Italy) (provided 850 to 882 mg EPA/DHA): EPA+DHA 0.86g/d
Control: identical placebo capsule containing olive oil
Compliance: not reported.
Length of intervention: 12 months

FOSTAR 2016

Methods

Fish Oil in knee OSTeoARthritis (FOSTAR)
RCT, parallel, (n3 EPA+DHA vs low n3), 24 months
Summary risk of bias: Low

Participants

Adults aged 40+ with knee osteoarthritis.
N: 101 int., 101 control.
Level of risk for CVD: Low
Male: 41% int., 60% control.
Mean age (SD): 60.8 (10) int., 61.1 (10) control
Age range: >40
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: None reported
Medications taken by 20-49% of those in the control group: not reported at baseline, but "during" includes vitamin D ~ 32%
Medications taken by some, but less than 20% of the control group: not reported at baseline, but "during" includes Glucocorticoid, HRT/antiresorptive, both ~ 10%
Location: Australia
Ethnicity: NR

Interventions

Type: supplementary food (enriched orange juice)
Comparison: high EPA & DHA vs low EPA & DHA plus ALA
Intervention: 1-3x a day drink of fruit juice mixed with day total = 15ml of fish oil supplement (18% EPA, 12% DHA, 4.5g/day total omega 3): EPA+DHA 4.5g/d
Control: Liquid oral oil 15ml sunola oil/day (which contains fish oil 2ml plus 13ml canola oil) (total omega-3 fat: ≥0.45 g EPA+DHA from 15ml
Compliance: Assessed by measuring the oil volume in returned bottles, compliance was >80% in both groups. Both groups had increases from baseline in plasma EPA and DHA with the high-dose group having substantially larger increases, consistent with compliance with study oil
Length of intervention: 24 months

Franzen 1993

Methods

RCT, parallel (n3 EPA+DHA vs MUFA), 12 months
Summary risk of bias:

Participants

Adults with documented coronary heart disease.
N: 15 int., 15 control.
Level of risk for CVD: High
Male: Unclear
Mean age (SD): 52 (9) int., 54 (7) control
Age range: NR
Smokers: 87% int., 100% control.
Hypertension: NR
Medications taken by at least 50% of those in the control group: aspirin, beta-blockers
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Lipid lowering medications were not allowed
Location: Germany
Ethnicity: NR

Interventions

Type: Fish oil capsules
Comparison: EPA & DHA vs MUFA
Intervention: 9x1g capsules/day of fish oils (20% EPA, 15% DHA,

3.15g/day total omega 3): EPA+DHA 3.15g/d
Control:9x1g capsules/day olive oil (which contains 6.3g/day MUFA, 1.35 g/day SFA, 1.35 g/d total omega 6 fat)
Compliance: Assessed by pill counts & FA in body tissue analysis.
Length of intervention: 12 months

Gill 2012

Methods

RCT, parallel, (n3 EPA+DHA vs unclear), 24 months
Summary risk of bias: Moderate or high

Participants

Adults with Metabolic syndrome.
N: unclear, total randomised 101
Level of risk for CVD: Low
Male: 47% total, no details by group.
Mean age (SD): 55 (10) total
Age range: 18-75
Smokers: 0% int., 0% control
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: USA
Ethnicity: Unclear

Interventions

Type: supplement (fish oil capsules)
Comparison: EPA & DHA vs placebo (not clear what)
Intervention: fO3FA capsules 1.8 g of EPA+DHA daily: EPA+DHA 1.8g/d
Control: matching placebo supplement
Compliance: NR.
Length of intervention: 12 months

GISSI-HF

Methods

GISSI Heart Failure (GISSI-HF)
RCT, parallel, 2 arms (n3 EPA+DHA vs MUFA), 3.9 years
Summary risk of bias: Moderate or high

Participants

Patients with chronic heart failure
N: 3494 int, 3481control
Level of risk for CVD: High
Male: 77.8% int, 78.8% control
Mean age: 67 (11) int,67 (11) control
Age range: 18+ years
Smokers: 14.4% int, 13.9% control
Hypertension: 54.0% int, 55.2% control
Medications taken by at least 50% of those in the control group: ACE inhibitors, Beta blockers, diuretics
Medications taken by 20-49% of those in the control group: Spironolactone, digitalis, oral anticoagulants, aspirin, nitrates, statin
Medications taken by some, but less than 20% of the control group: ARBs, other antiplatelets, calcium channel blockers, Amiodarone
Location: Italy
Ethnicity: Unclear

Interventions

Type: supplement (capsule)
Comparison: EPA & DHA vs MUFA
Intervention: 866mg EPA, 1039mg DHA, Total Omega-3 Fat: 1905 mg. I capsule per day of 1g n-3 in average ratio EPA:DHA of 1:1.2: EPA+DHA 1.91g/d
Control:1g/d matching olive oil placebo capsule
Compliance: Unclear
Length of intervention: Median 3.9 years

GISSI-P 1999

Methods

GISSI Prevention (GISSI-P)
RCT, 2x2 (n3 EPA+DHA vs nil), also randomisation to vitamin E capsule or

	nil), 42 months Summary risk of bias: Moderate or high
Participants	People with recent (≤3 months) myocardial infarction N: 5666 int., 5658 control (99.9% follow up at study end) Level of risk for CVD: High Male: 85.7% int., 84.9 % control Mean age (SD): 59.3 (10.6) int., 59.5 (10.5) years control Age range: <50 to >80 Smokers: 42.6% int., 42.3% control Hypertension: 36.2% int., 34.9% control Medications taken by at least 50% of those in the control group: anti-platelet Medications taken by 20-49% of those in the control group: ACE inhibitors, beta-blockers Medications taken by some, but less than 20% of the control group: lipid lowering Location: Italy Ethnicity: NR
Interventions	Type: supplement (capsule) Comparison: EPA & DHA vs nil Intervention: Omacor gelatine capsules, 1/d (850-882 mg/d EPA + DHA daily, ratio 1:2): EPA+DHA 0.86g/d Control: nil (no placebo) Compliance: capsule counts, 11.6% had stopped taking Omacor by 12 mo., 28.5% by the end of the study Duration of intervention: median follow up 40 mo.

Greenfield 1993

Methods	RCT, parallel, 3 arms (n3 EPA vs n6 GLA vs MUFA), 6 months Summary risk of bias: moderate to high
Participants	People with stable (treatment unchanged for at least 6 weeks) ulcerative colitis (diagnosed by standard endoscopic, histological and radiological criteria) for more than a year and receiving less than 10mg prednisolone/day. N: 16 int.1, 19 int.2, 8 control. (analysed: 13 int.1, 13 int.2, 7 cont.) Level of risk for CVD: Low Male: 75% int.1, 68.4% int.2, 62.5% control. Mean age (SEM): 57.3(4.4) int.1, 51.3(3.4) int.2, 35 (6.8) control Age range: NR Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: 5ASA (mesalazine/ sulphasalazine) Medications taken by 20-49% of those in the control group: Medications taken by some, but less than 20% of the control group: Rectal steroids Location: UK Ethnicity: NR
Interventions	Type: supplement (capsules containing EPA+DHA or borage/EPO or olive oil) Comparison: EPA + DHA vs n6 vs MUFA Intervention 1: 6g/d (6 capsules) containing 1.116g/d EPA & 0.726g/d DHA (total n3 PUFA 1.842g/d PLUS 0.318g/d n6 PUFA)*: EPA+DHA 1.84g/d Intervention 2: 1.5g/d (6 capsules) containing 0.840g/d LA & 0.232g/d GLA (total n6 PUFA 1.072g/d)* Control: olive oil 6g/day (6 capsules)* *each patient received a loading dose of 12 capsules per day for one month at the start of the trial followed by 6 capsules daily for the remaining 5 months All oils provided by Seven Seas Healthcare, Kingston upon Hull, UK Compliance: erythrocyte FA composition Duration of intervention: 24 wks./6 months

HARP - Sacks 1995

Methods	Harvard Atherosclerosis Reversibility Project (HARP) RCT, (n3 EPA+DHA vs MUFA), 24 months Summary risk of bias: Moderate or high
Participants	Patients with coronary heart disease N: 41 int., 39 control (99.9% follow up at study end) Level of risk for CVD: High Male: 93.5% int., 92.9 % control Mean age (SD): 62 (7) int., 62 (7) years control Age range: 30-75 Smokers: 0% (exclusion criteria) Hypertension: 48% int., 36% control Medications taken by at least 50% of those in the control group: Beta blockers, antiplatelet agents Medications taken by 20-49% of those in the control group: Calcium channel blockers, nitrates Medications taken by some, but less than 20% of the control group: ACE inhibitors, oral hypoglycaemic drugs Location: USA Ethnicity: NR
Interventions	Type: supplement (capsule) Comparison: LCN3 vs MUFA Intervention: 12 fish oil capsules/day (Promega, Parke-Davis) in divided doses, preferably after meals. Each fish oil capsule contained 500 mg of n-3 polyunsaturated fatty acids composed of EPA (240 mg), DHA (160 mg) and other (100 mg) (mainly DPA) providing total daily dose of 6g of n-3 fatty acids: EPA+DHA 4.8g/d Control: olive oil capsules identical in appearance to the fish oil capsules. Compliance: capsule counts and serum level measurements. Adherence averaged 80% int., and 90% control with significant levels of adipose n-3 fatty acids in the fish oil group. Duration of intervention: average 28 months

Hashimoto 2012

Methods	RCT, parallel, (n3 EPA+DHA vs MUFA), 12 months Summary risk of bias: Moderate or high
Participants	Healthy older people from Japan N: 57 int., 54 control. (analysed, int: 53 cont: 48) Level of risk for CVD: Low Male: 63% int., 61% control. Mean age (SD): 72.0 (7.6) int., 72.9 (7.8) control Age range: NR but ≥57 years inclusion criteria Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: Japan Ethnicity: Japanese
Interventions	Type: food supplement (fish sausage with EPA+DHA or olive oil) Comparison: EPA & DHA vs MUFA Intervention: 2 fish sausages/d (including 1.72g/d DHA + 0.4g/d EPA, Resara, Maruha Nichiro Foods): EPA+DHA 2.12g/d Control: 2 fish sausages/d (including 0.1g/d DHA + 0.02g/d EPA plus olive oil). The sausages were indistinguishable re colour taste and flavour. Compliance: Sausages eaten were recorded in a diary and assessed monthly to encourage compliance. Plasma DHA and EPA levels increased in the intervention group, and decreased in controls Duration of intervention: 12 months

Hashimoto 2016

Methods	RCT, parallel, (n3 DHA vs low n3 DHA), 12 months Summary risk of bias: Moderate or high
Participants	Healthy older people from Japan N: 43 int., 32 control. (analysed, int: 39 cont: 27) Level of risk for CVD: Low Male: 12% int., 16% control. Mean age (SD): 87.6 (3.3) int., 89.6 (5.1) control Age range: NR but ≥75 years inclusion criteria Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: Japan Ethnicity: Japanese
Interventions	Type: food supplement (fish sausage with EPA+DHA or olive oil) Comparison: EPA & DHA vs MUFA Intervention: daily fish sausages (including 0.86g DHA + 0.20g EPA, Resara, Maruha Nichiro Corp): EPA+DHA 1.06g/d Control: daily fish sausages/d (including 0.05g DHA + 0.02g EPA, Kururunpack, Maruha Nichiro Corp). Compliance: Unclear how well sausages were eaten, but erythrocyte DHA fell in control group and was maintained in the intervention group. Erythrocyte plasma membrane EPA was statistically significantly higher in the intervention group than control at 12 months. Duration of intervention: 12 months

Hawthorne 1992

Methods	RCT, parallel arm, placebo controlled (n3 EPA vs MUFA), 12 months Summary risk of bias: moderate-high
Participants	Individuals with established diagnosis of ulcerative colitis diagnosed on the basis of rectal biopsy and barium enema or colonoscopy. Entry restricted to patients who had had two or more relapses in the previous three years. N: 46 int., 50 control [entry in relapse: 26 int., 30 cont; entry in remission: 20 int., 20 cont] (analysed – int: 45 cont: 42; states ITT analysis but figures reported are for those who completed the trial only) Level of risk for CVD: Low Male: 69% int., 40.5% control. Mean age (SD): 44 int.; 49 cont. (SD not reported) Age range: 17-73 int., 20-77 control Smokers: 2.2% int., 2.4% control Hypertension: NR Medications taken by at least 50% of those in the control group: sulphasalazine or mesalazine (71%) Medications taken by 20-49% of those in the control group: all patients entering the trial in relapse appear to be on 20mg prednisolone or less = 27% control group Medications taken by some, but less than 20% of the control group: NSAIDs (5%) Location: UK Ethnicity: NR UC distribution in colorectum: Whole colorectum: 33% int., 43% control Left-sided disease only: 27% int., 24% control Sigmoid disease only: 38% int., 33% control Proctitis only: 2% int.; 0% control Mean duration of colitis (years): 7 int., 9 cont. Median number of relapses in previous year: 2 int., 3 cont.
Interventions	Type: supplement (free fish oil triglyceride concentrate HiEPA or olive oil) Comparison: EPA+DHA vs MUFA Intervention: 20mls free oil per day (including 25% EPA + 6% DHA, or 4.5g/d EPA plus 1.08g/d DHA; Scotia Pharmaceuticals, Surrey, UK):

EPA+DHA 5.58g/d
Control: 20mls olive oil per day (including 73% MUFA; Scotia Pharmaceuticals, Surrey, UK)
Compliance: count of bottles of oil used during each two month period, adiposity (red cell membrane EPA incorporation), 2 x 7-day semi-weighted diet diaries in both first and last 2m of study (pts enrolled in Nottingham only, n=76). Median consumption of oil: 20ml daily in both arms; bottle counts: intervention - median 650 (360-720) ml/month; control – median 635 (270-720) ml/month, with no fall during the year. Good compliance confirmed by red cell membrane incorporation of EPA in int. group only throughout follow-up period.
Duration of intervention: 12 months

HERO-Tapsell 2009

Methods

Healthy Eating to Reduce Overweight in people with type 2 diabetes (HERO)
RCT, parallel, (n3 ALA vs low n3), 12 months
Summary risk of bias: Moderate or high

Participants

Overweight adults with non-insulin treated diabetes
N: 26 int., 24 control. (analysed, int: 18 cont: 17)
Level of risk for CVD: Moderate
Male %: NR
Mean age (SD): 54 (8.7), not reported by arm.
Age range: 33-70
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: lipid lowering drugs, oral hypoglycaemics
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Australia
Ethnicity: NR

Interventions

Type: food supplement (walnuts)
Comparison: ALA vs nil
Intervention: 30g/d snack portions of walnuts (provided 10% MUFA, 10% E PUFA, and a P/S ratio of 1.0) and advised not to take fish oil supplements: ALA dose unclear
Control: No supplements.
Both groups were given low-fat isocaloric dietary advice (30% E fat (10% E SFA, 15% E MUFA; 5% E PUFA, P/S ratio of 0.5), 20% E protein and 50% E CHO) plus advice to brisk walk 30 min x 3 times/week.
Compliance: measured by erythrocyte membrane fatty acid levels which were similar in both groups.
Duration of intervention: 12 months

Higashihara 2010

Methods

RCT, parallel, (n3 EPA vs nil), 24 months
Summary risk of bias: Moderate or high

Participants

Prostate cancer patients whose PSA levels were less than 0.2 ng/ml 3 months after prostatectomy (n=62)
N: 34 int., 34 control. (analysed, int: 32 cont: 30)
Level of risk for CVD: low
Male: 100% int., 100% control.
Mean age (SD): 58 (5) int., 58 (7) control
Age range: unclear
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Japan
Ethnicity: NR

Interventions	Type: supplement / food / supplemented food Comparison: EPA capsule vs nil Intervention: 2.4g/d EPA ethyl ester: EPA 2.4g/d Epadel-S, purity >98%; Mochida Pharmaceutical Co., Ltd., Tokyo, Japan) Control: nil Compliance: erythrocyte fatty acids assessed at baseline, 6 and 24 months. EPA, DHA and DPA all statistically significantly higher in intervention group than control at 24 months. Duration of intervention: 24 months

Huang 1996

Methods	RCT, parallel, (n3 EPA+DHA vs n6 LA), 12 months Summary risk of bias: Moderate or high
Participants	Post-surgery patients with Dukes A or B adenocarcinoma of the colon or rectum or severely dysplastic adenomatoid polyps N: 17 int., 10 control. (analysed, int: 12 cont: unclear) Level of risk for CVD: low Male: NR Mean age (SD): NR Age range: NR Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: USA Ethnicity: NR
Interventions	Type: supplement Comparison: n3 EPA vs n6 Intervention: n3 capsules: 9x 1g/d. EPA: 9x 0.44= 4g DHA: 9 x 0.24 = 2g. Total 4g/d EPA + 2g/d DHA: EPA+DHA 6.0g/d Control: corn oil capsules Compliance: *plasma fatty acid levels and capsule counts assessed (82% capsule counts)* Duration of intervention: 12 months

IFOMS- Sirtori 1997

Methods	Italian Fish Oil Multicentre Study (IFOMS) RCT, parallel, (N3 EPA+DHA vs MUFA), 6 months Summary risk of bias: Moderate or high
Participants	Patients with hypertriglyceridemia N: 470 int., 465 control. (analysed, int: 442 cont: 426) Level of risk for CVD: Moderate Male: 62.6% int., 62.2% control Mean age (SD): 58.2 (9.09) int., 58.8 (8.99) control Age range: NR Smokers: NR Hypertension: 67% int., 68% control Medications taken by at least 50% of those in the control group: Antihypertensives Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: Italy Ethnicity: NR
Interventions	Type: supplement (n-3 or olive oil capsules) Comparison: n-3 vs MUFA Intervention: n-3 capsules (3g/d for 2 months [1.53g EPA and 1.05g DHA], then 2g/d [1.02g EPA and 0.70g DHA] for 4 months, Escapent, Italy): EPA+DHA 1.72g/d Control: Olive oil capsules (3g/d for 2 months, then 2g/d for 4 months) Compliance: Pill counts and plasma and erythrocyte EPA and DHA Duration of intervention: 6 months (followed by a 6 month open phase)

Jackson 2016

Methods	RCT, parallel, (n3 DHA vs low n3), 6 months Summary risk of bias: Moderate or high
Participants	Population: Healthy adults with subjective memory deficit (MMSE ≥26, MAC-Q score > 24) N: 33 int., 32 control. (analysed, int: 30 cont: 28) Level of risk for CVD: Low Male: 39% int., 36% control. Mean age (SD): 60.3 (4.9) int., 59.6 (5.3) control Age range: 50-70 Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: UK Ethnicity: NR Depression: General population (low risk) Anxiety: General population (low risk)
Interventions	Type: supplement Comparison: DHA-rich fish oil vs high oleic acid sunflower oil & fish oil Intervention: 4 x 500 mg DHA rich tuna oil (896mg DHA, 128mg EPA) / day: EPA+DHA 1.02g/d Control: 2.24 g high oleic acid sunflower oil and 120 mg fish oil (32 mg DHA + EPA) / day (Efalex Active 50+, a dietary supplement containing a number of potentially cognition enhancing components including DHA, phosphatidylserine, vitamin B12, folic acid and Ginkgo biloba), Compliance: Duration of intervention: 6 months

JELIS 2007

Methods	Japan EPA Lipid Intervention Study (JELIS) RCT, parallel, 2arm (n3 EPA vs nil), 5 years Summary risk of bias: Moderate or high
Participants	People with hypercholesterolaemia N: int., 9326, control 9319 (analysed int 9326, cont 9319) Level of risk for CVD: Moderate (Patients with hypercholesterolaemia) Male: 32% int., 31% control Mean age (SD): 61 (8) int. 61 (9) control Age range: 40-75 yrs. Smokers: 20% int., 18% control Hypertension: 36% int., 35% control Medications taken by at least 50% of those in the control group: statins Medications taken by 20-49% of those in the control group: Calcium channel blockers, other antihypertensives Medications taken by some, but less than 20% of the control group: beta blockers, antiplatelet, hypoglycaemics, nitrates Location: Japan Ethnicity: Japanese
Interventions	Type: supplement (EPA capsule) Comparison 1: EPA vs nil Intervention: 3 x 2 x 300mg capsules/d EPA ethyl ester (total dose of 1.8g/d EPA), after meals: EPA 1.8g/d Control: Nothing (though all in both groups received "appropriate" dietary advice). All patients in both groups were on statins. Compliance: Monitored by local physicians and measuring plasma fatty acids concentrations. Study drug regimens, 71% adhered EPA int., 73% adhered EPA control, 74% adhered statin. Duration of intervention: maximum 5 years, mean 4.7 (1.1) years.

Kremer 1995

Methods	RCT, 4 x parallel arm, placebo controlled (n3 EPA+DHA vs n6 LA), 6 months / 7 months Summary risk of bias: moderate to high
Participants	Individuals with definite or classic active rheumatoid arthritis as demonstrated by the presence of three of the following four criteria: ≥6 tender joints, ≥3 swollen joints, ≥30 min morning stiffness, a Westergren ESR of ≥28 mmol/hour. N: 37 int., 29 control (analysed – int: 15 cont: 14) Level of risk for CVD: Low Male: 43.5% int., 46.2% control. Mean age (SD): 58 int.; 57 cont. (SD not reported) Age range: NR Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: None reported Medications taken by 20-49% of those in the control group: prednisolone (mean 4.5mg/day) 23%; hydroxychloroquine 34% Medications taken by some, but less than 20% of the control group: methotrexate (11%), intramuscular gold (11%), sulphasalazine (11%), D-penicillamine (8%), Auranofin (4%), Azathioprine (4%) Location: USA Ethnicity: NR Baseline Westergren ESR (mean +/- SEM): int. 31 +/- 3.9 mm/hr; cont. 41 +/- 8.1 mm/hr
Interventions	Type: supplement (fish oil capsule or corn oil) Comparison: EPA+DHA vs MUFA/SFA Intervention: 130mg/kg/day (including 44% EPA + 24% DHA; supplied by National marine Fisheries Association for the National Institutes of Health): EPA+DHA ~6.2g/d Control: 9 x corn oil capsules per day, capsule weight unspecified (supplier not reported) Compliance: capsule count showed 93% overall compliance in patients consuming fish oil and 88% overall compliance in patients taking corn oil. Authors state that analysis of 3-day food diaries revealed a consistent pattern of nutrient intake in both study groups (data not shown). Duration of intervention: 6/7 months (depending on allocation)

Kumar 2012

Methods	RCT, parallel, (n3 EPA+DHA vs nil), 12 months Summary risk of bias: Moderate or high
Participants	Patients with persistent atrial fibrillation (AF) on warfarin N: 92 int., 90 control (91 and 87 analysed ITT). Level of risk for CVD: high Male %: 82.4 int., 72.4 control Mean age (SD): 63 (10) int., 61(13) control. Age range: 18-85 (inclusion criteria) Smokers: 22.2% int., 11.5% control Hypertension: 45.6% int., 58.6% control Medications taken by at least 50% of those in the control group: Anti-arrhythmic drugs, Renin-Angiotensin System inhibitors. Medications taken by 20-49% of those in the control group: Statins Medications taken by some, but less than 20% of the control group: NR Location: Australia Ethnicity: NR
Interventions	Type: fish oil capsule Comparison: EPA+DHA vs nil Intervention: 6 capsules/day of a fish oil preparation containing a total dose of 1.02 g of EPA and 0.72 g DHA. Participants in the omega-3 group were asked to continue fish oils till a maximum of 1 year or till return of persistent AF: EPA+DHA 1.74g/d Control: No supplements. Patients were advised not to take any fish oil

supplements
All patients underwent cardioversion following randomisation.
Compliance: was monitored on a weekly basis via telephone and during follow-up by using a pill count plus serum EPA and DHA levels that were significantly increased.
Duration of intervention: 1 year (or AF recurrence)

Kumar 2013

Methods

RCT, parallel, (n3 EPA+DHA vs nil), 12 months
Summary risk of bias: Moderate or high

Participants

Patients >60 years with sinoatrial node disease and dual chamber pacemakers
N: 39 int., 39 control (only 18 vs 39 for 12 months analyses).
Level of risk for CVD: Moderate/high
Male %: 46% int., 56% control
Mean age (SD): 78 (7) int., 77(8) control.
Age range: NR
Smokers: NR
Hypertension: 72%
Medications taken by at least 50% of those in the control group: Statin, Renin-Angiotensin System inhibitors.
Medications taken by 20-49% of those in the control group: Anti-arrhythmic drugs
Medications taken by some, but less than 20% of the control group: NR
Location: Australia
Ethnicity: NR

Interventions

Type: Omega 3 capsule
Comparison: EPA+DHA vs nil
Intervention: a triglyceride preparation containing a total of 6 g/day of omega-3 polyunsaturated fatty acids of which 1.8 g/day were n-3 (1.02 g EPA and 0.72 g DHA): EPA+DHA 1.84g/d
Control: No supplements.
Compliance: measured by weekly dietary history and pill count. Fatty acid status measured at randomisation and between 1-3 months post randomisation (blood samples).
Duration of intervention: median 378 days

Lalia 2015

Methods

RCT, parallel, (n3 EPA+DHA vs MUFA), 6 months
Summary risk of bias: Moderate or high

Participants

Insulin resistant adults
N: 16 int., 15 control. (analysed, int: 14 cont: 11)
Level of risk for CVD: low
Male: 36% int., 18% control.
Mean age (SD): 35.3 (2.9) int., 32.6 (2.5) control
Age range: NR (recruitment criterion was ≥18 years)
Smokers: 0% (exclusion criterion)
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR (Those taking medications that might affect muscle metabolism, such as beta-blockers, corticosteroids, anticoagulants were excluded)
Location: USA
Ethnicity: NR

Interventions

Type: supplement
Comparison: EPA+DHA vs ethyl oleate
Intervention: EPA+DHA as 2x2 softgel capsules/d (2.7g/d EPA+ 1.2g/d DHA): EPA+DHA 3.9g/d
Control: ethyl oleate as 2x2 softgel capsules/d (4.8g/d ethyl oleate)
Compliance: plasma EPA and DHA assessed, both levels were higher in the intervention group at 6 months (p values between 0.05 and 0.10).

Duration of intervention: 6 months

Lau 1993

Methods

RCT, parallel arm, double-blind, placebo controlled (n3 EPA+DHA vs nil), 12 months
Summary risk of bias: moderate to high

Participants

Individuals with definite or classical rheumatoid arthritis as defined by the 1987 American Rheumatism Association criteria and requiring use of non-steroidal anti-inflammatory medication (NSAIDs).
N: 32 int., 32 control (analysed – not reported, drop-out rate suggests int: 23, cont: 16 as no ITT analysis reported)
Level of risk for CVD: Low
Male: 28% int., 31% cont.
Mean age (SD): 49.3 int.; 53.4 cont. (SD not reported)
Age range: 26-73 int., 27-70 cont.
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: None reported
Medications taken by 20-49% of those in the control group: Diclofenac (28.1%)
Medications taken by some, but less than 20% of the control group: Piroxicam (18.8%), Ibuprofen (12.5%), Naproxen (9.4%), Fenbufen (9.4%), Aspirin (9.4%), Ketoprofen (6.3%), Indomethacin (3.1%), Orudis (3.1%)
Location: Scotland
Ethnicity: NR/British
Baseline ESR (mean + range): int. 27 (5-87) mm/hr; cont. 28.5 (5-85) mm/hr
Baseline CRP (mean + range): int. 1.1 (0-8) mg/l; cont. 1.3 (0-4.3) mg/l

Interventions

Type: supplement (fish oil capsule or air-filled capsule)
Comparison: EPA+DHA vs air
Intervention: 10 capsules per day (including 1.71g EPA + 1.14g DHA [MaxEPA]; manufactured and supplied by Glaxo Pharmaceuticals Ltd.: EPA+DHA 2.85g/d
Control: 10 air-filled capsules per day (supplier not reported)
Compliance: capsule count undertaken but result not reported. In MaxEPA treatment group: EPA levels significantly elevated at 6m & 12m and returned to baseline at 15m; DHA significantly elevated at 12m, which persisted to 15m. No significant changes in the levels of EPA, DHA or AA in red cell membrane in placebo group.
Duration of intervention: 12 months (but followed up for 15m)

Lee 2012

Methods

RCT, parallel, (n3 DHA+EPA vs n6 LA), 12 months
Summary risk of bias: Moderate or high

Participants

Population: elderly individuals aged 60 and above, living in 15 low to middle socioeconomic public flats.
N: 18 int., 18 control. (analysed, int: 17 cont: 18)
Level of risk for CVD: Low
Male: 17.6% int., 28% control.
Mean age (SD): 66.4 (5.1) int., 63.5 (3.0) control
Age range: NR
Smokers: 11.8% int; 16.7% control
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Malaysia
Ethnicity: NR
Depression: General population (low risk)
Anxiety: General population (low risk)

Interventions

Type: supplement

Comparison: Docosahexaenoic acid-concentrated fish oil vs corn oil (n6)
Intervention: 3x 1-g soft gelatine capsule daily, containing 430mg of DHA and 150mg of EPA (EPAX 1050TG; EPAX AS, Lysaker, Norway): EPA+DHA 1.75g/d
Control: Isocaloric placebo corn oil 0.6g linoleic acid. (EPAX AS, Lysaker, Norway)
Compliance: Monthly capsule counts found compliance was high: capsule consumption rate 94.5% int., 93.8% control
Duration of intervention: 12 months

Li 2015

Methods

2x parallel arm, prospective, unblinded RCT (n3 EPA+DHA vs nil), 6 months
Summary risk of bias: moderate-high

Participants

People diagnosed with pathological non-alcoholic steatohepatitis (NASH)
N: 39 int., 39 control (analysed: 39 int., 39 cont.)
Level of risk for CVD: Moderate
Male: 87.2% int., 92.3% control.
Mean age (SD): 52.6 (6.6) int., 50.4 (7.2) control
Age range: NR
Smokers: 59% int., 56.4% cont.
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: China
Ethnicity: NR

Interventions

Type: supplement (oil containing PUFA or normal saline)
Comparison: higher EPA+DHA n3 vs lower EPA+DHA n3
Intervention: 50mls PUFA oil (with 1:1 ratio of EPA+DHA) Manufacturer not stated: EPA+DHA unclear
Control: normal saline (volume not stated)
Compliance: NR
Duration of intervention: 24 wks./6 months

Loeschke 1996

Methods

RCT, parallel, (n3 EPA+DHA vs n6 LA), 24 months
Summary risk of bias: Moderate to high

Participants

People with ulcerative colitis in remission
N: 31 int., 33 control. (analysed, int: 31 cont: 33)
Level of risk for CVD: low
Male: 48% int., 55% control.
Mean age (SD) years: 40 (13) int., 39 (11) control
Age range: NR
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: 5-ASA
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Germany
Ethnicity: NR

Interventions

Type: supplement
Comparison: fish oil (LCn3) vs maize oil (n6)
Intervention: 2 capsules 3x/d, each capsule contained 1ml of 85% ethyl esters of LC n-3 fatty acids from fish oil (Fresenius AG, Homburg). Included 1 IU/ml tocopherol and orange flavour: EPA+DHA 5.1g/d
Control: 2 capsules 3x/d of maize oil (Fresenius AG, Homburg). Included 1 IU/ml tocopherol and orange flavour.
Compliance: assessed by detailed interview and capsule count, blood samples were drawn at every presentation. 2 intervention and 1 control participant were found to be noncompliant.
Duration of intervention: 24 months

Lorenz-Meyer 1996

Methods	RCT- parallel, 2 arms (n3 EPA+DHA vs n6 LA), 12 months Summary risk of bias: Moderate or high
Participants	People with Crohn's Disease in remission (but with a recent relapse) N: 70 int., 63 control Level of risk for CVD: Low Male: 35.7% int, 27.0% cont Mean age (SD): 29.5 (9.6) int, 31.8 (10.9) cont Age range: 17-62 int, 17-65 cont Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: Methylprednisolone (All for 1st 8 weeks) Medications taken by 20-49%: NR Medications taken by some, but <20%: NR Location: Germany Ethnicity: NR
Interventions	Type: supplement (fish oil) Comparison: EPA & DHA vs omega 6 Intervention: 2x3 1g gelatine capsules/d of ethylester fish oil concentrate (3.3g/d EPA + 1.8g/d DHA): EPA+DHA 5.1g/d Control: 2x3 1g gelatine capsules/d of corn oil Compliance: Pill count, 5 non-compliant patients, among compliant patients, 18 were censored (for not using the medication for three continuous weeks) Duration of intervention: 12 months

Mantzaris 1996

Methods	RCT, parallel arm, placebo-controlled (n3 EPA+DHA Vs MUFA), 12 months Summary risk of bias: moderate to high
Participants	People with ulcerative colitis in clinical, endoscopic & histological remission N: 27 int., 23 control. (analysed, int: 22 cont: 18) Level of risk for CVD: Low Male: 45% int., 50% control. Mean age (SD): 35 int., 37 control (no SD) Age range: 18-65 int., 17-60 cont. Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: oral mesalazine (1.2g tid) 100% Medications taken by 20-49% of those in the control group: Medications taken by some, but less than 20% of the control group: Location: Greece Ethnicity: NR
Interventions	Type: supplement (oil containing EPA+DHA or olive oil) Comparison: EPA+DHA vs MUFA Intervention: 20ml/d oil containing 3.2g/d EPA & 2.1g/d DHA, manufactured as MaxEPA: EPA+DHA 5.3g/d Control: 20ml/day olive oil Compliance: unclear Duration of intervention: 12 months

MAPT 2017

Methods	Omega-3 Fatty Acids and/or Multi-domain Intervention in the Prevention of Age-related Cognitive Decline (MAPT) RCT, parallel, (n3 EPA+DHA vs non-fat), 36 months Summary risk of bias: Low
Participants	Population: People aged at least 70 years without dementia but with memory complaint, IADL limitation or slow gait speed N: 840 int (groups 1&3), 840 control (groups 2&4) randomised. Numbers

	analysed differ by outcome Level of risk for CVD: Low Male: 37.2% int., 34.5% control. (combined groups) Mean age (SD): 75·6(4·7) & 74.4 (4.4)int., 75·1 (4·3) & 75 (4.1)control Age range: NR Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: France and Monaco Ethnicity: NR Depression: General population (low risk) Anxiety: General population (low risk)
Interventions	Type: supplement Comparison: LCn3 vs paraffin oil Intervention: Arm 1: omega 3 (V0137 CA 800 mg/d DHA; 225mg/d EPA in soft caps): EPA+DHA 1.03g/d Arm 3: omega 3 (V0137 CA 800 mg/d DHA; 225mg/d EPA in soft caps) plus multi-domain intervention (nutrition, physical exercise, cognitive stimulation, social activities): EPA+DHA 1.03g/d Control: Arm 2: paraffin oil capsules containing flavoured paraffin oil. All capsules were supplied by Pierre Fabre Médicament (Castres, France). Arm 4: placebo capsules plus multi-domain intervention (nutrition, physical exercise, cognitive stimulation, social activities) Compliance: Adherence to study interventions was assessed every 6 months. For supplementation, adherence was assessed by counting the number of capsules returned by participants (or based on treatment dates if the number of capsules was missing). Furthermore, biological samples were obtained at baseline and after 12 months to assess concentrations of DHA and EPA in red blood cell membranes. Duration of intervention: 36 months

MARGARIN - Bemelmans 2002

Methods	Mediterranean alpha-linolenic enriched Groningen dietary intervention study (MARGARIN) RCT, factorial 2x2 (n3 ALA vs n6 LA), 2 years Summary risk of bias: Low
Participants	Hypercholesteraemic adults with 2 or more CVD risk factors N: total 282 randomised; 114 int (51 with nutrition education, 58 without NE) 157 control (52 with NE, 105 without NE) Level of risk for CVD: moderate (multiple cardiovascular risk factors, 10 yr. IHD risk ~20%) Male: 41.9% int., 45.7% control Mean age (SD): 54.4 (9.5) int, 53.9 (9.8) control Age range: 30-70 Smokers: 49.1% int., 49.3% control Hypertension: 52.9% int., 45.3% control (on anti-hypertensives) Medications taken by at least 50% of those in the control group: Antihypertensives Medications taken by 20-49%: NR Medications taken by some, but <20%: NR Location: the Netherlands Ethnicity: NS
Interventions	Type: supplement (ALA enriched margarine) Intervention: Provided with ALA rich margarine (80% fat of which 15% was ALA & 46% LA) to be eaten ad libitum: ALA 6g/d Control: Provided with linoleic rich margarine (80% fat of which 0.3% was ALA & 58% LA), identical in taste and packaging. Both margarines contained 0.66 mg/g vitamin E, 9 µg/g vitamin A & 0.023 µg/g vitamin D. Comparison: ALA vs omega 6 Compliance: serum fatty acids used to assess, ALA rose by 0.47 mol% (SD

0.04) & 0.36 mol% (SD 0.04) int arms (with & without NE) and fell by 0.06 mol% (SD 0.04) & 0.11 mol% (SD 0.03) control arms (with & without NE), significantly different.
Duration of intervention: 24 mo.

MARINA - Sanders 2011

Methods

Modulation of Atherosclerosis Risk by Increasing dose of N-3 fatty Acids (MARINA)
RCT, parallel, 4 arms (n-3 EPA+DHA at three different doses vs MUFA), 12 months
Summary risk of bias: Low

Participants

Non-smoking men and women aged 45-70y.
N: Int. 279 in 3 groups (G1 0.45g/d n=94, G2 0.9g/d n=93, G3 1.8g/d n=92)., cont: 88 (analysed G1 0.45g/d n=81, G2 0.9g/d n=80, G3 1.8g/d n=80, cont 71).
Level of risk for CVD: Low
Male: 38.7% int., 38.6% control.
Mean age (CI): G1:55 (53, 56), G2:55 (54, 56), G3: 55 (54, 57) int. 55 (54,57) control
Age range: 45-70
Smokers: 0% int., 0% control
Hypertension: 5.4% int., 5% control.
Medications taken by at least 50% of those in the control group: None
Medications taken by 20-49% of those in the control group: None
Medications taken by some, but less than 20% of the control group: Statins, antihypertensives, HRT, Thyroxine.
Location: UK
Ethnicity: G1: White 80.9%, black 4.3%, Asian 6.4%, Far Eastern 4.3%, Other 4.3%
G2: White 78.5%, black 6.5%, Asian 10.8%, Far Eastern 0%, Other 4.3%
G3: White 85.9%, black 1.1%, Asian 2.2%, Far Eastern 4.3%, Other 6.5%
Control: White 77.3%, black 10.2%, Asian 6.8%, Far Eastern 2.3%, Other 3.4%

Interventions

Type: supplement (fish oil capsules)
Comparison 1: EPA & DHA vs MUFA
Comparison 2: high EPA & DHA vs low EPA & DHA
Intervention: 3x1g oil gelatine capsule/day consisting of blend of EPA concentrate, DHA concentrate, Refined olive oil and 0.1wt% peppermint oil. Providing a daily dose of; 0.45g, 0.9g, or 1.8g per day (all with EPA/DHA ratio of 1.51): EPA+DHA 0.45g/d or 0.9g/d or 1.8g/d
Control: 3 gelatine capsules/ day containing refined olive oil + 0.1% peppermint oil
Compliance: measured by capsule counting and erythrocyte lipids for proportion of EPA/DHA @ baseline, 6m, 12m. 88.5% of participants consumed >90% of capsules provided. EPA and DHA in erythrocyte lipids increased in dose-dependent manner compared with placebo, indicating long-term compliance with intervention.
Length of intervention: 12 months

Martinez 2014

Methods

RCT, parallel, (n3 EPA+DHA vs unclear), 12 months
Summary risk of bias: Moderate or high

Participants

People treated for chronic periodontitis
N: 7 int., 8 control. (analysed, int: 7 cont: 8)
Level of risk for CVD: low
Male: 43% int., 38% control.
Mean age (SD) yrs.: 43.1 (6.0) int., 46.1 (11.6) control
Age range: NR
Smokers: 0% int., 13% control
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR

	Medications taken by some, but less than 20% of the control group: NR Location: Brazil Ethnicity: non-white 4 of 7 (57%) int, 2 of 8 (25%) placebo, others white
Interventions	Type: supplement Comparison: EPA+DHA vs "placebo" Intervention: 3 capsules/d EPA+DHA (Quintaessencia, 0.18g/d EPA, 0.12g/d DHA): EPA+DHA 0.9g/d Control: 3 capsules/d "placebo" - not defined (Quintaessencia) Compliance: assessed by return of empty capsule containers and weekly discussion about intake, difference between intervention and control at 12 months was statistically significant for EPA but not DHA or DPA. Duration of intervention: 12 months

Mate 1991

Methods	2 arm parallel RCT (n3 EPA+DHA vs nil), 24 months Summary risk of bias: moderate-high
Participants	People with Crohn's Disease in remission N: 19 int., 19 control. (analysed, int: 15 cont: 13) Level of risk for CVD: Low Male: 42% int., 58% control. Mean age (SD): 35 int., 34 control (no SD) Age range: NR Smokers: NR Hypertension: NR No meds allowed Location: Spain Ethnicity: NR
Interventions	Type: supplement/dietary advice (diet with high content fish oil [100-200g/wk. cold water fish meat OR 100g/wk. fish pate OR 250g/wk. fish oil supplements] or free diet) Comparison: more EPA+DHA vs less EPA+DHA Intervention: 100-200g/wk. cold water fish meat OR 100g/wk. fish pate OR 250g/wk. fish oil supplements (no dose or goal for omega 3 fats stated): EPA+DHA dose unclear Control: free diet Compliance: NR Duration of intervention: 24 months

MEMO - Van de Rest 2008

Methods	Mental health in Elderly Maintained with Omega-3 (MEMO) RCT, 3 arm parallel (n3 EPA-DHA high vs low dose vs MUFA), 6 months Summary risk of bias: Moderate or high
Participants	Independently living people aged at least 65 years N: 96 int high dose, 100 int low dose, 106 control. (analysed, 96 int high dose, 100 int low dose, 103 cont) Level of risk for CVD: low Male: 55% int high dose, 55% int low dose, 56% control Mean age (SD), years: 69.9 (3.4) int high dose, 69.5 (3.2) int low dose, 70.1 (3.7) control Age range: unclear, ≥65 years Smokers (current): 8% int high dose, 8% int low dose, 10% control Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR (pharmacologic antidepressants and medication for dementia were not allowed) Location: Netherlands Ethnicity: NR Depression: General population (low risk) Anxiety: General population (low risk)

Interventions	Type: supplement Comparison: high EPA+DHA vs low EPA+DHA vs MUFA Intervention high dose:1800mg/d EPA+DHA, 6 soft gelatine capsules/d, Banner pharmacaps: EPA+DHA 1.8g/d Intervention low dose: 400mg/d EPA+DHA, 6 soft gelatine capsules/d, Banner pharmacaps: EPA+DHA 0.4g/d Control: sunflower oil high in oleic, 6 soft gelatine capsules/d, Banner pharmacaps Compliance: "judged according to counts of capsules returned and a diary", “Adherence was excellent and did not differ between the treatment groups" Duration of intervention: 26 weeks

MENU - Rock 2016

Methods	Metabolism, Exercise and Nutrition at UCSD (MENU) RCT, parallel, (n3 ALA vs nil), 12 months Summary risk of bias: Moderate or high
Participants	Overweight and obese women, of whom half were insulin resistant N: 82 int., 81 control. (analysed, int: 65 cont: 61) Level of risk for CVD: low Male: 0% int., 0% control. Mean age (SD) yrs.: 51 (NR) int., 50 (NR) control Age range: 22-67 yrs. int, 25-72 cont Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: 10% were on cholesterol medications Location: USA Ethnicity: Hispanic 18% int, 14% cont; black 9% int, 3% cont; Asian American 1% int, 4% cont; white non-Hispanic 71% int, 78% cont.
Interventions	Type: food & advice Comparison: walnut rich moderate fat diet (ALA) vs moderate fat diet (MUFA) Intervention: advice to follow walnut-rich higher fat diet (35%E fat with limited SFA, MUFA encouraged, including 42g/d walnuts (provided by study), 45%E CHO, 20%E protein). Participants given print materials on diet & exercise, attended group sessions weekly for 1st 4 months, biweekly for next 2 months, then monthly to 1 year), provided web-based tracking for dietary constituents, scale, pedometer, measuring cups and exercise videos. Regular dietetic and group leader support. Clinic visits were at 0, 6 and 12 months: ALA dose unclear Control: Exactly as intervention for goals, materials and support except higher fat diet did not include walnuts (35%E fat with limited SFA, MUFA encouraged, 45%E CHO, 20%E protein) Compliance: Walnut consumption reported on form and nuts provided. Red blood cell ALA significantly higher in int at 12 months than control. Duration of intervention: 12 months

MIDAS 2010

Methods	Memory Improvement With Docosahexaenoic Acid Study (MIDAS) RCT, parallel, 2 arms (n3 DHA vs n6 LA), 24 weeks. Summary risk of bias: Low
Participants	Healthy older American people with subjective memory complaints (not meeting threshold for dementia diagnosis) N: 242 int., 243 control. (analysed, int: 219 cont: 218) Level of risk for CVD: Low Male: 44% int., 40% control. Mean age (SD): 70 (9.3) int., 70 (8.7) control Age range: NR but ≥55 years inclusion criteria Smokers: NR Hypertension: 43% (both arms)

Medications taken by at least 50% of those in the control group: Lipophilic statins
Medications taken by 20-49% of those in the control group: Other statins, diuretics, aspirin, multivitamins.
Medications taken by some, but less than 20% of the control group: ACE inhibitors, Ca++ channel blockers, Beta-blockers
Location: USA
Ethnicity: ~84% white American

Interventions

Type: supplement
Comparison: DHA vs corn and soy oil
Intervention: 3x 300mg capsule/d (total = 900mg/d DHA , *DSM Nutritional Products, Inc.*): DHA 0.9g/d
Control: 3 capsules/d (comprised of 50% corn oil & 50% soy oil).All capsules were orange-flavoured and orange colour to protect blinding.
Compliance: Capsule count at each visit, week 24 change from baseline plasma phospholipid DHA level. Change greater than 1.5 wt% (based on historical dose response plasma DHA levels) was considered compliant for the DHA group. Mean plasma DHA levels at 24 weeks met this criterion, and were significantly greater for intervention group compared to controls.
Duration of intervention: 24 weeks

Mita 2007

Methods

RCT, parallel, (n3 EPA vs nil), 2 years
Summary risk of bias:

Participants

Japanese type 2 diabetics
N: Int. 40, cont: 41 (analysed 30, 30).
Level of risk for CVD: Moderate
Male: 53% int., 67% control.
Mean age (SD): 59 (11.2) int. 61.2 (8.4) control
Age range: NR
Smokers: 40% int., 43% control
Hypertension: NR
Medications taken by at least 50% of those in the control group: Oral hypoglycaemics
Medications taken by 20-49% of those in the control group: Insulin, lipid-lowering drugs, antihypertensives.
Medications taken by some, but less than 20% of the control group: Antithrombotics
Location: Japan
Ethnicity: 100% Japanese

Interventions

Type: supplement (EPA oil capsules)
Comparison: EPA vs nil
Intervention: 1800mg/d EPA EPADEL capsules (Mochida Pharmaceutical Co Ltd Japan)- 98% pure ethyl-ester EPA (unclear how many caps): EPA+DHA 1.8g/d
Control: no intervention
Compliance: Checked during 3 month reviews throughout trial and 5 participants were excluded for poor compliance but no details on method or results.
Length of intervention: mean 2.1 (0.2) years

NAT2 2013

Methods

Nutritional AMD Treatment 2 (NAT2)
RCT, parallel, (n3 EPA+DHA vs MUFA), 36 months
Summary risk of bias: Low

Participants

Patients with early age related macular degeneration
N: 150 int., 150 control.
Level of risk for CVD: High (92.5% intervention and 79.8 controls had past CVD)
Male: 31.3% int., 39.5% control.
Mean age (SD): 73.9 (6.6) int., 73.2 (6.8) control
Age range: 55-85

	Smokers: 6.7% int., 8.5% control Hypertension: 58% total (not reported by study arm) Medications taken by at least 50% of those in the control group: lipid lowering medication Medications taken by 20-49% of those in the control group: Agents acting on Renin-Angiotensin system, anti-inflammatory and anti-rheumatic products. Medications taken by some, but less than 20% of the control group: Insulin or blood sugar lowering drugs Location: France Ethnicity: Unclear
Interventions	Type: Supplement (fish oil capsule) Comparison: EPA & DHA vs MUFA Intervention: 3 daily fish oil capsules (EPA: 270mg/d DHA: 840mg/d) and vitamin E: 6mg/d: EPA+DHA 1.11g/d Control: 3x 602mg olive oil capsules a day containing 0.2g total PUFA and vitamin E: 0.09g/day. Compliance: assessed during visits from unused capsules and serum PUFA levels. Overall compliance over the 3 years; 69.4% intervention, 70.5% control. Length of intervention: 36 months

NEURAPRO-E 2017

Methods	A comparison study of fish oil capsules and psychological therapy versus placebo capsules and psychological therapy in patients at risk of developing a psychotic disorder (NEURAPRO-E) RCT, parallel, (n3 EPA+DHA vs mixed fats), 6 months Summary risk of bias: Moderate or high
Participants	Population: Young people at ultra-high risk for psychotic disorders N: 153 int., 151 control. (analysed, int: 114 cont: 111) Level of risk for CVD: Male: 45.7% for all participants. Mean age (SD): 19.1 (4.6) for all participants Age range: NR Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: Australia, Switzerland, Germany, China, Austria, Singapore, Netherlands Ethnicity: NR Depression: Long term condition (high risk) Anxiety: Long term condition (high risk)
Interventions	Type: supplement Comparison: n-3 capsules vs paraffin & coconut oil Intervention: Omega-3 fatty acids: 2.8g of marine fish oil containing approximately 1.4g Eicosapentaenoic acid (EPA)/Docosahexaenoic acid (DHA) in 4 X 0.700g capsules, administered orally, daily. Plus cognitive behavioural case management (CBCM): A manualised intervention of cognitive-behavioural therapy (CBT) embedded within case management: EPA+DHA 1.4g/d Control: The placebo capsule will match the fish oil capsules in size and appearance contain paraffin/coconut oil, tocopherols to match the content in the active ingredient and a small proportion of the fish oil to ensure the placebo capsules have the same odour as the active capsules. Plus CBCM. Compliance: Patient compliance was assessed by monthly pill counts over the first 6 months of the study, as well as through the measurement of the essential fatty acid content of red blood cells from blood samples collected at baseline and 6 months after study entry (or at the transition assessment

if applicable).
There were 66 adherent participants (43.1%) in the ω-3 PUFA group and 62 in the placebo group (41.1%). However, a total of 83 participants had missing data for the capsule counts (ω-3 PUFA, 35; placebo, 48), 9 of whom (10.8%) transitioned to psychosis. To avoid losing participants from the analysis, these 83 individuals were assumed to be nonadherent
Duration of intervention: 6 months

Nigam 2014

Methods
RCT, parallel, (n3 ALA vs n6 LA vs MUFA), 6 months
Summary risk of bias: Moderate or high

Participants
People with non-alcoholic fatty liver disease
N: 30 n6 int., 33 ALA int, 30 MUFA control. (analysed 30 n6 int., 30 ALA int, 30 MUFA control)
Level of risk for CVD: moderate
Male: 100% n6 int., 100% ALA int, 100% MUFA control
Mean age (SD): 36.2 (7.1) n6 int., 38.0 (6.4) ALA int, 37.2 (6.2) MUFA control
Age range: NR but 20-50years were the inclusion criteria
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: India
Ethnicity: NR

Interventions
Type: food
Comparisons: n6 vs MUFA, also ALA vs MUFA, also ALA vs n6
n6 Intervention: to use up to 20g/d of soybean or safflower oil for cooking (15-24% MUFA, 50-60% PUFA, n6/n3 7 for soya or >100 for safflower)
ALA Intervention: to use up to 20g/d of canola oil for cooking (61% MUFA, 7% SFA, 21%n6 PUFA, 11% ALA): ALA 2.2g/d
Control: to use up to 20g/d of olive oil for cooking (70% MUFA, 15% SFA, 9%n6 PUFA, 1% ALA)
Compliance: Assessed using FFQ, 24 hour recall and 3 day food diary (unclear how many or how often). Paper states that 1 person was excluded from the canola group for non-compliance but this was not defined. No further compliance details.
Duration of intervention: 6 months

Niki 2016

Methods
RCT, parallel, (n3 EPA vs nil (both with strong statin)), 6 months
Summary risk of bias: Moderate or high

Participants
Patients with angina and hypertension treated with strong statins
N: 48 int., 47 control, but only 62 received treatment (?) (analysed, int: 29 cont: 30)
Level of risk for CVD: high
Male: 72% int., 63% control.
Mean age (SD): 68.1 (10.1) int., 69.4 (10.7) control
Age range: NR
Smokers: 0% both arms
Hypertension: 100% both arms
Medications taken by at least 50% of those in the control group: statins, aspirin (100%), thienopyridine (anti-platelet, 100%)
Medications taken by 20-49% of those in the control group: ACE inhibitors 23%, Angiotensin II receptor blocker 37%, calcium channel blocker 43%, beta-blockers 30%
Medications taken by some, but less than 20% of the control group: NR
Location: Japan
Ethnicity: NR

Interventions
Type: supplement
Comparison: EPA ester vs nil

Intervention: 1.8g/d EPA ester (brand and form unclear): EPA 1.8g/d
Control: nil
Compliance: NR
Duration of intervention: 6 months

Nishio 2014

Methods
RCT, parallel, (n3 EPA vs nil, both with statin), 9 months
Summary risk of bias: Moderate or high

Participants
People with untreated dyslipidaemia and thin-cap fibroatheroma
N: 16 int., 15 control. (analysed, int: 15 cont: 15)
Level of risk for CVD: High (all were at increased risk, and over half had had ACS)
Male: 87% int., 87% control.
Mean age (SD) yrs.: 61 (12.6) int., 63.8 (9.5) control
Age range: NR
Smokers: 80% int., 60% control
Hypertension: 73% int., 67% control
Medications taken by at least 50% of those in the control group: aspirin (100%), Clopidogrel (100%), ACE-I or ARB (60%)
Medications taken by 20-49% of those in the control group: beta-blockers (20%), calcium channel blockers (33%)
Medications taken by some, but less than 20% of the control group: antidiabetic agents (13%)
Location: Japan
Ethnicity: NR

Interventions
Type: supplement
Comparison: EPA vs nil
Intervention: 1.8g/d EPA plus rosuvastatin (dose adjusted to reach LDL <70mg/dl or <1.8mmol/l): EPA 1.8g/d
Control: no placebo, just rosuvastatin (dose adjusted to reach LDL <70mg/dl or <1.8mmol/l)
Compliance: assessed using blood lipids, statistically significant difference in EPA/AA ratio in blood lipids at 9 months between arms (p=0.0001)
Duration of intervention: 9 months

Nodari 2009

Methods
RCT, parallel, (n3 EPA+DHA vs MUFA), 6 months
Summary risk of bias: Moderate or high

Participants
People with cardiomyopathy and frequent or repetitive ventricular arrhythmia
N: 22 int., 22 control. (analysed, int: 21 cont: 20)
Level of risk for CVD: high
Male: 95% int., 86% control.
Mean age (SD) yrs.: 61.1 (11.2) int., 64.8 (9.5) control
Age range: NR
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: ACE inhibitors 77%, beta blockers 100%, aldosterone 54%, furosemide 95%, amiodarone 95%
Medications taken by 20-49% of those in the control group: ARBs 23%
Medications taken by some, but less than 20% of the control group: NR
Location: Italy
Ethnicity: NR

Interventions
Type: supplement
Comparison: EPA+DHA vs y
Intervention: 5x1g capsules for 1 month then 1 capsule/d for the remaining 5 months (later stable dose 0.87g/d EPA plus 1.44g/d DHA): EPA+DHA 2.31g/d
Control: 5x1g capsules for 1 month then 1 capsule/d of olive oil for the remaining 5 month, of identical appearance to intervention
Compliance: assessed by plasma EPA, DHA and DPA, which increased in

	the intervention, but not the control, group Duration of intervention: 6 months

Nodari 2011 AF

Methods	RCT, parallel, (n3 DHA+EPA vs MUFA), 12 months Summary risk of bias: Moderate or high
Participants	Patients with persistent atrial fibrillation with at least 1 relapse after cardioversion N: 102 int., 103 control. (analysed, int: 94 cont: 94) Level of risk for CVD: high Male: 70% int., 63% control. Mean age (SD): 70 (6) int., 69 (9) control Age range: NR (18-80 inclusion criteria) Smokers: 10% int., 9.1% control. Hypertension: 47% int., 40% control. Medications taken by at least 50% of those in the control group: beta-blockers, ACE inhibitors, anticoagulant therapy, amiodarone. Medications taken by 20-49% of those in the control group: Diuretics, antiplatelet, statins. Medications taken by some, but less than 20% of the control group: calcium channel blockers. Location: Italy Ethnicity: NR
Interventions	Type: supplement (Omacor) Comparison: EPA & DHA vs MUFA Intervention: 2x1g/d Omacor (total 1.7g/d EPA+DHA at a ratio of 0.9 to 1.5): EPA+DHA 1.7g/d Control: 2x1g/d olive oil (gelatine capsules identical in appearance to Omacor) Compliance: No details Duration of intervention: 12 months

Nodari 2011 HF

Methods	RCT, parallel, (n3 DHA+EPA vs MUFA), 12 months Summary risk of bias: Moderate or high
Participants	People with heart failure (non-ischaemic dilated cardiomyopathy) N: 67 int., 66 control. (analysed, int: 67 cont: 66) Level of risk for CVD: high Male: 95.5% int., 84.9% control. Mean age (SD): 61 (11) int., 64 (9) control Age range: NR (18-75 inclusion criteria) Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: beta-blockers, ACE inhibitors, furosemide, amiodarone, aldosterone blockers Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: statins, ARB Location: Italy Ethnicity: NR
Interventions	Type: supplement (Omacor) Comparison: EPA & DHA vs MUFA Intervention: 2x1g/d Omacor (1.7g/d EPA+DHA at a ratio of 0.9 to 1.5): EPA+DHA 1.7g/d Control: 2x1g/d olive oil (gelatine capsules identical in appearance to Omacor) Compliance: Pill counts - participants were withdrawn if <80% capsules taken (none were withdrawn). Fatty acid EPA+DHA 0.83% in intervention group, 0.41% in control group. Duration of intervention: 12 months

Nogueira 2016

Methods	RCT, parallel, (n3 EPA+DHA vs non-fat), 6 months Summary risk of bias: Moderate or high
Participants	Patients with non-alcoholic steatohepatitis N: 32 int., 28 control. (analysed, int: 27 cont: 23) Level of risk for CVD: Low Male: 14.8% int., 21.7% control Mean age (SD): 52.5 (7.2) int., 53.9 (6.8) control Age range: NR Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: Brazil Ethnicity: NR
Interventions	Type: supplement (capsules with n-3 PUFA or mineral oil) Comparison: n-3 (EPA+DHA+ALA) vs nil Intervention: 3 capsules/d omega 3 (including 0.6g/d ALA, 0.194g/d EPA + 0.15g/d DHA, Amway): EPA+DHA 0.345g/d plus ALA 0.6g/d Control: 3 capsules/d placebo mineral oil capsules Compliance: Plasma fatty acid changes Duration of intervention: 6 months

Nomura 2009

Methods	RCT, parallel, (n3 EPA vs nil, both with statins), 6 months Summary risk of bias: Moderate or high
Participants	Hyperlipidaemic type 2 diabetics N: 72 int., 64 control. (analysed, int: 72 cont: 64) Level of risk for CVD: Moderate Male:52.9% in both groups combined Mean age (SD): 65 (3) in both groups combined Age range: NR Smokers: 11% in both groups combined Hypertension: 44% in both groups combined Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: Insulin, aspirin, Ticlopidine, Ca-antagonists, ARBs, sulfonylureas, alpha-glucoside inhibitors Location: Japan Ethnicity: NR
Interventions	Type: supplement (EPA + Pitavastatin vs Pitavastatin) Comparison: EPA vs none Intervention: Daily capsules (1.8g/d EPA + 2mg/d Pitavastatin): EPA 1.8g/d Control: Daily capsules (2mg/d Pitavastatin) Compliance: NR Duration of intervention: 6 months

Norouzi 2014

Methods	RCT, parallel, (n3 EPA+DHA vs unclear), 14 months Summary risk of bias: Moderate or high
Participants	Patients with chronic traumatic spinal cord injury. N: 55 int., 55 control. (analysed, int: 54 cont: 50) Level of risk for CVD: low Male: 81.5% int., 82% control. Mean age (SD): 51.15 (13.43) int., 54.12 (11.76) control Age range: 15-74 int., 30-74 control Smokers: 0% (exclusion criteria) Hypertension: NR

	Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: Iran Ethnicity: NR
Interventions	Type: supplement (n-3 capsules) Comparison: EPA & DHA vs placebo (unclear what) Intervention: 2 MorDHA capsules (providing 870mg DHA and 130mg EPA) per day: EPA+DHA 1.0g/d Control: 2 placebo capsules per day. Both capsules were similar in colour, shape, and taste. Both groups received one calcium capsules per day consisting of 1000mg calcium and 400IU vitamin D. Compliance: Pill counts - compliance averaged 80% in both groups. Duration of intervention: 14 months

Norwegian - Natvig 1968

Methods	Norwegian Vegetable Oil Experiment of 1965-6 RCT, parallel, 2 arms (n3 ALA vs n6 LA), 1 year. Risk of bias: Moderate or high
Participants	Men working in Norwegian companies aged 50-59 years N: 6716 int., 6690 control Level of risk for CVD: Low (working men, though a few had had a previous MI or angina) Male: 100% Mean age (SD): Unclear Age range: 50-59 Smokers: Unclear (~48% non-smokers) Hypertension: Unclear Medications taken by at least 50% of those in the control group: NS Medications taken by 20-49% of those in the control group: NS Medications taken by some, but less than 20% of the control group: NS Location: Norway Ethnicity: Unclear
Interventions	Type: supplement (oil) Comparison: ALA vs omega 6 Intervention: linseed oil, 10 ml /d (55% ALA), 5.5g/d ALA, 1.5g/d linoleic: ALA 5.5g/d Control: sunflower oil, 10 ml/d (1.4% ALA), 0.1g/d ALA, 6.3g/d linoleic. Vitamin E was added to both oils. Compliance: 73% were still taking the linseed oil at 1 yr., 72% were still taking their sunflower oil at 1 yr. (unclear how this was ascertained). Duration of intervention: 12 mo.

NutriStroke 2009

Methods	NutriStroke RCT, parallel, (n3 EPA+DHA vs nil), 12 months Summary risk of bias: Moderate or high
Participants	People in a rehabilitation unit who had survived a stroke N: 38 int., 34 control. (analysed, int: 32 cont: 20) Level of risk for CVD: high Male: 74% int., 56% control. Mean age (SD): 61.3 (13.6) n3, 66.3 (11.4) n3+antiox int., 68.4 (12.6) placebo, 65.1 (12.8) antiox - control Age range: NR Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: Italy Ethnicity: NR

Interventions

Type: supplement (capsule)
Comparison: fish oil vs placebo
Intervention: fish oil gelatine capsules including 250mg DHA & 250mg EPA, as well as diet rich in vitamins and omega 3: EPA+DHA 0.5g/d
Control: "identical to supplement but contained no antioxidants or polyunsaturated fatty acids" as well as diet rich in vitamins and omega 3
Compliance: Appears to have been assessed at meetings or on the phone monthly, but results unclear.
Duration of intervention: 12 months

Nye 1990

Methods

Randomisation: parallel, 3 groups (n3 EPA vs MUFA vs aspirin & dipyridamole), 1 year
Risk of bias: Moderate or high

Participants

People undergoing PTCA
N: 36 int., 37 control (also 35 allocated to arm 3, aspirin and dipyridamole)
Level of risk for CVD: High (people undergoing angioplasty)
Male: 78% int., 76% control
Mean age (SD): 54 (8) int., 55 (8) control years
Age range: Unclear
Smokers: Unclear
Hypertension: Unclear
Medications taken by at least 50% of those in the control group: NS
Medications taken by 20-49% of those in the control group: NS
Medications taken by some, but less than 20% of the control group: NS
Location: New Zealand
Ethnicity: Unclear

Interventions

Type: supplement (capsules)
Comparison: EPA vs MUFA
Intervention: MaxEPA capsules 12/d (2.2g EPA): EPA 2.2g/d
Control: olive oil capsules, 12/d, identical to MaxEPA. Both capsules had vitamin E.
Compliance: no data
Length of intervention: 12 mo.

OFAMI - Nilsen 2001

Methods

Omacor Following Acute Myocardial Infarction (OFAMI)
RCT, parallel, 2 arms (n3 EPA+DHA vs n6 LA), 2 years
Summary risk of bias: Moderate or high

Participants

Patients recruited 4-8 days after confirmed MI
N: 150 int., 150 control
Level of risk for CVD: High
Male: 77% int., 82% control
Mean age (SD): 64.4 int., 63.6 control (no SD)
Age range: 28-86 int., 29-87 control
Smokers: 39% int., 38% control
Hypertension: 29% int., 23% control
Medications taken by at least 50% of those in the control group: B-blockers, aspirin
Medications taken by 20-49% of those in the control group: statins, ACE inhibitors
Medications taken by some, but less than 20% of the control group: diuretics, warfarin
Location: Norway
Ethnicity: Unclear

Interventions

Type: supplement (capsules)
Comparison: EPA & DHA vs omega 6
Intervention: Omacor capsules 4/d: EPA+DHA 3.5g/d
Control: corn oil capsules, 4/d
Compliance: assessed by questionnaire and capsule count, 82% int group had complete compliance after 6 weeks, 86% of controls
Length of intervention: 24 mo.

OFAMS 2012

Methods	Omega-3 Fatty Acid Treatment in Multiple Sclerosis (OFAMS) RCT, parallel, (n3 EPA+DHA vs n6 LA), 6 months Summary risk of bias: Moderate to high
Participants	Population: Relapsing remitting multiple sclerosis N: 46 int., 46 control. (analysed, int: 46 cont: 45) Level of risk for CVD: Low Male: 34% int., 36% control. Mean age (SD): 38.8 (8.4) int., 38.3 (8.4) control Age range: NR Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: Norway Ethnicity: NR Depression: Long term condition (high risk) Anxiety: Long term condition (high risk)
Interventions	Type: supplement Comparison: EPA & DHA vs corn oil Intervention: 5 capsules/day 1-g Triomar capsules (Pronova Biocare), containing 60% ω-3 fatty acids: 270 mg of eicosapentaenoic acid (EPA) and 170 mg of docosahexaenoic acid per gram. Four international units of α-tocopherol per gram were added for antioxidative protection: EPA+DHA 2.2g/d Control: 5 1g capsules/day corn oil Compliance: Sera samples for total monounsaturated and unsaturated fatty acids, saturated fatty acids, and n-3 and n-6 fatty acids were collected at baseline and months 6, 12, and 24 Duration of intervention: 6 months

OFFER 2015

Methods	Omega-3 Fatty Acids Efficacy in First-episode of Schizophrenia (OFFER) RCT, parallel, (n3 EPA+DHA vs MUFA), 6 months Summary risk of bias: Low
Participants	Population: people with first episode of schizophrenia aged 16–35 N: 36 int., 35 control. (analysed, int: 32 cont: 33) Level of risk for CVD: Low Male: 52.8% int., 65.7% control. Mean age (SD): 23.2 (4.8) int., 23.3 (4.8) control Age range: NR Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: benzodiazepines (51.4%) Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: antidepressants (17.1%); mood stabilizers (11.4%); anticholinergics (8.6%) Location: Poland Ethnicity: NR Depression: Current / Historical / Long term condition (high risk) / General population (low risk) Anxiety: Current / Historical / Long term condition (high risk) / General population (low risk)
Interventions	Type: supplement Comparison: capsules with EPA & DHA vs olive oil Intervention: The active treatment was yellow gel capsules filled with concentrated fish oil containing 0.33 g of EPA and 0.22 g of DHA in each capsule. The daily dose of 4 capsules provided 2.2 g of n-3 PUFA, i.e.: 1.32 g/day of EPA plus 0.88 g/day of DHA: EPA+DHA 2.2g/d

Control: Placebo capsules were prepared to match the active treatment in appearance and flavour. The placebo contained also a scant amount of fish oil to provide a comparable taste and smell of the different capsules.
The study medication (concentrated fish oil and placebo) was provided by Marinex International Sp. z o.o. and shipped from Scandinavian Laboratories, Inc. Mt. Bethel, PA, USA
Compliance: Adherence to study intervention was monitored through patient/parent self-report and pill count at each medication appointment
Duration of intervention: 6 months

OMEGA - Senges 2009

Methods

Effect of Omega 3 fatty acids on reduction of sudden cardiac death after MI (OMEGA)
2 arm, parallel RCT (n3 EPA+DHA vs MUFA), 12mo
Summary risk of bias: Low

Participants

People who have had an acute myocardial infarction
N: 1940 int.,1911 control (analysed for primary endpoints 1919 int., 1885 control)
Level of risk for CVD: High
Male: 75.1% int., 73.7% control
Age (Median): 64.0, int., 64.0 control
Age range: Unclear (upper & lower quartiles 54-72)
Smokers: 35.9% int, 37.5% control
Hypertension: 66.9% int, 66.1% control
Medications taken by at least 50% of those in the control group: statins, ACE inhibitors, beta-blockers, Clopidogrel, aspirin.
Medications taken by 20-49%: diuretics
Medications taken by some, but <20%: AT1 receptor blockers, vitamin K antagonist, calcium channel blockers, digitalis, amiodarone, oral antidiabetics, insulin.
Location: Germany
Ethnicity: NS

Interventions

Type: supplement (capsules)
Comparison: EPA & DHA vs MUFA
Intervention: 1x1g/d Pronova BiCare soft gelatine capsule 'zodin' omega-3 acid ethyl esters (460mg/d EPA and 386mg/d DHA): EPA+DHA 0.846g/d
Control: 1x1g/d olive oil capsule identical to intervention
Compliance: 93.1% of int group and 93.2% of control participants took >70% of capsules
Duration of intervention: 12 months

OMEGA-Remodel 2016

Methods

Effect of Fish Oil Supplementation in People who have recently had a heart attack (OMEGA-Remodel)
RCT, parallel, (n3 EPA+DHA vs n6 LA), 6 months
Summary risk of bias: Moderate or high

Participants

People after acute MI
N: 180 int., 178 control. (analysed, int: 180 cont: 178)
Level of risk for CVD: high
Male: 82% int., 79% control.
Mean age (SD) yrs.: 60 (10) int., 58 (10) control
Age range: NR
Smokers: 13% int., 20% control
Hypertension: 66% int., 63% control
Medications taken by at least 50% of those in the control group: dual antiplatelet, beta blockers, statins, ACE inhibitors or ARBs
Medications taken by 20-49% of those in the control group: nil
Medications taken by some, but less than 20% of the control group: calcium channel blocker, aldosterone antagonists, insulin, nitroglycerin, diuretics
Location: US
Ethnicity: NR

Interventions	Type: supplement Comparison: EPA+DHA vs corn oil Intervention: 4x1g/d fish oil capsules with meals (Lovaza including 1.86g/d EPA plus 1.5g/d DHA, GlaxoSmithKline). Encouraged to avoid over the counter fish oil and follow usual post-MI dietary instructions with no specific advice on omega 3 intake: EPA+DHA 3.36g/d Control: 4x1g/d corn oil capsules with meals (including 2.4g/d LA and no EPA or DHA). Encouraged to avoid over the counter fish oil and follow usual post-MI dietary instructions with no specific advice on omega 3 intake Compliance: 2-monthly scripted telephone interviews to assess pill counts (also tolerance and adverse events), also red blood cell fatty acids. DPA, DHA and EPA were all significantly higher in intervention than control participants at 6 months. Duration of intervention: 6 months

OmegAD 2008

Methods	Omega-3 and Alzheimer's Disease (OMEGA AD) RCT, cross-over, (n3 EPA+DHA vs. n6 LA), 6 months. Summary risk of bias: Moderate or high
Participants	People in Sweden with mild to moderate Alzheimer's disease and stable comorbidities. N: 103 int., 101 control (analysed int: 91 cont: 87). Level of risk for CVD: Low. Male: 43% int., 54% control. Mean age (SD): 72.6 (9.0) int., 72.9 (8.6) control. Age range: NR. Smokers: 9% int., 10% control. Hypertension: NR Medications taken by at least 50% of those in the control group: ACE inhibitors Medications taken by 20-49% of those in the control group: acetylsalicylic acid, antidepressants. Medications taken by some, but less than 20% of the control group: neuroleptic agents, statins herbal medications Location: Sweden Ethnicity: NR Depression: Long term condition (high risk) Anxiety: Long term condition (high risk)
Interventions	Type: Supplement Comparison: DHA+EPA vs. corn oil Intervention: Four 1-g capsules daily, each containing 430 mg DHA and 150 mg EPA (daily total = 1.72g/d DHA and 600 mg EPA: EPAX1050TG; Pronova Biocare A/S, Lysaker, Norway): EPA+DHA 2.32g/d Control: 4 capsules/d (comprised of mostly corn oil as well as total 600 mg/d of linoleic acid). Compliance: Blood samples for analyses of serum fatty acid levels were Obtained to assess compliance with the n-3 fatty acid therapy. The patients in the n-3–treated group showed mean 2.4-and 3.6-fold increases in the ratios of DHA and EPA, respectively, in serum after the first 6 months. Corresponding mean values for the placebo-treated patients were 0.95 and 0.96, respectively. Duration of intervention: 6 months

OPAL - Dangour 2010

Methods	Older People And n- 3 Long-chain polyunsaturated fatty acid (OPAL) 2 arm, parallel, RCT, 12mo (n3 EPA+DHA vs MUFA) Summary risk of bias: Low
Participants	Healthy cognitively normal adults aged 70-79 N: 434 int., 433 control (analysed 376 int., 372 control) Level of risk for CVD: Low Male: 53.4% int., 56.6% control Mean age (SD): 74.7 (2.5) int., 74.6 (2.7) control Age range: 70-79 years

Smokers: NR
Hypertension: 54.9% int, 56.9% control
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49%: NR
Medications taken by some, but <20%: NR
Location: England and Wales
Ethnicity: NR

Interventions

Type: supplement (capsules)
Comparison: EPA & DHA vs MUFA
Intervention: 2x 650 mg capsule/d Ocean Nutrition vanilla flavoured soft gelatine capsule (total daily dose of 200mg EPA and 500mg DHA): EPA+DHA 0.7g/d
Control: 2 x 650mg olive oil capsule identical to intervention
Compliance: Count returned capsules. Capsules not returned (Int., median: 0.95; IQR:0.82, 1.00; control median: 0.95; IQR: 0.81, 1.00). Fatty acid data: EPA, int., 49.9, 2.7 (mean, SD); control, 39.1, 3.1. DHA, int., 95.6, 3.1; control, 70.7, 2.9. ALA: int., 21.5, 0.8; control, 22.0, 0.9.
Length of intervention: 24 mo.

OPTILIP 2006

Methods

Quantification of the Optimal n6/n3 ratio in the UK Diet (OPTILIP)
RCT, parallel, (n3 EPA+DHA vs n3 ALA vs nil), 6 months
Summary risk of bias: Moderate or high

Participants

Men and postmenopausal women aged 45-70 years
N: 308 randomised overall (analysed, n-3 int: 61; ALA int: 53; cont: 44)
Level of risk for CVD: Low
Male: 57% n-3 int., 60% ALA int; 68% control.
Mean age (SD): n-3 int., 62; ALA int., 60; control 58 years (SD not reported)
Age range: 45-70 years overall
Smokers: 16% overall
Hypertension: 41% overall
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: HRT
Medications taken by some, but less than 20% of the control group: BP medication, lipid lowering medication, thyroxine
Location: UK
Ethnicity: NR

Interventions

Type: food supplements (spread, oil, canned fish in varying quantities)
Comparison: long chain n-3 vs low long chain n-3; and high ALA vs low ALA
Intervention: **For n-3 group**: Advice to increase oily fish to 2 portions/wk., provided 2 cans tinned salmon and salmon pate/wk. (John West and Arctic Fjord), and supplements of 20g/d spread (n-3 EPA & DHA content 2.0g/100g + ALA 5.3g/100g, Unilever) and 16g/d oil (ALA content 0.3g/100g, Anglia Oils) giving overall diet ratio of n-6:n-3 of 3:1: EPA+DHA & ALA unclear
For high linolenate group: No advice to increase oily fish, provided 2 cans tuna/wk. (John West), and supplements of 20g/d spread (ALA 5.0g/100g, Unilever) and 16g/d oil (ALA content 8.9g/100g, Anglia Oils) giving overall diet ratio of n-6:n-3 of 3:1: EPA+DHA & ALA unclear
Control: No advice to increase oily fish, provided 2 cans tuna/wk. (John West), and supplements of 20g/d spread (ALA 0.5g/100g, Unilever) and 16g/d oil (ALA content 0.3g/100g, Anglia Oils); otherwise habitual diet, giving overall diet ratio of n-6:n-3 of 10:1
Compliance: Dietary record and erythrocyte EPA and DHA
Duration of intervention: 6 months

ORIGIN 2013

Methods

Outcome Reduction With Initial Glargine Intervention (ORIGIN)
RCT, 2x2 factorial, (n3 EPA+DHA vs MUFA), 72 months
Summary risk of bias: Moderate or high

Participants	People at high risk of CV events with impaired fasting glucose, impaired glucose tolerance or diabetes N: 6319 int., 6292 control. (analysed, int: 6281 cont: 6255) Level of risk for CVD: moderate Male: 65.4% int., 64.7% control. Mean age (SD): 63.5 (7.8) int., 63.6 (7.9) control Age range: unclear, eligible if aged ≥50years Smokers: current smokers 12.1% int, 12.6% control Hypertension: 78.7% int, 80.3% cont Medications taken by at least 50% of those in the control group: ACE inhibitor or ARB, aspirin or other antiplatelet, beta-blocker, statin, glucose lowering drug. Medications taken by 20-49%: calcium-channel blocker Medications taken by some, but less than 20%: thiazide diuretics, anticoagulant Location: 40 study locations in Europe and the Americas Ethnicity: unclear
Interventions	Type: supplement capsule (Omacor) Comparison: EPA & DHA vs MUFA Intervention: 1 gelatine capsule/d Omacor containing at least 900mg ethyl esters of n-3 fats (465mgEPA + 375mgDHA): EPA+DHA 0.84g/d Control: 1x1g gelatine capsule/d olive oil Compliance: methods of assessment unclear, but reported that "rates of adherence to the study-drug regimen were similar in the two groups with 96% of patients continuing to receive the study drug at 1 year.... and 88% at the end of the study". Length of intervention: 74 months mean follow up (Median 6.2 years)

ORL 2013

Methods	Omega-3 fatty acids randomized long-term trial (ORL) RCT- parallel, 3 arms (n3 EPA+DHA high dose vs low dose vs n3 EPA), 12 mo. Summary risk of bias: Moderate or high
Participants	Population: Japanese adults with hypertriglyceridaemia N: 171 int (4g TAK), 165 control (2g TAK). Level of risk for CVD: Moderate Male: 70.8% int., 71.5% control Mean age (SD): 55.9 (10.12) int., 56 (10.95) control Age range: 20-74 Smokers (current): 27.5% int., 31.5% control Hypertension: 66.7% int., 67.3% control Medications taken by at least 50% of those in the control group: HMG-CoA reductase inhibitor Medications taken by 20-49%: Statin Medications taken by some, but less than 20%: NR Location: Japan Ethnicity: unclear
Interventions	Type: supplement (TAK-085 capsules) Comparison: EPA & DHA higher vs lower dose Intervention: 1x2/d capsule each containing 2g of TAK-085 (1g of fatty acid in TAK-085 capsules contains approximately 465 mg of EPA-E plus 375 mg of DHA-E). Total dose of 1.86g/d EPA & 1.5 g/d DHA: EPA+DHA 3.36g/d Control: 1 capsule/d containing 2g of TAK-085 (1g of fatty acid in TAK-085 capsules contains approximately 465 mg of EPA-E plus 375 mg of DHA-E). Total dose of 0.93g/d EPA & 0.75g/d DHA. Compliance: monitored every 4 weeks, mean rate of compliance reported as >96% in each group. Length of intervention: 12 months

Palma 2015

Methods	RCT, parallel, (n3 EPA+DHA vs unclear, both with antipsychotic

	medication), 12 months Summary risk of bias: Moderate or high
Participants	Population: People with schizophrenia N: 30 int., 30 control. (analysed, int: 29 cont: 24) Level of risk for CVD: Low Male: NR. Mean age (SD): NR Age range: NR Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: Spain Ethnicity: NR Depression: Long term condition (high risk) Anxiety: Long term condition (high risk)
Interventions	Type: supplement Comparison: n-3 plus antipsychotics vs antipsychotics Intervention: Omacor capsules with 840mg EPA plus 465mg DHA: EPA+DHA 1.31g/d Control: None stated Compliance: NR Duration of intervention: 12 months

Patch 2005

Methods	RCT, parallel, (n3 EPA+DHA vs nil), 6 months Summary risk of bias: Moderate or high
Participants	Healthy overweight people with mild TG elevation N: 40 int., 45 control. (analysed, int: 38 cont: 37) Level of risk for CVD: Low Male: 48% int., 51% control. Mean age (SD): 50.4 (14.5) int., 50.2 (9.4) control Age range: NR but inclusion criteria were 20-65 years Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR (Those taking antihypertensives were excluded) Location: Australia Ethnicity: NR
Interventions	Type: supplemented food Comparison: foods supplemented with omega 3 vs non-supplemented foods Intervention: 8 portions/d of foods supplemented with microencapsulated cod fish oil (Maritex), providing 1.0g/d of a mixture of EPA+DHA: EPA+DHA 1.0g/d Control: 8 portions/d of un-supplemented foods Compliance: assessed by daily logs, 3d weight food intake, erythrocyte fatty acids, and erythrocyte EPA and DHA were higher in intervention than control at 6 months, but statistical significance unclear Duration of intervention: 6 months

Pomponi 2014

Methods	RCT, parallel, (n3 DHA+EPA vs n6 LA), 6 months Summary risk of bias: Moderate or high
Participants	Population: Adults with mild to moderate Parkinson's disease N: 12 int., 12 control. (analysed, int: 12 cont: 12) Level of risk for CVD: Low Male: 41.6% int., 50% control.

	Mean age (SD): 64.0 (4.9) int., 64.0 (9.8) control Age range: NR Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: Italy Ethnicity: NR Depression: Long term condition (high risk) (but excluded patients with current and prior depression and current anti-depressant use or psychotherapy) Anxiety: Long term condition (high risk) and Current (At the beginning of this trial anxiety was present in 83% and 100%, respectively for DHA group and placebo group)
Interventions	Type: supplement Comparison: DHA & EPA vs placebo Intervention: Daily dose of 800mg DHA and 290mg EPA for 6 months. EPA 150mg/g as triglyceride, 145mg/g as fatty acid and DHA 430mg//g as triglyceride 400mg/g as fatty acid per capsule. Provided by Catalent Italy SpA: EPA+DHA 1.09g/d Control: Equicaloric amount of corn oils. From Catalent Italy, Spa Compliance: NR Duration of intervention: 6 months

Pratt 2009

Methods	RCT, parallel, (n3 EPA+DHA vs n6 LA), 6 months Summary risk of bias: Moderate or high
Participants	People with paroxysmal or persistent AF N: 332 int., 331 control. (analysed, int: 293-322 cont: 291-323) Level of risk for CVD: high Male: 60% int., 53% control. Mean age (SD): 59.8 (13.4) int., 61.2 (12.3) control Age range: NR (inclusion criterion was ≥18 years Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: Angiotensin converting enzyme inhibitors or angiotensin II receptor blocker 37%, statins 45% Medications taken by some, but less than 20% of the control group: antiarrhythmic drugs Location: USA Ethnicity: 4% African American, 92% White, 4% other
Interventions	Type: supplement Comparison: prescription omega 3 vs corn oil Intervention: 4x1g/d prescription omega 3 capsules (Lovaza, 1.86g/d EPA, 1.5g/d DHA) after 1 week of double (loading) dose: EPA+DHA 3.36g/d Control: 4x1g/d corn oil capsules (assume 1 week loading dose also) Compliance: method of assessment unclear, but 3/332 excluded for non-adherence Duration of intervention: 1 week loading dose plus 24 weeks standard dose, 25 week total

Proudman 2015

Methods	RCT, parallel, (n3 EPA+DHA vs low n3), 12 months Summary risk of bias: Low
Participants	Patients with rheumatoid arthritis <12 months duration, DMARD-naive. N: 87 int., 53 control. (analysed, int: 75 cont: 47) Level of risk for CVD: low Male: 29% int., 25% control. Mean age (SD): 56.1 (15.9) int., 55.5 (14.1) control

Age range: Unclear
Smokers: 65.1% int., 54.7% control (includes current & previous smokers).
Hypertension: NR
Medications taken by at least 50% of those in the control group: Triple DMARD therapy (SSZ 0.5g/d, HCQ 200mg twice/day and MTX 10mg once per week).
Medications taken by 20-49% of those in the control group: NSAIDS
Medications taken by some, but less than 20% of the control group: Oral or parenteral steroids
Location: Australia
Ethnicity: NR

Interventions

Type: supplement (fish oil)
Comparison: high EPA & DHA vs low EPA & DHA
Intervention: 10 ml/d fish oil concentrate (BLT Incromega TG3525) providing 3.2g/d EPA + 2.3g/d DHA: EPA+DHA 5.5g/d
Control: 10 ml/d sunola oil: capelin oil (2:1) providing 0·21 g EPA + 0·19 g DHA/d as TAG (0.40g/day EPA + DHA).
Compliance: Consumption checked at each visit. 100% compliance would be consumption of 3650 mL oil at 12 months. The fish oil group was less compliant than the control group with median intakes of 2482 mL and 3248 mL, respectively (p=0.015, Mann-Whitney U test). This provided an average daily intake of EPA+DHA of 3.7 g and 0.36 g in the fish oil and control groups, respectively.
Duration of intervention: 12 months

Puri 2005

Methods

RCT, parallel (n3 EPA vs non-fat), 2 arm, 12mo
Summary risk of bias: Low

Participants

People with Huntington's Disease
N: 67 int., 68 control. (analysed, int: 39 cont: 44)
Level of risk for CVD: Low
Male: 57% int., 44% control.
Mean age (SD): 50 (9.3) int., 49 (9.0) control
Age range: NR
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: antidepressants
Medications taken by some, but <20%: neuroleptics
Location: UK, USA, Canada, Australia
Ethnicity: Caucasian (Black, Asian) 94% (4%, 1%) int, 97% (3%, 0%) control

Interventions

Type: supplement (ethyl-EPA)
Comparison: EPA vs paraffin (non-fat)
Intervention: 2x2x500mg capsules/d, Total dose of 2 g/day ethyl-EPA (code name LAX-101, purity 95%): EPA+DHA 1.9g/d
Control: 2x2x500mg capsules/d liquid paraffin
Compliance: 38 were excluded for protocol violations, 4 int and 16 control were non-compliant with capsules
Duration of intervention: 12 months

Raitt 2005

Methods

RCT, parallel, (n3 EPA+DHA vs MUFA), 24 months
Summary risk of bias: Moderate or high

Participants

People with implantable cardioverter defibrillators and recent sustained ventricular tachycardia or ventricular fibrillation (VT/VF)
N: 100 int., 100 control.
Level of risk for CVD: High
Male: 86% int., 86% control.
Mean age (SD): 63 (13) int., 62 (13) control
Age range: NR but 18-75 inclusion criteria
Smokers: NR

Hypertension: 46% int, 55% control
Medications taken by at least 50% of those in the control group: diuretic, beta blockers, ACE inhibitors
Medications taken by 20-49% of those in the control group: digoxin, statins
Medications taken by some, but less than 20% of the control group: calcium channel blocker
Location: USA
Ethnicity: Caucasian 94% int, 97% control

Interventions

Type: supplement (fish oil capsules vs olive oil capsules)
Comparison: EPA & DHA vs MUFA
Intervention: 1.8g/d fish oil capsules (Hoffman LaRoche, including ethyl esters of EPA and DHA, 0.76g/d EPA, 0.54g/d DHA): EPA+DHA 1.3g/d
Control: 1.8g/d olive oil capsules (Hoffman LaRoche, 73% oleic acid)
Compliance: while control group plasma and platelet DHA and EPA did not change, there were increases of 2-8.3% in the intervention group
Duration of intervention: 24 months (Median 718 days)

Ramirez-Ramirez 2013

Methods

RCT, parallel, (n3 EPA+DHA vs n6 LA), 12 months
Summary risk of bias: Moderate or high

Participants

People with relapsing remitting multiple sclerosis
N: 25 int., 25 control. (analysed, int: 20 cont: 19)
Level of risk for CVD: low
Male: 83% int., 82% control (but these appear unlikely)
Mean age (SD) yrs.: 35.1 (7.6) int., 34.9 (7.8) control
Age range: NR but 18-55 were inclusion criteria
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: 100% treated with interferon beta1b for at least 1 year before the trial began
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Mexico
Ethnicity: NR

Interventions

Type: supplement
Comparison: DHA+EPA vs sunflower oil
Intervention: 4g/d omega Rx capsules (Dr Sears zone diet, with excipient of glycerine, water, tocopherol, sunflower oil, titanium dioxide, includes 0.8g/d EPA plus 1.6g/d DHA): EPA+DHA 2.4g/d
Control: excipient only (Perfect Source Natural Products, glycerine, water, tocopherol, sunflower oil, titanium dioxide)
Compliance: consumption diary plus pills returned at each visit, adherence calculated (correct formula?? pills consumed x100/pills returned), optimal adherence was considered to be >80%,, 1 int and 3 control were excluded due to compliance <80%. Blood DHA and EPA were significantly different at 12 months.
Duration of intervention: 12 months

Rebello 2015

Methods

RCT, parallel, (n3 ALA vs mixed fat), 24 wks.
Summary risk of bias: Moderate to high

Participants

Healthy older people from USA
N: 3 int., 3 control. (analysed, int: 2 cont: 2)
Level of risk for CVD: Low
Male: 50% int., 50% control.
Mean age (SD): NR
Age range: 58-78 years
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR

	Location: USA Ethnicity: Not reported
Interventions	Type: food supplement (Yoghurt with added canola oil or added Medium Chain Triglyceride Oil (MCT oil, Nestle™)) Comparison: PUFA vs. SFA Intervention: Yogurt with added 56g canola oil (about 65% MUFA, & 28% PUFA, typically):ALA unclear Control: Yogurt with added 56 g/d MCTs (type of saturated fat) Compliance: Measured but Not reported; one participant dropped due to non-compliance Duration of intervention: 24 wks.

Reed 2014

Methods	RCT, parallel, 3 arms (n3 EPA+DHA vs n6 GLA), 18 months Summary risk of bias: Moderate to high
Participants	Adults with rheumatoid arthritis N: 53 int., 52 control (28 int., 24 control analysed). Level of risk for CVD: Low Male: 13.2% int., 23.1% control. Mean age (SD): 57.3 (12.3) int., 60.3 (9.2) control Age range: NR but 18-85 inclusion criteria Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: Methotrexate, DMARDS, and TNF blockers Medications taken by 20-49% of those in the control group: Corticosteroids and TNF blockers Medications taken by some, but less than 20% of the control group: NR Location: USA Ethnicity: black/African-American: int (fish oil): 7.8% cont (Borage oil): 7.8 %
Interventions	Type: supplement (fish oil vs Borage oil) Comparison: EPA & DHA vs Omega 6 Intervention: 7 fish oil (2.1 g EPA:1.4 g DHA) capsules and 6 sunflower seed oil capsules daily = 13 capsules divided doses: EPA+DHA 3.5g/d Control: 6 borage seed oil (1.8 gm GLA) capsules plus 7 sunflower seed oil capsules daily Compliance: assessed by capsule counts and patient report. Patient report indicates that 45% of patients reported ever missing a dose (borage: 42%, fish 48%). Median total capsules missed (excluding those with 0) were 182 (borage: 164, fish 169). Duration of intervention: 18 months

Risk and Prevention 2013

Methods	Evaluation of the Efficacy of n-3 PUFA in Subjects at High Cardiovascular Risk (Risk and Prevention) RCT, parallel, (n3 EPA+DHA vs MUFA), 60 months? Summary risk of bias: Moderate or high
Participants	Patients with multiple cardiovascular risk factors N: 6244 int., 6269 control. (analysed, int: 6239 cont: 6266) Level of risk for CVD: high Male: 62.3% int., 60.6% control. Mean age (SD): 63.9 (9.3) int., 64.0 (9.6) control Age range: NR Smokers: 22.1% int., 21.4% control. Hypertension: 84.6% int., 84.5% control. Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: ACE inhibitor; ARB; Diuretic agent; Calcium-channel blocker; Beta-blocker; Oral hypoglycaemic drug; Statin; Antiplatelet agent. Medications taken by some, but less than 20% of the control group: Insulin Location: Italy

Ethnicity: NR

Interventions

Type: supplement (n-3 capsules)
Comparison: EPA & DHA vs MUFA
Intervention: 1g/d n-3 capsules polyunsaturated fatty acid ethyl esters (EPA and DHA content 850-882 mg with an average ratio of 1.0 to 1.2): EPA+DHA 0.86g/d
Control: 1g/d olive oil capsules
Compliance: measured by self-report during follow up visits but no results reported.
Duration of intervention: 60 months

Romero 2013

Methods

RCT, parallel, (n3 EPA+DHA vs nil), 6 months
Summary risk of bias: Moderate to high

Participants

Population: patients with mild cognitive impairment
N: 15 int., 15 control. (analysed, int: 13 cont: 13)
Level of risk for CVD: low
Male: NR int., NR control.
Mean age (SD): NR int., NR control, but mean age for total population given as 72.5 years
Age range: NR
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Spain
Ethnicity: NR

Interventions

Type: Omega-3 food supplement
Comparison: omega-3 supplement vs no omega-3
Intervention: 2 ACUTIL capsules per day: 500 mg DHA + 80 EPA per day: EPA+DHA 0.58g/d
Control: no omega-3
Compliance: NR
Duration of intervention: 6 months

Rossing 1996

Methods

RCT, parallel, (n3 EPA+DHA vs MUFA), 12 months
Summary risk of bias: Moderate or high

Participants

Adults with insulin-dependent diabetes mellitus, diabetic nephropathy and normal BP
N: 18 int., 18 control. (analysed, 17 int, 15 cont)
Level of risk for CVD: moderate
Male: 64% int., 67% control.
Mean age (SD) years: 32 (7) int., 34 (10) control
Age range: 18-55 years
Smokers: 50% int., 47% control.
Hypertension: NR
Medications taken by at least 50% of those in the control group: insulin
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Denmark
Ethnicity: NR

Interventions

Type: supplement
Comparison: fish oil vs olive oil
Intervention: cod-liver oil emulsion (Pharma-Vinci A/S Denmark). EPA 2g, DHA 2.6g: EPA+DHA 4.6g/d
Control: olive oil emulsion (Pharma-Vinci A/S Denmark)
Compliance: assessed through omega 3 incorporation in platelets, and the paper reports significantly higher omega 3 levels in platelets at 12 months.
Duration of intervention: 12 months

Sandhu 2016

Methods	RCT, parallel 5 arms (combined G4&5 Lovaza n-3 +/-raloxifene vs G1&3 control +/- raloxifene), (Lovaza n-3 vs control), 24 months Summary risk of bias: Moderate or high
Participants	Healthy postmenopausal women (50% normal weight, 30% overweight, 20% obese) with high breast density detected on their routine screening mammograms N: 54 & 53 int., 53 & 53 control. Level of risk for CVD: low Male: 0% int., 0% control. Mean age (SD): 56.56(6.9) & 57.85(5.1) int., 57.11(5.9) & 57.68(5.1) control Age range: NR Smokers: 0% int., 0% control. Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: USA Ethnicity: NR
Interventions	Type: supplement (n-3 capsules) Comparison: EPA & DHA vs nil Intervention: G4, Lovaza 4 g per day. Lovaza is the FDA-approved n-3FA formulation containing 465 mg of EPA & 375 mg of DHA per gram, total dose; 1860 mg/d EPA, 1500mg/d DHA. G5 as G4 plus 30 mg raloxifene/day Control: G1, No treatment G3, 30mg raloxifene/day Compliance: measured by pill count, recorded at follow-up visits and further verified by serum fatty acids monitoring. Compliance was 94±2% (S.E.) at 6 months and 97±2% (S.E.) at 12 months. Only two subjects had a compliance <85% (84% and 81%). Duration of intervention: 24 months

Sasaki 2012

Methods	RCT, parallel, (n3 EPA vs nil, both arms had statins), 6 months Summary risk of bias: Moderate or high
Participants	Type 2 diabetic patients with dyslipidaemia and statin treated N: 15 int., 14 control. (analysed, int: 15 cont: 13) Level of risk for CVD: Moderate Male: 54% int., 46% control Mean age (SD): 65.5 (5.4) int., 69.2 (7.7) control Age range: NR Smokers: 13% int., 21% control Hypertension: NR Medications taken by at least 50% of those in the control group: Statin Medications taken by 20-49% of those in the control group: Sulfonylurea, metformin, insulin, ACE inhibitor or ARB, aspirin Medications taken by some, but less than 20% of the control group: Calcium channel blocker Location: Japan Ethnicity: NR
Interventions	Type: supplement (EPA + statin or statin alone) Comparison: EPA vs nil Intervention: 1.8g/d purified EPA preparation (Epadel, Mochida Pharmaceutical Co. Ltd) + statin: EPA 1.8g/d Control: Statin alone Compliance: NR Duration of intervention: 6 months

Sawada 2016

Methods	RCT, parallel, (n3 EPA vs nil), 6 months Summary risk of bias: Moderate or high
Participants	Newly-diagnosed impaired glucose metabolism patients with coronary artery disease N: 59 int., 59 control. (analysed, int: 54 cont: 53) Level of risk for CVD: High Male: 81.5% int., 81.1% control. Mean age (SD): 67.8 (9.1) int., 68.9 (8.8) control Age range: NR Smokers: 9.3% int., 7.5% control Hypertension: 88.9% int., 92.5% control Medications taken by at least 50% of those in the control group: Statin, calcium channel blocker, ACEI/ARB Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: Japan Ethnicity: NR
Interventions	Type: supplement (EPA capsules or nil) Comparison: EPA vs nil Intervention: 2x capsules/d (including 1800mg EPA, EPADEL, Mochida Pharmaceutical Co Ltd) Control: "no EPA" Compliance: NR Duration of intervention: 6 months

SCIMO - von Schacky 1999

Methods	Study on prevention of Coronary atherosclerosis with Marine Omega 3 fatty acids (SCIMO) RCT, parallel (n3 EPA+DHA vs mixed fats), 2 years Summary risk of bias: Low
Participants	People with angiographically proven coronary artery disease N: 112 int., 111 control (analysed 82 int., 80 control) Level of risk for CVD: High Male: 82% int., 78.6% control Mean age (SD): 57.8 (9.7) int., 58.9 (8.1) control Age range: Unclear (18-75 inclusion criteria) Smokers: 16.2% int., 22.3% control Hypertension: 53.1% int., 45.5% control (history of high blood pressure) Medications taken by at least 50% of those in the control group: Platelet inhibitors, Beta-blockers. Medications taken by 20-49% of those in the control group: Long-term nitrate therapy, Lipid-lowering agents, ACE inhibitors, diuretics, calcium antagonists, other antihypertensive agents and digitalis. Medications taken by some, but less than 20% of the control group: Nitrates only on demand. Location: Germany Ethnicity: NR
Interventions	Type: supplement (capsule) Comparison: EPA & DHA vs average European fat composition Intervention: concentrated fish oil capsules, 6x 1g capsules/d for first 3 mo., 3x 1g/d for rest of study (4g/d EPA +DHA + DPA + ALA for first 3 mo., then 2g/d): EPA+DHA 2.0g/d Control: capsules containing fat which replicated the fat composition of the average European diet, 6/d for first 3 mo., 3/d for rest of study, opaque soft gelatine capsules identical to fish capsules in identical screw-top containers Compliance: capsule count, overall 2284 (SD 313) capsules taken of 2460 prescribed for each person, erythrocyte phospholipids rose from 4.6 to 11.8% at 24 mo. in int., and didn't alter from baseline in controls Length of intervention: 24 mo.

Shimizu 1995

Methods	RCT, parallel, (n3 EPA vs nil), 12 months

Summary risk of bias: Moderate or high

Participants

Non-insulin dependent diabetic patients
N: 29 int., 16 control. (analysed, NR)
Level of risk for CVD: Moderate
Male: 34.5% int., 75% control
Mean age (SD): 66.3 (13.5) int., 58.6 (7.2) control
Age range: NR
Smokers: NR
Hypertension: 37.9% int., 43.8% control
Medications taken by at least 50% of those in the control group: Sulfonylurea
Medications taken by 20-49% of those in the control group: Insulin, antihypertensives
Medications taken by some, but less than 20% of the control group: NR
Location: Japan
Ethnicity: NR

Interventions

Type: supplement (EPA-E capsules or nil)
Comparison: EPA vs nil
Intervention: 3 capsules/d (total 0.9g/d EPA, Mochida Pharmaceuticals): EPA 0.9g/d
Control: Unclear
Compliance: Capsule count (no data provided)
Duration of intervention: 12 months

Shinto 2014

Methods

RCT, parallel (n3 EPA+DHA vs n6 LA), 12 months
Summary risk of bias:

Participants

Patients aged 55 or more with probable Alzheimer dementia diagnosis.
N: 13 int., 13 control.
Level of risk for CVD: Low
Male: 61% int. 46% control.
Mean age (SD): 75.9 (8.1) int., 75.2 (10.8) control
Age range: 55+ (inclusion criteria)
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: anti-cholinesterases or memantine
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Lipid lowering medications and many other drugs were not allowed
Location: USA
Ethnicity: 100% white

Interventions

Type: Fish oil capsules
Comparison: EPA & DHA vs n-6
Intervention: 3x1g capsules/day of fish oils (975 mg EPA, 675 mg DHA per day): EPA+DHA 1.65g/d
Control:3x1g capsules/day soybean oil (which contains 5% fish oil)
Both groups had a placebo lipoic acid tablet and lemon flavoured capsules
Compliance: Assessed by pill counts & FA in RBCs membranes. Results showed increased EPA & DHA levels in the intervention group
Length of intervention: 12 months

SHOT - Eritsland 1996

Methods

SHunt Occlusion Trial (SHOT)
RCT, parallel (n3 EPA+DHA vs nil), 4 arms, 1 year
Summary risk of bias: medium or high

Participants

People admitted for coronary bypass grafting
N: 317 int., 293 control
Level of risk for CVD: High
Male: 86% int., 88 % control
Mean age (SD): 59.9 (8.7) int., 59.4 (8.8) control

Age range: Unclear
Smokers: 19% int., 20% control
Hypertension: 20% int., 25% control
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: Antihypertensives.
Medications taken by some, but less than 20% of the control group: NR
Location: Norway
Ethnicity: NR

Interventions

Type: supplement (capsule)
Comparison: EPA & DHA vs nil
Intervention: Omacor capsules, 4/d (3.3g EPA + DHA daily): EPA+DHA 3.3g/d
Control: nil
Compliance: capsule count, 88% taken, serum EPA + DHA rose in the intervention group (176 to 257 mg/L at 9 mo.) and fell in the control group (170 to 169 mg/L at 9 mo.)
Length of intervention: 12 mo.

Sianni 2013

Methods

RCT, parallel, (n3 EPA+DHA vs unclear), 12 months (not sure if randomised)
Summary risk of bias: Moderate or high

Participants

Patients with hypertension and paroxysmal or persistent atrial fibrillation (AF)
N: 268 int., 60 control.
Level of risk for CVD: moderate
Male: NR
Mean age (SD) years: 62 (6), not reported by arm
Age range: NR
Smokers: NR
Hypertension: 100%
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Greece
Ethnicity: NR

Interventions

Type: supplement
Comparison: fish oil vs unclear placebo
Intervention: omega-3 fatty acids in dose of 4 g/day: EPA+DHA unclear
Control: Placebo, no further details
Compliance: no details
Duration of intervention: 12 months

Sinn 2012

Methods

RCT, 3 arms in parallel, (n3 EPA+DHA (mainly EPA) vs n3 EPA+DHA (mainly DHA) . vs n6 LA), 6 months.
Summary risk of bias: Low

Participants

Older Australian people with few comorbidities and mild cognitive impairment
N: 18 Int EPA, 18 Int DHA, 18 control. (analysed, Int EPA: 13, Int DHA: 16, cont=LA group: 11)
Level of risk for CVD: Low
Male: 82% IntEPA, 72% IntDHA, 47% = LA group
Mean age (SD): 74.88 (5.06) intEPA, 74.22 (7.00) IntDHA, 73 (3.96) = LA group
Age range: NR, but eligibility criteria > 65 yrs.
Smokers: 12% IntEPA, 0% IntDHA, 0% = LA group
Hypertension: NR
Medications taken by at least 50% of those in the control group = LA group: NR
Medications taken by 20-49% of those in the control group = LA group: NR

	Medications taken by some, but less than 20% of the control group = LA group: NR Location: Australia Ethnicity: NR Depression: General population (low risk) Anxiety: General population (low risk)
Interventions	Type: supplement capsules (EPA rich, DHA rich or LA rich) Comparison: EPA rich vs. DHA vs rich (both n-3 rich) vs. safflower oil (linoleic acid rich, n-6 rich) InterventionEPA: 4 capsules/d (total dose = 1.67g/d EPA + 160 mg/d DHA): EPA+DHA 1.83g/d InterventionDHA: 4 capsules/d (total dose = 1.55g/d DHA + 400 mg/d EPA): EPA+DHA 1.95g/d Control=LA group: 4 capsules/d (total dose = 2.2g/d LA). How identical supplements in each arm were to each other is not reported; but ability participants had poor ability to correctly guess which supplement they had. Compliance: Capsule count and comparisons of FA levels in erythrocytes. No p-values reported for erythrocyte data, but capsule consumption was 93% on average (range = 82-97%). Duration of intervention: 6 months

Skoldstam 1992

Methods	RCT, parallel, (n3 EPA+DHA vs mixed fats), 6 months Summary risk of bias: Moderate or high
Participants	People with stable rheumatoid arthritis N: 23 int., 23 control. (analysed, int: 22 cont: 21) Level of risk for CVD: low Male: 18% int., 33% control. Mean age (SD) yrs.: 58 (NR) int., 55 (NR) control Age range: 40-73yrs int., 28-70yrs control Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NSAID (86% of whole group), Medications taken by 20-49% of those in the control group: DMARDS (42% of whole group) Medications taken by some, but less than 20% of the control group: NR Location: Sweden Ethnicity: NR
Interventions	Type: supplement Comparison: fish oil (n3) vs vegetable oil capsules (n6 and MUFA) Intervention: 10x1g MaxEPA capsules/d (1.8g/d EPA plus 1.2g/d DHA plus 10mg alpha tocopherol) and asked to maintain usual diet: EPA+DHA 3.0g/d Control: 10x1g vegetable oil capsules/d (maize, corn and peppermint oils, <2.5% n3) and asked to maintain usual diet Compliance: blood fatty acids were measured, with significant differences between arms for EPA, DHA and DPA at 6 months. Duration of intervention: 6 months

SMART Tapsell 2013

Methods	SMART trial (from the Smart Foods Centre) RCT, 3-arm parallel, (n3 EPA+DHA vs lower dose n3 EPA+DHA vs MUFA) 12 months Summary risk of bias: Moderate or high
Participants	Overweight adults N: Fish +S int 41, Fish 43, control 42. (analysed, Fish +S int 21, Fish 25, control 18) Level of risk for CVD: low Male: 27% Fish + S int, 23% Fish int, 28% control. Mean age (SD) years: unclear by arm, overall 45.1 (8.4) Age range: NR but 18-60 years eligible

Smokers: NR but 5.9% overall
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Australia
Ethnicity: NR

Interventions

Type: supplement and food
Comparison: Fish plus fish oil supplements vs Fish plus olive oil supplements vs olive oil supplements
Intervention, Fish + S: hypocaloric diet aiming at 30%E from fat, 25%E from protein, 45%E from CHO, plus 180g fish/week plus capsules including 420mg/d EPA + 210mg/d DHA (Blackmores Promega Heart): EPA+DHA 0.63g/d plus fish
Intervention, Fish: hypocaloric diet aiming at 30%E from fat, 25%E from protein, 45%E from CHO, plus 180g fish/week plus capsules including 1g olive oil/d: EPA+DHA unclear
Control: hypocaloric diet aiming at 30%E from fat, 25%E from protein, 45%E from CHO, plus capsules including 1g olive oil/d
Compliance: Assessed through diet histories (fish) and erythrocyte fatty acid supplements (capsules), but results not reported
Duration of intervention: 12 months

Smith 2015

Methods

RCT, parallel, (n3 EPA+DHA vs n6 LA), 6 months
Summary risk of bias: Moderate or high

Participants

Healthy older adults
N: 40 int., 20 control. (analysed, int: 29 cont: 15)
Level of risk for CVD: low
Male: 34% int., 33% control.
Mean age (SD) yrs.: 68 (5) int., 69 (7) control
Age range: NR
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: USA
Ethnicity: NR

Interventions

Type: supplement
Comparison: LCn3 vs n6
Intervention: 4x1g/d capsules of n3 acid ethyl esters (Lovaza, GlaxoSmithKline, 1.86g/d EPA + 1.5g/d DHA, equivalent to 200-400g/d freshwater fish): EPA+DHA 3.36g/d
Control: 4x1g/d capsules of corn oil (capsules looked identical to Lovaza capsules)
Compliance: Assessed using pill count, participants were given excess pills and asked to return the remainder at study end. Mean compliance according to pills returned was 94% in intervention, 92% in control.
Duration of intervention: 6 months

SO927 Hershman 2015

Methods

RCT, parallel, (n3 EPA+DHA vs n6 LA), 6 months
Summary risk of bias: Moderate or high

Participants

Women with early stage breast cancer receiving an aromatase inhibitor with musculoskeletal pain
N: 131 int., 131 control. (analysed, int: 102 cont: 107)
Level of risk for CVD: low
Male: 0% int., 0% control.
Mean age (SD) yrs.: 59.5 (NR) int., 59.1 (NR) control
Age range: NR
Smokers: NR

Hypertension: NR
Medications taken by at least 50% of those in the control group: all an aromatase inhibitors
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Canada
Ethnicity: int 93% white of whom 6% reported Hispanic ethnicity, 4% black, 1% Asian. Control 82% white of whom 7% reported Hispanic ethnicity, 12% black, 2% Asian.

Interventions

Type: supplement
Comparison: EPA+DHA vs soy and corn oil
Intervention: 6 fish oil capsules/d (Ocean Nutrition, 3.36g/d EPA plus 1.68g/d DHA) coloured with carob and flavoured with lemon/lime: EPA+DHA 5.04g/d
Control: 6 capsules/d of soybean and corn oil blend, coloured with carob and flavoured with lemon/lime
Compliance: Assessed by researcher review of intake calendar and capsule count. 2 control and one intervention participants were excluded due to non-compliance but it is not clear what level of compliance was required.
Duration of intervention: 6 months

SOFA 2006

Methods

Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA)
2 arm, parallel RCT (n3 EPA+DHA vs n6 LA), 12mo
Summary risk of bias: Low

Participants

People with previous ventricular arrhythmias & implantable cardioverter defibrillators
N: 273 int., 273 control (273 int, 273 cont analysed)
Level of risk for CVD: High
Male: 84% int., 85 % control
Mean age (SD): 60.5 (12.8) int., 62.4 (11.4) control
Age range: Unclear (18 years and older)
Smokers: 16% int., 8% control
Hypertension: 53% int., 49% control
Medications taken by at least 50% of those in the control group: beta-blockers
Medications taken by 20-49% of those in the control group: lipid lowering, antiarrhythmic medications (combined)
Medications taken by some, but less than 20% of the control group: amiodarone, sotalol
Location: 8 countries in Europe
Ethnicity: NS

Interventions

Type: supplement (capsule)
Comparison: EPA & DHA vs MUFA & omega 6
Intervention: 2g/d (4 capsules) purified fish oil. 961mg n-3 PUFAS (464mg EPA + 335mg DHA and 162mg other n-3 PUFAs) daily. 3000ppm vitamin E (Loders Croklann, Wormeveer): EPA+DHA 0.8g/d
Control: 2g/d high-oleic acid sunflower oil. 3000ppm vitamin E (Loders Croklann, Wormeveer).
Compliance: Daily diary, checked by research nurses every 4 months. Judging by capsule count, 207 patients in the fish oil group and 218 in the placebo took more than 80% of their capsules. N-3 fatty acid composition in serum cholesterol levels was measured at baseline and the end of the trial. The EPA concentration in serum cholesterol esters increased in the expected range. No data provided.
Length of intervention: 12 mo.

Sofi 2010

Methods

2 arm, parallel RCT (n3 EPA+DHA vs MUFA), 12mo
Summary risk of bias: high

Participants

Non-alcoholic fatty liver disease patients

N: 6 int., 5 control
Level of risk for CVD: low
Male: 66.7% int., 100 % control
Median age: 55 int., 54 control
Age range: 30-41 int., 42-70 control
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Italy
Ethnicity: NR

Interventions

Type: supplement (oil)
Comparison: EPA & DHA vs MUFA
Intervention:6.5 ml/d olive oil enriched with n-3 (t-Omega 3, tFarma srl, Italy) plus dietary recommendations. (0.83g n-3, 0.47g EPA, 0.24g DHA): EPA+DHA 0.71g/d
Control: 6.5 ml/d olive oil plus dietary recommendations
Compliance: was verified by counting the empty boxes on return but no data reported
Length of intervention: 12 mo.

Stonehouse 2013

Methods

RCT, parallel, (n3 DHA vs MUFA), 6 months
Summary risk of bias: Low

Participants

pop: Healthy men and women 18-45 years
N: 115 int., 113 control. (analysed, int: 85 cont: 91)
Level of risk for CVD: Low
Male: 37.4% int., 35.4% control.
Mean age 33.4 (7.8) int., 33.2 (7.9) control
Age range: 18-45 allowed.
Smokers: 0% (exclusion criterion)
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: New Zealand
Ethnicity: European 78.2% int, 80.9% control.

Interventions

Type: supplement
Comparison: DHA (n3) vs high oleic sunflower oil
Intervention: 3 capsules/d. In total 2.25 g/d, comprised of 1.16 g DHA/d, 60 mg/d DPA and 0.17 g EPA/d: EPA+DHA 1.39g/d
Control: 3 capsules/d with total dose = 2.25 g/d, comprised of 1.61 g/d oleic acid, at least 160 mg/d PUFA and at least 150 mg/d SFA.
Compliance: Treatment compliance was determined with combination of weekly diary records, pill-counting of leftover capsules, and analysis of erythrocyte LC n23 PUFA levels. P-values < 0.001 for erythrocyte level differences of active FAs in supplements.
Duration of intervention: 6 months

SU.FOL.OM3 Galan 2010

Methods

Supplementation en Folates et Omega 3 (SU.FOL.OM3)
RCT, 2x2 factorial (n3 EPA+DHA vs non-fat), 4 years
Summary risk of bias: Low

Participants

People with a history of MI, unstable angina or ischemic stroke
N: control: 1248, int: 1253
Level of risk for CVD: High
Male: 80.85% int., 78.25% control
Mean age (SD): 61.1 (8.8) int., 60.8 (8.7) control
Age range: 53-68 int, 54-68 control
Smokers: 11.1% int., 10.4% control
Hypertension: NR

	Medications taken by at least 50% of those in the control group: beta blockers, aspirin or antiplatelets, lipid lowering, ACE inhibitors Medications taken by 20-49%: NR Medications taken by some, but <20%: calcium channel blocker, angiotensin II receptor blockers. Location: France Ethnicity: NR
Interventions	Type: supplement (capsule) Comparison: EPA & DHA vs unclear placebo Intervention: 2 gelatine capsules Pierre Fabre omega 3 (400mg/d EPA and 200mg/d DHA): EPA+DHA 0.6g/d Control: 2 gelatine capsules/d placebo (liquid paraffin with fish flavour) Compliance: Tested by questionnaire, response rate was on average 96%. Out of this, 86% complied. Duration of intervention: 4 years

Tajalizadekhoob 2011

Methods	RCT, parallel, (n3 EPA+DHA vs mixed fats), 6 months Summary risk of bias: Moderate or high
Participants	Population: Elderly residents of the Kahrizak Charity Foundation (physically handicapped or elderly individuals with no financial resources are cared for free of charge). N: 33 int., 33 control. (analysed, int: 32 cont: 29) Level of risk for CVD: Low Male: 30.3% int., 30.3% control. Mean age 79.64 (SD 7.39) int: 79.73 (SD 7.01) control Age range: NR Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: SSRIs, TCAs Location: Iran Ethnicity: NR Depression: Long term condition (high risk) and general population (low risk) Anxiety: Long term condition (high risk) and general population (low risk)
Interventions	Type: supplement Comparison: fish oil capsule vs placebo capsule Intervention: One hard gelatine capsule containing one gram of fish oil was used daily for the drug group. Each capsule contained cod liver oil, glycerol, water, and fish oil and was comprised of 180 mg eicosapentaenoic acid (EPA) and 120 mg DHA. The cod liver oil and fish oil were obtained from cold water fish: EPA+DHA 0.3g/d Control: The placebo was a hard gelatine capsule containing medium-chain triglycerides (MCTs) derivate from coconut oil, glycerol, and water, which appeared similar to the fish oil capsules of the drug group. Compliance: The drugs were given to the participants daily. Participants took the drugs under the supervision of the individual responsible for the administration of the drugs. The individual reported the drug intake of each participant. She was responsible to report whether any of the participants did not agree to take the drug and returned the drug to the research office. The participants were not coerced into taking the drugs and had a choice of not accepting the treatment. The staff were strictly responsible to report non-adherence to the drug treatment. Duration of intervention: 6 months

Tande 2016

Methods	2 arm, parallel RCT (n3 EPA+DHA vs MUFA), 12mo Summary risk of bias:

Participants	Healthy male and female volunteers with BMI 25-35 kg/m^2 N: 64 int., 63 control (50 int, 50 cont analysed) Level of risk for CVD: low Male: 42% int., 43 % control Mean age (SD): 50.7 (7.7) int., 49 (9.4) control Age range: Unclear (18 years and older) Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: Norway Ethnicity: NR
Interventions	Type: supplement (capsule) Comparison: EPA & DHA vs MUFA Intervention: 2 x 500 mg Calanus oil capsules twice daily (2g/d, Ayanda AS (Norway), blister packs of 60 capsules each). The Calanus oil contained approximately 85% wax ester with a sum of neutral lipids>90%: EPA+DHA and ALA unclear Control: identical capsules of olive oil. Compositional analysis indicated that the fatty acid content of the olive oil was primarily oleic acid (76.9%), palmitic acid (10.2%), and linoleic acid (7.7%). Compliance: assessed through the return of unused capsules. Compliance rate reported for both intervention and placebo groups was good (86-88%). Length of intervention: 12 months

Tani 2017

Methods	Single-centre, prospective, open-label RCT (n3 EPA+DHA vs nil), 6 months Summary risk of bias: moderate-high
Participants	People with stable coronary artery disease on statin therapy N: 55 int., 55 control. (analysed, int: 53 cont: 53) Level of risk for CVD: High Male: 92% int., 83% control. Mean age (SD): 68 (11) int., 66 (11) control Age range: 35-80y eligible Smokers: 8% int., 11% control Hypertension: 81% int., 68% control Medications taken by at least 50% of those in the control group: Antiplatelets (98%), Ca channel blockers (62%), Strong statins (72%) Medications taken by 20-49% of those in the control group: ACE inhibitor/ Angiotensin receptor blocker (49%), β blocker (38%), Moderate statin (26%) Medications taken by some, but less than 20% of the control group: Location: Japan Ethnicity: NR
Interventions	Type: supplement (capsules containing EPA or no treatment) Comparison: Higher EPA Vs lower EPA Intervention: 1800mg/d capsules (2x900mg) containing 1.8g/d EPA (total n3 PUFA 1.8g/d) manufactured by Mochida Pharmaceuticals, Tokyo, Japan: EPA+DHA 1.8g/d Control: No treatment. Compliance: Serum fatty acid status data Duration of intervention: 6 months

Tapsell 2004

Methods	RCT, parallel, (n3 ALA vs nil), 6 months Summary risk of bias: Moderate or high
Participants	Patients with type 2 diabetes N: 17 int., 20 control. (analysed, int: 16 cont: 19) Level of risk for CVD: Moderate Male: 29.4% int., 64.7% control. Mean age (SD): 57.7 (9.0) int., 59.3 (7.1) control

Age range: 35-75 years overall
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Australia
Ethnicity: NR

Interventions

Type: supplemented food (walnuts + advice for modified low fat diet, or advice for modified low fat diet alone)
Comparison: ALA vs nil
Intervention: 30g/d walnuts + advice for modified low fat diet: ALA dose unclear
Control: Advice for modified low fat diet only
Compliance: Diet history and 3-d food record
Duration of intervention: 6 months

Tardivo 2015

Methods

RCT, parallel, (n3 EPA+DHA vs nil), 6 months
Summary risk of bias: Moderate or high

Participants

Postmenopausal women with metabolic syndrome
N: 44 int., 43 control. (analysed, int: 44 cont: 43 - paper states ITT analysis, but there were dropouts, below)
Level of risk for CVD: moderate
Male: 0% int., 0% control.
Mean age (SD) years: 55.1 (6.6) int., 55.0 (7.3) control
Age range: NR but inclusion criteria were 45-70 years
Smokers: 21% overall (not reported by arm)
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Brazil
Ethnicity: NR

Interventions

Type: supplement
Comparison: EPA+DHA vs nil
Intervention: 3 capsules/d EPA+DHA (Proepa, Ache, providing 0.54g/d EPA plus 0.36g/d DHA with 6mg/d alpha-tocopherol) plus dietary advice on energy intake (encouraging weight loss for those overweight), with 5-6 meals/d, 45-60%E CHO, 10-35%E protein, 20-35%E fat, SFA<7%E, MUFA 10-15%E, individualised to usual dietary intake: EPA+DHA 0.9g/d
Control: dietary advice on energy intake (encouraging weight loss for those overweight), with 5-6 meals/d, 45-60%E CHO, 10-35%E protein, 20-35%E fat, SFA<7%E, MUFA 10-15%E, individualised to usual dietary intake.
Compliance: Assessed in intervention with count of returned capsule containers at each visit, but no results of this mentioned, not in control as no placebo used.
Duration of intervention: 6 months

Tartibian 2011

Methods

RCT, 2x2 design, parallel, (n3 EPA+DHA vs nil), 6 months (the other intervention is aerobic exercise)
Summary risk of bias: Moderate or high

Participants

Sedentary postmenopausal women
N: 21 int with exercise, 20 int alone, 20 exercise alone, 18 no intervention (analysed NR)
Level of risk for CVD: low
Male: 0% int., 0% control.
Mean age (SD) yrs.: 59.7 (2.3) int with exercise, 63.1 (7.5) int alone, 61.4 (6.9) exercise alone, 58.9 (8.1) no int
Age range: NR
Smokers: NR

Hypertension: NR
Medications taken by at least 50% of those in the control group: Nil, inclusion criteria were that that participants took no medications
Medications taken by 20-49% of those in the control group: nil
Medications taken by some, but less than 20% of the control group: nil
Location: Iran
Ethnicity: NR

Interventions

Type: supplement
Comparison: EPA+DHA vs nil (plus or minus aerobic exercise)
Intervention: omega 3 capsules (Viva omega 3 fish oil, each containing 180mgEPA plus 120mg DHA): EPA+DHA 0.9g/d
Control: Nil
2x2 study, plus or minus an aerobic exercise programme
Compliance: assessed by pill counts was 96%, neutrophil cell membrane EPA and DHA appear to be significantly higher at 6 months in the intervention groups
Duration of intervention: 6 months

Terano 1999

Methods

RCT, parallel, (n3 EPA+DHA vs nil), 12 months.
Summary risk of bias: Moderate to high.

Participants

pop:
N: 10 int., 10 control. (analysed, int: 10 cont: 10)
Level of risk for CVD: High: all had "dementia of CVD".
Male: 10% int., 10% control.
Mean age (SD): 82.7 (6.4) int., 83.3 (5.3) control
Age range: NR
Smokers: 0% (not allowed at residence)
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Japan
Ethnicity: NR

Interventions

Type: supplement
Comparison: more DHA vs no supplement (open label)
Intervention: 6 capsules to create daily dose = 720 mg/d: DHA 0.72g/d
Control: no capsules
Compliance: Nurses who gave capsules made sure they were swallowed; strictly controlled intake of all participants so unlikely any "always takers".
Duration of intervention: 12 months

THIS DIET 2008

Methods

The Heart Institute of Spokane Diet Study (THIS DIET)
RCT- parallel (n3 EPA+DHA vs nil) 24 months
Summary risk of bias: Moderate or high

Participants

Recent survivors of first myocardial infarction (within <6 weeks).
N: 51 int., 50 control.
Level of CVD risk: High
Male: 80% int., 68% control.
Mean age (SD): 58(10) int., 58 (9) control.
Age range: unclear
Smokers: 25% int., 30% control.
Hypertension: 43% int., 50% control (uncontrolled or secondary hypertension excluded)
Medications taken by at least 50% of those in the control group: Aspirin, statins, beta blockers, and ACE inhibitors or angiotensin receptor blockers.
Medications taken by 20-49%: NR
Medications taken by some, but <20%: NR
Location: USA
Ethnicity: int. 98% white race control 94% white race

Interventions

Type: Dietary advice (to follow a Mediterranean style diet high in n-3)
Comparison: EPA & DHA vs placebo (unclear what)
Intervention: Mediterranean style diet high in n-3 (>0.75%E from omega 3 fats, unclear how much was EPA and DHA and how much was ALA). Dietary counselling group sessions; two in first month then at months 3, 6, 12 and 24. Sessions focused on behaviour modification and practical aspects of assigned diet including recipes, shopping and dining out: EPA+DHA dose unclear
Control: Dietary advice (to follow the American Heart Association Step II diet). Same number of group sessions as intervention.
The 2 diets were low in saturated fat (<7% kcal) and cholesterol (<200 mg/day); the Mediterranean-style diet was distinguished by greater omega-3 fat intake (>0.75% kcal).
Compliance: Participants were required to attend six sessions and only invited but not required to attend extra sessions. 3-day food diaries were reviewed with dietitians. Compliance results not stated.
Length of intervention: 24 months

TREND-HD 2008

Methods

Trial of Ethyl-EPA in Treating Mild to Moderate Huntington's Disease (TREND-HD)
RCT, parallel, (n3 EPA vs non-fat), 6 months
Summary risk of bias: Moderate or high

Participants

Population: People with Huntington's disease
N: 158 int., 158 control. (analysed, int: 152 cont: 156)
Level of risk for CVD: Low
Male: 56% int., 43% control.
Mean age (SD): 52.3 (9.8) int., 53.3 (10.2) control
Age range: NR
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: United States and Canada
Ethnicity: white 145 int, 149 control.
Depression: Long term condition (high risk)
Anxiety: Long term condition (high risk)

Interventions

Type: supplement
Comparison: Ethyl-EPA vs placebo
Intervention: 2 x 500mg capsules ethyl-EPA (>95% purity, 0.2% DL-α-tocopherol) /day: EPA+DHA 0.95g/d
Control: 2 x 500mg light paraffin oil (0.2% DL-α-tocopherol) / day
Compliance: Not measured
Duration of intervention: 6 months

Veleba 2015

Methods

RCT, parallel, 2x2 (n3 EPA+DHA vs n6 LA, plus or minus pioglitazone), 6 months
Summary risk of bias: Moderate or high

Participants

Overweight/obese type 2 diabetic patients treated with metformin
N: 17 n-3; 17 n-3 + Pio; 18 Pio; 17 control. (analysed, n-3: 16; n-3+Pio 14; Pio 17; cont: 13)
Level of risk for CVD: Moderate
Male: 66% in all groups combined
Age median: 59.5 n-3; 60.5 n-3+Pio: 62.0 Pio; 62.0 control
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: Metformin
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Czech Republic

	Ethnicity: NR
Interventions	Type: supplement (capsules with EPA+DHA; Pio+EPA+DHA; Pio alone; or corn oil) Comparison: EPA+DHA vs low EPA+DHA Intervention: **n-3 arm:** 5g/d omega-3 concentrate (including 0.75g/d EPA + 2g/d DHA, EPAX, Aalesund): EPA+DHA 2.75g/d **n-3+ pioglitazone arm:** as for n-3 + 15mg/d pioglitazone (Pio, Takeda): EPA+DHA 2.75g/d **Pio arm**: 15mg/d pioglitazone alone **Control:** 5g/d corn oil capsules (EPAX, Aalesund) Compliance: Serum omega-3 PhL index Duration of intervention: 24 weeks

WAHA 2016

Methods	The Walnut and Healthy Aging Study (WAHA) 2 arm, parallel RCT (n3 ALA vs nil), 2 years Summary risk of bias: Moderate to high
Participants	Middle aged healthy adults N: 362 int., 346 control (only preliminary data on 260 int., and 254 control is available) Level of risk for CVD: low Male: 32.6% int., 31.5% control Mean age (SD): 69.4 (3.8) int., 68.9 (3.5) control Age range: 63-79 (inclusion criteria) Smokers: 4.4% int., 1.2% control Hypertension: 52.8% int., 52.9% control Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: Spain and USA Ethnicity: NR
Interventions	Type: supplement (food) Comparison: ALA vs nil Intervention: 15% of daily energy intake as walnuts. The estimated amount of walnuts ranged from 1 to 2 oz/d (~30–60g/d). Sachets for daily consumption containing 30, 45, or 60 g of raw, pieced walnuts were provided as 8-week allotments to be eaten daily, preferably as the raw product, either as a snack or by incorporating them into shakes, yogurts, cereals, or salads. To improve participants' compliance, 1-kg extra walnut allowances were provided every 2 months to take into account family needs: LA unclear g/d Control: Usual diet without walnut. Compliance: assessed by dietitians through FFQs, recount of empty packages, and changes in FAs concentrations. 95% consumed at least 1 oz./day. The proportion of α-linolenic acid in RBCs increased in the walnut group by 0.162% (95% CI, 0.143–0.181) and in the control group by 0.015% (CI, −0.005–0.035) (P<0.001). Length of intervention: 2 years (only 1 year results have partly been published)

Weinstock-Guttman 2005

Methods	RCT, parallel, (n3 EPA+DHA vs MUFA, both with low fat advice), 12 months Summary risk of bias: Moderate or high
Participants	Population: Adults with multiple sclerosis N: 15 int., 16 control. (analysed, int: 13 cont: 14) Level of risk for CVD: Low Male: 15.4% int., 14.3% control. Mean age (SD): 39.9 (10.0) int., 45.1 (7.7) control Age range: NR Smokers: NR Hypertension: NR

Medications taken by at least 50% of those in the control group: All patients received 400 units of Vitamin E, one multivitamin tablet (not containing any PUFA) and at least 500 mg calcium per day
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: USA
Ethnicity: NR

Interventions

Type: dietary advice plus supplement
Comparison: low fat diet (15% fat) with n-3 fish oils vs AHA Step I diet (fat ≤30%) with olive oil supplements
Intervention: 1.98g/d EPA, 1.32g/d DHA supplements (EPAX 5500 EE, Tishcon Corp) + low fat diet (<15% total calories): EPA+DHA 3.3g/d
Control: One 1g olive oil placebo capsules 6 times daily, moderate fat diet (<30% total calories) (American Heart Association Step 1 diet)
Compliance: Assessed by individual food records; int 69.2% control 66.7% compliance; also at 12 months there was a significant difference between the fatty acid status of the intervention and control groups in terms of EPA (p = 0.0270), as described in table 3 of the main paper
Duration of intervention: 12 months

WELCOME 2015

Methods

Wessex Evaluation of Fatty Liver and Cardiovascular Markers in NAFLD with Omacor Therapy (WELCOME)
RCT, parallel, (n3 EPA+DHA vs MUFA), 15-18 months
Summary risk of bias: Low

Participants

Patients with NAFLD
N: 51 int., 52 control. (analysed, 47 int., 48 control)
Level of risk for CVD: Moderate
Male: 49% int., 67% control.
Mean age (SD): 48.6 (11.1) int., 54 (9.6) control.
Age range: NR (18-75 inclusion criteria)
Smokers: 14.3% int., 11.8% control.
Hypertension: NR
Medications taken by at least 50% of those in the control group: lipid lowering drugs
Medications taken by 20-49% of those in the control group: Antihypertensives, metformin (data not provided by group)
Medications taken by some, but less than 20% of the control group: None reported
Location: UK
Ethnicity: NR

Interventions

Type: supplement (Omacor capsules)
Comparison: DHA & EPA vs MUFA
Intervention: 4g OMACOR per day (providing 1.84g EPA, 1.52 g DHA as ethyl esters)]: EPA+DHA 3.36g/d
Control: 4g olive oil capsules/ day (providing; ALA1%,Oleic acid 67%, palmitic acid 15%, stearic acid 2%, n-6 fat: 15%)
Compliance: was assessed by recording the returned unused capsules and quantification of erythrocyte EPA & DHA enrichment (a prespecified threshold of 2% for DHA & threshold of 0.7% for EPA enrichment)
Duration of intervention: 15-18 months

Westberg 1990

Methods

Double blind, crossover, placebo controlled RCT (n3 EPA vs MUFA), 6 months
Summary risk of bias: moderate-high

Participants

Individuals with a long-term diagnosis of systemic lupus erythematosus
N: 20 int., 20 control (analysed – int: 17 cont: 17)
Level of risk for CVD: Low
Male: 12% int., 12% control.
Mean age (SD): 44.2 (6.6) int.; 44.2 (6.6) cont.
Age range: 31-64 int., 31-64 cont.

Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: prednisolone (65%)
Medications taken by 20-49% of those in the control group: azathioprine (29.4%)
Medications taken by some, but less than 20% of the control group: cyclophosphamide (6%)
Location: Sweden
Ethnicity: NR

Interventions

Type: supplement (capsules of fish oil or olive oil)
Comparison: EPA+DHA vs MUFA/n6 FA
Intervention: 10-15 capsules MaxEPA per day calculated as 0.2g/kg body weight (including 18.6% EPA + 12.1% DHA, 5.3% n6FA [LA/AA]; supplied by Seven Seas Healthcare Ltd, Kingston-Upon-Hull, Yorkshire, England): EPA+DHA ~3.5g/d
Control: 10-15 capsules olive oil per day calculated as 0.2g/kg body weight (including 68.6% oleic acid and 12.4% n6FA; supplied by Seven Seas Healthcare Ltd, Kingston-Upon-Hull, Yorkshire, England)
Compliance: NR
Duration of intervention: 6 months

Witte 2012

Methods

RCT, parallel, (n3 EPA+DHA vs n6 LA), 6 months
Summary risk of bias: Moderate or high

Participants

Healthy older adults (aged 50 to 80 years)
N: 40 int., 40 control. (analysed, int: 32 cont: 33)
Level of risk for CVD: low
Male: 53% int., 55% control.
Mean age (SD): 65 (6.3) int., 62.9 (6.8) control
Age range: int 51-75 yrs., cont 50-75 yrs.
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Germany
Ethnicity: NR

Interventions

Type: supplement
Comparison: fish oil capsules vs sunflower oil capsules
Intervention: fish oil capsules, 4 capsules/d (including 1.32g/d EPA plus 0.88g/d DHA, provided by Via Vitamine), and advised not to change usual dietary habits: EPA+DHA 2.2g/d
Control: sunflower oil capsules, 4 capsules/d (provided by Via Vitamine), identical in shape and colour, and advised not to change usual dietary habits
Compliance: compliance assessed by capsule counts, questionnaire, and omega 3 index in erythrocyte membrane, capsule count suggested missed capsules were <5%
Duration of intervention: 6 months

Wright 2008

Methods

RCT, parallel, (n3 EPA+DHA vs MUFA), 6 months
Summary risk of bias: Low

Participants

People with systemic lupus erythematosus (SLE)
N: 30 int., 30 control. (analysed, int: 27 cont: 29)
Level of risk for CVD: low
Male: 3% int., 10% control.
Mean age (SD) yrs.: 48.5 (9.1) int., 47.6 (9.6) control
Age range: NR
Smokers: 17% int., 13% control
Hypertension: NR

Medications taken by at least 50% of those in the control group: hydroxychloroquine or chloroquine (63%)
Medications taken by 20-49% of those in the control group: prednisolone (33%), NSAIDs (27%), aspirin (27%)
Medications taken by some, but less than 20% of the control group: NR
Location: UK
Ethnicity: NR

Interventions

Type: supplement
Comparison: EPA+DHA vs MUFA
Intervention: 4 capsules/d Omacor (Solvay, 1.8g/d EPA plus 1.2g/d DHA): EPA+DHA 3.0g/d
Control: 4 identical capsules/d olive oil (MUFA, exact content unclear)
Compliance: assessed by capsule return and change in platelet membrane fatty acid composition, EPA and DHA composition was significantly higher at 24 weeks than baseline in the intervention group, but no data comparing intervention with control groups (control group stated not to have altered significantly).
Duration of intervention: 6 months

Zhang 2017

Methods

RCT, parallel, (n3 DHA vs n6 LA), 12 months
Summary risk of bias: Moderate to high

Participants

Otherwise healthy elderly people with mild cognitive impairment, in China.
N: 120 int., 120 control (analysed, int: 110 cont: 109)
Level of risk for CVD: Low
Male 35.8% int., 34.2% control
Mean age (SD): 74.5 (2.65) int., 74.6 (3.31) control
Age range: Eligibility criteria were age 65-85 at trial start
Smokers: 59.17% int., 61.67% control
Hypertension: 9.17% int., 7.50% control
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: China
Ethnicity: Assumed Chinese

Interventions

Type: supplement (capsule)
Comparison: DHA vs. corn oil (n6)
Intervention: 1 capsule twice a day, with meals, including 2 grams algal DHA (50% DHA by weight). Martek Biosciences, Columbia, MD.
Control: Corn oil, Orange flavoured and orange colour to protect the study blind.
Compliance: Participants were asked to return any remaining tablets. Compliance was defined as a ratio = actually taken/should have taken. Achieved 97% for intervention, 95% for control. Serum levels of DHA also measured, DHA at 6m barely higher in intervention than in controls.
Duration of intervention: 12 months

Zheng 2016

Methods

RCT, parallel, (n3 EPA+DHA vs n3 ALA vs n6 LA), 6 months
Summary risk of bias: Moderate or high

Participants

People with type 2 diabetes mellitus
N: 63 fish oil int., 61 flaxseed oil int, 61 control. (analysed, 58 fish oil int., 53 flaxseed oil int, 55 control)
Level of risk for CVD: moderate
Male: 33% fish oil int., 60% flaxseed oil int, 48% control
Mean age (SD) yrs.: 59.7 (8.8) fish oil int., 59.7 (11.1) flaxseed oil int, 59.1 (10.0) control
Age range: men 35-80 years, women menopause to 80 years (inclusion criteria)
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: diabetic

	medication Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: China Ethnicity: NR
Interventions	Type: supplement Comparison: fish oil (LCn3) vs flaxseed oil (ALA) vs corn oil (n6) Fish oil Intervention: 4 capsules/d fish oil (1.2g/d EPA, 0.8g/d DHA), Neptunus Bioengineering: EPA+DHA 2.0g/d Flaxseed oil Intervention: 4 capsules/d flaxseed oil (2.5g/d ALA), Neptunus Bioengineering: ALA 2.5g/d Control: 4 capsules/d corn oil (2.1g/d LA), Neptunus Bioengineering Compliance: evaluated by measurement of erythrocyte phospholipid fatty acid compositions at baseline and end, counting empty bottles returned to study centres at days 90 and 180, and monthly phone contact. Sig diff of EPA and DHA between fish oil and corn oil groups at 6 months, and of ALA between flaxseed oil and corn oil at 6 months. Duration of intervention: 6 months

Özaydin 2011

Methods	RCT, parallel, (n3 EPA+DHA vs nil, both arms with amiodarone), 12 months Summary risk of bias: Moderate or high
Participants	Patients with persistent atrial fibrillation (AF) referred for cardioversion N: 23 int., 24 control. Level of risk for CVD: High Male: 47.8% int., 37.5% control. Mean age (SD): 62 (12) int., 61 (11) control Age range: 37-81 Smokers: NR Hypertension: 57% int., 50% control. Medications taken by at least 50% of those in the control group: All patients received Amiodarone (an antiarrhythmic medication) Medications taken by 20-49% of those in the control group: Beta-blockers, statins, ACEIs and ARBs Medications taken by some, but less than 20% of the control group: Calcium antagonists Location: Turkey Ethnicity: NR
Interventions	Type: Supplement (capsule) Comparison: LCN3 vs nil Intervention: 2g/d n3 PUFA (Marincap, Kocak, Turkey). 4x 500 mg capsules providing EPA 18% (360mg/d); DHA 12% (240mg/d): EPA+DHA 0.6g/d Control: no placebo. Amiodarone was given to both groups. Compliance: No details Duration of intervention: 12 months or AF recurrence

Footnotes
ALA = alpha-linolenic acid
BMI = body mass index
BP = blood pressure
CABG = coronary artery bypass grafting
CHD = coronary heart disease
chol = cholesterol
CVD = cardiovascular disease
DBP = diastolic blood pressure
DHA = docosahexaenoic acid
DM = diabetes mellitus
DPA = docosapentaenoic acid
E = dietary energy
EPA = eicosapentaenoic acid or icosapentaenoic acid
FA = fatty acid

FFQ = food frequency questionnaire
FH = family history
HDL = high density lipoprotein
H/O = personal history of
HRT = hormone replacement therapy
HT = hypertension
LCn3: long-chain omega 3 fats including EPA, DPA and DHA
MI = myocardial infarction
mo. = months
MUFA = mono-unsaturated fatty acids
n3 = omega 3
n6 = omega 6
PUFA = poly-unsaturated fatty acids
PTCA = percutaneous
P/S = poly-unsaturated / saturated fat ratio
SBP = systolic blood pressure
SFA = saturated fatty acids
TG = serum triglycerides
TIA = transient ischaemic attack
USA = United States of America
veg = vegetables
WHO = World Health Organization
yrs. = years

Appendix 3. Baseline dietary intake data (before intervention starts)

This chapter has been omitted from this version of the report.

Appendix 4. Dietary intake during the study intervention period

This chapter has been omitted from this version of the report.

Appendix 5. Fatty acid status measures

This chapter has been omitted from this version of the report.

Appendix 6. Dosage table for omega 3 interventions

This chapter has been omitted from this version of the report.

Appendix 7. References to included studies

ADCS-Quinn 2010

[ClinicalTrials.gov: NCT00440050]

Quinn JF, Raman R, Thomas RG, Yurko-Mauro K, Nelson EB, Van Dyck C, Galvin JE, Emond J, Jack CR Jr, Weiner M, Shinto L, Aisen PS. Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: a randomized trial. JAMA 2010;304(17):1903-11. [CRSREF: 2715755]

AFFORD 2014

[ClinicalTrials.gov: NCT01235130; ISRCTN: ISRCTN52203885]

* Nigam A, Talajic M, Roy D, Nattel S, Lambert J, Nozza A, et al. Fish oil for the reduction of atrial fibrillation recurrence, inflammation, and oxidative stress. Journal of the American College of Cardiology 2014;64(14):1441-8.

Nigam A, Talajic M, Roy D, Nattel S, Lambert J, Nozza A, et al. Multicentre trial of fish oil for the reduction of atrial fibrillation recurrence, inflammation and oxidative stress: The atrial fibrillation fish oil research study. Canadian Journal of Cardiology 2013;1):S383.

Almallah 1998

Published and unpublished data [CRSSTD: 2715805]

Almallah YZ, Ewen SW, El Tahir A, Mowat NA, Brunt PW, Sinclair TS et al. Distal proctocolitis and n-3 polyunsaturated fatty acids (n-3 PUFAs): the mucosal effect in situ. Journal of Clinical Immunology 2000;20(1):68-76. [CRSREF: 2715806]

Almallah YZ, Ewen SW, Mowat NA, Brunt PW, Sinclair TS, Heys SD et al. Immunohistological modulation after nutritional supplementation with omega-3 essential fatty acids in patients with inflammatory bowel disease [abstract]. British Juurnal of Surgery 1998;85:690-1. [CRSREF: 2715807]

Almallah YZ, O'Hanrahan T, Richardson S, Mowat NA, Brunt PW, Sinclair TS et al. Eicosapentaenoic acid and docosahexaenoic acid in the treatment of patients with distal procto-colitis [abstract]. British Journal of Surgery 1996;83 Suppl 1:2. [CRSREF: 2715808]

Almallah YZ, O'Hanrahan T, Richardson S, Mowat NA, Brunt PW, Sinclair TS et al. Inhibition of natural cytotoxicity with eicosapentaenoic and docosahexaenoic acids: possible mechanisms [abstract]. British Journal of Surgery 1996;83:685. [CRSREF: 2715809]

Almallah YZ, Richardson S, O'Hanrahan T, Mowat NA, Brunt PW, Sinclair TS et al. Distal procto-colitis, natural cytotoxicity, and essential fatty acids. American Journal of Gastroenterology 1998;93(5):804-9. [CRSREF: 2715810]

AlphaOmega - ALA

[CRSSTD: 2715616; ClinicalTrials.gov: NCT00127452]

Brouwer IA, Geleijnse JM, Klaasen VM, Smit LA, Giltay EJ, de Goede J, et al. Effect of alpha linolenic acid supplementation on serum prostate specific antigen (PSA): results from the alpha omega trial. PLoS ONE [Electronic Resource] 2013;8(12):e81519.

Eussen SR, Geleijnse JM, Giltay EJ, Rompelberg CJ, Klungel OH, Kromhout D. Effects of n-3 fatty acids on major cardiovascular events in statin users and non-users with a history of myocardial infarction. European Heart Journal 2012;33(13):1582-8.

Geleijnse J, Giltay E, Kromhout D. Effects of n-3 fattyacids on cognitive decline: A randomized double-blind, placebo-controlled trial in stable myocardial infarction patients. Alzheimer's and Dementia 2011;1):S512.

Geleijnse JM, Giltay EJ, Kromhout D. Effects of n-3 fatty acids on cognitive decline: a randomized, double-blind, placebo-controlled trial in stable myocardial infarction patients. Alzheimer's & Dementia 2012;8(4):278-87.

Geleijnse JM, Giltay EJ, Schouten EG, de Goede J, Oude Griep LM, Teitsma-Jansen AM, Katan MB, Kromhout D; Alpha Omega Trial Group.. Effect of low doses of n-3 fatty acids on cardiovascular diseases in 4,837 post-myocardial infarction patients: design and baseline characteristics of the Alpha Omega Trial. The American Heart Journal 2010;159(4):539-46. [CRSREF: 2715617; DOI: 10/1016/j.ahj.2009.12.033]

Giltay EJ, Geleijnse JM, Heijboer AC, de Goede J, Oude Griep LM, Blankenstein MA, et al. No effects of n-3 fatty acid supplementation on serum total testosterone levels in older men: the Alpha Omega Trial. International Journal of Andrology 2012;35(5):680-7.

Giltay EJ, Geleijnse JM, Kromhout D. Effects of n-3 fatty acids on depressive symptoms and dispositional optimism after myocardial infarction. American Journal of Clinical Nutrition 2011;94(6):1442-50.

Hoogeveen E, Gemen E, Geleijnse M, Kusters R, Kromhout D, Giltay E. Effects of N-3 fatty acids on decline of kidney function after myocardial infarction: Alpha omega trial. Nephrology Dialysis Transplantation 2012;27:ii64.

Hoogeveen EK, Geleijnse JM, Kromhout D, Giltay EJ. No effect of n-3 fatty acids on high-sensitivity C-reactive protein after myocardial infarction: the Alpha Omega Trial. European Journal of Preventive Cardiology 2014;21(11):1429-36.

Hoogeveen EK, Geleijnse JM, Kromhout D, Stijnen T, Gemen EF, Kusters R, et al. Effect of omega-3 fatty acids on kidney function after myocardial infarction: the Alpha Omega Trial. Clinical Journal of The American Society of Nephrology: CJASN 2014;9(10):1676-83.

Kromhout D, Geleijnse JM, de Goede J, Oude Griep LM, Mulder BJ, de Boer MJ, et al. n-3 fatty acids, ventricular arrhythmia-related events, and fatal myocardial infarction in postmyocardial infarction patients with diabetes. Diabetes Care 2011;34(12):2515-20.

* Kromhout D, Giltay EJ, Geleijnse JM; Alpha Omega Trial Group.. n-3 fatty acids and cardiovascular events after myocardial infarction. The New England Journal of Medicine 2010;363(18):2015-26. [CRSREF: 2715618]

AlphaOmega - EPA+DHA

[CRSSTD: 2715616; ClinicalTrials.gov: NCT00127452]

Brouwer IA, Geleijnse JM, Klaasen VM, Smit LA, Giltay EJ, de Goede J, et al. Effect of alpha linolenic acid supplementation on serum prostate specific antigen (PSA): results from the alpha omega trial. PLoS ONE [Electronic Resource] 2013;8(12):e81519.

Eussen SR, Geleijnse JM, Giltay EJ, Rompelberg CJ, Klungel OH, Kromhout D. Effects of n-3 fatty acids on major cardiovascular events in statin users and non-users with a history of myocardial infarction. European Heart Journal 2012;33(13):1582-8.

Geleijnse J, Giltay E, Kromhout D. Effects of n-3 fattyacids on cognitive decline: A randomized double-blind, placebo-controlled trial in stable myocardial infarction patients. Alzheimer's and Dementia 2011;1):S512.

Geleijnse JM, Giltay EJ, Kromhout D. Effects of n-3 fatty acids on cognitive decline: a randomized, double-blind, placebo-controlled trial in stable myocardial infarction patients. Alzheimer's & Dementia 2012;8(4):278-87.

Geleijnse JM, Giltay EJ, Schouten EG, de Goede J, Oude Griep LM, Teitsma-Jansen AM, Katan MB, Kromhout D; Alpha Omega Trial Group.. Effect of low doses of n-3 fatty acids on cardiovascular diseases in 4,837 post-myocardial infarction patients: design and baseline characteristics of the Alpha Omega Trial. The American Heart Journal 2010;159(4):539-46. [CRSREF: 2715617; DOI: 10/1016/j.ahj.2009.12.033]

Giltay EJ, Geleijnse JM, Heijboer AC, de Goede J, Oude Griep LM, Blankenstein MA, et al. No effects of n-3 fatty acid supplementation on serum total testosterone levels in older men: the Alpha Omega Trial. International Journal of Andrology 2012;35(5):680-7.

Giltay EJ, Geleijnse JM, Kromhout D. Effects of n-3 fatty acids on depressive symptoms and dispositional optimism after myocardial infarction. American Journal of Clinical Nutrition 2011;94(6):1442-50.

Hoogeveen E, Gemen E, Geleijnse M, Kusters R, Kromhout D, Giltay E. Effects of N-3 fatty acids on decline of kidney function after myocardial infarction: Alpha omega trial. Nephrology Dialysis Transplantation 2012;27:ii64.

Hoogeveen EK, Geleijnse JM, Kromhout D, Giltay EJ. No effect of n-3 fatty acids on high-sensitivity C-reactive protein after myocardial infarction: the Alpha Omega Trial. European Journal of Preventive Cardiology 2014;21(11):1429-36.

Hoogeveen EK, Geleijnse JM, Kromhout D, Stijnen T, Gemen EF, Kusters R, et al. Effect of omega-3 fatty acids on kidney function after myocardial infarction: the Alpha Omega Trial. Clinical Journal of The American Society of Nephrology: CJASN 2014;9(10):1676-83.

Kromhout D, Geleijnse JM, de Goede J, Oude Griep LM, Mulder BJ, de Boer MJ, et al. n-3 fatty acids, ventricular arrhythmia-related events, and fatal myocardial infarction in postmyocardial infarction patients with diabetes. Diabetes Care 2011;34(12):2515-20.

* Kromhout D, Giltay EJ, Geleijnse JM; Alpha Omega Trial Group.. n-3 fatty acids and cardiovascular events after myocardial infarction. The New England Journal of Medicine 2010;363(18):2015-26. [CRSREF: 2715618]

AREDS2 2014

Published and unpublished data [ISRCTN: NCT00345176]

Age-Related Eye Disease Study, Chew EY, Clemons TE, SanGiovanni JP, Danis RP, Ferris FL III, et al. Secondary analyses of the effects of lutein/zeaxanthin on age-related macular degeneration progression: AREDS2 report No. 3. JAMA Ophthalmology 2014;132(2):142-9.

Age-Related Eye Disease Study, Chew EY, SanGiovanni JP, Ferris FL, Wong WT, Agron E, et al. Lutein/zeaxanthin for the treatment of age-related cataract: AREDS2 randomized trial report no. 4. JAMA Ophthalmology 2013;131(7):843-50.

Age-Related Eye Disease Study, Huynh N, Nicholson BP, Agron E, Clemons TE, Bressler SB, et al. Visual acuity after cataract surgery in patients with age-related macular degeneration: age-related eye disease study 2 report number 5. Ophthalmology 2014;121(6):1229-36.

Chew EY, Clemons TE, Agron E, Launer LJ, Grodstein F, Bernstein PS, et al. Effect of Omega-3 Fatty Acids, Lutein/Zeaxanthin, or Other Nutrient Supplementation on Cognitive Function: The AREDS2 Randomized Clinical Trial. JAMA 2015;314(8):791-801.

Chew EY, Clemons TE. In reply: Making sense of the evidence from the age-related eye disease study 2 randomized clinical trial. JAMA Ophthalmology 2014;132(8):1031-2.

Group Areds Research, Chew EY, Clemons T, SanGiovanni JP, Danis R, Domalpally A, et al. The Age-Related Eye Disease Study 2 (AREDS2): study design and baseline characteristics (AREDS2 report number 1). Ophthalmology 2012;119(11):2282-9.

* Writing Group for the AREDS Research Group, Bonds DE, Harrington M, Worrall BB, Bertoni AG, Eaton CB, et al. Effect of long-chain omega-3 fatty acids and lutein + zeaxanthin supplements on cardiovascular outcomes: results of the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. JAMA Internal Medicine 2014;174(5):763-71.

Baldassarre 2006

[CRSSTD: 2715625]

Baldassarre D, Amato M, Eligini S, Barbieri SS, Mussoni L, Frigerio B, Kozàkovà M, Tremoli E, Sirtori CR, Colli S.. Effect of n-3 fatty acids on carotid atherosclerosis and haemostasis in patients with combined hyperlipoproteinemia: a double-blind pilot study in primary prevention.. Annals of Medicine 2006;38(5):367-75. [CRSREF: 2715626; DOI: 10.1080/07853890600852880]

Baleztena 2015

[ClinicalTrials.gov: NCT01817101]

* Baleztena Gurrea J, Ruiz-Canela M, Pardo M, Castellanos MC, Gozalo MJ, Añorbe T, Bes-Rastrollo M. Utility of a food supplement rich in omega-3 fatty acids in the prevention of dementia, in relation to basal metabolism, in people of advanced age: randomised multicentre study [Utilidad de suplemento alimenticio rico en acidos grasos omega-3 en la prevencion de la demencia, en relacion con el nivel nutricional basal, en personas de edad avanzada: estudio aleatorizado multicentrico]. Rev Esp Geriatr Gerontol (Espec Cong) 2015;50(13):13 (OC 035). [Other:]

Bes-Rastrollo M, Baleztena J, Aguirre I, Ruiz-Canela M. Food supplement rich in omega-3 fatty acids in the prevention of dementia: multicenter randomized study [Complemento alimenticio rico enácidos grasos omega-3 en la prevención de lademencia: estudio aleatorizado multicéntrico]. Nutrición Clínicaen Medicina Libro de comunicaciones FESNAD 2015 2015;9(1):49 (067). [DOI: DOI:10.7400/NCM.2015.09.1.5025]

Bates 1989

Bates D, Cartlidge NE, French JM, Jackson MJ, Nightingale S, Shaw DA, et al. A double-blind controlled trial of long chain n-3 polyunsaturated fatty acids in the treatment of multiple sclerosis. Journal of Neurology, Neurosurgery & Psychiatry 1989;52(1):18-22.

Baxheinrich 2012

Baxheinrich A, Stratmann B, Lee-Barkey Y, Tschoepe D, Wahrburg U. Effects of a rapeseed oil-enriched hypoenergetic diet with a high content of alpha-linolenic acid on body weight and cardiovascular risk profile in patients with the metabolic syndrome. British Journal of Nutrition 2012;108:682-691.

Belch 1988

[CRSSTD: 2715820]

Belch JJ, Ansell D, Madhok R, O'Dowd A, Sturrock RD. Effects of altering dietary essential fatty acids on requirements for non-steroidal anti-inflammatory drugs in patients with rheumatoid arthritis: a double blind placebo controlled study. Annals of the Rheumatic Diseases 1988;47(2):96-104. [CRSREF: 2715821]

Belluzzi 1996

Published and unpublished data

Belluzzi, A., Brignola, C., Campieri, M., Pera, A., Boschi, S. & Miglioli, M. Effect of an enteric-coated fish-oil preparation on relapses in Crohn's Disease. New England Journal of Medicine 1996;334(24):1557-1560.

Berbert 2005

Berbert AA, Kondo, CRM, Almendra CM, Matsuo T, Dichi I. Supplementation of fish oil and olive oil in patients with rheumatoid arthritis. Nutrition 2005;21:131-136.

Berson 2004

[CRSSTD: 2715629]

* Berson EL, Rosner B, Sandberg MA, Weigel-DiFranco C, Moser A, Brockhurst RJ, et al. Clinical trial of docosahexaenoic acid in patients with retinitis pigmentosa receiving vitamin A treatment. Archives of Ophthalmology 2004;122(9):1297-305.

Berson EL, Rosner B, Sandberg MA, Weigel-DiFranco C, Moser A, Brockhurst RJ, et al. Further evaluation of docosahexaenoic acid in patients with retinitis pigmentosa receiving vitamin A treatment: subgroup analyses. Archives of Ophthalmology 2004;122(9):1306-14.

Bo 2017

[Other: ChiCTR-TRC-14004625]

* Bo Y, Zhang X, Wang Y, You J, Cui H, Zhu Y, Pang W, Liu W, Jiang Y, Lu Q. The n-3 Polyunsaturated Fatty Acids Supplementation Improved the Cognitive Function in the Chinese Elderly with Mild Cognitive Impairment: A Double-Blind Randomized Controlled Trial. Nutrients 2017;9(1):E54. [DOI: 10.3390/nu9010054]

Boespflug 2016

[ClinicalTrials.gov: NCT01746303]

Boespflug EL, McNamara RK, Eliassen JC, Schidler MD, Krikorian R. Fish Oil Supplementation Increases Event-Related Posterior Cingulate Activation in Older Adults with Subjective Memory Impairment. J Nutr Health Aging 2016;20(2):161-9. [DOI: 10.1007/s12603-015-0609-6.]

Bonnema 1995

Published and unpublished data [CRSSTD: 2715834]

Bonnema SJ, Jespersen LT, Marving J, Gregersen G. Supplementation with olive oil rather than fish oil increases small arterial compliance in diabetic patients. Diabetes, Nutrition and Metabolism Clinical and Experimental 1995;8:81-7. [CRSREF: 2715835]

Brox 2001

Published and unpublished data [CRSSTD: 2715638]

* Brox J, Olaussen K, Osterud B, Elvevoll EO, Bjornstad E, Brattebog G et al. A long-term seal- and cod-liver-oil supplementation in hypercholesterolemic subjects. Lipids 2001;36(1):7-13. [CRSREF: 2715639]

Caldwell 2011

[ClinicalTrials.gov: NCT00681408]

Argo CK, Patrie JT, Lackner C, Henry TD, de Lange EE, Weltman AL, et al. Effects of n-3 fish oil on metabolic and histological parameters in NASH: a double-blind, randomized, placebo-controlled trial. Journal of hepatology 2015;62(1):190-7. [PubMed: 25195547]

Caldwell SH, Argo CK Henry TD, Lackner C et al. Dissociated histological and metabolic effects of omega-3 (3000mg/d) vs placebo with both exercise and diet in a double-blind randmozed controlled trial of NASH. Journal of Hepatology 2011**;**54:S8 [abstract]

Chih-Chiang Chin 2010

Unpublished data only [CRSSTD: 2716193; ClinicalTrials.gov: NCT01235533]

(Only Clinical trials entry)

Chiu 2008

[ClinicalTrials.gov: NCT00628017]

Chih-Chiang Chiu, Kuan-Pin Su, Tsung-Chi Cheng, Hsing-Cheng Liu, Ching-Jui Chang,Michael E. Dewey, Robert Stewart, Shih-Yi Huang. The effects of omega-3 fatty acids monotherapy in Alzheimer's disease and mildcognitive impairment: A preliminary randomized double-blindplacebo-controlled study. Progress in Neuro-sychopharmacology & Biological Psychiatry 2008;32:1538–1544.

Clark 2016

[ClinicalTrials.gov: NCT01241474]

* Clark LF, Thivierge MC, Kidd CA, McGeoch SC, Abraham P, Pearson DW, Horgan GW, Holtrop G, Thies F, Lobley GE. Fish oil supplemented for 9 months does not improve glycaemic control or insulin sensitivity in subjects with impaired glucose regulation: a parallel randomised controlled trial. British Journal of Nutrition 2016;115(1):75-86. [DOI: 10.1017/S0007114515004274]

Connor 1993

Published and unpublished data [CRSSTD: 2715860]

Connor WE, Prince MJ, Ullmann D, Riddle M, Hatcher L, Smith FE et al. The hypotriglyceridemic effect of fish oil in adult-onset diabetes without adverse glucose control. Annals of the New York Academy of Sciences 1993;683:337-40. [CRSREF: 2715861]

Ullmann D, Prince MJ, Riddle M, Connor WE, Smith F, Wilson D. The effects of dietary fish oil versus olive oil in diabetic patients [abstract]. Arteriosclerosis 1990;10:881A. [CRSREF: 2715862]

Darghosian 2015

[ClinicalTrials.gov: NCT00552084; DOI: 10.1016/j.amjcard.2014.10.022]

Darghosian L, Free M, Li J, Gebretsadik T, Bian A, Shintani A, McBride BF et al.. Effect of omega-three polyunsaturated fatty acids on inflammation, oxidative stress, and recurrence of atrial fibrillation.. American Journal of Cardiology 2015;115(2):196-201.

DART2 - Burr 2003

Published and unpublished data [CRSSTD: 2715655]

* Burr ML, Ashfield-Watt PA, Dunstan FD, Fehily AM, Breay P, Ashton T et al. Lack of benefit of dietary advice to men with angina: results of a controlled trial. European Journal of Clinical Nutrition 2003;57(2):193-200. [CRSREF: 2715656]

Ness AR, Ashfield-Watt PAL, Whiting JM, Smith GD, Hughes J, Burr ML. The long-term effect of dietary advice on the diet of men with angina: the diet and angina randomized trial. Journal of Human Nutrition and Dietetics 2004;17:1-3. [CRSREF: 2715657]

Ness AR, Gallacher JE, Bennett PD, Gunnell DJ, Rogers PJ, Kessler D et al. Advice to eat fish and mood: a randomised controlled trial in men with angina. Nutritional Neuroscience 2003;6(1):63-5. [CRSREF: 2715658]

DART - Burr 1989

Published and unpublished data [CRSSTD: 2715644]

* Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). Lancet 1989;2(8666):757-61. [CRSREF: 2715645]

Burr ML, Fehily AM, Rogers S, Welsby E, King S, Sandham S. Diet and reinfarction trial (DART): design, recruitment, and compliance. European Heart Journal 1989;10(6):558-67. [CRSREF: 2715646]

Burr ML, Fehily AM. Fatty fish and heart disease: a randomized controlled trial. World review of nutrition and dietetics 1991;66:306-12. [CRSREF: 2715647]

Burr ML, Fehily AM. Fish and the heart [letter]. Lancet 1989;ii:1451-2. [CRSREF: 2715648]

Burr ML, Holliday RM, Fehily AM, Whitehead PJ. Haematological prognostic indices after myocardial infarction: evidence from the diet and reinfarction trial (DART). European Heart Journal 1992;13(2):166-70. [CRSREF: 2715649]

Burr ML, Sweetham PM, Fehily AM. Diet and reinfarction [letter]. European Heart Journal 1994;15(8):1152-3. [CRSREF: 2715650]

Fehily AM, Vaughan-Williams E, Shiels K, Williams AH, Horner M, Bingham G et al. Factors influencing compliance with dietary advice: the Diet and Reinfarction Trial (DART). Journal of Human Nutrition and Dietetics 1991;4:33-42. [CRSREF: 2715651]

Fehily AM, Vaughan-Williams E, Shiels K, Williams AH, Horner M, Bingham G et al. The effect of dietary advice on nutrient intakes: evidence from the diet and reinfarction trial (DART). Journal of Human Nutrition & Dietetics 1989;2:4235. [CRSREF: 2715652]

Ness AR, Hughes J, Elwood PC, Whitley E, Smith GD, Burr ML. The long-term effect of dietary advice in men with coronary disease: follow-up of the Diet and Reinfarction Trial (DART). European Journal of Clinical Nutrition 2002;56(6):512-8. [CRSREF: 2715653]

Ness AR, Whitley E, Burr ML, Elwood PC, Smith GD, Ebrahim S. The long-term effect of advice to eat more fish on blood pressure in men with coronary disease: results from the diet and reinfarction trial. Journal of Human Hypertension 1999;13(11):729-33. [CRSREF: 2715654]

Dasarathy 2015

[ClinicalTrials.gov: NCT00323414]

Dasarathy S, Dasarathy J, Khiyami A, Yerian L, Hawkins C, Sargent R, McCullough A. Double blind randomized placebo controlled clinical trial of omega 3 fatty acids for the treatment of diabetic patients with nonalcoholic steatohepatitis. Journal of Clinical Gastroenterology 2015;49(2):137-144.

Delamaire 1991

[CRSSTD: 2716196]

Delamaire M, Durand F, Bouillaux M, Delambre C, Le-Goff MC, Allannic H. Influence of polyunsaturated fatty acid (MaxEPA) treatment on the haemorheological parameters of 28 IDD patients. Diabetologia 1991;34:A74. [CRSREF: 2716197]

Derosa 2009

Published and unpublished data [CRSSTD: 2715661]

Derosa G, Maffioli P, D'Angelo A, Salvadeo SA, Ferrari I, Fogari E, Gravina A, Mereu R, Randazzo S, Cicero AF. Effects of long chain omega-3 fatty acids on metalloproteinases and their inhibitors in combined dyslipidemia patients. Expert Opinion Pharmacother 2009;10(8):1239-47. [CRSREF: 2715662; DOI: 10.1517/14656560902865601]

Derosa 2011

[CRSSTD: 2715873; DOI: 10.1002/ejlt.201000504]

Derosa G, Cicero AFG, Fogari E, D'Angelo A, Bonaventura A, Maffioli P. Effects of n-3 PUFA on insulin resistance after an oral fat load. European Journal of Lipid Science and Technology 2011;113:950-60. [CRSREF: 2715874]

Derosa G, Cicero AFG, Fogari E, D'Angelo A, Bonaventura A, Romano D, Maffioli P. Effects of n-3 PUFAs on postprandial variation of metalloproteinases, and inflammatory and insulin resistance parameters in

dyslipidemic patients: evaluation with euglycemic clamp and oral fat load. Journal of Clinical LIpidology 2012;6:553-64. [DOI: 10.1016/j.jacl.2012.02.010]

Derosa 2016

Derosa G, Cicero AF, D'Angelo A, Borghi C, Maffioli P. Effects of n-3 pufas on fasting plasma glucose and insulin resistance in patients with impaired fasting glucose or impaired glucose tolerance. BioFactors (Oxford, England) 2016;42(3):316-22. [PubMed: 27040503]

Deslypere 1992

Published and unpublished data

Blok WL, Deslypere JP, Demacker PN, van der Ven-Jongekrijg J, Hectors MP, van der Meer JW, et al. Pro- and anti-inflammatory cytokines in healthy volunteers fed various doses of fish oil for 1 year. European journal of clinical investigation 1997;27(12):1003-8. [PubMed: 9466128]

Deslypere JP. Influence of supplementation with N-3 fatty acids on different coronary risk factors in men--a placebo controlled study. Verhandelingen - Koninklijke Academie voor Geneeskunde van Belgie 1992;54(3):189-216. [PubMed: 1413984]

Katan MB, Deslypere JP, van Birgelen AP, Penders M, Zegwaard M. Kinetics of the incorporation of dietary fatty acids into serum cholesteryl esters, erythrocyte membranes, and adipose tissue: an 18-month controlled study. Journal of lipid research 1997;38(10):2012-22. [PubMed: 9374124]

DIPP-Tokudome 2015

[Other: UMIN000000461]

Tokudome S, Kuriki K, Yokoyama Y, Sasaki M, Joh T, Kamiya T, et al. Dietary n-3/long-chain n-3 polyunsaturated fatty acids for prevention of sporadic colorectal tumors: a randomized controlled trial in polypectomized participants. Prostaglandins, leukotrienes, and essential fatty acids 2015;94:1-11. [PubMed: 25451556]

Tokudome S, Yokoyama Y, Kamiya T, Seno K, Okuyama H, Kuriki K, et al. Rationale and study design of dietary intervention in patients polypectomized for tumors of the colorectum. Japanese journal of clinical oncology 2002;32(12):550-3. [PubMed: 12578906]

DISAFF - Harrison 2003

Published and unpublished data [CRSSTD: 2715663; ISRCTN: ISRCTN16448451]

Harrison RA, Elton P. From pies to pilchards: dietary assistants increase consumption of oil rich fish [Abstract]. Journal of Epidemiology and Community Health 2000;Supplement:6. [CRSREF: 2715664]

Harrison RA, Elton PJ. Can an oil-rich fish diet improve treatment outcomes following cardioversion for atrial fibrillation? A randomised controlled trial. Study design and compliance [poster]. In: International Society for the Study of Fatty Acids and Lipids (ISSFAL). Montreal, Canada. 2003. [CRSREF: 2715665]

Harrison RA, Elton PJ. Is there a role for long-chain omega3 or oil-rich fish in the treatment of atrial fibrillation? Medical hypotheses 2005;64(1):59-63. [PubMed: 15533612]

Harrison RA, Purnell P, Elton PJ. Using community-based dietary assistants to increase the intake of oil-rich fish among older people [Abstract]. European Journal of Public Health 2003;13(Suppl 1):105. [CRSREF: 2715667]

Dodin 2005

Dodin S, Cunnane SC, Masse B, Lemay A, Jacques H, Asselin G, et al. Flaxseed on cardiovascular disease markers in healthy menopausal women: a randomized, double-blind, placebo-controlled trial. Nutrition (Burbank, Los Angeles County, Calif.) 2008;24(1):23-30. [PubMed: 17981439]

Dodin S, Lemay A, Jacques H, Legare F, Forest JC, Masse B. The effects of flaxseed dietary supplement on lipid profile, bone mineral density, and symptoms in menopausal women: a randomized, double-blind, wheat germ placebo-controlled clinical trial. The Journal of clinical endocrinology and metabolism 2005;90(3):1390-7. [PubMed: 15613422]

Doi 2014

[Other: UMIN000016723]

Doi M, Nosaka K, Miyoshi T, Iwamoto M, Kajiya M, Okawa K, et al. Early eicosapentaenoic acid treatment after percutaneous coronary intervention reduces acute inflammatory responses and ventricular arrhythmias in patients with acute myocardial infarction: a randomized, controlled study. International journal of cardiology 2014;176(3):577-82. [PubMed: 25305703]

Kazumasa Nosaka, Toru Miyoshi, Keisuke Okawa, Saori Tsukuda, Masahiro Sogo, Tomoyuki Nishibe, Naoaki Mastuo, Masayuki Doi.. Early initiation of eicosapentaenoic acid and statin treatment is associated with better clinical outcomes than statin alone in patients with acute coronary syndromes: 1-year outcomes of a randomized controlled study. In: Journal of the American College of Cardiology. Vol. 67. 2016:573.

M. Doi, K. Nosaka, T. Miyoshi, M. Iwamoto, M. Kajiya, K. Okawa, S. Tsukuda, N. Kawakita, F.Yokohama, K. Takeda.. Clinical outcomes of early initiation of pure eicosapentaenoic acid supplement after percutaneous coronary intervention in patients with acute coronary syndrome. In: European Heart Journal. Vol. 35 (Abstract Supplement). 2014:1156.

Nosaka Kazumasa, Miyoshi Toru, Iwamoto Mutsumi, Kajiya Masahito, Okawa Keisuke, Tsukuda Saori, et al. Early initiation of eicosapentaenoic acid and statin treatment is associated with better clinical outcomes than statin alone in patients with acute coronary syndromes: 1-year outcomes of a randomized controlled study. 2017;228:173-9.

DO IT - Einvik 2010

[CRSSTD: 2715668; ClinicalTrials.gov: NCT00764010]

Berstad P, Seljeflot I, Veierod MB, Hjerkinn EM, Arnesen H, Pedersen JI. Supplementation with fish oil affects the association between very long-chain n-3 polyunsaturated fatty acids in serum non-esterified fatty acids and soluble vascular cell adhesion molecule-1. Clinical Science 2003;105(1):13-20.

Eid HM, Arnesen H, Hjerkinn EM, Lyberg T, Ellingsen I, Seljeflot I. Effect of diet and omega-3 fatty acid intervention on asymmetric dimethylarginine. Nutrition & Metabolism 2006;3:4.

Eid HMA, Arnesen H, Hjerkinn EM, Lyberg T, Ellingsen I, Seljeflot I. Effect of diet and omega-3 fatty acid intervention on asymmetric dimethylarginine. Nutrition and Metabolism 2006;3:1-10.

Einvik G, Ekeberg O, Lavik JG, Ellingsen I, Klemsdal TO, Hjerkinn EM. The influence of long-term awareness of hyperlipidemia and of 3 years of dietary counseling on depression, anxiety, and quality of life. Journal of Psychosomatic Research 2010;68(6):567-72.

* Einvik G, Klemsdal TO, Sandvik L, Hjerkinn EM. A randomized clinical trial on n-3 polyunsaturated fatty acids supplementation and all-cause mortality in elderly men at high cardiovascular risk. European Journal of Cardiovascular Prevention & Rehabilitation 2010;17(5):588-92.

Ellingsen I, Hjerkinn EM, Arnesen H, Seljeflot I, Hjermann I, Tonstad S. Follow-up of diet and cardiovascular risk factors 20 years after cessation of intervention in the Oslo Diet and Antismoking study. European Journal of Clinical Nutrition 2006;60(3):378-85.

Furenes EB, Seljeflot I, Solheim S, Hjerkinn EM, Arnesen H, Furenes EB. Long-term influence of diet and/or omega-3 fatty acids on matrix metalloproteinase-9 and pregnancy-associated plasma protein-A in men at high risk of coronary heart disease. Scandinavian journal of clinical and laboratory investigation 2008;68(3):177-84.

Hjerkinn EM, Abdelnoor M, Breivik L, Bergengen L, Ellingsen I, Seljeflot I, et al. Effect of diet or very long chain omega-3 fatty acids on progression of atherosclerosis, evaluated by carotid plaques, intima-media thickness and by pulse wave propagation in elderly men with hypercholesterolaemia. European Journal of Cardiovascular Prevention & Rehabilitation 2006;13(3):325-33.

Hjerkinn EM, Seljeflot I, Ellingsen I, Berstad P, Hjermann I, Sandvik L, et al. Influence of long-term intervention with dietary counseling, long-chain n-3 fatty acid supplements, or both on circulating markers of endothelial activation in men with long-standing hyperlipidemia. American Journal of Clinical Nutrition 2005;81(3):583-9.

Lindman AS, Pedersen JI, Hjerkinn EM, Arnesen H, Veierod MB, Ellingsen I, et al. The effects of long-term diet and omega-3 fatty acid supplementation on coagulation factor VII and serum phospholipids with special emphasis on the R353Q polymorphism of the FVII gene. Thrombosis & Haemostasis 2004;91(6):1097-104.

Troseid M, Arnesen H, Hjerkinn EM, Seljeflot I. Serum levels of interleukin-18 are reduced by diet and n-3 fatty acid intervention in elderly high-risk men. Metabolism: Clinical & Experimental 2009;58(11):1543-9.

Troseid M, Seljeflot I, Weiss TW, Klemsdal TO, Hjerkinn EM, Arnesen H. Arterial stiffness is independently associated with interleukin-18 and components of the metabolic syndrome. Atherosclerosis 2010;209(2):337-9.

Ebrahimi 2009

Ebrahimi M, Ghayour-Mobarhan M, Azimi-Nezhad M, Shakeri A, Vejdani S, Tavallaei M, Akbarirad S, Parizadeh GA, Ferns. Dietary supplementation of omega-3 reduced antibody titers to heat shock protein 27 in metabolic syndrome subjects. 77th Congress of the European Atherosclerosis Society, April 26–29, 2008, Istanbul, Turkey 2008;PO29-494:138.

* Ebrahimi M, Ghayour-Mobarhan M, Rezaiean S, Hoseini M, Parizade SM, Farhoudi F, et al. Omega-3 fatty acid supplements improve the cardiovascular risk profile of subjects with metabolic syndrome, including markers of inflammation and auto-immunity. Acta Cardiologica 2009;64(3):321-7.

ELIA - Takaki 2011

[Other: UMIN000002171]

Takaki A, Umemoto S, Ono K, Seki K, Ryoke T, Fujii A, Itagaki T, Harada M, Tanaka M, Yonezawa T, Ogawa H, Matsuzaki M for ELIA study group. Add-on therapy of EPA reduces oxidative stress and inhibits the progression of aortic stiffness in patients with coronary artery disease and statin therapy: a randomized controlled study. Journal of Atherosclerosis and Thrombosis 2011;18:857-66. [Other:]

Emsley 2014

Emsley R, Chiliza B, Asmal L, du Plessis S, Phahladira L, van Niekerk E, van Rensburg SJ, Harvey BH. A randomized, controlled trial of omega-3 fatty acids plus an antioxidantfor relapse prevention after antipsychotic discontinuation infirst-episode schizophrenia. Schizophrenia Research 2014;158:230-35. [DOI: 10.1016/j.schres.2014.06.004]

EPE-A study 2014

Published and unpublished data [ClinicalTrials.gov: NCT01154985]

Sanyal AJ, Abdelmalek MF, Suzuki A, Cummings OW, Chojkier M. No significant effects of ethyl-eicosapentanoic acid on histologic features of nonalcoholic steatohepatitis in a phase 2 trial. Gastroenterology 2014;147(2):377-84.e1. [PubMed: 24818764]

EPIC-1 2008

Published and unpublished data [CRSSTD: 2715670; ClinicalTrials.gov: NCT00613197; DOI: 10.1001/JAMA.299.14.1690]

* Feagan BG, Sandborn WJ, Mittmann U, Bar-Meir S, D'Haens G, Bradette M, Cohen A, Dallaire C, Ponich TP, McDonald JW, Hébuterne X, Paré P, Klvana P, Niv Y, Ardizzone S, Alexeeva O, Rostom A, Kiudelis G, Spleiss J, Gilgen D, Vandervoort MK, Wong CJ, Zou GY, Donner A, Rutgeerts P. Omega-3 free fatty acids for the maintenance of remission in Crohn disease: the EPIC Randomized Controlled Trials. JAMA 2008;299(14):1690-7. [CRSREF: 2715671]

EPIC-2 2008

Published and unpublished data [CRSSTD: 2715672; ClinicalTrials.gov: NCT00074542; DOI: 10.1001/jama.299.14.1690]

* Feagan BG, Sandborn WJ, Mittmann U, Bar-Meir S, D'Haens G, Bradette M, Cohen A, Dallaire C, Ponich TP, McDonald JW, Hébuterne X, Paré P, Klvana P, Niv Y, Ardizzone S, Alexeeva O, Rostom A, Kiudelis G, Spleiss J, Gilgen D, Vandervoort MK, Wong CJ, Zou GY, Donner A, Rutgeerts P. Omega-3 free fatty acids for the maintenance of remission in Crohn disease: the EPIC Randomized Controlled Trials. JAMA 2008;229(14):1690-7. [CRSREF: 2715673]

EPOCH 2014

Published and unpublished data [Other: ACTRN2607000278437]

* Danthiir V, Burns NR, Nettelbeck T, Wilson C, Wittert G. The older people, omega-3, and cognitive health (EPOCH) trial design and methodology: a randomised, double-blind, controlled trial investigating the effect of long-chain omega-3 fatty acids on cognitive ageing and wellbeing in cognitively healthy older adults. Nutrition journal 2011;10:117. [PubMed: 22011460]

Danthiir V, Hosking D, Burns NR, Wilson C, Nettelbeck T, Calvaresi E, et al. Cognitive performance in older adults is inversely associated with fish consumption but not erythrocyte membrane n-3 fatty acids. The Journal of nutrition 2014;144(3):311-20. [PubMed: 24353345]

Eschen 2010

Eschen O, Christesen JH, La Rovere MT, Romano P, Sala P, Schmidt EB. Effects of marine n-3 fatty acids on circulating levels of soluble adhesion molecules in patients with chronic heart failure. Cellular and Molecular Biology 2010;56(1):43-49. [DOI: 10.1170/T878]

FAAT - Leaf 2005

[CRSSTD: 2715676; ClinicalTrials.gov: NCT00004559]

* Leaf A, Albert CM, Josephson M, Steinhaus D, Kluger J, Kang JX, et al. Prevention of fatal arrhythmias in high-risk subjects by fish oil n-3 fatty acid intake. Circulation 2005;112(18):2762-8.

Fakhrzadeh 2010

Fakhrzadeh H, Ghaderpanahi M, Sharifi F, Mirarefin M, Badamchizade Z, Kamrani A, Larijani B. Fatty acids on serum lipid profiles and insulin resistance of the elderly: a randomized controlled clinical trial. International Journal for Vitamin and Nutrition Research 2010;80(2):107-116.

Ghaderpanahi M, Fakhrzadeh H, Sharifi F, Mirarefin M, Badamchizade Z, Larijani B. The effects of fish oil supplementation on hematologic pattern of the elderly "Kahrizak Elderly Study". Iranian Journal of Diabetes and Lipid Disorders 2010;9:21-27.

Ferreira 2015

Ferreira JJ, Rosser A, Craufurd D, Squitieri F, Mallard N, Landwehrmeyer B. Ethyl-Eicosapentaenoic Acid Treatment in Huntington's Disease: A Placebo-Controlled Clinical Trial. Movement Disorders 2015;30(10):1426-9. [DOI: 10.1002/mds.26308]

Finnegan 2003

Published and unpublished data [CRSSTD: 2715890]

Finnegan YE, Howarth D, Minihane AM, Kew S, Miller GJ, Calder PC, Williams CM. Plant and marine derived (n-3) polyunsaturated fatty acids do not affect blood coagulation and fibrinolytic factors in moderately hyperlipidemic humans. Journal of Nutrition 2009;133(7):2210-3. [CRSREF: 2715891]

Finnegan YE, Minihane AM, Leigh-Firbank EC, Kew S, Meijer GW, Muggli R, Calder PC, Williams CM. Plant- and marine-derived n-3 polyunsaturated fatty acids have differential effects on fasting and postprandial blood lipid concentrations and on the susceptibility of LDL to oxidative modification in moderately hyperlipidemic subjects. American Journal of Clinical Nutrition 2003;77(4):783-95. [CRSREF: 2715892]

Kew S, Banerjee T, Minihane AM, Finnegan YE, Muggli R, Albers R, Williams CM, Calder PC. Lack of effect of foods enriched with plant- or marine-derived n-3 fatty acids on human immune function. American Journal of Clinical Nutrition 2003;77(5):1287-95. [CRSREF: 2715961]

Kew S, Banerjee T, Minihane AM, Finnegan YE, Williams CM, Calder PC. Relation between the fatty acid composition of peripheral blood mononuclear cells and measures of immune cell function in healthy, free-living subjects aged 25-72y. American Journal of Clinical Nutrition 2003;77:1278-86.

FISHGASTRO - Pot 2009

[CRSSTD: 2715678; Other:]

Pot GK, Geelen A, Majsak-Newman G, Harvey LJ, Nagengast FM, Witteman BJ, van de Meeberg PC, Hart AR, Williams MP, Przybylska-Phillips K, Dainty JR, Schaafsma G, Lund EK, Rijkers GT, Kampman E. Increased consumption of fatty and lean fish reduces serum c-reactive protein concentrations but not inflammation markers in feces and in colonic biopsies. J.Nutr 2010;140:371-376. [DOI: 10.3945/jn.109.113472]

Pot GK, Habermann N, Majsak-Newman G, Harvey LJ, Geelen A, Przybylska-Phillips K, Nagengast FM, Witteman BJ, van de Meeberg PC, Hart AR, Schaafsma G, Hooiveld G, Glei M, Lund EK, Pool-Zobel BL, Kampman E; FISHGASTRO Study Group. Increasing fish consumption does not affect genotoxicity markers in the colon in an intervention study. Carcinogenesis 2009;31(6):1087-1091. [DOI: 10.1093/carcin/bgp255]

* Pot GK, Majsak-Newman G, Geelen A, Harvey LJ, Nagengast FM, Witteman BJ, van de Meeberg PC, Timmer R, Tan A, Wahab PJ, Hart AR, Williams MP, Przybylska-Phillips K, Dainty JR, Schaafsma G, Kampman E, Lund EK; FISHGASTRO Study Group. Fish consumption and markers of colorectal cancer risk: a multicenter randomized controlled trial. Am J Clin Nutr 2009;90(2):354-361. [DOI: 10.3945/ajcn.2009.27630]

FLAX-PAD 2013

[ClinicalTrials.gov: NCT00781950]

Caligiuri SP, Aukema HM, Ravandi A, Guzman R, Dibrov E, Pierce GN. Flaxseed consumption reduces blood pressure in patients with hypertension by altering circulating oxylipins via an alpha-linolenic acid-induced inhibition of soluble epoxide hydrolase. Hypertension (Dallas, Tex. : 1979) 2014;64(1):53-9. [PubMed: 24777981]

Caligiuri SP, Rodriguez-Leyva D, Aukema HM, Ravandi A, Weighell W, Guzman R, et al. Dietary Flaxseed Reduces Central Aortic Blood Pressure Without Cardiac Involvement but Through Changes in Plasma Oxylipins. Hypertension (Dallas, Tex. : 1979) 2016;68(4):1031-8. [PubMed: 27528063]

Edel A, Rodriguez-Leyva D, Weighell W, La Vallee R, Aliani M, Guzman R, et al. Flaxseed lignan metabolites elicit antihypertensive effects in pad patients in the flax-pad trial. Annals of Nutrition and Metabolism 2013;63:1339.

Edel AL, Rodriguez-Leyva D, Maddaford TG, Caligiuri SP, Austria JA, Weighell W, et al. Dietary flaxseed independently lowers circulating cholesterol and lowers it beyond the effects of cholesterol-lowering medications alone in patients with peripheral artery disease. The Journal of nutrition 2015;145(4):749-57. [PubMed: 25694068]

Leyva DR, Zahradka P, Ramjiawan B, Guzman R, Aliani M, Pierce GN. The effect of dietary flaxseed on improving symptoms of cardiovascular disease in patients with peripheral artery disease: rationale and design of the FLAX-PAD randomized controlled trial. Contemporary clinical trials 2011;32(5):724-30. [PubMed: 21616170]

Pierce GN, Edel AL, LaVallee R, Caligiuri S, Aukema H, Ravandi A, et al. The use of dietary flaxseed to promote cardiovascular health. Acta Physiologica 2014;211:15.

Pierce GN, Rodriguez-Leyva D, Edel A, Guzman R, Aliani M. The clinical use of flaxseed as a powerful nutritional intervention to treat cardiovascular disease. Cardiology (Switzerland) 2013;126:201.

Rodriguez-Leyva D, Weighell W, Edel AL, LaVallee R, Dibrov E, Pinneker R, et al. Potent antihypertensive action of dietary flaxseed in hypertensive patients. Hypertension (Dallas, Tex. : 1979) 2013;62(6):1081-9. [PubMed: 24126178]

FORWARD 2013

Published and unpublished data [ClinicalTrials.gov: NCT00597220]

Macchia A, Grancelli H, Varini S, Nul D, Laffaye N, Mariani J, et al. Omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: results of the FORWARD (Randomized Trial to Assess Efficacy of PUFA for the Maintenance of Sinus Rhythm in Persistent Atrial Fibrillation) trial. Journal of the American College of Cardiology 2013;61(4):463-8. [PubMed: 23265344]

Macchia A, Varini S, Grancelli H, Nul D, Laffaye N, Ferrante D, et al. The rationale and design of the FORomegaARD Trial: A randomized, double-blind, placebo-controlled, independent study to test the efficacy of n-3 PUFA for the maintenance of normal sinus rhythm in patients with previous atrial fibrillation. American heart journal 2009;157(3):423-7. [PubMed: 19249410]

FOSTAR 2016

[Other: ACTRN12607000415404]

Chen JS, Hill CL, Lester S, Ruediger CD, Battersby R, Jones G, et al. Supplementation with omega-3 fish oil has no effect on bone mineral density in adults with knee osteoarthritis: a 2-year randomized controlled trial. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2016;27(5):1897-905. [PubMed: 26694596]

Hill C, Lester SE, Jones G. Response to 'Low-dose versus high-dose fish oil for pain reduction and function improvement in patients with knee osteoarthritis' by Chen et al. Annals of the rheumatic diseases 2016;75(1):e8. [PubMed: 26662278]

Hill CL, March LM, Aitken D, Lester SE, Battersby R, Hynes K, et al. Fish oil in knee osteoarthritis: a randomised clinical trial of low dose versus high dose. Annals of the rheumatic diseases 2016;75(1):23-9. [PubMed: 26353789]

Franzen 1993

Published and unpublished data [CRSSTD: 2715895]

Franzen D, Geisel J, Hopp HW, Oette K, Hilger HH. Long-term effects of low dosage fish oil on serum lipids and lipoproteins [Langzeiteffekte von niedrigdosiertem fischol auf serumlipide und lipoproteine]. Medizinische Klinik 1993;88(3):134-8. [CRSREF: 2715896]

Franzen D. Unknown. Catheterization and Cardiovascular Diagnosis 1993;28:301-10. [CRSREF: 2715897]

Gill 2012

[ClinicalTrials.gov: NCT00350194]

Edward A Gill, Michael A Chen, Pathmaja Paramsothy, Brian Fish, Daniel Isquith, Aarthi Thirumalai, Xue-Qiao Zhao.. Abstract 12697: Omega-3 Fatty Acids Effects on Carotid IMT in Metabolic Syndrome. In: Circulation. Vol. 130. 2014:A1269.

Edward A. Gill, Michael A. Chen, Arthi Thirumalai, Brian Fish, Pathmaja Paramsothy.. Omega-3 Fatty Acids Improve Dyslipidemia But Not Inflammatory Markers in Metabolic Syndrome. In: Journal of Clinical Lipidology. Vol. 6. 2012:278-9.

GISSI-HF

Unpublished data only [CRSSTD: 2715685]

Aleksova A, Masson S, Maggioni AP, Lucci D, Fabbri G, Beretta L, et al. n-3 polyunsaturated fatty acids and atrial fibrillation in patients with chronic heart failure: the GISSI-HF trial. European Journal of Heart Failure 2013;15(11):1289-95.

Canepa M, Temporelli PL, Rossi A, Gonzini L, Nicolosi GL, Staszewsky L, et al. Prevalence and prognostic impact of chronic obstructive pulmonary disease in patients with chronic heart failure. Data from the GISSI-Heart Failure trial. European Journal of Heart Failure 2016;18:442-3.

Cowie MR, Cure S, Bianic F, McGuire A, Goodall G, Tavazzi L.. Cost-effectiveness of highly purified omega-3 polyunsaturated fatty acid ethyl esters in the treatment of chronic heart failure: results of Markov modelling in a UK setting.. European Journal of Heart Failure 2011;13(6):681-9. [CRSREF: 2715686; DOI: 10.1093/eurjhf/hfr023]

Finzi A, Barlera S, Serra DM, Rossi MG, Ruggeri A, Mezzani A, et al. Antiarrhythmic effects of n-3 PUFA in patients with heart failure and an implantable cardioverter defibrillator in the GISSI-HF trial. European Heart Journal 2009;30:279.

Finzi AA, Latini R, Barlera S, Rossi MG, Ruggeri A, Mezzani A, Favero C, Franzosi MG, Serra D, Lucci D, Bianchini F, Bernasconi R, Maggioni AP, Nicolosi G, Porcu M, Tognoni G, Tavazzi L, Marchioli R.. Effects of n-3 polyunsaturated fatty acids on malignant ventricular arrhythmias in patients with chronic heart failure and implantable cardioverter-defibrillators: A substudy of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca (GISSI-HF) trial.. American Heart Journal 2011;161(2):338-43. [CRSREF: 2715687; DOI: 10.1016/j.ahj.2010.10.032]

Ghio S, Scelsi L, Latini R, Masson S, Eleuteri E, Palvarini M, Vriz O, Pasotti M, Gorini M, Marchioli R, Maggioni A, Tavazzi L; GISSI-HF investigators.. Effects of n-3 polyunsaturated fatty acids and of rosuvastatin on left ventricular function in chronic heart failure: a substudy of GISSI-HF trial.. European Journal of Heart Failure 2010;12(12):1345-53. [CRSREF: 2715688]

* Gissi-HF Investigators, Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G.. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial.. Lancet 2008;372(9645):1223-30. [CRSREF: 2715689; DOI: 10.1016/S01406736(08)61239-8]

La Rovere MT, Barlera S, Staszewsky L, Mezzani A, Midi P, Marchioli R, et al. Effect of n-3PUFA on heart rate variability. Data from the GISSI-HF holter substudy. Circulation. Conference: American Heart Association's Scientific Sessions 2011;124(21 SUPPL. 1).

La Rovere MT, Pinna GD, Maestri R, Barlera S, Bernardinangeli M, Veniani M, et al. Autonomic markers and cardiovascular and arrhythmic events in heart failure patients: still a place in prognostication? Data from the GISSI-HF trial. European Journal of Heart Failure 2012;14(12):1410-9.

La Rovere MT, Staszewsky L, Barlera S, Maestri R, Mezzani A, Midi P, et al. n-3PUFA and Holter-derived autonomic variables in patients with heart failure: data from the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca (GISSI-HF) Holter substudy. Heart Rhythm 2013;10(2):226-32.

Latini R, Masson S, Tacconi M, Bernasconi R, Dragani L, Milani V, et al. Circulating levels of n-3 polyunsaturated fatty acids in patients with chronic heart failure. Data from the GISSI-HF trial. European Heart Journal 2011;32:919.

Maggioni AP, Fabbri G, Lucci D, Marchioli R, Franzosi MG, Latini R, Nicolosi GL, Porcu M, Cosmi F, Stefanelli S, Tognoni G, Tavazzi L; GISSI-HF Investigators.. Effects of rosuvastatin on atrial fibrillation occurrence: ancillary results of the GISSI-HF trial.. Eupropean Heart Journal 2009;30(19):232736. [CRSREF: 2715690]

Marchioli R, Aldegheri MP, Borghese L, Franzosi MG, Latini R, Marfisi RM, et al. Time course analysis of the effect of n-3 PUFA on fatal and non fatal arrhythmias in heart failure: Secondary results of the GISSI-HF trial. European Heart Journal 2009;30:165.

Marchioli R, Cucchi G, Gualco A, Franzosi MG, Levantesi G, Maggioni AP, et al. Time course analysis of the effect of n-3 PUFA on fatal and non fatal heart failure: Secondary results of the GISSI-HF trial. European Heart Journal 2009;30:432.

Marchioli R, Franzosi MG, Latini R, Maggioni AP, Marfisi RM, Minneci C, et al. Prognostic ability of a Mediterranean dietary score in heart failure: Preliminary analysis of the GISSI-Heart failure Trial. European Heart Journal 2009;30:1026.

Marchioli R, Franzosi MG, Latini R, Maggioni AP, Marfisi RM, Nicolosi GL, et al. Effect of n-3 PUFA in heart failure patients with different dietary habits: Preliminary results of the GISSI-heart failure trial. European Heart Journal 2009;30:426.

Marchioli R, Franzosi MG, Levantesi G, Marfisi RM, Maggioni AP, Nicolosi GL, et al. Effect of n-3 PUFA according to fish intake: Preliminary results of GISSI-Heart Failure. European Heart Journal 2009;30:707.

Marchioli R, Levantesi G, Silletta MG, Barlera S, Bernardinangeli M, Carbonieri E, Cosmi F, Franzosi MG, Latini R, Lucci D, Maggioni AP, Moretti L, Nicolosi GL, Porcu M, Rossi MG, Tognoni G, Tavazzi L; GISSI-HF Investigators.. Effect of n-3 polyunsaturated fatty acids and rosuvastatin in patients with heart failure: results of the GISSI-HF trial.. Expert Reviews Cardiovascular Therapys 2009;7(7):735-48. [CRSREF: 2715691]

Masson S, Latini R, Milani V, Moretti L, Rossi MG, Carbonieri E, et al. Prevalence and prognostic value of elevated urinary albumin excretion in patients with chronic heart failure: data from the GISSI-Heart Failure trial. Circulation: Heart Failure 2010;3(1):65-72.

Masson S, Marchioli R, Mozaffarian D, Bernasconi R, Milani V, Dragani L, et al. Plasma n-3 polyunsaturated fatty acids in chronic heart failure in the GISSI-Heart Failure Trial: relation with fish intake, circulating biomarkers, and mortality. American Heart Journal 2013;165(2):208-15.

Røysland R, Masson S, Omland T, Milani V, Bjerre M, Flyvbjerg A, Di Tano G, Misuraca G, Maggioni AP, Tognoni G, Tavazzi L, Latini R; GISSI-HF Investigators.. Prognostic value of osteoprotegerin in chronic heart failure: The GISSI-HF trial.. American Heart Journal 2010;160(2):286-93. [CRSREF: 2715692; DOI: 10.1016/j.ahj.2010.05.015]

Tavazzi L, Tognoni G, Franzosi MG, Latini R, Maggioni AP, Marchioli R, Nicolosi GL, Porcu M; GISSI-HF Investigators.. Rationale and design of the GISSI heart failure trial: a large trial to assess the effects of n-3 polyunsaturated fatty acids and rosuvastatin in symptomatic congestive heart failure.. The European Journal of Heart Failure 2004;6(5):635-41. [CRSREF: 2715693; DOI: 10.1016/j.ejheart.2004.03.001]

GISSI-P 1999

[CRSSTD: 2715694]

Franzosi MG, Brunetti M, Marchioli R, Marfisi RM, Tognoni G, Valagussa F, GISSI-Prevenzione I. Cost-effectiveness analysis of n-3 polyunsaturated fatty acids (PUFA) after myocardial infarction: results from Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto (GISSI)-Prevenzione Trial. Pharmacoeconomics 2001;19(4):411-20. [CRSREF: 2715695]

* GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Lancet 1999;354:447-55. [CRSREF: 2715696]

Marchioli R, Barzi F, Bomba E, Chieffo C, Di Gregorio DDMR, Franzosi MG et al. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. Circulation 2002;105:1897-1903. [CRSREF: 2715697]

Marchioli R, Di Pasquale A. [The biochemical, pharmacological and epidemiological reference picture of the GISSI-Prevention. The Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico]. Giornale Italiano di Cardiologia 1993;23(9):933-64. [CRSREF: 2715698]

Marchioli R, Valagussa F. The results of the GISSI-Prevenzione trial in the general framework of secondary prevention. European Heart Journal 2000;21(12):949-52. [CRSREF: 2715699]

Marchioli R. Treatment with n-3 polyunsaturated fatty acids after myocardial infarction: results of GISSI-Prevenzione Trial. European Heart Journal Supplements 2001;3(Supplement D):D85-D97. [CRSREF: 2715700]

Greenfield 1993

Published and unpublished data [CRSSTD: 2715910]

Greenfield SM, Green AT, Teare JP, Jenkins AP, Punchard NA, Ainley CC et al. A randomized controlled study of evening primrose oil and fish oil in ulcerative colitis. Alimentary Pharmacology & Therapeutics 1993;7(2):159-66. [CRSREF: 2715911]

HARP - Sacks 1995

Published and unpublished data [CRSSTD: 2715701; Other: NCT00000461]

Pasternak RC, Brown LE, Stone PH, Silverman DI, Gibson CM, Sacks FM. Effect of combination therapy with lipid-reducing drugs in patients with coronary heart disease and "normal" cholesterol levels. A randomized, placebo-controlled trial. Harvard Atherosclerosis Reversibility Project (HARP) Study Group. Annals of internal medicine 1996;125(7):529-40. [PubMed: 8815751]

Sacks FM, Pasternak RC, Gibson CM, Rosner B, Stone PH. Effect on coronary atherosclerosis of decrease in plasma cholesterol concentrations in normocholesterolaemic patients. Harvard Atherosclerosis Reversibility Project (HARP) Group. Lancet (London, England) 1994;344(8931):1182-6. [PubMed: 7934538]

* Sacks FM, Stone PH, Gibson CM, Silverman DI, Rosner B, Pasternak RC. Controlled trial of fish oil for regression of human coronary atherosclerosis. HARP Research Group. J Am Coll Cardiol 1995;25(7):1492-1498. [CRSREF: 2715702]

Hashimoto 2012

Hashimoto M, Yamashita K, Kato S, Tamai T, Matsumoto I, Tanabe Y, et al. Beneficial effects of dietary docosahexaenoic acid intervention on cognitive function in elderly people with very mild dementia in Japan. Alzheimer's and Dementia 2011;1):S610-1.

M. Hashimoto, K. Yamashita, S. Kato, T. Tamai, Y. Tanabe, M. Mitarai, I. Matsumoto, M. Ohno.. Beneficial effects of daily dietary omega-3 polyunsaturated fatty acid supplementation on age related cognitive decline in elderly Japanese with very mild dementia: a 2-year randomized,double-blind, placebo-controlled trial. J Aging Res Clin Practice 2012;1(3):193-201.

Hashimoto 2016

Hashimoto M, Kato S, Tanabe Y, Katakura M, Mamun AA, Ohno M, et al. Beneficial effects of dietary docosahexaenoic acid intervention on cognitive function and mental health of the oldest elderly in Japanese care facilities and nursing homes. Geriatrics & gerontology international 2016. [PubMed: 26822516]

Hawthorne 1992

Published and unpublished data

Hawthorne AB, Daneshmend TK, Hawkey CJ, Belluzzi A, Everitt SJ, Holmes GKT, Malkinson C, Shaheen MZ, Willars JE. Treatment of ulcerative colitis with fish oil supplementation: a prospective 12 month randomised controlled trial. Gut 1992;33:922-928.

HERO-Tapsell 2009

Published and unpublished data [Other: ACTRN12607000600448]

Tan SY. Dietary manipulation and weight management. Doctor of Philosophy thesis, School of Health Sciences, University of Wollonong 2010.

* Tapsell LC, Batterham MJ, Teuss G, Tan SY, Dalton S, Quick CJ, et al. Long-term effects of increased dietary polyunsaturated fat from walnuts on metabolic parameters in type II diabetes. European journal of clinical nutrition 2009;63(8):1008-15. [PubMed: 19352378]

Higashihara 2010

* Higashihara, E, Itomura M, TerachiI T, Matsuda T, Kawakita M, Kameyama S, Fuse H, Chiba Y,Hamazaki T, Okegawa T, Tokunaga M, Murota T, Kawa G, Furuya Y, Akashi T, Hamazaki K and Takada H. Effects of Eicosapentaenoic Acid on Biochemical Failureafter Radical Prostatectomy for Prostate Cancer [in vivo]. 2010;24:561-566. [Other:]

Huang 1996

Published data only (unpublished sought but not used) [Other: ; Other:]

Huang YC, Jessup JM, Forse RA, Flickner S, Pleskow D, Anastopoulos HT et al. n-3 fatty acids decrease colonic epithelial cell proliferation in high-risk bowel mucosa. Lipids 1996;31:S313-S317. [CRSREF: 2715935]

IFOMS- Sirtori 1997

Published and unpublished data

Patti L, Maffettone A, Iovine C, Di Marino L, Annuzzi G, Riccardi G, Rivellese A. Long-term effects of fish oil on lipoprotein subfractions and low density lipoprotein size in non-insulin-dependent diabetic patients with hypertriglyderidemia. Atherosclerosis 1999;146:361-367.

Rivellese A, Maffettone A, Iovine C, Di Marino L, Annuzzi G, Mancini M, Riccardi G. Long-term effects of fish oil on insuin resistance and plasma lipoproteins in NIDDM patients with hypertriglyceridemia. Diabetes Care 1996;19(11):1207-2013.

Sirtori C, Crepaldi G, Manzato E, Mancini M, Rivellese A, Paoletti R, Pazzucconi F, Pamparana F, Stragliotto E. One-year treatment with ethyl esters of n-3 fatty acids in patients withhypertriglyceridemia and glucose intoleranceReduced triglyceridemia, total cholesterol and increased HDL-Cwithout glycemic alterations. Atherosclerosis 1998;137:419-427.

* Sirtori C, Paoletti R, Mancini M, Crepaldi G, Manzato E, Rivellese A, Pamparana F, Stragliotto E, on behalf of The Italian Fish Oil Multicenter Study. n-3 Fatty acids do not lead to an increased diabetic risk in patients with hyperlipidemia and abnormal glucose tolerance. American Journal of Clinical Nutrition 1997;65:1974-1881.

Jackson 2016

[Other: NCT01185379]

Jackson PA, Forster JS, Bell JG, Dick JR, Younger I, Kennedy DO. DHA Supplementation Alone or in Combination with Other Nutrients Does not Modulate Cerebral Hemodynamics or Cognitive Function in Healthy Older Adults. Nutrients 2016;8:86. [DOI: 10.3390/nu8020086; Other: NCT01185379]

JELIS 2007

Published and unpublished data [CRSSTD: 2715707; ClinicalTrials.gov: NCT00231738]

Cleland JG, Freemantle N, Coletta AP, Clark AL. Clinical trials update from the American Heart Association: REPAIR-AMI, ASTAMI, JELIS, MEGA, REVIVE-II, SURVIVE, and PROACTIVE. The European Journal of Heart Failure 2006;8(1):105-10. [CRSREF: 2715708; DOI: 10.1016/j.ejheart.2005.12.003]

Ishikawa Y, Yokoyama M, Saito Y, Matsuzaki M, Origasa H, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K, Matsuzawa Y; JELIS Investigators. Preventive effects of eicosapentaenoic acid on coronary artery disease in patients with peripheral artery disease. Circulation Journal 2010;74(7):1451-7. [CRSREF: 2715709; DOI: 10.1253/circj.CJ-09-0520]

Matsuzaki M, Yokoyama M, Saito Y, Origasa H, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K, Matsuzawa Y; JELIS Investigators. Incremental effects of eicosapentaenoic acid on cardiovascular events in statin-treated patients with coronary artery disease. Secondary prevention analysis from JELIS. Circulation Journal 2009;73(7):1283-90. [CRSREF: 2715710]

Oikawa S, Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K; JELIS Investigators. Suppressive effect of EPA on the incidence of coronary events in hypercholesterolemia with impaired glucose metabolism: Sub-analysis of the Japan EPA Lipid Intervention Study (JELIS). Atherosclerosis 2009;206(2):535-9. [CRSREF: 2715711; DOI: 10.1016/j.atherosclerosis.2009.03.029]

Origasa H, Yokoyama M, Matsuzaki M, Saito Y, Matsuzawa Y; JELIS Investigators. Clinical importance of adherence to treatment with eicosapentaenoic acid by patients with hypercholesterolemia. Circulation Journal 2010;74(3):510-7. [CRSREF: 2715712; DOI: 10.1253/circj.CJ-09-0746]

Saito Y, Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K; JELIS Investigators. Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS). Atherosclerosis 2008;200(1):135-40. [CRSREF: 2715713; DOI: 10.1016/j.atherosclerosis.2008.06.003]

Tanaka K, Ishikawa Y, Yokoyama M, Origasa H, Matsuzaki M, Saito Y, Matsuzawa Y, Sasaki J, Oikawa S, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K; JELIS Investigators. Reduction in the recurrence of stroke by eicosapentaenoic acid for hypercholesterolemic patients: subanalysis of the JELIS trial. Stroke 2008;39(8):2052-8. [CRSREF: 2715714; DOI: 10.1161/STROKEAHA.107.509455]

Yamanouchi D, Komori K. Eicosapentaenoic acid as the gold standard for patients with peripheral artery disease? - subanalysis of the JELIS trial -.. Circulation Journal 2010;74(7):1298-9. [CRSREF: 2715715; DOI: 10.1253/circj.CJ-10-0449]

* Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K; Japan EPA lipid intervention study (JELIS) Investigators. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet 2007;369(9567):1090-8. [CRSREF: 2715716]

Yokoyama M, Origasa H, for the JELIS Investigators. Effects of eicosapentaenoic acid on cardiovascular events in Japanese patients with hypercholesterolaemia: Rationale, design, and baseline characteristics of the Japan EPA Lipid Intervention Study (JELIS). American Heart Journal 2003;146:613-20. [CRSREF: 2715717]

Kremer 1995

* Kremer JM, Lawrence DA, Petrillo GF, Litts LL, Mullaly PM, Rynes RI, Stocker RP, Parhami N, Greenstein NS, Fuchs BR, Mathur A, Robinson DR, Sperling RI, Bigaouette J. Effects of high-dose fish oil on rheumatoid arthritis after stopping nonsteroidal antiinflammatory drugs: clinical and immune correlates. Arthritis & Rheumatism 1995;38(8):1107-1114.

Kumar 2012

[ClinicalTrials.gov: NCT00232219]

Kumar Saurabh, Sutherland Fiona, Morton Joseph B, Lee Geoffrey, Morgan John, Wong James, et al. Long-term omega-3 polyunsaturated fatty acid supplementation reduces the recurrence of persistent atrial fibrillation after electrical cardioversion. 2012;9(4):483-91.

Kumar 2013

[ClinicalTrials.gov: NCT00232245]

Kumar S, Sutherland F, Stevenson I, Lee JM, Garg ML, Sparks PB. Effects of long-term omega-3 polyunsaturated fatty acid supplementation on paroxysmal atrial tachyarrhythmia burden in patients with implanted pacemakers: results from a prospective randomised study. International journal of cardiology 2013;168(4):3812-7. [PubMed: 23890856]

Lalia 2015

[ClinicalTrials.gov: NCT01686568]

Lalia AZ, Johnson ML, Jensen MD, Hames KC, Port JD, Lanza IR. Effects of dietary n-3 fatty acids on hepatic and peripheral insulin sensitivity in insulin-resistant humans. Diabetes Care 2015;38:1228-37. [DOI: 10.2337/dc14-3101/-/DC1]

Lau 1993

Published and unpublished data

Lau CS, Morley KD, Belch JJF. Effects of fish oil supplementation on non-steroidal anti-inflammatory drug requirement in patients with mild rheumatoid arthritis: a double-blind placebo controlled study. British Journal of Rheumatology 1993;32:982-989.

Lee 2012

Lee KL, Shahar S, Chin A, Yusoff NAM. Docosahexaenoic acid-concentrated fish oil supplementation in subjects with mild cognitive impairment (MCI): a 12-month randomised, double-blind, placebo-controlled trial. Psychopharmacology 2013;225:605-12. [DOI: 10.1007/s00213-012-2848-0]

Lee LK, Shahar S, Chin A, Yusoff NAM, Rajab N, Aziz SA. Prevalence of gender disparities and predictors affecting the occurrence of mild cognitive impairment (MCI). Archives of Gerontology and Geriatrics 2012;54:185-191. [DOI: 10.1016/j.archger.2011.03.015]

Li 2015

Li Y-H, Yang L-H, Sha K-H, Liu T-G, Zhang L-G, Liu X-X. Efficacy of polyunsaturated fatty acid therapy on patients with nonalcoholic steatohepatitis. World Journal of Gastroenterology 2015;21(22):7008-7013. [DOI: 10.3748/wjg.v21.i22.7008]

Loeschke 1996

Published and unpublished data [CRSSTD: 2715720]

* Loeschke K, Ueberschaer B, Pietsch A, Gruber E, Ewe K, Wiebecke B et al. n-3 fatty acids only delay early relapse of ulcerative colitis in remission. Digestive diseases and sciences 1996;41(10):2087-94. [CRSREF: 2715721]

Lorenz-Meyer 1996

Published and unpublished data [CRSSTD: 2716000]

Lorenz-Meyer H, Bauer P, Nicolay C, Schulz B, Purrmann J, Fleig WE et al. Omega-3 fatty acids and low carbohydrate diet for maintenance of remission in Crohn's disease. A randomized controlled multicenter trial. Study Group Members (German Crohn's Disease Study Group). Scandinavian Journal of Gastroenterology 1996;31(8):778-85. [CRSREF: 2716001]

Mantzaris 1996

[CRSSTD: 2716218]

Mantzaris GJ, Archavlis E, Zografos C, Petraki K, Spiliades C, Triantafyllou G. A prospective, randomized, placebo-controlled study of fish oil in ulcerative colitis. Hellenic Journal of Gastroenterology 1996;9(2):138-41. [CRSREF: 2716219]

MAPT 2017

[ClinicalTrials.gov: NCT00672685]

Andrieu S, Guyonnet S, Coley N, Cantet C, Bonnefoy M, Bordes S et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. Lancet Neurology 2017;16:377-89. [DOI: 10.1016/S1474-4422(17)30040-6]

Carrie I, van Kan GA, Gillette-Guyonnet S, Andrieu S, Dartigues JF, Touchon J, et al. Recruitment strategies for preventive trials. The MAPT study (MultiDomain Alzheimer Preventive Trial). Journal of Nutrition, Health & Aging 2012;16(4):355-9.

Delrieu J, Andrieu S, Pahor M, Cantet C, Cesari M, Ousset PJ, Voisin T, Fougère B, Gillette S, Carrie I, Vellas B. Neuropsychological Profile of “Cognitive Frailty” Subjects in MAPT Study. J Prev Alzheimers Dis 2016;3(3):151-9. [DOI: 10.14283/jpad.2016.94]

Delrieu J, Payoux P, Hitzel A, Peiffer S, Abellan Van Kan G, Gillette S, et al. Multidomain alzheimer's disease preventive trial: Florbetapir ancillary study. Alzheimer's and Dementia 2011;1):S419.

Fougere B, Barreto PD, Goisser S, Soriano G, Guyonnet S, Andrieu S, Vellas B, MAPT Study Group. Red blood cell membrane omega-3 fatty acid levels and physical performance: Cross-sectional data from the MAPT study. Clinical Nutrition 2017;1-4. [DOI: 10.1016/j.clnu.2017.04.005]

Gillette S. The multidomain Alzheimer preventive trial (MAPT): A new approach for the prevention of Alzheimer's disease. Alzheimer's and Dementia 2009;(S4-02-05):145.

Gillette-Guyonnet S, Andrieu S, Dantoine T, Dartigues JF, Touchon J, Vellas B, et al. Commentary on "A roadmap for the prevention of dementia II. Leon Thal Symposium 2008." The Multidomain Alzheimer Preventive Trial (MAPT): a new approach to the prevention of Alzheimer's disease. Alzheimer's & Dementia 2009;5(2):114-21.

Gillette-Guyonnet S, Vellas B, Sandrine A, Charlotte D, Isabelle C. MAPT study: A 3-year randomized trial of omega 3 and/or multidomain intervention for the prevention of cognitive decline in frail elderly subjects-rationale, design and baseline data. Alzheimer's and Dementia 2011;1):S97-8.

Vellas B, Carrie I, Gillette-Guyonnet S, Touchon J, Dantoine T, Dartigues JF et al. MAPT Study: A multidomain approach for preventing ALzheimer's disease: Design and baseline data. Journal of Prevention of Alzheimers Disease 2014;1(1):13-22.

Vellas B, Carrie I, Guyonnet S, Touchon J, Dantoine T, Dartigues JF, et al. MAPT (multi-domain Alzheimer's prevention trial): Results at 36 months. Alzheimer's and Dementia 2015;1):331.

Vellas B, Touchon J, Weiner M. MAPT (multidomain Alzheimer preventive trial) imaging (MRI, FDG-PET, amyloid-PET) data. Journal of Nutrition, Health and Aging 2012;16 (9):812-5.

MARGARIN - Bemelmans 2002

Published data only (unpublished sought but not used) [CRSSTD: 2715722]

* Bemelmans WJ, Broer J, Feskens EJ, Smit AJ, Muskiet AJ, Lefrandt JD et al. Effect of an increased intake of alpha-linolenic acid and group nutritional education on cardiovascular risk factors: the Mediterranean alpha-linolenic enriched Groningen dietary intervention (MARGARIN) study. American Journal of Clinical Nutrition 2002;75:221-7. [CRSREF: 2715723]

Bemelmans WJ, Broer J, de Vries JH, Hulshof KF, May JF, Meyboom-De Jong B. Impact of Mediterranean diet education versus posted leaflet on dietary habits and serum cholesterol in a high risk population for cardiovascular disease. Public Health Nutrition 2000;3(3):273-83. [CRSREF: 2715724]

Bemelmans WJ, Lefrandt JD, Feskens EJ, Broer J, Tervaert JW, May JF, et al. Change in saturated fat intake is associated with progression of carotid and femoral intima-media thickness, and with levels of soluble intercellular adhesion molecule-1. Atherosclerosis 2002;163(1):113-20.

Bemelmans WJ, Lefrandt JD, Feskens EJ, van Haelst PL, Broer J, Meyboom-de Jong B, et al. Increased alpha-linolenic acid intake lowers C-reactive protein, but has no effect on markers of atherosclerosis. European Journal of Clinical Nutrition 2004;58(7):1083-9.

Bemelmans WJ, Muskiet FA, Feskens EJ, de Vries JH, Broer J, May JF, et al. Associations of alpha-linolenic acid and linoleic acid with risk factors for coronary heart disease. European Journal of Clinical Nutrition 2000;54(12):865-71.

Siero FW, Broer J, Bemelmans WJ, Meyboom-de Jong BM. Impact of group nutrition education and surplus value of Prochaska based stage-matched information on health-related cognitions and on Mediterranean nutrition behaviour. Health Education Research 2000;15(5):635-647.

MARINA - Sanders 2011

Published and unpublished data [CRSSTD: 2715725; ISRCTN: ISRCTN66664610]

Al-Hilal M, Alsaleh A, Maniou Z, Lewis FJ, Hall WL, Sanders TA, et al. Genetic variation at the FADS1-FADS2 gene locus influences delta-5 desaturase activity and LC-PUFA proportions after fish oil supplement. Journal of lipid research 2013;54(2):542-51. [PubMed: 23160180]

AlSaleh A, Maniou Z, Lewis FJ, Hall WL, Sanders TA, O'Dell SD. Interaction between a CSK gene variant and fish oil intake influences blood pressure in healthy adults. The Journal of nutrition 2014;144(3):267-72. [PubMed: 24401815]

Alsaleh A, Crepostnaia D, Maniou Z, Lewis FJ, Hall WL, Sanders TA, et al. Adiponectin gene variant interacts with fish oil supplementation to influence serum adiponectin in older individuals. The Journal of nutrition 2013;143(7):1021-7. [PubMed: 23658423]

Ana Margarida Pinto, A M, Hall WL, Sanders TAB. Effect of low doses of long chain n-3 PUFA intake on daytime heart rate variability: Results from the MARINA study. European Journal of Preventive Cardiology 2015;1):S146.

Hall WL, Hay G, Maniou Z, Seed PT, Chowienczyk PJ, Sanders TA. Effect of low doses of long chain n-3 polyunsaturated fatty acids on sleep-time heart rate variability: a randomized, controlled trial. International Journal of Cardiology 2013;168:4439-42.

Marina Study Team: Sanders TAB, Chowienczyk PJ, Hall W, Lewis F, Seed P, Maniou Z, Jiang B, Donald A, Connell K, McNeill K, Gray R, Sherwood R, O'Sullivan L. The influences of increasing intakes of EPA and DHA on vascular function and risk factors for cardiovascular disease. Food Standards Agency Project N02041. Final Report 2011.

Proudman S, Spargo L, Hall C, McWilliams L, Lee A, Maureen R, et al. Fish oil in rheumatoid arthritis: A randomised, double blind trial comparing high dose with low dose. Internal Medicine Journal 2012;42:2-3.

Sanders TA, Hall WL, Maniou Z, Lewis F, Seed PT, Chowienczyk PJ. Effect of low doses of long-chain n-3 PUFAs on endothelial function and arterial stiffness: a randomized controlled trial. The American journal of clinical nutrition 2011;94(4):973-80. [PubMed: 21865334]

Martinez 2014

Martinez GL, Koury JC, Martins MA, Nogueira F, Fischer RG, Gustafsson A, Figueredo CMS. Serum level changes of long chain-polyunsaturated fatty acids in patients undergoing periodontal therapy combined with one year of omega-3 supplementation: a pilot randomized clinical trial. J Periodontal Implant Sci 2014;44(4):169-77. [DOI: 10.5051/jpis.2014.44.4.169]

Mate 1991

Published and unpublished data

Mate J, Castanos R, Garcia-Samaniego J, Pajares JM. Does dietary fish oil maintain the remission of Crohn's Disease (CD): a study case control. Gastroenterology 1991;100(5, part 2):A228.

MEMO - Van de Rest 2008

[CRSSTD: 2715727]

Bouwens M, van de Rest O, Dellschaft N, Bromhaar MG, de Groot LC, Geleijnse JM, Müller M, Afman LA. Fish-oil supplementation induces antiinflammatory gene expression profiles in human blood mononuclear cells. Am J Clin Nutr 2009;90(2):415-24. [DOI: 10.3945/ajcn.2009.27680]

Van De Rest O, Geleijnse JM, Kok FJ, van Staveren WA, Dullemeijer C, Olderikkert MG, et al. Effect of fish oil on cognitive performance in older subjects: a randomized, controlled trial. Neurology 2008;71(6):430-8.

Van De Rest O, Geleijnse JM, Kok FJ, van Staveren WA, Hoefnagels WH, Beekman AT, et al. Effect of fish-oil supplementation on mental well-being in older subjects: a randomized, double-blind, placebo-controlled trial. American Journal of Clinical Nutrition 2008;88(3):706-13.

Van De Rest O, Geleijnse JM, Kok FJ, van Staveren WA, Olderikkert MG, Beekman AT, et al. Effect of fish oil supplementation on quality of life in a general population of older Dutch subjects: a randomized, double-blind, placebo-controlled trial. Journal of the American Geriatrics Society 2009;57(8):1481-6.

MENU - Rock 2016

[ClinicalTrials.gov: NCT01424007]

Le T, Flatt SW, Natarajan L, Pakiz B, Quintana EL, Heath DD, Rana BK, Rock CL. Effects of Diet Composition and Insulin Resistance Status on Plasma Lipid Levels in a Weight Loss Intervention in Women. J Am Heart Assoc 2016;5(1):e002771. [DOI: 10.1161/JAHA.115.002771]

* Rock CL, Flatt SW, Pakiz B, Quintana EL, Heath DD, Rana BK, Natarajan L. Effects of diet composition on weight loss, metabolic factors and biomarkers in a 1-year weight loss intervention in obese women examined by baseline insulin resistance status. Metabolism 2016;65(11):1605-13. [DOI: 10.1016/j.metabol.2016.07.008]

MIDAS 2010

[Other: NCT0027813]

Yurko-Mauro K, McCarthy D, Bailey-Hall E, Nelson EB, Blackwell A, MIDAS Investigators. Results of the MIDAS Trial: Effects of Docosahexaenoic acid on physiologica and safety parameters in age-related cognitive decline. 2009;P84.

Yurko-Mauro K, McCarthy D, Romb D, Nelson EB, Ryan AS, Blackwell A, Salem N, Stedman M; on behalf of the MIDAS Investigators. Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline. Alzheimer's & Dementia 2010;6:456-64. [Other: NCT0027813]

Mita 2007

[CRSSTD: 2715732]

Mita T, Watada H, Ogihara T, Nomiyama T, Ogawa O, Kinoshita J, Shimizu T, Hirose T, Tanaka Y, Kawamori R. Eicosapentaenoic acid reduces the progression of carotid intima-media thickness in patients with type 2 diabetes. Atherosclerosis 2007;191(1):162-7.

NAT2 2013

[ISRCTN: ISRCTN98246501]

Merle BM, Benlian P, Puche N, Bassols A, Delcourt C, Souied EH. Circulating omega-3 Fatty acids and neovascular age-related macular degeneration. Investigative ophthalmology & visual science 2014;55(3):2010-9. [PubMed: 24557349]

Merle BM, Richard F, Benlian P, Puche N, Delcourt C, Souied EH. CFH Y402H and ARMS2 A69S Polymorphisms and Oral Supplementation with Docosahexaenoic Acid in Neovascular Age-Related Macular Degeneration Patients: The NAT2 Study. PloS one 2015;10(7):e0130816. [PubMed: 26132079]

Querques G, Merle BM, Pumariega NM, Benlian P, Delcourt C, Zourdani A, et al. Dynamic Drusen Remodelling in Participants of the Nutritional AMD Treatment-2 (NAT-2) Randomized Trial. PloS one 2016;11(2):e0149219. [PubMed: 26901353]

Souied EH, Delcourt C, Querques G, Bassols A, Merle B, Zourdani A, et al. Oral docosahexaenoic acid in the prevention of exudative age-related macular degeneration: the Nutritional AMD Treatment 2 study. Ophthalmology 2013;120(8):1619-31. [PubMed: 23395546]

NEURAPRO 2017

[Other: ACTRN12608000475347]

Markulev C, McGorry PD, Nelson B, Yuen HP, Schaefer M, Yung AR. NEURAPRO-E study protocol: a multicentre randomized controlled trial of omega-3 fatty acids and cognitive-behavioural case management for patients at ultra high risk of schizophrenia and other psychotic disorders. Early Intervention in Psychiatry 2015;1-11. [DOI: 10.1111/eip.12260]

McGorry P, et al.. The neurapro-E study: A multicenter RCT of omega-3 fatty acids and cognitive-behavioural case management for patients at ultra high risk of schizophrenia and other psychotic disorders. Schizophrenia Bulletin 2015;41:S322-S323.

McGorry PD, Nelson B, Markulev C, Yuen HP, Schäfer MR, Mossaheb N, et al. Effect of ω-3 Polyunsaturated Fatty Acids in Young Peopleat Ultrahigh Risk for Psychotic DisordersThe NEURAPRO Randomized Clinical Trial. JAMA Psychiatry 2017;74(1):19-27. [DOI: 10.1001/jamapsychiatry.2016.2902]

Nigam 2014

Nigam P, Bhatt S, Misra A, Chadha DS, Vaidya M, Dasgupta J, Pasha QMA. Effect of 6-month intervention with cooking oils containing a high concentration of monounsaturated fatty acids (olive and canola oils) compared with control oil in male Asian Indians with nonalcoholic fatty liver disease. Diabetes Technology & Therapeutics 2014;16(4):255-60. [DOI: 10.1089/dia.2013.0178]

Niki 2016

* Niki T, Wakatsuki T, Yamaguchi K, Taketani Y, Oeduka H, Kusunose K, Ise T, Iwase T, Yamada H, Soeki T, Sata M. Effects of the Addition of Eicosapentaenoic Acid to Strong Statin Therapy on Inflammatory Cytokines and Coronary Plaque Components Assessed by Integrated Backscatter Intravascular Ultrasound. Circulation Journal 2016;80(2):450-60. [DOI: 10.1253/circj.CJ-15-0813]

Nishio 2014

Nishio R, Shinke T, Otake H, Nakagawa M, Nagoshi R, Inoue T, Kozuki A, Hariki H, Osue T, Taniguchi Y, Iwasaki M, Hiranuma N, Konishi A, Kinutani H, Shite J, Hirata K. Stabilizing effect of combined eicosapentaenoic acid and statin therapy on coronary think-cap fibroatheroma. Atherosclerosis 2014;234:114-9. [DOI: 10.1016/j.atherosclerosis.2014.02.025]

Nodari 2009

[CRSSTD: 2715736]

Nodari S, Metra M, Milesi G, Manerba A, Cesana BM, Gheorghiade M, et al. The role of n-3 PUFAs in preventing the arrhythmic risk in patients with idiopathic dilated cardiomyopathy. Cardiovascular Drugs & Therapy 2009;23(1):5-15.

Nodari 2011 AF

[ClinicalTrials.gov: NCT01198275]

Nodari S, Triggiani M, Campia U, Manerba A, Milesi G, Cesana BM, et al. n-3 polyunsaturated fatty acids in the prevention of atrial fibrillation recurrences after electrical cardioversion: a prospective, randomized study. Circulation 2011;124(10):1100-6. [PubMed: 21844082]

Nodari 2011 HF

Published and unpublished data [CRSSTD: 2715738; ClinicalTrials.gov: NCT01223703]

Nodari S, Triggiani M, Berlinghieri N, Milesi G, Foresti A, Gheorghiade M, et al. Effects of n-3 polyunsaturated fatty acids on left ventricular function and functional capacity in heart failure patients. European Heart Journal 2010;31:850.

* Nodari S, Triggiani M, Campia U, Manerba A, Milesi G, Cesana BM, et al. Effects of n-3 polyunsaturated fatty acids on left ventricular function and functional capacity in patients with dilated cardiomyopathy. Journal of the American College of Cardiology 2011;57(7):870-9.

Nodari S, Triggiani M, Campia U, Zhao L, Manerba A, Milesi G, et al. Plasma levels of n-3 polyunsaturated fatty acids and risk of hospitalization in patients with non-ischemic cardiomyopathy. Circulation. Conference: American Heart Association 2012;126(21 SUPPL. 1).

Nodari S. PUFAs and left ventricular function in heart failure (CS-PUFA-02) [study results]. ClinicalTrials.gov 2011.

Nogueira 2016

[ClinicalTrials.gov: NCT01992809]

Nogueira M, Alves V, Stefano J, Rodrigues L, Carrilho F, Waitzberg D, Oliveira C. Effects of omega-3 polyunsaturated fatty acids(PUFA) from fish and flaxseed oils on nonalcoholic steatohepatitis (NASH). Journal of Hepatology 2013;58:S409-S566.

Nogueira M, Oliveira C, Alves V, Stefano J, Rodrigues L, Torrinhas R, Cogliati B, Barbeiro H, Carrilho F, Waitzberg D. Omega-3 polyunsaturated fatty acids in treating non-alcoholic steatohepatitis: A randomized, double-blind, placebo-controlled trial. Clinical Nutrition 2016;35:578-586.

Nomura 2009

* Nomura S, Inami N, Shouzu A, Omoto S, Kimura Y, Takahashi N, Tanaka A, Urase F, Maeda Y, Ohtani H, Iwasaka T. The effects of pitavastatin, eicosapentanoic acid and combined therapy on platelet-derived microparticles and adiponectin in hyperlipidemic, diabetic patients. Platelets 2009;20(1):16-22.

Norouzi 2014

[ClinicalTrials.gov: NCT01311375]

Norouzi Javidan A, Sabour H, Latifi S, Abrishamkar M, Soltani Z, Shidfar F, et al. Does consumption of polyunsaturated fatty acids influence on neurorehabilitation in traumatic spinal cord-injured individuals? A double-blinded clinical trial. Spinal cord 2014;52(5):378-82. [PubMed: 24637568]

Sabour H, Norouzi Javidan A, Latifi S, Shidfar F, Heshmat R, Emami Razavi SH, et al. Omega-3 fatty acids' effect on leptin and adiponectin concentrations in patients with spinal cord injury: A double-blinded randomized clinical trial. The journal of spinal cord medicine 2015;38(5):599-606. [PubMed: 25096818]

Norwegian - Natvig 1968

[CRSSTD: 2715740]

* Natvig H, Borchgrevink CF, Dedichen J, Owren PA, Schiotz EH, Westlund K. A controlled trial of the effect of linolenic acid on incidence of coronary heart disease. The Norwegian vegetable oil experiment of 1965-66. Scandinavian Journal of Clinical & Laboratory Investigation - Supplement 1968;105:1-20. [CRSREF: 2715741]

Natvig H. [The effect of unsaturated fatty acids on the incidence of coronary infarction, etc]. Tidsskrift for Den Norske Laegeforening 1967;87(11):1033-41.

Nutristroke 2009

[CRSSTD: 2715742]

Garbagnati F, Cairella G, De Martino A, Multari M, Scognamiglio U, Venturiero V, Paolucci S. Is antioxidant and n-3 supplementation able to improve functional status in post-stroke patients? Results from the Nutristroke Trial. Cerebrovasc Dis 2009;27(4):375-83. [DOI: 10.1159/000207441]

Nye 1990

Ilsey CDJ, Nye ER, Sutherland W, Ram J, Ablett MB. Randomised placebo controlled trial of MAXEPA and aspirin/persantin after successful coronary angioplasty [abstract]. Australian & New Zealand Journal of Medicine 1987;17:559.

* Nye ER, Ablett MB, Robertson MC, Ilsley CD, Sutherland WH. Effect of eicosapentaenoic acid on restenosis rate, clinical course and blood lipids in patients after percutaneous transluminal coronary angioplasty. Australian and New Zealand Journal of Medicine 1990;20(4):549-52.

OFAMI - Nilsen 2001

Published and unpublished data [CRSSTD: 2715734; ClinicalTrials.gov: NCT01422317]

Aarsetoy H, Brugger-Andersen T, Hetland O, Grundt H, Nilsen DW. Long term influence of regular intake of high dose n-3 fatty acids on CD40-ligand, pregnancy-associated plasma protein A and matrix metalloproteinase-9 following acute myocardial infarction. Thrombosis & Haemostasis 2006;95(2):329-36.

Grundt H, Hetland O, Nilsen DW. Changes in tissue factor and activated factor XII following an acute myocardial infarction were uninfluenced by high doses of n-3 polyunsaturated fatty acids. Thrombosis & Haemostasis 2003;89(4):752-9.

Grundt H, Nilsen DW, Hetland O, Mansoor MA. Clinical outcome and atherothrombogenic risk profile after prolonged wash-out following long-term treatment with high doses of n-3 PUFAs in patients with an acute myocardial infarction. Clinical Nutrition 2004;23(4):491-500.

Grundt H, Nilsen DW, Mansoor MA, Hetland O, Nordoy A. Reduction in homocysteine by n-3 polyunsaturated fatty acids after 1 year in a randomised double-blind study following an acute myocardial infarction: no effect on endothelial adhesion properties. Pathophysiology of Haemostasis & Thrombosis 2003;33(2):88-95.

Grundt H, Nilsen DW, Mansoor MA, Nordoy A. Increased lipid peroxidation during long-term intervention with high doses of n-3 fatty acids (PUFAs) following an acute myocardial infarction. European Journal of Clinical Nutrition 2003;57(6):793-800.

Naesgaard PA, Grundt H, Brede C, Nilsen DW. The effect on vitamin D levels of long-term high-dose treatment with a concentrated omega-3 compound (omacor/lovaza) in patients hospitalized with a myocardial infarction. Circulation. Conference: American Heart Association's 2014;130(no pagination).

* Nilsen DW, Albrektsen G, Landmark K, Moen S, Aarsland T, Woie L. Effects of a high-dose concentrate of n-3 fatty acids or corn oil introduced early after an acute myocardial infarction on serum triacylglycerol and HDL cholesterol. American Journal of Clinical Nutrition 2001;74(1):50-6. [CRSREF: 2715735]

Poenitz V, Grundt H, Bottazzi B, Cuccovillo I, Mantovani A, Nilsen DW. Pentraxin 3 is uninfluenced by high doses of concentrated omega-3 fatty acids administered for 12 months following an acute myocardial infarction. Circulation. Conference: American Heart Association 2012;126(21 SUPPL. 1).

OFAMS 2012

[ClinicalTrials.gov: NCT00360906]

Torkildsen O, Wergeland S, Bakke S, Beiske AG, Bjerve KS, Hovdal H, et al. omega-3 fatty acid treatment in multiple sclerosis (OFAMS Study): a randomized, double-blind, placebo-controlled trial. Archives of neurology 2012;69(8):1044-51. [PubMed: 22507886]

OFFER 2015

[Other: NCT02210962]

Pawełczyk T, Grancow M, Kotlicka-Antczak M, Trafalska E, Gębski P, Szemraj J, Żurner N, Pawełczyk A. Omega-3 fatty acids in first-episode schizophrenia - a randomized controlledstudy of efficacy and relapse prevention (OFFER): rationale, design, and methods. BMC Psychiatry 2015;15:97. [DOI: 10.1186/s12888-015-0473-2]

Pawełczyk T, Grancow-Grabka M, Kotlicka-Antczak M, Trafalska E, Pawełczyk A. A randomized controlled study of the efficacy of six-month supplementation with concentrated fish oil rich in omega-3 polyunsaturated fatty acids in first episode schizophrenia. Journal of Psychiatric Research 2016;73(34):e44. [DOI: 10.1016/j.jpsychires.2015.11.013]

OmegAD 2008

Eriksdotter M, Vedin I, Falahati F, Freund-Levi Y, Hjorth E, Gerd Faxen-Irving G,Lars-Olof Wahlund LO, Marianne Schultzberg M, Hans Basun H, Tommy Cederholm T, Palmblad J. Plasma fatty acid profiles in relation to cognition and gender in Alzheimer patients during oral omega-3 fatty acid supplementation. The OmegAD study. Journal of Alzhiemer's Disease 2015;48(3):805-12.

Faxén Irving G, Freund-Levi Y, Eriksdotter-Jönhagen M, Basun H, Brismar K, Hjorth E, Palmblad J, Vessby B, Vedin I, Wahlund L, Cederholm T. N-3 fatty acid supplementation effects on weight and appetite in patients with Alzheimer's disease: The OmegAD Study. Journal of the American Geriatric Society 2009;57:11-17.

Faxén Irving G, Freund-Levi Y, Eriksdotter-Jönhagen M, Basun H, Hjorth E, Palmblad J, Vedin I, Cederholm T, Lars-Olof Wahlund. Effects on transthyretin in plasma and cerebrospinal fluid by DHA-rich n-3 fatty acid supplementation in patients with Alzheimer's Disease: The OmegAD study. Journal of Alzheimer's DIsease 2013;36:1-6.

Fjellström C, Starkenberg Å, Wesslén A, Tysén Bäckström A-C, Faxén Irving G and the OmegAD Study group. To be a good food provider: An exploratory study among spouses of persons with Alzheimers disease. American Journal of Alzheimer's Diseases and Other Dementias 2010;25:521-6.

Freund Levi Y, Eriksdotter-Jönhagen M, Cederholm T, Basun H, Faxén Irving G, Garlind A, VedinI, Vessby B, Wahlund LO, Palmblad J. Omega-3 fatty acid treatment of 174 patients with mild to moderate Alzheimer's disease (OmegAD): a randomized double-blind trial. Archives of Neurology 2006;63:1402-8.

Freund Levi Y, Vedin I, Cederholm, T, Basun H, Faxén Irving G, Eriksdotter M, Hjorth E, Schultzberg M, Vessby B, Wahlund L, Salem, Jr. N, Palmblad J. Transfer of n-3 fatty acids over the blood-brain barrier after dietary supplementation with a DHA rich n-3 fatty acid oil to Alzheimer disease patients. The OmegAD study. Journal of Internal Medicine 2014;275:428-36.

Freund-Levi Y, Basun H, Cederholm T, Faxén-Irving G, Garlind A, Grut M, Vedin I, Palmblad J, Wahlund LO, Eriksdotter-Jönhagen M.. Omega-3 supplementation in mild to moderate Alzheimer's disease: effects on neuropsychiatric symptoms. International Journal of Geriatric Psychiatry 2008;23:161-9.

Freund-Levi Y, Hjorth E, Lindberg C, Cederholm T, Faxen-Irving G, Vedin I, Palmblad J, Wahlund L-O, Schultzberg M, Basun H, Eriksdotter Jönhagen M. Effects of Omega-3 fatty acid on inflammatory markers

in CSF and plasma in Alzheimer's disease. The OmegAD study. Dementia and Geriatric Cognitive Disorders 2009;27:481-90.

Freund-Levi Y, Vedin I, Hjorth E, Basun H, Faxén Irving G, Schultzberg M, Eriksdotter M, Palmblad J, Vessby B, Wahlund LO, Cederholm T, Basu. Effects of supplementation with omega-3 fatty acids on oxidative stress and inflammation in patients with Alzheimer's disease: The OmegAD Study. Journal of ALzheimer's Disease 2014;42:823-31.

Hjorth E, Zhu M, Cortés Toro V, Vedin I, Palmblad J, Cederholm T, Freund-Levi Y, Faxen-Irving G, Wahlund L-O, Basun H, Eriksdotter M, Schultzberg M. Omega-3 fatty acids enhance phagocytosis of Alzheimer-related Ab42 by human microglia and decrease inflammatory markers. Journal of Alzheimer's Disease 2013;35:697-713.

Vedin I, Cederholm T, Freund Levi Y, Basun H, Garlind A, Faxen Irving G, Eriksdotter Jonhagen M, Vessby B, Wahlund L, Palmblad J. Effects of DHA rich n-3 fatty acid supplementation on cytokine release from blood mononuclear leukocytes. The OmegAD Study. American Journal of Clinical Nutrition 2008;87:1616-22.

Vedin I, Cederholm T, Freund-Levi Y, Basun H, Garlind A, Faxén Irving G, Eriksdotter-Jönhagen M, Wahlund L, Dahlman I, Palmblad J. Effects of DHA- rich n-3 fatty acid supplementation on gene expression changes in blood mononuclear leukocytes: the OmegAD study. PLOS One 2012;7:e35425.

Vedin T, Cederholm T, Freund-Levi Y, Basun H, Hjorth E, Faxén Irving G, Eriksdotter Jönhagen M, Schultzberg M, Wahlund L, Palmblad J. Reduced prostaglandin F2a release from blood mononuclear leukocytes after oral supplementation of n3 fatty acids: the OmegAD study. Journal of Lipid Research 2010;51:1179-85.

Wang X, Hjorth E, Vedin I, Eriksdotter M, Freund-Levi Y, Wahlund LO, Cederholm T, Palmblad J, Schultzberg M. Effects of n-3 FA supplementation on the release of pro-resolving lipid mediators by blood mononuclear cells: the OmegAD study. Journal of Lipid Research 2015;56(3):674-8.

OMEGA-Remodel 2016

[ISRCTN: NCT00729430]

Heydari B, Abdullah S, Pottala JV, Shah R, Abbasi S, Mandry D, Francis SA, Lumish H, Ghoshhajra BB, Hoffmann U, Appelbaum E, Feng JH, Blankstein R, Steigner M, McConnell JP, Harris W, Antman EM, Jerosch-Herold M, Kwong RK. Effect of Omega-3 Acid Ethyl Esters on Left Ventricular Remodeling After Acute Myocardial Infarction: The OMEGA-REMODEL Randomized Clinical Trial. Circulation 2016;134:378-91. [DOI: https://doi.org/10.1161/CIRCULATIONAHA.115.019949]

Heydari B, Abdullah S, Pottala JV, Shah RV, Abbasi SA, Mandry D, Lumish H, Hoffmann U, Appelbaum E, Feng J, Blankstein R, Steigner M, McConnell JP, Harris W, Jerosch-Herold M, Kwong RY. ST2 is reduced by high-dose omega-3 fatty acid treatment following acute MI and is correlated with reduction of the extracellular volume fraction of non-infarcted myocardium. Journal of Cardiovascular Magnetic Resonance 2016;18(suppl 1):O130.

Heydari B, Harris WS, Kwong RY. Response by Heydari et al to Letter Regarding Article, "Effect of Omega-3 Acid Ethyl Esters on Left Ventricular Remodeling After Acute Myocardial Infarction: The OMEGA-REMODEL Randomized Clinical Trial". Circulation 2017;135(2):e13-4. [DOI: 10.1161/CIRCULATIONAHA.116.025704]

OMEGA - Senges 2009

Published and unpublished data [CRSSTD: 2715747; ClinicalTrials.gov: NCT00251134]

Rauch B, Schiele R, Schneider S, Diller F, Victor N, Gohlke H, Gottwik M, Steinbeck G, Del Castillo U, Sack R, Worth H, Katus H, Spitzer W, Sabin G, Senges J. OMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. Circulation 2010;122(21):2152-9. [CRSREF: 2715748; DOI: 10.1161/CIRCULATIONAHA.110.948562]

Rauch B, Schiele R, Schneider S, Gohlke H, Diller F, Gottwik M, Steinbeck G, Heer T, Katus H, Zimmer R, Erdogan A, Pfafferott C, Senges J. Highly purified omega-3 fatty acids for secondary prevention of sudden cardiac death after myocardial infarction-aims and methods of the OMEGA-study. Cardiovascular Drugs Therapy 2006;20(5):365-75. [CRSREF: 2715749; DOI: 10.1007/s10557-006-0495-6]

OPAL - Dangour 2010

Published and unpublished data [CRSSTD: 2715750; ISRCTN: 72331636]

Dangour A. The OPAL study: Older people and n-3 long chain polyunsaturated fatty acids. Current Controlled Trials [www.controlled-trials.com] 2005.

* Dangour AD, Allen E, Elbourne D, Fasey N, Fletcher AE, Hardy P, et al. Effect of 2-y n-3 long-chain polyunsaturated fatty acid supplementation on cognitive function in older people: a randomized, double-blind, controlled trial. American Journal of Clinical Nutrition 2010;91(6):1725-32.

Dangour AD, Allen E, Elbourne D, Fletcher A, Richards M, Uauy R. Fish consumption and cognitive function among older people in the UK: baseline data from the OPAL study. Journal of Nutrition, Health & Aging 2009;13(3):198-202.

Dangour AD, Allen E, Elbourne D, Fletcher AE, Neveu MM, Uauy R, Holder G. n-3 fatty acids and retinal function. Ophthalmology 2013;120(3):643. [DOI: http://dx.doi.org/10.1016/j.ophtha.2012.09.043]

Dangour AD, Clemens F, Elbourne D, Fasey N, Fletcher AE, Hardy P, et al. A randomised controlled trial investigating the effect of n-3 long-chain polyunsaturated fatty acid supplementation on cognitive and retinal function in cognitively healthy older people: the Older People And n-3 Long-chain polyunsaturated fatty acids (OPAL) study protocol [ISRCTN72331636]. Nutrition Journal 2006;5:20.

OPTILIP 2006

Griffin M, Sanders T, Davies I, Morgan L, Millward D, Lewis F, Slaughter S, Cooper J, Miller G, Griffin B. Effects of altering the ratio of dietary n6 to n3 fatty acids on insulin sensitivity, lipoprotein size, and postprandial lipemia in men and postmenopausal women aged 45–70 y: the OPTILIP Study. American Journal of Clinical Nutrition 2006;84:1290-1298.

Sanders T, Lewis F, Slaughter S, Griffin B, Griffin M, Davies I, Millward J, Cooper J, Miller G. Effect of varying the ratio of n6 to n3 fatty acids by increasing the dietary intake of -linolenic acid, eicosapentaenoic and docosahexaenoic acid, or both on fibrinogen and clotting factors VII and XII in persons aged 45–70 y: the OPTILIP Study. American Journal of Clinical Nutrition 2006;84:513-522.

ORIGIN 2013

Unpublished data only [CRSSTD: 2716249; ClinicalTrials.gov: NCT00069784]

Bordeleau L, Yakubovich N, Dagenais G, Rosenstock J, Ryden LE, Spinas G, et al. Cancer outcomes in patients with dysglycemia on basal insulin: Results of the origin trial. Diabetes 2013;62:A72.

Bordeleau L, Yakubovich N, Dagenais GR, Rosenstock J, Probstfield J, Chang Yu P, et al. The association of basal insulin glargine and/or n-3 fatty acids with incident cancers in patients with dysglycemia. Diabetes Care 2014;37(5):1360-6.

Lonn EM, Bosch J, Diaz R, Lopez-Jaramillo P, Ramachandran A, Hancu N, et al. Effect of insulin glargine and n-3FA on carotid intima-media thickness in people with dysglycemia at high risk for cardiovascular events: the glucose reduction and atherosclerosis continuing evaluation study (ORIGIN-GRACE). Diabetes Care 2013;36(9):2466-74.

Maggioni AP, Fabbri G, Bosch J, Dyal L, Ryden LE, Gerstein HC, et al. Effects of n-3 fatty acids on long-term outcomes of high risk patients with type 2 diabetes mellitus or IGF/IGT with a recent myocardial infarction. European Heart Journal 2013;34:352.

Origin Trial Investigators, Bosch J, Gerstein HC, Dagenais GR, Diaz R, Dyal L, et al. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. New England Journal of Medicine 2012;367(4):309-18.

Origin Trial Investigators, Gerstein H, Yusuf S, Riddle MC, Ryden L, Bosch J. Rationale, design, and baseline characteristics for a large international trial of cardiovascular disease prevention in people with dysglycemia: the ORIGIN Trial (Outcome Reduction with an Initial Glargine Intervention). American Heart Journal 2008;155(1):26-32, 32.

Origin Trial Investigators, Gerstein HC, Bosch J, Dagenais GR, Diaz R, Jung H, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. New England Journal of Medicine 2012;367(4):319-28.

Punthakee Z, Gerstein HC, Bosch J, Tyrwhitt J, Jung H, Lee SF, et al. Cardiovascular and other outcomes postintervention with insulin glargine and omega-3 fatty acids (ORIGINALE). Diabetes Care 2016;39(5):709-16.

ORL-TAK 2013

[ClinicalTrials.gov: NCT01350999]

Tatsuno I, Saito Y, Kudou K, Ootake J. Long-term safety and efficacy of TAK-085 in Japanese subjects with hypertriglyceridemia undergoing lifestyle modification: the omega-3 fatty acids randomized long-term (ORL) study. Journal of clinical lipidology 2013;7(6):615-25. [PubMed: 24314359]

Özaydin 2011

[CRSSTD: 2715799]

Özaydin M, Erdoğan D, Tayyar S, Uysal BA, Doğan A, Içli A, Özkan E, Varol E, Türker Y, Arslan A. N-3 polyunsaturated fatty acids administration does not reduce the recurrence rates of atrial fibrillation and inflammation after electrical cardioversion: a prospective randomized study. Anadolu Kardiyoloji Dergisi 2011;11(4):305-9. [CRSREF: 2715800; DOI: 10.5152/akd.2011.080]

Palma 2015

Palma C. Omega 3 fatty acids supplementation in Schizophrenia. European Archives of Psychiatry and Clinical Neuroscience 2015;265(Supplement 1):S122.

Patch 2005

Mukaro VR, Costabile M, Murphy KJ, Hii CS, Howe PR, Ferrante A. Leukocyte numbers and function in subjects eating n-3 enriched foods: selective depression of natural killer cell levels. Arthritis Res Ther 2008;10(3):R57. [DOI: 10.1186/ar2426]

Murphy KJ, Meyer BJ, Mori TA, Burke V, Mansour J, Patch CS, Tapsell LC, Noakes M, Clifton PA, Barden A, Puddey IB, Beilin LJ, Howe PRC. Impact of foods enriched with n-3 long-chain polyunsaturated fatty acids on erythrocyte n-3 levels and cardiovascular risk factors. British Journal of Nutrition 2007;97(4):749-57. [DOI: https://doi.org/10.1017/S000711450747252X]

* Patch CS, Tapsell LC, Mori TA, Meyer BJ, Murphy KJ, Mansour J, Noakes M, Clifton PM, Puddey IB, Beilin LJ, Annison G, Howe PR. The use of novel foods enriched with long-chain n-3 fatty acids to increase dietary intake: a comparison of methodologies assessing nutrient intake. Journal of the American Dietetic Association 2005;105(12):1918-26.

Paty 1978

Paty, D.W., Cousin, H.K., Read, S. and Adlakha, K.. Linoleic acid in multiple sclerosis: failure to show any therapeutic benefit. Acta Neurologica Scandinavica 1978;58(1):53-58.

Pomponi 2014

Pomponi M, Loria G, Salvati S, Di Biase A, Conte G, Villella C, Righino E, Ciciarelli C, Bria P, La Torre G, Pomponi MFL, Janiri L, Bentivoglio AR. DHA effects in Parkinson disease depression. Basal Ganglia 2014;4:61-66. [DOI: 10.1016/j.baga.2014.03.004]

Pratt 2009

[ClinicalTrials.gov: NCT00402363]

* Kowey PR, Reiffel JA, Ellenbogen KA, Naccarelli GV, Pratt CM. Efficacy and Safety of Prescription Omega-3 Fatty Acids for the Prevention of Recurrent Symptomatic Atrial FibrillationA Randomized Controlled Trial. JAMA 2010;304(21):2363-72. [DOI: 10.1001/jama.2010.1735]

Pratt CM, Reiffel JA, Ellenbogen KA, Naccarelli GV, Kowey PR. Efficacy and safety of prescription omega-3-acid ethyl esters for the prevention of recurrent symptomatic atrial fibrillation: a prospective study. American Heart Journal 2009;158(2):163-9. [DOI: 10.1016/j.ahj.2009.05.024]

Proudman 2015

Published and unpublished data [Other: ACTRN12613000579796]

Proudman SM, Cleland LG, Metcalf RG, Sullivan TR, Spargo LD, James MJ. Plasma n-3 fatty acids and clinical outcomes in recent-onset rheumatoid arthritis. The British journal of nutrition 2015;114(6):885-90. [PubMed: 26283657]

Proudman SM, James MJ, Spargo LD, Metcalf RG, Sullivan TR, Rischmueller M, et al. Fish oil in recent onset rheumatoid arthritis: a randomised, double-blind controlled trial within algorithm-based drug use. Annals of the rheumatic diseases 2015;74(1):89-95. [PubMed: 24081439]

S. Proudman, L. Spargo, C. Hall, L. McWilliams, A. Lee, R. Maureen, R. Gibson, M. James, L. Cleland.. FISH OIL IN RHEUMATOID ARTHRITIS: A RANDOMISED, DOUBLE BLIND TRIAL COMPARING HIGH DOSE WITH LOW DOSE. In: Internal Medicine Journal. Vol. 42 (Suppl. 1). 2012:2-3.

Puri 2005

[CRSSTD: 2716228; ISRCTN: 79170611]

Puri BK, Leavitt BR, Hayden MR, Ross CA, Rosenblatt A, Greenamyre JT, Hersch S, Vaddadi KS, Sword A, Horrobin DF, Manku M, Murck H. Ethyl-EPA in Huntington disease: a double-blind, randomized, placebo-controlled trial. Neurology 2005;65(2):286-92. [CRSREF: 2716229]

Raitt 2005

[CRSSTD: 2715756; ClinicalTrials.gov: NCT00004558]

* Raitt MH, Connor WE, Morris C, Kron J, Halperin B, Chugh SS, et al. Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators: a randomized controlled trial. JAMA 2005;293(23):2884-91.

Ramirez-Ramirez 2013

Ramirez-Ramirez V, Macias-Islas MA, Ortiz GG, Pacheco-Moises F, Torres-Sanchez ED, Sorto-Gomez TE, Cruz-Ramos JA, Orozco-Aviña G, Celis de la Rosa AJ. Efficacy of fish oil on serum of TNF α , IL-1 β , and IL-6 oxidative stress markers in multiple sclerosis treated with interferon beta-1b. Ox Med Cell Longev 2013;2013:709493. [DOI: 10.1155/2013/709493]

Sorto-Gomez TE, Ortiz GG, Pacheco-Moises FP, Torres-Sanchez ED, Ramirez-Ramirez V, Macias-Islas MA, de la Rosa AC, Velázquez-Brizuela IE. Effect of fish oil on glutathione redox system in multiple sclerosis.. Am J Neurodegener Dis 2016;5(2):145-51.

Rebello 2015

[ClinicalTrials.gov: NCT01669200; Other:]

Rebello CJ, Keller JN, Liu AG, Johnson WD and Greenway FL. Pilot feasibility and safety study examining the effect of medium chain triglyceride supplementation in subjects with mild cognitive impairment: A randomized controlled trial. BBA Clinical 2015;3:123-125. [NCT: NCT01669200]

Reed 2014

Published and unpublished data [Other: NCT00072982]

Olendzki BC, Leung K, Van Buskirk S, Reed G, Zurier RB. Treatment of rheumatoid arthritis with marine and botanical oils: influence on serum lipids. Evidence-Based Complementary & Alternative Medicine: eCAM 2011;2011:827286.

Reed GW, Leung K, Rossetti RG, Vanbuskirk S, Sharp JT, Zurier RB. Treatment of rheumatoid arthritis with marine and botanical oils: an 18-month, randomized, and double-blind trial. Evidence-Based Complementary & Alternative Medicine: eCAM 2014;2014:857456.

Risk and Prevention 2013

Published and unpublished data [CRSSTD: 2716250; ClinicalTrials.gov: NCT00317707]

Efficacy of n-3 polyunsaturated fatty acids and feasibility of optimizing preventive strategies in patients at high cardiovascular risk: rationale, design and baseline characteristics of the Rischio and Prevenzione study, a large randomised trial in general practice. 2010;11(1):68.

* Roncaglioni MC, Tombesi M, Avanzini F, Barlera S, Caimi V, Longoni P, Marzona I, Milani V, Silletta MG, Tognoni G, Marchioli R. n-3 Fatty Acids in Patients with Multiple Cardiovascular Risk Factors. New England Journal of Medicine 2013;368(19):1800-8.

Visentin G, Risk & Prevention Study Grp. Towards evidence-based practice via practice-based evidence: the Italian experience. Family Practice 2008;25 Suppl 1:i71-4.

Romero 2013

[DOI: doi:10.1016/j.jns.2013.07.2126]

J. Romero Imbroda. Neurology Department, Hospital Comarcal de Melilla,Melilla, Spain. The role of Omega-3 fatty acids in patients with mild cognitiveimpairment by means of the PHOTOTEST. In: Journal of the Neurological Sciences. Vol. 333. 2013:e579–e628. [DOI: 10.1016/j.jns.2013.07.2126]

Rossing 1996

Published and unpublished data [CRSSTD: 2715765]

Myrup B, Rossing P, Jensen T, Parving H-H, Holmer G, Gram J, Kluft C, Jespersen J. Lack of effect of fish oil supplementation on coagulation and transcapillary escape rate of albumin in insulin-dependent diabetic patients with diabetic nephropathy. Scandinavian Journal of Clinical & Laboratory Investigation 2001;61(5):349-356. [CRSREF: 2715766]

* Rossing P, Hansen BV, Nielsen FS, Myrup B, Holmer G, Parving HH. Fish oil in diabetic nephropathy. Diabetes Care 1996;19(11):1214-1219. [CRSREF: 2715767]

Sandhu 2016

[ClinicalTrials.gov: NCT00723398]

Sandhu N, Schetter SE, Liao J, Hartman TJ, Richie JP, McGinley J, et al. Influence of Obesity on Breast Density Reduction by Omega-3 Fatty Acids: Evidence from a Randomized Clinical Trial. Cancer prevention research (Philadelphia, Pa.) 2016;9(4):275-82. [PubMed: 26714774]

Signori C, DuBrock C, Richie JP, Prokopczyk B, Demers LM, Hamilton C, et al. Administration of omega-3 fatty acids and Raloxifene to women at high risk of breast cancer: interim feasibility and biomarkers analysis from a clinical trial. European journal of clinical nutrition 2012;66(8):878-84. [PubMed: 22669332]

Sasaki 2012

[Other: UMIN000005783]

Sasaki J, Miwa T, Odawara M. Administration of highly purified eicosapentaenoic acid tostatin-treated diabetic patients further improves vascularfunction. Endocrine Journal 2012;59(4):297-304.

SCIMO - von Schacky 1999

Published and unpublished data [CRSSTD: 2715768]

Angerer P, Kothny W, Stork S, von Schacky C. Effect of dietary supplementation with omega-3 fatty acids on progression of atherosclerosis in carotid arteries. Cardiovascular Research 2002;54(1):183-90.

* von Schacky C, Angerer P, Kothny W, Theisen K, Mudra H. The effect of dietary omega-3 fatty acids on coronary atherosclerosis. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1999;130(7):554-562. [CRSREF: 2715769]

von Schacky C, Baumann K, Angerer P. The effect of n-3 fatty acids on coronary atherosclerosis: results from SCIMO, an angiographic study, background and implications. Lipids 2001;36 Suppl:S99-102.

Shimizu 1995

Published and unpublished data [CRSSTD: 2716096]

Shimizu H, Ohtani K, Tanaka Y, Sato N, Mori M, Shimomura Y. Long-term effect of eicosapentaenoic acid ethyl (EPA-E) on albuminuria of non-insulin dependent diabetic patients. Diabetes Res Clin Pract 1995;28(1):35-40. [CRSREF: 2716097]

Shinto 2014

[CRSSTD: 2715770; Other: NCT00090402]

Shinto L, Quinn J, Montine T, Dodge HH, Woodward W, Baldauf-Wagner S, et al. A randomized placebo-controlled pilot trial of omega-3 fatty acids and alpha lipoic acid in Alzheimer's disease. Journal of Alzheimer's disease : JAD 2014;38(1):111-20. [PubMed: 24077434]

Shinto L. Fish oil and alpha lipoic acid in treating Alzheimer's Disease. NCT00090402 2009.

SHOT - Eritsland 1996

Published and unpublished data [CRSSTD: 2715772]

Eritsland J, Arnesen H, Berg K, Seljeflot I, Abdelnoor M. Serum Lp(a) lipoprotein levels in patients with coronary artery disease and the influence of long-term n-3 fatty acid supplementation. Scandinavian journal of clinical and laboratory investigation 1995;55(4):295-300. [CRSREF: 2715773]

* Eritsland J, Arnesen H, Gronseth K, Fjeld NB, Abdelnoor M. Effect of dietary supplementation with n-3 fatty acids on coronary artery bypass graft patency. American Journal of Cardiology 1996;77(1):31-6. [CRSREF: 2715774]

Eritsland J, Arnesen H, Gronseth K, Fjeld NB, Abdelnoor M. Effect of supplementation with n-3 fatty acids on graft patency in patients undergoing coronary artery bypass operation. Results from SHOT study [abstract]. European Heart Journal 1994;15:29. [CRSREF: 2715775]

Eritsland J, Arnesen H, Seljeflot I, Hostmark AT. Long-term metabolic effects of n-3 polyunsaturated fatty acids in patients with coronary artery disease. American Journal of Clinical Nutrition 1995;61(4):831-6. [CRSREF: 2715776]

Eritsland J, Arnesen H, Seljeflot I, Kierulf P. Long-term effects of n-3 polyunsaturated fatty acids on haemostatic variables and bleeding episodes in patients with coronary artery disease. Blood coagulation & fibrinolysis 1995;6(1):17-22. [CRSREF: 2715777]

Eritsland J, Seljeflot I, Abdelnoor M, Arnesen H, Torjesen PA. Long-term effects of n-3 fatty acids on serum lipids and glycaemic control. Scandinavian journal of clinical and laboratory investigation 1994;54(4):273-80. [CRSREF: 2715778]

Eritsland J, Seljeflot I, Abdelnoor M, Arnesen H. Long-term influence of omega-3 fatty acids on fibrinolysis, fibrinogen, and serum lipids. Fibrinolysis 1994;8(2):120-5. [CRSREF: 2715779]

Eritsland J, Seljeflot I, Arnesen H, Abdelnoor M. Long-term effects of fish oil supplementation in patients with coronary artery disease: influence on lipoproteins, coagulation and fibrinolysis [abstract]. Thrombosis Research 1992;65:75. [CRSREF: 2715780]

Eritsland J, Seljeflot I, Arnesen H, Abdelnoor M. Long-term influence of omega-3 fatty acids on fibrinolysis, fibrinogen, and serum lipids [abstract]. Thrombosis and Haemostasis 1993;69:1065. [CRSREF: 2715781]

Eritsland J, Seljeflot I, Arnesen H, Westvik AB, Kierulf P. Effect of long-term, moderate-dose supplementation with omega-3 fatty acids on monocyte procoagulant activity and release of interleukin-6 in patients with coronary artery disease. Thromb Res 1995;77(4):337-46. [CRSREF: 2715782]

Sianni 2013

Sianni A, Matsoukis I, Ganotopoulou A, Paraskevas P, Asimis A, Tsivilis N, et al. PP128-SUN EFFECT OF OMEGA 3 FATTY ACIDS IN PATIENTS WITH HYPERTENSION AND ATRIAL FIBRILLATION. Clinical Nutrition32:S70-1.

Sinn 2012

[Other: ACTRN 12609000167268]

Sinn N, Milte CM, Street SJ, Buckley JD, Coates AM, Petkov J, Howe PRC. Effects of n-3 fatty acids, EPA v. DHA, on depressive symptoms, quality of life, memory and executive function in older adults with mild cognitive impairment: a 6-month randomised controlled trial. British Journal of Nutrition 2012;107:1682-1693. [DOI: 10.1017/S0007114511004788]

Skoldstam 1992

Published and unpublished data [CRSSTD: 2716114]

Skoldstam L, Borjesson O, Kjallman A, Seiving B, Akesson B. Effect of six months of fish oil supplementation in stable rheumatoid arthritis. A double-blind, controlled study. Scand J Rheumatol 1992;21(4):178-185. [CRSREF: 2716115]

SMART Tapsell 2013

[Other: ACTRN12608000425392]

Anil S, Charlton KE, Tapsell LC, Probst Y, Ndanuko R, Batterham MJ. Identification of dietary patterns associated with blood pressure in a sample of overweight Australians. J Hum Hypertens 2016;30(11):672-8. [DOI: 10.1038/jhh.2016.10]

* Tapsell LC, Batterham MJ, Charlton KE, Neale EP, Probst YC, O'Shea JE, et al. Foods, nutrients or whole diets: effects of targeting fish and LCn3PUFA consumption in a 12mo weight loss trial. BMC public health 2013;13:1231. [PubMed: 24369765]

Tapsell LC, Batterham MJ, Charlton KE. Effect of dietary restriction and n-3 PUFA supplementation on insulin resistance in obese adults. FASEB Journal 2010;24:733.9.

Smith 2015

[ClinicalTrials.gov: NCT01308957]

Smith GI, Julliand S, Reeds DN, Sinacore DR, Klein S, Mittendorfer B. Fish oil-derived n-3 PUFA therapy increases muscle mass and function in healthy older adults. Am J Clin Nutr 2015;102:115-22. [DOI: 10.3945/ajcn.114.105833]

SO927 Hershman 2015

[ISRCTN: NCT01385137]

Hershman DL, Unger JM, Crew KD, Moinpour CM, Minasian LM, Hansen L, et al. SWOG S0927: A randomized double blind placebo-controlled trial of omega-3-fatty acid for the control of aromatase inhibitor (AI)-induced musculoskeletal pain in women with early stage breast cancer. Cancer Research. Conference: 34th Annual CTRC AACR San Antonio Breast Cancer Symposium San Antonio, TX United States. Conference Start 2011;71(24 SUPPL. 3).

SOFA 2006

Published and unpublished data [CRSSTD: 2715785; ClinicalTrials.gov: NCT00110838]

Brouwer IA, Katan MB, Schouten EG, Camm AJ, Hauer RNW, Wever EFD et al. Rationale and design of a clinical trial on n-3 fatty acids and cardiac arrhythmia (SOFA) [abstract]. Annals of Nutrition & Metabolism 2001;45(Suppl 1):79. [CRSREF: 2715786]

Brouwer IA, Raitt MH, Dullemeijer C, Kraemer DF, Zock PL, Morris C, et al. Effect of fish oil on ventricular tachyarrhythmia in three studies in patients with implantable cardioverter defibrillators. European Heart Journal 2009;30(7):820-6.

* Brouwer IA, Zock PL, Camm AJ, Böcker D, Hauer RN, Wever EF, Dullemeijer C, Ronden JE, Katan MB, Lubinski A, Buschler H, Schouten EG; SOFA Study Group. Effect of fish oil on ventricular tachyarrhythmia and death in patients with implantable cardioverter defibrillators: the Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA) randomized trial. JAMA 2006;295(22):2613-9. [CRSREF: 2715787]

Brouwer IA, Zock PL, Wever EFD, Hauer RNW, Camm AJ, Bocker D et al. Rationale and design of a randomised controlled clinical trial on supplemental intake of n-3 fatty acids and incidence of cardiac arrhythmia: SOFA. European Journal of Clinical Nutrition 2003;57:1323-30. [CRSREF: 2715788]

Sofi 2010

Sofi F, Giangrandi I, Cesari F, Corsani I, Abbate R, Gensini GF, et al. Effects of a 1-year dietary intervention with n-3 polyunsaturated fatty acid-enriched olive oil on non-alcoholic fatty liver disease patients: a preliminary study. International journal of food sciences and nutrition 2010;61(8):792-802. [PubMed: 20465434]

Stonehouse 2013

Stonehouse et al.. DHA supplementation improved both memory and reaction time in healthy young adults: a randomized controlled trial. The American Journal of Clinical Nutrition 2013;97(5):1134-1143. [ACTRN: ACTRN12610000212055]

SU.FOL.OM3 Galan 2010

Published and unpublished data [CRSSTD: 2715789; ISRCTN: 41926726]

Ahluwalia N, Blacher J, Szabo De Edelenyi F, Faure P, Julia C, Hercberg S, et al. Prognostic value of multiple emerging biomarkers in cardiovascular risk prediction in patients with stable cardiovascular disease. Atherosclerosis 2013;228(2):478-84.

Andreeva VA, Galan P, Torres M, Julia C, Hercberg S, Kesse-Guyot E. Supplementation with B vitamins or n-3 fatty acids and depressive symptoms in cardiovascular disease survivors: ancillary findings from the SUpplementation with FOLate, vitamins B-6 and B-12 and/or OMega-3 fatty acids (SU.FOL.OM3) randomized trial. American Journal of Clinical Nutrition 2012;96(1):208-14.

Andreeva VA, Kesse-Guyot E, Barberger-Gateau P, Fezeu L, Hercberg S, Galan P. Cognitive function after supplementation with B vitamins and long-chain omega-3 fatty acids: ancillary findings from the SU.FOL.OM3 randomized trial. American Journal of Clinical Nutrition 2011;94(1):278-86. [CRSREF: 2715790]

Andreeva VA, Latarche C, Hercberg S, Briancon S, Galan P, Kesse-Guyot E. B vitamin and/or n-3 fatty acid supplementation and health-related quality of life: ancillary findings from the SU.FOL.OM3 randomized trial. PLoS ONE [Electronic Resource] 2014;9(1):e84844.

Andreeva VA, Touvier M, Kesse-Guyot E, Julia C, Galan P, Hercberg S. B vitamin and/or omega-3 fatty acid supplementation and cancer: ancillary findings from the supplementation with folate, vitamins B6 and B12, and/or omega-3 fatty acids (SU.FOL.OM3) randomized trial. Archives of Internal Medicine 2012;172(7):540-7.

Arnaud J, Bost M, Vitoux D, Labarere J, Galan P, Faure H, et al. Effect of low dose antioxidant vitamin and trace element supplementation on the urinary concentrations of thromboxane and prostacyclin metabolites. Journal of the American College of Nutrition 2007;26(5):405-11.

Astorg P, Bertrais S, Alessandri JM, Guesnet P, Kesse-Guyot E, Linard A, et al. Long-chain n-3 fatty acid levels in baseline serum phospholipids do not predict later occurrence of depressive episodes: a nested case-control study within a cohort of middle-aged French men and women. Prostaglandins Leukotrienes & Essential Fatty Acids 2009;81(4):265-71.

Astorg P, Couthouis A, Bertrais S, Arnault N, Meneton P, Guesnet P, et al. Association of fish and long-chain n-3 polyunsaturated fatty acid intakes with the occurrence of depressive episodes in middle-aged French men and women. Prostaglandins Leukotrienes & Essential Fatty Acids 2008;78(3):171-82.

Blacher J, Czernichow S, Paillard F, Ducimetiere P, Hercberg S, Galan P, et al. Cardiovascular effects of B-vitamins and/or N-3 fatty acids: the SU.FOL.OM3 trial. International Journal of Cardiology 2013;167(2):508-13.

Blacher J, Safar ME, Ly C, Szabo De Edelenyi F, Hercberg S, Galan P. Blood pressure variability: Cardiovascular risk integrator or independent risk factor. Journal of Human Hypertension 2015;29(2):122-6.

Czernichow S, Bruckert E, Oppert JM, Bertrais S, Paillard F, Astorg P, et al. Intake of added oils and fats among middle-aged French adults: relationships with educational level and region of residence. Journal of the American Dietetic Association 2005;105(12):1889-94.

Fezeu LK, Laporte F, Kesse-Guyot E, Andreeva VA, Blacher J, Hercberg S, et al. Baseline plasma fatty acids profile and incident cardiovascular events in the SU.FOL.OM3 trial: the evidence revisited. PLoS ONE [Electronic Resource] 2014;9(4):e92548.

Galan P, Briançon S, Blacher J, Czernichow S, Hercberg S. The scientific basis of the SU.FOL.OM3 study: a secondary intervention trial of folate, B6 and B12 vitamins and/or omega3 falty acid supplements in the prevention of recurrent ischemic events [Bases scientifiques de l'étude SUFOLOM3: essai de prévention secondaire visant à tester l'impact d'une supplémentation en folates, vitamines B6 et B12 et/ ou acides gras oméga-3 dans la prévention de la récidive de pathologies ischémiques]. Sang Thrombose Vaisseaux 2009;21(4):207-13. [CRSREF: 2715791]

Galan P, Briancon S, Blacher J, Czernichow S, Hercberg S. The SU.FOL.OM3 Study: a secondary prevention trial testing the impact of supplementation with folate and B-vitamins and/or Omega-3 PUFA on fatal and non fatal cardiovascular events, design, methods and participants characteristics. Trials 2008;9(35). [CRSREF: 2715792; DOI: 10.1186/1745-6215-9-35]

Galan P, Briancon S, Blacher J, Czernichow S, Hercberg S. The SU.FOL.OM3 Study: a secondary prevention trial testing the impact of supplementation with folate and B-vitamins and/or Omega-3 PUFA on fatal and non fatal cardiovascular events, design, methods and participants characteristics. Trials [Electronic Resource] 2008;9:35.

Galan P, Briancon S, Blacher J, Czernichow S, Hercberg S. The scientific basis of the SU.FOL.OM3 study: A secondary intervention trial of folate, B6 and B12 vitamins and/or omega3 falty acid supplements in the prevention of recurrent ischemic events. [French]. Sang Thrombose Vaisseaux 2009;21(4):207-13.

Galan P, Kesse-Guyot E, Czernichow S, Briancon S, Blacher J, Hercberg S; SU.FOL.OM3 Collaborative Group. Effects of B vitamins and omega 3 fatty acids on cardiovascular diseases: a randomised placebo controlled trial. BMJ 2010;341:c6273. [CRSREF: 2715793; DOI: 10.1136/bmj.c6273]

Galan P, de Bree A, Mennen L, Potier de Courcy G, Preziozi P, Bertrais S, Castetbon K, Hercberg S. Background and rationale of the SU.FOL.OM3 study: double-blind randomized placebo-controlled secondary prevention trial to test the impact of supplementation with folate, vitamin B6 and B12 and/or omega-3 fatty acids on the prevention of recurrent ischemic events in subjects with atherosclerosis in the coronary or cerebral arteries. The journal of nutrition, health and aging 2003;7(6):428-35. [CRSREF: 2715794]

Julia C, Meunier N, Touvier M, Ahluwalia N, Sapin V, Papet I, et al. Dietary patterns and risk of elevated C-reactive protein concentrations 12 years later. British Journal of Nutrition 2013;110(4):747-54.

Julia C, Touvier M, Meunier N, Papet I, Galan P, Hercberg S, et al. Intakes of PUFAs were inversely associated with plasma C-reactive protein 12 years later in a middle-aged population with vitamin E intake as an effect modifier. Journal of Nutrition 2013;143(11):1760-6.

Kesse-Guyot E, Peneau S, Hercberg S, Galan P, Vogt L, Escande M, et al. Thirteen-year prospective study between fish consumption, long-chain N-3 fatty acids intakes and cognitive function. Journal of Nutrition, Health and Aging 2011;15(2):115-20.

Latreille J, Kesse-Guyot E, Malvy D, Andreeva V, Galan P, Tschachler E, et al. Association between dietary intake of n-3 polyunsaturated fatty acids and severity of skin photoaging in a middle-aged Caucasian population. Journal of Dermatological Science 2013;72(3):233-9.

Latreille J, Kesse-Guyot E, Malvy D, Andreeva V, Galan P, Tschachler E, et al. Dietary Monounsaturated Fatty Acids Intake and Risk of Skin Photoaging. PLoS ONE 2012;7 (9) (no pagination)(e44490).

Pouchieu C, Chajes V, Laporte F, Kesse-Guyot E, Galan P, Hercberg S, et al. Prospective associations between plasma saturated, monounsaturated and polyunsaturated fatty acids and overall and breast

cancer risk - modulation by antioxidants: a nested case-control study. PLoS ONE [Electronic Resource] 2014;9(2):e90442.

Szabo De Edelenyi F, Vergnaud AC, Ahluwalia N, Julia C, Hercberg S, Blacher J, et al. Effect of B-vitamins and n-3 PUFA supplementation for 5 years on blood pressure in patients with CVD. British Journal of Nutrition 2012;107(6):921-7.

Touvier M, Kesse-Guyot E, Andreeva VA, Fezeu L, Charnaux N, Sutton A, et al. Modulation of the association between plasma intercellular adhesion molecule-1 and cancer risk by n-3 PUFA intake: a nested case-control study. American Journal of Clinical Nutrition 2012;95(4):944-50.

Vesin C, Galan P, Gautier B, Czernichow S, Hercberg S, Blacher J. Control of baseline cardiovascular risk factors in the SU-FOL-OM3 study cohort: does the localization of the arterial event matter? European Journal of Cardiovascular Prevention & Rehabilitation 2010;17(5):541-8.

de Bree A, Mennen LI, Hercberg S, Galan P. Evidence for a protective (synergistic?) effect of B-vitamins and omega-3 fatty acids on cardiovascular diseases. European Journal of Clinical Nutrition 2004;58(5):732-44.

Tajalizadekhoob 2011

Tajalizadekhoob Y, Sharifi F, Fakhrzadeh H, Mirarefin M, Ghaderpanahi M, Badamchizade Z, Azimipour S. The effect of low-dose omega 3 fatty acids on the treatment of mild to moderate depression in the elderly: a double-blind, randomized, placebo-controlled study. European Archives of Psychiatry and Clinical Neuroscience 2011;261:539-549. [DOI: 10.1007/s00406-011-0191-9]

Tande 2016

Tande KS, Vo TD, Lynch BS. Clinical safety evaluation of marine oil derived from Calanus finmarchicus. Regulatory toxicology and pharmacology : RTP 2016;80:25-31. [PubMed: 27233921]

Tani 2017

[DOI: 10.1007/s40256-016-0195-y; Other: UMIN000010452]

Tani S, Hiryama A, Atsumi W, Yagi T, Nagao K. Impact of adding eicosapentaenoic acid to strong statin therapy on serum pentraxin X3 level: a sixmonth,randomized control study. European Heart Journal 2015;36 (abstract supplement):180. [Other: Abstract P1127]

Tani S, Nagao K, Yagi T, Atsumi W, Hirayama A. impact of accing eicosapentaenoic acid to statin therapy on plasma pentraxin 3 level in patients with stable coronary artery disease: a 6-month, randomized controlled study. Am J Cardiovasc Drugs 2017;17:49-59. [DOI: 10.1007/s40256-016-0195-y]

Tapsell 2004

Published and unpublished data [CRSSTD: 2716130]

Gillen LJ, Tapsell LC, Patch CS, Owen A, Batterham M. Structured dietary advice incorporating walnuts achieves optimal fat and energy balance in patients with Type II Diabetes Mellitus. Journal of the American Dietetic Association 2005;105(7):1087-96. [CRSREF: 2716131; DOI: 10.1016/j.jada.2005.04.007]

Tapsell LC, Gillen LJ, Patch CS, Batterham M, Owen A, Baré M, Kennedy M. Including walnuts in a low-fat/modified-fat diet improves HDL cholesterol-to-total cholesterol ratios in patients with Type II Diabetes. Diabetes Care 2004;27(12):2777-83. [CRSREF: 2716132]

Tardivo 2015

[Other: RBR-5668v4]

Tardivo AP, Nahas-Neto J, Orsatti CL, Dias FB, Poloni PF, Schmitt EB, Nahas EAP. Effects of omega-3 on metabolic markers in postmenopausal women with metabolic syndrome. Climacteric 2015;18:290-8. [DOI: 10.3109/13697137.2014.981521]

Tartibian 2011

Tartibian B, Hajizadeh Maleki B, Kanaley J, Sadeghi K. Long-term aerobic exercise and omega-3 supplementation modulate osteoporosis through inflammatory mechanisms in post-menopausal women: a randomized, repeated measures study. Nutr Metab 2011;8:71. [DOI: 10.1186/1743-7075-8-71]

Terano 1999

Terano T, Fujishiro S, Ban K. Yamamoto K, Tanaka T, Noguchi Y, Tamura Y, Yazawa K,Hirayama T.. Docosahexaenoic acid supplementation improves the moderately severe dementia from thrombotic cerebrovascular diseases. Lipids 1999;34:S345-S346.

THIS DIET 2008

Published and unpublished data [ClinicalTrials.gov: NCT00269425]

Tuttle KR, Shuler LA, Packard DP, Milton JE, Daratha KB, Bibus DM, et al. Comparison of low-fat versus Mediterranean-style dietary intervention after first myocardial infarction (from The Heart Institute of Spokane Diet Intervention and Evaluation Trial). The American journal of cardiology 2008;101(11):1523-30. [PubMed: 18489927]

TREND-HD 2008

[CRSSTD: 2716238; ClinicalTrials.gov: NCT00146211]

Huntington Study Group TREND-HD Investigators. Randomized controlled trial of ethyl-eicosapentaenoic acid in Huntington disease: the TREND-HD study. Archives of Neurology 2008;65(12):1582-9. [CRSREF: 2716239]

Veleba 2015

[Other: EudraCT 2009-011106-42]

Veleba J, Kopecky Jr.J, Janovska P, Kuda O, Horakova O, Malinska H, Kazdova L, Oliyarnyk O, Skop V, Trnovska J, Hajek M, Skoch A, Flachs P, Bardova K, Rossmeis M, Olza J, Salim de Castro G, Calder P, Gardlo A, Fiserova E, Jensen J, Bryhn M, Kopecky J, Pelikanova T. Combined intervention with pioglitazone and n-3 fatty acids in metformin-treated type 2 diabetic patients: improvement of lipid metabolism. Nutrition and Metabolism 2015;12(52):DOI 10.1186/s12986-015-0047-9.

WAHA 2016

[ClinicalTrials.gov: NCT01634841]

Bitok, Edward, Rajaram, Sujatha, Ros, Emilio, et al. Does a Daily Walnut Supplement Given for a Year Result in Body Weight Gain? FASEB J April 2016;30:1157.5.

Huey, Lynnley, Bitok, Edward, Kazzi, Natalie, et al. Dietary compliance of walnut or no walnut intake in a 1-year randomized intervention trial among free-living elderly in the Walnuts and Healthy Aging Study (WAHA). FASEB J April 2016;30:1157.10.

Rajaram S, Valls-Pedret C, Cofan M, Sabate J, Serra-Mir M, Perez-Heras AM, et al. The Walnuts and Healthy Aging Study (WAHA): Protocol for a Nutritional Intervention Trial with Walnuts on Brain Aging. Frontiers in aging neuroscience 2016;8:333. [PubMed: 28119602]

* Ros, Emilio, Rajaram, Sujatha, Sala-Vila, Aleix, et al. Effect of a 1-Year Walnut Supplementation on Blood Lipids among Older Individuals: Findings from the Walnuts and Healthy Aging (WAHA) study. FASEB J April 2016;30(1 supplement):293.4.

Weinstock-Guttman 2005

Weinstock-Guttman B, Baier M, Park Y, Feichter J, Lee-Kwen P, Gallagher E, Venkatraman J, Meksawan K, Deinehert S, Pendergast D, Awad AB, Ramanathan M, Munschauer F, Rudick R. Low fat dietary intervention with n-3 fatty acid supplementation in multiple sclerosis patients. Prostaglandins, Leukotrienes and Essential Fatty Acids 2005;73:397-404. [DOI: 10.1016/j.plefa.2005.05.024]

WELCOME 2015

Published and unpublished data [ClinicalTrials.gov: NCT00760513]

Bhatia L, Scorletti E, Curzen N, Clough GF, Calder PC, Byrne CD. Improvement in non-alcoholic fatty liver disease severity is associated with a reduction in carotid intima-media thickness progression. Atherosclerosis 2016;246:13-20. [PubMed: 26748347]

Byrne CD, Targher G. Ectopic fat, insulin resistance, and nonalcoholic fatty liver disease: implications for cardiovascular disease. Arteriosclerosis, thrombosis, and vascular biology 2014;34(6):1155-61. [PubMed: 24743428]

Byrne CD, Targher G. Time to Replace Assessment of Liver Histology With MR-Based Imaging Tests to Assess Efficacy of Interventions for Nonalcoholic Fatty Liver Disease. Gastroenterology 2016;150(1):7-10. [PubMed: 26602219]

Clough GF, McCormick KG, Scorletti E, Bhatia L, Calder PC, Griffin MJ, et al. Higher body fat percentage is associated with enhanced temperature perception in NAFLD: results from the randomised Wessex Evaluation of fatty Liver and Cardiovascular markers in NAFLD with OMacor thErapy trial (WELCOME) trial. Diabetologia 2016;59(7):1422-9. [PubMed: 27106721]

McCormick KG, Scorletti E, Bhatia L, Calder PC, Griffin MJ, Clough GF, et al. Impact of high dose n-3 polyunsaturated fatty acid treatment on measures of microvascular function and vibration perception in non-alcoholic fatty liver disease: results from the randomised WELCOME trial. Diabetologia 2015;58(8):1916-25. [PubMed: 26021488]

Scorletti E, Bhatia L, McCormick KG, Clough GF, Nash K, Calder PC, et al. Design and rationale of the WELCOME trial: A randomised, placebo controlled study to test the efficacy of purified long chainomega-3

fatty acid treatment in non-alcoholic fatty liver disease [corrected]. Contemporary clinical trials 2014;37(2):301-11. [PubMed: 24556343]

Scorletti E, West AL, Bhatia L, Hoile SP, McCormick KG, Burdge GC, et al. Treating liver fat and serum triglyceride levels in NAFLD, effects of PNPLA3 and TM6SF2 genotypes: Results from the WELCOME trial. Journal of hepatology 2015;63(6):1476-83. [PubMed: 26272871]

Targher G, Byrne CD. Clinical Review: Nonalcoholic fatty liver disease: a novel cardiometabolic risk factor for type 2 diabetes and its complications. The Journal of clinical endocrinology and metabolism 2013;98(2):483-95. [PubMed: 23293330]

Westberg 1990

[CRSSTD: 2716169]

Westberg G & Tarkowski A. Effect of MaxEPA in patients with SLE. Scand J Rheumatology 1990;19:137-143.

Westberg G, Tarkowski A. Effect of MaxEPA in patients with SLE: a double blind crossover study [abstract]. Kidney International 1989;35:235. [CRSREF: 2716170]

Witte 2012

[ClinicalTrials.gov: NCT00996229]

Kulzow N, Witte AV, Kerti L, Grittner U, Schuchardt JP, Hahn A, et al. Impact of Omega-3 Fatty Acid Supplementation on Memory Functions in Healthy Older Adults. Journal of Alzheimer's Disease 2016;51(3):713-25.

* Witte AV, Kerti L, Hermannstadter HM, Fiebach JB, Schreiber SJ, Schuchardt JP, et al. Long-chain omega-3 fatty acids improve brain function and structure in older adults. Cerebral Cortex 2014;24(11):3059-68.

Witte V, Kerti L, Floel A. Effects of omega-3 supplementation on brain structure and function in healthy elderly subjects. Alzheimer's and Dementia 2012;1):441.

Wright 2008

Wright SA, O'Prey FM, McHenry MT, Leahey WJ, Devine AB, Duffy EM, Johnston DG, Finch MB, Bell AL, McVeigh GE. A randomised interventional trial of omega-3-polyunsaturated fatty acids on endothelial function and disease activity in systemic lupus erythematosus. Ann Rheum Dis 2008;67:841-8. [DOI: 10.1136/ard.2007.077156]

Zheng 2016

[ISRCTN: NCT01857167]

Li D, Zheng JS, Lin M, Wang L. Change of plasma metabolites in response to omega-3 fatty acids in Chinese patients with type 2 diabetes: A double-blinded randomized controlled trial. FASEB Journal. Conference: Experimental Biology 2015;29(1 Meeting Abstracts).

* Zheng JS, Lin M, Fang L, Yu Y, Yuan L, Jin Y, et al. Effects of n-3 fatty acid supplements on glycemic traits in Chinese type 2 diabetic patients: A double-blind randomized controlled trial. Molecular Nutrition & Food Research 2016;9:9.

Zheng JS, Lin M, Imamura F, Cai W, Wang L, Feng JP, et al. Serum metabolomics profiles in response to n-3 fatty acids in Chinese patients with type 2 diabetes: a double-blind randomised controlled trial. Scientific Reports 2016;6:29522.

Appendix 8. Characteristics of ongoing studies

This chapter has been omitted from this version of the report.

Appendix 9. Other references

Abdelhamid 2016

Abdelhamid A, Martin N, Bridges C, Song F, Deane KHO, Hooper L. Polyunsaturated fat intake for prevention of cardiovascular disease [Protocol]. Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.: CD012345. DOI: 10.1002/14651858.CD012345.

Al-khudhairy 2015

Al-Khudairy L, Hartley L, Clar C, Flowers N, Hooper L, Rees K. Omega 6 fatty acids for the primary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews 2015, Issue 11. Art. No.: CD011094. DOI: 10.1002/14651858.CD011094.pub2.

Anon 2005

Expression of concern. BMJ editors. BMJ 2005;331:266. [DOI: http://dx.doi.org/10.1136/bmj.331.7511.266]

Appel 1993

Appel LJ, Miller ER, Seidler AJ, Whelton PK. Does supplementation of diet with "fish oil" reduce blood pressure? A meta-analysis of controlled clinical trials. Archives of Internal Medicine 1993;153:1429-38.

Ballard-Barbash 1987

Ballard-Barbash R, Callaway CW. Marine fish oils: role in prevention of coronary artery disease. Mayo Clinic Proceedings 1987;62:113-8.

Bang 1972

Bang HO, Dyerberg J. Plasma lipids and lipoproteins in Greenlandic west coast eskimos. Acta Medica Scandinavica 1972;192:85-94.

Bang 1976

Bang HO, Dyerberg J, Hjorne N. The composition of food consumed by Greenland Eskimos. Acta medica Scandinavica 1976;200:69-73.

Berkley 1995

Berkley CS, Hoaglin DC, Mosteller F, Colditz GA. A random-effects regression model for meta-analysis. Statistics in Medicine 1995;14:395-411.

Bhatnagar 2003

Bhatnagar D, Durrington PN. Omega-3 fatty acids: their role in the prevention and treatment of atherosclerosis related risk factors and complications. International Journal of Clinical Practice 2003;57(4):305-14.

BNF 1999

British Nutrition Foundation. n-3 fatty acids and health: briefing paper. London: British Nutrition Foundation, 1999.

Bucher 2002

Bucher HC, Hengstler P, Schindler C, Meier G. N-3 polyunsaturated fatty adcids in coronary heart disease: a meta-analysis of randomized controlled trials. American Journal of Medicine 2002;112:298-304.

Burr 1993

Burr ML. Fish and ischaemic heart disease. Simopoulos AP (ed.): Nutrition in Health and Disease. World review of Nutrition and Dietetics 1993;72:49-60.

Calabresi 2004

Calabresi L, Villa B, Canavesi M, Sirtori CR, James RW, Bernini F et al. An omega-3 polyunsaturated fatty acid concentrate increases plasma high-density lipoprotein 2 cholesterol and paraoxonase levels in patients with familial combined hyperlipidemia. Metabolism 2004;53(2):153-8.

Chalmers 1990

Chalmers I, Adams M, Dickersin K et al. A cohort study of summary reports of controlled trials. JAMA 1990;263:1401-5.

Cordier 1998

Cordier S, Grasmick C, Paquier-Passelaigue M, Mandereau L, Weber J-P, Jouan M. Mercury exposure in French Guiana: levels and determinants. Archives of Environmental Health 1998;53(4):299-304.

De Backer 2003

De Backer G, Ambrosioni E, Borch-Johnson K, Brotons C, Cifkova R, Dallongeville J et al. European guidelines on cardiovascular disease prevention in clinical practice: third joint task force of European and other societies on cardiovascular disease prevention in clinical practice. European Journal of Cardiovascular Prevention and Rehabilitation 2003;10:S1-S78.

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple graphical test. BMJ 1997;315:629-34.

Falk 1999

Falk C, Hanrahan L, Anderson HA, Kanarek MS, Draheim L, Needham L et al. Body burden levels of dioxin, furans, and PCBs among frequent consumers of Great Lakes sport fish. Environmental Research, Section A 1999;80:S19-S25.

Finnegan 2003

Finnegan YE, Minihane AM, Leigh-Firbank EC, Kew S, Meijer GW, Muggli R et al. Plant- and marine-derived n-3 polyunsaturated fatty acids have differential effects on fasting and postprandial blood lipid concentrations and on the susceptibility of LDL to oxidative modification in moderately hyperlipidemic subjects. American Journal of Clincial Nutrition 2003;77:783-95.

FISH - Browning 2012

Published data only (unpublished sought but not used) [ISRCTN: SRCTN48398526]

Browning LM, Walker CG, Mander AP, West AL, Madden J, Gambell JM, et al. Incorporation of eicosapentaenoic and docosahexaenoic acids into lipid pools when given as supplements providing doses equivalent to typical intakes of oily fish. The American journal of clinical nutrition 2012;96(4):748-58. [PubMed: 22932281]

Walker CG, Browning LM, Mander AP, Madden J, West AL, Calder PC, et al. Age and sex differences in the incorporation of EPA and DHA into plasma fractions, cells and adipose tissue in humans. The British journal of nutrition 2014;111(4):679-89. [PubMed: 24063767]

Walker CG, Browning LM, Stecher L, West AL, Madden J, Jebb SA, et al. Fatty acid profile of plasma NEFA does not reflect adipose tissue fatty acid profile. The British journal of nutrition 2015;114(5):756-62. [PubMed: 26205910]

Walker CG, West AL, Browning LM, Madden J, Gambell JM, Jebb SA, et al. The Pattern of Fatty Acids Displaced by EPA and DHA Following 12 Months Supplementation Varies between Blood Cell and Plasma Fractions. Nutrients 2015;7(8):6281-93. [PubMed: 26247960]

Fitzgerald 1999

Fitzgerald EF, Deres DA, Hwang S-A, Bush B, Yang B-z, Tarbell A et al. Local fish consumption and serum PCB concentrations among Mohawk men at Akwesasne. Environmental Research: Section A 1999;80:S97-S103.

FSA 2000

Food Standards Agency UK. Dioxins and PCBs in the UK diet: 1997 Total diet study samples. Food Surveillance Information Sheet 2000;4/00. [Other: FSIS 4/00]

FSA 2002

Food Standards Agency UK. Dioxins and dioxin-like pcbs in fish oil supplements. Food Survey Information Sheet 2002;26/02.

FSA 2003

Food Standards Agency UK. Dioxins and dioxin-like PCBs in the UK diet: 2001 total diet study samples. Food Survey Information Sheet 2003;38:3.

Gapinski 1993

Gapinski JP, VanRuiswyk JV, Heudebert GR, Schectman GS. Preventing restenosis with fish oils following coronary angioplasty: a meta-analysis. Archives of Internal Medicine 1993;153:1595-601.

Geelen 2004

Geelen A, Brouwer IA, Zock PL, Katan MB. Antiarrhythmic effects of n-3 fatty acids: evidence from human studies. Current Opinion in Lipidology 2004;15:25-30.

GRADE Working Group 2004

GRADE Working Group. Grading quality of evidence and strength of recommendations. British Medical Journal 2004;328(7454):1490.

Hauck 1991

Hauck WW, Gilliss CL, Donner A, Gortner S. Randomisation by Cluster. Nursing Research 1991;40(6):356-8.

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.

Higgins 2011

Higgins JPT, Altman DG, Sterne JAC on behalf of the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT,Green S, editor(s). Cochrane handbook for systematic reviews of interventions Version 5.1.0 [updated March 2011]. Available from www.handbook.cochrane.org: The Cochrane Collaboration, 2011.

Hilbert 1998

Hilbert G, Lillemark L, Balchen S, Hojskov CS. Reduction of organochlorine contaminants from fish oil during refining. Chemosphere 1998;37(7):1241-52.

Hites 2004

Hites RA, Foran JA, Carpenter DO, Hamilton MC, Knuth BA, Schwager SJ. Global assessment of organic contaminants in farmed salmon. Science 2004;303:226-9.

Horton 2005

Horton R. Expression of concern: Indo-Mediterranean Diet Heart Study. The Lancet 2005;366(9483):354-356. [DOI: http://doi.org/10.1016/S0140-6736(05)67006-7]

Hovinga 1993

Hovinga ME, Sowers M, Humphrey HEB. Environmental exposure and lifestyle predictors of lead, cadmium, PCB and DDT levels in Great Lakes fish eaters. Archives of Environmental Health 1993;48(2):98-104.

Informed Health 2004

Informed Health Online. Our Dictionary of Research Terms for Consumers. www.informedhealthonline.org (Accessed July 2004).

Jacobs 1998

Jacobs MN, Santillo D, Johnston PA, Wyatt CL, French MC. Organochlorine residues in fish oil dietary supplements: comparison with industrial grade oils. Chemosphere 1998;37(9-12):1709-21.

JECFA 2001

Joint FAO/WHO Expert Committee on Food Additives. Summary of the fifty-seventh meeting of JEFCA. World Health Organization website 2001;Annex 4.

Kang 1996

Kang JX, Leaf A. Antiarrhythmic effects of polyunsaturated fatty acids: recent studies. Circulation 1996;94(7):1774-80.

Knapp 1989

Knapp HR. Omega-3 fatty acids, endogenous prostaglandins and blood pressure regulation in humans. Nutrition Reviews 1989;47(10):301-13.

Kris-Etherton 2002

Kris-Etherton PM, Harris WS, Appel LJ for the Nutrition Committee of the American Heart Association. Fish consumption, fish oil, omega 3 fatty acids, and cardiovascular disease. Circulation 2002;106:2747-57.

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J.. Chapter 6: Searching for studies. In: Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 (updated March 2011) edition. Available from www.cochrane-handbook.org: The Cochrane Collaboration, 2011.

Li 1999

Li D, Sinclair A, Wilson A, Nakkote S, Kelly F, Abedin L et al. Effect of dietary alpha-linolenic acid on thrombotic risk factors in vegetarian men. American Journal of Clinical Nutrition 1999;69:872-82.

Liem 1997

Liem AKD, Theelen RMC. Dioxins: chemical analysis, exposure and risk assessment. first edition. Utrecht: Universiteit Utrecht, 1997. [Other: ISBN 90 393 2012 8]

MAFF 1997

MAFF UK. Dioxins and polychlorinated bephenyls in fish oil dietary supplements and licensed medicines. Food Surveillance Information Sheet 1997;(106).

MAFF 1998A

MAFF UK. Concentrations of metals and other elements in marine fish and shellfish. Food Surveillance Information Sheet 1998;(151). [Other: FSIS 151]

MAFF 1998B

MAFF UK. Dioxins and PCBs in farmed trout in England and Wales. Food Surveillance Information Sheet 1998;145.

MAFF 1999

MAFF UK. Dioxins and PCBs in UK and imported marine fish. Food Surveillance Information Sheet 1999;184.

Mahaffey 1998

Mahaffey KR, Mergler D. Blood levels of total and organic mercury in residents of the upper St. Lawrence river basin, Quebec: association with age, gender, and fish consumption. Environmental Research: Section A 1998;77:104-14.

Marchioli 2004

Marchioli R. Update on the GISSI trial. Oral presentation at the ISSFAL conference, June 2004, Brighton UK.

Maurice-Bourgoin 00

Maurice-Bourgoin L, Quiroga I, Chincheros J, Courau P. Mercury distribution in waters and fishes of the upper Madeira rivers and mercury exposure in riparian Amazonian populations. Science of the Total Environment 2000;260:73-86.

Morris 1993

Morris MC, Sacks F, Rosner B. Does fish oil lower blood pressure? A meta-analysis of controlled trials. Circulation 1993;88:523-33.

Nettleton 1991

Nettleton JA. Omega-3 fatty acids: comparison of plant and seafood sources in human nutrition. Journal of the American Dietetic Association 1991;91:331-7.

O'Connor 1992

O'Connor GT, Malenka DJ, Olmstead EM, Johnson PS, Hennekens CH. A meta-analysis of randomised trials of fish oil in prevention of restenosis following coronary angioplasty. American Journal of Preventive Medicine 1992;8:186-92.

Pawlosky 2001

Pawlosky RJ, Hibbeln JR, Novotny JA, Salem N Jr. Physiological compartmental analysis of alpha-linolenic acid metabolism in adult humans. Journal of Lipid Research 2001;42:1257-65.

Peterson 1994

Peterson DE, Kanarek MS, Kuykendall MA, Diedrich JM, Anderson HA, Remington PL. Fish consumption patterns and blood mercury levels in Wisconsin Chippewa Indians. Archives of Environmental Health 1994;49(1):53-8.

Radack 1989

Radack K, Deck C. The effects of omega-3 polyunsaturated fatty acids on blood pressure: a methodologic analysis of the evidence. Journal of the American College of Nutrition 1989;8(5):376-85.

Retraction 2004

Singh RB. Retraction. British Medical Journal In press.

Salonen 1995

Salonen JT, Seppanen K, Nyyssonen K, Korpela H, Kauhanen J, Kantola M et al. Intake of mercury from fish, lipid peroxidation, and the risk of myocardial infarction and coronary, cardiovascular, and any death in eastern Finnish men. Circulation 1995;91:645-55.

Sharp 1998

Sharp S. Meta-analysis regression. Stata Technical Bulletin 1998;42:16-22.

SIGN 2002

Scottish Intercollegiate Guidelines Network. Cardiac rehabilitation: a national clinical guideline. Edinburgh: SIGN, 2002.

Simopoulos 1992

Simopoulos AP, Norman HA, Gillaspy JE, Duke JA. Common purslane: a source of omega-3 fatty acids and antioxidants. Journal of the American College of Nutrition 1992;11(4):374-82.

USFDA 1995

US FDA. Mercury in fish: cause for concern? FDA Consumer, web site www.fda.gov 1995;(May). [Other: September 1994, revised May 1995]

USFDA 2000

U.S. Food and Drug Administration. Letter regarding dietary supplement health claim for omega-3 fatty acids and coronary heart disease. US FDA web site, www.fda.gov 2000;Docket No. 91N-0103.

White 2005

White C. Suspected research fraud: difficulties of getting at the truth. BMJ 2005;331(7511):281-8. [DOI: 10.1136/bmj.331.7511.281]

Wood 1998

Wood D, Durrington P, Poulter N, McInnes G, Rees A, Wray R et al. Joint British Recommendations on prevention of coronary heart disease in clinical practice. Heart 1998;80:S1-S29.

Appendix 10. Other published versions of this review

Hooper 2004

Hooper L, Harrison RA, Summerbell CD, Moore H, Worthington HV, Ness A, Capps N, Davey Smith G, Riemersma R,Ebrahim S. Omega 3 fatty acids for prevention and treatment of cardiovascular disease. Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No.: CD003177. DOI: 10.1002/14651858.CD003177.pub2.