



**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]

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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**

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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 $\Omega 3$ 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/ictcp/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 participate 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 given 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).

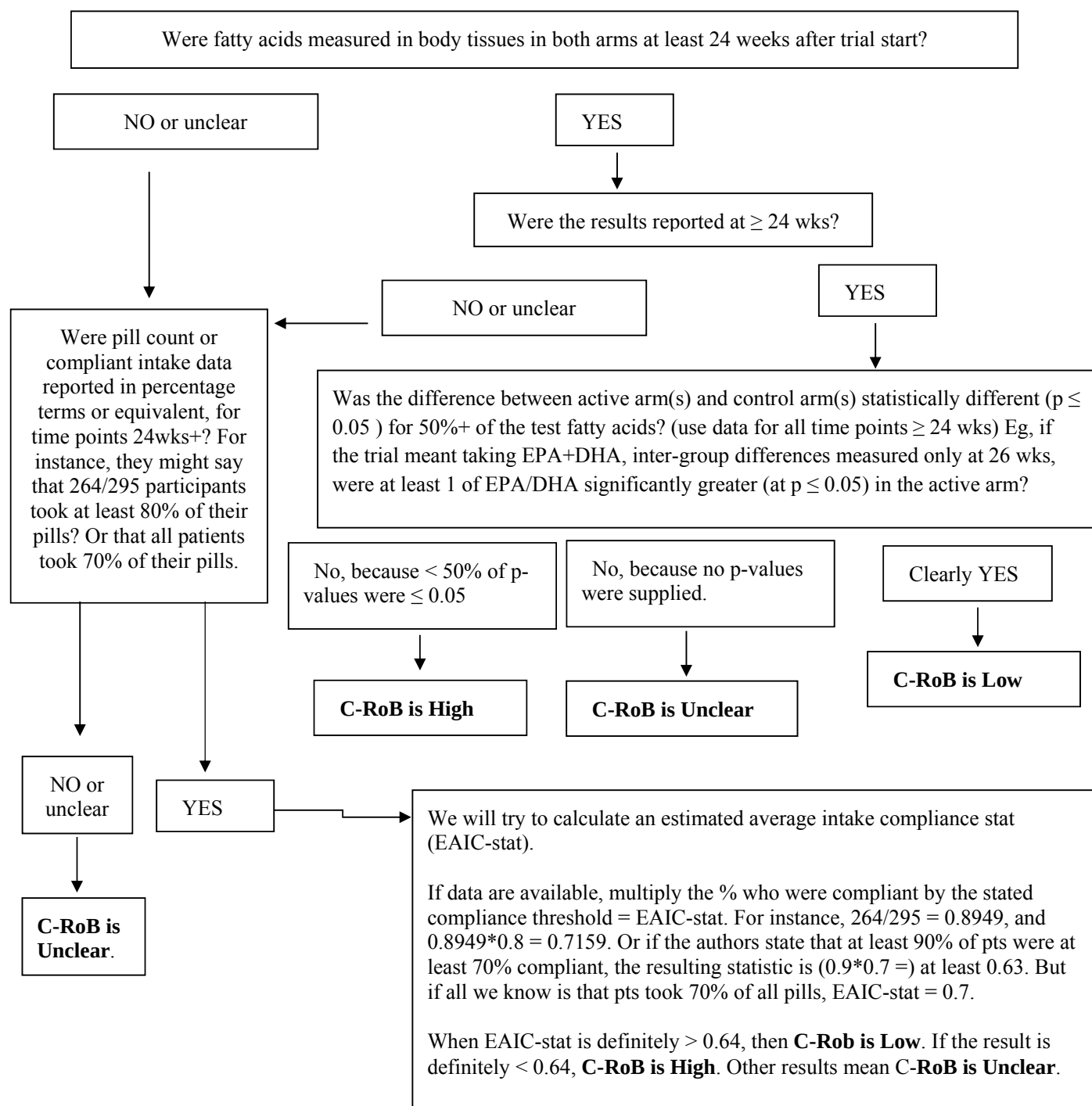


Figure 2.1. Schema for use in assessing compliance (part of risk of bias).

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 $\leq 150\text{mg/d}$, >150 to 250mg/d , >250 to 400mg/d , >400 to 2400mg/d , >2.4 to 4.4g/d , $>4.4\text{g/d}$, ALA low $<5\text{g/d}$, ALA high $\geq 5\text{g/d}$, unknown dose)
4. By baseline intake of long chain omega 3,
 - o Low intake: $<100\text{mg/d}$ EPA+DHA or $<1100\text{mg/d}$ total n3 or $<0.5\%$ E from total n3 or $<50\text{mg/d}$ DHA or $<50\text{mg/d}$ EPA or $\leq 1\text{g/d}$ ALA
 - o Moderate intake: $100\text{--}250\text{mg/d}$ EPA+DHA or $1100\text{--}2250\text{mg/d}$ total n3 or $0.5\text{--}1.5\%$ E from total n3 or $50\text{--}150\text{mg/d}$ DHA or $50\text{--}150\text{mg/d}$ EPA or $>1\text{--}2\text{g/d}$ ALA
 - o High intake: $>250\text{mg/d}$ EPA+DHA or $>2250\text{mg/d}$ total n3 or $>1.5\%$ E from total n3 or $>150\text{mg/d}$ DHA or $>150\text{mg/d}$ EPA or $>2\text{g/d}$ 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
 - o Short duration: 6 months to <1 year in study
 - o Medium duration: 1 to <2 years in study
 - o Medium-long duration: 2 to <4 years in study
 - o 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)
 - o Completed
- ❖ Omit studies confounded by dietary aims other than those around dietary fat (eg with fruit and veg aims or weight reduction aims)
 - o Completed
- ❖ Assess and analyse by baseline intakes
 - o Baseline intakes have been collated and data extracted, see Appendix 3,
 - o Analysis by baseline intakes has not been possible due to very limited baseline intake data
- ❖ Assess and analyse by foods vs supplements
 - o 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
 - o We have subgrouped primary outcomes by intervention type.
- ❖ Assess and analyse by medication used in control group
 - o Medication use has been data extracted and collated, and collated in the Table of Characteristics in Appendix 2, under Participants.
 - o 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
 - o These inclusion criteria have been used
 - o 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
 - o 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
 - o Funding information has been removed from risk of bias assessment and appears in the table of characteristics instead.
 - o 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
 - o Schema for assessment of compliance has been developed, see methodology section
 - o Body measures of fatty acids are collated in Appendix 5.
 - o 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.

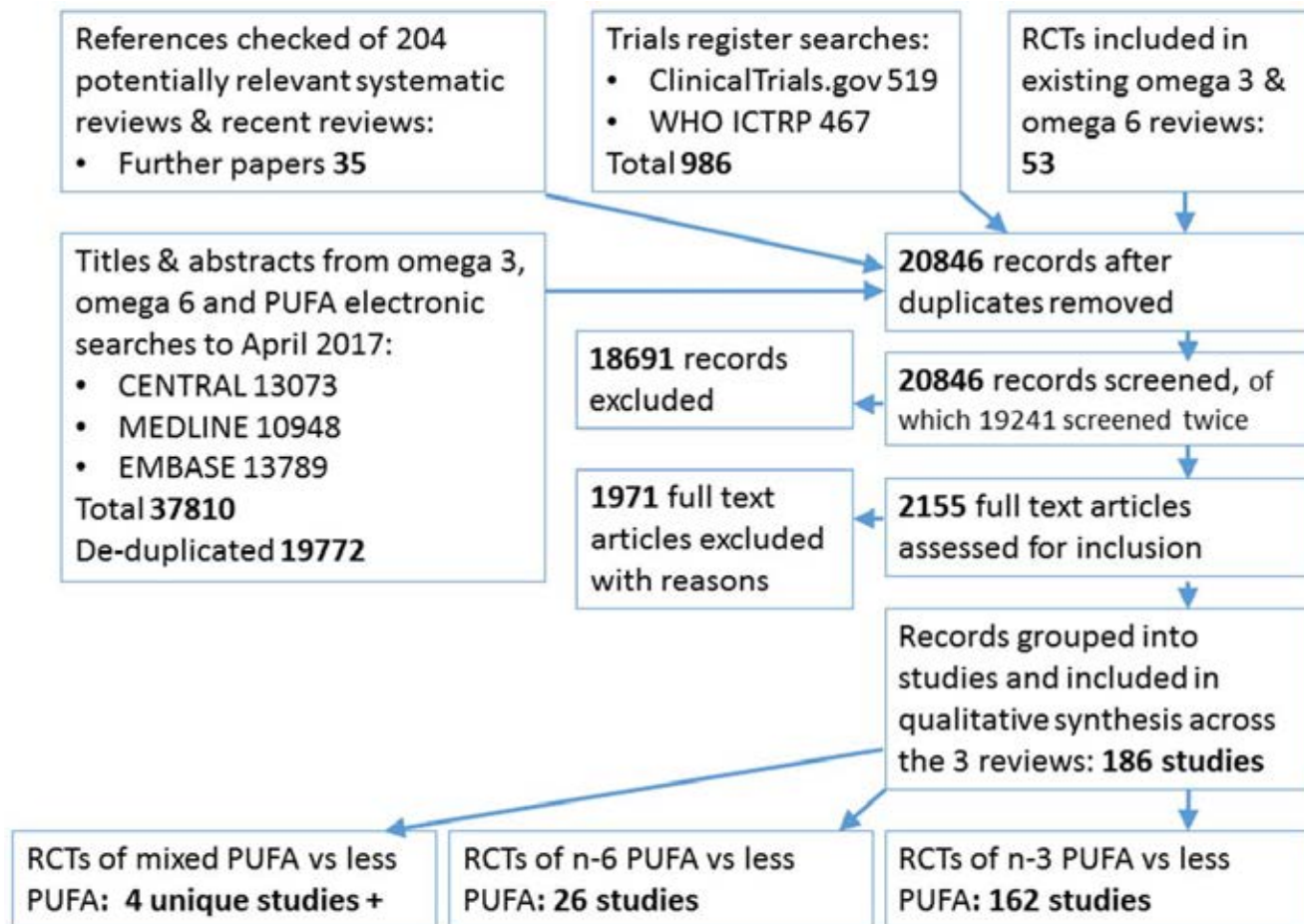


Figure 2.2. Flow diagram for this set of reviews. *Please note that some of the n3 PUFA trials mentioned in this flowchart no longer appear in this version of the report as they relate to outcomes not mentioned here.*

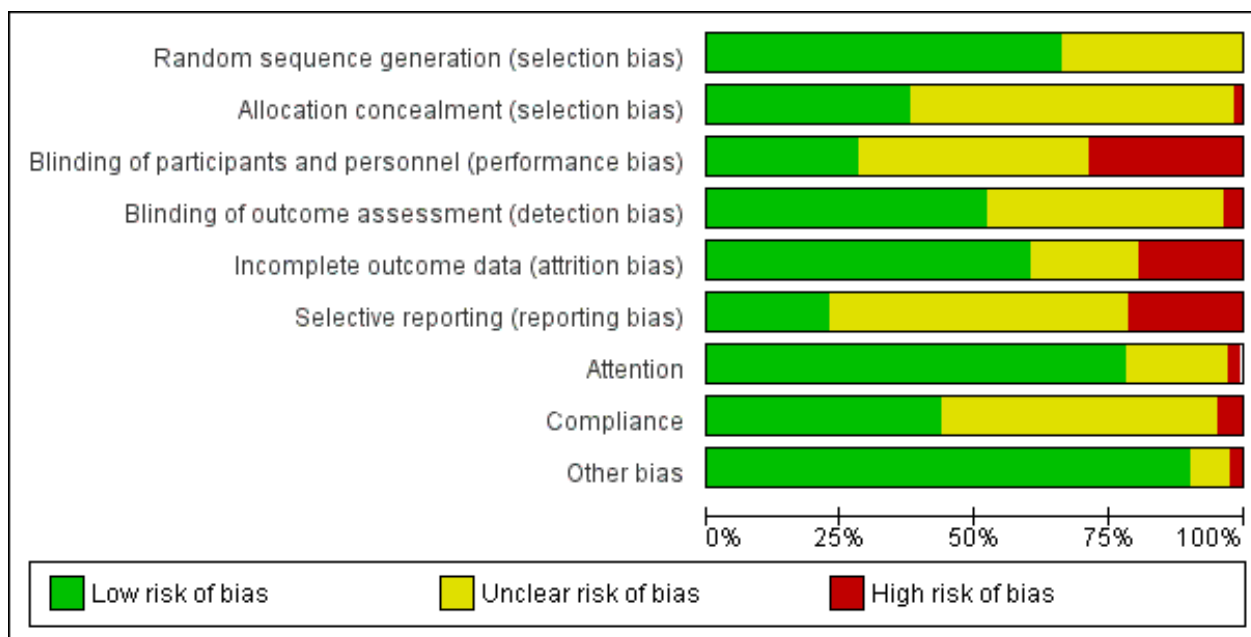


Figure 2.3. Risk of bias summary for all the RCTs in the sets of reviews

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.

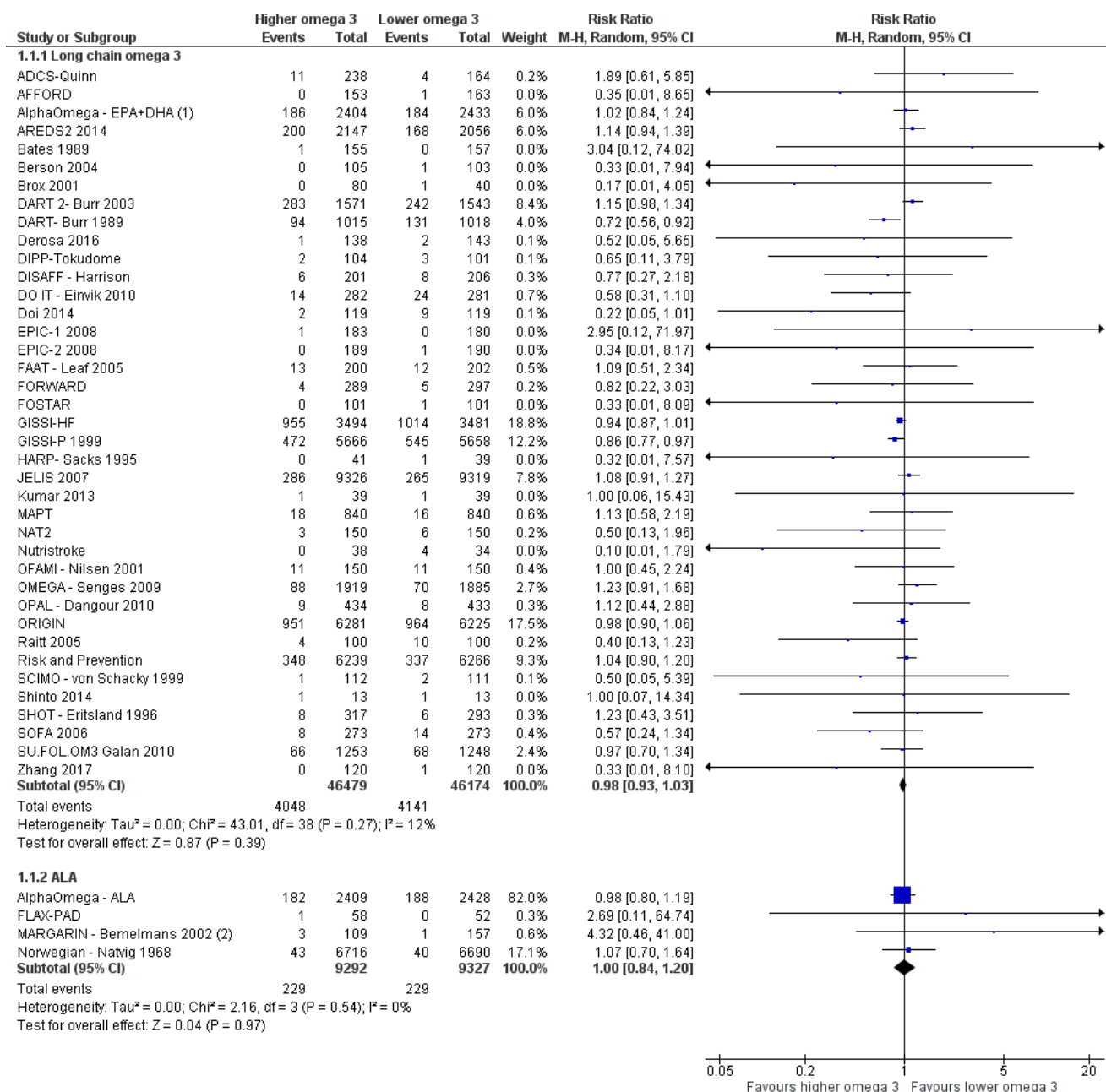


Figure 3.1. Forest plot including all studies with data on mortality from any cause, where at least one death occurred, subgrouped by long-chain omega-3 fats (LCn3, including fish oils, EPA and DHA) and ALA (from plant sources), and including risk of bias assessment.

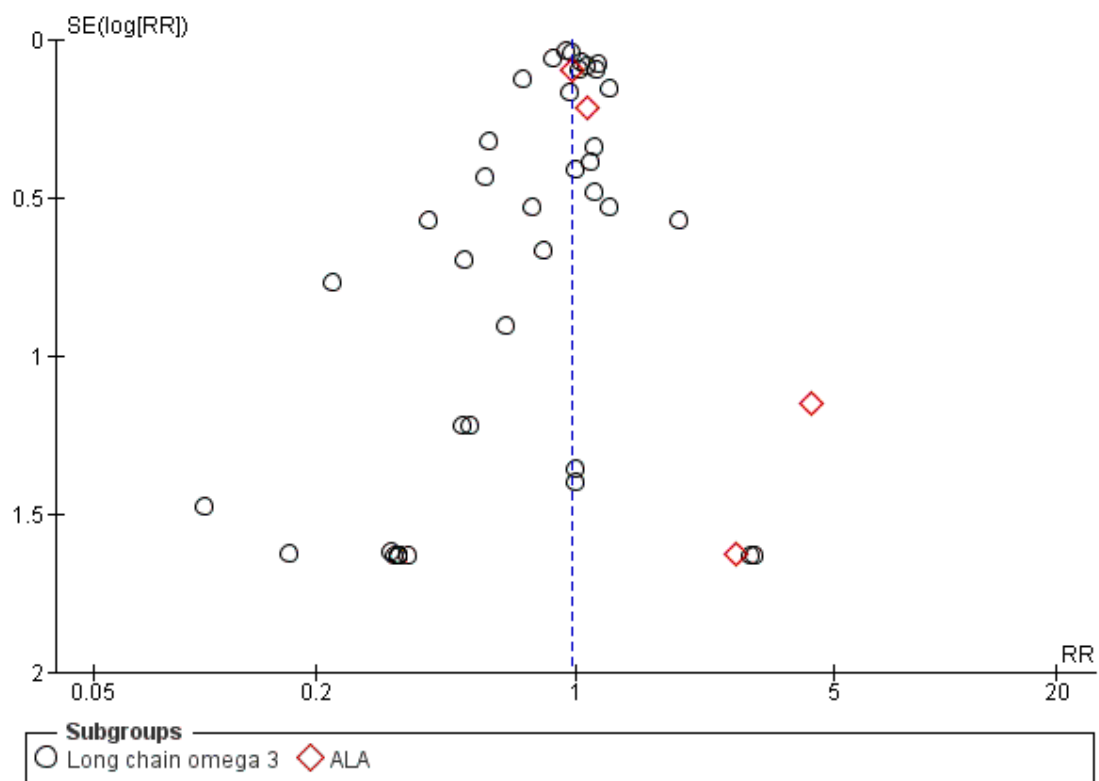


Figure 3.2. Funnel plot of all-cause mortality data.

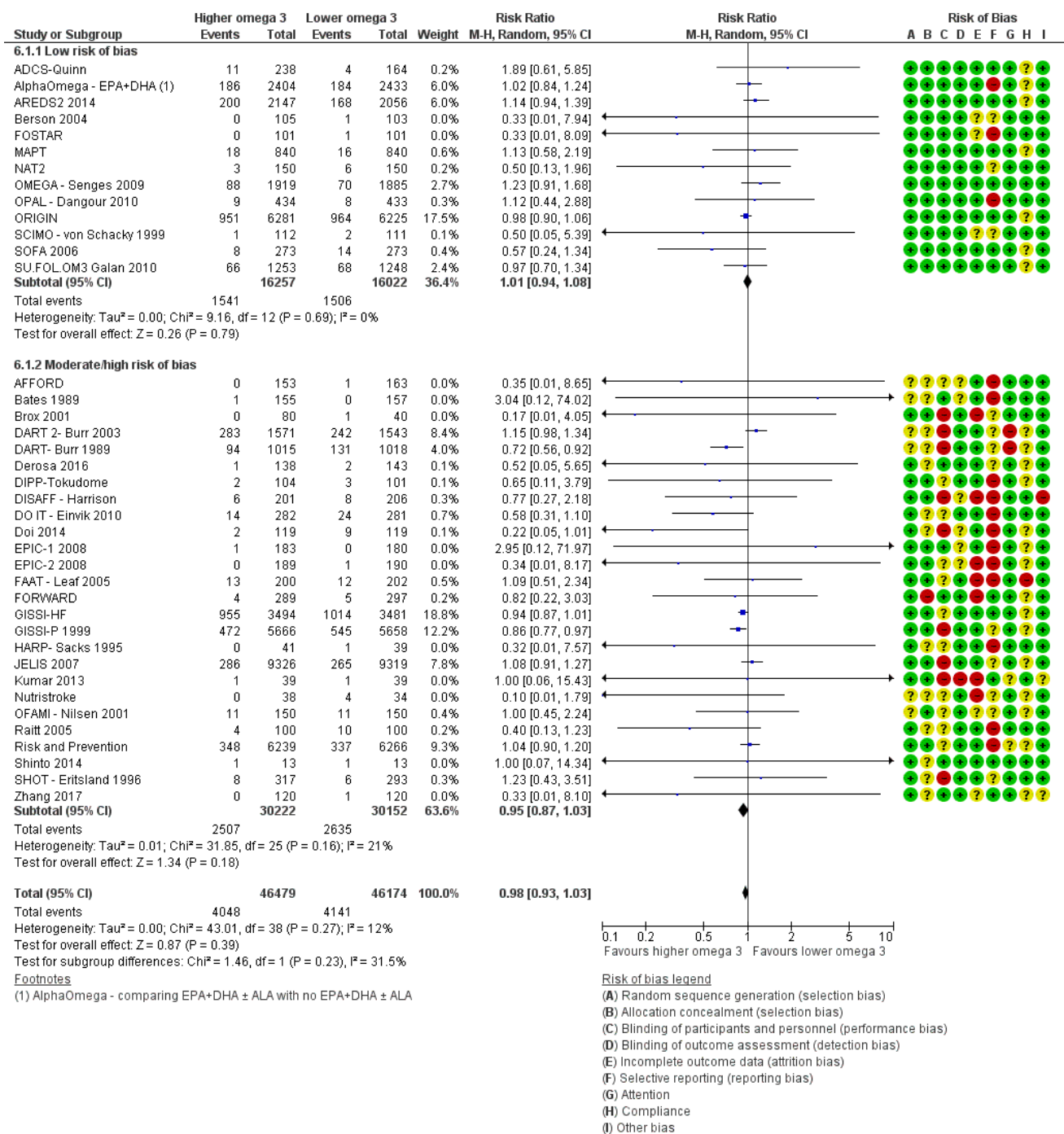
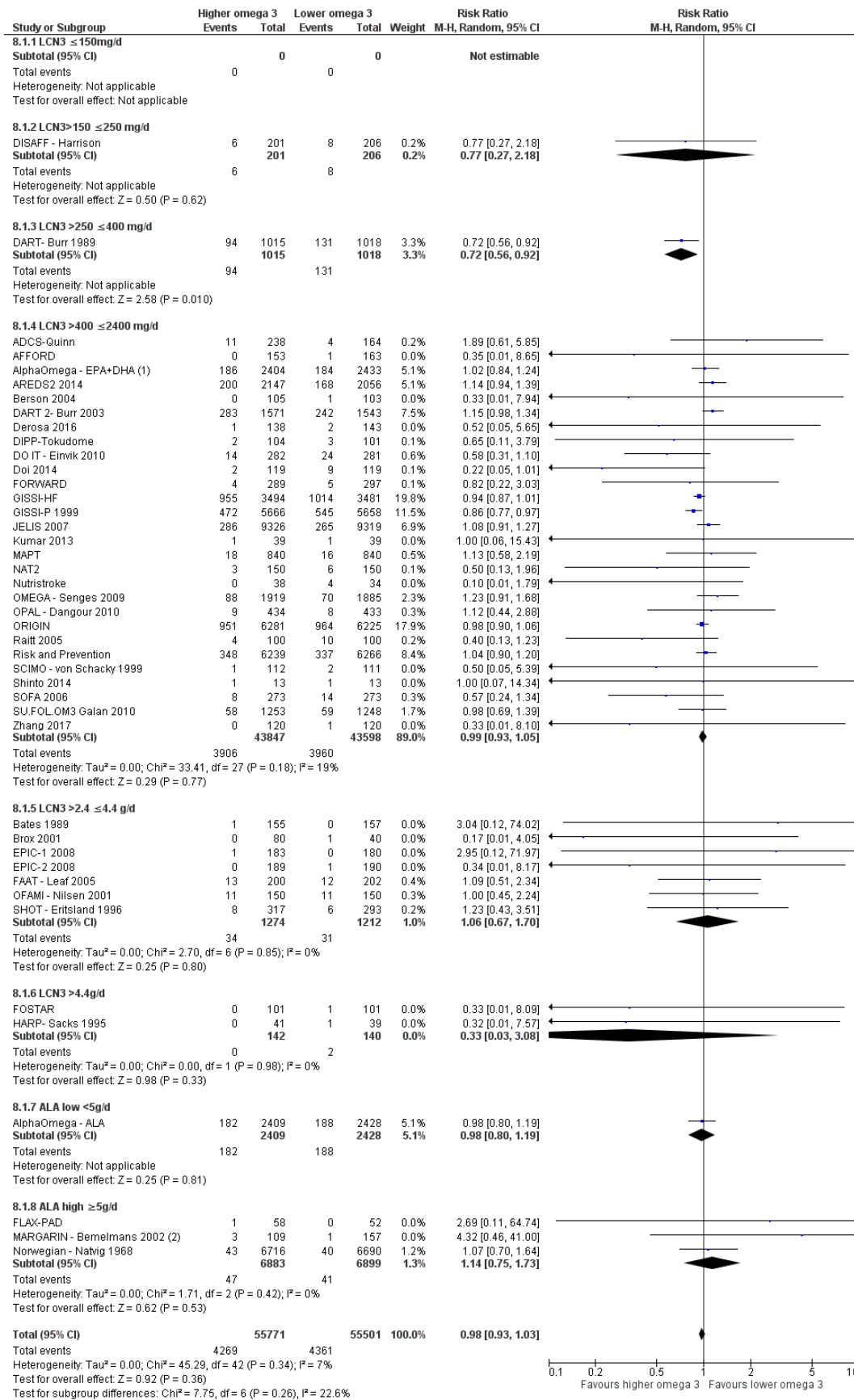


Figure 3.3. Forest plot of all-cause mortality, sensitivity analysis limiting to studies at low summary risk of bias (shown as subgrouped by risk of bias).



Footnotes
(1) AlphaOmega - comparing EPA+DHA ± ALA with no EPA+DHA ± ALA
(2) MARGARIN study - comparing ALA ± EPA+DHA with no ALA ± EPA+DHA

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

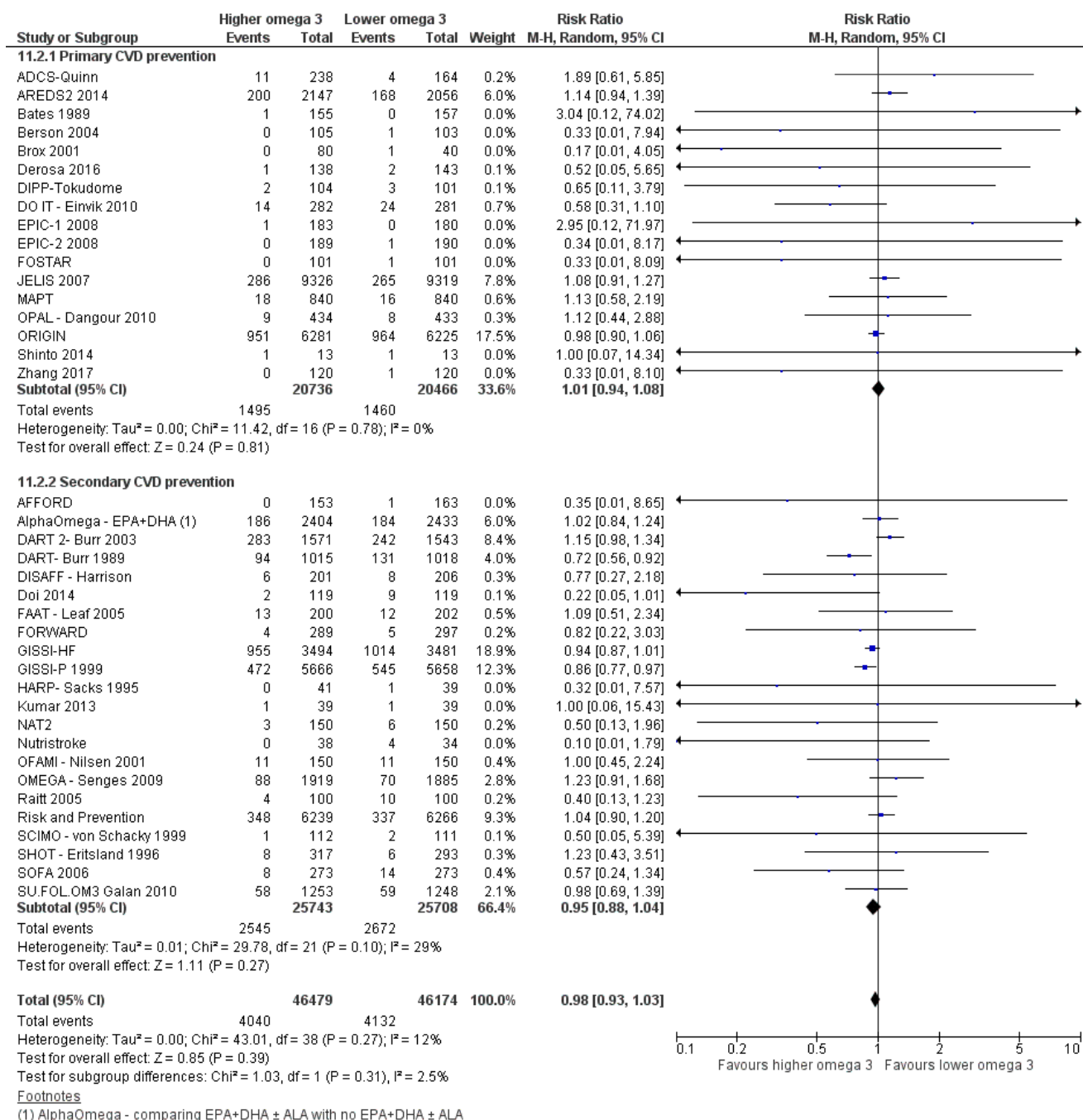


Figure 3.5. Forest plot of all-cause mortality, subgrouped by primary or secondary prevention of CVD.

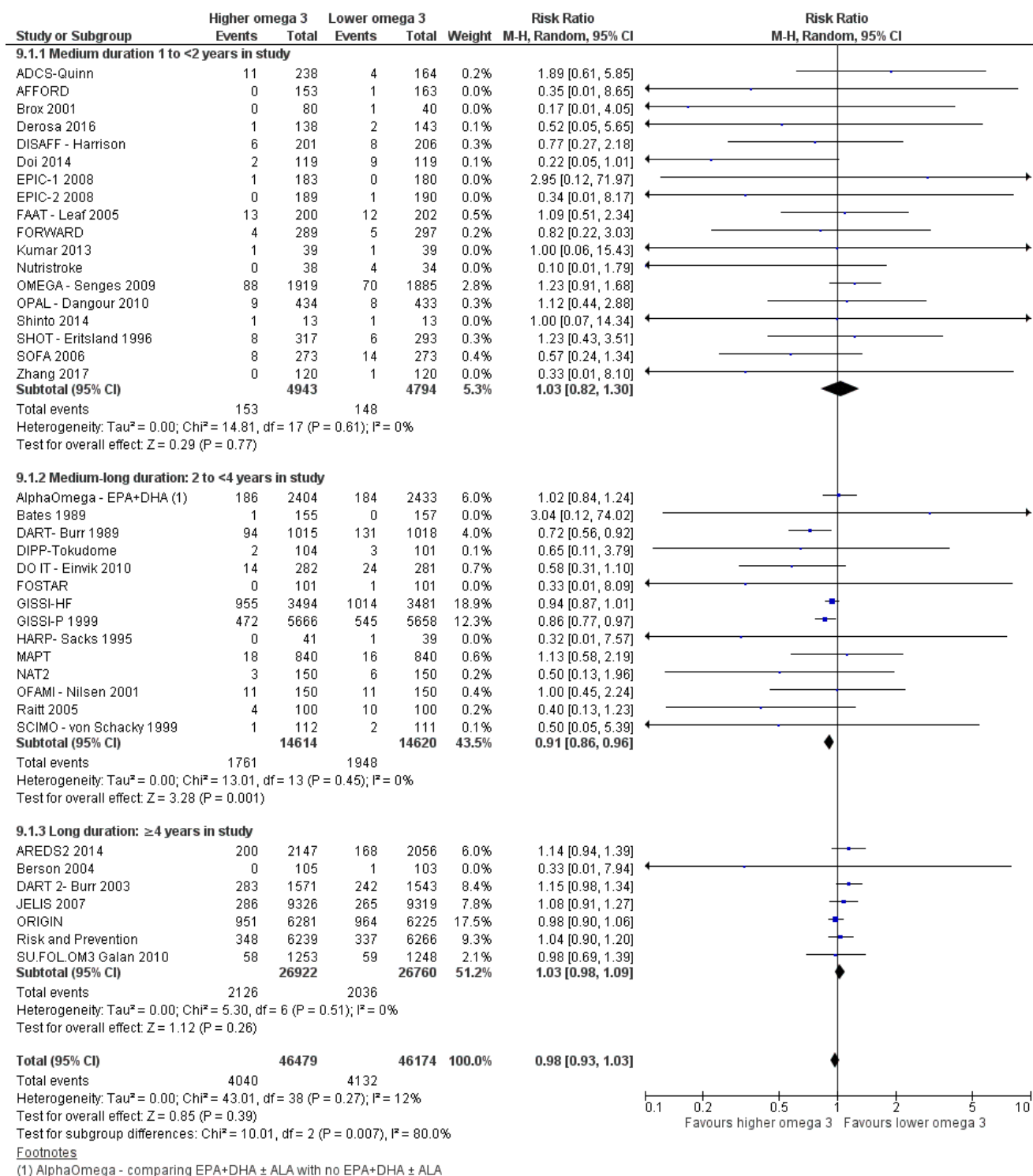


Figure 3.6. Forest plot of all-cause mortality, subgrouped by duration of intake.

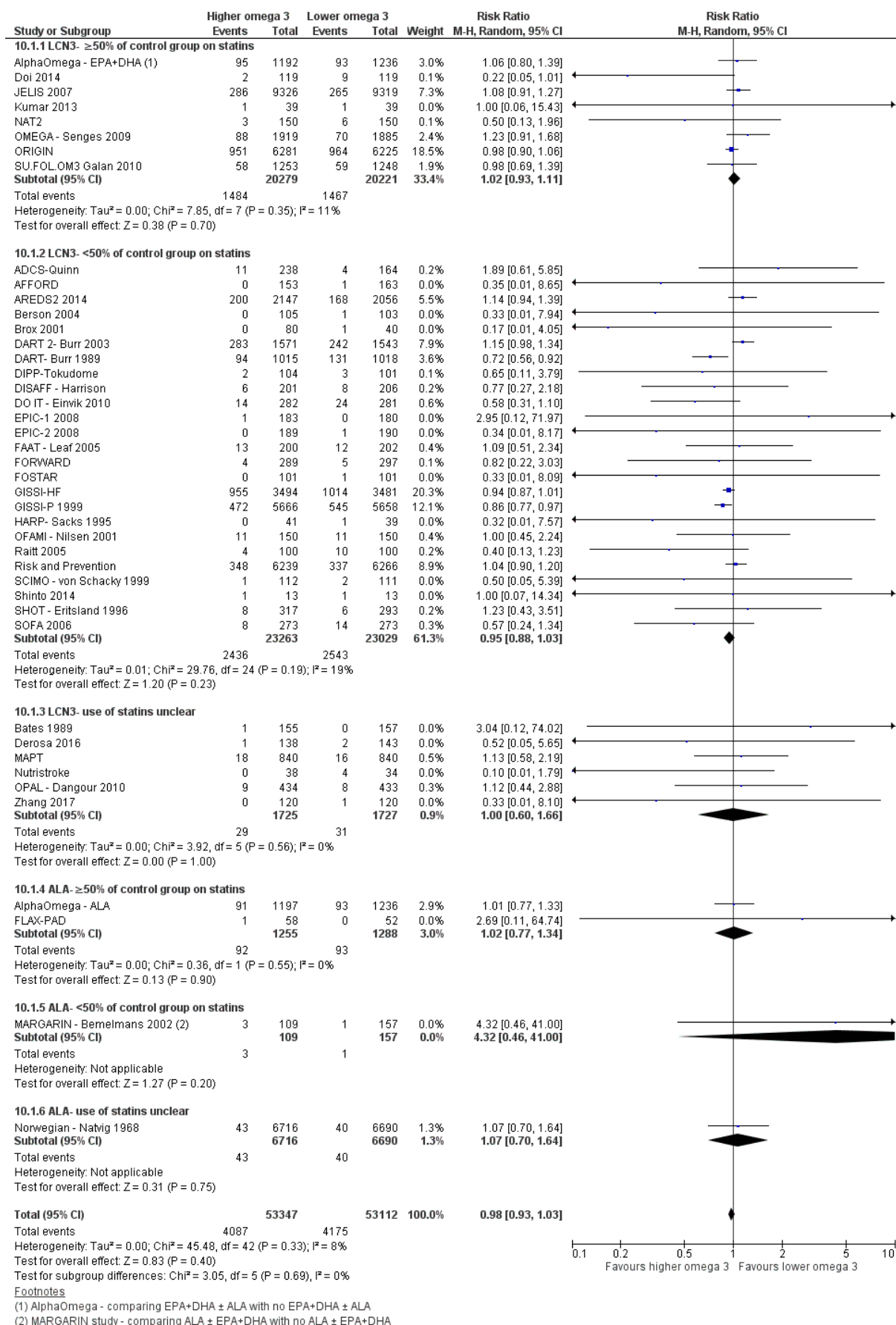


Figure 3.7. Forest plot of all-cause mortality, subgrouped by statin use through the trial

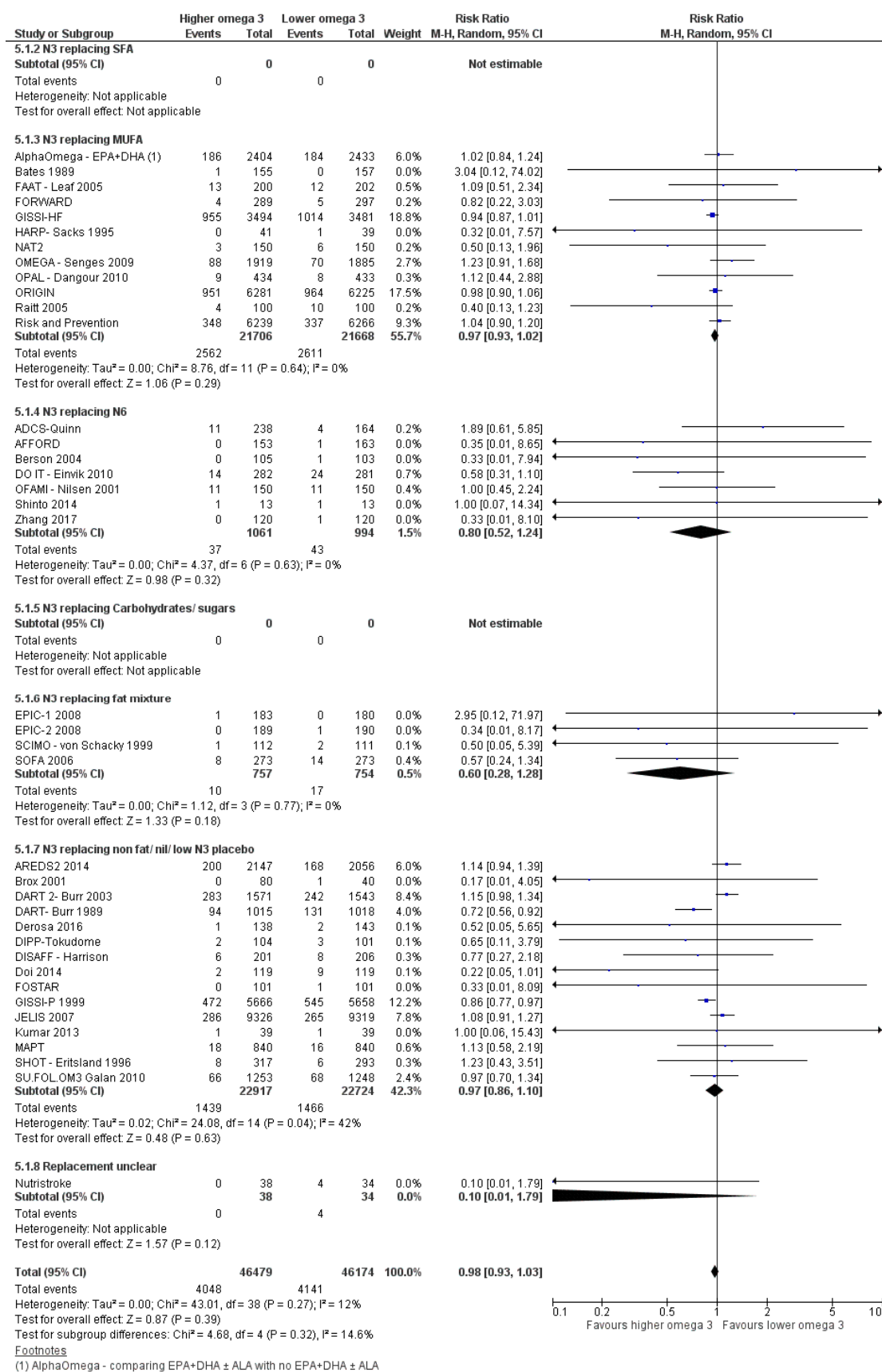


Figure 3.8. Forest plot of all-cause mortality, subgrouped by what omega 3 is replacing

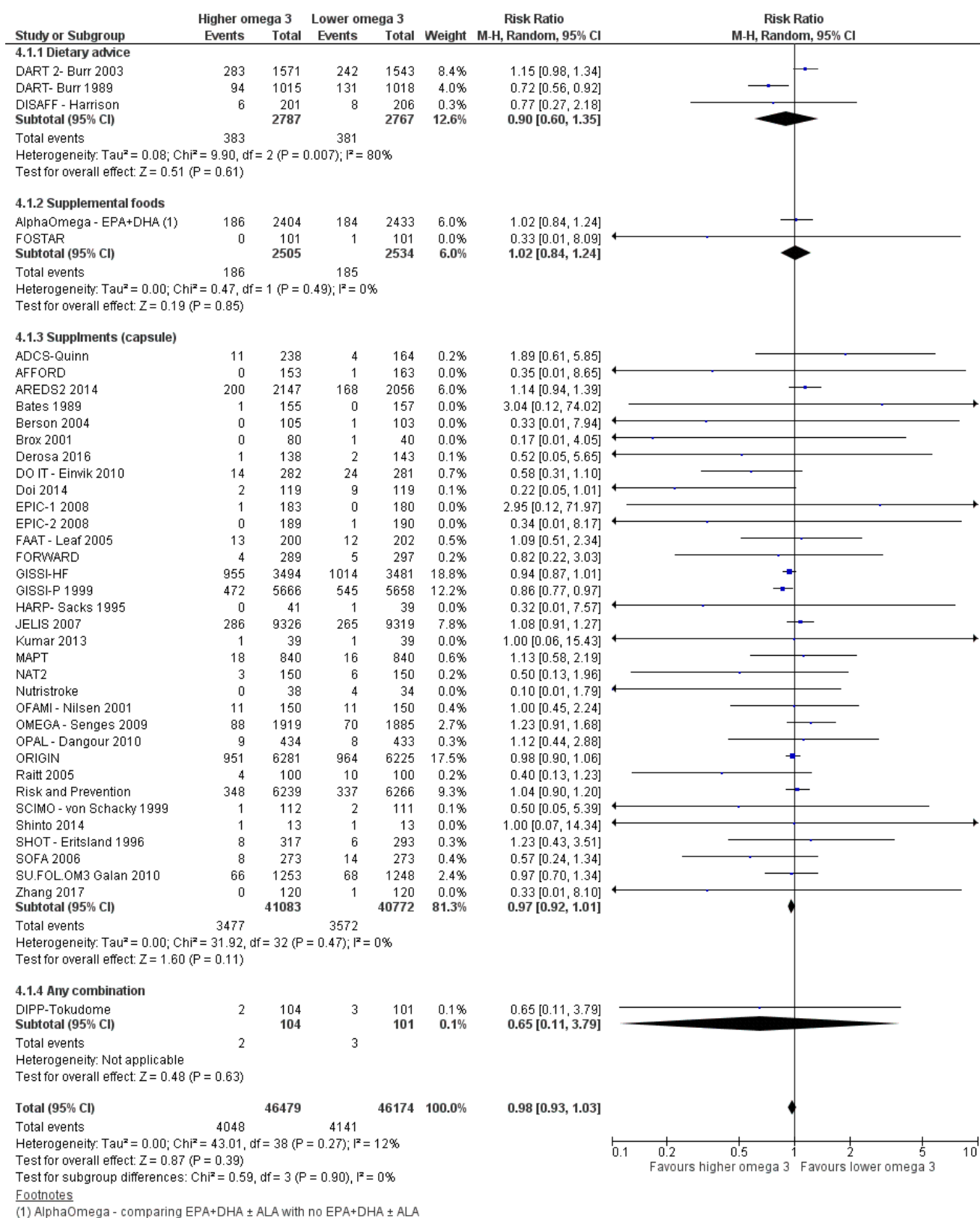


Figure 3.9. Forest plot of all-cause mortality, subgrouped by type of intervention

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.

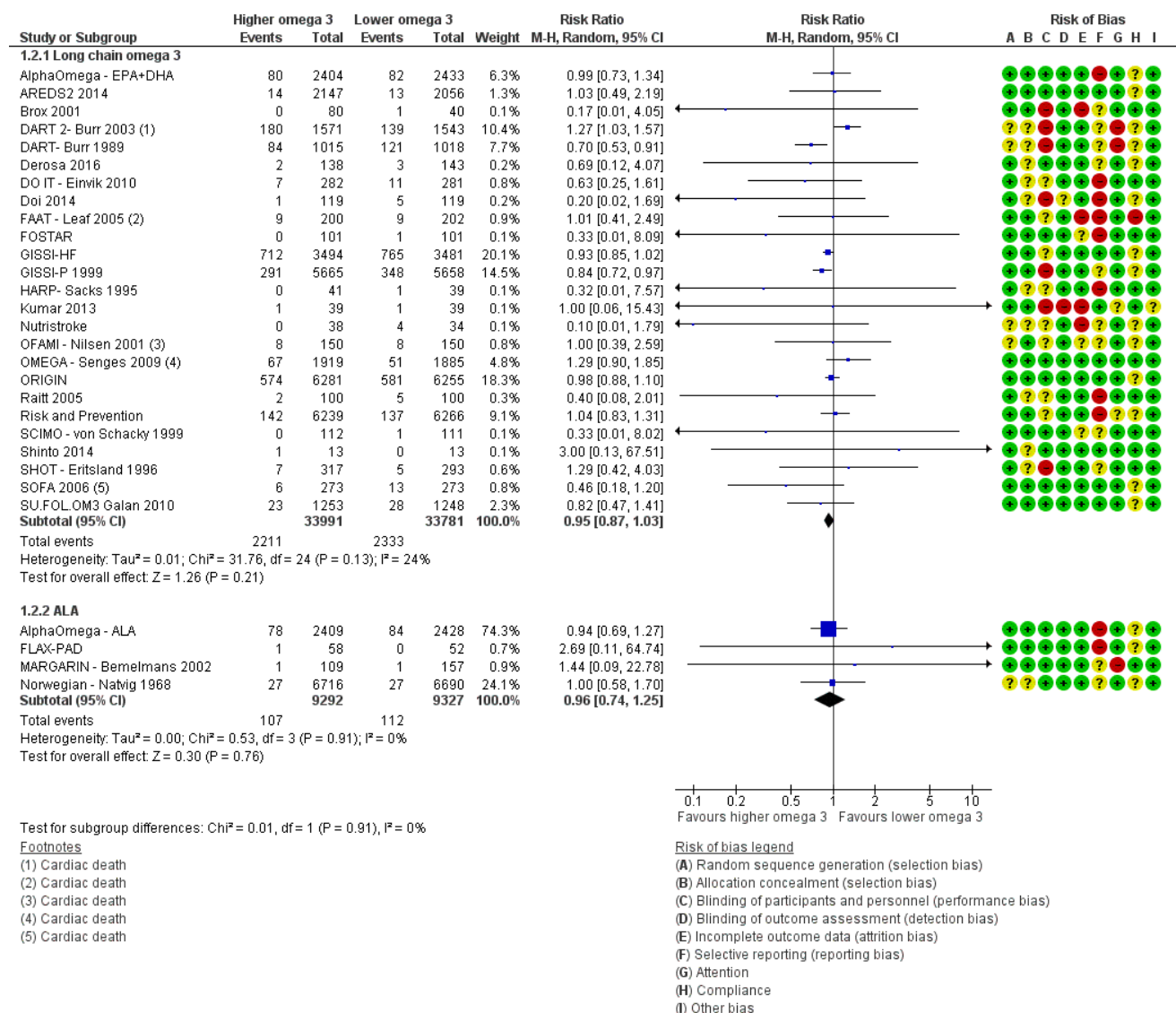


Figure 4.1. Meta-analysis of the effect of omega 3 fats on cardiovascular deaths, subgrouped by LCn3 or ALA intervention.

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.

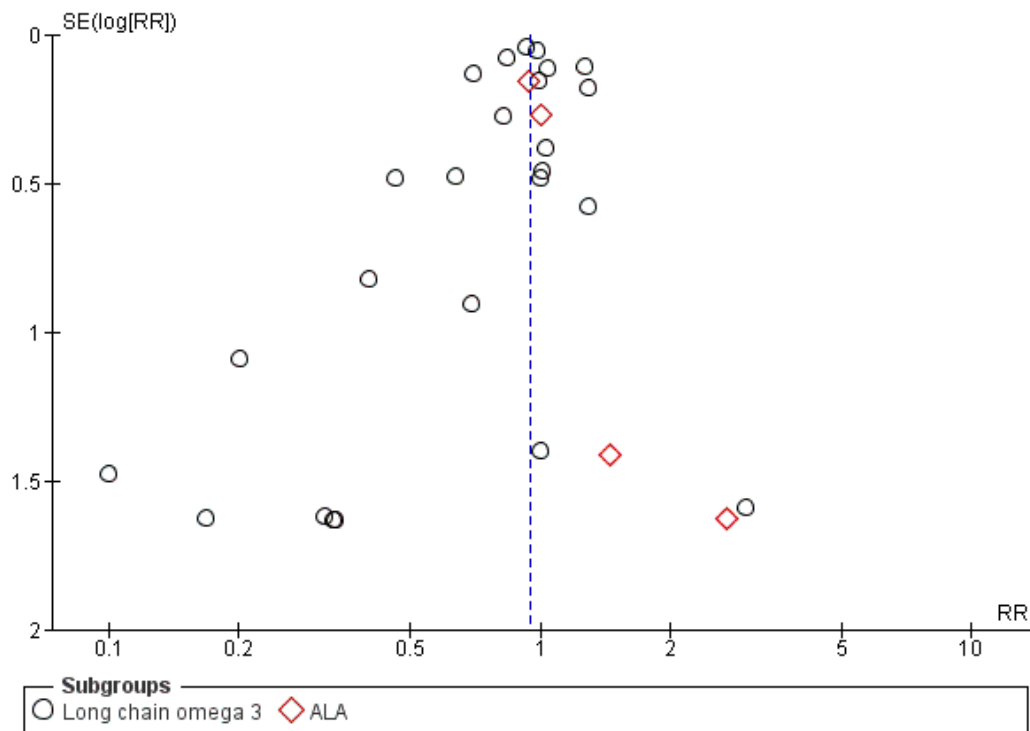


Figure 4.2. Funnel plot of the effect of omega 3 fats on cardiovascular deaths.

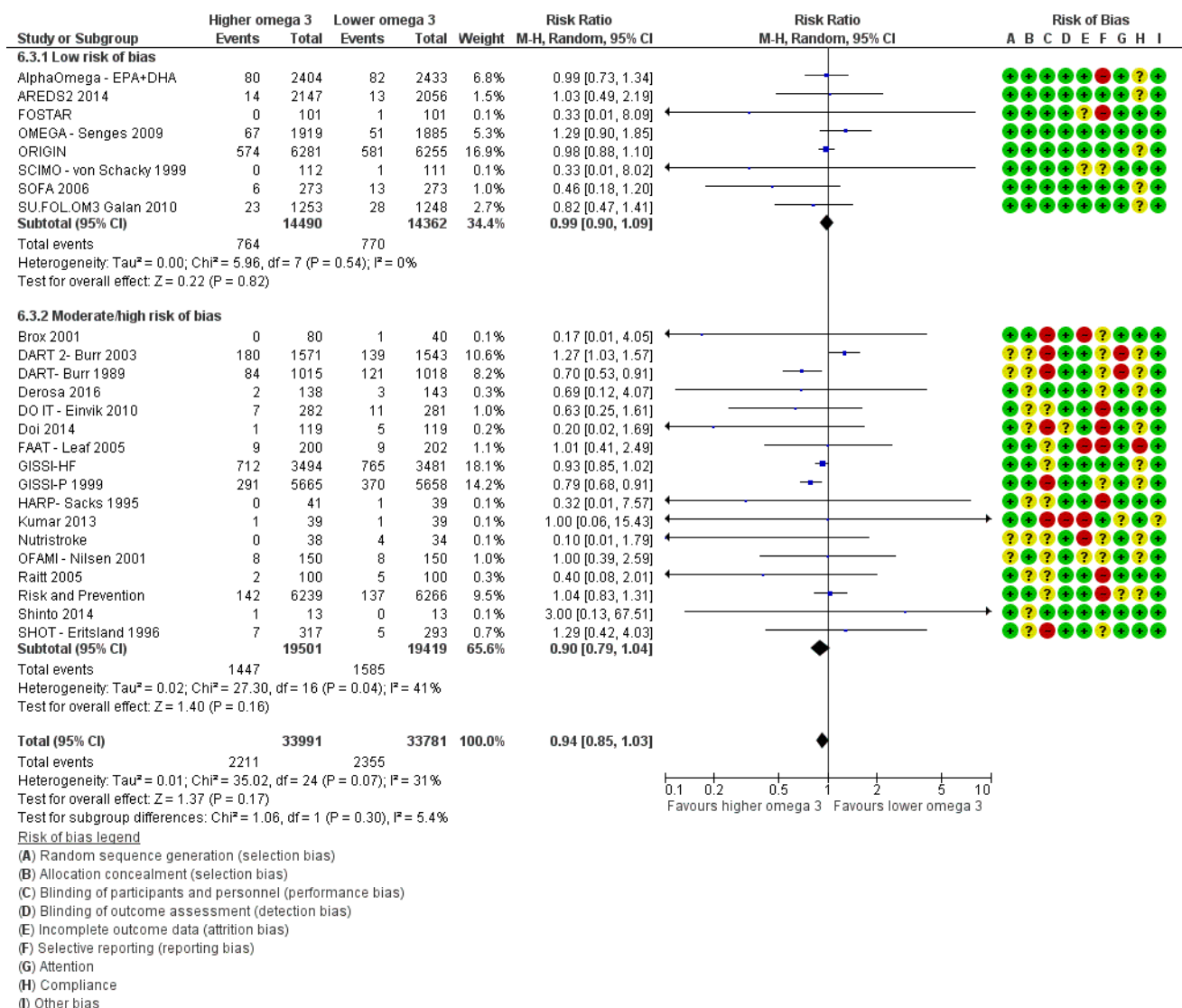


Figure 4.3. Meta-analysis of the effect of LCn3 fats on cardiovascular deaths, sensitivity analysis limiting to studies at low summary risk of bias (shown as subgrouped by risk of bias).

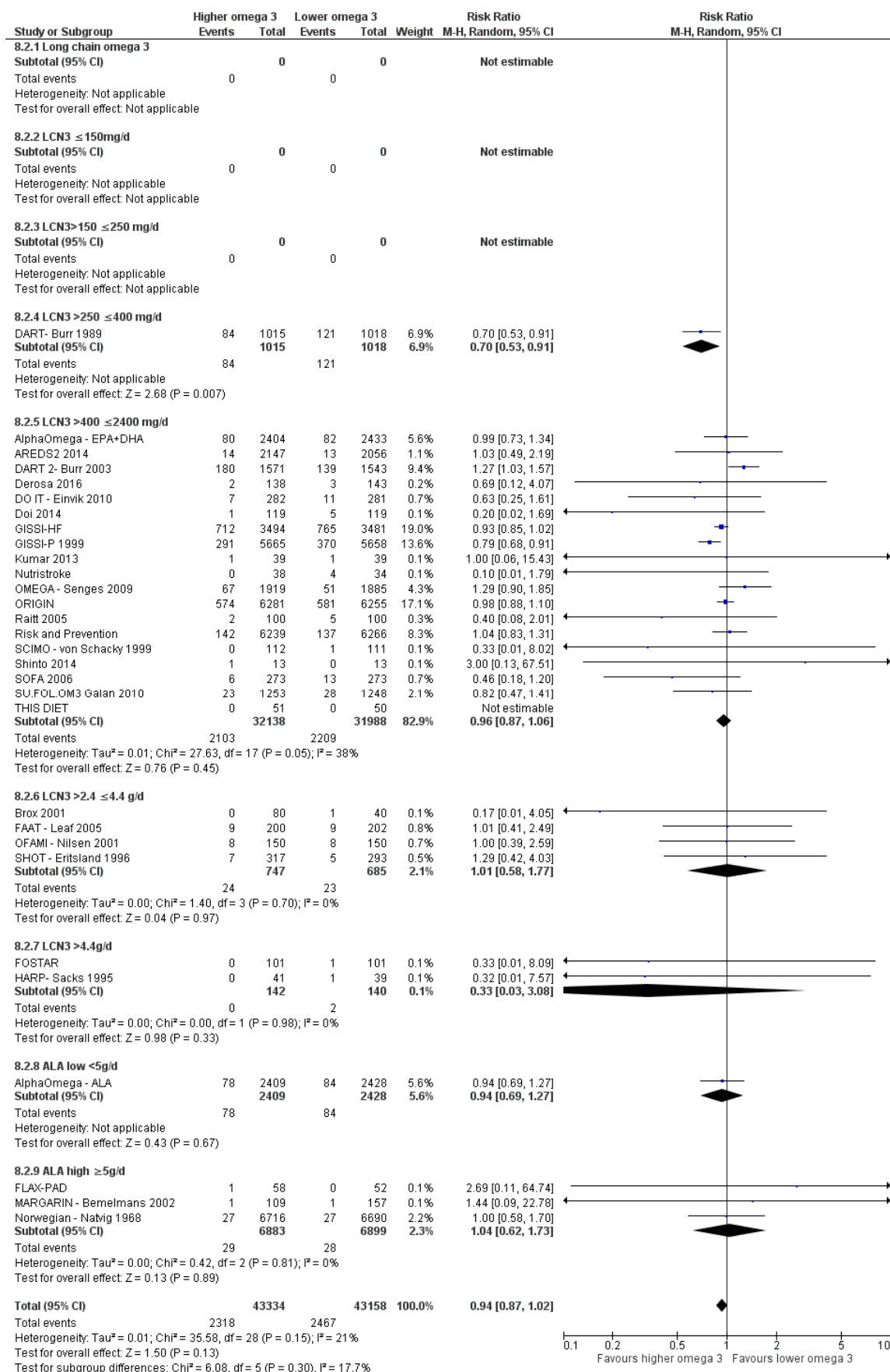


Figure 4.4. Meta-analysis of the effect of omega 3 fats on cardiovascular deaths, subgrouped by dose.

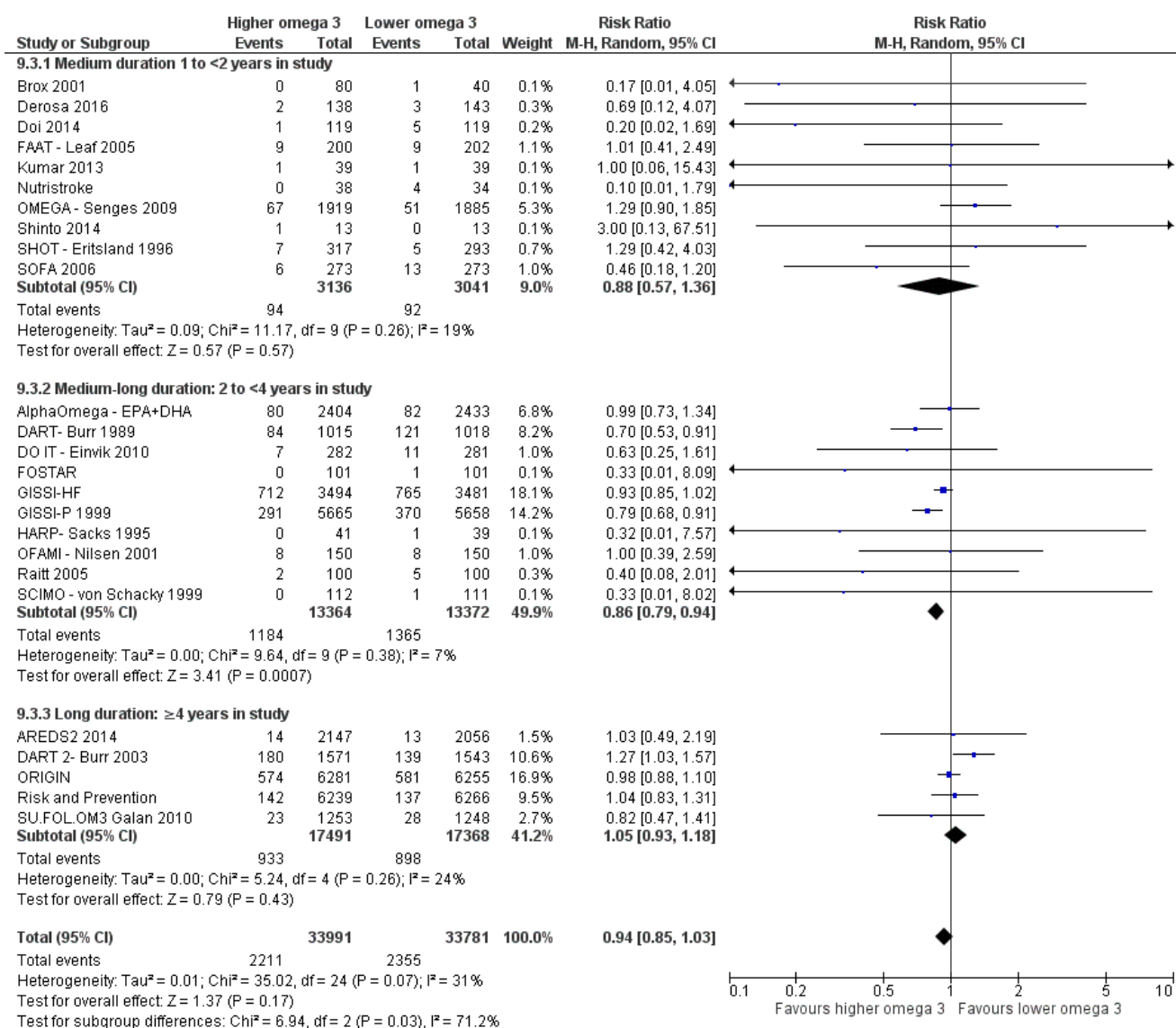


Figure 4.5. Meta-analysis of the effect of LCn3 fats on cardiovascular deaths, subgrouped by duration.

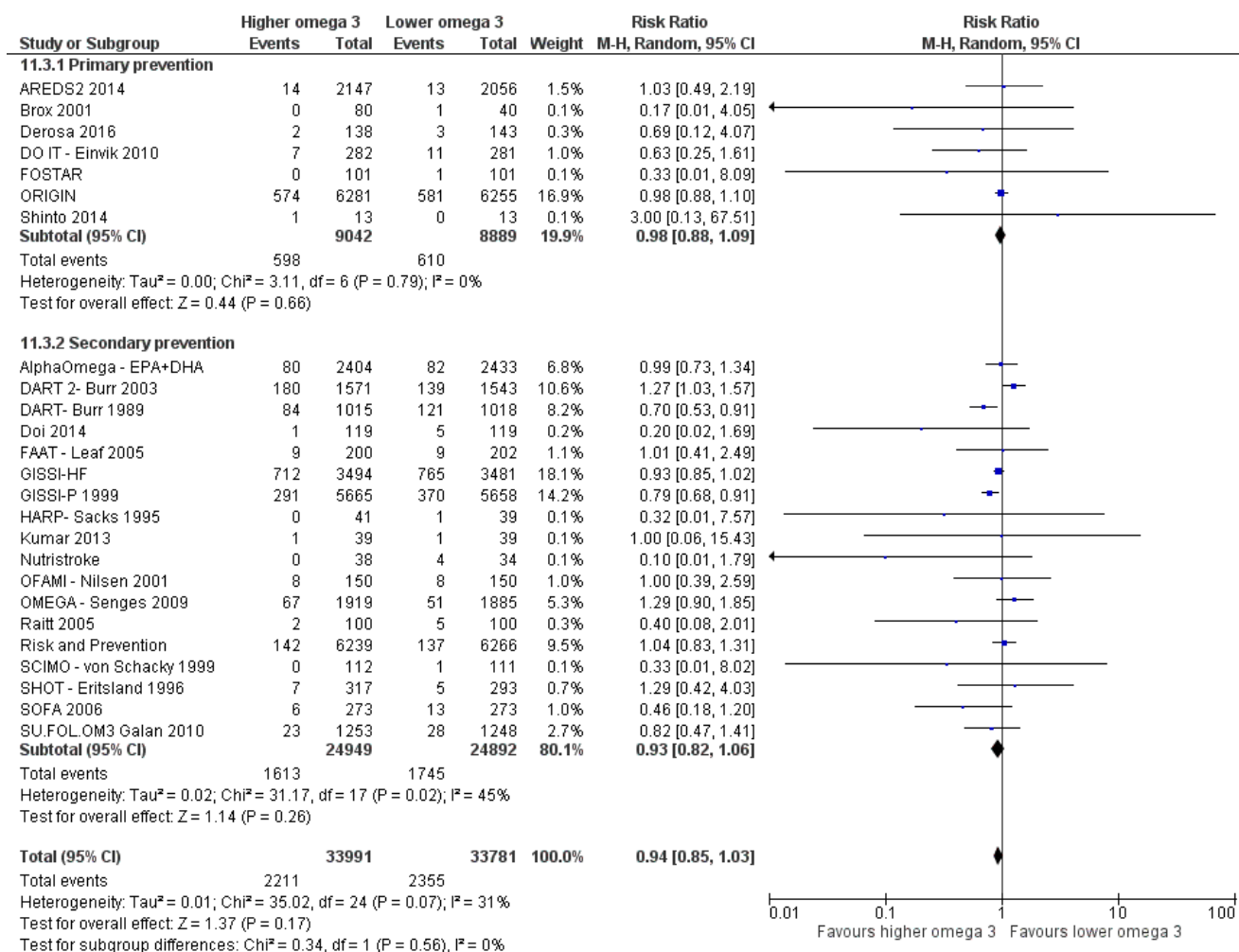


Figure 4.6. Meta-analysis of the effect of LCn3 fats on cardiovascular deaths, subgrouped by primary or secondary CVD prevention.

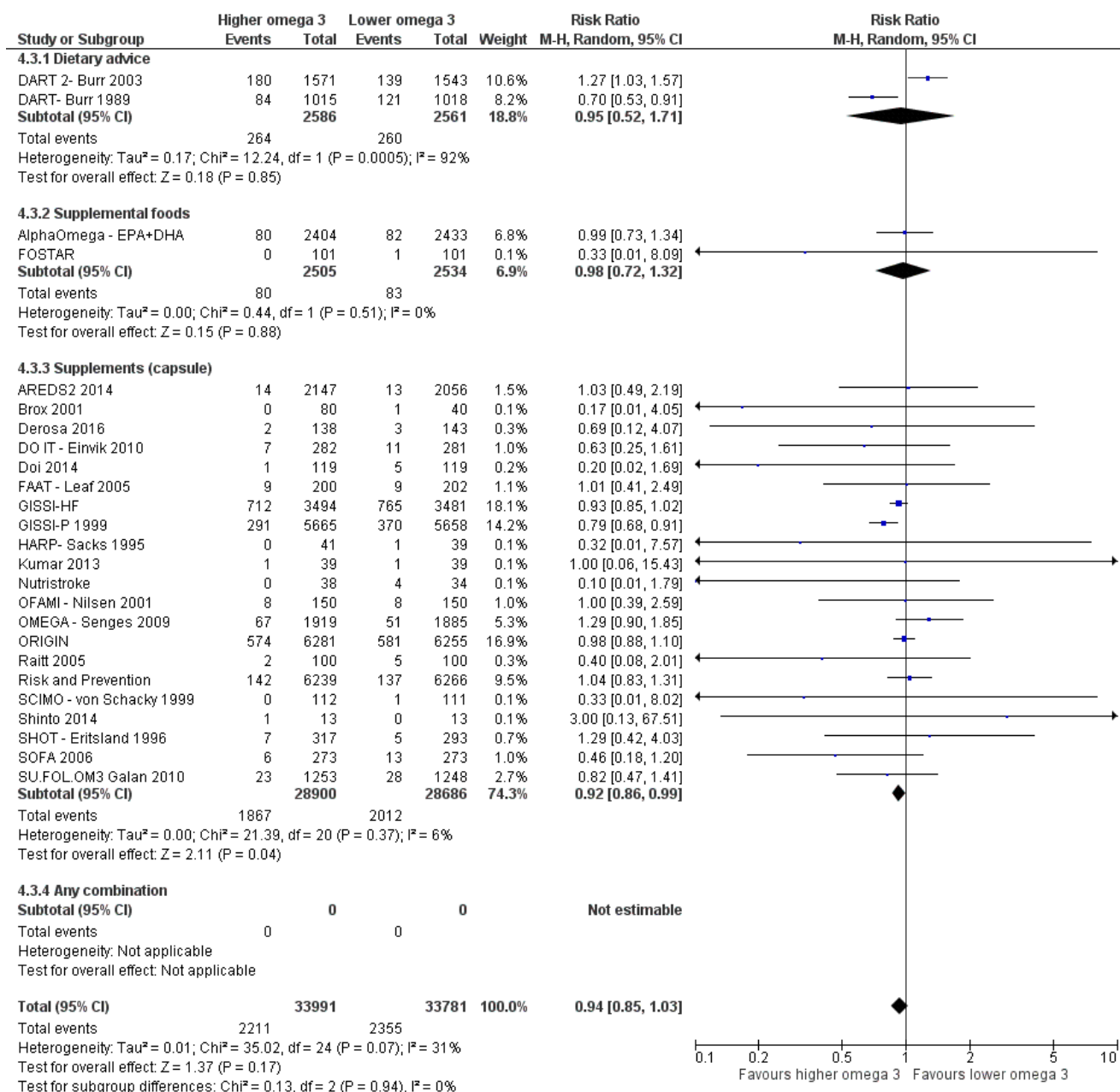


Figure 4.7. Meta-analysis of the effect of LCn3 fats on cardiovascular deaths, subgrouped by type of intervention.

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.

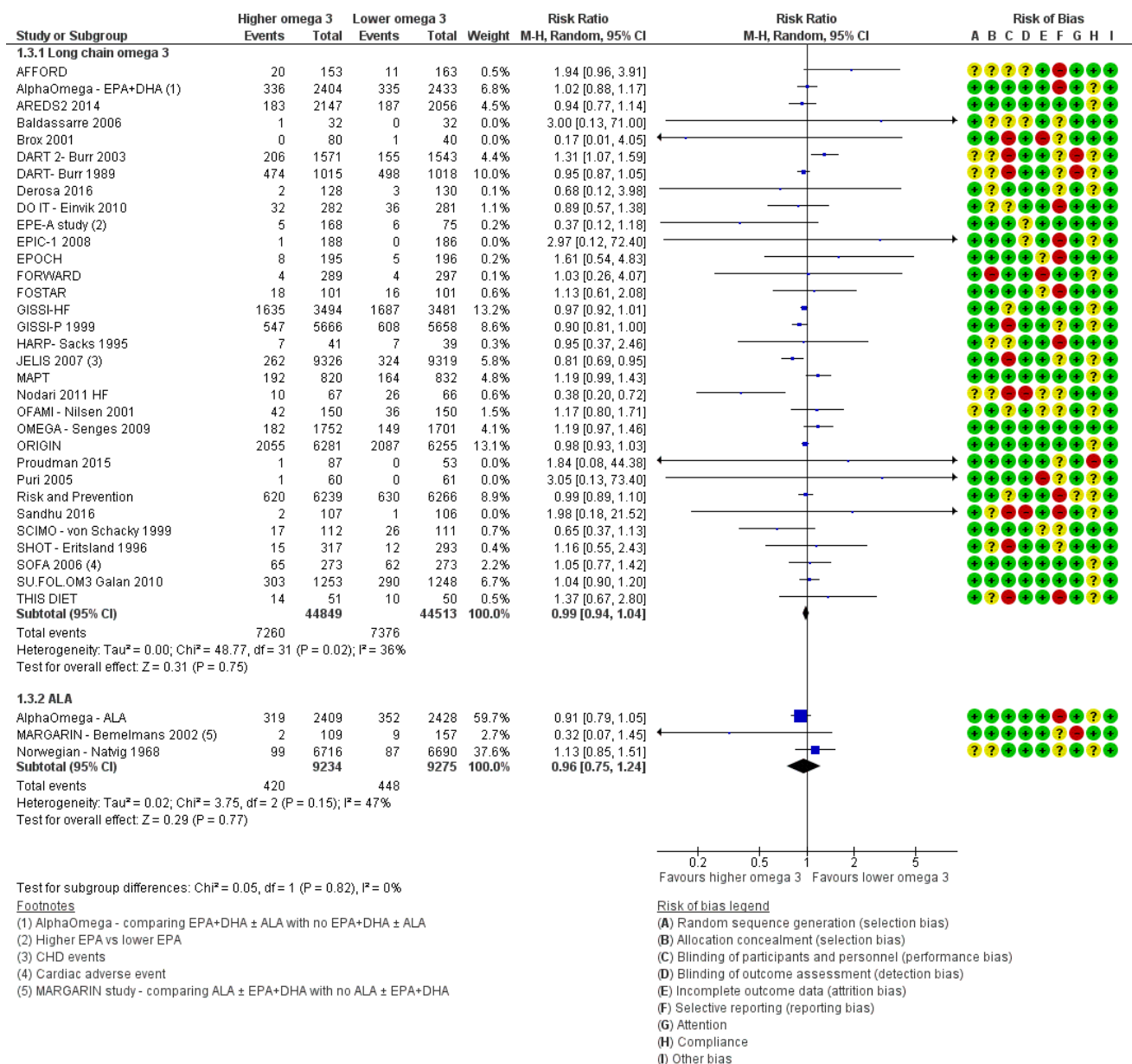


Figure 4.8. Meta-analysis of effects of omega 3 fats on cardiovascular events, subgrouped by LCn3 or ALA interventions.

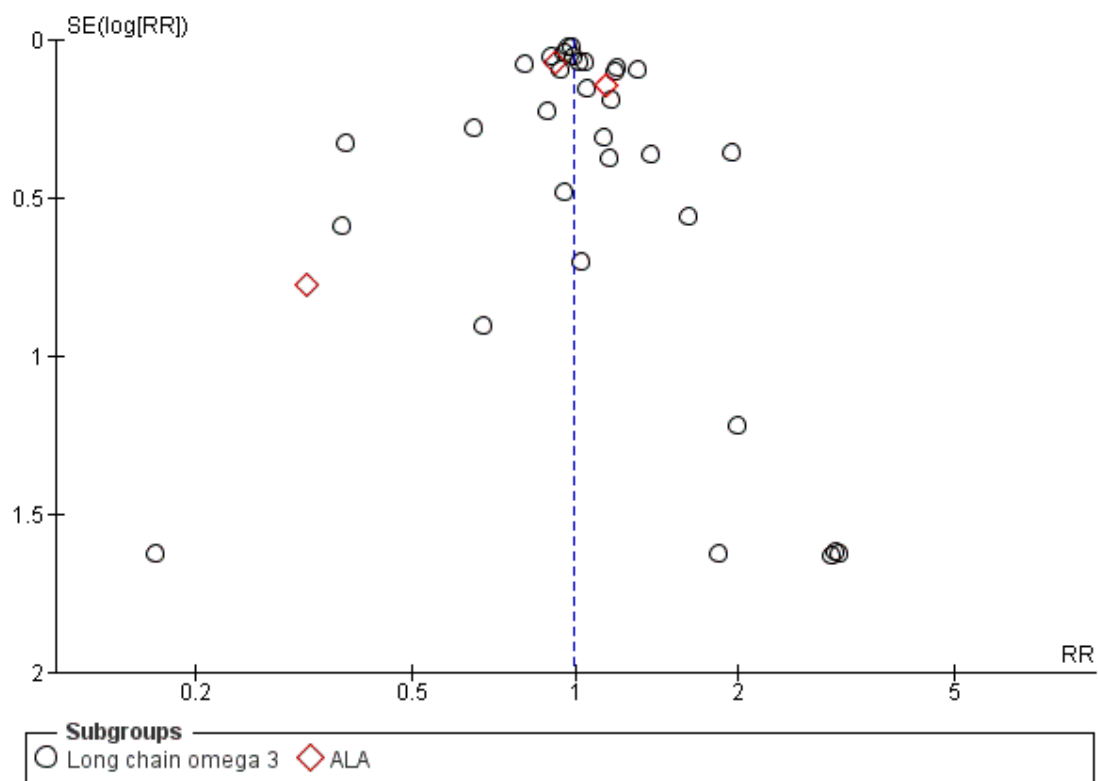


Figure 4.9. Funnel plot of effects of omega 3 fats on cardiovascular events

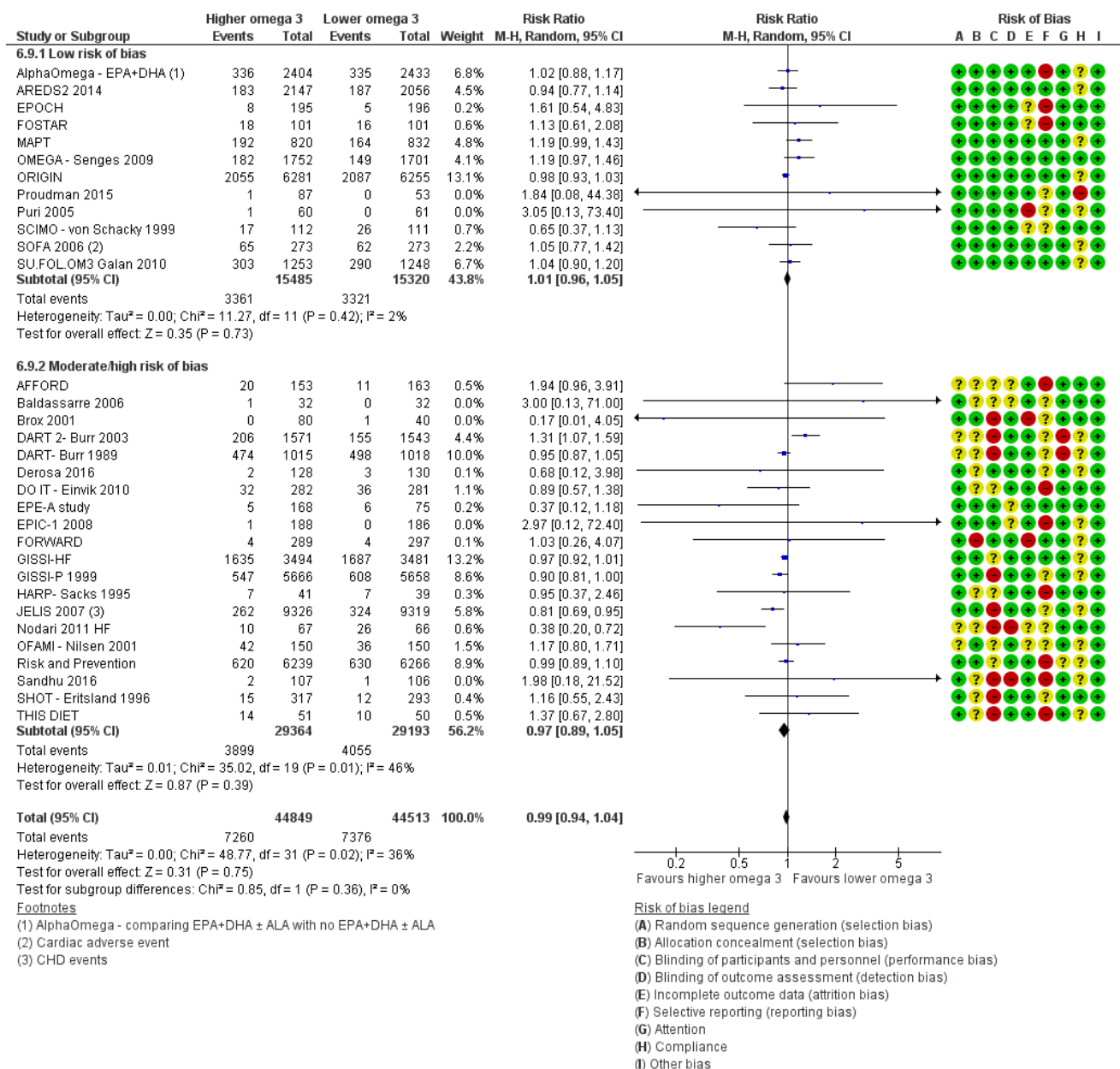


Figure 4.10. Meta-analysis of effects of long chain omega 3 fats on cardiovascular events, sensitivity analysis limiting to studies at low summary risk of bias (shown as subgrouped by risk of bias).

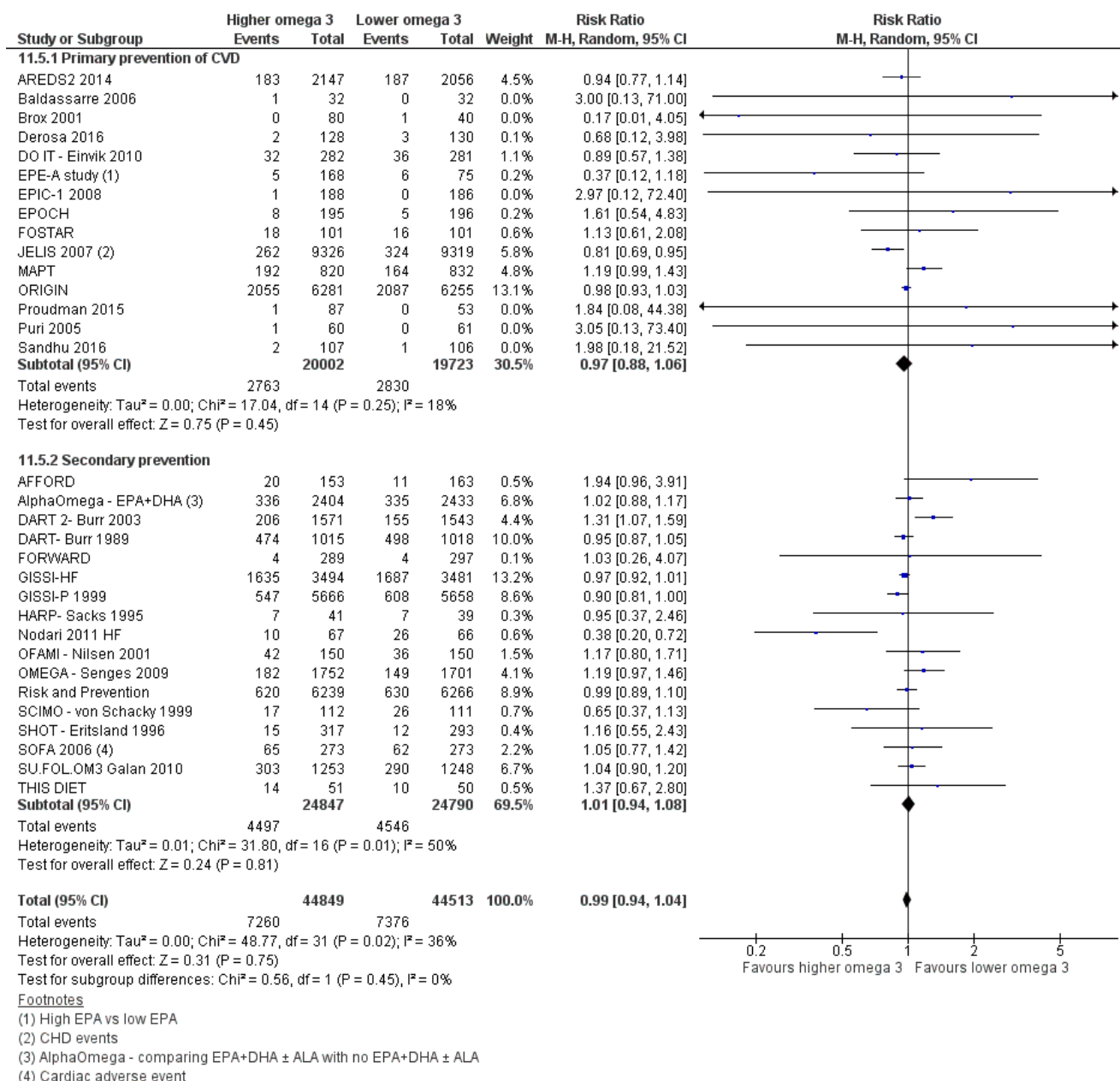


Figure 4.11. Meta-analysis of effects of long chain omega 3 fats on cardiovascular events, subgrouped by primary and secondary prevention.

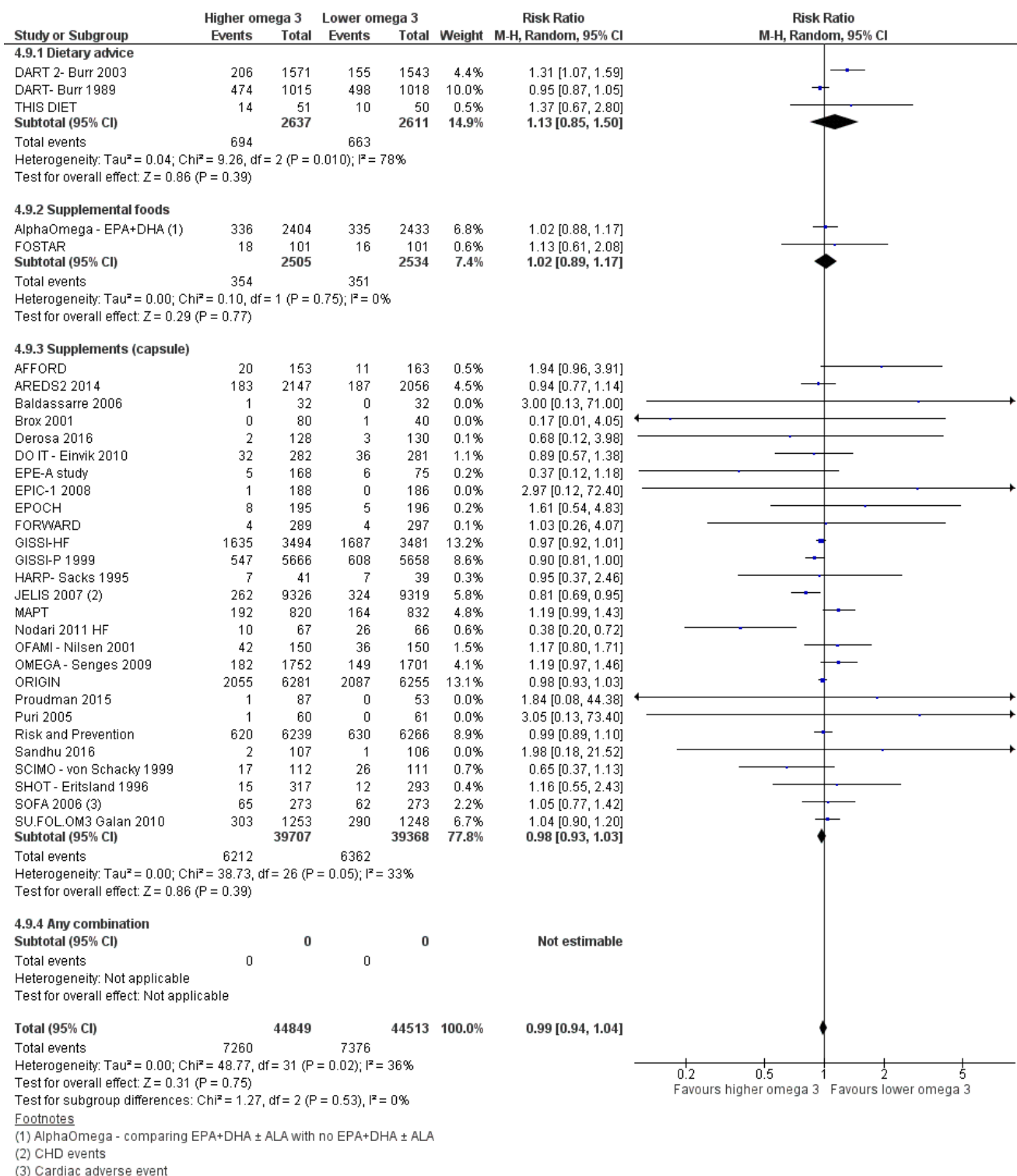


Figure 4.12. Meta-analysis of effects of long chain omega 3 fats on cardiovascular events, subgrouped by intervention type (dietary advice, supplement etc.).

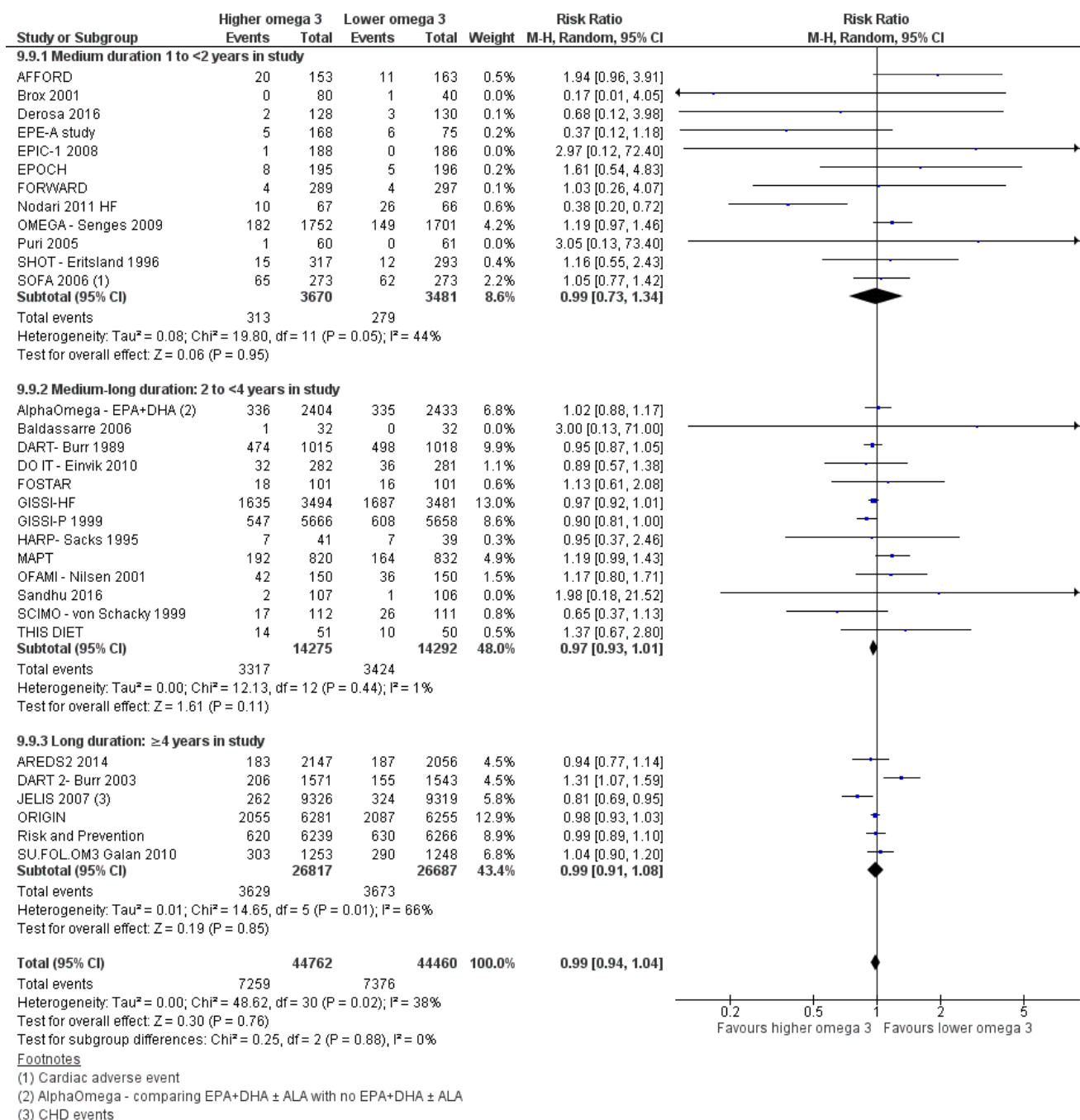


Figure 4.13. Meta-analysis of effects of long chain omega 3 fats on cardiovascular events, subgrouped by duration of intervention.

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.

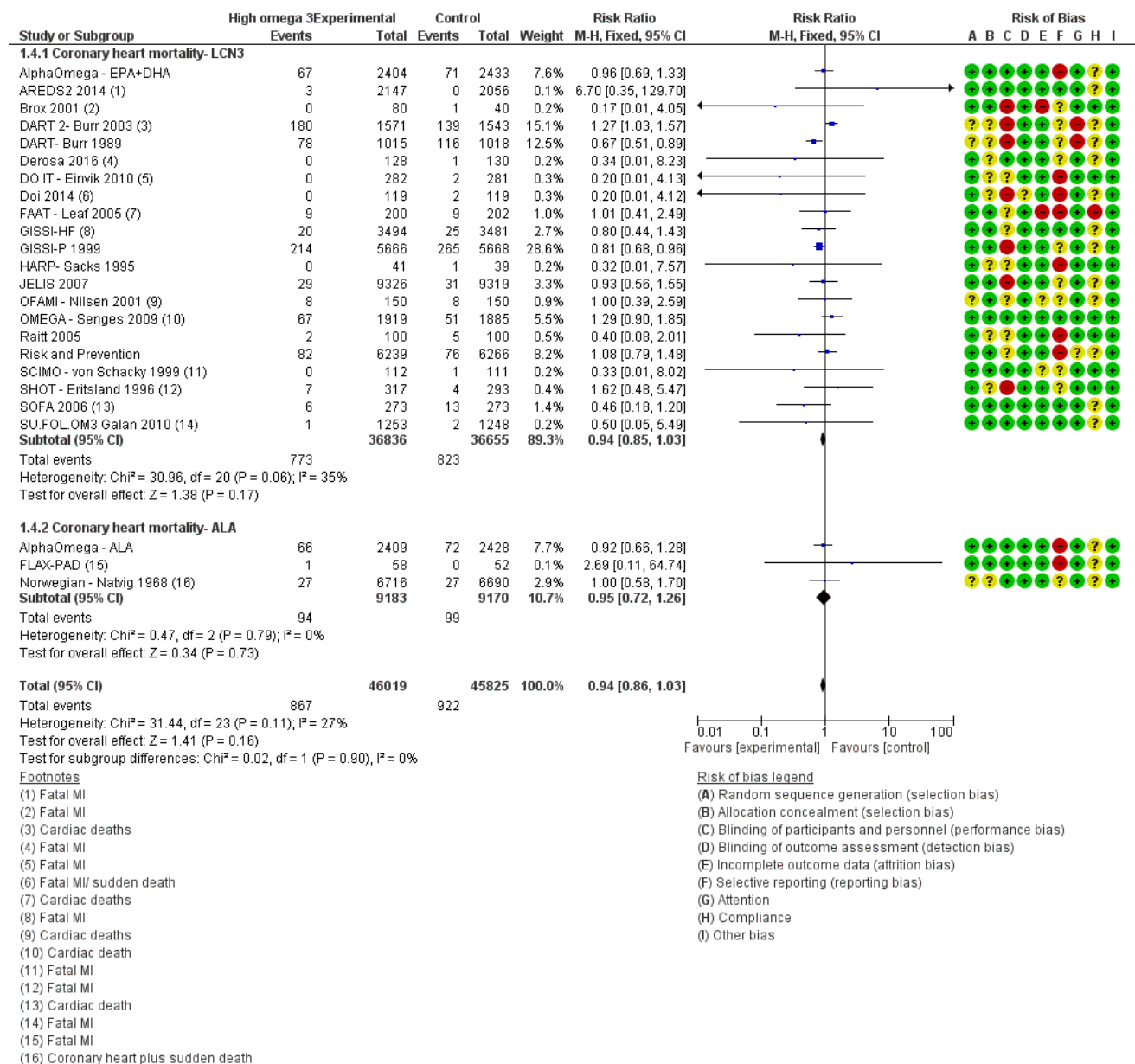


Figure 4.15. Sensitivity analysis. Forest plot of the effect of LCn3 fats on coronary heart disease deaths, using fixed effects meta-analysis.

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).

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.

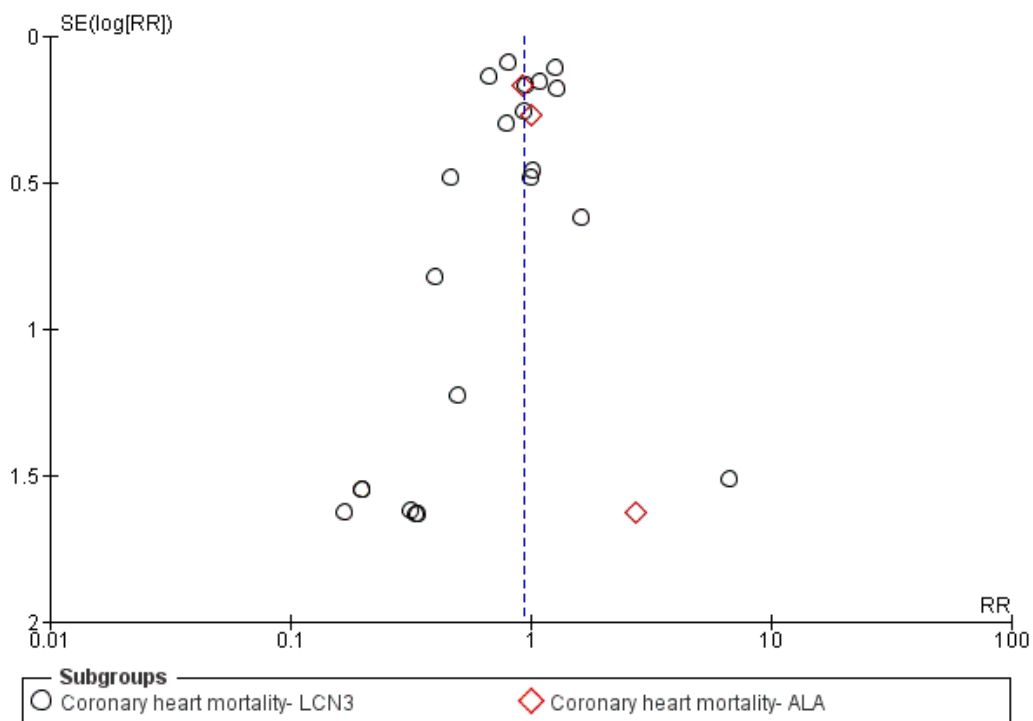


Figure 4.18. Meta-analysis of the effect of LCn3 fats on coronary heart disease deaths, sensitivity analysis limiting to studies at low summary risk of bias (shown as subgrouped by risk of bias to allow analysis of the contrast between the two sets of trials).



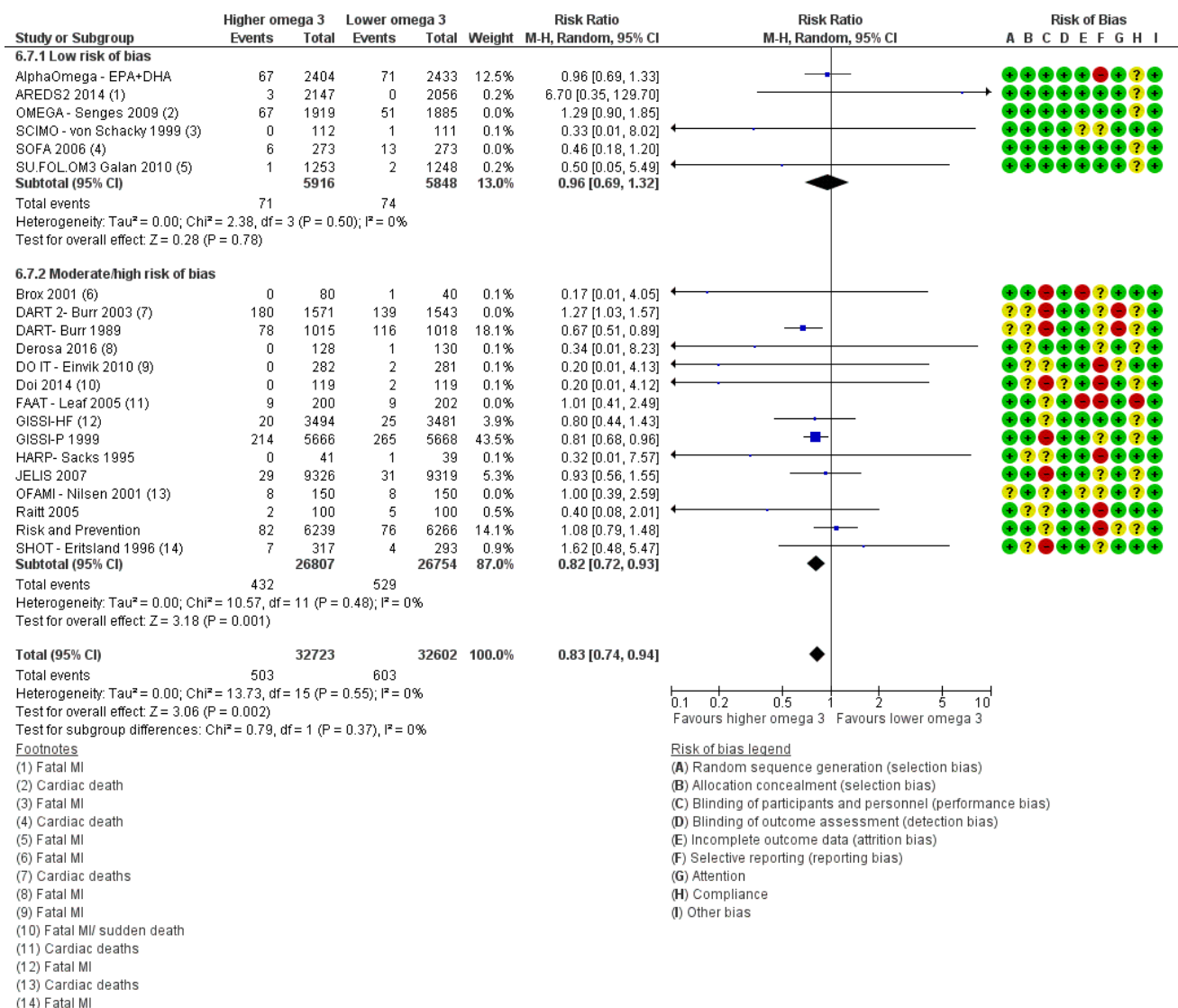


Figure 4.19. Sensitivity analysis. Forest plot of the effect of LCN3 fats on coronary heart disease deaths, subgrouped by risk of bias, omitting studies only reporting cardiac death.

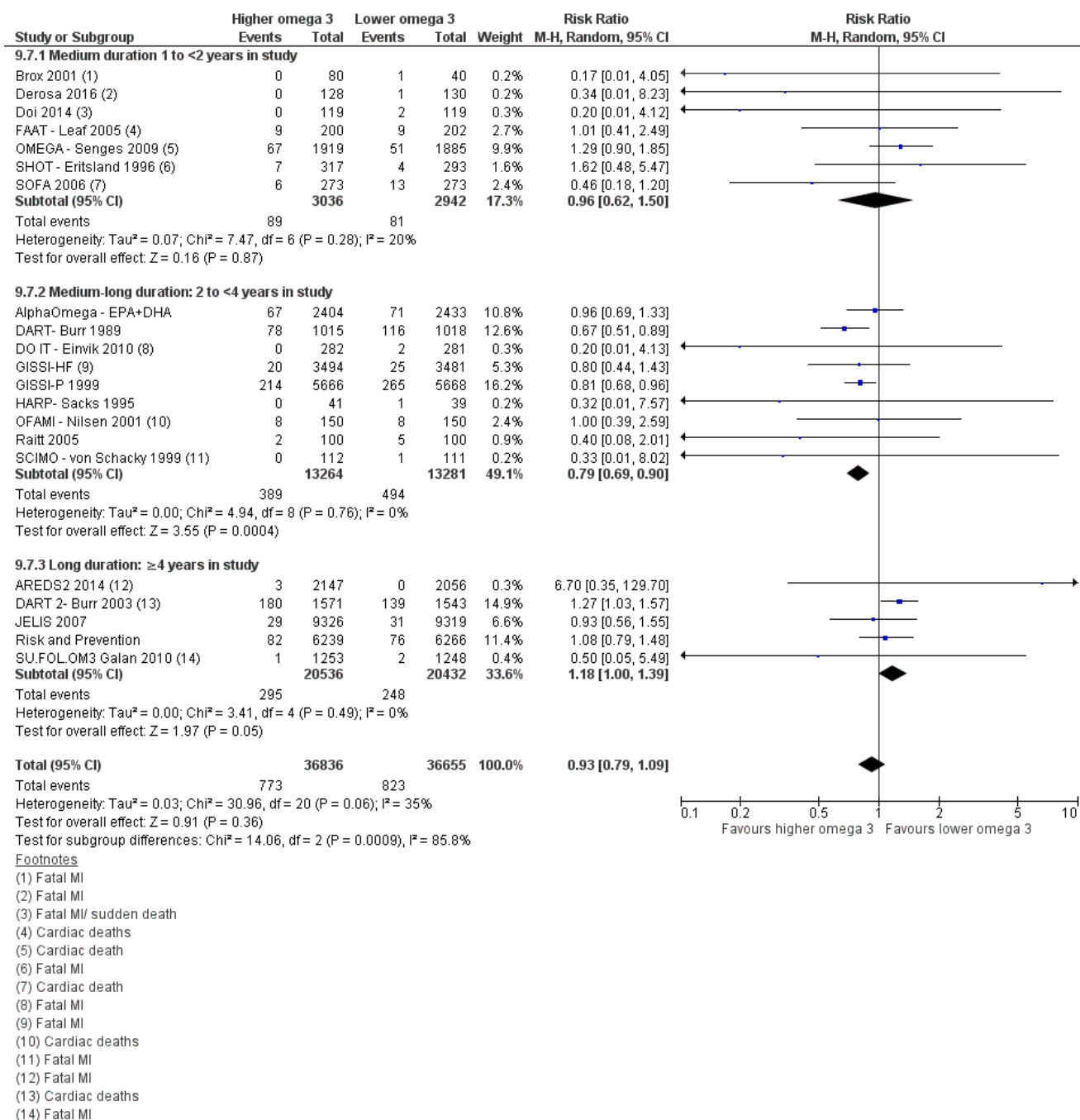


Figure 4.20. Meta-analysis of the effect of LCn3 fats on coronary heart disease deaths, subgrouped by duration of intervention.

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.

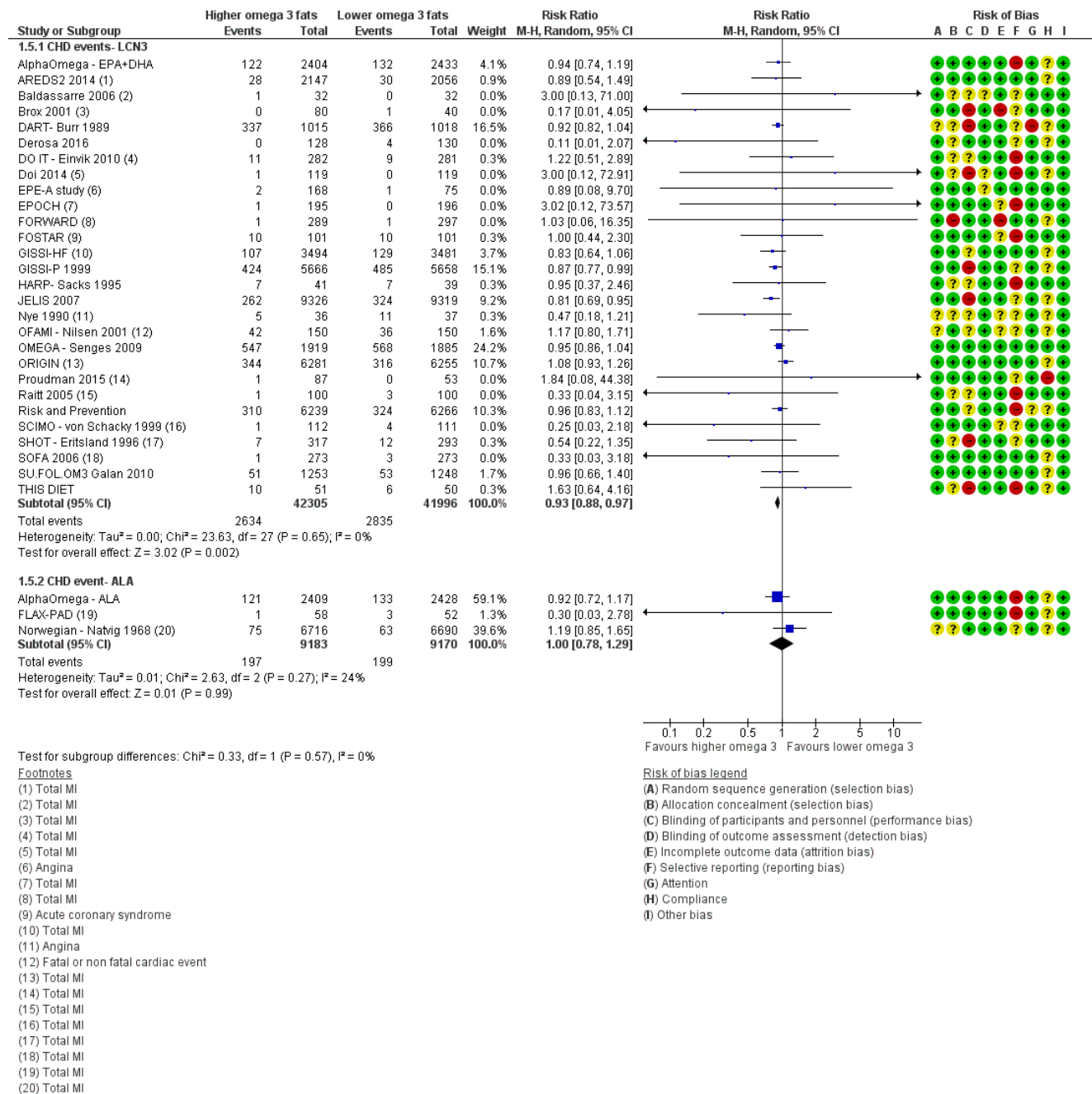


Figure 4.21. Meta-analysis of the effect of LCn3 fats on coronary heart disease, subgrouped by LCn3 and ALA.

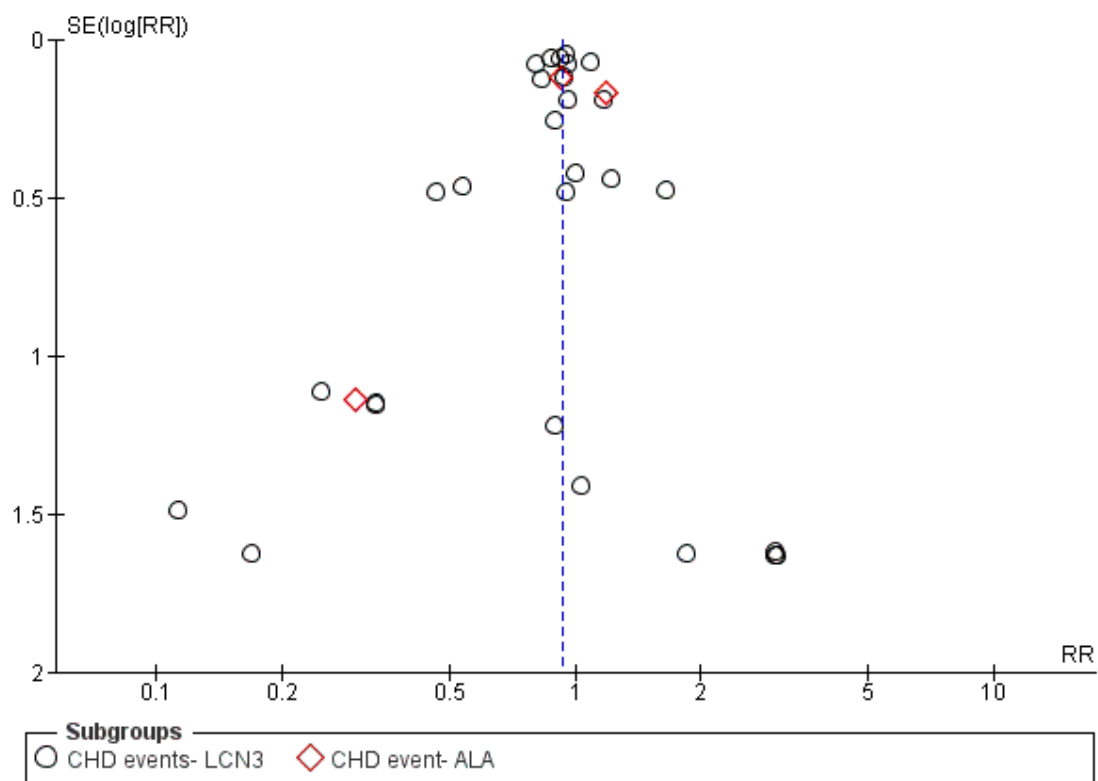


Figure 4.22. Funnel plot for meta-analysis of the effect of LCN3 fats on coronary heart disease.

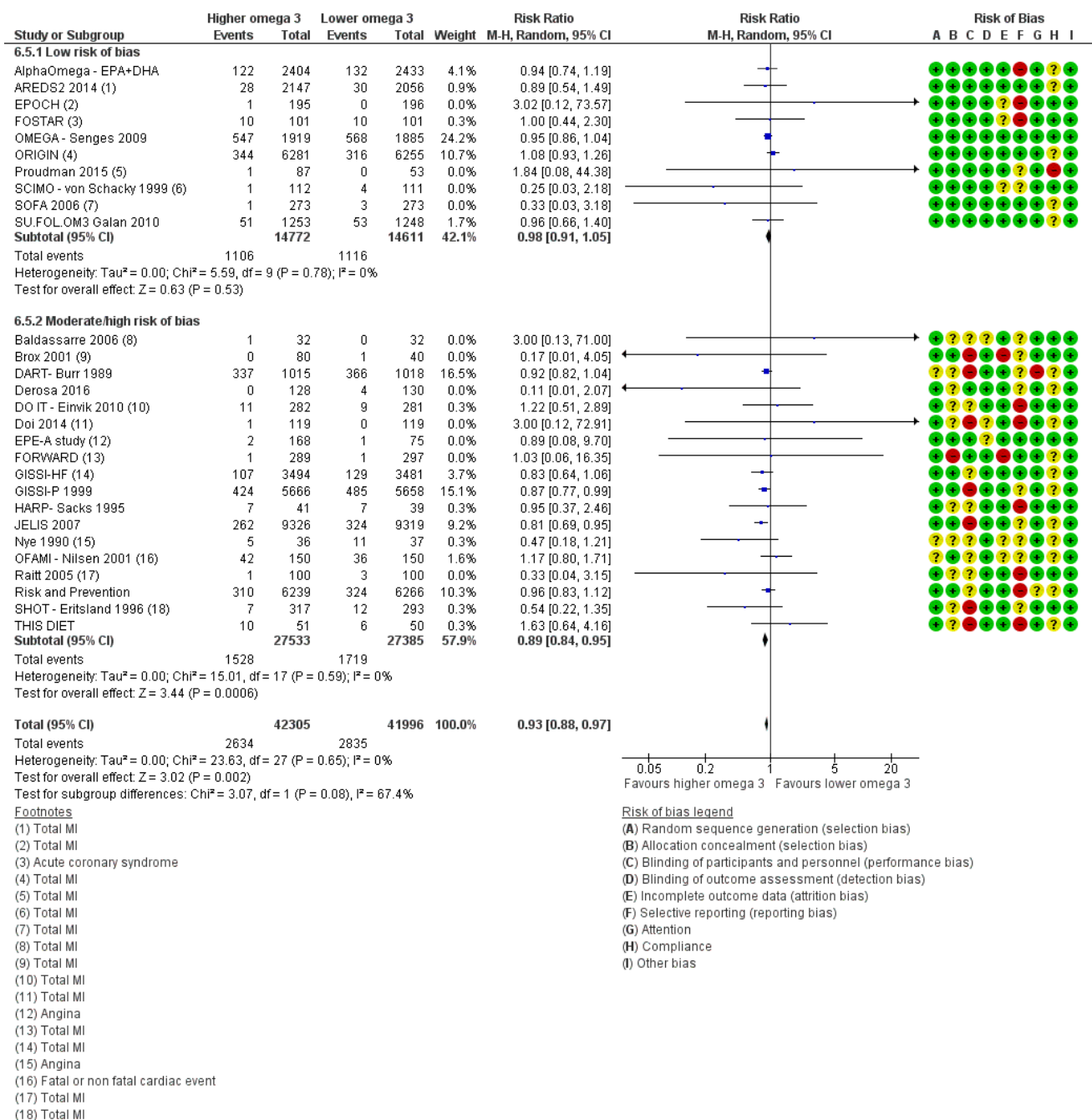


Figure 4.23. Meta-analysis of the effect of LCN3 fats on coronary heart disease, sensitivity analysis omitting trials at moderate to high summary risk of bias (shown subgrouped by summary risk of bias to allow readers to contrast effects in the two sets of studies).

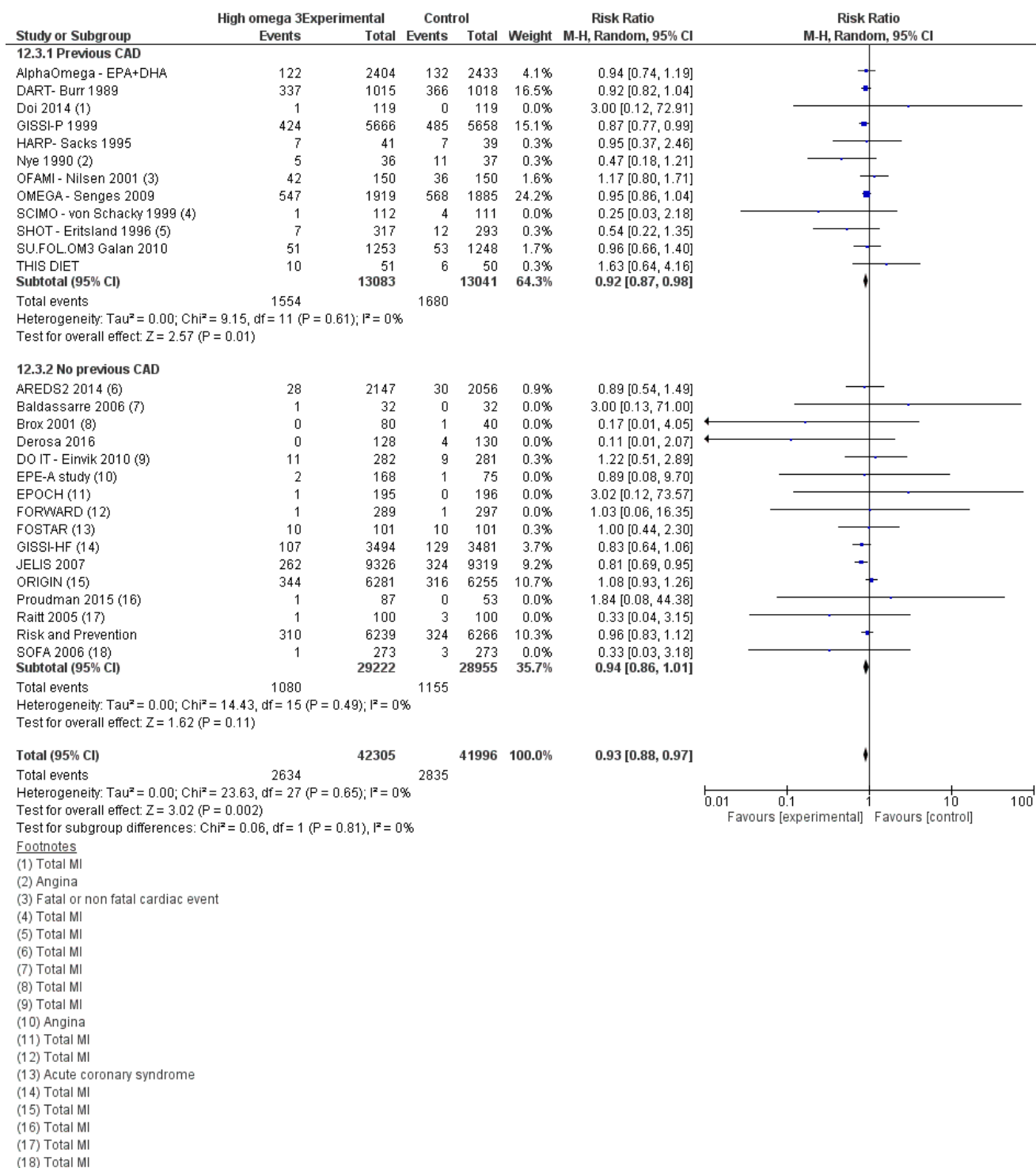


Figure 4.24. Meta-analysis of the effect of LCn3 fats on coronary heart disease, subgrouped by previous CAD history.

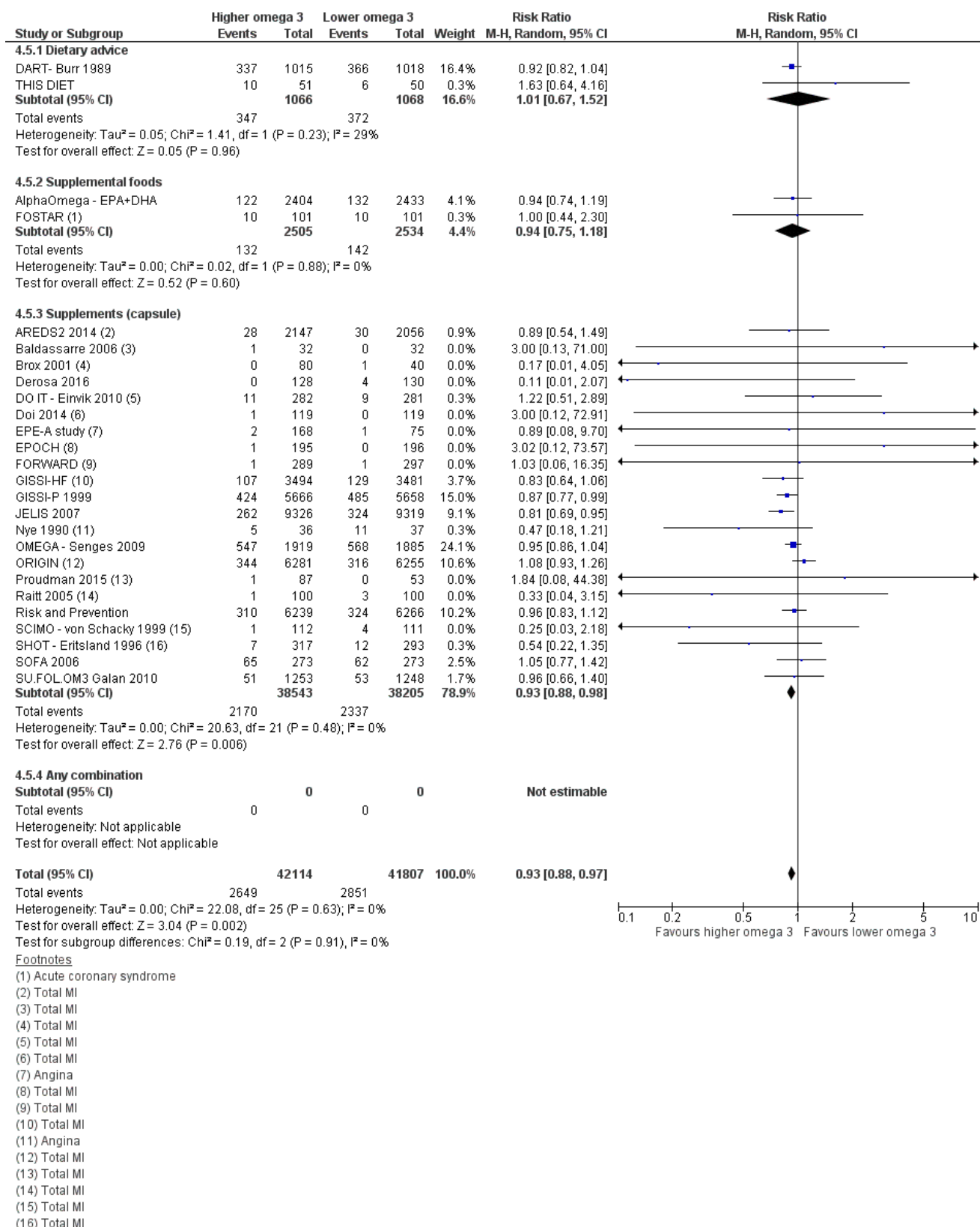


Figure 4.25. Meta-analysis of the effect of LCn3 fats on coronary heart disease, subgrouped by type of intervention.

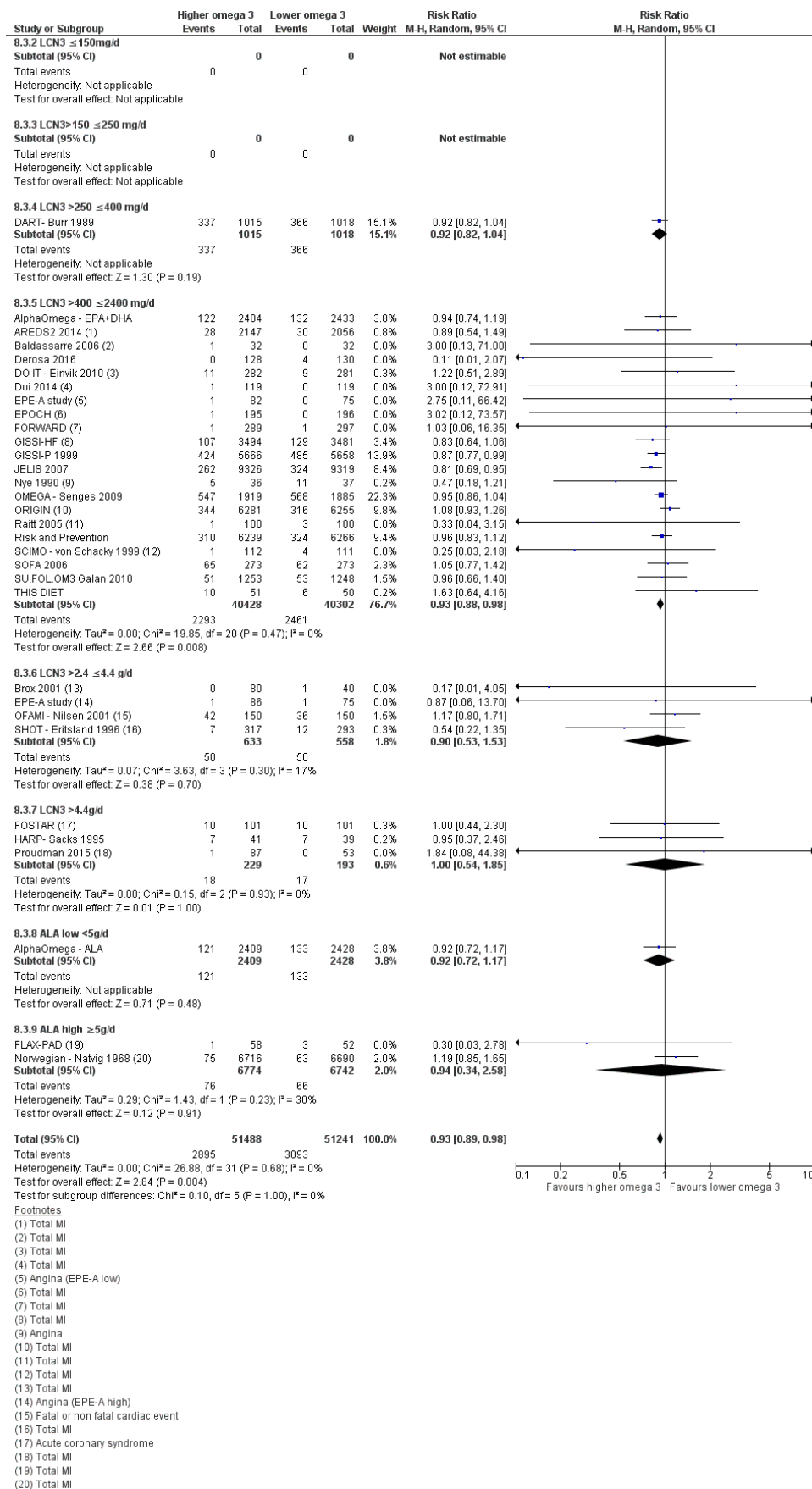


Figure 4.26. Meta-analysis of the effect of LCN3 fats on coronary heart disease, subgrouped by dose.

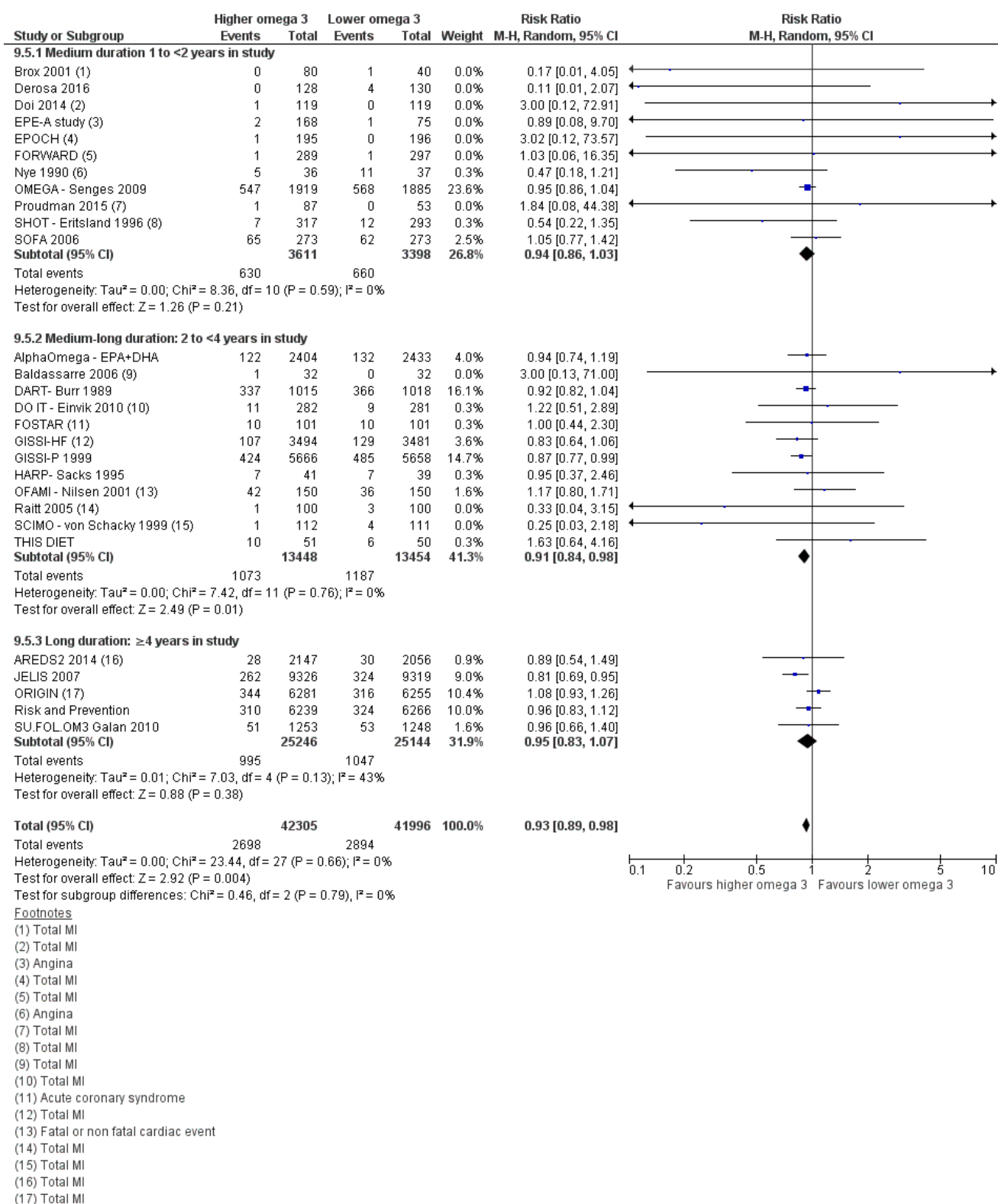


Figure 4.27. Meta-analysis of effects of omega 3 fats on CHD, subgrouped by duration.

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, I^2 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.

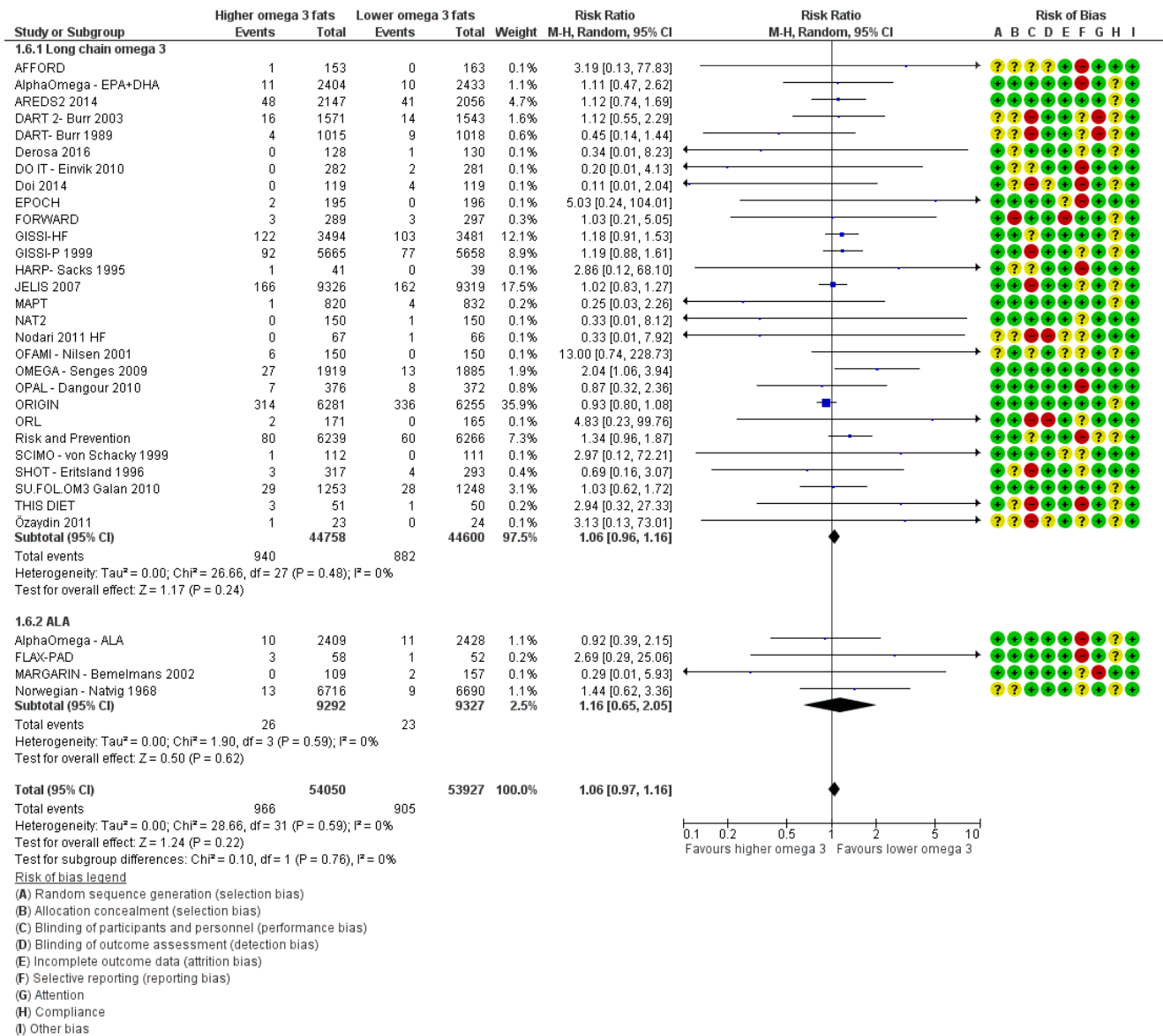


Figure 4.28. Meta-analysis of effects of omega 3 fats on stroke, subgrouped by LCN3 or ALA.

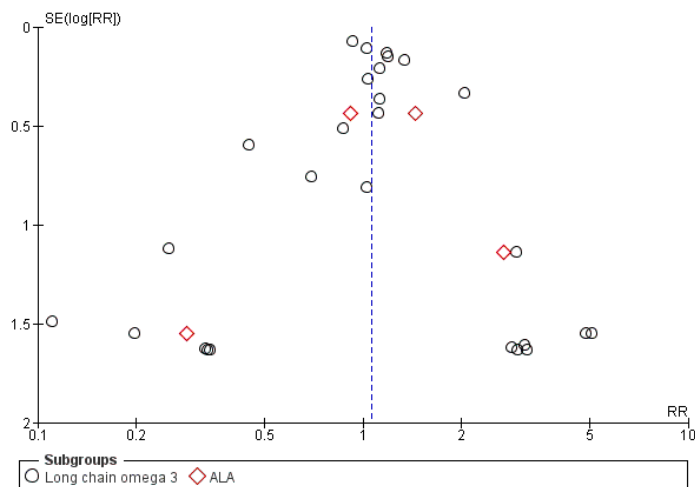


Figure 4.29. Funnel plot for effect of omega 3 fats on stroke.

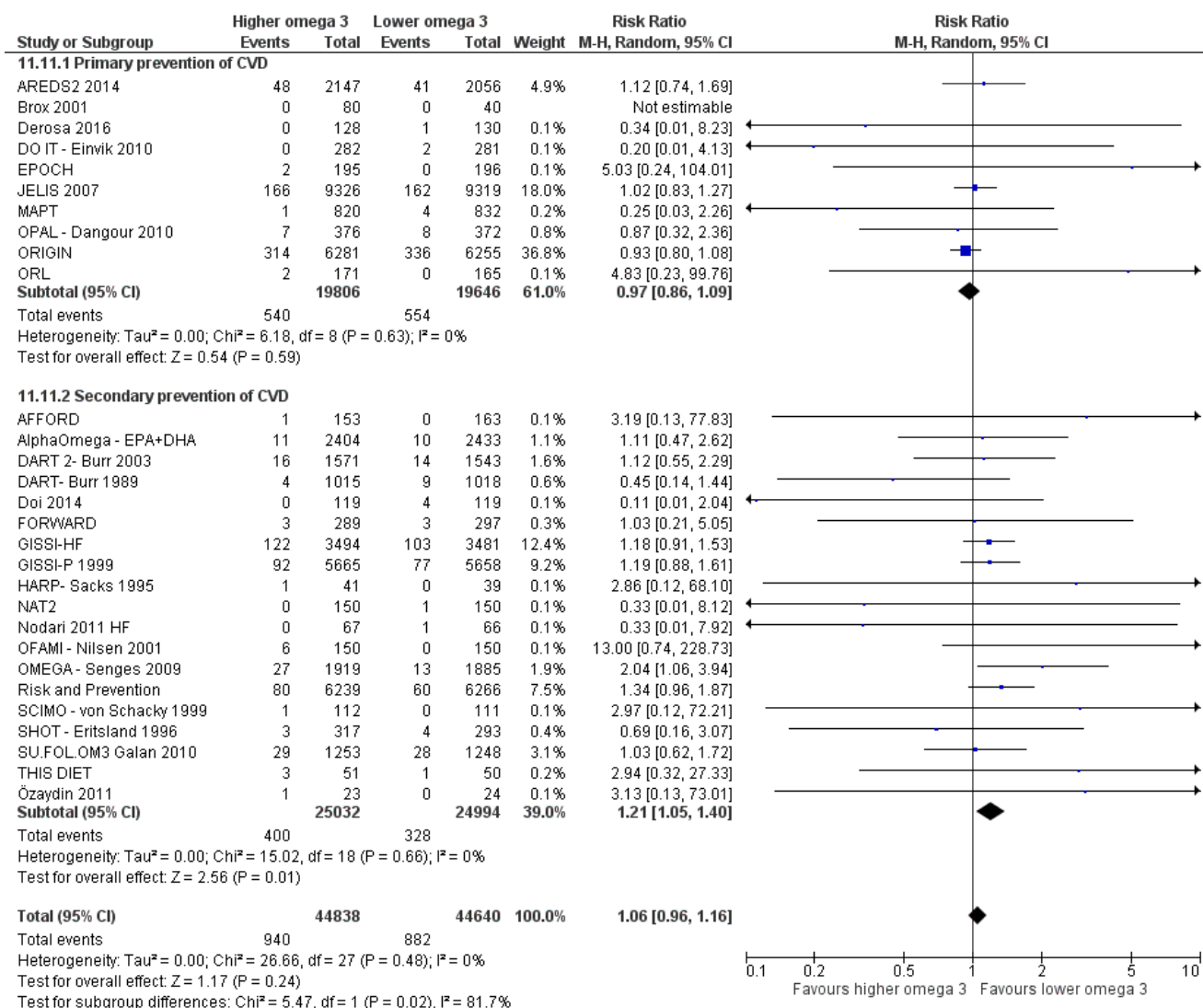


Figure 4.31. Meta-analysis of effects of omega 3 fats on stroke, subgrouped by primary (no existing CVD at baseline) or secondary prevention of CVD.

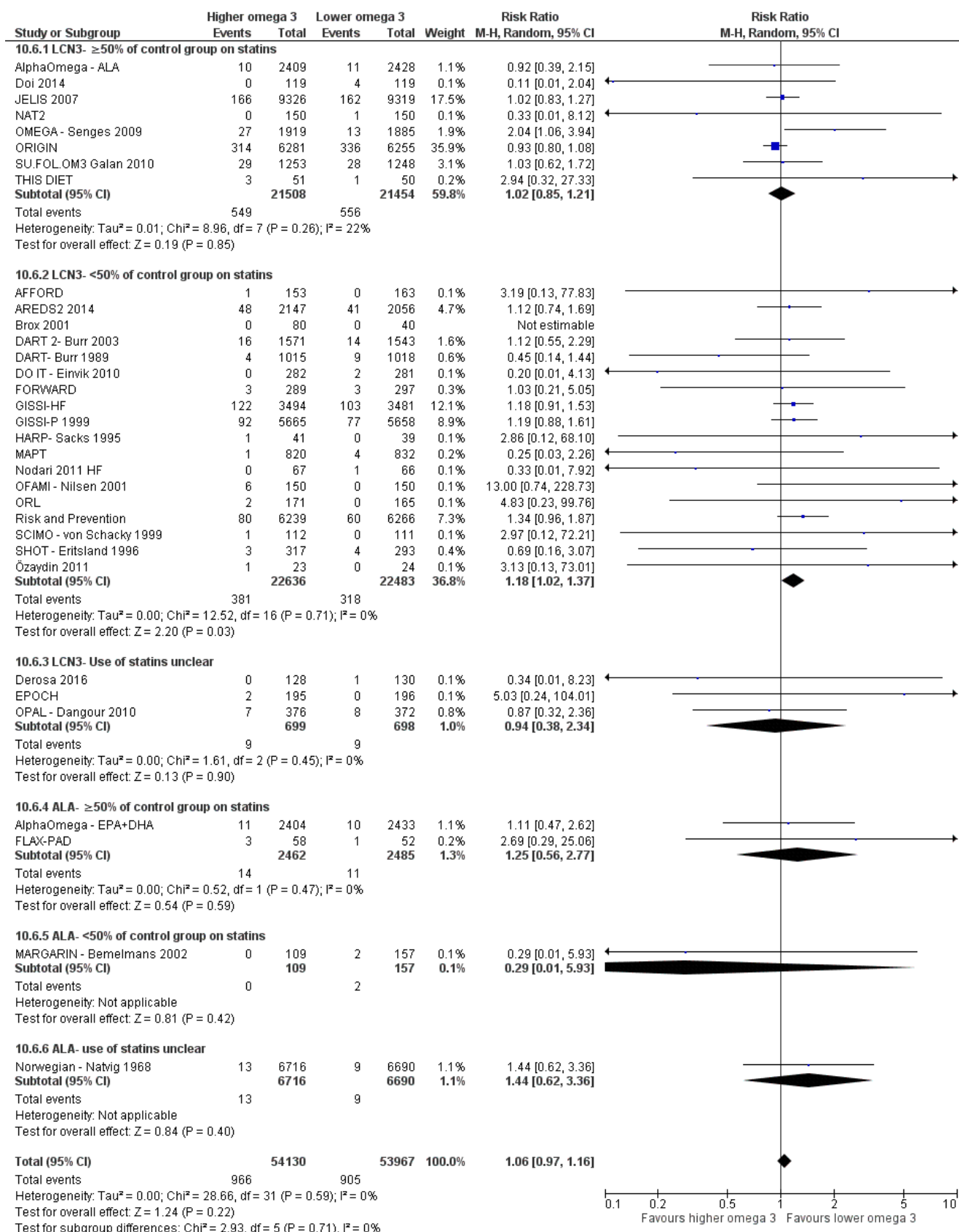


Figure 4.32. Meta-analysis of effects of omega 3 fats on stroke, subgrouped by use of statins.

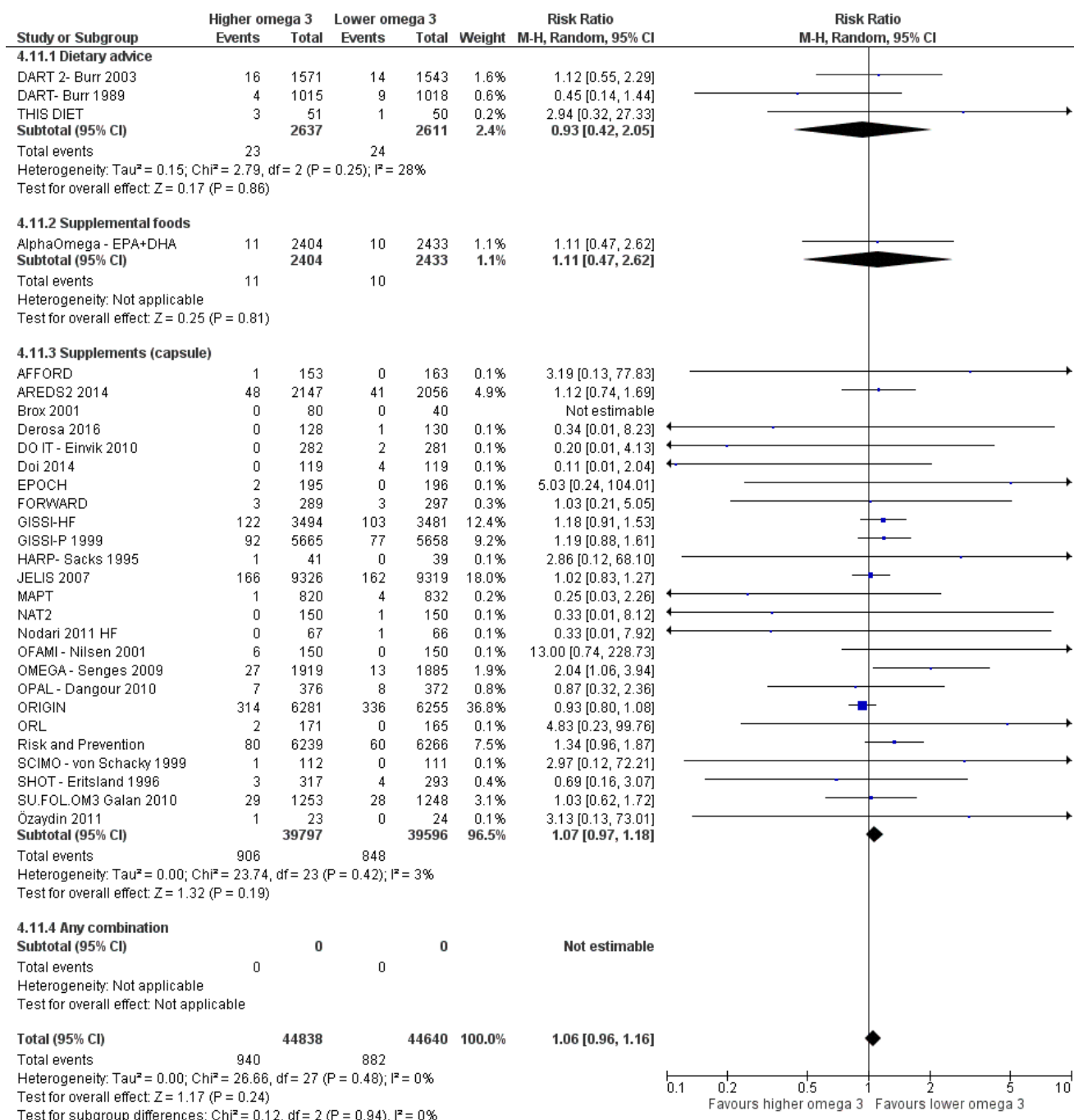


Figure 4.33. Meta-analysis of effects of omega 3 fats on stroke, subgrouped by type of intervention.

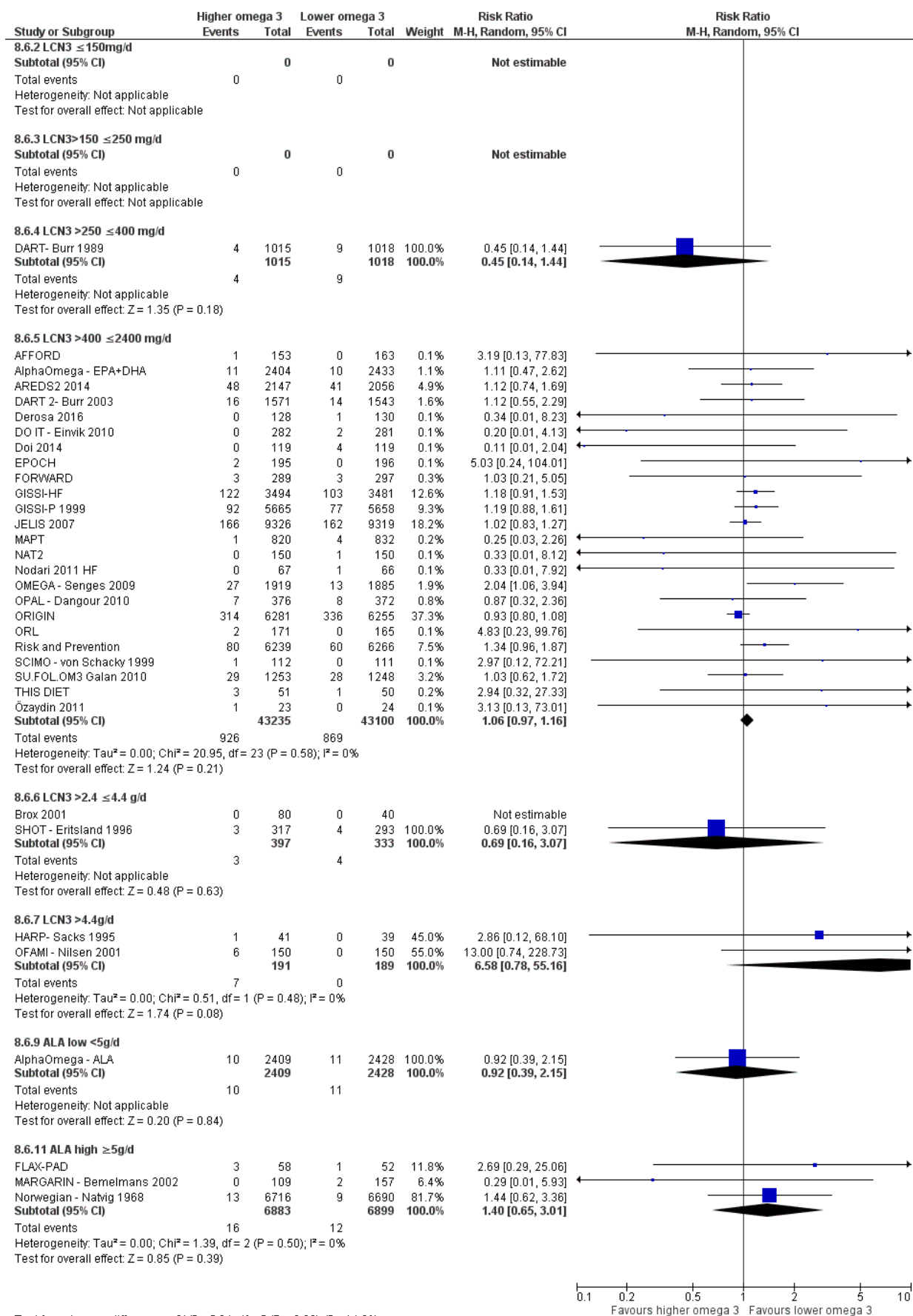


Figure 4.34. Meta-analysis of effects of omega 3 fats on stroke, subgrouped by omega 3 dose.

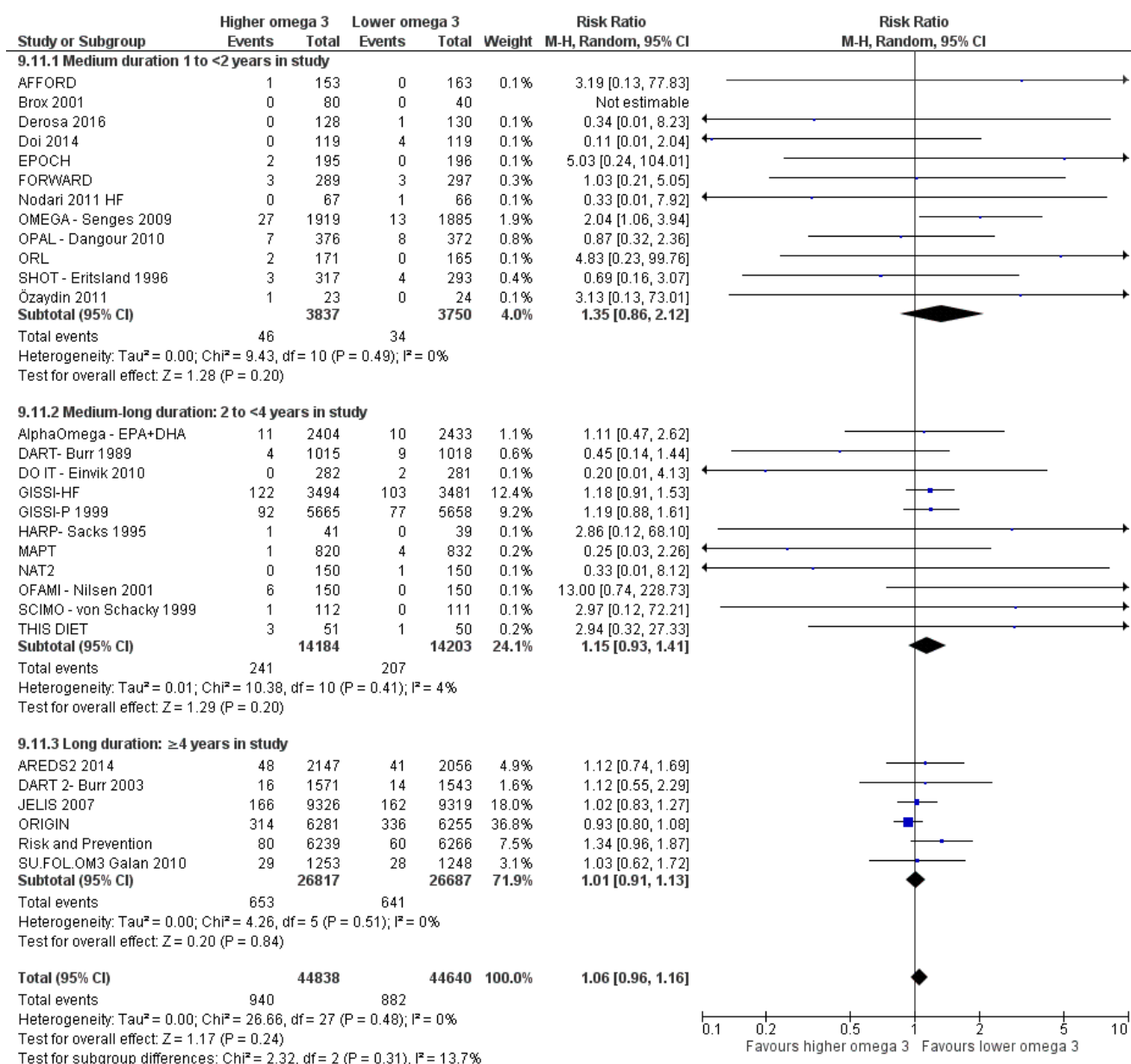


Figure 4.35. Meta-analysis of effects of omega 3 fats on stroke, subgrouped by duration.

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%).

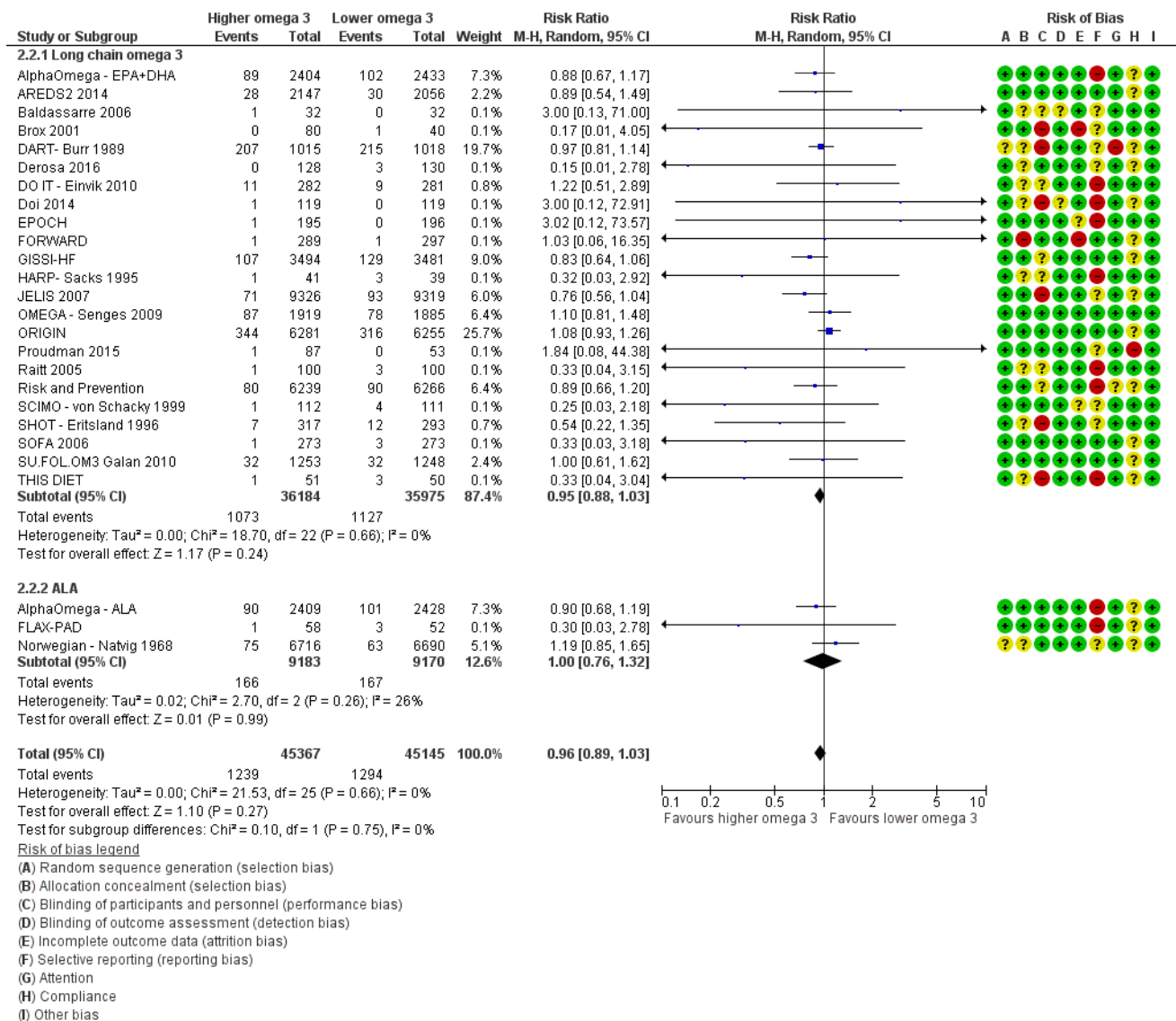


Figure 4.36. Meta-analysis of effects of omega 3 fats on MI (fatal or non-fatal combined), subgrouped by LCn3 or ALA intervention.

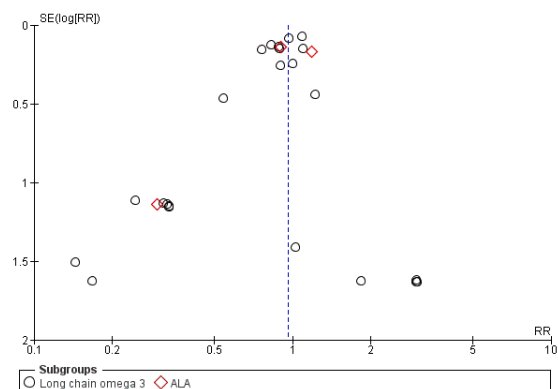


Figure 4.37. Funnel plot of effects of omega 3 fats on MI (fatal or non-fatal combined), subgrouped by LCn3 or ALA intervention.

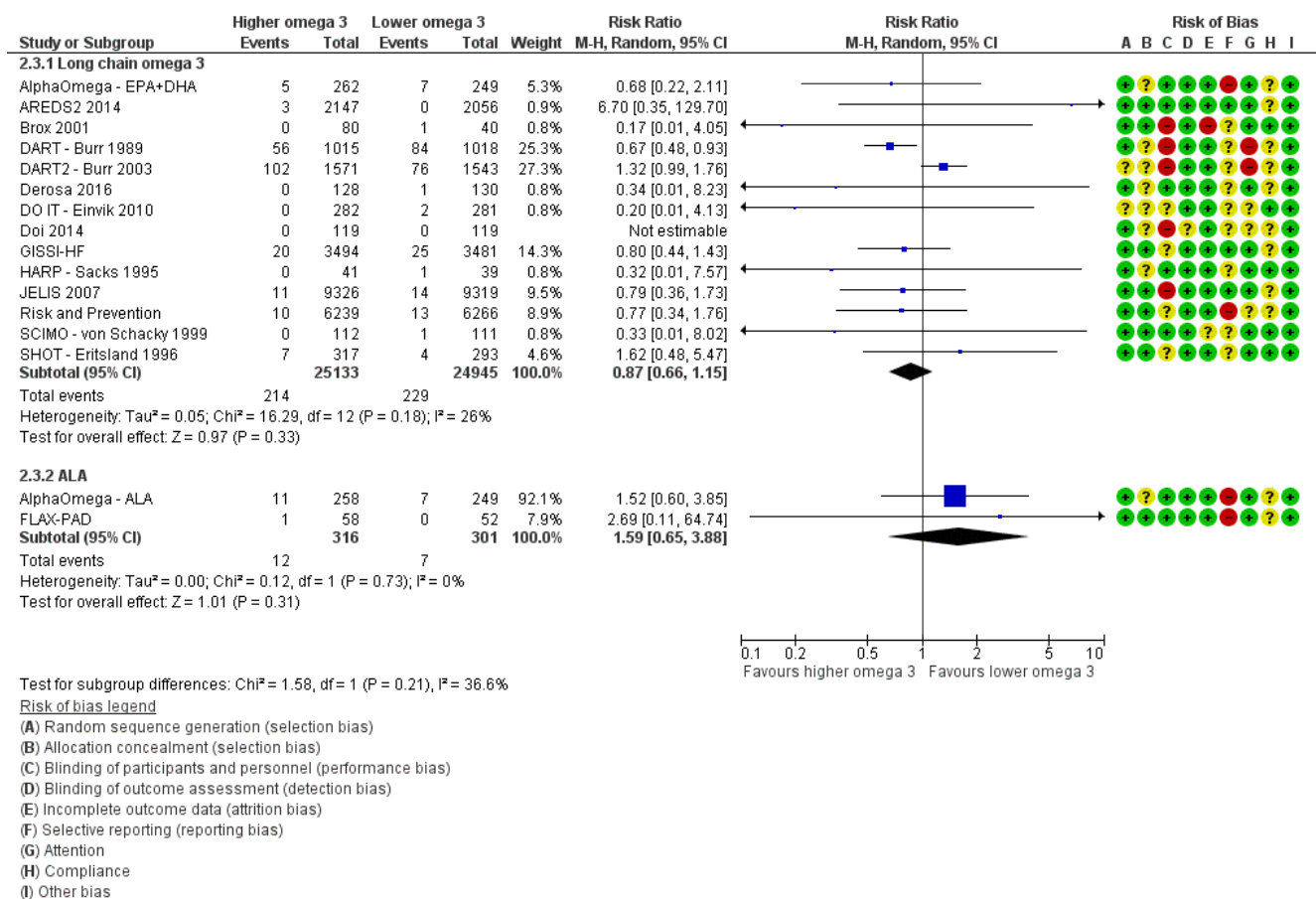


Figure 4.38. Meta-analysis of effects of omega 3 fats on fatal MI, subgrouped by LCn3 or ALA intervention.

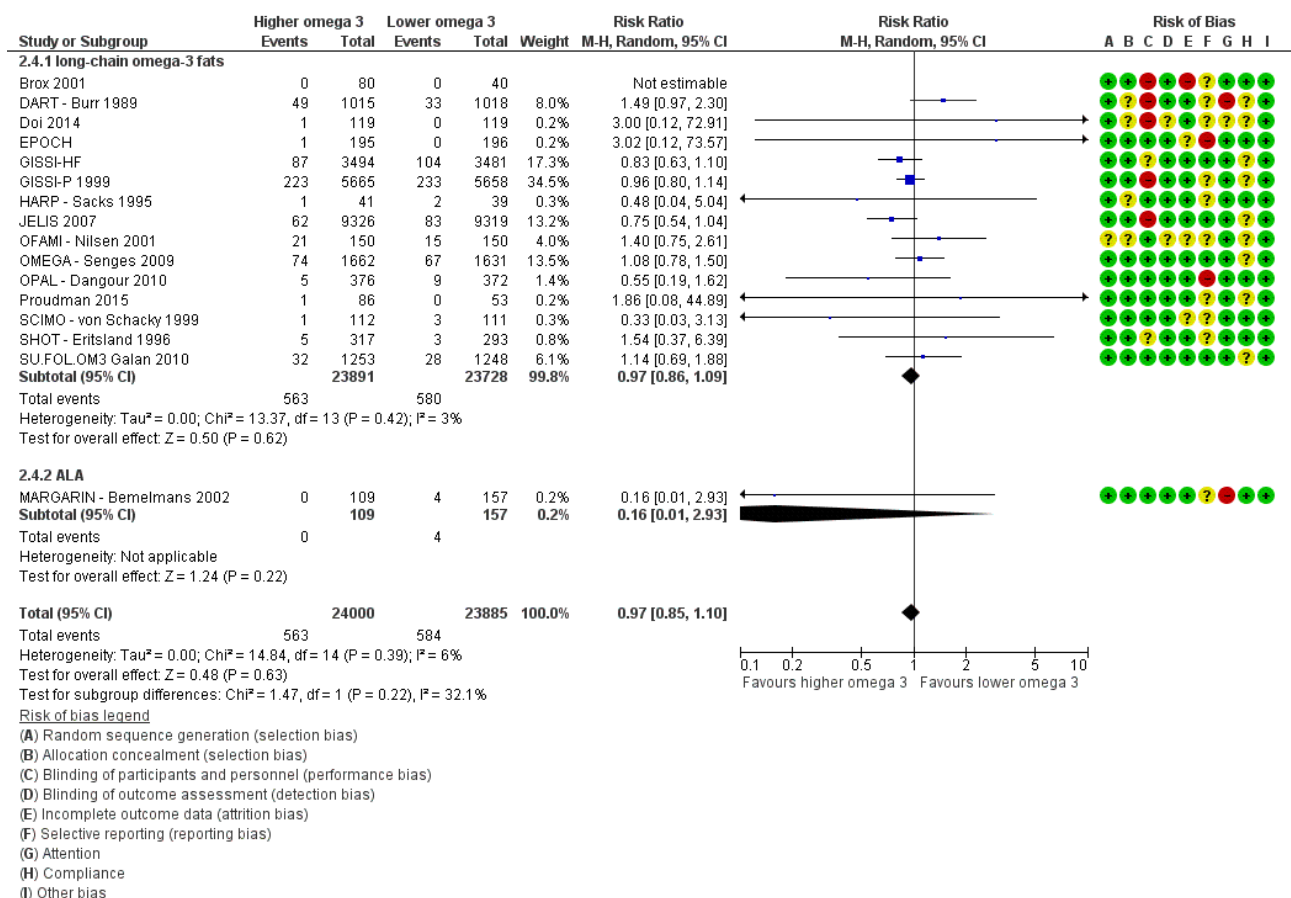


Figure 4.39. Meta-analysis of effects of omega 3 fats on non-fatal MI, subgrouped by LCN3 or ALA intervention.

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).

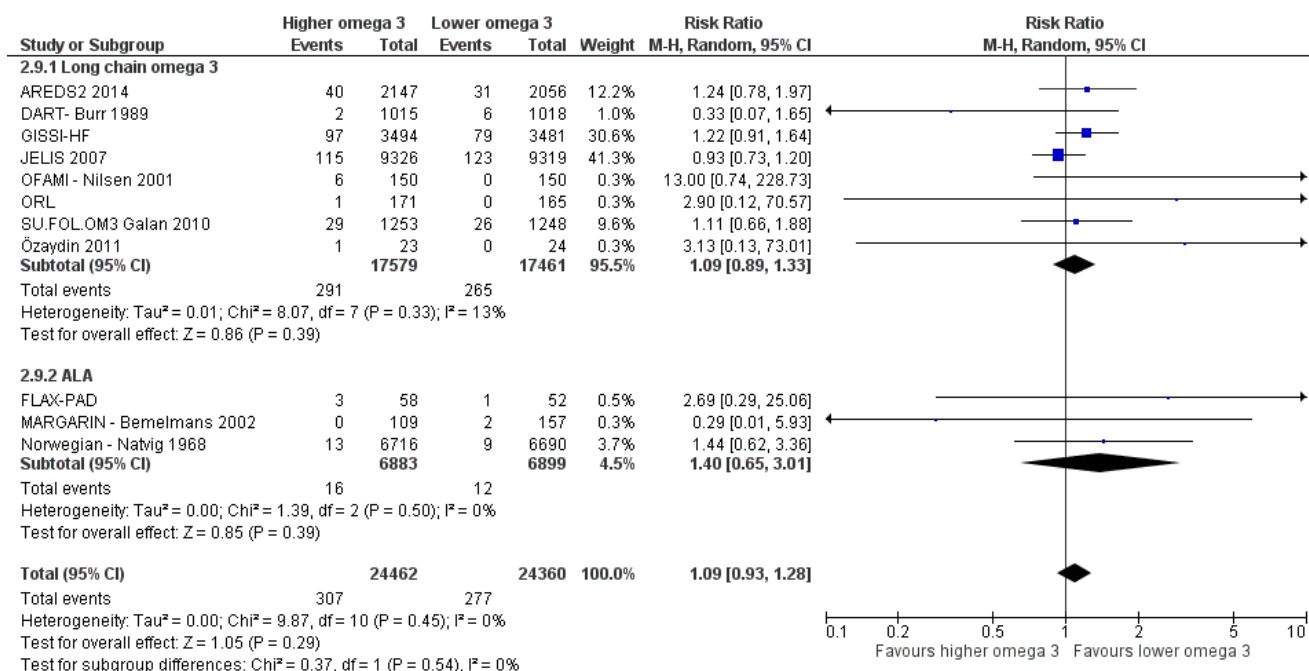


Figure 4.40. Meta-analysis of effects of omega 3 fats on ischaemic stroke, subgrouped by LCn3 or ALA intervention.

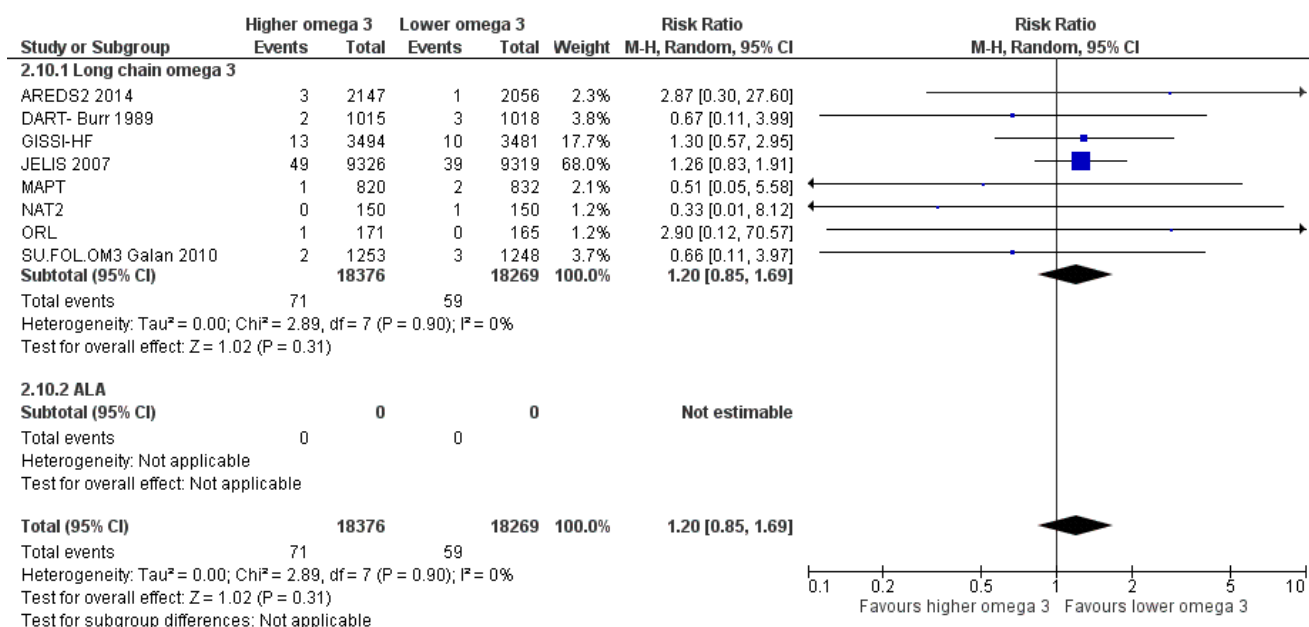


Figure 4.41. Meta-analysis of effects of omega 3 fats on haemorrhagic stroke, subgrouped by LCn3 or ALA intervention.

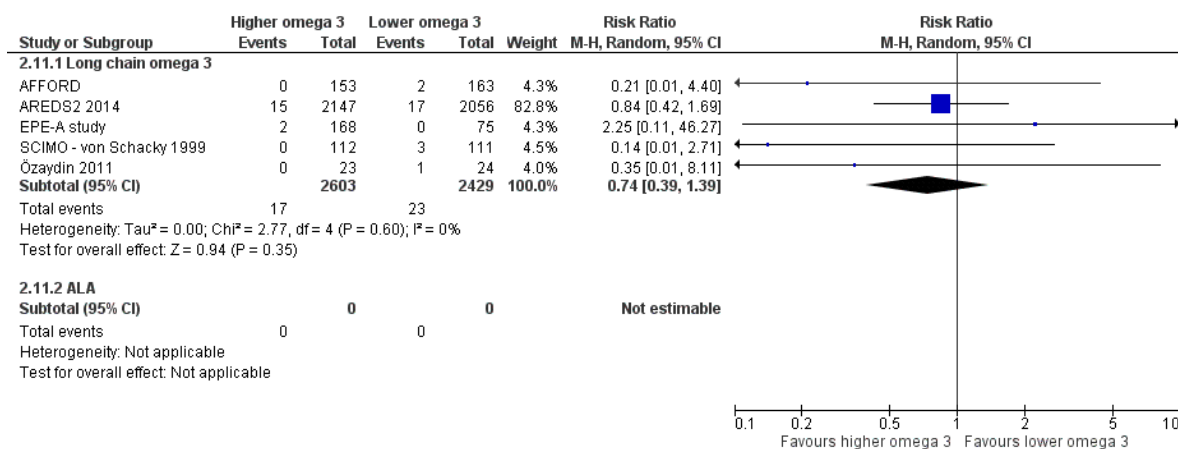


Figure 4.42. Meta-analysis of effects of omega 3 fats on transient ischaemic events (TIA), subgrouped by LCN3 or ALA intervention.

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.

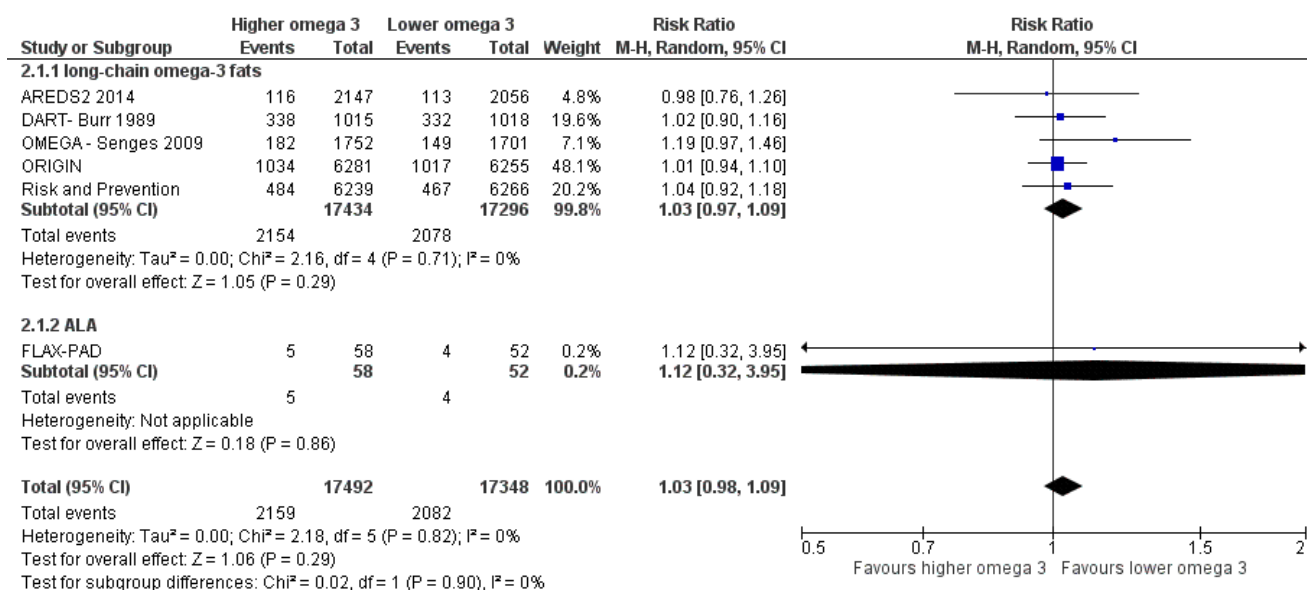


Figure 4.43. Meta-analysis of effects of omega 3 fats on MACCEs, subgrouped by LCN3 or ALA intervention.

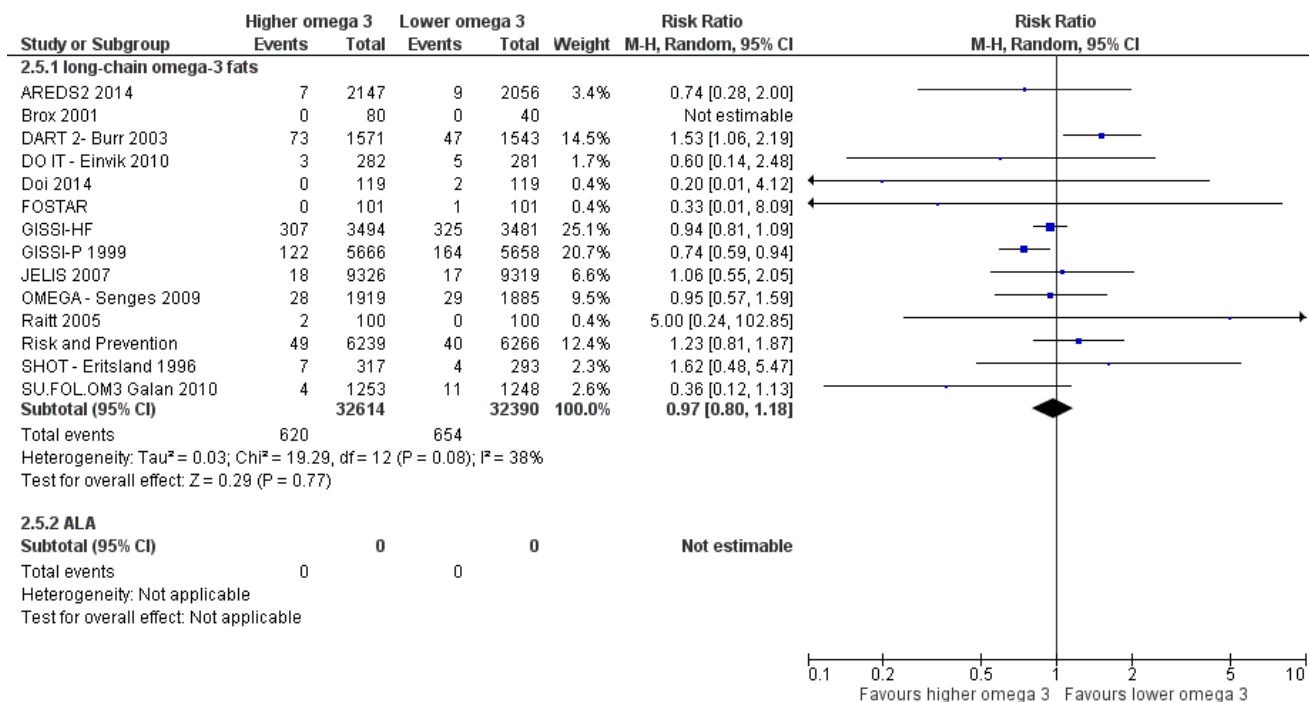


Figure 4.44. Meta-analysis of effects of omega 3 fats on sudden cardiac death, subgrouped by LCN3 or ALA intervention.

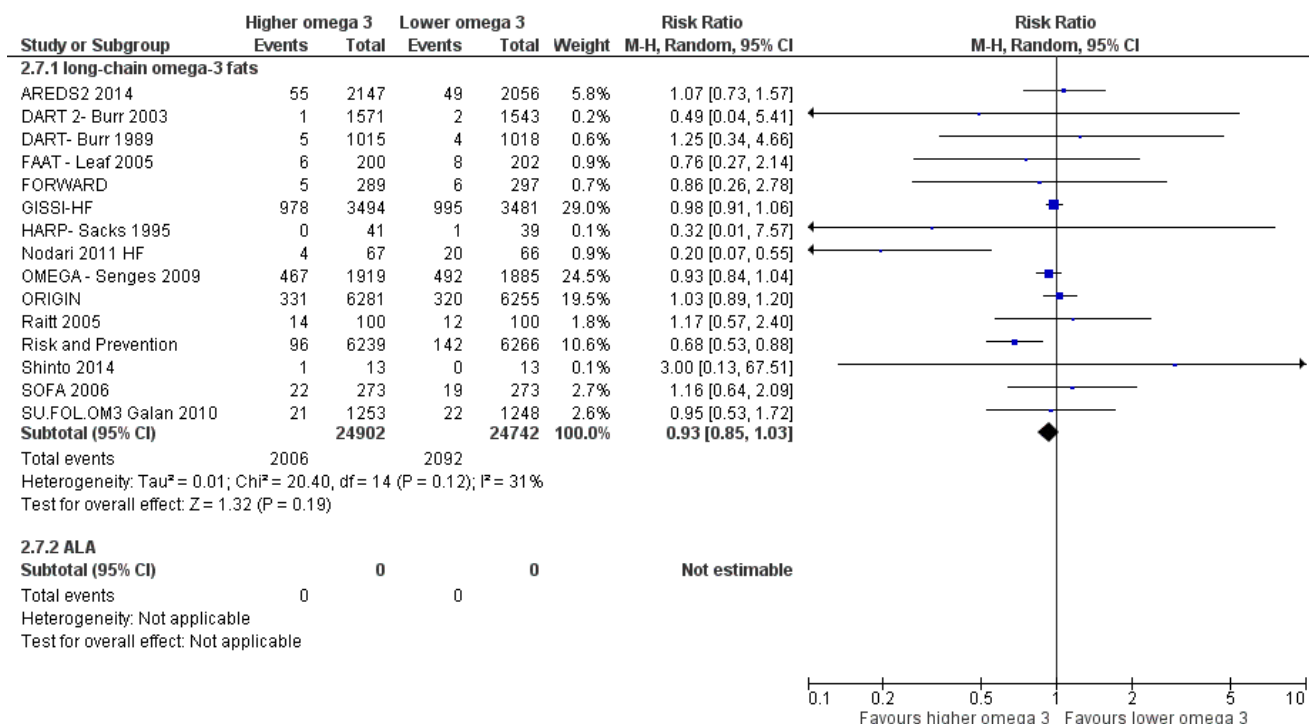


Figure 4.45. Meta-analysis of effects of omega 3 fats on heart failure diagnosis, subgrouped by LCN3 or ALA intervention.

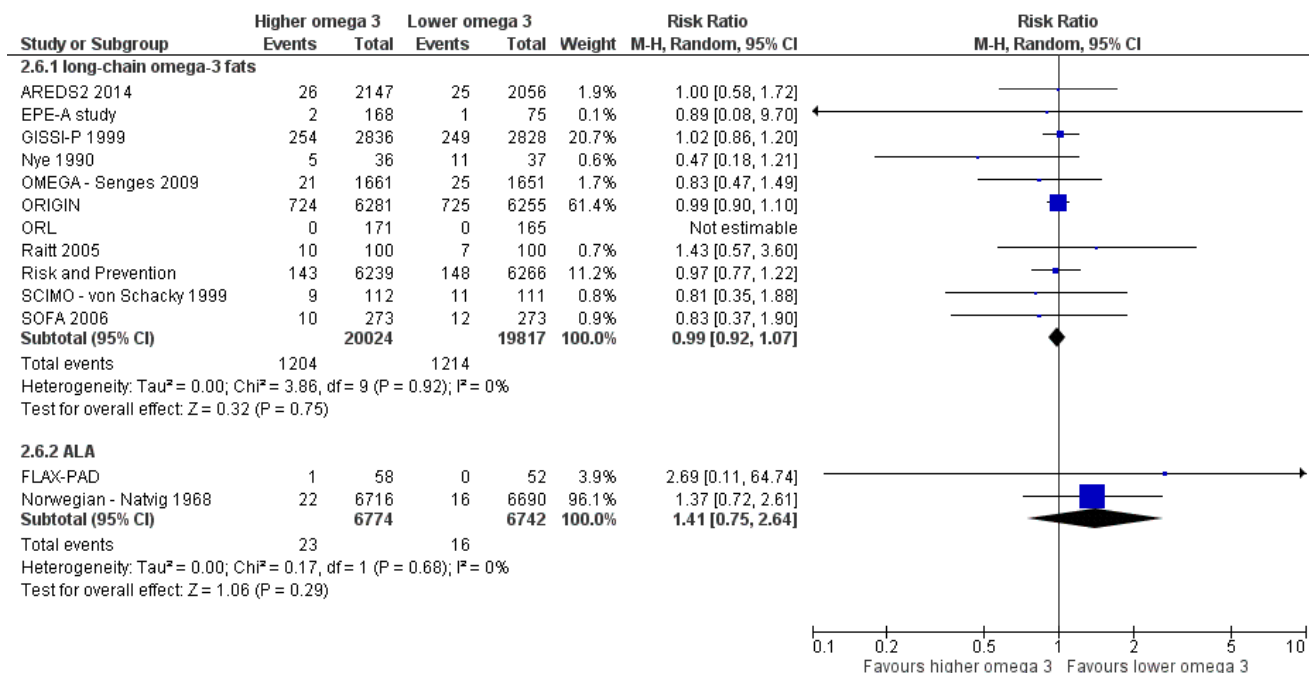


Figure 4.46. Meta-analysis of effects of omega 3 fats on angina, subgrouped by LCn3 or ALA intervention.

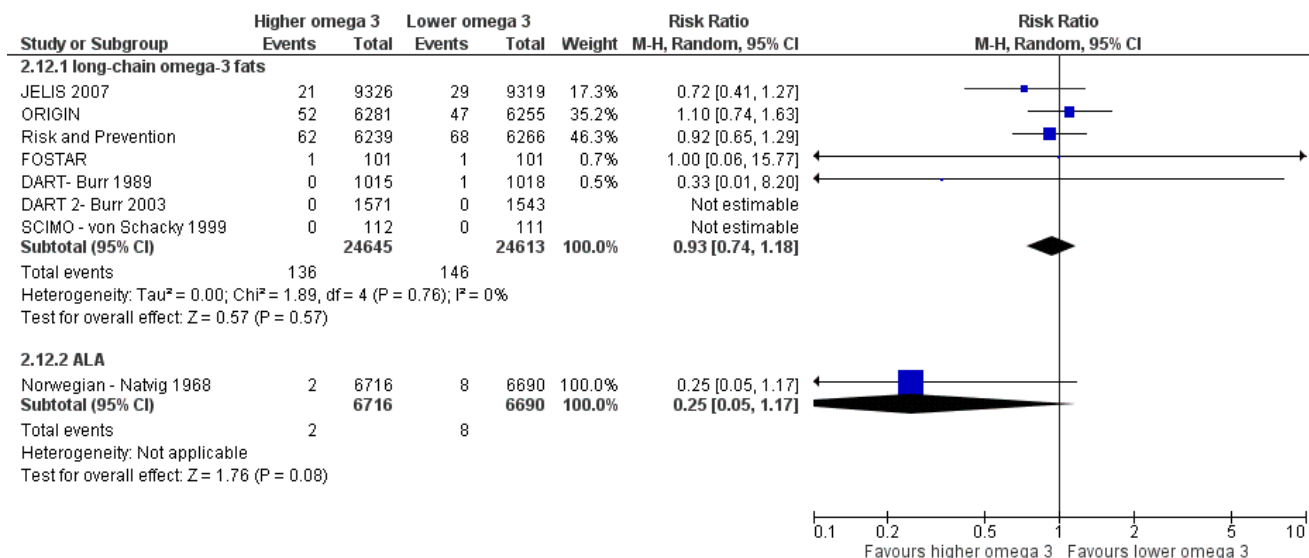


Figure 4.47. Meta-analysis of effects of omega 3 fats on peripheral vascular events, subgrouped by LCn3 or ALA intervention.

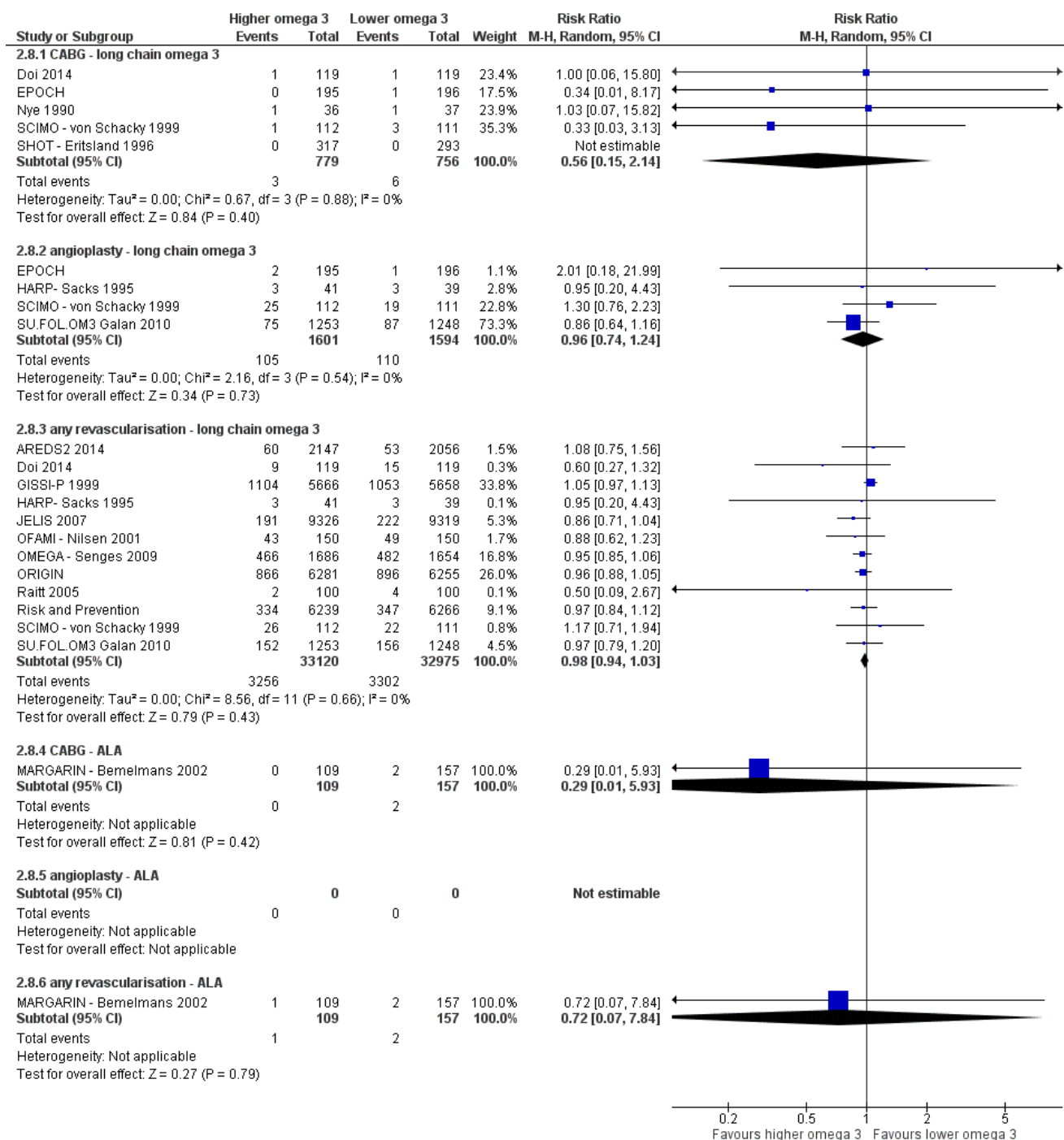


Figure 4.48. Meta-analysis of effects of omega 3 fats on revascularisation, subgrouped by LCN3 or ALA intervention.

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.

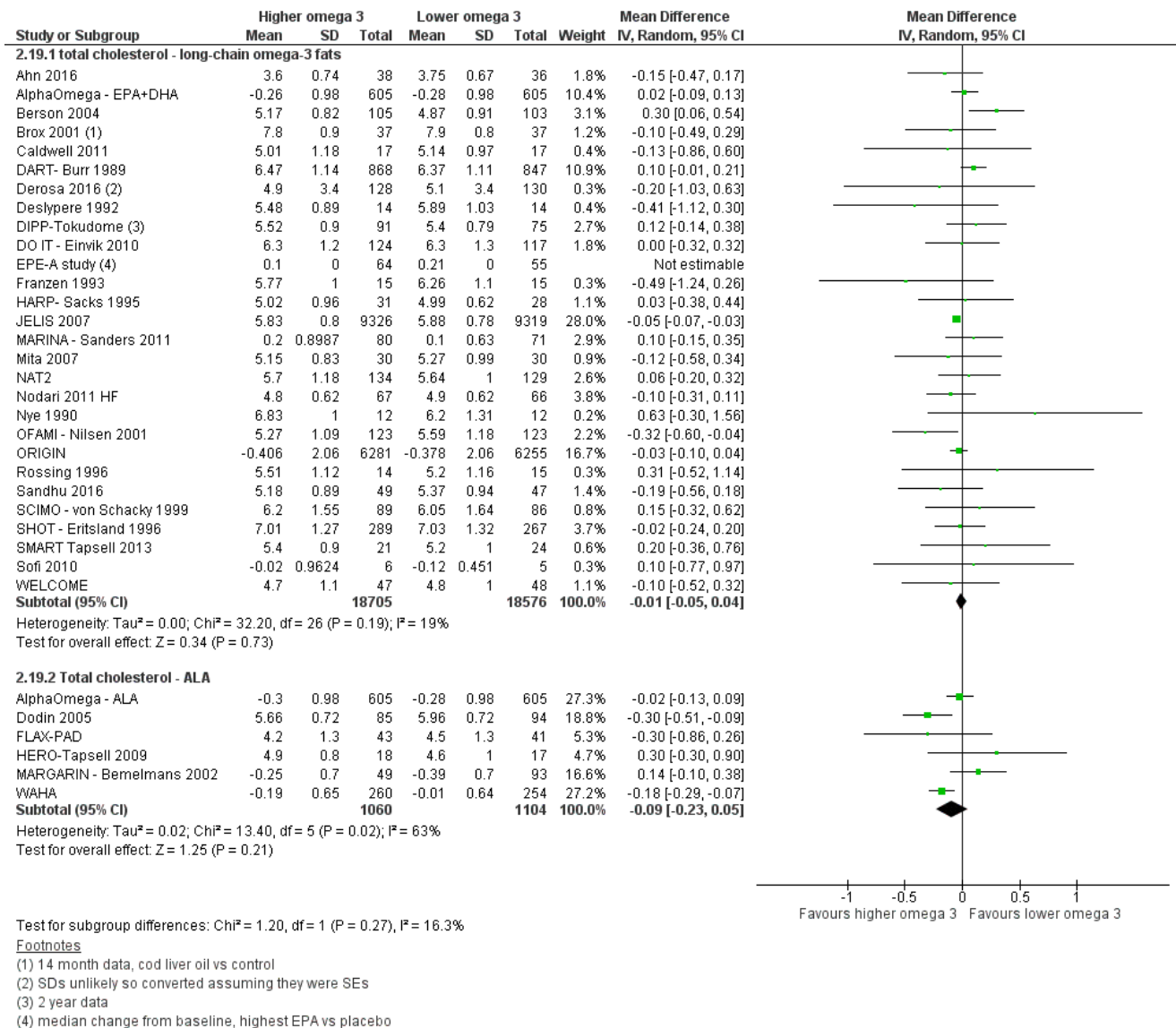


Figure 5.1. Meta-analysis of effects of omega 3 fats on serum total cholesterol, subgrouped by LCN3 or ALA intervention.

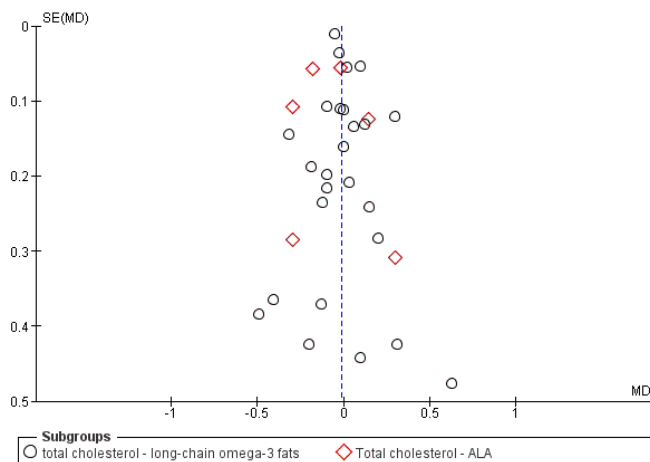


Figure 5.2. Funnel plot of effects of omega 3 fats on serum total cholesterol.

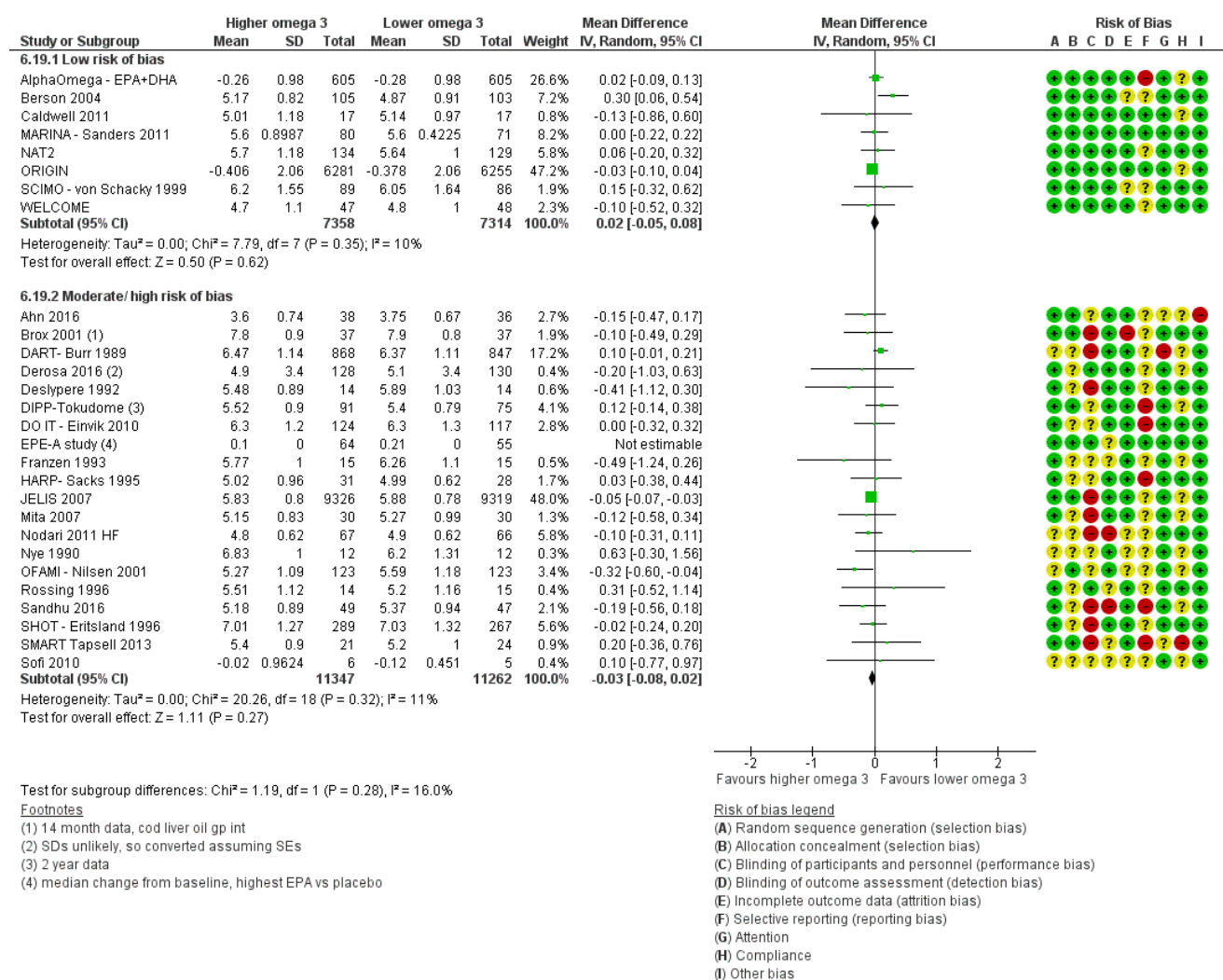


Figure 5.3. Meta-analysis of effects of LCn3 fats on serum total cholesterol, subgrouped by summary risk of bias.

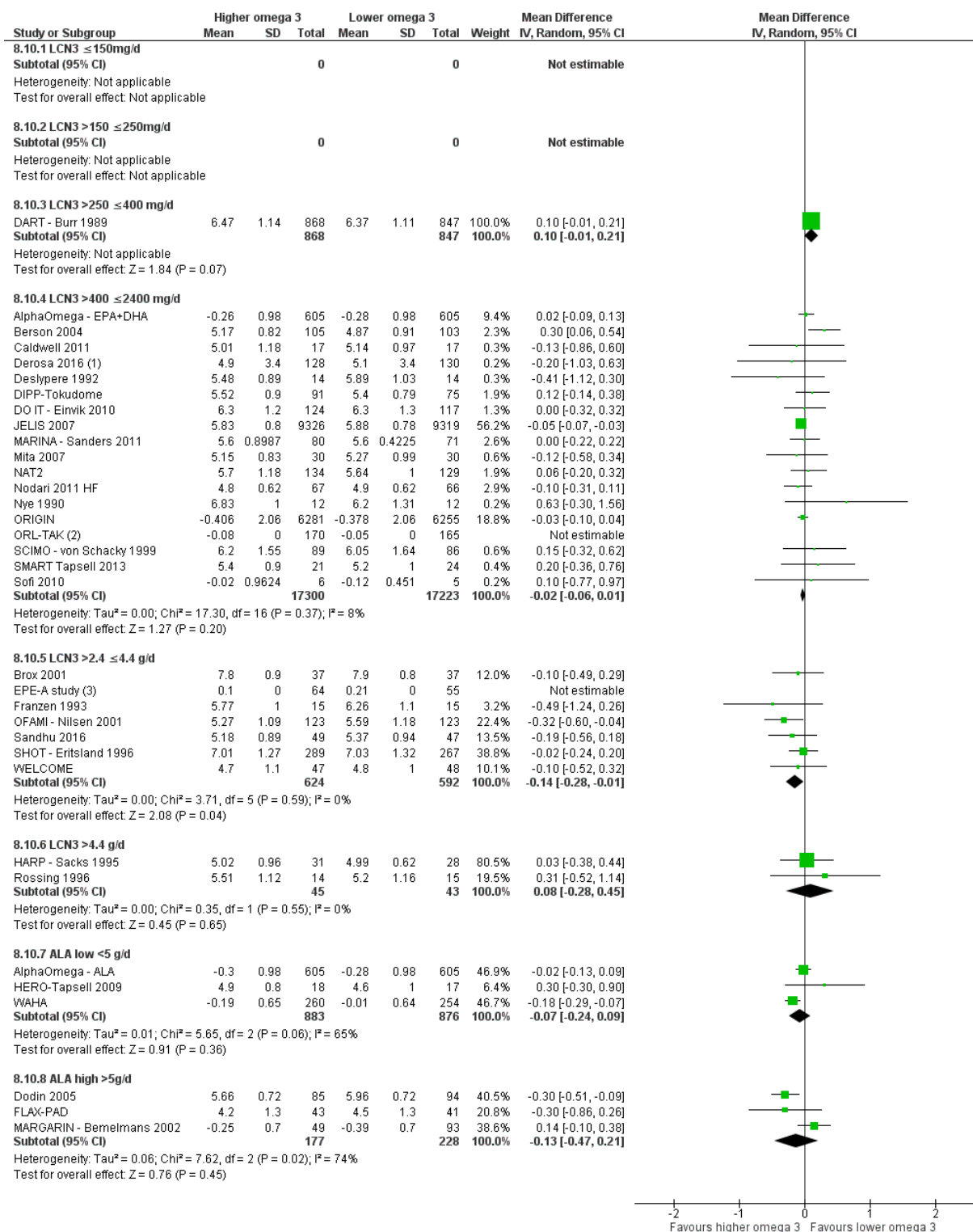


Figure 5.4. Meta-analysis of effects of omega 3 fats on serum total cholesterol, subgrouped by LCN3 or ALA dose.

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.

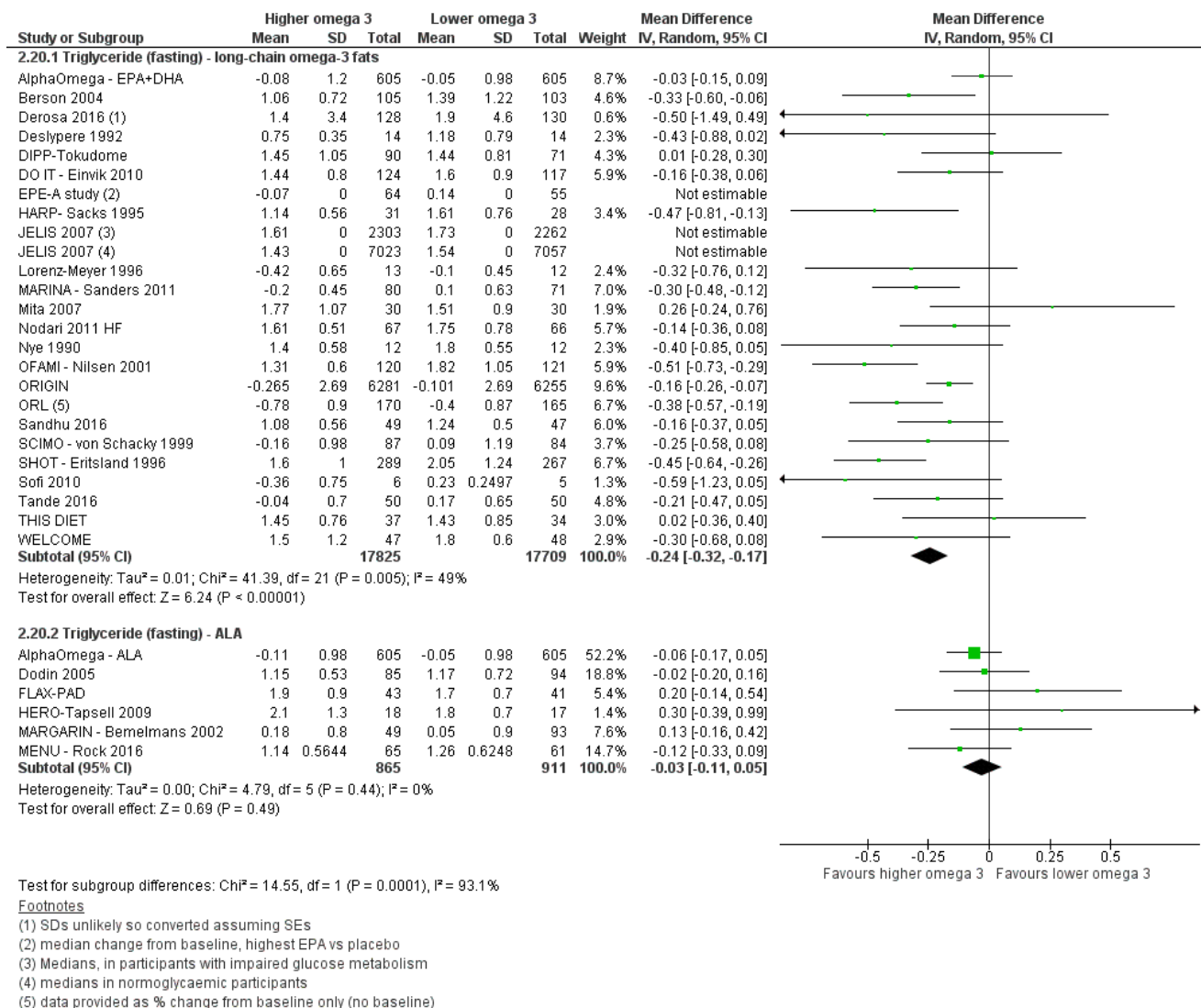


Figure 5.5. Meta-analysis of the effects of omega 3 fats on serum triglycerides, subgrouped by LCn3 or ALA.

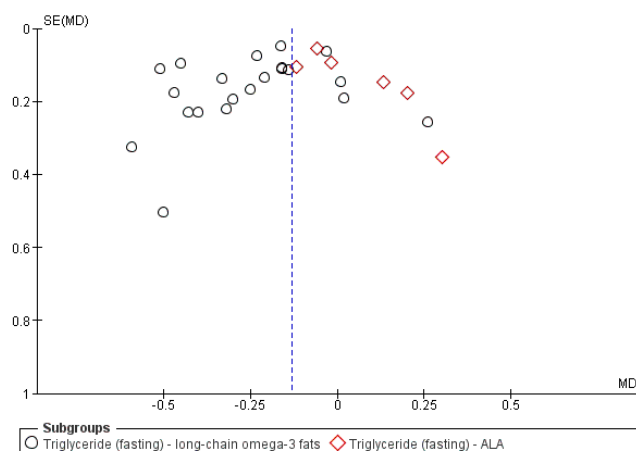


Figure 5.6. Funnel plot of the effects of omega 3 fats on serum triglycerides, subgrouped by LCn3 or ALA.

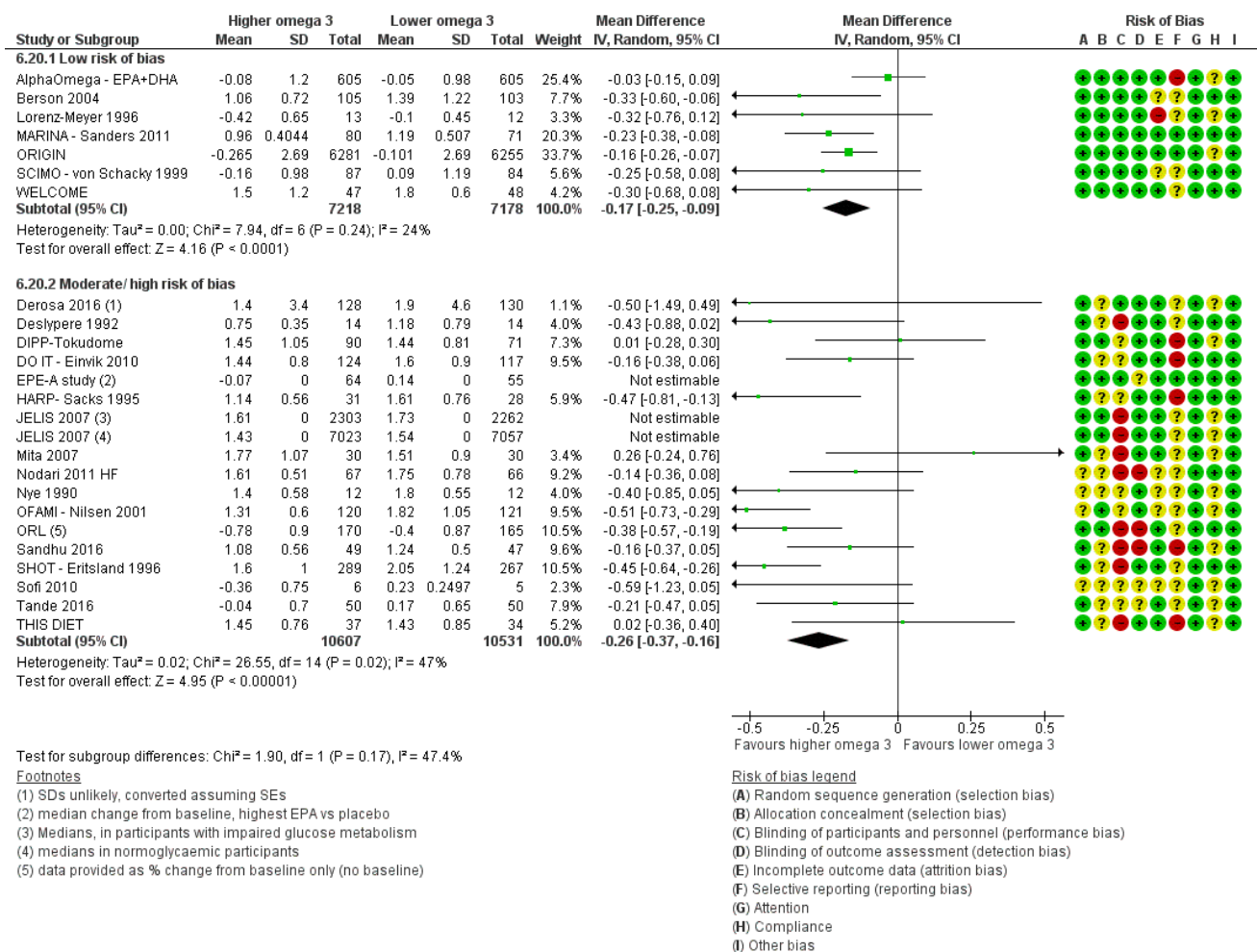


Figure 5.7. Meta-analysis of the effects of omega 3 fats on serum triglycerides, sensitivity analysis removing trials of moderate to high risk of bias (though shown as a subgrouping by summary risk of bias).

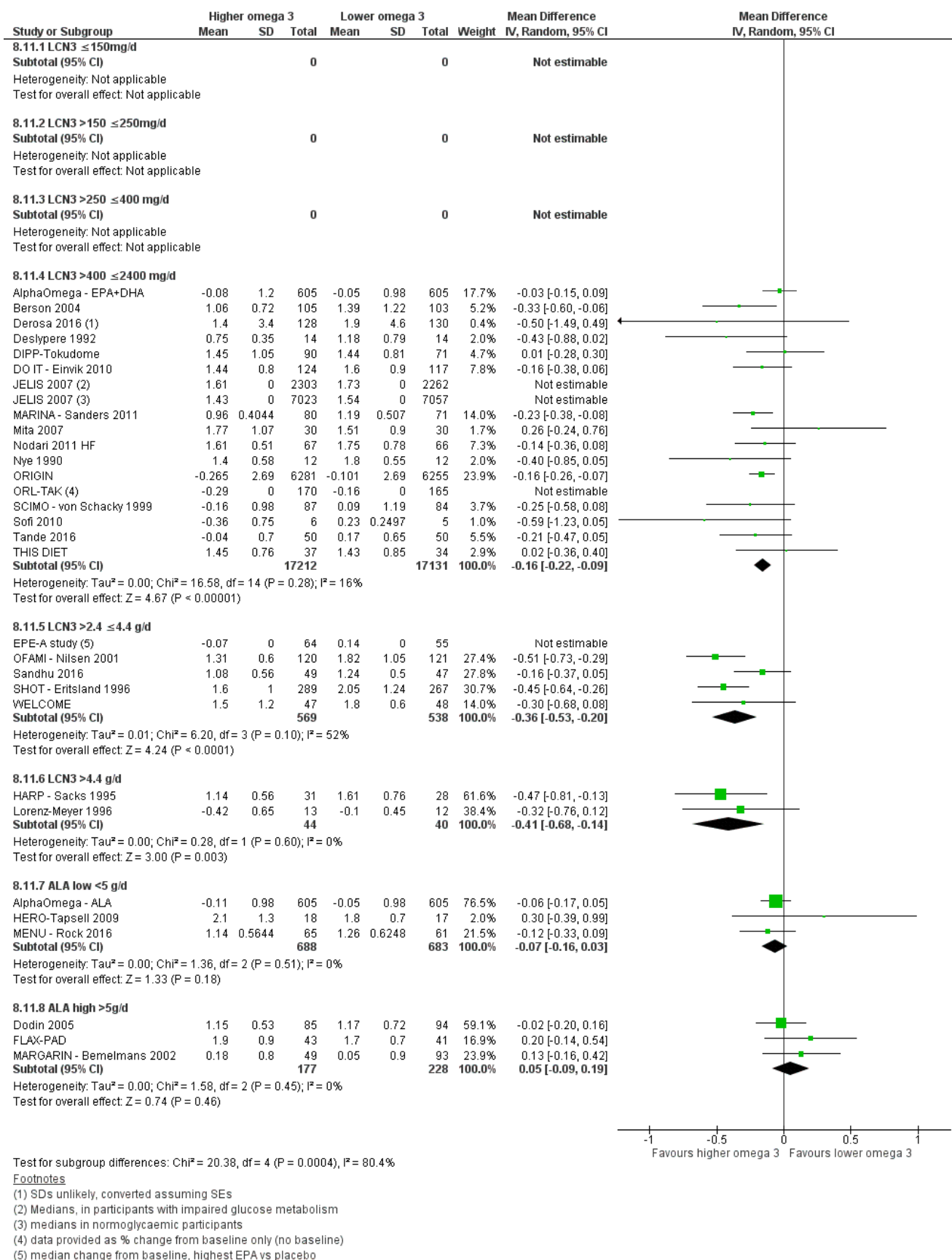


Figure 5.8. Meta-analysis of the effects of omega 3 fats on serum triglycerides (mmol/L), subgrouped by LCN3 and ALA dose.

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.

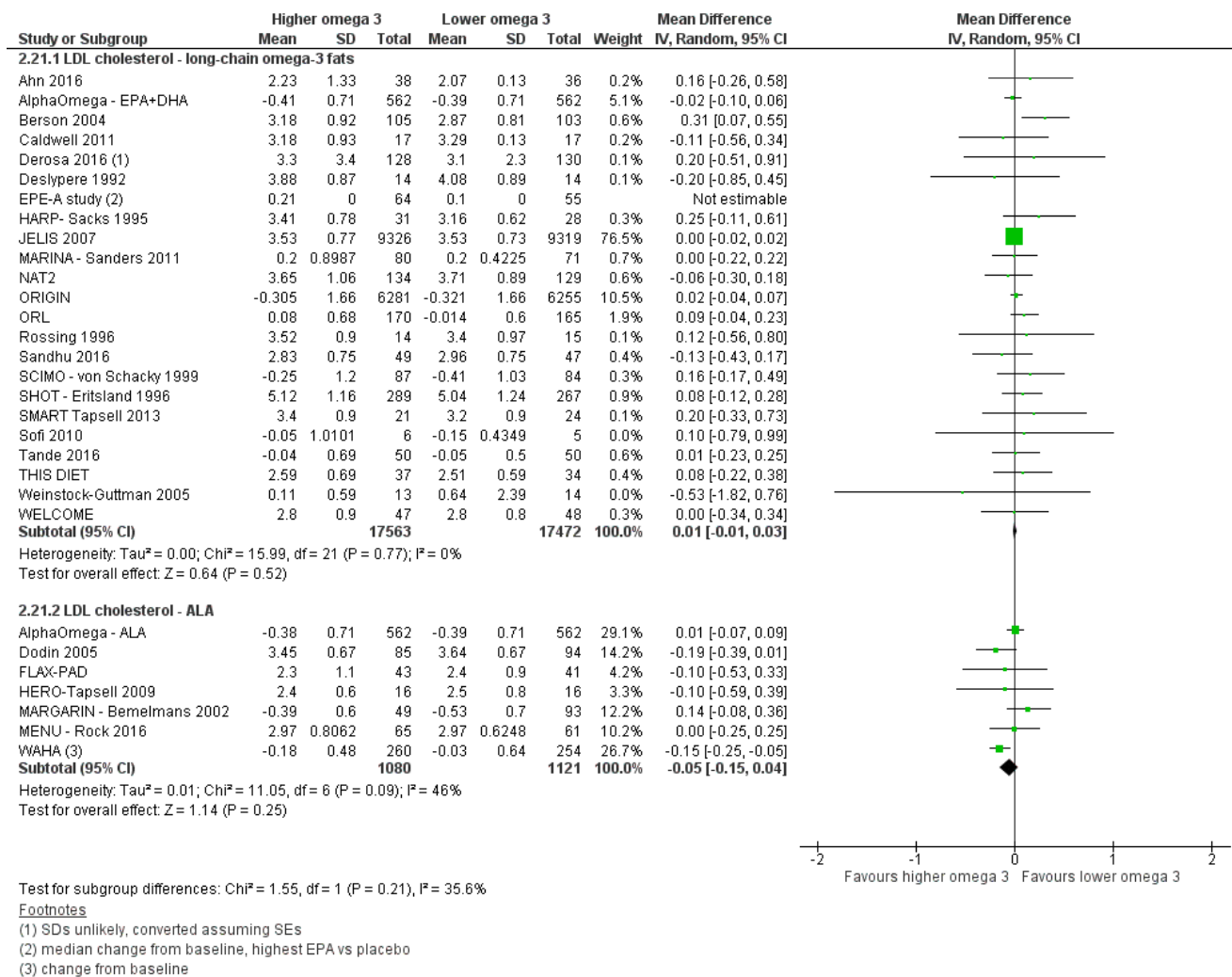


Figure 5.9. Meta-analysis of the effects of omega 3 fats on serum LDL (mmol/L), subgrouped by LCn3 and ALA.

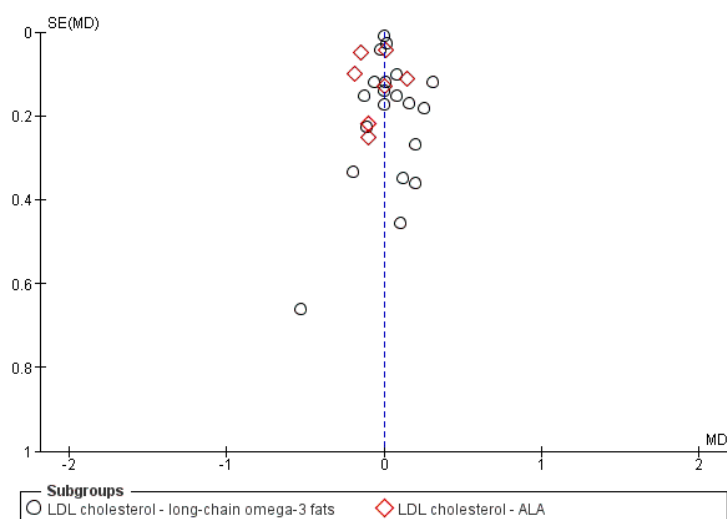


Figure 5.10. Funnel plot of the effects of omega 3 fats on LDL cholesterol.

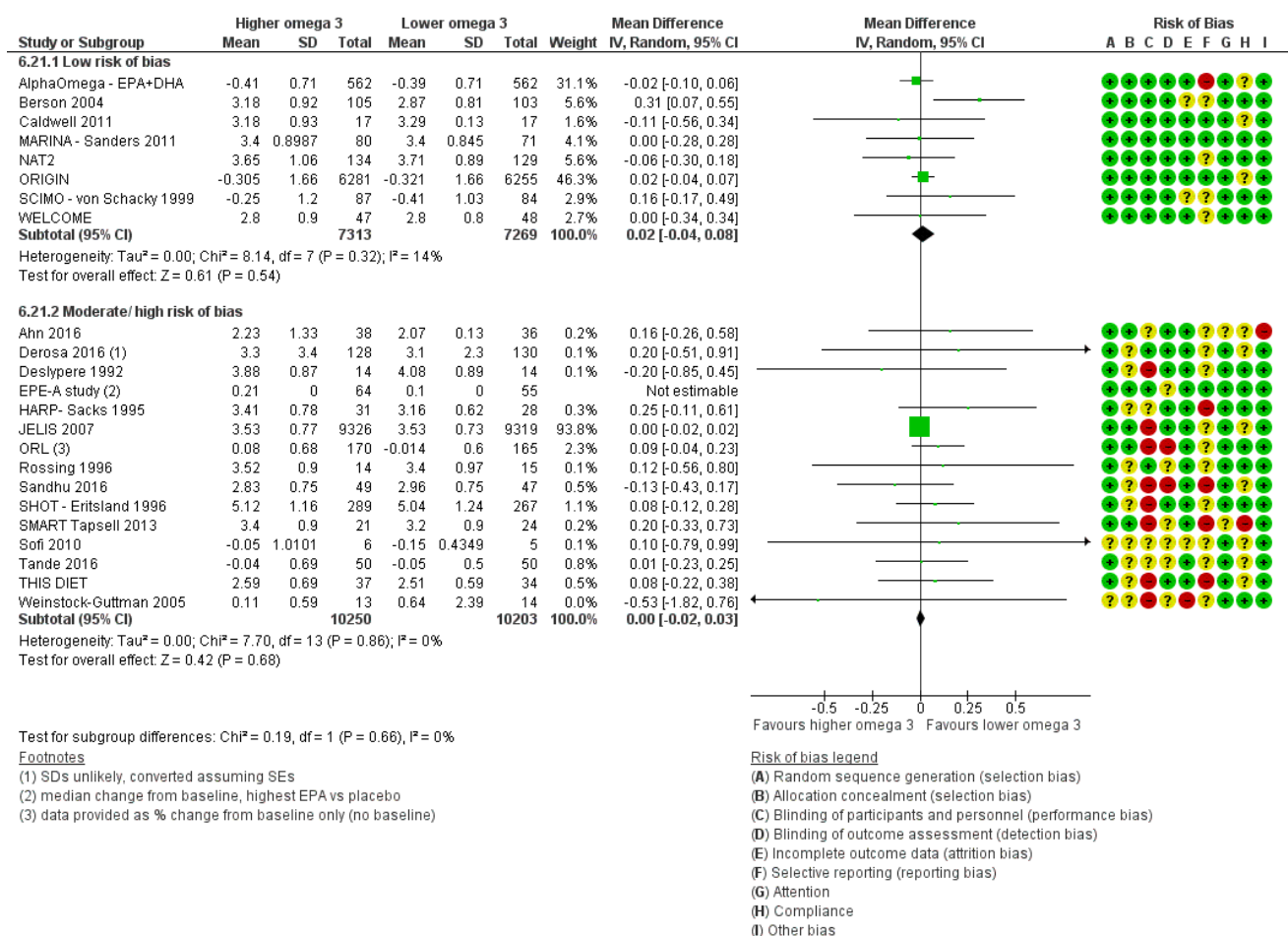


Figure 5.11. Meta-analysis of effects of omega 3 fats on serum LDL (in mmol/L), sensitivity analysis, removing trials at moderate to high risk of bias (shown in a separate subgroup).

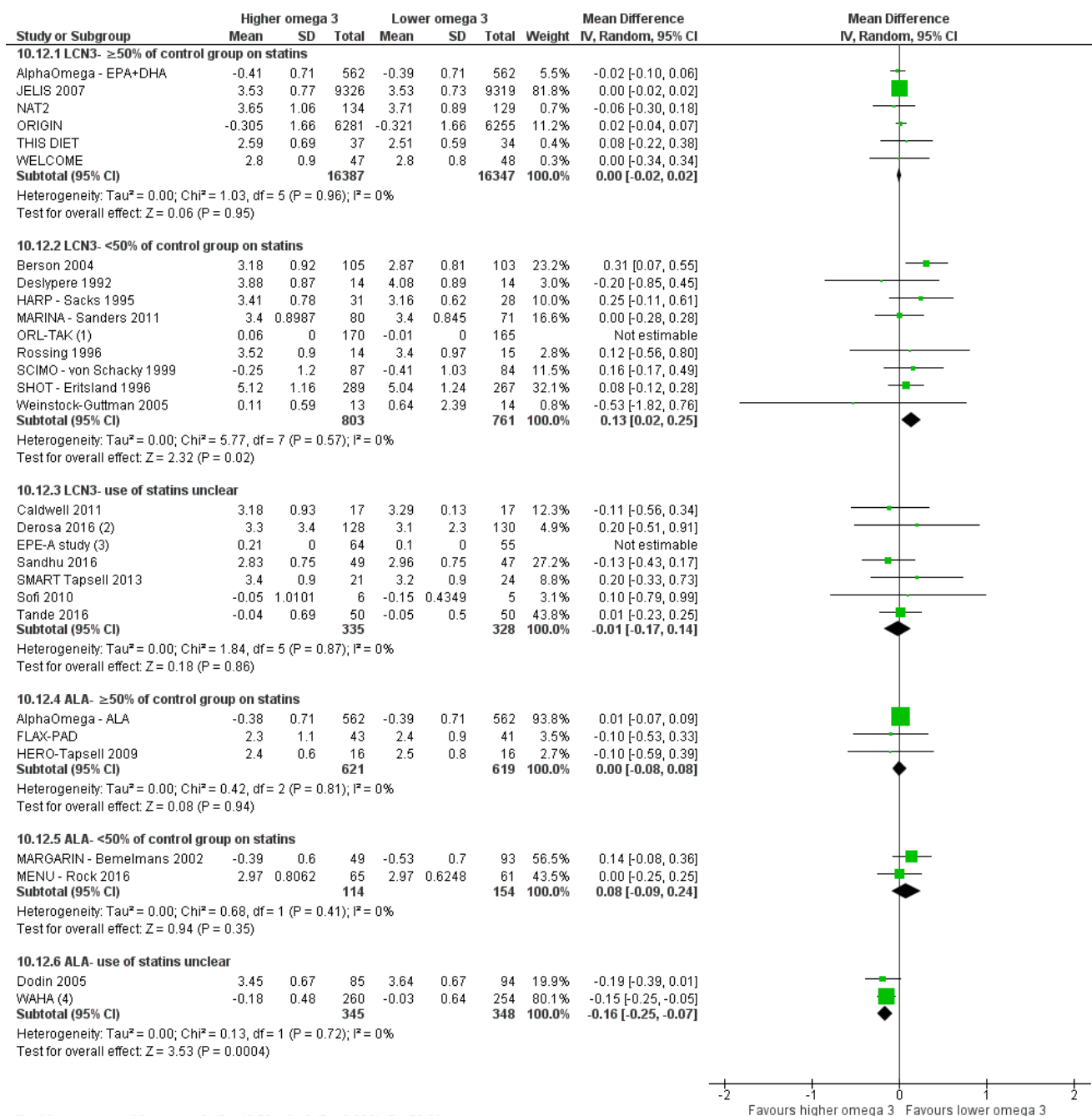


Figure 5.12. Meta-analysis of effects of omega 3 fats on serum LDL (in mmol/L), subgrouped by statin use.

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.

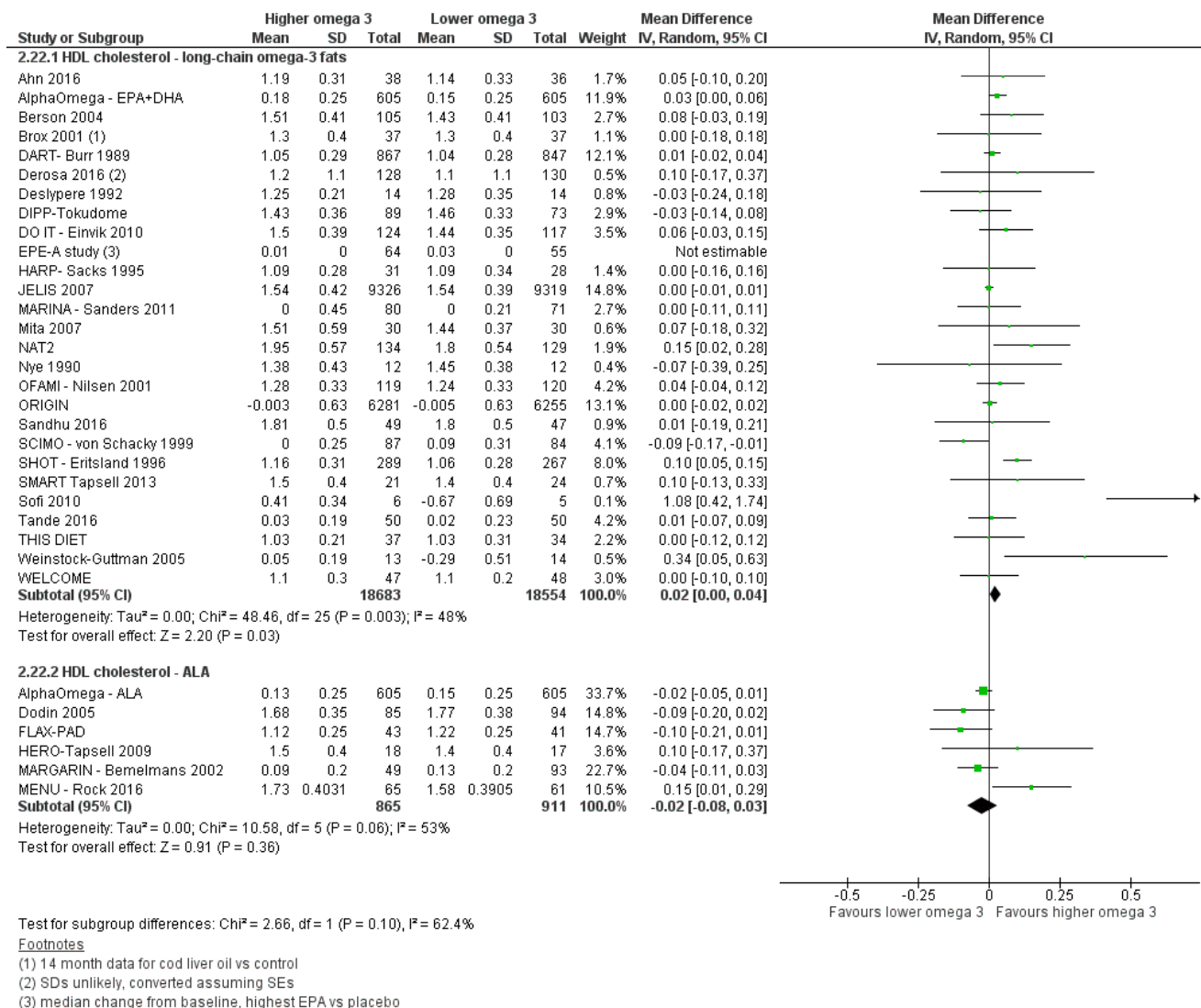


Figure 5.13. Meta-analysis of effects of omega 3 fats on serum HDL (in mmol/L), subgrouped by LCn3 or ALA intervention.

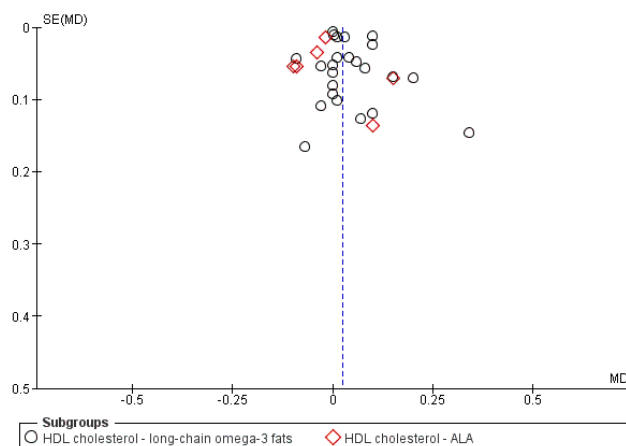


Figure 5.14. Funnel plot of effects of omega 3 fats on serum HDL (in mmol/L).

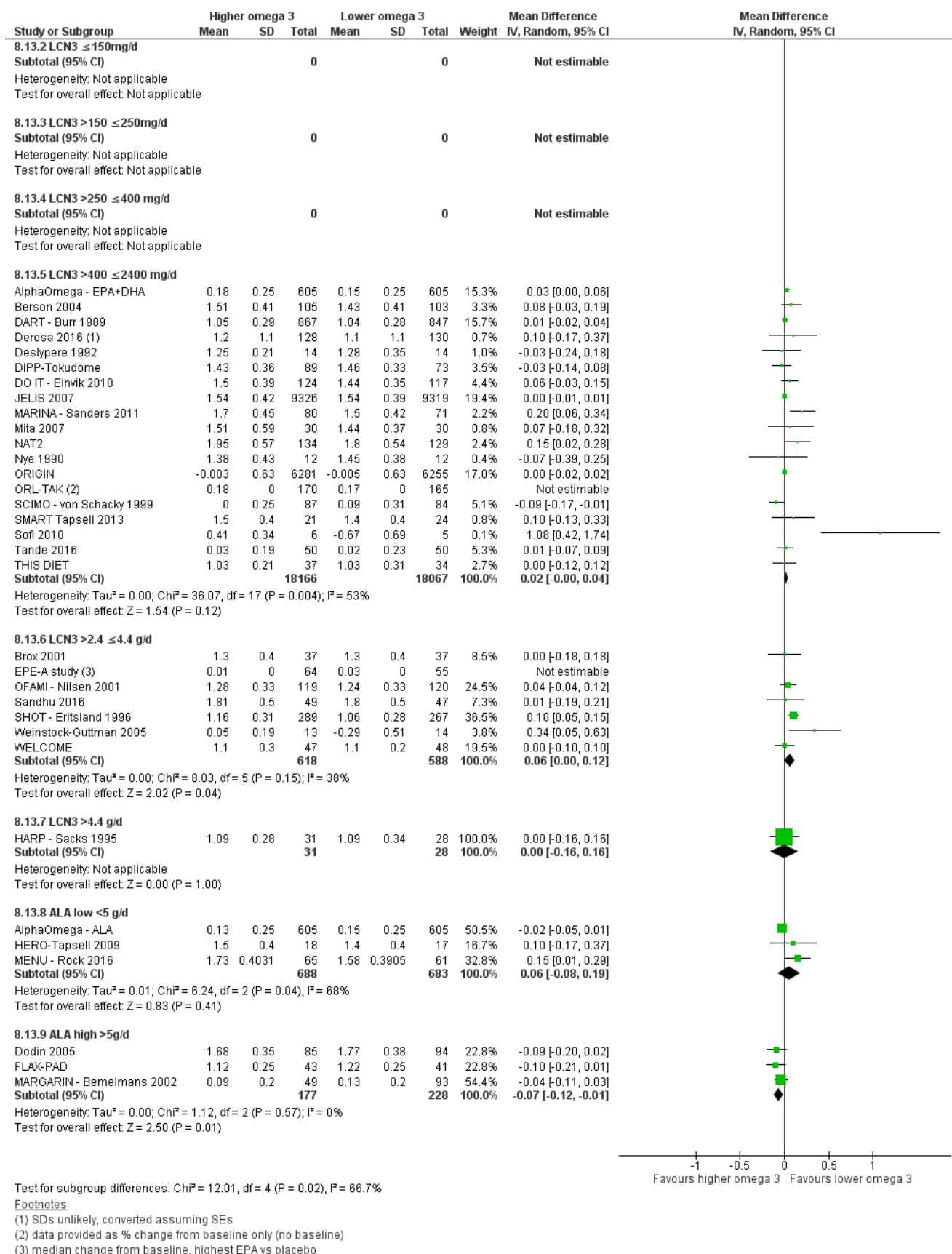


Figure 5.16. Meta-analysis of effects of omega 3 fats on serum HDL (in mmol/L), subgrouped by LCN3 or ALA dose.

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.

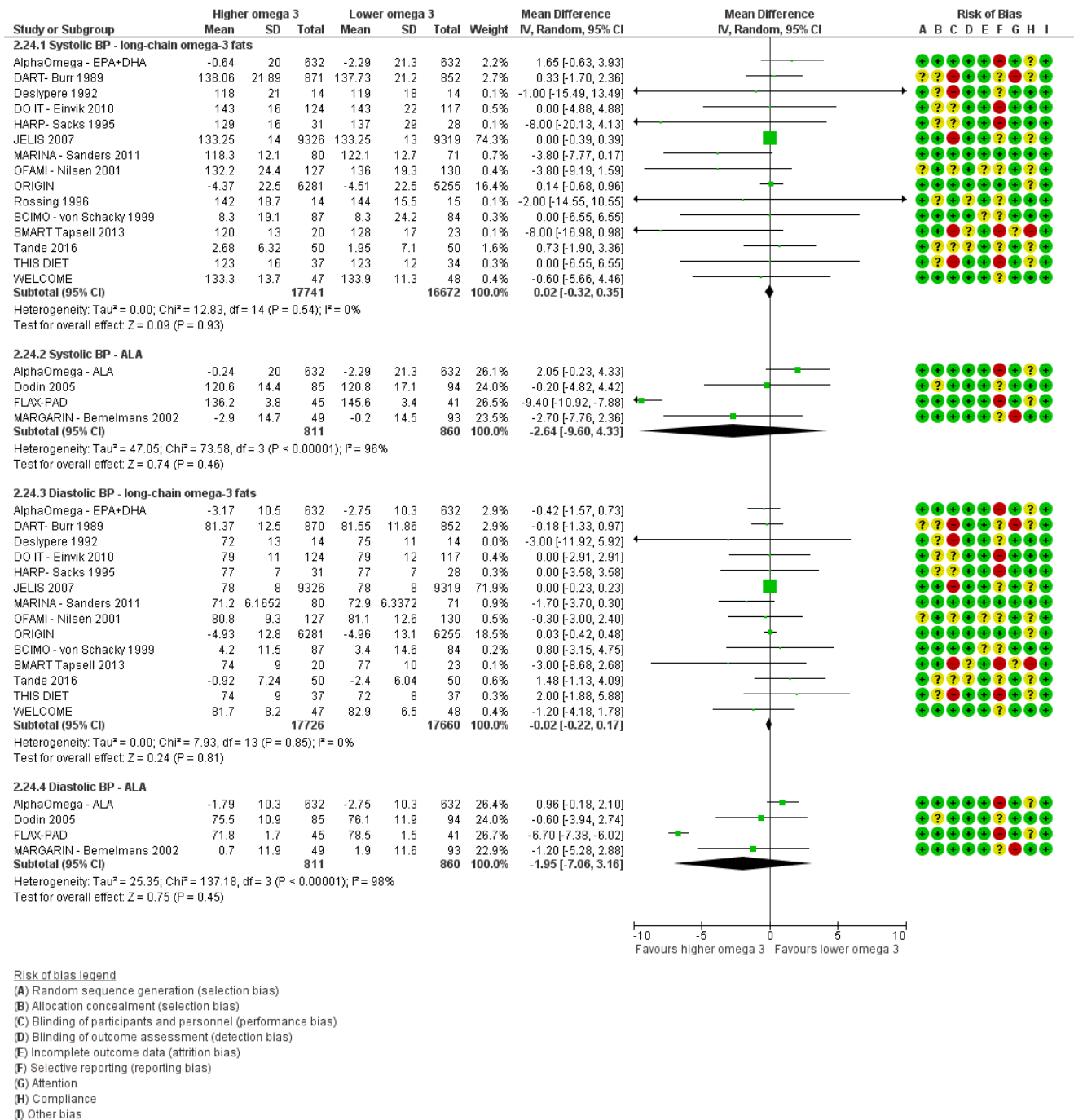


Figure 5.17. Meta-analysis of effects of long-chain and ALA omega 3 fats on systolic and diastolic blood pressure.

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%).

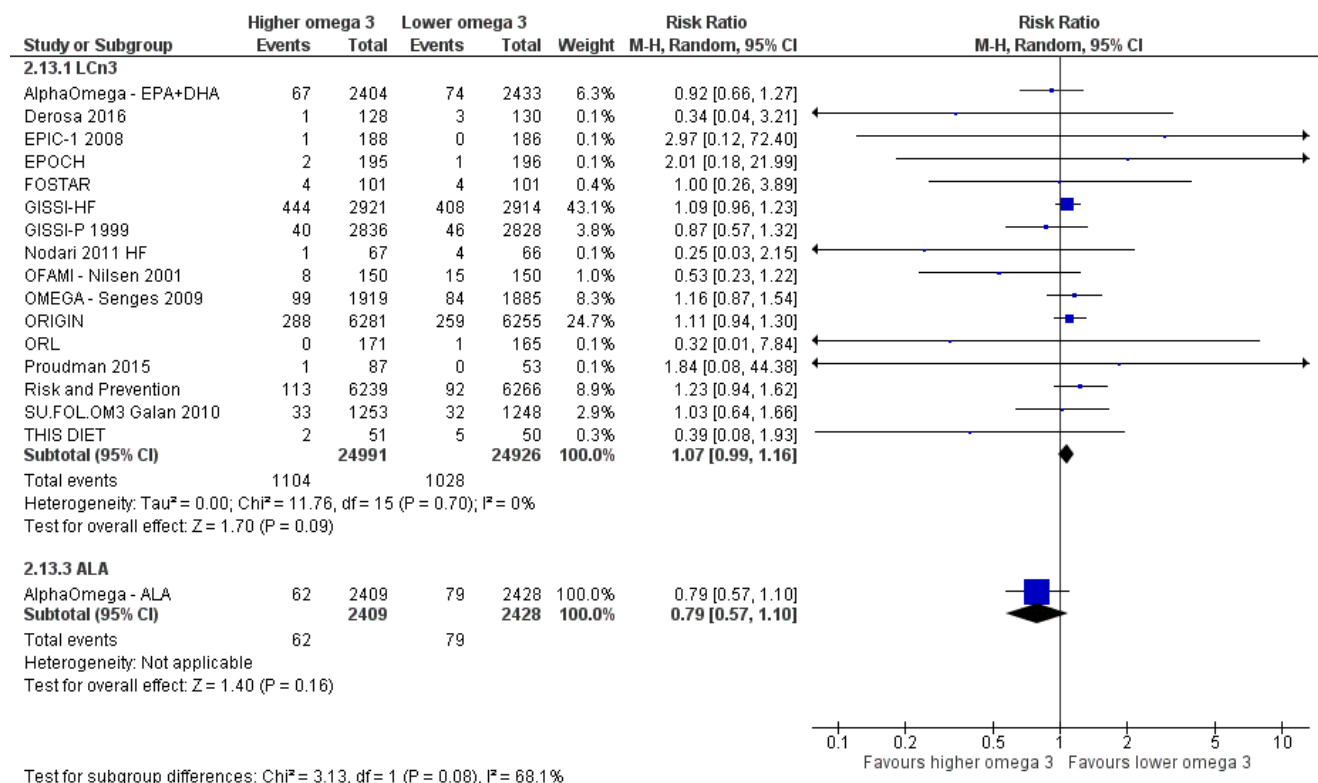


Figure 6.1. Meta-analysis of effects of LCn3 fats on new atrial or ventricular fibrillation or ventricular arrhythmia.

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.

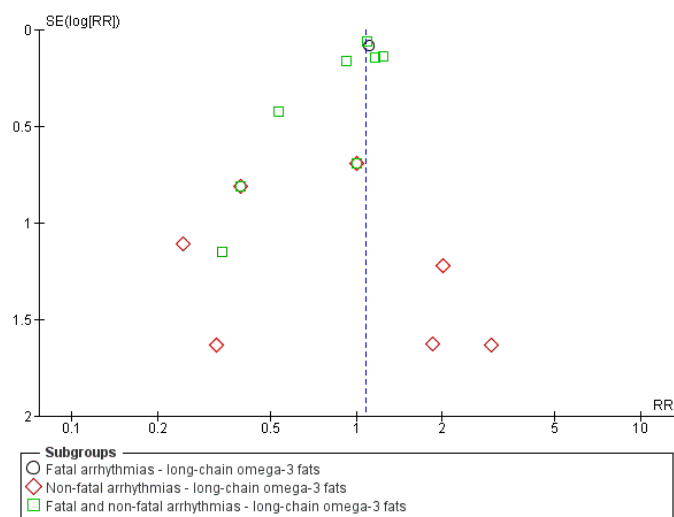


Figure 6.2. Funnel plot of LCn3 fats on new atrial fibrillation.

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.

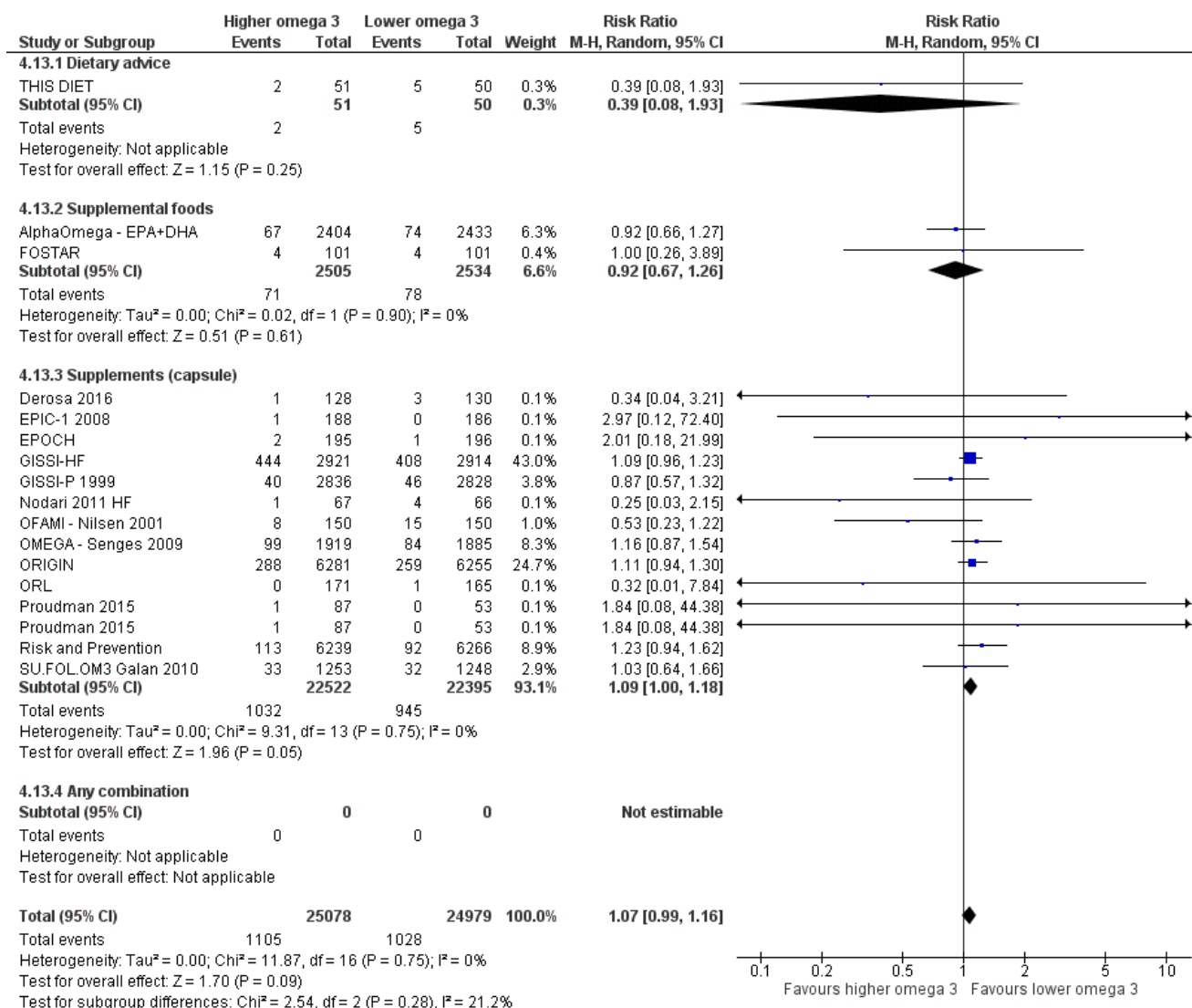


Figure 6.3. Meta-analysis of LCn3 fats on new atrial fibrillation, subgrouping by type of intervention.

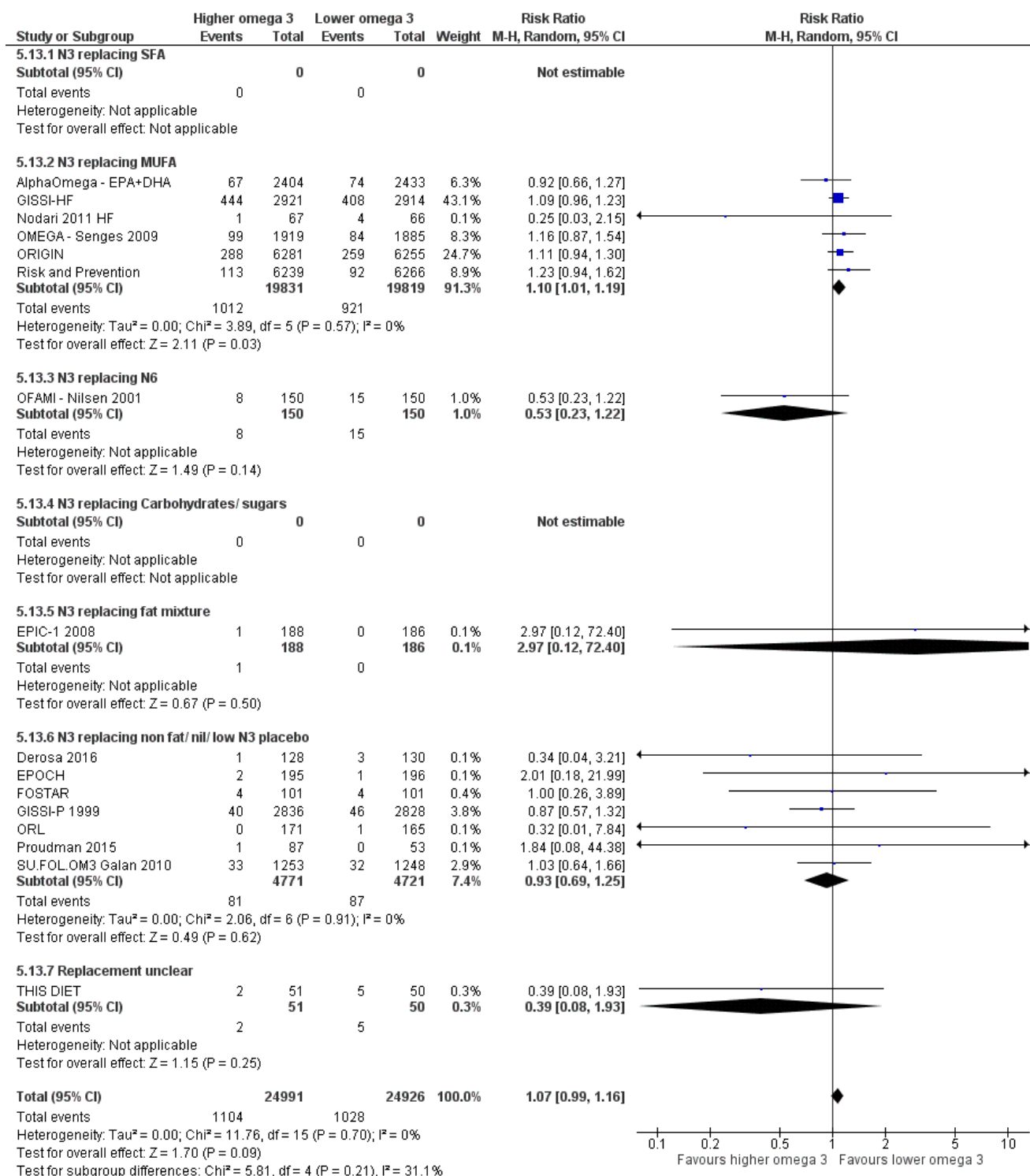


Figure 6.4. Meta-analysis of effects of omega 3 fats on new atrial fibrillation, subgrouping by replacement.

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.

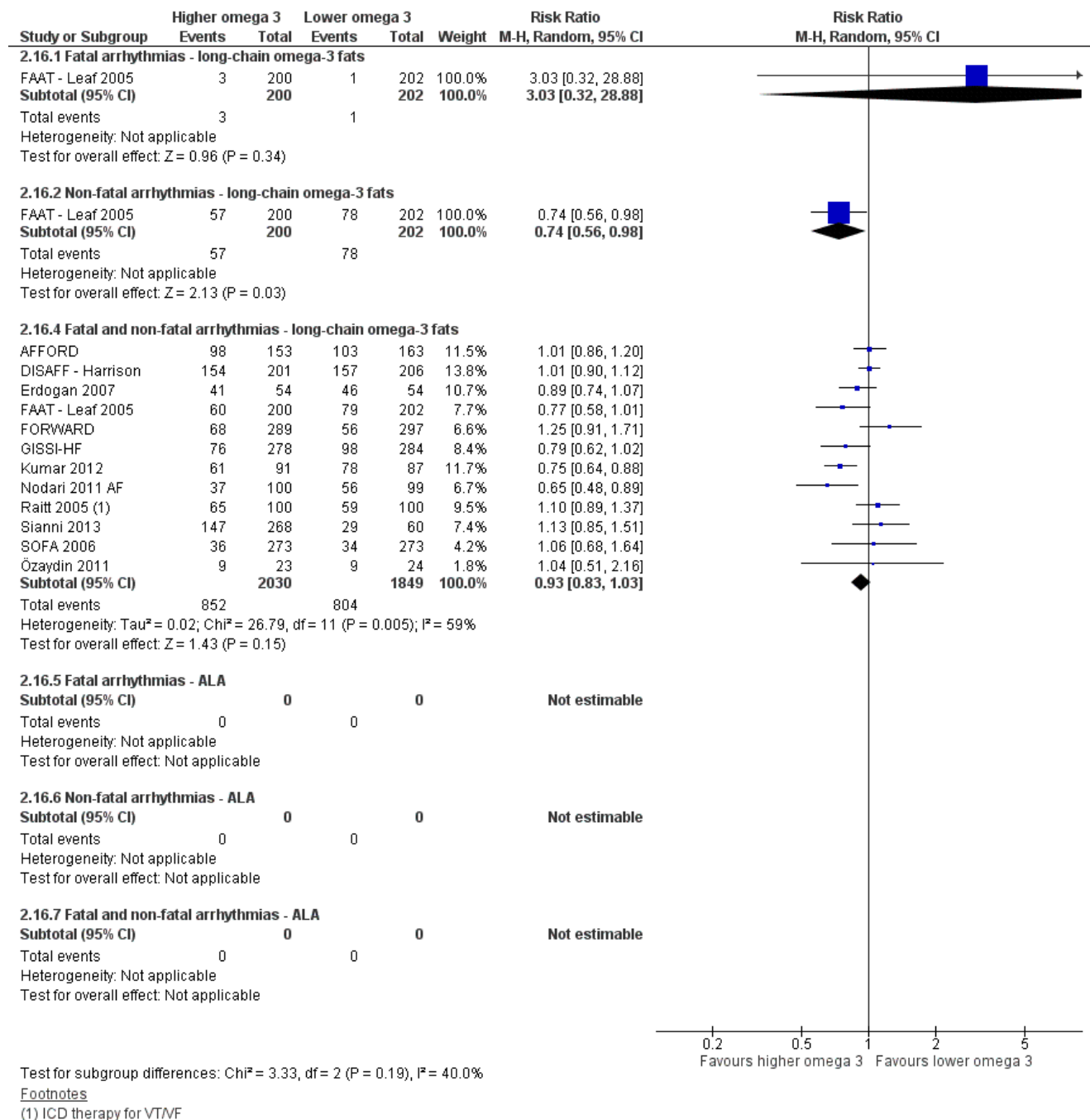


Figure 6.5. Meta-analysis of effects of omega 3 fats on recurrent atrial fibrillation.

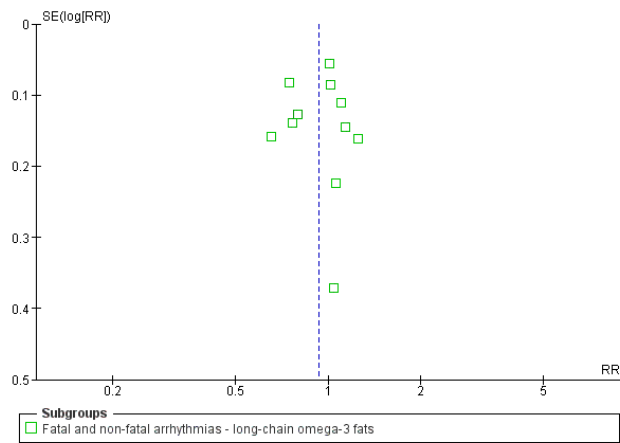


Figure 6.6. Funnel plot of effects of LCn3 fats on recurrence of arrhythmias

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

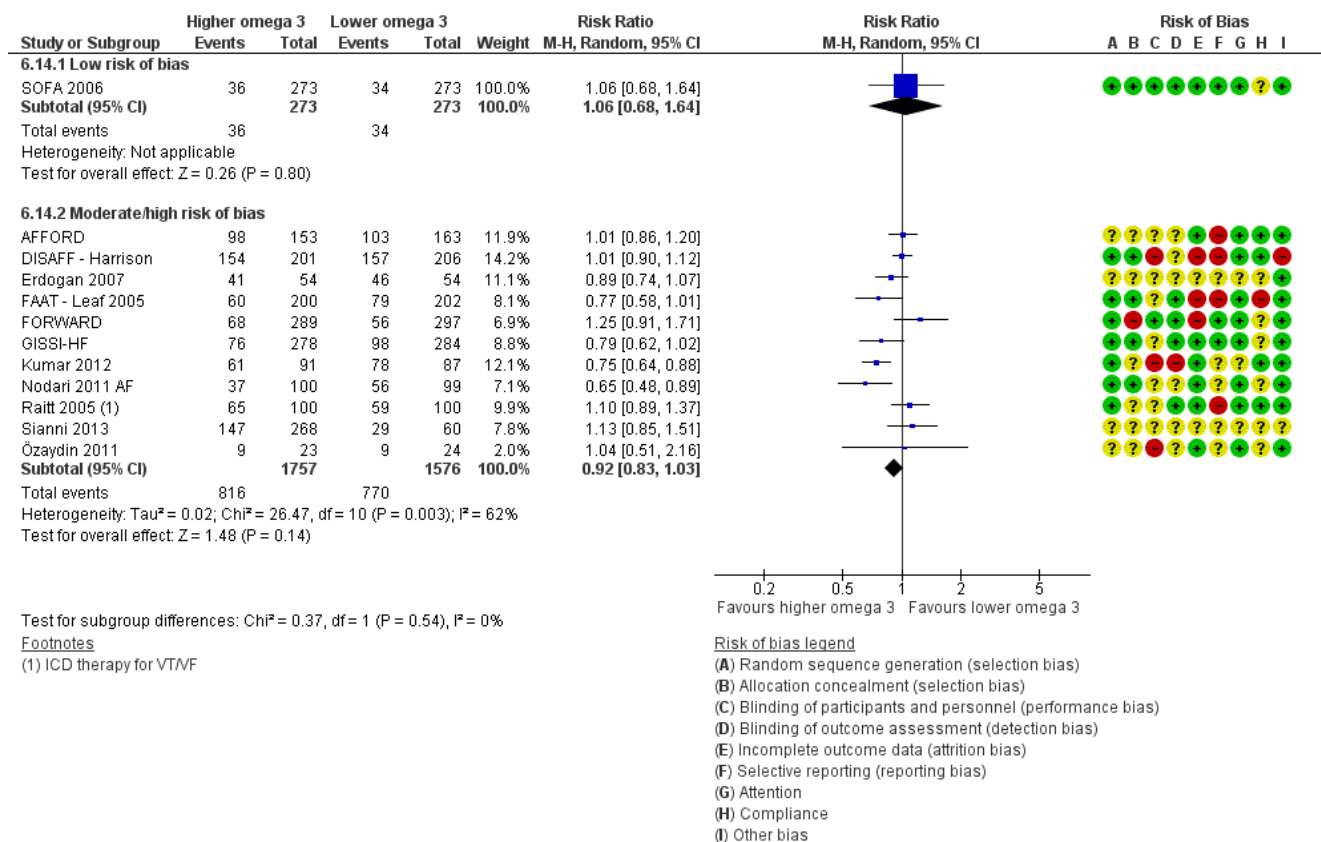


Figure 6.7. Meta-analysis of the effects of LCn3 fatty acids on recurrent arrhythmia, sensitivity analysis removing trials of moderate to high summary risk of bias (shown as subgrouping by summary risk of bias).

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)	⊕⊕⊕○ MODERATE of	CRITICAL

								0.6%		0 fewer per 1000 (from 1 fewer to 1 more)	no effect	
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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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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 I² 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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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)	⊕⊕○○ LOW	IMPORTANT

¹ Effect did not alter when analysis was limited to studies at low summary risk of bias.

² I² 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 I² 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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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)	⊕⊕○○ 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 I² 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 I² 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 scyliorhinus*)
 #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 scyliorhinus* 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 alphaslinolen*).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 scyliorhinus* 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) <u>sic</u> 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 Omega 3 fats and health, Abridged version, 1 August 2017, page 128

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-naïve 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 (Pikazol) 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 Prodotti 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: Antiarrhythmics, 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: β-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

Participants

Summary risk of bias: Moderate or high
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 compliance. 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 (Società 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, 3481 control
 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. 1 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: $9 \times 0.44 = 4\text{g}$ DHA: $9 \times 0.24 = 2\text{g}$. Total 4g/d EPA + 2g/d DHA: EPA+DHA 6.0g/d Control: corn oil capsules Compliance: <i>plasma fatty acid levels and capsule counts assessed (82% capsule counts)</i> 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 $\geq$ 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 Omega 3 fats and health, Abridged version, 1 August 2017, page 161

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	Hypercholesterolaemic 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 , <i>DSM Nutritional Products, Inc.</i>): 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

Participants	medication), 12 months Summary risk of bias: Moderate or high 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

Interventions	Location: USA Ethnicity: Not reported 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

Interventions	Ethnicity: NR 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 Omega 3 fats and health, Abridged version, 1 August 2017, page 188

Participants	Summary risk of bias: Moderate or high 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
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	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/m² 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

Interventions	Ethnicity: NR 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 Participants Interventions	The Walnut and Healthy Aging Study (WAHA) 2 arm, parallel RCT (n3 ALA vs nil), 2 years Summary risk of bias: Moderate to high 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 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 Participants	RCT, parallel, (n3 EPA+DHA vs MUFA, both with low fat advice), 12 months Summary risk of bias: Moderate or high 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 $\leq$30%) with olive oil supplements Intervention: 1.98g/d EPA, 1.32g/d DHA supplements (EPAX 5500 EE, Tishcon Corp) + low fat diet (<15% total calories): EPA+DHA 3.3g/d Control: One 1g olive oil placebo capsules 6 times daily, moderate fat diet (<30% total calories) (American Heart Association Step 1 diet) Compliance: Assessed by individual food records; int 69.2% control 66.7% compliance; also at 12 months there was a significant difference between the fatty acid status of the intervention and control groups in terms of EPA ($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

Interventions	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 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
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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.

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OMEGA-Remodel 2016

[ISRCTN: NCT00729430]

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Appendix 8. Characteristics of ongoing studies

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

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Appendix 10. Other published versions of this review

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