Supplementary materials for Brown et al.

Increasing omega-3, omega-6, and total dietary polyunsaturated fat for prevention and treatment of type 2 diabetes mellitus: systematic review of randomised controlled trials

Contents

Supplementary Text. Results section in greater detail.

Description of studies

We included 83 RCTs that measured at least one of our primary outcomes, of the 311 completed trials in our database [1]. These 83 RCTs (85 comparisons) had randomised 121,070 participants. Their characteristics, risk of bias assessments and bibliographic references are detailed in Additional Table 1.

Of these 83 RCTs, ten were assessed as at low summary risk of bias: [2-11] at low risk for random sequence generation, allocation concealment, and blinding of outcome assessment in dietary trials, and in supplement-type trials additionally at low risk for blinding of participants and personnel, see Additional Figure 1.

Half the studies were conducted in Europe (41), 16 in North America; 3 in South America; 15 in Asia; 6 in Australia, and two in locations across at least 2 continents. 26 studies specifically recruited participants with diabetes or impaired glucose metabolism (of which one recruited type 1 diabetics). We attempted to contact authors of 52 included trials, of which we received information on methodology and/or results relating to 36 trials (see acknowledgements).

Effects of omega-3

Sixty six trials assessed effects of LCn3 of which ten were at low summary risk of bias. Twelve trials assessed effects of ALA, of which five also assessed LCn3 in separate arms, and of which a single trial was at low summary risk of bias.[2] Nineteen trials compared omega-3 with omega-6 fats of which one was at low summary risk of bias.[12] GRADE summary of findings are shown in Table 1 (main paper), full details of LCn3 analyses, including sensitivity analyses and subgrouping are in Additional Tables 2 to 6, ALA analyses in Additional Tables 7 to 11, comparing increased omega-3 to increased omega-6 in Additional Table 12 and secondary outcomes in Additional Tables 13 and 14.

Effect of omega-3 on diagnosis of diabetes and pre-diabetes

LCn3 may have little or no effect on risk of diagnosis of T2DM (low-quality evidence, downgraded once each for imprecision and publication bias). Seventeen trials randomised participants to LCn3 or control for at least 24 weeks and reported at least one new diagnosis of diabetes. Over 58,000

participants were included, and 2196 diabetes diagnoses recorded, with little or no effect of LCn3 on diagnosis risk (RR 1.00, 95% CI 0.85 to 1.17, I^2 45%, Figure 1). This did not differ when restricted to trials of ≥12 months (RR 1.01, 95% CI 0.86 to 1.19, I^2 47%, 2185 diagnoses, 58535 participants in 15 trials).

Sensitivity analyses using fixed effects meta-analysis or limiting to larger trials, trials with trials registry entries, and those at low risk from compliance confirmed little or no effect. Sensitivity analyses only including studies at low summary risk of bias (RR 0.76, 95% CI 0.49 to 1.19, I^2 72%, Additional Table 2), as well as trials with no industry funding suggested protection from diabetes diagnosis though with very wide confidence intervals that included both benefit and harm from increased LCn3. The suggested benefit was due to a single trial[5] of 258 participants with baseline impaired fasting glucose or glucose intolerance randomised to 18 months of LCn3 or placebo, reporting 7 developing diabetes in the intervention arm, 38 in control (data verified with study authors, Additional Figures 2 & 3).

The funnel plot suggested that some smaller studies with reduced incidence of diabetes diagnosis with LCn3 may be missing, however formal statistical tests did not suggest important bias, although they are of low power to detect bias (Begg's test p=0.537, Harbord's test p=0.950, Peter's test p=0.134). We are not aware of missing studies (Additional Figure 4).

There were no significant differences between subgroups when subgrouping by LCn3 dose, type of intervention, replacement, age, sex, baseline diabetes risk (Additional Figure 5), use of diabetic medication or duration (Additional Table 2). The lack of suggestion of dose or duration effects undermines belief in a true effect (Additional Figures 6-7). There was no suggestion that effects differed by whether the intervention was dietary fish or fish oil capsules (though evidence on effects of dietary advice on eating oily fish was very limited), or whether the LCn3 was replacing monounsaturated fats, omega-6, carbohydrate or other non-fat placebos (Additional Figures 8-9).

Effects of ALA on diabetes diagnosis are uncertain as the evidence is of very low-quality (downgraded once for inconsistency and twice for imprecision). Two RCTs randomising 18,243 participants to ALA or control reported 230 new diabetes diagnoses with a risk ratio of 0.68 (95% CI 0.33 to 1.39, I^2 59%). This did not alter greatly in fixed effects analysis, limiting to the single trial at low summary risk of bias or at low risk from compliance bias. One trial was 12 months, the other 40 months duration (Additional Table 7). We are not aware of any missing studies.

We considered the subgroup of studies which replaced omega-6 with omega-3 with particular interest as, if the theory that omega-3 and omega-6 fats have opposing roles is correct, we would expect to see strongest effects when omega-3 replaces dietary omega-6. As the data were very

weak (limited events, no trials at low summary risk of bias, confidence intervals including important benefits and harms) the effect of replacing omega-6 with omega-3 fats on diabetes diagnosis is unclear (RR 0.67, 95% CI 0.35 to 1.28, I^2 5%, 43 diagnoses in 14,002 participants, three trials, Additional Table 12).

We found no RCTs that assessed effects of LCn3 or ALA on pre-diabetes diagnosis.

Effect of omega-3 on glycated haemoglobin

LCn3 probably has little or no effect on glycated haemoglobin (HbA1c, moderate level evidence, downgraded once for risk of bias). Data from 32,798 participants suggested no effect of LCn3 on HbA1c (MD -0.02%, 95% CI -0.07 to 0.04, I^2 49%, 17 comparisons, mean baseline HbA1c was 6.5% Figure 2). This lack of effect was not altered in fixed effects meta-analysis or other sensitivity analyses (Additional Table 3). No meta-analysis of trials at low summary risk of bias was possible, but the single trial at low summary risk of bias,[8] reported the same median value in both arms. Limiting to RCTs of ≥12 months duration did not alter the lack of effect on HbA1c (MD -0.00%, 95% CI -0.07 to 0.06, I^2 68%). All but one of the included studies,[13] gave supplementary capsules.

Data from 14 further trials were missing (with baseline inequalities or data collected but not fully reported, 7 of which are shown in Figure 2 and confirm lack of effect on HbA1c). The funnel plot did not suggest publication bias (Additional Figure 10), and this was borne out by formal statistical tests (Egger's test p=0.977, Begg's test p=0.902)

There were no dose or duration effects (Additional Figures 11-12), but there were statistically significant differences (p=0.01) between subgroups by baseline diabetes risk (no effect in the general population, a small reduction of HbA1c in those at risk of diabetes, and an equivalent small increase in HbA1c in those with existing diabetes, Additional Figure 13). However, only two small trials included 172 participants at increased diabetes risk, and three further trials were not included in analysis due to missing variance data. Two of these suggested exactly the same HbA1c in intervention and control arms, the other suggested slightly higher HbA1c in the intervention arm, so these trials contradict the results of the meta-analysis. After imputing standard deviations for the missing trials, the difference between subgroups by baseline diabetes risk was no longer statistically significant (p=0.21). There was a statistically significant difference between subgroups by replacement (replacement of omega-6 by LCn3 suggested a small but statistically significant HbA1c reduction (MD -0.15%, 95% CI -0.24 to -0.06, I^2 0%, in 841 participants, Additional Figure 14). This was interpreted as little or no effect as this represented a <5% change from baseline. One further study reported data (unsuitable for pooled analysis) suggesting higher

HbA1c in the omega-3 arm (contradicting the effects in pooled analysis). There were no other statistically significant differences between subgroups.

ALA may have little or no effect on HbA1c (low-quality evidence, downgraded once each for risk of bias and imprecision). Three RCTs suggested no effect on HbA1c (MD 0.01%, 95% CI -0.43 to 0.45, I^2 0%, 178 participants, mean baseline HbA1c 7.0%), and we are not aware of any missing studies. This lack of effect was not altered by fixed effects analysis, or limiting to trials at low risk from compliance, but no included studies were at low summary risk of bias. Further sensitivity analyses and subgrouping were not carried out (Additional Table 8). Limiting to trials of ≥12 months, a single study remained [14], suggesting that increasing ALA may increase HbA1c (MD 0.40%, 95% CI -0.59 to 1.39) but with wide confidence intervals.

As mentioned above, there was little or no effect of omega-3 vs omega-6 on glycated haemoglobin (MD -0.15%, 95% CI -0.24 to -0.06, I^2 0%, 841 participants, six trials, Additional Table 12) as all of the confidence interval suggested change of <5% of baseline. No included trials were at low summary risk of bias.

Effect of omega-3 on HOMA-IR

LCn3 may have little or no effect on HOMA-IR (low-quality evidence, downgraded once each for imprecision and publication bias). HOMA-IR is a measure of insulin resistance that takes both fating insulin and fasting glucose into account. Lower HOMA-IR, like lower glucose, HbA1c or insulin levels, indicates better glucose control. Thirteen trials randomising 1064 participants included HOMA-IR data in pooled analysis, while four further trials provided data without variance and three trials were unsuitable for pooling (due to baseline differences). There was little effect on HOMA-IR (MD 0.06, 95% CI -0.21 to 0.33, I^2 18%, mean baseline HOMA-IR was 4.6, Figure 5).

Sensitivity analyses did not suggest different results except when limiting studies to those that randomised ≥100 participants, in which the three larger trials suggested a reduction in HOMA-IR with increased LCn3 (MD -1.15, 95% CI -2.61 to 0.30, I^2 0%, 697 participants, Additional Figure 16, Additional Table 4). However of the three larger trials that could not be included in the meta-analysis two suggested higher HOMA-IR in the LCn3 arms, and one suggested the same HOMA-IR level. There were no statistically significant differences between any sets of subgroups, and no suggestion of differential effects by dose or duration.

We downgraded for risk of bias due to different effects of the larger trials, and surprising weightings of individual studies in the meta-analyses, suggesting that there may be some data problems. The funnel plot suggests that studies with higher HOMA-IR in the LCn3 arm may be

missing (Additional Figure 17), though this was not supported by formal statistical tests (Egger's test p=0.187, Begg's test p=0.951)

ALA may have little or no effect on HOMA-IR (low-quality evidence, downgraded once for imprecision and once for risk of bias and publication bias combined). Four trials assessed the effects of ALA on HOMA, three of which were pooled (MD 0.10, 95% CI -0.50 to 0.70, I^2 0%, 294 participants, mean baseline HOMA-IR was 3.4). The suggestion of little or no effect did not alter with fixed effects analysis or limiting to trials at low risk of compliance problems, but no included trials were at low summary risk of bias. The study not included in meta-analysis suggested slightly increased HOMA-IR with increased LCn3.

There was little or no reduction in HOMA-IR with omega-3 vs omega-6 (MD -0.23, 95%CI -1.35 to 0.88, I^2 60%, 328 participants, 6 comparisons). Three further RCTs reported data unsuitable for pooling, two of which suggested higher HOMA-IR with increased omega-3, as did the single trial at low summary risk of bias. Data were of very low-quality.

Effect of omega-3 on fasting insulin

LCn3 may have little or no effect on fasting insulin (low-grade evidence, downgraded once each for risk of bias and imprecision). Seventeen trials suggested little or no effect of supplementation of LCn3 over ≥6 months on fasting serum insulin (MD 1.02 pmol/L, 95% CI -4.34 to 6.37, I^2 43%, 2077 participants, mean baseline insulin 98 pmol/L; Figure 4), but we are aware of fifteen further missing studies, although the funnel plot did not suggest missing data (Additional Figure 18, Egger's test p=0.976, Begg's test p=0.711).

This lack of effect did not alter with fixed effects meta-analysis, or limiting to low risk of compliance, or other sensitivity analyses, but limiting to trials at low summary risk of bias suggested increased fasting serum insulin with increased LCn3 (MD 25.27 pmol/L, 95% CI 4.11 to 46.4, I^2 0%, 387 participants, Additional Table 5). There were no statistically significant differences between subgroups except for sex (p=0.03), diabetic medication use (p=0.02) and duration (p=0.04) where the single trial in which most participants used diabetic medication and the single trial with a duration of 2-4 years both suggested a significant reduction in insulin with increased LCn3. Subgrouping by sex suggested similar effects in the single trials of men and women, with a different effect in men and women combined, which does not suggest differential effects by sex. Similarly there was no suggestion that as trial duration lengthened fasting insulin increased or decreased with increasing LCn3 (Additional Figure 19).

ALA may increase fasting insulin (low-quality evidence, downgraded once each for risk of bias and imprecision). Eight trials assessed effects of ALA on fasting serum insulin, six of which were

pooled, suggesting increased fasting insulin (MD 5.3 pmol/L, 95% CI -4.68 to 15.27, I^2 0%, 469 participants) of 7% from 80pmol/L at baseline. This did not alter in fixed effects analysis or limiting to trials at low risk from compliance bias, but no trials were at low summary risk of bias. Other sensitivity analyses and subgroupings were not carried out as there were too few trials.

Data comparing omega-3 to omega-6 on fasting insulin were highly heterogeneous, with unimportant insulin reductions (MD -3.23 pmol/L, 95% CI -21.73 to 15.28, I^2 67%, 690 participants in 8 comparisons, Additional Table 12). Six RCTs had data unsuitable for pooling, while the single trial at low summary risk of bias suggested increased insulin with higher omega-3. Data were of very low-quality.

Effect of omega-3 on fasting glucose

LCn3 may have little or no effect on fasting serum or plasma glucose (low-quality evidence, downgraded once each for risk of bias and publication bias). Forty eight trials (33 contributing to meta-analysis), assessed effects of increasing LCn3 on fasting serum or plasma glucose. Pooling suggested little or no effect - a statistically significant glucose increase from baseline of <1% (MD 0.04 mmol/L, 95% CI 0.02 to 0.07, I^2 0%, 35,156 participants, mean baseline glucose 6.2 mmol/L, Figure 3). There was little or no effect using fixed effects meta-analysis or when limiting to studies at low risk from compliance, larger trials, registered trials and those without industry funding, Additional Table 6. The two studies at low summary risk of bias suggested reduction in glucose with increased LCn3 but with very wide confidence intervals (MD -0.45mmol/L, 95% CI -1.49 to 0.59, I^2 54%, 353 participants).

The funnel plot did not suggest publication bias (Additional Figure 20), and neither did the formal tests (Egger's test p=0.205, Begg's test p=0.273) but we are aware of 15 further studies (some of which are shown in Figure 3). Almost 70% of the weight in this analysis came from a single large trial, JELIS,[15] with longer duration than most included trials (five years) and suggested slight but unimportant glucose increases with LCn3. There were no significant differences between subgroups for dose, age, sex, type of intervention, replacement, diabetic medication use, baseline diabetes risk or duration (Additional Table 6).

ALA probably has little or no effect on fasting glucose (moderate-quality evidence, downgraded once for risk of bias). Nine trials assessed effects of ALA on fasting serum glucose, of which seven contributed to meta-analysis (MD -0.07mmol/L glucose, 95% CI -0.16 to 0.02, I^2 0%, 648 participants, mean baseline glucose 6.2 mmol/L, one missing trial also suggesting slightly lower glucose in the higher ALA arm and the other was unclear, Figure 5). Sensitivity analyses by fixed effects and low risk from compliance did not differ from the main analysis, but no included trials

were at low summary risk of bias (Additional Table 11). There were no statistically significant differences between subgroups and too few trials to interpret the funnel plot.

There was little or no effect of increasing omega-3 vs omega-6 on fasting plasma glucose (MD -0.03 mmol/L, 95% CI -0.11 to 0.05, I^2 10%, 1641 participants, 14 comparisons, none of which were at low summary risk of bias, Additional Table 12). Five further studies provided unusable data.

Effects of omega-6

Eleven trials compared omega-6 with something other than omega-3, so were included in this comparison. Because none of the eleven trials were at low summary risk of bias, all outcomes were downgraded for risk of bias. No outcomes included at least ten trials, so we did not carry out additional sensitivity analyses, subgrouping or funnel plots. Figures 1 to 5 (main paper) show meta-analysis forest plots, Table 2 (main paper) shows GRADE summary of findings, while full details of omega-6 analyses on primary outcomes, including sensitivity analyses, are in Additional Tables 15 to 20.

Effect of omega-6 on diagnosis of diabetes or pre-diabetes

Effects of omega-6 fats on T2DM diagnosis are unclear as quality of evidence was very low (downgraded once for risk of bias, twice for imprecision). Two RCTs randomised 2087 participants to omega-6 fats or control and reported three new diagnosis of diabetes (Figure 1). This did not alter in fixed effects analysis, neither trial was at low summary risk of bias or low risk from compliance problems. No included studies reported pre-diabetes outcomes.

Effect of omega-6 on glycated haemoglobin

Omega-6 fats may have little or no effect on HbA1c (low-quality evidence, downgraded once each for risk of bias and imprecision). The suggestion of little or no effect (MD 0.00%, 95% CI -1.01 to 1.01, I^2 0%, 64 participants in 2 RCTs, mean baseline HbA1c was 7.9%) was not altered in fixed effects meta-analysis, or when limited to trials with low risk from compliance bias, but no trials were at low summary risk of bias. We are aware of one further study that collected HbA1c data but did not report it [16], and one where data were too unbalanced at baseline to use. [17]

Effect of omega-6 on HOMA-IR

The effect of increasing omega-6 on HOMA-IR is unclear as the evidence is of very low-quality (downgraded for once for risk of bias and twice for indirectness). A single small trial of 6 months duration suggested higher HOMA-IR with higher omega-6 (MD 1.50, 95% CI 0.59 to 2.41, 60 participants, mean baseline HOMA-IR was 2.4), and must be considered very cautiously. A further small trial provided data not used due to baseline differences. [18]

Effect of omega-6 on fasting serum insulin

Effects on fasting insulin are unclear as data are very low-quality (downgraded once each for risk of bias, inconsistency and imprecision). The meta-analysis of data from 124 participants in three trials was highly heterogeneous with wide confidence intervals (MD 14.71 pmol/L, 95% CI -19.81 to 49.24, I^2 77%, mean baseline insulin was 55.4 pmol/L). Fixed effects analysis did not alter effects, limiting to the study with low compliance risk suggested no effect, and there were no trials at low summary risk of bias. One study [19] was too different at baseline to use in meta-analysis.

Effect of omega-6 on fasting glucose

The effect of omega-6 fats on plasma glucose is unclear as the quality of evidence is very low (downgraded once each for risk of bias, publication bias and imprecision). Three RCTs, each of 6 months duration, reported fasting serum glucose. None were at low summary risk of bias (MD -0.09mmol/L, 95% CI -0.39 to 0.20, I^2 0%, 134 participants, mean baseline glucose was 7.1 mmol/L). Lack of effect did not alter in fixed effects meta-analysis, but the single trial at low risk from compliance suggested a small reduction in glucose. We are aware of four further trials that assessed serum glucose but did not report it or reported arms with very different baseline glucose levels.

Effects of total PUFA

When assessing effects of polyunsaturated fats on diabetes diagnosis we included eight studies [18-25] of ≥6 months duration that stated an aim to increase total PUFA or to increase both omega-3 and omega-6 fats. Most were also omega-6 trials (comparing omega-6 with something other than omega-3), except PREDIMED and Moore [24-26]. As none were at low summary risk of bias, all outcomes were downgraded for risk of bias. With only eight trials, we did not carry out additional sensitivity analyses, subgrouping or funnel plots. Table 3 shows GRADE summary of findings,

forest plots are shown in Figures 1 to 5, full details of PUFA analyses of primary outcomes, including sensitivity analyses are in Additional Tables 21 to 26.

Effect of total PUFA on diagnosis of diabetes or pre-diabetes

The effect of increasing total PUFA on risk of diabetes diagnosis is unclear as the evidence was of very low-quality (downgraded once for risk of bias and twice for imprecision). Three eligible RCTs provided data suggesting potential harm (RR 1.08, 95% CI 0.81 to 1.43, I^2 0%, 175 diagnoses in 4481 participants). The effect size was unaltered with fixed effects analysis (RR 1.08, 95% CI 0.81 to 1.44), and no studies were at low summary risk of bias or low risk of compliance bias.

We found no RCTs that assessed the effect of total PUFA on measures of pre-diabetes.

Effect of total PUFA on glycated haemoglobin

Increasing total PUFA may make little or no difference to HbA1c (low-quality evidence, downgraded once each for risk of bias and imprecision). There was little or no effect of PUFAs on HbA1c (MD 0.08%, 95% CI -0.41 to 0.56, I^2 0%, in 172 participants, 3 trials, mean baseline HbA1c was 8.6%). This did not alter in fixed-effects analysis or when limiting to trials at low risk of compliance bias.

Effect of total PUFA on HOMA-IR

The effect of increasing total PUFA on HOMA-IR is unclear as the evidence is of very low-quality (downgraded for risk of bias, indirectness and imprecision). A subgroup of one trial, not at low summary risk of bias or risk from compliance, suggested a small decrease in HOMA-IR (MD -0.34, 95%CI -0.88 to 0.20, 93 participants, mean baseline HOMA-IR was 1.8). A further trial[18] provided unusable data.

Effect of total PUFA on fasting serum insulin

Increasing total PUFA may make little or no difference to fasting insulin (low-quality evidence, downgraded for risk of bias and imprecision), (MD -0.60pmol/L, 95% CI -10.33 to 9.14, I^2 0%, 157 participants, 3 trials, mean baseline insulin was 62 pmol/L). This was unchanged using fixed

effects meta-analysis or in the single trial at low risk from compliance. Two studies provided unusable data.[19 24]

Effect of total PUFA on fasting glucose

Increasing total PUFA may have little or no effect on fasting glucose (low-quality data, downgraded for risk of bias and imprecision (MD -0.04mmol/L, 95% CI -0.18 to 0.11, I^2 0%, 182 participants, 3 trials, mean baseline fasting glucose was 8.1 mmol/L). There was little or no effect in fixed effects analysis, the suggestion of a small reduction in glucose in the single study at low risk from compliance. Two further studies[19 18] provided unusable data due to large differences between arms at baseline, and one did not report numerical data.[24]

Secondary outcomes

Secondary outcomes were planned as serum lipids, adiposity, all-cause mortality and diabetic mortality but are only reported in Additional Tables 13, 14, 20 & 26 as effects of omega-3, omega-6 and total PUFA on mortality, lipids and adiposity have been formally systematically reviewed in sister reviews assessing effects in RCTs of at least 12 months duration.[27-29]

Tables

Supplementary Table A. Table of characteristics and risk of bias assessments for each of the included studies

AlphaOmega - ALA 2011 [30-32]

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 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 and consumed 20.6 (2.8) g of margarine/d. Length of intervention: 40 months.
Outcomes	Main study outcome: Cardiovascular disease events. Dropouts: 91 died, 98 discontinued int., 93 died, 93 discontinued control. Available outcomes: deaths, MI, cardiovascular events, ventricular arrhythmia, Incident cardiovascular disease, authors provided information on diabetes diagnosis Response to contact: Yes
Notes	The study has three intervention arms (ALA margarine, EPA/DHA margarine, mixture of the two interventions). This table represents the ALA only intervention. Outcome data is used for the ALA group where reported separately or for the combined (ALA arm, ALA + EPA/DHA arm) Study funding: Netherlands Heart Foundation, National Institutes of Health and Unilever R&D (latter provided unrestricted grant for distribution of trial margarines).

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	On the computer by a random number generator before the start of the trial.
Allocation concealment (selection bias)	Low risk	Author confirmed allocation was concealed from clinicians/ researchers.
Blinding of participants and personnel (performance bias)	Low risk	The 4 types of margarine were “similar in taste, texture and colour". A trained test panel did not perceive a fishy taste or odour. Randomisation tables were stored in safely under supervision.
Blinding of outcome assessment (detection bias)	Low risk	Randomisation tables were stored in safely under supervision. There was an independent statistician for data analysis. "Events were coded by three members

		of the end-point adjudication committee who were unaware of the identity of the patient, the identity of the treating physician and the patients assigned study group".
Incomplete outcome data (attrition bias)	Low risk	All patients were followed up for events computerised linkage with municipal registries. 2531 patients were only followed up for baseline anthropometric and medical measurements.
Selective reporting (reporting bias)	High risk	Sudden cardiac death endpoint omitted. Registered in August 2005, recruitment was from 2002 to 2006. Outcomes papers published in 2010.
Attention	Low risk	All participants appear to have had similar frequency and quantity of attention and follow up
Compliance	Low risk	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 and consumed 20.6 (2.8) g of margarine/d
Other bias	Low risk	None noted

AlphaOmega - EPA+DHA [30-32]

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.

Outcomes Main study outcome: Cardiovascular disease events.
Dropouts: 95 died, 119 discontinued int., 93 died, 93 discontinued control.
Available outcomes: deaths, MI, cardiovascular events, ventricular arrhythmia, Incident cardiovascular disease, authors provided information on diabetes diagnosis
Response to contact: Yes

Notes The study has three intervention arms (ALA margarine, EPA/DHA margarine, mixture of the two interventions). This table represents the EPA/DHA only intervention. Outcome data is used for the EPA/DHA group where available or for the combined (EPA/DHA arm, EPA/DHA & ALA arm)
Study funding: Netherlands Heart Foundation, National Institutes of Health and Unilever R&D (latter provided unrestricted grant for distribution of trial margarines).

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	On the computer by a random number generator before the start of the trial.
Allocation concealment (selection bias)	Low risk	Author confirmed allocation was concealed from clinicians/ researchers.
Blinding of participants and personnel (performance bias)	Low risk	The 4 types of margarine were “similar in taste, texture and colour". A trained test panel did not perceive a fishy taste or odour. Randomisation tables were stored in safely under supervision.
Blinding of outcome assessment (detection bias)	Low risk	Randomisation tables were stored in safely under supervision. There was an independent statistician for data analysis. "Events were coded by three members of the end-point adjudication committee who were unaware of the identity of the patient, the identity of the treating physician and the patients assigned study group".
Incomplete outcome data (attrition bias)	Low risk	All patients were followed up for events computerised linkage with municipal registries. 2531 patients were only followed up for baseline anthropometric and medical measurements.
Selective reporting (reporting bias)	High risk	Sudden cardiac death endpoint omitted. Registered from August 2005, recruitment was from 2002 to 2006. Outcomes papers published in 2010.
Attention	Low risk	All participants appear to have had similar frequency and quantity of attention and follow up
Compliance	Low risk	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 and consumed 20.6 (2.8) g of margarine/d
Other bias	Low risk	None noted

AREDS2 2014 [3 33]

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: Low

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 supp 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.

Outcomes Main study outcome: Development of advanced AMD
Dropouts: Int 200 died, 165 discontinued, 80 were lost to follow up.
Cont 168 died, 140 discontinued, 61 were lost to follow up.
Available outcomes: deaths, cardiovascular death, MI, stroke, angina, heart failure, revascularization, cognition, eye health, (authors provided data on diabetes diagnosis, depression diagnosis, breast cancer)
Response to contact: Yes

Notes Study funding: National Eye Institute/National Institutes of Health, Department of Health and Human Services.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"random block design was implemented using the AREDS2 Advantage Electronic Data Capture system by the AREDS2 Coordinating Center"
Allocation concealment (selection bias)	Low risk	Each treatment was assigned 5 bottle numbers. Bottle numbers were issued via an electronic randomisation system for each participant once study eligibility was verified. The assigned bottle number was used to distribute the study treatment(s). AREDS2 Coordinating centre personnel involved in creating the randomisation system had access to the bottle number/treatment assignments.
Blinding of participants and personnel (performance bias)	Low risk	"Participants, investigators, study coordinators, and all other study personnel are masked to treatment assignment".
Blinding of outcome assessment (detection bias)		The coordinating centre randomly assigned the event to a study adjudicator, who made the final determination of these study end points through review of the medical records and applying the end point criterion defined a priori. All adjudicators were masked to study assignment.
Incomplete outcome data (attrition bias)	Low risk	<20% attrition over 5 years, balanced reasons for drop outs.
Selective reporting (reporting bias)	Low risk	Outcomes in Trials Registry entry appear to all be reported (NCT00345176). Entry received June 2006, recruitment Sep 2006 – Oct 2012.
Attention	Low risk	Participants, investigators, study coordinators, and all other study personnel are masked to treatment assignment, so attention bias not feasible
Compliance	Unclear risk	Assessed by pill count - 84% of participants in each group took at least 75% of study medications
Other bias	Low risk	None noted

ASCEND 2018 [11 34]

Methods A Study of Cardiovascular Events iN Diabetes (ASCEND)
RCT, parallel, 2 × 2 factorial (n-3 EPA + DHA vs MUFA) also randomised to aspirin vs placebo), median 7.4 years
Summary risk of bias: low

Participants Patients with diabetes, without apparent vascular disease
N: 7740 intervention, 7740 control (ITT so 7740 in each arm analysed)
Level of risk for CVD: moderate (DM)
Men: intervention 62.6%, control 62.6%
Age in years (SD): intervention 63.3 (9.2), control 63.3 (9.2)
Age range: 40+ years

Smokers: intervention 8.3%, control 8.3%
Hypertension: intervention 61.6%, control 61.6%
Medications taken by at least 50% of those in the control group: statins, metformin, ACE inhibitors or ARBs
Medications taken by 20%-49% of those in the control group: aspirin, insulin, sulphonylurea, calcium channel blockers
Medications taken by some, but less than 20% of the control group: NSAID, thiazolidinedione, beta-blockers, thiazide or related diuretics, PPI
Location: UK
Ethnicity: white 96.5% intervention, 96.5% control

Interventions Type: supplement (capsule)
Comparison: EPA + DHA vs MUFA
Intervention: 840mg/d EPA+DHA (460mg/d EPA plus 380mg/d DHA) as 1 capsule daily, provided by Mylan, Solvay and Abbott.
Arm 1: omega-3 (1 g/d: 0.41 g EPA, 0.34 g DHA) and placebo tablets for aspirin
Arm 3: omega-3 (1 g/d) and aspirin (100 mg/d)
Control: 1 capsule/d of olive oil provided by Mylan, Solvay and Abbott.
Arm 2: aspirin (100 mg/d) and olive oil placebo capsule
Arm 4: olive oil placebo and placebo tablets for aspirin
Compliance: assessed through posted questionnaires, suggesting 77% compliance in intervention group, 76% in control. 10% also took over-the-counter fish oil.
Length of intervention: mean 7.4 years

Outcomes Main study outcome: serious vascular events (first of MI, stroke, TIA or vascular death)
Dropouts: intervention 2879 stopped taking meds for some reason, but were included in analysis; control 2938 stopped taking meds, but were included in analysis
Available outcomes: deaths, cardiovascular death, MI, stroke, heart failure, revascularisation, atrial fibrillation, diabetes complications, cancer diagnosis, breast cancer, prostate cancer (and other types of cancer), TIA, IBD, dementia, depressive disorders, anxiety, suicidal and injurious behaviour, Parkinsons' disease, body weight, serum cholesterol, HDL cholesterol, HbA1c
Response to contact: not yet attempted

Notes NCT00135226
Trial website: ascend.medsci.ox.ac.uk; rum.ctsu.ox.ac.uk/ascend
Study funding: British Heart Foundation, medications provided by Mylan, Solvay and Abbott.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using minimisation
Allocation concealment (selection bias)	Low risk	Almost no direct contact with trial personnel - all via questionnaires and GP appointments, central randomisation appears to follow consent
Blinding of participants and personnel (performance bias)	Low risk	Blinding of participants, care providers, investigators and outcome assessors stated in trials register. This appears feasible given the dispersed design with mainly postal contact.
Blinding of outcome assessment (detection bias)	Low risk	Outcomes self-reported (questionnaire) but investigated by masked adjudication committee
Incomplete outcome data (attrition bias)	Low risk	Intention to treat analysis
Selective reporting (reporting bias)	Low risk	Prospective trial registration (registered Aug 2005, recruitment June 2005 to July 2011), and all outcomes in register reported (plus extensive adverse event list)
Attention	Low risk	Almost no contact that could differ between groups
Compliance	Unclear risk	All information was via questionnaires, so unclear.
Other bias	Low risk	None noted.

Balfego 2016 [13]

Methods RCT, parallel, (LCn3 vs lower LCn3), 6 months

Summary risk of bias: Moderate or high

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

Interventions
Type: supplemented food (sardine-enriched diet or control diet)
Comparison: n3 vs lower n3
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

Outcomes
Main study outcome: Metabolic control, inflammation and gut microbiota
Dropouts: 2 int., 1 control
Available outcomes: Weight, BMI, glucose, insulin, HOMA, HbA1c, inflammatory markers (weight and BMI not used due to baseline differences)
Response to contact: No contact attempted

Notes
Study funding: Catalunya-La Pedrera Foundation, Government of Catalonia

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using online software
Allocation concealment (selection bias)	Unclear risk	An external person was involved in allocating
Blinding of participants and personnel (performance bias)	High risk	Sardine vs control diet
Blinding of outcome assessment (detection bias)	Unclear risk	NR
Incomplete outcome data (attrition bias)	Low risk	Balanced drop outs and <10% in 6 months
Selective reporting (reporting bias)	Unclear risk	Retrospectively registered
Attention	Unclear risk	Not specified and diets differ (sardines or control diet)
Compliance	Low risk	Significant increase in EPA and DHA erythrocyte fatty acids in the intervention group at intervention end
Other bias	Low risk	None noted

Baxheinrich 2012 [35]

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: supplementary food (advice to consume hypo-energetic 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)
PUFA Dose: (intended) increase 3.5g/d ALA, **1.6%E n-3, 1.6%E PUFA**
Compliance: Dietary record
Duration of intervention: 6 months

Outcomes Main study outcome: Body weight and cardiovascular risk profile
Dropouts: 6 int., 7 control
Available outcomes: Adiposity, lipids, glucose, insulin (BP and metabolic syndrome- 6 months only)
Response to contact: No contact attempted

Notes Study funding: Union for Promoting Oil and Protein Plants and the International Foundation for the Promotion of Nutrition Research and Nutrition Education

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned"
Allocation concealment (selection bias)	Unclear risk	As above
Blinding of participants and personnel (performance bias)	High risk	Appears open- control participants consumed a different oil once weekly
Blinding of outcome assessment (detection bias)	Unclear risk	NR
Incomplete outcome data (attrition bias)	Low risk	Analysis for completers only. Similar drop-out and reasons by arm
Selective reporting (reporting bias)	Unclear risk	No registry or protocol identified
Attention	Low risk	Counselling about lifestyle, dietary behaviour and physical activity was identical for both groups
Compliance	Low risk	Significant difference in dietary intake for ALA recorded at 6 months
Other bias	Low risk	None identified

Bonnema 1995 [36]

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

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

Interventions Type: supplement
Comparison: fish oil capsules vs olive oil capsules
Intervention: 6x1g fish oil capsules (Pikasol) daily (with conventional diabetic diet) including 2g/d EPA plus 1.32g/d DHA: EPA+DHA 3.32g/d
Control: 6x1g olive oil capsules daily (with conventional diabetic diet)
PUFA Dose: (intended) increase 3.32g/d EPA+DHA, **1.5%E n-3, 1.5%E PUFA**
Compliance: Capsule count, average daily consumption was >95% expected amount

Duration of intervention: 6 months

Outcomes Main study outcome: peripheral arterial compliance
Dropouts: 0 int., 1 control
Available outcomes: glucose, HbA1c, total & HDL cholesterol (BP, urinary albumin, serum creatinine, arterial & venous compliance - these not used, TG not used as 2 arms very different at baseline), no deaths or CVD events occurred, insulin doses not altered. 2 in intervention group, 0 in control developed albumin excretion.
Response to contact: yes

Notes Study funding: Esbjerg Fonden, Fonden for laegevidenskabelig forskning i Rignkoebing, Ribe and Soenderjyllands Amter, capsules from Lube Ltd, Denmark.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was done by sealed envelopes", and was "blinded through a third person without involvement of the investigators"
Allocation concealment (selection bias)	Low risk	As above.
Blinding of participants and personnel (performance bias)	Unclear risk	Authors replied to reviewers stating that the recipients and providers were unaware of the assigned treatment, but it is unclear how this was achieved given that fish oil is easy to taste.
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear.
Incomplete outcome data (attrition bias)	Low risk	One withdrawal only of 28 randomised, due to adverse effects
Selective reporting (reporting bias)	Unclear risk	No trials registry entry or study protocol identified.
Attention	Unclear risk	Participants all visited every 2 months, no suggestion of differential treatment
Compliance	Low risk	Pill counts suggested high compliance.
Other bias	Low risk	None noted

Burr 2003 - DART2 [37]

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

Outcomes	Main study outcome: total mortality Dropouts: none for mortality Available outcomes: total and CV deaths, sudden death, stroke, heart failure, cancer deaths, diagnosis type 2 diabetes. Response to contact: Yes
Notes	Some of each group were also advised on high fruit, veg and oat diets, and those who received neither fish nor fruit advice received 'non-specific' dietary advice. All those whose BMI >30 in both groups received weight reduction advice. Study funding: Probably British Heart Foundation, Seven Seas Ltd, Novex Pharma Ltd and the Fish Foundation (these were acknowledged)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Pre-prepared sequentially numbered enveloped opened by dietitian (unclear if envelopes were opaque)
Blinding of participants and personnel (performance bias)	High risk	Dietary advice, so not possible for participants to be blinded to intervention
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors were not aware of study allocation (Prof Burr stated he did not know assignments)
Incomplete outcome data (attrition bias)	Low risk	Hospital notes and death registers were flagged to catch all outcome data
Selective reporting (reporting bias)	Unclear risk	No study protocol was found, or trials registry entry
Attention	High risk	More attention was paid to those given dietary advice
Compliance	Unclear risk	Postal dietary questionnaire suggested dietary EPA intake increased by 2.4g/week int., 0.2g /week control
Other bias	Low risk	None noted

Caldwell 2011 [4 12]

Methods	RCT, parallel, (n3 EPA+DHA or n6 LA), 12 months Summary risk of bias: Low
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 n-3, 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
Outcomes	Main study outcome: NASH activity score Dropouts: 3 int., 3 control Available outcomes: Lipids, measures of adiposity, insulin, HOMA-IR (glucose available but unbalanced at baseline)

Response to contact: yes

Notes Data on; BMI, weight, visceral fat, TG and glucose were not used as they were different between groups at baseline.
Study funding: study was supported by NIH NCCAM Grant 5R21AT2901–2 and 5 M01 RR00847. Study medication and identical appearing placebo was provided at no charge by Nordic Natural. RBC phospholipid profile was performed by Metametrix (www.metametrix.com). M30, M65, adiponectin, and IGFBP-1 electro chemiluminescence assays were performed by Wellstat Diagnostics (www.wellstatdiagnostics.com).

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomized to N-3 or placebo using a stratified block 1:1 randomization scheme. An independent biostatistician generated the randomization list which was confidentially forwarded to the Investigational Pharmacy
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias)	Low risk	All staff and subjects were blinded to therapy assignment throughout the study period. Both capsules were identical.
Blinding of outcome assessment (detection bias)	Low risk	Participants blinded for main outcome (NASH activity score)
Incomplete outcome data (attrition bias)	Low risk	15% drop outs explained and equal in both groups
Selective reporting (reporting bias)	Low risk	The trial was prospectively registered
Attention	Low risk	Both groups had the same attention
Compliance	Unclear risk	No details on compliance measurement
Other bias	Low risk	None noted

Clark 2016 [38]

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)
PUFA Dose: (intended) increase 3.9g/d EPA+DHA, **1.8%E n-3, 1.8%E PUFA**
Compliance: monthly capsule count plus phospholipid composition of erythrocyte membranes
Duration of intervention: 9 months

Outcomes Main study outcome: insulin sensitivity
Dropouts: NR (36 randomised, 16 int, 17 cont analysed)

Available outcomes: Diabetes diagnosis, weight, %body fat, lipids, fasting glucose & insulin , HOMA2-IR, , fasting endogenous glucose production, branched chain amino acids, C-peptide measured but not used)
Response to contact: Yes (data provided)

Notes Study funding: core grant from the Scottish Government to the Rowett Institute, EPAX AS provided the intervention and control capsules.
Diabetes diagnosis: only data on confirmed diagnosis were used. Data provided by authors included participants with raised HbA1c not used.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Author confirmed the Statistician (head of the local Biomathemenatics and Statistics (BioSS) team) generated a random list (computer generated) for oil distribution; the contents of this list were known only to him.
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias)	Unclear risk	"Capsules of the two oils were identical in outward appearance and were provided via the double-blind procedure in similar containers labelled sequentially under the supervision of an independent nutritionist. Neither volunteers nor researchers knew which treatment was allocated.". However no information provided on capsules taste or smell.
Blinding of outcome assessment (detection bias)	Low risk	Author confirmed: At the end of the trial and following data analysis, the final codes were disclosed by the Statistician. So throughout the trial neither the volunteers nor the Experimenters knew which oil was allocated to whom
Incomplete outcome data (attrition bias)	Low risk	3 dropouts only of 36 randomised (8%), reasons provided
Selective reporting (reporting bias)	Unclear risk	All outcomes mentioned in the registry were presented, but study started in Feb 2009 and study was registered in Nov 2010, unclear how many participants had completed by this time
Attention	Low risk	Intervention and control participants appeared to have the same time and procedures at each appointment
Compliance	Low risk	Erythrocyte membrane long chain omega 3 fatty acids were significantly different in intervention and control participants
Other bias	Low risk	None noted

Connor 1993 [39 40]

Methods RCT, cross-over, (n3 EPA+DHA vs MUFA), 6 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: 15/16 pts were on oral hypoglycaemic agents
Medications taken by 20-49% of those in the control group: insulin
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)
PUFA Dose: (intended) increase 6.0g/d EPA+DHA, **2.7%E n-3, 2.7%E PUFA**
Compliance: Plasma fatty acids
Duration of intervention: 2 consecutive 6 month periods of intervention or control

Outcomes Main study outcome: Lipids and diabetic control
Dropouts: 0 int., 0 control
Available outcomes: Lipids, glucose (plasma and urinary), HbA1c, weight, mortality
Response to contact: yes

Notes Author response confirming no mortality/ cardiovascular events
Study funding: Institutes of health, Oregon sea grant

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomized" "coin"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Unclear risk	No details
Blinding of outcome assessment (detection bias)	Unclear risk	No details
Incomplete outcome data (attrition bias)	Low risk	No drop outs
Selective reporting (reporting bias)	Unclear risk	No registry or protocol identified
Attention	Low risk	Identical treatment is described
Compliance	Unclear risk	No p-values supplied
Other bias	Low risk	None noted

DART fat 1989 [20 41 42]

Methods Diet And Reinfarction Trial (DART)
RCT, n6 LA vs mixed fats, 2 years
Summary risk of bias: Moderate or high

Participants Men recovering from an MI
CVD risk: high
Control: randomised 1015, analysed unclear
Intervention: randomised 1018, analysed unclear
Mean years in trial: control 1.9, randomised 1.9
% male: 100%
Age: mean control 56.8, intervention 56.4
Age range: all <70 years
Smokers: control 62.7%, int 61.2%
Hypertension: cont 23.3%, int 24%
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: beta-blockers, other anti-hypertensives, anti-anginals
Medications taken by some, but less than 20% of the control group: anti-coagulant, aspirin, other anti-platelet, digoxin, other cardiac drugs
Location: UK
Ethnicity: NR

Interventions Type: dietary advice
Comparison: ↑ polyunsaturated oil and margarines (n6) vs usual dietary fats
Intervention aims: reduce fat intake to 30%E, increase P/S to 1.0 (using polyunsaturated oils and margarines), weight reducing advice if BMI>30 (dietitians provided the participants and their wives with initial individual advice and a diet information sheet, participants were revisited for further advice,

recipes, encouragement at 1, 3, 6, 9, 12, 15, 18 and 21 months)
Control aims: no dietary advice on fat, weight reducing advice if BMI>30 (dietitians provided 'sensible eating' advice without specific information on fats)
Dose: (intake data) int group 11%E SFA, P/S 0.85, PUFA 9.4%E. Cont group 15%E SFA, P/S 0.45, PUFA 6.6%E. **Increase 2.8%E PUFA, most of which n-6.**
Baseline n-6: unclear, 6.6%E PUFA, most of which was n-6
Compliance: unclear
Duration of intervention: 2 years

Outcomes Main study outcomes: mortality, reinfarction
Dropouts: all followed for events regardless of compliance (ITT)
Available outcomes: cardiovascular events (cardiovascular deaths plus non-fatal MI), cancer deaths, total MI, non-fatal MI, total and HDL cholesterol, diagnosis type 2 diabetes
Response to contact: Yes, Professor Burr provided additional data and information on methodology

Notes Note: This was a 2x2x2 factorial trial, and so some in each group were randomised to increased fatty fish and/or increased cereal fibre.
Study funding: Welsh Scheme for Development of Health and Social Research, Welsh Heart Research Foundation, Flora Project (commercial), Health Promotion Research Trust

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	randomised using sealed envelopes
Allocation concealment (selection bias)	Unclear risk	Unclear if envelopes were opaque
Blinding of participants and personnel (performance bias)	High risk	Impossible to blind trials where participants need to make their own dietary changes
Blinding of outcome assessment (detection bias)	Low risk	"outcome assessors were not aware of study allocation" (Prof Burr, personal communication). Method of blinding not stated
Incomplete outcome data (attrition bias)	Low risk	GPs contacted for information on mortality and morbidity when patients did not attend
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry located
Attention	High risk	More attention was given to those given dietary advice
Compliance	Unclear risk	NR
Other bias	Low risk	None found

DART fish 1989 [20 41 42]

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: Moderate 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, Aspirin/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

Outcomes Main study outcome: total mortality, reinfarction, CHD death
Dropouts: none for mortality
Available outcomes: total and CV deaths, MI, CHD events, lipids, blood pressure, cancer deaths, diagnosis type 2 diabetes
Response to contact: Yes

Notes Some of each group were also advised on low fat and high PUFA and/or high fibre diets, all participants who smoked were advised to stop and all with a BMI >30 were given weight reduction advice, regardless of randomisation arm. The low fat high PUFA comparison was included in the omega 6 review.
Study funding: By the Welsh Scheme for the Development of Health and Social Research, the Welsh Heart Foundation and the Health Promotion, Research Trust. Seven Seas Health Care and Duncan Flockhart provided MaxEPA capsules

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomised", NB: change to Low following email from Lee on 4.9.17
Allocation concealment (selection bias)	Unclear risk	Pre-prepared sequentially numbered enveloped opened by dietitian (unclear if envelopes were opaque)
Blinding of participants and personnel (performance bias)	High risk	Blinding of dietary advice (or lack of it) is not possible
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors were not aware of study allocation (Prof Burr stated he did not know assignments)
Incomplete outcome data (attrition bias)	Low risk	Hospital notes and death registers were flagged to catch all outcome data
Selective reporting (reporting bias)	Unclear risk	No study protocol or trials register entry was found
Attention	High risk	More attention was paid to those given dietary advice
Compliance	Unclear risk	7 day weighed food diary of a random sub-sample indicated intake of 2.5g/week EPA int., 0.8g/week EPA control
Other bias	Low risk	None noted

Dasarathy 2015 [43]

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: inclusion criteria required stable regiment of anti-diabetic agents.
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
Outcomes	Main study outcome: Histology and liver function Dropouts: 0 int., 0 control Available outcomes: Adiposity, lipids, glucose, HOMA, HbA1c, insulin (BMI, total cholesterol, triglycerides and insulin not used due to baseline differences) Response to contact: No
Notes	Study funding: National Institutes of Health

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“using a random numbers table”
Allocation concealment (selection bias)	Unclear risk	No methodology supplied
Blinding of participants and personnel (performance bias)	Low risk	Capsules had no visual/odour/taste differences
Blinding of outcome assessment (detection bias)	Low risk	“codes were broken only after primary analysis was completed”
Incomplete outcome data (attrition bias)	Low risk	All included in analysis
Selective reporting (reporting bias)	Unclear risk	Not all registry outcomes clearly reported
Attention	Low risk	No suggestion of this
Compliance	Unclear risk	Pill count or intake data not reported in percentage terms or equivalent
Other bias	Low risk	None noted

de Luis 2016 [44]

Methods	RCT, single blind, placebo-controlled (n3 DHA vs MUFA), 6 months Summary risk of bias: Moderate or high
Participants	Generally healthy individuals with obesity (BMI 30-35) N: 17 int., 17 control. (analysed, int: 14 cont: 15) Level of risk for CVD: low Male: 35.7% int., 46.7% control. Mean age (SD): 47.4(9.1) int., 44.3(11.7) control Age range: 18-65 (inclusion) 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: supplement (capsules/pills containing DHA or olive oil Comparison: Higher DHA vs MUFA Intervention: 500mg/d DHA for first 60 days followed by 250mg/d until 180 days manufactured by Polaris, Pleuven, France Control: placebo pill containing 5 ml olive oil **PUFA Dose**: (intended) increase average 0.33g/d EPA+DHA, **0.2%E n-3, 0.2%E PUFA** Compliance: Erythrocyte fatty acid status Duration of intervention: 6 months
Outcomes	Main study outcome: modification in inflammation-resolving eicosanoid levels Dropouts: 3 int., 2 control Available outcomes: body weight; waist circumference; BMI; fat mass; HOMA-IR; plasma glucose levels; insulin levels; serum total cholesterol, triglyceride, HDL & LDL concentrations; resistin, leptin, adiponectin levels; inflammatory markers: CRP, IL-6, TNF-alpha; red cell membrane fatty acid status

(LDL not used due to baseline differences)
Response to contact: Yes (details provided)

Notes No conflicts of interest declared; PNKDIET, SLU, Spain provided free of charge the diet of the ketogenic phases in both groups & oral supplementation of DHA/placebo

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	randomised using table of numbers
Allocation concealment (selection bias)	Unclear risk	Unclear, no details provided.
Blinding of participants and personnel (performance bias)	High risk	Single blinded, only participants blinded. Insufficient detail regarding appearance, smell or taste of intervention or placebo to assess blinding performance
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information provided
Incomplete outcome data (attrition bias)	High risk	Outcome data reported for 85.3% of randomised participants
Selective reporting (reporting bias)	Low risk	Primary outcome reported matches trials register
Attention	Low risk	Participants in both arms appear to have identical follow-up
Compliance	Low risk	Measured by fatty acid status data. C-RoB low as p<0.05 in FA DHA levels between arms at 6m
Other bias	Low risk	None noted

DeFina 2010 [45]

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

Participants Sedentary men and women with a BMI between 26 and 40
N: 64 int., 64 control. (analysed, int: 64 cont: 64)
Level of risk for CVD: Low
Male: 31.3% int., 31.3% control.
Mean age (SD): 45.6 (8.3) int., 47.0 (7.8) control
Age range: 30-60 years
Smokers: NR
Hypertension: 17.2% int., 18.8% 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: supplement (capsules with n3 EPA+DHA; or soybean plus corn oil)
Comparison: n3 EPA+DHA vs n6 LA
Intervention: 5 capsules/d (including 3.0g EPA+DHA in ratio 5:1, Cooper Advanced Omega-3): EPA+DHA 3.0g/d
Control: 5 capsules/d (soybean and corn oil in ratio 1:1)
Compliance: Plasma fatty acids, pill counts, 3-d dietary records
Duration of intervention: 6 months

Outcomes Main study outcome: Weight loss and body composition
Dropouts: 23 int., 22 control
Available outcomes: Anthropometrics, lipids, glucose, insulin, fatty acids. Profile of mood states (POMS). CRP measured, not reported (BP 6 months not used; insulin and HDL cholesterol not used, baseline differences)
Response to contact: Yes, methodological details provided

Notes Study funding: Cooper Concepts Inc.

Risk of bias table

Bias	Authors'	Support for judgement

	judgement	
Random sequence generation (selection bias)	Low risk	Author confirmed: *Participants were randomized to intervention and control arms using a sex and 2-level BMI stratified random block method. The clinical observers were blinded to the randomization process.*
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias)	Unclear risk	States capsules were identical in colour, shape, and flavour; but smell not reported
Blinding of outcome assessment (detection bias)	Unclear risk	NR
Incomplete outcome data (attrition bias)	Low risk	Attrition >20%, however balanced by arm, reasons given and intention-to-treat analysis
Selective reporting (reporting bias)	Unclear risk	No registry or protocol identified
Attention	Low risk	Schedule appears comparable and differs only by capsule
Compliance	Low risk	Significant increase in plasma EPA and DHA in intervention group
Other bias	Low risk	None noted

Delamaire 1991 [46]

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

Participants
People with well-controlled insulin-dependant 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

Outcomes
Main study outcome: haemorheological parameters
Dropouts: NR
Available outcomes: (sheer rate viscosity, erythrocyte aggregation, fibrinogen - not used)
No usable outcomes were reported, but blood sugar parameters were clearly collected as the abstract states "glycaemic balance was unchanged in either group".
Response to contact: No

Notes
Study funding: NR
Only abstract found. No replies despite several attempts to contact the author.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	Unclear risk	Not reported

Blinding of outcome assessment (detection bias)	Unclear risk	Not reported, but biochemistry type outcomes so likely low risk
Incomplete outcome data (attrition bias)	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry found
Attention	Unclear risk	Not reported
Compliance	Unclear risk	Not reported
Other bias	Low risk	None noted

Derosa 2009 [47]

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

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

Interventions Type: supplement
Comparison: omega 3 capsules vs sugar pills
Intervention: 1.125g/d EPA plus 1.875g/d DHA as ethylic esters, split over 3 meals (SPA Societa Produtti Antibiotici): EPA+DHA 3.0g/d
Control: pills of sucrose, mannitol and mineral salts, 3g/d split over 3 meals
PUFA Dose: (intended) increase 3.0g/d EPA+DHA, **1.4%E n-3, 1.4%E PUFA**
Compliance: assessed by pill count returned at clinic visits, but compliance data not reported
Duration of intervention: 6 months

Outcomes Main study outcome: lipid profile, coagulation, inflammatory and fibrinolytic parameters
Dropouts: 4 of 168 int., 3 of 165 control
Available outcomes: lipids, glucose, insulin, HOMA, hsCRP (no deaths or MI occurred, 1 cancer diagnosed in each arm but 6 month data), PAI1, homocysteine and several inflammatory markers reported but not used, BMI provided but too different at baseline to use
Response to contact: Author contacted but this trial not discussed

Notes Study funding: SPA (Societa Produtti Antibiotici) provided medication and paid for publication charges, no other funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was done using a drawing of envelopes containing randomization codes prepared by a statistician. A copy of the code was provided only to the responsible person performing the statistical analysis. The code was only broken after a database lock, but could have been broken for individual subjects in case of an emergency."
Allocation concealment (selection bias)	Unclear risk	As above- no information provided on opacity of envelopes.
Blinding of participants and personnel (performance bias)	High risk	No suggestion that pills were similar, and given different compositions there were unlikely to be
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear, code was masked, but participants were likely to have known their allocation

Incomplete outcome data (attrition bias)	Unclear risk	Low dropout level, though no explanations of attrition provided
Selective reporting (reporting bias)	Unclear risk	No trials registry entry or protocol found
Attention	Low risk	Appointments appeared similar in schedule and duration between arms
Compliance	Unclear risk	No body tissue levels or pill count data provided
Other bias	Low risk	None noted

Derosa 2011 [48 49]

Methods RCT, parallel, (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
PUFA Dose: (intended) increase 2.55g/d EPA+DHA, **1.2%E n-3, 1.2%E PUFA**
Compliance: measured by counting the number of pills returned at the time of specified clinic visits, no data found
Length of intervention: 6 months

Outcomes Main study outcome: insulin-resistance
Dropouts: 6 int, 4 control
Available outcomes: weight, lipids, fasting glucose, HOMA-IR, other markers of insulin sensitivity, hsCRP, s-ICAM, s-VCAM, TNF alpha, E-selectin, IL-6 (BP reported but not used as 6 month data, metalloproteinases reported, fasting insulin, HOMA, BMI reported but not used as too unbalanced at baseline)
Response to contact: yes

Notes Study funding: NR, "The authors certify that they have no affiliation with, or financial involvement in, any organization or entity with a direct financial interest in the subject matter or materials discussed in the manuscript"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomisation was done using a drawing of envelopes containing randomisation codes prepared by a statistician"
Allocation concealment (selection bias)	Unclear risk	Unclear whether envelopes were thick enough to be opaque
Blinding of participants and personnel (performance bias)	Unclear risk	n-3 and placebo supplied as identical, opaque, white capsules in coded bottles to ensure the blind status of the study - However no information provided on capsules taste or smell

Blinding of outcome assessment (detection bias)	Low risk	States "double blind", and code only broken after database lock
Incomplete outcome data (attrition bias)	Unclear risk	Numbers shown at baseline don't add up to the total number randomised, but ITT analysis for those receiving at least one dose of the capsules
Selective reporting (reporting bias)	Unclear risk	No registry entry or protocol found
Attention	Unclear risk	Frequency of contact appears similar for both groups, and blinded
Compliance	Unclear risk	Unclear as data not provided on compliance
Other bias	Low risk	None noted

Derosa 2016 [5]

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

Participants Caucasian overweight/obese patients with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) but not on meds affecting glucose metabolism
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

Outcomes Main study outcome: insulin-resistance
Dropouts: 23 across arms (no details on groups but stated that there were no difference between groups)
Available outcomes: weight, BMI, lipids, diabetes mellitus, HOMA, insulin, authors provided information on mortality, cardiovascular mortality, CHD, stroke, MI, glucose, depression, atrial fibrillation
Response to contact: Yes

Notes Glucose data is provided by impaired fasting glucose or impaired glucose intolerance groups
Study funding: "The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties"

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Randomization was done using a drawing of envelopes containing randomisation codes prepared by a statistician.
Allocation concealment (selection bias)	Low risk	Authors replied that the researcher who recruited participants was not aware of which arm the participant would be allocated to, but methodology for this not provided.
Blinding of participants and personnel (performance bias)	Low risk	Both n-3 PUFAs and placebo were supplied as identical, opaque, white capsules in coded bottles to ensure the blind status of the study.
Blinding of outcome assessment (detection bias)	Low risk	A copy of the code was provided only to the person performing the statistical analysis.
Incomplete outcome data (attrition bias)	Low risk	An intention to treat analysis was conducted for patients who received 1 dose of study medication
Selective reporting (reporting bias)	Unclear risk	No trial registry or protocol found
Attention	Low risk	No difference reported
Compliance	Unclear risk	Measured by counting the number of pills returned at the time of specified clinic visits
Other bias	Low risk	None noted

Deslypere 1992 [50-52]

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 vit 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.

Outcomes Main study outcome: Effect on coronary risk factors
Dropouts: None
Available outcomes: deaths (nil), CVD events (nil), Lipids, BP, HbA1c, weight (measured but not reported)
Response to contact: Yes

Notes Study funding: capsules supplied by Labaz (Brussels Belgium). The placebo capsules contained olive oil (Puget) and palm oil (Loders-Kroklaan, Wormerveer). Financial support by Sanofi-Labaz.
Data entered for high fish oil versus placebo groups

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	"The manufacturer provided envelopes containing numbers corresponding with boxes of capsules. For each enrolled subject, random envelope was opened." author correspondence
Allocation concealment (selection bias)	Low risk	No further details, but method (above) suggests that the person enrolling a participant would have been blinded to allocation, and authors confirm this.
Blinding of participants and personnel (performance bias)	High risk	Although double blind, the fishy taste of the active treatment was not matched.
Blinding of outcome assessment (detection bias)	Low risk	Authors confirmed outcome assessors were unaware until afterwards.
Incomplete outcome data (attrition bias)	Low risk	No drop outs
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registry record
Attention	Low risk	No difference between groups
Compliance	Low risk	Significant difference in EPA concentration
Other bias	Low risk	None noted

DIPP-Tokudome 2015 [53 54]

Methods Dietary Intervention for Patients Polypectomized for tumours of the colorectum (DIPP)
RCT, parallel, 2 arms (n3 EPA+DHA + 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 + ALA vs nil
Intervention: advice to 1) Reduce total fat intake, 2) Decrease consumption of n-6 PUFAs, increase intake of n-3 PUFAs from fish/marine foods
3) Increase intake of n-3 PUFAs from perilla oil rich in ALA, 4) Take 8 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

Outcomes Main study outcome: Number and size of colorectal tumours
Dropouts: 3 int., 5 control
Available outcomes: All-cause mortality, dietary intake, plasma fatty acids, lipids, side effects, glucose.
Response to contact: Yes (methodological details provided)

Notes Study funding: All were either government or charity grants.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly allocated using random digit number for allocation of participants.
Allocation concealment (selection bias)	Low risk	Author confirmed "Allocation information was blinded to clinicians and researchers"

Blinding of participants and personnel (performance bias)	Unclear risk	From the 2015 paper, 'The attending physicians as well as the participants were blinded to the assignment information'. However, in the discussion section they say 'complete participant blinding could not have been achieved because free living participants might have exchanged information on their dietary intervention, say in the hospital waiting room'. Author confirmed blinding
Blinding of outcome assessment (detection bias)	Low risk	'physicians, including colonoscopists, a scientist who conducted blood and specimen analyses, and pathologists were blinded'.
Incomplete outcome data (attrition bias)	Low risk	All those randomised were accounted for.
Selective reporting (reporting bias)	High risk	The researchers chose not to report data on the number, size and pathological type of the colorectal tumours as they said they would in the trials register. They reported more outcomes in the paper than initially stated. UMIN000000461 Registered 03/08/2006, recruitment completed 01/03/2007
Attention	Low risk	Participants were given equal follow-up.
Compliance	Unclear risk	paper reported satisfactory compliance but this was not defined
Other bias	Low risk	None noted

DO IT - Einvik 2010 [55]

Methods Diet and Omega 3 Intervention Trial on Atherosclerosis (DO IT)
Randomisation: RCT, parallel, 2x2 factorial (n3 DHA+EPA vs n6 LA also dietary advice intervention), 36 months
Summary risk of bias: Moderate or high

Participants Elderly men with long standing dyslipidaemia or hypertension (a subset of Oslo Diet heart study)
N: Int 282 (140 n-3 capsules + 142 n-3 capsules & dietary advice), Control 281 (142 placebo capsules + 139 placebo capsules & dietary advice)
Level of risk for CVD: Moderate
Male: Int 100%, Control 100%
Mean age (SD): Int 70.4 (2.9), Control 69.7 (3.0) years
Age range: 64-76 years
Smokers: Int 35%, Control 33%
Hypertension: Int 29%, Control 27%
Medications taken by at least 50% of those in the control group: None
Medications taken by 20-49% of those in the control group: statins and Acetylsalicylic acid.
Medications taken by some, but less than 20% of the control group: βeta-blockers, ACE-inhibitors, and Nitrates.
Location: Norway
Ethnicity: NR

Interventions Type: supplement/ capsule (also dietary advice as the factorial intervention)
Comparison: EPA & DHA vs omega 6
Intervention: 2x2 capsules/d inc 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 inc 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.

Outcomes Main study outcome: atherosclerosis progression.
Dropouts: Int 14 died, 20 others discontinued, Control 24 died, 18 others discontinued.
Available outcomes: Mortality, cardiovascular deaths, CHD events, CV events, MI, stroke, diabetes, glucose, lipids, cancer diagnosis, cancer deaths, sudden death (authors have provided additional information on HADS depression and anxiety, and diabetes diagnosis, glucose, HbA1c, insulin)
Response to contact: Yes

Notes The other 2x2 intervention was dietary advice to increase both omega 3 and omega 6 fats. These data were included in the total PUFA review.
Study funding: Norwegian Cardiovascular Council, Norwegian retail company RIMI, vegetable oil and

margarine supplied by the Norwegian food company Mills DA and placebo capsules by LUBE.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Permuted block randomisation
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias)	Unclear risk	Capsules of fish oil or placebo taken, but unclear whether blinded and if so, how well or successfully
Blinding of outcome assessment (detection bias)	Low risk	"Mortality data were supplied from the Norwegian Cause of Death Registry, and all clinical events were confirmed by hospital records and verified by an independent cardiologist"
Incomplete outcome data (attrition bias)	Low risk	No attrition as deaths and events collected from centralised register
Selective reporting (reporting bias)	Unclear risk	Trials registry entry submitted after the outcomes papers were published
Attention	Low risk	No suggestion of attention bias between verum and placebo supplement arms
Compliance	Low risk	Pharmacy records suggested that >90% of supplements were taken, and plasma EPA and DHA were raised in intervention compared to control participants.
Other bias	Low risk	None noted

Dodin 2005 [56 57]

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

Outcomes
Main study outcome: Bone mineral density
Dropouts: 26 int., 17 control (but 13/17 had an endpoint evaluation)
Available outcomes: Weight, BMI, QoL, Blood Pressure, lipids, glucose, adverse events, dietary intake, plasma fatty acids
Response to contact: Yes

Notes
Authors replied to tell us that there were no deaths or CV events during the study
Study funding: Not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation schedule was prepared by the clinical unit of the research centre using computer generated randomisation in blocks of four to eight
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Low risk	Subjects, investigators, staff, and statisticians were blinded to dietary assignments for the duration of the study. “a local baker prepared loaves of bread. Each week, the loaves of bread were delivered in sealed, opaque unmarked wrappers to the Department of Food and Nutrition Sciences at Laval University. The seeds were ground up and vacuum-packed in the same laboratory. The Department of Food and Nutrition Sciences was responsible for labelling the bags of bread and packages of seeds with the subject’s randomization number. Bread and packages of seeds were provided on a 3-month basis. The foods that both groups received was similar in appearance and packaging and was kept frozen until consumption to avoid essential fatty acid
Blinding of outcome assessment (detection bias)	Low risk	Subjects, investigators, staff, and statisticians were blinded to dietary assignments for the duration of the study
Incomplete outcome data (attrition bias)	Low risk	Intention to treat analysis. Loss to follow up 10%, reasons given.
Selective reporting (reporting bias)	Unclear risk	No protocol or clinical trial registry entry found
Attention	Low risk	All participants had same number of visits
Compliance	Low risk	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
Other bias	Low risk	None noted

Dullaart 1992 [19]

Methods RCT, parallel, 2 arms (n6 vs mixed fats), 2 years
Summary risk of bias: Moderate or high

Participants Type I diabetics with elevated urinary albumin
CVD risk: moderate
Control: randomised 20, analysed 20
Intervention: randomised 18, analysed 16
% male: 81% int., 75% control
Age: mean(SD) control 41(14), intervention 44(12)
Age range: Unclear (21-65 inclusion)
Smokers: control 55%, int 50%
Hypertension: cont 10%, int 6%
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: anti-hypertensives
Location: Netherlands
Ethnicity: NR

Interventions Type: dietary advice
Comparison: LA (n6) vs usual diet
Intervention: Diet advice given at every visit throughout the 2-year period to increase linoleic acid

achieving a polyunsaturated: saturated fatty acid ratio close to 1.0. Advice to replace butter or saturated margarines by polyunsaturated margarines and to restrict the intake of saturated fat from meat and milk products
Control: to continue their usual diet. All participants were urged not to alter total fat and protein content.
Dose: (intake data) int group 13%E SFA, P/S 0.985, PUFA 9.4%E. Cont group 15%E SFA, P/S 0.45, PUFA 6.6%E. **Increase 2.8%E PUFA, most of which n-6.**
Baseline n-6: unclear, 6.6%E PUFA, most of which was n-6
Compliance: unclear
Duration of intervention: 2 years

Outcomes Main study outcomes: albuminurea and lipids
Dropouts: int 2 of 20, cont 4 of 20
Available outcomes: weight, HDL cholesterol, TGs, HbA1c (total cholesterol, glucose, insulin reported but too different at baseline to use, LDL not reported in control group, renal outcomes such as GFR, albuminurea, mean arterial pressure not used)
Response to contact: Yes

Notes Most outcomes are estimated from figures.
Study funding: Dutch Diabetes Research Fund

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"patients were stratified according to sex and randomised in blocks of ten men and six women"
Allocation concealment (selection bias)	Low risk	assigned using opaque sealed envelopes by independent statistical investigator with no contact with participants
Blinding of participants and personnel (performance bias)	High risk	No information on blinding. Participants could not be blinded as they received dietary advice.
Blinding of outcome assessment (detection bias)	Unclear risk	No details
Incomplete outcome data (attrition bias)	Unclear risk	No details on drop outs apart from the exclusion of 2 intervention participants from the trial due to pregnancy and decision not to participate.
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration.
Attention	High risk	Intervention groups received diet advice at every visit. As the control group were advised to stick with their usual diet, it seems likely that the intervention group received more time on dietary advice.
Compliance	High risk	Compliance poor as assessed by biomarkers
Other bias	Low risk	None noted

Ebrahimi 2009 [58 59]

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
PUFA Dose: (intended) increase 3.0g/d EPA+DHA, **1.4%E n-3, 1.4%E PUFA**
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

Outcomes Main study outcome: "several anthropometric and biochemical parameters"
Dropouts: 13/60 int., 17/60 control (this probably combines dropouts and exclusions)
Available outcomes: weight, BMI, total chol, HDL & LDL chol, fasting glucose (TGs and hsCRP provided as medians, BP given but only 6 months, heat shock protein not relevant)
Response to contact: No contact attempted

Notes Study funding: Mashhad University of Medical Science Research Council

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly allocated" - no further details
Allocation concealment (selection bias)	Unclear risk	no information
Blinding of participants and personnel (performance bias)	High risk	No placebo used
Blinding of outcome assessment (detection bias)	Unclear risk	Blinding not mentioned
Incomplete outcome data (attrition bias)	High risk	30/120 (25%) lost over 6 months
Selective reporting (reporting bias)	Unclear risk	No protocol or trials register entry found
Attention	High risk	Paper states that weekly visits were used to promote and assess compliance, but presumably these did not happen in the control group as there was no placebo to encourage or assess.
Compliance	Unclear risk	Unclear how many did not comply fully (and so were excluded)
Other bias	Low risk	None noted

EPE-A 2014 [60]

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

Participants People with non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD)
N: 86 high dose, 82 low dose, 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% high dose, 41.5% low dose, 42.7% control.
Mean age (SD): 47.8 (11.1) high dose, 47.8 (12.5) low dose, 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 low dose: 94% high dose: 87% cont: 90.7%
African American low dose: 3.7% high dose: 2.3% cont: 4.0%
Others low dose: 2.4% high dose: 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- content NR
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

Outcomes Main study outcome: Histological Response in Standardized Scoring of Liver Biopsies and change in ALT level.
Dropouts: 22 high dose, 27 low dose, 20 control
Available outcomes: cardiac events, deaths (none), adverse events, cancers (weight, BMI, lipids, glucose, HbA1c, HOMA, hsCRP (all reported as medians so not useable in meta-analyses)
Response to contact: Yes

Notes Data combined for the two intervention groups for binary outcomes and higher dose data used for continuous outcomes.
Study funding: supported entirely by Mochida Pharmaceuticals

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation using an interactive voice-response system was used to assign subjects in a 1:1:1 ratio between the 2 arms for each site separately. Subjects were stratified by the presence of type 2 diabetes. The total fraction of such individuals was capped at 40% of the study cohort
Allocation concealment (selection bias)	Low risk	As above (remote computer-generated randomisation)
Blinding of participants and personnel (performance bias)	Low risk	Author confirmed researchers and outcome assessors were blinded to treatment allocation and pills were identical with respect to size, colour and gross smell.
Blinding of outcome assessment (detection bias)	Unclear risk	No details
Incomplete outcome data (attrition bias)	High risk	Number and characteristics of participants lost to follow-up similar across arms, however <80% provided outcome data relevant to this systematic review.
Selective reporting (reporting bias)	Low risk	Registered Jun 2010, study started June 2010, completed Oct 2012. All outcomes in trials registry entry were also reported in the trials registry. Secondary outcomes reported were not planned (compared with first version of clinicaltrials.gov entry).
Attention	Low risk	All participants had same follow-up visits.
Compliance	Low risk	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
Other bias	Low risk	None noted

EPOCH 2014 [6 61]

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 (1.72 g/d DHA and 0.60 g/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

Outcomes Main study outcome: Change in cognitive performance
Dropouts: NR
Available outcomes: Author reported MI, stroke, revascularisation, arrhythmias, CV events. Planned outcomes, not reported in publications, included: cognitive outcomes, functional outcomes, glucose, BP, lipids, plasma fatty acids, blood pressure, inflammation and oxidative stress.
Response to contact: Yes

Notes Authors reported some events, but don't appear to be published.
Study funding: EPAX donated the Omega-3 concentrate and Blackmores Pty Ltd donated the placebo and packaging of the Omega-3 concentrate. The trial was supported by the Brailsford Robertson Award 2007-2008 (University of Adelaide and CSIRO Food and Nutritional Sciences), and is funded by a National Health and Medical Research Project Grant (#578800).

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Age-stratified, permuted-block randomisation, with mixed block-sizes (two to eight, size unknown to study investigators), 1:1 allocation. Computer generated randomisation schedule.
Allocation concealment (selection bias)	Low risk	An independent researcher prepared allocation to treatment.
Blinding of participants and personnel (performance bias)	Low risk	The researchers, project staff, and participants remained blinded to treatment allocation until the trial was completed and the database locked. However no information provided on capsules appearance, taste or smell.
Blinding of outcome assessment (detection bias)	Low risk	As above
Incomplete outcome data (attrition bias)	Unclear risk	No data for each group presented, and no attrition data presented.
Selective reporting (reporting bias)	High risk	Only cognitive functions reported for whole population (not by arm). No secondary outcomes reported (MMSE; perceived health status, depressive symptoms, positive and negative affect, life satisfaction, self-reported cognitive functioning, and functional capacity; blood pressure; biomarkers of glucose, glycated haemoglobin, triglycerides, total cholesterol, HDL, LDL, homocysteine, CRP, MDA, and telomere length). ACTRN2607000278437 Date registered: 18/05/2007. Participant recruitment period unclear.
Attention	Low risk	All had the same contact and attention
Compliance	Unclear risk	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 but results not reported
Other bias	Low risk	None noted

Fakhrzadeh 2010 [62 63]

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

Participants Elderly residents (65 years 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

Outcomes Main study outcome: Lipids, insulin resistance
Dropouts: 10 in both groups combined
Available outcomes: Lipid profiles, insulin, glucose, HOMA-IR (glucose, insulin and HOMA-IR data not useable- baseline differences)
Response to contact: Yes

Notes Study funding: Tehran University of Medical Science

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned"
Allocation concealment (selection bias)	Unclear risk	As above
Blinding of participants and personnel (performance bias)	Unclear risk	"participants and investigators were blinded to the intervention"
Blinding of outcome assessment (detection bias)	Unclear risk	As above
Incomplete outcome data (attrition bias)	Unclear risk	Drop out numbers by group unclear
Selective reporting (reporting bias)	Unclear risk	No registry or protocol identified
Attention	Unclear risk	Not reported and blinding unclear
Compliance	Unclear risk	Nurses observed participants taking capsules
Other bias	Low risk	None noted

Ferrara 2000 [21]

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

Participants Hypertensive patients

N: 23 overall (analysed, int: 23 cont: 23)
Level of risk for CVD: Moderate
Male: 43% int., 43% control.
Mean age (SD): NR
Age range: 25-70 years
Smokers: NR
Hypertension: All
Medications taken by at least 50% of those in the control group: Antihypertensives
Medications taken by 20-49% of those in the control group: (atenolol, nifedipine, lisinopril)
Medications taken by some, but less than 20% of the control group: (hydrochlorothiazide, doxazosin)
Location: Italy
Ethnicity: NR

Interventions Type: supplemented food (diets enriched with sunflower oil or olive oil)
Comparison: PUFA vs MUFA
Intervention: Spoons of sunflower oil added after cooking (40g men, 30g women): assuming 59% LA, 23.6g/d LA men, 17.7g/d women
Control: Spoons of olive oil added after cooking (40g men, 30g women)
PUFA Dose: (intended) increase ~20g/d LA, **9%E n-6, 9%E PUFA**
Compliance: 7-d food records
Duration of intervention: 6 months

Outcomes Main study outcome: Antihypertensive use and BP
Dropouts: none
Available outcomes: BMI, weight, lipids, glucose
Response to contact: No contact attempted

Notes Study funding: NR

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)		"randomly assigned"
Allocation concealment (selection bias)	Unclear risk	"randomly assigned"
Blinding of participants and personnel (performance bias)	Unclear risk	"double-blind"- however, given as spoonfuls of oil (olive oil and sunflower oil)
Blinding of outcome assessment (detection bias)	Unclear risk	BP measures by author "unaware of the patient's dietary treatment". Method of blinding not described
Incomplete outcome data (attrition bias)	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	No registry or protocol identified
Attention	Low risk	The study only differed by the content of the spoonfuls of oil added to participants diets. Assessment schedule did not appear to differ between the two arms.
Compliance	Unclear risk	3 patients not fully compliant, however included in the analysis "since they had complied with the indications for the intake of MUFA or PUFA"
Other bias	Low risk	None noted

Finnegan 2003 [64]

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 inc 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

Outcomes Main study outcome: fasting and postprandial insulin and glucose
Dropouts: NR but 50 were lost across all 5 arms
Available outcomes: weight, lipids, glucose, insulin, TNFα, IL-1,2,4,6&10 (postprandial TG and glucose AUC and IAUCs, coagulation and fibrinolytic factors, BP, phagocytic activity, oxidative burst, thymidine and interferon gamma reported but not used)
Response to contact: No contact attempted

Notes Study funding: DEFRA, BBSRC, Roche Vitamins & Unilever research under the Agri-Food LINK programme

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blocked stratified randomisation
Allocation concealment (selection bias)	Unclear risk	No methods discussed
Blinding of participants and personnel (performance bias)	Unclear risk	Reported as "double blind" but their similarity in appearance, taste and packaging was not discussed
Blinding of outcome assessment (detection bias)	Unclear risk	As above
Incomplete outcome data (attrition bias)	High risk	25% of participants were lost
Selective reporting (reporting bias)	Unclear risk	No trials registry entry or protocol found
Attention	Low risk	No suggestion of differential attention in the 5 groups
Compliance	Low risk	Statistically significant changes in fatty acids
Other bias	Low risk	None noted

Gill 2012 [65 66]

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

Outcomes Main study outcome: Change in Carotid IMT
Dropouts: Unclear
Available outcomes: lipids, insulin and glucose are stated as secondary outcomes but no usable data published
Response to contact: No

Notes Results cannot be used as numbers are not reported by study arm
Study funding: Unclear, but mentions that Pfizer, NIH & "Northwest Lipids Clinic" are partners.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Unclear risk	No data
Blinding of outcome assessment (detection bias)	Unclear risk	No data
Incomplete outcome data (attrition bias)	Unclear risk	No data
Selective reporting (reporting bias)	High risk	Inadequate detail in reporting as no full text publication found; Gill 2014 does give detail on carotid IMT, but not on other primary or secondary outcomes. The trial was prospectively registered (registered July 2006, unclear when recruitment started, final data collection 2011, first data published 2012).
Attention	Unclear risk	No data
Compliance	Unclear risk	No details
Other bias	Unclear risk	No data

GISSI-P 1999 [67 68]

Methods Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico - Prevention (GISSI-P)
RCT, 2x2 (n3 EPA+DHA vs 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 months, 28.5% by the end of the study
Duration of intervention: median follow up 40 months

Outcomes Main study outcome: All-cause mortality, CV mortality, stroke, MI
Dropouts: Unclear (however, all randomised were included in analyses)
Available outcomes: total , sudden and CV deaths, MI, stroke, angioplasty or CABG, Angina, CHD, diagnosis type 2 diabetes, cancer diagnosis, cancer death, combined CV events, side effects
Response to contact: No

Notes Numbers are slightly different in different publications (Lancet 1999 paper used as main source). Half of both groups were on vitamin E supplements (300 mg/d synthetic α-tocopherol) as this was the other 2x2 intervention
Study funding: Bristol Meyers Squibb, Pharmacia Upjohn, Societa Produtti Antibiotici, Pfizer

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Telephone/computer network, stratified by hospital, based on a biased coin algorithm
Allocation concealment (selection bias)	Low risk	Randomisation by telephone with the coordinating centre
Blinding of participants and personnel (performance bias)	High risk	No placebo intervention (capsule vs nil) so participants not blinded
Blinding of outcome assessment (detection bias)	Low risk	"validation of clinical events ... was assured by an ad-hoc committee of expert cardiologists and neurologists blinded to patients treatment assignment"
Incomplete outcome data (attrition bias)	Low risk	Clearly described, good follow up (<28% dropped out over 3.5 years)
Selective reporting (reporting bias)	Unclear risk	No study protocol or trials registry entry was found
Attention	Low risk	Slight as no placebo, otherwise similar
Compliance	Unclear risk	Capsule counts, 11.6% had stopped taking Omacor by 12 months, 28.5% by the end of the study
Other bias	Low risk	None noted

GLAMT 1993 [69]

Methods Gamma linolenic acid multicentre trial (GLAMT)
RCT, 2 arm, parallel (n-6 GLA vs non-fat), 1 year
Summary risk of bias: Moderate or high

Participants People with mild diabetic neuropathy
CVD risk: moderate
Control: randomised 57, analysed 48 (with at least one evaluation)
Intervention: randomised 54, analysed 52
Mean years in trial: control 1.0, randomised 1.0
% male: cont 79%, int 67%
Age, mean (SD) years: control 52.9 (11.4), intervention 53.3 (11.1)
Age range: unclear
Smokers: unclear
Hypertension: unclear
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: UK & Finland
Ethnicity: NR

Interventions Type: Supplement
Comparison: GLA (n-6) vs placebo (paraffin)

Control aims: 12 capsules/d paraffin
Intervention aims: 12 capsules/d evening primrose oil (EP4, equivalent to Epogam): 0.48g/d GLA
Dose: increase 0.48g/d GLA, 0.48g/d or 4kcal or **0.2%E n-6**
Baseline n-6: unclear
Compliance: unclear
Duration of intervention: 1 year

Outcomes Main study outcome: measures of diabetic neuropathy
Dropouts: cont 17, int 10
Available outcomes: MI, cancer (no deaths, glucose and HbA1c appear to have been analysed but are not available)
Response to contact: No

Notes Study funding: Scotia Pharmaceuticals

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	Described as double blind, and "Active and placebo capsules were indistinguishable in taste or appearance"
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear, though study described as double blind no methods or statement of blinding of outcome assessors was mentioned
Incomplete outcome data (attrition bias)	High risk	Reasons for withdrawal usually given, but high and dissimilar
Selective reporting (reporting bias)	Unclear risk	No clear protocol or trials registry entry found
Attention	Low risk	Capsule only intervention and provided to all, other follow ups appeared consistent for all
Compliance	Unclear risk	NR
Other bias	Low risk	None identified

Heine 1989 [22]

Methods RCT, cross-over, (n6 LA vs mixed fat), 6 months
Summary risk of bias: Moderate or high

Participants Non-insulin dependent diabetic patients
N: 17 patients overall (analysed, int: 14 cont: 14)
Level of risk for CVD: Moderate
Male: 57% int., 57% control.
Mean age (SD): 51.9 (11.6) int., 51.9 (11.6) control
Age range: 30-70 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: Glibenclamide
Medications taken by some, but less than 20% of the control group: Gliclazide, tolbutamide
Location: The Netherlands
Ethnicity: NR

Interventions Type: supplemented food (oils and margarines with LA or SFA)
Comparison: LA vs SFA
Intervention: LA enriched oils and margarines (P:S ratio 1.0): LA quantity unclear
Control: Substitution of LA oils and margarines for SFA (P:S ratio 0.3)
PUFA Dose: (intended) increase unclear
Compliance: 1-wk dietary recall and assessment of fatty acids of cholesteryl esters
Duration of intervention: 30 weeks

Outcomes Main study outcome: Lipoproteins and insulin sensitivity
Dropouts: 3 overall

Available outcomes: Lipids, glucose, HbA1c, weight, insulin (HDL subfractions as means over the period and BP at 6 months not used)
Response to contact: No contact attempted

Notes Study funding: NR

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomized"
Allocation concealment (selection bias)	Unclear risk	"randomized"
Blinding of participants and personnel (performance bias)	Unclear risk	NR
Blinding of outcome assessment (detection bias)	Unclear risk	NR
Incomplete outcome data (attrition bias)	High risk	Drop out >20% in 3 months
Selective reporting (reporting bias)	Unclear risk	No registry or protocol identified
Attention	Low risk	The study only differed by the content of the oils and margarines. The assessment schedule was not stated to differ between the two arms
Compliance	Low risk	Dietary recall confirmed by significant increase in LA in the intervention group
Other bias	Low risk	None noted

HERO-Tapsell 2009 [14 70]

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

Outcomes Main study outcome: change in body weight and % body fat.
Dropouts: 8 int., 5 control
Available outcomes: all-cause mortality (nil deaths), weight, lipids, glucose, insulin, HbA1c and other measures of adiposity.
Response to contact: No contact attempted

Notes Body fat % was too different between groups at baseline hence data not used.

Study funding: California Walnuts Commission

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was conducted using a computerized random number generator by a researcher independent of the subject interface
Allocation concealment (selection bias)	Unclear risk	No further details
Blinding of participants and personnel (performance bias)	High risk	**"**Subjects, but not dietitians, were blinded to the type of overall diet (a pre-packaged 30 g snack portion of walnuts was given to the walnut group unbeknown to the controls)" However, there was no placebo supplement so blinding not truly feasible.
Blinding of outcome assessment (detection bias)	Unclear risk	Paper states "code was concealed from the researchers collecting data, as well as from subjects." However as participants could not be blinded outcome assessors may not have been (problem for measures of adiposity, not for biochemical measures).
Incomplete outcome data (attrition bias)	High risk	High drop-out rate 35 of 50 analysed (30% attrition rate)
Selective reporting (reporting bias)	Unclear risk	Trial registered but post analysis
Attention	Low risk	Both groups appear to have had same level of attention.
Compliance	High risk	ALA levels almost exactly the same in both intervention and control
Other bias	Low risk	None noted.

Houtsmuller 1979 [71-74]

Methods RCT, parallel, (increase n6 LA vs usual diet), 72 months maximum
Summary risk of bias: Moderate or high

Participants Adults with newly diagnosed diabetes
N: 51 int., 51 control. (analysed unclear int, unclear cont)
Level of risk for CVD: moderate
Male: 56% overall (not stated by intervention arm)
Mean age (SD): NR int., NR 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: statins (probably)
Location: The Netherlands
Ethnicity: NR

Interventions Type: dietary advice
Comparison: increased PUFA vs usual diet
Intervention: aims total fat 40%E, 1/3 linoleic acid, CHO 45%E, protein 15%E; methods unclear, surveyed by dietitian. Intervention appears to be delivered by dietitian but no clear details on format or frequency.
Control: aims SFA 35%E, CHO 50%E, protein 15%E; methods unclear, surveyed by dietitian
Compliance by biomarkers: good, serum total cholesterol significantly reduced in intervention compared to control (-0.47mmol/L, 95% CI -0.76 to -0.18), no significant differences in men, but significant improvements in women from 3 years.
Compliance by dietary intake: unclear (not reported)
Total fat intake: not reported
Saturated fat intake: not reported
PUFA intake: not reported
PUFA n-3 intake: not reported
PUFA n-6 intake: not reported
MUFA intake: not reported

CHO intake: not reported
Protein intake: not reported
Trans fat intake: not reported
Duration of intervention: 72 months

Outcomes Main study outcome: progression of diabetic retinopathy
Dropouts: unclear int., unclear control
Available outcomes: cardiovascular events (total MI and angina), total cholesterol, TGs (data read off graph), CHD mortality (fatal MI), CHD events (MI, angina), progression of retinopathy
Response to contact: No

Notes Study funding: Dutch Heart Foundation
Author contact: Attempted but no contact established

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants matched in pairs then randomised
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding of participants and personnel (performance bias)	Unclear risk	Unclear, though unlikely as dietary advice provided.
Blinding of outcome assessment (detection bias)	Unclear risk	Blinding of outcome assessors not mentioned.
Incomplete outcome data (attrition bias)	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs, trialists asked for data - unclear if any data missing
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry found
Attention	Unclear risk	Unclear as methods unclear
Compliance	Low risk	Compliance good assessed by biomarkers (serum total cholesterol)
Other bias	High risk	Some concerns around fraud in the first authors later research on diet in cancer. No allegations found regarding his research in diabetes (but much information is in Dutch). Numbers of events are not clear by arm and assumed from adding across various publications.

IFOMS- Sirtori 1997 [75-77]

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)
PUFA Dose: (intended) increase ~2.0g/d EPA+DHA, **0.9%E n-3, 0.9%E PUFA**
Compliance: Pill counts and plasma and erythrocyte EPA and DHA

Duration of intervention: 6 months (followed by a 6 month open phase)

Outcomes Main study outcome: Lipids and glucose metabolism
Dropouts: 28 int., 39 control
Available outcomes: Mortality (nil), lipids, glucose, OGTT (area under curve), HbA1c, insulin
Response to contact: Yes

Notes Study funding: Consiglio delle Ricerche of Italy and by a grant-in-aid by Pharmacia and Upjohn, Milan, Italy

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	SAS system “randomized-block technique”
Allocation concealment (selection bias)	Unclear risk	Not detailed
Blinding of participants and personnel (performance bias)	Unclear risk	Not detailed
Blinding of outcome assessment (detection bias)	Unclear risk	Not detailed
Incomplete outcome data (attrition bias)	Low risk	Intention to treat analysis and seemingly balanced drop outs
Selective reporting (reporting bias)	Unclear risk	No registry or protocol identified
Attention	Unclear risk	Not detailed and blinding unclear
Compliance	Unclear risk	Overall compliance >90% (by pill count)
Other bias	Low risk	None noted

JELIS 2007 [78 79]

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 years
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.

Outcomes Main study outcome: major coronary events
Dropouts: 1766 int., 1582 control (but all had endpoint evaluation)
Available outcomes: Major coronary events: sudden cardiac death, fatal or non-fatal MI, unstable angina, angioplasty or CABG. Also all-cause mortality, stroke, peripheral artery disease, cancer, lipids, rise in blood sugar, fasting glucose, HbA1c.

Response to contact: No

Notes Study funding: Mochida Pharmaceutical Company

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Statistical Co-ordination centre: “permitted block randomisation with a block size of 4”
Allocation concealment (selection bias)	Low risk	Centralised. Statistical coordinating centre (see above).
Blinding of participants and personnel (performance bias)	High risk	Not blinded as there was no placebo, “Open label blinded end point”
Blinding of outcome assessment (detection bias)	Low risk	"Clinical endpoints ... reported by local physicians were checked by members of a regional organizing committee in a blinded fashion. Then an endpoints adjudication committee ... confirmed them once a year without knowledge of the treatment allocation".
Incomplete outcome data (attrition bias)	Low risk	Well documented, ITT analysis, drop out numbers low.
Selective reporting (reporting bias)	Unclear risk	NCT00231738 registered October 2005, recruitment Nov 1996 to Nov 1999, main results published 2007. Rationale & design paper published in 2003 (reported baseline characteristics, so before completed follow up, but after data collection began). All reported outcomes appear to have been published.
Attention	Low risk	Slight, as no placebo provided to control group, but only capsules to intervention group. Otherwise two groups appeared to be treated equally.
Compliance	Unclear risk	Monitored by local physicians and measuring plasma fatty acids concentrations. Study drug regimens,71% adhered EPA int., 73% adhered EPA control, 74% adhered statin.
Other bias	Low risk	None noted

Krebs 2006 [80]

Methods RCT, parallel, (n3 EPA+DHA vs n6 LA, both with weight loss programme), 6 months
Summary risk of bias: Moderate or high

Participants Overweight hyperinsulinaemic women
N: 39 int., 38 control. (analysed, int: 35 cont: 32)
Level of risk for CVD: Moderate
Male: 0% int., 0% control.
Mean age (SD): 44.7 (13.2) in both groups combined
Age range: 21-69 years
Smokers: 0 (smokers were excluded)
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 (capsules with n3 EPA+DHA or LA+oleic acid)
Comparison: n3 EPA+DHA vs n6 LA, both with weight loss programme
Intervention: Weight loss programme plus 5 capsules/d (including 1.3g EPA+ 2.9g DHA, EPAX, Pronova): EPA+DHA 4.2g/d
Control: Weight loss programme plus 5 capsules/d (including 2.8g LA + 1.4g oleic acid, Pronova): LA 2.8g/d
Compliance: Plasma and adipose fatty acids
Duration of intervention: 6 months

Outcomes Main study outcome: Cardiovascular risk factors
Dropouts: 4 int., 6 control
Available outcomes: Adiposity, insulin, glucose, HOMA, HbA1c, lipids, inflammatory markers (BP 6

months not used). All as geometric means. Change data for weight, fat mass, waist circumference, triglycerides, AUC insulin
Response to contact: No contact attempted

Notes 3 arm study, with the no weight-loss arm not discussed here
Study funding: Medical Research Council and SMILES

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned"
Allocation concealment (selection bias)	Unclear risk	"randomly assigned"
Blinding of participants and personnel (performance bias)	Unclear risk	"double blind"
Blinding of outcome assessment (detection bias)	Unclear risk	"double blind"
Incomplete outcome data (attrition bias)	High risk	>10% lost over 6 months
Selective reporting (reporting bias)	Unclear risk	No registry or protocol identified
Attention	Low risk	For the arms discussed here, schedules appeared comparable and only differed by capsule content
Compliance	Low risk	Significant increase in n-3 and DHA in adipose tissue of intervention group
Other bias	Low risk	None noted

Lalia 2015 [81]

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)
PUFA Dose: (intended) increase 3.9g/d EPA+DHA, **1.8%E n-3, 1.8%E PUFA**
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

Outcomes Main study outcome: hepatic and peripheral insulin sensitivity
Dropouts: 2 of 16 int., 4 of 15 control
Available outcomes: BMI, glucose, insulin, HOMA-IR (weight, lipids, CRP, IL-6 too different at baseline to use, leptin & adiponectin reported but not used)
Response to contact: No contact attempted

Notes Study funding: Clinical and translational science award, Strickland Career Development Award, Sancilio & Co supplied materials for the study, senior author was member of the Sancilio Scientific Advisory Board.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomly assigned individuals to groups based on a table prepared by a statistician"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Unclear risk	Reported as "double blind" but no further details of how this was attained or whether it was successful provided.
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	High risk	31 randomised, 25 completed so 20% dropout over 6 months. Further 4 participants missed out on several measures.
Selective reporting (reporting bias)	Low risk	All outcomes reported in trials register were reported in the paper or on the registry site. Study registered in Sept 2012, data collection began in Dec 2012.
Attention	Low risk	Appeared similar in both arms
Compliance	High risk	Difference in lipid composition between arms was not statistically significant
Other bias	Low risk	None noted

Martinez 2014 [82]

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) years: 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

Outcomes Main study outcome: serum fatty acids
Dropouts: 0 int., 0 control
Available outcomes: periodontal outcomes (probing depth, clinical attachment levels, visible plaque index, bleeding on probing), lipids, hsCRP, leucocytes, HbA1c, Insulin, glucose (all reported as medians, so not useable in meta-analyses).
Response to contact: No contact attempted

Notes Study funding: Not reported
Author contact: Not yet

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	"randomly assigned using a coin toss"
Allocation concealment (selection bias)	Unclear risk	No further detail
Blinding of participants and personnel (performance bias)	Unclear risk	Unclear how similar intervention and control were
Blinding of outcome assessment (detection bias)	Low risk	Probable as paper states "bottles were not decoded until all of the follow up evaluations and statistical analyses had been performed to ensure proper double-blind study protocol"
Incomplete outcome data (attrition bias)	Low risk	No participants were lost
Selective reporting (reporting bias)	Unclear risk	No protocol or trials register entry found
Attention	Low risk	Capsules provided monthly, discussion about intake weekly, dental follow up every 4 months
Compliance	Unclear risk	Only EPA but not DHA or DPA was significantly different at 12 months (due to small sample size?)
Other bias	Low risk	None noted

MENU - Rock 2016 [83 84]

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) years: 51 (NR) int., 50 (NR) control
Age range: 22-67 years 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

Outcomes
Main study outcome: body weight
Dropouts: 13 of 82 int., 12 of 81 control
Available outcomes: weight, waist circumference, HDL and LDL cholesterol, triglycerides, insulin, glucose, HOMA-IR, HOMA-beta, CRP and IL-6 (estradiol, SHBG, nutrient gene interactions, physical activity and heart rate also presented)
Response to contact: No

Notes
Study funding: National Cancer Inst and California Walnut Commission
Author contact: Not yet

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation stratified by age and insulin resistance
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	High risk	Open study, participants were advised on their diets extensively
Blinding of outcome assessment (detection bias)	Unclear risk	Blinding not mentioned, so unclear for their primary outcome, weight.
Incomplete outcome data (attrition bias)	Low risk	Paper states ITT analysis but 25 dropouts (15%) not included in 1 year data, but dropout reasons clear.
Selective reporting (reporting bias)	Low risk	Pre-registered, all mentioned outcomes reported at 12 months.
Attention	Low risk	Appear very equal.
Compliance	Low risk	Statistically significant difference between intervention and control arms for ALA in blood cell membranes at 12 months
Other bias	Low risk	None noted

Mita 2007 [85]

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

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

Outcomes Main study outcome: Progression of diabetic macroangiopathy measured by carotid intima-media thickness and brachial-ankle pulse wave velocity.
Dropouts: 10 int., 11 control
Available outcomes: BMI, lipids, BP, HbA1c, cancer diagnosis.
Response to contact: No contact attempted

Notes Blood pressure data not used as groups are different at baseline.
Study funding: Not stated

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients randomly divided into two groups matched for age an d gender
Allocation concealment (selection bias)	Unclear risk	No details

Blinding of participants and personnel (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	Low risk	Assessors of main study outcomes were blinded to the treatment
Incomplete outcome data (attrition bias)	Low risk	Drop out (26%) over 2 years. All dropouts explained, however, 5 were excluded for poor compliance but no clear predefined protocol for exclusion.
Selective reporting (reporting bias)	Unclear risk	No protocol
Attention	Low risk	All participants had the same contact
Compliance	Unclear risk	Compliance measured but no clear methods or reported results.
Other bias	Low risk	None noted

Moore 2006 [24]

Methods RCT, 5 arms in parallel, (high LCn3 & high ALA vs high LCn3 & n6 vs low LCn3 & high ALA vs low LCn3 & n6, also a control arm), 6 months
Summary risk of bias: moderate to high

Participants Overweight or obese adults
N: high LCn3 & high ALA 32 (analysed 29), high LCn3 & n6 32 (analysed 27), low LCn3 & high ALA 30 (analysed 22), low LCn3 & n6 29 (analysed 27)
Level of risk for CVD: moderate
Men: 33% overall
Mean age in years (SD): 50 (9) overall
Age range: not reported
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: food - oily or white fish plus fat spreads and cooking oils
Comparison: high LCn3 & high ALA vs high LCn3 & n6 vs low LCn3 & high ALA vs low LCn3 & n6, also a control arm
Intervention: study foods were collected from trial every 4 weeks
high LCn3 & high ALA: 2 portions oily fish/wk or 4.5g/wk LCn3, rapeseed oil for oils and fats
high LCn3 & n6: 2 portions oily fish/wk or 4.5g/wk LCn3, sunflower oil for oils and fats
low LCn3 & high ALA: 2 portions white fish/wk or 0.7g/wk LCn3, rapeseed oil for oils and fats
low LCn3 & n6: 2 portions white fish/wk or 0.7g/wk LCn3, sunflower oil for oils and fats
Control: no intervention
Compliance: assessed by food diary and by plasma fatty acids - suggesting good compliance
Length of intervention: 24 weeks

Outcomes Main study outcome: cardiovascular risk factors
Dropouts: 2, 5, 7, 3 dropped out
Available outcomes: adiposity (weight, waist, DXA%), lipids, BP, inflammatory markers (plasma cytokines, leptin, acute phase proteins, TNF alpha, ACT reported but not in enough detail to include in meta-analysis), insulin sensitivity (glucose and insulin, but only states "no significant group x time interactions").
Response to contact: not yet attempted

Notes Study funding: not stated but Matthew foods provided fat spreads

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	minimisation was used to assign participants and ensure groups were balanced

Allocation concealment (selection bias)	Unclear risk	unclear
Blinding of participants and personnel (performance bias)	High risk	Not blinded as foods were used
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear
Incomplete outcome data (attrition bias)	Low risk	Clearly described
Selective reporting (reporting bias)	Unclear risk	No trials registry or protocol found
Attention	Low risk	Food interventions so equivalent attention likely
Compliance	Low risk	Good changes in plasma fatty acids
Other bias	Low risk	None noted

MUFFIN Miller 2016 [18]

Methods RCT, prospective, open label, parallel group (n6 LA vs MUFA), 6 months
Summary risk of bias: Moderate or high

Participants Middle-aged men and women with metabolic syndrome
N: total randomised: 88 (analysed: int: 16; cont: 23)
Level of risk for CVD: Moderate
Male: 40% of all participants; NR by group.
Mean age (SD): 60.9 (8.5) for all participants; NR by group
Age range: 38-76 (all participants)
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: statins, ACE inhibitors
Medications taken by some, but less than 20% of the control group: NR
Location: USA
Ethnicity: 79% of total participants were African-American

Interventions Type: food supplement (PUFA enriched muffins with safflower oil or MUFA enriched with high oleic acid sunflower oil)
Comparison: PUFA vs MUFA
Intervention: 3x 3.5oz PUFA enriched muffins per day (including 27.6g/d PUFA; prepared in the metabolic kitchen of the USDA [Beltsville, MD]): PUFA 27.6g/d
Control: 3x 3.5oz MUFA enriched muffins per day (including 30.9g/d MUFA; prepared in the metabolic kitchen of the USDA [Beltsville, MD])
PUFA Dose: (intended) increase 27.6g/d LA, **12.4%E n-3, 12.4%E PUFA**
Compliance: 7-day food records at baseline and at end of 6m testing, including number of muffins consumed.
Duration of intervention: 6 months

Outcomes Main study outcome: Cardiometabolic benefit
Dropouts: 49 in total (n=88/110 randomised post AHA dietary baseline phase; n=39 completed 6-month dietary intervention)
Available outcomes: Adiposity, insulin, lipids, Inflammatory markers: hs-CRP, IL-8, TNFα (glucose and HOMA reported but not used due to baseline differences; BP 6 months, not used)
Response to contact: No contact attempted

Notes Supported by the Baltimore VA Geriatric Research Education and Clinical Center and Nutrition Obesity Research Center. No conflicts of interest declared

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation stated but no method
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel	Unclear risk	Taste blinded for participants but no information about

(performance bias)		personnel blinding
Blinding of outcome assessment (detection bias)	Unclear risk	No detail provided for relevant outcomes
Incomplete outcome data (attrition bias)	High risk	Primary outcomes reported only for participants who completed the trial (39/88)
Selective reporting (reporting bias)	Unclear risk	No study registration or protocol was found
Attention	Low risk	Follow up appeared identical
Compliance	Unclear risk	No data provided regarding muffin compliance over trial; FA status data provided for 34/88 participants only
Other bias	Low risk	None noted

Nigam 2014 [86]

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: Asian Indians

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)
Dietary counselling was given to all participants.
PUFA Dose: unclear
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

Outcomes Main study outcome: blood glucose control
Dropouts: 0 of 30 n6 int., 3 of 33 ALA int, 0 of 30 MUFA control
Available outcomes: glucose, insulin, HOMA, serum triglycerides, adiposity, (also disposition index, liver span, LFTs provided but not used)
Response to contact: No contact attempted

Notes Study funding: Dalmin Continental
Comparisons used: ALA vs MUFA for the effect n3, N6 vs MUFA for the effect of N6, ALA vs LA for n3 vs n6 comparison.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Paper states "randomly allocated by computer-generated number"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	High risk	Appears to be an open study without blinding

Blinding of outcome assessment (detection bias)	High risk	Open label, no further details
Incomplete outcome data (attrition bias)	Low risk	3 of 93 dropped out (3%), reasons given
Selective reporting (reporting bias)	Unclear risk	No protocol or trial register entry found
Attention	Low risk	The study only differed by the content of the oils, but the assessment schedule was not stated to differ between the two arms
Compliance	Unclear risk	Not reported
Other bias	Low risk	None noted

Niki 2016 [87]

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
PUFA Dose: (intended) increase 1.8g/d EPA, **0.8%E n-3, 0.8%E PUFA**
Compliance: NR
Duration of intervention: 6 months

Outcomes Main study outcome: inflammatory cytokines
Dropouts: 2 int., 1 control
Available outcomes: HDL and LDL cholesterol, glucose, HbA1c, hs-CRP, TNF alpha, IL-6 (no deaths, MI or revascularisation occurred in either arm, TG reported but too different at baseline, PTX3, MMP-3, MMP-9, MCP-1, BP, lumen, plaque & lipid volume reported but not used)
Response to contact: No contact attempted

Notes Study funding: NR, senior author received lecture fees from 3 pharmaceutical companies

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"allocated to 2 groups using computer assisted permuted-block randomization with random block size of 4–6"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	High risk	Open label (no placebo)
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear, assessors blinded to clinical characteristics, but unclear if blinded to to allocation
Incomplete outcome data (attrition bias)	High risk	While 95 were allocated only 62 were treated (unclear what this means in terms of control group who received no placebo)

Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry located
Attention	Low risk	There appear to have been similar numbers and duration of appointments
Compliance	Unclear risk	Not reported
Other bias	Low risk	None noted

Nodari 2011 HF [88]

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 (gelatin 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

Outcomes Main study outcome: Left ventricular function and functional capacity
Dropouts: 0 int., 0 control
Available outcomes: hospitalisation for cardiovascular reasons, hospitalisation for worsening heart failure, lipids, blood glucose, serum cytokine (No deaths)
Response to contact: No

Notes Study funding: Centro per lo Studio ed il Trattamento dello Scompenso Cardiaco, one author was a consultant for 8 pharmaceutical companies

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised"
Allocation concealment (selection bias)	Unclear risk	not described
Blinding of participants and personnel (performance bias)	High risk	Paper states that placebo and verum were identical and that the study was double blind, but blinding of participants not checked. Author confirmed investigators not blinded.
Blinding of outcome assessment (detection bias)	High risk	Author confirmed assessors not blinded.
Incomplete outcome data (attrition bias)	Unclear risk	Unclear whether all participants were assessed for all outcomes (eg hospitalisation), but some outcomes report no attrition.
Selective reporting (reporting bias)	Unclear risk	NCT01223703 - study registration Oct 2010, recruitment Nov 2007 to June 2009. Retrospective. All outcomes reported.
Attention	Low risk	No suggestion of this, and investigators appeared blinded (so could not differ in attention provided by

		allocation)
Compliance	Low risk	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.
Other bias	Low risk	None noted

Nogueira 2016 [89 90]

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
PUFA Dose: (intended) increase 1.0g/d EPA+DHA+ALA, **0.5%E n-3, 0.5%E PUFA**
Compliance: Plasma fatty acid changes
Duration of intervention: 6 months

Outcomes Main study outcome: NAS activity
Dropouts: 5 int., 5 control
All Outcomes collected but unusable due to unclear interpretation about % improvement: Lipids, anthropometrics, glucose, insulin, HbA1c, inflammatory markers
Response to contact: No, author contacted (July 2017) but no reply.

Notes Study funding: University of Sao Paulo.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated sequence
Allocation concealment (selection bias)	Unclear risk	"Included patients were enrolled in the study by two trained investigators following this randomization sequence"
Blinding of participants and personnel (performance bias)	Unclear risk	Double-blind and "identical" capsules. However no information provided as to their smell and taste.
Blinding of outcome assessment (detection bias)	Unclear risk	With the exception of an independent dietician, staff remained blinded until the end of the statistical analysis of the trial
Incomplete outcome data (attrition bias)	Low risk	8% Drop outs balanced by group, with reasons given
Selective reporting (reporting bias)	Unclear risk	Not all outcomes clearly reported
Attention	Low risk	No suggestion of this
Compliance	Low risk	Significant change in plasma fatty acids
Other bias	Low risk	None noted

Nomura 2009 [91]

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

Outcomes Main study outcome: Platelet-derived microparticles and adiponectin
Dropouts: NR
Available outcomes: Lipids and HbA1c (HbA1c not in useable format- baseline differences)
Response to contact: No contact attempted

Notes A third arm (EPA only) was also included (n=55)
Study funding: Grant from the Japan Foundation of Neuropsychiatry and Hematology Research, grant for Advanced Medical Care from the Ministry of Health and Welfare of Japan, and a grant from the Ministry of Education, Science and Culture of Japan

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly selected"
Allocation concealment (selection bias)	Unclear risk	As above
Blinding of participants and personnel (performance bias)	Unclear risk	Not reported
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Unclear risk	Not reported and blinding not clear
Selective reporting (reporting bias)	Unclear risk	No registry or protocol identified
Attention	Unclear risk	Not reported
Compliance	Unclear risk	Not reported
Other bias	Low risk	None noted

Norwegian - Natvig 1968 [92 93]

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 year, 72% were still taking their sunflower oil at 1 year (unclear how this was ascertained).
Duration of intervention: 12 months

Outcomes Main study outcome: morbidity and mortality
Dropouts: survival status was traced for all but 4 included men, health status was missing for about 80 men in total or 0.6%.
Available outcomes: total and CV deaths, MI, angina, stroke, peripheral vascular disease, combined CV events, diagnosis type 2 diabetes, total cholesterol (subgroup)
Response to contact: Not attempted as study published in the 1960s

Notes Study funding: Not stated

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Paper states "simple randomisation" without clarification
Allocation concealment (selection bias)	Unclear risk	Few details provided
Blinding of participants and personnel (performance bias)	Low risk	Paper states that the workplace doctors who administered the trial locally were sent bottles for each participant marked only with their trial number, and that "appearance and taste of the products were so similar that most participants were unable to identify the type"
Blinding of outcome assessment (detection bias)	Low risk	Company physicians recorded health status, and were also blinded to intervention (as above)
Incomplete outcome data (attrition bias)	Low risk	Detailed description, and those who left employment during the study were followed up for survival and morbidity via the main health system
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registration found
Attention	Low risk	As company physicians administered oils and assessed outcomes but were blind to treatment arm there could not be attention bias
Compliance	Unclear risk	73% were still taking the linseed oil at 1 year, 72% were still taking their sunflower oil at 1 year (unclear how this was ascertained)
Other bias	Low risk	None noted

OFAMI - Nilsen 2001 [94]

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 months

Outcomes Main study outcome: CV events
Dropouts: unclear
Available outcomes: total and CV deaths, MI, unstable angina, interventions, combined CV events, BMI, lipids, BP (authors provided additional data on glucose, AF, stroke)
Response to contact: Yes

Notes Study funding: Pharmacia-Upjohn and Pronova

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned" - Pharmacia was responsible for randomisation
Allocation concealment (selection bias)	Low risk	Author confirmed allocation was concealed
Blinding of participants and personnel (performance bias)	Low risk	Identical capsules containing either Omacor or corn oil were supplied by Pharmacia in collaboration with Pronova. Double blinding stated, but taste not reported as masked and blinding of participants not checked
Blinding of outcome assessment (detection bias)	Low risk	Author stated: all analyses was performed without the knowledge of outcome.
Incomplete outcome data (attrition bias)	Unclear risk	Number of drop outs was unclear
Selective reporting (reporting bias)	Unclear risk	Trials registry NCT01422317. Outcomes reported in trials registry appear to have been published, but registration was retrospective.
Attention	Low risk	All participants appear to have been reviewed at the same intervals
Compliance	Unclear risk	Assessed by questionnaire and capsule count, 82% int group had complete compliance after 6 weeks, 86% of controls
Other bias	Low risk	None noted

OPAL - Dangour 2010 [7 95-97]

Methods Older People And n- 3 Long-chain polyunsaturated fatty acid (OPAL)
2 arm, parallel, RCT, 24mo (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 gelatin 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. α-linoleic: int., 21.5, 0.8; control, 22.0, 0.9.
Length of intervention: 24 months

Outcomes Main study outcome: Delayed onset of cognitive decline
Dropouts: Control: 78(8-died, 53-withdrew, 17-discontinued intervention but provided data) Int: 67(9-died, 49-withdrew, 9-discontinued intervention but provided data)
Available outcomes: deaths, MI, arrhythmias, stroke, diabetes, lipids
Response to contact: Yes

Notes Study funding: UK Food Standards Agency, NHS R&D provided support costs.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were "selected in random blocks". "Research nurses telephoned a central computerized randomization service to obtain treatment allocation codes".
Allocation concealment (selection bias)	Low risk	Central allocation via telephone
Blinding of participants and personnel (performance bias)	Low risk	Identical capsules (vanilla-flavoured, dark-brown coloured). Supplements packaged into identical pots, each containing 180 capsules, labelled by staff not involved in the study. All project staff were unaware of group assignments until after data analysis.
Blinding of outcome assessment (detection bias)	Low risk	All project staff were unaware of group assignments until after data analysis.
Incomplete outcome data (attrition bias)	Low risk	Participants who discontinued the supplements invited to an interview at 24 months. Dropouts explained and similar in both arms (int 49 withdrew, control 53 withdrew, 12%).
Selective reporting (reporting bias)	High risk	ISRCTN72331636. Trial registered 2004, before study began. Protocol published 2006. Publication of first results 2010. Many outcomes, such as depression and BP were stated in trials registry entry but not reported.
Attention	Low risk	All participants had the same review schedule, and staff were unaware of assignments
Compliance	Low risk	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. α-linoleic: int., 21.5, 0.8; control, 22.0, 0.9
Other bias	Low risk	None noted

OPTILIP 2006 [98 99]

Methods Quantification of the Optimal n6/n3 ratio in the UK Diet (OPTILIP)
RCT, parallel, 5 arms (n3 EPA+DHA vs n3 ALA vs n6 LA), 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

Outcomes Main study outcome: Lipids, insulin sensitivity and clotting factors
Dropouts: 48 overall
Available outcomes: Insulin, glucose, HOMA, QUICKI, lipids (geometric means- triglycerides not used for ALA comparison and insulin not used for n-3 comparison due to baseline differences)
Response to contact: No

Notes 5 arms overall- the "moderate linolenate diet" and the "n-3 + linolenate diet" not discussed here
Study funding: Food Standards Agency (with supplemented foods supplied as detailed above)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned"
Allocation concealment (selection bias)	Unclear risk	As above
Blinding of participants and personnel (performance bias)	High risk	Fish increase requested for n-3 group so participants unblinded
Blinding of outcome assessment (detection bias)	Unclear risk	NR
Incomplete outcome data (attrition bias)	Unclear risk	Numbers randomised to each group and therefore drop outs by group unclear
Selective reporting (reporting bias)	Unclear risk	No registry or protocol identified
Attention	Unclear risk	NR
Compliance	Low risk	Significant increase in EPA/DHA content of erythrocytes in n-3 groups
Other bias	Low risk	None identified

ORIGIN 2012 [100-103]

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

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 gelatin capsule/d Omacor containing at least 900mg ethyl esters of n-3 fats (465mgEPA + 375mgDHA): EPA+DHA 0.84g/d
Control: 1x1g gelatin 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)

Outcomes Main study outcome: Composite of the First Occurrence of Cardiovascular (CV) Death, Nonfatal Myocardial Infarction (MI) or Nonfatal Stroke
Dropouts: 38 int., 37 control (some of the remainder did not have final outcome status, were lost or withdrew consent, but were included in analysis)
Available outcomes: mortality, CV mortality, fatal arrhythmia, MI, stroke, heart failure, angina, revascularization, breast cancer, cancer diagnoses and cancer deaths, BP, lipids (HbA1c given as medians only)
Response to contact: Yes

Notes The other 2x2 assignment was to insulin glargine versus standard care, and is not discussed here. Results are reported here for the trial duration and not the follow up post trial (The ORIGIN and Legacy Effects, ORIGINALE).
Study funding: From Sanofi Aventis, Omacor provided by Pronova Biocare

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomized by an automated telephone randomization system (using randomly varying block sizes)"
Allocation concealment (selection bias)	Low risk	as above
Blinding of participants and personnel (performance bias)	Low risk	Study described as "double blind" and placebo described as identical. Blinding of patients, investigators, local and central trials personnel described. However no information provided as to the capsule's smell and taste
Blinding of outcome assessment (detection bias)	Low risk	"all primary and secondary outcomes were adjudicated with the use of prespecified definitions by a committee whose members were unaware of study-group assignments"
Incomplete outcome data (attrition bias)	Low risk	Almost all participants were included in outcomes
Selective reporting (reporting bias)	Low risk	NCT00069784 - registered Oct 2003, study started Aug 2003, final data collection Dec 2011. Most outcomes appear to have been reported in various publications (cardiovascular events only reported by glargine randomisation).
Attention	Low risk	No suggestion of differences between groups
Compliance	Unclear risk	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".
Other bias	Low risk	None noted

ORL - Tatsuno 2013 [104]

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 months
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

Outcomes Main study outcome: Safety outcomes and adverse events
Dropouts: 8 G1, 14 G2, 21 G3
Available outcomes: TG, LDL, adverse events (including CVD events, cancers, diagnosis type 2 diabetes), CRP, waist circumference, weight, blood pressure (Nil death) (Total cholesterol and HDL reported as %change from baseline, but not used as baseline not reported).
Response to contact: No

Notes A third arm of EPA-E 1.8g supplementation is not used here. Outcome data used TAK-4 vs TAK-2
Study funding: Funded by Takeda Pharmaceutical Company

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was stratified according to statin use and performed by an independent registration centre
Allocation concealment (selection bias)	Low risk	Randomization was stratified according to statin use and performed by an independent registration centre
Blinding of participants and personnel (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	High risk	Open label
Incomplete outcome data (attrition bias)	Low risk	All participants were accounted for and analysed for main outcomes
Selective reporting (reporting bias)	Low risk	Trials registry entry May 2011, study start date Nov 2009, completion Nov 2011, so partially retrospective. However, entry appears to reflect reported outcomes.
Attention	Low risk	Capsules, follow up appeared identical
Compliance	Low risk	Monitored every 4 weeks, mean rate of compliance reported as >96% in each group
Other bias	Low risk	None noted

Patch 2005 [105 106]

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
PUFA Dose: (intended) increase 1.0g/d EPA+DHA, **0.5%E n-3, 0.5%E PUFA**
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

Outcomes Main study outcome: TG
Dropouts: 2 of 40 int., 8 of 45 control
Available outcomes: weight, TG, glucose, CRP, waist/hip ratio (insulin, total cholesterol, BMI too different at baseline to use, BP reported but only 6 months, urinary thromboxane, creatinine, number and function of leukocytes reported but not used)
Response to contact: No contact attempted

Notes Study funding: Linkage grant from Australian Research Council, Goodman Fielder Ltd (Sydney) provided financial support and product development expertise.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation to balance groups according to baseline TG and BMI
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Low risk	**"**Intervention foods (enriched with long-chain n-3 fatty acids) and equivalent control foods (not enriched) were supplied to all subjects in unmarked packages with one of two codes. The content of the study foods was blinded to subjects as well as researchers."
Blinding of outcome assessment (detection bias)	Low risk	As above
Incomplete outcome data (attrition bias)	Unclear risk	Numbers included differ by paper
Selective reporting (reporting bias)	Unclear risk	No protocol or trials register found
Attention	Low risk	Timing and attention appear to be similar by arm
Compliance	Unclear risk	Unclear whether erythrocyte fatty acids differed statistically significantly by arm
Other bias	Low risk	None noted

Pratt 2009 [107 108]

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

Outcomes Main study outcome: prevention of recurrent symptomatic AF
Dropouts: 39 of 332 discontinued int., 40 of 331 discontinued control
Collected outcomes: HbA1c increase, TG increase: but these not useable, only described qualitatively. Also major depression diagnosis, suicide (cancer diagnoses, atrial fibrillation and many related outcomes reported but only 6 months data, details adverse event data)
Response to contact: No contact attempted

Notes Study funding: GlaxoSmithKline

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Clinical research organisation generated the randomisation schedule
Allocation concealment (selection bias)	Low risk	"site personnel telephoned into an interactive voice response system to obtain a randomization number and were assigned blinded study medication bottles"
Blinding of participants and personnel (performance bias)	Unclear risk	"blinded medication bottles" suggests blinding but no mention of similarity or taste
Blinding of outcome assessment (detection bias)	Low risk	"biweekly transtelephonic monitoring was used to document asymptomatic recurrences of AF... investigators were blinded to the monitoring results"
Incomplete outcome data (attrition bias)	High risk	79 of 663 discontinued (12%), reasons provided, similar discontinuation in both arms
Selective reporting (reporting bias)	Low risk	Trials registry entry in Nov 2006, same month as first data collection. All outcomes in trials registry are reported in publication or on trials register.
Attention	Low risk	Both arms appear to have had similar schedule, duration and type of appointments
Compliance	Unclear risk	Almost no information
Other bias	Low risk	None noted

PREDIMED 2013 [25 109-121]

Methods PREvención con DIeta MEDiterránea (PREDIMED)
RCT, parallel, 3 arms (high PUFA vs low PUFA) 60 months
Summary risk of bias: Moderate to high

Participants Men aged 55 to 80 years and women aged 60 to 80 years, free of CVD but with diabetes or at least 3

CVD risk factors
N: Int (Med with nuts) 2454, Cont (Med with olive oil) 2543 - also low fat arm, not discussed here, 2450
Level of risk for CVD: Moderate
Male: Int 46%, Cont 41.3%
Mean age (SD): Int 67 (6), Cont 67 (6) years
Age range: 55-80 years
Smokers: Int 14.5%, Cont 13.9% (current smokers)
Hypertension: Int 82.4%, Cont 82.1%
Medications taken by at least 50% of those in the control group: nil
Medications taken by 20-49% of those in the control group: ACE inhibitors, diuretics, other antihypertensives, statins, oral hypoglycaemics, antiplatelet therapy
Medications taken by some, but less than 20% of the control group: insulin, non-statin lipid lowering, hormone replacement therapy
Location: Spain
Ethnicity: white from Europe 97%, Hispanic from Central or South America 1-2%, other 1.5%

Interventions Type: Dietary advice and food supplement
Comparison: PUFA vs MUFA
Intervention: Mediterranean dietary advice plus 30g/d mixed nuts (15g walnuts, 7.5g hazelnuts, 7.5g almonds, provided, rich in ALA and linoleic) - intensive education on diet with individual and up to 20 group sessions with dietitian.
Control: Mediterranean dietary advice plus 1 L/week extra-virgin olive oil (provided) - intensive education on diet with individual and up to 20 group sessions with dietitian.
Compliance: Scores on the 14-item Mediterranean-diet screener increased for the participants in both Mediterranean diet groups. Participants in the two Mediterranean-diet groups significantly increased weekly servings of fish (by 0.3 servings) and legumes (by 0.4 servings) compared with the low fat arm. Participants assigned to a Mediterranean diet with extra-virgin olive oil and those assigned to a Mediterranean diet with nuts significantly increased their consumption of extra virgin olive oil (to 50 and 32 g per day, respectively) and nuts (to 0.9 and 6 servings per week, respectively).
Duration of intervention: 56 months median.

Outcomes Main study outcome: Cardiovascular disease events.
Dropouts: Int 6.3% lost to follow up for ≥2 years, Cont 3.6% lost to follow up for ≥2 years.
Available outcomes: deaths, CV mortality, stroke, MI, cardiovascular events, diagnosis type 2 diabetes, glucose, insulin, HOMA, metabolic syndrome
Response to contact: No

Notes Study funding: Mainly governmental funding, but olive oil and nuts were provided by companies

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Tables of random allocation were centrally elaborated. However the main paper [114] was retracted and republished [25] following a statistical analysis suggesting that baseline variables did not appear consistent with randomisation [122]. The republication states that partners were included in the trial without randomisation (in the same arms as family members) and that some clinics allocated by clinic rather than applying the protocol specified individual randomisation. This puts allocation concealment of some participants at high risk.
Allocation concealment (selection bias)	High risk	Study nurses in charge of the random allocation were independent of the nursing staff, allocation was performed centrally. But see note above
Blinding of participants and personnel (performance bias)	High risk	Olive oil and nuts arms could not be blinded to participants
Blinding of outcome assessment (detection bias)	Low risk	"All medical records related to end points were examined by the end-point adjudication committee, whose members were unaware of the study-group assignments."
Incomplete outcome data (attrition bias)	Low risk	"We used four sources of information to identify end points: repeated contacts with participants, contacts with family physicians, a yearly review of medical records, and consultation of the National Death Index."

		Attrition was <10% per year, explained and balanced.
Selective reporting (reporting bias)	High risk	Many outcomes in the trials registry entry are not reported by allocated group for the full set of study participants (for example, cognition)
Attention	Low risk	Appears very similar between the two Mediterranean diet groups
Compliance	Unclear risk	Not reported
Other bias	High risk	Retraction and republication in 2018 due to randomisation problems not reported in the initial publication. However, new outcome data not provided.

Proudman 2015 [9 123 124]

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

Outcomes Main study outcome: Disease-modifying anti-rheumatic drugs (DMARD) failure and remission.
Dropouts: 11 int., 6 control
Available outcomes: Mortality (Nil death), adverse events including CVD, DAS score, diabetes.
Response to contact: Yes

Notes DAS scores are reported as median and IQR in Proudman 2012 abstract
Study funding: The study was supported by 'the National Health Medical Research Council of Australia and Royal Adelaide Hospital Research Committee. Melrose Health has provided support for ongoing studies.' The oil used in the study was made by the Royal Adelaide Hospital Pharmacy

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'The randomisation schedule was prepared using an online random number generator and involved randomly permuted blocks of size six.'
Allocation concealment (selection bias)	Low risk	'Randomisation was performed by the RAH pharmacy, which also prepared and provided the study oils in 500 mL identical dark brown bottles labelled with consecutive study numbers'
Blinding of participants and personnel (performance bias)	Low risk	'Both participants and investigators/assessors were blinded to the group allocation. Although the control oil was paler in colour than the fish oil, this was not

		evident in the brown bottles. The 'fishy' odour of each oil was similar.'
Blinding of outcome assessment (detection bias)	Low risk	Both participants and investigators/assessors were blinded to the group allocation' 'Investigators and subjects remained blinded for all withdrawals.'
Incomplete outcome data (attrition bias)	Low risk	The flow of all study participants shown in Figure 2, 12% drop out, similar rates between groups
Selective reporting (reporting bias)	Unclear risk	Outcomes reported in trial register matched with the outcomes reported in publications. However, the study was retrospectively registered - registered in 2013, recruitment began in 2001.
Attention	Low risk	No difference between groups
Compliance	High risk	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 (68%) and 3248 mL (89%), 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
Other bias	Low risk	None noted

REDUCE-IT 2018[125 126]

Methods	Reduction of Cardiovascular Events with EPA - Intervention Trial (REDUCE-IT) RCT, parallel, (LCn3 vs paraffin oil), median 4.9 years Summary risk of bias: moderate or high
Participants	Patients (45 years+) with hypertriglyceridaemia, and with cardiovascular disease or with DM and another risk factor, and on statin (58% had T2DM) N: intervention 4089 randomised, control 4090 randomised (analysed, intervention: 4083 control: 4077) Level of risk for CVD: moderate (w DM) and high (with CVD) Men: 71.6% intervention, 70.8% control Age median (IQ range) years: median 64 (57-69) intervention, 64 (57-69) control Age range: not reported, those with CVD included if at least 45 years, those with DM if at least 50 years old Smokers: not reported Hypertension: not reported Medications taken by at least 50% of those in the control group: 100% treated with statins to be randomised Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but less than 20% of the control group: ezetimbe Location: 11 countries including USA, Netherlands, Ukraine, Russia, South Africa, Poland, India, Romania, Australia, New Zealand Ethnicity: white 90.3% intervention, 90.2% control
Interventions	Type: supplement Comparison: EPA vs paraffin Intervention: EPA ethyl ester derived from fish oil (AMR101 4 g/d, Amarin), 3.99g/d EPA plus 8mg/d vitamin E (2 capsules twice a day) Control: 3.73g/d light liquid paraffin oil in 4 capsules (2 capsules twice a day) Compliance: serum EPA assessed, expressed as medians, ~26µg/ml at baseline, at 1 year rose to 144 in intervention group, 23.3 in control. Duration of intervention: median 4.9 years (max 6.2 years)
Outcomes	Main study outcome: composite of cardiovascular death, MI, stroke, coronary revascularisation and hospitalisation for unstable angina Dropouts: 6 intervention, 13 control Available outcomes: deaths, CVD deaths, CVD events, MACCEs, stroke, MI, sudden cardiac death, new angina, heart failure, amputations due to PVD, atrial fibrillation, revascularisation, DM, TIA, HT, (lipid levels and CRP provided as medians) Response to contact: not yet attempted

Notes NCT01492361
Study funding: study designed, run and funded by Amarin (who produce the intervention capsules)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	stratified randomisation
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel stated to be blinded, not clearly stated that containers were identical but capsular content was identical
Blinding of outcome assessment (detection bias)	Low risk	Adjudication was by independent clinical endpoint committee unaware of assignment
Incomplete outcome data (attrition bias)	Low risk	Low levels of participant loss
Selective reporting (reporting bias)	Low risk	Only 2 outcomes mentioned in trials register, both reported plus many more. Registered Nov 2011, recruitment Nov 2011 to Aug 2016.
Attention	Low risk	Appeared similar
Compliance	Low risk	Median serum EPA rose in intervention but not in control
Other bias	Unclear risk	Some changes in inclusion criteria (levels of TG included) during trial

Risk & Prevention 2013 [127 128]

Methods Evaluation of the Efficacy of n-3 PUFA in Subjects at High Cardiovascular Risk (Risk and Prevention)
RCT, parallel, (n3 EPA+DHA vs MUFA), 60 months?
Summary risk of bias: Moderate or high

Participants Patients with multiple cardiovascular risk factors
N: 6244 int., 6269 control. (analysed, int: 6239 cont: 6266)
Level of risk for CVD: high
Male: 62.3% int., 60.6% control.
Mean age (SD): 63.9 (9.3) int., 64.0 (9.6) control
Age range: NR
Smokers: 22.1% int., 21.4% control.
Hypertension: 84.6% int., 84.5% control.
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: ACE inhibitor; ARB; Diuretic agent; Calcium-channel blocker; Beta-blocker; Oral hypoglycaemic drug; Statin; Antiplatelet agent.
Medications taken by some, but less than 20% of the control group: Insulin
Location: Italy
Ethnicity: NR

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

Outcomes Main study outcome: composite of time to death from cardiovascular causes or hospital admission for cardiovascular causes
Dropouts: Int., 5 (withdrew consent before baseline), 43 lost to follow-up, 1115 stopped treatment. 6239 analysed.
Control: 3 (withdrew consent before baseline), 39 lost to follow-up, 1218 stopped treatment. 6266 analysed
Available outcomes: mortality, CV mortality, CV events, coronary related events and mortality, MI, AF, heart failure, side effects, stroke, cancer diagnosis, cancer death. Authors provided data on which participants developed diabetes, glucose and HbA1c.

Response to author contact: yes

Notes All continuous outcomes change data are reported as LSM hence not used.
Study funding: "The steering committee had the full and sole responsibility for planning and coordinating the study, analyzing and interpreting the data, and preparing the manuscript and submitting it for publication. Società Prodotti Antibiotici, Pfizer, and Sigma Tau funded the trial but had no role in the study design, planning, conduct, or analysis or in the interpretation or reporting of the results"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Treatment was centrally assigned by means of telephone on the basis of a concealed, computer-generated randomization list, stratified according to general practitioner."
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias)	Unclear risk	"Patients, general practitioners, coordination and statistical staff, and outcome assessors were unaware of the study assignments until the final analyses were completed." However, there was no mention of placebo appearance or other methods of blinding, so unclear.
Blinding of outcome assessment (detection bias)	Low risk	"Patients, general practitioners, coordination and statistical staff, and outcome assessors were unaware of the study assignments until the final analyses were completed." "All events included in the primary efficacy end point were documented with the use of a narrative summary and supporting documentation and were adjudicated on the basis of prespecified criteria by an ad hoc committee consisting of a cardiologist, an internist, and a neurologist who were unaware of the study assignments"
Incomplete outcome data (attrition bias)	Low risk	"Analyses were performed in the intention-to-treat population, except for a prespecified per protocol analysis of the primary end point in patients with no major protocol violations who did not permanently stop treatment." Figures differ in Visentin 2008: (*p. i73) "*At the end of March 2006, 12 521 patients have been Randomized"; ... "After 1-year of follow-up, 2.5% of the patients withdrawn from the trial and 5% of the patients discontinued treatment. The reasons for drug discontinuation were 1.7% for side effects (mainly gastrointestinal) and 3.3% others (clinical or patient's refusal)…After 1-year of follow-up, 1.0% had CV death and 3.4% hospitalization for CV events (primary end point)"
Selective reporting (reporting bias)	High risk	Primary endpoint was amended part way through study. Differences in groupings of cardiovascular events in tables 2; S4 and S5. For hospital admissions notes each patient could have more than one cardiovascular cause
Attention	Unclear risk	Does not state attention differs or is the same between groups- regularly see GP for follow-up
Compliance	Unclear risk	No results
Other bias	Low risk	None noted

Rose 1965 [23]

Methods RCT, 2 arm parallel (n-6 LA vs MUFA), 24 months
Summary risk of bias: Moderate to high

Participants Patients with Ischaemic Heart Disease (IHD)
CVD risk: high
N: 28 int., 26 control (analysed 15 int., 12 control)
% male: NR
Mean age: 52.6 int., 55 control (no SDs)
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: Dietary advice+ test oil provided
Comparison: n-6 vs MUFA
Intervention: 80 g/day corn oil to be taken in three equal doses at meal-times plus patients were instructed to avoid fried foods, fatty meat, sausages, pastry, ice-cream, cheese, cakes, milk, eggs, butter were restricted. Corn oil supplement of
Control: 80g/day olive oil plus patients were instructed to avoid fried foods, fatty meat, sausages, pastry, ice-cream, cheese, cakes, milk, eggs, butter were restricted: assuming 80% LA in corn oil, 64g/d LA
Compliance: measured based on the number of oil cans and patients' own statement. Mean intake was 64 g/day int., 58g/day control. However, this mean is only for people still in the trial.
Duration of intervention: 2 years

Outcomes Main study outcome: Occurrence of infraction
Dropouts: 6 int., 11 control?, details provided in table but unclear how many dropped out.
Available outcomes: major CVD events, MI (fatal & non-fatal), sudden death, diagnosis type 2 diabetes, serum cholesterol.
Response to contact: Not attempted as trial conducted in the 1960s

Notes Study funding: No details
The study had a third control arm (no intervention) which has not been used here.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	When a new patient was accepted for the trial a sealed envelope was opened containing the allocation instructions. In the case of patients allocated to an oil group the instructions referred only to a code number.
Allocation concealment (selection bias)	Unclear risk	As above, opacity of envelope unclear
Blinding of participants and personnel (performance bias)	Low risk	The physicians in charge knew which patients were receiving oil, but they did not know until the end of the trial the kind of oil that they were receiving.
Blinding of outcome assessment (detection bias)	Low risk	The electrocardiograms were assessed without the knowledge of the patients treatment group
Incomplete outcome data (attrition bias)	Low risk	52% int., and 57% control remained in the trial after 24 months. However, the list of reasons and complications is provided.
Selective reporting (reporting bias)	Unclear risk	No trial registry record or protocol found
Attention	Low risk	Both groups were given oil, and appear to have the same level of attention
Compliance	High risk	Compliance poor; assessed by biomarkers
Other bias	Low risk	None noted

Rossing 1996 [129 130]

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

Outcomes Main study outcome: diabetic nephropathy
Dropouts: 1 int., 3 control (though 3 further intervention participants are not included in all data)
Available outcomes: breast cancer, total & LDL cholesterol, systolic BP (TGs reported as medians so not used, albuminurea, fractional albumin clearance, trascapillary escape rate of albumin, prothrombin fragment reported as geometric means or medians, HbA1c, HDL and BP too different at baseline to include, GFR not relevant)
Response to contact: No

Notes Study funding: supported by The Danish Heart Association. Eskisol Fish oil and placebo oil emulsions were provided by Pharma-Vinci A/S, Frederiksvaerk, Denmark.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomized using concealed randomization to receive either fish oil or olive oil in blocks of 4 according to their glomerular filtration rate."
Allocation concealment (selection bias)	Unclear risk	No further details
Blinding of participants and personnel (performance bias)	Low risk	"Active and placebo (olive oil) were given as emulsions with orange flavour. At the end patients were allowed to guess about treatment and ~50% were right"
Blinding of outcome assessment (detection bias)	Unclear risk	No details.
Incomplete outcome data (attrition bias)	Low risk	Drop outs similar between groups although relatively high for small sample size. 3 drop-outs from fish oil and 1 from control due to side effects. Intention to treat analysis appears to have been given for albuminuria only.
Selective reporting (reporting bias)	Unclear risk	No trials registry entry or protocol found
Attention	Low risk	Time and attention appear to be the same. All patients were given dietary advice.
Compliance	Low risk	Reports significantly higher omega 3 levels in platelets at 12 months for the intervention group.
Other bias	Low risk	None noted

Sandhu 2016 [131 132]

Methods RCT, parallel 5 arms (only G1&4 are reported here), (n-3 EPA + DHA 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 int., 53 control. (analysed, int: 49 cont: 47)
Level of risk for CVD: low
Male: 0% int., 0% control.
Mean age (SD): 56.56 (6.9) int., 57.11 (5.9) 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: 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
Control: No treatment
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

Outcomes Main study outcome: change in breast density.
Dropouts: 5 int., 6 control
Available outcomes: Cardiovascular events, breast cancer, lipids, dietary intake, plasma FAs, adverse events (including one incidence of hyperglycaemia)
Response to contact: Yes

Notes The study had five arms: group 1, no treatment, control; group 2, raloxifene 60 mg orally daily; group 3, raloxifene 30 mg orally daily; group 4, Lovaza 4 g orally daily; and group 5, Lovaza 4g per day plus raloxifene 30mg orally daily. Data here is presented for groups 1 and 4.
Study funding: The authors thank GlaxoSmith Kline and Eli Lilly for their generous supply of Lovaza and raloxifene, respectively. This work has been funded by Susan G. Komen for the Cure, KG081632 (A. Manni) and pilot funds from the Penn State Hershey Cancer Institute (K. El-Bayoumy) (Sandhu 2016 Pg 281, Col 2)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sandhu 2016 pg 276: 'each study participant was randomly assigned with equal probability to one of the following five groups. A block randomization scheme was used to ensure balance treatment allocation during the course of enrolment.'
Allocation concealment (selection bias)	Unclear risk	No description of concealment of allocation
Blinding of participants and personnel (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	High risk	Open label
Incomplete outcome data (attrition bias)	Low risk	<20% lost over 2 years, detailed reasons provided, no suggestion these are unbalanced.
Selective reporting (reporting bias)	High risk	Biomarkers of oxidative stress (Urinary 8-(isoprostane) F-2α and 8OHdG, Lymphocyte 8-OHdG, DNA etheno adducts), Urinary 2-OHE1, 4-OHE1, and 16α-OHE1, Serum level of C-reactive protein and IL-6, Serum level of IGF-I and IGFBP-3, complete blood count mentioned in trial registry but not reported in Sandhu 2016. (More outcomes reported than in registry – diet, physical activity levels, adverse events). NCT00723398 First received: July 24, 2008, study start date March 2009.
Attention	Low risk	Participants assessed at baseline, 1-year and 2-year follow-up

Compliance	Unclear risk	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%).
Other bias	Low risk	None noted

Sasaki 2012 [133]

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
PUFA Dose: (intended) increase 1.8g/d EPA+DHA, **0.8%E n-3, 0.8%E PUFA**
Compliance: NR
Duration of intervention: 6 months

Outcomes Main study outcome: Endothelial outcome
Dropouts: 0 int., 1 control?
Available outcomes: BMI, glucose, HbA1c, lipids (LDL used)
Response to contact: No contact attempted

Notes Data for triglycerides and HDL cholesterol not used due to baseline differences
Study funding: Self-funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned"
Allocation concealment (selection bias)	Unclear risk	As above
Blinding of participants and personnel (performance bias)	Unclear risk	Not reported
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	Low drop out with reason provided
Selective reporting (reporting bias)	High risk	Appears secondary outcomes not reported and retrospectively registered
Attention	Unclear risk	Not reported and blinding unclear
Compliance	Unclear risk	Not reported
Other bias	Low risk	None noted

Sawada 2016 [134]

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; no anti-diabetics were 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: Japan
Ethnicity: NR

Interventions Type: supplement (EPA capsules or nil)
Comparison: EPA vs nil
Intervention: 2x capsules/d (including 1.8g/d EPA, EPADEL, Mochida Pharmaceutical Co Ltd): EPA 1.8g/d
Control: "no EPA"
PUFA Dose: (intended) increase 1.8g/d EPA, **0.8%E n-3, 0.8%E PUFA**
Compliance: NR
Duration of intervention: 6 months

Outcomes Main study outcome: Hyperglycaemia, hyperlipemia and endothelial dysfunction
Dropouts: 5 int., 6 control
Available outcomes: Type 2 diabetes and impaired glucose tolerance, glucose, HbA1c, HOMA, CRP, lipids, weight, BMI, (HOMA medians only, FPG not used due to baseline differences, BP 6 months not used)
Response to contact: No contact attempted

Notes Study funding: No grant support for the present study but all authors declare that they have no competing interests

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed by means of random, permuted blocks of four in sealed envelopes
Allocation concealment (selection bias)	High risk	This study was open-label, single-blinded
Blinding of participants and personnel (performance bias)	High risk	Patients knew whether they were intervention or control and no placebo capsule mentioned for the control group
Blinding of outcome assessment (detection bias)	Unclear risk	NR
Incomplete outcome data (attrition bias)	Low risk	Drop outs balanced and less than 10% over 6 months
Selective reporting (reporting bias)	Low risk	Registry outcomes reported
Attention	Low risk	All patients saw a dietitian and treatment only differs by capsule
Compliance	Low risk	EPA/AA ratio significantly increased in intervention group at 6 months
Other bias	Low risk	None noted

Schirmer 2007 [135]

Methods RCT, 2 arm, parallel (n6 GLA vs MUFA), 1 year
Summary risk of bias: Moderate to high

Participants Formerly obese adults with a recent minimum weight loss of 12 kg, a current BMI of < 34, otherwise health.
CVD risk: low

N: 23 int., 22 control (analysed only completers 13 int., 17 control)
% male: 8% int., 6% control.
Mean age: 44.2 (10.1) int., 52.6 (8.1) control
Age range: NR
Smokers: NR
Hypertension: 0%
Medications taken by at least 50% of those in the control group: Anorexigenic agent
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 (capsule)
Comparison: n-6 (GLA) vs MUFA
Intervention: 5g/day of 500mg borage oil capsules providing 0.89g/d GLA.
Control: 5g/day of identical 500mg olive oil capsules.
Subjects in both groups were required to take a balanced multivitamin-mineral supplement daily, which included 80 mg of d-alpha-tocopherol.
Compliance: participants maintained daily intake records and measurement of adipose GLA.
Duration of intervention: 1 years (results reported only for participants completing a minimum of 5o weeks)

Outcomes Main study outcome: measures of adiposity
Dropouts: unclear, only one withdrew after randomisation but trial was terminated and only reported on 30/45 completers
Available outcomes: weight, fat weight. (Fasting blood glucose & blood pressure measured but not reported)
Response to contact: No

Notes Study funding: Supported in part by a gift from Shaklee Technica

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Low risk	**"**Both oil supplements were administered in a double-blind protocol as identical 500 mg capsules".
Blinding of outcome assessment (detection bias)	Low risk	"The initial study was terminated, and all remaining subjects were assessed over a 6-wk period. Unblinding revealed"…"the monitoring of their weights (simple ANOVA of group means while investigators and subjects remained unaware of treatment)"
Incomplete outcome data (attrition bias)	High risk	"At the termination of the randomized placebo-controlled trial, 45 subjects remained in the study" Mentions one dropped out between randomisation & treatment commencement but no details/explanation of remaining drop outs/ non completers
Selective reporting (reporting bias)	Unclear risk	No protocol or trial register entry
Attention	Low risk	Appears to be similar, both groups took capsules
Compliance	Low risk	Adipose GLA was significantly higher in intervention group compared to control (P < 0.0001)
Other bias	Low risk	None noted

Shimizu 1995 [136]

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

Participants Non-insulin dependent diabetic patients
N: 29 int., 16 control. (analysed, NR)
Level of risk for CVD: Moderate

Male: 34.5% int., 75% control
Mean age (SD): 66.3 (13.5) int., 58.6 (7.2) control
Age range: NR
Smokers: NR
Hypertension: 37.9% int., 43.8% control
Medications taken by at least 50% of those in the control group: Sulfonylurea
Medications taken by 20-49% of those in the control group: Insulin, antihypertensives
Medications taken by some, but less than 20% of the control group: NR
Location: Japan
Ethnicity: NR

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

Outcomes Main study outcome: Albuminuria
Dropouts: Unclear
Available outcomes: deaths (nil), CV events (nil), side effects (nil overall), BP, lipids, glucose, HbA1c (treated as not useable due to baseline differences)
Response to contact: Yes

Notes Data for lipids, glucose, HbA1c not used due to baseline differences, dropouts unclear
Study funding: NR

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Each doctor picked up an envelope which contained a treatment group allocation
Allocation concealment (selection bias)	High risk	Author response: Recruiters were aware of treatment allocation
Blinding of participants and personnel (performance bias)	High risk	Author response: recipients and providers aware of treatment
Blinding of outcome assessment (detection bias)	Unclear risk	No details
Incomplete outcome data (attrition bias)	Unclear risk	NR
Selective reporting (reporting bias)	Unclear risk	No registry or protocol identified
Attention	Unclear risk	NR and no blinding
Compliance	Unclear risk	NR
Other bias	Low risk	None noted

SHOT - Eritsland 1996 [137-146]

Methods SHunt Occlusion Trial (SHOT)
RCT, parallel (n3 EPA+DHA vs nil), 4 arms, 1 year
Summary risk of bias: Moderate 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 months) and fell in the control group (170 to 169 mg/L at 9 months)
Length of intervention: 12 months

Outcomes Main study outcome: CABG graft patency
Dropouts: 15 int., 14 control
Available outcomes: deaths, CV deaths, MI, stroke, repeat CABG, combined CV events, lipids, glucose, side effects (insulin data provided, but too different at baseline to use)
Response to contact: Yes

Notes The study had 4 arms; aspirin, warfarin, fish oil+ aspirin & warfarin+ fish oil. The first 2 groups are combined as the control and the last two combined as intervention.
Dietary assessment suggested total diet plus supplement intakes as follows: 2.7 g/d EPA + DHA at baseline, 5.5 g/d at 9 months int., 2.5g/d at baseline, 2.2g/d at 9 mo control group
Study funding: Funded in part by Pronova and Nycomed Pharma

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers were provided in consecutively sealed envelopes generated centrally
Allocation concealment (selection bias)	Unclear risk	As above but envelopes not reported as opaque.
Blinding of participants and personnel (performance bias)	High risk	Open trial, no blinding apart from outcome assessors so participants and study personnel were aware of assignments. However, author suggested in personal communication that participants were not aware of their assignments.
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors (radiologists) reported as blinded
Incomplete outcome data (attrition bias)	Low risk	Reasons for attrition and exclusions stated, numbers clear, dropouts <20% per year.
Selective reporting (reporting bias)	Unclear risk	No study protocol or trials register entry was found
Attention	Low risk	Appeared equivalent between arms
Compliance	Low risk	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)
Other bias	Low risk	No further bias noted

SMART Tapsell 2013 [147-149]

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

Outcomes Main study outcome: total % body fat
Dropouts: Fish + Supplement int. 20, Fish int 18, control 24.
Available outcomes: weight, BMI, lipids, BP, fasting glucose, % body fat (leptin, TG, fasting insulin not used as only medians provided with IQ range)
Response to contact: Yes

Notes To assess effects of omega 3 fats the best comparison in this study is Fish + S vs Fish, so numerical data reflect this comparison. Study funding: Australian National Health and Medical Research Council, fish and olive oil capsules were provided free by Blackmores Australia

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**"**A researcher independent of the subject interface undertook the randomisation of participants into diet groups (stratified by sex and block randomised...)"
Allocation concealment (selection bias)	Low risk	**"**Randomisation was performed centrally, off-site and and the holder of the allocation schedule provided the codes to a single researcher who was independent to the subject interface. The placebo and active ingredient capsules were coded off-site. The codes were kept from the researchers collecting dietary data and delivering treatment. Allocation concealment was maintained as the persons responsible for screening eligible participants for inclusion in the trial was unaware to which supplement group the subject would be allocated. Different dietitians collected the dietary data and provided dietary advice"
Blinding of participants and personnel (performance bias)	High risk	As above, but impossible to blind participants to the fish advice
Blinding of outcome assessment (detection bias)	Unclear risk	As above
Incomplete outcome data (attrition bias)	Low risk	Very high levels of attrition, though intention to treat analyses carried out.
Selective reporting (reporting bias)	High risk	We were unable to find data on 24 hour energy expenditure, oxidation or heart rate which were stated as primary and secondary outcomes in the trials registry. ACTRN12608000425392 Trial registered 26/08/2008. Participants recruited between 8/07/2008-26/02/2009.
Attention	Unclear risk	While dietary education was for 1 hour then six further half hour follow ups plus written materials and monthly newsletters plus dietary interviews it is not clear whether this was in all arms or only some of them.
Compliance	High risk	"Of the 12 month completers, 57% were judged to be compliant, 39% (n = 7) for the control group who reported <180 g fish/week, 48% (n = 12) for the Fish group who reported ≥180 g fish/week, and 85% (n = 17) for the Fish + S group who reported ≥180 g fish/week or ≥90% supplements". However, erythrocyte (EPA+DHA)/total fatty acids x 100 was significantly different for the fish oil supplemented

		group compared to the two others - but it was only measured in around half of the participants as the others dropped out, so presumably were non-compliant.
Other bias	Low risk	None noted.

Smith 2015 [150]

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) years: 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

Outcomes Main study outcome: Muscle mass and function
Dropouts: 11 of 40 int., 5 of 20 control
Available outcomes: weight, body fat, intermuscular fat content, TG, HDL & LDL cholesterol, fasting glucose (glucose 2 hours post GTT, LFTs, BP not used)
Response to contact: No contact attempted

Notes Study funding: NIH, Clinical Translational Science Award, study drugs were a gift from GlaxoSmithKline

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned" - no further details
Allocation concealment (selection bias)	Unclear risk	As above
Blinding of participants and personnel (performance bias)	Unclear risk	Stated "double blind" and that capsules appeared identical. However no information provided as to their smell and taste.
Blinding of outcome assessment (detection bias)	Unclear risk	Stated "double blind" but no details as to method
Incomplete outcome data (attrition bias)	High risk	14 of 60 (27%) lost over 24 weeks
Selective reporting (reporting bias)	Low risk	Trials register entry made Feb 2011, study started June 2011 so prospective. Outcomes stated in trials register were all stated in paper.
Attention	Unclear risk	Follow up schedule unclear
Compliance	Unclear risk	Pill count suggests compliance with intervention and control capsules was greater than 90%
Other bias	Low risk	None noted

Sofi 2010 [151]

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

Outcomes Main study outcome: Fatty liver status
Dropouts: unclear
Available Outcomes: lipids, glucose, insulin, HOMA, BMI (not in usable format)
Response to contact: No contact attempted

Notes Study funding: Oil supplied by tFarma and funding not stated.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The patients were randomized into two groups"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Unclear risk	No details
Blinding of outcome assessment (detection bias)	Unclear risk	No details
Incomplete outcome data (attrition bias)	Unclear risk	Numbers analysed for liver health are for those randomised. Numbers analysed for other outcomes not stated. No mention of dropouts.
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration
Attention	Low risk	Both groups received same contact
Compliance	Unclear risk	Measured but no results reported
Other bias	Low risk	None noted

Spadaro 2008 [152]

Methods RCT, parallel, (high LCn3s vs low LCn3s, not specific which LCn3s), 6 months
Summary risk of bias: Moderate or high

Participants People with non-alcoholic fatty liver disease (NAFLD)
N: 20 int., 20 control. (analysed, int: 18 cont: 18)
Level of risk for CVD: moderate
Male: 61% int., 44% control.
Mean age (SD) years: 50.2 (12.9) int., 51.3 (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: Italy
Ethnicity: NR

Interventions Type: supplement
Comparison: PUFA vs nil
Intervention: 2g/d PUFA (in capsule form), plus American Heart Association dietary advice (50%E CHO, 20%E protein, 30%E fats), overweight and obese participants were encouraged to lose weight by reducing total energy intake
Control: American Heart Association dietary advice (50%E CHO, 20%E protein, 30%E fats), overweight and obese participants were encouraged to lose weight by reducing total energy intake
n3 Dose: (intended) increase 2.0g/d**, 0.9%E n3**
Compliance: Evaluated using a questionnaire, no results presented
Duration of intervention: 6 months

Outcomes Main study outcome: fatty liver status
Dropouts: 2 int., 2 control
Available outcomes: lipids, TNF alpha, BMI, HOMA-IR (LFTs, degree of steatosis presented but not used)
Response to contact: No contact attempted

Notes Study funding: NS
Author contact: Not yet

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned into two study groups using random sampling numbers"
Allocation concealment (selection bias)	Unclear risk	No further data
Blinding of participants and personnel (performance bias)	High risk	No placebo, open study
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear, not stated, though mostly biochemical outcomes
Incomplete outcome data (attrition bias)	Low risk	2 lost of 20 from each arm, 10% lost in 6 months. Reasons given, balanced.
Selective reporting (reporting bias)	Unclear risk	No protocol or trials register entry found
Attention	Low risk	The study only differed by the additional capsules, but the assessment schedule was not stated to differ between the two arms
Compliance	Unclear risk	Not stated
Other bias	Low risk	None noted

Tande 2016 [153]

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

Participants Healthy male and female volunteers with BMI 25-35 kg/m^2
N: 64 int., 63 control (50 int, 50 cont analysed)
Level of risk for CVD: low
Male: 42% int., 43 % control
Mean age (SD): 50.7 (7.7) int., 49 (9.4) control
Age range: Unclear (18 years and older)
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR

	Location: Norway Ethnicity: NR
Interventions	Type: supplement (capsule) Comparison: EPA & DHA vs MUFA Intervention: 2 x 500 mg Calanus oil capsules twice daily 2g/d, Ayanda AS (Norway) blister packs of 60 capsules each. The Calanus oil contained approximately 85% wax ester with a sum of neutral lipids>90%: EPA+DHA and ALA unclear Control: identical capsules of olive oil. Compositional analysis indicated that the fatty acid content of the olive oil was primarily oleic acid (76.9%), palmitic acid (10.2%), and linoleic acid (7.7%). Compliance: assessed through the return of unused capsules. Compliance rate reported for both intervention and placebo groups was good (86-88%). Length of intervention: 12 months
Outcomes	Main study outcome: Safety of Calanus oil consumption Dropouts: 14 int, 13 control. Available Outcomes: BMI, waist-hip ratio, BP, pulse, HbA1c, ESR, CRP, lipids, glucose tolerance, insulin, clinical chemistry parameters, adverse events (authors report no cardiovascular events, deaths or diabetes diagnoses occurred) Response to contact: Reply from authors, providing details of methodology
Notes	Study funding: Funding was provided by Calanus AS.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**"**Randomization of the study subjects into the intervention group or the placebo group was performed by the University Hospital of North Norway clinical research unit and was stratified by gender." Author reply stated "Randomization was performed by competent people at the drugstore affiliated to the University Hospital, with no interconnection, formally or materially with the research department from where the study was managed. Randomization was performed prior to recruiting subjects."
Allocation concealment (selection bias)	Unclear risk	As above, unclear
Blinding of participants and personnel (performance bias)	Low risk	Subjects of the placebo group received identical capsules at similar daily doses as the intervention group. However no information provided as to their smell and taste. Also unclear if investigators were blinded. Author reply stated "Each study subject was given a randomization number, which carried the name of the person, date of birth and treatment information (intervention or control). The randomization number was the only information made available to the study personnel, and the code was managed by personnel outside the research department. This code was broken after the completion of all analysis with all primary data processed."
Blinding of outcome assessment (detection bias)	Low risk	As above
Incomplete outcome data (attrition bias)	Low risk	All drop outs (~20%) are explained
Selective reporting (reporting bias)	Unclear risk	No trials registry entry or protocol found
Attention	Low risk	Appear to be similar in both groups
Compliance	Unclear risk	"levels of DHA and EPA in the blood were generally higher in the Calanus oil group over baseline values relative to the placebo controls" but no data provided
Other bias	Low risk	None noted

Tapsell 2004 [154 155]

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
PUFA Dose: (intended) increase unclear
Compliance: Diet history and 3-d food record
Duration of intervention: 6 months

Outcomes Main study outcome: Cholesterol
Dropouts: 1 int., 1 control
Available outcomes: Mortality and cardiovascular events (nil), anthropometrics (not useable), lipids, HbA1c
Response to contact: Yes

Notes Author confirmed no deaths or cardiovascular events
Data for anthropometrics, total and LDL cholesterol not used due to baseline differences
3 arm trial: Low fat (unmodified) arm not discussed here
Study funding: California Walnut Commission

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly allocated"
Allocation concealment (selection bias)	Unclear risk	"randomly allocated"
Blinding of participants and personnel (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	Unclear risk	NR
Incomplete outcome data (attrition bias)	Low risk	Low drop out and balanced across arms
Selective reporting (reporting bias)	Unclear risk	No registry or protocol identified
Attention	Unclear risk	Unclear since open label (in low fat arm not discussed fully here, participants received fewer phone calls)
Compliance	High risk	Majority of p values for differences in fatty acid status >0.05
Other bias	Low risk	None noted

Tardivo 2015 [156]

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.
PUFA Dose: (intended) increase 0.9g/d EPA+DHA, **0.4%E n-3, 0.4%E PUFA**
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

Outcomes Main study outcome: metabolic and inflammatory markers
Dropouts: 11 of 44 int., 13 of 43 control
Available outcomes: waist circumference, body fat%, BMI, lipids, glucose, insulin, HOMA-IR, CRP, IL-6, TNF alpha (also IL-1beta, BP not used)
Response to contact: No contact attempted

Notes Funding: FAPESP - Fundação de Amparo a Pesquisa do Estado de São Paulo, Faculdade de Medicina de Botucatu da Universidade Estadual Paulista UNESP, Julio de Mesquita Filho

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	All given a number from 1 to 87, and randomised using a centralised computer (SAS)
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	High risk	Open trial, no placebo
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated, biochemistry outcomes primarily
Incomplete outcome data (attrition bias)	High risk	11 of 44 in int, and 13 of 43 in control lost over 6 months (28%)
Selective reporting (reporting bias)	Unclear risk	RBR-5668v4 Registration Date: Feb, 3, 2013, Enrollment between 1/2/2011-22/12/2011. All outcomes reported.
Attention	Low risk	Appointments were 2 monthly to review and encourage dietary changes
Compliance	Unclear risk	Not reported
Other bias	Low risk	None noted

THIS DIET 2008 [157]

Methods The Heart Insitute 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: Asprin, 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

Outcomes Main study outcome: a composite of end points including all-cause and cardiac death, MI, hospital admissions for HF, unstable angina, or stroke.
Dropouts: none for primary outcomes.
Available outcomes: total and CVD deaths (nil deaths), CV events, stroke, MI, diagnosis of DM, lipids, blood pressure, albuminuria, CRP, creatinine and dietary intake. (Authors supplied further data on newly diagnosed DM, glucose and insulin data, cancers, depression, atrial fibrillation, waist, BMI and weight, but BMI and weight too different at baseline to use)
Response to contact: yes, further data supplied as above

Notes The study compared the 2 intervention groups to a non-randomised usual care control group (not reported here)
Study funding: No funding details is provided but some reported conflict of interests for one of the the co-authors.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sealed envelopes concealing the allocation sequence were prepared by a research coordinator. Assignment was stratified by diabetes mellitus status using 10-envelope blocks. Envelopes were selected in the prepared order from a locked drawer by a study dietitian to assign interventions
Allocation concealment (selection bias)	Unclear risk	As above, but opacity of envelopes is not stated.
Blinding of participants and personnel (performance bias)	High risk	Neither the intervention team nor participants could be blinded to dietary assignment.
Blinding of outcome assessment (detection bias)	Low risk	The PI was blinded for the purpose of adjudicating clinical end points and adverse events by the removal of identifiers from records used for review.
Incomplete outcome data (attrition bias)	Low risk	Primary outcomes data provided for all randomised
Selective reporting (reporting bias)	High risk	NCT00269425 Trial was registered in 2005, data collection started in Oct 2000, January 2008 (Final data collection date for primary outcome measure), publication 2008. A number of the outcomes from the registration were not reported e.g. Cardiovascular revascularization, Peripheral revascularization or amputation, Doubling of serum creatinine, dialysis or

		kidney transplant, New hypertension. Also, numerous secondary measures were reported that were not in the original registration.
Attention	Low risk	Both arms had the same contact and attention.
Compliance	Unclear risk	No details
Other bias	Low risk	None noted

Veleba 2015 [158]

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

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

Interventions Type: supplement (capsules with EPA+DHA; Pio+EPA+DHA; Pio alone; or corn oil)
Comparison: EPA+DHA vs low EPA+DHA
Intervention: **n-3 arm:** 5g/d omega-3 concentrate (including 0.75g/d EPA + 2g/d DHA, EPAX, Aalesund): EPA+DHA 2.75g/d
n-3+ pioglitazone arm: as for n-3 + 15mg/d pioglitazone (Pio, Takeda): EPA+DHA 2.75g/d
Pio arm: 15mg/d pioglitazone alone
Control: 5g/d corn oil capsules (EPAX, Aalesund)
PUFA Dose: (intended) increase 2.75g/d EPA+DHA, **1.2%E n-3, 1.2%E PUFA**
Compliance: Serum omega-3 PhL index
Duration of intervention: 24 weeks

Outcomes Main study outcome: Insulin sensitivity and triacylglycerol
Dropouts: 1 n-3; 3 n-3+Pio; 1 Pio; 4 control
Available outcomes: Insulin, weight, BMI, lipids, glucose, HbA1c, inflammatory markers (as medians and interquartile range)
Response to contact: No contact attempted

Notes 4 arm trial, 2x2, omega 3 and pioglitazone interventions
Study funding: Ministry of Health of the Czech Republic

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed using a computer-based algorithm arranging experimental units in blocks of four"
Allocation concealment (selection bias)	Unclear risk	"The randomization code was kept secret and revealed after the clean-file procedure had been completed when all data had been filled in the case report forms"
Blinding of participants and personnel (performance bias)	Unclear risk	"double blind"
Blinding of outcome assessment (detection bias)	Unclear risk	"double blind"
Incomplete outcome data (attrition bias)	High risk	Drop out >20% in the control arm
Selective reporting (reporting bias)	High risk	EudraCT 2009-011106-42. Unclear if prospectively registered. Registered on 26/05/2009. Some outcomes not reported e.g. liver and muscle

		(musculus tibialis) fat content, body fat distribution: fat quantity in different departments (subcutaneous, visceral)
Attention	Unclear risk	No specific statement and blinding unclear (open for pioglitazone arm)
Compliance	Low risk	Serum omega-3 PhL index significantly increased in response to omega-3
Other bias	Low risk	None noted

Vijayakumar 2014 [17 159 160]

Methods RCT, 2 arms, parallel (n6 LA vs SFA), 2 years
Summary risk of bias: Moderate or High

Participants People with stable coronary artery disease
CVD risk: high
Intervention (sunflower oil): 100 randomised, analysed at 2 years 94
Control (coconut oil): 100 randomised, analysed at 2 years 96
Mean years in trial: 2
% male: Int 92.9%, Cont 93.9%
Age, mean (SD) years: Int 59.0 (8.9), Cont 59.0 (8.4)
Age range: unclear
Smokers, ex: Int 57.1%, Cont 54.1%
Hypertension: Int 55.1%, 58.2%
Medications taken by at least 50% of those in the control group: statins
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: fibrates, nicotinic acid
Location: India
Ethnicity: NR

Interventions Type: Supplement (cooking oil)
Comparison: sunflower oil (n6) vs coconut oil (SFA)
Intervention aims: whole family to use branded sunflower oil for cooking (15%E provided in form of sunflower oil)
Control aims: whole family to use branded coconut oil for cooking (15%E provided in form of coconut oil)
Dose: increase **15%E n-6**
Baseline n-6: unclear
Compliance: unclear
Duration of intervention: 2 years

Outcomes Main study outcome: cardiovascular risk factors
Dropouts: Int 6 lost, Cont 4 lost
Available outcomes: lipids, death, re-vascularisation, (glycaemic control, weight, BMI available but unbalanced at baseline)
Response to contact: yes, authors supplied outcome and methodological information

Notes Study funding: Coconut development board, Amrita Institute of Medical Science and Research. Sponsors had no role in study design or analysis.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation with 5 blocks of 40
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias)	Unclear risk	Unlikely as participants and their families used branded oils
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear
Incomplete outcome data (attrition bias)	Low risk	5% withdrawals. Clear, with reasons
Selective reporting (reporting bias)	Unclear risk	Unclear, no protocol or trials register entry found
Attention	Low risk	Unlikely as cooking oil was the intervention, and

		assessments appeared similarly timed
Compliance	Unclear risk	NR
Other bias	Low risk	None noted

Wang 2016 [161]

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

Participants Type 2 diabetic patients with abdominal obesity
N: 50 int., 50 control. (analysed, int: 49 cont: 50)
Level of risk for CVD: Moderate
Male: 30.6% int., 40% control.
Mean age (SD): 64.6 (5.5) int., 66.3 (5.1) control
Age range: 60 years plus
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: Oral agents
Medications taken by 20-49% of those in the control group: Insulin, anti-hypertensives
Medications taken by some, but less than 20% of the control group: NR
Location: China
Ethnicity: Chinese

Interventions Type: supplement (capsules with EPA+DHA or corn oil)
Comparison: Fish oil vs corn oil
Intervention: 4x1g fish oil capsules/d (containing 1.34g EPA + 1.07g DHA, By-Health Co. China): EPA+DHA 2.41g/d
Control: 4x1g corn oil capsules/d
Compliance: Monthly check-ins and returning empty bottles. Serum fatty acid composition at baseline and trial end
Duration of intervention: 6 months

Outcomes Main study outcome: Glycaemic control and dyslipidaemia
Dropouts: 1 int., 0 control
Available outcomes: Anthropometrics, lipids, glucose, HbA1c, insulin, HOMA-IR (insulin and HOMA not used due to baseline differences; BP 6mths only)
Response to contact: No contact attempted

Notes Study funding: Grant from the National Natural Science Foundation of China, the nutrition research foundation from the Chinese Nutrition Society, the Fundamental Research Funds for the Central Universities, and the Graduate Research and Innovation Projects of Colleges in Jiangsu Province.
Commercial supply of capsules

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers were generated through the statistics software of SAS PROC PLAN procedure programming
Allocation concealment (selection bias)	Unclear risk	Both participants and investigators were blinded for treatment allocation until the completion of the final data analysis
Blinding of participants and personnel (performance bias)	Low risk	Identical-looking capsules and participants were asked to swallow the whole capsules before their main meals to avoid unmasking
Blinding of outcome assessment (detection bias)	Unclear risk	Both participants and investigators were blinded for treatment allocation until the completion of the final data analysis
Incomplete outcome data (attrition bias)	Low risk	Low drop out (1 participant with reason)
Selective reporting (reporting bias)	High risk	C-reactive protein not reported
Attention	Low risk	Participant seen at the same points and asked to maintain stable diet, medications and physical activity

Compliance	Low risk	Significant increase in serum EPA and DHA in the intervention group
Other bias	Low risk	None noted

WELCOME 2014 [162-166]

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: Anti-hypertensives, 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 erthrocyte EPA & DHA enrichment (a prespecified threshold of 2% for DHA & threshold of 0.7% for EPA enrichment)
Duration of intervention: 15-18 months

Outcomes Main study outcome: Changes in mean liver fat %, changes in two liver fibrosis scores, change in serum biomarkers
Dropouts: 4 int., 4 control
Available outcomes: weight, BMI, lipids, blood pressure, glucose, insulin sensitivity, body fat measures, liver enzymes, HbA1c, serum n-3 FAs, authors provided details of diabetes diagnoses, %body fat, BP and carotid intima media thickness. HbA1c not used (baseline differences)
Response to contact: Yes

Notes Study funding: Omacor and placebo were provided by Pronova Biopharma through Abbott Laboratories, Southampton, UK. This work was support- ed by a National Institute for Health Research (NIHR) Southampton Biomedical Research Unit grant and by a Diabetes UK allied health research training fellowship awarded to KGM (Diabetes UK. BDA 09/ 0003937). CDB, PCC and ES are supported in part by the NIHR Southampton Biomedical Research Centre (McCormick-2015, p9)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were block randomised by an independent clinical trials pharmacist to treatment with identical capsules by mouth of either n-3 fatty acid ethyl esters (4 g/day Omacor; Pronova, Sandefjord, Norway) or placebo (4 g/day olive oil) for a minimum of 15 months and a maximum of 18 months (McCormick-2015, p2). Patients were randomised according to standardized procedures (computerized block randomisation) by a re- search pharmacist at University Hospital Southampton NHS Foundation Trust. Simple randomisation in blocks of four, either to trial medication or placebo was used. (Scorletti-2014, p2)

Allocation concealment (selection bias)	Low risk	Participants were block randomised by an independent clinical trials pharmacist to treatment with identical capsules by mouth of either n-3 fatty acid ethyl esters (4 g/day Omacor; Pronova, Sandefjord, Norway) or placebo (4 g/day olive oil) for a minimum of 15 months and a maximum of 18 months (McCormick-2015, p2). Only the clinical trials pharmacist was unblinded, and randomisation group allocation was concealed from all study members throughout the trial. (McCormick-2015, p2).
Blinding of participants and personnel (performance bias)	Low risk	Paper states that only the clinical trials pharmacist was unblinded, and randomisation group allocation was concealed from all study members throughout the trial. However, the trial register record states "single blind (investigator)". Although the capsules were identical, no information provided as to their smell and taste.
Blinding of outcome assessment (detection bias)	Low risk	As above
Incomplete outcome data (attrition bias)	Low risk	The ITT analysis included all patients randomized who had complete data (baseline and end-of-study measurements), regardless of whether they were later found to be ineligible, a protocol violator, given the wrong treatment allocation, or never treated). (Scorletti 2014, p4)
Selective reporting (reporting bias)	Unclear risk	Prospectively registered Sept 2008, study start Sept 2009, end Feb 2017. Outcome data for cardiac function not yet published (but expected soon, study only completed in Feb 2017) though other cardiovascular measures reported.
Attention	Low risk	Both groups had the same attention
Compliance	Low risk	Almost 90% reached compliance threshold. Was assessed by recording the returned unused capsules and quantification of erthrocyte EPA & DHA enrichment (prespecified threshold of 2% for DHA & threshold of 0.7% for EPA enrichment)" Enrichment was highly variable in the intervention group, 5 and 6 participants did not reach the prespecified threshold for EPA and DHA enrichment, respectively. In the placebo group, we expected no enrichment between baseline and end of study, but 3 and 4 participants reached the thresholds set for the DHA +EPA group, for EPA and DHA, respectively (Fig. 2). One participant in the placebo group admitted to taking cod liver oil during the study and another markedly increased consumption of fish."
Other bias	Low risk	None noted

Witte 2012 [167-169]

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 years, cont 50-75 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: 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

Outcomes Main study outcome: brain function
Dropouts: 7 of 40 int., 6 of 40 control
Available outcomes: glucose, HbA1c, hsCRP, TNF alpha, IL-6, BMI, TG, cognition including executive function, memory, sensorimotor speed, attention and mood (there were no deaths in either arm, weight, % body fat, insulin and serum total cholesterol were too different at baseline to use, BP data not used as only 6 mo, MRI imaging data, carotid intima media thickness not used)
Response to contact: No contact attempted

Notes There was a 3rd arm to this study, testing calorie restriction - we have not used these data.
Study funding: Deutsche Forschungsgemeinschaft, Else-Kroner Fresenius Stiftung, Bundesministerium fur Bildung und Forschung. Capsules provided by Via Vitamine.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"block randomisation"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Unclear risk	"subjects and investigators were blinded to the treatment group" and capsules described as identical in shape and colour but no information provided as to taste or smell
Blinding of outcome assessment (detection bias)	Low risk	As above
Incomplete outcome data (attrition bias)	Low risk	Less than 20% lost to follow up, loss similar in each arm and described
Selective reporting (reporting bias)	Low risk	Trials register entry Oct 2009, data collection started Nov 2009. All outcomes mentioned in trials register, and many more, reported in publications.
Attention	Low risk	No suggestion of difference between arms
Compliance	Low risk	Appears to be a statistically significant difference between arms in omega 3 index at study end
Other bias	Low risk	None noted

Zheng 2016 [170-172]

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) years: 59.7 (8.8) fish oil int., 59.7 (11.1) flaxseed oil int, 59.1 (10.0) control
Age range: men 35-80 years, women menopause to 80 years (inclusion criteria)
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: diabetic medication
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: China
Ethnicity: NR

Interventions Type: supplement
Comparison: fish oil (LCn3) vs flaxseed oil (ALA) vs corn oil (n6)
Fish oil Intervention: 4 capsules/d fish oil (1.2g/d EPA, 0.8g/d DHA), Neptunus Bioengineering: EPA+DHA 2.0g/d
Flaxseed oil Intervention: 4 capsules/d flaxseed oil (2.5g/d ALA), Neptunus Bioengineering: ALA 2.5g/d
Control: 4 capsules/d corn oil (2.1g/d LA), Neptunus Bioengineering
Compliance: evaluated by measurement of erythrocyte phospholipid fatty acid compositions at baseline and end, counting empty bottles returned to study centres at days 90 and 180, and monthly phone contact. Sig diff of EPA and DHA between fish oil and corn oil groups at 6 months, and of ALA between flaxseed oil and corn oil at 6 months.
Duration of intervention: 6 months

Outcomes Main study outcome: insulin resistance
Dropouts: 5 of 63 fish oil int., 8 of 61 flaxseed oil int, 6 of 61 control
Available outcomes: glucose, insulin, HbA1c, HOMA, lipids (some unbalanced at baseline so not used, liver and renal function markers not used)
Response to contact: No contact attempted

Notes Study funding: National Basic Research Program of China, National Natural Science Foundation of China, Ph.D. Programs Foundation of Ministry of Education of China, Cambridge Initiative – Nutrition.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**"**randomly allocated to one of the three treatments by computer-generated random numbers with a block size of six, allocation sequence generated by J.S.Z."
Allocation concealment (selection bias)	Unclear risk	"Doctors/nurses at each study centre enrolled and assigned participants to the intervention groups"
Blinding of participants and personnel (performance bias)	Unclear risk	Capsules had "identical appearance", standardised to 1g each, study reported as **"**double blind". "All the patients were given four bottles of capsules at baseline, and given another four bottles at 90 days"… "None of the participants or the nurses/physicians in the study centers knew the oil types during the intervention."… "capsules were kept in white bottles (90 capsules/bottle), which were labelled as Oil A, Oil B, and Oil C for the three types of capsules." No attempt mentioned to mask flavour or smell of fish oil.
Blinding of outcome assessment (detection bias)	Low risk	"None of the participants or the nurses/physicians in the study centers knew the oil types during the intervention" and outcomes biochemical.
Incomplete outcome data (attrition bias)	Unclear risk	Clear about numbers and time of dropout, but no reasons. Attrition <20% each arm.
Selective reporting (reporting bias)	Low risk	Only insulin resistance mentioned in trials register entry (registered before participant recruitment), but many other outcomes reported.
Attention	Low risk	Appears similar across groups
Compliance	Low risk	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.
Other bias	Low risk	None noted.

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
MI = myocardial infarction
mo = months
MUFA = mono-unsaturated fatty acids
n-3 = omega 3
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

Supplementary Table B. Effect of higher vs lower LCn3 on diagnosis of T2DM

Factor assessed	Subgroup	Number of comparisons	Number of participants	Risk Ratio (M-H, Random, 95%CI)	I^2 for subgroup, %	Chi^2 test for subgroup differences, p-value
Random effects	Nil	17	58643	1.00 [0.85, 1.17]	45	NA
SENSITIVITY ANALYSES						
Fixed effects	Nil	17	58643	1.01 [0.93, 1.09]	45	NA
Summary risk of bias	Low summary risk of bias	6	9616	0.76 [0. 49, 1.19]	72	0.17
	Moderate or high risk of bias	11	49027	1.05 [0.96, 1.15]	0	
Compliance risk	Low	8	10024	0.97 [0.81, 1.18]	0	NA
Industry Funding	None	4	4620	0.53 [0.22, 1.27]	85	NA
Lack of Trial Register	Either before 2010 or after 2010 with a trial register	16	58385	1.03 [0.95, 1.12]	0	NA
Trial size	≥ 100 participants	14	58440	1.01 [0.85, 1.19]	51	NA
SUBGROUPS						
Type of intervention	Dietary advice	1	101	0.98 [0.06, 15.25]	NA	0.61
	Supplemental foods	1	4837	0.93 [0.71, 1.21]	NA	
	Supplements (capsules)	13	48558	0.98 [0.81, 1.20]	56	
	Any combination	2	5147	2.56 [0.60, 11.01]	0	
Replacement	LCn3 vs SFA	0	0	Not estimable	NA	0.38
	LCn3 vs MUFA	4	18138	1.05 [0.91, 1.22]	0	
	LCn3 vs n6	2	596	1.00 [0.44, 2.28]	0	
	LCn3 vs CHO	0	0	Not estimable	NA	
	LCn3 vs non-fat or nil or low n3	10	39808	0.95 [0.70, 1.29]	67	
	LCn3 vs unclear	1	101	0.98 [0.06, 15.25]	NA	
	ALA vs. n6	1	13406	0.40 [0.15, 1.03]	NA	
Primary or	General population (no elevated risk)	13	54885	1.04 [0.96, 1.13]	0	0.17

secondary prevention						
	Higher risk group but not diagnosed with T2DM	4	3758	0.46 [0.14, 1.49]	83	
Diabetic medication use	DM meds used by up to 50%	11	50547	1.03 [0.94, 1.12]	0	0.78
	DM meds used by 50%+	0	0	Not estimable	NA	
	DM med use unclear	6	8096	0.92 [0.44, 1.94]	77	
Trial duration	Duration 6 mo to <12 mo	2	108	0.38 [0.10, 1.42]	0	0.22
	Duration 12 to <24mo	5	1521	0.85 [0.29, 2.46]	77	
	Duration 24 to <48 mo	5	15756	0.99 [0.89, 1.10]	0	
	Duration 48+ mo	5	41258	1.12 [0.98, 1.28]	0	
LCn3 dose	LCn3 ≤150mg/d	0	0	Not estimable	NA	0.70
	LCn3 >150 to ≤250mg/d	0	0	Not estimable	NA	
	LCn3 >250 to ≤400mg/d	1	4837	0.93 [0.71, 1.21]	NA	
	LCn3 >400 to ≤2400mg/d	11	49843	0.96 [0.76, 1.20]	62	
	LCn3 >2.4g/d to ≤4.4g/d	4	3856	1.10 [0.80, 1.51]	0	
	LCn3 >4.4g/d	1	139	1.86 [0.08, 44.89]	NA	
Sex	Male & female	14	52933	0.98 [0.82, 1.17]	53	0.50
	Male only	3	5710	1.27 [0.61, 2.67]	0	
	Female only	0	0	Not estimable	0	
Age	Mean age <50 years	0	0	Not estimable	-	0.91
	Mean age 50 to <60 years	8	11217	0.90 [0.42, 1.95]	67	
	Mean age 60-70 years	7	43139	1.07 [0.92, 1.24]	11	
	Mean age >70 years	2	4287	1.04 [0.81, 1.34]	0	

Supplementary Table C. Effect of higher vs lower LCn3 on HbA1c, %

Factor assessed	Subgroup	Number of comparisons	Number of participants	Mean Difference (IV, Random*, 95% CI)	I^2 for subgroup, %	Chi^2 test for subgroup differences, p-value
Main analysis	Nil	16	32798	-0.02 [-0.07, 0.04]	49	NA
SENSITIVITY ANALYSIS						
Fixed effects	Nil	16	32798	-0.00 [-0.02, 0.02]	49	NA
Summary risk of bias	Not appropriate - all at moderate or high risk of bias	NA	NA	NA	NA	NA
Compliance Risk of Bias	Low	7	918	-0.11 [-0.21, -0.01]	31	NA
Industry Funding	None indicated	3	236	0.04 [-0.34, 0.42]	74	NA
Lack of Trial Register	Either before 2010 or after 2010 with a trial register	13	32602	-0.02 [-0.08, 0.04]	57	NA
Trial size	≥ 100 participants	7	32358	-0.02 [-0.09, 0.04]	71	0.80
SUBGROUPS						
Type of intervention	Dietary advice	0	0	Not estimable	NA	0.12
	Supplemental foods	1	32	0.20 [-0.08, 0.48]	NA	
	Supplement (capsules)	15	32766	-0.02 [-0.08, 0.03]	49	
	Any combination	0	0	Not estimable	NA	
Replacement	LCn3 vs SFA	0	0	Not estimable	NA	0.008
	LCn3 vs MUFA	5	13079	0.01 [-0.04, 0.05]	0	
	LCn3 vs n6	5	788	-0.15 [-0.24, -0.06]	0	
	LCn3 vs CHO	0	0	Not estimable	NA	
	LCn3 vs non-fat or nil or low n3	6	18931	0.02 [-0.08, 0.12]	64	
	LCn3 vs unclear	0	0	Not estimable	NA	
Primary or secondary	General population (no elevated risk)	7	3225	-0.00 [-0.06, 0.06]	60	0.01

Factor assessed	Subgroup	Number of comparisons	Number of participants	Mean Difference (IV, Random*, 95% CI)	I^2 for subgroup, %	Chi^2 test for subgroup differences, p-value
prevention	Higher risk group but not diagnosed with T2DM	2	172	-0.15 [-0.25, -0.04]	0	
	Existing diagnosis of T2DM	7	401	0.16 [-0.05, 0.37]	0	
Diabetic medication use	DM meds used by up to 50%	11	32457	-0.02 [-0.08, 0.04]	61	0.28
	DM meds used by 50%+	5	341	0.17 [-0.18, 0.52]	0	
	DM meds use unclear	0	0	Not estimable	NA	
Trial duration	Duration 6 to <12 mo	10	986	-0.05 [-0.16, 0.06]	15	0.71
	Duration 12 to <24 mo	2	128	0.02 [-0.24, 0.28]	0	
	Duration 24 to <48 mo	2	534	0.04 [-0.54, 0.63]	78	
	Duration 48+ mo	3	31150	0.02 [-0.03, 0.07]	63	
LCn3 dose	LCn3 ≤150mg/d	0	0	Not estimable	NA	0.28
	LCn3 >150 to ≤250mg/d	0	0	Not estimable	NA	
	LCn3 >250 to ≤400mg/d	0	0	Not estimable	NA	
	LCn3 >400 to ≤2400mg/d	11	32570	-0.03 [-0.09, 0.03]	61	
	LCn3 >2.4g/d to ≤4.4g/d	2	127	-0.01 [-0.28, 0.26]	0	
	LCn3 >4.4g/d	2	53	0.61 [-0.44, 1.67]	0	
	LCn3 dose unclear	1	32	0.20 [-0.08, 0.48]	NA	
Sex	Male & female	14	32296	0.01 [-0.04, 0.05]	34	0.17
	Male only	2	502	-0.14 [-0.33, 0.06]	42	
	Female only	0	0	Not estimable	-	
Age	Mean age <50 years	2	137	0.11 [-0.34, 0.56]	0	0.52
	Mean age 50 to <60 years	4	587	0.08 [-0.12, 0.29]	0	
	Mean age 60-70 years	10	32074	-0.03 [-0.09, 0.04]	66	
	Mean age >70 years	0	0	Not estimable	-	

Supplementary Table D. Effect of higher vs lower LCn3 on HOMA-IR

Factor assessed	Subgroup	Number of comparisons	Number of participants	Mean Difference (IV, Random, 95% CI)	I^2 (%) for subgroup	Chi^2 test for subgroup differences, p-value
Main analysis	Nil	13	1064	0.06 [-0.21, 0.33]	18	NA
SENSITIVITY ANALYSIS						
Fixed effects	Nil	13	1064	0.11 [-0.08, 0.30]	17	NA
Summary risk of bias	Low	2	292	0.01 [-5.28, 5.29]	62	0.98
	Moderate or high	11	772	0.07 [-0.18, 0.33]	16	
Compliance Risk of Bias	Low	4	205	0.18 [-0.27, 0.63]	38	NA
Industry Funding	No industry funding indicated	4	521	-0.38 [-1.24, 0.47]	0	NA
Lack of Trial Register	Either before 2010 or after 2010 with a trial register	10	758	0.06 [-0.22, 0.34]	24	NA
Trial size	≥ 100 participants	3	697	-1.15 [-2.61, 0.30]	0	NA
SUBGROUPS						
Type of intervention	Dietary advice	0	NA	NA	NA	0.72
	Supplemental foods	2	43	-0.46 [-2.32, 1.40	0	
	Supplement (capsules)	10	976	-0.07 [-0.53, 0.39]	36	
	Any combination	1	45	0.10 [-0.19, 0.39]	NA	
Replacement	LCn3 vs SFA	0	NA	NA	NA	0.78
	LCn3 vs MUFA	3	65	0.14 [-0.21, 0.50]	0	
	LCn3 vs n6	4	215	0.20 [-1.47, 1.86]	52	
	LCn3 vs CHO	0	NA	NA	NA	
	LCn3 vs non-fat or nil or low n3	6	784	-0.02 [-0.31, 0.28]	1	
	LCn3 vs unclear	0	NA	NA	NA	
Primary or secondary	General population (no elevated risk)	3	400	0.14 [-0.09, 0.37]	0	0.42

Factor assessed	Subgroup	Number of comparisons	Number of participants	Mean Difference (IV, Random, 95% CI)	I^2 (%) for subgroup	Chi^2 test for subgroup differences, p-value
prevention	Higher risk group but not diagnosed with T2DM	7	482	-0.23 [-0.93, 0.47]	39	
	Existing diagnosis of T2DM	3	182	-0.70 [-2.50, 1.10]	28	
Diabetic medication use	DM meds used by up to 50%	9	802	0.16 [-0.04, 0.36]	0	0.34
	DM meds used by 50%+	2	150	-0.19 [-4.60, 4.22]	57	
	DM meds use unclear	2	112	-0.46 [-1.26, 0.35]	0	
Trial duration	Duration 6 to <12 mo	9	716	-0.04 [-0.46, 0.37]	31	0.59
	Duration 12 to <24 mo	4	348	0.09 [-0.20, 0.39]	0	
	Duration 24 to <48 mo	0	NA	NA	NA	
	Duration 48+ mo	0	NA	NA	NA	
LCn3 dose	LCn3 ≤150mg/d	0	NA	NA	NA	0.20
	LCn3 >150 to ≤250mg/d	1	29	0.20 [-0.17, 0.57]	NA	
	LCn3 >250 to ≤400mg/d	0	NA	NA	NA	
	LCn3 >400 to ≤2400mg/d	5	281	-0.72 [-1.47, 0.03	3	
	LCn3 >2.4g/d to ≤4.4g/d	4	640	0.21 [-0.37, 0.80]	9	
	LCn3 >4.4g/d	1	37	3.00 [-2.78, 8.78]	NA	
	LCn3 dose unclear	2	77	0.09 [-0.20, 0.38]	0	
Sex	Male & female	12	977	0.09 [-0.19, 0.37]	18	0.34
	Male only	0	0	Not estimable	-	
	Female only	1	87	-0.40 [-1.37, 0.57]	=	
Age	Mean age <50 years	5	170	0.13 [-0.09, 0.36]	0	0.37
	Mean age 50 to <60 years	7	862	-0.43 [-1.20, 0.34]	46	
	Mean age 60-70 years	1	32	-0.30 [-2.42, 1.82]	-	
	Mean age >70 years	0	0	Not estimable	-	

Supplementary Table E. Effect of higher vs lower LCn3 on fasting insulin, pmol/L

Factor assessed	Subgroup	Number of comparisons	Number of participants	Mean Difference (IV, Random, 95% CI)	I^2 for subgroup, %	Chi^2 test for subgroup differences
Main analysis	nil	17	2077	1.02 [-4.34, 6.37]	43	NA
SENSITIVITY ANALYSIS						
Fixed effects	nil	17	2077	0.61 [-1.41, 2.62]	43	NA
Summary risk of bias	Low summary risk of bias	3	387	25.27 [4.11, 46.44]	0	0.02
	Moderate to high summary risk of bias	14	1690	-0.16 [-5.17, 4.86]	38	
Compliance risk of bias	Low	8	844	2.73 [-8.30, 13.77]	66	NA
Industry Funding	None indicated	4	484	0.87 [-6.39, 8.14]	0	NA
Lack of Trial Register	Either before 2010 or after 2010 w trial register	14	1708	0.35 [-5.71, 6.41]	51	NA
Trial size	≥ 100 participants	7	1625	-6.21 [-16.21, 3.79]	49	0.06
SUBGROUPS						
Type of intervention	Dietary advice	0	0	Not estimable	NA	0.26
	Supplemental foods	3	104	9.05 [-5.46, 23.56]	0	
	Supplement (capsule)	14	1973	0.03 [-5.94, 5.99]	50	
	Any combination	0	0	Not estimable	NA	
Replacement	LCn3 vs SFA	0	0	Not estimable	NA	0.88
	LCn3 vs MUFA	6	674	3.69 [-5.18, 12.56]	35	
	LCn3 vs n6	5	548	-0.47 [-26.06, 25.12]	77	
	LCn3 vs CHO	0	0	Not estimable	NA	
	LCn3 vs non-fat or nil or low n3	5	810	0.92 [-6.19, 8.04]	0	
	LCn3 vs unclear	1	45	0.41 [-1.86, 2.68]	NA	
Primary or secondary	General population (no elevated risk)	8	1377	0.68 [-5.58, 6.95]	44	0.35

Factor assessed	Subgroup	Number of comparisons	Number of participants	Mean Difference (IV, Random, 95% CI)	I^2 for subgroup, %	Chi^2 test for subgroup differences
prevention	Higher risk group but not diagnosed with T2DM	7	555	4.85 [-6.67, 16.37]	33	
	Existing diagnosis of T2DM	2	145	-25.28 [-65.37, 14.82]	51	
Diabetic medication use	DM meds used by up to 50%	14	1852	2.55 [-2.49, 7.59]	37	0.02
	DM meds used by 50%+	1	113	-45.10 [-83.39, -6.81]	NA	
	DM meds use unclear	2	112	-13.33 [-33.49, 6.83]	0	
Trial duration	Duration 6 to <12 mo	10	1227	-0.01 [-7.89, 7.86]	40	0.04
	Duration 12 to <24 mo	6	543	6.50 [-3.22, 16.23]	38	
	Duration 24 to <48 mo	1	307	-18.80 [-35.84, -1.76]	NA	
	Duration 48+ mo	0	0	Not estimable	NA	
LCn3 dose	LCn3 ≤150mg/d	0	0	Not estimable	NA	0.28
	LCn3 >150 to ≤250mg/d	1	29	3.47 [-7.71, 14.65]	NA	
	LCn3 >250 to ≤400mg/d	0	0	Not estimable	NA	
	LCn3 >400 to ≤2400mg/d	9	1179	-2.50 [-9.24, 4.23]	52	
	LCn3 >2.4 to ≤4.4g/d	5	737	14.31 [-2.12, 30.74]	25	
	LCn3 >4.4g/d	0	0	Not estimable	NA	
	LCn3 dose unclear	2	132	2.58 [-11.94, 17.11]	0	
Sex	Male & female	15	1683	2.96 [-2.19, 8.11]	35	0.03
	Male only	1	307	-18.80 [-35.84, -1.76]	-	
	Female only	1	87	-14.00 [-38.20, 10.20]	-	
Age	Mean age <50 years	5	233	0.58 [-1.61, 2.78]	0	0.71
	Mean age 50 to <60 years	9	1398	2.79 [-10.61, 16.20]	60	
	Mean age 60-70 years	3	446	-5.83 [-22.30, 10.63]	61	
	Mean age >70 years	0	0	Not estimable	-	

Supplementary Table F. Effect of higher vs lower LCn3 on fasting plasma glucose, mmol/L

Factor assessed	Subgroup	Number of comparisons	Number of participants	Mean Difference (IV, Random, 95% CI)	I^2 for subgroup, %	Chi^2 test for subgroup differences, p-value
Main analysis	Nil	34	35156	0.04 [0.02, 0.07]	0	NA
SENSITIVITY ANALYSIS						
Fixed effects	Nil	34	35156	0.04 [0.02, 0.07]	0	NA
Summary risk of bias	Low RoB	2	353	-0.45 [-1.49, 0.59]	54	0.36
	Moderate to high RoB	32	34803	0.04 [0.02, 0.07]	0	
Compliance Risk of Bias	Low	13	2150	-0.07 [-0.16, 0.02]	0	NA
Industry Funding	None	6	728	-0.06 [-0.50, 0.39]	48	NA
Lack of Trial Register	Before 2010 or after 2010 w trial register	27	34508	0.05 [0.02, 0.07]	0	NA
Trial size	≥ 100 participants	15	34184	0.03 [-0.02, 0.08]	18	NA
SUBGROUPS						
Type of intervention	Dietary advice	None	NA	Not estimable	NA	0.11
	Supplemental foods	2	106	-0.00 [-0.26, 0.26]	0	
	Supplements (capsules)	29	34779	0.05 [0.02, 0.07]	0	
	Any combination	3	271	-0.13 [-0.29, 0.04]	0	
Replacement	LCn3 vs SFA	None	NA	Not estimable	NA	0.86
	LCn3 vs MUFA	10	13371	0.05 [-0.01, 0.12]	0	
	LCn3 vs n6	10	1320	0.01 [-0.11, 0.14]	31	
	LCn3 vs CHO	NA	NA	Not estimable	NA	
	LCn3 vs non-fat or nil or low n3	14	20465	0.04 [0.02, 0.07]	0	
	LCn3 vs unclear	0	0	Not estimable	NA	
Primary or secondary prevention	General population (no elevated risk)	20	34220	0.04 [0.02, 0.07]	0	0.63
	Higher risk group but not	7	568	0.00 [-0.19, 0.20]	0	

Factor assessed	Subgroup	Number of comparisons	Number of participants	Mean Difference (IV, Random, 95% CI)	I^2 for subgroup, %	Chi^2 test for subgroup differences, p-value
	diagnosed with T2DM					
	Existing diagnosis of T2DM	7	368	0.24 [-0.19, 0.67]	0	
Diabetic medication use	DM meds used by up to 50%	26	34736	0.04 [0.02, 0.07]	0	0.25
	DM meds used by 50%+	5	308	0.42 [-0.16, 1.00]	0	
	DM med use unclear	2	112	-0.21 [-0.68, 0.26]	0	
Trial duration	Duration 6 to <12 mo	21	1959	0.02 [-0.07, 0.11]	0	0.07
	Duration 12 to <24 mo	7	1142	-0.06 [-0.17, 0.04]	1	
	Duration 24 to <48 mo	3	905	-0.09 [-0.27, 0.09]	5	
	Duration 48+ mo	3	31150	0.05 [0.03, 0.08]	0	
LCn3 dose	LCn3 ≤150mg/d	0	0	Not estimable	NA	0.34
	LCn3 >150 to ≤250mg/d	1	29	0.00 [-0.31, 0.31]	NA	
	LCn3 >250 to ≤400mg/d	0	0	Not estimable	NA	
	LCn3 >400 to ≤2400mg/d	15	32847	0.04 [-0.01, 0.08]	11	
	LCn3 >2.4 to ≤4.4g/d	13	2034	0.01 [-0.10, 0.11]	0	
	LCn3 >4.4g/d	2	69	1.12 [0.04, 2.19]	6	
	LCn3 dose unclear	3	177	-0.01 [-0.14, 0.12]	0	
Sex	Male & female	31	34582	0.05 [0.02, 0.07]	0	0.10
	Male only	1	487	-0.20 [-0.46, 0.06]	-	
	Female only	1	87	-0.30 [-0.93, 0.33]	-	
Age	Mean age <50 years	7	391	-0.01 [-0.11, 0.10]	3	0.09
	Mean age 50 to <60 years	15	2415	-0.06 [-0.18, 0.05]	0	
	Mean age 60-70 years	11	32350	0.05 [0.02, 0.08]	2	
	Mean age >70 years	0	0	Not estimable	-	

Supplementary Table G. Effect of higher vs lower ALA on diagnosis of type 2 diabetes

Factor assessed	Subgroup	Number of comparisons	Number of participants	Risk Ratio (M-H, Random, 95%CI)	I^2 %
Main analysis	Nil	2	18243	0.68 [0.33, 1.39]	59
Fixed effects	Nil	2	18243	0.82 [0.63, 1.05]	59
Summary risk of bias	Low risk of bias	1	4837	0.87 [0.67, 1.14]	NA
Compliance risk	Nil	1	4837	0.87 [0.67, 1.14]	NA

Supplementary Table H. Effect of higher vs lower ALA on HbA1c, %

Factor assessed	Subgroup	Number of comparisons	Number of participants	Mean Difference (IV, Random*, 95% CI)	I^2 %
Main analysis	Nil	3	178	0.01 [-0.43, 0.45]	0%
Fixed effects	Nil	3	178	0.01 [-0.43, 0.45]	0%
Summary risk of bias	Not appropriate - all at moderate or high risk of bias	NA	NA	NA	NA
Compliance risk	Nil	1	108	-0.10 [-1.02, 0.82]	NA

Supplementary Table I. Effect of higher vs lower ALA on HOMA-IR

Factor assessed	Subgroup	Number of comparisons	Number of participants	Mean Difference (IV, Random*, 95% CI)	I^2 %
Main analysis	Nil	3	294	0.10 [-0.50, 0.70]	0
Fixed effects	Nil	3	294	0.10 [-0.50, 0.70]	0
Summary risk of bias	Not appropriate - all at moderate or high risk of bias	NA	NA	NA	NA
Compliance bias	Nil	2	234	-0.10 [-0.87, 0.68]	0

Supplementary Table J. Effect of higher vs lower ALA on fasting insulin, pmol/L

Factor assessed	Subgroup	Number of comparisons	Number of participants	Mean Difference (IV, Random*, 95% CI)	I^2 %
Main analysis	Nil	6	469	5.30 [-4.68, 15.27]	0
Fixed effects	Nil	6	469	5.30 [-4.68, 15.27]	0
Summary risk of bias	Not appropriate - all at moderate or high risk of bias	NA	NA	NA	NA
Compliance risk	Nil	4	374	2.02 [-9.07, 13.12]	0

Supplementary Table K. Effect of higher vs lower ALA on fasting plasma glucose, mmol/L

Factor assessed	Subgroup	Number of comparisons	Number of participants	Mean Difference (IV, Random*, 95% CI)	I^2 %
Main analysis	Nil	7	648	-0.07 [-0.16, 0.02]	0
Fixed effects	Nil	7	648	-0.07 [-0.16, 0.02]	0
Summary risk of bias	Not appropriate - all at moderate or high risk of bias	NA	NA	NA	NA
Compliance risk	Nil	5	553	-0.06 [-0.15, 0.03]	0

Supplementary Table L. Effects of omega-3 compared to more omega-6 on primary outcomes

Factor assessed	Number of comparisons	Number of participants	Risk Ratio (M-H, Random, 95%CI)	I^2 for subgroup, %
Diagnosis of T2DM	3	14002	0.67 [0.35, 1.28]	5
HbA1c %	6	841	-0.15 [-0.24, -0.06]	0
Fasting insulin	8	690	-3.23 [-21.73, 15.28]	67
Fasting glucose	14	1641	-0.03 [-0.11, 0.05]	10
HOMA-IR	6	328	-0.23 [-1.35, 0.88]	60

Supplementary Table M. Effects of higher vs lower LCn3 on secondary outcomes within this review.

Outcome	Number of comparisons	Number of participants	Mean Difference (IV, Random, 95% CI)	Heterogeneity, I^2, %	Percentage change from mean baseline
All-cause mortality	14	69584	0.99 [0.91, 1.07]	40	NA
Serum cholesterol, mmol/L	34	37914	0.01 [-0.04, 0.05]	69	<1%
Serum triglycerides, mmol/L	35	18205	-0.16 [-0.22, -0.11]	54	~10%
Serum HDL, mmol/L	35	37982	0.03 [0.01, 0.04]	61	~3%
Serum LDL, mmol/L	29	35743	0.01 [-0.02, 0.04]	30	<1%
Weight, kg	17	16659	1.06 [0.30, 1.82]	56	1-2%
BMI, kg/m^2	17	15192	0.34 [0.01, 0.66]	52	1-2%
%body fat	6	478	-0.53 [-2.78, 1.72]	54	1-2%
Waist circumference, cm	4	353	0.51 [0.16, 0.87]	0	<1%
Waist:hip ratio	2	162	0.00 [-0.01, 0.01]	0	0
Total Body fat, kg	3	110	0.87 [0.47, 1.27]	0	~4%

Supplementary Table N. Effects of higher vs lower ALA on secondary outcomes within this review.

Outcome	Number of comparisons	Number of participants	Mean Difference (IV, Random*, 95% CI)	Heterogeneity, I^2, %
All-cause mortality	2	15939	1.03 [0.81, 1.30]	0
Serum cholesterol, mmol/L	6	1672	-0.06 [-0.20, 0.08]	39
Triglycerides, mmol/L	9	1893	0.01 [-0.08, 0.10]	26
Serum HDL, mmol/L	8	1812	-0.01 [-0.05, 0.02]	18
Serum LDL, mmol/L	7	1709	-0.03 [-0.10, 0.04]	0
Weight, kg	7	552	-1.07 [-3.24, 1.10]	61
BMI, kg/m^2	4	1580	-0.39 [-1.61, 0.82]	79
%body fat	1	81	-2.00 [-5.11, 1.11]	NA
Waist circumference, cm	4	279	-0.69 [-3.52, 2.14]	49
Waist:hip ratio	None	NA	NA	NA
Total Body fat, kg	None	NA	NA	NA

Supplementary Table O. Effect of higher vs lower omega-6 on diagnosis of type 2 diabetes

Factor assessed	Subgroup	Number of comparisons	Number of participants	Risk Ratio (M-H, Random, 95%CI)	I^2 for subgroup, %
Main analysis	Nil	2	2087	1.52 [0.19, 12.05]	0
Fixed effects	Nil	2	2087	1.60 [0.22, 11.77]	0
Summary risk of bias	Not appropriate – none at low summary risk of bias	NA	NA	NA	NA
Compliance bias	Not appropriate – none at low risk of bias from compliance	NA	NA	NA	NA

Supplementary Table P. Effect of higher vs lower omega-6 on HbA1c, %

Factor assessed	Subgroup	Number of comparisons	Number of participants	Mean Difference (IV, Random*, 95% CI)	I^2 for subgroup, %
Main analysis	Nil	2	64	0.00 [-1.01, 1.01]	0
Fixed effects	Nil	2	64	0.00 [-1.01, 1.01]	0
Summary risk of bias	Not appropriate - all at moderate or high risk of bias	NA	NA	NA	NA
Compliance bias	Nil	1	28	0.00 [-1.94, 1.94]	NA

Supplementary Table Q. Effect of higher vs lower omega-6 on HOMA-IR

Factor assessed	Subgroup	Number of comparisons	Number of participants	Mean Difference (IV, Random*, 95% CI)	I^2 for subgroup, %
Main analysis	Nil	1	60	1.50 [0.59, 2.41]	NA
Fixed effects	Nil	1	60	1.50 [0.59, 2.41]	NA
Summary risk of bias	Not appropriate - all at moderate or high risk of bias	NA	NA	NA	NA
Compliance bias	Not appropriate – none at low risk of bias from compliance	NA	NA	NA	NA

Supplementary Table R. Effect of higher vs lower omega-6 on fasting insulin, mmol/L

Factor assessed	Subgroup	Number of comparisons	Number of participants	Mean Difference (IV, Random*, 95% CI)	I^2 for subgroup, %
Main analysis	Nil	3	124	14.71 [-19.81, 49.24]	77
Fixed effects	Nil	3	124	9.02 [-5.99, 24.04]	77
Summary risk of bias	Not appropriate – none at low summary risk of bias	NA	NA	NA	NA
Compliance bias	Nil	1	28	0.00 [-19.24, 19.24]	NA

Supplementary Table S. Effect of higher vs lower omega-6 on fasting glucose, mmol/L

Factor assessed	Subgroup	Number of comparisons	Number of participants	Mean Difference (IV, Random*, 95% CI)	I^2 for subgroup, %
Main analysis	Nil	3	134	-0.09 [-0.39, 0.20]	0
Fixed effects	Nil	3	134	-0.09 [-0.39, 0.20]	0
Summary risk of bias	Not appropriate - all at moderate or high risk of bias	NA	NA	NA	NA
Compliance bias	Nil	1	28	-0.30 [-2.24, 1.64]	NA

Supplementary Table T. Effects of higher vs lower omega-6 on secondary outcomes within this review.

Outcome	Number of comparisons	Number of participants	Mean Difference (IV, Random*, 95% CI)	Heterogeneity, I^2, %
All-cause mortality	3	2287	0.98 [0.77, 1.25]	0
Serum cholesterol, mmol/L	6	2114	-0.20 [-0.38, -0.02]	40
Triglycerides, mmol/L	7	495	-0.03 [-0.16, 0.10]	14
Serum HDL, mmol/L	6	2086	-0.03 [-0.11, 0.05]	73
Serum LDL, mmol/L	3	257	-0.04 [-0.22, 0.14]	0
Weight, kg	6	399	1.29 [-1.13, 3.71]	26
BMI, kg/m^2	3	296	0.49 [-0.70, 1.68]	73
%body fat	1	190	-0.10 [-1.03, 0.83]	NA
Waist circumference, cm	1	60	1.20 [-1.81, 4.21]	NA
Waist: hip ratio	1	190	-0.01 [-0.02, 0.00]	NA

Supplementary Table U. Effect of higher vs lower total PUFA on diagnosis of type 2 diabetes

Factor assessed	Subgroup	Number of comparisons	Number of participants	Risk Ratio (M-H, Random, 95%CI)	I^2 for subgroup, %
Main analysis	Nil	3	4481	1.08 [0.81, 1.43]	0%
Fixed effects	Nil	3	4481	1.08 [0.81, 1.44]	0%
Summary risk of bias	Not appropriate - all at moderate or high risk of bias	NA	NA	NA	NA
Compliance bias	Not appropriate – none at low risk of bias from compliance	NA	NA	NA	NA

Supplementary Table V. Effect of higher vs lower total PUFA on HbA1c, %

Factor assessed	Subgroup	Number of comparisons	Number of participants	Mean Difference (IV, Random*, 95% CI)	I^2 for subgroup, %
Main analysis	Nil	3	172	0.08 [-0.41, 0.56]	0
Fixed effects	Nil	3	172	0.08 [-0.41, 0.56]	0
Summary risk of bias	Not appropriate - all at moderate or high risk of bias	NA	NA	NA	NA
Compliance bias	Nil	1	28	0.00 [-1.94, 1.94]	NA

Supplementary Table W. Effect of higher vs lower total PUFA on HOMA-IR

Factor assessed	Subgroup	Number of comparisons	Number of participants	Mean Difference (IV, Random*, 95% CI)	I^2 for subgroup, %
Main analysis	Nil	1	93	-0.34 [-0.88, 0.20]	NA
Fixed effects	Nil	1	93	-0.34 [-0.88, 0.20]	NA
Summary risk of bias	Not appropriate - all at moderate or high risk of bias	NA	NA	NA	NA
Compliance bias	Not appropriate – none at low risk of bias from compliance	NA	NA	NA	NA

Supplementary Table X. Effect of higher vs lower total PUFA on fasting insulin, mmol/L

Factor assessed	Subgroup	Number of comparisons	Number of participants	Mean Difference (IV, Random*, 95% CI)	I^2 for subgroup, %
Main analysis	Nil	3	157	-0.60 [-10.33, 9.14]	0%
Fixed effects	Nil	3	157	-0.60 [-10.33, 9.14]	0%
Summary risk of bias	Not appropriate - all at moderate or high risk of bias	NA	NA	NA	NA
Compliance bias	Nil	1	28	0.00 [-19.24, 19.24]	NA

Supplementary Table Y. Effect of higher vs lower total PUFA on fasting glucose, mmol/L

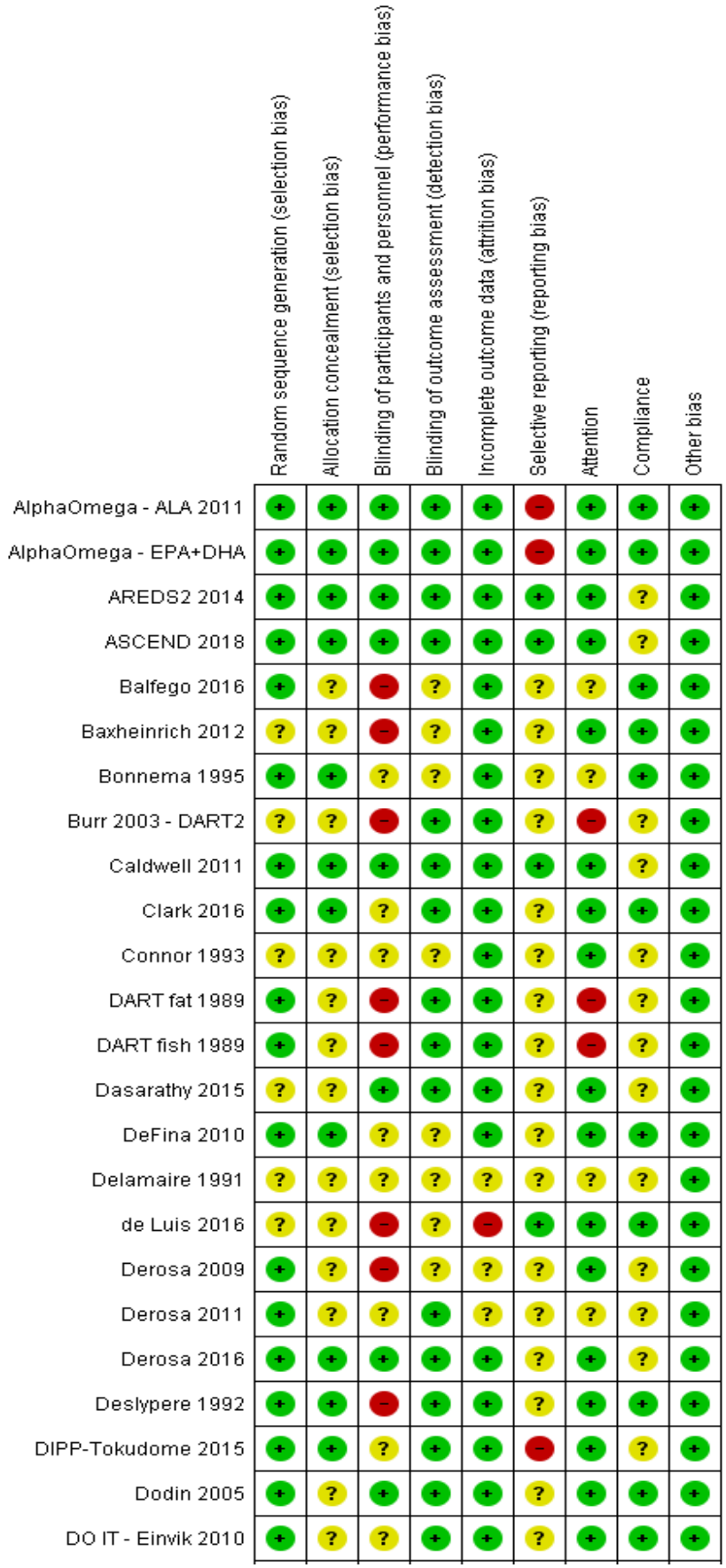
Factor assessed	Subgroup	Number of comparisons	Number of participants	Mean Difference (IV, Random*, 95% CI)	I^2 for subgroup, %
Main analysis	Nil	3	182	-0.04 [-0.18, 0.11]	0
Fixed effects	Nil	3	182	-0.04 [-0.18, 0.11]	0
Summary risk of bias	Not appropriate - all at moderate or high risk of bias	NA	NA	NA	NA
Compliance bias	Nil	1	28	-0.30 [-2.24, 1.64]	NA

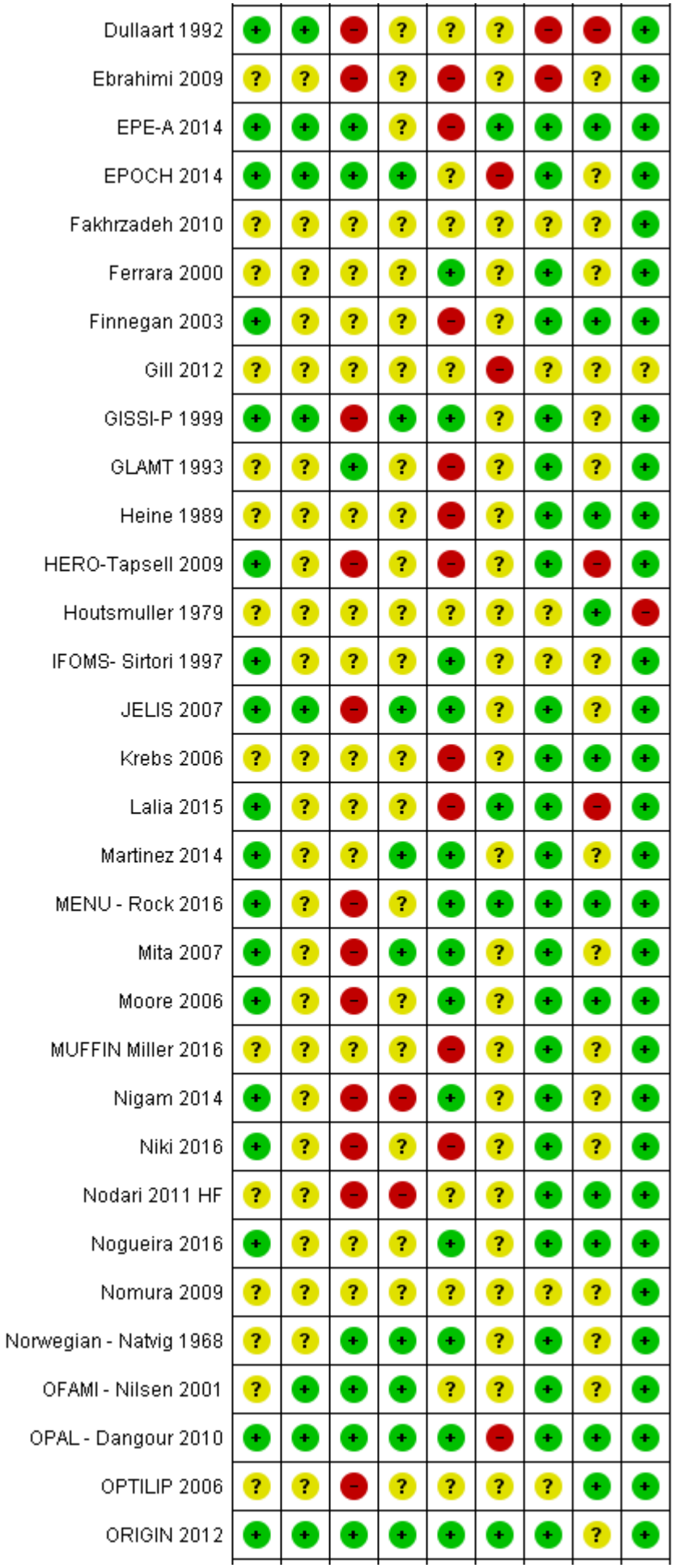
Supplementary Table Z. Effects of higher vs lower total PUFA on secondary outcomes within this review.

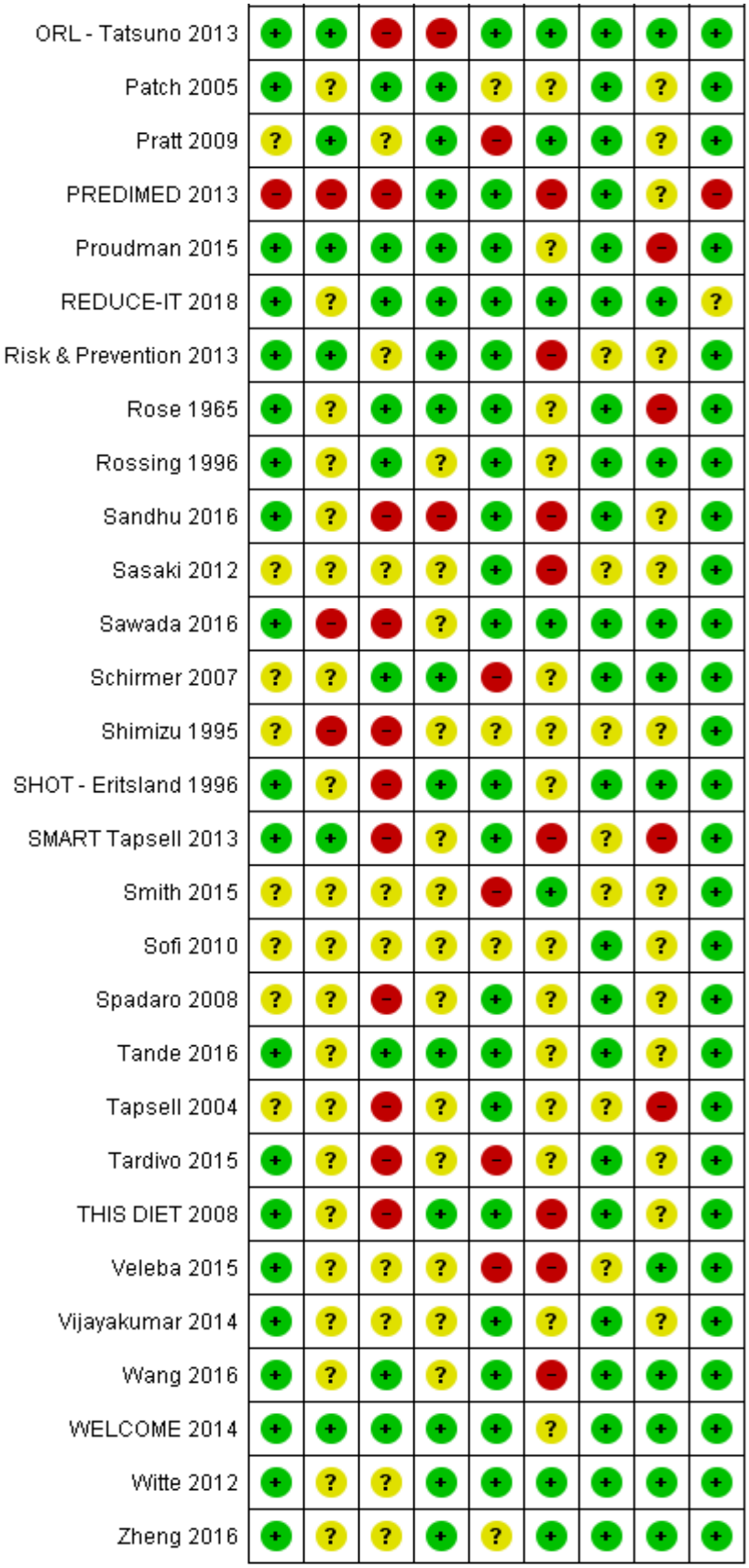
Outcome	Number of comparisons	Number of participants	Mean Difference (IV, Random*, 95% CI)	Heterogeneity, I^2, %
All-cause mortality	3	7084	1.01 [0.85, 1.20]	0%
Serum cholesterol, mmol/L	6	2146	-0.20 [-0.30, -0.10]	2%
Triglycerides, mmol/L	5	467	-0.08 [-0.20, 0.05]	0%
Serum HDL, mmol/L	5	2154	-0.00 [-0.02, 0.02]	0%
Serum LDL, mmol/L	3	385	-0.12 [-0.41, 0.17]	57%
Weight, kg	5	3772	0.36 [-0.06, 0.77]	0%
BMI, kg/m^2	2	578	0.22 [-0.09, 0.53]	49%
Waist circumference, cm	1	653	-0.22 [-1.04, 0.59]	0%
%body fat	1	214	0.80 [-0.39, 1.99]	NA
Body fat, kg	1	214	0.00 [-1.12, 1.12]	NA

Supplementary Figures

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

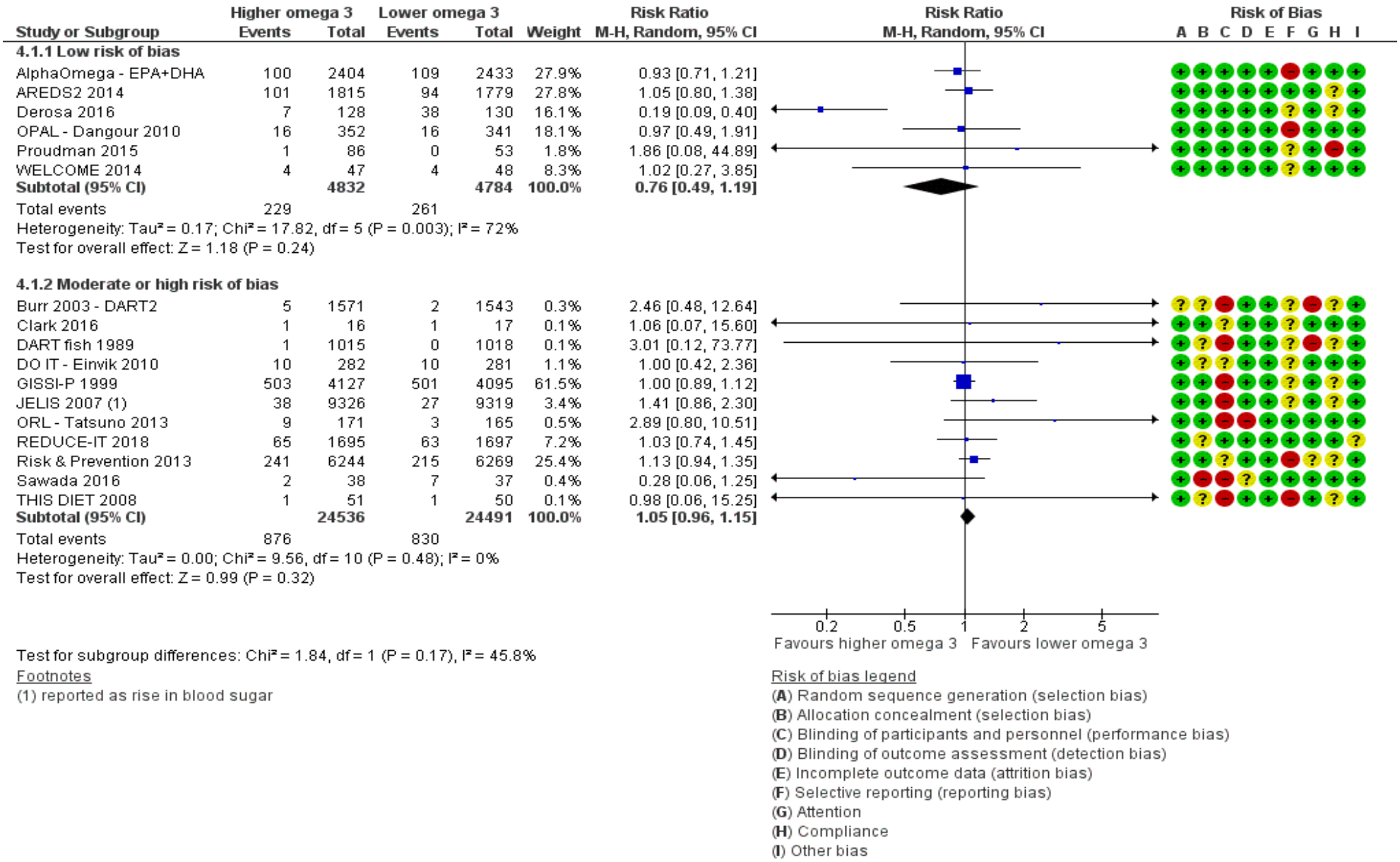



Dullaart 1992
Ebrahimi 2009
EPE-A 2014
EPOCH 2014
Fakhrzadeh 2010
Ferrara 2000
Finnegan 2003
Gill 2012
GISSI-P 1999
GLAMT 1993
Heine 1989
HERO-Tapsell 2009
Houtsmuller 1979
IFOMS- Sirtori 1997
JELIS 2007
Krebs 2006
Lalia 2015
Martinez 2014
MENU - Rock 2016
Mita 2007
Moore 2006
MUFFIN Miller 2016
Nigam 2014
Niki 2016
Nodari 2011 HF
Nogueira 2016
Nomura 2009
Norwegian - Natvig 1968
OFAMI - Nilsen 2001
OPAL - Dangour 2010
OPTILIP 2006
ORIGIN 2012

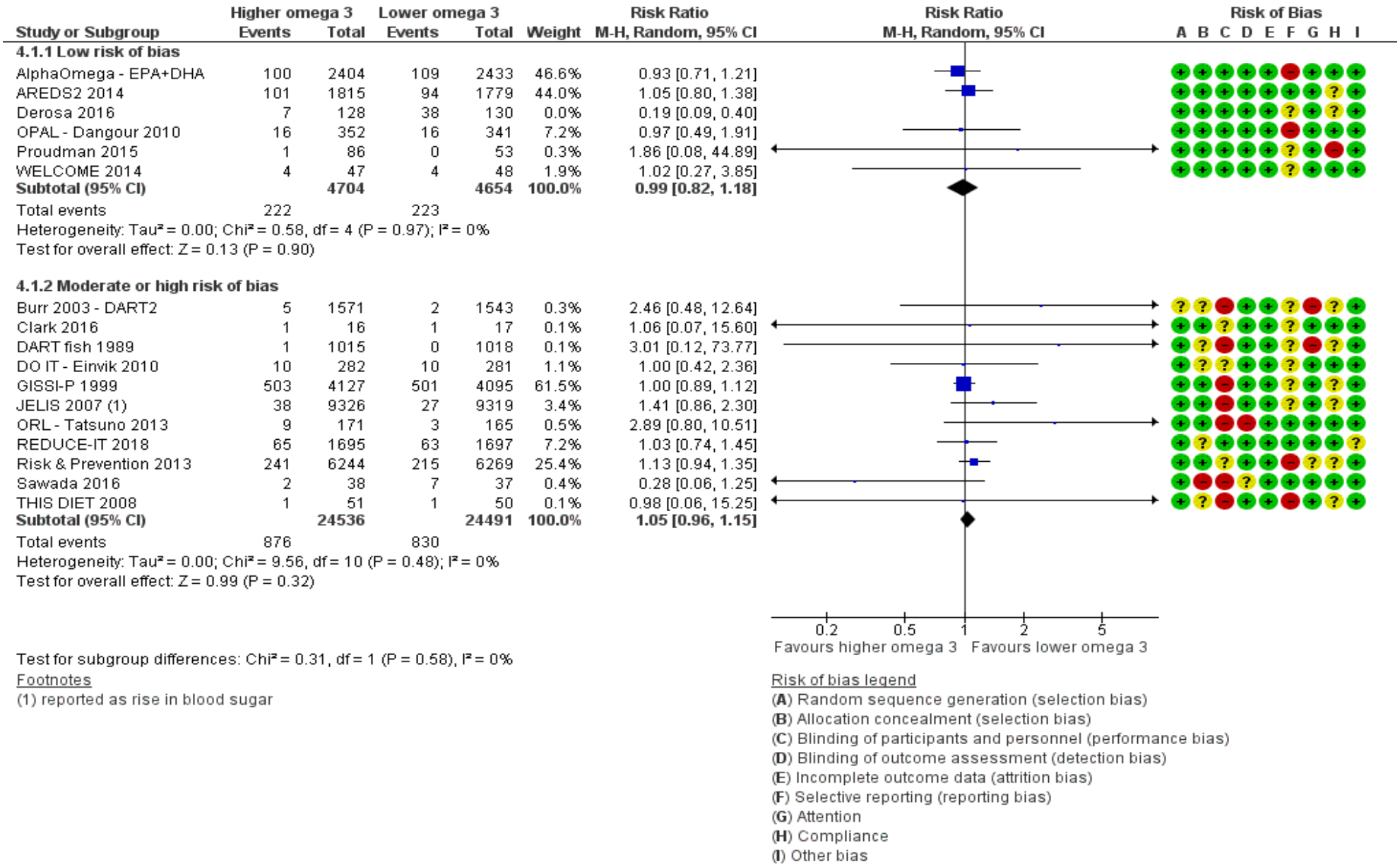


Footnote:
+ means low risk of bias for that study/domain
- means high risk of bias for that study/domain
? means unclear risk of bias for that study/domain

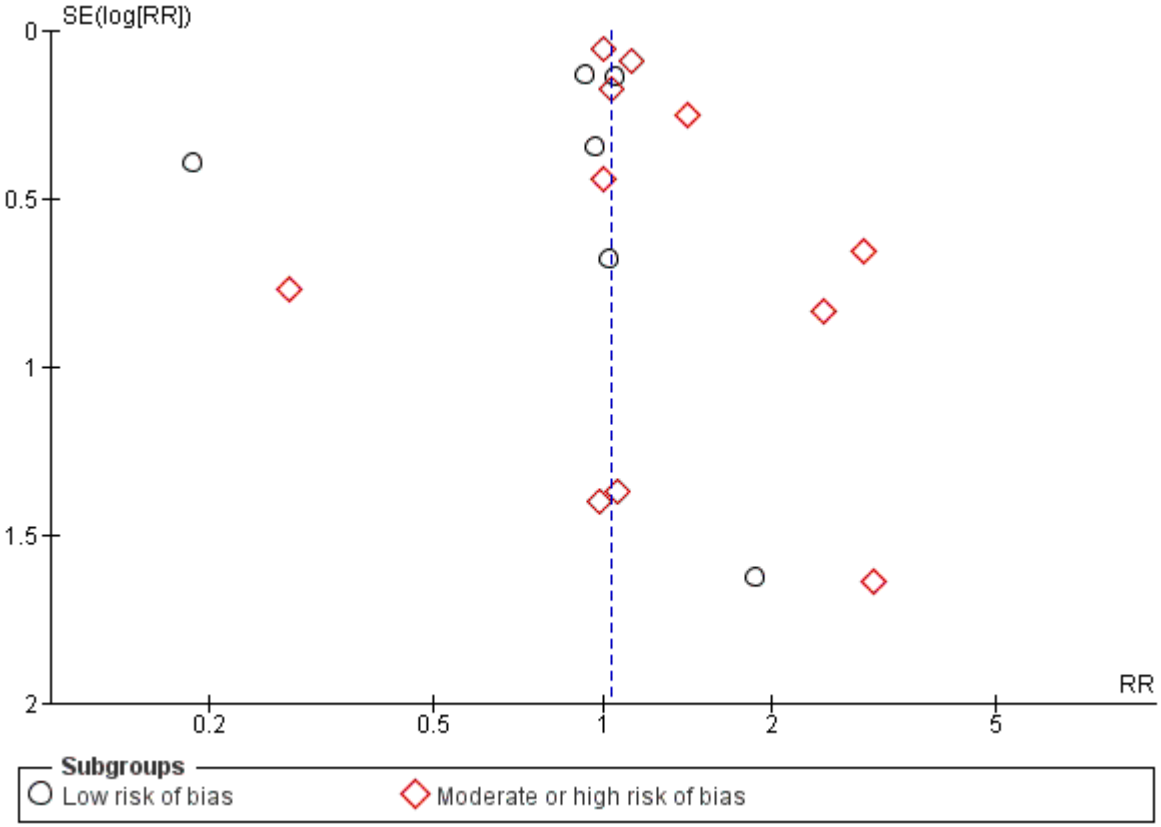
Reasoning behind decisions in this table are given in Additional Table 1.



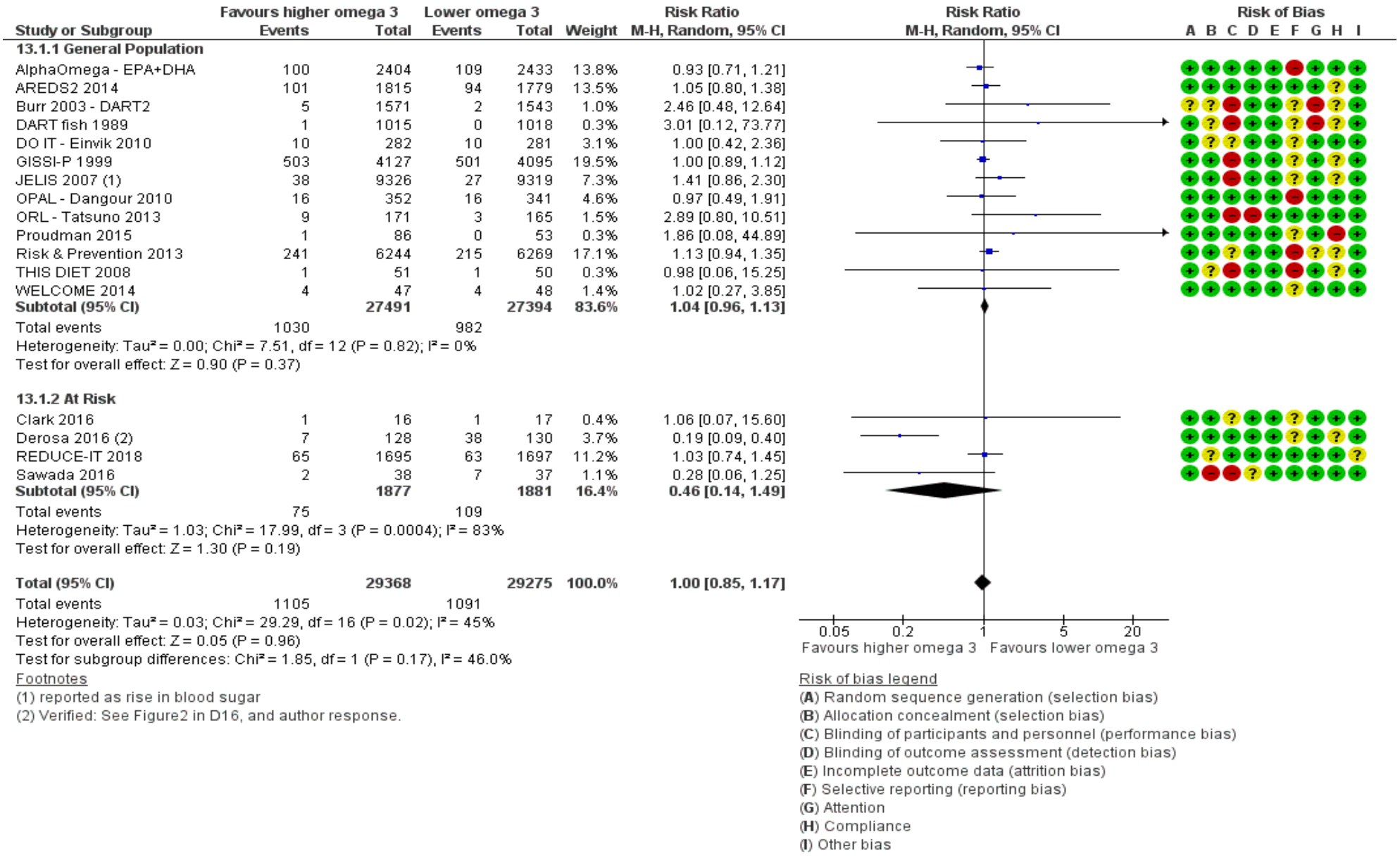
Supplementary Figure B. Meta-analysis of effects of LCn3 on type 2 diabetes diagnosis. Sensitivity analysis by summary risk of bias.



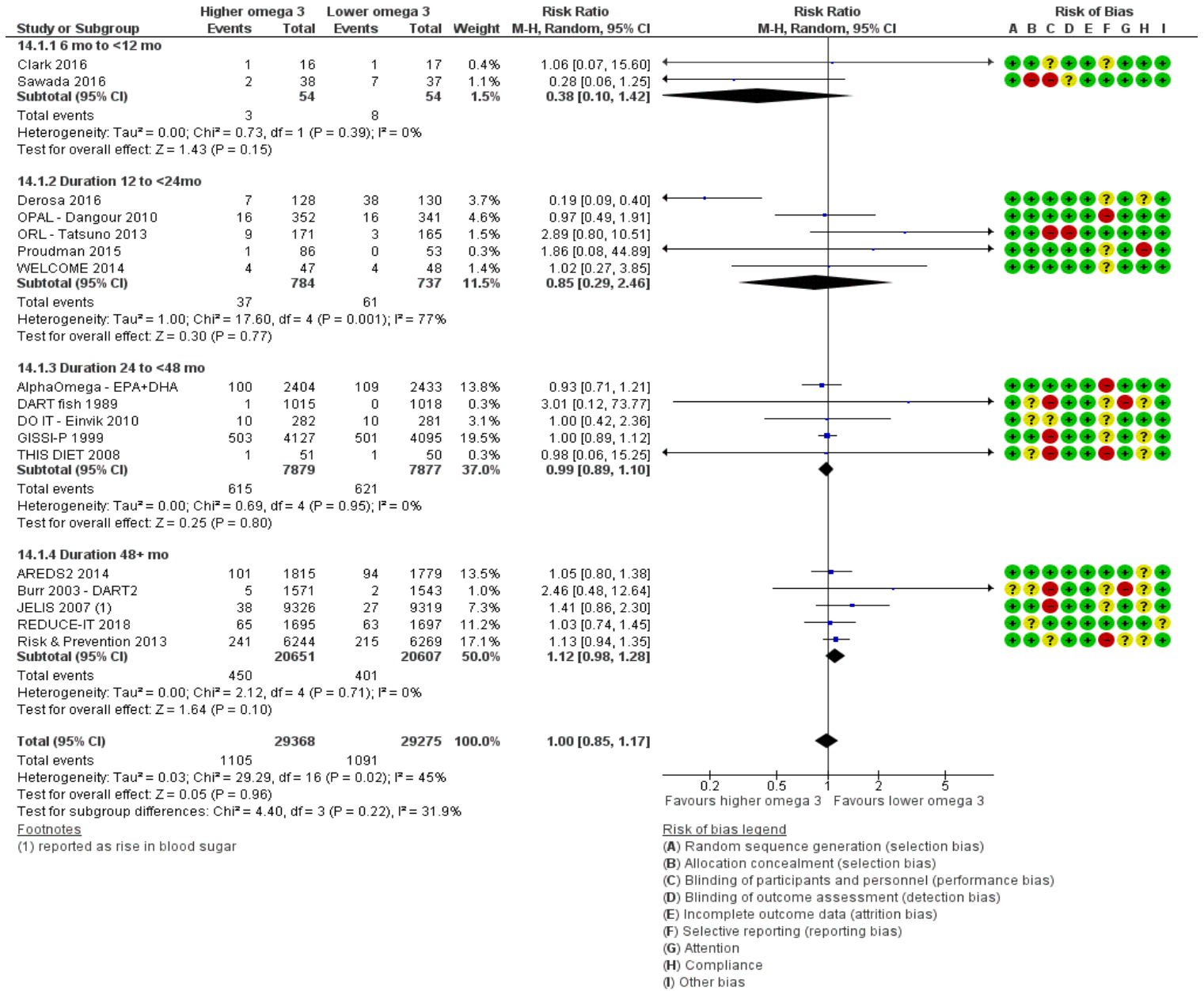
Supplementary Figure C. Meta-analysis of effects of LCn3 on type 2 diabetes diagnosis. Sensitivity analysis by summary risk of bias, omitting Derosa 2016.



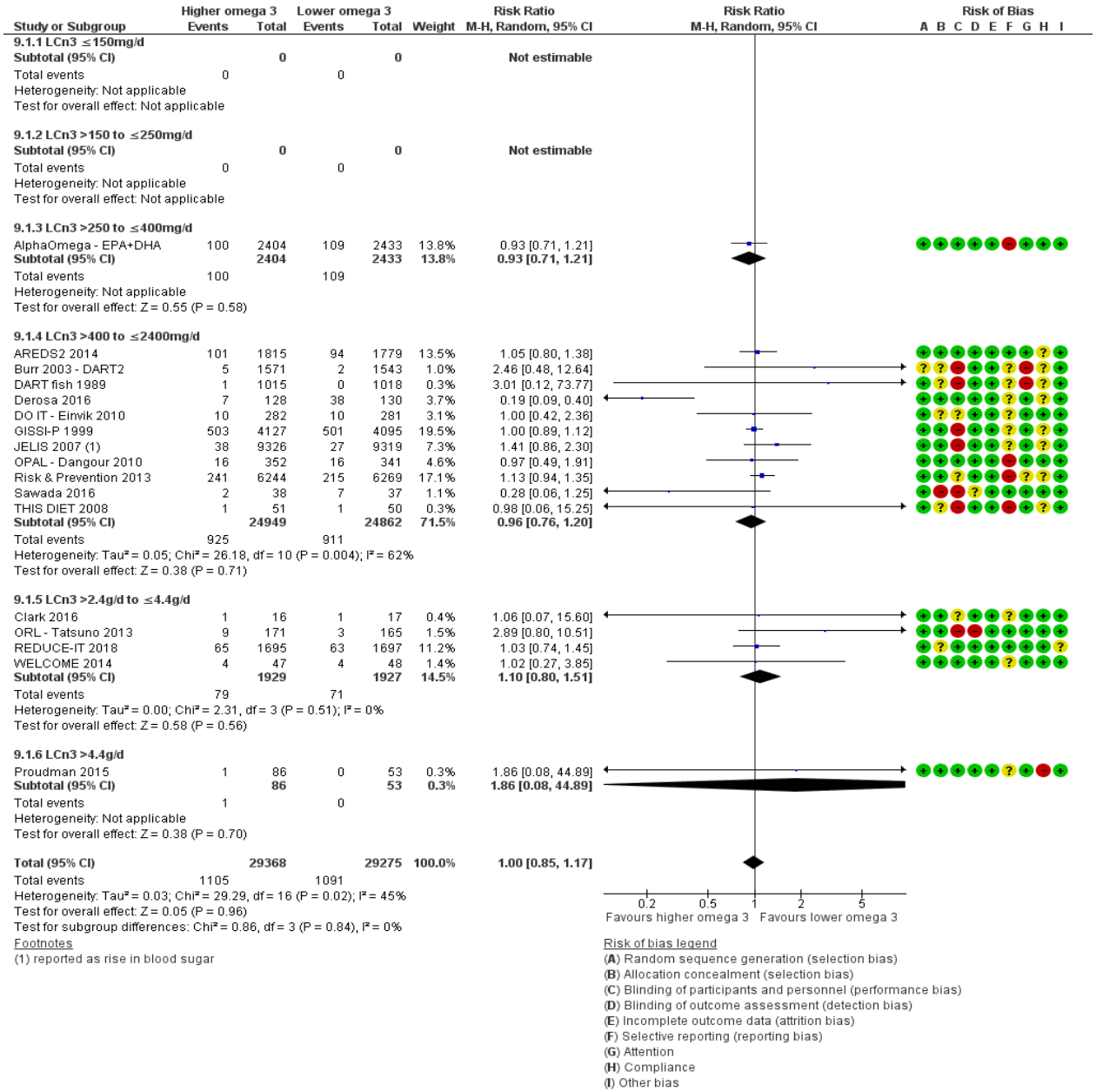
Supplementary Figure D. Funnel plot of effects of LCn3 on type 2 diabetes diagnosis. Several small trials with results suggesting that increased LCn3 is associated with reduced risk of diabetes diagnosis may be missing. Adding these trials back in would tend to reduce the RR a small amount.



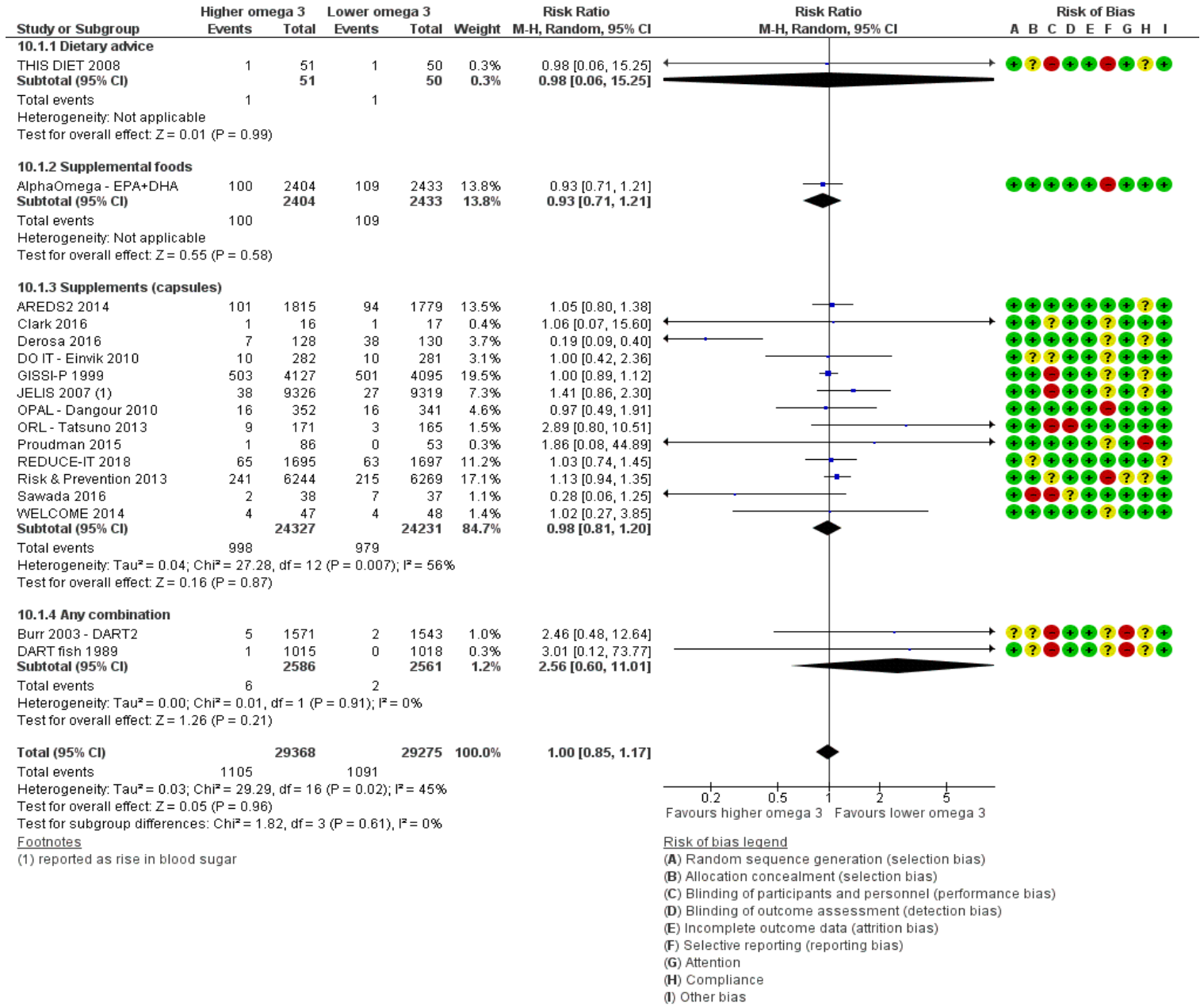
Supplementary Figure E. Meta-analysis of effects of LCn3 on type 2 diabetes diagnosis. Subgroup analysis assessing effects by baseline diabetes risk



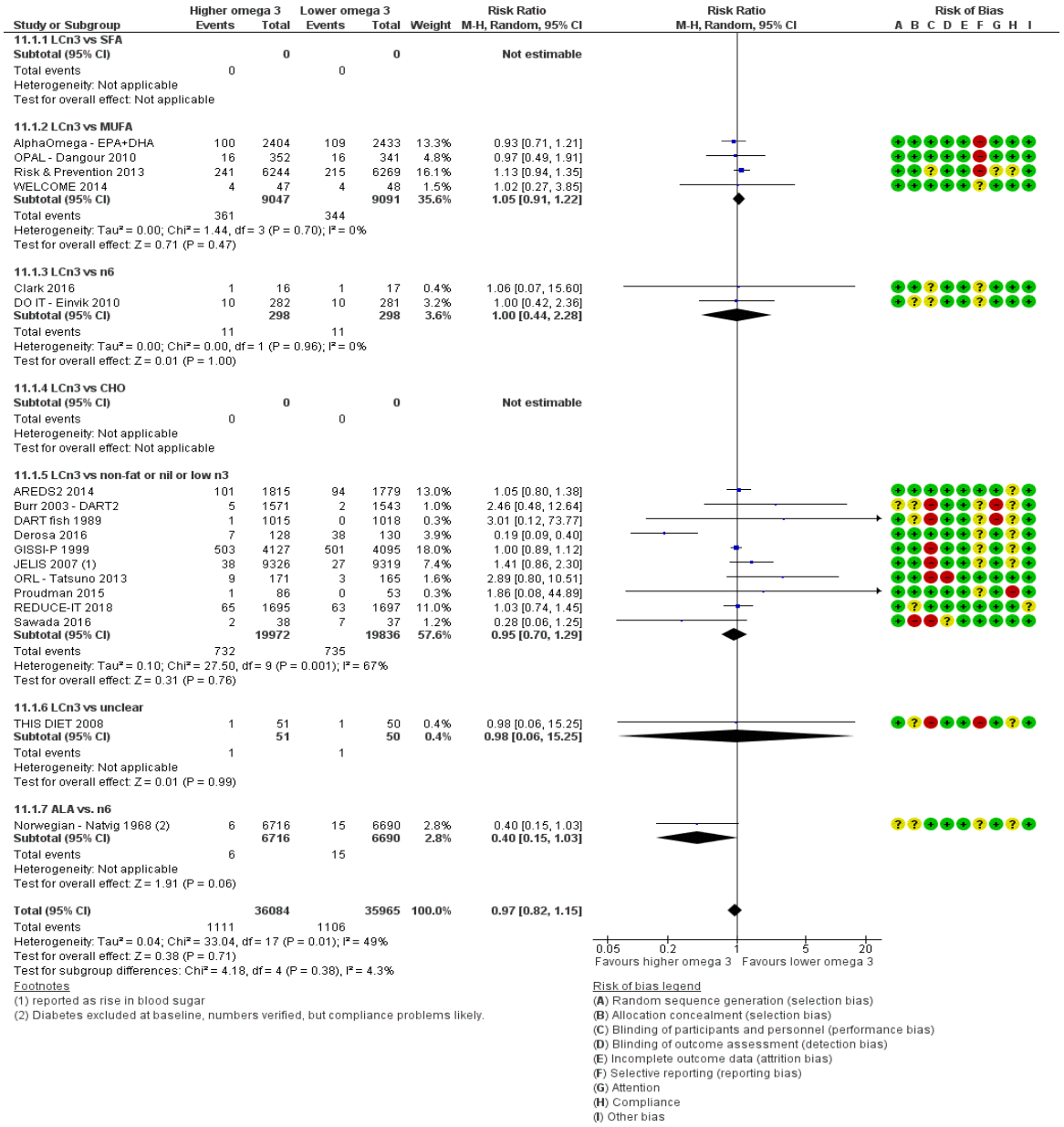
Supplementary Figure F. Meta-analysis of effects of LCn3 on risk of type 2 diabetes diagnosis, subgrouping by trial duration.



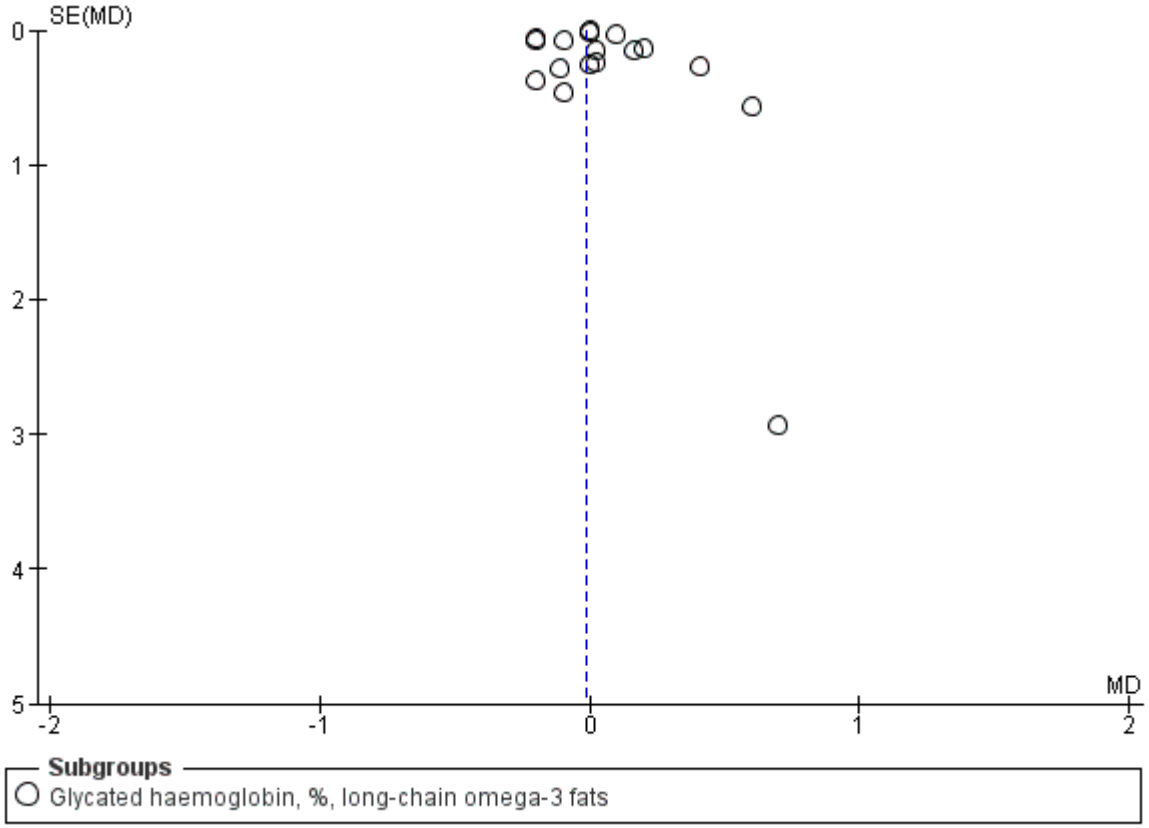
Supplementary Figure G. Meta-analysis of effects of LCn3 on risk of type 2 diabetes diagnosis, subgrouping by LCn3 dose.



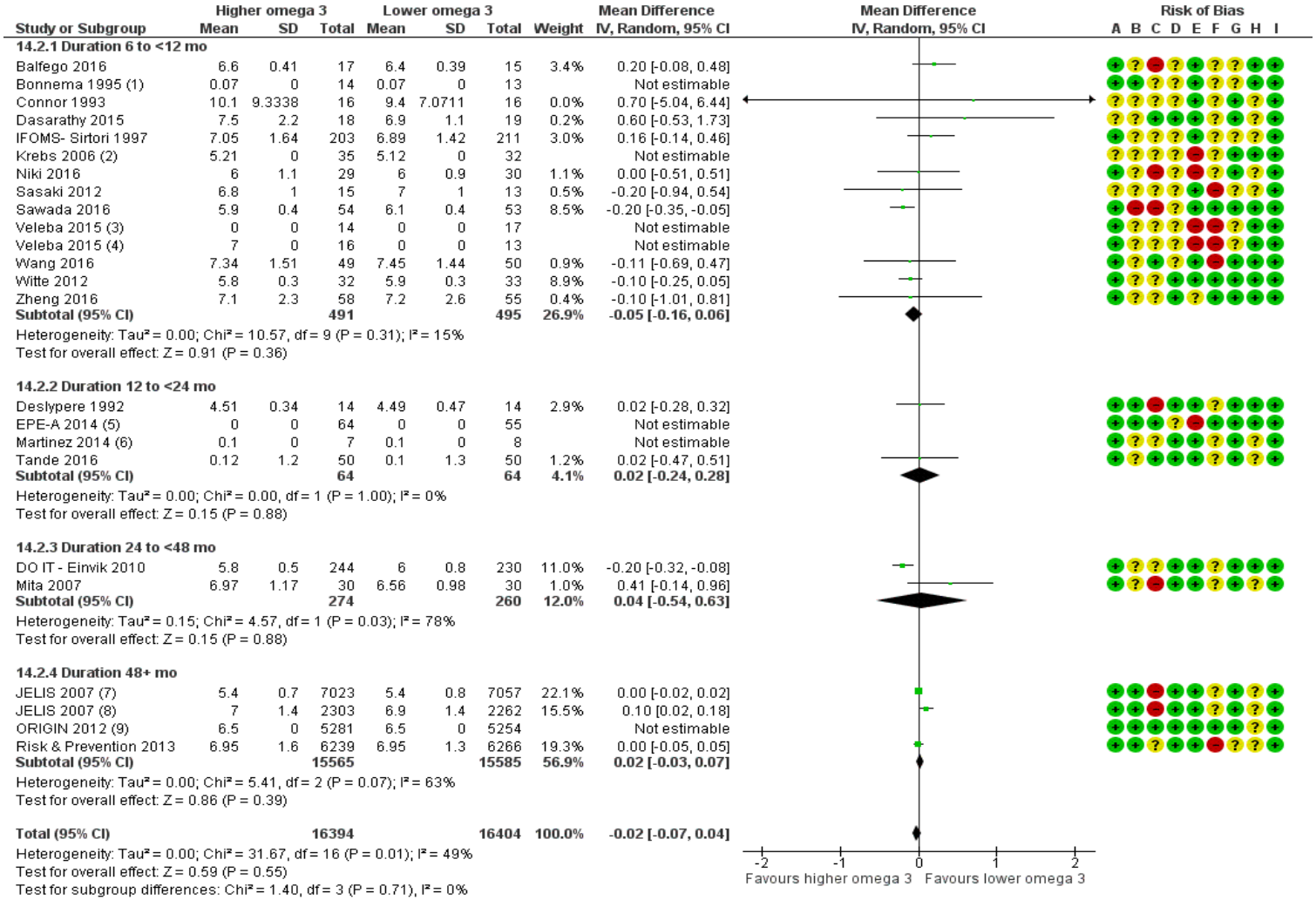
Supplementary Figure H. Meta-analysis of effects of LCn3 on risk of type 2 diabetes diagnosis, subgrouping by type of intervention.



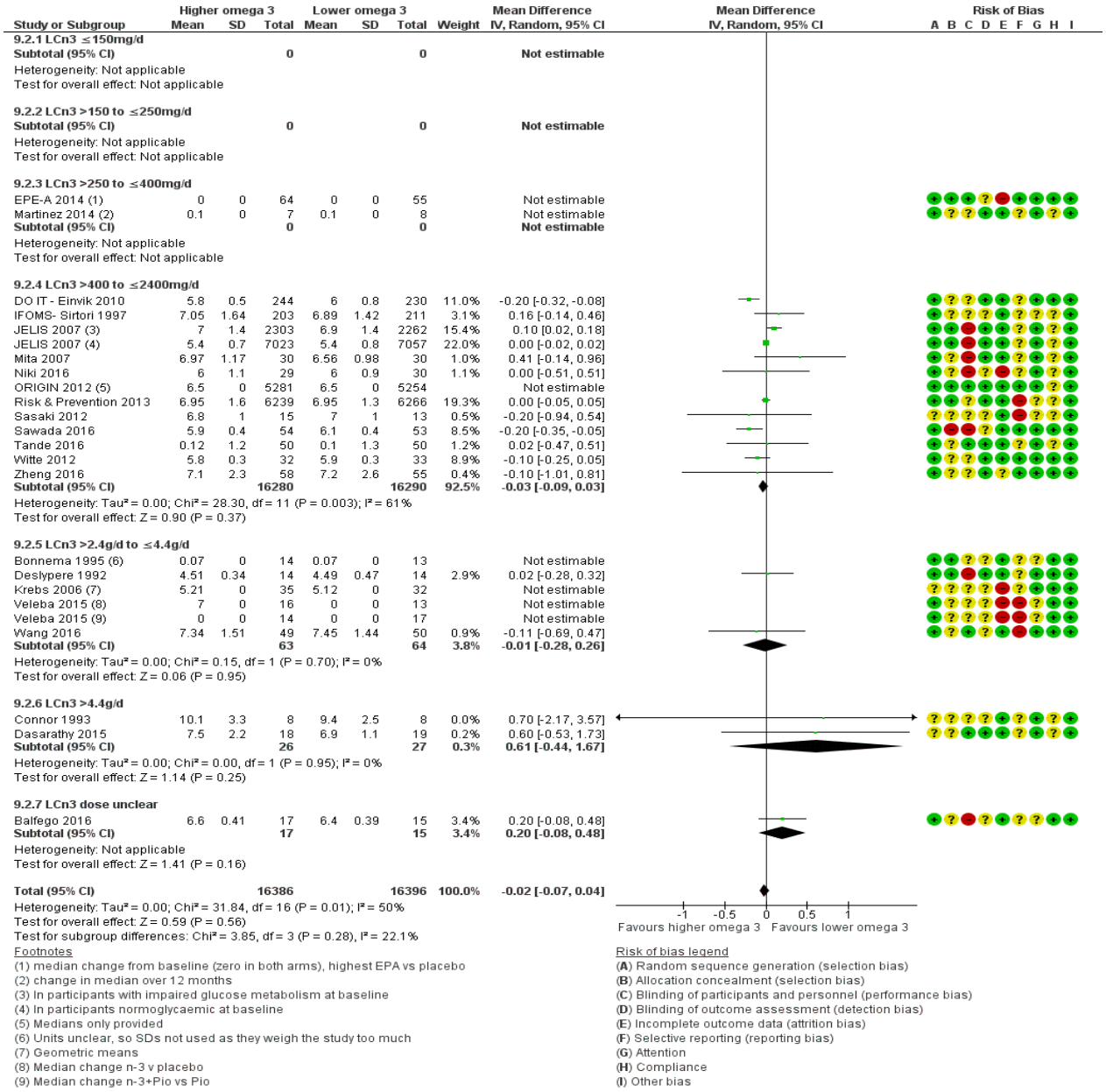
Supplementary Figure I. Meta-analysis of effects of LCn3 on risk of type 2 diabetes diagnosis, subgrouping by macronutrient replaced by LCn3.



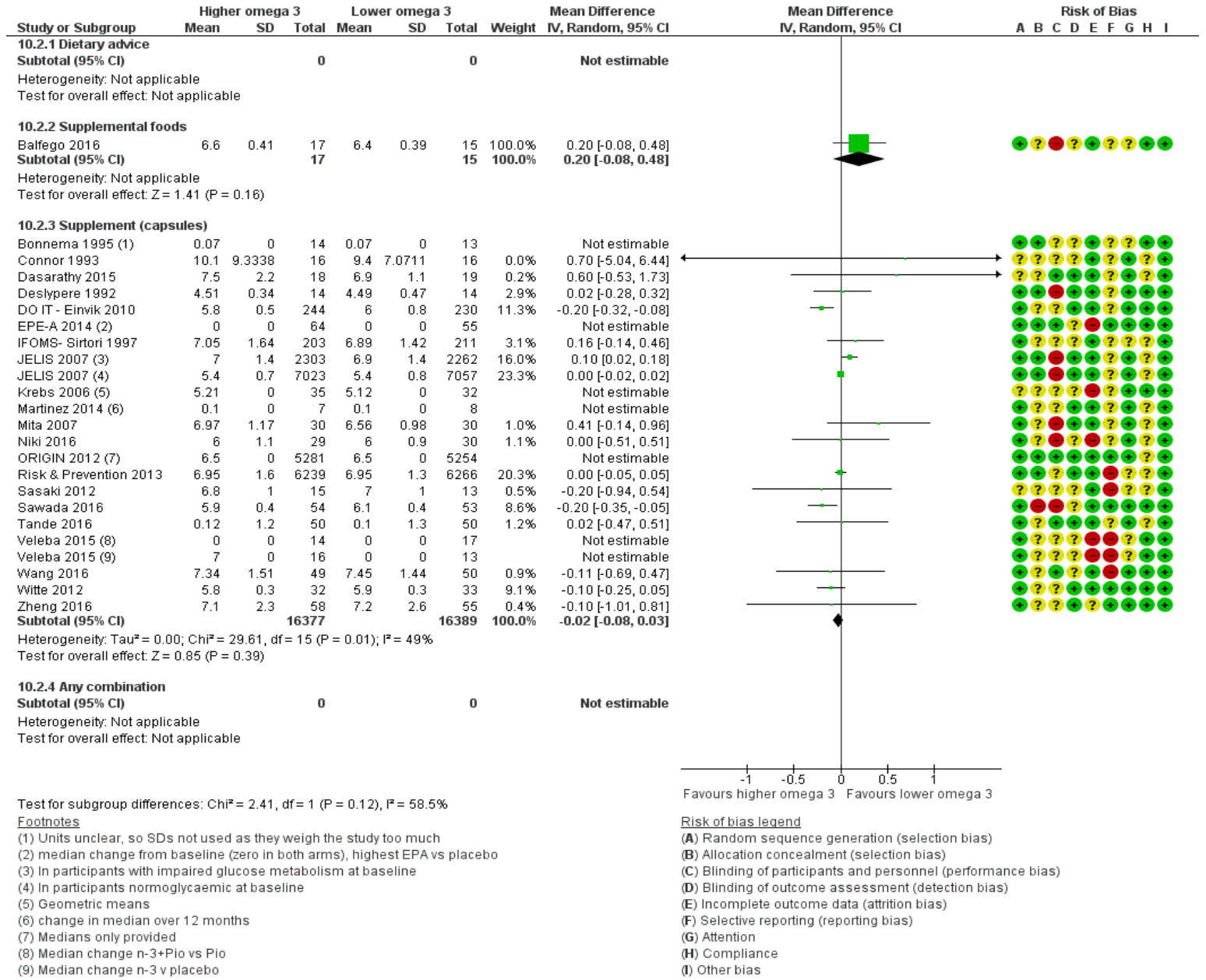
Supplementary Figure J. Funnel plot of effects of LCn3 on HbA1c. This is difficult to interpret, but does not clearly suggest publication bias.



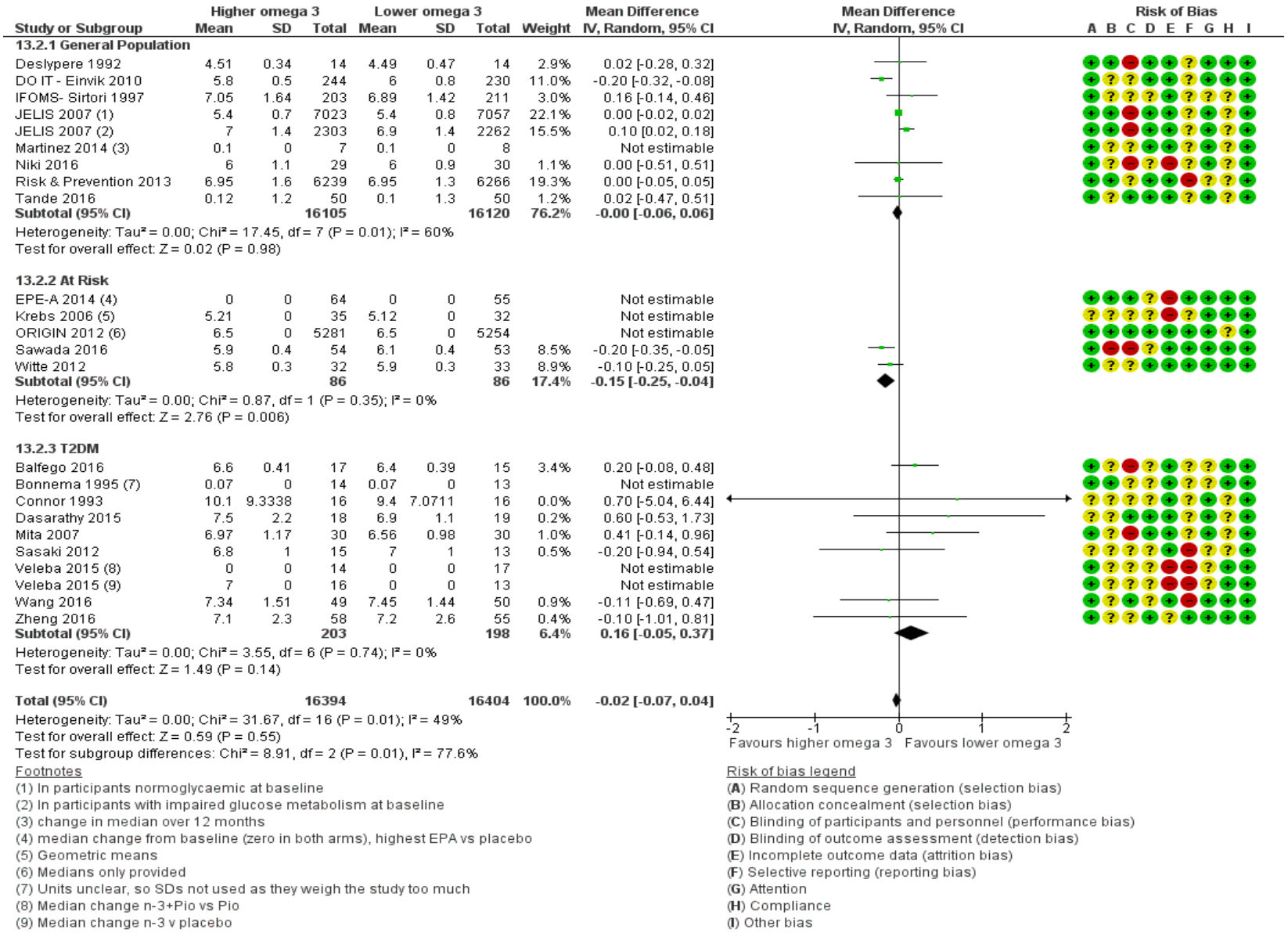
Supplementary Figure K. Meta-analysis of effects of LCn3 on HbA1c, %, subgrouping by trial duration.



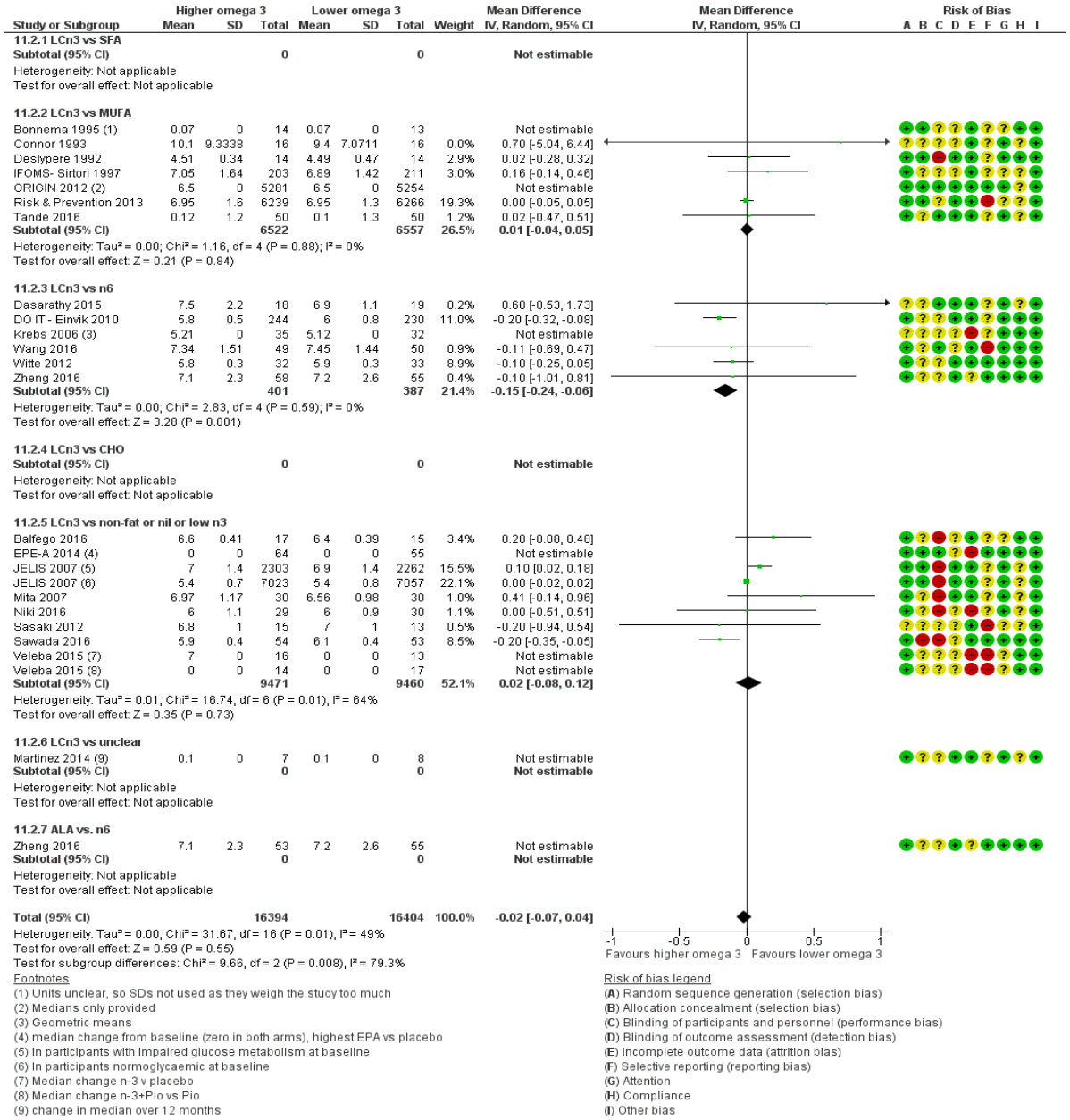
Supplementary Figure L. Meta-analysis of effects of LCn3 on HbA1c, %, subgrouping by LCn3 dose.



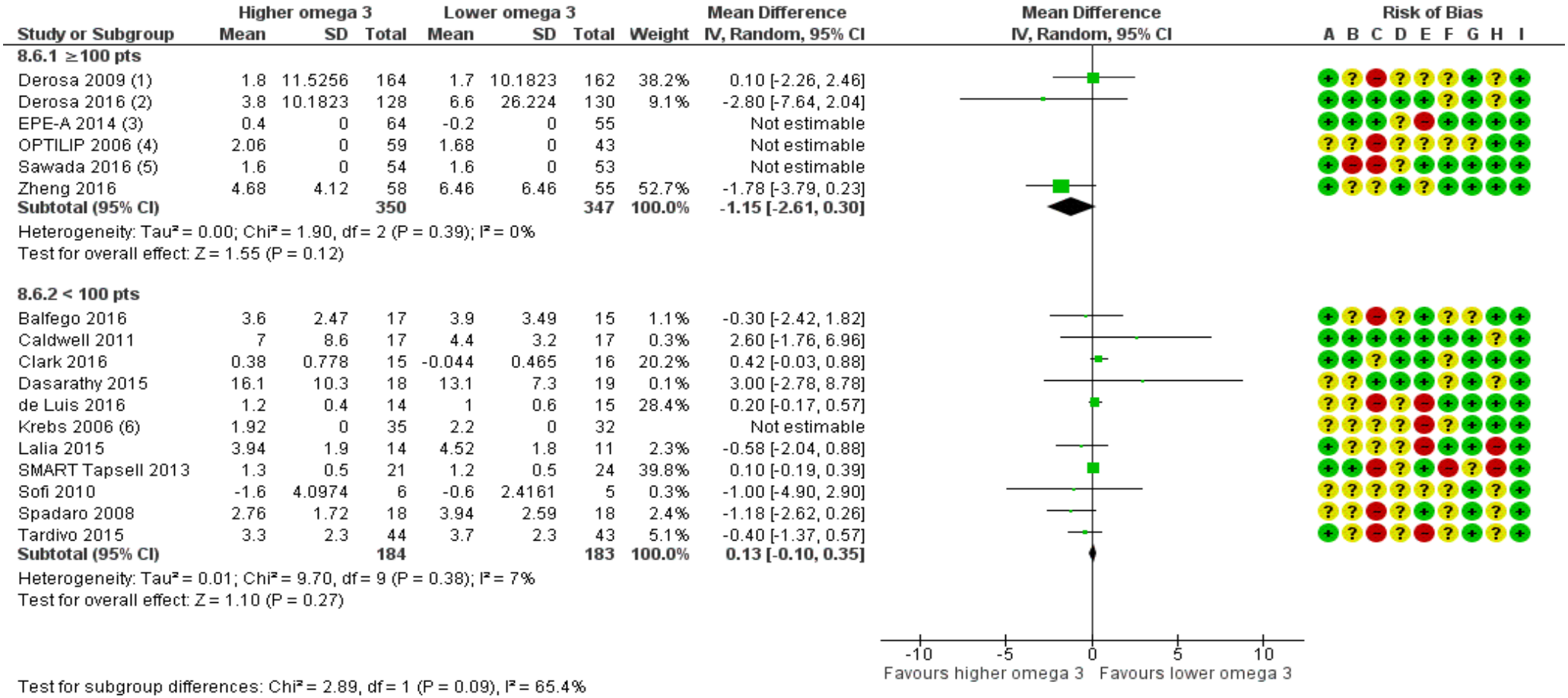
Supplementary Figure M. Meta-analysis of effects of LCn3 on HbA1c, %, subgrouping by intervention type.



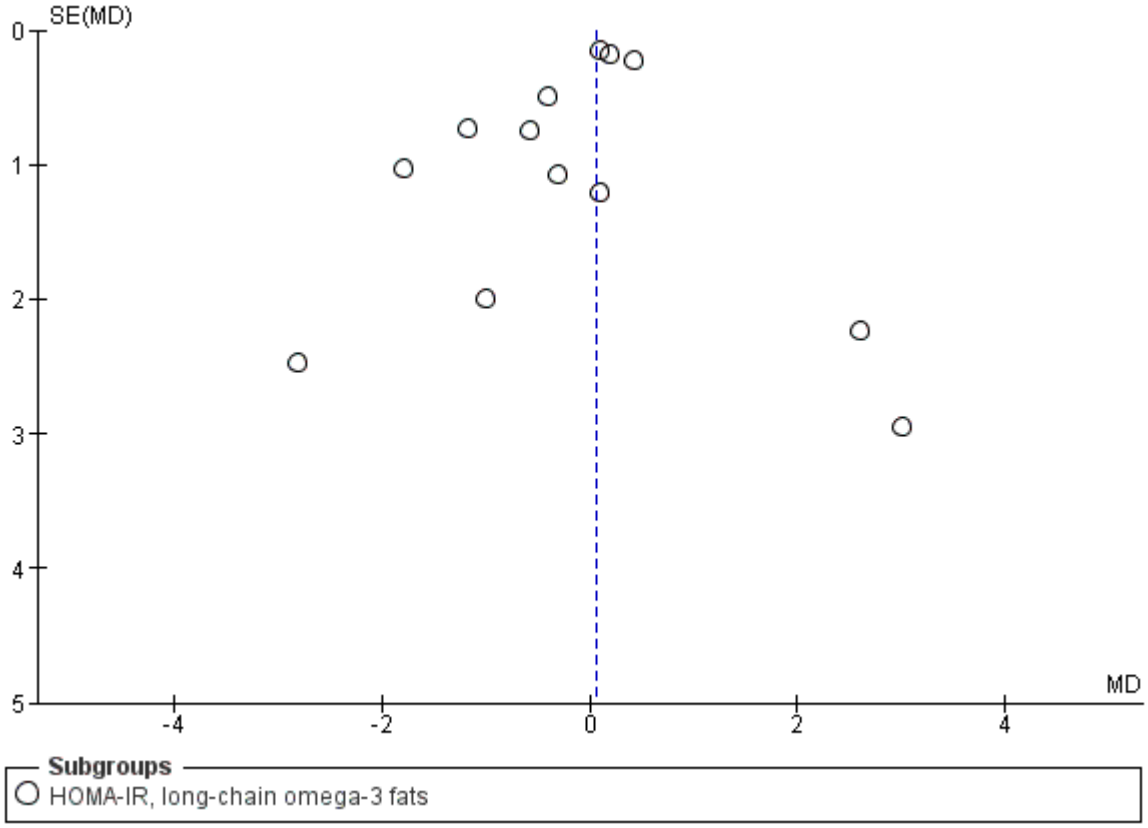
Supplementary Figure N. Meta-analysis of effects of LCn3 on HbA1c, %, subgrouping by baseline risk of diabetes.



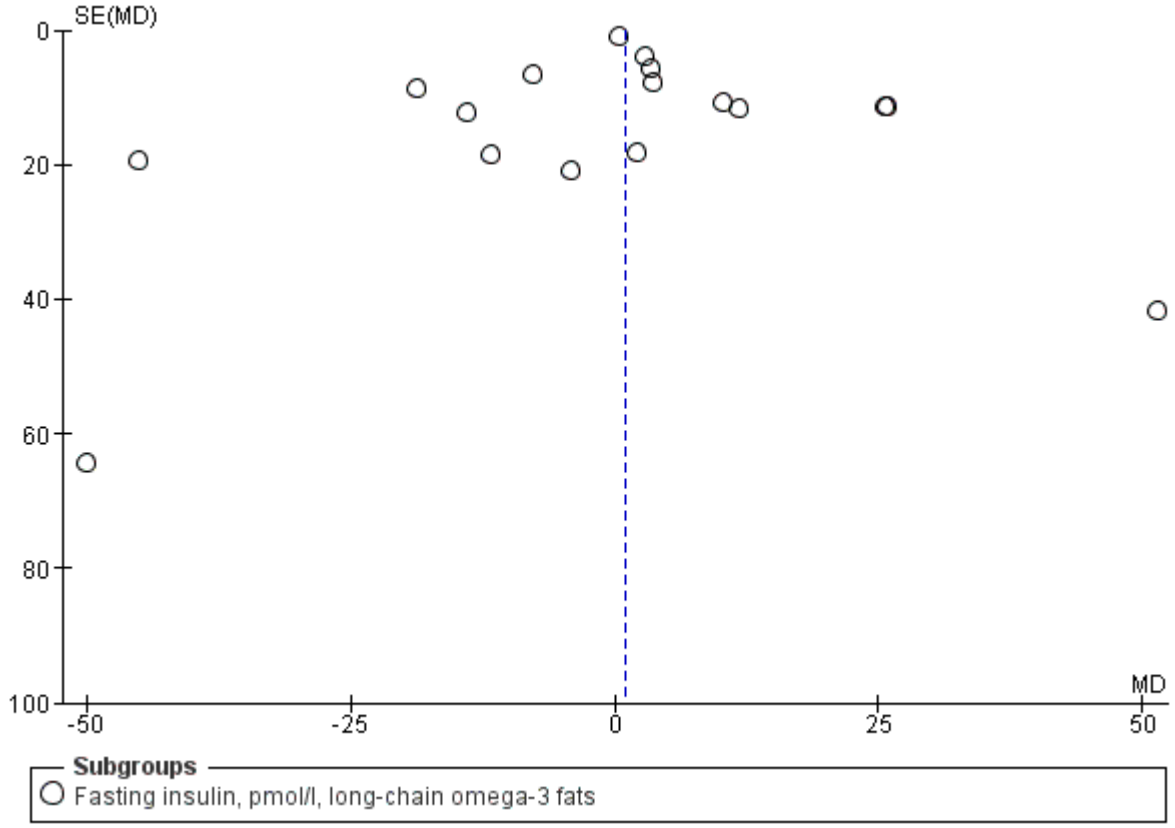
Supplementary Figure O. Meta-analysis of effects of LCn3 on HbA1c, %, subgrouping by intervention type.



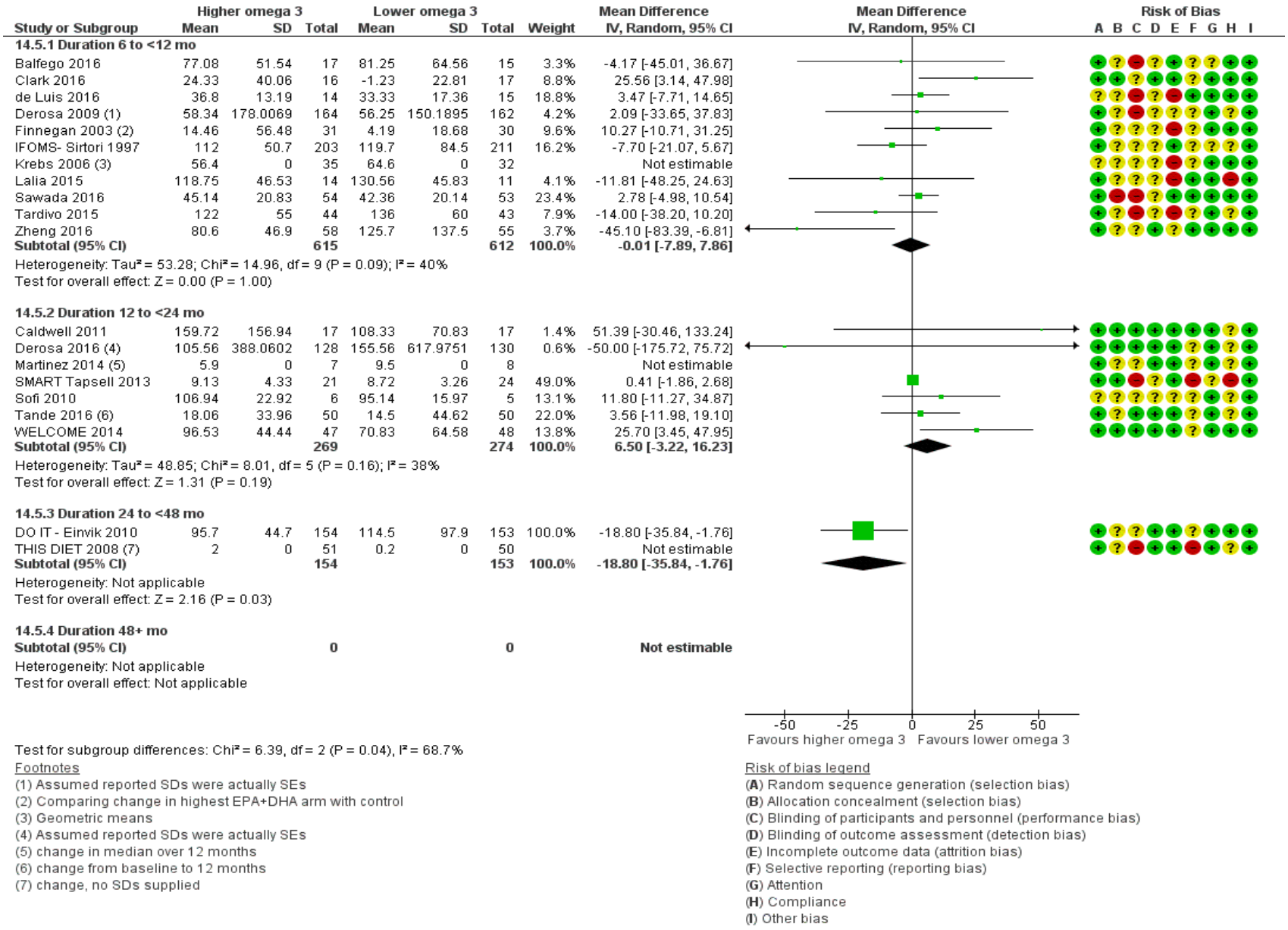
Supplementary Figure P. Meta-analysis of effects of LCn3 on HOMA-IR, sensitivity analysis by study size (≥100 participants randomised)



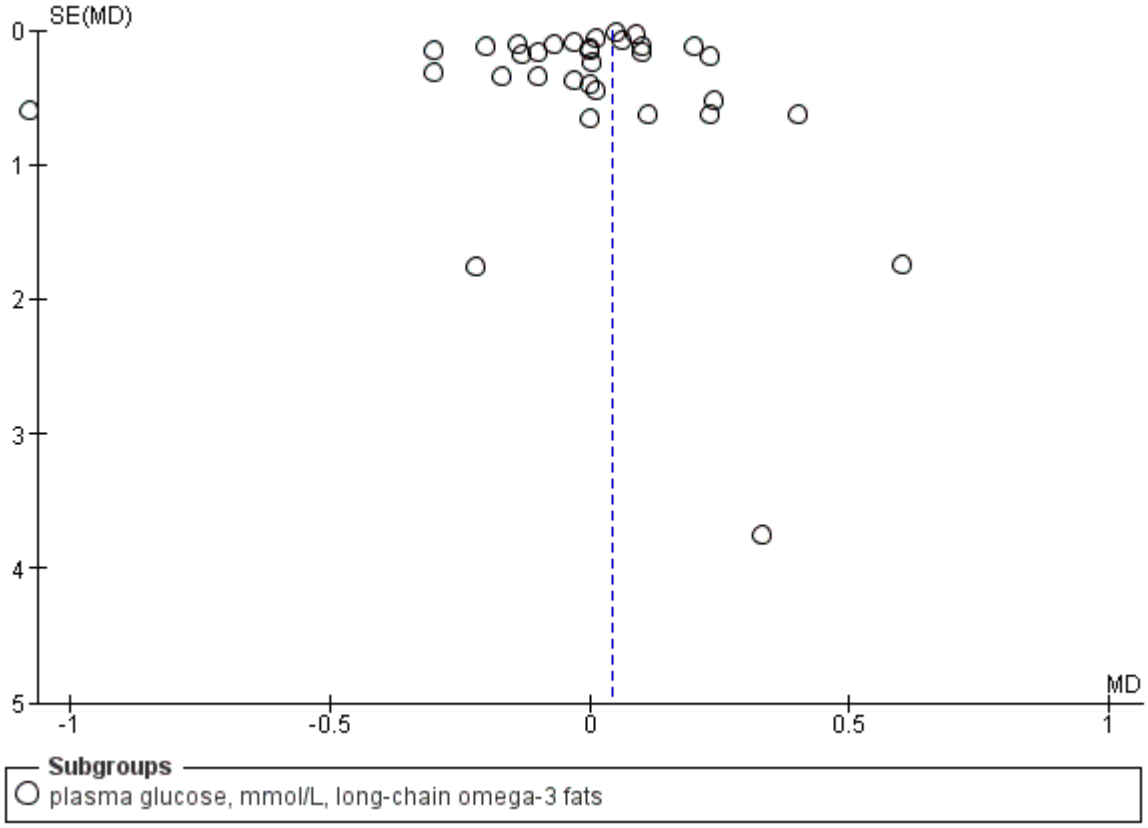
Supplementary Figure Q. Funnel plot of effects of LCn3 on HOMA-IR, suggesting that some trials where raising LCn3 increased HOMA-IR may be missing. Adding these trials in would tend to increase the mean difference.



Supplementary Figure R. Funnel plot of effects of LCn3 on fasting serum insulin, difficult to interpret but suggesting little publication bias.



Supplementary Figure S. Meta-analysis of effects of LCn3 on fasting serum insulin, subgrouping by trial duration. While there are statistically significant differences between subgroups there is no trend (effects neither strengthen nor weaken as trials lengthen).



Supplementary Figure T. Funnel plot of effects of LCn3 on fasting glucose, difficult to interpret but suggesting little publication bias.

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