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[Intervention Review]

Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease

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ABSTRACT

Background

Omega-3 polyunsaturated fatty acids from oily fish (long-chain omega-3 (LCn3)), including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)), as well as from plants (alpha-linolenic acid (ALA)) may benefit cardiovascular health. Guidelines recommend increasing omega-3-rich foods, and sometimes supplementation, but recent trials have not confirmed this.

Objectives

To assess the effects of increased intake of fish- and plant-based omega-3 fats for all-cause mortality, cardiovascular events, adiposity and lipids.

Search methods

We searched CENTRAL, MEDLINE and Embase to February 2019, plus ClinicalTrials.gov and World Health Organization International Clinical Trials Registry to August 2019, with no language restrictions. We handsearched systematic review references and bibliographies and contacted trial authors.

Selection criteria

We included randomised controlled trials (RCTs) that lasted at least 12 months and compared supplementation or advice to increase LCn3 or ALA intake, or both, versus usual or lower intake.

Data collection and analysis

Two review authors independently assessed trials for inclusion, extracted data and assessed validity. We performed separate random-effects meta-analysis for ALA and LCn3 interventions, and assessed dose-response relationships through meta-regression.

Main results

We included 86 RCTs (162,796 participants) in this review update and found that 28 were at low summary risk of bias. Trials were of 12 to 88 months' duration and included adults at varying cardiovascular risk, mainly in high-income countries. Most trials assessed LCn3

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supplementation with capsules, but some used LCn3- or ALA-rich or enriched foods or dietary advice compared to placebo or usual diet. LCn3 doses ranged from 0.5 g a day to more than 5 g a day (19 RCTs gave at least 3 g LCn3 daily).

Meta-analysis and sensitivity analyses suggested **little or no effect of increasing LCn3** on **all-cause mortality** (risk ratio (RR) 0.97, 95% confidence interval (CI) 0.93 to 1.01; 143,693 participants; 11,297 deaths in 45 RCTs; high-certainty evidence), **cardiovascular mortality** (RR 0.92, 95% CI 0.86 to 0.99; 117,837 participants; 5658 deaths in 29 RCTs; moderate-certainty evidence), **cardiovascular events** (RR 0.96, 95% CI 0.92 to 1.01; 140,482 participants; 17,619 people experienced events in 43 RCTs; high-certainty evidence), **stroke** (RR 1.02, 95% CI 0.94 to 1.12; 138,888 participants; 2850 strokes in 31 RCTs; moderate-certainty evidence) or **arrhythmia** (RR 0.99, 95% CI 0.92 to 1.06; 77,990 participants; 4586 people experienced arrhythmia in 30 RCTs; low-certainty evidence). Increasing LCn3 may **slightly reduce coronary heart disease mortality (number needed to treat for an additional beneficial outcome (NNTB) 334**, RR 0.90, 95% CI 0.81 to 1.00; 127,378 participants; 3598 coronary heart disease deaths in 24 RCTs, low-certainty evidence) and **coronary heart disease events** (**NNTB 167**, RR 0.91, 95% CI 0.85 to 0.97; 134,116 participants; 8791 people experienced coronary heart disease events in 32 RCTs, low-certainty evidence). Overall, effects did not differ by trial duration or LCn3 dose in pre-planned subgrouping or meta-regression. There is little evidence of effects of eating fish.

Increasing ALA intake probably makes **little or no difference to all-cause mortality** (RR 1.01, 95% CI 0.84 to 1.20; 19,327 participants; 459 deaths in 5 RCTs, moderate-certainty evidence),**cardiovascular mortality** (RR 0.96, 95% CI 0.74 to 1.25; 18,619 participants; 219 cardiovascular deaths in 4 RCTs; moderate-certainty evidence), **coronary heart disease mortality** (RR 0.95, 95% CI 0.72 to 1.26; 18,353 participants; 193 coronary heart disease deaths in 3 RCTs; moderate-certainty evidence) and **coronary heart disease events** (RR 1.00, 95% CI 0.82 to 1.22; 19,061 participants; 397 coronary heart disease events in 4 RCTs; low-certainty evidence). However, increased ALA may slightly **reduce risk of cardiovascular disease events** (**NNTB 500**, RR 0.95, 95% CI 0.83 to 1.07; but RR 0.91, 95% CI 0.79 to 1.04 in RCTs at low summary risk of bias; 19,327 participants; 884 cardiovascular disease events in 5 RCTs; low-certainty evidence), and probably slightly reduces risk of **arrhythmia** (**NNTB 91**, RR 0.73, 95% CI 0.55 to 0.97; 4912 participants; 173 events in 2 RCTs; moderate-certainty evidence). Effects on **stroke are unclear**.

Increasing LCn3 and ALA had little or no effect on serious adverse events, adiposity, lipids and blood pressure, except increasing LCn3 reduced triglycerides by ~15% in a dose-dependent way (high-certainty evidence).

Authors' conclusions

This is the most extensive systematic assessment of effects of omega-3 fats on cardiovascular health to date. Moderate- and low-certainty evidence suggests that increasing LCn3 slightly reduces risk of coronary heart disease mortality and events, and reduces serum triglycerides (evidence mainly from supplement trials). Increasing ALA slightly reduces risk of cardiovascular events and arrhythmia.

PLAIN LANGUAGE SUMMARY

Omega-3 intake for cardiovascular disease

Review question

We reviewed randomised trials (where participants have an equal chance of being assigned to either treatment) examining effects of increasing fish- and plant-based omega-3 fats on heart and circulatory disease (called cardiovascular diseases, which include heart attacks and stroke), fatness and blood fats (lipids, including cholesterol, triglycerides, high-density lipoprotein (HDL – 'good' cholesterol) and low-density lipoprotein (LDL – 'bad' cholesterol)).

Background

The main types of omega-3 fats are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), both found in fish, and alpha-linolenic acid (ALA) found in plant foods. Many people believe that taking omega-3 supplements reduces risk of heart disease, stroke and death.

Trial characteristics

The evidence is current to February 2019. The review included 86 trials involving 162,796 people. These trials assessed effects of greater omega-3 intake versus lower omega-3 intake for at least a year on heart and circulatory disease. Twenty-eight trials were very trustworthy (well-designed so as not to give biased results). Participants were adults, some with existing illness and some healthy, living in North America, Europe, Australia and Asia. Most EPA and DHA trials provided capsules, few gave oily fish.

Key results

Increasing EPA and DHA has little or no effect on deaths and cardiovascular events (high-certainty evidence) and probably makes little or no difference to cardiovascular death, stroke, or heart irregularities (moderate-certainty evidence). However, increasing EPA and DHA may slightly reduce risk of coronary death and coronary events (low-certainty evidence, coronary events are illnesses of arteries supplying the heart). To prevent one person having a coronary event, 167 people would need to increase their EPA and DHA, and 334 people would need to increase their EPA and DHA to prevent one person dying from coronary disease. EPA and DHA reduce triglycerides by about 15% but do not affect fatness or other lipids (high-certainty evidence).

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Eating more ALA (for example, by increasing walnuts or enriched margarine) probably makes little or no difference to all-cause, cardiovascular or coronary deaths or coronary events but probably slightly reduces cardiovascular events and heart irregularities (moderate- or low-certainty evidence). To prevent one person having a coronary event, 500 people would need to increase their ALA, 91 people to prevent one person having arrhythmia.

There is little evidence of effects of eating fish. EPA and DHA reduce triglycerides. EPA, DHA and ALA may be slightly protective of some heart and circulatory diseases.

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Summary of findings for the main comparison. High versus low long-chain omega-3 fats for preventing cardiovascular disease and mortality (primary outcomes)

High versus low long-chain omega-3 fats for preventing cardiovascular disease and mortality (primary outcomes)

Patient or population: adults with or without existing CVD
Setting: participants were living at home for most or all of the duration of their trials. Most trials were carried out in high-income economies (World Bank 2018), but four were carried out in upper-middle-income countries (Argentina, Iran, Turkey and China). No trials took place wholly in low- or low-middle income countries.
Intervention: higher intake of LCn3 fats
Comparison: lower intake of LCn3 fats

The intervention was dietary supplementation, a provided diet or advice on diet. Supplementation may have been in oil or capsule form or as foodstuffs provided, to be consumed by mouth (excluding enteral and parenteral feeds and enemas). The foodstuffs or supplements must have been oily fish or fish oils as a food, oil, made into a spreading fat, or supplementing another food (such as bread or eggs). Refined eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) or concentrated fish or algal oils, were also accepted.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with lower LCn3	Risk with higher LCn3				
All-cause mortality – deaths Assessed with number of participants dying of any cause, whether reported as an outcome or a reason for dropout Duration: range 12-88 months	80 per 1000	78 per 1000 (74 to 81)	RR 0.97 (0.93 to 1.01)	143,693 (45 RCTs)	⊕⊕⊕⊕ High[a]	LCn3 fat intake makes little or no difference to risk of all-cause mortality
Cardiovascular mortality – cardiovascular deaths Assessed with deaths from any cardiovascular cause. Where this was not available, we used cardiac death instead where known Duration: range 12-88 months	50 per 1000	46 per 1000 (43 to 49)	RR 0.92 (0.86 to 0.99)	117,837 (29 RCTs)	⊕⊕⊕⊖ Moderate[b]	LCn3 fat intake probably makes little or no difference to risk of cardiovascular death
Cardiovascular events Assessed with number of participants experiencing any cardiovascular event	128 per 1000	123 per 1000 (118 to 129)	RR 0.96 (0.92 to 1.01)	140,482 (43 RCTs)	⊕⊕⊕⊕ High[c]	LCn3 fat intake makes little or no difference to risk of cardiovascular events

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Duration: range 12-88 months						
Coronary heart disease mortality – CHD deaths Assessed with coronary deaths, or where these were not reported, IHD death, fatal MI or cardiac death (in that order) Duration: range 12-88 months	29 per 1000	26 per 1000 (24 to 29)	RR 0.90 (0.81 to 1.00)	127,378 (24 RCTs)	⊕⊕⊖⊖ Low[d]	Increasing LCn3 fat intake may slightly reduce CHD mortality (**NNTB 334**, 95% CI 200 to infinity; NNTB 1000 for primary prevention; NNTB 200 for secondary prevention)
Coronary heart disease events – CHD events Assessed with number of participants experiencing the first outcome in this list reported for each trial: CHD or coronary events; total MI; acute coronary syndrome; or angina (stable and unstable) Duration: range 12-88 months	68 per 1000	62 per 1000 (58 to 66)	RR 0.91 (0.85 to 0.97)	134,116 (32 RCTs)	⊕⊕⊖⊖ Low[e]	Increasing LCn3 fat intake may slightly reduce the risk of CHD events (**NNTB 167**, 95% CI 100 to 500; NNTB 200 for primary prevention; NNTB 143 for secondary prevention)
Stroke Assessed with number of participants experiencing at least 1 fatal or non-fatal, ischaemic or haemorrhagic stroke Duration: range 12-88 months	20 per 1000	21 per 1000 (19 to 23)	RR 1.02 (0.94 to 1.12)	138,888 (31 RCTs)	⊕⊕⊕⊖ Moderate[f]	LCn3 fat intake probably makes little or no difference to risk of experiencing a stroke
Arrhythmias Assessed with number of participants experiencing fatal or nonfatal, new or recurrent arrhythmia, including atrial fibrillation, ventricular tachycardia and ventricular fibrillation Duration: range 12-88 months	57 per 1000	56 per 1000 (52 to 60)	RR 0.99 (0.92 to 1.06)	77,990 (30 RCTs)	⊕⊕⊖⊖ Low[g]	Increasing LCn3 fat intake may make little or no difference to risk of arrhythmia
Harms: bleeding Assessed with number of participants experiencing bleeding events Duration: range 12-72 months	16 per 1000	**18 per** 1000 (14 to 22)	**RR 1.12** (0.91 to 1.37)	80,147 (11 RCTs)	⊕⊖⊖⊖ Very low[h]	The effect of LCn3 fat intake on bleeding is unclear as the evidence is of very low certainty
Harms: pulmonary embolus or DVT	5 per 1000	**6 per** 1000 (2 to 14)	**RR 1.15** (0.44 to 2.98)	3546 (5 RCTs)	⊕⊖⊖⊖ Very low[i]	The effect of LCn3 fat intake on pulmonary embolus or

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	Assessed with number of participants experiencing pulmonary embolus or DVT Duration: range 18-36 months			DVT is unclear as the evidence is of very low certainty

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CHD: coronary heart disease; **CI**: confidence interval; **CVD:** cardiovascular disease; **DHA:** docosahexaenoic acid; **DVT**: deep vein thrombosis; **EPA:** eicosapentaenoic acid; **IHD**: ischaemic heart disease; **LCn3:** long-chain omega-3; **MI**: myocardial infarction; **RCT**: randomised controlled trial; **RR**: risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]**All-cause mortality, long-chain omega-3 (LCn3)**

- **Risk of bias**: effect size moved closer to no effect (risk ratio (RR) 1.0) when analysis was limited to trials at low summary risk of bias and low risk of compliance bias (adding weight to the suggestion of little or no effect) but did not alter with fixed-effect meta-analysis or results in the analysis limited to larger trials. It was further noted by the World Health Organization Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health that although many of the trials had issues with blinding, the tendency for lack of blinding is an overestimation of effect. This is less of a concern for this outcome, as the pooled effect was approaching null and not statistically significant. Not downgraded.
- **Inconsistency**: I^2 statistic was less than 60% and I^2 reduced when analysis was limited to trials at low summary risk of bias. This adds weight to the suggestion of little or no effect. Not downgraded.
- **Indirectness**: representative, generalisable adult population including men and women, including healthy participants and participants with cardiovascular disease (CVD) risk factors or previous CVD as well as non-CVD health problems. Low- and middle-income countries were represented but underrepresented. Not downgraded.
- **Imprecision**: tight confidence intervals, very large numbers of participants took part in long-term randomised controlled trials (RCTs) with consistent results. Given the lack of a statistically significant effect in this very large set of participants, any effect appears too small to be individually relevant. Not downgraded.
- **Publication bias**: the funnel plot suggested that some small trials with higher numbers of events in the intervention group might be missing. If such missing trials were added back in, the RR would rise. This adds weight to the suggestion of little or no effect. Not downgraded.

[b]**Cardiovascular mortality, LCn3**

- **Risk of bias**: effect size moved closer to no effect (RR 1.0) when analysis was limited to trials at low summary risk of bias and with fixed-effect analysis (adding weight to the suggestion of little or no effect) but did not alter when the analyses were limited to trials at low risk of compliance bias or larger trials. It was further noted by the WHO NUGAG Subgroup on Diet and Health that although many of the RCTs had issues with blinding, the tendency for lack of blinding is an overestimation of effect. This is less of a concern for this outcome, as the pooled effect was approaching null. Not downgraded.
- **Inconsistency**: I^2 statistic was less than 60% and I^2 reduced when analysis was limited to trials at low summary risk of bias. This adds weight to the suggestion of little or no effect. Not downgraded.
- **Indirectness**: representative, generalisable adult population including men and women, including healthy participants and participants with CVD risk factors or previous CVD as well as non-CVD health problems. All trials were conducted in high-income countries. Not downgraded.
- **Imprecision**: 95% confidence intervals do not exclude important benefits. Downgraded once.
- **Publication bias**: the funnel plot suggested that some small trials with higher numbers of events in the intervention group might be missing. If such missing trials were added back in, the RR would rise. This adds weight to the suggestion of little or no effect. Not downgraded.

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[c]**Cardiovascular events, LCn3**

- **Risk of bias**: effect size moved closer to no effect (RR 1.0) when analysis was limited to trials at low summary risk of bias (adding weight to the suggestion of little or no effect) but did not alter with fixed-effect meta-analysis or results in the analysis limited to larger trials. It was further noted by the WHO NUGAG Subgroup on Diet and Health that although many of the RCTs had issues with blinding, the tendency for lack of blinding is an overestimation of effect. This is less of a concern for this outcome, as the pooled effect was approaching null and not statistically significant. Not downgraded.
- **Inconsistency**: I^2 statistic was less than 60% and I^2 reduced when analysis was limited to trials at low summary risk of bias. This adds weight to the suggestion of little or no effect. Not downgraded.
- **Indirectness**: representative, generalisable adult population including men and women, including healthy participants and participants with CVD risk factors or previous CVD as well as non-CVD health problems. Low- and middle-income countries were represented but underrepresented. Not downgraded.
- **Imprecision**: very large numbers of participants took part in long-term RCTs with consistent results. Given the lack of an important effect in this very large set of participants, any effect appears too small to be individually relevant. The 95% confidence intervals excluded important benefits or harms. Not downgraded.
- **Publication bias**: the funnel plot suggested that some small trials with higher numbers of events in the intervention group might be missing. If such missing trials were added back in, the RR would rise. This adds weight to the suggestion of little or no effect. Not downgraded.

[d]**Coronary heart disease mortality, LCn3**

- **Risk of bias**: effect size more than 8% was retained when analysis was limited to trials at low summary risk of bias, low risk of compliance bias and larger trials. Not downgraded.
- **Inconsistency**: I^2 statistic was less than 60%. Not downgraded.
- **Indirectness**: representative, generalisable adult population including men and women, including healthy participants and participants with CVD risk factors or previous CVD as well as non-CVD health problems. All trials were conducted in high-income countries. Not downgraded.
- **Imprecision**: large numbers of participants took part in long-term RCTs with consistent results. As 95% confidence intervals did not exclude lack of effect we downgraded once.
- **Publication bias**: the funnel plot suggested that some small trials with higher numbers of events in the intervention group might be missing. If such missing trials were added back in the RR would rise. This weakens the suggestion of an effect. Downgraded once.

[e]**Coronary heart disease events, LCn3**

- **Risk of bias**: effect size moved closer to no effect (RR 1.0) when analysis was limited to trials at low summary risk of bias, but increased when limiting trials to those at low risk of compliance problems and larger trials. There was a small protective effect in the main analysis and some sensitivity analyses, but not in sensitivity analyses limiting to RCTs at low summary risk of bias or using fixed-effect analysis. The suggestion of a dose response in meta-regression was lost when REDUCE-IT 2019 data were omitted. We summarised this as suggesting a true effect of around 8%. This is on the borderline of little or no effect and a more than 8% effect. Downgraded twice.
- **Inconsistency**: I^2 statistic was less than 60%. Not downgraded.
- **Indirectness**: representative, generalisable adult population including men and women, including healthy participants and participants with CVD risk factors or previous CVD as well as non-CVD health problems. Low- and middle-income countries were represented but underrepresented. Not downgraded.
- **Imprecision**: 95% confidence interval did not include the null. Not downgraded.
- **Publication bias**: no suggestion from the funnel plot of publication bias. Not downgraded.

[f]**Stroke, LCn3**

- **Risk of bias**: effect size consistently suggested little or no effect for all sensitivity analyses. It was further noted by the WHO NUGAG Subgroup on Diet and Health that although many of the RCTs had issues with blinding, the tendency for lack of blinding is an overestimation of effect. This is less of a concern for this outcome, as the pooled effect was approaching null and not statistically significant. Not downgraded.
- **Inconsistency**: I^2 statistic was less than 60%. Not downgraded.
- **Indirectness**: representative, generalisable adult population including men and women, including healthy participants and participants with CVD risk factors or previous CVD as well as non-CVD health problems. Low- and middle-income countries were represented but underrepresented. Not downgraded.
- **Imprecision**: very large numbers of participants took part in long-term RCTs with consistent results. Given the lack of a statistically significant effect in this very large set of participants any effect appears too small to be individually relevant. However, as 95% confidence intervals do not exclude important harms, we downgraded once.
- **Publication bias**: the funnel plot did not suggest any small trial bias. Not downgraded.

[g]**Arrhythmias, LCn3**

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- **Risk of bias**: effect size remained similar in most sensitivity analyses, but suggested harm when limited to trials at low summary risk of bias. Downgraded once.
- **Inconsistency**: I^2 statistic was less than 60%. Not downgraded.
- **Indirectness**: representative, generalisable adult population including men and women, including healthy participants and participants with CVD risk factors or previous CVD as well as non-CVD health problems. Low- and middle-income countries were represented but underrepresented. Not downgraded.
- **Imprecision**: As 95% confidence intervals of the sensitivity analysis excluding trials at higher risk of bias included both harm and no effect, and there was a statistically significant difference in effect size between trials at low summary risk of bias and other trials, we downgraded once.
- **Publication bias**: funnel plot not interpretable as trials all of a similar size and weight. Not downgraded.

[h]**Bleeding, LCn3**
- **Risk of bias**: effect size changed direction (from harmful to protective) when analysis limited to trials at low summary risk of bias. Downgraded once.
- **Inconsistency**: I^2 statistic was less than 60%. Not downgraded.
- **Indirectness**: representative, generalisable adult population including men and women, including healthy participants and participants with CVD risk factors or previous CVD as well as non-CVD health problems. Low- and middle-income countries not represented. Not downgraded.
- **Imprecision**: 95% confidence intervals do not exclude large and important benefits or harms. Downgraded twice.
- **Publication bias**: insufficient trials for funnel plot. Not downgraded.

[i]**Pulmonary embolus or DVD, LCn3**
- **Risk of bias**: effect size suggested greater harm when analysis limited to trials at low summary risk of bias. Downgraded once.
- **Inconsistency**: I^2 statistic was less than 60%. Not downgraded.
- **Indirectness**: representative, generalisable adult population including men and women, including healthy participants and participants with CVD risk factors or previous CVD as well as non-CVD health problems. Low- and middle-income countries not represented. Not downgraded.
- **Imprecision**: 95% confidence intervals do not exclude large benefits or large harms. Downgraded twice.
- **Publication bias**: insufficient trials for funnel plot. Not downgraded.

Summary of findings 2. High versus low alpha-linolenic acid omega-3 fats for preventing cardiovascular disease (primary outcomes)

High versus low alpha-linolenic omega-3 fats for preventing cardiovascular disease (primary outcomes)

Patient or population: adults with or without existing CVD

Setting: participants were living at home for most or all of the duration of their trials. Most trials were carried out in high-income economies (World Bank 2018), but four were carried out in upper-middle-income countries (Argentina, Iran, Turkey and China). No trials took place in low- or low- to middle-income countries.
Intervention: higher intake of ALA
Comparison: lower intake of ALA

The intervention was dietary supplementation, a provided diet or advice on diet. Supplementation may have been in oil or capsule form or as foodstuffs provided, to be consumed by mouth (excluding enteral and parenteral feeds and enemas). The foodstuffs or supplements must have been refined ALA: linseed (flax); canola (rapeseed); perilla; purslane; mustard seed; candlenut; stillingia; or walnut, as a food, oil, made into a spreading fat or supplementing another food (such as bread or eggs). For ALA sources the product consumed had to have an omega-3 fat content of at least 10% of the total fat content.

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants (trials)	Certainty of the evidence (GRADE)	Comments

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	Risk with lower ALA	Risk with higher ALA				
All-cause mortality – deaths Assessed with number of participants dying of any cause, whether reported as an outcome or a reason for dropout Duration: range 12-40 months	24 per 1000	24 per 1000 (20 to 28)	RR 1.01 (0.84 to 1.20)	19,327 (5 RCTs)	⊕⊕⊕⊖ Moderate[a]	ALA intake probably makes little or no difference to risk of all-cause mortality
Cardiovascular mortality – cardiovascular deaths Assessed with deaths from any cardiovascular cause. Where this was not available, we used cardiac death instead where known. Duration: range 12-40 months	12 per 1000	12 per 1000 (9 to 15)	RR 0.96 (0.74 to 1.25)	18,619 (4 RCTs)	⊕⊕⊕⊖ Moderate[b]	ALA intake probably makes little or no difference to risk of cardiovascular mortality
Cardiovascular events Assessed with number of participants experiencing any cardiovascular event Duration: range 12-40 months	47 per 1000	45 per 1000 (39 to 50)	RR 0.95 (0.83 to 1.07)	19,327 (5 RCTs)	⊕⊕⊖⊖ Low[c]	Increasing ALA intake may slightly reduce the risk of cardiovascular events. (**NNTB 500**, 95% CI 125 to −334; NNTB 500 in primary prevention; NNTB 84 in secondary prevention)
Coronary heart disease mortality – CHD deaths Assessed with: coronary deaths, or where these were not reported, IHD death, fatal MI or cardiac death (in that order) Duration: range 12-40 months	11 per 1000	10 per 1000 (8 to 14)	RR 0.95 (0.72 to 1.26)	18,353 (3 RCTs)	⊕⊕⊕⊖ Moderate[d]	ALA intake probably has little or no effect on risk of CHD mortality
Coronary heart disease events Assessed with number of participants experiencing the first outcome in this list reported for each trial: CHD or coronary events; total MI; acute coronary syndrome; or angina (stable and unstable) Duration: range 12-40 months	21 per 1000	21 per 1000 (17 to 26)	RR 1.00 (0.82 to 1.22)	19,061 (4 RCTs)	⊕⊕⊖⊖ Low[e]	ALA intake may make little or no difference to CHD events
Stroke	2 per 1000	3 per 1000 (2 to 5)	RR 1.15 (0.66 to 2.01)	19,327 (5 RCTs)	⊕⊖⊖⊖ Very low[f]	The effect of ALA intake on stroke is unclear as the ev-

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Assessed with: number of participants experiencing at least one fatal or non-fatal, ischaemic or haemorrhagic stroke Duration: range 12 to 40 months						idence is of very low certainty
Arrhythmias Assessed with number of participants experiencing fatal or nonfatal, new or recurrent arrhythmia, including atrial fibrillation, ventricular tachycardia and ventricular fibrillation Duration: range 12-40 months	40 per 1000	29 per 1000 (22 to 39)	RR 0.73 (0.55 to 0.97)	4912 (2 RCTs)	⊕⊕⊕⊖ Moderate[g]	ALA intake probably slightlyreduces the risk of arrhythmias. (**NNTB 91**, 95% CI 56 to 1000; assessment by primary or secondary prevention not possible)
Harms: bleeding Assessed with number of participants experiencing bleeding events	The effect of ALA intake on bleeding is unclear as no trials reported this outcome.					
Harms: pulmonary embolus or DVT Assessed with number of participants experiencing pulmonary embolus or DVT Duration: 24 months	3 per 1000	**1 per** 1000 (0 to 23)	**RR 0.32** (0.01 to 7.80)	708 (1 RCT)	⊕⊖⊖⊖ Very low[h]	The effect of ALA intake on pulmonary embolus or DVT is unclear as the evidence is of very low certainty

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
ALA: alpha-linolenic acid; **CHD**: coronary heart disease; **CI**: confidence interval; **DVT**: deep vein thrombosis; **IHD**: ischaemic heart disease; **MI**: myocardial infarction; **RCT**: randomised controlled trial; **RR**: risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]**All-cause mortality, alpha-linolenic acid (ALA)**

- **Risk of bias**: there was little or no effect in the main meta-analysis or in any sensitivity analysis. Not downgraded.
- **Inconsistency**: I^2 statistic was less than 60%. Not downgraded.
- **Indirectness**: representative, generalisable adult population including men and women, including healthy participants and participants with cardiovascular disease (CVD) risk factors or previous CVD as well as non-CVD health problems. All trials were conducted in high-income countries. Not downgraded.
- **Imprecision**: large numbers of participants took part in long-term RCTs with consistent results. However, as 95% confidence intervals do not exclude important benefits or harms we downgraded once.

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- **Publication bias**: insufficient trials for funnel plot. Not downgraded.

[b]**Cardiovascular mortality, ALA**

- **Risk of bias**: there was little or no effect in the main analysis, or in any sensitivity analysis. Not downgraded.
- **Inconsistency**: I^2 statistic was less than 60%. Not downgraded.
- **Indirectness**: representative, generalisable adult population including men and women, including healthy participants and participants with CVD risk factors or previous CVD as well as non-CVD health problems. All trials were conducted in high-income countries. Not downgraded.
- **Imprecision**: large numbers of participants took part in RCTs in long-term trials with consistent results. However, as 95% confidence intervals do not exclude important benefits or harms we downgraded once.
- **Publication bias**: insufficient trials for funnel plot. Not downgraded.

[c]**Cardiovascular events, ALA**

- **Risk of bias**: there was little or no effect in the main analysis, with larger trials and in fixed-effect analysis, and a 9%-10% reduction in risk when data were limited to RCTs at low summary risk of bias or at low risk from compliance problems. Downgraded once.
- **Inconsistency**: I^2 statistic was less than 60%. Not downgraded.
- **Indirectness**: representative, generalisable adult population including men and women, including healthy participants and participants with CVD risk factors or previous CVD as well as non-CVD health problems. All trials were conducted in high-income countries. Not downgraded.
- **Imprecision**: As 95% confidence intervals do not exclude important benefits we downgraded once.
- **Publication bias**: insufficient trials for funnel plot. Not downgraded.

[d]**Coronary heart disease mortality, ALA**

- **Risk of bias**: all sensitivity analyses suggested little or no effect. Not downgraded.
- **Inconsistency**: I^2 statistic was less than 60%. Not downgraded.
- **Indirectness**: representative, generalisable adult population including men and women, including healthy participants and participants with CVD risk factors or previous CVD as well as non-CVD health problems. All trials were conducted in high-income countries. Not downgraded.
- **Imprecision**: As 95% confidence intervals do not exclude important benefits or harms we downgraded once.
- **Publication bias**: insufficient trials for funnel plot. Not downgraded.

[e]**Coronary heart disease events, ALA**

- **Risk of bias**: there was little or no effect in the main analyses, in fixed-effect meta-analysis, in larger trials or when limiting to trials at low risk of compliance bias, but some risk reduction (9%) when data were limited to RCTs at low summary risk of bias. Downgraded once.
- **Inconsistency**: I^2 statistic was less than 60%. Not downgraded.
- **Indirectness**: representative, generalisable adult population including men and women, including healthy participants and participants with CVD risk factors or previous CVD as well as non-CVD health problems. All trials were conducted in high-income countries. Not downgraded.
- **Imprecision**: as 95% confidence intervals do not exclude important benefits or harms we downgraded once.
- **Publication bias**: insufficient trials for funnel plot. Not downgraded.

[f]**Stroke, ALA**

- **Risk of bias**: the main analysis, fixed-effect analysis, and larger trials suggest increased risk of stroke with more ALA, but there was little or no effect when data were limited to RCTs at low summary risk of bias, and a suggestion of benefit when limited to trials with low risk of compliance problems. Downgraded twice.
- **Inconsistency**: I^2 statistic was less than 60%. Not downgraded.
- **Indirectness**: representative, generalisable adult population including men and women, including healthy participants and participants with CVD risk factors or previous CVD as well as non-CVD health problems. All trials were conducted in high-income countries. Not downgraded.
- **Imprecision**: only 49 participants experienced strokes in the included trials; 95% confidence intervals do not exclude important benefits or harms, downgraded once.
- **Publication bias**: insufficient trials for funnel plot. Not downgraded.

[g]**Arrhythmias, ALA**

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- **Risk of bias**: increasing ALA reduced the risk of arrhythmia in the main analysis, and also in all sensitivity analyses. Not downgraded.
- **Inconsistency**: I^2 statistic was less than 60%. Not downgraded.
- **Indirectness**: two trials, which included adults with previous myocardial infarction or successful cardioversion in high-income countries. Not downgraded.
- **Imprecision**: as 95% confidence intervals do not exclude little or no effect we downgraded once.
- **Publication bias**: insufficient trials for funnel plot. Not downgraded.

[h]**Pulmonary embolus or DVD, ALA**

- **Risk of bias**: the single trial was not at low summary risk of bias. Downgraded once.
- **Inconsistency**: with one trial no inconsistency. Not downgraded.
- **Indirectness**: healthy men and women, no participants with CVD risk factors or previous CVD; low- and middle-income countries not represented. Not downgraded.
- **Imprecision**: only one event included in a single trial. Downgraded twice.
- **Publication bias**: insufficient trials for funnel plot. Not downgraded.

Summary of findings 3. High versus low omega-3 fats for modification of cardiovascular disease risk factors (adiposity and lipids): key outcomes

High versus low omega-3 fats for modification of CVD risk factors (adiposity and lipids)

Patient or population: adults with or without existing CVD

Setting: participants were living at home for most or all of the duration of their trials. Most trials were carried out in high-income economies (World Bank 2018), but four were carried out in upper-middle income countries. No trials took place in low- or low-middle income countries.

Intervention: higher omega-3 intake (LCn3 or ALA)
Comparison: lower omega-3 intake (LCn3 or ALA)

The intervention was dietary supplementation, a provided diet or advice on diet. Supplementation may have been in oil or capsule form or as foodstuffs provided, to be consumed by mouth (excluding enteral and parenteral feeds and enemas). The foodstuffs or supplements must have been oily fish; fish oils; linseed (flax), canola (rapeseed), perilla, purslane, mustard seed, candlenut, stillingia or walnut as a food, oil, made into a spreading fat or supplementing another food (such as bread or eggs). For ALA sources the product consumed had to have an omega-3 fat content of at least 10% of the total fat content. Refined eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) or ALAs, or concentrated fish or algal oils, were also accepted.

Outcomes All in trials of 12 to 72 months' duration	Anticipated absolute effects* (95% CI)		№ of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with low omega-3	Risk with high omega-3			
Measures of adiposity, LCn3 - weight, kg	Mean body weight was 81.2 kg	MD 0.00 kg lower (0.69 lower to 0.70 higher)	17,000 (14 RCTs)	⊕⊕⊕⊕ High[a]	LCn3 intake makes little or no difference to body weight
Measures of adiposity, LCn3 - BMI, kg/m^2	Mean BMI was 27.3 kg/m^2	MD 0.06 higher (0.14 lower to 0.25 higher)	15,474 (15 RCTs)	⊕⊕⊕⊕ High[b]	LCn3 intake makes little or no difference to BMI
Serum total cholesterol, LCn3 – TC, mmol/L	Mean TC was 5.61 mmol/L	MD 0.01 lower (0.05 lower to 0.03 higher)	38,469 (30 RCTs)	⊕⊕⊕⊕	LCn3 intake makes little or no difference to serum TC

				High[c]	
Serum triglyceride,LCn3 - fasting TG, mmol/L	Mean TG was 1.59 mmol/L	MD 0.24 lower (0.31 lower to 0.16 lower)	43,998 (27 RCTs)	⊕⊕⊕⊕ High[d]	Increasing LCn3 intake reduces serum TG by about 0.24 mmol/L or 15%
Serum high-density lipoprotein, LCn3 – HDL, mmol/L	Mean HDL was 1.32 mmol/L	MD 0.03 higher (0.01 to 0.05 higher)	46,604 (30 RCTs)	⊕⊕⊕⊕ High[e]	Increasing LCn3 intake has little or no effect on serum HDL
Serum low-density lipoprotein, LCn3 – LDL, mmol/L	Mean LDL was 3.27 mmol/L	MD 0.01 higher (0.01 lower to 0.03 higher)	43,454 (25 RCTs)	⊕⊕⊕⊕ High[f]	LCn3 intake makes little or no difference to serum LDL.
Measures of adiposity, ALA – weight, kg	Mean weight was 80.9 kg	MD 1.49 lower (4.17 lower to 1.18 higher)	664 (4 RCTs)	⊖⊖⊖⊖ Very low[g]	The effect of ALA intake on body weight is unclear as the evidence is of very low certainty
Measures of adiposity, ALA – BMI, kg/m^2	Mean BMI was 27.4 kg/m^2	MD 0.42 lower (1.53 lower to 0.69 higher)	1581 (3 RCTs)	⊖⊖⊖⊖ Very low[h]	The effect of ALA intake on BMI is unclear as the evidence is of very low certainty
Serum total cholesterol, ALA – TC, mmol/L	Mean TC was 5.02 mmol/L	MD 0.09 lower (0.23 lower to 0.05 higher)	2164 (6 RCTs)	⊕⊕⊖⊖ Low[i]	ALA intake may make little or no difference to serum TC
Serum triglyceride, ALA - fasting TG, mmol/L	Mean TG was 1.48 mmol/L	MD 0.03 lower (0.11 lower to 0.05 higher)	1776 (6 RCTs)	⊕⊕⊕⊖ Moderate[j]	ALA intake probably makes little or no difference to serum TG
Serum high-density lipoprotein, ALA – HDL, mmol/L	Mean HDL was 1.49 mmol/L	MD 0.02 lower (0.08 lower to 0.03 higher)	1776 (6 RCTs)	⊕⊕⊕⊖ Moderate[k]	ALA intake probably has little or no effect on serum HDL
Serum low-density lipoprotein, ALA – LDL, mmol/L	Mean LDL was 2.88 mmol/L	MD 0.05 lower (0.15 lower to 0.04 higher)	2201 (7 RCTs)	⊕⊕⊕⊖ Moderate[l]	ALA intake probably has little or no effect on serum LDL

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
__ALA__: alpha-linolenic acid; __BMI__: body mass index; __CI__: confidence interval; __DHA:__ docosahexaenoic acid; __EPA:__ eicosapentaenoic acid; __HDL__: high-density lipoprotein; __LCn3__: long-chain omega-3 fatty acids; __LDL__: low-density lipoprotein; __MD__: mean difference; __RCT__: randomised controlled trial; __TC__: total cholesterol; __TG__: triglycerides

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]**Measures of adiposity, weight, long-chain omega-3 (LCn3)**

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- **Risk of bias**: there was little or no effect in the main analysis or in any sensitivity analysis. Not downgraded.
- **Inconsistency**: I^2 statistic was less than 60%. Not downgraded.
- **Indirectness**: representative, generalisable adult population including men and women, including healthy participants and participants with previous CVD. However, low- and middle-income countries were underrepresented. Not downgraded.
- **Imprecision**: large numbers of participants took part in long-term randomised controlled trials (RCTs) with consistent results; 95% confidence intervals exclude important benefits or harms. Not downgraded.
- **Publication bias**: funnel plot was not interpretable, no clear small trial bias. However, we are aware of several trials whose data could not be included. Not downgraded.

[b]**Measures of adiposity, body mass index (BMI), LCn3**

- **Risk of bias**: there was little or no effect in the main analysis or in any sensitivity analysis. Not downgraded.
- **Inconsistency**: I^2 statistic was less than 60%. Not downgraded.
- **Indirectness**: representative, generalisable adult population including men and women, including healthy participants and participants with previous CVD. However, low- and middle-income countries were underrepresented. Not downgraded.
- **Imprecision**: large numbers of participants took part in long-term RCTs with consistent results. 95% confidence intervals exclude important benefits or harms. Not downgraded.
- **Publication bias**: funnel plot was not interpretable, no clear small trial bias. However, we are aware of several trials whose data could not be included. Not downgraded.

[c]**Lipids, serum total cholesterol, LCn3**

- **Risk of bias**: there was little or no effect in the main analysis or in any sensitivity analysis. Not downgraded.
- **Inconsistency**: I^2 statistic was less than 60%. Not downgraded.
- **Indirectness**: representative, generalisable adult population including men and women, including healthy participants and participants with previous CVD. However, low- and middle-income countries were not represented. Not downgraded.
- **Imprecision**: the 95% CI excluded important benefits or harms. Not downgraded.
- **Publication bias**: funnel plot did not suggest clear small trial bias. However, we are aware of several trials whose data could not be included; not downgraded.

[d]**Lipids, serum triglycerides, LCn3**

- **Risk of bias**: there was a greater than 5% (and statistically significant) effect overall and in all sensitivity analyses, including when data were limited to RCTs at low summary risk of bias. Not downgraded.
- **Inconsistency**: I^2 statistic was less than 60%. Not downgraded.
- **Indirectness**: representative, generalisable adult population including men and women, including healthy participants and participants with previous CVD. However, low- and middle-income countries were not represented. Not downgraded.
- **Imprecision**: large numbers of participants took part in long-term RCTs with consistent results. 95% confidence intervals exclude harm and lack of effect. Not downgraded.
- **Publication bias**: funnel plot was not interpretable, but results of fixed-effect and random-effects analyses were similar, suggesting little small trial bias. However, we are aware of several trials whose data could not be included. Not downgraded.

[e]**Lipids, high-density lipoprotein (HDL), LCn3**

- **Risk of bias**: the suggested little or no effect (less than 5% increase) in HDL with increased LCn3 was apparent in all sensitivity analyses. Not downgraded.
- **Inconsistency**: I^2 statistic was less than 60%. Not downgraded.
- **Indirectness**: representative, generalisable adult population including men and women, including healthy participants and participants with previous CVD. However, low- and middle-income countries were not represented. Not downgraded.
- **Imprecision**: 95% confidence intervals exclude harms or benefits. Not downgraded.
- **Publication bias**: funnel plot suggested no clear small trial bias. However, we are aware of several trials whose data could not be included. Not downgraded.

[f]**Lipids, low-density lipoprotein (LDL), LCn3**

- **Risk of bias**: there was little or no effect in the main analysis or in any sensitivity analysis. Not downgraded.
- **Inconsistency**: I^2 statistic was less than 60%. Not downgraded.

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- **Indirectness**: representative, generalisable adult population including men and women, including healthy participants and participants with previous CVD. However, low- and middle-income countries were not represented. Not downgraded.
- **Imprecision**: 95% confidence intervals excluded important benefits or harms. Not downgraded.
- **Publication bias**: funnel plot did not suggest clear small trial bias, and results of fixed-effect and random-effects analyses were similar. However, we are aware of several trials whose data could not be included. Not downgraded.

[g]**Measures of adiposity, weight, alpha-linolenic acid (ALA)**

- **Risk of bias**: no included trials were at low summary risk of bias. Downgraded once.
- **Inconsistency**: I^2 statistic was greater than 60%. Downgraded once.
- **Indirectness**: representative, generalisable adult population including men and women, including healthy participants and participants with previous CVD. However, low- and middle-income countries were not represented. Not downgraded.
- **Imprecision**: 95% confidence intervals included both benefits and harms. Downgraded once.
- **Publication bias**: funnel plot was not interpretable, but effects in fixed-effect and random-effects meta-analysis were different suggesting that small trial bias may be present. We are aware of several trials whose data could not be included. Downgraded once.

[h]**Measures of adiposity, BMI, ALA**

- **Risk of bias**: the main analysis and some sensitivity analyses suggested that ALA reduced BMI, but this was not seen when trials were limited to those at low summary risk of bias. Downgraded once.
- **Inconsistency**: I^2 statistic was greater than 60%. Downgraded once.
- **Indirectness**: representative, generalisable adult population including men and women, including healthy participants and participants with previous CVD. However, low- and middle-income countries were not represented. Not downgraded.
- **Imprecision**: 95% confidence intervals include benefits and harms. Downgraded once.
- **Publication bias**: funnel plot was not interpretable, but effects of fixed-effect and random-effects analyses were distinct, suggesting some small trial bias. We are aware of several trials whose data could not be included. Downgraded once.

[i]**Lipids, serum total cholesterol, ALA**

- **Risk of bias**: there was little or no effect in the main analysis or in any sensitivity analysis. Not downgraded.
- **Inconsistency**: I^2 statistic was greater than 60%. Downgraded once.
- **Indirectness**: representative, generalisable adult population including men and women, including healthy participants and participants with previous CVD. However, low- and middle-income countries were not represented. Not downgraded.
- **Imprecision**: the main analysis included both benefits and harms. Downgraded once.
- **Publication bias**: funnel plot was not interpretable, no clear small trial bias, fixed-effect and random-effects meta-analysis suggested similar effects. We are aware of several trials whose data could not be included. Not downgraded.

[j]**Lipids, serum triglycerides, ALA**

- **Risk of bias**: there was little or no effect in the main analysis or in any sensitivity analysis. Not downgraded.
- **Inconsistency**: I^2 statistic was less than 60%. Not downgraded.
- **Indirectness**: representative, generalisable adult population including men and women, including healthy participants and participants with previous CVD. However, low- and middle-income countries were not represented. Not downgraded.
- **Imprecision**: 95% confidence intervals included benefits. Downgraded once.
- **Publication bias**: funnel plot was not interpretable, no clear small trial bias and fixed-effect and random-effects analysis results were similar. We are aware of several trials whose data could not be included. Not downgraded.

[k]**Lipids, HDL, ALA**

- **Risk of bias**: there was little or no effect in the main analysis and all sensitivity analyses. Not downgraded.
- **Inconsistency**: I^2 statistic was less than 60%. Not downgraded.

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- **Indirectness**: representative, generalisable adult population including men and women, including healthy participants and participants with previous CVD. However, low- and middle-income countries were not represented. Not downgraded.
- **Imprecision**: 95% confidence interval includes harms. Downgraded once.
- **Publication bias**: funnel plot was not interpretable, effects of fixed-effect and random-effects meta-analysis was very similar suggesting lack of small trial bias. We are aware of several trials whose data could not be included. Not downgraded.

/Lipids, LDL, ALA

- **Risk of bias**: little or no effect in main analysis and all sensitivity analyses. Not downgraded.
- **Inconsistency**: I^2 statistic was less than 60%. Not downgraded.
- **Indirectness**: representative, generalisable adult population including men and women, including healthy participants and participants with previous CVD. However, low- and middle-income countries were not represented. Not downgraded.
- **Imprecision**: for main analysis 95% confidence interval included benefits. Downgraded once.
- **Publication bias**: funnel plot was not interpretable, effects of fixed-effect and random-effects meta-analysis were similar suggesting no small trial bias. We are aware of several trials whose data could not be included. Not downgraded.

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BACKGROUND

Description of the condition

Cardiovascular diseases are disorders of the heart and blood vessels. They comprise cerebrovascular disease (including stroke and transient ischaemic attack), coronary heart disease (including heart attack or myocardial infarction and angina), peripheral arterial disease (diseases of the blood vessels to the arms and legs), deep vein thrombosis and pulmonary embolism (blood clots formed in the legs which can move to the heart and lungs), as well as rheumatic and congenital heart disease (WHO 2017); these last two are not discussed in this review. Globally, 31% of all deaths are due to cardiovascular disease, more than from any other cause (WHO 2017). Of the estimated 17.7 million people who died from cardiovascular diseases in 2015, around 7.4 million were due to coronary heart disease and 6.7 million due to stroke. Of 17 million premature deaths in 2015 caused by non-communicable diseases, 82% were in low- and middle-income countries, and 37% were caused by cardiovascular diseases (WHO 2017).

Description of the intervention

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

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

How the intervention might work

Proposed mechanisms for the protective role of omega-3 fats against cardiovascular diseases include: lowering the blood pressure; altering the lipid profile, especially reduced serum triglyceride concentration; modulating arterial lipoprotein lipase levels; reducing thrombotic tendency; producing anti-inflammatory effects and anti-arrhythmic effects; improving vascular endothelial function and insulin sensitivity; and increasing plaque stability and paraoxonase levels (Bhatnagar 2003; BNF 1999; Calabresi 2004; Chang 2013; Geelen 2004).

Given that most omega-3 fats are ingested in the form of oily fish or fish oil (often fish liver) capsules, reports of high levels of various toxic compounds such as mercury, dioxins and polychlorinated biphenyls (PCBs) in oily fish and fish oils are concerning (Bourdon 2010; FSA 2000; Levine 2005; Liem 1997; MAFF 1998A; SACN COT 2004; USFDA 1995). These are all fat soluble and accumulate over time in the body, so harm may be exhibited only after long-term fish consumption or supplementation with fish oils. Animal intervention trials and human cohorts who have suffered accidental exposure to dioxins and PCBs suggest that pre-natal exposure may cause sub-fertility problems, and adult exposures may lead to an excess of total cancers (JECFA 2001). Human cohorts exposed to high levels of mercury exhibit neurological problems (USFDA 1995). As many people eat oily fish once or twice a week or take fish oil supplements, it is important to explore the potentially harmful effects of fish-associated omega-3 intake. It is also possible that omega-3 fats themselves may exhibit harm, for example through extension of bleeding times or suppression of normal immune responses (USFDA 2000).

Cardiovascular effects of eating more oily fish may differ from those of taking a fish oil supplement because fish (not fish oil) is a rich source of nutrients including selenium, iodine, zinc, calcium and protein. Fish in the diet may also displace a variety of other foods including sources of saturated or trans fats, so it could alter cardiovascular disease risk in other ways.

Why it is important to do this review

There is a great deal of public belief in the cardiovascular benefits of omega-3 fats. Analysis of US National Health and Nutrition Examination Survey data from 2003 to 2008 suggests that in the USA, adults' mean LCn3 intakes were greater from dietary supplements (0.72 g/d EPA and DHA) than from foods (0.41 g/d, Papanikolaou 2014). But public health advice differs across countries. For example, the National Institute for Health and Clinical Excellence in the UK now encourages fish intake but discourages supplementation: "people with or at high risk of CVD [cardiovascular disease] should be advised to consume at least 2 portions of fish per week, including a portion of oily fish". However, it advises that omega-3 fatty acid compounds "should not be offered for primary or secondary prevention of CVD [cardiovascular disease]" (NICE 2016). The American Heart Association (AHA) also "recommends eating fish (particularly fatty fish) at least two times (two servings) a week". Although the AHA suggests that omega-3 intake via foods is preferable, it is more positive about omega-3 supplements: "those with coronary artery disease may not get enough omega-3 by diet alone. These people may want to talk to their doctor about supplements" (AHA 2016). These recommendations are balanced with a warning about potential excessive bleeding in those taking doses of more than 3 g/d omega-3 fatty acids (presumably LCn3 fats). The AHA have issued updated guidelines on use of omega-3 fats to treat raised triglycerides, suggesting that "prescription n-3 FAs [fatty acids, meaning LCn3] (EPA+DHA or EPA-only) at a dose of 4 g/d (>3 g/d total EPA+DHA) are an effective and safe option for reducing triglycerides as monotherapy or as an adjunct to other lipid-lowering agents" (Skulas-Ray 2019). Such recommendations, and resulting increased fish consumption, have potentially negative long-term consequences for our marine ecosystems (Brunner 2009).

Epidemiological trials have supported the relationship between high omega-3 intake and lower cardiovascular disease rates (Ballard-Barbash 1987; Burr 1993; Kris-Etherton 2002). However, these associations could be due to other characteristics of people who choose to eat fish. In many societies eating fish is associated with better social status and a health-conscientious life view (Cade 2007), so eating fish is highly confounded by dietary quality, socioeconomic status and other markers of healthy lifestyles. As

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an example, the global attributable burden of eating a diet low in seafood omega-3 fats was estimated as 1.1% of global disability-adjusted life-years (DALYs; 95% confidence interval (CI) 0.8 to 1.5), "with 22% of ischaemic heart disease DALYs attributable to low seafood intake" (Engell 2013). The data sources are not described, but when the estimate was derived from randomised controlled trials (RCTs) alone, rather than cohort trials and RCTs combined, the estimated global attributable burden was much smaller, 0.5% (95% CI −0.5 to 1.4). Information concerning cause and effect is more reliably supplied by intervention trials in which participants are randomly allocated to receive fish oil or advice to eat more fish.

Systematic reviews of RCTs have had various findings. A recent version of this review (Abdelhamid 2018a), included 79 long-term RCTs and more than 112,000 participants, finding no effects of omega-3 fats on all-cause mortality or cardiovascular outcomes. Other systematic reviews have suggested a lack of effect for omega-3 fats on all-cause mortality or a variety of cardiovascular diseases (Campbell 2013; Chowdhury 2012; Khoueiry 2013; Kotwal 2012; Kwak 2012; Mariani 2013; Rizos 2012; Zheng 2014). However, some reviews have highlighted particular outcomes or circumstances in which cardiovascular disease prevention was evident: after heart surgery (He 2013), for preventing sudden cardiac death (Zhao 2009), for reducing cardiovascular disease mortality and sudden cardiac death, although with no effect on all-cause mortality (Trikalinos 2012), for cardiovascular disease mortality (Sethi 2016), and for reducing the risk of stroke in women, albeit with no effect on stroke overall (Larsson 2012). Kwak 2012 reported marginal effects on cardiovascular death, though these were lost when a poor-quality trial was removed, and a few others have reported only positive effects in their abstracts (reductions in cardiovascular events, cardiac death and coronary events) (Delgado-Lista 2012). These disparate findings have fuelled both debate and confusion. A recent extensive Agency for Healthcare Research and Quality review meta-analysed risk factors extensively but suggested there was only limited RCT data to assess the effects of omega-3 fats on clinical cardiovascular disease outcomes (Balk 2016). The publication recently of a suite of large-scale and long-term trials of LCn3 (ASCEND 2018; REDUCE-IT 2019; VITAL 2019), has prompted the need to update Abdelhamid 2018a.

This systematic review and meta-analysis aimed to assess the evidence on the effects of omega-3 fats (LCn3 and ALA separately) on all-cause mortality and cardiovascular diseases. It also aimed to assess potentially harmful effects of omega-3 fats or compounds associated with consuming LCn3 fats, such as excessive bleeding. A related review has formally systematically reviewed potential harms such as excessive cancers, rather than simply examining trials included in this review for cancer outcomes (Hanson 2019). We assessed mechanisms of action such as lipid and body weight changes and antiarrhythmic effects as primary or secondary outcomes in this review, and we have systematically reviewed these outcomes in a formal way by including trials that assessed adiposity, lipids and arrhythmic events, even where no cardiovascular disease events occurred or were reported. The World Health Organization (WHO) is currently updating its guidance on polyunsaturated fatty acid (PUFA) intake in adults and children. This is one of a set of systematic reviews commissioned by WHO in order to inform and contribute to the development of updated WHO recommendations. Sister systematic reviews have assessed effects of omega-3, omega-6 and total polyunsaturated fats on inflammation and inflammatory bowel disease (Thorpe 2017), diabetes and glucose metabolism (Brown 2019), depression and anxiety (Deane 2019), cognition and dementia (Brainard 2019), cancers (Hanson 2019) and functional status (Abdelhamid 2019). Separate reviews assess effects of omega-6 fats and total polyunsaturated fat on mortality and cardiovascular outcome (Abdelhamid 2018b; Hooper 2018), and provide a detailed database of the relevant trials for use by others (Hooper 2019).

The results of this review including GRADE assessments were discussed and reviewed by the WHO Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health as part of WHO's guideline development process.

OBJECTIVES

To assess the effects of increased intake of fish- and plant-based omega-3 for all-cause mortality, cardiovascular events, adiposity and lipids.

The primary review question was, 'Do long-chain omega-3 fats (LCn3, fish-based omega-3 fats) or ALA (plant-based omega-3 fats) alter risk of all-cause mortality, cardiovascular deaths, cardiovascular events, coronary heart disease deaths, coronary heart disease events, stroke, arrhythmia, adiposity and lipids?'

Secondary questions include the following.

- If omega-3 fatty acids confer protection:
  - does protection occur equally in those at low and at high risk of cardiovascular disease?
  - does protection depend on the dose of omega-3 fats taken per day?
  - do effects differ between dietary and supplemental omega-3 sources?
  - does protection depend on trial summary risk of bias?
- Is protection or harm stronger with longer trial duration?
- Are effects of omega-3 fatty acids dependent on baseline triglyceride levels or diabetic status?

The latter was suggested by WHO NUGAG and added post-hoc specifically for this update.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled clinical trials that included diet advice or dietary supplementation to promote omega-3 fatty acid intake versus placebo, no supplementation, usual diet or lower-dose omega-3. One of our outcomes had to be measured and available (through publications or contact with trial authors), and trials had to follow participants for at least 12 months (52 weeks or 360 days). For advice trials, follow-up must have been at least 12 months following advice, and for trials where participants received food or supplementation, provision must have continued for at least 12 months. We accepted randomisation of individuals or of clusters as long as there were at least six clusters randomised.

Careful work by Browning suggests that supplements of EPA and DHA equivalent to one weekly portion of oily fish results in 95% of maximal incorporation by 5 days for EPA in plasma

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phosphatidylcholine (95% CI 0 to 18 days) to 273 days for DHA into blood mononuclear cells (95% CI 0 to 670 days; FISH 2012). While this suggests individual variability, on average all compartments except blood mononuclear cells had equilibrated by 117 days (both EPA and DHA into plasma phosphatidylcholine, plasma cholesteryl esters, plasma nonesterified fatty acids, plasma triglycerides, erythrocytes and platelets). The authors stated, "EPA and DHA reached a maximum in platelets in 3–4 weeks and 1–2 months, respectively, and in blood mononuclear cells in 6–9 months". For this reason we chose 12 months as the minimum duration of intervention, as it allows equilibration of most body compartments with EPA and DHA as well as time for this change in body composition to have some effect on cardiovascular risk or mortality.

In previous reviews of dietary effects on cardiovascular outcomes, we limited trials to at least two years' duration (Hooper 2015), as the proposed mechanism of effects was via LDL cholesterol, atherosclerosis and its sequelae, and this takes time to develop. The 4S trial showed separation of the survival curves at around two years (Scandinavian Simvastatin Survival Study Group 1994). Potential mechanisms for effects of PUFAs are broader, including what could be rapid effects on arrhythmias or inflammation, so we decided to include trials of at least 12 months to ensure we did not miss these effects.

Types of participants

Trials in adults (18 years or older, men and women) at any risk of cardiovascular disease (with or without existing cardiovascular disease) were eligible, including those in participants with increased risk of cancer, those undergoing or who have undergone coronary artery bypass grafting or angioplasty, and those with current or previous cardiovascular disease, nephritis in systemic lupus erythematosus, breast cysts, diabetes mellitus, rheumatoid arthritis, multiple sclerosis, psoriasis, hay fever, asthma or ulcerative colitis. Including these populations allows us to understand both development and progression of cardiovascular disease (primary and secondary prevention). We excluded participants who were pregnant or acutely ill (with acute-stage cancer, undergoing heart or renal transplantation, with HIV or AIDS, on haemodialysis, with IgA glomerulonephritis, or any other renal problem except in diabetes).

Types of interventions

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

We excluded trials using multiple risk factor interventions on lifestyle factors (such as weight reduction, smoking or physical activity goals), or differential dietary interventions not involving dietary fats, except where that other intervention was a direct replacement for polyunsaturated fats or the effect of diet or supplementation could be separated out from the other interventions.

Trials were eligible if they compared the effect of dietary advice or supplementation to increase omega-3 fats with the usual diet, no advice, no supplementation, placebo or lower-dose omega-3.

Types of outcome measures

Primary outcomes

Primary outcomes included numbers of participants experiencing:

- all-cause mortality (deaths);
- cardiovascular mortality (cardiovascular deaths);
- cardiovascular events (cardiovascular events);
- coronary heart disease mortality (coronary heart disease deaths);
- coronary heart disease events;
- stroke; and
- arrhythmia (atrial fibrillation).

We analysed coronary heart disease using the first of the following to be reported: number of participants experiencing coronary heart disease or coronary events, total myocardial infarction, acute coronary syndrome or angina (stable and unstable). This meant that if trial authors reported coronary heart disease events, we used these in analysis; where trials did not report coronary heart disease events but did report total myocardial infarction, we used that (and so on). Combined cardiovascular events included fatal and non-fatal myocardial infarction, angina, stroke, heart failure, peripheral arterial disease, sudden death and non-scheduled cardiovascular interventions – coronary artery bypass surgery or angioplasty. We included all available outcomes where we could be sure that the same participant was not being counted twice.

At the request of WHO NUGAG Subgroup on Diet and Health, we added coronary heart disease mortality post hoc as a primary outcome. Data used were the first of the following list reported: coronary death, ischaemic heart disease death, fatal myocardial infarction, cardiac death. We only used cardiac death when no other outcomes in this category were available, and we ran a sensitivity analysis omitting cardiac death. The reason for excluding cardiac death in sensitivity analysis was that it goes slightly outside our area of interest, including other causes of death in addition to coronary heart disease, such as cardiomyopathies and congenital and valvular heart diseases. We wanted to include cardiac death in the main analysis as we felt that otherwise we would be missing some important cases of coronary heart mortality, but we decided to exclude it in sensitivity analysis as we were potentially including a few outcomes that coronary heart disease mortality did not encompass.

Secondary outcomes

Secondary outcomes included:

- major adverse cerebrovascular or cardiovascular events (MACCEs) or individual cardiovascular events (total, fatal or non-

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fatal myocardial infarction, sudden cardiac death, angina, heart failure, revascularisation, peripheral arterial disease or acute coronary syndrome);
- body weight and other measures of adiposity; and
- lipids (total, LDL or HDL cholesterol and triglycerides).

We defined MACCEs as participants experiencing myocardial infarction, unstable angina, stroke or death. We did not consider trials that did not provide data on all these health events for this outcome.

The review included trials if any of their participants experienced or were assessed for any primary or secondary outcome. These could have been reported in publications (as outcomes or reasons for dropout or adverse events), supplied by trial authors, or which clearly happened even if exact numbers were not available. However, as almost all trials note if a death or cardiovascular event occurs in a trial participant (so all trials assessed for our primary outcomes) we only included trials where at least one event occurred, or where a continuous outcome was measured.

Tertiary outcomes

We extracted the following outcomes where available within included trials.

- Blood pressure
- Serious adverse events (any other reported illnesses)
- Side effects
- Dropouts
- Quality-of-life measures
- Economic costs

We originally intended to assess type 2 diabetes diagnoses, measures of glucose metabolism, cancers, breast cancer, neurocognitive outcomes such as dementia, depression and anxiety within included trials. However, as part of the larger set of reviews we formally systematically reviewed effects of omega-3 fats on type 2 diabetes diagnoses and measures of glucose metabolism (Brown 2019), cancers including breast cancer (Hanson 2019), neurocognitive outcomes such as dementia (Brainard 2019), irritable bowel disease (IBD) and inflammatory factors (Thorpe 2017), depression and anxiety (Deane 2019), and functional outcomes (Abdelhamid 2019), so a partial assessment within this review would be unhelpful and potentially misleading. For this reason we exclude these specific outcomes from our reporting of serious adverse events.

Key outcomes

When the World Health Organization (WHO) NUGAG Subgroup on Diet and Health requested this review update they named the following as key outcomes to inform their planned dietary guidance.

- All-cause mortality
- Cardiovascular disease mortality
- Cardiovascular disease events
- Coronary heart disease mortality
- Coronary heart disease events
- Stroke
- Arrhythmia (atrial fibrillation)
- Serum lipids including total cholesterol, fasting triglycerides, high-density lipoprotein (HDL) and low-density lipoprotein (LDL)
- Measures of adiposity (body weight and body mass index (BMI)

We were not able to make all of these outcomes into primary outcomes (as the number of primary outcomes are restricted for Cochrane Reviews). However, because WHO NUGAG Subgroup on Diet and Health will use these outcomes to underpin guidance, we carried out sensitivity analyses, subgroup analyses and GRADE assessment of certainty of evidence for them, even when they were not primary outcomes.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases on 13 February 2019 to identify reports of relevant randomised clinical trials:

- Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 2) in the Cochrane Library;
- Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE (Ovid, 1946 to 12 February 2019);
- Embase Classic and Embase (Ovid, 1947 to 2019 week 6).

We applied date limits to the terms from the original strategies so that the search included only new records (Appendix 1). The RCT filter for MEDLINE was the Cochrane sensitivity and precision-maximising RCT filter, and for Embase, we applied the terms as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011).

Appendix 2 shows the MEDLINE search strategy for the original version of this review (Hooper 2004), Appendix 3 and Appendix 4 show searches used to update the previous version of this review (Abdelhamid 2018a).

For the previous (27 April 2017) update we also ran searches for a new systematic review of the effects of polyunsaturated fats on cardiovascular disease (Abdelhamid 2018b), as well as updating and extending a Cochrane Review of the effects of omega-6 polyunsaturated fats on health outcomes (Hooper 2018). We ran searches for these reviews using the same RCT filters (Appendix 4). The results of these searches were de-duplicated against the omega-3 searches, and all the titles and abstracts assessed as a single set for all three reviews. We created a data set of RCTs that lasted at least six months and compared higher versus lower omega-6, omega-3 or total PUFA in adults. We used this data set as the wider study pool from which we selected included trials for all reviews (Abdelhamid 2018a; Abdelhamid 2018b; Abdelhamid 2019; Brainard 2019; Brown 2019; Deane 2019; Hanson 2019; Hooper 2018; Hooper 2019; Thorpe 2017). We did not repeat these additional searches in 2019.

We also searched two trials registers, ClinicalTrials.gov (clinicaltrials.gov), and the WHO International Clinical Trials Registry Platform (ICTRP, www.who.int/ictrp/en), to 31 July 2019 for registry entries for relevant completed and ongoing trials.

Searching other resources

We assessed titles and abstracts retrieved during these electronic searches for relevant RCTs and also relevant systematic reviews.

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We handsearched the included trials in all relevant systematic reviews up to April 2017 for new trials and additional publications of included trials. We contacted authors of all large included trials (at least 100 participants) included up to April 2017 and some smaller trials for further trial data, methodological details and references to trials not yet identified, including published, unpublished or ongoing trials.

For all included trials we carefully searched and data-extracted trials registry entries, protocols, supplementary materials, letters, conference abstracts and additional publications to help us locate complete data sets.

Data collection and analysis

Selection of studies

At least two review authors independently assessed titles and abstracts resulting from the electronic and bibliographic searches. We rejected titles and abstracts on initial screen only if the review author could determine from the title and abstract that the article was not a report of a RCT; did not address omega-3 intake (or total polyunsaturated fat or omega-6 fat for the other two reviews); were exclusively in children or young adults (less than 18 years old), pregnant women or the critically ill; were of less than 12 months' duration; or if the intervention was multi-factorial and we could not separate out the effect of dietary fat.

We rejected trials only when it was certain that no primary or secondary outcome events occurred, and none of the secondary outcome risk factors were measured. When we could not reject a title or abstract with certainty, we obtained the full text of the article for further evaluation. We made attempts to obtain full-text translations or evaluations, or both, of all potentially relevant non-English articles.

We used an in/out form to assess full-text papers and trials for inclusion (or otherwise) into the review. We contacted the authors of all potentially included RCTs for further information on trial methodology and outcomes. Two review authors independently decided on inclusion of full-text RCTs, resolving any differences by discussion and, when necessary, in consultation with the review author team.

Data extraction and management

We designed a data extraction form for this review, which each of the review authors tested on a common 'training' trial (SCIMO 1999), and we adapted the form as needed. We extracted data concerning participants, interventions, and outcomes, as described above in the selection criteria section. We extracted dichotomous data from dietary advice trials at the latest point available in the trial (regardless of the amount of reinforcement of the original dietary message), while for supplement trials, we extracted dichotomous data to the point that supplementation or the trial ended, whichever was earlier. We extracted continuous data at the nearest time point to 12 months and also the latest point available in fixed-term trials, but in trials where participants were followed up for varying durations (aside from dropouts), we extracted the participants' data from the first time point following the mean trial duration. We never used data from periods following the end of a trial in meta-analysis.

We also extracted data on risk of bias, assessed using the Cochrane 'Risk of bias' tool, along with data on potential effect modifiers, including existing cardiovascular disease (primary or secondary prevention), trial duration, intensity of intervention (dietary advice, diet provided, supplemental foods, supplements (capsules) and any combination), LCn3 fats or ALA and dose, replacement, medications used (including statins, antihypertensive, antiarrhythmic or antithrombotic medication), fatty acid data (from plasma, platelets or adipose tissue) and smoking status.

For primary and secondary dichotomous outcomes, we extracted numbers of participants experiencing an outcome and total numbers of participants randomised (or in whom the outcome was assessed where known) for each trial arm. For continuous outcomes, we extracted the number of participants assessed, means and standard deviations of the final readings in each treatment arm; we calculated standard deviations from other variance data where appropriate. Where data were available on both change and final readings, we used data on change.

Two review authors independently extracted original reports of trial results. We resolved differences between review authors' results by discussion and, when necessary, in consultation with a third review author or the review author team.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each included trial, using Cochrane criteria (Higgins 2017), including in the domains of sequence generation; allocation concealment; blinding of participants and personnel, blinding of outcome assessors; incomplete outcome data; and selective outcome reporting. Additional review-specific criteria included similarity of type and intensity of intervention in both arms (attention) and evidence of appropriate moderate to high compliance (to establish that the intervention group were receiving a different intake of omega-3 fats than the control group). Table 1 presents specific details of how we interpreted these criteria for this review.

In brief, we considered a trial to be at low risk of attention bias when participants were given the same amount of time and attention from trial staff and health professionals whether they were in the intervention or control arms, and at low risk of compliance bias when adherence was assessed, results of that assessment were clearly reported for both intervention and control arms, and where most participants appeared to have taken at least 75% of the intended PUFA dose.

Summary risk of bias

Schulz 1995 found that poorly concealed allocation was associated with a 40% greater effect size, so randomisation and allocation concealment are core issues for all trials. Lack of blinding is associated with bias, though smaller levels of bias than lack of allocation concealment (Savovic 2012), especially in trials with objectively measured outcomes (Wood 2008), such as those we primarily used in our review. Although we originally planned to assess summary risk of bias for all included trials in the same way across the whole set of reviews (Abdelhamid 2018a; Abdelhamid 2018b; Abdelhamid 2019; Brainard 2019; Brown 2019; Deane 2019; Hanson 2019; Hooper 2018; Hooper 2019; Thorpe 2017), we adopted a different approach after discussing the different nature

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of supplement trials compared to dietary advice or food provision trials with the WHO NUGAG Subgroup on Diet and Health.

We considered supplement or capsule type trials to be at low summary risk of bias where we judged randomisation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessors to be adequate. We considered all other trials to be at moderate or high risk of bias (a single category).

We considered dietary advice or all-food-provided type trials to be at low summary risk of bias where we judged randomisation, allocation concealment, and blinding of outcome assessors to be adequate. We considered all other trials to be at moderate or high risk of bias (a single category).

Measures of treatment effect

We pooled dichotomous data using risk ratios (RR) to describe effect sizes and continuous data using mean differences (MD). Where effects were described by different but comparable measures or scales in different trials, we planned to combine them using standardised mean difference (SMD), but this was not needed in this review.

Unit of analysis issues

We considered that we could reduce patient numbers in cluster-randomised trials to an effective sample size, as described by Hauck 1991, however, we identified no such trials. For combined outcomes (e.g. combined cardiovascular events), we made attempts to add numbers of individuals experiencing specific outcomes within trials, but only where we could be certain that we were not counting individual participants more than once within any one of our review outcome categories.

For trials with intervention arms providing different omega-3 doses, we combined data for the intervention groups for binary outcomes and used higher-dose data versus control for continuous outcomes. We used arms with different doses separately when subgrouping by dose. Where factorial trials ran more than one intervention included in this review (AlphaOmega - ALA 2010; AlphaOmega - EPA+DHA 2010), we did not pool both comparisons in the same meta-analysis.

Dealing with missing data

We sought trials registry entries and trial protocols to help us assess which trials measured each outcome. Where trials appeared to have collected – but did not report – data, we wrote to trial authors to ask for information. We wrote to authors of all trials that randomised at least 100 participants as well as to those of many smaller trials (although not to all due to limited resources), prioritising our efforts on larger trials that would tend to provide more information to the review. For larger trials where we found no trials registry entry or protocol, we wrote to trial authors to ask whether they had collected information on any outcomes of interest that we had not yet located. Where it was clear that data existed but could not be located to use within the review, we noted this and assessed the potential effect of this missing data on effect sizes narratively.

A recent meta-analysis of effects of omega-3 fats on cardiovascular outcomes, Aung 2018, worked with 10 large RCTs in depth to formulate their outcome data to match precisely between trials. It is difficult as a reviewer to access complex outcomes (such as 'cardiovascular events') where we need to count people experiencing events, rather than counting events - events are additive, but people experiencing events are not (a participant experiencing a stroke, non-fatal myocardial infarction and angina must be counted as only one person experiencing cardiovascular events, rather than three events). As the review had worked with trial authors to optimise their data, we used data from this review to both fill in missing data (some data had not been previously published) and also to update our data where the data in Aung 2018 differed from previously reported data for any outcome. The trials that this applies to, those included in Aung 2018, were AlphaOmega - ALA 2010; AlphaOmega - EPA+DHA 2010; AREDS2 2014; DO IT 2010; GISSI-HF 2008; GISSI-P 1999; JELIS 2007; OMEGA 2009; ORIGIN 2012; Risk & Prevention 2013; SU.FOL.OM3 2010.

Assessment of heterogeneity

We assessed heterogeneity using the I^2 test and assumed it to be important when I^2 test value was more than 60% (Higgins 2003).

Assessment of reporting biases

We used funnel plots to assess for evidence of bias for primary outcomes where at least 10 trials contributed to the meta-analysis (Egger 1997). We also compared effects from random-effects and fixed-effect meta-analyses to understand whether small study effects may be important (Page 2019), alongside reporting known missing data (above).

Data synthesis

Primary measures of interest were effects of dietary advice or supplementation of fish-based (LCn3) fats, and ALAs, on primary outcomes. We separated out effects of LCn3 and ALA in all analyses and thus present two separate sets of results: one for LCn3 and one for ALA.

We combined treatment/control differences in the outcomes across trials using risk ratios (RR) or mean differences (MD) in random-effects meta-analysis. For combined outcomes (e.g. combined cardiovascular events), we made attempts to add numbers of individuals experiencing specific outcomes within trials, but only where we were certain that we were not counting individual participants more than once within any one of our review outcome categories. However, individuals may have been counted for more than one of the review outcomes (in separate forest plots).

Subgroup analysis and investigation of heterogeneity

We explored the effects of LCn3 and ALA separately on all primary review outcomes and also on key review outcomes where these were secondary outcomes in our review and included at least six trials by subgrouping. The planned subgroup analyses were as follows.

- Type of intervention: dietary advice, supplemental foods (for example margarine fortified with rapeseed, tins of sardines or oils to use in cooking) provided by the trial, supplements (capsules or oils) provided to take as medicine or any combination
- Replacement of saturated fatty acids, mono-unsaturated fatty acids (MUFA), omega-6 fats, fat mixture, carbohydrates or sugars, non-fat or no placebo, or unclear, with LCn3 or ALA
- Primary prevention versus secondary prevention of cardiovascular disease (where trials that recruited participants

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for cardiovascular disease at baseline were considered secondary prevention trials, and trials that did not recruit on the basis of cardiovascular disease, so may include some or no people with existing cardiovascular disease, were considered primary prevention trials)

- LCn3 dose: at least 150 mg/d, 250 mg/d, 400 mg/d from all sources including supplements (above or below each threshold); low dose 0.4 g/d to 2.4 g/d, medium dose 2.5 g/d to 4.4 g/d, and high dose ≥ 4.5 g/d of combined LCn3 fats;
- ALA dose: higher versus lower levels of intake (≥ 5 g/d versus < 5 g/d);
- Trial duration: trials with medium follow-up (12 to 23 months), medium follow-up (24 to 47 months) and long follow-up (≥ 48 months)
- Statin use (< 50% of control group on statins, ≥ 50% of control group on statins, use of statins unclear)
- Baseline LCn3 intake, and baseline ALA intake

There were insufficient data on baseline omega-3 or ALA intake (or intake in control groups, which could have been used as a proxy) to subgroup by baseline omega-3 or ALA intake.

Post-hoc, WHO NUGAG asked us to assess whether effects of omega-3 fats differed by baseline triglyceride or diabetes status. We carried out post-hoc subgroups on primary outcomes whenever the other subgroups were created, including the following.

- Triglyceride status: raised triglycerides at baseline (inclusion criteria relate to triglycerides and mean triglycerides in control group at baseline were > 200 mg/dL or > 2.26 mmol/L) versus normal triglycerides (triglycerides did not relate to inclusion criteria, or mean triglycerides in control group at baseline was < 200 mg/dL or < 2.26 mmol/L)
- Diabetes status: diabetic at baseline (at least half of participants had diabetes) versus diabetes risk factors at baseline (insulin resistance, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis or obesity) versus inclusion criteria that did not relate to diabetic status.

Meta-regression

We used meta-regression to further explore effects of LCn3 dose, ALA dose, omega-6 dose, total PUFA dose (looking for evidence of dose response for each), trial duration, primary or secondary prevention, food or capsule intervention (food included dietary advice and supplemental foods), and risk of bias (summary risk of bias low or moderate to high) on primary outcomes. We performed random-effects meta-regression using the STATA 16 command meta regress (Berkley 1995; Sharp 1998): log(e) risk ratio versus (dose or primary/secondary prevention or type of intervention or risk of bias or duration), weighted by the standard error of the log(e) risk ratio. Where there were no events in one arm, we added 0.1 to the numbers for both groups (so a trial with 10 people experiencing stroke in one arm but none in the other arm would be entered as 10.1 and 0.1). We analysed all included trials (of at least 12 months' duration) that reported each outcome from this review and its sister reviews (omega-3 trials from this review, omega-6 trials from Hooper 2018, and total PUFA trials from Abdelhamid 2018b). We carried out meta-regression of each variable singly, then a multivariate meta-regression of the three variables with lowest P values in single regression for each outcome. Given that we generally included data from fewer than 40 trials and there were some missing data for some trials, we did not run meta-regressions with more than three variables at one time.

Sensitivity analysis

We carried out sensitivity analyses on all primary outcomes (regardless of the number of included trials) and on key outcomes that were secondary outcomes in this review.

We used sensitivity analyses to assess robustness of results to:

- trial quality (removing trials at moderate or high summary risk of bias);
- trial size (retaining only trials that randomised at least 100 participants across all trial arms);
- fixed-effect analysis; and
- compliance (retaining only trials where we assessed compliance as conferring low risk of bias).

We tabulated the type and frequency of side effects and adverse effects (with the other extracted data on adverse effects) and compared between different trials and designs.

'Summary of findings' tables

We interpreted outcome data as follows.

1. Is there an effect? (options were 'increased risk', 'decreased risk', or 'little or no effect'). Our main outcome measure was RR so we decided on existence of an effect using RR. RR more than 8% (RR < 0.92 or > 1.08) for the highest-certainty evidence suggested increased or decreased risk (otherwise little or no effect). The presence or not of an effect was decided on the RR for the main analysis and sensitivity analyses, the highest-certainty evidence (the main analysis, the sensitivity analyses of trials at low summary risk of bias and at low risk of compliance problems).
2. For continuous outcomes, we considered increasing ALA or LCn3 to have little or no effect unless effect sizes represented at least 5% change from baseline (or 2% in the case of cumulative outcomes such as adiposity).
3. We assessed certainty of evidence using GRADE assessment (GRADE Working Group 2004), for key outcomes. We used the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of the body of evidence as it related to the trials that contributed data to the meta-analyses for the prespecified outcomes. We used methods and recommendations described in Section 8.5 (Higgins 2017), and Chapter 11 (Schünemann 2017), of the *Cochrane Handbook for Systematic Reviews of Interventions*, plus GRADEpro GDT software (GRADEpro GDT). We justified all decisions to downgrade the certainty of trials using footnotes and made comments to aid readers' understanding of the review.
4. Where there was a suggested effect, we assessed the size of effect using the number needed to treat for an additional beneficial outcome (NNTB), number needed to treat for an additional harmful outcome (NNTH) or absolute risk reduction (ARR).

We included three 'Summary of findings' tables: for effects of LCn3 on primary outcomes (Summary of findings for the main comparison), effects of ALA on primary outcomes (Summary of

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findings 2), and for key outcomes that were not included in the review primary outcomes (measures of adiposity and serum lipids, Summary of findings 3).

RESULTS

Description of studies

Results of the search

During the 2019 update, we assessed a further 2419 publications for inclusion and included another seven trials (Figure 1). We found that six previously ongoing trials had published relevant results (Broutset 2007; DREAM Asbell 2018; ENRGISE 2018; ASCEND 2018; REDUCE-IT 2019; VITAL 2019), so we included them in the review, and we included a further trial (not previously ongoing, HEARTS 2017). We assessed 29 registry entries from ClinicalTrials.gov and 88 entries from WHO ICTRP, of which seven were newly included as ongoing trials (NCT03806426; EVAPORATE 2016; MTG 2018; NCT03784963; LO-MAPT 2018; POSEIDON 2018; ACTRN12618000761268 2018), and one is awaiting assessment, as it appears to fulfil all inclusion criteria, except that trial duration is unclear (IRCT20100123003140N21). VITAL 2019 had a number of substudies registered with different trial registration numbers, which we included as part of the included VITAL 2019 trial (noted in the Characteristics of included studies), even though most are ongoing. This provided 86 RCTs (over 421 documents) included in this review.

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Figure 1. Study flow diagram

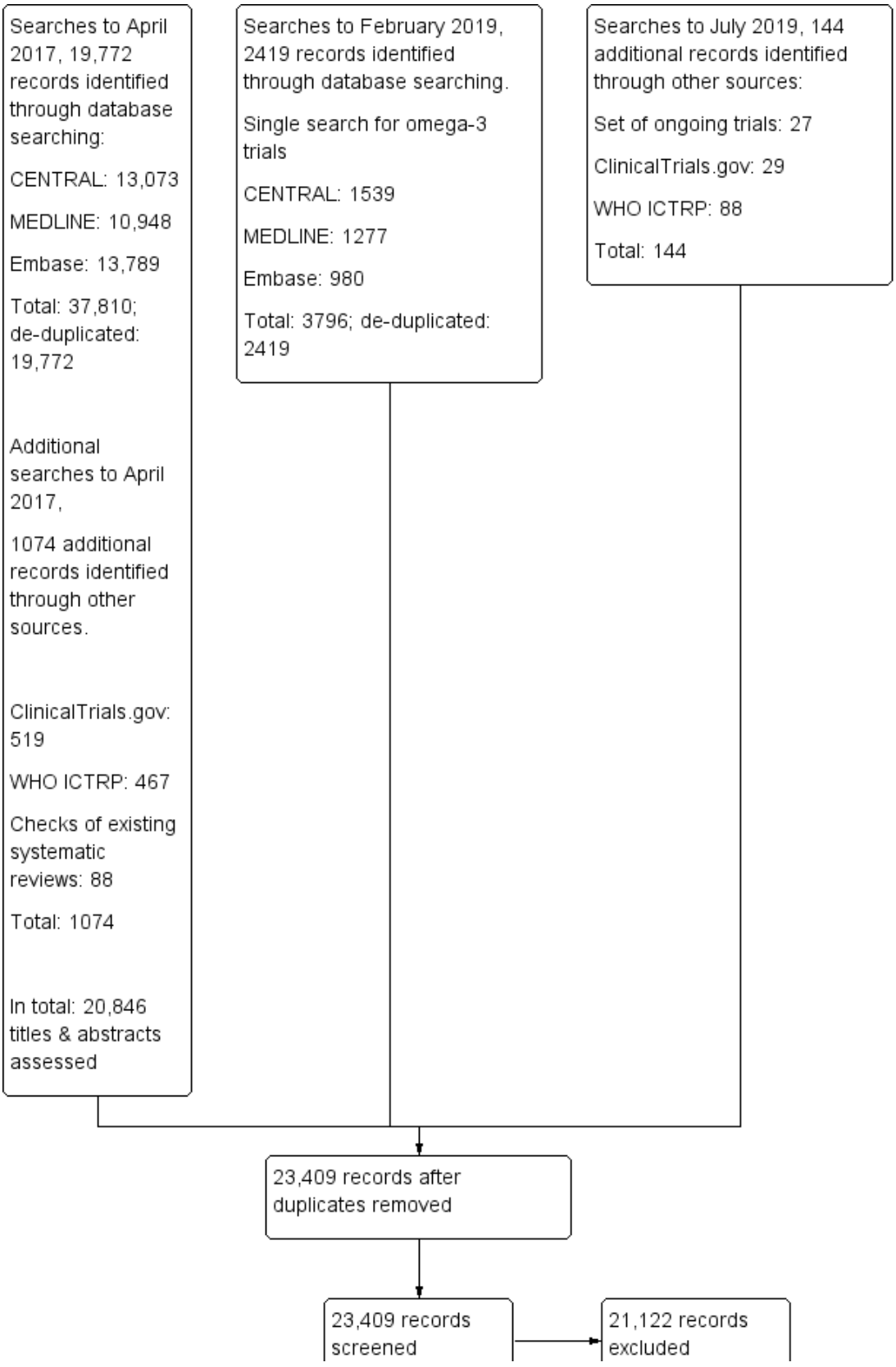

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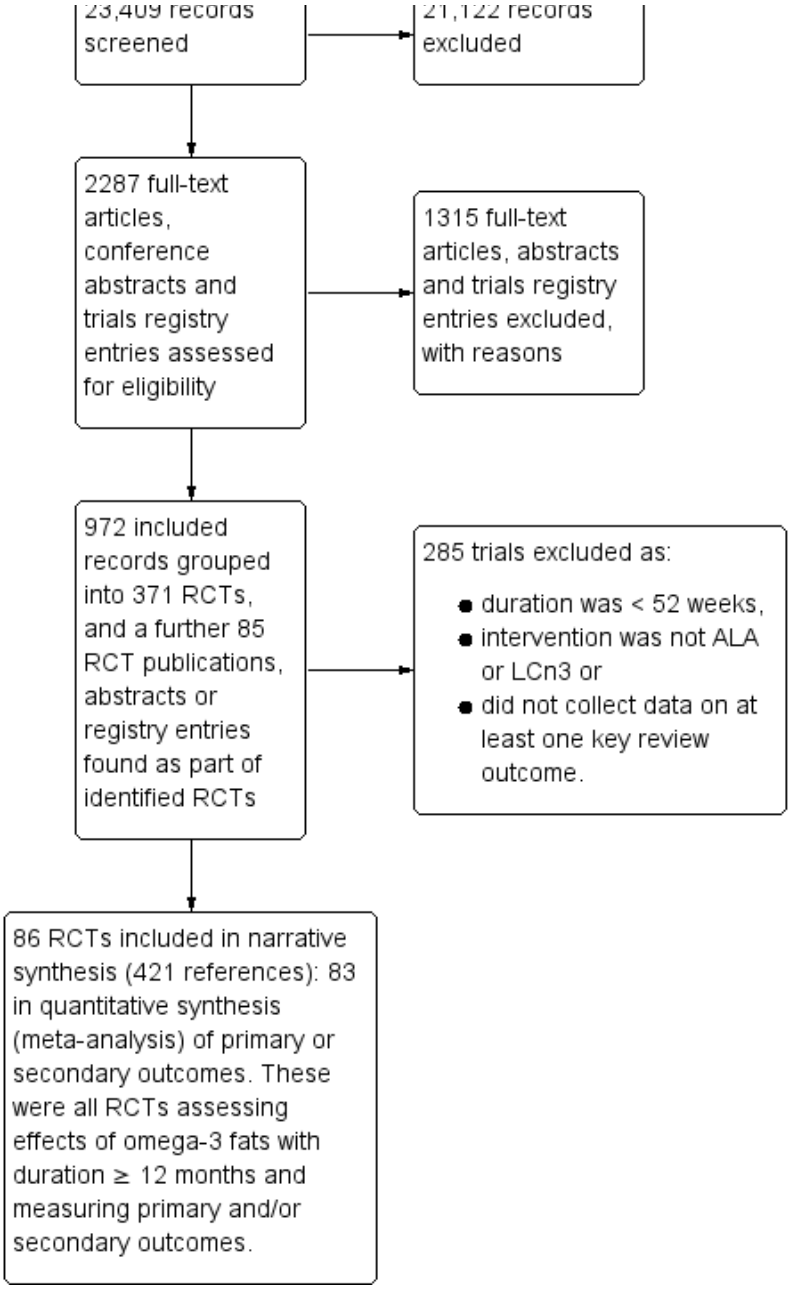
Figure 1. (Continued)



Of these 86 RCTs, we included 83 in meta-analyses. Three trials clearly collected relevant data but did not report them in a format that we could use in meta-analyses (Gill 2012; Ramirez-Ramirez 2013; Reed 2014; Figure 1).

Using the data provided in Aung 2018, we updated the data for 10 trials already included in this review (AlphaOmega - ALA 2010; AlphaOmega - EPA+DHA 2010; AREDS2 2014; DO IT 2010; GISSI-HF 2008; GISSI-P 1999; JELIS 2007; OMEGA 2009; ORIGIN 2012; Risk & Prevention 2013; SU.FOL.OM3 2010). This has allowed us to include additional outcomes for some trials, and use updated numbers for others.

Included studies

The 86 included RCTs randomised 162,796 participants, adding 31% to the number of participants with this update (we included 112,059 participants in the previous version of this review, Abdelhamid 2018a). Fifteen trials (16 comparisons) randomised at least 1000 participants (AlphaOmega - ALA 2010; AlphaOmega - EPA+DHA 2010; ASCEND 2018; AREDS2 2014; DART 1989; DART2 2003; GISSI-HF 2008; GISSI-P 1999; JELIS 2007; Norwegian 1968; OMEGA 2009; ORIGIN 2012; REDUCE-IT 2019; Risk & Prevention 2013; SU.FOL.OM3 2010; VITAL 2019), of which one was a 2x2 factorial trial, which included both interventions (AlphaOmega - ALA 2010; AlphaOmega - EPA+DHA 2010). Most of these larger trials assessed effects of LCn3 fats, but two trials/arms assessed effects of ALA (AlphaOmega - ALA 2010; Norwegian 1968).

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Participants had cardiovascular disease at baseline in 35 of the trials (secondary prevention), and the remaining 50 trials were of primary prevention, while one was mixed (REDUCE-IT 2019).

Most trials assessed effects of LCn3 fats.

- Sixty-nine trials increased LCn3 intake using supplementary capsules or medicinal oils (ADCS 2010; AFFORD 2013; Ahn 2016; AREDS2 2014; ASCEND 2018; Baldassarre 2006; Bates 1989; Berson 2004; Brox 2001; Caldwell 2011; Derosa 2016; Deslypere 1992; Doi 2014; DO IT 2010; DREAM Asbell 2018; ENRGISE 2018; EPE-A 2014 (as two different doses); EPIC-1 2008; EPIC-2 2008; EPOCH 2014; Erdogan 2007; FAAT 2005; FORWARD 2013; Franzen 1993; Gill 2012; GISSI-HF 2008; GISSI-P 1999; HARP 1995; HEARTS 2017; JELIS 2007; Kumar 2012; Kumar 2013; Lorenz-Meyer 1996; MAPT 2017; MARINA 2011; Mita 2007; NAT2 2013; Nodari 2011 AF; Nodari 2011 HF; Norouzi 2014; Nutristroke 2009; Nye 1990; OFAMI 2001; OMEGA 2009; OPAL 2010; ORIGIN 2012; ORL 2013; Özaydin 2011; Proudman 2015; Puri 2005; Raitt 2005; Ramirez-Ramirez 2013; REDUCE-IT 2019; Reed 2014; Risk & Prevention 2013; Rossing 1996; Sandhu 2016; SCIMO 1999; seAFOod Hull 2018; Shinto 2014; SHOT 1996; Sianni 2013; SOFA 2006; Sofi 2010; SU.FOL.OM3 2010; Tande 2016; VITAL 2019; WELCOME 2015; Zhang 2017).
- Two trials used supplemented or supplemental foods, either enriched margarine (AlphaOmega - EPA+DHA 2010) or orange juice (FOSTAR 2016) to increase LCn3.
- Four increased LCn3 fats using dietary advice (DART 1989; DART2 2003; DISAF 2003; THIS DIET 2008).
- Three provided some combination of these interventions to increase LCn3 (DIPP 2015; SMART 2013; Weinstock-Guttman 2005).

Doses of LCn3 ranged from 0.5 g/d of EPA and DHA to more than 5 g/d (19 RCTs had a dose of LCn3 < 1 g/d, 27 a dose of 1 to < 2 g/d, 12 of 2 to < 3 g/d, 19 RCTs had a dose of 3 or more g/d LCn3, 1 did not clearly state their dose).

Fewer trials assessed the effects of ALA on health outcomes.

- One trial used supplementary capsules or medicinal oils to increase ALA (Norwegian 1968).
- Seven increased ALA using supplemented or supplemental foods, such as enriched margarine, bread, walnuts or other enriched food products (AlphaOmega - ALA 2010; Broutset 2007; Dodin 2005; FLAX-PAD 2013; HERO 2009; MARGARIN 2002; WAHA 2016).
- One used a combination of these to increase ALA (MENU 2016).

One trial provided an intervention combining LCn3 and ALA as capsules (DIPP 2015). However, trial authors did not state the ALA dose, so we treated the trial as an LCn3 intervention.

Control groups received olive, corn, sunflower oils, other types of fats (including medium-chain triglycerides and fat replicating the composition of an average European diet), other 'inert' or ill-defined substances (liquid paraffin, aluminium hydroxide, 'placebo' not described), different dietary advice or foods without the omega-3 enrichment, or no treatment/no placebo. These control groups or replacements are shown for each key outcome when subgrouping by replacement (for example Analysis 1.6 shows effects of increasing LCn3 on all-cause mortality, grouped by replacement).

The main trial outcome was cardiovascular in 51 trials. Twenty-one trials (22 comparisons) aimed to measure death or cardiovascular events (AlphaOmega - ALA 2010; AlphaOmega - EPA+DHA 2010; ASCEND 2018; DART 1989; DART2 2003; Doi 2014; FAAT 2005; FLAX-PAD 2013; GISSI-HF 2008; GISSI-P 1999; JELIS 2007; Norwegian 1968; Nye 1990; OFAMI 2001; OMEGA 2009; ORIGIN 2012; REDUCE-IT 2019; Risk & Prevention 2013; SOFA 2006; SU.FOL.OM3 2010; THIS DIET 2008; VITAL 2019).

Thirty-two trials aimed to measure various cardiovascular risk factors or progression of cardiovascular health.

- Atrial fibrillation recurrence or sinus rhythm (AFFORD 2013; Broutset 2007; DISAF 2003; Erdogan 2007; FAAT 2005; FORWARD 2013; Kumar 2012; Kumar 2013; Nodari 2011 AF; Özaydin 2011; Raitt 2005; Sianni 2013)
- Atherosclerosis progression/regression (Ahn 2016; DO IT 2010; HARP 1995; HEARTS 2017; SCIMO 1999)
- Left ventricular function (Nodari 2011 HF)
- Coronary artery bypass graft patency (SHOT 1996)
- Lipids and other cardiovascular disease risk factors (Brox 2001; Deslypere 1992; Franzen 1993; MARGARIN 2002)
- Diabetes, insulin or glucose-based outcomes (Derosa 2016; Rossing 1996)
- Endothelial function or carotid intima-media thickness (Baldassarre 2006; Gill 2012; MARINA 2011; Mita 2007)
- Body weight and adiposity (HERO 2009; MENU 2016; SMART 2013)

Thirty-five RCTs assessed effects on other health states.

- Cognitive measures (ADCS 2010; EPOCH 2014; MAPT 2017; OPAL 2010; Shinto 2014; WAHA 2016; Zhang 2017)
- Eye health (AREDS2 2014; Berson 2004; DREAM Asbell 2018; NAT2 2013)
- Multiple sclerosis outcomes (Bates 1989; Weinstock-Guttman 2005)
- Cancer or pre-cancer outcomes (DIPP 2015; seAFOod Hull 2018; VITAL 2019)
- Bone health (Dodin 2005)
- Liver health (Caldwell 2011; EPE-A 2014; Sofi 2010; WELCOME 2015)
- Gastrointestinal health (Crohn's; EPIC-1 2008; EPIC-2 2008; Lorenz-Meyer 1996)
- Arthritis outcomes (FOSTAR 2016; Proudman 2015; Reed 2014)
- Functional status (ENRGISE 2018; Nutristroke 2009)
- Neurological function after spinal injury or in Huntington's disease (Norouzi 2014; Puri 2005)
- Safety outcomes and adverse events (ORL 2013; Tande 2016)
- Breast health (Sandhu 2016)
- Inflammatory markers (Ramirez-Ramirez 2013 plus ENRGISE 2018)

Most trials took place in high-income economies (World Bank 2018), but four were in upper-middle-income countries: Argentina (FORWARD 2013), Iran (Norouzi 2014), Turkey (Özaydin 2011), and

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China (Zhang 2017). No trials took place exclusively in low- or low-to middle-income countries. REDUCE-IT 2019 was a multi-centre trial that randomised participants in the USA, Netherlands, Ukraine, Russia, South Africa, Poland, India, Romania, Australia and New Zealand.

We identified a further 25 ongoing trials, which we describe in the table of Characteristics of ongoing studies. At the time of writing this review, all of these trials appear unpublished, and some were recruiting or delivering interventions or had recently been completed, and trial authors were presumably analysing data and writing up results. Others appear overdue for publication, and their status is unclear – they may constitute missing data.

Excluded studies

We read the full texts of over 1000 papers, so the full list of excluded trials is too extensive to add to this review. The main reason for exclusion of full-text papers was duration of less than 12 months (this was often unclear in abstracts, so we collected full-text papers to check).

We initially included several trials into our wider data set that we later excluded (Singh 1992; Singh 1997; Singh 1997; Singh 2002). Their exclusion was due to expressions of concern published by the *BMJ* and *The Lancet* (BMJ 2005; Horton 2005; White 2005). These expressions of concern followed extensive examination of the conduct, results and publication of these trials and questioned the veracity of data behind several trials published by RB Singh. Another trial that would otherwise have been included was retracted and so not included (Matsuyama 2005).

Risk of bias in included studies

We assessed summary risk of bias as low in 28 RCTs (29 comparisons: ADCS 2010; AlphaOmega - ALA 2010; AlphaOmega - EPA+DHA 2010; AREDS2 2014; ASCEND 2018; Berson 2004; Caldwell 2011; Derosa 2016; DREAM Asbell 2018; EPOCH 2014; FLAX-PAD 2013; FORWARD 2013; FOSTAR 2016; Lorenz-Meyer 1996; MAPT 2017; MARGARIN 2002; MARINA 2011; NAT2 2013; OMEGA 2009; OPAL 2010; ORIGIN 2012; Proudman 2015; Puri 2005; Reed 2014; SCIMO 1999; SOFA 2006; SU.FOL.OM3 2010; VITAL 2019; WELCOME 2015), and we deemed it to be moderate to high in the remainder. Our definition of low summary risk of bias is in the section Assessment of risk of bias in included studies. Figure 2 itemises risk of bias by domain and trial.

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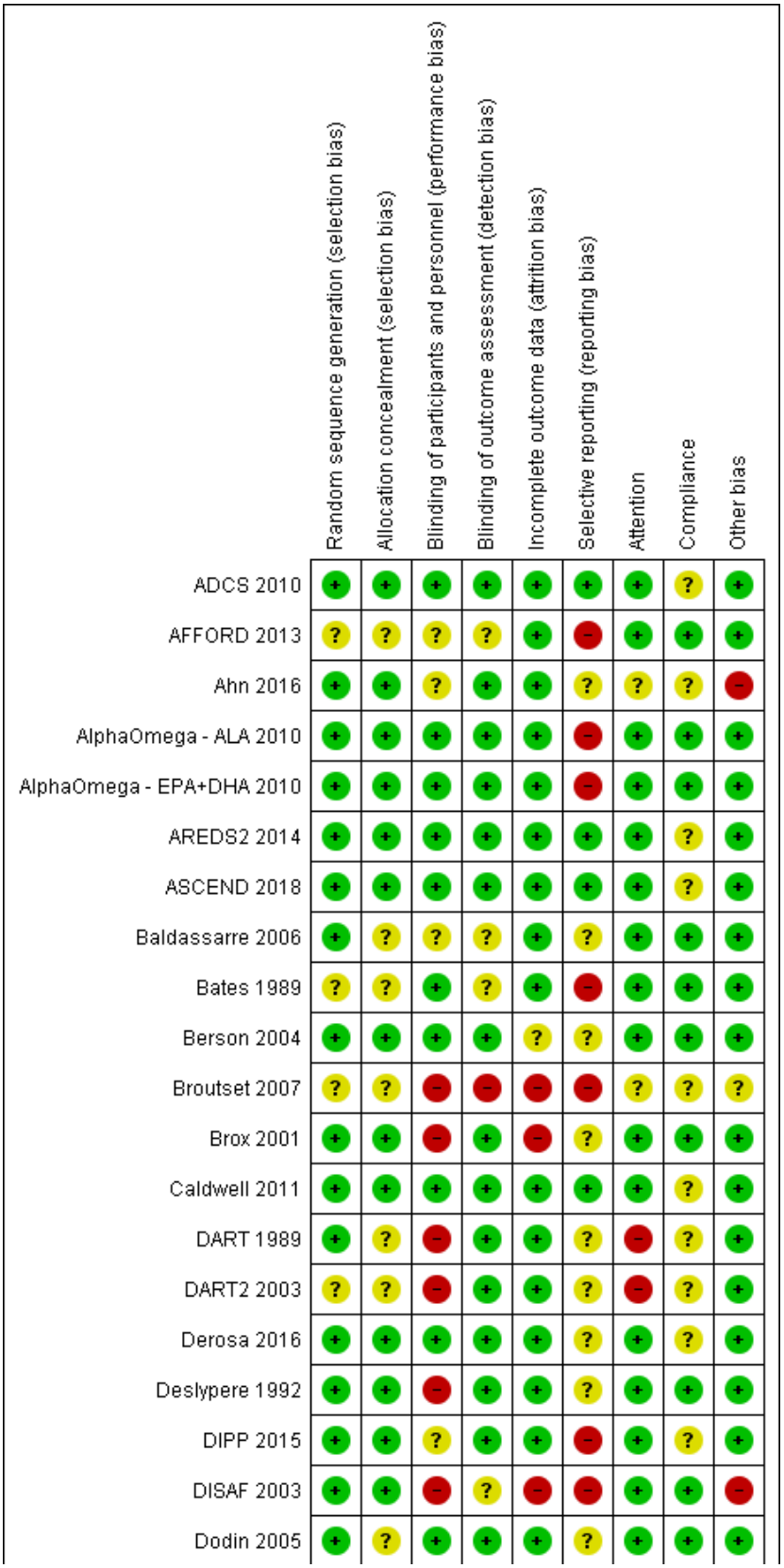
Figure 2. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study



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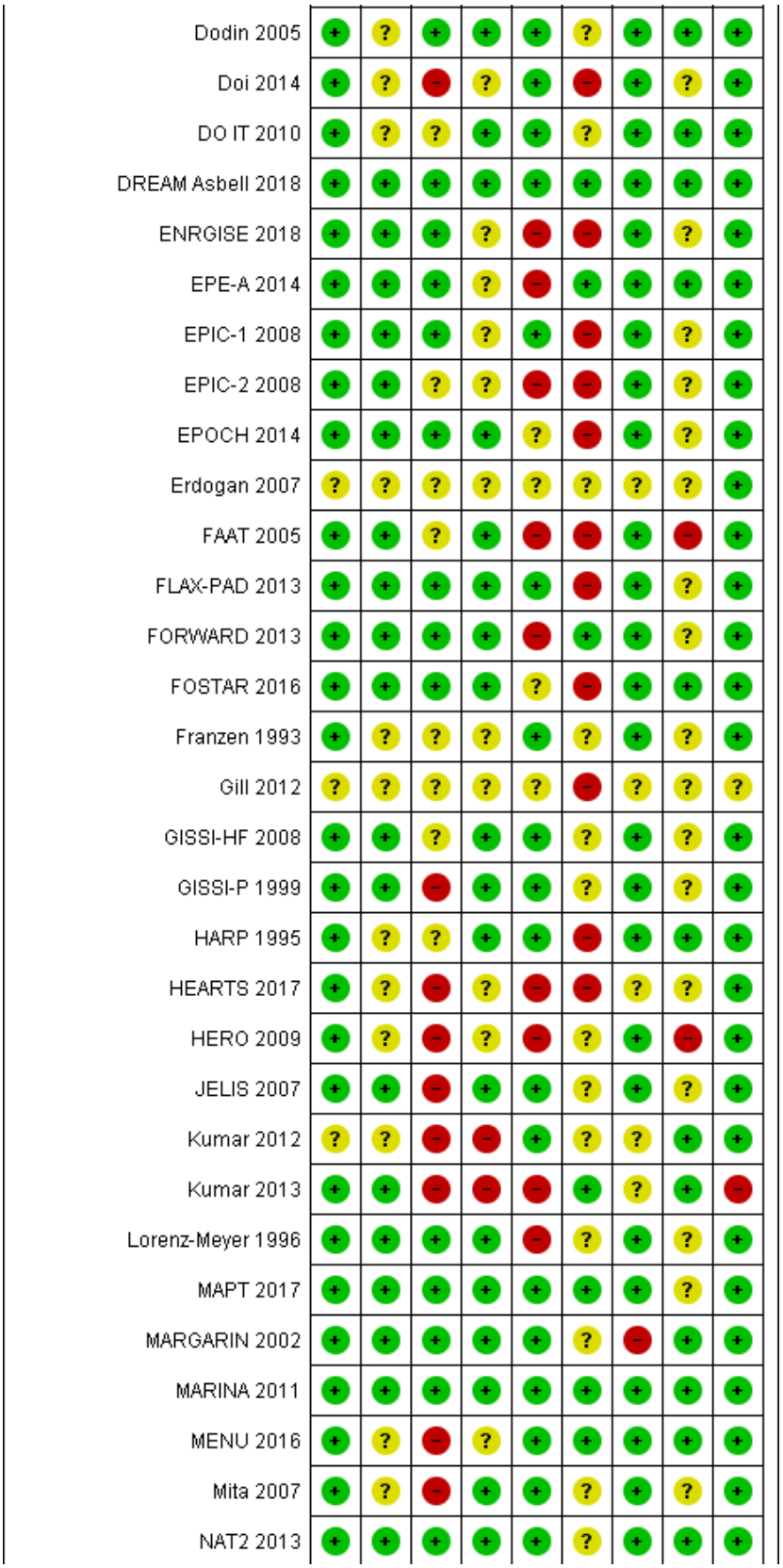

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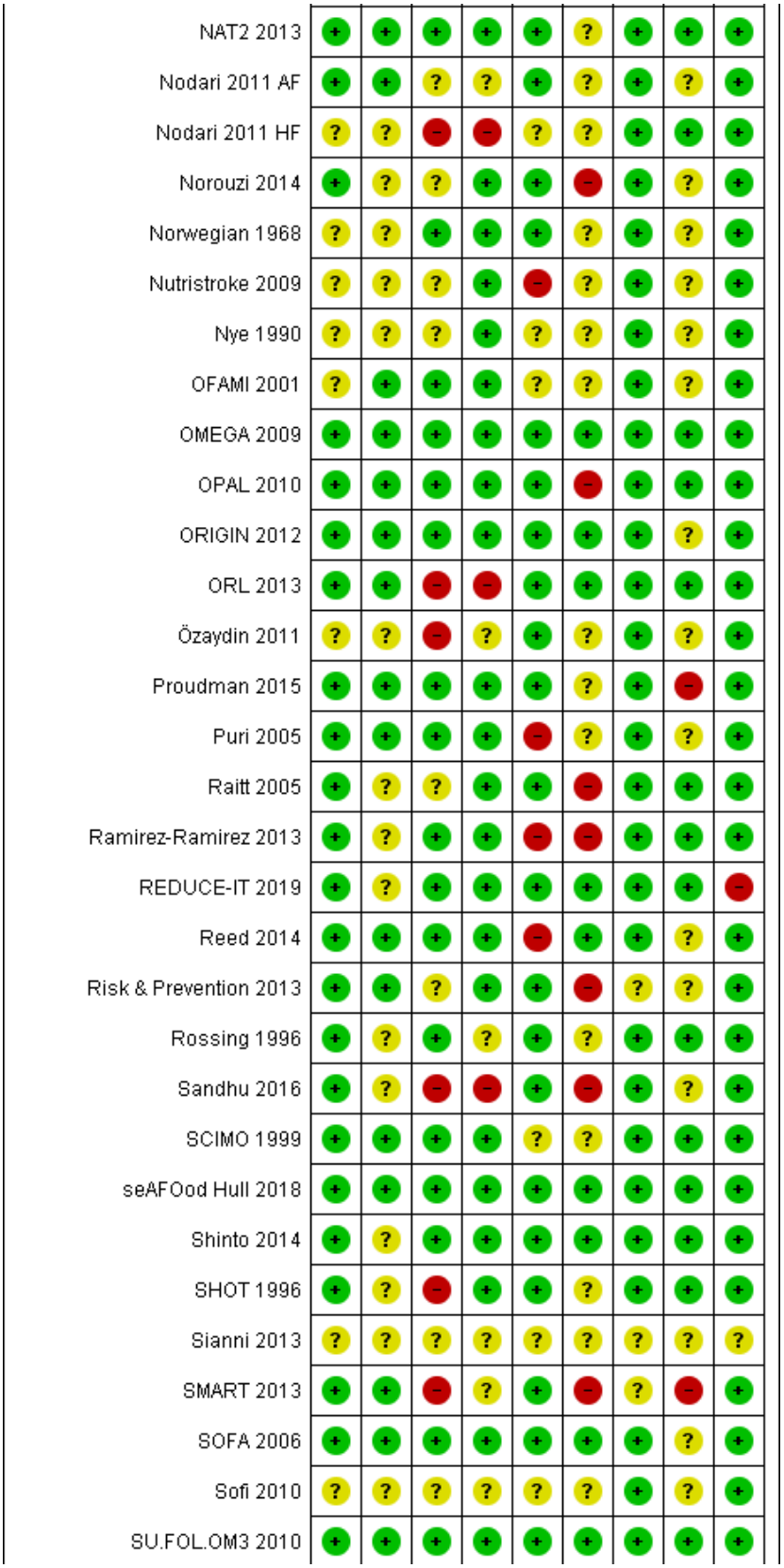

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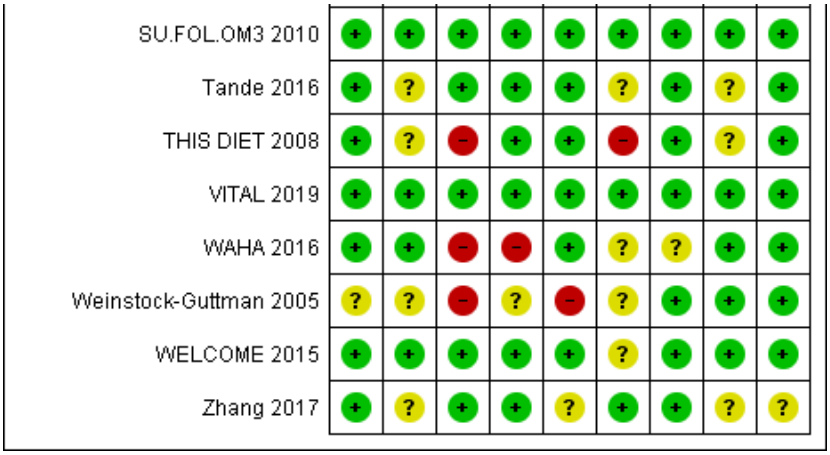

Allocation

Of the 86 RCTs (87 RCT arms as AlphaOmega - ALA 2010 and AlphaOmega - EPA+DHA 2010 which include the same participants are represented twice) described in the 'Risk of bias' summary (Figure 2), 69 trials (70 arms) described randomisation well enough to merit an assessment of low risk (the remainder were unclear), and 49 trials (50 arms) described adequate allocation concealment (the remaining 37 were unclear).

Blinding

We considered blinding of participants and personnel to be at low risk of bias in 42 of the 86 trials (43 arms). Lack of blinding of participants put 24 trials at high risk of bias, while the remaining 20 trials were at unclear risk. Blinding of outcome assessors put 57 trials (58 arms) at low risk of detection bias and at seven at high risk; this aspect was unclear in the remainder. We found that 37 trials (38 arms) were at low risk of both performance and detection bias.

Incomplete outcome data

We found that 57 trials (58 arms) were at low risk of attrition bias, 17 at high risk, and the remaining 12 at unclear risk.

Selective reporting

We determined that 22 trials had a pre-published trials registry entry or protocol and reported all planned outcomes appropriately so we considered them at low risk of selective reporting. Twenty-five trials (26 arms) were at high risk of selective reporting, omitting reports on either pre-stated outcomes or time points. We judged the remaining 39 trials to be at unclear risk of reporting bias as we could not find any protocol or prospective trial registry entry (often trials were published prior to trial registration availability).

Other potential sources of bias

We assessed risk of bias due to lack of compliance and attention bias and also noted other sources of bias. We found four trials to be at high risk of compliance bias (FAAT 2005; HERO 2009; Proudman 2015; SMART 2013), while 37 trials (38 arms) provided evidence of good compliance, and the remaining 45 trials were unclear. We noted a high risk of attention bias in three trials where intervention participants potentially had more dedicated time for dietary advice or follow-up (DART 1989; DART2 2003; MARGARIN 2002). Eleven trials did not provide enough details to assess so we considered them to be at unclear risk of attention bias (Ahn 2016; Broutset 2007; Erdogan 2007; Gill 2012; HEARTS 2017; Kumar 2012; Kumar 2013; Risk & Prevention 2013; Sianni 2013; SMART 2013; WAHA 2016), while we thought the remaining 72 trials (73 arms) were at low risk of attention bias. We judged four trials to be at high risk of other potential biases: Ahn 2016 because it is unclear whether it was placebo-controlled, and there was concern over reported standard deviations; DISAF 2003 because the trial stopped early; Kumar 2013 due to concerns over design; and REDUCE-IT 2019 because some data were presented for opposite arms in different publications. Four trials were at unclear risk due to insufficient methodological detail being provided (Broutset 2007; Gill 2012; Sianni 2013; Zhang 2017).

Effects of interventions

See: **Summary of findings for the main comparison** High versus low long-chain omega-3 fats for preventing cardiovascular disease and mortality (primary outcomes); **Summary of findings 2** High versus low alpha-linolenic acid omega-3 fats for preventing cardiovascular disease (primary outcomes); **Summary of findings 3** High versus low omega-3 fats for modification of cardiovascular disease risk factors (adiposity and lipids): key outcomes

Primary outcomes

See Summary of findings for the main comparison for a GRADE summary of our evidence on effects of long-chain omega-3 (LCn3) fats (including eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA)) on our primary outcomes.

Effects of long-chain omega-3 fats on primary health outcomes

All-cause mortality (LCn3)

High-certainty evidence showed little or no effect of LCn3 on all-cause mortality.

There was little or no effect of increasing LCn3 fats on all-cause mortality, despite 11,297 deaths in more than 143,000 participants (RR 0.97, 95% CI 0.93 to 1.01; I^2 = 5%; Analysis 1.1). The funnel plot suggested that some small trials with higher numbers of deaths in the intervention group might be missing (Figure 3), indicating small study bias, though there was almost no difference between random-effects and fixed-effect analysis. If any such missing trials

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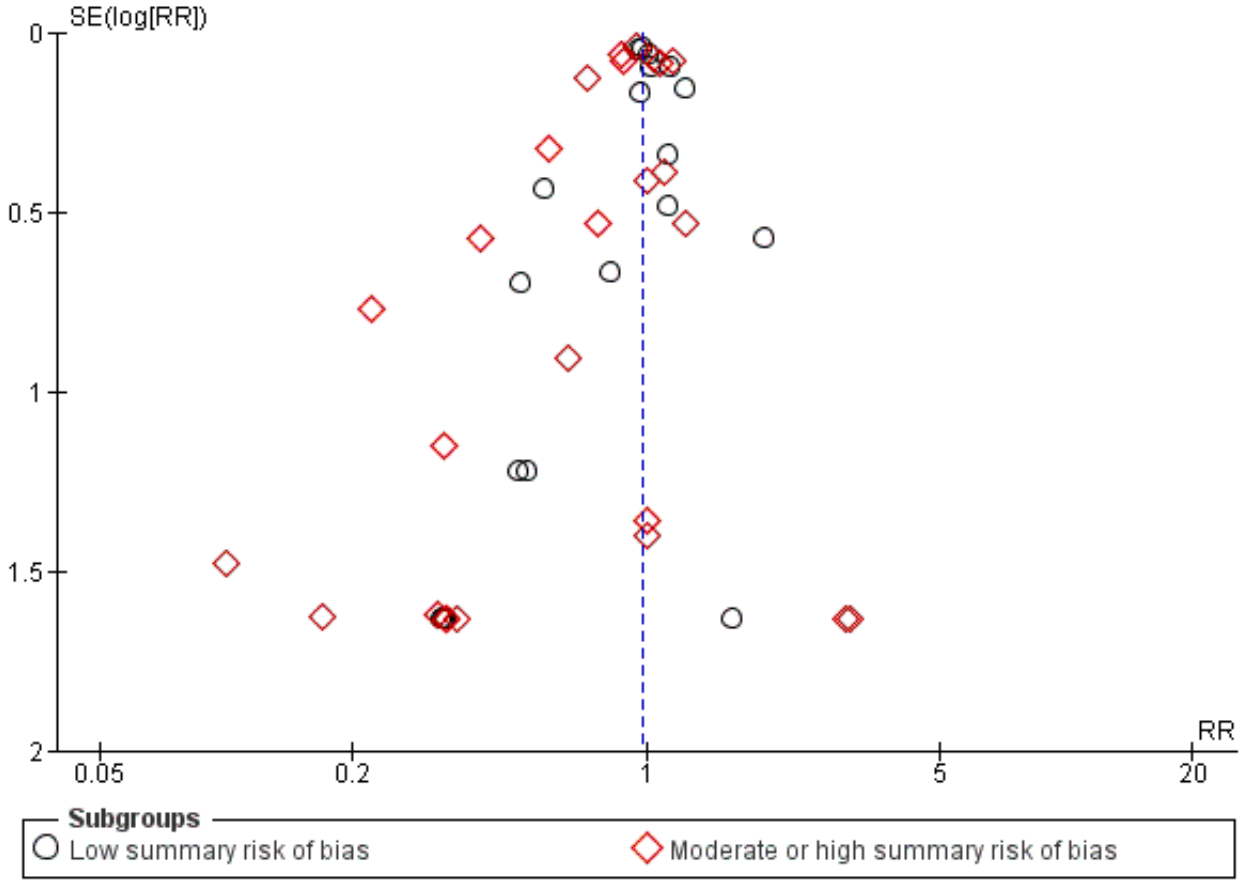
were added back in the RR would rise slightly (towards the null value of 1.0).

Figure 3. Funnel plot of comparison 1. High versus low long-chain omega-3 fats (primary outcomes), outcome 1.3, all-cause mortality, sensitivity analysis by summary risk of bias



Sensitivity analyses using fixed-effect meta-analysis did not alter the lack of effect on all-cause mortality (RR 0.97, 95% CI 0.93 to 1.00; Analysis 1.2). Removing RCTs not at low summary risk of bias left us with 19 RCTs involving over 75,000 participants, 5579 of whom died, suggesting no effect of LCn3 on mortality (RR 0.99, 95% CI 0.95 to 1.04; I^2 = 0%; Analysis 1.3). This lack of effect was also evident in sensitivity analyses limited to trials at low risk of compliance bias and to larger trials (Analysis 1.4).

The lack of effect for LCn3 on mortality did not differ by replacement with MUFA, omega-6 fats or other types of placebo compounds (Analysis 1.6). There was no suggestion of any dose effect for LCn3 fats on mortality (Analysis 1.5), and subgroups with RRs further away from 1.00 had wide 95% confidence intervals. The lack of effect did not differ by primary versus secondary prevention (Analysis 1.9), statin use (Analysis 1.10), mode of intervention (dietary advice, supplemental foods, or capsules, Analysis 1.7), baseline triglycerides (Analysis 1.11) or baseline diabetic status (Analysis 1.12). While there was some suggestion of a small risk reduction in total mortality with LCn3 in trials with medium to long duration (2 to < 4 years, RR 0.91, 95% CI 0.86 to 0.96) and this subgroup was clearly different from other durations (test for subgroup differences P = 0.03), the effect was not evident in shorter (1 to < 2 years) or longer trials (≥ 4 years, RR 1.00, 95% CI 0.96 to 1.05). Because of the lack of effect in longer trials, we did not assume any duration effects (Analysis 1.8).

As there was no suggestion of any effect of LCn3 fats on all-cause mortality, we did not carry out meta-regression.

GRADE assessment suggested that the finding of little or no effect of LCn3 on all-cause mortality was supported by high-certainty evidence (not downgraded, Summary of findings for the main comparison).

Cardiovascular disease mortality (LCn3)

Moderate-certainty evidence suggests that LCn3 fat intake probably makes little or no difference to cardiovascular deaths.

Twenty-nine trials in 117,837 participants, 5658 of whom died of cardiovascular disease, reported on cardiovascular mortality (RR 0.92, 95% CI 0.86 to 0.99; I^2 = 22%; Analysis 1.13). The funnel plot suggested that some smaller trials with more cardiovascular deaths in the intervention group were missing (some small study bias, Figure 4). If this were the case then adding the missing trials would increase the RR slightly towards the null (no effect). This was

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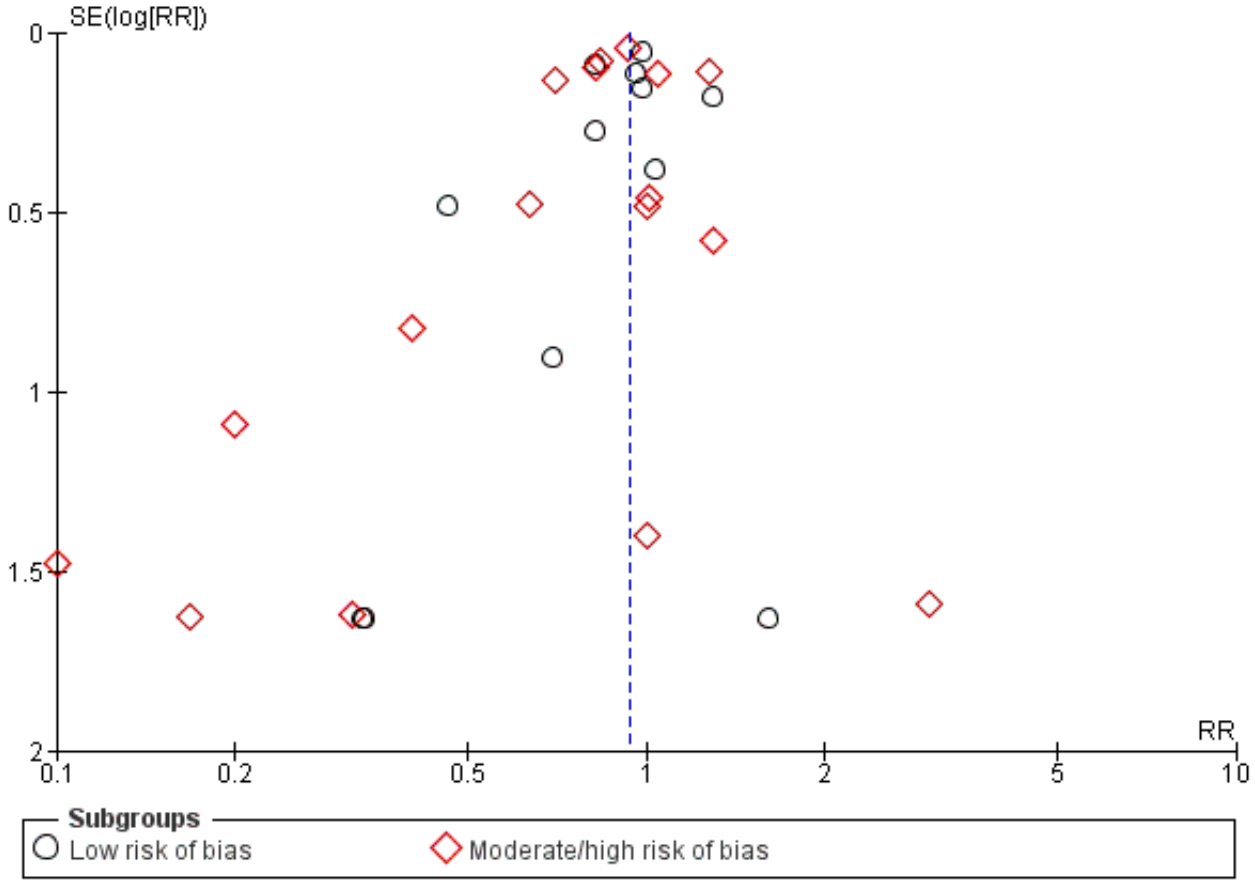
supported by the fixed-effect meta-analysis effect being closer to the null than the random-effects model.

Figure 4. Funnel plot of comparison 1. High vs low long-chain omega-3 fats (primary outcomes), outcome 1.15, cardiovascular disease mortality, sensitivity analysis by summary risk of bias



Fixed-effect meta-analysis suggested little or no effect on cardiovascular disease mortality risk (RR 0.93, 95% CI 0.88 to 0.97; Analysis 1.14). Sensitivity analyses removing RCTs not at low summary risk of bias left 12 RCTs in 71,019 participants, 2266 of whom died, also suggesting little or no effect of LCn3 on cardiovascular disease mortality (RR 0.95, 95% CI 0.88 to 1.03; I^2 = 0%; Analysis 1.15). Removing trials not at low risk of compliance bias and retaining only larger trials produced similar effects to the main analysis (Analysis 1.16).

There were no statistically significant differences between subgroups and no differential effects by replacement (Analysis 1.18), mode of intervention (Analysis 1.19), duration (Analysis 1.20), primary or secondary prevention (Analysis 1.21), statin use (Analysis 1.22), omega-3 dose (Analysis 1.17), baseline triglyceride level (Analysis 1.23) or diabetes status (Analysis 1.24). There was no suggestion of a dose-response effect.

Meta-regression to assess effects of LCn3 dose, ALA, omega-6 and total PUFA dose, trial duration, intervention type, primary or secondary prevention and risk of bias (as well as a single multiple regression of the three factors with the smallest P values) showed no association between these factors and risk of cardiovascular mortality (all P values were > 0.2, Table 2). We saw no suggestion of dose-response or duration effects.

The suggestion of a marginally protective effect disappeared in trials at low summary risk of bias, the funnel plot suggests that the true risk ratio is slightly higher than the main estimate, and there was no suggestion of dose or duration effects; thus we summarised the evidence as showing little or no effect of LCn3 on cardiovascular disease mortality. GRADE assessment suggested moderate-certainty evidence that LCn3 fat intake probably makes little or no difference to cardiovascular deaths (downgraded once for imprecision).

Combined cardiovascular events (LCn3)

High-certainty evidence suggests that LCn3 intake makes little or no difference to risk of cardiovascular events.

There was little or no effect of increasing LCn3 fats on cardiovascular events (RR 0.96, 95% CI 0.92 to 1.01; I^2 = 44%; Analysis 1.25). Analyses included 17,619 participants with cardiovascular events in 140,482 participants in 43 trials. The funnel plot suggested that some smaller trials with more participants experiencing cardiovascular events in the intervention group were

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missing (some small study bias, not shown). If this were the case then adding the missing trials would increase the RR. However effect sizes were the same in fixed-effect and random-effects analyses suggesting any bias is limited.

Sensitivity analyses removing trials at moderate to high risk of bias left 16 trials, including 73,000 participants, 7951 of whom had cardiovascular disease events, with no suggestion of any effect of LCn3 fats (RR 0.98, 95% CI 0.95 to 1.02; I^2 = 0%; Analysis 1.27). Sensitivity analyses including trials at low risk of compliance bias, at low risk of small study bias and using fixed-effect meta-analysis did not suggest any effect of LCn3 on cardiovascular disease events (Analysis 1.26; Analysis 1.28).

In subgroup analysis there was no suggestion of a dose-response effect (Analysis 1.29). Effects did not differ by replacement (Analysis 1.30), baseline cardiovascular disease risk (Analysis 1.33), type of intervention (Analysis 1.31), statin use (Analysis 1.34), LCn3 dose (Analysis 1.29), trial duration (Analysis 1.32), baseline triglycerides (Analysis 1.35) or baseline diabetic status (Analysis 1.36), and there were no important differences between subgroups.

Meta-regression suggested a negative relationship between LCn3 dose and risk of cardiovascular disease events (P = 0.02), suggesting reduction in cardiovascular disease risk at higher LCn3 doses, as would be expected from a dose response. However, when the single outlying trial REDUCE-IT 2019 (with a large effect size and high dose) was omitted, the P value was 0.997 suggesting no relationship between LCn3 dose and risk of cardiovascular disease events. The effect was also moderated in the multiple regression (P = 0.07). Meta-regression did not suggest associations between ALA, omega-6 or total PUFA dose, trial duration, intervention type, primary or secondary prevention, risk of bias or the single multiple regression of the three factors with the smallest P values (Table 3).

GRADE assessment suggested high-certainty evidence that LCn3 intake makes little or no difference to risk of cardiovascular events (not downgraded).

Coronary heart disease mortality (LCn3)

Low-certainty evidence suggests that increasing LCn3 fat intake may slightly reduce coronary heart mortality (NNTB 334).

Increasing LCn3 fats reduced the risk of coronary heart mortality by 10% (RR 0.90, 95% CI 0.81 to 1.00; I^2 = 35%) in 24 trials reporting 3598 events in more than 127,000 participants (Analysis 1.37). Sensitivity analyses using a fixed-effect model suggested little or no effect on coronary heart disease mortality (RR 0.92, 95% CI 0.86 to 0.98; Analysis 1.38).

Retaining only RCTs at low summary risk of bias, meta-analysis of 10 trials with more than 70,000 participants and 1180 coronary heart disease deaths suggested that increasing LCn3 fats reduced coronary heart disease deaths (RR 0.89, 95% CI 0.76 to 1.04; I^2 = 22%; Analysis 1.39). Sensitivity analyses retaining only trials with low risk of compliance bias suggested a 17% reduction in risk with LCn3, retaining only larger trials suggested a 13% reduction (Analysis 1.40). The funnel plot suggested that some smaller trials with higher RRs were missing, and if added back these would increase the RR. The presence of such small study bias is supported by the reduction in effect size in fixed-effect compared to random-effects meta-analysis (random-effects meta-analysis weighs information from small trials more heavily).

When we added this outcome we prespecified that we would use the first of the following list reported in any trial: coronary death, ischaemic heart disease death, fatal myocardial infarction and cardiac death. We used cardiac death only when no other outcomes in this category were available, and we ran a sensitivity analysis omitting cardiac death as it potentially includes other causes of death in addition to coronary heart disease, such as cardiomyopathies and congenital and valvular heart diseases (though numbers are likely to be small). Omitting cardiac death resulted in a 19% reduction in coronary heart disease deaths with LCn3 (RR 0.81, 95% CI 0.73 to 0.90, I^2 = 0%, 18 trials including 106,676 participants, Analysis 1.41).

There were no statistically significant differences between subgroups for LCn3 dose (Analysis 1.42), type of intervention (Analysis 1.44), duration (Analysis 1.45), primary or secondary prevention (Analysis 1.46), statin use (Analysis 1.47), baseline coronary artery disease status (Analysis 1.48), replacement (Analysis 1.43), baseline triglycerides (Analysis 1.49) or diabetes status (Analysis 1.50).

Meta-regression to assess associations between LCn3 dose and risk of coronary heart disease mortality found no relationship (P = 0.89, Table 4). Similarly we saw no relationships between ALA dose, omega-6 dose, total PUFA dose, duration, intervention type, primary or secondary prevention, or risk of bias and coronary heart disease deaths (all P values were > 0.40, Table 4). Multiple regression of the three factors with the smallest P value found no factors associated with risk of coronary heart disease deaths. We saw no suggestion of dose or duration effects.

The NNTB is 334 (95% CI 200 to infinity), so 334 people would need to increase their LCn3 intake to prevent one death from coronary heart disease. If we assess NNTB by primary or secondary prevention of cardiovascular disease, people without previous cardiovascular disease (needing primary prevention) have an NNTB of 1000 (95% CI NNTB 334 to NNTH 1000), while those with existing cardiovascular disease have an NNTB of 200 (95% CI NNTB 112 to NNTH 500).

The suggestion of a small protective effect was seen across sensitivity analyses, excepting fixed-effect analysis. We summarised the evidence as indicating that increasing LCn3 reduces coronary heart disease mortality. GRADE assessment suggested low-certainty evidence that LCn3 fat intake may slightly reduce coronary heart mortality (downgraded once for imprecision and once for publication bias).

Coronary heart disease events (LCn3)

Low-certainty evidence suggests that LCn3 fat intake may slightly reduce the risk of coronary heart events (NNTB 167).

The main meta-analysis suggested a 9% reduction in people experiencing coronary heart disease events with higher intake of LCn3 fats (RR 0.91, 95% CI 0.85 to 0.97; I^2 = 37%; 32 trials, 8777 events, 134,116 participants; Analysis 1.51). The funnel plot did not suggest serious small study bias (Figure 5), but effect sizes in fixed-effect meta-analysis were slightly smaller.

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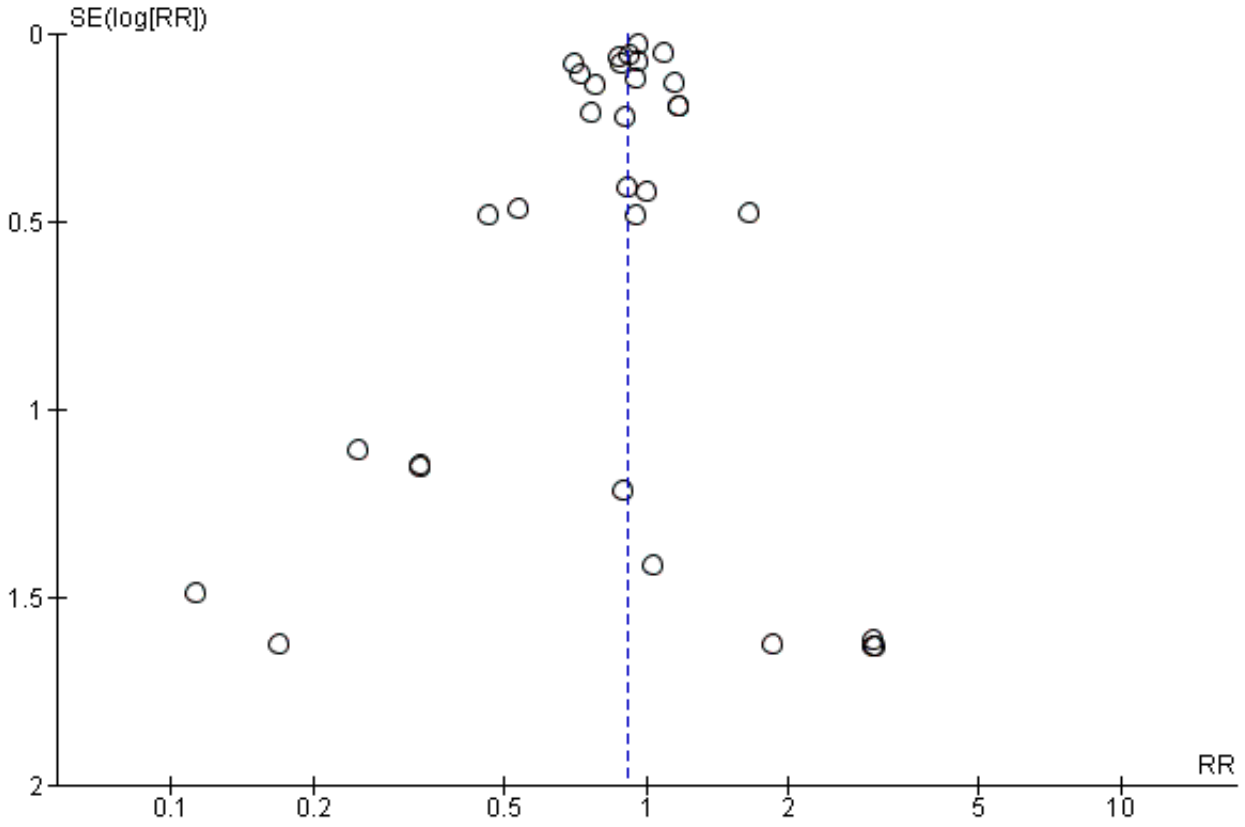
Figure 5. Funnel plot of comparison 1. High vs low long-chain omega-3 fats (primary outcomes), outcome 1.51, coronary heart disease events (overall)



The size of any effect was reduced in sensitivity analyses using a fixed-effect model (RR 0.93, 95% CI 0.89 to 0.96; Analysis 1.52) and when we limited trials to those at low summary risk of bias (RR 0.93, 95% CI 0.82 to 1.05, I^2 = 38%, Analysis 1.53), but increased when analyses were limited to trials with good compliance and to larger trials (Analysis 1.54).

There were no statistically significant differences between subgroups (Analysis 1.55; Analysis 1.56; Analysis 1.57; Analysis 1.58; Analysis 1.59; Analysis 1.60; Analysis 1.61; Analysis 1.63), except for subgrouping by baseline triglyceride, where the subgroup of trials with raised triglyceride suggested a greater reduction in coronary heart disease events (Analysis 1.62).

Meta-regression suggested a negative relationship between LCn3 dose and risk of coronary heart disease events (P = 0.02), suggesting reduction in coronary heart disease risk at higher LCn3 doses, as would be expected from a dose response. This was weakened in the single multiple regression of the three factors with the smallest P value (P = 0.06). When we omitted the single outlying trial REDUCE-IT 2019, meta-regression no longer suggested any relationship between LCn3 dose and risk of coronary heart disease events (P = 0.81). Meta-regression did not suggest associations between ALA, omega-6 or total PUFA dose, trial duration, intervention type, primary or secondary prevention, or risk of bias and risk of coronary heart disease events (Table 5).

167 people would need to increase their LCn3 intake for one person to avoid a coronary heart disease event (NNTB 167, 95% CI 100 to 500). If we separate this out for people without existing cardiovascular disease the NNTB is 200 for primary prevention (95% CI NNTB 112 to NNTB infinity), and the NNTB is 143 for people with existing cardiovascular disease, secondary prevention, (95% CI NNTB 91 to NNTH 500).

While there was a small protective effect in the main analysis and some sensitivity analyses, but not in sensitivity analyses limiting to RCTs at low summary risk of bias or using fixed-effect analysis, there was also a suggestion of a dose response. We summarised this as suggesting a true effect of around 8%. GRADE assessment suggested low-certainty evidence that increasing LCn3 fat intake may slightly reduce risk of coronary heart events (downgraded twice for risk of bias).

Stroke (LCn3)

Moderate-certainty evidence suggests that LCn3 fat intake probably makes little or no difference to risk of experiencing a stroke.

Increasing intake of LCn3 appears to have little effect on risk of stroke (RR 1.02, 95% CI 0.94 to 1.12; I^2 = 11%; 31 trials reported 2850 strokes; Analysis 1.64), and the funnel plot did not suggest small study bias (not shown).

Sensitivity analyses removing trials not at low summary risk of bias left 14 trials with 1684 participants experiencing strokes, suggesting

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little or no effect of LCn3 fats on stroke (RR 0.99, 95% CI 0.90 to 1.09; I^2 = 0%; Analysis 1.66). Using fixed-effect meta-analysis and sensitivity analysis removing trials with risk from poor compliance and smaller trials all suggested no effect of increased LCn3 (Analysis 1.66; Analysis 1.68).

When trials reported stroke type separately, the risk of haemorrhagic stroke was increased (RR 1.23, 95% CI 0.93 to 1.64; I^2 = 0%; 197 participants with events), while ischaemic stroke was unaltered (RR 0.98, 95% CI 0.79 to 1.20; I^2 = 47%; 985 people with events in 10 trials; Analysis 1.68). Six trials reported only 152 participants experiencing transient ischaemic attack, suggesting a 10% increase in risk but with very wide confidence intervals (transient ischaemic attacks were not included in any other stroke categories; Analysis 1.68). Subgrouping did not suggest important differences by intervention type, replacement, statin use, trial duration, baseline triglycerides or diabetic status (Analysis 1.70; Analysis 1.71; Analysis 1.72; Analysis 1.74; Analysis 1.75; Analysis 1.76). Subgrouping by dose suggested important differences in effect at different doses, but there was no pattern to these effects so they were assumed to be spurious (Analysis 1.69). There was a suggestion of increased stroke risk in people with cardiovascular disease at baseline (RR 1.21, 95% CI 1.05 to 1.40; I^2 = 0%; with differences in effect size between subgroups by primary or secondary prevention, P = 0.002; Analysis 1.73).

Meta-regression to assess effects of LCn3 dose did not find any clear dose response on risk of stroke (P = 0.12, Table 6). Univariate meta-regression suggested that trials of longer duration showed smaller risk ratios (or lower risk, P = 0.03), and this effect was retained in the multivariate regression (P = 0.03). There were no clear relationships between dose of any PUFA type, risk of bias, or use of food or capsules, and only trial duration remained statistically significant in multivariate meta-regression.

Analyses consistently suggested little or no effect of LCn3 on stroke risk, and there were no dose-response relationships, though there is a possible increase in risk of haemorrhagic stroke with increased LCn3. GRADE assessment suggests moderate-certainty evidence that LCn3 fat intake probably makes little or no difference to risk of experiencing a stroke (downgraded once for imprecision).

Arrhythmia (LCn3)

Low-certainty evidence suggests that LCn3 fat intake may slightly increase the risk of arrhythmia (NNTH 1000).

There was little or no effect of LCn3 fats on incidence of new or recurrent (fatal and non-fatal) arrhythmias (RR 0.99, 95% CI 0.92 to 1.06; I^2 = 44%; 4586 events in more than 77,000 participants; Analysis 1.77). The funnel plot was not interpretable as trials were clustered (not shown), but the effect size moved above 1 in fixed-effect meta-analysis, suggesting that some trials suggesting harm from increased LCn3 may be missing.

Sensitivity analyses removing trials not at low summary risk of bias left 12 trials with 1602 events (> 41,000 participants), suggesting a 9% increase in risk of arrhythmia with increased LCn3 (RR 1.09, 95% CI 0.99 to 1.20, I^2 = 0%, Analysis 1.79). Restricting the analysis to trials at low summary risk of bias removed heterogeneity, and there was a statistically significant difference in effect size between subgroups at low versus moderate to high risk of bias (P = 0.04, Analysis 1.79). Using fixed-effect methodology did not alter the apparent lack of effect of LCn3 on arrhythmia (Analysis 1.78), and sensitivity analysis by compliance and trial size also suggested little or no effect of LCn3 on arrhythmia (Analysis 1.80).

Subgrouping by new or recurrent arrhythmias suggested differences between subgroups, with LCn3 increasing the risk of new arrhythmias and having little or no effect on the risk of recurrent arrhythmia (Analysis 1.81). There were also statistically significant differences between subgroups by fatality, suggesting that LCn3 increases the risk of fatal arrhythmia, but protects against non-fatal arrhythmia (Analysis 1.82), primary or secondary prevention, suggesting harm in primary prevention, little or no effect in secondary prevention (Analysis 1.87) and duration, suggesting little or no effect in trials of up to four years' duration and harm in longer trials (Analysis 1.86). Subgroup analyses by type of intervention, replacement, statin use, dose and baseline triglyceride did not suggest statistically significant differences between subgroups (Analysis 1.83; Analysis 1.84; Analysis 1.85; Analysis 1.88; Analysis 1.89). Subgrouping by diabetes status suggested significant differences between subgroups, with little or no effect of increasing LCn3 on arrhythmia for those recruited without specific diabetes risk factors, but increased risk of arrhythmia in those with diabetes risk factors and in those with diabetes at baseline (Analysis 1.90).

Meta-regression suggested a positive relationship between trial duration and risk ratio, such that longer trials appeared to increase arrhythmia risk (P = 0.03; Table 7). This relationship was lost when we controlled for primary or secondary prevention and ALA dose (P = 0.42). There was also a relationship between arrhythmia with primary versus secondary prevention, suggesting greater risk ratio (harm) in primary prevention (P = 0.03; Table 7). There were no other suggested relationships, and neither of these relationships were maintained in multivariate analysis.

Overall, the trials at lower risk of bias, and the longer trials, suggested slight harm from increasing LCn3. This suggests that there may be some harm associated with increasing LCn3 on arrhythmia risk, and fatal arrhythmia, particularly in the longer term and in primary prevention. One thousand people would need to increase their LCn3 intake for one additional person to experience arrhythmia (NNTH 1000, 95% CI 200 to −334). GRADE assessment suggested low-certainty evidence that LCn3 fat intake may slightly increase the risk of arrhythmia (downgraded once for risk of bias and once for imprecision).

Effects of alpha-linolenic acid (ALA) on primary health outcomes

See Summary of findings 2 for a summary of our evidence on effects of ALA on our primary outcomes.

As there were fewer than 10 trials for all ALA analyses we did not create or assess funnel plots, though we did run sensitivity analyses and subgroups. We assessed ALA dose-response and duration effects in meta-regression of all included LCn3, ALA, omega-6 and total PUFA trials (but not of ALA trials alone as there were too few trials to carry out meta-regression with any reliability). None of the trials that increased ALA intakes were in participants with raised baseline triglycerides, increased risk of diabetes or diabetes at baseline, so we did not subgroup by baseline triglycerides or diabetic status.

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All-cause mortality (ALA)

Moderate-certainty evidence suggests that ALA intake probably makes little or no difference to all-cause mortality.

There was little or no effect of increasing ALA omega-3 fats on all-cause mortality, with 459 deaths in more than 19,000 participants involved in five trials (RR 1.01, 95% CI 0.84 to 1.20; I^2 = 0%; Analysis 4.1).

Sensitivity analyses removing trials not at low summary risk of bias left three trials with 375 deaths, again suggesting little or no effect (RR 1.02, 95% CI 0.72 to 1.45; I^2 = 3%; Analysis 4.3). Other sensitivity analyses all suggested little or no effect (Analysis 4.2; Analysis 4.4).

Subgrouping by ALA dose, trial duration, statin use, replacement, primary or secondary prevention, or intervention type did not result in any significant differences between subgroups (Analysis 4.5; Analysis 4.6; Analysis 4.7; Analysis 4.8; Analysis 4.9; Analysis 4.10). As there was no suggestion of effect in any subgroup, we did not carry out meta-regression.

GRADE assessment suggested that ALA intake probably makes little or no difference to all-cause mortality (moderate-certainty evidence, downgraded once for imprecision).

Cardiovascular mortality (ALA)

Moderate-certainty evidence suggests that increasing ALA intake probably has little or no effect on cardiovascular mortality.

Four trials contributed data to this outcome. There was little or no effect of increasing ALA omega-3 fats on cardiovascular mortality (RR 0.96, 95% CI 0.74 to 1.25; I^2 = 0%; Analysis 4.11), but confidence intervals were very wide. Analyses included 219 cardiovascular disease deaths in more than 18,000 participants. All sensitivity analyses suggested little or no effect of increasing ALA (Analysis 4.12; Analysis 4.13; Analysis 4.14).

Subgrouping by ALA dose, trial duration, replacement, intervention type, statin use, or primary or secondary prevention did not suggest important differences between subgroups (Analysis 4.15; Analysis 4.16; Analysis 4.17; Analysis 4.18; Analysis 4.19; Analysis 4.20). Meta-regression to assess for effects of ALA dose on cardiovascular mortality did not suggest dose effects (P = 0.88; Table 2).

GRADE assessment suggested that increasing ALA intake probably has little or no effect on cardiovascular mortality (moderate-certainty evidence, downgraded once for imprecision).

Cardiovascular events (ALA)

GRADE assessment suggested low-certainty evidence that increasing ALA intake may slightly reduce the risk of cardiovascular events (NNTB 500).

There was little or no effect on risk of cardiovascular events in five trials with increased ALA intake (RR 0.95, 95% CI 0.83 to 1.07; I^2 = 0%; 884 out of > 19,000 participants experienced at least one cardiovascular event; Analysis 4.21). Sensitivity analyses removing trials at moderate to high risk of bias left three trials in which 691 of more than 5000 enrolled participants experienced at least one cardiovascular event, suggesting a 9% reduction in risk of cardiovascular disease events with higher ALA (RR 0.91, 95% CI 0.79 to 1.04; I^2 = 0%; Analysis 4.23). Fixed-effect analysis, and limiting to larger trials, suggested little or no effect on cardiovascular disease event risk (Analysis 4.22; Analysis 4.24), while trials at low risk of compliance bias suggested a 10% reduction in risk (Analysis 4.24).

Subgrouping by ALA dose, trial duration, replacement, intervention type, statin use, or primary or secondary prevention did not suggest significant differences between subgroups (Analysis 4.25; Analysis 4.26; Analysis 4.27; Analysis 4.28; Analysis 4.29; Analysis 4.30). Meta-regression to assess for effects of ALA dose on cardiovascular events did not suggest dose effects (P = 0.67; Table 3).

The NNTB was 500 (95% CI 125 to −334), so 500 people would need to increase their ALA intake to prevent one person experiencing a cardiovascular event. The NNTB for primary prevention was 500 (95% CI 125 to −112), the NNTB for secondary prevention was 84 (95% CI 35 to 143). GRADE assessment suggested that increasing ALA intake may reduce the risk of cardiovascular events by a small amount (low-certainty evidence, downgraded once for risk of bias and once for imprecision).

Coronary heart disease mortality (ALA)

GRADE assessment suggested that increasing ALA intake probably has little or no effect on coronary heart disease mortality.

Three trials reported 193 coronary heart disease deaths in more than 18,000 participants, suggesting little or no effect on coronary heart disease mortality with increased ALA (RR 0.95, 95% CI 0.72 to 1.26; I^2 = 0%; Analysis 4.31). No sensitivity analyses suggested benefits or harms (Analysis 4.32; Analysis 4.33; Analysis 4.34).

Subgrouping by ALA dose, trial duration, replacement, intervention type, statin use, primary or secondary prevention, or previous history of coronary artery disease did not suggest important differences between subgroups (Analysis 4.35; Analysis 4.36; Analysis 4.37; Analysis 4.38; Analysis 4.39; Analysis 4.40; Analysis 4.41), and meta-regression did not suggest dose effects (P = 0.94; Table 4).

GRADE assessment suggested that increasing ALA intake probably has little or no effect on coronary heart disease mortality (moderate-certainty evidence, downgraded once for imprecision).

Coronary heart disease events (ALA)

Low-certainty evidence suggests that ALA intake may make little or no difference to coronary heart disease events.

Four trials contributed data to this outcome, with 397 of more than 19,000 participants experiencing at least one coronary heart disease event. There was little or no effect on coronary heart disease risk with increased ALA (RR 1.00, 95% CI 0.82 to 1.22 I^2 = 2%; Analysis 4.42). Sensitivity analyses using fixed-effect meta-analysis did not alter the lack of effect (RR 1.00, 95% CI 0.82 to 1.21; Analysis 4.43). Removing trials not at low summary risk of bias left two trials with almost 5000 participants, suggesting a 9% reduction in risk of a coronary heart disease event (RR 0.91, 95% CI 0.71 to 1.15; Analysis 4.44), though little or no effect was seen when restricting analysis to larger trials or those with better compliance (Analysis 4.45).

Subgrouping by ALA dose, trial duration, replacement, intervention type, statin use, primary or secondary prevention, or previous history of coronary artery disease did not suggest important differences between subgroups (Analysis 4.46; Analysis 4.47; Analysis 4.48; Analysis 4.49; Analysis 4.50; Analysis 4.51; Analysis

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4.52). Meta-regression did not suggest a correlation between ALA dose and coronary heart disease events (P = 0.18; Table 5).

Given the differences in sensitivity analyses, GRADE assessment suggested that ALA intake may make little or no difference to coronary heart disease events (low-certainty evidence, downgraded once for risk of bias and once for imprecision).

Stroke (ALA)

The effect of ALA intake on stroke is unclear, as the evidence is of very low certainty.

Five RCTs included more than 19,000 participants, of whom 51 experienced a stroke, suggesting a 15% increase in stroke risk with increased ALA (RR 1.15, 95% CI 0.66 to 2.01; I^2 = 0%; Analysis 4.53). Sensitivity analyses removing trials not at low summary risk of bias left three trials with 27 stroke events and no suggestion of effect (Analysis 4.55). Using a fixed-effect model suggested a 23% increased risk of stroke (Analysis 4.54), while removing trials at high risk of bias due to compliance suggested a 15% reduction in stroke risk, larger trials suggested a 15% greater stroke risk (Analysis 4.56).

Subgrouping by ALA dose, trial duration, replacement, intervention type, statin use, or primary or secondary prevention did not result in significant differences between subgroups (Analysis 4.57; Analysis 4.58; Analysis 4.59; Analysis 4.60; Analysis 4.61; Analysis 4.62). When examining data reported by type of stroke, only three trials reported on 28 ischaemic strokes, with no clear effects, and no trials reported haemorrhagic stroke (Analysis 4.63). Meta-regression did not suggest any relationship between ALA dose and risk of stroke (P = 0.73; Table 6).

The effect of ALA on stroke is unclear as the evidence is of very low certainty (downgraded twice for risk of bias and once for imprecision).

Arrhythmia (ALA)

Moderate-certainty evidence suggested that ALA intake probably slightly reduces the risk of arrhythmias (NNTB 91).

Two trials reported effects of ALA on arrhythmia, with 173 arrhythmias in 4912 participants, suggesting a 27% reduction in arrhythmia but with wide confidence intervals (RR 0.73, 95% CI 0.55 to 0.97, I^2 = 0%, Analysis 4.64). All sensitivity analyses suggested that ALA reduced arrhythmia (Analysis 4.65; Analysis 4.66; Analysis 4.67). There was no suggestion of a dose-response relationship between ALA and arrhythmia risk in meta-regression (P = 0.45; Table 7).

The NNTB was 91 (95% CI 56 to 1000) so 91 people would need to increase their ALA intake for one person to avoid experiencing arrhythmia. With only two trials it was not possible to estimate NNTB by primary or secondary prevention. GRADE assessment suggested that ALA intake probably slightly reduces the risk of arrhythmias (moderate-certainty evidence, downgraded once for imprecision).

Secondary outcomes

See Summary of findings 3 for a summary of our evidence on effects of LCn3 fats and ALA on serum lipids and measures of adiposity.

Effects of long-chain omega-3 fats (EPA, DHA and DPA) on secondary health outcomes

We did not carry out sensitivity analyses or subgrouping on secondary outcomes, except for adiposity and lipids, which were key outcomes. We did carry out some post hoc sensitivity analyses to further assess effects of LCn3 on myocardial infarction, to ascertain whether the suggested protection was stable to sensitivity analyses.

Major adverse cerebrovascular or cardiovascular events (LCn3)

Five trials reported on major adverse cerebrovascular or cardiovascular events (MACCEs) in more than 34,000 participants, 4232 of whom suffered from a MACCE, suggesting little or no effect of LCn3 fats (RR 1.03, 95% CI 0.97 to 1.09; I^2 = 0%; Analysis 2.1).

Myocardial infarction (LCn3)

Twenty-seven trials (> 133,000 participants) reported on total (fatal and non-fatal) myocardial infarction. Meta-analyses suggested that increasing LCn3 fats resulted in a reduction in total myocardial infarction (RR 0.88, 95% CI 0.81 to 0.96; I^2 = 25%; 3992 people experiencing at least one myocardial infarction; Analysis 2.2). This was confirmed in fixed-effect analysis (Analysis 2.3), sensitivity analyses limited to trials without compliance problems and to those that randomised at least 100 participants (Analysis 2.5), but analyses limited to trials at low summary risk of bias suggested little or no effect of LCn3 on myocardial infarction (RR 0.93, 95% CI 0.83 to 1.05; I^2 = 20%; > 71,000 participants in 13 trials reporting on 1885 people experiencing at least one myocardial infarction; Analysis 2.4). This undermines a true protective effect of LCn3 on myocardial infarction.

We ran subgroup analyses by fatality at the request of the WHO NUGAG Subgroup on Diet and Health, finding no significant difference between fatal and non-fatal myocardial infarction subgroups (P = 0.20; Analysis 2.6).

Sudden cardiac death (LCn3)

There was little or no effect of LCn3 fats on sudden cardiac death (RR 0.93, 95% CI 0.77 to 1.11; I^2 = 41%; 1422 deaths, 14 trials in > 73,000 people; Analysis 2.7).

Angina (LCn3)

Meta-analysis of 13 trials involving more than 48,000 participants, 2829 of whom reported new or worsening angina, suggested little or no effect of increasing LCn3 fats (RR 0.99, 95% CI 0.92 to 1.06; I^2 = 0%; Analysis 2.8).

Heart failure (LCn3)

Meta-analysis suggested little or no effect of LCn3 fatty acids on heart failure diagnosis in 17 trials with 4651 people experiencing events (RR 0.94, 95% CI 0.87 to 1.02; I^2 = 23%; Analysis 2.9). Sensitivity analysis limiting to the seven trials at low summary risk of bias also suggested little or no effect (RR 0.97, 95% CI 0.89 to 1.05; I^2 = 0%; 2017 participants experiencing heart failure). We concluded that there was little or no effect of LCn3 on risk of heart failure.

Revascularisation (LCn3)

Meta-analysis suggested little or no effect of LCn3 fats on revascularisation, all types combined (RR 0.93, 95% CI 0.86 to

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1.00; I^2 = 56%; 10,793 participants experiencing revascularisation; Analysis 2.10).

Peripheral arterial disease (LCn3)

Meta-analysis suggested that LCn3 had little or no effect on risk of peripheral arterial disease (RR 0.95, 95% CI 0.76 to 1.18; I^2 = 0%; 6 trials, 325 events in > 57,000 participants; Analysis 2.11). Sensitivity analysis, limiting to trials at low summary risk of bias, suggested that increasing LCn3 increased the risk of peripheral arterial disease by 10% (Analysis 2.13), other sensitivity analyses all suggested little or no effect (Analysis 2.12; Analysis 2.14). The data suggest that there is little or no effect of LCn3 on risk of peripheral arterial disease.

Acute coronary syndrome (LCn3)

There were limited data on effects of increasing LCn3 fats on acute coronary syndrome (RR 1.19, 95% CI 0.71 to 2.00; I^2 = 0%; 2 trials, 55 events in > 2000 participants; Analysis 2.15).

Body weight, body mass index (BMI) and other measures of adiposity (LCn3)

Body weight

High-certainty evidence shows that increasing LCn3 intake makes little or no difference to body weight.

Fourteen trials reported on the effect of increasing LCn3 on body weight and were included in meta-analysis, suggesting little or no effect in 17,000 participants (mean difference (MD) 0.00 kg, 95% CI −0.69 to 0.70; I^2 = 42%; Analysis 2.16). Sensitivity analysis limited to trials at low summary risk of bias, low risk from compliance, larger trials or fixed-effect analysis (not shown) did not alter this lack of effect (Analysis 2.17; Analysis 2.18; Analysis 2.19).

Subgroup analysis by intervention type, primary or secondary prevention, statin use and trial duration did not suggest important differences between subgroups (Analysis 2.22; Analysis 2.23; Analysis 2.24; Analysis 2.25). There was a marginally significant difference between dose subgroups (P = 0.05; Analysis 2.20) and increased body weight when participants received very high LCn3 doses (> 4.4 g/d LCn3, MD 1.51 kg, 95% CI 0.28 to 2.75; I^2 = 0%; 2 trials, 261 participants; Analysis 2.20). Subgrouping by replacement suggested differences between subgroups (P = 0.001; Analysis 2.21), with reduced body weight when LCn3 replaced saturated fatty acids or carbohydrates but increased weight when LCn3 replaced nil or low LCn3 (Analysis 2.21).

Several trials clearly measured body weight but did not report it in a useable way (Baldassarre 2006; Caldwell 2011; Deslypere 1992; EPE-A 2014; MARINA 2011; Nutristroke 2009). Body weight is commonly measured in healthcare settings, so there may be considerably more missing data than this. The funnel plot was not easily interpretable but small differences in effect size between fixed-effect and random-effects meta-analysis supports the possibility of a small amount of small study bias.

GRADE offers high-certainty evidence that LCn3 intake makes little or no difference to body weight (not downgraded).

Body mass index (BMI)

High-certainty evidence shows that LCn3 intake makes little or no difference to BMI.

Fifteen trials, 13 of which we included in meta-analysis, reported on BMI, suggesting little or no effect of LCn3 on BMI (MD 0.06 kg/m^2, 95% CI −0.14 to 0.25; I^2 = 39%; > 15,000 participants; Analysis 2.26). This lack of effect was also apparent in sensitivity analyses limited to trials at low summary risk of bias (Analysis 2.28), with good compliance or with large trial size (Analysis 2.29), as well as fixed-effect analysis (Analysis 2.27). Subgroup analyses by primary or secondary prevention, intervention type, statin use and trial duration did not suggest important differences between subgroups (Analysis 2.32; Analysis 2.33; Analysis 2.34; Analysis 2.35). There were significant differences between subgroups when subgrouped by replacement, suggesting lower BMI when LCn3 replaced saturated fatty acids or carbohydrate, and increased BMI when LCn3 replaced nil or low LCn3 (P = 0.02; Analysis 2.31). There was also a suggestion that increasing LCn3 increased BMI when the dose was above 2.4 g/d (Analysis 2.30).

Several trials clearly measured BMI but did not report it in a useable way (Caldwell 2011; EPE-A 2014; Nutristroke 2009; Ramirez-Ramirez 2013; Sofi 2010), suggesting that missing data may be an issue with this outcome. The funnel plot was not interpretable, but effect sizes from random-effects and fixed-effect meta-analysis were similar suggesting minimal small study bias.

GRADE offers high-certainty evidence that LCn3 intake makes little or no difference to BMI (not downgraded).

Other measures of adiposity

Few trials reported on other measures of adiposity (percentage body fat, percentage visceral fat, waist circumference, waist/hip ratio, abdominal circumference and hip circumference) with some suggesting higher adiposity and some lower adiposity in groups with more LCn3 (Analysis 2.36).

Serum lipids (LCn3)

Several trials clearly measured lipids but did not report them in a way that we could include in our meta-analyses. These included Baldassarre 2006, Gill 2012, Ramirez-Ramirez 2013 and Reed 2014. Further trials assessed but did not report triglycerides (Ahn 2016; Caldwell 2011; Franzen 1993; Rossing 1996), or HDL and LDL cholesterol (Franzen 1993). Because of the volume of potentially missing data, small study bias may potentially bias these outcomes.

Serum total cholesterol

High-certainty evidence shows that LCn3 intake makes little or no difference to serum total cholesterol.

Thirty trials provided data on long-term effects of LCn3 fats on serum total cholesterol, suggesting little or no effect in more than 38,000 participants (MD −0.01 mmol/L, 95% CI −0.05 to 0.03, I^2 = 14%, Analysis 2.37). Sensitivity analyses using a fixed-effect model, or limited to trials at low summary risk of bias, low risk of compliance issues, and larger trials also suggested little or no effect of LCn3 on serum total cholesterol (Analysis 2.38; Analysis 2.39; Analysis 2.40). Subgrouping by duration, primary or secondary prevention and statin use did not suggest any differential effects of LCn3 (Analysis 2.44; Analysis 2.45; Analysis 2.46). There were almost significant differences between subgroups by dose but no logical sequence suggesting no true dose-response effect (P = 0.05; Analysis 2.41). There were also subgroup differences for replacement and intervention type but there were no subgroups with changes of at least 5% of baseline (Analysis 2.42; Analysis 2.43).

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GRADE assessment suggests high-certainty evidence that LCn3 intake makes little or no difference to serum total cholesterol (not downgraded).

Serum triglycerides

High-certainty evidence suggests that increasing LCn3 intake reduces serum triglycerides, in a dose-dependent manner, by around 15%.

LCn3 fats significantly reduced serum triglycerides in more than 43,000 participants in 23 trials (MD −0.24 mmol/L, 95% CI −0.31 to −0.16; I^2 = 48%; Analysis 2.47). This effect was not lost in sensitivity analysis excluding trials at moderate to high risk of bias, those without clear compliance or small trials, or using fixed-effect analysis (Analysis 2.48; Analysis 2.49; Analysis 2.50). Subgrouping suggested that the reduction of serum triglycerides did not differ between subgroups by primary or secondary prevention, statin use, replacement, intervention type or trial duration (Analysis 2.52; Analysis 2.53; Analysis 2.54; Analysis 2.55; Analysis 2.56). There was a suggestion of a dose-response relationship with greater reductions in triglycerides at higher LCn3 doses, with significant differences between subgroups (P = 0.04; Analysis 2.51).

GRADE assessment suggests high-certainty evidence that increasing LCn3 intake reduces serum triglycerides in a dose-dependent manner (not downgraded).

HDL cholesterol

High-certainty evidence suggests that LCn3 intake has little or no effect on HDL cholesterol.

Thirty trials including more than 46,000 participants suggested little or no effect (an increase of < 5%) in serum HDL cholesterol with increased LCn3 (MD 0.03 mmol/L, 95% CI 0.01 to 0.05; P = 0.005, I^2 = 50%; Analysis 2.57). The finding of little or no effect was retained in all sensitivity analyses (Analysis 2.58; Analysis 2.59; Analysis 2.60). There were no significant differences between subgroups in any analysis and no suggestion of a dose-response relationship (Analysis 2.61; Analysis 2.62; Analysis 2.63; Analysis 2.64; Analysis 2.65; Analysis 2.66).

GRADE assessment suggests high-certainty evidence that LCn3 intake has little or no effect on HDL cholesterol (not downgraded).

LDL cholesterol

GRADE assessment suggests high-certainty evidence that LCn3 intake makes little or no difference to LDL cholesterol.

There was little or no effect of increasing LCn3 on serum LDL cholesterol in over 43,000 participants from 25 trials (MD 0.01 mmol/L, 95% CI −0.01 to 0.03; I^2 = 0%; Analysis 2.67). This lack of effect did not alter in any sensitivity analysis (Analysis 2.68; Analysis 2.69; Analysis 2.70). We saw no statistically significant differences between subgroups except for with regard to statin use, where there was a less than 5% increase in LDL cholesterol in nine trials where statin use was low (Analysis 2.71; Analysis 2.72; Analysis 2.73; Analysis 2.74; Analysis 2.75; Analysis 2.76).

GRADE assessment provides high-certainty evidence that LCn3 intake makes little or no difference to LDL cholesterol (not downgraded).

Effects of ALA on secondary health outcomes

We did not plan any sensitivity or subgroup analyses on secondary outcomes, except for the key outcomes of adiposity and lipids. As fewer than 10 ALA trials were available for these outcomes, we carried out only sensitivity analyses.

Major adverse cerebrovascular or cardiovascular events (ALA)

One trial reported on MACCEs in 110 participants, nine of whom experienced an event. There were insufficient data to suggest any effect of ALA on MACCEs (RR 1.12, 95% CI 0.32 to 3.95; Analysis 5.1).

Myocardial infarction (ALA)

Three trials reported that 333 out of more than 18,000 participants experienced a fatal or non-fatal myocardial infarction, suggesting little or no effect of ALA on myocardial infarction (RR 1.00, 95% CI 0.76 to 1.32; I^2 = 26%; Analysis 5.2). We carried out subgroup analyses by fatality at the request of the WHO NUGAG Subgroup on Diet and Health, and these suggested no significant differences between fatal and non-fatal myocardial infarction subgroups (P = 0.36; Analysis 5.3).

Sudden cardiac death (ALA)

No trials assessed effects of ALA on sudden cardiac death.

Angina (ALA)

Two trials assessed the effects of increasing ALA on diagnosis of new or worsening angina (39 of > 13,000 participants experienced this). There were insufficient data to suggest any effect of ALA on angina (RR 1.41, 95% CI 0.75 to 2.64; I^2 = 0%; Analysis 5.4).

Heart failure (ALA)

No trials assessed effects of ALA on heart failure.

Revascularisation (ALA)

Only one trial (3 events in 266 participants) reported on the effects of increased ALA on revascularisation (RR 0.72, 95% CI 0.07 to 7.84; 3 events; Analysis 5.5) or CABG specifically (RR 0.29, 95% CI 0.01 to 5.93; 2 events; Analysis 5.5). There were insufficient data to suggest any effect of ALA on revascularisation.

Peripheral arterial disease (ALA)

Meta-analysis suggested no clear effect of ALA on peripheral arterial disease in a single trial (RR 0.25, 95% CI 0.05 to 1.17; 10 of the > 13,000 participants experienced peripheral arterial disease; Analysis 5.6). There were insufficient data to suggest any effect of ALA on the outcome.

Acute coronary syndrome (ALA)

No trials assessed effects of ALA on acute coronary syndrome.

Body weight, body mass index (BMI) and other measures of adiposity (ALA)

The effect of LCn3 intake on body weight and BMI is unclear as the evidence is of very low certainty.

Four trials reported on the effect of ALA on body weight in 664 participants, suggesting some weight reduction in those taking more ALA but with extremely high heterogeneity (MD −1.49 kg, 95% CI −4.17 to 1.18; I^2 = 73%; Analysis 5.7). Sensitivity analysis using

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fixed-effect meta-analysis suggested little or no effect of ALA on body weight (Analysis 5.8), while no trials were at low summary risk of bias (Analysis 5.9). Retaining only trials at low risk for compliance bias or only larger trials suggested weight reduction with ALA (Analysis 5.10). There were no significant differences between subgroups by intervention type, dose, duration, replacement, statin use, or primary or secondary prevention of cardiovascular disease (Analysis 5.11; Analysis 5.12; Analysis 5.13; Analysis 5.14; Analysis 5.15; Analysis 5.16). GRADE assessment suggests that the effect of ALA intake on body weight is unclear, as the evidence is of very low certainty (downgraded once each for risk of bias, inconsistency, publication bias and imprecision).

Three trials reported on BMI, suggesting a reduction in BMI with increased ALA (MD −0.42 kg/m^2, 95% CI −1.53 to 0.69; I^2 = 65%; 1581 participants; Analysis 5.17), again with high heterogeneity. Sensitivity analyses using fixed-effect analysis or only retaining trials at low summary risk of bias suggested a small increase in BMI with ALA (Analysis 5.18; Analysis 5.19), while limiting to trials at low risk of compliance bias or eliminating smaller trials suggested a small reduction in BMI with increased ALA (Analysis 5.20). There were no statistically significant differences between subgroups differentiated by replacement or statin use (Analysis 5.23; Analysis 5.25), but there were differences by dose; subgrouping by dose suggested greater reduction of BMI in trials giving more ALA (P = 0.03; Analysis 5.21). All included trials gave supplemental foods (Analysis 5.22). There were greater reductions in BMI in shorter trials (P = 0.02; Analysis 5.24) and in primary prevention trials (P = 0.03; Analysis 5.26), but the inclusion of Dodin 2005 in any subgroup tended to differentiate that group from the others. GRADE assessment suggests that the effect of ALA intake on BMI is unclear, as the evidence is of very low certainty (downgraded once each for risk of bias, inconsistency, publication bias and imprecision).

One trial reported on visceral adipose tissue, suggesting no clear effect. Three trials reported on waist circumference. Meta-analysis of two of these suggested that increasing ALA resulted in reduced weight circumference (MD −1.59 cm, 95% CI −3.10 to −0.07; I^2 = 0%; Analysis 5.27). However, the single trial that we could not include in the meta-analysis due to lack of information on variance suggested effects in the opposite direction. Sensitivity analyses (only retaining trials at low summary risk of bias, not shown) removed all trials.

Serum lipids (ALA)

Serum total cholesterol

Low-certainty evidence suggests that ALA intake may make little or no difference to serum total cholesterol.

Six trials provided data on the long-term effects of ALA on serum total cholesterol, suggesting that increased ALA intake has little or no effect on total cholesterol, with high heterogeneity (MD −0.09 mmol/L, 95% CI −0.23 to 0.05; I^2 = 63%; in > 2000 participants; Analysis 5.28). The suggestion of little or no effect did not alter in any sensitivity analyses (Analysis 5.29; Analysis 5.30; Analysis 5.31). All trials provided food supplements (Analysis 5.33), but subgroup analyses suggested greater (though still small) reductions in total cholesterol in trials of shorter duration (P = 0.02; Analysis 5.35). Other differences between subgroups resulted from effect groups where ALA replacement or statin use was 'unclear' (Analysis 5.34; Analysis 5.36), or there were no differences (Analysis 5.32; Analysis 5.37). GRADE assessment suggests low-certainty evidence that ALA intake may make little or no difference to serum total cholesterol (downgraded once each for imprecision and inconsistency).

Serum triglycerides

Moderate-certainty evidence suggests that increasing ALA intake probably makes little or no difference to serum triglycerides.

There was little or no effect of ALA on serum triglycerides in 1776 participants in six trials (MD −0.03 mmol/L, 95% CI −0.11 to 0.05; I^2 = 0%; Analysis 5.38). There was little or no effect of ALA in sensitivity analysis removing trials of moderate to high risk of bias (Analysis 5.40), in fixed-effect meta-analysis (Analysis 5.39), or limiting by compliance bias or trial size (Analysis 5.41). Subgrouping suggested no important differential effects by dose, duration, replacement, intervention type, statin use, or primary or secondary prevention (Analysis 5.42; Analysis 5.43; Analysis 5.44; Analysis 5.45; Analysis 5.46; Analysis 5.47). GRADE assessment suggests moderate-certainty evidence that ALA intake probably makes little or no difference to serum triglycerides (downgraded once for imprecision).

HDL cholesterol

Moderate-certainty evidence suggests that ALA probably has little or no effect on HDL cholesterol.

There was little or no effect of ALA on HDL cholesterol in 1776 participants of six trials (MD −0.02 mmol/L, 95% CI −0.08 to 0.03; I^2 = 53%; Analysis 5.48), or in any sensitivity analyses (Analysis 5.49; Analysis 5.50; Analysis 5.51). A further trial, WAHA 2016, also measured HDL but did not provide data in a useable format for meta-analysis. There were no statistically significant differences between subgroups (Analysis 5.52; Analysis 5.53; Analysis 5.54; Analysis 5.55; Analysis 5.56; Analysis 5.57). GRADE assessment suggests moderate-certainty evidence that ALA probably has little or no effect on HDL cholesterol (downgraded once for imprecision).

LDL cholesterol

Moderate-certainty evidence suggests that ALA intake probably makes little or no difference to LDL cholesterol.

There was little or no effect of increasing ALA on LDL cholesterol in 2201 participants of seven trials (MD −0.05 mmol/L, 95% CI −0.15 to 0.04; I^2 = 46%; Analysis 5.58), with similar effects in all sensitivity analyses (Analysis 5.59; Analysis 5.60; Analysis 5.61). Subgrouping suggested no differences in effect by ALA dose or primary or secondary prevention (Analysis 5.62; Analysis 5.63; Analysis 5.64; Analysis 5.66; Analysis 5.67), but there was a statistically significant difference between trials of longer and shorter duration, though little or no effect in both groups (Analysis 5.65). GRADE assessment suggests moderate-certainty evidence that ALA intake may make little or no difference to LDL cholesterol (downgraded once for imprecision).

Tertiary outcomes

Effects of long-chain omega-3 fats (EPA, DHA and DPA) on tertiary health outcomes

We extracted these outcomes from trials that we included for other outcomes, so we did not assess them completely or systematically. We did not carry out sensitivity analyses or subgrouping for these outcomes. We are aware of missing data for some of these outcomes, including blood pressure in Ramirez-Ramirez 2013.

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Blood pressure (LCn3)

Seventeen included trials (> 35,000 participants) contributed data on effects of LCn3 fats on blood pressure. Meta-analysis suggested little or no effect of LCn3 on systolic (MD 0.01 mmHg, 95% CI −0.31 to 0.34; I^2 = 0%; Analysis 3.1) or diastolic (MD −0.02 mmHg, 95% CI −0.22 to 0.17; I^2 = 0%; Analysis 3.1) blood pressure in trials of at least one year.

Serious adverse effects (LCn3)

As part of the larger set of reviews, we formally systematically reviewed effects of omega-3 fats on type 2 diabetes diagnoses, measures of glucose metabolism (Brown 2019), cancers including breast cancer (Hanson 2019), neurocognitive outcomes such as dementia (Brainard 2019), irritable bowel disease (IBD) and inflammatory factors (Thorpe 2017), depression and anxiety (Deane 2019), and functional outcomes (Abdelhamid 2019), so we do not present these outcomes here.

We collected data on the following potentially important health outcomes (Analysis 3.2).

- Any serious adverse event (RR 1.00, 95% CI 0.94 to 1.06; I^2 = 0%; 3 trials, > 9000 participants, 2668 events).
- Bleeding (RR 1.12, 95% CI 0.91 to 1.37; I^2 = 44%; 11 trials, > 80,000 participants, 1324 events). Assessed as being very low-certainty evidence, so the effect of LCn3 on bleeding is unclear (Summary of findings for the main comparison).
- Serious gastrointestinal events (RR 1.34, 95% CI 0.64 to 2.80; I^2 22%; 3 trials, 774 participants, 49 events).
- Pulmonary embolus or DVT (RR 1.15, 95% CI 0.44 to 2.98; I^2 = 0%; 5 trials, > 3000 participants, 20 events). Assessed as being very low-certainty evidence, so the effect of LCn3 on pulmonary embolus or DVT is unclear (Summary of findings for the main comparison).
- Progression to advanced age-related macular degeneration (RR 0.96, 95% CI 0.90 to 1.02; 1 trial, > 4000 participants, 2049 events).
- Thrombophlebitis: no data identified
- Urolithiasis: no data identified

Side effects (non-serious, LCn3)

To assess side effects we collected data on the following potential side effects (Analysis 3.3).

- Withdrawal due to side effects: the data suggest more participants taking LCn3 fats dropped out because of side effects (RR 1.16, 95% CI 0.99 to 1.36; I^2 = 1%; 23 trials, > 16,000 participants, 620 dropouts).
- Increased abdominal pain or discomfort: data suggest an association with higher LCn3 (RR 1.05, 95% CI 0.91 to 1.20; I^2 = 16%; 9 trials, > 41,000 participants, 10,040 events).
- Diarrhoea: the data suggested an increased risk with increased LCn3 (RR 1.02, 95% CI 0.87 to 1.19; I^2 = 49%; 13 trials, > 37,000 participants, 12,303 events).
- Nausea: risk increased with LCn3 (RR 1.20, 95% CI 0.96 to 1.49; I^2 = 54%; 8 trials, > 35,000 participants, 7639 events).
- Any gastrointestinal side effect: risk also appeared to increase with LCn3, albeit with very high heterogeneity (RR 1.10, 95% CI 0.97 to 1.26; I^2 = 74%; 33 trials, > 895,000 participants, 6651 events).
- Skin problems, including itching or rashes: these were not affected by LCn3 in a meta-analysis with high heterogeneity (RR 1.11, 95% CI 0.52 to 2.37; I^2 = 68%; 9 trials, > 36,000 participants, 293 events).
- Headache or worsening migraine: there were limited data on this outcome (RR 0.85, 95% CI 0.51 to 1.40; I^2 = 0%; 4 trials, 1526 participants, 60 events).
- Reflux: there were limited data (RR 1.23, 95% CI 0.79 to 1.91; I^2 = 32%; 3 trials, > 8000 participants, 282 events).
- Joint, lumbar and muscle pain: meta-analysis of data from three trials suggested that LCn3 had little or no effect on such pain (RR 0.95, 95% CI 0.74 to 1.23; > 27,000 participants, 989 people experienced pain).
- All side effects: there was no suggestion that LCn3 increased or decreased all side effects combined in a meta-analysis with very high heterogeneity (RR 1.01, 95% CI 0.95 to 1.08; I^2 = 79%; 14 trials, > 39,000 participants, 9863 people with at least one side effect).

Dropouts (LCn3)

Included trials reported 6643 dropouts in over 56,000 participants in 35 trials, suggesting no difference in dropout rates between intervention and control arms (RR 0.97, 95% CI 0.90 to 1.04; I^2 = 28%; Analysis 3.4).

Quality of life, economic costs (LCn3)

We found no data on quality-of-life outcomes or economic costs.

Effects of ALA on tertiary health outcomes

We extracted these outcomes from trials that we included for other outcomes, so we did not assess them completely or systematically. We did not carry out sensitivity analyses or subgrouping for these outcomes.

Blood pressure (ALA)

Four included trials (1671 participants) contributed data on effects of ALA on blood pressure. Meta-analysis suggested little or no effect of ALA on systolic (MD −0.87 mmHg, 95% CI −4.48 to 2.75; I^2 = 58%; Analysis 6.1) or diastolic (MD −1.42 mmHg, 95% CI −4.40 to 1.57; I^2 = 74%; Analysis 6.1) blood pressure in trials of at least one year. The heterogeneity in these results reflect a single trial, FLAX-PAD 2013, that showed large diastolic and systolic blood pressure effects. The other (larger) trials did not suggest such effects.

Serious adverse effects (ALA)

As part of the larger set of reviews we formally systematically reviewed effects of omega-3 fats on type 2 diabetes diagnoses and measures of glucose metabolism (Brown 2019), cancers including breast cancer (Hanson 2019), neurocognitive outcomes such as dementia (Brainard 2019), irritable bowel disease (IBD) and inflammatory factors (Thorpe 2017), depression and anxiety (Deane 2019), and functional outcomes (Abdelhamid 2019), so we do not present these outcomes here.

We collected data on the following potentially important health outcomes (Analysis 6.2).

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- Any serious adverse event: no data identified
- Bleeding: no data identified
- Serious gastrointestinal effects: no data identified
- Pulmonary embolus or DVT: only one event was identified in a single trial, so there were insufficient data to assess effects. GRADE assessment suggested very low-certainty evidence (downgraded once for risk of bias and twice for imprecision (Summary of findings 2).
- Progression to advanced age-related macular degeneration: no data identified
- Thrombophlebitis: there were insufficient data to assess effects (RR 1.59, 95% CI 0.72 to 3.51; 1 trial, > 13,000 participants, 26 events).
- Urolithiasis: there were insufficient data to assess effects (RR 0.80, 95% CI 0.47 to 1.36; 1 trial, > 13,000 participants, 54 events).

Side effects (non-serious, ALA)

To assess potential side effects, we collected data on the following (Analysis 6.3).

- Dropouts due to side effects: data suggested that ALA increased the risk of withdrawal, although there was high heterogeneity (RR 2.10, 95% CI 0.66 to 6.71; I^2 = 62%; 5 trials, > 3000 participants, 68 events).
- Abdominal pain or discomfort: no data identified
- Diarrhoea: a single trial identified 10 participants with diarrhoea, suggesting a higher risk of diarrhoea with greater ALA intake (RR 3.82, 95% CI 0.82 to 17.88).
- Nausea: there were insufficient data to assess effects of ALA (RR 6.29, 95% CI 0.33 to 118.93; 1 trial, 110 participants, 3 events).
- Any gastrointestinal side effect: there were insufficient data to assess effects of ALA (RR 2.06, 95% CI 0.62 to 6.80; I^2 = 58%; 4 trials, > 3000 participants, 49 events). The high heterogeneity suggests that gastrointestinal side effects may be collected in different ways in different trials.
- Skin problems, including itching or rashes: no data identified
- Headache or worsening migraine: no data identified
- Reflux: no data identified
- All side effects combined: no data identified

Dropouts (ALA)

Included trials reported 558 dropouts in over 3000 participants in six trials, suggesting slightly similar dropout rates in participants taking higher and lower ALA (RR 1.08, 95% CI 0.92 to 1.25; I^2 = 0%; Analysis 6.4).

Quality of life, economic costs (ALA)

We found no data on quality of life outcomes or economic costs.

DISCUSSION

Summary of main results

We included 86 randomised controlled trials (162,796 participants), of which 28 were at low summary risk of bias (randomisation, allocation concealment, selection and detection bias all at low risk for supplementation trials; randomisation, allocation concealment and detection bias all at low risk for dietary advice trials). This compares to 79 RCTs including 112,059 participants, of which 25 were at low summary risk of bias in the previous review (Abdelhamid 2018a). Trials of 12 to 88 months' duration included adults at varying levels of cardiovascular risk, mainly in high-income countries. Most trials assessed LCn3 supplementation with capsules, but some used LCn3- or ALA-rich or enriched foods or dietary advice compared to placebo or usual diet.

Pooled trial results suggested there is probably little or no effect of increasing LCn3 fats on risk of all-cause mortality, cardiovascular deaths, cardiovascular events, stroke or arrhythmias (moderate- and high-certainty evidence). But in this update we found low-certainty evidence suggesting that increasing LCn3 intake may reduce coronary heart disease mortality (NNTB 334) and coronary heart disease events (NNTB 167). These are small effects and have not been apparent in the more limited data sets of the past.

Limiting LCn3 analyses to trials at low summary risk of bias moved the effect size towards 1.0 (the null value) for most primary outcomes except coronary heart disease mortality and arrhythmia. We found no suggestion of dose responses in subgrouping but there were suggestions of dose response by LCn3 dose in meta-regression for cardiovascular disease events and coronary heart disease events. These results apply to supplemental LCn3 intake. We did not see important differences in LCn3 trials between those providing oily fish (dietary source) or EPA/DHA capsules (supplemental source), but as few trials provided whole fish health effects may differ.

Increasing ALA intake suggested moderate- and low-certainty evidence of little or no effect on all-cause mortality, cardiovascular mortality, coronary heart disease mortality or events, but low-certainty evidence suggested a small protection from cardiovascular events (NNTB 500) and moderate-certainty evidence, protection from arrhythmia (NNTB 91). Effects on stroke were unclear. Data were more limited than for LCn3, and there were too few trials for informative funnel plots or subgroup analyses. These suggested that benefits of ALA need to be considered with caution, as effects were small, and few trials addressed the outcomes.

Meta-analyses suggested little or no effect of increasing LCn3 fats intake on secondary outcomes: major adverse cerebrovascular or cardiovascular events, fatal or non-fatal myocardial infarction, or both, sudden cardiac death, new or worsening angina, heart failure, revascularisation, peripheral arterial disease or acute coronary syndrome. There were very limited data on effects of ALA on these outcomes.

High-certainty evidence suggested that increasing LCn3 has little or no effect on measures of adiposity (body weight or BMI), but effects of ALA on measures of adiposity were unclear as the evidence was of very low-certainty. High-certainty evidence shows that increasing LCn3 reduces serum triglycerides by ~15% in a dose-dependent manner, but moderate-certainty evidence suggests little or no effect of ALA on triglycerides. High-certainty evidence showed no effect of increasing LCn3 on total, HDL or LDL cholesterol in these long-term trials, while moderate- and low-certainty evidence suggested little or no effect of increasing ALA on these lipids. Within the included trials we assessed effects on blood pressure, serious adverse effects, side effects and dropouts. There was no suggestion that blood pressure or risk of adverse events such as bleeding differed by LCn3 or ALA intake. Thus, proposed mechanisms for omega-3 activity, including lowering of blood pressure, reduced

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thrombotic tendency and anti-arrhythmic effects are not apparent in long-term trials of adult humans, but LCn3 does lower serum triglyceride levels.

The review has provided some answers for its secondary questions.

- If omega-3 fatty acids confer protection:
  - does protection occur equally in those at low and at high risk of cardiovascular disease? There is no evidence of differential effects on mortality or cardiovascular health by primary or secondary cardiovascular disease prevention, except in the case of LCn3 and arrhythmia, where there is a suggestion of harm in primary prevention, little or no effect in secondary prevention. However, because the underlying risk of an event is different in primary and secondary prevention the NNTB differs in these two groups. For example, in assessing the effects of LCn3 on coronary heart disease mortality the NNTB is 334 (95% CI 200 to infinity), so 334 people would need to increase their LCn3 intake to prevent one death from coronary heart disease. If we assess NNTB by primary or secondary prevention of cardiovascular disease, people without previous cardiovascular disease (needing primary prevention) have an NNTB of 1000 (95% CI NNTB 334 to NNTH 1000), while those with existing cardiovascular disease have an NNTB of 200 (NNTB 91 to NNTH 500). When assessing effects of LCn3 on coronary heart disease events, the NNTB overall is 167 (95% CI 100 to 500), while the NNTB is 200 for primary prevention (95% CI NNTB 112 to NNTB infinity) and 143 for people with existing cardiovascular disease, secondary prevention (NNTB 143, 95% CI NNTB 91 to NNTH 500).
  - does protection depend on the dose of omega-3 fats taken per day? We ran subgroup analyses for primary and key outcomes and meta-regression for primary outcomes but found no evidence of differential effects by LCn3 or ALA dose on any outcomes except LCn3 on serum triglycerides, cardiovascular disease events and coronary heart disease events, where there were statistically significantly greater reductions with higher LCn3 dose.
  - do effects differ between dietary and supplemental omega-3 sources? We assessed this question by looking for statistically significant differences between subgroups but found no evidence of differential effects by dietary or supplemental LCn3 or ALA sources. However, few of the LCn3 trials advised or gave fish, most gave supplemental fish oils, so our ability to assess effects of eating more oily whole fish are limited.
  - does protection depend on trial summary risk of bias? Some analyses suggested a protective effect of LCn3 fats, but these effects disappeared when analyses were limited to trials at low summary risk of bias. The stronger trials with higher internal validity suggested few or no effects of LCn3 on mortality or most cardiovascular disease outcomes, but effects of LCn3 were greater for coronary heart disease mortality and arrhythmia when limited to the trials at low summary risk of bias. On the other hand, for all-cause mortality, cardiovascular disease mortality and events and coronary heart disease mortality and events, ALA trials at low summary risk of bias suggested greater protection with higher ALA than in the main analysis (including trials of all levels of summary risk of bias).
- Is protection or harm stronger with longer trial duration? In subgroup analyses for primary and key outcomes and in meta-regression for primary outcomes, there was no evidence that longer trials increased the effect of LCn3 or ALA. The exceptions were effects of LCn3 on stroke (where trials of longer duration showed smaller risk ratios, or lower risk) and arrhythmia (where the risk of arrhythmia was higher in longer trials).
- Are effects of omega-3 fatty acids dependent on baseline triglyceride levels or diabetic status? In subgroup analyses for primary outcomes we found no evidence that increasing LCn3 had different effects in trials with higher baseline triglycerides or with diabetes or diabetes risk factors, however few trials had raised triglycerides or diabetes at baseline so the assessment was not well powered. The exception was when assessing coronary heart disease events, where the subgroup of three trials with raised triglyceride suggested a greater reduction in coronary heart disease events (Analysis 1.62), this effect relied on REDUCE-IT 2019. No trials of increased ALA had raised baseline triglycerides or diabetes, so effects could not be assessed for ALA.

Overall completeness and applicability of evidence

We searched very carefully to find all trials relevant to this review and located 86 trials randomising 162,796 participants to higher and lower omega-3 fats (LCn3 or ALA) for at least 12 months.

To reduce selection bias, we contacted authors of trials that appeared to have randomised appropriate participants to appropriate intervention and comparator but may not have published relevant outcomes (to April 2017). If trial authors had assessed any of our outcomes, we requested data and included the trial. This enabled us to include several additional trials. We also contacted authors of all included trials that randomised at least 100 participants (and most smaller trials to April 2017) to request data on any further outcomes (as well as on methodological issues) that may have been recorded but not reported. We tried to contact 72 of the 86 included trials (all except Baldassarre 2006; HERO 2009; Mita 2007; Nutristroke 2009; Özaydin 2011; Shinto 2014; Sofi 2010; and the newly added trials ASCEND 2018; Broutset 2007; DREAM Asbell 2018; ENRGISE 2018; HEARTS 2017; REDUCE-IT 2019; VITAL 2019). This allowed us to collect useful additional data on outcomes such as deaths and cardiovascular events that we would not have had access to otherwise. For all trials we carefully searched out and data extracted trials registry entries, protocols, supplementary materials, letters, conference abstracts and additional publications to help us locate additional data.

Most of our newly included trials were previously ongoing. We have detailed 25 remaining ongoing trials, of which seven are newly ongoing, that appear to be unpublished at the time of writing (Characteristics of ongoing studies). We have labelled these trials as ongoing, although some appear overdue for publication, and their status is unclear – they may constitute missing data. We tried to contact authors of all 'overdue' ongoing trials, and some stated that publications are forthcoming; others did not reply. We suspect that if trial authors have not published outcomes, it is likely that any protective health effects did not reach statistical significance. Given that existing trials suggest no effects of omega-3 fats on cardiovascular health outcomes, any missing data may not affect outcomes greatly; however, for completeness we would prefer to include all available data.

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Post hoc, we followed advice to assess differences in effects between EPA and DHA within the review. However, most LCn3 trials provided or advised changes resulting in increased intakes of both EPA and DHA (as in natural fish oil), though in different ratios. Only three trials provided data on DHA only (ADCS 2010; Berson 2004; Zhang 2017), and six provided data on EPA only (Doi 2014; JELIS 2007; Mita 2007; Nye 1990; Puri 2005; REDUCE-IT 2019). Unfortunately, for any single outcome, only two or three of these trials were represented, so our ability to assess differential effects of the DHA-only and EPA-only interventions was very limited, and we have not presented these analyses or attempted to draw any information from them.

Quality of the evidence

Figure 2 displays risk of bias of included trials. Of the 86 RCTs, 28 were at low summary risk of bias (at low risk of selection bias, performance bias and detection bias, plus low risk of performance bias in supplemental trials). We assessed the validity of evidence in meta-analyses by running sensitivity analyses that removed trials not at low summary risk of bias. Funnel plots for LCn3 trials suggested that there may be missing trials for all primary outcomes except stroke and arrhythmia, and in all cases adding such trials back in would move effect sizes closer to no effect (RR 1.0). This lack of effect in the trials at lowest risk of bias (with suggestions of effect in trials at moderate to high risk of bias) supported our interpretation of lack of effect of LCn3 fats on many of our primary outcomes.

However, the increased numbers of trials, of longer trials and of greater numbers of people randomised within included trials (up by 31% in this review from the previous iteration, Abdelhamid 2018a), has increased our power to see small effects of increasing LCn3. We pre-stated that effect sizes needed to be greater than 8% (RR < 0.92 or > 1.08) to suggest an important effect. Effect sizes of 9% or 10% are still small, and for the outcomes that have reached this level of effectiveness in this review NNTBs are still very large. The effects of LCn3 and ALA we are seeing on cardiovascular diseases and triglycerides are small.

Potential biases in the review process

Potential adverse effects include cancers and neurological problems associated with polychlorinated biphenyls (PCBs) or mercury in fish oils, and bleeds associated with reductions in clotting (see How the intervention might work). We have collated any data on bleeds, including haemorrhagic stroke, in this review, though we did not ask trial authors specifically for additional data on these outcomes. Unfortunately there were insufficient data on serious harms (bleeding and pulmonary embolism or deep vein thrombosis) to assess these potential harms. We have not collated data on cancers (Hanson 2019), and neurological problems (Brainard 2019), within this review but have formally systematically reviewed them elsewhere. This approach is preferable to including data on these outcomes from within included trials, which would be incomplete and potentially underpowered to show important effects.

One problem with cardiovascular disease outcomes is that they are collected together in a variety of ways, depending on the trial. For example, in assessing coronary heart disease mortality, we prespecified that we would include the first of the following list reported in any trial: coronary death, ischaemic heart disease death, fatal myocardial infarction, cardiac death. Each included trial collates outcome data in its own way, so we had to adapt to this in our analysis. One way to get around this problem would be to ask trial authors to go back to their original datasets to assess outcomes in a single prespecified way. This was done by a recent meta-analysis that included only 10 trials but was able to formulate their outcome data to match between trials (Aung 2018). In doing this they were able to include data on outcomes that we were not able to access. For example, numbers of coronary heart disease deaths for GISSI-HF 2008 have risen considerably in this version of the review, as we were able to include data on coronary heart disease deaths from a greater range of sources than were previously published: sudden cardiac deaths, deaths due to ventricular arrhythmias, and heart failure in patients with coronary heart disease, myocardial infarction, or deaths occurring after coronary revascularisation or heart transplant. Their data are also richer with regard to summing people with events (rather than numbers of events). Numbers of events are relatively easy to extract from published papers, but are not additive across composite endpoints such as cardiovascular disease events or coronary heart disease events (as a single individual may have experienced a stroke and a heart attack as well as onset of angina, but should be counted once only within any one composite outcome - counting events would lead to their inclusion twice in coronary heart disease events and three times for cardiovascular disease events). For that reason previous versions of this review have been conservative in the data we have used, but use of the Aung 2018 data has allowed more data inclusion. The next section discusses similarities and differences between this review and Aung 2018, but their findings were highly similar. For example, effects of LCn3 on coronary heart disease mortality, our meta-analytic estimate of effect of LCn3 was RR 0.90, (95% CI 0.81 to 1.00; I^2 = 35%) in 24 trials reporting 3598 coronary heart disease deaths (Analysis 1.37), while theirs was RR 0.93 (95% CI 0.83 to 1.03) in 10 trials reporting 2695 coronary heart disease deaths.

While we tried hard to locate all available trials and collect additional outcome data where possible, there was evidence from funnel plots of some small study bias. Some smaller trials showing increased risk of cardiovascular disease outcomes with omega-3 fats may be missing from some of the meta-analyses. If these trials were replaced they would tend to increase risk ratios. This suggests that there is some underlying small study bias within the review.

Underlying risks vary from trial to trial. For example, the risk of death in GISSI-HF 2008 was 28% in people with heart failure at baseline, but less than 4% in the healthy population recruited to VITAL 2019. Despite this there was little suggestion of heterogeneity between trials (I^2 = 5%; Analysis 1.1). Where there have been suggestions of effects we have translated these into benefits or harms in both higher- and lower-risk populations to clarify.

Given that the many LCn3 trials at moderate to high risk of bias appear to be inflating any protective effects, and that small trial bias is also inflating any protective effects, it is justified to view with skepticism the occasional suggestion of a protective effect. We do see some protective effects, but they are small. Given the very large number of subgroup analyses we carried out, it is also important to treat the occasional subgroup analysis that throws up a statistically significant difference between subgroups very cautiously.

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A secondary question asked by this review was about differential effects of dietary and supplemental LCn3 fats. LCn3 interventions included dietary advice (advice to eat more oily fish), supplemental foods (LCn3 fats incorporated into other foods such as margarine) and supplements or capsules (by far the greatest proportion of trials). Dietary fish is likely to have different health effects, as it may take the place of less healthy foods in the diet (leading to reduced saturated fat intake, for example) and provides many nutrients in addition to omega-3 fats (such as protein, selenium, iodine, calcium, magnesium, etc.). There were only four LCn3 dietary advice trials with event data (DART 1989; DART2 2003; DISAF 2003; THIS DIET 2008), and two of these also provided fish oil capsules when participants did not want to eat more fish (DART 1989; DART2 2003). We found no statistically significant differences between dietary advice subgroups and supplemental foods or capsule subgroups for primary outcomes. This may mean that health effects between the two types of intervention are not different, but it is likely that our analysis was underpowered to see any such differences if they exist.

Population LCn3 status varies widely across the world, from over 8% of fatty acids in Japan, Scandinavia and other areas with non-Westernised dietary patterns to less than 4% in North, South and Central America; Europe; the Middle East; Southeast Asia; and Africa (Stark 2016). We hypothesised that additional LCn3 might have greater health effects in people whose usual LCn3 intake was relatively low, but unfortunately we were not able to ascertain baseline LCn3 intake or status for most of our included trials. However, most of the included trials were carried out in areas of the world with lower LCn3 status, so we would expect to see effects of increasing LCn3 in most included trials if such effects exist.

Agreements and disagreements with other studies or reviews

One potential difference between the findings of this review and some other trials and reviews is our running sensitivity analyses assessing effects exclusively in trials at low summary risk of bias. This clarified the lack of effect of LCn3 fats on stroke, which otherwise appeared slightly harmful. On the other hand, these sensitivity analyses suggested protective effects of LCn3 on coronary heart disease mortality and ALA on cardiovascular events. The effectiveness or lack of effectiveness of LCn3 on coronary heart disease events is harder to call. The main analysis suggests a 9% reduction in coronary heart disease events, but sensitivity analyses limiting trials to those at low summary risk of bias, or fixed-effect analysis suggested 7% and 8% reductions, while limiting to trials with low risk of compliance problems or to larger trials suggested reductions of 16% and 11% respectively. We have suggested that this implies that LCn3 does slightly reduce risk of coronary heart disease events, but the interpretation that there was little or no effect is also logical.

There was no suggestion that blood pressure or risk of adverse events such as bleeding differed by LCn3 or ALA intake. This suggests that possible mechanisms for omega-3 activity, including lowering of blood pressure, reduced thrombotic tendency and anti-arrhythmic effects are not important in most adults, though LCn3 does lower serum triglyceride levels. We did not systematically review blood pressure data so may have missed a few long-term trials (though not many) – missing data from included trials is likely to be a bigger issue. Of the 15 included trials that reported blood pressure outcomes, nine reported numbers of hypertensive participants at baseline, ranging from 5% in MARINA 2011 to 79% of participants in ORIGIN 2012. Effects did not differ by proportions of hypertensive participants (I^2 was 0% for both systolic and diastolic blood pressure; Analysis 3.1).

Nearly 20 years ago, the GISSI-P 1999 trial suggested that LCn3 had its primary effects in reducing sudden cardiac death. However, the forest plot clearly shows that subsequent trials have not seen this effect individually or in aggregate (Analysis 2.7).

The scope of this review is similar to that of the extensive Agency for Healthcare Research and Quality review (Balk 2016), so we have compared our results with theirs. Given that our review included 86 RCTs randomising more than 162,000 participants, who experienced over 11,000 deaths and more than 5000 cardiovascular disease deaths, we were surprised to read that Balk and colleagues characterised the body of evidence as having "limited data ... from RCTs on the effect of n-3 FA on clinical CVD [cardiovascular disease] outcomes" (Balk 2016). This appears to be because the Balk review excluded RCTs of people with non-cardiovascular disease and non-diabetes-related diseases at baseline, while we included them. While Balk 2016 excluded some trials that we included, it did not include any trials providing all-cause mortality data that we excluded. This meant that in analysing effects on all-cause mortality, Balk 2016 included 18 RCTs randomising 81,027 participants experiencing 8480 deaths, while we included more than 143,000 participants randomised to high or low LCn3 or ALA experiencing 11,297 deaths. Balk 2016 excluded trials that we included, such as AREDS2 2014, a high-quality trial with 368 deaths in more than 4000 participants with age-related macular degeneration. This sort of population appeared ideal to us for assessment of omega-3 fats on primary prevention of cardiovascular disease, as these people tend to be elderly but there is no clear reason why omega-3 fats would affect cardiovascular disease differently in this population than in other older adults at usual cardiovascular disease risk.

Despite these slight differences in approach, we obtained very similar effect estimates to Balk 2016. We meta-analysed effects of LCn3 and ALA trials, finding an RR for all-cause mortality of 0.97 (95% CI 0.93 to 1.01; I^2 = 5%), compared to a pooled RR for all-cause mortality of 0.97 (95% CI 0.92 to 1.03) in Balk 2016. While that review seldom pooled their results, we can compare our results with theirs where they did. Despite our slightly different inclusion criteria, our results are very comparable (Table 8).

A recent individual meta-analysis of 10 large trials in almost 78,000 people at high risk of cardiovascular disease found no associations of LCn3 with coronary heart disease mortality (RR 0.93, 99% CI 0.83 to 1.03), nonfatal myocardial infarction (RR 0.97, 99% CI 0.87 to 1.08), coronary heart disease events (RR 0.96, 95% CI 0.90 to 1.01) or major vascular events (RR 0.97, 95% CI 0.93 to 1.01; Aung 2018). Aung 2018 included individual patient data from the participants of large, long trials (randomising at least 500 participants and following them for at least one year) (AlphaOmega - EPA+DHA 2010; AREDS2 2014; DO IT 2010; GISSI-HF 2008; GISSI-P 1999; JELIS 2007; OMEGA 2009; ORIGIN 2012; Risk & Prevention 2013; SU.FOL.OM3 2010), and this review includes all these trials. Their review had the advantage of being able to ensure that they had complete and equivalent data for all of their key outcomes from all the trials, reducing the risk of publication bias (and this review has incorporated some of their data to improve and extend our data

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set), but the disadvantage of missing all the data from many large LCn3 trials such as DART 1989, DART2 2003, FORWARD 2013, MAPT 2017, SHOT 1996 and SOFA 2006, all LCn3 trials randomising at least 500 participants. It also missed large trials of LCn3 in lower-risk participants such as OPAL 2010, and large trials of ALA such as MARGARIN 2002, Norwegian 1968 and WAHA 2016, as well as all the smaller trials. However, though taking different approaches, the numerical results of this review and Aung 2018 are also very similar (Table 8). Aung 2018 has been updated with data from the three largest recent trials (ASCEND 2018; REDUCE-IT 2019; VITAL 2019), published as Hu 2019. This review, Balk 2016, Aung 2018 and Hu 2019 addressed the analysis of the data in slightly different ways, creating sensitivity analyses for each other. The fact that they came to similar numerical conclusions reassures us that our conclusions are solidly based. However, the risk ratios for coronary heart disease mortality and events have fallen in this update of the review and crossed the line to suggest small beneficial effects of LCn3.

Cardiovascular diseases and cancers are both major non-communicable killers, so overall assessment of the utility of increasing omega-3 fats will depend on effects on both sets of outcomes. Figure 6 summarises the information on absolute effects of LCn3 and ALA on cardiovascular and cancer outcomes (focusing on outcomes where risk ratios were < 0.92 or > 1.08). The cancer data come from a sister review (Hanson 2019). Combining data from the two reviews suggests that for every 1000 men increasing their intake of LCn3, three will avoid dying from coronary heart disease, six will avoid a coronary heart disease event, one will avoid the diagnosis of arrhythmia and three additional men will be diagnosed with prostate cancer. Similarly, for every 1000 men increasing their intake of ALA two will avoid a cardiovascular disease event and 11 will avoid diagnosis of arrhythmia but three additional men will be diagnosed with prostate cancer (Figure 6). These small negative effects on cancer outcomes for men attenuate the small beneficial effects of LCn3 and ALA on cardiovascular outcomes.

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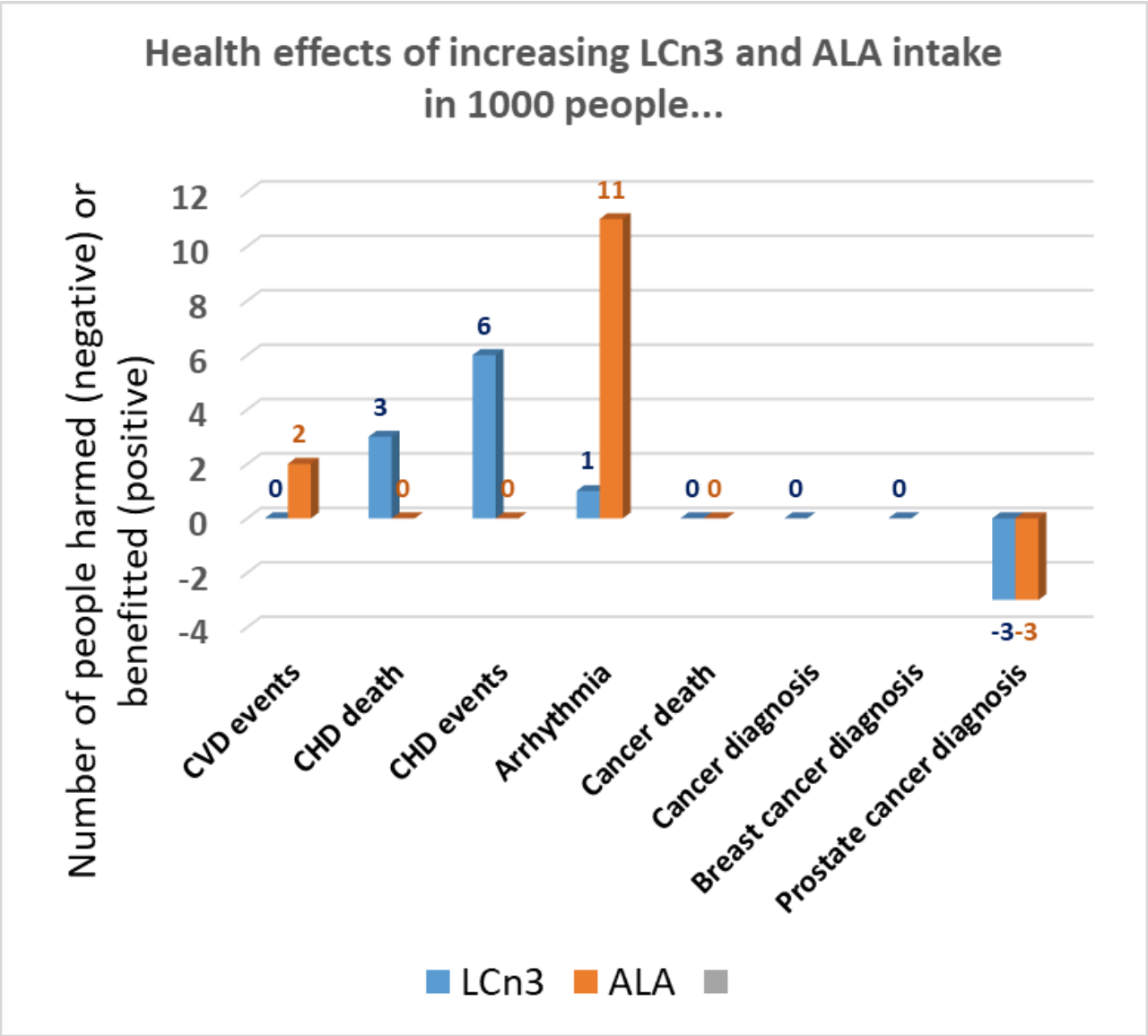
Figure 6. Assessment of health effects across cancers and cardiovascular outcomes. Bars above zero suggest the number of people who would benefit out of 1000 people consuming more long-chain omega-3 (LCn3) or alpha-linolenic acid (ALA), bars below zero suggest the number of people who would be harmed out of 1000 people consuming more LCn3 or ALA. Cardiovascular disease (CVD) data are from this review, cancer data from a sister review (Hanson 2019). CHD: coronary heart disease.



AUTHORS' CONCLUSIONS

Implications for practice

We found high-certainty evidence that long-chain omega-3 fats (LCn3) do not have important positive or negative effects on mortality or cardiovascular events and moderate-certainty evidence that they have little or no effect on cardiovascular disease mortality, stroke or arrhythmia in primary or secondary prevention. However, we found low-certainty evidence that LCn3 slightly reduces risk of coronary heart disease mortality (number needed to treat for an additional beneficial outcome (NNTB) 334, NNTB 200 in secondary prevention, NNTB 1000 in primary prevention), and coronary heart disease events (NNTB 167, NNTB 143 in secondary prevention, NNTB 200 in primary prevention). As these effects are very small (and numbers needed to treat for an additional benefit high), supplemental LCn3 fats are probably not useful for preventing or treating cardiovascular disease. LCn3 fats can help to reduce serum triglycerides, though they do not appear to affect body fatness or other lipid fractions.

An NNTB of 167 means that 167 people will need to take LCn3 supplements for around four years each so that one of those people avoids a coronary heart disease event. The other 166 people receive no benefit. Similarly, an NNTB of 334 means that 334 people need to take LCn3 supplements for around four years each for one person to avoid death from coronary heart disease, the other 333 people do not benefit.

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How does an NNTB of 143 or 500 compare with effective medications in cardiovascular disease prevention? Could we compare, for example, with the use of statins in secondary prevention of myocardial infarction or ezetimibe added to statins after acute coronary syndrome? In the 4S trial (Scandinavian Simvastatin Survival Study Group 1994), 8% of the participants taking simvastatin died, and 12% of those taking the placebo died, a difference of 4%, so the NNTB was 25. Twenty-five people needed to take simvastatin for around five years to prevent one person dying. Most of us decide to take statins post-myocardial infarction. Ten-year NNTBs for statins in primary prevention when used according to appropriate guidance are around 30, to prevent one case of atherosclerotic cardiovascular disease (Mortensen 2019). The IMPROVE-IT trial showed that giving ezetimibe in addition to statin to 50 people with acute coronary syndrome for seven years each prevents one person from having a cardiovascular event (Turgeon 2015).

Individuals may make differing decisions about whether an NNTB of 143 is useful. Perhaps NNTBs should be noted on fish oil supplement packages: “If 143 people with existing cardiovascular disease take this supplement for 5 years each then one of those 143 people will avoid a coronary event (such as a heart attack). If 1000 people without existing cardiovascular disease take this supplement for 5 years each then one person will avoid dying from coronary heart disease”. Then each of us could decide whether this is the way we wish to spend our money, on omega-3 supplements or a different cardiovascular treat such as a pair of running shoes, healthy fruit or fish, or a relaxation class.

Most evidence on LCn3 fats came from trials of capsules of fish oil or eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA) mixtures. While we did not see important differences between trials of supplemental capsules and trials of oily fish, there were few trials of oily fish. Fish and seafood are nutrient-dense and rich in a variety of other nutrients (such as vitamin D, calcium, iodine, selenium) so are useful foods even without cardiovascular benefits. In light of the evidence in this review it would be appropriate to review official recommendations supporting supplemental LCn3 fatty acid intake.

We found low-certainty evidence that increasing ALA may slightly reduce risk of cardiovascular disease events (NNTB 500) and moderate-certainty evidence that increasing ALA probably reduces risk of arrhythmia (NNTB 91). However, there is probably little or no effect on all-cause or cardiovascular mortality, coronary heart disease mortality or coronary heart disease events (low- and moderate-certainty evidence). As with LCn3, effects of ALA were very small; 91 people would need to increase their ALA intake to prevent one person developing arrhythmia, and 500 would need to take more ALA to prevent one person experiencing a cardiovascular disease event. We found no evidence that ALA affected adiposity or serum lipids. Trials of ALA gave ALA-rich or enriched foods such as walnuts or ALA-enriched margarine.

Implications for research

There are several large ongoing trials of supplemental LCn3 fats (see Characteristics of ongoing studies, and large parts of VITAL 2019 are ongoing). We suggest that given the minimal protective effects suggested for omega-3 fats in the large number of trials to date, no further trials should be initiated until the ongoing trials have reported. Ongoing and completed trials should make data on baseline LCn3 intake, and details of deaths, cardiovascular outcomes, lipids, adiposity and blood pressure available, as well as other key health outcomes, regardless of their primary outcomes.

Further large and high-certainty trials of ALA carried out in lower- and higher-income countries, and that assess baseline ALA intake and use biomarkers to assess compliance would be helpful to clarify the cardiovascular effects of ALA. Similarly trials of dietary fish would be helpful.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ADCS 2010

Methods	Alzheimer's Disease Cooperative Study (ADCS) RCT, parallel, (n-3 DHA vs n-6 LA), 18 months Summary risk of bias: low
Participants	Individuals with mild to moderate Alzheimer's disease N: 238 intervention, 164 control Level of risk for CVD: low Men: 52.9% intervention, 40.2% control Mean age in years (SD): 76 (9.3) intervention, 76 (7.8) control Age range: unclear Smokers: 24.4% intervention, 21.9% control Hypertension: not reported Medications taken by at least 50% of those in the control group: cholinesterase inhibitor, memantine Medications taken by 20%-49% of those in the control group: none Medications taken by some, but < 20% of the control group: none Location: USA Ethnicity: not reported
Interventions	Type: supplement (capsule) Comparison: DHA vs omega-6 Intervention: 2 × 1 g algal-derived DHA capsules (Neuromins)/d for a total daily dose of 2 g, each capsule contain 45%-55% of DHA and does not contain EPA (950 mg soft-gel capsules, which contain approximately 510 mg DHA). Dose: +DHA 1.02 g/d Control: 2 × 1 g placebo capsules/d (made up of corn or soy oil) Compliance: measured by pill counts at every visit Length of intervention: 18 months
Outcomes	Main trial outcome: change in the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) and change in the Clinical Dementia Rating (CDR) Dropouts: 67 intervention, 40 control (discontinued treatment but included in main analyses)

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ADCS 2010 *(Continued)*

	Available outcomes: mortality, measures of cognition, baseline and change in plasma DHA, adverse events Response to contact: no data provided
Notes	Trial funding; quote: "grant UO1-AG10483 from the National Institute on Aging. The National Institute on Aging was not otherwise involved in the design and conduct of the study, or in the analysis of data or preparation of the manuscript". "The placebo and DHA study drugs were provided by Martek Biosciences. Martek also provided plasma and cerebrospinal fluid measurements of FAs, as well as partial financial support for the magnetic resonance imaging sub study. (Martek Biosciences produces nutritional supplements from cultivated fungi and microalgae). Martek employees participated in design of the study and in revision of the manuscript, but were not involved in data management or data analysis." (Quinn 2010, p. 1910).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved with a centralised interactive voice response system, using a block design with a block size of 5 (3 in the DHA group and 2 in the placebo group.
Allocation concealment (selection bias)	Low risk	Randomisation was achieved with a centralised interactive voice response system, using a block design with a block size of 5 (3 in the DHA group and 2 in the placebo group.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo capsules (made up of corn or soy oil) were identical in appearance. The adequacy of blinding was assessed by questionnaires completed by caregivers, trial co-ordinators, and site physicians.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The adequacy of blinding was assessed by questionnaires completed by caregivers, trial co-ordinators, and site physicians with results showing no difference between groups and the majority did not know.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis. At 12 months data were available for > 80%
Selective reporting (reporting bias)	Low risk	Prospectively registered February 2007, trial started February 2007, completed May 2009. Primary outcomes were rate of change in ADAS-Cog11 and CDR-SOB, which are both reported in main report. NPI and ADL were secondary outcomes also reported.
Attention	Low risk	Both trial arms had the same follow-up and care.
Compliance	Unclear risk	Measured by pill count at every visit. 28% intervention and 24% control discontinued supplement with a minority discontinuing due to adverse events. A further 8% were excluded for < 80% compliance in both intervention and control arms.
Other bias	Low risk	None noted

AFFORD 2013

Methods	Multi-centre study to evaluate the effect of n-3 FAs on arrhythmia recurrence in atrial fibrillation (AFFORD)

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AFFORD 2013 *(Continued)*

	RCT, parallel, (n-3 EPA + DHA vs n-6), 12 months
	Summary risk of bias: moderate or high
Participants	People with symptomatic paroxysmal or persistent AF
	N: 165 intervention, 172 control (Analysed, intervention: 153 control: 163)
	Level of risk for CVD: high
	Men: 69% intervention, 65% control
	Mean age in years (SD): 60 (12) intervention, 62 (13) control
	Age range: not reported
	Smokers: not reported
	Hypertension: 45% intervention, 42% control
	Medications taken by at least 50% of those in the control group: oral anticoagulant
	Medications taken by 20%-49%: beta-blockers, ACE inhibitors, ARBs
	Medications taken by some, but < 20%: none
	Location: Canada
	Ethnicity: not reported
Interventions	Type: supplement (fish oil)
	Comparison: EPA + DHA vs omega-6 safflower oil
	Intervention: 4 × 1 g enteric-coated fish oil capsules/d (1.6 g/d EPA + 0.8 g/d DHA, Genuine Health, Toronto, Ontario, Canada). Dose: +2.4 g/d EPA + DHA, Control: 4 ×1 g matching placebo capsules, 4 g/d safflower oil
	Compliance: omega-3 index increased in intervention group, but not control, over the trial
	Duration of intervention: 6-16 months
Outcomes	Main trial outcome: AF recurrence
	Dropouts: 21 intervention, 19 control
	Available outcomes: all-cause mortality, stroke, AF recurrence, TIA, CV events, CRP (not usable)
	Response to contact: no
Notes	We contacted trial authors about QoL, resource use and dietary habits
	Trial funding: Canadian Institutes for Health Research and the Heart and Stroke Foundation of Quebec

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"[R]andomised"
Allocation concealment (selection bias)	Unclear risk	Not described

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AFFORD 2013 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blind, but blinding not described or tested
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	An independent events committee adjudicated AF recurrences, bleeding, strokes, TIAs, and deaths, but unclear if blinded to allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participant flow well described. ITT analysis
Selective reporting (reporting bias)	High risk	NCT01235130 registered July 2010, recruitment March 2009-March 2012, follow-up finished December 2012. Results published 2014, but no data on QoL, resource utilisation, or dietary habits (stated in registry) found
Attention	Low risk	No problem with attention bias
Compliance	Low risk	Omega-3 index measured
Other bias	Low risk	None noted

Ahn 2016

Methods	RCT, parallel, (EPA + DHA + statins vs statins), 12 months Summary risk of bias: moderate to high
Participants	Statin-treated coronary artery disease (CAD) patients undergoing percutaneous coronary intervention N: 38 intervention, 36 control Level of risk for CVD: high Men: 63.2% intervention, 72.2% control Mean age in years (SD): 59.6 (9.1) intervention, 60.7 (0.8) [sic] control Age range: unclear Smokers: 36.8% intervention, 58.3% control Hypertension: 50% in both groups Medications taken by at least 50% of those in the control group: aspirin, clopidogrel, ACE inhibitors/ARB, beta-blockers, atorvastatin Medications taken by 20%-49% of those in the control group: cilostazol Medications taken by some, but < 20% of the control group: rosuvastatin, nitrates, calcium antagonists Location: South Korea Ethnicity: not reported
Interventions	Type: supplement (capsule) Comparison: EPA + DHA vs nil

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Ahn 2016 *(Continued)*

	Intervention: 3 g of ω-3 PUFA containing 1395 mg of EPA and 1125 mg of DHA/d. No further details. Dose: +2.52 g/d EPA + DHA Control: unclear whether control group were given placebo or only statins Compliance: unclear how it was measured but reported good compliance with no numbers Length of intervention: 12 months
Outcomes	Main trial outcome: change in atherosclerotic burden Dropouts: none Available outcomes: lipids (TG reported as median, IQR so not used), atheroma volume, neointimal volume index Response to contact: no
Notes	Trial funding: the trial was supported by clinical research grant from Pusan National University Hospital

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Simple randomisation was carried out using random number tables to assign each participant to the intervention or control group
Allocation concealment (selection bias)	Low risk	Participants were assigned randomisation numbers sequentially on recruitment to the trial, and the randomisation codes were retained by the clinical research co-ordinator.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The personnel responsible for randomisation as well as those performing laboratory measurements were blinded to the randomisation assignments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts reported
Selective reporting (reporting bias)	Unclear risk	No protocol or trial register entry found
Attention	Unclear risk	No details
Compliance	Unclear risk	No details on how it was measured and no FA levels reported
Other bias	High risk	It's unclear whether the trial was placebo-controlled or the control group had no intervention. Also, some of the SDs appear to be incorrectly reported.

AlphaOmega - ALA 2010

Methods	RCT, (n-3 ALA vs MUFA), 40 months

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AlphaOmega - ALA 2010 *(Continued)*

	Summary risk of bias: low
Participants	60-80 year-olds with previous MI N: 1197 ALA intervention, 1236 control (1212 ALA + EPA/DHA intervention group) Level of risk for CVD: high Men: 77.9% intervention, 78.7% control Mean age in years (SD): 69.0 (5.6) intervention, 68.9 (5.6) control Age range: 60-80 years Smokers: 17.4% intervention, 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: not reported Medications taken by some, but < 20% of the control group: antiarrythmic drugs, antidiabetic drugs Location: the Netherlands Ethnicity: not reported
Interventions	Type: supplementary margarine Comparsion: ALA vs MUFA Intervention 20 g/d enriched margarine incorporating: 2 g ALA. 8 × 250 g margarine tubs delivered every 12 weeks. Dose: average achieved +1.9 g/d ALA Control: 20 g/d margarine. No additional n-3 PUFAs. Identical margarine (oleic acid) placebo Compliance: unused margarine tubs were returned- daily intakes of margarine and n-3 FAs were calculated on the basis of the amount unused. Adherence was measured by levels of FAs in plasma cholesteryl esters, margarine and questionnaires. 90.5% of participants adhered to the protocol and consumed 20.6 (SD 2.8) g/d of margarine. Length of intervention: 40 months
Outcomes	Main trial outcome: CVD events Dropouts: 91 died, 98 discontinued intervention, 93 died, 93 discontinued control Available outcomes: deaths, MI, CVD events, ventricular arrhythmia, incident CVD Response to contact: yes (data provided)
Notes	The trial has 3 intervention arms (ALA margarine, EPA/DHA margarine, mixture of the 2 interventions). This table represents the ALA-only intervention. Outcome data are used for the ALA group where reported separately or for the combined (ALA arm, ALA + EPA/DHA arm) Trial funding: Netherlands Heart Foundation, National Institutes of Health and Unilever R&D (latter provided unrestricted grant for distribution of trial margarines)

Risk of bias

Bias	Authors' judgement	Support for judgement

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AlphaOmega - ALA 2010 *(Continued)*

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	Trial author confirmed allocation was concealed from clinicians/ researchers
Blinding of participants and personnel (performance bias) All outcomes	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 safely under supervision.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Randomisation tables were stored safely under supervision. There was an independent statistician for data analysis. Quote: "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) All outcomes	Low risk	All participants were followed up for events, computerised linkage with municipal registries. 2531 participants 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 2002-2006. 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 FAs were calculated on the basis of the amount unused. Adherence was measured by levels of FAs in plasma cholesteryl esters, margarine and questionnaires. 90.5% of participants adhered to the protocol and consumed 20.6 (SD 2.8) g/d of margarine
Other bias	Low risk	None noted

AlphaOmega - EPA+DHA 2010

Methods	RCT, (EPA + DHA vs MUFA), 40 months Summary risk of bias: low
Participants	60-80 year-olds with previous MI N: 1192 EPA/DHA intervention, 1236 control (1212 ALA + EPA/DHA intervention group) Level of risk for CVD: high Men: 78.1% intervention, 78.7% control Mean age in years (SD): 69.1 (5.6) intervention, 68.9 (5.6) control Age range: 60-80 years Smokers: 16.8%, intervention, 18% control Hypertension: unclear

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AlphaOmega - EPA+DHA 2010 *(Continued)*

	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: not reported Medications taken by some, but < 20% of the control group: antiarrythmic drugs, antidiabetic drugs Location: the Netherlands Ethnicity: not reported
Interventions	Type: supplementary margarine Comparison 1: EPA + DHA vs MUFA Intervention: 20 g/d enriched margarine incorporating 400 mg EPA-DHA (240 mg EPA and 160 mg DHA). Dose: average achieved 376 mg/d EPA + DHA Control: 20 g/d margarine. No additional n-3 PUFAs. Identical margarine (oleic acid) placebo Compliance: unused margarine tubs were returned; daily intakes of margarine and n-3 FAs were calculated on the basis of the amount unused. Adherence was measured by levels of FAs in plasma cholesteryl esters, margarine and questionnaires. 90.5% of participants adhered to the protocol. Length of intervention: 40 months
Outcomes	Main trial outcome: CVD events Dropouts: 95 died, 119 discontinued intervention, 93 died, 93 discontinued control Available outcomes: deaths, MI, CVD events, ventricular arrhythmia, incident CVD Response to contact: yes (data provided)
Notes	The trial has 3 intervention arms (ALA margarine, EPA/DHA margarine, mixture of the 2 interventions). This table represents theEPA/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) Trial funding: Netherlands Heart Foundation, National Institutes of Health and Unilever R&D (latter provided unrestricted grant for distribution of trial margarines)

Risk of bias

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) All outcomes	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 safely under supervision.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Randomisation tables were stored safely under supervision. There was an independent statistician for data analysis. Quote: "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) All outcomes	Low risk	All participants were followed up for events computerised linkage with municipal registries. 2531 participants were only followed up for baseline anthropometric and medical measurements.

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AlphaOmega - EPA+DHA 2010 *(Continued)*

Selective reporting (reporting bias)	High risk	Sudden cardiac death endpoint omitted. Registered from August 2005, recruitment was from 2002-2006. 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 FAs were calculated on the basis of the amount unused. Adherence was measured by levels of FAs in plasma cholesteryl esters, margarine and questionnaires. 90.5% of participants adhered to the protocol and consumed 20.6 (SD 2.8) g/d margarine
Other bias	Low risk	None noted

AREDS2 2014

Methods	Age-Related Eye Disease Study 2 (AREDS2) RCT, parallel, 2 × 2 factorial (n-3 EPA + DHA vs nil) also randomised to lutein and zeaxanthin vs nil), 5 years Summary risk of bias: low
Participants	People aged 50-85 years at high risk of progression to advanced age-related macular degeneration (AMD) N: 2147 intervention (1068 DHA/EPA, 1079 DHA/EPA + lutein/zeaxanthin), 2056 control (1012 placebo, 1044 lutein/zeaxanthin) Level of risk for CVD: low (however ˜20% had previous CV event) Men: intervention 42.1%, control 44.4% Age in years: intervention median 74.6 (IQR 11.1), control median 74 (IQR 11.1) Age range: 68-79 years Smokers: intervention 6.3%, control 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 < 20% of the control group: NSAID, paracetamol Location: USA Ethnicity: white 96.5% intervention, 96.6% control; Hispanic: 2.6 intervention, 1.3 control
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 (500 mg/d), Vitamin E (440 IU/d), beta-carotene (15 mg/d), zinc oxide (80 mg/d) and cupric oxide (2 mg/d). Dose: +1 g/d EPA + DHA Control: standard AREDS supplement of Vitamin C (500 mg/d), Vitamin E (400IU/d), beta-carotene (15 mg/d), zinc oxide (80 mg/d) and cupric oxide (2 mg/d).

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AREDS2 2014 *(Continued)*

	Compliance: assessed by pill count. 84% of participants in each group took at least 75% of trial medications Length of intervention: 60 months
Outcomes	Main trial outcome: development of advanced AMD Dropouts: intervention 200 died, 165 discontinued, 80 were lost to follow-up; control 168 died, 140 discontinued, 61 were lost to follow-up Available outcomes: deaths, CV death, MI, stroke, angina, heart failure, revascularisation, cognition, eye health, (trial authors provided data on diabetes diagnosis, depression diagnosis, breast cancer) Response to contact: yes (data provided)
Notes	Trial funding: National Eye Institute/National Institutes of Health, Department of Health and Human Services

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "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 trial eligibility was verified. The assigned bottle number was used to distribute the trial treatment(s). AREDS2 Co-ordinating centre personnel involved in creating the randomisation system had access to the bottle number/treatment assignments.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Participants, investigators, study coordinators, and all other study personnel are masked to treatment assignment". However, no information was given regarding the taste, smell, or appearance of the active or placebo capsules.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The co-ordinating centre randomly assigned the event to a trial adjudicator, who made the final determination of these trial endpoints through review of the medical records and applying the endpoint criterion defined a priori. All adjudicators were masked to trial assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 20% attrition over 5 years, balanced reasons for dropouts
Selective reporting (reporting bias)	Low risk	Outcomes in trials registry entry appear to all be reported (NCT00345176). Entry received June 2006, recruitment September 2006–October 2012
Attention	Low risk	Participants, investigators, trial co-ordinators, and all other trial 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 trial medications
Other bias	Low risk	None noted

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ASCEND 2018

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	People with diabetes, without apparent vascular disease (94% of participants in both arms had type 2 DM, TG unclear) 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 < 20% of the control group: NSAID, thiazolidinedione, beta-blockers, thiazide or related diuretics, PPI Location: UK Ethnicity: white 96.5% intervention, 96.5% control Indian/Pakistani/Bangladeshi 1.2% intervention, 1.2% control African/Caribbean 0.9% intervention, 0.9% control
Interventions	Type: supplement (capsule) Comparison: EPA + DHA vs MUFA Intervention: 840 mg/d EPA+DHA (460 mg/d EPA plus 380 mg/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 trial 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

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ASCEND 2018 *(Continued)*

	Available outcomes: deaths, CV death, MI, stroke, heart failure, revascularisation, AF, diabetes complications, cancer diagnosis, breast cancer, prostate cancer (and other types of cancer), TIA, IBD, dementia, depressive disorders, anxiety, suicidal and injurious behaviour, Parkinson's 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 Trial funding: British Heart Foundation, medications provided by Mylan, Solvay and Abbott

Risk of bias

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) All outcomes	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) All outcomes	Low risk	Outcomes self-reported (questionnaire) but investigated by masked adjudication committee
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis
Selective reporting (reporting bias)	Low risk	Prospective trial registration (registered August 2005, recruitment June 2005-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

Baldassarre 2006

Methods	RCT, (n-3 EPA + DHA vs MUFA), 24 months Summary risk of bias: moderate or high
Participants	45-70-year-olds with combined hyperlipoproteinaemia (mean baseline TG > 3 mmol/L) N: 32 intervention, 32 control Level of risk for CVD: moderate

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Baldassarre 2006 *(Continued)*

	Men: 29% intervention, 29% control Mean age in years (SD): 53.7 (7.2) intervention, 53.7 (6.9) control Age range: 45-70 years (inclusion) Smokers: 28.1% intervention, 28.1% control Hypertension: none (exclusion criteria) Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported (participants on HRT, anti-hypertensive drugs, lipid-lowering drugs, or who smoked > 10 cigarettes were excluded) Location: Italy Ethnicity: not reported
Interventions	Type: capsules Comparsion: LCn3 vs MUFA Intervention: 1 g × 6 soft gelatin capsules/d of FA mixture (19% EPA), 13% DHA, 19% palmitic acid, 18% oleic acid, 2% LA and 29% other minor components) providing 1.08 g/d EPA, 0.72 g/d DHA, 0.01 g/d tocopherol acetate, divided to 3 doses. Dose: 1.8 g/d EPA + DHA Control: 1 g × 6 opaque identical soft gelatin capsules/d of olive oil divided in 3 doses Compliance: assessed by counting returned capsules at each visit and by measuring EPA and DHA levels at month 24 Length of intervention: 24 months
Outcomes	Main trial outcome: carotid atherosclerosis measures Dropouts: 2 intervention, 5 control Available outcomes: deaths (nil), MI (lipids, weight, BP and heart rate reported but not in a usable format; lipid data were presented at various times without clear numerical data, suggesting falls in TGs in the intervention but not control arms, and rises in LDL and HDL cholesterol in intervention but not control arms. For the other outcomes the text states "a rise in body weight (+ 3%, P < 0.01) was observed at the end of the study in both groups. Blood pressure and heart rate were unchanged". Effects on IMT and platelets also reported but not used) Response to contact: not yet attempted
Notes	Trial funding: supported by Institut De Recherche Pierre Fabre, Departement Recherche Clinique

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An appropriate software was used to obtain 2 groups balanced for sex, age and smoking
Allocation concealment (selection bias)	Unclear risk	No further details
Blinding of participants and personnel (performance bias)	Unclear risk	Double-blind and placebo capsules were opaque and identical-looking to intervention. However no information provided on capsules taste or smell

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Baldassarre 2006 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	All dropouts are accounted for. "One patient left the study after 3 months because he moved to another city and was therefore excluded from statistical analyses. Two patients were excluded because of major deviation from the protocol during the follow-up (anti-hypertensive assumption) and four because of non-compliance on the basis of returning capsules (compliance < 70%). The final analysed group included 57 patients (30 on active treatment)."
Selective reporting (reporting bias)	Unclear risk	No protocol or trial register record
Attention	Low risk	Both groups had the same contact and number of visits.
Compliance	Low risk	Pill count, we know they excluded 4/64 who returned > 70% of capsules. So 60/64 had > 70% compliance with significant increase in serum EPA and DHA in the intervention group.
Other bias	Low risk	None noted

Bates 1989

Methods	RCT, parallel, (n-3 EPA + DHA vs MUFA), 24 months Summary risk of bias: moderate or high
Participants	People with MS N: 155 intervention, 157 control (analysed, intervention: 145 control: 147) Level of risk for CVD: low Men: 34.2% intervention, 30.6% control Mean age in years (SD): 34.0 (6.6) intervention, 33.7 (6.3) control Age range: not reported but 16-45 years inclusion criteria Smokers: not reported Hypertension: not reported Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49%: not reported Medications taken by some, but < 20%: not reported Location: UK Ethnicity: not reported
Interventions	Type: supplement (fish oil capsule) Comparison: EPA + DHA vs MUFA

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Bates 1989 *(Continued)*

	Intervention: 20 × 0.5 g/d capsules MaxEPA fish body oil (10 g/d fish oil providing 1.71 g/d EPA + 1.14 g/d DHA +10 IU/d vitamin E), plus all advised to reduce animal fat and ensure plentiful omega-6 fats. Dose: +2.85 g/d EPA + DHA Control: 20 × 0.5 g/d capsules olive oil (10 g/d olive oil), plus all advised to reduce animal fat and ensure plentiful omega-6 fats. All capsules contained 0.5 IU vit E and 100 ppm dodecyl gallate to minimise peroxide formation Compliance: serum EPA and DHA rose in intervention group but fell in controls Duration of intervention: 24 months (5 years mentioned but outcomes not reported)
Outcomes	Main trial outcome: MS progress Dropouts: 10 intervention, 10 control Available outcomes: all-cause mortality, progress of MS, rate of MS relapse Response to contact: yes (no data provided)
Notes	Trial funding: Multiple Sclerosis Society of Great Britain and Northern Ireland, but Marfleet Refining provided fish oil and placebo capsules

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised"
Allocation concealment (selection bias)	Unclear risk	No further details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Paper states research was "double blind" and control capsules "had the same appearance and flavour as the fish oil capsules and were packed and dispensed in identical fashion"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low risk at reported time points
Selective reporting (reporting bias)	High risk	No protocol or trials registration entries found. Study was intended to run for 5 years, but outcomes only appear to be reported for the first 2 years.
Attention	Low risk	Unlikely as each had capsules
Compliance	Low risk	Serum EPA and DHA rose in intervention group but fell in controls
Other bias	Low risk	Not noted

Berson 2004

Methods	RCT, parallel, (n-3 DHA vs n-6 LA), 48 months

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Berson 2004 *(Continued)*

	Summary risk of bias: low
Participants	People with retinitis pigmentosa aged 18-55 years N: 221 randomised overall, analysed 105 intervention, 103 control Level of risk for CVD: low Men: 48% intervention, 54% control Mean age in years (SD): 37.8 (6.5) intervention, 36.0 (7.2) control Age range: unclear (18-55 inclusion criterion) Smokers: not reported Hypertension: not reported Medications taken by at least 50% of those in the control group: vitamin A Medications taken by 20%-49% of those in the control group: multivitamins Medications taken by some, but < 20% of the control group: not reported Location: USA Ethnicity: unclear (6% of the trial population were minorities)
Interventions	Type: supplement (DHA capsules) Comparison: DHA vs omega-6 Intervention: 6 × 500 mg capsules/d of DHA (1.2 g/d DHA plus 1.8 g vegetable oil) plus < 0.0006 mg/d tocopherols plus 15,000 IU retinyl palmitate (vitamin A). Dose: +1.2 g/d DHA Control: 6 × 500 mg capsules/d of soy and corn oils (half each) with 120 mg/d ALA, plus < 0.0006 mg/d tocopherols plus 15000 IU retinyl palmitate (vitamin A) Compliance: 92% of capsules taken by both intervention and control groups (assessed by monthly calendars). Plasma DHA much higher in intervention than control Length of intervention: 48 months
Outcomes	Main trial outcome: retinal degeneration Dropouts: 5 or 6 intervention, 7 or 8 control Available outcomes: mortality, cancer diagnoses, lipids, eyesight Response to contact: yes (no data provided)
Notes	Trial funding: National Eye Institute and Foundation Fighting Blindness

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Random numbers available only to programmer who provided assignments to data manager, all staff in contact with participants were masked to group assignment

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Berson 2004 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	States that all staff in contact with participants were masked to group assignment, as were participants. However no information was provided regarding the taste, smell and appearance of the active and placebo capsules
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All assessments were performed blind to trial allocation. Each ocular examination was performed without review of previous records. All serum samples were analysed without knowledge of treatment group assignment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Numbers of dropouts and reasons for dropouts not stated. 221 participants randomised, data presented on 208 participants
Selective reporting (reporting bias)	Unclear risk	No trials registry entry or protocol found
Attention	Low risk	Staff in contact with participants were masked, so unable to bias time, etc
Compliance	Low risk	92% of capsules taken by both intervention and control groups (assessed by monthly calendars), Plasma DHA much higher in intervention than control
Other bias	Low risk	None noted

Broutset 2007

Methods	RCT, parallel, (ALA vs unclear), 12 months Summary risk of bias: moderate to high
Participants	People aged 18-77 years with successful AF electrical cardioversion N: 98 randomised overall, analysed 40 intervention, 35 control Level of risk for CVD: high Men: % unclear, but both sexes enrolled Mean age in years (SD): unclear Age range: unclear (18-77 inclusion criterion) Smokers: not reported Hypertension: not reported Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: France Ethnicity: unclear
Interventions	Canola margarine and oil, rich in ALA, vs a conventional diet (control), for 1 year Type: enriched foods (canola margarine and oil rich in ALA) Comparison: ALA vs unclear

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Broutset 2007 *(Continued)*

	Intervention: ALA dose of canola margarine and oil unclear Control: conventional diet (ALA dose unclear) Compliance: not reported Duration of intervention: 12 months
Outcomes	Main trial outcome: length of time to first recurrence of AF Dropouts: 98 recruited, 75 analysed, 23 dropouts, unclear which arms Available outcomes: AF recurrence Response to contact: yes (no data provided)
Notes	NCT00410020, registered December 2006 Checked for updates and publications, 2 August 2019. 2007 abstract found (no further publication)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Allocation stated as randomised in trials register, but no method provided
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Trials register suggests open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Trials register suggests open-label trial
Incomplete outcome data (attrition bias) All outcomes	High risk	98 recruited, 75 analysed (23% dropout) over 12 months
Selective reporting (reporting bias)	High risk	Only 1 of the several outcomes and analyses in trials register reported
Attention	Unclear risk	Unclear
Compliance	Unclear risk	Unclear
Other bias	Unclear risk	None noted

Brox 2001

Methods	RCT, parallel, 3 arms (n-3 EPA + DHA from cod liver vs n-3 EPA + DHA from seal oil vs nil), 14 months Summary risk of bias: moderate or high
Participants	People with moderate hypercholesterolaemia (mean baseline TG 204 mg/dL)

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Brox 2001 *(Continued)*

	N: 40 seal oil, 40 cod liver oil, 40 control (numbers analysed vary by outcome) Level of risk for CVD: moderate (dyslipidaemia) Men: 53% seal oil, 50% cod liver oil, 48% control Mean age in years: 53.2 seal oil, 55.0 cod liver oil, 55.8 control Age range: 43-66 years Smokers: unclear Hypertension: unclear Medications taken by at least 50% of those in the control group: none allowed Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: Norway Ethnicity: not reported
Interventions	Type: supplement (oil) Comparison: EPA + DHA vs nil Intervention: intervention: seal oil – 15 mL/d (2.6 g, 1.1 g/d EPA + 1.5/d DHA) (total n-3 3.9 g/d, total PUFA 4.2 g/d): SO dose: EPA + DHA 2.6 g/d Cod liver oil – 15 mL/d (3.3 g, 1.5 g /d EPA + 1.8 g/d DHA) (total n-3 4.1 g/d, total PUFA 4.35 g/d): cod liver oil dose: EPA + DHA 3.3 g/d Control: nil, no supplement Compliance: serum omega-3 FAs, rose from around 1 mmoL/L to 2.4 (seal oil), 2.1 (cod liver oil) and 1.2 mmoL/L (control) Length of intervention: 14 months
Outcomes	Main trial outcome: serum lipids Dropouts: 8 seal oil, 2 cod liver oil, 1 control Available outcomes: total and CV deaths, MI, combined CV events, lipids, adverse events Response to contact: yes (author provided methodological details)
Notes	Data of 2 intervention groups combined for dichotomous outcomes and cod liver oil vs control data used for continuous outcomes Trial funding: the trial was supported by the programme Medical Research in Finnmark County, University of Tromsø

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	J Brox stated (personal communication, January 2017): "The randomization of the 120 participants was done by first generating 3 groups (seal oil, cod liver oil, control), then giving each participant a number (1-120), 'putting all the numbers into the same hat' and blindly drawing one number at the time from the hat. The first 40 numbers (1-40) were allocated to the seal oil group, the

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Brox 2001 *(Continued)*

		next 40 numbers (41-80) to the cod liver oil group and the rest (81-120) were allocated to the control group."
Allocation concealment (selection bias)	Low risk	J Brox stated (personal communication, January 2017): "The researcher/clinician who invited the participants had no knowledge of to which group the participants would be allocated."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "controls were aware – not given a supplement"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	J Brox stated (personal communication, 2003): "All the persons involved in the drawing & analysing of blood were unaware of treatment. The technicians analysing the blood did not have any personal contact with the participants except K. Olaussen who did the FA analysis … she only had access to the sample numbers not names and code. The participants did not know their number (says elsewhere that K Olaussen did not know allocations). The only outcome assessor was J Brox who did not have personal contact with participants, randomising, collecting results or analysing process." "The only assessor was J Brox who did not have any personal contact with the participants, had nothing to do with the randomising or analysing process, or the collecting of results."
Incomplete outcome data (attrition bias) All outcomes	High risk	Control group 3 dropouts, seal oil group 10 dropouts, cod liver oil 3 dropouts. So substantial differences in rates of dropouts between the groups
Selective reporting (reporting bias)	Unclear risk	No trial protocol or trials register entry was found
Attention	Low risk	No suggestion of differential attention
Compliance	Low risk	Serum omega-3 FAs, rose from around 1 mmoL/L to 2.4 (seal oil), 2.1 (cod liver oil) and 1.2 mmoL/L (control)
Other bias	Low risk	No further bias noted

Caldwell 2011

Methods	RCT, parallel, (n-3 EPA + DHA vs n-6 LA), 12 months Summary risk of bias: low
Participants	Participants with non-cirrhotic NASH (53% obese, mean 3.1 metabolic syndrome criteria, 35% diabetic, mean TG 191 mg/dL) N: 20 intervention, 21 control (analysed 17 intervention, 17 control) Level of risk for CVD: moderate Men: 35.3% intervention, 41.2% control Mean age in years (SD): 46.4 (12.1) intervention, 47.2 (12) control Age range: 25-72 years Smokers: not reported Hypertension: not reported

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Caldwell 2011 *(Continued)*

	Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: USA Ethnicity: intervention, 100% white, control 94.% white, 5.9% other
Interventions	Type: supplement (capsule) Comparison: EPA + DHA vs omega-6 Intervention: 3 × 1 g fish oil capsules/d (Nordic Natural) for a total 2.1 g/d n-3, each capsule contained 70% of n-3 (1050 mg EPA, 750 mg DHA + 300 mg other n-3). Dose: 1.8 g/d EPA + DHA Control: 3 × 1 g/d identical placebo (soybean) capsules containing 8% fish oils Both groups had dietary counselling on caloric intake and physical activity Compliance: unclear (measured n-6-n-3 ratio due to its link to hepatic lipid composition) Length of intervention: 12 months
Outcomes	Main trial outcome: NASH activity score Dropouts: 3 intervention, 3 control Available outcomes: lipids (TG too unbalanced at baseline to use), measures of adiposity (weight, BMI, visceral fat – all unbalanced at baseline so not used), fasting glucose, insulin, HOMA-IR, QUICKI (also NASH progression, hepatic fat, ALT, VO_2 max, activity level, markers of cell injury, adiponectin not used) Response to contact: yes, change data supplied for BMI and body weight, confirmed no deaths, CV events, diabetes, depression, breast cancer or IBD diagnoses
Notes	Data on; BMI, weight, visceral fat, TG and glucose were not used as they were different between groups at baseline. Trial funding: trial was supported by NIH NCCAM Grant 5R21AT2901–2 and 5 M01 RR00847. Trial 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised to n-3 or placebo using a stratified block 1:1 randomisation scheme. An independent biostatistician generated the randomisation list which was confidentially forwarded to the Investigational pharmacy
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All staff and participants were blinded to therapy assignment throughout the trial period. Both capsules were identical. However no information provided on capsules' taste or smell

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Caldwell 2011 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded for main outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	15% dropouts 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

DART 1989

Methods	Diet And Reinfarction Trial (DART) – oily fish advice (or capsule) arm RCT – parallel, 2 × 2 × 2 factorial (n-3 EPA + DHA vs nil or fat advice vs not, oily fish advice (or capsule) vs not, dietary fibre advice vs not)), 2 years Summary risk of bias: moderate or high
Participants	Men recovering from MI N: 1015 intervention, 1018 Level of risk for CVD: high (post-MI) Men: 100% Mean age, SD: 56.7 intervention, 56.4 control (SDs not stated) Age range: unclear Smokers: 61.7% intervention, 62.2% control Hypertension: 22.7% intervention, 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 SFA + MUFA (by dietary achievement below) Intervention: advised to eat at least 2 weekly portions of 200-400 g fatty fish (mackerel, herring, kipper, pilchard, sardine, salmon, trout). If this was not possible, given MaxEPA capsules, 3/d (0.5 g EPA/d). 191/883 participants were taking MaxEPA at 2 years. Advice was reinforced 3-monthly. Dose: aimed for 0.5 g/d EPA

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DART 1989 *(Continued)*

	Control: no such dietary advice or capsules Compliance: 7-day weighed food diary of a random subsample indicated intake of 2.5 g/week EPA intervention, 0.8 g/week EPA control **Dietary achievements** Total fat intake, percentage of energy (%E) (through trial): control 35 (SD 6), intervention 31 (SD 7) (MD −4.00, 95% CI −4.57 to −3.43); significant reduction Saturated fat intake, %E (through trial): control 15 (SD 3), intervention 11 (SD 3), (MD −4.00, 95% CI −4.26 to −3.74); significant reduction PUFA intake (through trial), %E: control 7 (SD unclear), intervention 9 (SD unclear), (MD 2.00, 95% CI 1.57 to 2.43 assuming SDs of 5) significant increase PUFA n-3 intake: EPA, control 0.6 (SD 0.7) g/week, intervention 2.4 (SD 1.4) g/week PUFA n-6 intake: not reported MUFA intake (through trial), %E: control 13 (SD unclear), intervention 11 (SD unclear) (MD −2.00, 95% CI −2.43 to −1.57 assuming SDs of 5); significant reduction CHO intake (through trial), %E: control 44 (SD 6),intervention 46 (SD 7) (MD 2.00, 95% CI 1.43 to 2.57); significant increase Protein intake (through trial), %E: control 17(SD 4), intervention 18 (SD 4) (MD 1.00, 95% CI 0.65 to 1.35); significant increase Trans fat intake: not reported Length of intervention: 24 months
Outcomes	Main trial outcome: total mortality, reinfarction, CHD death Dropouts: none for mortality Available outcomes: total and CV deaths, MI, CHD events, lipids, BP, cancer deaths Response to contact: yes (data provided)
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 kg/m^2 were given weight-reduction advice, regardless of randomisation arm. The low fat high PUFA comparison was included in the omega-6 review. Trial 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomised" confirmed by trial author
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

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DART 1989 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were not aware of trial allocation (Prof Burr stated he did not know assignments)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Hospital notes and death registers were flagged to catch all outcome data
Selective reporting (reporting bias)	Unclear risk	No trial 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 2.5 g/week EPA intervention, 0.8 g/week EPA control
Other bias	Low risk	None noted

DART2 2003

Methods	Diet and Angina Randomised Trial (DART2) RCT, 2 × 2, (oily fish or capsules n-3 EPA + DHA vs nil, also no specific advice, also fruit, vegetables and oats vs no specific advice), 3-9 years Summary risk of bias: moderate or high
Participants	Men treated for angina N: 1571 intervention, 1543 control (all analysed for events) Control level of risk for CVD: high Men: 100% Mean age in years (SD): 61.1 (NR) intervention, 61.1 (NR) control Age range: unclear Smokers: 25% intervention, 23% control Hypertension: 49% intervention, 47% control Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49%: lipid-lowering, beta-blockers Medications taken by some, but < 20% of the control group: not reported Location: UK Ethnicity: not reported
Interventions	Type: dietary advice (to eat more oily fish or take fish oil capsules) Comparison: EPA + DHA vs unclear (not total fat, SFA or alcohol, presumably CHO and/or protein but not clear)

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DART2 2003 *(Continued)*

	Intervention: most (1109) advised to eat at least 2 weekly portions of fatty fish or take MaxEPA capsules, 3/d (0.5 g EPA/d). But 462 participants were sub-randomised to receive only fish oil capsules, not dietary fish advice. Dose: aimed for 0.5 g/d EPA. Control: non-specific sensible eating advice that did not include either of the interventions Compliance: postal dietary questionnaire suggested dietary EPA intake increased by 2.4 g/week intervention, 0.2 g/week control **Dietary achievements** Total fat intake, (change from baseline to 6 months): control −8.6 g/d (SD 20.9), intervention −5.2 (g/d SD 21.4) (MD 3.4 g/d) Saturated fat intake, (change from baseline to 6 months): control −3.5 g/d (SD 9.3), intervention −2.8 g/d (SD 9.4), (MD 0.7 g/d) PUFA intake (change from baseline to 6 months): control −1.6 g/d (SD 5.4), intervention −0.1 g/d (SD 5.8) (MD 1.5 g/d) PUFA n-3 intake (change from baseline to 6 months): EPA, control 0.12 g/week (SD 0.73), intervention 2.65 g/week (SD 1.35) (MD 2.53 g/week) 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: 36-108 months
Outcomes	Main trial outcome: total mortality Dropouts: none for mortality Available outcomes: total and CV deaths, sudden death, stroke, heart failure, cancer deaths Response to contact: yes (data provided)
Notes	Some of each group were also advised on high fruit, vegetables and oat diets, and those who received neither fish nor fruit advice received 'non-specific' dietary advice. All those whose BMI > 30 kg/m^2 in both groups received weight reduction advice. Trial funding: probably British Heart Foundation, Seven Seas Ltd, Novex Pharma Ltd and the Fish Foundation (these were acknowledged)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "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) All outcomes	High risk	Dietary advice, so not possible for participants to be blinded to intervention

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DART2 2003 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were not aware of trial allocation (Prof Burr stated he did not know assignments)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Hospital notes and death registers were flagged to catch all outcome data
Selective reporting (reporting bias)	Unclear risk	No trial 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 2.4 g/week intervention, 0.2 g/week control
Other bias	Low risk	None noted

Derosa 2016

Methods	RCT, parallel, (n-3 PUFA capsules vs placebo), 18 months Summary risk of bias: low
Participants	White overweight/obese people with IFG or IGT (mean baseline TG 182 mg/dL) N: 138 intervention, 143 control (analysed 128 intervention, 130 control) Level of risk for CVD: low Men: 50.72% intervention, 48.95% control Mean age in years (SD): 53.4 (11.2) intervention, 54.8 (12.1) control Age range: unclear Smokers: not reported Hypertension: not reported Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: Italy Ethnicity: white
Interventions	Type: capsule (n-3 PUFA) Comparison: EPA + DHA vs CHO + SFA Intervention: 3 × 1 g capsule/d n-3 PUFAs (ethylic esters, each 1-g capsule of n-3 PUFAs contains highly concentrated ethyl esters of omega-3 FAs, primarily EPA, and DHA in the proportion of 0.9–1.5). Dose: unclear (approx 2-3 g/d) Control: placebo (a capsule containing sucrose, mannitol and mineral salts, magnesium stearate (a saturated fat) and silicon dioxide, used as anti-caking agents)

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Derosa 2016 *(Continued)*

	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/d and 35 g/d of fibre). Individuals were also encouraged to increase their physical activity by walking briskly for 20-30 min, 3-5 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 trial outcome: insulin resistance Dropouts: 23 across arms (no details on groups but stated that there were no differences between groups) Available outcomes: mortality, CV mortality, CHD event, stroke, combined CVD events, MI, AF, weight, BMI, lipids, DM Response to contact: yes (data provided)
Notes	Trial 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

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)	Low risk	Trial author stated that allocation was concealed from clinicians and researchers, but no methodology provided
Blinding of participants and personnel (performance bias) All outcomes	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 trial. However no information provided on capsules' taste or smell
Blinding of outcome assessment (detection bias) All outcomes	Low risk	A copy of the code was provided only to the person performing the statistical analysis
Incomplete outcome data (attrition bias) All outcomes	Low risk	An ITT analysis was conducted for participants who received 1 dose of trial 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

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Deslypere 1992

Methods	RCT 4 arms, (n-3 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 intervention, 14 control Level of risk for CVD: low Men: 100% Mean age in years (SD): 56.2 (16.5) (not reported by arm) Age range: 21-87 Smokers: none Hypertension: not reported Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported (no medications influencing lipid metabolism or NSAIDs were allowed) Location: the Netherlands Ethnicity: not reported
Interventions	Type: capsules Comparsion: LCn3 vs MUFA Intervention 9 capsules (9 g vol)/d, of which 3, 6 or 9 were fish oil (Labaz, Brussels, Belgium) and any remainder were placebo (providing respectively 1.12; 2.24 or 3.37 g n-3 FA/day). Dose: 1.12 g/d; 2.24 g/d or 3.37 g/d EPA + DHA) Control: 9 placebo capsules made up of olive oil (Puget Marseille, France) and Palmoil (Loders-Kroklaan Wormerveen, the Netherlands) with the same SFA, cholesterol and vitamin E as the fish oil capsules Compliance: assessed by counting remaining capsules every 2 months and by measuring EPA concentration. Excellent compliance reported and shown by the EPA concentration results Length of intervention: 12 months
Outcomes	Main trial outcome: effect on coronary risk factors Dropouts: none Available outcomes: deaths (nil), CVD events (nil), lipids, BP, HbA1c, weight (measured but only text suggests "no significant changes in the anthropometric parameters (weight, length, waist, hip and thigh circumferences) during the trial"), IL-6, TNF-alpha and several IL-1s (IL-6 reported as below detection range, for the others there was "no significant difference between the two treatment groups at any point in time") Response to contact: yes
Notes	Trial 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

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Deslypere 1992 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (trial author correspondence): "The manufacturer provided envelopes containing numbers corresponding with boxes of capsules. For each enrolled subject, random envelope was opened."
Allocation concealment (selection bias)	Low risk	Allocation concealed from all this way
Blinding of participants and personnel (performance bias) All outcomes	High risk	Although double-blind, the fishy taste of the active treatment was not matched (trial author states that the fishy taste was clear in the intervention capsules)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial authors confirmed outcome assessors were unaware until afterwards
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
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 2015

Methods	Dietary Intervention for Patients Polypectomized for tumours of the colorectum (DIPP) RCT, parallel, 2 arms (n-3 EPA + DHA + n-3 ALA vs unclear), 24 months Summary risk of bias: moderate or high
Participants	People previously polypectomised for colorectal tumours N: 104 intervention, 101 control Level of risk for CVD: low Men: 73.1% intervention, 74.3% control Mean age in years (SD): 58.3 (9.5) intervention, 59.7 (8.9) control Age range: 35-75 Smokers: 65.4% intervention, 61.4% control Hypertension: not reported Medications taken by at least 50% of those in the control group: supplements

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DIPP 2015 *(Continued)*

	Medications taken by 20%-49% of those in the control group: none Medications taken by some, but < 20% of the control group: oral contraceptive pills Location: Japan Ethnicity: not reported
Interventions	Type: advice + supplement (fish oil capsules) Comparison: EPA + DHA + ALA vs unclear Intervention: advice to reduce total fat intake, decrease consumption of n-6 PUFAs, increase intake of n-3 PUFAs from fish/marine foods, increase intake of n-3 PUFAs from perilla oil rich in ALA, take 8 capsules of fish oil/d (equivalent to 96 mg/d of EPA and 360 mg/d of DHA). Dose: 456 mg/d EPA + DHA and unknown dose of ALA Control: advice to decrease intake of fats/oils as a whole Compliance: measured via semi-quantitative food frequency questionnaire, plasma FA concentrations, FA compositions in the membranes of red blood cells and the sigmoid colon. Reported satisfactorily high compliance with protocol in both groups but no figures provided Length of intervention: 24 months
Outcomes	Main trial outcome: number and size of colorectal tumours Dropouts: 3 intervention, 5 control Available outcomes: all-cause mortality, dietary intake, plasma FAs, lipids, side effects, glucose Response to contact: yes (methodological details provided)
Notes	Trial funding: all were either government or charity grants

Risk of bias

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) All outcomes	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) All outcomes	Low risk	Quote: "physicians, including colonoscopists, a scientist who conducted blood and specimen analyses, and pathologists were blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All those randomised were accounted for

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DIPP 2015 *(Continued)*

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 3 August 2006, recruitment completed 1 March 2007
Attention	Low risk	Participants were given equal follow-up
Compliance	Unclear risk	Reported satisfactorily high compliance with protocol was noted in both groups but no figures
Other bias	Low risk	None noted

DISAF 2003

Methods	Dietary Intervention Study for AF (DISAF) RCT, parallel, 2 arms (n-3 EPA + DHA vs unclear), 12 months Summary risk of bias: moderate or high
Participants	People presenting for 1st treatment of acute/persistent AF or flutter, confirmed by ECG N: intervention 201, control 206 Level of risk for CVD: high (people with AF) Men: intervention 64.7%, control 63.6% Mean age in years (SD): intervention 67.7 (9.4), control 68.7 (9.5) Age range: unclear Smokers: intervention 10.9%, control 12.1% Hypertension: intervention 48.2%, control 40.8% Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: antiarrhythmics, antithrombotics Medications taken by some, but < 20% of the control group: not reported Location: UK Ethnicity: white British
Interventions	Type: dietary advice Comparison: EPA + DHA vs unclear Intervention: dietary assistants gave advice and support to eat 2-3 portions of oily fish/week (providing up to 10 g LCn3/ week), plus 2-3 portions of fruit and vegetables/d. Dose: 1.4 g/d EPA + DHA Control: dietary assistants gave advice and support to eat 2-3 portions of fruit and vegetables/d. No other health/lifestyle given as part of the trial Compliance: assessed red blood cell FAs and found some increases in EPA and DHA in intervention compared to control (no further intake data)

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DISAF 2003 *(Continued)*

	Length of intervention: 12 months
Outcomes	Main trial outcome: sinus rhythm after 12 months Dropouts: unclear Available outcomes: deaths, AF recurrence Response to contact: yes (data provided)
Notes	Trial funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was by phone to an independent randomisation office, which used pre-printed random number tables
Allocation concealment (selection bias)	Low risk	Randomisation was by phone to an independent randomisation office, which used pre-printed random number tables
Blinding of participants and personnel (performance bias) All outcomes	High risk	Dietary advice was clear, so allocation known by participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	High risk	Some discrepancies between papers, reasons unclear
Selective reporting (reporting bias)	High risk	ISRCTN16448451 registered 23 January 2004, recruitment from 1 July 1998-1 July 2002; some secondary outcomes were not reported
Attention	Low risk	Intervention (advice to eat more oil-rich fish, fruit and vegetables) and control (advice to eat more fruit and vegetables) groups appeared to be given equivalent time and attention
Compliance	Low risk	Assessed red blood cell FAs and found some increases in EPA and DHA in intervention compared to control
Other bias	High risk	The trial was stopped early

DO IT 2010

Methods	Diet and Omega-3 Intervention Trial on atherosclerosis (DO IT) Randomisation: RCT, parallel, 2 × 2 factorial, (n-3 DHA + EPA vs n-6 LA also dietary advice intervention), 36 months Summary risk of bias: moderate or high
Participants	Elderly men with longstanding dyslipidaemia or hypertension (a subset of Oslo Diet heart trial) (mean baseline TG 1.8 mmol/L)

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DO IT 2010 *(Continued)*

	N: intervention 282 (140 n-3 capsules + 142 n-3 capsules and dietary advice), control 281 (142 placebo capsules + 139 placebo capsules and dietary advice) Level of risk for CVD: moderate Men: intervention 100%, control 100% Mean age in years (SD): intervention 70.4 (2.9), control 69.7 (3.0) years Age range: 64-76 years Smokers: intervention 35%, control 33% Hypertension: intervention 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 < 20% of the control group: β-blockers, ACE inhibitors and nitrates Location: Norway Ethnicity: not reported
Interventions	Type: supplement/capsule (also dietary advice as the factorial intervention) Comparison: EPA + DHA vs omega-6 Intervention: 2 × 2 capsules/d including 2.4 g/d of omega-3 PUFA (Pikasol, 0.84 g/d EPA plus 0.48 g/d DHA plus 8.4 mg/d tocopherols). Dose: 1.32 g/d EPA + DHA Control: 2 × 2 capsules/d including 4 g/d corn oil (2.24 g/d linoleic, 1.28 g/d oleic acid, 16 mg/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 trial outcome: atherosclerosis progression Dropouts: intervention 14 died, 20 others discontinued, control 24 died, 18 others discontinued Available outcomes: mortality, CV deaths, CHD events, CV events, MI, stroke, diabetes, glucose, lipids, cancer diagnosis, cancer deaths, sudden death, BMI (waist circumference reported as median, IQR) Response to contact: yes (data provided)
Notes	The other 2 × 2 intervention was dietary counselling to increase both omega-3 and omega-6 fats as well as fruit and vegetables. Trial 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Permuted block randomisation, no clear mechanism provided
Allocation concealment (selection bias)	Unclear risk	No details provided

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DO IT 2010 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	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) All outcomes	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) All outcomes	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

Methods	RCT, parallel, (n-3 ALA vs unclear), 12 months Summary risk of bias: moderate or high
Participants	Healthy menopausal women N: 101 intervention, 98 control (analysed, intervention: 85 control: 94) Level of risk for CVD: low Men: 0% intervention, 0% control Mean age in years (SD): 54.0 (4.0) intervention, 55.4 (4.5) control Age range: 49-65 Smokers: 8% intervention, 6% control Hypertension: not reported Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: Canada Ethnicity: French Canadian
Interventions	Type: food supplement (flaxseed) Comparison: ALA vs unclear (probably includes lipids, CHO and protein, but not clear)

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Dodin 2005 *(Continued)*

	Intervention: 40 g/d flaxseed incorporated into diets (providing 21,071 g total lignans, 180 calories, 16 g lipids (57% ALA), and 11 g total dietary fibre). Dose: 9.1 g/d ALA Control: 40 g/d wheat germ incorporated into diets (providing 196 g total lignans, 144 calories, 4 g lipids (6.9% ALA), and 6 g total dietary fibre Compliance: 1st morning urine collection was performed at randomisation and at month 12 to measure urinary lignin levels. In addition, trial 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 trial outcome: bone mineral density Dropouts: 26 intervention, 17 control (but 13/17 had an endpoint evaluation) Available outcomes: weight, BMI, QoL, BP, lipids, glucose, adverse events, dietary intake, plasma FAs Response to contact: yes
Notes	Trial authors replied to tell us that there were no deaths or CV events during the trial Trial funding: not reported

Risk of bias

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 4-8
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, investigators, staff, and statisticians were blinded to dietary assignments for the duration of the trial. Quote: "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 FA"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, investigators, staff, and statisticians were blinded to dietary assignments for the duration of the trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT 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

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Dodin 2005 *(Continued)*

Compliance	Low risk	1st morning urine collection was performed at randomisation and at month 12 to measure urinary lignin levels. In addition, trial 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

Doi 2014

Methods	RCT, parallel, (n-3 EPA vs nil), 12 months Summary risk of bias: moderate or high
Participants	People having percutaneous coronary intervention after acute MI N: 119 intervention, 119 control analysed Level of risk for CVD: high Men: 77% intervention, 76% control Mean age in years (SD): 70 (11) intervention, 71 (12) control Age range: unclear Smokers: 28% intervention, 32% control Hypertension: 71% intervention, 69% control Medications taken by at least 50% of those in the control group: aspirin, ticlopidine, beta-blockers, statins (as part of treatment) Medications taken by 20%-49% of those in the control group: ARB/ACE inhibitors Medications taken by some, but < 20% of the control group: none Location: Japan Ethnicity: not reported
Interventions	Type: supplement (EPA) Comparison: EPA vs nil Intervention: purified EPA ethyl esters (> 98%) 1800 mg EPA/day within 24 h after percutaneous coronary intervention plus statins. Dose: 1.8 g/d EPA Control: statins with no EPA Compliance: not reported Length of intervention: 12 months
Outcomes	Main trial outcome: CV events Dropouts: 1 intervention, 2 control Available outcomes: mortality, stroke, MI, sudden death, CV death, revascularisation Response to contact: no

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Doi 2014 *(Continued)*

Notes	Trial funding: trial registry state "self-funded". The trial authors received honoraria from Mochida Pharmaceutical Co.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated, randomisation plan, which included stratification by age and sex
Allocation concealment (selection bias)	Unclear risk	Carried out by research technician but unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label but blind endpoint
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Data on outcomes were collected from clinical charts. Unclear if blinded. Diagnoses were confirmed by investigator blind to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 3 dropouts, similar rates between the groups and reasons given
Selective reporting (reporting bias)	High risk	Data collection completed before trial registry entry. Only 1% dropouts
Attention	Low risk	Timing of follow-up similar
Compliance	Unclear risk	Not reported
Other bias	Low risk	None observed

DREAM Asbell 2018

Methods	Dry Eye Assessment and Management (DREAM) Study RCT, parallel, (LCn-3 vs MUFA), 12 months Summary risk of bias: low
Participants	Adults with dry eye N: 349 intervention randomised, 186 control randomised Level of risk for CVD: low Men: 19% intervention, 19% control Mean age in years (SD): 58.3 (13.5) intervention, 57.5 (12.6) control Age range: unclear Smokers: unclear Hypertension: unclear

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DREAM Asbell 2018 *(Continued)*

	Medications taken by at least 50% of those in the control group: artificial tears Medications taken by 20%-49% of those in the control group: cyclosporine drops Medications taken by some, but < 20% of the control group: warm lid soaks, lid scrubs or baby shampoo Location: USA Ethnicity: intervention, white 76%, black 11%, other 13%; control white 72%; black 13%; other 15%
Interventions	Type: supplement (LCn3) Comparison: LCn3 vs MUFA Intervention: omega-3 supplements (2000 mg EPA + 1000 mg DHA/d as 5 gel caps). Dose: 3.0 g/d LCn3 Control: olive oil supplements (5 gel caps) Compliance: change in red cell FAs: EPA intervention +2.2% (SD 1.2), control 0.0 (SD 0.2); DHA intervention +1.6% (SD 1.2), control −0.1 (SD 0.7). P values for difference between arms < 0.001 for both Length of intervention: 12 months
Outcomes	Main trial outcome: OSDI score Dropouts: 24 intervention, 22 control Available outcomes: secondary: other eye health measures, SF-36, healthcare utilisation costs, cost-effectiveness. Reported as adverse events: mortality, adverse events by organ class, including breast cancer and other cancers, colitis, AF, atrial flutter, psychotic disorder, pulmonary embolism, DVT, HT, GI disorders, angina, arrhythmia, constipation, diarrhoea, IBS, cognitive disorder, anxiety, depression, diabetes diagnosis, QoL (SF-36) Response to contact: no
Notes	NCT02128763 Trial funding: National Eye Institute and National Instutes of Health

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assignment of active or placebo supplements was automatically sent electronically to the Investigational Drug Service. Randomization schedules were stratified by clinical centre. "Randomization was performed with the use of a Web-based module and was stratified according to clinical center with a permuted-block method with randomly chosen block sizes. Personnel at the Investigational Drug Service, University of Pennsylvania, mailed the supplements directly to the patients."
Allocation concealment (selection bias)	Low risk	Centralised randomisation, as above.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All subjects, clinical staff, and laboratory personnel were unaware of the assignment to active or placebo supplements." "Personnel at the Investigational Drug Service, University of Pennsylvania, mailed the supplements directly to the patients."

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DREAM Asbell 2018 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of 349 randomised to the intervention and 186 in control, 324 completed data collection in intervention (24 missed final visit and 1 died) and 164 in control (22 missed final visit), but all those randomised were assessed for adverse events.
Selective reporting (reporting bias)	Low risk	Trials register April 2014, recruitment began in November 2014. Outcomes reported mirror those in the trials register
Attention	Low risk	Treatment of both groups appeared identical.
Compliance	Low risk	Red cell EPA and DHA rose in intervention group compared to control
Other bias	Low risk	None noted

ENRGISE 2018

Methods	ENabling Reduction of low-Grade Inflammation in SEniors (ENRGISE) pilot study RCT, 2x2, (LCn-3 vs PUFA plus or minus losartan), 12 months Summary risk of bias: moderate to high
Participants	People aged ≥ 70 years with self-reported walking or stair-climbing difficulty N: 148 intervention randomised (122 fish oil only, 26 fish oil plus losartan), 141 control randomised (102 placebo only, 39 placebo plus losartan) Level of risk for CVD: low Men: 53% intervention, 53% control Mean age in years (SD): 78 (5.6) intervention, 77 (5.3) control Age range: unclear (70+ years inclusion criteria, including participants in their 90s) Smokers: unclear Hypertension: int fish oil only 79%, intervention fish oil plus losartan 42%, control placebo only 70%, control placebo plus losartan 56% Medications taken by at least 50% of those in the control group: unclear Medications taken by 20%-49% of those in the control group: unclear Medications taken by some, but < 20% of the control group: unclear Location: USA Ethnicity: white intervention 78% and 85%, control 79% and 69%; African American intervention 17% and 12%, control 17% and 21%; Hispanic intervention 3% and 0%, control 2% and 5%; other intervention 5% and 4%, control 4% and 10%
Interventions	Type: supplement (LCn3) Comparison: LCn3 vs PUFA

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ENRGISE 2018 *(Continued)*

	Intervention • Arm 1: omega-3 fish oil (1.4 g/d for 6 months, discontinued if AF or intolerance at 6 months, increased to 2.8 g/d if IL-6 remained high at 6 months) • Arm 4: omega-3 plus losartan Dose: 1.2 g/d LCn3 (0.8 g/d EPA plus 0.4 g/d DHA), increasing to 2.4 g/d (1.6 g/d EPA plus 0.8 g/d DHA) in some from 6-12 months Control: • Arm 2: losartan 25 mg/d • Arm 3: placebo corn oil (for omega-3) plus placebo cellulose (for losartan) • Arm 5: placebo corn oil (for omega-3) • Arm 6: placebo cellulose (for losartan) Fish oil and corn oil placebo sourced from Epax, 0.7 g gel capsules, identical shape, colour, weight Compliance: self-reported adherence at 12 months was excellent, very good or good in 85% intervention (fish oil), 77% control (placebo fish oil). 12% intervention and 19% control reported having discontinued. Pill counts also performed. Compliance unclear as self-reported Duration of intervention: 12 months
Outcomes	Main trial outcome: IL-6, 400-m walk test Dropouts: 24 intervention, 22 control Available outcomes: secondary: short physical performance battery, frailty, muscle strength using hand grip strength and knee dynamometry, SF-36, additional inflammatory markers (CRP and other novel markers). Reported as adverse events and serious adverse events: GI disorders, neoplasms, GI upset, "cardiac disorders" and "vascular disorders". Other measures at 12 months included anthropometry, vital signs, adverse events and medical history. (MMSE measured at baseline but not repeated) Response to contact: no
Notes	NCT02676466 Funding: National Institutes of Health and National Institute on Aging. Additional funding from US Dept of Agriculture, Tufts University and Claude D Pepper Older Americans Independence Centers. Abbott Laboratories paid for purchase of the trial drug and matching placebo Note: at update trial results had been submitted to ClinicalTrials.gov, but not yet posted. Further details may be available in the near future.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization used a permuted block algorithm (with random block lengths) and was concealed via the secure web-based data management system"
Allocation concealment (selection bias)	Low risk	Appears appropriate, as above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind. Placebo appears well matched to fish oil capsules

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ENRGISE 2018 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear, likely for biochemical measures, not clear for self-reported and interview measures
Incomplete outcome data (attrition bias) All outcomes	High risk	At 12 months 87% of those taking fish oil and 82% of those taking placebo had their IL-6 assessed, 76% and 68% had walk speed assessed. Appears to be a difference in retention rates
Selective reporting (reporting bias)	High risk	Primary outcomes and adverse events reported, but not secondary outcomes yet
Attention	Low risk	Likely that this was similar as placebo used
Compliance	Unclear risk	Only pill counts (not reported) and self-report assessed
Other bias	Low risk	None noted

EPE-A 2014

Methods	EPE-A RCT, parallel, 3 arms (n-3 EPA, low dose vs high dose vs unclear placebo), 12 months Summary risk of bias: moderate or high
Participants	People with NASH and NAFLD (mean BMI 33.6, mean TG 139 mg/dL, 30.7% diabetic) N: 86 intervention-high, 82 intervention low, 75 control (analysed 64, 55, 55 respectively, ITT analysis for primary outcomes) Level of risk for CVD: low (although 35% had type II diabetes) Men: 33.7% intervention-high, 41.5% intervention-low, 42.7% control Mean age in years (SD): 47.8 (11.1) intervention-high, 47.8 (12.5) intervention-low, 50.5 (12.5) control Age range: not reported Smokers: not reported Hypertension: not reported Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: USA Ethnicity: white intervention-low: 94%, intervention-high: 87%, control: 90.7% African American intervention-low: 3.7%, intervention-high: 2.3%, control: 4.0% Others intervention-low: 2.4%, intervention-high: 10.5%, control: 5.3%
Interventions	Type: supplement (omega-3 capsule) Comparison 1: high EPA vs low EPA (unclear what replaced EPA) Comparison 2: EPA vs unclear (placebo contents not reported)

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EPE-A 2014 *(Continued)*

	Intervention-high: EPA-E 2.7 g/d, 3 × EPA-E 300 mg capsules. Dose: 2.7 g/d EPA + DHA Intervention-low: EPA-E 1.8 g/d, 2 × EPA-E 300 mg capsules + 1 placebo capsule Dose: 1.8 g/d EPA + DHA Control: 3 × placebo capsules. The pills were identical with respect to size, colour and smell Compliance: 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 trial outcome: histological response in standardised scoring of liver biopsies and change in ALT level Dropouts: 22 intervention-high, 27 intervention-low, 20 control Available outcomes: cardiac events, deaths (none), angina, adverse events (weight, BMI, lipids, glucose, HbA1c, HOMA, hsCRP all reported as medians so not useable in meta-analyses) Response to contact: yes (provided methodological details)
Notes	Data combined for the 2 intervention groups for binary outcomes and higher dose data vs control used for continuous outcomes Trial funding: supported entirely by Mochida Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation using an interactive voice-response system to assign subjects in a 1:1:1 ratio between the 2 arms for each site separately. Participants were stratified by the presence of type 2 diabetes. The total fraction of such individuals was capped at 40% of the trial cohort
Allocation concealment (selection bias)	Low risk	As above (remote computer-generated randomisation)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind stated, but no further details. Trial author confirmed researchers and outcome assessors were blinded to treatment allocation and pills were identical with respect to size, colour and smell
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	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 June 2010, trial started June 2010, completed October 2012. All outcomes in trials registry entry were also reported in the trials registry. Secondary outcomes reported were not planned (compared with 1st version of clinicaltrials.gov entry)
Attention	Low risk	All participants had same follow-up visits

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EPE-A 2014 *(Continued)*

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

EPIC-1 2008

Methods	EPANOVA in Crohn's disease, study 1 (EPIC-1) RCT, parallel, 2-arm (omega-3 vs SFA as MCT), 52 weeks Summary risk of bias: moderate or high
Participants	Adults with quiescent Crohn's disease, CDAI score < 150 N: 188 intervention, 186 control Level of risk for CVD: low Men: 48.1% intervention, 41.1% control Mean age in years (SD): 40.5 (15.2) intervention, 38.2 (13.1) control Age range: 18-70 years Smokers: 30.6% intervention, 34.4% control Hypertension: unclear Medications taken by at least 50% of those in the control group: oral 5-ASA therapy, Systemic corticosteroids – prednisolone, budesonide Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: antibiotic therapy, topical rectal therapy, immune-modifying agents, immune modifiers/biologics Location: Canada, Europe, Israel, USA Ethnicity: not reported
Interventions	Type: supplement (capsule) Comparison: EPA + DHA vs SFA (MCTs of short SFAs) Intervention: 2 × 2 1 g gelatin capsules omega-3 free FAs (Epanova- 2.2 g EPA, 0.8 g DHA). Dose: 3 g/d EPA + DHA Control: 4 x1 g capsules MCT Compliance: pill counts, 79.2% adhered intervention, 75.6% adhered control Length of intervention: mean 52 weeks
Outcomes	Main trial outcome: Crohn's relapse-free time Dropouts: 80 intervention, 91 control Available outcomes: total deaths, non-fatal arrhythmias, cancer diagnoses, cancer deaths, adverse events Response to contact: yes (data provided)
Notes	Trial funding: Tillotts Pharma, trial authors had extensive financial disclosures

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EPIC-1 2008 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by number generator. Used a centralised randomisation procedure via interactive voice recognition system
Allocation concealment (selection bias)	Low risk	Centralised randomisation (see above)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinding stated, identical capsule (slow-release capsules). Neither investigator nor participant knew the allocation.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Trial states double-blind but does not state that outcome assessors were blinded or provide a mechanism for this
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of dropouts and reasons provided. 171 of 187 in intervention group and 174 of 184 in control group provided data for primary outcome, (7% dropout), though 80 in the intervention group and 91 in the control group terminated early.
Selective reporting (reporting bias)	High risk	Trials registration (NCT00613197) first received in 2008, but trial started in 2003 and was published in 2008
Attention	Low risk	As investigators were blinded attention bias was not possible.
Compliance	Unclear risk	Pill counts, 79.2% adhered intervention, 75.6% adhered control
Other bias	Low risk	No further bias noted

EPIC-2 2008

Methods	EPANOVA in Crohn's Disease, Study 2 (EPIC-2) RCT, parallel, 2 arms (omega-3 vs SFA - MCT), 58 weeks Summary risk of bias: moderate or high
Participants	Adults with a confirmed diagnosis of Crohn's Disease and a CDAI score < 150 who are responding to steroid induction therapy N: intervention, 189, control 190 (187 intervention, 188 control analysed) Level of risk for CVD: low (people with quiescent Crohn's disease) Men: 48.1% intervention, 41.1% control Mean age in years (SD): 38.5 (13.8) intervention, 40.0 (13.6) years control Age range: > 16 years Smokers: 25.1% intervention, 37.2% control Hypertension: unclear

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EPIC-2 2008 *(Continued)*

	Medications taken by at least 50% of those in the control group: systemic corticosteroids – prednisolone, budesonide (but tapered and discontinued during the trial) Medications taken by 20%-49% of those in the control group: only reported for prior 12 months Medications taken by some, but < 20% of the control group: only reported for prior 12 months Location: Canada, Europe, Israel, USA Ethnicity: not reported
Interventions	Type: supplement (capsule) Comparison: EPA + DHA vs SFA (MCTs of short SFAs) Intervention: 2 × 2 1 g gelatin capsules omega-3 free FAs (Epanova) providing total dose ˜2.2 g/d EPA, 0.8 g/d DHA. Dose: ˜3.0 g/d EPA + DHA Control: 2 × 2 1 g capsules MCT oil Compliance: measured by patient interviews and pill counts, 75.4% adhered intervention, 81.4% adhered control Length of intervention: mean 58 weeks
Outcomes	Main trial outcome: maintain Crohn's symptomatic remission Dropouts: 114 intervention, 112 control Available outcomes: mortality, CV events (nil), cancer diagnoses, adverse events Response to contact: yes (data provided)
Notes	Trial funding: Tillotts Pharma, trial authors had extensive financial disclosures

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by number generator. Used a centralised randomisation procedure via interactive voice recognition system
Allocation concealment (selection bias)	Low risk	Centralised randomisation (see above)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blinding stated, identical capsule (slow-release capsules). Neither investigator nor participant knew the allocation. However no information provided on capsules' taste or smell
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Trial states double-blind but does not state that outcome assessors were blinded or provide a mechanism for this
Incomplete outcome data (attrition bias) All outcomes	High risk	Number of dropouts and reasons provided, however 114 of 189 in intervention group and 112 of 190 in control group terminated early.
Selective reporting (reporting bias)	High risk	NCT00074542. First received 2003, trial start 2002. Published 2008. Some outcomes, such as QoL, stated in trials registry but not in published papers
Attention	Low risk	As investigators were blinded, attention bias was not possible.
Compliance	Unclear risk	Measured by participant interviews and pill counts, 75.4% adhered intervention, 81.4% adhered control

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EPIC-2 2008 *(Continued)*

Other bias	Low risk	No further bias noted

EPOCH 2014

Methods	Older People, Omega-3 and Cognitive Health (EPOCH) RCT, parallel (n-3 EPA + DHA vs MUFA), 18 months Summary risk of bias: low
Participants	Healthy older adults with no cognitive impairment N: 195 intervention, 196 control (reported by trial author) Level of risk for CVD: low Men: not reported Mean age in years (SD): not reported Age range: not reported, but 65-90 recruited Smokers: not reported Hypertension: not reported Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: Australia Ethnicity: not reported
Interventions	Type: supplement (fish oil capsules) Comparison: EPA + DHA vs MUFA Intervention: 4 capsules/d (1.72 g/d DHA and 0.60 g/d EPA). Dose: 2.32 g/d EPA + DHA Control: 4 capsules/d (3.960 g/d olive oil and 40 mg/d fish oil) Compliance: count of all unused supplements returned at 3-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 trial outcome: change in cognitive performance Dropouts: not reported Available outcomes: mortality (nil), MI, stroke, revascularisation, arrhythmias, CV events Response to contact: yes (data provided)
Notes	Trial authors reported some events, but don't appear to be published.

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EPOCH 2014 *(Continued)*

	Trial 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Age-stratified, permuted-block randomisation, with mixed block-sizes (2-8, size unknown to trial 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) All outcomes	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) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	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; BP; biomarkers of glucose, glycated haemoglobin, triglycerides, total cholesterol, HDL, LDL, homocysteine, CRP, MDA, and telomere length)
Attention	Low risk	All had the same contact and attention
Compliance	Unclear risk	Count of all unused supplements returned at 3-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

Erdogan 2007

Methods	RCT, parallel (n-3 EPA + DHA vs unclear), 12 months Summary risk of bias: moderate to high
Participants	People with successful external cardioversion N: unclear intervention, unclear control (54 analysed intervention, 54 control) Level of risk for CVD: high

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Erdogan 2007 *(Continued)*

	Men: 70% intervention, 74% control Mean age in years (SD): 65.0 (mean for whole group, SD not reported) Age range: not reported Smokers: not reported Hypertension: not reported Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: Germany Ethnicity: not reported
Interventions	Type: supplement (probably, not described) Comparison: high EPA + DHA vs unclear placebo Intervention: described only as "PUFA" but included in systematic review (Mariani 2013) by Erdogan et al on effects of n-3 PUFA. Dose: unclear Control: described only as "placebo" Compliance: not reported Length of intervention: 12 months
Outcomes	Main trial outcome: AF relapse Dropouts: not reported Available outcomes: recurrent AF (reported in Mariani 2013), mortality (none) Response to contact: no reply to date
Notes	Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as triple-blind, but no further details provided (only an abstract with some details in a related trial publication and some in a systematic review by the same author)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described, but analysis appears to have been carried out blind to intervention/control status

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Erdogan 2007 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number randomised not described
Selective reporting (reporting bias)	Unclear risk	Unclear, no trial registry entry or protocol found
Attention	Unclear risk	Not described
Compliance	Unclear risk	Not described
Other bias	Low risk	None noted

FAAT 2005

Methods	Fatty Acid Antiarrhythmia Trial – FAAT Randomisation: RCT, parallel, 2 arms, (n-3 EPA + DHA vs MUFA), 12 months Summary risk of bias: moderate or high
Participants	People with implanted cardioverter defibrillators N: intervention 200, control 202 Level of risk for CVD: high (patients with implanted cardioverter defibrillators) Men: intervention 84.5%, control 81.7% Mean age in years (SD): intervention 65.7 (11.6), control 65.3 (11.7) Age range: unclear Smokers: intervention 15%, control 11.4% Hypertension: unclear Medications taken by at least 50% of those in the control group: ACE inhibitors, beta-blockers Medications taken by 20%-49%: diuretics Medications taken by some, but < 20%: calcium channel blockers, amiodarone, sotalol, type 1 antiarrhythmics Location: USA Ethnicity: intervention 95.5% white, control 96.5% white
Interventions	Type: supplement/capsule Comparison: EPA + DHA vs MUFA Intervention: 4 ×1 g/d fish oil gelatin capsules, 2.6 g/d EPA + DHA (Pronova Biocare, quantities of EPA + DHA unclear). Dose: 2.6 g/d EPA + DHA Control: 4 ×1 g/d olive oil capsules, 4 g/d (in identical gelatin capsules, < 0.06 g/d EPA and < 0.06 g/d DHA) All were advised to use olive oil rather than the common plant seed oils for cooking, dressings, and sauces

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FAAT 2005 *(Continued)*

	Compliance: pill counts and platelet phospholipid data suggested greater omega-3 intake in intervention participants. 35% were non-compliers (36.5% intervention, 34.2% control) Duration of intervention: 12 months
Outcomes	Main trial outcome: fatal ventricular arrhythmias Dropouts: intervention 13 deaths, unclear number of dropouts, control 12 deaths, dropouts unclear Available outcomes: deaths, CV deaths, CVD events, deaths from heart failure, fatal arrhythmias, MI, angina Response to contact: yes (data provided)
Notes	Trial funding: the trial was supported in part by a grant from the NHLBI, NIH (HL62154)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation tables for each collaborating site, stratified by site
Allocation concealment (selection bias)	Low risk	Trial author confirmed allocation was concealed from investigators
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Trial referred to as "double blind" and gelatin capsules (verum and placebo) were stated as being of identical appearance but no discussion of taste or smell. Trial author confirmed that investigators and participants were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	VT and VF events were assessed blinded to allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Large numbers dropped out so some deaths, etc. may have been missed, 35% discontinued early due to non-compliance but were assessed at trial end, data censored for some participants
Selective reporting (reporting bias)	High risk	Trials registry data received September 2005, paper published November 2005
Attention	Low risk	Time and attention appeared similar between the 2 arms
Compliance	High risk	Pill counts and platelet phospholipid data suggested greater omega-3 intake in intervention participants. 35% were non-compliers (36.5% intervention, 34.2% control)
Other bias	Low risk	None noted

FLAX-PAD 2013

Methods	Effects of dietary flaxseed on symptoms of cardiovascular disease in patients with peripheral arterial disease (FLAX PAD) RCT, parallel, (n-3 ALA vs unclear), 12 months

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FLAX-PAD 2013 *(Continued)*

	Summary risk of bias: low
Participants	Patients with peripheral artery disease, over 40 years old N: 58 intervention, 52 control Level of risk for CVD: high (all had peripheral artery disease, 80% had hyperlipidaemia) Men: 74.1% intervention, 73.1% control Mean age in years (SD): 67.4 (8.06) intervention, 65.3 (9.4) control Age range: unclear Smokers: 19.2% intervention, 34.6% control Hypertension: 81% intervention, 69.2% control Medications taken by at least 50% of those in the control group: lipid-lowering medication, antihypertensives, antithrombotics Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: insulin or blood sugar-lowering drugs Location: Canada Ethnicity: unclear
Interventions	Type: food supplement (milled flaxseed) Comparison: ALA vs unclear (mix of wheat, wheat germ and mixed dietary oils) Intervention: food products (i.e. bagels, muffins, bars, pasta, buns, and milled seeds) containing 30 g of milled flaxseed daily. Dose: ˜6.8 g/d ALA (calculated based on 30 g milled flaxseed/d) Control: placebo food products (i.e. bagels, muffins, bars, pasta, buns, and milled seeds) containing a mixture of wheat, wheat bran, and mixed dietary oils to replace the flaxseed daily Compliance: plasma levels of enterolignans and the n-3 FA ALA were used as markers of dietary compliancy Length of intervention: 12 months
Outcomes	Main trial outcome: all-cause mortality, CV mortality, stroke, and MI Dropouts: 15 intervention, 11 control Available outcomes: BP, lipids, adverse events, plasma ALA Response to contact: yes (but no data provided)
Notes	Different intervention dropout figures reported in 2 publications (13 or 15) Trial funding: funded by government organisations but foods created and provided by a company

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly selected by a computer programme

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FLAX-PAD 2013 *(Continued)*

Allocation concealment (selection bias)	Low risk	Allocation was concealed. The person who determined if a participant was eligible for inclusion in the trial was unaware, when this decision was made, to which group the participant would be allocated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Product colour and texture were similar to disguise the composition of the product. Participants, personnel administering the intervention and those assessing the outcomes were blinded to group assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All personnel that collected or analysed data were blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised accounted for in main outcomes
Selective reporting (reporting bias)	High risk	Prospectively registered October 2008, trial start October 2008, primary outcome data completed March 2011, end date December 2017. Cardiovascular mortality and measures of adiposity not reported in a useable way
Attention	Low risk	Both groups had the same care
Compliance	Unclear risk	12 in intervention group and 8 in placebo group unwilling to comply with diet
Other bias	Low risk	None noted

FORWARD 2013

Methods	Randomised trial to assess efficacy of PUFA for the maintenance of sinus rhythm in persistent AF (FORWARD) RCT, parallel, (n-3 EPA + DHA vs MUFA), 12 months Summary risk of bias: low
Participants	People with paroxysmal AF N: 289 intervention, 297 control Level of risk for CVD: high Men: 57.8% intervention, 51.9% control Mean age in years (SD): 66.3 (12) intervention, 65.9 (10.5) control Age range: > 21 Smokers: 9% intervention, 6.2% control Hypertension: 92.2% intervention, 90.8% control Medications taken by at least 50% of those in the control group: aspirin, amiodarone, 'any antithrombotic treatment', beta-blockers Medications taken by 20%-49% of those in the control group: anticoagulants Medications taken by some, but < 20% of the control group: none reported

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FORWARD 2013 *(Continued)*

	Location: Argentina Ethnicity: not reported
Interventions	Type: supplement (capsule) Comparison: EPA + DHA vs MUFA Intervention: 1 capsule/d containing 1 g of n-3 PUFA (Societá Prodotti Antibiotici and SigmaTau, Italy) (provided 850 mg-882 mg EPA/DHA). Dose: 0.85 g/d EPA + DHA Control: identical placebo capsule containing olive oil Compliance: not reported Length of intervention: 12 months
Outcomes	Main trial outcome: survival free of AF Dropouts: 20 intervention, 25 control Available outcomes: mortality, MI, AF, heart failure, stroke, hospitalisation, side effects. Trial authors supplied further info on CVD events and methodology Response to contact: yes
Notes	Trial funding: through unrestricted grants provided by companies that supplied trial drugs, however "these companies did not have representatives on the Steering Committee" who terminated the trial after 1 year

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants were centrally assigned to receive either 1 g of n-3 PUFA or placebo in a ratio of 1:1" – computer generated in blocks of 4 and 6 stratified by trial location
Allocation concealment (selection bias)	Low risk	As above, centrally allocated. Communication from trial authors was ambiguous, stated that the person recruiting *was* aware of which arm the individual would be allocated to, but that the "study was double-blind, placebo-controlled."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Each study site will be supplied with study drug and placebo in identically appearing packaging". "Both placebo and active treatment have the same odour and produce a comparable degree of fishy aftertaste"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Patients, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of the treatment from the time of randomisation until database lock" "The adjudication committee members are unaware of participant allocation and assess all available data and documentation with reference to pre-established criteria".
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "the study was cut short by the trial steering committee due to 'a slower-than-expected recruitment rate and lower event rates'. This 'resulted in an underpowered clinical trial unable to verify its hypothesis'. Therefore the outcome data were not as complete as they were initially meant to be".
Selective reporting (reporting bias)	Low risk	Prospectively registered January 2008, trial start January 2008, completion August 2011. All outcomes in trials registry appear to have been reported

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FORWARD 2013 *(Continued)*

Attention	Low risk	Both intervention and control given the same exposure to research personnel. 2013 paper: "Clinical outcomes, adherence, and adverse events were assessed 2, 4, 8, and 12 months after randomization"
Compliance	Unclear risk	Not reported
Other bias	Low risk	None noted

FOSTAR 2016

Methods	Fish Oil in knee OSTeoARthritis (FOSTAR) RCT, parallel, (n-3 EPA + DHA vs low n-3), 24 months Summary risk of bias: low
Participants	Adults aged 40+ years with knee osteoarthritis N: 101 intervention, 101 control Level of risk for CVD: low Men: 41% intervention, 60% control Mean age in years (SD): 60.8 (10) intervention, 61.1 (10) control Age range: > 40 Smokers: not reported Hypertension: not reported Medications taken by at least 50% of those in the control group: none reported Medications taken by 20%-49% of those in the control group: not reported at baseline, but 'during' includes vitamin D ˜ 32% Medications taken by some, but < 20% of the control group: not reported at baseline, but 'during' includes glucocorticoid, HRT/anti-resorptive, both ˜ 10% Location: Australia Ethnicity: not reported
Interventions	Type: supplementary food (enriched orange juice) Comparison: high EPA + DHA vs low EPA + DHA plus ALA (replacement unclear, but low omega-3) Intervention: 1-3 × a day drink of fruit juice mixed with day total = 15 mL of fish oil supplement (18% EPA, 12% DHA, 4.5 g/day total omega-3). Dose: 4.5 g/d EPA + DHA Control: liquid oral oil 15 mL Sunola oil/day (which contains fish oil 2 mL plus 13 mL canola oil) (total omega-3 fat: ≥ 0.45 g EPA + DHA from 15 mL) Compliance: assessed by measuring the oil volume in returned bottles, compliance was > 80% in both groups. Both groups had increases from baseline in plasma EPA and DHA with the high-dose group having substantially larger increases, consistent with compliance with trial oil Length of intervention: 24 months
Outcomes	Main trial outcome: change in pain scale of WOMAC index

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FOSTAR 2016 *(Continued)*

	Dropouts: 18 intervention, 16 control Available outcomes: mortality, CVD events, adverse events, analgesic use, bone marrow density, weight gain and serum FAs Response to contact: yes
Notes	Data on QoL and pain score are presented in a figure and not in a usable format Trial funding: government funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random allocation sequence
Allocation concealment (selection bias)	Low risk	A security-protected central automated allocation procedure was used to allocate participants to one of the 2 treatment arms. This was performed centrally at 1 pharmacy and then used to allocate and administer the oil at each site
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Citrus flavouring was added to both oils to achieve comparable taste and optimise masking. Both were provided in identical dark 500-mL bottles with *similar* labelling. At the end of the trial, 52% of participants were unsure which group to which they had been allocated (50% high dose, 50% low dose). Of the remaining who thought they knew which group they were allocated, only 57% answered correctly, suggesting that blinding had been well maintained
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and staff involved in patient care and assessment of BMD remained blinded throughout the trial.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Oil intolerance in 1st year differed, others appear similar, but numbers confused
Selective reporting (reporting bias)	High risk	Prospectively registered August 2007, recruitment started July 2007, outcomes published 2016. Variety of outcomes such as QoL stated in trials registry but not published
Attention	Low risk	Same contact and instruction schedule for all participants
Compliance	Low risk	Assessed by measuring the oil volume in returned bottles, compliance was > 80% in both groups. Both groups had increases from baseline in plasma EPA and DHA with the high-dose group having substantially larger increases, consistent with compliance with trial oil
Other bias	Low risk	None noted

Franzen 1993

Methods	RCT, parallel (n-3 EPA + DHA vs MUFA), 12 months Summary risk of bias: moderate to high
Participants	Adults with documented CHD

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Franzen 1993 *(Continued)*

	N: 15 intervention, 15 control
	Level of risk for CVD: high
	Men: unclear
	Mean age in years (SD): 52 (9) intervention, 54 (7) control
	Age range: not reported
	Smokers: 87% intervention, 100% control
	Hypertension: not reported
	Medications taken by at least 50% of those in the control group: aspirin, beta-blockers
	Medications taken by 20%-49% of those in the control group: not reported
	Medications taken by some, but < 20% of the control group: not reported
	Lipid-lowering medications were not allowed
	Location: Germany
	Ethnicity: not reported
Interventions	Type: fish oil capsules
	Comparison: EPA + DHA vs MUFA
	Intervention: 9 × 1 g capsules/d of fish oils (20% EPA, 15% DHA, 3.15 g/d total omega-3). Dose: 3.15 g/d EPA + DHA
	Control: 9 × 1 g capsules/d olive oil (which contains 6.3 g/day MUFA, 1.35 g/day SFA, 1.35 g/d total omega-6 fat)
	Compliance: assessed by pill counts and FA in body tissue analysis
	Length of intervention: 12 months
Outcomes	Main trial outcome: blood lipids and FA in body tissues
	Dropouts: 0 intervention, 0 control
	Available outcomes: mortality (nil death), CVD events (nil), lipids (only TC used as the others were different at baseline), adverse events, serum FAs
	Response to contact: yes
Notes	Trial funding: unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list
Allocation concealment (selection bias)	Unclear risk	No details. They received their initial allocation in a sealed box in person; subsequent doses arrived in the post
Blinding of participants and personnel (performance bias)	Unclear risk	No further details beyond stating "double blind"

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Franzen 1993 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition
Selective reporting (reporting bias)	Unclear risk	No trial register or protocol found
Attention	Low risk	No difference between groups
Compliance	Unclear risk	Measured but no results
Other bias	Low risk	None noted

Gill 2012

Methods	RCT, parallel, (EPA + DHA vs unclear), 24 months
	Summary risk of bias: moderate or high
Participants	Adults with metabolic syndrome (mean baseline TG 157 mg/dL)
	N: unclear, total randomised 101
	Level of risk for CVD: low
	Men: 47% total, no details by group
	Mean age in years (SD): 55 (10) total
	Age range: 18-75 years
	Smokers: 0% intervention, 0% control
	Hypertension: not reported
	Medications taken by at least 50% of those in the control group: not reported
	Medications taken by 20%-49% of those in the control group: not reported
	Medications taken by some, but < 20% of the control group: not reported
	Location: USA
	Ethnicity: unclear
Interventions	Type: supplement (fish oil capsules)
	Comparison: EPA + DHA vs placebo (unclear what)
	Intervention: fO3FA capsules 1.8 g of EPA + DHA daily. Dose: 1.8 g/d EPA + DHA
	Control: matching placebo supplement
	Compliance: not reported

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Gill 2012 *(Continued)*

	Length of intervention: 12 months
Outcomes	Main trial outcome: change in carotid intima-media thickness 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 trial arm. Trial funding: unclear, but mentions that Pfizer, NIH and "Northwest Lipids Clinic" are partners

Risk of bias

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) All outcomes	Unclear risk	No data
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No data
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No data
Selective reporting (reporting bias)	High risk	Inadequate detail in reporting as no full-text publication found; Gill 2014 (see secondary ref under Gill 2012) 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 data
Other bias	Unclear risk	No data

GISSI-HF 2008

Methods	Gruppo Italiano per la Sperimentazione della Streptochinasi nell'Infarto miocardico – Heart Failure (GISSI-HF) RCT, parallel, 2 arms (n-3 EPA + DHA vs MUFA), 3.9 years Summary risk of bias: moderate or high

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GISSI-HF 2008 *(Continued)*

Participants	People with chronic heart failure N: 3494 intervention, 3481 control Level of risk for CVD: high Men: 77.8% intervention, 78.8% control Mean age: 67 (11) intervention, 67 (11) control Age range: ≥ 18 years Smokers: 14.4% intervention, 13.9% control Hypertension: 54.0% intervention, 55.2% control Medications taken by at least 50% of those in the control group: ACE inhibitors, beta-blockers, diuretics Medications taken by 20%-49% of those in the control group: spironolactone, digitalis, oral anticoagulants, aspirin, nitrates, statins Medications taken by some, but < 20% of the control group: ARBs, other antiplatelets, calcium channel blockers, amiodarone Location: Italy Ethnicity: unclear
Interventions	Type: supplement (capsule) Comparison: EPA + DHA vs MUFA Intervention: 1 capsule/d of 1 g n-3 mainly EPA and DHA as ethyl esters in the average ratio of 1:1.2. Dose: ˜0.866 g/d EPA + DHA Control: 1 g/d matching olive oil placebo capsule Compliance: unclear Length of intervention: median 3.9 years
Outcomes	Main trial outcome: time to death or admission to hospital for CV reasons Dropouts: 34 intervention, 46 control (1004 intervention and 1029 control stopped trial treatment) Available outcomes: mortality, CV mortality, MI, stroke, new heart failure, incident AF, resumed arrhythmia gatalitis Response to contact: yes (no data provided)
Notes	Trial funding: funders included Pfizer, AstraZeneca and others

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned (with stratification by site) to treatment groups
Allocation concealment (selection bias)	Low risk	Randomly assigned (with stratification by site) to treatment groups by a concealed computerised telephone randomisation system

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GISSI-HF 2008 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blinding stated, but taste not reported as masked and blinding of participants not checked
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All events "adjudicated blindly by an ad-hoc committee on the basis of pre-agreed definitions and procedures"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for attrition and exclusion were stated and addressed. Numbers in each intervention compared to numbers were similar.
Selective reporting (reporting bias)	Unclear risk	Published rationale and design (Tavazzi 2004, see secondary ref under GISSI-HF 2008) suggested primary outcomes were deaths and death or CV hospitalisation (published). Secondary outcomes not stated and no trials registry entry found
Attention	Low risk	Scheduled clinic visits at 1, 3, 6 months then 6-monthly until the end of the trial (for both arms)
Compliance	Unclear risk	No details
Other bias	Low risk	No further bias noted

GISSI-P 1999

Methods	Gruppo Italiano per la Sperimentazione della Streptochinasi nell'Infarto Miocardico – Prevention (GISSI-P) RCT, 2 × 2 (n-3 EPA + DHA vs nil), 42 months Summary risk of bias: moderate or high
Participants	People with recent (≤ 3 months) MI N: 5666 intervention, 5658 control (99.9% follow-up at trial end) Level of risk for CVD: high Men: 85.7% intervention, 84.9% control Mean age in years (SD): 59.3 (10.6) intervention, 59.5 (10.5) years control Age range: < 50 to > 80 Smokers: 42.6% intervention, 42.3% control Hypertension: 36.2% intervention, 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 < 20% of the control group: lipid-lowering Location: Italy Ethnicity: not reported

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GISSI-P 1999 *(Continued)*

Interventions	Type: supplement (capsule) Comparison: EPA + DHA vs nil Intervention: gelatin capsules of omega-3-acid ethyl esters 90 (Omacor), 1/d (850-882 mg/d EPA + DHA daily, ratio 1:2) Dose: ˜0.866 g/d EPA + DHA Control: nil (no placebo) Compliance: capsule counts, 11.6% had stopped taking Omacor by 12 months, 28.5% by the end of the trial Duration of intervention: median follow-up 40 months
Outcomes	Main trial 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, 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 2 × 2 intervention. Trial funding: Bristol Meyers Squibb, Pharmacia Upjohn, Societa Produtti Antibiotici, Pfizer

Risk of bias

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 co-ordinating centre
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo intervention (capsule vs nil) so participants not blinded
Blinding of outcome assessment (detection bias) All outcomes	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) All outcomes	Low risk	Clearly described, good follow-up (< 28% dropped out over 3.5 years)
Selective reporting (reporting bias)	Unclear risk	No trial protocol or trials registry entry was found
Attention	Low risk	Slight as no placebo, otherwise similar

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GISSI-P 1999 *(Continued)*

Compliance	Unclear risk	Capsule counts, 11.6% had stopped taking Omacor by 12 months, 28.5% by the end of the trial
Other bias	Low risk	No further bias noted

HARP 1995

Methods	Harvard Atherosclerosis Reversibility Project (HARP) RCT, (n-3 EPA + DHA vs MUFA), 24 months Summary risk of bias: moderate or high
Participants	People with CHD N: 41 intervention, 39 control (99.9% follow-up at trial end) Level of risk for CVD: high Men: 93.5% intervention, 92.9 % control Mean age in years (SD): 62 (7) intervention, 62 (7) years control Age range: 30-75 Smokers: 0% (exclusion criteria) Hypertension: 48% intervention, 36% control Medications taken by at least 50% of those in the control group: beta blockers, antiplatelet agents Medications taken by 20%-49% of those in the control group: calcium channel blockers, nitrates Medications taken by some, but < 20% of the control group: ACE inhibitors, oral hypoglycaemic drugs Location: USA Ethnicity: not reported
Interventions	Type: supplement (capsule) Comparison: LCn3 vs MUFA Intervention: 12 fish oil capsules/d (Promega, Parke-Davis) in divided doses, preferably after meals. Each fish oil capsule contained 500 mg of n-3 polyunsaturated FAs composed of EPA (240 mg), DHA (160 mg) and other (100 mg) (mainly DPA) providing total daily dose of 6 g of n-3 FAs. Dose: 6 g/d LCn3 Control: olive oil capsules identical in appearance to the fish oil capsules Compliance: capsule counts and serum level measurements. Adherence averaged 80% intervention, and 90% control with significant levels of adipose n-3 FAs in the fish oil group. Duration of intervention: average 28 months
Outcomes	Main trial outcome: regression of coronary artery lesions Dropouts: 10 intervention, 11 control Available outcomes: all-cause and CV deaths, fatal and non-fatal MI, stroke, angioplasty or CABG, unstable angina, CHD, cancer diagnosis, combined CV events, side effects Response to contact: yes
Notes	Trial funding: National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health, Bethesda, Maryland, Warner Lambert-Parke Davis, East Hanover, New Jersey; and by an Established Investigator Award to Dr Sacks from the American Heart Association, Dallas, Texas

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HARP 1995 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization" stratified by clinical management regime and total/HDL cholesterol ratio
Allocation concealment (selection bias)	Unclear risk	No further details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "patients and personnel responsible for lab measurements, cardiac catheterization, and analysis of angiography films were blinded to the treatment assignment". Although capsules were identical in appearance, no information on their taste and smell
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "patients and personnel responsible for lab measurements, cardiac catheterization, and analysis of angiography films were blinded to the treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition rate over 28 months and all reasons are well documented
Selective reporting (reporting bias)	High risk	Trial registered retrospectively after publication
Attention	Low risk	Nothing in description implies the arms were treated differently
Compliance	Low risk	Very clear ($P < 0.001$) differences between arms for the 3 main n-3 components in the fish oil
Other bias	Low risk	None noted

HEARTS 2017

Methods	Slowing HEART diSease with lifestyle and omega-3 fatty acids (HEARTS) RCT, (LCn3 vs nil), 30 months Summary risk of bias: moderate or high
Participants	People with stable coronary artery disease on statins N: 143 intervention randomised, 126 in ITT analysis, 142 control randomised, 114 in ITT analysis Level of risk for CVD: high Men: 84.9% intervention, 85.1% control Mean age in years (SD): 62.5 (7.8) intervention, 63.5 (7.6) years control Age range: unclear (21-80 years were eligible) Smokers: unclear Hypertension: 79% intervention, 89% control Medications taken by at least 50% of those in the control group: statins, aspirin, ACE-I, beta-blockers

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HEARTS 2017 *(Continued)*

	Medications taken by 20%-49% of those in the control group: ARB, hydrochlorothiazide, calcium-channel blocker Medications taken by some, but < 20% of the control group: furosemide Location: USA Ethnicity: not reported
Interventions	Type: supplement (capsule) Comparison: LCn3 vs nil Intervention: LCn3 ethyl esters from fish oil (Lovaza, GlaxoSmithKline), 4 x 1000 mg capsules/d. 3.36 g/d LCn3 (1.86 g/d EPA, 1.5 g/d DHA) Control: nil (no placebo) Compliance: unclear Duration of intervention: 30 months
Outcomes	Main trial outcome: coronary noncalcified plaque volume Dropouts: 10 intervention, 11 control Available outcomes: coronary artery plaque (% atheroma volume, maximum % diameter stenosis, minimal luminal diameter, number of participants with categorical variables of maximal stenosis > 50%, number with 3-vessel disease > 20%, number of participants with stenosis of 0%-29%, 30%-49%, 50%-69% and > 70% stenosis, remodeling index), physical function, pain, stiffness, exercise, inflammatory markers (CRP, PAI-1, serum amyloid A, matrix metalloproteinase -9 (MMP-9), IL-6, TNF-a, IL-1b, VCAM-1, ICAM-1, adiponectin serum nitrotyrosine), pericardial fat, insulin resistance, NASH, cognitive function, exercise capacity, urinary microalbumin. Serious adverse events reported include cardiac and GI, non-serious adverse events cardiac, atypical chest pain, dental, pulmonary, GI, musculoskeletal and more. Mortality, BP, measures of adiposity, glucose metabolism, lipids and blood count data also reported in publications. Response to contact: not attempted
Notes	NCT01624727 Trial funding: National Heart, Lung and Blood Institute, Harvard internal funding. GlaxoSmithKline donated the Lavaza

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was computer allocated in blocks of 4 and stratified by presence or absence of diabetes mellitus".
Allocation concealment (selection bias)	Unclear risk	Unclear (no further information provided)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial, no placebo used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Plaque analysis was performed independently by 2 readers blinded to treatment allocation. Unclear whether outcome assessors were blinded for other outcomes
Incomplete outcome data (attrition bias)	High risk	143 intervention randomised, 126 in ITT analysis (17 missing), 142 control randomised, 114 in ITT analysis (28 missing)

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HEARTS 2017 *(Continued)*
All outcomes

Selective reporting (reporting bias)	High risk	Several outcomes do not appear to be published yet (for example, inflammatory markers, pain, physical function)
Attention	Unclear risk	Unclear, possible as open label
Compliance	Unclear risk	Unclear, not reported
Other bias	Low risk	None noted

HERO 2009

Methods	Healthy Eating to Reduce Overweight in people with type 2 diabetes (HERO) RCT, parallel, (n-3 ALA vs low n-3 (nil)), 12 months Summary risk of bias: moderate or high
Participants	Overweight adults with non-insulin treated diabetes (mean baseline TG 2.4 mmol/L) N: 26 intervention, 24 control (analysed, intervention: 18 control: 17) Level of risk for CVD: moderate Male %: not reported Mean age in years (SD): 54 (8.7), not reported by arm Age range: 33-70 years Smokers: not reported Hypertension: not reported Medications taken by at least 50% of those in the control group: lipid-lowering drugs, oral hypoglycemics Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: Australia Ethnicity: not reported
Interventions	Type: food supplement (walnuts) Comparison: ALA vs nil Intervention: 30 g/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 not reported. Dose: ˜3 g/d ALA based on 30 g/d intake of walnuts 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 × 3 times/week Compliance: measured by erythrocyte membrane FA levels, which were similar in both groups

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HERO 2009 *(Continued)*

	Duration of intervention: 12 months
Outcomes	Main trial outcome: change in body weight and % body fat Dropouts: 8 intervention, 5 control Available outcomes: all-cause mortality (nil deaths), weight, visceral adipose tissue, lipids, glucose, insulin, HbA1c (body fat % and subcutaneous adipose tissue measured but too different at baseline to use) Response to contact: not yet attempted
Notes	Body fat % was too different between groups at baseline hence data not used Trial funding: California Walnuts Commission

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was conducted using a computerised 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) All outcomes	High risk	Quote: "Subjects, but not dietitians, were blinded to the type of overall diet (a prepackaged 30 g snack portion of walnuts was given to the walnut group unbeknown to the controls)". However, there was no placebo supplement, so blinding easily broken
Blinding of outcome assessment (detection bias) All outcomes	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) All outcomes	High risk	High dropout rate 35 of 50 analysed (30% attrition rate)
Selective reporting (reporting bias)	Unclear risk	Trial was registered postanalysis
Attention	Low risk	Both groups appear to have had same level of attention
Compliance	High risk	ALA levels almost exactly the same in intervention and control
Other bias	Low risk	None noted

JELIS 2007

Methods	Japan Eicosapentaenoic acid Lipid Intervention Study (JELIS) RCT, parallel, 2-arm (EPA capsule vs nil), 5 years Summary risk of bias: moderate or high
Participants	People with hypercholesterolaemia (mean baseline TG 1.7mmol/L)

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JELIS 2007 *(Continued)*

	N: intervention, 9326, control 9319 (analysed intervention 9326, control 9319) Level of risk for CVD: moderate (people with hypercholesterolaemia) Men: 32% intervention, 31% control Mean age in years (SD): 61 (8) intervention 61 (9) control Age range: 40-75 years Smokers: 20% intervention, 18% control Hypertension: 36% intervention, 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 < 20% of the control group: beta-blockers, antiplatelet, hypoglycemics, nitrates Location: Japan Ethnicity: Japanese
Interventions	Type: supplement (EPA capsule) Comparison 1: EPA vs nil Intervention: 3 × 2 × 300 mg capsules/d EPA ethyl ester (total dose of 1.8 g/d EPA), after meals. Dose: 1.8 g/d EPA Control: nothing (though all in both groups received "appropriate" dietary advice). All participants in both groups were on statins Compliance: monitored by local physicians and measuring plasma FA concentrations trial drug regimens, 71% adhered EPA intervention, 73% adhered EPA control, 74% adhered statin Duration of intervention: maximum 5 years, mean 4.7 (1.1) years
Outcomes	Main trial outcome: major coronary events Dropouts: 1766 intervention, 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	Trial funding: Mochida Pharmaceutical Company

Risk of bias

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 co-ordinating centre (see above)

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JELIS 2007 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded as there was no placebo. Quote: "[o]pen label blinded end point"
Blinding of outcome assessment (detection bias) All outcomes	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) All outcomes	Low risk	Well documented, dropout numbers low
Selective reporting (reporting bias)	Unclear risk	NCT00231738 registered October 2005, recruitment November 1996-November 1999, main results published 2007. Rationale and 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 2 groups appeared to be treated equally
Compliance	Unclear risk	Monitored by local physicians and measuring plasma FA concentrations. Trial drug regimens,71% adhered EPA intervention, 73% adhered EPA control, 74% adhered statin
Other bias	Low risk	No further bias noted

Kumar 2012

Methods	RCT, parallel, (fish oil vs nil), 12 months Summary risk of bias: moderate or high
Participants	People with persistent AF on warfarin N: 92 intervention, 90 control (91 and 87 analysed ITT) Level of risk for CVD: high Male %: 82.4 intervention, 72.4 control Mean age in years (SD): 63 (10) intervention, 61(13) control Age range: 18-85 years (inclusion criteria) Smokers: 22.2% intervention, 11.5% control Hypertension: 45.6% intervention, 58.6% control Medications taken by at least 50% of those in the control group: anti-arrhythmic drugs, renin-angiotensin system inhibitors Medications taken by 20%-49% of those in the control group: statins Medications taken by some, but < 20% of the control group: not reported Location: Australia

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Kumar 2012 *(Continued)*

	Ethnicity: not reported
Interventions	Type: fish oil capsule Comparison: EPA + DHA vs nil Intervention: 6 capsules/d of a fish oil preparation containing a total dose of 1.02 g of EPA and 0.72 g DHA. Participants in the omega-3 group were asked to continue fish oils till a maximum of 1 year or till return of persistent AF. Dose: 1.7 g/d EPA + DHA Control: no supplements. Participants were advised not to take any fish oil supplements. All participants underwent cardioversion following randomisation. Compliance: was monitored on a weekly basis via telephone and during follow-up by using a pill count plus serum EPA and DHA levels, which were significantly increased Duration of intervention: 1 year (or AF recurrence)
Outcomes	Main trial outcome: AF recurrence Dropouts: 4 intervention, 0 control Available outcomes: all-cause mortality (nil death), AF recurrence, time to AF recurrence, adverse events Response to contact: contact not yet established
Notes	Trial funding: the trial was funded in part by the National Heart Foundation of Australia and the Pfizer Cardiovascular Lipid Research Grant.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomised to a control or an omega-3 group in a 1:1 fashion (no details of method)
Allocation concealment (selection bias)	Unclear risk	No further details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label with no placebo control
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis was conducted
Selective reporting (reporting bias)	Unclear risk	Trial registered 2005 but data collection started 2003
Attention	Unclear risk	Intervention group had capsules, while control group did not. Potential for greater contact and checking with intervention group on this basis, although otherwise both groups seem to have had the same care.

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Kumar 2012 *(Continued)*

Compliance	Low risk	EPA and DHA levels were significantly higher in intervention group
Other bias	Low risk	None noted

Kumar 2013

Methods	RCT, parallel, (fish oil vs nil), 12 months Summary risk of bias: moderate or high
Participants	People > 60 years with sinoatrial node disease and dual chamber pacemakers N: 39 intervention, 39 control randomised (18 intervention vs 39 control at 12 months) Level of risk for CVD: moderate/high Male %: 46% intervention, 56% control Mean age in years (SD): 78 (7) intervention, 77(8) control Age range: not reported Smokers: not reported Hypertension: 72% Medications taken by at least 50% of those in the control group: statins, renin-angiotensin system inhibitors Medications taken by 20%-49% of those in the control group: anti-arrhythmic drugs Medications taken by some, but < 20% of the control group: not reported Location: Australia Ethnicity: not reported
Interventions	Type: omega-3 capsule Comparison: EPA + DHA vs nil Intervention: a TG preparation containing a total of 6 g/d of omega-3 polyunsaturated FAs of which 1.8 g/d were n-3 (1.02 g EPA and 0.72 g DHA). Dose: 1.8 g/d EPA + DHA Control: no supplements Compliance: measured by weekly dietary history and pill count. FA status measured at randomisation and between 1-3 months post randomisation (blood samples). Duration of intervention: median 378 days
Outcomes	Main trial outcome: AF burden Dropouts: 1 intervention, 0 control Available outcomes: all-cause mortality, CV mortality, AF (frequency and duration but not recurrence so not used), adverse events Response to contact: written but no contact yet
Notes	Trial funding: unclear

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Kumar 2013 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using sequentially numbered, opaque, sealed envelopes.
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label design
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "At each visit, stored AT/AF diagnostic data were retrieved in an unblinded fashion"
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 1 lost, and reason explained. 21 of the 39 randomised to the intervention were crossed over to control at 6 months so 12-month outcomes are reported for 17/18 intervention while baseline characteristics are reported for the 39 participants.
Selective reporting (reporting bias)	Low risk	Trial prospectively registered and outcomes stated were reported
Attention	Unclear risk	As only the intervention group had supplements there was potential for attention differences. Other contact appears the same.
Compliance	Low risk	EPA was 3-fold higher and DHA 1.8 fold higher compared with controls. EPA and DHA did not change significantly in controls upon repeat testing
Other bias	High risk	Odd design – 21 of the 39 randomised to the intervention were crossed over to control at 6 months

Lorenz-Meyer 1996

Methods	RCT- parallel, 2 arms (omega-3 vs corn oil), 12 months Summary risk of bias: low
Participants	People with Crohn's disease in remission (but with a recent relapse) N: 70 intervention, 63 control Level of risk for CVD: low Men: 35.7% intervention, 27.0% control Mean age in years (SD): 29.5 (9.6) intervention, 31.8 (10.9) control Age range: 17-62 years intervention, 17-65 years control Smokers: not reported Hypertension: not reported

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Lorenz-Meyer 1996 *(Continued)*

	Medications taken by at least 50% of those in the control group: methylprednisolone (all for 1st 8 weeks) Medications taken by 20%-49%: not reported Medications taken by some, but < 20%: not reported Location: Germany Ethnicity: not reported
Interventions	Type: supplement (fish oil) Comparison: EPA + DHA vs omega-6 Intervention: 2 × 3 1 g gelatin capsules/d of ethylester fish oil concentrate (3.3 g/d EPA + 1.8 g/d DHA). Dose: 5.1 g/d EPA + DHA Control: 2 × 3 1 g gelatin capsules/d of corn oil Compliance: pill count, 5 non-compliant participants, among compliant participants, 18 were censored (for not using the medication for 3 continuous weeks) Duration of intervention: 12 months
Outcomes	Main trial outcome: Crohn's disease duration of remission Dropouts: unclear Available outcomes: mortality (nil), Crohn's disease activity and relapses, TG Response to contact: yes (methodological details provided)
Notes	There was a 3rd arm of dietary advice (for low CHO diet) Trial funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised within the centres in blocks of 6 (block size blinded to the centres)
Allocation concealment (selection bias)	Low risk	Trial author reported allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind conditions were intended for the verum-placebo comparisons". Trial author stated that capsules were identical in appearance (taste not mentioned).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome was relapses "classified in a blind fashion by a primary endpoint committee"
Incomplete outcome data (attrition bias) All outcomes	High risk	Participants were accounted for based on the main outcome of the trial (relapses), however 20% omitted from analyses and numbers confusing

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Lorenz-Meyer 1996 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No trials registry entry or protocol found
Attention	Low risk	All participants were seen by their physician in the respective centre after regular time intervals (1, 2, 3, 6, 9 and 12 months).
Compliance	Unclear risk	Pill count, 5 non-compliant participants, among compliant participants, 18 were censored (for not using the medication for 3 continuous weeks). 23 of 133 non-compliant
Other bias	Low risk	None noted

MAPT 2017

Methods	Multidomain Alzheimer Preventive Trial (MAPT) 4 arms RCT, parallel, (n-3 ± multidomain intervention vs placebo (paraffin) ± multidomain intervention), 36 months Summary risk of bias: low
Participants	Population: people aged ≥ 70 years without dementia but with memory complaint, IADL limitation or slow gait speed N: 840 intervention (arms 1 and 3), 840 control (arms 2 and 4) randomised. Numbers analysed differ by outcome Level of risk for CVD: low Men: 37.2% intervention, 34.5% control (combined groups) Mean age in years (SD): 75.6 (4.7) and 74.4 (4.4) intervention, 75.1 (4.3) and 75 (4.1) control Age range: not reported Smokers: not reported Hypertension: not reported Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: France and Monaco Ethnicity: not reported
Interventions	Type: supplement (capsule) Comparison: EPA + DHA vs paraffin oil (non-fat) Intervention Arm 1: omega-3 (V0137 CA 800 mg/d DHA; 225 mg/d EPA in soft capsules). Dose for arms 1 and 3: 1.025 g/d EPA + DHA Arm 3: omega-3 (V0137 CA 800 mg/d DHA; 225 mg/d EPA in soft capsules) plus multi-domain intervention (nutrition, physical exercise, cognitive stimulation, social activities)

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MAPT 2017 *(Continued)*

	Control: Arm 2: placebo capsules containing flavoured paraffin oil. All capsules were supplied by Pierre Fabre Médicament (Castres, France) Arm 4: placebo capsules plus multi-domain intervention (nutrition, physical exercise, cognitive stimulation, social activities) Compliance: adherence to trial interventions was assessed every 6 months. For supplementation, adherence was assessed by counting the number of capsules returned by participants (or based on treatment dates if the number of capsules was missing). Furthermore, biological samples were obtained at baseline and after 12 months to assess concentrations of DHA and EPA in red blood cell membranes. Duration of intervention: 36 months
Outcomes	Main trial outcome: change in cognitive function) Dropouts: 200 intervention, 194 control Available outcomes: mortality, CVD events, haemorrhagic stroke, adverse events, functional capacity, other cognitive functions, safety and tolerability Response to contact: no
Notes	Trial funding: Gérontopôle of Toulouse, the French Ministry of Health (PHRC 2008, 2009), the Pierre Fabre Research Institute (manufacturer of the PUFA supplement), Exhonit Therapeutics, and Avid Radiopharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned (1:1:1:1) to the combined intervention (i.e. the multidomain intervention plus PUFAs), the multidomain intervention plus placebo, PUFAs only, or placebo only. A computer-generated randomisation procedure (done by ClinInfo, a subcontractor) was used with block sizes of 8 and stratification by centre.
Allocation concealment (selection bias)	Low risk	A clinical research assistant, who was not involved in the assessment of participants, used a centralised interactive voice response system to identify which group to allocate the participant to, and which lot number to administer.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants and trial staff were blinded to PUFA or placebo assignment – both sets of capsules looked and tasted identical. In view of the nature of the multidomain intervention, the trial was unblinded for this component, but the independent neuropsychologists who were trained to assess cognitive outcomes were blinded to group assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All participants and trial staff were blinded to PUFA or placebo assignment—both sets of capsules looked and tasted identical. In view of the nature of the multidomain intervention, the trial was unblinded for this component, but the independent neuropsychologists who were trained to assess cognitive outcomes were blinded to group assignment. Data analysts were not blinded to group assignment, but 2 data managers, 1 statistician (CC) and 2 physicians (SA and BV) did a blinded data review.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1680 participants were enrolled and randomly allocated, the modified ITT population (N = 1525), i.e. 155 excluded (9% over 3 years)

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MAPT 2017 *(Continued)*

Selective reporting (reporting bias)	Low risk	Protocol registered ClinicalTrials.gov (NCT00672685) – outcomes match report. "Because of advances in the field since our trial was designed in 2007, we decided to modify the primary outcome from one cognitive test to a composite cognitive score, which is now thought to be a better endpoint." This protocol amendment was submitted to the local ethical committee on 2 February 2015 and was subsequently approved
Attention	Low risk	Both groups assessed at baseline, 6, 12, 24, 36 months. Groups 1 and 2 only differed by content of capsules.
Compliance	Unclear risk	Adherence to trial interventions was assessed every 6 months, by counting the number of capsules returned (or based on treatment dates if the number of capsules was missing). Biological samples were obtained at baseline and after 12 months to assess concentrations of DHA and EPA in red blood cell membranes, but outcomes not reported
Other bias	Low risk	None noted

MARGARIN 2002

Methods	Mediterranean alpha-linolenic enriched Groningen dietary intervention trial (MARGARIN) RCT, factorial 2 × 2 (ALA-rich margarine vs LA-rich margarine, also nutrition education vs no education but this is not included), 2 years Summary risk of bias: low
Participants	Hypercholestrolemic adults with ≥ 2 CVD risk factors (mean baseline TG 1.9 mmol/L) N: total 282 randomised; 114 intervention (51 with nutrition education, 58 without nutrition education) 157 control (52 with nutrition education, 105 without nutrition education) Level of risk for CVD: moderate (multiple CV risk factors, 10-year IHD risk ˜20%) Men: 41.9% intervention, 45.7% control Mean age in years (SD): 54.4 (9.5) intervention, 53.9 (9.8) control Age range: 30-70 Smokers: 49.1% intervention, 49.3% control Hypertension: 52.9% intervention, 45.3% control (on anti-hypertensives) Medications taken by at least 50% of those in the control group: antihypertensives Medications taken by 20%-49%: not reported Medications taken by some, but < 20%: not reported Location: the Netherlands Ethnicity: not reported
Interventions	Type: supplementary food (ALA-enriched margarine) Intervention: provided with ALA-rich margarine (80% fat of which 15% was ALA and 46% LA) to be eaten as desired. Dose: average intake 6.3 g/d ALA (was also 1 g/d ALA in the control group).

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MARGARIN 2002 *(Continued)*

	Control: provided with linoleic-rich margarine (80% fat of which 0.3% was ALA and 58% LA), identical in taste and packaging. Both margarines contained 0.66 mg vitamin E/g, 9 micro-g vitamin A/g and 0.023 micro-g vitamin D/g Comparison: ALA vs omega-6 Compliance: serum FAs used to assess, ALA rose by 0.47 mol % (SD 0.04) and 0.36 mol % (SD 0.04) intervention arms (with and without nutrition education) and fell by 0.06 mol % (SD 0.04) and 0.11 mol % (SD 0.03) control arms (with and without nutrition education), significantly different Duration of intervention: 24 months
Outcomes	Main trial outcome: CV risk factors and IHD risk Dropouts: unclear Available outcomes: total and CV deaths, non-fatal MI, stroke, CABG and angioplasty, BMI, lipids, BP Response to contact: yes
Notes	Trial funding: Prevent fund and Unilever Research Other intervention (2 × 2) was educational, teaching a multifactorial dietary intervention. It was excluded as multifactorial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random allocation, allocated by an independent trial co-ordination centre that organised masked distribution of margarines
Allocation concealment (selection bias)	Low risk	Allocated by an independent trial co-ordination centre that organised masked distribution of margarines
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind; the 2 margarines are described as identical as to taste and packaging (though not reported as checked)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	2 independent physicians, a cardiologist and a general practitioner validated and classified results in a blinded fashion
Incomplete outcome data (attrition bias) All outcomes	Low risk	The number randomised to each arm was unclear, but 1 publication clarifies (55 randomised to each arm, 51 intervention and 52 control analysed)
Selective reporting (reporting bias)	Unclear risk	No trial protocol or trials registry entry was found.
Attention	High risk	There was no difference in attention between margarine types, but the dietary-advice group spent more time with trial staff than the control group, and some (not quite randomly allocated) were sent individual motivational letters (Siero 2000, see secondary ref under MARGARIN 2002).
Compliance	Low risk	Serum FAs used to assess, ALA rose by 0.47 mol % (SD 0.04) and 0.36 mol % (SD 0.04) intervention arms (with and without nutrition education) and fell by 0.06 mol % (SD 0.04) and 0.11 mol % (SD 0.03) control arms (with and without nutrition education), Significantly different
Other bias	Low risk	No further bias noted

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MARINA 2011

Methods	Modulation of Atherosclerosis Risk by INcreasing dose of n-3 fatty Acids (MARINA) RCT, parallel, 4 arms (n-3 PUFA 3 different doses or olive oil placebo), 12 months Summary risk of bias: low
Participants	Non-smoking men and women aged 45-70 years N: intervention. 279 in 3 groups (G1 0.45 g/d n = 94, G2 0.9 g/d n = 93, G3 1.8 g/d n = 92); control: 88 (analysed G1 0.45 g/d n = 81, G2 0.9 g/d n = 80, G3 1.8 g/d n = 80, control 71) Level of risk for CVD: low Men: 38.7% intervention, 38.6% control Mean age in years (CI): G1: 55 (53, 56), G2: 55 (54, 56), G3: 55 (54, 57) intervention 55 (54,57) control Age range: 45-70 Smokers: 0% intervention, 0% control Hypertension: 5.4% intervention, 5% control Medications taken by at least 50% of those in the control group: none Medications taken by 20%-49% of those in the control group: none Medications taken by some, but < 20% of the control group: statins, antihypertensives, HRT, thyroxine Location: UK Ethnicity: G1: white 80.9%, black 4.3%, Asian 6.4%, East Asian 4.3%, other 4.3% G2: white 78.5%, black 6.5%, Asian 10.8%, East Asian 0%, other 4.3% G3: white 85.9%, black 1.1%, Asian 2.2%, East Asian 4.3%, other 6.5% Control: white 77.3%, black 10.2%, Asian 6.8%, East Asian 2.3%, other 3.4%
Interventions	Type: supplement (fish oil capsules) Comparison 1: EPA + DHA vs MUFA Comparison 2: high EPA + DHA vs low EPA + DHA Intervention: 3 × 1 g oil gelatin capsule/d consisting of blend of EPA concentrate, DHA concentrate, refined olive oil and 0.1% peppermint oil. Providing a daily dose of: 0.45 g, 0.9 g, or 1.8 g/d (all with EPA/DHA ratio of 1.51). Dose: 1.8 g/d EPA + DHA (G3 used for outcomes) Control: 3 gelatin capsules/ day containing refined olive oil + 0.1% peppermint oil Compliance: measured by capsule counting and erythrocyte lipids for proportion of EPA/DHA @ baseline, 6 months, 12 months. 88.5% of participants consumed > 90% of capsules provided. EPA and DHA in erythrocyte lipids increased in dose-dependent manner compared with placebo, indicating long-term compliance with intervention. Length of intervention: 12 months
Outcomes	Main trial outcome: endothelial function, arterial stiffness Dropouts: 38 intervention (13,13,12), 17 control Available outcomes: lipids, dietary intake, CRP, BP (supine and ambulatory – numeric data not provided, but trial states that there were no significant differences between arms). Weight data not used as

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MARINA 2011 *(Continued)*

	baseline is different between groups (FMD, arterials stiffness, carotid intima media thickness, heart rate variability, heart rate, endothelial progenitor cells reported but not used) Contact with trial authors: yes (many outcomes above provided in end of trial report from trial authors)
Notes	Outcome data used G3 (highest dose) vs placebo for continuous outcomes and combined the 3 intervention groups vs placebo for dichotomous outcomes Trial funding: Food Standards Agency

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the random allocation sequence was generated with a computer program by using the process of minimisation to balance age, sex and ethnicity between treatment groups."
Allocation concealment (selection bias)	Low risk	Quote: "We enrolled eligible participants and the study database program allocated a serious of capsules to the participant. The treatments associated with the capsule codes were concealed from all investigators and associated clinical staff until the data analysis was complete. The code breaker was an employee of MedSciNet who constructed the trial database."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "We enrolled eligible participants and the study database program allocated a serious of capsules to the participant. The treatments associated with the capsule codes were concealed from all investigators and associated clinical staff until the data analysis was complete. The code breaker was an employee of MedSciNet who constructed the trial database." "blends of the test fat with 0.1% peppermint oil to disguise the fish taste of the EPA and DHA" (peppermint oil in both intervention and control capsules)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "We enrolled eligible participants and the study database program allocated a serious of capsules to the participant. The treatments associated with the capsule codes were concealed from all investigators and associated clinical staff until the data analysis was complete. The code breaker was an employee of MedSciNet who constructed the trial database."
Incomplete outcome data (attrition bias) All outcomes	Low risk	15% withdrawal, reasons for attrition reported
Selective reporting (reporting bias)	Low risk	Outcomes published match trials register. Registered September 2008, trial started June 2008, ended December 2010, main publication 2011
Attention	Low risk	No difference between groups
Compliance	Low risk	Statistically significant difference in erythrocyte omega-3 fats at 12 months between different arms
Other bias	Low risk	None noted

MENU 2016

Methods	Metabolism, Exercise and Nutrition at UCSD (MENU) RCT, parallel, (ALA as walnut-rich moderate-fat diet vs MUFA as moderate-fat diet), 12 months

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MENU 2016 *(Continued)*

	Summary risk of bias: moderate or high
Participants	Overweight and obese women, of whom half were insulin-resistant (mean baseline TG 124 mg/dL) N: 82 intervention, 81 control (analysed, intervention: 65 control: 61) Level of risk for CVD: low Men: 0% intervention, 0% control Mean age (SD) years: 51 (not reported) intervention, 50 (not reported) control Age range: 22-67 years intervention, 25-72 years control Smokers: not reported Hypertension: not reported Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: 10% were on cholesterol medications Location: USA Ethnicity: Hispanic 18% intervention, 14% control; black 9% intervention, 3% control; Asian American 1% intervention, 4% control; white non-Hispanic 71% intervention, 78% control
Interventions	Type: food and 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 42 g/d walnuts (provided by trial), 45%E CHO, 20%E protein). Participants given print materials on diet and 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. Dose: ˜4.2 g/d ALA (calculated based on 42 g/d intake of walnuts) 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 intervention at 12 months than control Duration of intervention: 12 months
Outcomes	Main trial outcome: body weight Dropouts: 13 of 82 intervention, 12 of 81 control Available outcomes: weight, waist circumference, HDL and LDL cholesterol, TG, 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 reply received to date
Notes	Trial funding: National Cancer Institute and California Walnut Commission

Risk of bias

Bias	Authors' judgement	Support for judgement

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MENU 2016 *(Continued)*

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) All outcomes	High risk	Open trial, participants were advised on their diets extensively
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not mentioned, so unclear for their primary outcome, weight
Incomplete outcome data (attrition bias) All outcomes	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

Methods	RCT, parallel, (EPA capsules vs nil), 2 years Summary risk of bias: moderate to high
Participants	Japanese people with type 2 diabetes (mean baseline TG 1.5mmol/L) N: intervention. 40, control: 41 (analysed 30, 30) Level of risk for CVD: moderate Men: 53% intervention, 67% control Mean age in years (SD): 59 (11.2) intervention 61.2 (8.4) control Age range: not reported Smokers: 40% intervention, 43% control Hypertension: not reported Medications taken by at least 50% of those in the control group: oral hypoglycemics Medications taken by 20%-49% of those in the control group: insulin, lipid-lowering drugs, antihypertensives Medications taken by some, but < 20% of the control group: antithrombotics Location: Japan

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Mita 2007 *(Continued)*

	Ethnicity: 100% Japanese
Interventions	Type: supplement (EPA oil capsules) Comparison: EPA vs nil Intervention: 1800 mg/d EPA EPADEL capsules (Mochida Pharmaceutical Co Ltd Japan): 98% pure ethyl-ester EPA (unclear how many caps). Dose: ˜1.8 g/d EPA 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 trial outcome: progression of diabetic macroangiopathy measured by carotid intima-media thickness and brachial-ankle pulse wave velocity Dropouts: 10 intervention, 11 control Available outcomes: BMI, lipids, BP, HbA1c, cancer diagnosis Response to contact: not yet attempted
Notes	BP data not used as groups are different at baseline Trial funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants randomly divided into 2 groups matched for age and gender
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors of main trial outcomes were blinded to the treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rate (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

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NAT2 2013

Methods	Nutritional AMD Treatment-2 (NAT2) RCT, parallel, (EPA + DHA vs MUFA), 36 months Summary risk of bias: low
Participants	People with early AMD N: 150 intervention, 150 control Level of risk for CVD: high (92.5% intervention and 79.8 controls had past CVD) Men: 31.3% intervention, 39.5% control Mean age in years (SD): 73.9 (6.6) intervention, 73.2 (6.8) control Age range: 55-85 Smokers: 6.7% intervention, 8.5% control Hypertension: 58% total (not reported by trial arm) Medications taken by at least 50% of those in the control group: lipid-lowering medication Medications taken by 20%-49% of those in the control group: agents acting on renin-angiotensin system, anti-inflammatory and anti-rheumatic products Medications taken by some, but < 20% of the control group: insulin or blood sugar-lowering drugs Location: France Ethnicity: unclear
Interventions	Type: supplement (fish oil capsule) Comparison: EPA + DHA vs MUFA Intervention: 3 daily fish oil capsules containing 1110 total n-3 FAs (EPA: 270 mg/d DHA: 840 mg/d) and vit E: 6 mg/d. Dose: 1.1 g/d EPA + DHA Control: 3 × 602 mg/d olive oil capsules containing 0.2 g total PUFA and vitamin E: 0.09 g/d Compliance: assessed during visits from unused capsules and serum PUFA levels Overall compliance over the 3 years; 69.4% intervention, 70.5% control Length of intervention: 36 months
Outcomes	Main trial outcome: time to occurrence of choroidal new vessels in the trial eye from prospective assessment of fluorescein angiography Dropouts: 29 intervention, 34 control Available outcomes: all-cause mortality, plasma lipids, adverse events, serum FAs Response to contact: yes (no added data)
Notes	TG data not used as presented as median (5th-95th percentile) Trial funding: Laboratoire Chauvin, Bausch & Lomb Inc
Risk of bias	

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NAT2 2013 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QL Ranclin software was used to generate the randomisation list before enrolment. Both participants and trial personnel were blinded to the treatment assignment
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The capsules had the same appearance, the same size, and the same weight (602 mg) in both DHA and placebo groups. No masking flavour was added to the capsules, which were otherwise odourless
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial author confirmed blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Any temporary discontinuation of the treatment was considered to be a deviation from the trial protocol. Discontinuation for more than 5 months was considered to be a major deviation from the trial protocol. Participants who dropped out were taken into account in the survival analysis and occurrence of choroidal new vessels and were counted at last angiography performed.
Selective reporting (reporting bias)	Unclear risk	ISRCTN98246501. Retrospectively registered May 2007, recruitment started December 2003, completed November 2008, key publication 2013
Attention	Low risk	Same amount of time spent with both trial arms
Compliance	Low risk	Assessed during visits from unused capsules and serum PUFA levels. Overall compliance over the 3 years; 69.4% intervention, 70.5% control
Other bias	Low risk	None noted

Nodari 2011 AF

Methods	RCT, parallel, (DHA + EPA vs MUFA), 12 months Summary risk of bias: moderate or high
Participants	People with persistent AF with at least 1 relapse after cardioversion N: 102 intervention, 103 control (analysed, intervention: 94 control: 94) Level of risk for CVD: high Men: 70% intervention, 63% control Mean age in years (SD): 70 (6) intervention, 69 (9) control Age range: not reported (18-80 inclusion criteria) Smokers: 10% intervention, 9.1% control Hypertension: 47% intervention, 40% control Medications taken by at least 50% of those in the control group: beta-blockers, ACE inhibitors, anticoagulant therapy, amiodarone

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Nodari 2011 AF *(Continued)*

	Medications taken by 20%-49% of those in the control group: diuretics, antiplatelet, statins Medications taken by some, but < 20% of the control group: calcium channel blockers Location: Italy Ethnicity: not reported
Interventions	Type: supplement (omega-3-acid ethyl esters 90: Omacor) Comparison: EPA + DHA vs MUFA Intervention: 2 × 1 g/d Omacor (total 1.7 g/d EPA + DHA at a ratio of 0.9:1.5). Dose: 1.7 g/d EPA + DHA Control: 2 × 1 g/d olive oil (gelatin capsules identical in appearance to Omacor) Compliance: no details Duration of intervention: 12 months
Outcomes	Main trial outcome: probability of maintenance of sinus rhythm Dropouts: 6 intervention, 5 control Available outcomes: adverse events, AF recurrence (nil death) Response to contact: no
Notes	Trial funding: 'Centro per lo Studio ed il Trattamento dello Scompenso Cardiaco' of the University of Brescia, Brescia, Italy. The work of Dr Campia was supported by National Institutes of Health grant K12 HL083790-01a1

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random assignment followed a computer-generated randomisation list obtained using blocks of size 4
Allocation concealment (selection bias)	Low risk	The randomisation schedule was kept in the research pharmacy area and was available only to unblinded pharmacy personnel until after the database was locked. At that time, the unblinded participant treatment information was made available to the investigators.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo gelatin capsules identical in appearance to Omacor. However no information provided as to their smell and taste.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were accounted for. ITT analysis for main outcomes
Selective reporting (reporting bias)	Unclear risk	NCT01198275. Registered retrospectively in September 2010, trial started January 2006, completed May 2008, main publication 2011
Attention	Low risk	No difference between groups

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Nodari 2011 AF *(Continued)*

Compliance	Unclear risk	No details
Other bias	Low risk	None noted

Nodari 2011 HF

Methods	RCT, parallel, (DHA + EPA vs MUFA), 12 months Summary risk of bias: moderate or high
Participants	People with heart failure (non-ischaemic dilated cardiomyopathy) N: 67 intervention, 66 control (analysed, intervention: 67 control: 66) Level of risk for CVD: high Men: 95.5% intervention, 84.9% control Mean age in years (SD): 61 (11) intervention, 64 (9) control Age range: not reported (18-75 inclusion criteria) Smokers: not reported Hypertension: not reported 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: not reported Medications taken by some, but < 20% of the control group: statins, ARB Location: Italy Ethnicity: not reported
Interventions	Type: supplement (Omacor) Comparison: EPA + DHA vs MUFA Intervention: 2 × 1 g/d Omacor (1.7 g/d EPA + DHA at a ratio of 0.9:1.5) Control: 2 × 1 g/d olive oil (gelatin capsules identical in appearance to Omacor) Compliance: pill counts – participants were withdrawn if < 80% capsules taken (none were withdrawn). FA EPA + DHA 0.83% in intervention group, 0.41% in control group. Duration of intervention: 12 months
Outcomes	Main trial outcome: left ventricular function and functional capacity Dropouts: 0 intervention, 0 control Available outcomes: mortality (nil death), combined CVD events, AF, BMI, hospitalisation for CV reasons, hospitalisation for worsening heart failure, lipids, blood glucose (but too different at baseline to use), serum cytokine Response to contact: yes

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Nodari 2011 HF *(Continued)*

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Paper states that placebo and verum were identical and that the trial was double-blind, but blinding of participants not checked. Trial author confirmed investigators not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Trial author confirmed assessors not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether all participants were assessed for all outcomes (e.g. hospitalisation), but some outcomes report no attrition
Selective reporting (reporting bias)	Unclear risk	NCT01223703 – trial registration October 2010, recruitment November 2007-June 2009. Retrospective
Attention	Low risk	No suggestion of this, and investigators appeared blinded (so could not differ in attention provided by allocation)
Compliance	Low risk	See characteristics table
Other bias	Low risk	None noted

Norouzi 2014

Methods	RCT, parallel, (MorDHA capsules vs unclear placebo), 14 months Summary risk of bias: moderate or high
Participants	People with chronic traumatic spinal cord injury N: 55 intervention, 55 control (analysed, intervention: 54 control: 50) Level of risk for CVD: low Men: 81.5% intervention, 82% control Mean age in years (SD): 51.15 (13.43) intervention, 54.12 (11.76) control Age range: 15-74 years intervention, 30-74 years control Smokers: 0% (exclusion criteria) Hypertension: not reported

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Norouzi 2014 *(Continued)*

	Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: Iran Ethnicity: not reported
Interventions	Type: supplement (n-3 capsules) Comparison: EPA + DHA vs placebo (unclear what) Intervention: 2 MorDHA capsules (providing 870 mg DHA and 130 mg EPA)/d. Dose: 1 g/d DHA + EPA Control: 2 placebo capsules/d. Both capsules were similar in colour, shape, and taste. Both groups received 1 calcium capsule/d consisting of 1000 mg calcium and 400 IU vitamin D. Compliance: pill counts – compliance averaged 80% in both groups Duration of intervention: 14 months
Outcomes	Main trial outcome: professionals' evaluation of neurological function Dropouts: 1 intervention, 5 control Available outcomes: functional measures (total and subscales), BMI, leptin and adiponectin concentration Response to contact: no
Notes	Trial funding: PhD university funding. Omega-3 capsules were provided by Minami Nutrition Co (Aartselaar, Belgium) and placebo capsules were supplied by Zahravi Pharmaceutical Co. (Tabriz, Iran). Calcium capsules were provided by Darou Pakhsh Pharm Co. (Tehran, Iran) Data were collected at the beginning of the trial and after 14 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using permuted balanced block randomisation method
Allocation concealment (selection bias)	Unclear risk	No further detail on allocation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated as double-blind but content of placebo not stated and no report of attempt to mask n-3 FA taste
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unclear, few details
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was 1 in intervention group, 5 in control group, so minor; "the two most common reasons for dropouts were experiencing GI side effects or difficulty to maintain scheduled clinic visits"

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Norouzi 2014 *(Continued)*

Selective reporting (reporting bias)	High risk	Some of the outcomes stated in the trial register were not reported. Registered March 2011, trial start November 2010, completion April 2012
Attention	Low risk	No difference between groups
Compliance	Unclear risk	Pill counts – compliance averaged 80% in both groups
Other bias	Low risk	None noted

Norwegian 1968

Methods	Norwegian vegetable oil experiment of 1965-6 RCT, parallel, 2 arms (ALA linseed oil vs omega-6 sunflower oil), 1 year Risk of bias: moderate or high
Participants	Men working in Norwegian companies aged 50-59 years N: 6716 intervention, 6690 control Level of risk for CVD: low (working men, though a few had had a previous MI or angina) Men: 100% Mean age in years (SD): unclear Age range: 50-59 years Smokers: unclear (˜48% non-smokers) Hypertension: unclear Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: Norway Ethnicity: unclear
Interventions	Type: supplementary food (oil) Comparison: ALA vs omega-6 Intervention: linseed oil, 10 mL/d (55% ALA), 5.5 g/d ALA, 1.5 g/d linoleic. Dose: 5.5 g/d ALA Control: sunflower oil, 10 mL/d (1.4% ALA), 0.1 g/d ALA, 6.3 g/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 trial 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%

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Norwegian 1968 *(Continued)*

	Available outcomes: total and CV deaths, MI, angina, stroke, PVD, combined CV events, total cholesterol (subgroup) Response to contact: no
Notes	Trial funding: not stated

Risk of bias

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) All outcomes	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) All outcomes	Low risk	Company physicians recorded health status, and were also blinded to intervention (as above)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Detailed description, and those who left employment during the trial 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	No further bias noted

Nutristroke 2009

Methods	Nutristroke RCT, parallel, (diet rich in vitamins and omega-3 plus omega-3 supplement vs diet rich in vitamins and omega-3), 12 months Summary risk of bias: moderate or high
Participants	People in a rehabilitation unit who had survived a stroke N: 38 intervention, 34 control (analysed, intervention: 32 control: 20) Level of risk for CVD: high Men: 74% intervention, 56% control

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Nutristroke 2009 *(Continued)*

	Mean age in years (SD): 61.3 (13.6) n-3, 66.3 (11.4) n-3 + antioxidant intervention, 68.4 (12.6) placebo, 65.1 (12.8) antioxidant – control Age range: not reported Smokers: not reported Hypertension: not reported Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: Italy Ethnicity: not reported
Interventions	Type: supplement (capsule) Comparison: fish oil vs unclear placebo Intervention: fish oil gelatin capsules including 250 mg DHA + 250 mg EPA. Dose: 0.5 g/d EPA + DHA Control: "identical to supplement but contained no antioxidants or polyunsaturated fatty acids" Compliance: appears to have been assessed at meetings or on the phone monthly, but results unclear Duration of intervention: 12 months
Outcomes	Main trial outcome: functional status in stroke survivors Dropouts: 6 intervention, 14 control Available outcomes: mortality and CV mortality, lipids (6 months), albumin and lymphocyte counts (6 months), Barthel Index (functional status), neurological impairment (not reported by intervention group), mobility, adiposity (no numerical data presented; quote: "there were no statistically significant differences in body weight, BMI, arm circumference and triceps skin fold at the different time points") Response to contact: not yet attempted
Notes	2 × 2 trial that also had an antioxidant supplementary focus (supplementary vitamins C and E, beta carotene and polyphenols) Trial funding: Italian Ministry of Health, Sigma-Tau Health Science provided omega-3 capsules

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized by means of a specific list"
Allocation concealment (selection bias)	Unclear risk	Randomisation methodology not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "the placebo was identical to the supplement but contained no antioxidants or polyunsaturated fatty acids; no patient, research assistant, investigator or any other medical or nursing staff could distinguish the placebo from the supplements during the study". However, only one placebo discussed and unclear whether it was a placebo capsule (for omega-3) or pill (for antioxidants)

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Nutristroke 2009 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "assays were quality control checked by internal standard and calibration curve in a random and double blind way"
Incomplete outcome data (attrition bias) All outcomes	High risk	High rates of dropouts
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry found
Attention	Low risk	All assessments and treatments appear equal across the intervention groups
Compliance	Unclear risk	Appears to have been assessed at meetings or on the phone monthly, but results unclear
Other bias	Low risk	None noted

Nye 1990

Methods	Randomisation: parallel, 3 groups (omega-3 vs olive oil vs aspirin and dipyridamole), 1 year Risk of bias: moderate or high
Participants	People undergoing PTCA N: 36 intervention, 37 control (also 35 allocated to arm 3, aspirin and dipyridamole) Level of risk for CVD: high (people undergoing angioplasty) Men: 78% intervention, 76% control Mean age in years (SD): 54 (8) intervention, 55 (8) control years Age range: unclear Smokers: unclear Hypertension: unclear Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: New Zealand Ethnicity: unclear
Interventions	Type: supplement (capsules) Comparison: EPA vs MUFA Intervention: MaxEPA capsules 12/d (2.2 g EPA). Dose: 2.2 g/d EPA Control: olive oil capsules, 12/d, identical to MaxEPA. Both capsules included vitamin E Compliance: no data

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Nye 1990 *(Continued)*

	Length of intervention: 12 months
Outcomes	Main trial outcome: angina, restenosis Dropouts: none Available outcomes: angina, interventions, lipids (Nil death) Response to contact: no
Notes	Trial funding: Medical Research Council of New Zealand and Scherer Ltd (who supplied MaxEPA and the olive oil capsules)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly divided without exclusions into 3 groups"
Allocation concealment (selection bias)	Unclear risk	Unclear, no further info
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States that placebo capsules were identical to the MaxEPA, and "neither the patient nor the attending cardiologist knew which capsules were being used" (but no masking of taste was reported, and participant guesses as to allocation were not reported)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "neither the patient, nor the attending cardiologist knew which capsules were being used" ... "Angioplasty was repeated electively at one year or before where symptoms recurred, and assessed without knowledge of the patient's treatment group."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Some participants were lost to follow-up and reasons for this were unclear
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registration found
Attention	Low risk	No suggestion of attention bias, symptomatic participants were reviewed between scheduled visits, otherwise all on the same schedule
Compliance	Unclear risk	No data
Other bias	Low risk	No further bias noted

OFAMI 2001

Methods	Omacor Following Acute Myocardial Infarction (OFAMI) RCT, parallel, 2 arms (omega-3 vs corn oil), 2 years Summary risk of bias: moderate or high
Participants	Participants recruited 4-8 days after confirmed MI N: 150 intervention, 150 control

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OFAMI 2001 *(Continued)*

	Level of risk for CVD: high Men: 77% intervention, 82% control Mean age in years (SD): 64.4 intervention, 63.6 control (no SD) Age range: 28-86 years intervention, 29-87 years control Smokers: 39% intervention, 38% control Hypertension: 29% intervention, 23% control Medications taken by at least 50% of those in the control group: beta-blockers, aspirin Medications taken by 20%-49% of those in the control group: statins, ACE inhibitors Medications taken by some, but < 20% of the control group: diuretics, warfarin Location: Norway Ethnicity: unclear
Interventions	Type: supplement (capsules) Comparison: EPA + DHA vs omega-6 Intervention: 4 gelatin capsules of omega-3-acid ethyl esters 90 (Omacor, Pronova A/S, Oslo, Norway), each is 1 g containing 850-882 mg EPA and DHA as concentrated ethylesters Dose ˜3.4- 3.5 g/d EPA + DHA Control: corn oil capsules, 4/d, each contains 1 g of corn oil Compliance: assessed by questionnaire and capsule count, 82% intervention group had complete compliance after 6 weeks, 86% of controls Length of intervention: 24 months
Outcomes	Main trial outcome: CV events Dropouts: unclear Available outcomes: total and CV deaths, MI, unstable angina, interventions, combined CV events, BMI, lipids, BP (trial authors provided additional data on glucose, AF, stroke) Response to contact: yes
Notes	Trial funding: Pharmacia-Upjohn and Pronova

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned" – Pharmacia was responsible for randomisation. Trial author response: participants were randomised in blocks of 4
Allocation concealment (selection bias)	Low risk	Trial author confirmed allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical capsules containing either Omacor or corn oil. Double-blinding stated, but taste not reported as masked and blinding of participants not checked

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OFAMI 2001 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial author stated: all later analyses performed without the knowledge of outcome
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of dropouts 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% intervention group had complete compliance after 6 weeks, 86% of controls
Other bias	Low risk	No further bias noted

OMEGA 2009

Methods	Effect of omega-3 FAs on reduction of sudden cardiac death after MI (OMEGA) 2 arm, parallel RCT (omega-3 vs olive oil), 12 months Summary risk of bias: low
Participants	People who had had an acute MI N: 1940 intervention, 1911 control (analysed for primary endpoints 1919 intervention, 1885 control) Level of risk for CVD: high Men: 75.1% intervention, 73.7% control Age (median): 64.0 years, intervention, 64.0 years control Age range: unclear (upper and lower quartiles 54-72) Smokers: 35.9% intervention, 37.5% control Hypertension: 66.9% intervention, 66.1% control Medications taken by at least 50% of those in the control group: statins, ACE inhibitors, beta-blockers, clopidogrel, aspirin Medications taken by 20%-49%: diuretics Medications taken by some, but < 20%: AT1 receptor blockers, vitamin K antagonist, calcium channel blockers, digitalis, amiodarone, oral antidiabetics, insulin Location: Germany Ethnicity: not reported
Interventions	Type: supplement (capsules) Comparison: EPA + DHA vs MUFA Intervention: 1 × 1 g/d Pronova BiCare soft gelatin capsule 'zodin' omega-3 acid ethyl esters (460 mg/d EPA and 386 mg/d DHA). Dose: 0.85 g/d EPA + DHA

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OMEGA 2009 *(Continued)*

	Control: 1 × 1 g/d olive oil capsule identical to intervention Compliance: 93.1% of intervention group and 93.2% of control participants took > 70% of capsules Duration of intervention: 12 months
Outcomes	Main trial outcome: sudden cardiac death, cardiac arrest Dropouts: control: 26 (8 lost to follow-up, 2 withdrew before allocation, 16 excluded) intervention: 21 Available outcomes: deaths, CV mortality, MACCE, MI, arrhythmias, heart failure, stroke, revascularisation, lipids; trial authors supplied information on angina, depression, cancers, AF Response to contact: yes
Notes	Trial funding: Tromsdorff Arzneimittel commissioned the research

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation code generated by alpha med PHARBIL, done in blocks of 8. Randomisation was stratified by centre.
Allocation concealment (selection bias)	Low risk	Appearance of the drugs or the drug containers did not allow participants and physicians to deduce the trial arm. 4-digit number on a concealed container
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Capsules for placebo and intervention looked the same, randomisation code unknown to investigator (taste and smell not mentioned)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Classification of adverse events blinded to allocation, and there was a blinded endpoint committee for all prespecified outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All events were documented by the investigators and reported to the assigned clinical research organisation and the sponsor. The data safety monitoring board judged any imbalances between the trial arms.
Selective reporting (reporting bias)	Low risk	NCT00251134 registered in 2005. Trial start date: 2003, Completed: 2008, trial design: 2006, Published paper: 2010. All trials registry primary and secondary outcomes reported
Attention	Low risk	Capsules for both arms
Compliance	Low risk	93.1% of intervention group and 93.2% of control participants took > 70% of capsules. EAIC 0.65 intervention, and control
Other bias	Low risk	None noted

OPAL 2010

Methods	Older People And n-3 Long-chain PUFA (OPAL) 2-arm, parallel, RCT, (omega-3 vs MUFA), 12 months Summary risk of bias: low

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OPAL 2010 *(Continued)*

Participants	Healthy cognitively normal adults aged 70-79 years N: 434 intervention, 433 control (analysed 376 intervention, 372 control) Level of risk for CVD: low Men: 53.4% intervention, 56.6% control Mean age in years (SD): 74.7 (2.5) intervention, 74.6 (2.7) control Age range: 70-79 years Smokers: not reported Hypertension: 54.9% intervention, 56.9% control Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49%: not reported Medications taken by some, but < 20%: not reported Location: England and Wales Ethnicity: not reported
Interventions	Type: supplement (capsules) Comparison: EPA + DHA vs MUFA Intervention: 2 × 650 mg capsule/d Ocean Nutrition vanilla flavoured soft gelatin capsule (total daily dose of 200 mg EPA and 500 mg DHA). Dose: 0.7 g/d EPA + DHA Control: 2 × 650 mg olive oil capsule identical to intervention Compliance: count returned capsules Capsules not returned: • intervention - median: 0.95; IQR: 0.82, 1.00 • control - median: 0.95; IQR: 0.81, 1.00 Fasting serum FAs, mg/L, mean (SD) • EPA: intervention 49.9, (2.7); control 39.1 (3.1) • DHA: intervention 95.6 (3.1); control, 70.7 (2.9) • ALA intervention 21.5 (0.8); control 22.0 (0.9) Length of intervention: 24 months
Outcomes	Main trial outcome: delayed onset of cognitive decline Dropouts: control: 78 (8 died, 53 withdrew, 17 discontinued intervention but provided data); intervention: 67 (9 died, 49 withdrew, 9 discontinued intervention but provided data) Available outcomes: deaths, MI, arrhythmias, stroke, diabetes, lipids Response to contact: yes
Notes	Trial funding: UK Food Standards Agency, National Health Service Research & Development provided support costs
Risk of bias	

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OPAL 2010 *(Continued)*

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) All outcomes	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 trial. All project staff were unaware of group assignments until after data analysis.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All project staff were unaware of group assignments until after data analysis.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants who discontinued the supplements invited to an interview at 24 months. Dropouts explained and similar in both arms (intervention 49 withdrew, control 53 withdrew)
Selective reporting (reporting bias)	High risk	ISRCTN72331636. Trial registered 2004, before trial 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 (intervention - median: 0.95; IQR: 0.82, 1.00; control - median: 0.95; IQR: 0.81, 1.00). Fasting serum FAs, mg/L, mean (SD): EPA, intervention 49.9 (2.7); control 39.1 (3.1). DHA, intervention 95.6 (3.1); control 70.7 (2.9). ALA: intervention 21.5 (0.8); control 22.0 (0.9)
Other bias	Low risk	No further bias noted

ORIGIN 2012

Methods	Outcome Reduction with Initial Glargine INtervention (ORIGIN) RCT, 2 × 2 factorial, (n-3 vs MUFA), 72 months Summary risk of bias: low
Participants	People at high risk of CV events with IFG, IGT or diabetes (mean baseline TG 140 mg/dL, 88.4% had diabetes) N: 6319 intervention, 6292 control (analysed, intervention: 6281 control: 6255) Level of risk for CVD: moderate Men: 65.4% intervention, 64.7% control Mean age in years (SD): 63.5 (7.8) intervention, 63.6 (7.9) control Age range: unclear, eligible if aged ≥ 50 years Smokers: current smokers 12.1% intervention, 12.6% control

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ORIGIN 2012 *(Continued)*

	Hypertension: 78.7% intervention, 80.3% control 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 < 20%: thiazide diuretics, anticoagulant Location: 40 trial 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 900 mg ethyl esters of n-3 fats (465 mg EPA + 375 mg DHA). Dose: 0.84 g/d EPA + DHA Control: 1 × 1 g 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 trial outcome: composite of the 1st occurrence of CV death, nonfatal MI or nonfatal stroke Dropouts: 38 intervention, 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, revascularisation, breast cancer, cancer diagnoses and cancer deaths, BP, lipids (HbA1c given as medians only) Response to contact: yes but no data provided
Notes	The other 2 × 2 assignment was to insulin glargine vs 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). Trial funding: Sanofi Aventis, Omacor provided by Pronova Biocare

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "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) All outcomes	Low risk	Trial described as "double blind" and placebo described as identical. Blinding of participants, investigators, local and central trials personnel described. However, no information provided as to the capsules' smell and taste
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "all primary and secondary outcomes were adjudicated with the use of prespecified definitions by a committee whose members were unaware of study-group assignments"

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ORIGIN 2012 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Almost all participants were included in outcomes
Selective reporting (reporting bias)	Low risk	NCT00069784 – registered October 2003, trial started August 2003, final data collection December 2011. Most outcomes appear to have been reported in various publications (CV 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 2013

Methods	Omega-3 FAs randomised long-term (ORL) RCT- parallel, 3 arms (TAK-085 2 g, TAK-085 4 g, and EPA-E 1.8 g, n-3 vs unclear), 12 months Summary risk of bias: moderate or high
Participants	Population: Japanese adults with hypertriglyceridaemia (mean baseline TG 263 mg/dL) N: 171 intervention (4 g TAK), 165 control (2 g TAK) Level of risk for CVD: moderate Men: 70.8% intervention, 71.5% control Mean age in years (SD): 55.9 (10.12) intervention, 56 (10.95) control Age range: 20-74 Smokers (current): 27.5% intervention, 31.5% control Hypertension: 66.7% intervention, 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 < 20%: not reported Location: Japan Ethnicity: unclear
Interventions	Type: supplement (TAK-085 capsules) Comparison: EPA + DHA higher vs lower dose Intervention: 1 × 2/d capsule each containing 2 g of TAK-085 (1 g of FA in TAK-085 capsules contains approximately 465 mg of EPA-E plus 375 mg of DHA-E). Total dose of 1.86 g/d EPA + 1.5 g/d DHA. Dose: ˜3.4 g/d EPA + DHA) (difference of +1.7 g/d from control arm) Control: 1 capsule/d containing 2 g of TAK-085 (1 g of FA in TAK-085 capsules contains approximately 465 mg of EPA-E plus 375 mg of DHA-E). Total dose of 0.93 g/d EPA + 0.75 g/d DHA. Dose: 1.7 g/d EPA + DHA

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ORL 2013 *(Continued)*

	Compliance: monitored every 4 weeks, mean rate of compliance reported as > 96% in each group Length of intervention: 12 months
Outcomes	Main trial outcome: safety outcomes and adverse events Dropouts: group 1: 8, group 2: 14, group 3 (not analysed): 21 Available outcomes: adverse events (including CVD events, cancers), CRP, waist circumference, weight, BP (nil death), lipids provided as % change from baseline, but no baseline data available, so not used in meta-analyses Response to contact: no
Notes	A 3rd arm of EPA-E 1.8 g supplementation is not used here. Outcome data used TAK-4 vs TAK-2 Trial funding: Takeda Pharmaceutical Company

Risk of bias

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

Proudman 2015

Methods	RCT, parallel, (EPA + DHA fish oil vs omega-6 Sunola oil), 12 months Summary risk of bias: low

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Proudman 2015 *(Continued)*

Participants	People with RA < 12 months' duration, DMARD-naive N: 87 intervention, 53 control (analysed, intervention: 75 control: 47) Level of risk for CVD: low Men: 29% intervention, 25% control Mean age in years (SD): 56.1 (15.9) intervention, 55.5 (14.1) control Age range: unclear Smokers: 65.1% intervention, 54.7% control (includes current and previous smokers) Hypertension: not reported Medications taken by at least 50% of those in the control group: triple DMARD therapy (SSZ 0.5 g/d, HCQ 200 mg twice/day and MTX 10 mg once/week) Medications taken by 20%-49% of those in the control group: NSAIDS Medications taken by some, but < 20% of the control group: oral or parenteral steroids Location: Australia Ethnicity: not reported
Interventions	Type: supplement (fish oil) Comparison: high EPA + DHA vs omega-6 (low EPA + DHA with Sunola oil) Intervention: 10 mL/d fish oil concentrate (BLT Incromega TG3525) providing 5.5 g/day (3.2 EPA + 2.3 DHA). Dose: 5.5 g/d EPA + DHA Control: 10 mL/d Sunola oil:capelin oil (2:1) providing 0.21 g EPA + 0.19 g DHA/d as TAG (0.40 g/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 trial outcome: DMARD failure and remission Dropouts: 11 intervention, 6 control Available outcomes: mortality (nil death), adverse events including CVD, DAS score, diabetes, authors supplied methodology data plus BMI change Response to contact: yes
Notes	DAS scores are reported as median and IQR in Proudman 2012 abstract (see secondary ref under Proudman 2015) Trial funding: National Health Medical Research Council of Australia and Royal Adelaide Hospital Research Committee. Melrose Health provided support for ongoing trials. The oil was made by the Royal Adelaide Hospital Pharmacy

Risk of bias

Bias	Authors' judgement	Support for judgement

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Proudman 2015 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "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	Quote: "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) All outcomes	Low risk	Quote: "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) All outcomes	Low risk	Both participants and investigators/assessors were blinded to the group allocation. Quote: "Investigators and subjects remained blinded for all withdrawals."
Incomplete outcome data (attrition bias) All outcomes	Low risk	The flow of all trial participants shown in FIGURE 2
Selective reporting (reporting bias)	Unclear risk	Outcomes reported in trial register matched with the outcomes reported in publications. However, the trial 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

Puri 2005

Methods	RCT, parallel (ethyl-EPA vs paraffin), 2 arm, 12 months Summary risk of bias: low
Participants	People with Huntington's disease N: 67 intervention, 68 control (analysed, intervention: 39 control: 44) Level of risk for CVD: low Men: 57% intervention, 44% control Mean age in years (SD): 50 (9.3) intervention, 49 (9.0) control Age range: not reported Smokers: not reported Hypertension: not reported Medications taken by at least 50% of those in the control group: not reported

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Puri 2005 *(Continued)*

	Medications taken by 20%-49% of those in the control group: antidepressants Medications taken by some, but < 20%: neuroleptics Location: Australia, Canada, UK, USA Ethnicity: intervention: 94% white, 4% black, 1% Asian; control: 97%, 3%, 0%, respectively
Interventions	Type: supplement (ethyl-EPA) Comparison: EPA vs paraffin (non-fat) Intervention: 2 × 2 × 500 mg capsules/d, total dose of 2 g/d ethyl-EPA (code name LAX-101, purity 95%). Dose: 1.9 g/d EPA Control: 2 × 2 × 500 mg capsules/d liquid paraffin Compliance: 38 were excluded for protocol violations, 4 intervention and 16 control were non-compliant with capsules Duration of intervention: 12 months
Outcomes	Main trial outcome: functional status in Huntington's disease Dropouts: 7 intervention, 7 control Available outcomes: measures of functional capacity, CV events, cancers (nil deaths) Response to contact: yes (no additional data provided)
Notes	Trial funding: Amarin Neuroscience Ltd. (formerly known as Laxdale Ltd.), provided organisation, funding and salaries

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "After screening and acceptance... patients were assigned to treatment by receiving a numbered pack supplied by a clinical trials packaging organization ... independent of all other aspects of the trial. Randomization was stratified in a block size of four, with the appropriate number of blocks allocated to each center. PCI Clinical Services held the randomization code until the database had been closed and all patients had been assigned"
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "[p]lacebo and ethyl-EPA capsules were of identical appearance" (though taste and smell not reported)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Randomisation described as "double-blind", "neither the patients nor the participating medical staff had access to this code during the course of the study"
Incomplete outcome data (attrition bias) All outcomes	High risk	Clearly reported and complete, however > 20% attrition

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Puri 2005 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry identified
Attention	Low risk	Unlikely
Compliance	Unclear risk	38 were excluded for protocol violations, 4 intervention and 16 control were non-compliant with capsules
Other bias	Low risk	None noted

Raitt 2005

Methods	RCT, parallel, (fish oil or olive oil), 24 months Summary risk of bias: moderate or high
Participants	People with implantable cardioverter defibrillators and recent sustained VT/VF N: 100 intervention, 100 control Level of risk for CVD: high Men: 86% intervention, 86% control Mean age in years (SD): 63 (13) intervention, 62 (13) control Age range: not reported but 18-75 inclusion criteria Smokers: not reported Hypertension: 46% intervention, 55% control Medications taken by at least 50% of those in the control group: diuretic, beta blockers, ACE inhibitors Medications taken by 20%-49% of those in the control group: digoxin, statins Medications taken by some, but < 20% of the control group: calcium channel blocker Location: USA Ethnicity: 94% white in intervention group, 97% in control group
Interventions	Type: supplement (fish oil capsules vs olive oil capsules) Comparison: EPA + DHA vs MUFA Intervention: 1.8 g/d fish oil capsules (Hoffman LaRoche, including ethyl esters of EPA and DHA, 0.76 g/d EPA, 0.54 g/d DHA). Dose: 1.3 g/d EPA + DHA Control: 1.8 g/d olive oil capsules (Hoffman LaRoche, 73% oleic acid) Compliance: while control group plasma and platelet DHA and EPA did not change, there were increases of 2%-8.3% in the intervention group Duration of intervention: 24 months (median 718 days)
Outcomes	Main trial outcome: time to 1st episode of VT/VF Dropouts: 17 intervention, 26 control

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Raitt 2005 *(Continued)*

	Available outcomes: deaths, CV death, MI, angina, revascularisation, arrhythmias, sudden cardiac death, cancer Response to contact: yes but no data provided
Notes	Trial funding: NIH and Hoffman LaRoche

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer generated block randomisation scheme"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participant blinding unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	implanted cardioverter defibrillator traces were viewed by researchers blinded to allocation, "double blind placebo-controlled"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Almost all participants were included in outcome assessment, well described
Selective reporting (reporting bias)	High risk	NCT registered in February 2000, trial carried out from February 1999-January 2004. Most outcomes stated in registry entry reported, but QoL missing
Attention	Low risk	Capsules were the only different interventions between arms, little opportunity for attention bias
Compliance	Low risk	While control group plasma and platelet DHA and EPA did not change, there were increases of 2%-8.3% in the intervention group
Other bias	Low risk	None noted

Ramirez-Ramirez 2013

Methods	RCT, parallel, (fish oil vs sunflower oil), 12 months Summary risk of bias: moderate or high
Participants	People with relapsing remitting MS N: 25 intervention, 25 control (analysed, intervention: 20 control: 19) Level of risk for CVD: low Men: 83% intervention, 82% control (but these appear unlikely) Mean age (SD) years: 35.1 (7.6) intervention, 34.9 (7.8) control Age range: not reported but 18-55 years were inclusion criteria

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Ramirez-Ramirez 2013 *(Continued)*

	Smokers: not reported Hypertension: not reported Medications taken by at least 50% of those in the control group: 100% treated with interferon beta1b for at least 1 year before the trial began Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: Mexico Ethnicity: not reported
Interventions	Type: supplement Comparison: DHA + EPA vs n6 Intervention: 4 g/d omega Rx capsules (Dr Sears zone diet, with excipient of glycerin, water, tocopherol, sunflower oil, titanium dioxide, includes 0.8 g/d EPA plus 1.6 g/d DHA). Dose: 2.4 g/d EPA + DHA Control: excipient only (Perfect Source Natural Products, glycerin, water, tocopherol, sunflower oil, titanium dioxide) Compliance: consumption diary plus pills returned at each visit, adherence calculated (correct formula?? pills consumed × 100/pills returned), optimal adherence was considered to be > 80%, 1 intervention and 3 control were excluded due to compliance < 80%. Blood DHA and EPA were significantly different at 12 months. Duration of intervention: 12 months
Outcomes	Main trial outcome: TNF-alpha Dropouts: 5 of 25 intervention, 6 of 25 control Available outcomes: TNF-alpha, IL-6, IL-1 beta, nitric oxide catabolites, MS relapse, disability EDSS, liver and renal function tests, haemoglobin, leucocytes, platelets, oxidative outcomes (glucose and lipids data collected but not reported, for BMI and BP paper reports "no difference through study") Response to contact: not yet attempted
Notes	Trial funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence (blocks of 4)
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "capsules were identical in appearance, packaging and labelling", "physicians and patients were blind to the intervention", and there was a rosemary flavour to mask.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "an independent physician evaluated the EDSS score and collected samples at each clinic visit"

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Ramirez-Ramirez 2013 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Loss of 11/50 over 1 year, 22% loss
Selective reporting (reporting bias)	High risk	Paper reports analysis of glucose and lipids but these are not reported
Attention	Low risk	Appeared similar, reviewed every 3 months
Compliance	Low risk	Blood DHA and EPA were significantly different at 12 months
Other bias	Low risk	None noted

REDUCE-IT 2019

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	People (45 years+) with hypertriglyceridaemia, and with CVD or with DM and another risk factor, and on statin (58% had DM at baseline, mean baseline TG > 200 mg/dL) N: intervention 4089 randomised, control 4090 randomised (analysed, intervention: 4083 control: 4077) Level of risk for CVD: moderate (with DM in 29.3% of both intervention and control groups) and high (with CVD, 70.7% of both groups) 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, 45.4% intervention and 46.6% control groups aged 65+ years. 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, 54% of both groups on anti-diabetic medication, 95% on antihypertensives, 80% on antiplatelets, 52% on ACE, 71% on beta blockers. Medications taken by 20%-49% of those in the control group: 27% on ARB Medications taken by some, but < 20% of the control group: 6% on ezetimibe, 9% on anticoagulant Location: 11 countries including USA, Netherlands, Ukraine, Russia, South Africa, Poland, India, Romania, Australia, New Zealand (westernised 71%, Eastern Europe 26%, Asia Pacific 3%) 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), 3.99 g/d EPA plus 8 mg/d vitamin E (2 capsules twice/d) Control: 3.73 g/d light liquid paraffin oil in 4 capsules (2 capsules twice a day)

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REDUCE-IT 2019 *(Continued)*

	Compliance: serum EPA assessed, expressed as medians, ~26 µg/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 trial outcome: composite of CV 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, AF, revascularisation, DM, TIA, HT (lipid levels and CRP provided as medians). CVD event data provided by diabetes and TG status Response to contact: not yet attempted
Notes	NCT01492361 Trial funding: trial designed, run and funded by Amarin (who produce the intervention capsules)

Risk of bias

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) All outcomes	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) All outcomes	Low risk	Adjudication was by independent clinical endpoint committee unaware of assignment
Incomplete outcome data (attrition bias) All outcomes	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 November 2011, recruitment November 2011 to August 2016
Attention	Low risk	Appeared similar
Compliance	Low risk	Median serum EPA rose in intervention but not in control
Other bias	High risk	CHD and MI data suggest fewer participants in the intervention arm experienced these outcomes, BUT this is contradicted in Bhatt JACC 2019 (online figure 3), which suggests the data are the wrong way around (suggesting worse outcomes with higher omega-3). Analyses have assumed main data set correct. Some changes in inclusion criteria (levels of TG included) during trial.

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Reed 2014

Methods	RCT, parallel, 3 arms (fish oil or borage oil), 18 months Summary risk of bias: low
Participants	Adults with RA N: 53 intervention, 52 control (28 intervention, 24 control analysed) Level of risk for CVD: low Men: 13.2% intervention, 23.1% control Mean age in years (SD): 57.3 (12.3) intervention, 60.3 (9.2) control Age range: not reported but 18-85 inclusion criteria Smokers: not reported Hypertension: not reported Medications taken by at least 50% of those in the control group: MTX, DMARDs, and TNF blockers Medications taken by 20%-49% of those in the control group: corticosteroids and TNF blockers Medications taken by some, but < 20% of the control group: not reported Location: USA Ethnicity: black/African-American: intervention (fish oil): 7.8% control (borage oil): 7.8%
Interventions	Type: supplement (fish oil vs borage oil) Comparison: EPA + DHA vs omega-6 Intervention: 7 fish oil (2.1 g EPA:1.4 g DHA) capsules and 6 sunflower seed oil capsules daily = 13 capsules divided doses. Dose: 3.5 g/d EPA + DHA Control: 6 borage seed oil (1.8 g GLA) capsules plus 7 sunflower seed oil capsules daily Compliance: assessed by capsule counts and participant report. Participant report, indicates that 45% of participants reported ever missing a dose (borage: 42%, fish 48%). Median total capsules missed (excluding those with 0) were 182 (borage: 164, fish 169) Duration of intervention: 18 months
Outcomes	Main trial outcome: RA modified DAS Dropouts: 25 intervention, 28 control Available outcomes: mortality (nil death), CVD events (nil), DAS score, CDAI score. Trial authors suggested that LDL and total cholesterol were reduced in the intervention group at 18 months, and HDL was increased in both intervention and control at 18 months, while DBP was reduced in the intervention group at 18 months, but no numbers provided. CRP and ESR data were provided combined for the intervention and control arms in the trial author response, so not useable Response to contact: yes, trial authors supplied details of methodology but no usable outcome data
Notes	A 3rd arm (45 participants) were given a combination of both oils but not discussed here Trial funding: National Institutes of Health Grant RO1-AT000309 from the National Center for Complementary and Alternative Medicine

Risk of bias

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Reed 2014 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Trial author stated "stratified random block, stratified by site using random blocks of 3 & 6"
Allocation concealment (selection bias)	Low risk	No methodology provided in the paper, but the trial author suggested concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, all capsules were identical in appearance and colour, they were shipped in opaque plastic bottles to the University of Massachusetts University Hospital pharmacy, from where they were distributed to participating centres. However no information provided as to their smell and taste.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial author confirmed outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Trial authors mention ITT analysis but shows completers analysis. Numbers of participants are not provided for all outcomes measured. Provided results for the overall group (69 participants table 3a) while the flow diagram states there are 74 completers. 51% dropped out.
Selective reporting (reporting bias)	Low risk	Trial prospectively registered in 2003, estimated trial completion November 2008, published in 2014. Both outcomes reported in registry are reported in the publication.
Attention	Low risk	All participants were evaluated at 3-month intervals, by the same examiner.
Compliance	Unclear risk	Assessed by capsule counts and participant report. Participant report, indicates that 45% of participants reported ever missing a dose (borage: 42%, fish 48%). Median total capsules missed (excluding those with 0) were 182 (borage: 164, fish 169)
Other bias	Low risk	None noted

Risk & Prevention 2013

Methods	RCT, parallel, (n-3 vs olive oil), 60 months Summary risk of bias: moderate or high
Participants	Patients with multiple CV risk factors (59.9% had diabetes) N: 6244 intervention, 6269 control (analysed, intervention: 6239 control: 6266) Level of risk for CVD: high Men: 62.3% intervention, 60.6% control Mean age in years (SD): 63.9 (9.3) intervention, 64.0 (9.6) control Age range: not reported Smokers: 22.1% intervention, 21.4% control Hypertension: 84.6% intervention, 84.5% control Medications taken by at least 50% of those in the control group: not reported

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Risk & Prevention 2013 *(Continued)*

	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 < 20% of the control group: insulin Location: Italy Ethnicity: not reported
Interventions	Type: supplement (n-3 capsules) Comparison: EPA + DHA vs MUFA Intervention: 1 g/d n-3 capsules polyunsaturated FA ethyl esters (EPA and DHA content 850-882 mg with an average ratio of 1.0:1.2). Dose: ˜0.87 g/d EPA + DHA Control: 1 g/d olive oil capsules Compliance: measured by self-report during follow-up visits but no results reported Duration of intervention: 60 months
Outcomes	Main trial outcome: composite of time to death from CV causes or hospital admission for CV causes Dropouts: intervention: 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 Trial authors provided data on diabetes diagnosis, glucose and HbA1c. Response to contact: yes
Notes	All continuous outcomes change data are reported as least squares mean hence not used. Trial funding, quote: "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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "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) All outcomes	Unclear risk	Quote: "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.

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Risk & Prevention 2013 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Patients, general practitioners, coordination and statistical staff, and outcome assessors were unaware of the study assignments until the final analyses were completed." Quote: "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) All outcomes	Low risk	Quote: "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 GI) and 3.3% others (clinical or patient's refusal)… After 1-year of follow-up, 1.0% had CV death and 3.4% hospitalisation for CV events (primary end point)"
Selective reporting (reporting bias)	High risk	Primary endpoint was amended part way through trial. Differences in groupings of CV events in tables 2; S4 and S5. For hospital admissions notes each participant could have > 1 CV cause
Attention	Unclear risk	Does not state attention differs or is the same between groups- regularly see GP for follow-up and blinding not clear
Compliance	Unclear risk	No results
Other bias	Low risk	None noted

Rossing 1996

Methods	RCT, parallel, (fish oil vs olive oil), 12 months Summary risk of bias: moderate or high
Participants	Adults with insulin-dependent DM, diabetic nephropathy and normal BP (mean baseline TG 1.0 mmol/L) N: 18 intervention, 18 control (analysed, 17 intervention, 15 control) Level of risk for CVD: moderate Men: 64% intervention, 67% control Mean age (SD) years: 32 (7) intervention, 34 (10) control Age range: 18-55 years Smokers: 50% intervention, 47% control Hypertension: not reported Medications taken by at least 50% of those in the control group: insulin Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported

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Rossing 1996 *(Continued)*

	Location: Denmark Ethnicity: not reported
Interventions	Type: supplement Comparison: EPA + DHA vs MUFA Intervention: cod-liver oil emulsion (Pharma-Vinci A/S Denmark). EPA 2 g, DHA 2.6 g, total PUFA 4.6 g/d. Dose: 4.6 g/d EPA + DHA 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 trial outcome: diabetic nephropathy Dropouts: 1 intervention, 3 control (though 3 further intervention participants are not included in all data) Available outcomes: mortality (nil), breast cancer, total and LDL cholesterol, SBP (TGs reported as medians so not used, albuminurea, fractional albumin clearance, transcapillary escape rate of albumin, prothrombin fragment reported as geometric means or medians, HbA1c, HDL and DBP too different at baseline to include, GFR, PAI1, TPA, fibrinogen, etc. not relevant) Response to contact: yes
Notes	Trial funding: the Danish Heart Association. Eskisol Fish oil and placebo oil emulsions were provided by Pharma-Vinci A/S, Frederiksvaerk, Denmark

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomised using concealed randomisation 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) All outcomes	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) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts similar between groups although relatively high for small sample size. 3 dropouts from fish oil and 1 from control due to side effects. ITT analysis appears to have been given for albuminuria only
Selective reporting (reporting bias)	Unclear risk	No trials registry entry or protocol found

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Rossing 1996 *(Continued)*

Attention	Low risk	Time and attention appear to be the same. All participants 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

Methods	RCT, parallel, 5 arms (combined groups 4 and 5 omega-3-acid ethyl esters (Lovaza) n-3 ± raloxifene vs control groups 1 and 3 ± raloxifene), 24 months Summary risk of bias: moderate or high
Participants	Healthy postmenopausal women (50% normal weight, 30% overweight, 20% obese) with high breast density detected on their routine screening mammograms N: 54 + 53 intervention, 53 + 53 control Level of risk for CVD: low Men: 0% intervention, 0% control Mean age in years (SD): 56.56 (6.9) + 57.85 (5.1) intervention, 57.11 (5.9) + 57.68 (5.1) control Age range: not reported Smokers: 0% intervention, 0% control Hypertension: not reported Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: USA Ethnicity: not reported
Interventions	Type: supplement (n-3 capsules) Comparison: EPA + DHA vs nil Intervention: group 4, Lovaza 4 g/d. Lovaza is the FDA-approved n-3 FA formulation containing 465 mg of EPA + 375 mg of DHA per gram, total dose; 1860 mg/d EPA, 1500 mg/d DHA. Group 5 as group 4 plus 30 mg raloxifene/d. Dose: 3.36 g/d EPA + DHA Control: group 1, no treatment; group 3, 30 mg raloxifene/d Compliance: measured by pill count, recorded at follow-up visits and further verified by serum FA monitoring. Compliance was 94% (SE 2%) at 6 months and 97% (SE 2%) at 12 months. Only 2 participants had a compliance < 85% (84% and 81%). Duration of intervention: 24 months
Outcomes	Main trial outcome: change in breast density Dropouts: 5 intervention, 6 control

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Sandhu 2016 *(Continued)*

	Available outcomes: CV events, breast cancer, lipids, dietary intake, plasma FAs, adverse events (including 1 incidence of hyperglycaemia) Response to contact: yes
Notes	The trial had 5 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 4 g/d plus raloxifene 30 mg orally daily. Data here are combined for groups 4 and 5 vs 1 and 3 for binary outcomes and group 1 vs 4 used for continuous outcomes Trial funding: GlaxoSmith Kline and Eli Lilly provided Lovaza and raloxifene, respectively. Funded by Susan G Komen for the Cure, KG081632 (A Manni) and pilot funds from the Penn State Hershey Cancer Institute (K El-Bayoumy)

Risk of bias

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) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	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 CRP 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)
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 FA monitoring. Compliance was 94% (SE 2%) at 6 months and 97% (SE 2%) at 12 months. Only 2 participants had a compliance < 85% (84% and 81%)
Other bias	Low risk	None noted

SCIMO 1999

Methods	Study on prevention of coronary atherosclerosis with marine omega-3 FAs (SCIMO)

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SCIMO 1999 *(Continued)*

	RCT, parallel (omega-3 vs average European fats), 2 years Summary risk of bias: low
Participants	People with angiographically proven coronary artery disease N: 112 intervention, 111 control (analysed 82 intervention, 80 control) Level of risk for CVD: high Men: 82% intervention, 78.6% control Mean age in years (SD): 57.8 (9.7) intervention, 58.9 (8.1) control Age range: unclear (18-75 inclusion criteria) Smokers: 16.2% intervention, 22.3% control Hypertension: 53.1% intervention, 45.5% control (history of high BP) Medications taken by at least 50% of those in the control group: platelet inhibitors, beta-blockers Medications taken by 20%-49% of those in the control group: long-term nitrate therapy, lipid-lowering agents, ACE inhibitors, diuretics, calcium antagonists, other antihypertensive agents and digitalis Medications taken by some, but < 20% of the control group: nitrates only on demand Location: Germany Ethnicity: not reported
Interventions	Type: supplement (capsule) Comparison: EPA + DHA vs SFA + MUFA (average European fat composition) Intervention: concentrated fish oil capsules, 6 x 1 g capsules/d for first 3 months, 3 × 1 g/d for rest of trial (4 g/d EPA +DHA + DPA + ALA for first 3 months, then 2 g/d). Dose: ˜2 g/d LCn3 Control: capsules containing fat that replicated the fat composition of the average European diet, 6/d for first 3 months, 3/d for rest of trial, opaque soft gelatin capsules identical to fish capsules in identical screw-top containers Compliance: capsule count, overall 2284 (SD 313) capsules taken of 2460 prescribed for each person, erythrocyte phospholipids rose from 4.6% to 11.8% at 24 months in intervention, and didn't alter from baseline in controls Length of intervention: 24 months
Outcomes	Main trial outcome: changes in stenosis on angiography Dropouts: unclear Available outcomes: mortality, MI, CV events, revascularisation, angina, stroke, cancer diagnosis, weight, lipids, BP, side effects Response to contact: yes
Notes	Asked participants to guess treatment allocation, of those in intervention 63/90 were unsure, 5/90 guessed placebo and 22/90 guessed fish oil; of those in control 66/85 were unsure, 9/85 guessed placebo and 10/85 guessed fish oil Trial funding: Pronova provided capsules and funds for trial monitoring but it was stated that the funders played no part in analysis or publication
Risk of bias	

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SCIMO 1999 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified, and for the resulting 9 strata "a random sequence of study group assignments was computer generated by the trial monitor"
Allocation concealment (selection bias)	Low risk	Sealed, sequential numbered envelopes used (opaque not stated, but provided only a random number which linked to a specific container of capsules).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo and fish oil capsules "looked identical and were made of soft opaque gelatin and each contained 1 g of a fatty acid mixture". These were provided in identical containers with identical labels with a randomisation number. Participants were told that capsules differed in composition but not in taste.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding is described and is very strong for angiographic outcomes, but there is no description of how CV events were assessed or recorded. However outcomes assessors were probably the same assessors and so blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear for how many participants clinical events were assessed (though described in detail for angiographic outcomes), so trial flow unclear
Selective reporting (reporting bias)	Unclear risk	No trial trials register entry or protocol was found
Attention	Low risk	As trial personnel were unaware of assignments bias in attention was not possible
Compliance	Low risk	Capsule count, overall 2284 (SD 313) capsules taken of 2460 prescribed for each person, erythrocyte phospholipids rose from 4.6% to 11.8% at 24 months in intervention and didn't alter from baseline in controls
Other bias	Low risk	No further bias noted

seAFOod Hull 2018

Methods	Systematic Evaluation of Aspirin and Fish Oil (seAFOod) polyp prevention trial RCT, parallel, 2x2 (n3 EPA vs SFA MCT), 12 months (also randomised to aspirin arm) Summary risk of bias: low
Participants	NHS Bowel Cancer Screening Programme patients (55-73 years) identified as "high risk" (≥ 5 small adenomas; or ≥ 3 adenomas with at least 1 being ≥ 10 mm in diameter) after their 1st screening colonoscopy N: 356 intervention, 353 control (analysed 314 intervention, 326 control) Level of risk for CVD: low Male: 80% intervention, 80% control Mean age (SD): 65 or 66 years intervention, 65 years control (IQR 62-69) Age range: unclear (55-73 inclusion criteria) Smokers: 12% intervention, 17% control Hypertension: not reported Medications taken by at least 50% of those in the control group: nil Medications taken by 20-49% of those in the control group: statins (28%)

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seAFOod Hull 2018 *(Continued)*

	Medications taken by some, but < 20% of the control group: metformin (8%), PPI (11%), others 1% or less Location: England, UK Ethnicity: not reported
Interventions	Type: supplement (capsule) Comparison: EPA vs capric and caprylic acid MCTs Intervention: Arm 1: EPA (ALFA capsules: 2 x 500 mg twice/d = 2 g/d EPA) and aspirin placebo (1/d) Arm 2: EPA placebo (capric and caprylic acid triglycerides: 2/d) and enteric-coated aspirin (1/d = 300 mg/d) Control: Arm 3: EPA (ALFA capsules: 2 x 500 mg twice/d = 2 g/d) and enteric-coated aspirin (1/d = 300 mg/d) Arm 4: EPA placebo (cparic and caprylic acid triglycerides: 2/d) and aspirin placebo (1/d) Identical looking capsules and pills Compliance: capsule count, 95% capsules taken by all arms, red blood cell EPA at 12 months was ~1.5% FAs in intervention, ~0.5% in control (as at baseline) Oily fish intake: 42% of intervention and 40% control ate ≥ 1 portions of oily fish/week at 12 months Length of intervention: 12 months
Outcomes	Main trial outcome: number of participants with ≥ 1 adenomas at 12 months Dropouts: 40 intervention, 27 control Available outcomes: mortality, colorectal adenoma counts (and various types of severity e.g. number of "advanced" adenomas per participant, number of "high risk" participants re-classified as "intermediate risk", number participants with ≥ 1 advanced adenomas, adenoma region in the colorectum, total number of adenomas per participant, number of participants with colorectal cancer, levels of bioactive lipid mediators e.g. omega-3), adverse events (red blood cell lipids, oily fish intake) Response to contact: not yet attempted
Notes	ISRCTN05926847 EudraCT 2010-020943-10 www.seafood-trial.co.uk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation used a secure web-based system with treatment assignment established by pseudorandom code, using random permuted blocks of randomly varying size
Allocation concealment (selection bias)	Low risk	As above, allocation of participants not revealed to anyone until data lock
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Idential looking placebos were used for both interventions

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seAFOod Hull 2018 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and outcome assessors blinded to allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Few drop-outs, ITT analysis
Selective reporting (reporting bias)	Low risk	Outcomes in registry entry appear in paper
Attention	Low risk	All capsules, no scope for attention bias
Compliance	Low risk	Good compliance by all counts
Other bias	Low risk	None noted

Shinto 2014

Methods	RCT, parallel (fish oil capsule vs soybean oil capsule), 12 months Summary risk of bias: moderate to high
Participants	People aged ≥ 55 with probable Alzheimer dementia diagnosis N: 13 intervention, 13 control Level of risk for CVD: low Men: 61% intervention 46% control Mean age in years (SD): 75.9 (8.1) intervention, 75.2 (10.8) control Age range: 55+ (inclusion criteria) Smokers: not reported Hypertension: not reported Medications taken by at least 50% of those in the control group: anti-cholinesterases or memantine Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Lipid-lowering medications and many other drugs were not allowed Location: USA Ethnicity: 100% white
Interventions	Type: fish oil capsules Comparison: EPA + DHA vs n-6 Intervention: 3 × 1 g capsules/d of fish oils (975 mg EPA, 675 mg DHA/d). Dose: 1.65 g/d EPA + DHA Control: 3 × 1 g capsules/d soybean oil (which contains 5% fish oil) Both groups had a placebo lipoic acid tablet and lemon-flavoured capsules

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Shinto 2014 *(Continued)*

	Compliance: assessed by pill counts and FA in red blood cell membranes. Results showed increased EPA + DHA levels in the intervention group. Length of intervention: 12 months
Outcomes	Main trial outcome: F2-isoprostane levels (oxidative stress measure) Dropouts: 2 intervention, 2 control Available outcomes: mortality, CVD events, adverse events, serum FAs, measures of cognition (ADAS Cog and MMSE), ADL, IADL (also F2 isoprostane) Response to contact: not attempted
Notes	Trial funding: National Institutes of Health/National Institute of Aging (NIH/NIA) and NIH General Clinical Research

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised by a computer-generated scheme that was stratified by smoking status
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Capsules matched for taste and flavour. Blinding assessed at the end and majority of staff and participants were unaware of treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	15% dropouts explained and included
Selective reporting (reporting bias)	Low risk	NCT00090402 first received: 25 August 2004, trial start date April 2004. More secondary outcomes reported than included in the trial register entry
Attention	Low risk	Both arms seem to have had the same contact
Compliance	Low risk	Compliance measured and FAs levels reported. Results showed increased EPA + DHA levels in the intervention group
Other bias	Low risk	None noted

SHOT 1996

Methods	SHunt Occlusion Trial (SHOT) RCT, parallel (omega-3 vs nil), 4 arms, 1 year Summary risk of bias: moderate or high

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SHOT 1996 *(Continued)*

Participants	People admitted for CABG N: 317 intervention, 293 control Level of risk for CVD: high Men: 86% intervention, 88% control Mean age in years (SD): 59.9 (8.7) intervention, 59.4 (8.8) control Age range: unclear Smokers: 19% intervention, 20% control Hypertension: 20% intervention, 25% control Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: antihypertensives Medications taken by some, but < 20% of the control group: not reported Location: Norway Ethnicity: not reported
Interventions	Type: supplement (capsule) Comparison: EPA + DHA vs nil Intervention: 4 fish-oil concentrate soft gelatin capsules/d (Omacor; Pronova AS, Oslo, Norway) containing 51% EPA and 32% DHA ethyl esters and 3.7 mg vitamin E as an antioxidant. Dose: 3.3 g/d EPA + DHA Control: no treatment Compliance: capsule count, 88% taken, serum EPA + DHA rose in the intervention group (176-257 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 trial outcome: CABG graft patency Dropouts: 15 intervention, 14 control Available outcomes: deaths, CV deaths, MI, stroke, repeat CABG, combined CV events, lipids, side effects Response to contact: yes
Notes	The trial had 4 arms; aspirin; warfarin; fish oil + aspirin; and warfarin + fish oil. We combined the first 2 groups as the control and the last 2 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 intervention, 2.5 g/d at baseline, 2.2 g/d at 9 months control group Trial funding: in part by Pronova and Nycomed Pharma

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers were provided in consecutively sealed envelopes generated centrally

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SHOT 1996 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Envelopes not reported as opaque
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial, no blinding apart from outcome assessors so participants and trial personnel were aware of assignments. However, trial author suggested in personal communication that participants were not aware of their assignments.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors (radiologists) reported as blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for attrition and exclusions stated, numbers clear, dropouts < 20% per year
Selective reporting (reporting bias)	Unclear risk	No trial 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 (176-257 mg/L at 9 months) and fell in the control group (170-169 mg/L at 9 months)
Other bias	Low risk	No further bias noted

Sianni 2013

Methods	RCT, parallel, (fish oil vs unclear placebo), 12 months Summary risk of bias: moderate or high
Participants	People with hypertension and paroxysmal or persistent AF N: 268 intervention, 60 control Level of risk for CVD: moderate Men: not reported Mean age (SD) years: 62 (6), not reported by arm Age range: not reported Smokers: not reported Hypertension: 100% Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: Greece Ethnicity: not reported

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Sianni 2013 *(Continued)*

Interventions	Type: supplement Comparison: fish oil vs unclear placebo Intervention: omega-3 FAs with no further details. Dose: 4 g/d omega-3 Control: placebo, no further details Compliance: no details Duration of intervention: 12 months
Outcomes	Main trial outcome: AF recurrence and BP Dropouts: no details Available outcomes: new AF episodes, BP (not in a usable format) Response to contact: no
Notes	Trial funding: unclear The trial's only publication was a conference abstract.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details, probably randomised but unclear
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details
Selective reporting (reporting bias)	Unclear risk	No protocol or trial register record found
Attention	Unclear risk	No details
Compliance	Unclear risk	No details
Other bias	Unclear risk	No details

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SMART 2013

Methods	SMART trial (from the Smart Foods Centre) RCT, 3-arm parallel, (fish + S: hypocaloric diet plus fish plus fish oil capsules vs fish: hypocaloric diet plus fish plus olive oil capsules vs control: hypocaloric diet plus olive oil capsules), 12 months Summary risk of bias: moderate or high
Participants	Overweight adults (mean baseline TG 1.3 mmol/L) N: fish + S intervention 41, fish 43, control 42. (analysed, fish + S intervention 21, fish 25, control 18) Level of risk for CVD: low Men: 27% fish + S intervention, 23% fish intervention, 28% control Mean age (SD) years: unclear by arm, overall 45.1 (8.4) Age range: not reported but 18-60 years eligible Smokers: not reported but 5.9% overall Hypertension: not reported Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: Australia Ethnicity: not reported
Interventions	Type: supplement and food Comparison: EPA + DHA vs MUFA (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 180 g fish/week plus capsules including 420 mg/d EPA + 210 mg/d DHA (Blackmores Promega Heart). Dose: 0.63 g/d EPA + DHA Intervention, fish: hypocaloric diet aiming at 30% E from fat, 25% E from protein, 45% E from CHO, plus 180 g fish/week plus capsules including 1 g olive oil/d Control: hypocaloric diet aiming at 30% E from fat, 25% E from protein, 45% E from CHO, plus capsules including 1 g olive oil/d Compliance: assessed through diet histories (fish) and erythrocyte FA supplements (capsules), but results not reported Duration of intervention: 12 months
Outcomes	Main trial outcome: total % body fat Dropouts: fish + supplement intervention 20, fish intervention 18, control 24 Available outcomes: weight, BMI, lipids, BP, fasting glucose, fasting insulin, % body fat (leptin also reported), no deaths or CV events occurred (trial authors' report) Response to contact: trial authors provided data on CVD events (none) and mean/SD data for TGs and fasting insulin

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SMART 2013 *(Continued)*

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "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	Quote: "Randomisation was performed centrally, off-site 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) All outcomes	High risk	As above, but impossible to blind participants to the fish advice
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Very high levels of attrition, though ITT analyses carried out
Selective reporting (reporting bias)	High risk	We were unable to find data on 24-h energy expenditure, oxidation or heart rate, which were stated as primary and secondary outcomes in the trials registry.
Attention	Unclear risk	While dietary education was for 1 h then 6 further half-h 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	Quote: "Of the 12 months 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 FAs × 100 was significantly different for the fish-oil-supplemented group compared to the 2 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

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SOFA 2006

Methods	Study on Omega-3 Fatty Acids and ventricular arrhythmia (SOFA) 2-arm, parallel RCT (n-3 EPA + DHA vs MUFA and n6), 12 months Summary risk of bias: low
Participants	People with previous ventricular arrhythmias and implanted cardioverter defibrillator N: 273 intervention, 273 control (273 intervention, 273 control analysed) Level of risk for CVD: high Men: 84% intervention, 85 % control Mean age in years (SD): 60.5 (12.8) intervention, 62.4 (11.4) control Age range: unclear (≥ 18 years) Smokers: 16% intervention, 8% control Hypertension: 53% intervention, 49% control Medications taken by at least 50% of those in the control group: beta-blockers Medications taken by 20%-49% of those in the control group: lipid-lowering, antiarrythmic medications (combined) Medications taken by some, but < 20% of the control group: amiodarone, sotalol Location: 8 countries in Europe Ethnicity: not reported
Interventions	Type: supplement (capsule) Comparison: EPA + DHA vs MUFA + omega-6 Intervention: 2 g/d (4 capsules) purified fish oil. 961 mg n-3 PUFAS (464 mg EPA + 335 mg DHA and 162 mg other n-3 PUFAs) daily. 3000 ppm vitamin E (Loders Croklann, Wormeveer). Dose: 0.8 g/d EPA + DHA Control: 2 g/d high-oleic acid sunflower oil. 3000 ppm vitamin E (Loders Croklann, Wormeveer) Compliance: daily diary, checked by research nurses every 4 months. Judging by capsule count, 207 participants in the fish-oil group and 218 in the placebo took > 80% of their capsules. N-3 FA composition in serum cholesterol levels was measured at baseline and the end of the trial. The EPA concentration in serum cholesterol esters increased in the expected range. No data provided Length of intervention: 12 months
Outcomes	Main trial outcome: spontaneous VTs and all-cause mortality Dropouts: 33 intervention (23 partial follow-up), 33 control (14 partial follow-up) Available outcomes: deaths, MI, new angina, new heart failure, no fatal arrhythmias, cancer, CV events, side effects Response to contact: yes but no data provided
Notes	Trial funding: Wageningen Centre for Food Sciences (alliance of major Dutch food industries and others)

Risk of bias

Bias	Authors' judgement	Support for judgement

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SOFA 2006 *(Continued)*

Random sequence generation (selection bias)	Low risk	Participants using beta-blockers were separately randomised in blocks of 2. A computer randomisation programme randomly took the first treatment of a block. The second participant in a block of 2 always received the opposite treatment.
Allocation concealment (selection bias)	Low risk	Treatments (blinded medication numbers) were centrally assigned by a telephone allocation service.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinding. Bottles contained capsules labelled with medication numbers that were unidentifiable for participants as well as investigators. Fish oil and placebo capsules had identical appearance. Difference could not be tasted if swallowed with water (as suggested)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "blinded endpoint adjudication committee"
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis. Did a partial follow-up on some participants who dropped out due to non-compliance
Selective reporting (reporting bias)	Low risk	NCT00110838, trial registered in May 2005, end of trial January 2005, trial results published in 2006. However, rationale and design paper (stating outcomes) published in 2003. Outcomes in the 2006 paper appear to be the same as in Rationale paper
Attention	Low risk	Unlikely as intervention blinded to investigators and only intervention was capsules
Compliance	Unclear risk	Daily diary, checked by research nurses every 4 months. Judging by capsule count, 207 participants in the fish-oil group and 218 in the placebo took > 80% of their capsules. N-3 FA composition in serum cholesterol levels was measured at baseline and the end of the trial. The EPA concentration in serum cholesterol esters increased in the expected range. No data provided
Other bias	Low risk	No further bias noted

Sofi 2010

Methods	2-arm, parallel RCT (enriched olive oil vs olive oil), 12 months Summary risk of bias: moderate or high
Participants	People with NAFLD patients (mean TG 143 mg/dL, mean BMI 29.3) N: 6 intervention, 5 control Level of risk for CVD: low Men: 66.7% intervention, 100% control Median age: 55 intervention, 54 control Age range: 30-41 intervention, 42-70 control Smokers: not reported Hypertension: not reported

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Sofi 2010 *(Continued)*

	Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: Italy Ethnicity: not reported
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) containing 0.47 g EPA, 0.24 g DHA plus dietary recommendations. Dose: 0.83 g/d EPA + DHA 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 trial outcome: fatty liver status Dropouts: unclear Available outcomes: lipids, glucose, insulin, HOMA, (BMI not in usable format, also liver function tests, oxidative markers, adiponectin, fatty liver and steatosis outcomes) Response to contact: not yet attempted
Notes	Trial funding: oil supplied by tFarma and funding not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomized into two groups"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	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

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Sofi 2010 *(Continued)*

Other bias	Low risk	None noted

SU.FOL.OM3 2010

Methods	Supplementation en Folates et omega-3 (SU.FOL.OM3) RCT, 2 × 2 factorial (LCn3 omega-3 vs paraffin (non-fat), also B vitamin comparison), 4 years Summary risk of bias: low
Participants	People with a history of MI, unstable angina or ischaemic stroke N: control: 1248, intervention: 1253 Level of risk for CVD: high Men: 80.85% intervention, 78.25% control Mean age in years (SD): 61.1 (8.8) intervention, 60.8 (8.7) control Age range: 53-68 years intervention, 54-68 years control Smokers: 11.1% intervention, 10.4% control Hypertension: not reported Medications taken by at least 50% of those in the control group: beta-blockers, aspirin or antiplatelets, lipid-lowering, ACE inhibitors Medications taken by 20%-49%: not reported Medications taken by some, but < 20%: calcium channel blocker, angiotensin II receptor blockers Location: France Ethnicity: not reported
Interventions	Type: supplement (capsule) Comparison: EPA + DHA vs non fat placebo Intervention: 2 gelatin capsules Pierre Fabre omega-3 (400 mg/d EPA and 200 mg/d DHA) Control: 2 gelatin capsules/d placebo (liquid paraffin with fish flavour) Compliance: tested by questionnaire, response rate was on average 96%. Out of this, 86% complied Duration of intervention: 4 years
Outcomes	Main trial outcome: composite of MI, cerebral vascular ischaemic accident or CV deaths Dropouts: control: 145 (66 withdrew, 11 lost to follow-up, 68 deaths), intervention: 134 (61 withdrew, 7 lost to follow-up, 66 deaths) Available outcomes: deaths, CV death, non fatal MI, stroke, CV events, coronary events, cancer events, Geriatric Depression Scale score, trial authors provided additional information on outcomes and methodology Response to contact: yes (data provided)
Notes	The other factorial intervention was B-vitamins (560 µg methyl-tetrahydrofolate, 3 mg B-6, 20 µg B12) vs placebo

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SU.FOL.OM3 2010 *(Continued)*

	Trial funding: French Ministry of Research, Ministry of Health, Sodexo, Candia, Unilever, Danone, Roche, Merck

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Used computerized block randomisation with stratification by sex, age, prior CVD, and city of residence". "Permuted block randomisation (with a block size randomly selected as 8) was used".
Allocation concealment (selection bias)	Low risk	Allocation of participants was programmed by the statistical co-ordinating centre, who sent participants sufficient treatment capsules for 1 year in an appropriately labelled package
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All subjects and investigators were blinded to treatment allocation", and placebo capsules looked and tasted "identical to the active supplementation". Fish oil flavour was used in placebos.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome investigators were blinded to allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attritions and exclusions were well described. Only 10% loss over 4 years, well balanced
Selective reporting (reporting bias)	Low risk	ISRCTN41926726 registered 2005, 2003 publication on background and rationale, recruitment started April 2003, 2008 protocol, recruitment ended June 2009, 2010 results published. Outcomes in registry entry appear to have been published.
Attention	Low risk	Not likely as capsules used
Compliance	Low risk	Quote: "Allocation to omega 3 fatty acids increased plasma concentrations of omega 3 fatty acids by 37% compared with placebo" (appears statistically significantly different, though not explicitly stated) … "The overall response rate for return of completed questionnaires was 99%, 96%, 94%, and 95% at 6, 12, and 24 months and at the end of the trial, respectively. About 86% of those who returned a questionnaire reported that they were compliant with the study treatment and compliance was similar in all four groups"
Other bias	Low risk	No further bias noted

Tande 2016

Methods	2-arm, parallel RCT (Calanus (marine) oil vs olive oil), 12 months Summary risk of bias: moderate to high
Participants	Healthy male and female volunteers with BMI 25-35 kg/m^2 (mean baseline TG 1.4 mmol/L) N: 64 intervention, 63 control (50 intervention, 50 control analysed) Level of risk for CVD: low Men: 42% intervention, 43 % control Mean age in years (SD): 50.7 (7.7) intervention, 49 (9.4) control

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Tande 2016 *(Continued)*

	Age range: unclear (≥ 18 years) Smokers: not reported Hypertension: not reported Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: Norway Ethnicity: not reported
Interventions	Type: supplement (capsule) Comparison: EPA + DHA vs MUFA Intervention: 2 × 500 mg Calanus oil capsules twice daily to provide a daily dose of 2 g. Supplements were provided by Ayanda AS (Norway) as blister packs of 60 capsules each. The Calanus oil contained approximately 85% wax ester with a sum of neutral lipids > 90%. Dose: 2 g/d EPA + DHA Control: identical capsules of olive oil. Compositional analysis indicated that the FA 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 trial outcome: safety of Calanus oil consumption Dropouts: 14 intervention, 13 control Available outcomes: BMI, waist-hip ratio, BP, pulse, HbA1c, ESR, CRP, lipids, glucose tolerance, insulin, clinical chemistry parameters, adverse events (no CVD events, deaths or other major health outcomes occurred according to trial author reply) Response to contact: trial author replied with methodological and event information
Notes	Trial funding: Calanus AS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "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 that "[r]andomization 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) All outcomes	Low risk	Participants in the placebo group received identical capsules at similar daily doses to the intervention group. However, no information provided as to their smell and taste. Also unclear if investigators were blinded. Trial author reply stated "Each trial 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 trial personnel, and the code was managed by personnel outside the research department. This code was broken after the completion of all

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Tande 2016 *(Continued)*

		analysis with all primary data processed." Blinding of participants only possible for fish plus supplementation vs fish plus placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	All dropouts (~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	Quote: "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

THIS DIET 2008

Methods	The Heart Institute of Spokane diet study (THIS-DIET) RCT- parallel, EPA + DHA vs MUFA, 24 months Summary risk of bias: moderate or high
Participants	Recent survivors of 1st MI (within < 6 weeks) N: 51 intervention, 50 control Level of CVD risk: high Men: 80% intervention, 68% control Mean age in years (SD): 58 (10) intervention, 58 (9) control Age range: unclear Smokers: 25% intervention, 30% control Hypertension: 43% intervention, 50% control (uncontrolled or secondary hypertension excluded) Medications taken by at least 50% of those in the control group: aspirin, statins, beta-blockers, and ACE inhibitors or ARBs Medications taken by 20%-49%: not reported Medications taken by some, but < 20%: not reported Location: USA Ethnicity: intervention 98% white; control 94% white
Interventions	Type: dietary advice (to follow a Mediterranean style diet high in n-3) Comparison: EPA + DHA vs MUFA (biggest dietary change)

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THIS DIET 2008 *(Continued)*

	Intervention: Mediterranean-style diet high in n-3. Dietary counselling group sessions; 2 in 1st 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. Aim to increase omega-3 fat intake to > 0.75% kcal. Dose: ~1.5 g/d omega-3 fat, or 0.31% E by intake assessment 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/d); the Mediterranean-style diet was distinguished by greater omega-3 fat intake (> 0.75% kcal). Compliance: participants were required to attend 6 sessions and only invited but not required to attend extra sessions. 3-day food diaries were reviewed with dietitians. Compliance results not stated **Dietary achievements:** Total fat intake, % E (at 24 months): control 29.7 (SD 9.3), intervention 29.1 (SD 8.6) Saturated fat intake, % E (at 24 months): control 8.0 (SD 2.9), intervention 7.9 (SD 3.2) PUFA intake, % E (at 24 months): control 5.7 (SD 3.1), intervention 5.7 (SD 2.4) PUFA n-3 intake, % E: control 0.46 (SD 0.38), intervention 0.67 (SD 0.35) g/week PUFA n-6 intake: not reported MUFA intake, % E (at 24 months): control 10.3 (SD 5.1), intervention 9.7 (SD 3.6) CHO intake, % E (at 24 months): control 54 (SD 11), intervention 54 (SD 10) Protein intake, % E (at 24 months): control 17 (SD 2), intervention 18 (SD 3) Trans fat intake: not reported Length of intervention: 24 months
Outcomes	Main trial outcome: a composite of endpoints including all-cause and cardiac death, MI, hospital admissions for heart failure, unstable angina, or stroke Dropouts: none for primary outcomes Available outcomes: total and CVD deaths (nil deaths), CV events, stroke, MI, diagnosis of DM, BMI and weight (different at baseline hence not used), waist circumference, lipids, BP, albuminuria, CRP, creatinine and dietary intake (trial authors supplied further data on newly diagnosed DM, glucose and insulin data, cancers, depression, AF) Response to contact: yes further data supplied as above
Notes	The trial compared the 2 intervention groups to a non-randomised usual-care control group (not reported here) Trial funding: no funding details is provided but some reported conflict of interests for one trial author.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sealed envelopes concealing the allocation sequence were prepared by a research co-ordinator. Assignment was stratified by DM status using 10-envelope blocks. Envelopes were selected in the prepared order from a locked drawer by a trial dietitian to assign interventions

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THIS DIET 2008 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	As above but opacity of envelopes is not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Neither the intervention team nor participants could be blinded to dietary assignment.
Blinding of outcome assessment (detection bias) All outcomes	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) All outcomes	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 October 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. CV revascularisation, peripheral revascularisation 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

VITAL 2019

Methods	Vitamin D and omega-3 triaL (VITAL) RCT- parallel 2x2 (LCn3 vs MUFA), median 5.3 years Summary risk of bias: low
Participants	Multi-ethnic population of > 25,000 apparently healthy adults (men ≥ 50 years, women ≥ 55 years) without cancer or CVD at baseline N: 12,933 intervention, 12,938 control (analysed int 12,933, control 12,938) Level of CVD risk: low Men: 49.4% intervention, 49.5% control Mean age in years (SD): 67.2 (7.1) intervention, 67.1 (7.1) control Age range: unclear Smokers: 7.2% intervention, 7.2% control Hypertension: 49.3% intervention, 50.22% control Medications taken by at least 50% of those in the control group: antihypertensives Medications taken by 20%-49%: cholesterol-lowering medication, aspirin, multivitamins

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VITAL 2019 *(Continued)*

	Medications taken by some, but < 20%: post-menopausal hormones Location: USA Ethnicity: intervention 71.5% white, 20.1% black, 3.9% Hispanic, 1.6% Asian; control 71.2% white, 20.2% black, 4.1% Hispanic, 1.5% Asian
Interventions	Type: supplement Comparison: LCn3 vs MUFA Intervention: Arm 1: omega-3, 1 capsule/d, Omacor fish oil, ProNova. EPA + DHA 840 mg/d: 465 mg EPA; 375 mg DHA provided in calendar packs and placebo D3 Arm 3: omega-3 as in Arm 1 and vitamin D3 (1/d, 2000 IU) Control: Arm 2: placebo omega-3 and vitamin D3 (1/d, 2,000IU) Arm 4: placebo omega-3 and placebo D3 Dose: 840 mg/d LCn3, or 0.38% E Compliance: % of participants who reported taking at least 2/3 of capsules - intervention 75.8%, control 75.7% at 5 years. N3 index was measured in ˜10% who volunteered - unclear if representative Dietary achievements: not mentioned Duration of intervention: median 5.3 years, range 3.8-6.1 years
Outcomes	Main trial outcome: reduction in risk for total cancer and CVD events (a composite of MI, stroke, and CV mortality) Dropouts: none for primary outcomes (ITT) Available outcomes: death, CVD death, total stroke (also ischaemic and haemorrhagic stroke, stroke death), total MI, fatal MI, revascularisation (percutaneous coronary intervention and CABG), any cancer diagnosis, breast cancer diagnosis, prostate and colorectal cancer diagnoses, cancer deaths, CVD events (CV death, MI and stroke), side effects (various trial registry entries also suggest diabetes, hypertension, cognitive decline, autoimmune conditions, infections, chronic respiratory disease, depression, bone health, fractures, chronic knee pain, body composition, physical disability, falls, plasma biomarker measures) Response to contact: not yet attempted
Notes	NCT01169259 www.vitalstudy.org Trial funding: NIH with some additional funding e.g. Quest Diagnostics analysed vitamin D, Omacor donated by Pronova BioPharma and matching placebos VITAL substudies (most of which are ongoing) include: • VITAL adiposity-NCT01785004 (assessing effects on adiposity) • VITAL AMD-NCT01782352 (assessing effects on age-related macular degeneration) • VITAL bone-NCT01747447 (assessing effects on bone) • VITAL breast-NCT02239874 (assessing effects on breast tissue and mammographic density) • VITAL Cog-NCT01669915 (assessing effects on cognition) • VITAL Dep-NCT01696435 (assessing effects on depression)

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VITAL 2019 *(Continued)*

- VITAL DKD-NCT01684722 (assessing effects on diabetic kidney disease)
- Vital DM-NCT01633177 (assessing prevention of diabetes)
- VITAL Echo-NCT01630213 (assessing effects on cardiac structure & function)
- VITAL eye-NCT01880463 (assessing effects on dry eye disease)
- VITAL HF-NCT02271230 (assessing effects on heart failure)
- VITAL HT- NCT01653678 (assessing effects on hypertension)
- VITAL infection-NCT01758081 (assessing effects on infectious diseases)
- VITAL Lung-NCT01728571 (assessing effects on respiratory function)
- VITAL fractures-NCT01704859 (assessing effects on fractures)
- VITAL anemia- NCT01632761 (assessing effects on anaemia)
- VITAL Rythm-NCT02178410 (assessing effects on AF)
- VITAL inflam-NCT01351805 (assessing effects on autoimmune disease and inflammation)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was computer-generated within sex, race and 5-year age groups in blocks of 8
Allocation concealment (selection bias)	Low risk	Computer randomisation and lack of direct contact with trial staff probably ensured adequate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo described as "matching", no contact with trial personnel except via mailed questionnaire
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Endpoints committee were unaware of trial-group assignments
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis
Selective reporting (reporting bias)	Low risk	All outcomes of the main trial are reported. Other subtrials have not yet reported.
Attention	Low risk	No contact with trial personnel, little opportunity for attention bias
Compliance	Low risk	Compliance appears acceptable though lipid data were in a small self-selected sample
Other bias	Low risk	None noted

WAHA 2016

Methods	The WAlnut and Healthy Aging study (WAHA) 2-arm, parallel RCT (ALA vs unclear), 2 years Summary risk of bias: moderate to high
Participants	Middle-aged healthy adults

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WAHA 2016 *(Continued)*

	N: 362 intervention, 346 control (only preliminary data on 312 participants from 1 of the 2 centres is available) Level of risk for CVD: low Men: 32.6% intervention, 31.5% control Mean age in years (SD): 69.4 (3.8) intervention, 68.9 (3.5) control Age range: 63-79 (inclusion criteria) Smokers: 4.4% intervention, 1.2% control Hypertension: 52.8% intervention, 52.9% control Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: Spain and USA Ethnicity: not reported
Interventions	Type: supplement (food) Comparison: ALA vs unclear (usual diet plus walnuts vs usual diet) Intervention: 15% of daily energy intake as walnuts. The estimated amount of walnuts ranged from about 30–60 g/day (1-2 ounces). Sachets for daily consumption containing 30 g, 45 g, or 60 g of raw, pieced walnuts were provided as 8-week allotments to be eaten daily, preferably as the raw product, either as a snack or by incorporating them into shakes, yogurts, cereals, or salads. To improve participants' compliance, 1-kg extra walnut allowances were provided every 2 months to take into account family needs. Dose: ˜5 g/d ALA Control: usual diet without walnut Compliance: assessed by dietitians through FFQs, recount of empty packages, and changes in FA concentrations. 95% consumed at least 30 g/d. The proportion of ALA in red blood cells increased in the walnut group by 0.16% (95% CI 0.14 to 0.18) and in the control group by 0.02% (95% CI −0.01 to 0.04; P < 0.001). No data on dietary intake provided. Length of intervention: 2 years (only 1-year results have partly been published)
Outcomes	Main trial outcome: change in cognitive decline (results not yet published) Dropouts: 36 intervention, 21 control (after 1 year) Available outcomes: lipids (for TG and HDL only data states "no between diet differences were observed"), weight (waist circumference was provided but without variance, abstract stated that "there were no significant changes in body fat and waist-to-hip ratio over time and between the two groups"). Trial authors provided data on mortality, CVD events, cancer deaths and diagnoses, IBD diagnosis (no CVD deaths). Cognitive, ophthalmological, inflammatory markers, glycaemic status and other outcomes are not yet available. Response to contact: trial authors provided additional outcome and methodology data.
Notes	Trial funding: Calfornia Walnut Commission The 2-year results as well the full 1-year results are yet to be published. Outcome data reported are for only for participants from 1 centre (USA)

Risk of bias

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WAHA 2016 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized to either the control or walnut group using a computerized random number table with stratification by center, sex, and age range. Couples entering the trial were treated as one number and were randomized into the same group".
Allocation concealment (selection bias)	Low risk	Trial author reply states, "Baseline subject data was collected before randomization. Randomization was done by the clinician, pressing the key on the computer. Since this was a dual center (Barcelona and Loma Linda) trial, a single computer software randomized participants for both the centers."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind. "An unavoidable limitation of the study is not being able to blind participants to the intervention since it consists of a whole food" Rajaram 2017.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Trial author reply states "Study personnel not in contact with the subjects were blind to the treatment assignment. So (lab technicians, ophthalmology technician, neuro cognitive testers) were not aware of the treatment assignment. Of course clinicians who were visited by subjects every two months, knew the treatment assignment". This suggests that allocation was known by physicians, so high risk for event data
Incomplete outcome data (attrition bias) All outcomes	Low risk	38/362 dropouts in intervention group = 10.5%. 34/346 dropouts in control group = 9.8%. Similar dropout in groups over 2 years
Selective reporting (reporting bias)	Unclear risk	Although prospectively registered, no full results paper published – results from conference abstracts only report some secondary outcomes
Attention	Unclear risk	Not enough details
Compliance	Low risk	ALA levels were significantly higher in the intervention group
Other bias	Low risk	None noted

Weinstock-Guttman 2005

Methods	RCT, parallel, (low-fat diet (15% fat) with n-3 fish oils vs AHA Step I diet (fat ≤ 30%) with olive oil supplements), 12 months Summary risk of bias: moderate or high
Participants	Population: adults with MS N: 15 intervention, 16 control (analysed, intervention: 13, control: 14) Level of risk for CVD: low Men: 15.4% intervention, 14.3% control Mean age in years (SD): 39.9 (10.0) intervention, 45.1 (7.7) control Age range: not reported Smokers: not reported

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Weinstock-Guttman 2005 *(Continued)*

	Hypertension: not reported Medications taken by at least 50% of those in the control group: all participants received 400 units of vitamin E, 1 multivitamin tablet (not containing any PUFA) and at least 500 mg calcium/d Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: USA Ethnicity: not reported
Interventions	Type: dietary advice plus supplement Comparison: EPA + DHA vs MUFA (low-fat diet (15% fat) with n-3 fish oils vs AHA Step I diet (fat ≤ 30%) with olive oil supplements) Intervention: 1.98 g/d EPA, 1.32 g/d DHA supplements (EPAX 5500 EE, Tishcon Corp) + low fat diet (< 15% total calories). Dose: 3.3 g/d EPA + DHA Control: one 1 g olive oil placebo capsules 6 times/d, moderate-fat diet (< 30% total calories) (AHA Step 1 diet) Compliance: assessed by individual food records; intervention 69.2% control 66.7% compliance; also at 12 months there was a significant difference between the FA status of the intervention and control groups in terms of EPA (P = 0.027), as described in table 3 of the main paper Duration of intervention: 12 months
Outcomes	Main trial outcome: physical component scale (PCS) Dropouts: 3 intervention, 7 control Available outcomes: Mental Health Inventory, Modified Fatigue Impact Scale, weight change, HDL and LDL cholesterol, adverse events (MS relapse, TNF-alpha, ICAM-1, VCAM-1 and other inflammatory markers, SF-36 not used) Response to contact: no
Notes	Trial funding: National Multiple Sclerosis Society (PP0620T), Mellen Center Foundation and ''The Jog for the Jake'' grant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States "randomly assigned", no further details
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Patients knew the percentage of dietary fat but did not know the assignment of capsules oil supplementation."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported

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Weinstock-Guttman 2005 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Discrepancy in numbers of participants discontinued and numbers analysed. Per-protocol analysis
Selective reporting (reporting bias)	Unclear risk	No protocol or trials register entry found
Attention	Low risk	Treated equally
Compliance	Low risk	Assessed by individual food records; intervention 69.2% control 66.7% compliance. At 12 months there was a significant difference between the EPA status of the intervention and control groups (P = 0.027)
Other bias	Low risk	None noted

WELCOME 2015

Methods	Wessex Evaluation of fatty Liver and Cardiovascular Markers in NAFLD with Omacor Therapy (WELCOME) RCT, parallel, (DHA + EPA vs MUFA), 15-18 months Summary risk of bias: low
Participants	Patients with NAFLD (mean TG 1.4mmol/L, mean BMI 32.0, 9% diabetic) N: 51 intervention, 52 control (analysed, 47 intervention, 48 control) Level of risk for CVD: moderate Men: 49% intervention, 67% control Mean age in years (SD): 48.6 (11.1) intervention, 54 (9.6) control Age range: not reported (18-75 years inclusion criteria) Smokers: 14.3% intervention, 11.8% control Hypertension: not reported Medications taken by at least 50% of those in the control group: lipid-lowering drugs Medications taken by 20%-49% of those in the control group: antihypertensives, metformin (data not provided by group) Medications taken by some, but < 20% of the control group: none reported Location: UK Ethnicity: not reported
Interventions	Type: supplement (Omacor capsules) Comparison: DHA + EPA vs MUFA Intervention: 4 g OMACOR/d (providing 1.84 g EPA, 1.52 g DHA as ethyl esters). Dose: 3.36 g/d EPA + DHA Control: 4 g olive oil capsules/d (providing; ALA 1%, oleic acid 67%, palmitic acid 15%, stearic acid 2%, n-6 fat: 15%)

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WELCOME 2015 *(Continued)*

	Compliance: was assessed by recording the returned unused capsules and quantification of erthrocyte EPA + DHA enrichment (a prespecified threshold of 2% for DHA and threshold of 0.7% for EPA enrichment) Duration of intervention: 15-18 months
Outcomes	Main trial outcome: changes in mean liver fat %, changes in 2 liver fibrosis scores, change in serum biomarkers Dropouts: 4 intervention, 4 control Available outcomes: weight, BMI, lipids, BP, glucose, insulin sensitivity, body fat measures, liver enzymes, HbA1c, serum n-3 FAs, trial authors provided details of diabetes diagnoses, % body fat, BP and carotid intima media thickness Response to contact: yes
Notes	Trial funding: 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. Omacor and placebo were provided by Pronova Biopharma through Abbott Laboratories, Southampton, UK

Risk of bias

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 FA ethyl esters (4 g/d Omacor; Pronova, Sandefjord, Norway) or placebo (4 g/d olive oil) for a minimum of 15 months and a maximum of 18 months (McCormick-2015, p2). Patients were randomised according to standardised procedures (computerised block randomisation) by a research pharmacist at University Hospital Southampton NHS Foundation Trust. Simple randomisation in blocks of 4, either to trial medication or placebo was used. (Scorletti-2014, p 2). (See secondary refs for WELCOME 2015)
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 FA ethyl esters (4 g/d Omacor; Pronova, Sandefjord, Norway) or placebo (4 g/d 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 trial members throughout the trial. (McCormick-2015, p 2). (See secondary refs for WELCOME 2015)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Paper states that only the clinical trials pharmacist was unblinded, and randomisation group allocation was concealed from all trial 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) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	The ITT analysis included all participants randomised who had complete data (baseline and end-of-trial measurements), regardless of whether they were later found to be ineligible, a protocol violator, given the wrong treatment al-

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WELCOME 2015 *(Continued)*

		location, or never treated) (Scorletti 2014, p 4; see secondary ref for WELCOME 2015)
Selective reporting (reporting bias)	Unclear risk	Prospectively registered September 2008, trial start September 2009, end February 2017. Outcome data for cardiac function not yet published, though other CV measures reported – take as ongoing as recent end date
Attention	Low risk	Both groups had the same attention
Compliance	Low risk	Assessed by recording the returned unused capsules and quantification of erthrocyte EPA + DHA enrichment (a prespecified threshold of 2% for DHA and threshold of 0.7% for EPA enrichment). Quote: "Enrichment was highly variable in the DHA+EPA group and 5 and 6 participants in the DHA+EPA group 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 trial in all participants in this group, but 3 and 4 participants reached the thresholds set for the DHA+EPA group, for EPA and DHA, respectively. One participant in the placebo group admitted to taking cod liver oil during the trial and another markedly increased consumption of fish." 10 of 95 non-compliant
Other bias	Low risk	None noted

Zhang 2017

Methods	RCT, parallel, (n-3 DHA vs n-6 LA), 12 months Summary risk of bias: moderate to high
Participants	Otherwise healthy elderly people with mild cognitive impairment N: 120 intervention, 120 control (analysed, intervention: 110 control: 109) Level of risk for CVD: low Men: 35.8% intervention, 34.2% control Mean age in years (SD): 74.5 (2.65) intervention, 74.6 (3.31) control Age range: eligibility criteria were age 65-85 years at trial start Smokers: 59.17% intervention, 61.67% control Hypertension: 9.17% intervention, 7.50% control Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: China Ethnicity: assumed Chinese
Interventions	Type: supplement (capsule) Comparison: DHA vs corn oil (n-6) Intervention: 1 capsule twice a day, with meals, including 2 g algal DHA (45%-55% DHA by weight). Martek Biosciences, Columbia, MD. Dose: ˜1 g/d DHA

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Zhang 2017 *(Continued)*

	Control: corn oil, orange-flavoured and orange colour to protect the trial blind Compliance: participants were asked to return any remaining tablets. Compliance was defined as a ratio (actually taken/should have taken). Achieved 97% for intervention, 95% for control. Serum levels of DHA also measured, DHA at 6 months barely higher in intervention than in controls Duration of intervention: 12 months
Outcomes	Main trial outcome: cognitive function and hippocampal volume Dropouts: 10 intervention, 11 control Available outcomes: mortality, cognitive outcomes and cerebral volume measurements Response to contact: no reply to date
Notes	Trial funding: Chinese Nutrition Society (CNS) Nutrition Research Foundation- DSM Research Fund

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated, also statistics analyst ignorant to this trial used random number table
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo capsules … identical in appearance. All capsules were orange-flavoured and orange colour to protect the trial blind. Packaged into identical pots, each containing 180 capsules, and labelled by staff who were not involved in the trial. A blinding key linked each participant to his or her assigned treatment. This key was kept by an investigator not involved in any data collection or analyses, in a secure electronic file. The code was revealed at the completion of the trial following analyses of the main trial aims.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All project staff were unaware of group assignments until the completion of the trial and after data analysis
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	They did not describe how they imputed missing data (lost contact with participants, but called this an ITT analysis). Overall well matched and not high attrition
Selective reporting (reporting bias)	Low risk	Registered trial prospectively. Outcomes match protocol
Attention	Low risk	"Adherence was encouraged and monitored throughout the trial by telephone assessment at 15 time points, and by blood assay at baseline" 6 months and 12 months. This and assessments were described as same for both arms
Compliance	Unclear risk	Quote: "participants were requested to return any remaining tablets in order to measure compliance, together with the replenishment of capsules for the following month." Compliance … defined "as a ratio = actually taken/should have taken". "Adherence was encouraged and monitored throughout the trial by telephone assessment at 15 time points, and by blood assay at baseline" 6 months and 12 months On compliance tree, leads to "No, because no P values were supplied" therefore risk of compliance bias unclear

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Zhang 2017 *(Continued)*

Other bias	Unclear risk	Although the register says single-blind, the publication very clearly describes a double-blind RCT

Özaydin 2011

Methods	RCT, parallel, (n-3 fish oil + amiodarone vs amiodarone), 12 months Summary risk of bias: moderate or high
Participants	People with persistent AF referred to cardioversion N: 23 intervention, 24 control Level of risk for CVD: high Men: 47.8% intervention, 37.5% control Mean age in years (SD): 62 (12) intervention, 61 (11) control Age range: 37-81 Smokers: not reported Hypertension: 56.5% intervention, 50% control Medications taken by at least 50% of those in the control group: all participants received amiodarone (an antiarrhythmic medication) Medications taken by 20%-49% of those in the control group: beta-blockers, statins, ACE inhibitors and ARBs Medications taken by some, but < 20% of the control group: calcium antagonists Location: Turkey Ethnicity: not reported
Interventions	Type: supplement (capsule) Comparison: LCn3 vs nil Intervention: 2 g/d n-3 PUFA (Marincap, Kocak, Turkey). 4 × 500 mg capsules providing EPA 18% (360 mg/d); DHA 12% (240 mg/d). Dose: 0.6 g/d EPA + DHA Control: no placebo. Amiodarone was given to both groups. Compliance: no details Duration of intervention: 12 months or AF recurrence
Outcomes	Main trial outcome: AF recurrence (endpoint) Dropouts: no details Available outcomes: all-cause mortality (nil death), stroke, TIA, AF recurrence (hyperthyroidism diagnosis, hospitalisation) Response to contact: not yet attempted
Notes	Trial funding: unclear

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Özaydin 2011 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Unclear risk	Quote: "randomised"; no further details
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	All were accounted for
Selective reporting (reporting bias)	Unclear risk	No trial registry entry or protocol found
Attention	Low risk	Both groups seem to have the same care
Compliance	Unclear risk	No information
Other bias	Low risk	None noted

ACE: angiotensin-converting enzyme; **ADAS**: Alzheimer's Disease Assessment Scale; **ADL**: activities of daily living; **AF**: atrial fibrillation; **AHA**: American Heart Association; **ALA:** alpha-linolenic acid; **AMD:** age-related macular degeneration; **BMI**: body mass index; **ALT**: alanine transaminase; **ARB**: angiotensin-receptor blocker; **BMD**: bone mineral density; **BMI**: body mass index; **BP**: blood pressure; **CABG**: coronary artery bypass grafting; **CAD:** coronary artery disease; **CDAI**: Clinical Disease Activity Index; **CHD**: coronary heart disease; **CHO**: carbohydrate; **CI:** confidence interval; **CV**: cardiovascular;**CRP**: C-reactive protein; **CVD**: cardiovascular disease; **DAS**: Disease Activity Score; **DBP**: diastolic blood pressure; **DHA**: docosahexaenoic acid; **DM**: diabetes mellitus; **DMARD**: disease-modifying antirheumatic drugs; **DPA**: docosapentaenoic acid; **E**: dietary energy; **EC:** enteric coated; **ECG**: electrocardiogram; **EDSS**: Expanded Disability Status Scale; **EPA**: eicosapentaenoic acid; **ESR**: erythrocyte sedimentation rate; **FA**: fatty acid; **FFQ**: food frequency questionnaire; **FH**: family history; **FMD**: flow-mediated dilation; **GFR**: glomular filtration rate; **GI:** gastrointestinal; **GLA**: gamma linolenic acid; **HbA1c**: glycated haemoglobin; **HCQ**: hydroxychloroquine; **HDL**: high-density lipoprotein; **H/O**: personal history of; **HOMA-IR**: homeostatic model assessment of insulin resistance; **HRT**: hormone replacement therapy; **HT**: hypertension; **IADL**: instrumental activities of daily living; **IBD**: inflammatory bowel disease; **ICAM-1**: intercellular adhesion molecule 1; **ICD:** implanted cardioverter defibrillator; **IFG:** impaired fasting glucose; **IGT:** impaired glucose tolerance; **IHD:** ischaemic heart disease; **IL**: interleukin;**IMT**: immune-mediated thrombocytopenia; **IQR**: interquartile range; **ITT:** intention-to-treat; **LA:** linolenic acid (an omega-6 fatty acid);**LCn3**: long-chain omega-3 fatty acids; **LDL**: low-density lipoprotein; **MACCE:** major adverse cerebrovascular or cardiovascular events; **MCT:** medium-chain triglycerides; **MD**: mean difference; **MDA**: malondialdehyde; **MI**: myocardial infarction; **MMP-9:** Matrix metallopeptidase 9; **MMSE**: Mini–Mental State Examination; **MS**: multiple sclerosis; **MUFA**: mono-unsaturated fatty acids; **MTX**: methotrexate;**n-3**: omega-3; **NAFLD:** non-alcoholic fatty liver disease; **NASH**: non-alcoholic steatohepatitis; **n-3:** omega-3 fats; **NSAID**: non-steroidal anti-inflammatory drug; **OSDI:** ocular surface disease index; **PAI1**: plasminogen activator inhibitor-1; **PCI:** percutaneous coronary intervention; **PI**: principal investigator;**PPI:** proton pump inhibitors; **PTCA**: percutaneous transluminal coronary angioplasty; **P/S**: polyunsaturated/saturated fat ratio; **PUFA**: polyunsaturated fatty acids; **PVD:** peripheral vascular disease; **QoL**: quality of life; **QUICKI**: quantitative insulin sensitivity check index; **RA**: rheumatoid arthritis; **RCT**: randomised controlled trial; **SBP**: systolic blood pressure; **SD**: standard deviation;**SE**: standard error; **SFA**: saturated fatty acids; **SHBG:** sex hormone-binding globulin; **SSZ**: sulfasalazine; **TAG**: triacylglycerol; **TC:** total cholesterol; **TG**: serum triglycerides; **TIA**: transient ischaemic attack; **TNF**: tumour necrosis factor; **VCAM-1**: vascular cell adhesion molecule 1; **VF:** ventricular fibrillation; **VO2 max:** maximal oxygen uptake; **VT:** ventricular tachycardia; **WHO**: World Health Organization; **WOMAC:** Western Ontario and McMaster Universities Arthritis Index

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Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alekseeva 2000	Trial not randomised
Baleztena 2015	No relevant outcomes measured
Belch 1988	No relevant outcomes measured
Belluzzi 1996	Trial authors confirmed no relevant outcomes measured
Berthoux 1992	Participants not adult humans, or participants unwell at baseline
Borchgrevink 1966	Mean duration of intervention 10 months (range 3-16 months)
Busnach 1998	Participants not adult humans, or participants unwell at baseline
CANN 2015	Intervention is multifactorial (FA/flavanoid blend)
Cappelli 1997	Participants not adult humans, or participants unwell at baseline
CARES 2015	Multisupplement intervention
Cheng 1990a	No appropriate control group
Cheng 1990b	No appropriate control group
Clark 1993	No relevant outcomes measured
Clark 1994	Participants not adult humans, or participants unwell at baseline
Clark 2001	Participants not adult humans, or participants unwell at baseline
Clausen 1989	Multifactorial intervention (cannot separate effects of omega-3 fats from those of other dietary, behavioural or drug interventions)
Diskin 1990	No omega-3 supplementation or dietary advice
Donadio 1994	Participants not adult humans, or participants unwell at baseline
Doyle 2001	Multifactorial intervention (cannot separate effects of omega-3 fats from those of other dietary, behavioural or drug interventions)
Dry 1991	No relevant outcomes measured
Ezaki 1999	Trial not randomised
Feher 2005	Intervention is multifactorial (omega-3 given with coenzyme Q and other compounds vs placebo)
FISH 2012	No clinical outcomes collected (confirmed by corresponding author, 30 November 2016)
Fonolla 2009	Intervention was milk enriched with EPA and DHA but also other vitamins and minerals - multifactorial dietary intervention
Fonolla-Joya 2016	Intervention was milk enriched with EPA and DHA but also other vitamins and minerals - multifactorial dietary intervention

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Study	Reason for exclusion
Franzen 1989	Trial not randomised
Galarraga 2008	9-month intervention period
Gapparova 2000	Trial not randomised
Gazso 1992	No omega-3 supplementation or dietary advice
Geusens 1994	No relevant outcomes measured
Gogos 1998	Participants not adult humans, or participants unwell at baseline
Greatrex 2000	Trial not randomised
Griffin 1999	Trial not randomised
Hamazaki 1984	Participants not adult humans, or participants unwell at baseline
Hansen 1996	Multi-factorial intervention (cannot separate effects of omega-3 fats from those of other dietary, behavioural or drug interventions)
Harris 1991	No appropriate control group
Hashimoto 2012	No relevant outcomes measured
Hashimoto 2016	No relevant outcomes measured
Hawthorne 1992	Trial authors confirmed no relevant outcomes measured
Hogg 1995	Participants not adult humans, or participants unwell at baseline
HOPE epilepsy 2012	Trial recruitment was suspended due to lack of funding
Huang 1996	No relevant outcomes measured
Huang 2008	Intervention was 9 months and no relevant outcomes
InTrePad 2013	Trial never run, withdrawn due to lack of funding (see trials register)
ISRCTN38354847	The proposed 1-year trial was never conducted
Junker 1990	Follow-up not at least a year
Kachorovskii 1977	No omega-3 supplementation or dietary advice
Kanorskii 2007	LCn3 compared to sotalol (group 1), sotalol and perindopril (group 2), sotalol, perindopril and rosuvastatin (group 3), so no useful control group
Karlsson 1998	Multifactorial intervention (cannot separate effects of omega-3 fats from those of other dietary, behavioural or drug interventions)
Kaul 1992	Intervention duration 6 months
Khan 2003	Intervention was 8 months

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Study	Reason for exclusion
Konya 2000	Trial not randomised
Kremer 1995	< 1 year duration
Kruger 1998	No relevant outcomes measured
Kurabayashi 2000	< 1 year duration
Lau 1993	Trial authors confirmed no relevant outcomes
Leaf 1995	Trial not randomised
Lee 2010	Trial authors confirmed no relevant outcomes measured
Leng 1998	Multifactorial intervention (cannot separate effects of omega-3 fats from those of other dietary, behavioural or drug interventions)
LipiDiDiet 2016	Multifactorial dietary intervention that included omega-3 fats but many other nutrition components
Loeschke 1996	No relevant outcomes measured
LUTEGA 2013	Multisupplement intervention
Lyon Diet Heart 1994	Multifactorial intervention (cannot separate effects of omega-3 fats from those of other dietary interventions)
Maachi 1995	Participants not adult humans, or participants unwell at baseline
Macsai 2008	No relevant outcomes measured
Mansel 1990	Not an omega-3 intervention
Mantzaris 1996	No relevant outcomes measured
Mate-Jimenez 1991	Trial authors confirmed no relevant outcomes
Matsuyama 2005	Publication retracted (fraudulent)
Middleton 2002	Unbalanced intervention as the intervention arm contains additional GLA
MoodFOOD 2016	Multisupplement intervention
NAYAB 2017	No planned relevant outcomes. Follow-up < 12 months
NCT01235533	48 weeks' intervention planned in trials register entry
NCT01784042	Not randomised. Trial appears not to have been funded
NU-AGE 2014	Multifactorial dietary intervention
NutriMEMO 2014	Mutlisupplement intervention
OFAMS 2012	No relevant outcomes measured

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Study	Reason for exclusion
Okuda 1996	No appropriate control group
OLIVE 1998	Trial was not funded and did not achieve full recruitment (info provided by co-author)
Oslo DIET HEART 1970	Multifactorial intervention (cannot separate effects of omega-3 fats from those of other dietary, behavioural or drug interventions)
Pogozheva 1997	Trial not randomised
Pogozheva 2000	Trial not randomised
Puri 2008	Trial authors confirmed no relevant outcomes
Quazi 1994	Trial not randomised, < 1 year intervention
Sacks 1994	< 1 year intervention
Saynor 1988	Trial not randomised
Saynor 1992	No appropriate control group
Selvais 1995	Intervention was < 1 year
Shimizu 1995	Trial authors confirmed no relevant outcomes
Singh 1992	Expressions of concern issued by *BMJ* and *Lancet* regarding research by this first author (BMJ 2005; Horton 2005)
Singh 1997	Expressions of concern issued by*BMJ* and *Lancet* regarding research by this first author (BMJ 2005; Horton 2005)
Singh 2002	Expressions of concern issued by*BMJ* and *Lancet* regarding research by this first author (BMJ 2005; Horton 2005)
Tariq 1989	Participants not adult humans, or participants unwell at baseline and intervention is < 1 year
Terano 1999	Trial authors confirmed no relevant outcomes during trial
Tomer 2001	No relevant outcomes. Measured lipids but unclear baseline and endpoint is probably 4 weeks
Torjesen 1997	Multifactorial intervention (cannot separate effects of omega-3 fats from those of other dietary, behavioural or drug interventions)
VSDR 2015	The supplement (Nutrof Omega) contained DHA, Vitamins C, E, B1, B2, B3, B6, B9, B12, Zn, Mn, Se, Cu, lutein and zeaxanthin (multifactorial dietary intervention)
Wheaton 2010	Participants were not a minimum of 18 years old
Yasui 2001	No appropriate control group
Zinger 1987	Trial not randomised

DHA: docosahexaenoic acid; **EPA**: eicosapentaenoic acid; **FA**: fatty acid; **GLA**: gamma linolenic acid

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Characteristics of studies awaiting assessment *[ordered by study ID]*

IRCT20100123003140N21

Methods	RCT
Participants	People aged 50-70 years with Parkinson's disease
Interventions	Each for unclear duration Intervention: daily 2 capsules of omega-3 capsules with an EPA of 180 mg and DHA of 120 mg from the Zahravi Pharmaceuticals Company Control: 2 capsules each day, in combination with soy oil, from Zahrawi Pharmaceuticals Company
Outcomes	Primary: inflammatory factors (IL-1β, IL-6, TNF-α, IL-10) and lipids Secondary: anthropometry, physical activity
Notes	Status unclear as duration is unclear, also unclear whether complete or ongoing but no trial results found

DHA: docosahexaenoic acid; **EPA:** eicosapentaenoic acid; **IL:** interleukin; **RCT:** randomised controlled trial; **TNF:** tumour necrosis factor

Characteristics of ongoing studies *[ordered by study ID]*

AC Omega3 2014

Trial name or title	Aboriginal cardiovascular omega-3 randomised controlled trial (AC Omega3)
Methods	RCT
Participants	Indigenous Australian adults with stable coronary artery disease
Interventions	Each for 12 months: Arm 1: omega-3 (1800 mg/d AlaskOmega: 3 capsules/d: 400 mg EPA and 200 mg DHA) Arm 2: placebo mixed oil capsules (1000 mg/d: 3 capsules/d containing palm oil, gelatin, glycerol, sunflower oil, rapeseed oil, mixed tocopherols, and a "small amount" of fish oil (for taste to aid blinding)
Outcomes	Primary: serum non-HDL-C Secondary: TG, total cholesterol, LDL cholesterol, HDL cholesterol, lipid functionality by cholesterol efflux and CETP, heart rate variability, platelet function and thrombosis markers, inflammation markers, cumulative combined rate of major adverse cardiac events (including death, non-fatal MI, unstable angina, non-fatal stroke, revascularisation and cardiac-related hospital admissions)
Starting date	Registered on trials registry: 10 July 2014 Trial start date: 1 October 2014 Estimated trial completion date: data collection completed November 2017
Contact information	Alex Brown (PI), Wardliparingga Aboriginal Unit, Adelaide, Australia, alex.brown@sahmri.com
Notes	ACTRN12614000732684 Alex Brown contacted in 2016: confirmed trial is actively recruiting

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AC Omega3 2014 *(Continued)*

	Checked for updates and publications, none found, 2 August 2019

ACTRN12618000761268 2018

Trial name or title	A 56 week, double-blind, randomised trial to evaluate the efficacy of testosterone, with and without DHA supplementation on cerebral amyloid load in known brain amyloid-PET positive men with subjective memory complaints
Methods	RCT
Participants	Older men (6-80 years) concerned about their memory
Interventions	Each for 56 weeks Intervention: testosterone 1000 mg/4 mL plus 1720 mg of DHA (4 capsules/d) Control: testosterone 1000 mg/4 mL plus placebo-DHA (Also arm 3: placebo-testosterone plus placebo-DHA)
Outcomes	Primary: brain amyloid levels Secondary: composite score of cognitive functioning derived from scores on California Verbal Learning Test –Second Edition (CVLT-II), Brief Visuospatial Memory Test – Revised (BVMT-R), Logical Memory subtest of the Wechsler Memory Scale-R, Executive Abilities: Methods and Instruments for Neurobehavioral Evaluation and Research Battery (NIH EXAMINER), Boston Naming Test (BNT), Controlled Oral Word Association Test (COWAT), and the WAIS-III Digit Span and Digit Symbol Coding Tasks; as well as a change in global cognition measured by the Montreal Cognitive Assessment (MoCA)
Starting date	Registered on trials registry: 21 March 2018 Trial start date: 16 April 2018 Estimated trial completion date: unclear - likely 2020
Contact information	Kevin Taddei, k.taddei@ecu.edu.au
Notes	ACTRN12618000761268 Added 2 August 2019

AFORRD 2010

Trial name or title	Atorvastatin in factorial with omega-3 fatty acid risk reduction in diabetes (AFORRD)
Methods	RCT
Participants	People with type 2 diabetes with no known CVD and not taking lipid-lowering therapy, adults (> 18 years) N: intervention 397, control 403 (analysed intervention 371, control 361)
Interventions	Each for 12 months: Arm 1: atorvastatin (Lipitor 20 mg/d) and olive oil placebo (2 g/d)

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AFORRD 2010 *(Continued)*

	Arm 2: omega-3 (Omacor 2 g/d: 46% EPA, 38% DHA) and placebo tablets for atorvastatin Arm 3: atorvastatin (Lipitor 20 mg/d) and Omega-3 (Omacor 2 g/d: 46% EPA, 38% DHA) Arm 4: placebo tablets for atorvastatin and olive oil placebo (2 g/d)
Outcomes	Primary: lipid profiles Secondary: phytosterol changes, HbA1c, estimated CVD risk using the UK Prospective Diabetes Study risk engine
Starting date	Registered on trials registry: 4 April 2004 Trial start date: 1 November 2004 Estimated trial completion date: 31 July 2006
Contact information	Rury Holman, Oxford Centre for Diabetes
Notes	ISRCTN76737502 Rury Holman contacted in 2016: confirmed results are not yet published, but planned Checked for updates and publications, none found, 2 August 2019

Bartold 2010

Trial name or title	Clinical efficacy of fish oil as adjunct therapy for patients with chronic periodontitis
Methods	RCT
Participants	People (25-80 years, non-smokers) with newly diagnosed severe but non-aggressive periodontitis
Interventions	Each for 13 months: Arm 1: fish oil rich in EPA (6 × 500 mg capsules/d: 277 mg EPA; 27 mg DHA) and standard periodontal treatment (scaling and debridement) Arm 2: fish oil rich in DHA (6 × 500 mg capsules/d: 66 mg EPA; 258 mg DHA) and standard periodontal treatment Arm 3: soya oil placebo (6 × 500 mg capsules/d) and standard periodontal treatment
Outcomes	Primary: probing pocket depth, clinical attachment level (CAL) Secondary: inflammatory biomarkers in gingival crevicular fluid, erythrocyte omega-3, CRP
Starting date	Registered on trials registry: 23 July 2010 Trial start date: July 2010 Estimated trial completion date: unclear
Contact information	Mark Bartold, University of Adelaide, mark.bartold@adelaide.edu.au
Notes	ACTRN12610000594022 PhD, Boram Park, available giving 4 month outcome data for pilot trial N = 33 participants Mark Bartold written to in 2016. Confirmed preparing full publications for submission

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Bartold 2010 *(Continued)*

	Checked for updates and publications, none found, 2 August 2019

Beyond Aging Project 2015

Trial name or title	Beyond ageing project phase 2: a selective prevention trial using novel pharmacotherapies in an older age cohort at risk for depression
Methods	RCT
Participants	Older adults (60+ years) at risk of depression (K-10 score ranging from 16-29) who initially participated in the first Beyond Ageing Project
Interventions	Each for 12 months: Arm 1: omega-3 (4 capsules, total 2 g/d: 1200 mg EPA and 800 mg DHA) and placebo microcrystalline cellulose (1 capsule) Arm 2: paraffin oil placebo (4 capsules) and sertraline hydrochloride (1 capsule, 50 mg) Arm 3: paraffin oil placebo (4 capsules) and placebo microcrystalline cellulose (1 capsule)
Outcomes	Primary: depressive symptoms (PHQ-9, patient health questionnaire 9) Secondary: cognitive decline, MMSE, brain metabolism, hippocampal volume, anxiety (assessed using GAD-7), disability (WHODAS-II), sleeping problems (PSQI, Pittsburgh Sleep Quality Index), exercise (Active Australian Survey)
Starting date	Registered on trials registry: 12 January 2010 Trial start date: June 2011 Estimated trial completion date: main results expected in 2017
Contact information	Ian Hickie (PI), Brain and Mind Centre, University of Sydney, ian.hickie@sydney.adu.au
Notes	ACTRN12610000032055 Checked for updates and publications, 2 August 2019. Trials registry updated in January 2019, suggests last participant recruited January 2019, recruitment 205 (aim was 450), states that results are not currently available in journal or other format.

Chandrakala 2010

Trial name or title	Long-term effects of a reduced fat diet intervention in pre-diabetes
Methods	RCT
Participants	Participants with pre-diabetes, IFG or IGT, 201 participants discussed in 1 abstract, 134 in a later abstract
Interventions	Each for 3 years: Arm 1: reduced-fat diet (fat content ≤ 20% total energy, ratio of PUFA/SFA 0.8;1.0) Arm 2: normal/control diet

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Chandrakala 2010 *(Continued)*

Outcomes	Incidence of diabetes, BMI, lipids, insulin, plasma glucose, HbA1c, BP, nutritional intake
Starting date	Registered on trials registry: no registration found Trial start date: not stated Estimated trial completion date: not stated
Contact information	Chandrakala Galla, chandrakala.galla@gmail.com; Arpana Gaddam, dr.arpanag@gmail.com
Notes	We wrote to trial authors in 2016: Dr Gaddam confirmed work submitted as a PhD but not published in full. Requested copy of PhD thesis, but no reply to date. Funding: DiabetOmics India Checked for updates and publications, none found, 2 August 2019

ChiCTR-TRC-12002014

Trial name or title	Influence of different sources of n-3 fatty acid on plasma lipid in moderately hypercholesterolaemic subjects
Methods	RCT
Participants	Adults (40-65 years) with mild to moderate hypercholesterolaemia
Interventions	Arm 1: EPA/DHA 1.8 g/d Arm 2: EPA/DHA 3.6 g/d Arm 3: ALA 4 g/d Arm 4: placebo
Outcomes	FAs, lipids, cytokines (IL-6, IL-1a)
Starting date	Registered on trials registry: 13 March 2012 Trial start date: unclear Estimated trial completion date: unclear
Contact information	Su Yixiang, Sun-Yat Sen University, China, suyx@mail.sysu.edu.cn; Zhou Quan, Guangzhou Medical University, joan_zq@126.com
Notes	ChiCTR-TRC−12002014 Su Yixiang and Zhou Quan contacted in 2016: no response Checked for updates and publications, none found, 2 August 2019

DO HEALTH

Trial name or title	Vitamin D3- omega3- home exercise- healthy ageing and longevity trial (DO-HEALTH)

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DO HEALTH *(Continued)*

Methods	RCT
Participants	Community-dwelling adults ≥ 70 years, 50% of seniors enrolled based on a fall in the year before enrolment
Interventions	Each for 3 years: Arm 1: omega-3 (1 g/d, ratio EPA:DHA = 1:2) and vitamin D3 (2000 IU/d) capsules and strength home exercise (3 × 30 min/week) Arm 2: omega-3 (1 g/d, ratio EPA:DHA = 1:2) and vitamin D3 (2000 IU/d) capsules and flexibility home exercise (3 × 30 min/week) Arm 3: omega-3 (1 g/d, ratio EPA:DHA = 1:2) and placebo capsules and strength home exercise (3 × 30 min/week) Arm 4: omega-3 (1 g/d, ratio EPA:DHA = 1:2) and placebo capsules and flexibility home exercise (3 × 30 min/week) Arm 5: placebo and vitamin D3 (2000 IU/d) capsules and strength home exercise (3 × 30 min/week) Arm 6: placebo and vitamin D3 (2000 IU/d) capsules and flexibility home exercise (3 × 30 min/week) Arm 7: placebo and placebo capsules and strength home exercise (3 × 30 min/week) Arm 8: placebo and placebo capsules and flexibility home exercise (3 × 30 min/week)
Outcomes	Primary: non-vertebral fractures, functional decline, BP, cognitive decline, rate of any infection Secondary: other fractures, falls, pain in knee osteoarthritis, musculoskeletal changes, GI symptoms, mental and oral health, QoL, life-expectancy, CVD events, cancer, glucose measures, cost-benefit. All endpoints supported by a DO-HEALTH biomarker trial
Starting date	Registered on trials registry: 6 December 2012 Trial start date: December 2012 Estimated trial completion date: November 2017 Actual trial completion date: January 2018
Contact information	Heike Bischoff-Ferrari (PI), Centre on Aging and Mobility, University of Zurich
Notes	NCT01745263 EudraCT: 2012−001249-41 www.do-health.eu Checked for updates and publications, 2 August 2019. *Lancet* letter by Bischoff in February 2019 gave no results but referred to the "soon to be published DO-HEALTH trial". Website provides no results after December 2017 newsletter, no publications noted

EVAPORATE 2016

Trial name or title	Effect of Vascepa on improving coronary atherosclerosis in people with high triglycerides taking statin therapy (EVAPORATE)
Methods	RCT

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EVAPORATE 2016 *(Continued)*

Participants	Adults (30-85 years) with raised TG (200-499 mg/dL)
Interventions	Each for 18 months: Intervention: EPA (Vascepa) 4 gm/d Control: placebo (not specified)
Outcomes	Primary: progression rates of low attenuation plaque Secondary: morphology of non-calcified coronary atherosclerotic plaque (NCP), markers of inflammation (Lp-PLA2), changes in LDL and HDL cholesterol, composition of non-calcified coronary atherosclerotic plaque (NCP)
Starting date	Registered on trials registry 6 October 2016 Trial start date: 14 September 2016 Estimated trial completion date: September 2019
Contact information	Matthew J. Budoff, Principal Investigator, Los Angeles Biomedical Research Institute
Notes	NCT02926027 Added 2 August 2019

LO-MAPT 2018

Trial name or title	Prevention of cognitive decline in older adults with low DHA/EPA index in red blood cells (LO-MAPT)
Methods	RCT (18 months) followed by 18 months open-label
Participants	Older adults (≥ 70 years) with low DHA/EPA status (red blood cell DHA/EPA index ≤ 4.83%) and subjective memory complaints or family history of Alzheimer's disease
Interventions	Each for 18 months: Intervention: 3/d 1 g softgel vegetarian capsules of DHA-O; each 1 g capsule of DHA-0 providing 324 mg DHA and 185 mg EPA (total daily DHA + EPA dose = 1.53 g/d) Control: 3/d 1 g vegetarian control capsules (containing a 1:1 ratio of corn oil and soy oil)
Outcomes	Primary: composite z-score of cognitive performance Secondary: FCSRT Test, MMSE score, Category Naming Test (CNT)
Starting date	Registered on Trials Registry 1 October 2018 Trial start date: 17 April 2018 Estimated trial completion date: April 2022
Contact information	Bruno Vellas, vellas.b@chu-toulouse.fr
Notes	NCT03691519 Added 2 August 2019

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MAPT PLUS

Trial name or title	Long-term effects of interventional strategies to prevent cognitive decline in elderly (MAPT PLUS)
Methods	RCT – extension of MAPT trial
Participants	Participants of MAPT trial
Interventions	Follow-up 2 year extension of participants in MAPT, after completion of MAPT interventions
Outcomes	Primary: cognitive and functional status (Grober and Buschke test) Secondary: markers of cerebral atrophy, cost-effectiveness
Starting date	Registered on trials registry: 30 December 2011 Trial start date: December 2011 Estimated trial completion date: December 2018
Contact information	Bruno Vellas (PI), University Hospital, Toulouse, vellas.b@chu-toulouse.fr
Notes	NCT01513252 Bruno Vellas written to in 2016- no response Checked for updates and publications, none found, 2 August 2019

MTG 2018

Trial name or title	Improving metabolic health in patients with diastolic dysfunction (MTG)
Methods	RCT 2 x 2
Participants	People aged 40-60 years, who were previously sedentary obese and middle aged, at high risk for development of HF
Interventions	Each for 12 months: Intervention: 2 g/d omega-3 fish oil Control: 1 g/d olive oil Both with yoga or high-intensity exercise (2 x 2)
Outcomes	Primary: myocardial TG Secondary: cardiorespiratory fitness, arterial stiffness, diastolic function and left ventricular mass and volume
Starting date	Registered on trials registry: 27 February 2018 Trial start date: 1 June 2015 Estimated trial completion date: 1 June 2019
Contact information	Benjamin D Levine, University of Texas Southwestern Medical Center

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MTG 2018 *(Continued)*

Notes	NCT03448185 Added 2 August 2019

NCT00010868

Trial name or title	Omega 3 fatty acids in bipolar disorder prophylaxis
Methods	RCT
Participants	People aged 18-65 with bipolar disorder
Interventions	Each for 12 months: Arm 1: omega-3 Arm 2: placebo
Outcomes	Prophylactic efficacy
Starting date	Trial Registration entry: 2 February 2001 Trial start date: July 2000 Estimated trial completion: July 2004
Contact information	Andrew Stoll, Mclean Hospital
Notes	NCT00010868 The PI, Andrew Stoll, appears to have been struck off the medical register in Massachusetts in 2011 (Commonwealth of Massachusetts Board of Registration in Medicine, Adjudicatory Case number 2011−026) so it has not been possible to contact him and no publication of results has been found. Checked for updates and publications, none found, 2 August 2019

NCT00309439

Trial name or title	Studies of serum PSA (prostate specific antigen) to help resolve the current implication of alpha-linolenic acid and prostate cancer
Methods	RCT
Participants	Adults 18-77 years
Interventions	Arm 1: ALA-rich diet Arm 2: control (not detailed)
Outcomes	Prostate specific antigen, AF
Starting date	Registered on trials registry: 29 March 2006 Trial start date: unclear

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NCT00309439 *(Continued)*

	Estimated trial completion date: unclear
Contact information	David Jenkins, University of Toronto, nutritionproject@smh.toronto.on.ca
Notes	NCT00309439 David Jenkins contacted in 2016: confirmed not published in full and data incomplete Checked for updates and publications, none found, 2 August 2019

NCT02211560

Trial name or title	Investigating a phosphatidylserine based dietary approach for the management of mild cognitive impairment
Methods	RCT
Participants	People with mild cognitive impairment (MCI) aged 65-85 years
Interventions	Each for 24 months: Arm 1: phosphatidylserine omega-3 (DHA-enriched) Arm 2: placebo cellulose capsules
Outcomes	Primary: selective reminding test (SRT) Secondary: MMSE, neurological battery test (NBT), dementia (DSM-4 criteria), mini sleep questionnaire (MSQ), Hamilton Anxiety rating scale (HAM-A), safety and adverse events
Starting date	Registered on trials registry: 6 August 2014 Trial start date: September 2014 Estimated trial completion date: September 2019
Contact information	Nadia Niemerzyanski, nadiaN@enzymotec.com; Yael Richter, yaelr@enzymotec.com
Notes	NCT02211560 Checked for updates and publications, 2 August 2019. Trial terminated early due to poor recruitment, 97 recruited, no results posted or published.

NCT02295059

Trial name or title	Omega 3 fatty acids and ERPR(-)HER2(±) breast cancer prevention
Methods	RCT
Participants	Women at risk for recurrent breast cancer- with prior diagnosis of stage 0-III breast cancer and completion of surgery, chemotherapy or trastuzumab or radiation therapy
Interventions	Each for 12 months: Arm 1: omega-3 high-dose capsules (5 g/d EPA + DHA)

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NCT02295059 *(Continued)*

	Arm 2: omega-3 low-dose capsules (0.9 g/d EPA + DHA)
Outcomes	Primary: breast adipose tissue metabolites Secondary: cytomorphology or cell proliferation of mammary epithelial cells, DNA promoter methylation and pro-inflammatory gene expression in mammary epithelial and adipose tissue
Starting date	Registered on trials registry: 14 October 2014 Trial start date: August 2014 Estimated trial completion date: January 2020
Contact information	Anitra Sumbry, anitra.sumbry@osumc.edu; Lisa Yee (PI), Ohio State University
Notes	NCT02295059 Checked for updates and publications, none found, 2 August 2019

NCT02719327

Trial name or title	Impact of icosapent ethyl on Alzheimer's disease (AD) biomarkers in preclinical adults
Methods	RCT
Participants	Cognitively healthy adults aged 50-70 years whose parents had AD
Interventions	Each for 18 months: Arm 1: icosapent ethyl EPA (Vascepa) 4 g/d gel capsule Arm 2: matching gel capsule placebo
Outcomes	Primary: cerebral blood flow by MRI Secondary: cerebrospinal fluid biomarkers of AD, cognitive performance (Preclinical Alzheimer's Cognitive Composite, PACC)
Starting date	Registered on trials registry: 21 March 2016 Trial start date: December 2016 Estimated trial completion date: November 2021
Contact information	Cynthia Carlsson, cynthia.carlsson@va.gov; Elena Beckman, elena.beckman@va.gov
Notes	NCT02719327 Checked for updates and publications, none found, 2 August 2019

NCT03784963

Trial name or title	Efficacy of omega-3 fatty acid therapy in preventing gastrointestinal bleeding in patients with continuous-flow left ventricular assist devices (CF-LVAD)
Methods	RCT

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NCT03784963 *(Continued)*

Participants	Adults (aged ≥ 18 years) with CF-LVAD or scheduled to receive a CF-LVAD implant
Interventions	Each for 1 year: Intervention: 4 g/d Nature Made Ultra Omega-3 fish oil Control: no fish oil
Outcomes	Primary: markers of angiogenesis including angiopoietin-1, angiopoietin-2, VEGF, TNF alpha and CRP Secondary: GI bleeding, changes in the microbiome
Starting date	Registered on trials registry: 24 December 2018 Trial start date: 23 January 2019 Estimated trial completion date: 1 January 2021
Contact information	Nir Uriel, nuriel@medicine.bsd.uchicago.edu
Notes	NCT03784963 Added 2 August 2019

NCT03806426

Trial name or title	Effect of EPA-FFA on polypectomy in familial adenomatous polyposis
Methods	RCT
Participants	Adults (18-65 years) with familial adenomatous polyposis
Interventions	Each for 2 years: Intervention: Eicosapentaenoic acid free fatty acid (EPA-FFA), 500 mg capsule, 2 x 500 mg capsules to be taken twice daily for 24 months Control: placebo, 500 mg capsule, 2 x 500 mg capsules to be taken twice daily for 24 months
Outcomes	Primary: total number of polypectomies and numbers of proctectomies at 24 months Secondary: change in polyp number and change in InSIGHT Polyposis Staging System (IPSS) score
Starting date	Registered on trials registry: 16 January 2019 Trial start date: 5 December 2018 Estimated trial completion date: 1 March 2021
Contact information	Justin Slagel, CEO, info@slapharma.com

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NCT03806426 *(Continued)*

Notes	NCT03806426 First added 2 August 2019

OMEMI 2014

Trial name or title	Omega-3 fatty acids in elderly patients with myocardial infarction study (OMEMI)
Methods	RCT
Participants	Elderly people (70-82 years) with acute MI
Interventions	Each for 24 months: Arm 1: omega-3 capsules, 3/d (Pikasol, total of 1.8 g/d EPA + DHA) and standard therapy Arm 2: corn oil placebo, 3/d and standard therapy
Outcomes	Primary: composite of total mortality, first non-fatal recurring acute MI, stroke and revascularisation Secondary: new onset AF, adipose tissue, serum FAs, markers of endothelial function, inflammation, coagulation and fibrinolytic activity, genes associated with atherothrombosis
Starting date	Registered on trials registry: 16 April 2013 Trial start date: November 2012 Estimated trial completion date: November 2019
Contact information	Svein Solheim, Center for Clinical Heart Research, Oslo University Hospital, arnljot.tveit@vestre-viken.no
Notes	NCT01841944 Checked for updates and publications, none found, 2 August 2019

POSEIDON 2018

Trial name or title	Pilot study of omega-3 and vitamin D in high-dose in type I diabetic patients (POSEIDON)
Methods	RCT
Participants	Adults with new or established type 1 diabetes
Interventions	For 1 year Intervention: omega-3 fats and vitamin D Control: vitamin D
Outcomes	Primary: Mixed Meal Tolerance Test (MMTT) Secondary: haemoglobin A1c, insulin requirements, adverse events
Starting date	Registered on trials registry: 23 January 2018

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POSEIDON 2018 *(Continued)*

	Trial start date: 23 July 2018 Estimated trial completion date: December 2023
Contact information	David Baidal, dbaidal@med.miami.edu
Notes	NCT03406897 Added 2 August 2019

Shinto 2015

Trial name or title	N-3 PUFA for vascular cognitive aging
Methods	RCT
Participants	Older adults (≥ 80 years) at high risk for cognitive decline and dementia of Alzheimer's type
Interventions	Each for 3 years: Arm 1: omega-3 fish oil (1.65 g/d EPA + DHA) Arm 2: soybean oil placebo (1.65 g/d)
Outcomes	Primary: total cerebral white matter volume Secondary: biomarkers of endothelial health, total brain atrophy, medial temporal lobe atrophy, ventricular expansion, trail making test part B, digit symbol WAIS-R, cerebral blood flow, fractional anisotropy within frontal gyri
Starting date	Registered on trials registry: 24 September 2013 Trial start date: May 2014 Estimated trial completion date: August 2019
Contact information	Alena Borgatti, borgatti@ohsu.edu; James Dursch, dursch@ohsu.edu; Gene Bowman and Lynne Shinto (PIs), Oregon Health and Science University
Notes	NCT01953705 Checked for updates and publications, none found, 2 August 2019

STRENGTH 2015

Trial name or title	A long-term outcomes study to assess statin residual risk reduction with EpaNova in high CVD risk patients with hypertriglyceridemia (STRENGTH)
Methods	RCT
Participants	Adults with hypertriglyceridaemia and low HDL and high risk for CVD
Interventions	Each for 3-5 years Arm 1: omega-3 carboxylic acid capsule (Epanova, not < 800 mg/g) and statin (once daily)

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STRENGTH 2015 *(Continued)*

	Arm 2: corn oil placebo capsule and statin (once daily)
Outcomes	Primary: time to 1st occurrence of any component of the composite MACE (CVD death, nonfatal MI, nonfatal stroke, emergent/elective coronary revascularisation, hospitalisation for unstable angina) Secondary: composite measure of CVD events that include the first occurrence of CVD death, non-fatal MI and non-fatal stroke; composite measure of coronary events that include the first occurrence of cardiac death; first occurrence of individual components of MACE; time to CVD death. Other measures include: all-cause mortality, new AF, thrombotic events, heart failure events
Starting date	Trial Registration entry: 2 April 2014 Trial start date: October 2014 Estimated trial completion: September 2020
Contact information	AstraZeneca Clinical Study Information Centre, information.center@astrazeneca.com. PIs Steven Nissen (Cleveland Clinic), Michael Lincoff (Cleveland Clinic) Stephen Nicholls (Adelaide Clinical Research)
Notes	NCT02104817 EudraCT: 2014−001069−28 Checked for updates and publications, none found, 2 August 2019

SUPERIORSVG 2010

Trial name or title	Surgical and pharmacological novel interventions to improve overall results of saphenous vein graft patency in coronary artery bypass grafting surgery (SUPERIOR SVG)
Methods	RCT
Participants	Adults having CABG using SVG
Interventions	Each for 12 months: Arm 1: fish oil supplements (2 × 1 g/d Ocean Nutrition capsules: 55% fish oils EPA:DHA 33%:22%) and SVG conventionally harvested Arm 2: placebo and SVG conventionally harvested Arm 3: fish oil supplements (2 × 1 g/d Ocean Nutrition capsules: 55% fish oils EPA:DHA 33%:22%) and SVG no-touch harvest Arm 4: placebo and SVG no-touch harvest
Outcomes	Primary: proportion of grafts occluded Secondary: significant stenosis, adverse SVG harvesting events, composite outcome of all-cause mortality, non-fatal MI and repeat revascularisation
Starting date	Registered on trials registry: 12 January 2010 Trial start date: July 2011 Estimated trial completion date: December 2016
Contact information	Stephen Fremes, Sunnybrook Health Sciences Centre (PI)

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SUPERIORSVG 2010 *(Continued)*

Notes	NCT01047449 Checked for updates and publications, 2 August 2019. Results of the surgical intervention found (Deb 2019), but no results yet for the omega-3 intervention.

UMIN000012825

Trial name or title	Effect of PUFA on vascular healing process in hypercholesterolemic patients with ACS
Methods	RCT
Participants	Hypercholesterolemic patients (20-80 years) with acute coronary syndrome who have received successful OCT-guided PCI
Interventions	Each for 12 months: Arm 1: intensive lipid-lowering therapy with both statin and EPA + DHA Arm 2: intensive lipid-lowering therapy with both statin and EPA Arm 3: standard lipid-lowering therapy with statins
Outcomes	Primary: changes in OCT parameter Secondary: lipids, serum plasma profile, inflammatory parameters, adverse CVD events
Starting date	Registered on trials registry: 1 February 2014 Trial start date: 1 February 2014 Estimated trial completion date: not stated Date of final participant recruitment: 30 June 2019
Contact information	Shiro Uemura (PI), Nara Medical University, Japan, suemura@naramed-u.ac.jp
Notes	UMIN000012825 Checked for updates and publications, none found, 2 August 2019

ACS: acute coronary syndrome; **AD**: Alzheimer's disease; **AF**: atrial fibrillation; **BMI**: body mass index; **BP:** blood pressure; **CABG**: coronary artery bypass graft; **CETP**: cholesteryl ester transfer protein; **CHD**: coronary heart disease; **CRP:** C-reactive protein; **CVD**: cardiovascular disease; **DHA**: docosahexaenoic acid; **EPA**: eicosapentaenoic acid; **FA:** fatty acid(s); **FCSRT:** Free and Cued Selective Reminding Test; **GAD-7**: generalised anxiety disorder 7; **GI:** gastrointestinal; **HbA1c**: glycated haemoglobin; **HDL**: high-density lipoprotein; **IFG**: impaired fasting glucose; **IGT**: impaired glucose tolerance; **IL**: interleukin; **LDL**: low-density lipoprotein; **MACE**: major adverse coronary event; **MI**: myocardial infarction; **MMSE:** Mini–Mental State Examination; **MRI**: magnetic resonance imaging; **OCT**: optical coherence tomography; **OSDI**: ocular surface disease index; **PCI**: percutaneous coronary intervention; **PHQ-9**: patient health questionnaire 9; **PI**: principal investigator; **PSA**: prostate specific antigen; **PSQI**: Pittsburgh Sleep Quality Index; **PUFA**: polyunsaturated fatty acids; **QoL:** quality of life; **RCT**: randomised controlled trial; **SFA**: saturated fatty acids; **SVG**: saphenous vein graft; **TG:** serum triglycerides; **TNF:** tumour necrosis factor; **VEGF:** vascular endothelial growth factor; **WAIS-R:** Wechsler Adult Intelligence Scale - revised

DATA AND ANALYSES

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Comparison 1. High vs low LCn3 omega-3 fats (primary outcomes)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality (overall) - LCn3	45	143693	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.93, 1.01]
2 All-cause mortality -LCn3 - sensitivity analysis (SA) fixed-effect	45	143693	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.93, 1.00]
3 All-cause mortality - LCn3 - SA by summary risk of bias	45		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Low summary risk of bias	19	75741	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.95, 1.04]
3.2 Moderate or high summary risk of bias	26	67952	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.87, 1.01]
4 All-cause mortality - LCn3 - SA by compliance and study size	44		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 SA - low risk of compliance bias	22	50929	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.90, 1.05]
4.2 SA - 100+ randomised	41	143437	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.93, 1.01]
5 All-cause mortality - LCn3 - subgroup by dose	45	143693	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.93, 1.01]
5.1 LCn3 ≤ 150 mg/d	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 LCn3 > 150 ≤ 250 mg/d	1	407	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.27, 2.18]
5.3 LCn3 > 250 ≤ 400 mg/d	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.56, 0.92]
5.4 LCn3 > 400 ≤ 2400 mg/d	31	129505	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.94, 1.03]
5.5 LCn3 > 2.4 ≤ 4.4 g/d	10	11466	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.77, 1.04]
5.6 LCn3 > 4.4 g/d	2	282	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.03, 3.08]
6 All-cause mortality - LCn3 - subgroup by replacement	45		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 LCn3 replacing SFA	6	3988	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.56, 0.91]
6.2 LCn3 replacing MUFA	18	88062	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.93, 1.01]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.3 LCn3 replacing N-6	8	2601	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.51, 1.10]
6.4 LCn3 replacing CHO	1	281	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.05, 5.65]
6.5 LCn3 replacing nil/low n-3 placebo	11	47844	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.86, 1.08]
6.6 LCn3 replacement unclear	5	4000	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.77, 1.43]
7 All-cause mortality - LCn3 - subgroup by intervention type	45	143693	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.93, 1.01]
7.1 Dietary advice	3	5554	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.60, 1.35]
7.2 Supplemental foods	2	5039	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.84, 1.24]
7.3 Supplements (capsule)	39	132895	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.93, 1.00]
7.4 Any combination	1	205	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.11, 3.79]
8 All-cause mortality - LCn3 - subgroup by duration	45	143693	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.93, 1.01]
8.1 Medium duration 1 to < 2 years in study	20	10981	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.82, 1.29]
8.2 Medium-long duration: 2 to < 4 years in study	15	29519	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.86, 0.96]
8.3 Long duration: ≥ 4 years in study	10	103193	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.96, 1.05]
9 All-cause mortality - LCn3 - subgroup by primary or secondary prevention	45	143693	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.93, 1.01]
9.1 Primary CVD prevention	21	83797	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.95, 1.05]
9.2 Secondary CVD prevention	23	51736	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.88, 1.03]
9.3 Mixed primary & secondary CVD prevention	1	8160	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.75, 1.03]
10 All-cause mortality - LCn3 - subgroup by statin use	45	143693	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.93, 1.01]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 LCn3 ≥ 50% of control group on statins	11	66834	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.92, 1.04]
10.2 LCn3 < 50% of control group on statins	29	73719	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.91, 1.03]
10.3 LCn3 - use of statins unclear	5	3140	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.58, 1.63]
11 All-cause mortality - LCn3 - subgroup by baseline TG	45	143693	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.93, 1.01]
11.1 Baseline TG not restricted	43	135413	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.94, 1.01]
11.2 Baseline TG raised	2	8280	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.54, 1.36]
12 All-cause mortality - LCn3 - subgroup by baseline DM	45	143693	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.93, 1.01]
12.1 Normal diabetes risk	40	94761	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.92, 1.04]
12.2 Diabetes risk factors at baseline	2	12787	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.90, 1.06]
12.3 Diabetes at baseline	3	36145	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.89, 1.03]
13 Cardiovascular mortality (overall) - LCn3	29	117837	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.86, 0.99]
14 CVD mortality - LCn3 - SA fixed-effect	29	117837	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.88, 0.97]
15 CVD mortality - LCn3 - SA by summary risk of bias	29		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
15.1 Low risk of bias	12	71019	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.88, 1.03]
15.2 Moderate/high risk of bias	17	46818	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.80, 1.02]
16 CVD mortality - LCn3 - SA by compliance and study size	28		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
16.1 SA - low risk of compliance bias	15	47829	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.82, 1.04]
16.2 SA - 100+ randomised	24	91710	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.85, 1.00]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17 CVD mortality - LCn3 - subgroup by dose	30	117938	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.86, 0.99]
17.1 LCn3 ≤ 150 mg/d	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.2 LCn3 > 150 ≤ 250 mg/d	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.3 LCn3 > 250 ≤ 400 mg/d	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.53, 0.91]
17.4 LCn3 > 400 ≤ 2400 mg/d	21	105477	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.88, 1.03]
17.5 LCn3 > 2.4 ≤ 4.4 g/d	6	10146	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.70, 1.01]
17.6 LCn3 > 4.4 g/d	2	282	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.03, 3.08]
18 CVD mortality - LCn3 - subgroup by replacement	30		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
18.1 N-3 replacing SFA	3	2537	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.53, 0.90]
18.2 N-3 replacing MUFA	15	86128	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.86, 1.00]
18.3 N-3 replacing N-6	4	1435	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.41, 1.19]
18.4 N-3 replacing carbohydrates/sugars	1	281	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.12, 4.07]
18.5 N-3 replacing nil/low n-3 placebo	8	27252	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.74, 0.93]
18.6 Replacement unclear	3	3388	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.13, 2.88]
19 CVD mortality - LCn3 - subgroup by intervention type	29	117837	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.86, 0.99]
19.1 Dietary advice	2	5147	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.52, 1.71]
19.2 Supplemental foods	2	5039	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.72, 1.32]
19.3 Supplements (capsule)	25	107651	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.87, 0.97]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.4 Any combination	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
20 CVD mortality - LCn3 - subgroup by duration	29	117837	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.86, 0.99]
20.1 Medium duration 1 to < 2 years in study	11	6712	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.64, 1.37]
20.2 Medium-long duration: 2 to < 4 years in study	10	26736	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.82, 0.95]
20.3 Long duration: ≥ 4 years in study	8	84389	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.86, 1.07]
21 CVD mortality - LCn3 - subgroup by primary or secondary prevention	29	117837	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.86, 0.99]
21.1 Primary prevention	10	59817	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.86, 1.02]
21.2 Secondary prevention	18	49841	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.83, 1.06]
21.3 Mixed primary & secondary prevention	1	8179	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.67, 0.99]
22 CVD mortality - LCn3 - subgroup by statin uses	29	117837	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.86, 0.99]
22.1 LCn3 - ≥ 50% of control group on statins	8	47653	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.82, 1.04]
22.2 LCn3 - < 50% of control group on statins	18	69296	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.84, 1.03]
22.3 LCn3- Use of statins unclear	3	888	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.13, 2.05]
23 CVD mortality - LCn3 - subgroup by baseline TG	29	117837	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.86, 0.99]
23.1 Baseline TG not restricted	27	109538	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.87, 1.01]
23.2 Baseline TG raised	2	8299	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.67, 0.99]
24 CVD mortality - LCn3 - subgroup by baseline DM	29	117837	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.86, 0.99]
24.1 Normal diabetes risk	24	68856	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.84, 1.03]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24.2 Diabetes risk factors at baseline	2	12817	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.88, 1.10]
24.3 Diabetes at baseline	3	36164	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.75, 1.01]
25 Cardiovascular events (overall) - LCn3	43	140482	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.92, 1.01]
26 CVD events - LCn3 - SA fixed effect	43	140482	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.94, 0.99]
27 CVD events - LCn3 - SA by summary risk of bias	43		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
27.1 Low summary risk of bias	16	73000	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.95, 1.02]
27.2 Moderate or high summary risk of bias	27	67482	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.86, 1.02]
28 CVD events - LCn3 - SA by compliance and study size	42		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
28.1 SA - low risk of compliance bias	18	47699	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.81, 1.06]
28.2 SA - 100+ randomised	38	140162	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.92, 1.02]
29 CVD events - LCn3 - subgroup by dose	43		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
29.1 LCn3 ≤ 150 mg/d	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
29.2 LCn3 > 150 ≤ 250 mg/d	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
29.3 LCn3 > 250 ≤ 400 mg/d	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.88, 1.05]
29.4 LCn3 > 400 ≤ 2400 mg/d	31	127458	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.93, 1.03]
29.5 LCn3 > 2.4 ≤ 4.4 g/d	9	10644	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.73, 1.14]
29.6 LCn3 > 4.4 g/d	3	422	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.65, 1.81]
30 CVD events - LCn3 - subgroup by replacement	43		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
30.1 N-3 replacing SFA	4	2888	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.87, 1.04]
30.2 N-3 replacing MUFA	18	86416	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.94, 1.00]
30.3 N-3 replacing n-6	7	2180	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.86, 1.32]
30.4 N-3 replacing carbohydrates/sugars	1	258	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.12, 3.98]
30.5 N-3 replacing nil/low n-3 placebo	13	48169	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.84, 1.06]
30.6 Replacement unclear	4	3631	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.50, 1.64]
31 CVD events - LCn3 - subgroup by intervention type	43	140482	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.92, 1.01]
31.1 Dietary advice	3	5248	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.86, 1.49]
31.2 Supplemental foods	2	5039	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.89, 1.17]
31.3 Supplements (capsule)	38	130195	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.90, 1.00]
31.4 Any combination	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
32 CVD events - LCn3 - subgroup by duration	43	140482	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.92, 1.01]
32.1 Medium duration 1 to < 2 years in study	19	8396	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.69, 1.07]
32.2 Medium-long duration: 2 to < 4 years in study	15	29052	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.95, 1.03]
32.3 Long duration: ≥ 4 years in study	9	103034	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.88, 1.03]
33 CVD events - LCn3 - subgroup by primary or secondary prevention	43	140482	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.92, 1.01]
33.1 Primary prevention of CVD	19	81391	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.91, 1.02]
33.2 Secondary prevention	23	50912	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.93, 1.05]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
33.3 Mixed primary & secondary prevention	1	8179	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.68, 0.85]
34 CVD events - LCn3 - subgroup by statin use	43	140482	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.92, 1.01]
34.1 LCn3 - ≥ 50% of control group on statins	11	66333	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.86, 1.01]
34.2 LCn3 - < 50% of control group on statins	25	71031	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.93, 1.04]
34.3 LCn3 - use of statins unclear	7	3118	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.51, 1.43]
35 CVD events - LCn3 - subgroup by baseline TG	43	140478	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.91, 1.00]
35.1 Baseline TG not restricted	41	135344	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.92, 1.01]
35.2 Baseline TG raised	3	5134	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.67, 0.90]
36 CVD events - LCn3 - subgroup by baseline diabetes	43	140479	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.91, 1.00]
36.1 Normal diabetes risk	37	91281	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.93, 1.04]
36.2 Diabetes risk factors at baseline	4	16426	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.72, 1.07]
36.3 Diabetes at baseline	3	32772	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.76, 1.05]
37 Coronary heart disease mortality (overall) - LCn3	24	127378	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.81, 1.00]
38 CHD mortality - LCn3 - SA fixed effect	24	127378	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.86, 0.98]
39 CHD mortality - LCn3 - SA by summary risk of bias	24		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
39.1 Low summary risk of bias	10	70259	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.76, 1.04]
39.2 Moderate or high summary risk of bias	14	57119	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.79, 1.06]
40 CHD mortality - LCn3 - SA by compliance and study size	23		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
40.1 SA - low risk of compliance bias	10	38809	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.67, 1.03]
40.2 SA - 100+ randomised	22	114762	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.77, 0.98]
41 CHD mortality - LCn3 - SA omitting cardiac death	18	106676	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.73, 0.90]
41.1 Low risk of bias	7	53373	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.68, 0.97]
41.2 Moderate/high risk of bias	11	53303	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.71, 0.94]
42 CHD mortality - LCn3 - subgroup by dose	24	127378	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.81, 1.00]
42.1 LCn3 ≤ 250 mg/d	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
42.2 LCn3 > 250 ≤ 400 mg/d	2	5147	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.50, 1.74]
42.3 LCn3 > 400 ≤ 2400 mg/d	18	121329	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.83, 0.99]
42.4 LCn3 > 2.4 ≤ 4.4g/d	3	822	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.49, 1.78]
42.5 LCn3 > 4.4g/d	1	80	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.57]
43 CHD mortality - LCn3 - subgroup by replacement	23		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
43.1 N-3 replacing SFA	3	2514	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.51, 0.88]
43.2 N-3 replacing MUFA	13	85492	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.81, 1.00]
43.3 N-3 replacing n-6	3	1409	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.33, 1.09]
43.4 N-3 replacing carbohydrates/sugars	1	258	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.23]
43.5 N-3 replacing nil/low n-3 placebo	7	37651	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.70, 0.94]
44 CHD mortality - LCn3 - subgroup by intervention type	24	127378	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.81, 1.00]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
44.1 Dietary advice	2	5147	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.50, 1.74]
44.2 Supplemental foods	1	4837	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.69, 1.33]
44.3 Supplements (capsule)	21	117394	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.83, 0.98]
44.4 Any combination	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
45 CHD mortality - LCn3 - subgroup by duration	24	127378	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.81, 1.00]
45.1 Medium duration 1 to < 2 years in study	7	5978	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.58, 1.23]
45.2 Medium-long duration: 2 to < 4 years in study	9	26545	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.77, 0.94]
45.3 Long duration: ≥ 4 years in study	8	94855	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.83, 1.16]
46 CHD mortality - LCn3 - subgroup by primary or secondary prevention	24	127378	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.81, 1.00]
46.1 Primary prevention	8	77676	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.75, 1.07]
46.2 secondary prevention	16	49702	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.79, 1.04]
47 CHD mortality - LCn3 - subgroup by statin use	24	127378	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.81, 1.00]
47.1 LCn3 - ≥ 50% of control group on statins	7	58041	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.78, 1.09]
47.2 LCn3 - < 50% of control group on statins	16	69079	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.77, 1.03]
47.3 LCn3 - use of statins unclear	1	258	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.23]
48 CHD mortality - LCn3 - subgroup by CAD history	24	127378	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.81, 1.00]
48.1 Previous CAD	11	29074	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.71, 1.10]
48.2 No previous CAD	13	98304	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.84, 1.03]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
49 CHD mortality - LCn3 - subgroup by baseline TG	24	127378	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.81, 1.00]
49.1 Baseline TG not restricted	23	127258	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.81, 1.00]
49.2 Baseline TG raised	1	120	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.01, 4.05]
50 CHD mortality - LCn3 - subgroup by baseline DM	24	127378	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.81, 1.00]
50.1 Normal diabetes risk	20	86599	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.77, 0.99]
50.2 Diabetes risk factors at baseline	2	12794	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.92, 1.25]
50.3 Diabetes at baseline	2	27985	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.67, 1.25]
51 Coronary heart disease events (overall) - LCn3	32	134116	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.85, 0.97]
52 CHD events - LCn3 - SA fixed effect	32	134116	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.89, 0.96]
53 CHD events - LCn3 - SA by summary risk of bias	32		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
53.1 Low summary risk of bias	14	71578	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.82, 1.05]
53.2 Moderate or high summary risk of bias	18	62538	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.83, 0.97]
54 CHD events - LCn3 - SA by compliance and study size	31		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
54.1 SA - low risk of compliance bias	14	47497	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.74, 0.95]
54.2 SA - 100+ randomised	29	133899	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.84, 0.95]
55 CHD events - LCn3 - subgroup by dose	32		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
55.1 LCn3 ≤ 150 mg/d	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
55.2 LCn3 > 150 ≤ 250 mg/d	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
55.3 LCn3 > 250 ≤ 400 mg/d	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.82, 1.04]
55.4 LCn3 > 400 ≤ 2400 mg/d	23	122081	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.87, 0.99]
55.5 LCn3 > 2.4 ≤ 4.4 g/d	6	9655	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.63, 1.22]
55.6 LCn3 > 4.4 g/d	3	422	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.54, 1.85]
56 CHD events - LCn3 - subgroup by replacement	32		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
56.1 N-3 replacing SFA	3	2514	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.16, 1.75]
56.2 N-3 replacing MUFA	17	86305	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.89, 1.02]
56.3 N-3 replacing n-6	4	1549	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.78, 1.53]
56.4 N-3 replacing carbohydrates/sugars	1	258	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 2.07]
56.5 N-3 replacing nil/low n-3 placebo	9	46105	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.72, 0.92]
56.6 Replacement unclear	2	445	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.45, 2.17]
57 CHD events - LCn3 - subgroup by intervention type	32	134116	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.85, 0.97]
57.1 Dietary advice	2	2134	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.67, 1.52]
57.2 Supplemental foods	2	5039	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.75, 1.20]
57.3 Supplements (capsule)	28	126943	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.83, 0.98]
57.4 Any combination	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
58 CHD events - LCn3 - subgroup by duration	32	134116	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.85, 0.97]
58.1 Medium duration 1 to < 2 years in study	11	7009	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.64, 1.25]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
58.2 Medium-long duration: 2 to < 4 years in study	13	27187	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.90, 0.99]
58.3 Long duration: ≥ 4 years in study	8	99920	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.74, 0.98]
59 CHD events - LCn3 - subgroup by primary or secondary prevention	32	134116	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.85, 0.97]
59.1 Primary prevention of CVD	13	78716	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.75, 1.02]
59.2 Secondary prevention of CVD	18	47221	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.91, 0.99]
59.3 Mixed primary & secondary prevention	1	8179	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.60, 0.82]
60 CHD events - LCn3 - subgroup by statin use	32	134116	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.85, 0.97]
60.1 LCn3 - ≥ 50% of control group on statins	11	66679	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.80, 1.07]
60.2 LCn3 - < 50% of control group on statins	18	66545	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.89, 0.97]
60.3 LCn3 - use of statins unclear	3	892	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.11, 3.83]
61 CHD events - LCn3 subgroup by CAD history	32	134116	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.85, 0.97]
61.1 Previous CAD	13	26409	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.87, 1.02]
61.2 No previous CAD	18	99528	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.86, 1.00]
61.3 Mixed - some previous CAD	1	8179	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.60, 0.82]
62 CHD events - LCn3 - subgroup by baseline TG	32	134116	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.85, 0.97]
62.1 Baseline TG not restricted	29	125753	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.89, 0.99]
62.2 Baseline TG raised	3	8363	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.60, 0.82]
63 CHD events - LCn3 - subgroup by baseline DM	32	134116	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.85, 0.97]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
63.1 Normal diabetes risk	26	84915	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.88, 0.97]
63.2 Diabetes risk factors at baseline	3	13037	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.45, 1.95]
63.3 Diabetes at baseline	3	36164	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.70, 1.01]
64 Stroke (overall) - LCn3	31	138888	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.94, 1.12]
65 Stroke - LCn3 - SA fixed effect	31	138888	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.94, 1.09]
66 Stroke - LCn3 - SA by summary risk of bias	31		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
66.1 Low risk of bias	14	73390	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.90, 1.09]
66.2 Moderate/high risk of bias	17	65498	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.87, 1.26]
67 Stroke - LCn3 - SA by compliance and study size	30		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
67.1 SA - low risk of compliance bias	14	48501	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.80, 1.19]
67.2 SA - 100+ randomised	29	138761	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.93, 1.12]
68 Stroke - LCn3 - subgroup by stroke type	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
68.1 Ischaemic stroke - LCn3	10	69090	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.79, 1.20]
68.2 Haemorrhagic stroke - LCn3	10	70695	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.93, 1.64]
68.3 Transient ischaemic attack (TIA)	6	13211	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.76, 1.60]
69 Stroke - LCn3 - subgroup by dose	31	138888	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.94, 1.12]
69.1 LCn3 ≤ 150 mg/d	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
69.2 LCn3 > 150 ≤ 250 mg/d	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
69.3 LCn3 > 250 ≤ 400 mg/d	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.14, 1.44]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
69.4 LCn3 > 400 ≤ 2400 mg/d	26	127686	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.96, 1.12]
69.5 LCn3 > 2.4 ≤ 4.4 g/d	2	8789	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.57, 0.94]
69.6 LCn3 > 4.4 g/d	2	380	Risk Ratio (M-H, Random, 95% CI)	6.58 [0.78, 55.16]
70 Stroke - LCn3 - subgroup by replacement	31		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
70.1 N-3 replacing SFA	3	2514	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.19, 1.50]
70.2 N-3 replacing MUFA	16	86603	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.94, 1.14]
70.3 N-3 replacing n-6	3	1179	Risk Ratio (M-H, Random, 95% CI)	2.08 [0.18, 24.31]
70.4 N-3 replacing carbohydrates/sugars	1	258	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.23]
70.5 N-3 replacing nil/low n-3 placebo	9	47398	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.80, 1.17]
70.6 Replacement unclear	2	3450	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.61, 2.43]
71 Stroke - LCn3 - subgroup by intervention type	31	138888	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.94, 1.12]
71.1 Dietary advice	3	5248	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.42, 2.05]
71.2 Supplemental foods	1	4837	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.47, 2.62]
71.3 Supplements (capsule)	27	128803	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.93, 1.13]
71.4 Any combination	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
72 Stroke - LCn3 - subgroup by duration	31	138888	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.94, 1.12]
72.1 Medium duration 1 to < 2 years in study	11	7467	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.86, 2.12]
72.2 Medium-long duration: 2 to < 4 years in study	11	28387	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.93, 1.41]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
72.3 Long duration: ≥ 4 years in study	9	103034	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.08]
73 Stroke - LCn3 - subgroup by primary or secondary prevention	31	138888	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.94, 1.12]
73.1 Primary prevention of CVD	11	80683	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.90, 1.07]
73.2 Secondary prevention of CVD	19	50026	Risk Ratio (M-H, Random, 95% CI)	1.21 [1.05, 1.40]
73.3 Mixed primary & secondary prevention	1	8179	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.57, 0.95]
74 Stroke - LCn3 - subgroup by statin use	31	138888	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.94, 1.12]
74.1 LCn3 - ≥ 50% of control group on statins	10	66621	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.84, 1.10]
74.2 LCn3 - < 50% of control group on statins	18	70870	Risk Ratio (M-H, Random, 95% CI)	1.14 [1.01, 1.29]
74.3 LCn3 - use of statins unclear	3	1397	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.38, 2.34]
75 Stroke - LCn3 - subgroup by baseline TG	31	138888	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.94, 1.12]
75.1 Baseline TG not restricted	29	130373	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.96, 1.12]
75.2 Baseline TG raised	2	8515	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.25, 4.00]
76 Stroke - LCn3 - subgroup by baseline DM	31	138888	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.94, 1.12]
76.1 Normal diabetes risk	25	89594	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.98, 1.22]
76.2 Diabetes risk factors at baseline	3	13130	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.80, 1.08]
76.3 Diabetes at baseline	3	36164	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.73, 1.30]
77 Arrythmia (overall) - LCn3	30	77990	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.92, 1.06]
78 Arrythmia - LCn3 - SA fixed effects	30	77990	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.98, 1.09]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
79 Arrhythmia- LCn3 - SA by summary risk of bias	30	77990	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.92, 1.06]
79.1 Low summary risk of bias	12	41816	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.99, 1.20]
79.2 Moderate to high risk of bias	18	36174	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.86, 1.04]
80 Arrhythmia- LCn3 - SA by compliance and study size	29		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
80.1 SA - low risk of compliance bias	12	21628	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.88, 1.12]
80.2 SA - 100+ randomised	29	77943	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.91, 1.06]
81 Arrhythmia - LCn3 - subgroup by new or recurrent	30		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
81.1 New arrhythmia	19	74111	Risk Ratio (M-H, Random, 95% CI)	1.09 [1.01, 1.17]
81.2 Recurrent arrhythmia	12	4425	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.84, 1.03]
82 Arrhythmia - LCn3 - subgroup by fatality	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
82.1 Fatal arrhythmias - LCn3	2	12938	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.95, 1.31]
82.2 Non-fatal arrhythmias - LCn3	8	2079	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.57, 0.96]
83 Arrhythmia - LCn3 - subgroup by dose	30	77990	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.92, 1.06]
83.1 LCn3 ≤ 150 mg/d	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
83.2 LCn3 > 150 ≤ 250 mg/d	1	407	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.90, 1.12]
83.3 LCn3 > 250 ≤ 400 mg/d	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
83.4 LCn3 > 400 ≤ 2400 mg/d	20	67015	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.90, 1.08]
83.5 LCn3 > 2.4 ≤ 4.4 g/d	5	9790	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.58, 1.32]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
83.6 LCn3 > 4.4 g/d	2	342	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.32, 3.83]
83.7 Unclear LCn3 dose	2	436	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.76, 1.28]
84 Arrhythmia - LCn3 - subgroup by replacement	30		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
84.1 N-3 replacing SFA	2	632	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.10, 5.67]
84.2 N-3 replacing MUFA	15	58652	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.91, 1.11]
84.3 N-3 replacing n-6	4	1302	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.86, 1.16]
84.4 N-3 replacing carbohydrates/sugars	1	258	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.04, 3.21]
84.5 N-3 replacing nil/low n-3 placebo	5	16569	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.70, 1.30]
84.6 Replacement unclear	5	1381	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.91, 1.08]
85 Arrhythmia - LCn3 - subgroup by intervention type	30	77990	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.92, 1.06]
85.1 Dietary advice	2	508	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.44, 1.72]
85.2 Supplemental foods	2	5039	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.67, 1.26]
85.3 Supplements (capsule)	26	72443	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.91, 1.08]
85.4 Any combination	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
86 Arrhythmia - LCn3 - subgroup by duration	30	77990	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.92, 1.06]
86.1 Medium duration 1 to < 2 years in study	18	9088	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.84, 1.04]
86.2 Medium-long duration: 2 to < 4 years in study	7	17701	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.84, 1.10]
86.3 Long duration: ≥ 4 years in study	5	51201	Risk Ratio (M-H, Random, 95% CI)	1.13 [1.03, 1.25]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
87 Arrhythmia - LCn3 - subgroup by primary or secondary prevention3	30	77990	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.92, 1.06]
87.1 Primary prevention	10	30580	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.98, 1.22]
87.2 Secondary prevention	19	39231	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.87, 1.03]
87.3 Mixed primary & secondary prevention	1	8179	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.99, 1.50]
88 Arrhythmia - LCn3 - subgroup by statin use	30	77990	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.92, 1.06]
88.1 LCn3 - ≥ 50% of control group on statins	7	47438	Risk Ratio (M-H, Random, 95% CI)	1.10 [1.00, 1.21]
88.2 LCn3 - < 50% of control group on statins	19	29467	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.85, 1.04]
88.3 LCn3 - use of statins unclear	4	1085	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.80, 1.18]
89 Arrythmia - LCn3 - subgroup by baseline TG	30	77990	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.92, 1.06]
89.1 Baseline TG not restricted	28	69475	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.90, 1.05]
89.2 Baseline TG raised	2	8515	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.99, 1.50]
90 Arrythmia - LCn3 - subgroup by baseline DM	30	77990	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.92, 1.06]
90.1 Normal diabetes risk	24	28696	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.87, 1.03]
90.2 Diabetes risk factors at baseline	3	13130	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.93, 1.29]
90.3 Diabetes at baseline	3	36164	Risk Ratio (M-H, Random, 95% CI)	1.16 [1.02, 1.31]

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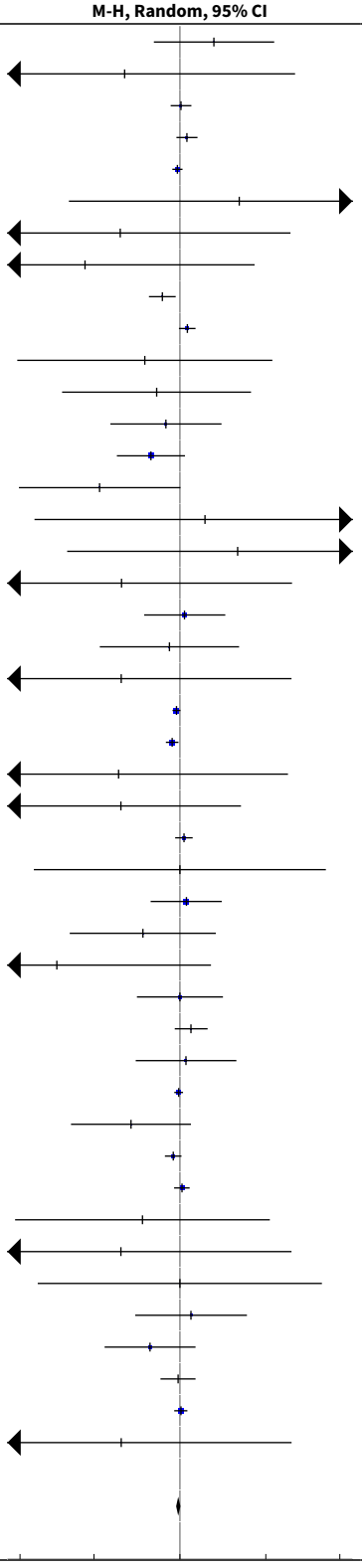
Analysis 1.1. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 1 All-cause mortality (overall) - LCn3.

Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 fats n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ADCS 2010	11/238	4/164		0.12%	1.89[0.61,5.85]
AFFORD 2013	0/153	1/163		0.02%	0.35[0.01,8.65]
AlphaOmega - EPA+DHA 2010	186/2404	184/2433		3.69%	1.02[0.84,1.24]
AREDS2 2014	200/2147	168/2056		3.68%	1.14[0.94,1.39]
ASCEND 2018	752/7740	788/7740		12.5%	0.95[0.87,1.05]
Bates 1989	1/155	0/157		0.02%	3.04[0.12,74.02]
Berson 2004	0/105	1/103		0.02%	0.33[0.01,7.94]
Brox 2001	0/80	1/40		0.02%	0.17[0.01,4.05]
DART 1989	94/1015	131/1018		2.33%	0.72[0.56,0.92]
DART2 2003	283/1571	242/1543		5.52%	1.15[0.98,1.34]
Derosa 2016	1/138	2/143		0.03%	0.52[0.05,5.65]
DIPP 2015	2/104	3/101		0.05%	0.65[0.11,3.79]
DISAF 2003	6/201	8/206		0.14%	0.77[0.27,2.18]
DO IT 2010	14/282	24/281		0.37%	0.58[0.31,1.1]
Doi 2014	2/119	9/119		0.07%	0.22[0.05,1.01]
DREAM Asbell 2018	1/349	0/186		0.02%	1.6[0.07,39.15]
EPIC-1 2008	1/183	0/180		0.02%	2.95[0.12,71.97]
EPIC-2 2008	0/189	1/190		0.02%	0.34[0.01,8.17]
FAAT 2005	13/200	12/202		0.26%	1.09[0.51,2.34]
FORWARD 2013	4/289	5/297		0.09%	0.82[0.22,3.03]
FOSTAR 2016	0/101	1/101		0.02%	0.33[0.01,8.09]
GISSI-HF 2008	955/3494	1014/3481		17.24%	0.94[0.87,1.01]
GISSI-P 1999	472/5666	545/5658		8.97%	0.86[0.77,0.97]
HARP 1995	0/41	1/39		0.02%	0.32[0.01,7.57]
HEARTS 2017	1/143	3/142		0.03%	0.33[0.03,3.14]
JELIS 2007	286/9326	265/9319		5.05%	1.08[0.91,1.27]
Kumar 2013	1/39	1/39		0.02%	1[0.06,15.43]
MAPT 2017	18/840	16/840		0.34%	1.13[0.58,2.19]
NAT2 2013	3/150	6/150		0.08%	0.5[0.13,1.96]
Nutristroke 2009	0/38	4/34		0.02%	0.1[0.01,1.79]
OFAMI 2001	11/150	11/150		0.24%	1[0.45,2.24]
OMEGA 2009	88/1919	70/1885		1.57%	1.23[0.91,1.68]
OPAL 2010	9/434	8/433		0.17%	1.12[0.44,2.88]
ORIGIN 2012	951/6281	964/6225		15.21%	0.98[0.9,1.06]
Raitt 2005	4/100	10/100		0.12%	0.4[0.13,1.23]
REDUCE-IT 2019	274/4083	310/4077		5.52%	0.88[0.75,1.03]
Risk & Prevention 2013	348/6239	337/6266		6.27%	1.04[0.9,1.2]
SCIMO 1999	1/112	2/111		0.03%	0.5[0.05,5.39]
seAFOod Hull 2018	0/356	1/353		0.02%	0.33[0.01,8.09]
Shinto 2014	1/13	1/13		0.02%	1[0.07,14.34]
SHOT 1996	8/317	6/293		0.14%	1.23[0.43,3.51]
SOFA 2006	8/273	14/273		0.21%	0.57[0.24,1.34]
SU.FOL.OM3 2010	66/1253	68/1248		1.37%	0.97[0.7,1.34]
VITAL 2019	493/12933	485/12938		8.34%	1.02[0.9,1.15]
Zhang 2017	0/120	1/120		0.02%	0.33[0.01,8.1]
Total (95% CI)	**72083**	**71610**		**100%**	**0.97[0.93,1.01]**
Total events: 5569 (Favours higher omega 3), 5728 (Lower omega 3 fats)					



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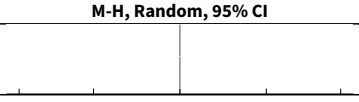
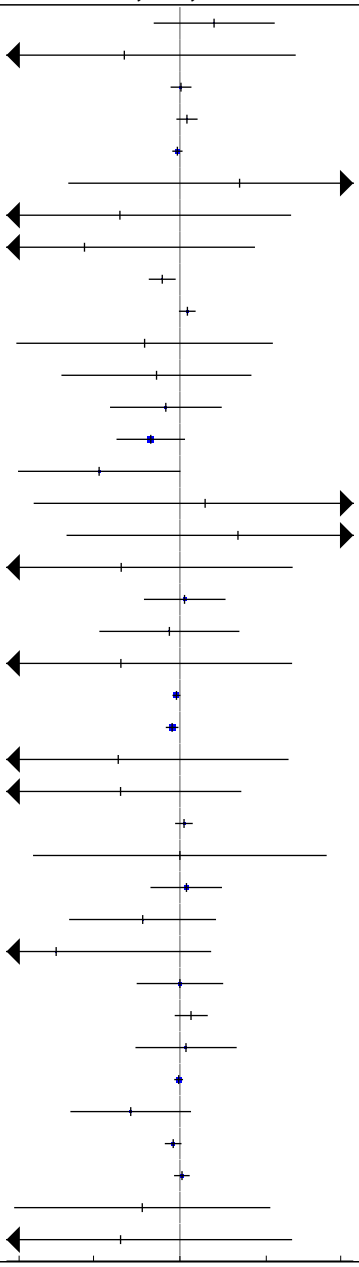
Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 fats n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0; Chi²=46.47, df=44(P=0.37); I²=5.31%					
Test for overall effect: Z=1.55(P=0.12)					



Favours higher omega 3 — Favours lower omega 3

Analysis 1.2. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 2 All-cause mortality -LCn3 - sensitivity analysis (SA) fixed-effect.

Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 fats n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
ADCS 2010	11/238	4/164		0.08%	1.89[0.61,5.85]
AFFORD 2013	0/153	1/163		0.03%	0.35[0.01,8.65]
AlphaOmega - EPA+DHA 2010	186/2404	184/2433		3.18%	1.02[0.84,1.24]
AREDS2 2014	200/2147	168/2056		2.99%	1.14[0.94,1.39]
ASCEND 2018	752/7740	788/7740		13.71%	0.95[0.87,1.05]
Bates 1989	1/155	0/157		0.01%	3.04[0.12,74.02]
Berson 2004	0/105	1/103		0.03%	0.33[0.01,7.94]
Brox 2001	0/80	1/40		0.03%	0.17[0.01,4.05]
DART 1989	94/1015	131/1018		2.28%	0.72[0.56,0.92]
DART2 2003	283/1571	242/1543		4.25%	1.15[0.98,1.34]
Derosa 2016	1/138	2/143		0.03%	0.52[0.05,5.65]
DIPP 2015	2/104	3/101		0.05%	0.65[0.11,3.79]
DISAF 2003	6/201	8/206		0.14%	0.77[0.27,2.18]
DO IT 2010	14/282	24/281		0.42%	0.58[0.31,1.1]
Doi 2014	2/119	9/119		0.16%	0.22[0.05,1.01]
DREAM Asbell 2018	1/349	0/186		0.01%	1.6[0.07,39.15]
EPIC-1 2008	1/183	0/180		0.01%	2.95[0.12,71.97]
EPIC-2 2008	0/189	1/190		0.03%	0.34[0.01,8.17]
FAAT 2005	13/200	12/202		0.21%	1.09[0.51,2.34]
FORWARD 2013	4/289	5/297		0.09%	0.82[0.22,3.03]
FOSTAR 2016	0/101	1/101		0.03%	0.33[0.01,8.09]
GISSI-HF 2008	955/3494	1014/3481		17.68%	0.94[0.87,1.01]
GISSI-P 1999	472/5666	545/5658		9.49%	0.86[0.77,0.97]
HARP 1995	0/41	1/39		0.03%	0.32[0.01,7.57]
HEARTS 2017	1/143	3/142		0.05%	0.33[0.03,3.14]
JELIS 2007	286/9326	265/9319		4.61%	1.08[0.91,1.27]
Kumar 2013	1/39	1/39		0.02%	1[0.06,15.43]
MAPT 2017	18/840	16/840		0.28%	1.13[0.58,2.19]
NAT2 2013	3/150	6/150		0.1%	0.5[0.13,1.96]
Nutristroke 2009	0/38	4/34		0.08%	0.1[0.01,1.79]
OFAMI 2001	11/150	11/150		0.19%	1[0.45,2.24]
OMEGA 2009	88/1919	70/1885		1.23%	1.23[0.91,1.68]
OPAL 2010	9/434	8/433		0.14%	1.12[0.44,2.88]
ORIGIN 2012	951/6281	964/6225		16.85%	0.98[0.9,1.06]
Raitt 2005	4/100	10/100		0.17%	0.4[0.13,1.23]
REDUCE-IT 2019	274/4083	310/4077		5.4%	0.88[0.75,1.03]
Risk & Prevention 2013	348/6239	337/6266		5.85%	1.04[0.9,1.2]
SCIMO 1999	1/112	2/111		0.03%	0.5[0.05,5.39]
seAFOod Hull 2018	0/356	1/353		0.03%	0.33[0.01,8.09]



Favours higher omega 3 — Favours lower omega 3

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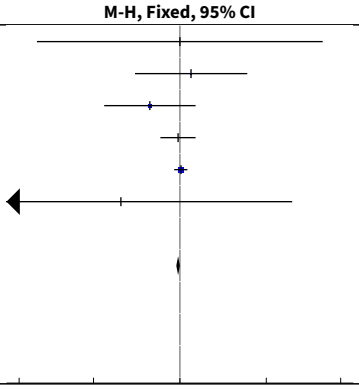
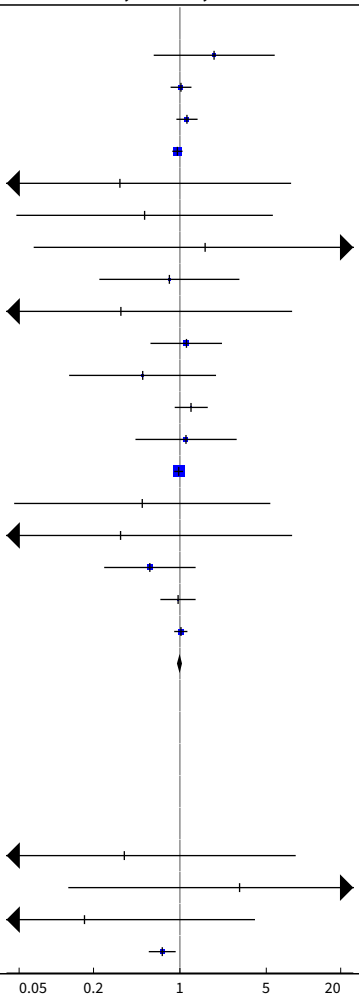
Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 fats n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Shinto 2014	1/13	1/13		0.02%	1[0.07,14.34]
SHOT 1996	8/317	6/293		0.11%	1.23[0.43,3.51]
SOFA 2006	8/273	14/273		0.24%	0.57[0.24,1.34]
SU.FOL.OM3 2010	66/1253	68/1248		1.19%	0.97[0.7,1.34]
VITAL 2019	493/12933	485/12938		8.44%	1.02[0.9,1.15]
Zhang 2017	0/120	1/120		0.03%	0.33[0.01,8.1]
Total (95% CI)	**72083**	**71610**		**100%**	**0.97[0.93,1]**
Total events: 5569 (Favours higher omega 3), 5728 (Lower omega 3 fats)					
Heterogeneity: Tau²=0; Chi²=46.47, df=44(P=0.37); I²=5.31%					
Test for overall effect: Z=1.88(P=0.06)					



Analysis 1.3. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 3 All-cause mortality - LCn3 - SA by summary risk of bias.

Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 fats n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Low summary risk of bias					
ADCS 2010	11/238	4/164		0.19%	1.89[0.61,5.85]
AlphaOmega - EPA+DHA 2010	186/2404	184/2433		6.46%	1.02[0.84,1.24]
AREDS2 2014	200/2147	168/2056		6.45%	1.14[0.94,1.39]
ASCEND 2018	752/7740	788/7740		27.54%	0.95[0.87,1.05]
Berson 2004	0/105	1/103		0.02%	0.33[0.01,7.94]
Derosa 2016	1/138	2/143		0.04%	0.52[0.05,5.65]
DREAM Asbell 2018	1/349	0/186		0.02%	1.6[0.07,39.15]
FORWARD 2013	4/289	5/297		0.15%	0.82[0.22,3.03]
FOSTAR 2016	0/101	1/101		0.02%	0.33[0.01,8.09]
MAPT 2017	18/840	16/840		0.56%	1.13[0.58,2.19]
NAT2 2013	3/150	6/150		0.13%	0.5[0.13,1.96]
OMEGA 2009	88/1919	70/1885		2.62%	1.23[0.91,1.68]
OPAL 2010	9/434	8/433		0.28%	1.12[0.44,2.88]
ORIGIN 2012	951/6281	964/6225		36.44%	0.98[0.9,1.06]
SCIMO 1999	1/112	2/111		0.04%	0.5[0.05,5.39]
seAFOod Hull 2018	0/356	1/353		0.02%	0.33[0.01,8.09]
SOFA 2006	8/273	14/273		0.34%	0.57[0.24,1.34]
SU.FOL.OM3 2010	66/1253	68/1248		2.28%	0.97[0.7,1.34]
VITAL 2019	493/12933	485/12938		16.38%	1.02[0.9,1.15]
Subtotal (95% CI)	**38062**	**37679**		**100%**	**0.99[0.95,1.04]**
Total events: 2792 (Favours higher omega 3), 2787 (Lower omega 3 fats)					
Heterogeneity: Tau²=0; Chi²=11.1, df=18(P=0.89); I²=0%					
Test for overall effect: Z=0.23(P=0.82)					
1.3.2 Moderate or high summary risk of bias					
AFFORD 2013	0/153	1/163		0.06%	0.35[0.01,8.65]
Bates 1989	1/155	0/157		0.06%	3.04[0.12,74.02]
Brox 2001	0/80	1/40		0.06%	0.17[0.01,4.05]
DART 1989	94/1015	131/1018		7%	0.72[0.56,0.92]



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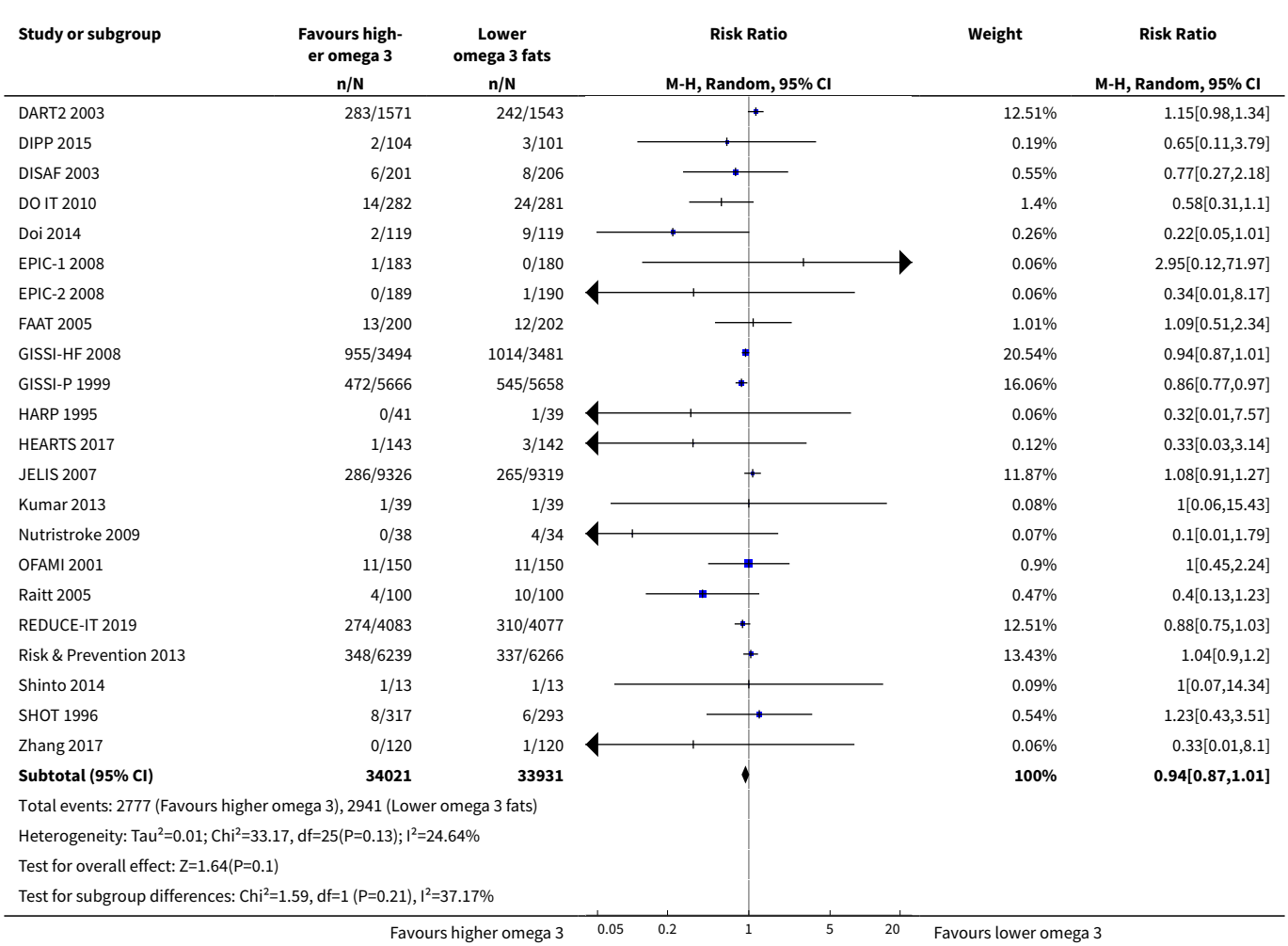
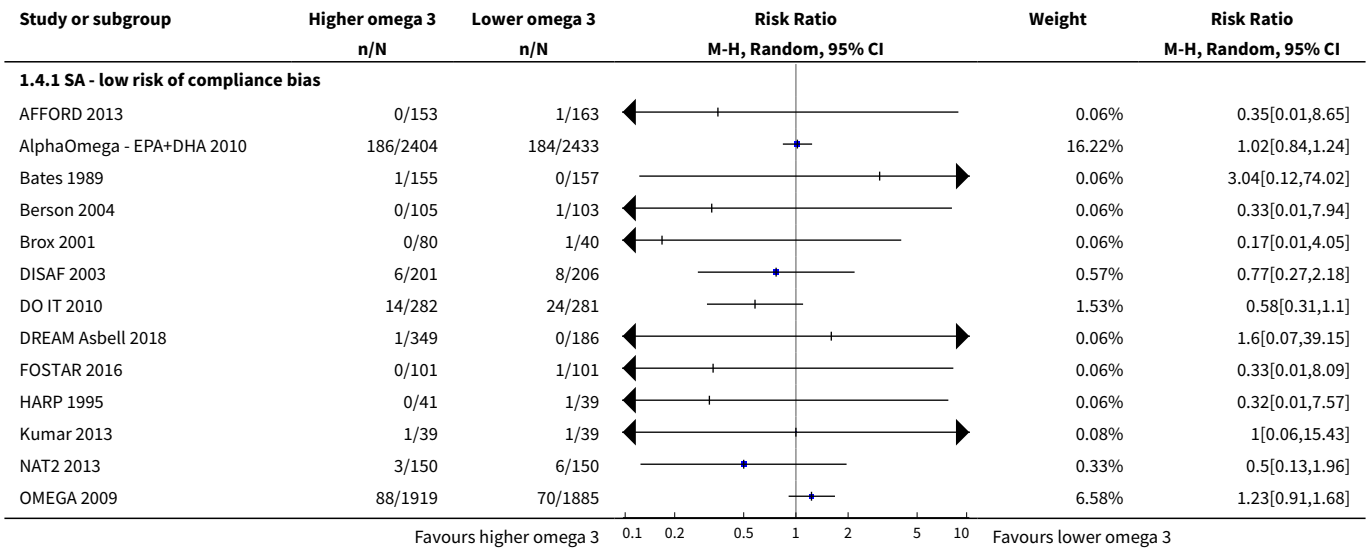


Analysis 1.4. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 4 All-cause mortality - LCn3 - SA by compliance and study size.



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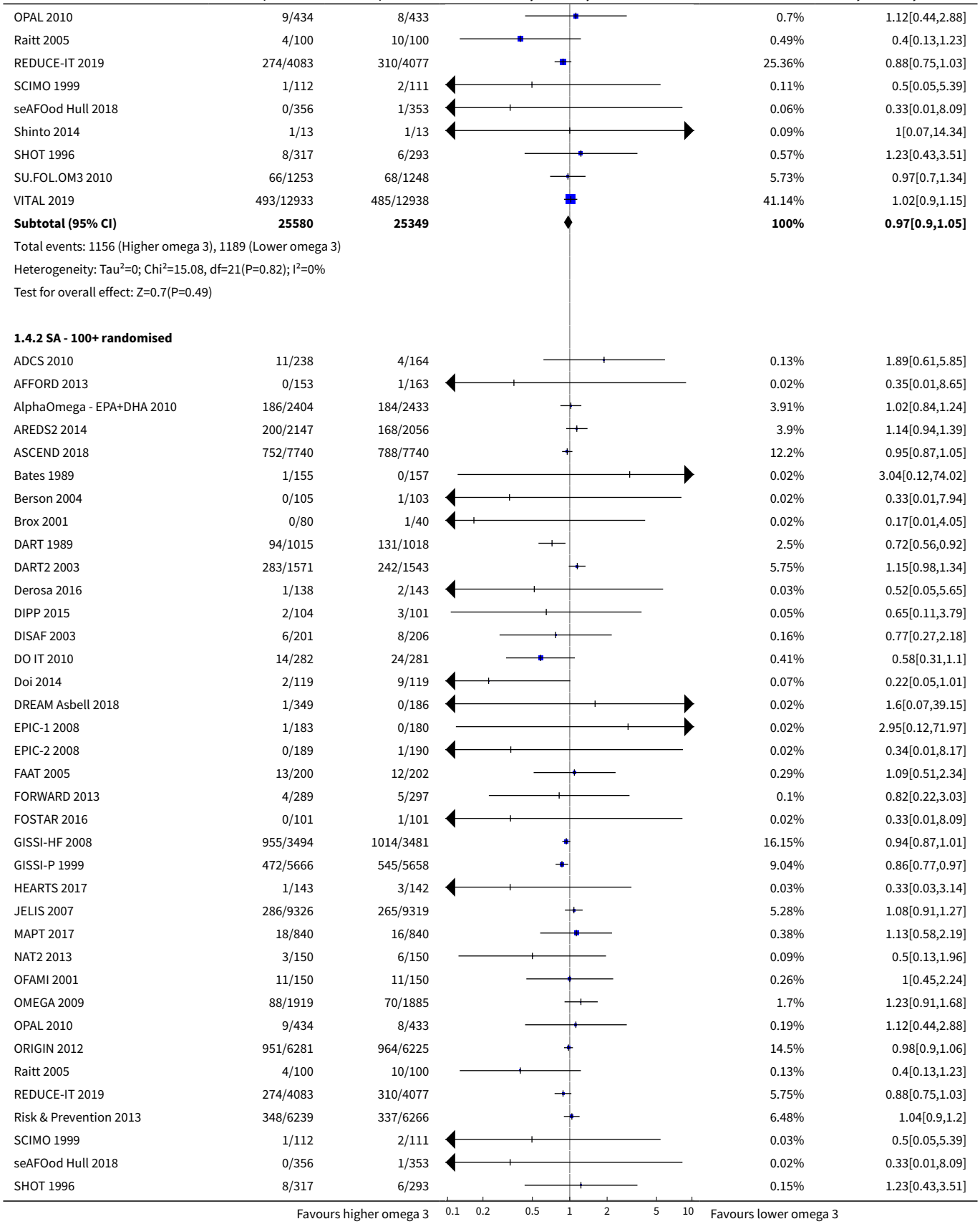

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
OPAL 2010	9/434	8/433		0.7%	1.12[0.44,2.88]
Raitt 2005	4/100	10/100		0.49%	0.4[0.13,1.23]
REDUCE-IT 2019	274/4083	310/4077		25.36%	0.88[0.75,1.03]
SCIMO 1999	1/112	2/111		0.11%	0.5[0.05,5.39]
seAFOod Hull 2018	0/356	1/353		0.06%	0.33[0.01,8.09]
Shinto 2014	1/13	1/13		0.09%	1[0.07,14.34]
SHOT 1996	8/317	6/293		0.57%	1.23[0.43,3.51]
SU.FOL.OM3 2010	66/1253	68/1248		5.73%	0.97[0.7,1.34]
VITAL 2019	493/12933	485/12938		41.14%	1.02[0.9,1.15]
Subtotal (95% CI)	**25580**	**25349**		**100%**	**0.97[0.9,1.05]**
Total events: 1156 (Higher omega 3), 1189 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=15.08, df=21(P=0.82); I^2=0%					
Test for overall effect: Z=0.7(P=0.49)					
1.4.2 SA - 100+ randomised					
ADCS 2010	11/238	4/164		0.13%	1.89[0.61,5.85]
AFFORD 2013	0/153	1/163		0.02%	0.35[0.01,8.65]
AlphaOmega - EPA+DHA 2010	186/2404	184/2433		3.91%	1.02[0.84,1.24]
AREDS2 2014	200/2147	168/2056		3.9%	1.14[0.94,1.39]
ASCEND 2018	752/7740	788/7740		12.2%	0.95[0.87,1.05]
Bates 1989	1/155	0/157		0.02%	3.04[0.12,74.02]
Berson 2004	0/105	1/103		0.02%	0.33[0.01,7.94]
Brox 2001	0/80	1/40		0.02%	0.17[0.01,4.05]
DART 1989	94/1015	131/1018		2.5%	0.72[0.56,0.92]
DART2 2003	283/1571	242/1543		5.75%	1.15[0.98,1.34]
Derosa 2016	1/138	2/143		0.03%	0.52[0.05,5.65]
DIPP 2015	2/104	3/101		0.05%	0.65[0.11,3.79]
DISAF 2003	6/201	8/206		0.16%	0.77[0.27,2.18]
DO IT 2010	14/282	24/281		0.41%	0.58[0.31,1.1]
Doi 2014	2/119	9/119		0.07%	0.22[0.05,1.01]
DREAM Asbell 2018	1/349	0/186		0.02%	1.6[0.07,39.15]
EPIC-1 2008	1/183	0/180		0.02%	2.95[0.12,71.97]
EPIC-2 2008	0/189	1/190		0.02%	0.34[0.01,8.17]
FAAT 2005	13/200	12/202		0.29%	1.09[0.51,2.34]
FORWARD 2013	4/289	5/297		0.1%	0.82[0.22,3.03]
FOSTAR 2016	0/101	1/101		0.02%	0.33[0.01,8.09]
GISSI-HF 2008	955/3494	1014/3481		16.15%	0.94[0.87,1.01]
GISSI-P 1999	472/5666	545/5658		9.04%	0.86[0.77,0.97]
HEARTS 2017	1/143	3/142		0.03%	0.33[0.03,3.14]
JELIS 2007	286/9326	265/9319		5.28%	1.08[0.91,1.27]
MAPT 2017	18/840	16/840		0.38%	1.13[0.58,2.19]
NAT2 2013	3/150	6/150		0.09%	0.5[0.13,1.96]
OFAMI 2001	11/150	11/150		0.26%	1[0.45,2.24]
OMEGA 2009	88/1919	70/1885		1.7%	1.23[0.91,1.68]
OPAL 2010	9/434	8/433		0.19%	1.12[0.44,2.88]
ORIGIN 2012	951/6281	964/6225		14.5%	0.98[0.9,1.06]
Raitt 2005	4/100	10/100		0.13%	0.4[0.13,1.23]
REDUCE-IT 2019	274/4083	310/4077		5.75%	0.88[0.75,1.03]
Risk & Prevention 2013	348/6239	337/6266		6.48%	1.04[0.9,1.2]
SCIMO 1999	1/112	2/111		0.03%	0.5[0.05,5.39]
seAFOod Hull 2018	0/356	1/353		0.02%	0.33[0.01,8.09]
SHOT 1996	8/317	6/293		0.15%	1.23[0.43,3.51]

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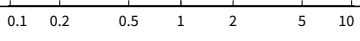
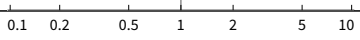
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
SOFA 2006	8/273	14/273		0.23%	0.57[0.24,1.34]
SU.FOL.OM3 2010	66/1253	68/1248		1.49%	0.97[0.7,1.34]
VITAL 2019	493/12933	485/12938		8.45%	1.02[0.9,1.15]
Zhang 2017	0/120	1/120		0.02%	0.33[0.01,8.1]
Subtotal (95% CI)	**71952**	**71485**		**100%**	**0.97[0.93,1.01]**
Total events: 5567 (Higher omega 3), 5721 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=43.61, df=40(P=0.32); I²=8.28%					
Test for overall effect: Z=1.43(P=0.15)					
Test for subgroup differences: Chi²=0, df=1 (P=0.97), I²=0%					



Favours higher omega 3 — Favours lower omega 3

Analysis 1.5. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 5 All-cause mortality - LCn3 - subgroup by dose.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 LCn3 ≤ 150 mg/d					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 3), 0 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.5.2 LCn3 > 150 ≤ 250 mg/d					
DISAF 2003	6/201	8/206		0.14%	0.77[0.27,2.18]
Subtotal (95% CI)	**201**	**206**		**0.14%**	**0.77[0.27,2.18]**
Total events: 6 (Higher omega 3), 8 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.5(P=0.62)					
1.5.3 LCn3 > 250 ≤ 400 mg/d					
DART 1989	94/1015	131/1018		2.33%	0.72[0.56,0.92]
Subtotal (95% CI)	**1015**	**1018**		**2.33%**	**0.72[0.56,0.92]**
Total events: 94 (Higher omega 3), 131 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.58(P=0.01)					
1.5.4 LCn3 > 400 ≤ 2400 mg/d					
ADCS 2010	11/238	4/164		0.12%	1.89[0.61,5.85]
AFFORD 2013	0/153	1/163		0.02%	0.35[0.01,8.65]
AlphaOmega - EPA+DHA 2010	186/2404	184/2433		3.69%	1.02[0.84,1.24]
AREDS2 2014	200/2147	168/2056		3.68%	1.14[0.94,1.39]
ASCEND 2018	752/7740	788/7740		12.5%	0.95[0.87,1.05]
Berson 2004	0/105	1/103		0.02%	0.33[0.01,7.94]
DART2 2003	283/1571	242/1543		5.52%	1.15[0.98,1.34]
Derosa 2016	1/138	2/143		0.03%	0.52[0.05,5.65]
DIPP 2015	2/104	3/101		0.05%	0.65[0.11,3.79]
DO IT 2010	14/282	24/281		0.37%	0.58[0.31,1.1]
Doi 2014	2/119	9/119		0.07%	0.22[0.05,1.01]
FORWARD 2013	4/289	5/297		0.09%	0.82[0.22,3.03]



Favours higher omega 3 — Favours lower omega 3

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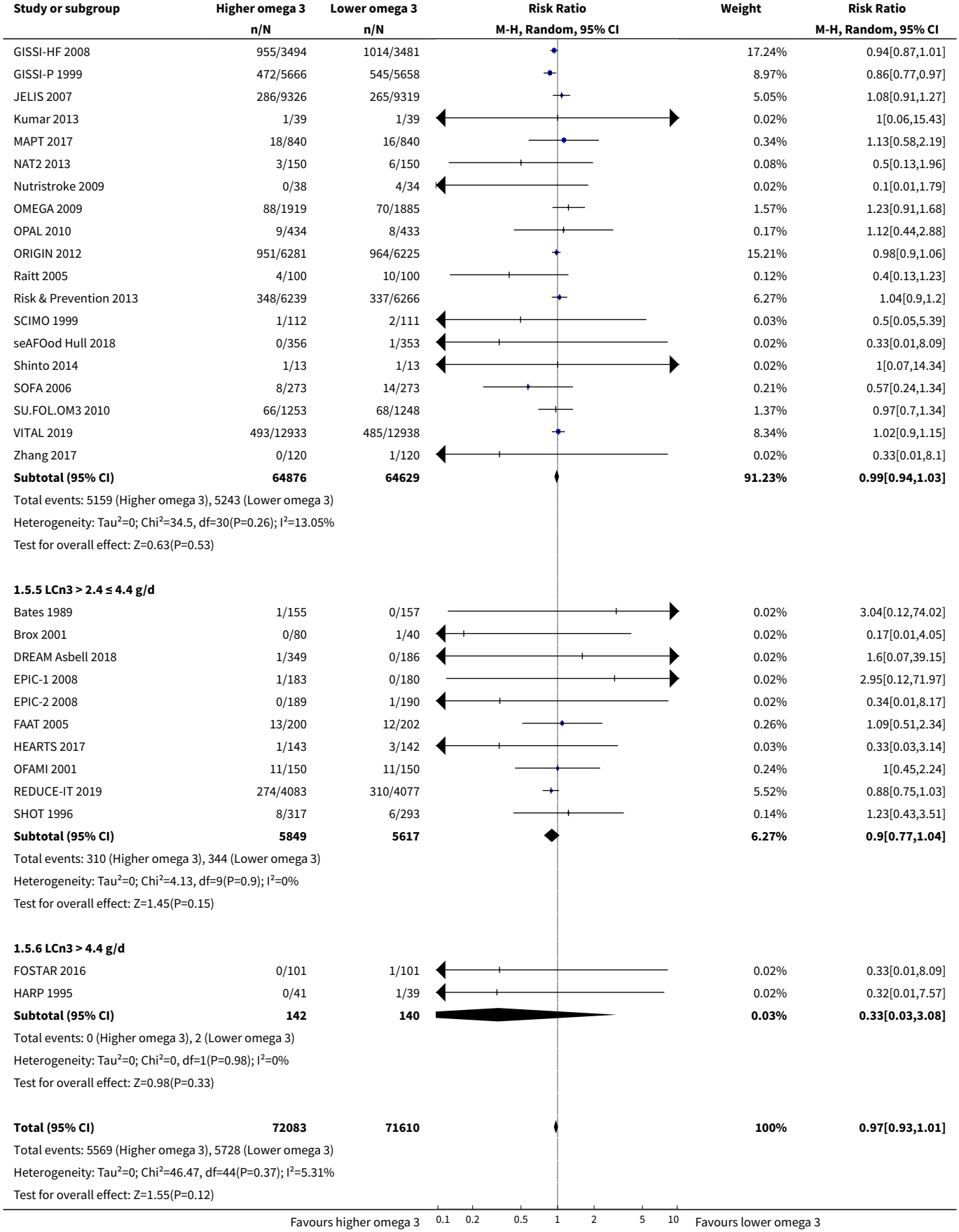

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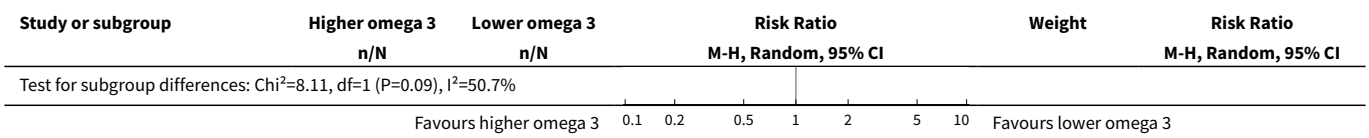
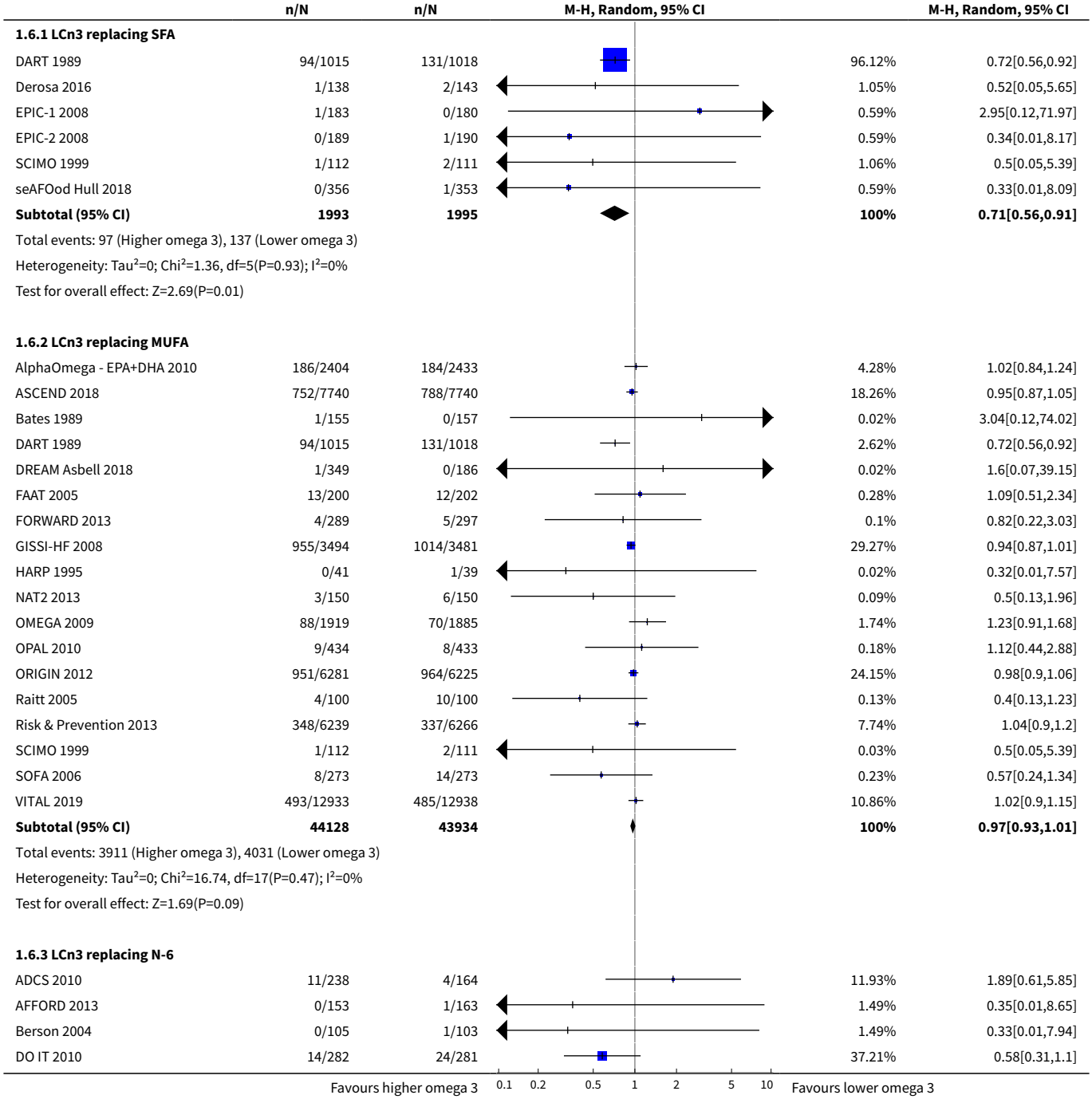


Analysis 1.6. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 6 All-cause mortality - LCn3 - subgroup by replacement.



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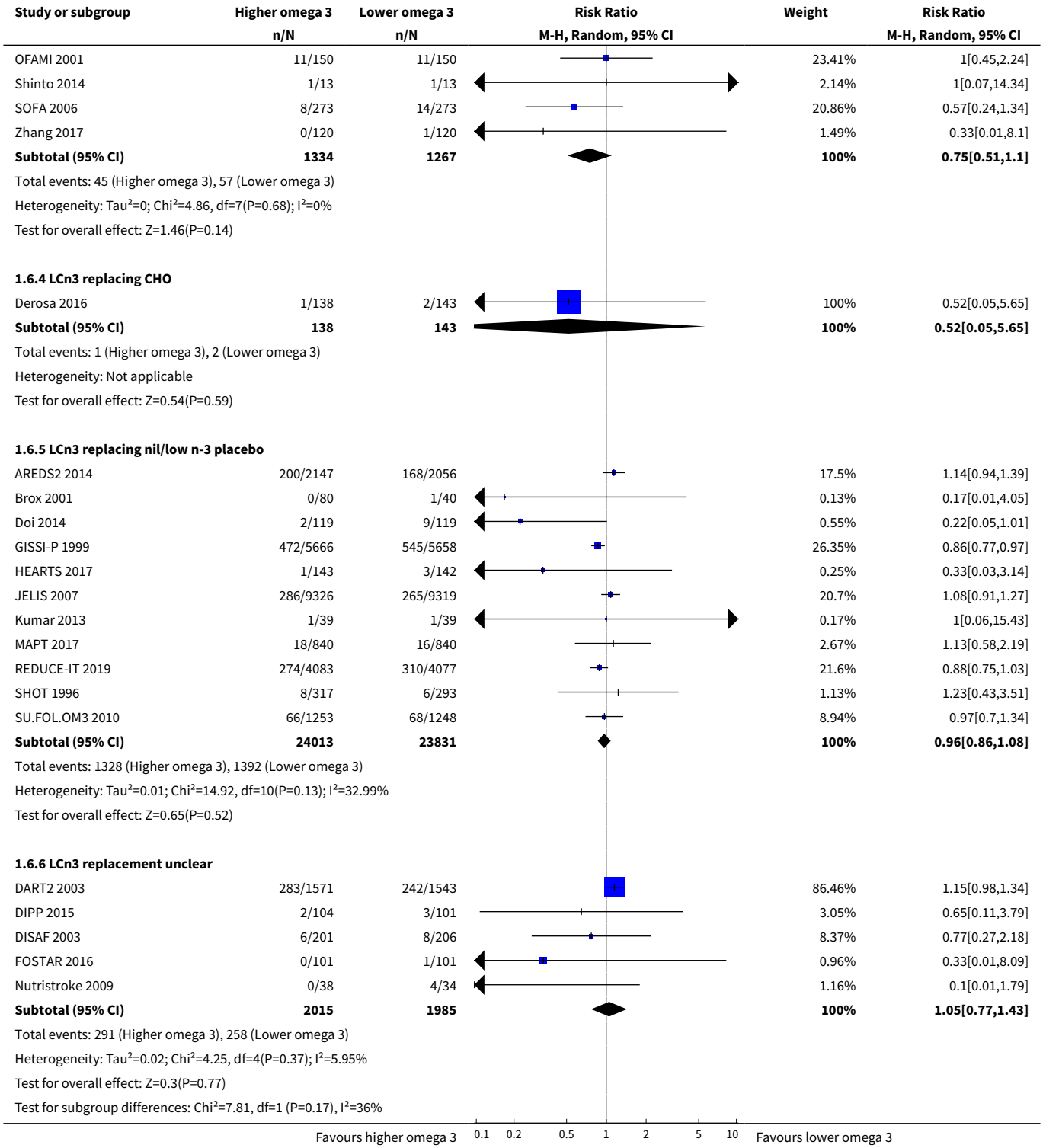

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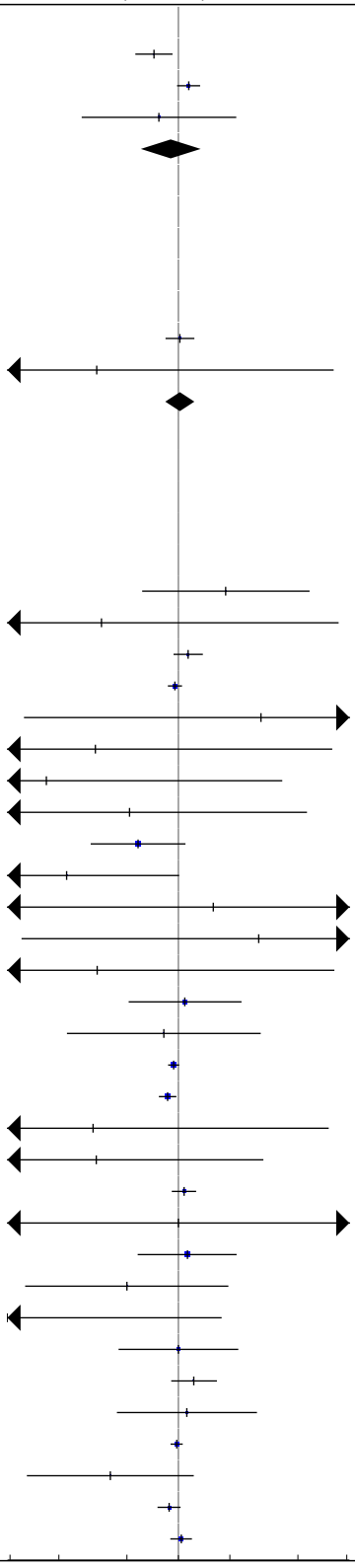
Analysis 1.7. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 7 All-cause mortality - LCn3 - subgroup by intervention type.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 Dietary advice					
DART 1989	94/1015	131/1018		2.33%	0.72[0.56,0.92]
DART2 2003	283/1571	242/1543		5.52%	1.15[0.98,1.34]
DISAF 2003	6/201	8/206		0.14%	0.77[0.27,2.18]
Subtotal (95% CI)	**2787**	**2767**		**8%**	**0.9[0.6,1.35]**
Total events: 383 (Higher omega 3), 381 (Lower omega 3)					
Heterogeneity: Tau^2=0.08; Chi^2=9.9, df=2(P=0.01); I^2=79.81%					
Test for overall effect: Z=0.51(P=0.61)					
1.7.2 Supplemental foods					
AlphaOmega - EPA+DHA 2010	186/2404	184/2433		3.69%	1.02[0.84,1.24]
FOSTAR 2016	0/101	1/101		0.02%	0.33[0.01,8.09]
Subtotal (95% CI)	**2505**	**2534**		**3.7%**	**1.02[0.84,1.24]**
Total events: 186 (Higher omega 3), 185 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.47, df=1(P=0.49); I^2=0%					
Test for overall effect: Z=0.19(P=0.85)					
1.7.3 Supplements (capsule)					
ADCS 2010	11/238	4/164		0.12%	1.89[0.61,5.85]
AFFORD 2013	0/153	1/163		0.02%	0.35[0.01,8.65]
AREDS2 2014	200/2147	168/2056		3.68%	1.14[0.94,1.39]
ASCEND 2018	752/7740	788/7740		12.5%	0.95[0.87,1.05]
Bates 1989	1/155	0/157		0.02%	3.04[0.12,74.02]
Berson 2004	0/105	1/103		0.02%	0.33[0.01,7.94]
Brox 2001	0/80	1/40		0.02%	0.17[0.01,4.05]
Derosa 2016	1/138	2/143		0.03%	0.52[0.05,5.65]
DO IT 2010	14/282	24/281		0.37%	0.58[0.31,1.1]
Doi 2014	2/119	9/119		0.07%	0.22[0.05,1.01]
DREAM Asbell 2018	1/349	0/186		0.02%	1.6[0.07,39.15]
EPIC-1 2008	1/183	0/180		0.02%	2.95[0.12,71.97]
EPIC-2 2008	0/189	1/190		0.02%	0.34[0.01,8.17]
FAAT 2005	13/200	12/202		0.26%	1.09[0.51,2.34]
FORWARD 2013	4/289	5/297		0.09%	0.82[0.22,3.03]
GISSI-HF 2008	955/3494	1014/3481		17.24%	0.94[0.87,1.01]
GISSI-P 1999	472/5666	545/5658		8.97%	0.86[0.77,0.97]
HARP 1995	0/41	1/39		0.02%	0.32[0.01,7.57]
HEARTS 2017	1/143	3/142		0.03%	0.33[0.03,3.14]
JELIS 2007	286/9326	265/9319		5.05%	1.08[0.91,1.27]
Kumar 2013	1/39	1/39		0.02%	1[0.06,15.43]
MAPT 2017	18/840	16/840		0.34%	1.13[0.58,2.19]
NAT2 2013	3/150	6/150		0.08%	0.5[0.13,1.96]
Nutristroke 2009	0/38	4/34		0.02%	0.1[0.01,1.79]
OFAMI 2001	11/150	11/150		0.24%	1[0.45,2.24]
OMEGA 2009	88/1919	70/1885		1.57%	1.23[0.91,1.68]
OPAL 2010	9/434	8/433		0.17%	1.12[0.44,2.88]
ORIGIN 2012	951/6281	964/6225		15.21%	0.98[0.9,1.06]
Raitt 2005	4/100	10/100		0.12%	0.4[0.13,1.23]
REDUCE-IT 2019	274/4083	310/4077		5.52%	0.88[0.75,1.03]
Risk & Prevention 2013	348/6239	337/6266		6.27%	1.04[0.9,1.2]



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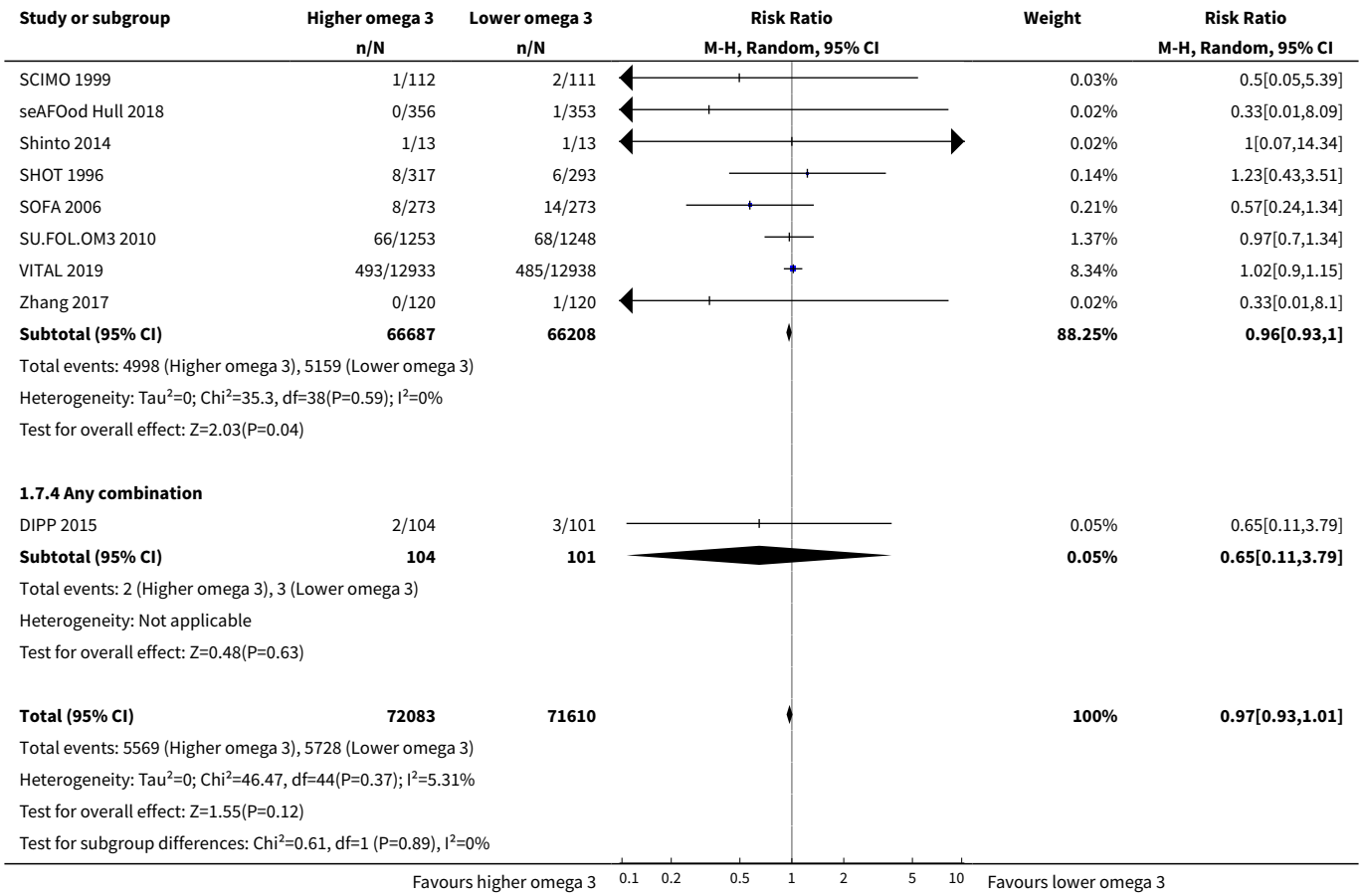
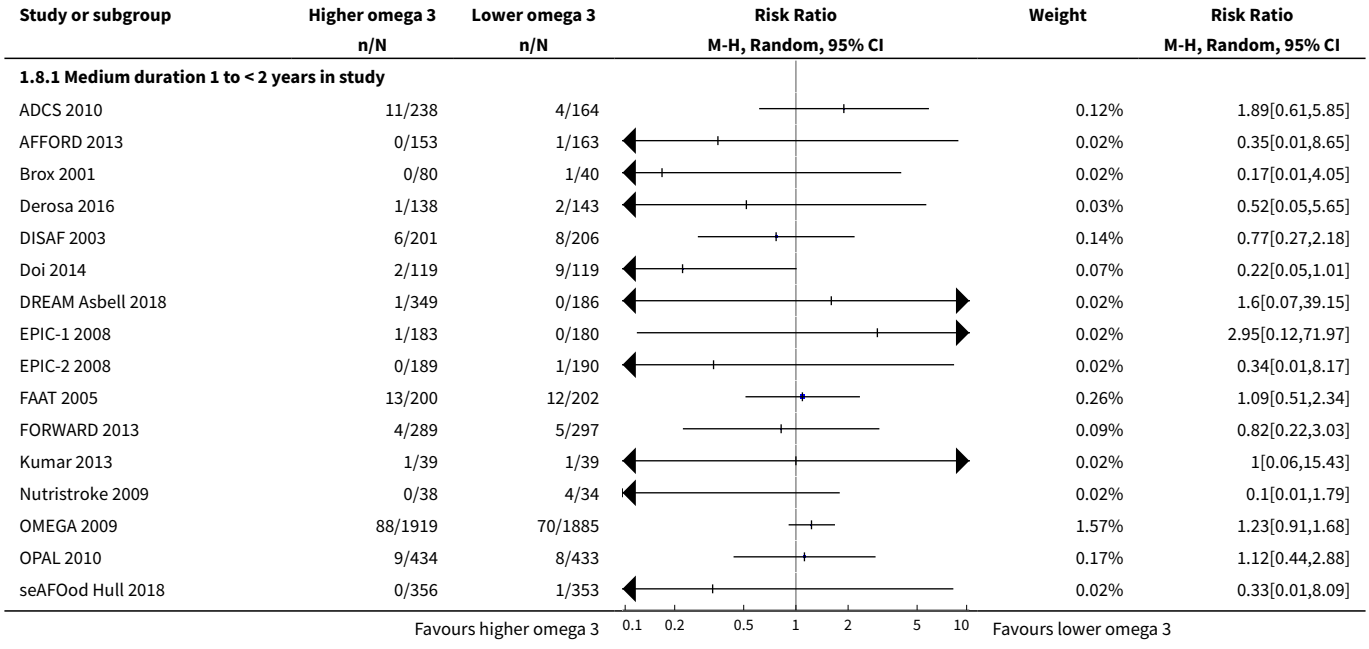


Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
SCIMO 1999	1/112	2/111		0.03%	0.5[0.05,5.39]
seAFOod Hull 2018	0/356	1/353		0.02%	0.33[0.01,8.09]
Shinto 2014	1/13	1/13		0.02%	1[0.07,14.34]
SHOT 1996	8/317	6/293		0.14%	1.23[0.43,3.51]
SOFA 2006	8/273	14/273		0.21%	0.57[0.24,1.34]
SU.FOL.OM3 2010	66/1253	68/1248		1.37%	0.97[0.7,1.34]
VITAL 2019	493/12933	485/12938		8.34%	1.02[0.9,1.15]
Zhang 2017	0/120	1/120		0.02%	0.33[0.01,8.1]
Subtotal (95% CI)	**66687**	**66208**		**88.25%**	**0.96[0.93,1]**
Total events: 4998 (Higher omega 3), 5159 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=35.3, df=38(P=0.59); I²=0%					
Test for overall effect: Z=2.03(P=0.04)					
1.7.4 Any combination					
DIPP 2015	2/104	3/101		0.05%	0.65[0.11,3.79]
Subtotal (95% CI)	**104**	**101**		**0.05%**	**0.65[0.11,3.79]**
Total events: 2 (Higher omega 3), 3 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.48(P=0.63)					
Total (95% CI)	**72083**	**71610**		**100%**	**0.97[0.93,1.01]**
Total events: 5569 (Higher omega 3), 5728 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=46.47, df=44(P=0.37); I²=5.31%					
Test for overall effect: Z=1.55(P=0.12)					
Test for subgroup differences: Chi²=0.61, df=1 (P=0.89), I²=0%					

Analysis 1.8. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 8 All-cause mortality - LCn3 - subgroup by duration.



Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Medium duration 1 to < 2 years in study					
ADCS 2010	11/238	4/164		0.12%	1.89[0.61,5.85]
AFFORD 2013	0/153	1/163		0.02%	0.35[0.01,8.65]
Brox 2001	0/80	1/40		0.02%	0.17[0.01,4.05]
Derosa 2016	1/138	2/143		0.03%	0.52[0.05,5.65]
DISAF 2003	6/201	8/206		0.14%	0.77[0.27,2.18]
Doi 2014	2/119	9/119		0.07%	0.22[0.05,1.01]
DREAM Asbell 2018	1/349	0/186		0.02%	1.6[0.07,39.15]
EPIC-1 2008	1/183	0/180		0.02%	2.95[0.12,71.97]
EPIC-2 2008	0/189	1/190		0.02%	0.34[0.01,8.17]
FAAT 2005	13/200	12/202		0.26%	1.09[0.51,2.34]
FORWARD 2013	4/289	5/297		0.09%	0.82[0.22,3.03]
Kumar 2013	1/39	1/39		0.02%	1[0.06,15.43]
Nutristroke 2009	0/38	4/34		0.02%	0.1[0.01,1.79]
OMEGA 2009	88/1919	70/1885		1.57%	1.23[0.91,1.68]
OPAL 2010	9/434	8/433		0.17%	1.12[0.44,2.88]
seAFOod Hull 2018	0/356	1/353		0.02%	0.33[0.01,8.09]

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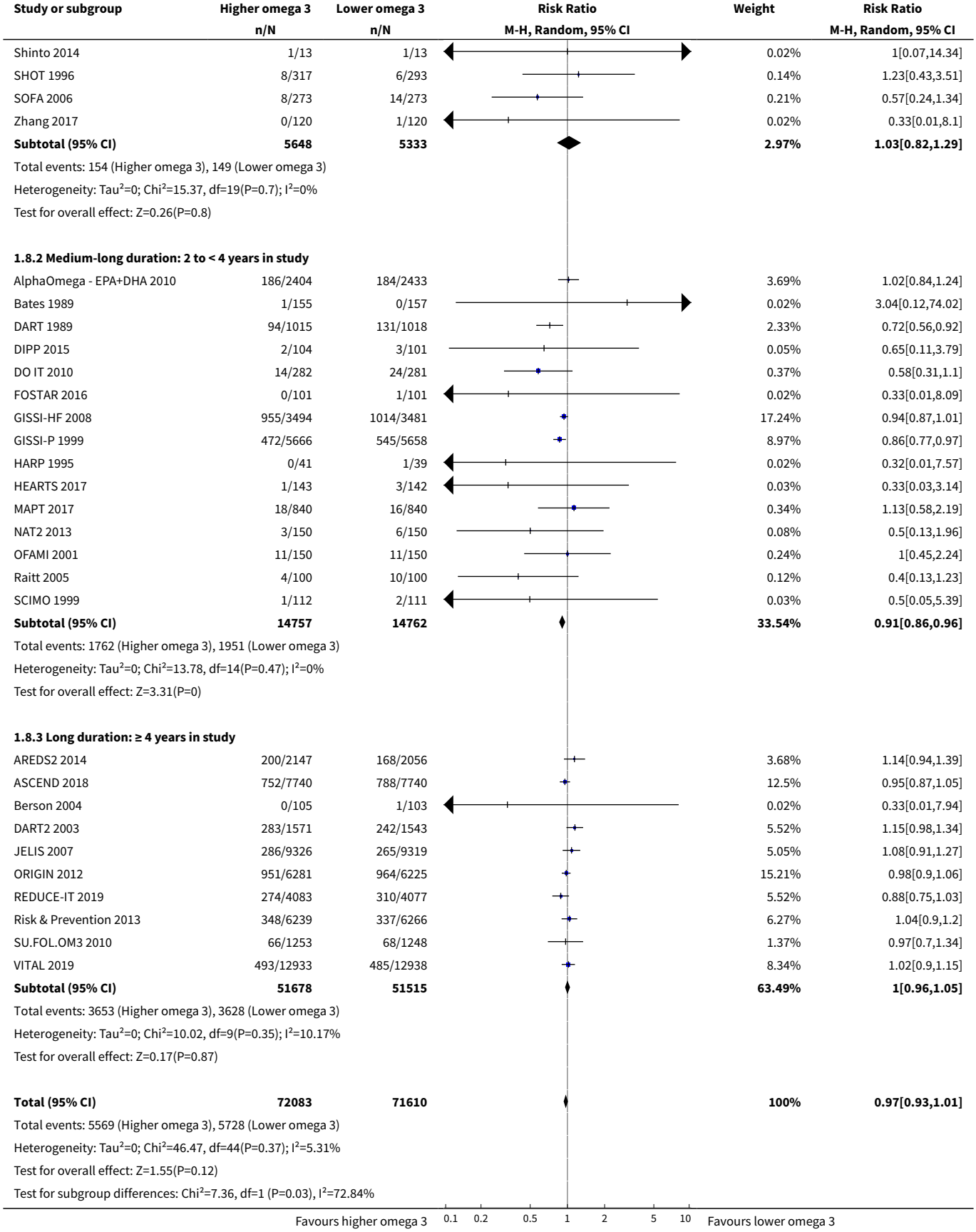

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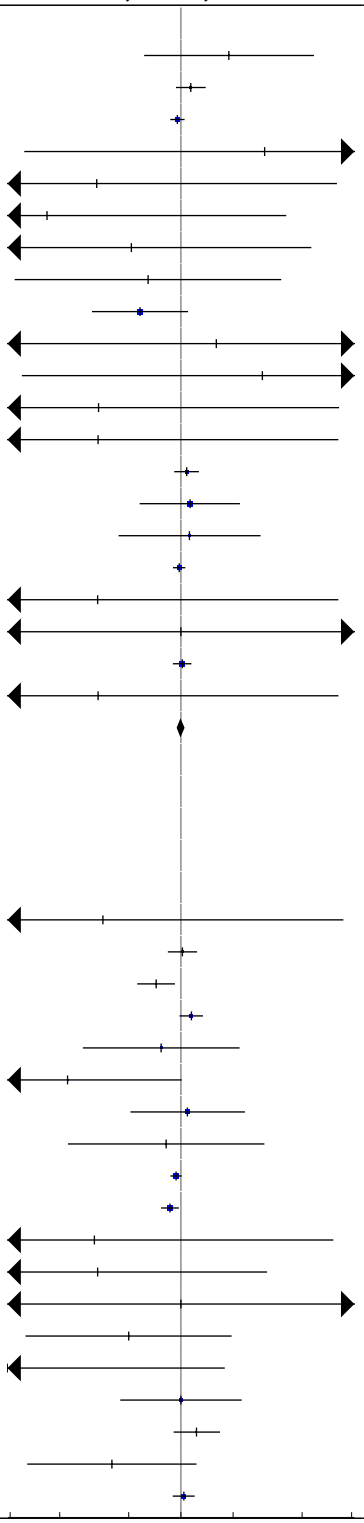
Analysis 1.9. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 9 All-cause mortality - LCn3 - subgroup by primary or secondary prevention.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.9.1 Primary CVD prevention					
ADCS 2010	11/238	4/164		0.12%	1.89[0.61,5.85]
AREDS2 2014	200/2147	168/2056		3.68%	1.14[0.94,1.39]
ASCEND 2018	752/7740	788/7740		12.5%	0.95[0.87,1.05]
Bates 1989	1/155	0/157		0.02%	3.04[0.12,74.02]
Berson 2004	0/105	1/103		0.02%	0.33[0.01,7.94]
Brox 2001	0/80	1/40		0.02%	0.17[0.01,4.05]
Derosa 2016	1/138	2/143		0.03%	0.52[0.05,5.65]
DIPP 2015	2/104	3/101		0.05%	0.65[0.11,3.79]
DO IT 2010	14/282	24/281		0.37%	0.58[0.31,1.1]
DREAM Asbell 2018	1/349	0/186		0.02%	1.6[0.07,39.15]
EPIC-1 2008	1/183	0/180		0.02%	2.95[0.12,71.97]
EPIC-2 2008	0/189	1/190		0.02%	0.34[0.01,8.17]
FOSTAR 2016	0/101	1/101		0.02%	0.33[0.01,8.09]
JELIS 2007	286/9326	265/9319		5.05%	1.08[0.91,1.27]
MAPT 2017	18/840	16/840		0.34%	1.13[0.58,2.19]
OPAL 2010	9/434	8/433		0.17%	1.12[0.44,2.88]
ORIGIN 2012	951/6281	964/6225		15.21%	0.98[0.9,1.06]
seAFOod Hull 2018	0/356	1/353		0.02%	0.33[0.01,8.09]
Shinto 2014	1/13	1/13		0.02%	1[0.07,14.34]
VITAL 2019	493/12933	485/12938		8.34%	1.02[0.9,1.15]
Zhang 2017	0/120	1/120		0.02%	0.33[0.01,8.1]
Subtotal (95% CI)	**42114**	**41683**		**46.03%**	**0.99[0.95,1.05]**
Total events: 2741 (Higher omega 3), 2734 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=12.97, df=20(P=0.88); I^2=0%					
Test for overall effect: Z=0.23(P=0.82)					
1.9.2 Secondary CVD prevention					
AFFORD 2013	0/153	1/163		0.02%	0.35[0.01,8.65]
AlphaOmega - EPA+DHA 2010	186/2404	184/2433		3.69%	1.02[0.84,1.24]
DART 1989	94/1015	131/1018		2.33%	0.72[0.56,0.92]
DART2 2003	283/1571	242/1543		5.52%	1.15[0.98,1.34]
DISAF 2003	6/201	8/206		0.14%	0.77[0.27,2.18]
Doi 2014	2/119	9/119		0.07%	0.22[0.05,1.01]
FAAT 2005	13/200	12/202		0.26%	1.09[0.51,2.34]
FORWARD 2013	4/289	5/297		0.09%	0.82[0.22,3.03]
GISSI-HF 2008	955/3494	1014/3481		17.24%	0.94[0.87,1.01]
GISSI-P 1999	472/5666	545/5658		8.97%	0.86[0.77,0.97]
HARP 1995	0/41	1/39		0.02%	0.32[0.01,7.57]
HEARTS 2017	1/143	3/142		0.03%	0.33[0.03,3.14]
Kumar 2013	1/39	1/39		0.02%	1[0.06,15.43]
NAT2 2013	3/150	6/150		0.08%	0.5[0.13,1.96]
Nutristroke 2009	0/38	4/34		0.02%	0.1[0.01,1.79]
OFAMI 2001	11/150	11/150		0.24%	1[0.45,2.24]
OMEGA 2009	88/1919	70/1885		1.57%	1.23[0.91,1.68]
Raitt 2005	4/100	10/100		0.12%	0.4[0.13,1.23]
Risk & Prevention 2013	348/6239	337/6266		6.27%	1.04[0.9,1.2]



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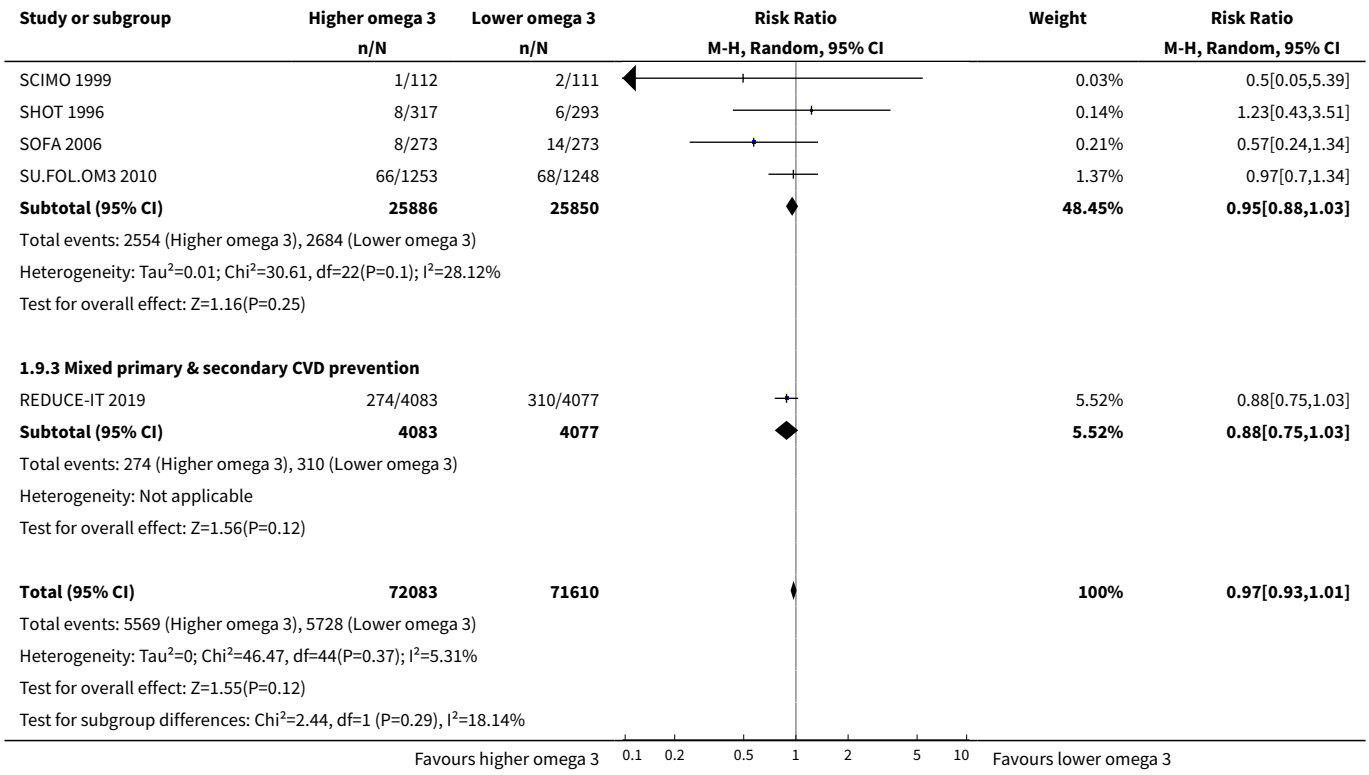
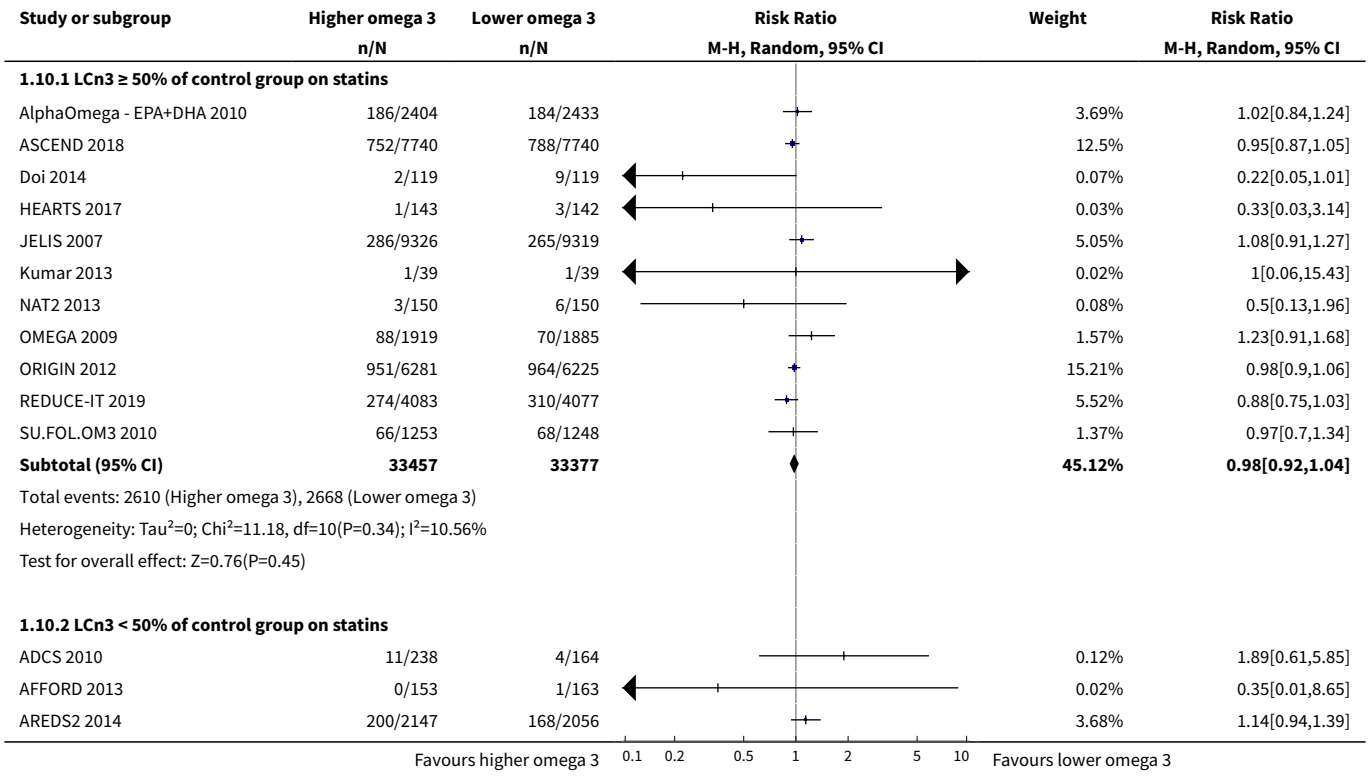


Analysis 1.10. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 10 All-cause mortality - LCn3 - subgroup by statin use.



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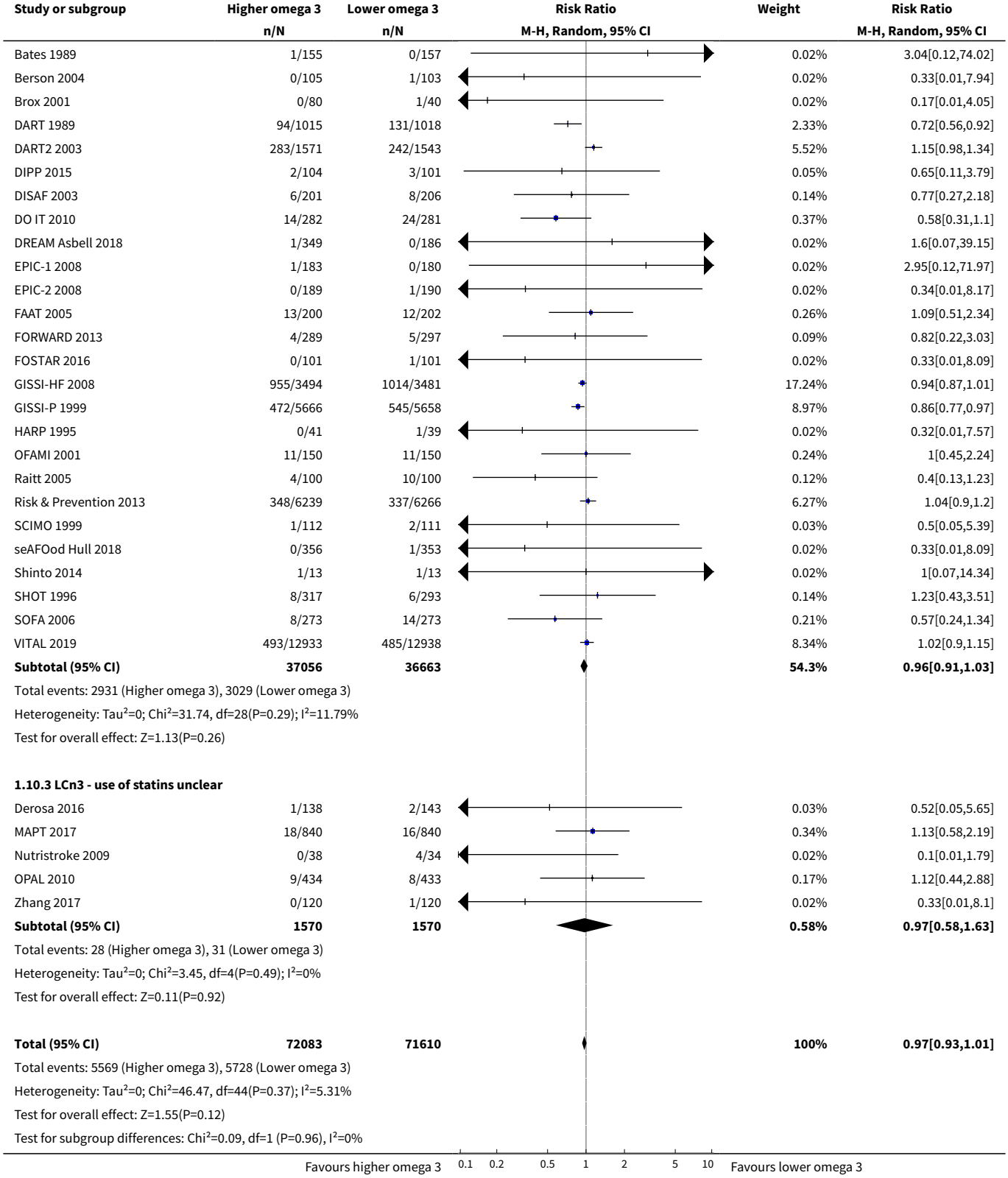

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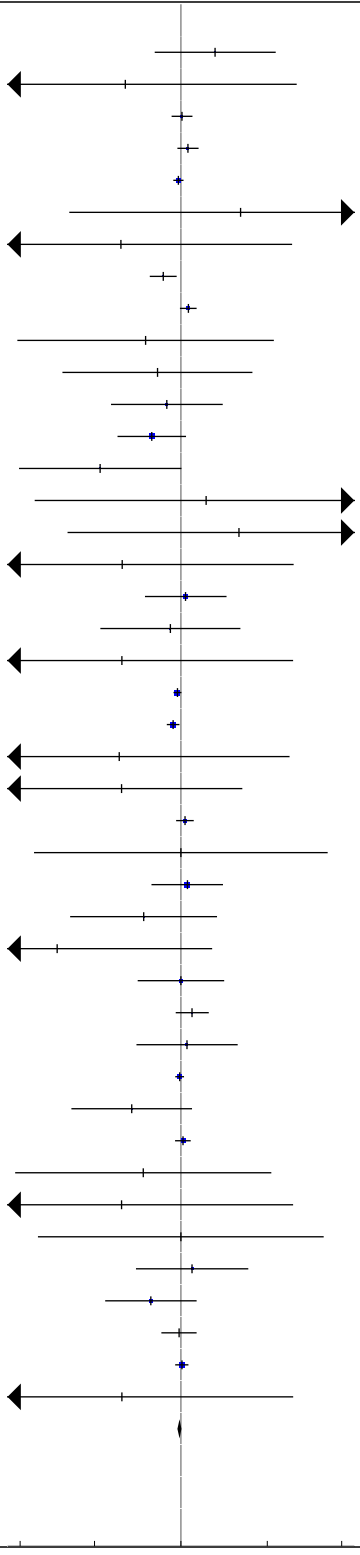
Analysis 1.11. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 11 All-cause mortality - LCn3 - subgroup by baseline TG.

Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 fats n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.11.1 Baseline TG not restricted					
ADCS 2010	11/238	4/164		0.12%	1.89[0.61,5.85]
AFFORD 2013	0/153	1/163		0.02%	0.35[0.01,8.65]
AlphaOmega - EPA+DHA 2010	186/2404	184/2433		3.69%	1.02[0.84,1.24]
AREDS2 2014	200/2147	168/2056		3.68%	1.14[0.94,1.39]
ASCEND 2018	752/7740	788/7740		12.5%	0.95[0.87,1.05]
Bates 1989	1/155	0/157		0.02%	3.04[0.12,74.02]
Berson 2004	0/105	1/103		0.02%	0.33[0.01,7.94]
DART 1989	94/1015	131/1018		2.33%	0.72[0.56,0.92]
DART2 2003	283/1571	242/1543		5.52%	1.15[0.98,1.34]
Derosa 2016	1/138	2/143		0.03%	0.52[0.05,5.65]
DIPP 2015	2/104	3/101		0.05%	0.65[0.11,3.79]
DISAF 2003	6/201	8/206		0.14%	0.77[0.27,2.18]
DO IT 2010	14/282	24/281		0.37%	0.58[0.31,1.1]
Doi 2014	2/119	9/119		0.07%	0.22[0.05,1.01]
DREAM Asbell 2018	1/349	0/186		0.02%	1.6[0.07,39.15]
EPIC-1 2008	1/183	0/180		0.02%	2.95[0.12,71.97]
EPIC-2 2008	0/189	1/190		0.02%	0.34[0.01,8.17]
FAAT 2005	13/200	12/202		0.26%	1.09[0.51,2.34]
FORWARD 2013	4/289	5/297		0.09%	0.82[0.22,3.03]
FOSTAR 2016	0/101	1/101		0.02%	0.33[0.01,8.09]
GISSI-HF 2008	955/3494	1014/3481		17.24%	0.94[0.87,1.01]
GISSI-P 1999	472/5666	545/5658		8.97%	0.86[0.77,0.97]
HARP 1995	0/41	1/39		0.02%	0.32[0.01,7.57]
HEARTS 2017	1/143	3/142		0.03%	0.33[0.03,3.14]
JELIS 2007	286/9326	265/9319		5.05%	1.08[0.91,1.27]
Kumar 2013	1/39	1/39		0.02%	1[0.06,15.43]
MAPT 2017	18/840	16/840		0.34%	1.13[0.58,2.19]
NAT2 2013	3/150	6/150		0.08%	0.5[0.13,1.96]
Nutristroke 2009	0/38	4/34		0.02%	0.1[0.01,1.79]
OFAMI 2001	11/150	11/150		0.24%	1[0.45,2.24]
OMEGA 2009	88/1919	70/1885		1.57%	1.23[0.91,1.68]
OPAL 2010	9/434	8/433		0.17%	1.12[0.44,2.88]
ORIGIN 2012	951/6281	964/6225		15.21%	0.98[0.9,1.06]
Raitt 2005	4/100	10/100		0.12%	0.4[0.13,1.23]
Risk & Prevention 2013	348/6239	337/6266		6.27%	1.04[0.9,1.2]
SCIMO 1999	1/112	2/111		0.03%	0.5[0.05,5.39]
seAFOod Hull 2018	0/356	1/353		0.02%	0.33[0.01,8.09]
Shinto 2014	1/13	1/13		0.02%	1[0.07,14.34]
SHOT 1996	8/317	6/293		0.14%	1.23[0.43,3.51]
SOFA 2006	8/273	14/273		0.21%	0.57[0.24,1.34]
SU.FOL.OM3 2010	66/1253	68/1248		1.37%	0.97[0.7,1.34]
VITAL 2019	493/12933	485/12938		8.34%	1.02[0.9,1.15]
Zhang 2017	0/120	1/120		0.02%	0.33[0.01,8.1]
Subtotal (95% CI)	**67920**	**67493**		**94.46%**	**0.97[0.94,1.01]**
Total events: 5295 (Favours higher omega 3), 5417 (Lower omega 3 fats)					
Heterogeneity: Tau^2=0; Chi^2=43.92, df=42(P=0.39); I^2=4.36%					
Test for overall effect: Z=1.27(P=0.2)					



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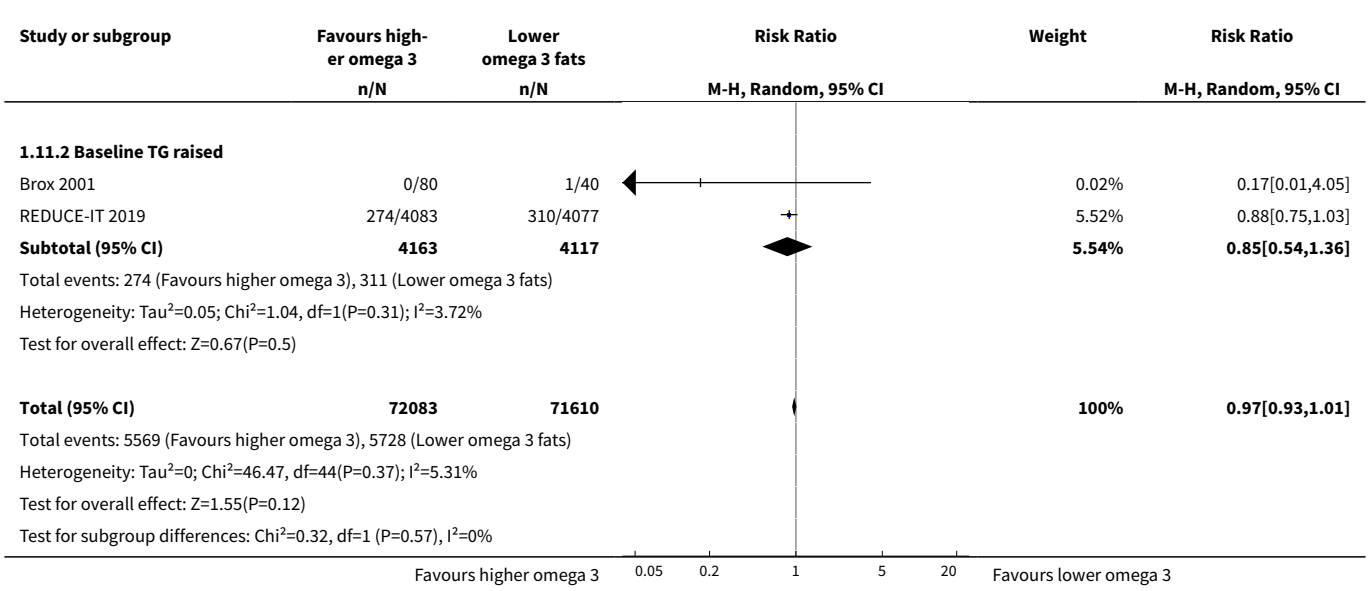
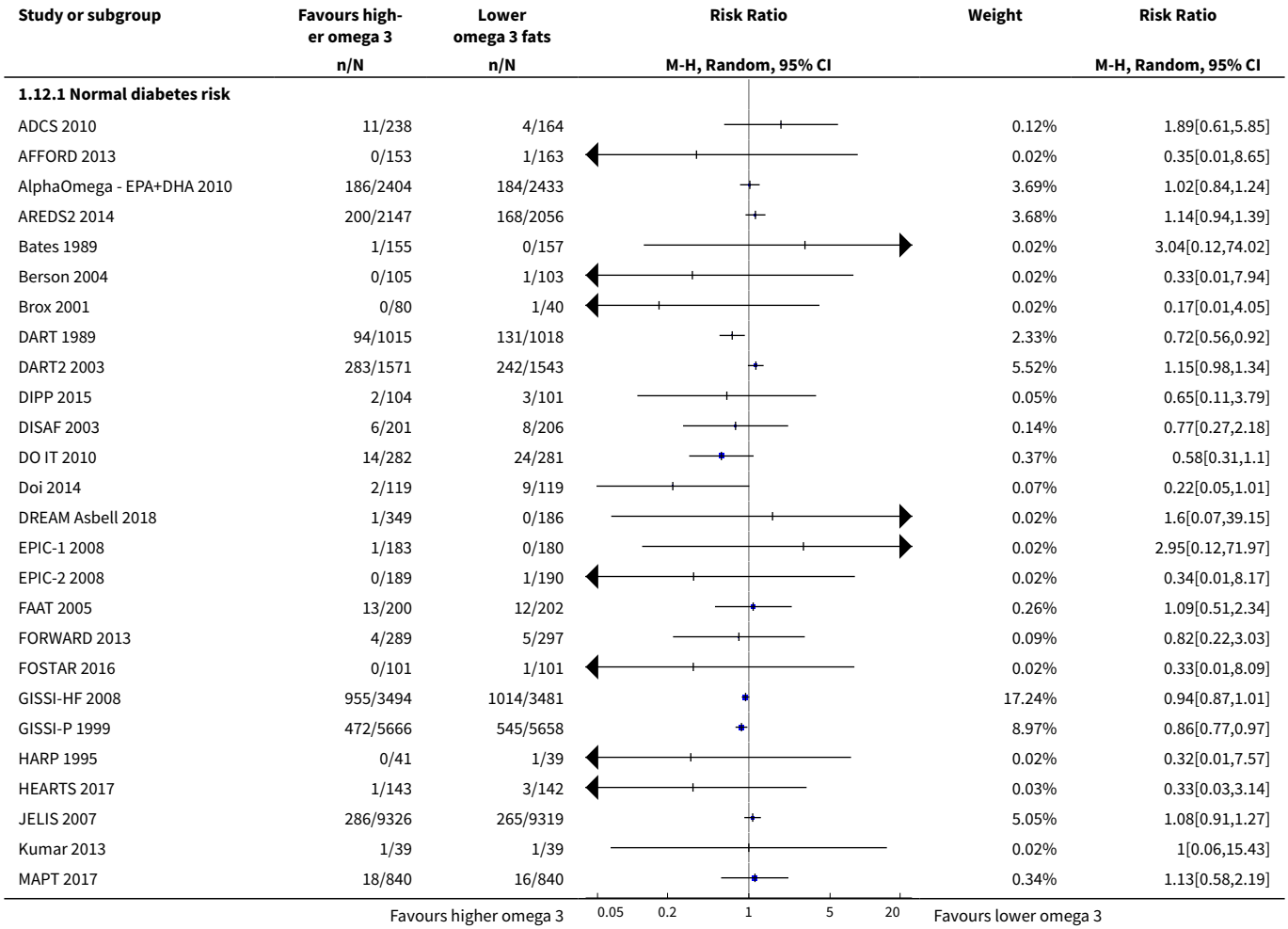


Analysis 1.12. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 12 All-cause mortality - LCn3 - subgroup by baseline DM.



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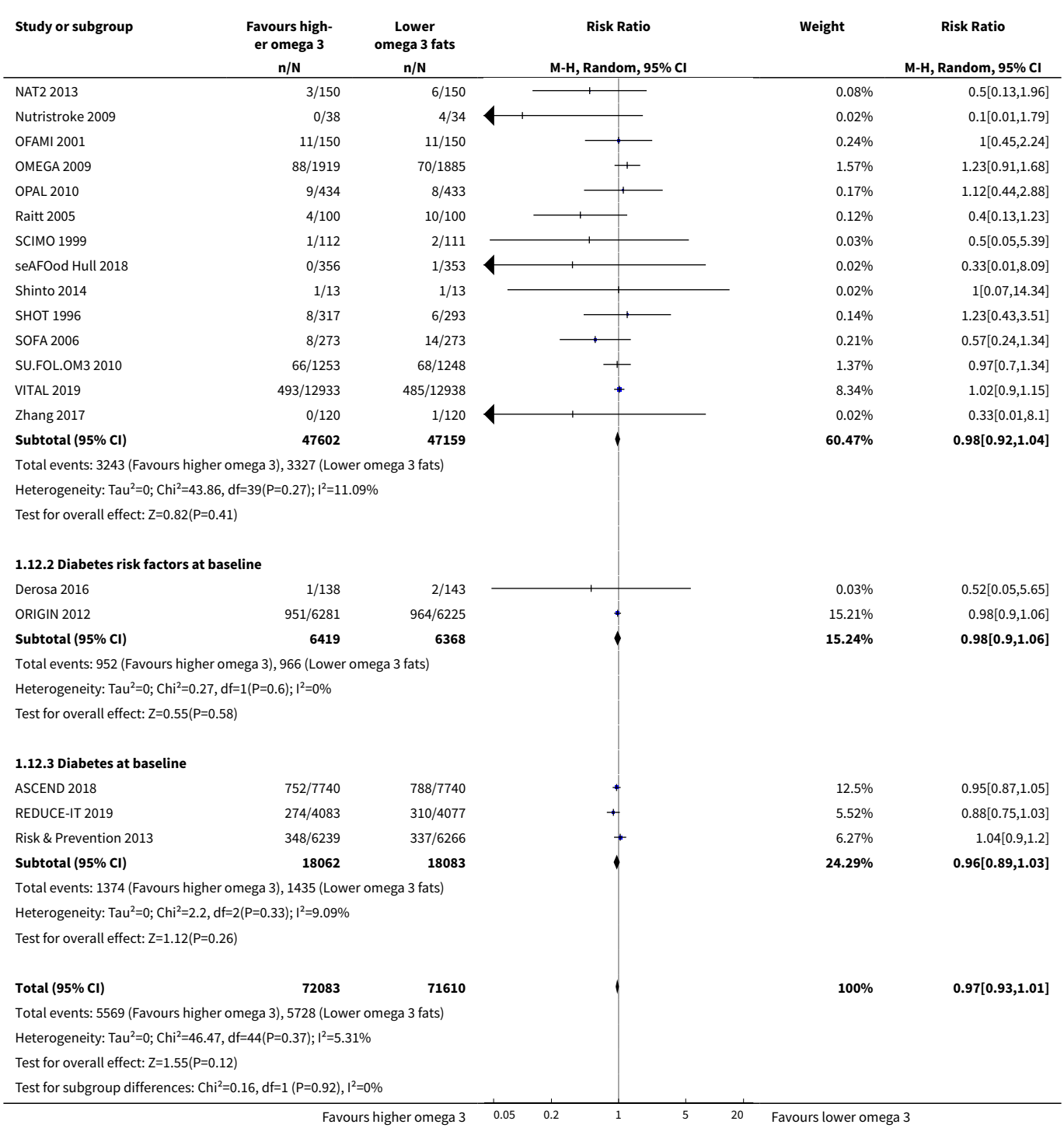

Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 fats n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
NAT2 2013	3/150	6/150		0.08%	0.5[0.13,1.96]
Nutristroke 2009	0/38	4/34		0.02%	0.1[0.01,1.79]
OFAMI 2001	11/150	11/150		0.24%	1[0.45,2.24]
OMEGA 2009	88/1919	70/1885		1.57%	1.23[0.91,1.68]
OPAL 2010	9/434	8/433		0.17%	1.12[0.44,2.88]
Raitt 2005	4/100	10/100		0.12%	0.4[0.13,1.23]
SCIMO 1999	1/112	2/111		0.03%	0.5[0.05,5.39]
seAFOod Hull 2018	0/356	1/353		0.02%	0.33[0.01,8.09]
Shinto 2014	1/13	1/13		0.02%	1[0.07,14.34]
SHOT 1996	8/317	6/293		0.14%	1.23[0.43,3.51]
SOFA 2006	8/273	14/273		0.21%	0.57[0.24,1.34]
SU.FOL.OM3 2010	66/1253	68/1248		1.37%	0.97[0.7,1.34]
VITAL 2019	493/12933	485/12938		8.34%	1.02[0.9,1.15]
Zhang 2017	0/120	1/120		0.02%	0.33[0.01,8.1]
Subtotal (95% CI)	**47602**	**47159**		**60.47%**	**0.98[0.92,1.04]**
Total events: 3243 (Favours higher omega 3), 3327 (Lower omega 3 fats)					
Heterogeneity: Tau^2=0; Chi^2=43.86, df=39(P=0.27); I^2=11.09%					
Test for overall effect: Z=0.82(P=0.41)					
1.12.2 Diabetes risk factors at baseline					
Derosa 2016	1/138	2/143		0.03%	0.52[0.05,5.65]
ORIGIN 2012	951/6281	964/6225		15.21%	0.98[0.9,1.06]
Subtotal (95% CI)	**6419**	**6368**		**15.24%**	**0.98[0.9,1.06]**
Total events: 952 (Favours higher omega 3), 966 (Lower omega 3 fats)					
Heterogeneity: Tau^2=0; Chi^2=0.27, df=1(P=0.6); I^2=0%					
Test for overall effect: Z=0.55(P=0.58)					
1.12.3 Diabetes at baseline					
ASCEND 2018	752/7740	788/7740		12.5%	0.95[0.87,1.05]
REDUCE-IT 2019	274/4083	310/4077		5.52%	0.88[0.75,1.03]
Risk & Prevention 2013	348/6239	337/6266		6.27%	1.04[0.9,1.2]
Subtotal (95% CI)	**18062**	**18083**		**24.29%**	**0.96[0.89,1.03]**
Total events: 1374 (Favours higher omega 3), 1435 (Lower omega 3 fats)					
Heterogeneity: Tau^2=0; Chi^2=2.2, df=2(P=0.33); I^2=9.09%					
Test for overall effect: Z=1.12(P=0.26)					
Total (95% CI)	**72083**	**71610**		**100%**	**0.97[0.93,1.01]**
Total events: 5569 (Favours higher omega 3), 5728 (Lower omega 3 fats)					
Heterogeneity: Tau^2=0; Chi^2=46.47, df=44(P=0.37); I^2=5.31%					
Test for overall effect: Z=1.55(P=0.12)					
Test for subgroup differences: Chi^2=0.16, df=1 (P=0.92), I^2=0%					

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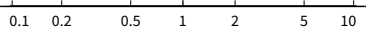
Analysis 1.13. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 13 Cardiovascular mortality (overall) - LCn3.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
AlphaOmega - EPA+DHA 2010	80/2404	82/2433		4.46%	0.99[0.73,1.34]
AREDS2 2014	14/2147	13/2056		0.87%	1.03[0.49,2.19]
ASCEND 2018	196/7740	240/7740		8.9%	0.82[0.68,0.98]
Brox 2001	0/80	1/40		0.05%	0.17[0.01,4.05]
DART 1989	84/1015	121/1018		5.51%	0.7[0.53,0.91]
DART2 2003	180/1571	139/1543		7.64%	1.27[1.03,1.57]
Derosa 2016	2/138	3/143		0.16%	0.69[0.12,4.07]
DO IT 2010	7/282	11/281		0.57%	0.63[0.25,1.61]
Doi 2014	1/119	5/119		0.11%	0.2[0.02,1.69]
DREAM Asbell 2018	1/349	0/186		0.05%	1.6[0.07,39.15]
FAAT 2005	9/200	9/202		0.61%	1.01[0.41,2.49]
FOSTAR 2016	0/101	1/101		0.05%	0.33[0.01,8.09]
GISSI-HF 2008	712/3494	765/3481		16.46%	0.93[0.85,1.02]
GISSI-P 1999	291/5665	348/5658		11.18%	0.84[0.72,0.97]
HARP 1995	0/41	1/39		0.05%	0.32[0.01,7.57]
Kumar 2013	1/39	1/39		0.07%	1[0.06,15.43]
Nutristroke 2009	0/38	4/34		0.06%	0.1[0.01,1.79]
OFAMI 2001	8/150	8/150		0.55%	1[0.39,2.59]
OMEGA 2009	67/1919	51/1885		3.37%	1.29[0.9,1.85]
ORIGIN 2012	574/6281	581/6255		14.63%	0.98[0.88,1.1]
Raitt 2005	2/100	5/100		0.19%	0.4[0.08,2.01]
REDUCE-IT 2019	174/4089	213/4090		8.37%	0.82[0.67,0.99]
Risk & Prevention 2013	142/6239	137/6266		6.66%	1.04[0.83,1.31]
SCIMO 1999	0/112	1/111		0.05%	0.33[0.01,8.02]
Shinto 2014	1/13	0/13		0.05%	3[0.13,67.51]
SHOT 1996	7/317	5/293		0.39%	1.29[0.42,4.03]
SOFA 2006	6/273	13/273		0.55%	0.46[0.18,1.2]
SU.FOL.OM3 2010	23/1253	28/1248		1.59%	0.82[0.47,1.41]
VITAL 2019	142/12933	148/12938		6.79%	0.96[0.76,1.21]
Total (95% CI)	**59102**	**58735**		**100%**	**0.92[0.86,0.99]**
Total events: 2724 (Higher omega 3), 2934 (Lower omega 3)					
Heterogeneity: Tau²=0.01; Chi²=35.85, df=28(P=0.15); I²=21.89%					
Test for overall effect: Z=2.18(P=0.03)					



Analysis 1.14. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 14 CVD mortality - LCn3 - SA fixed-effect.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
AlphaOmega - EPA+DHA 2010	80/2404	82/2433		2.77%	0.99[0.73,1.34]
AREDS2 2014	14/2147	13/2056		0.45%	1.03[0.49,2.19]
ASCEND 2018	196/7740	240/7740		8.16%	0.82[0.68,0.98]
Brox 2001	0/80	1/40		0.07%	0.17[0.01,4.05]
DART 1989	84/1015	121/1018		4.11%	0.7[0.53,0.91]
DART2 2003	180/1571	139/1543		4.77%	1.27[1.03,1.57]

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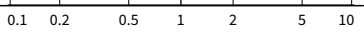
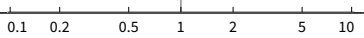
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Derosa 2016	2/138	3/143		0.1%	0.69[0.12,4.07]
DO IT 2010	7/282	11/281		0.37%	0.63[0.25,1.61]
Doi 2014	1/119	5/119		0.17%	0.2[0.02,1.69]
DREAM Asbell 2018	1/349	0/186		0.02%	1.6[0.07,39.15]
FAAT 2005	9/200	9/202		0.3%	1.01[0.41,2.49]
FOSTAR 2016	0/101	1/101		0.05%	0.33[0.01,8.09]
GISSI-HF 2008	712/3494	765/3481		26.05%	0.93[0.85,1.02]
GISSI-P 1999	291/5665	348/5658		11.83%	0.84[0.72,0.97]
HARP 1995	0/41	1/39		0.05%	0.32[0.01,7.57]
Kumar 2013	1/39	1/39		0.03%	1[0.06,15.43]
Nutristroke 2009	0/38	4/34		0.16%	0.1[0.01,1.79]
OFAMI 2001	8/150	8/150		0.27%	1[0.39,2.59]
OMEGA 2009	67/1919	51/1885		1.75%	1.29[0.9,1.85]
ORIGIN 2012	574/6281	581/6255		19.79%	0.98[0.88,1.1]
Raitt 2005	2/100	5/100		0.17%	0.4[0.08,2.01]
REDUCE-IT 2019	174/4089	213/4090		7.24%	0.82[0.67,0.99]
Risk & Prevention 2013	142/6239	137/6266		4.65%	1.04[0.83,1.31]
SCIMO 1999	0/112	1/111		0.05%	0.33[0.01,8.02]
Shinto 2014	1/13	0/13		0.02%	3[0.13,67.51]
SHOT 1996	7/317	5/293		0.18%	1.29[0.42,4.03]
SOFA 2006	6/273	13/273		0.44%	0.46[0.18,1.2]
SU.FOL.OM3 2010	23/1253	28/1248		0.95%	0.82[0.47,1.41]
VITAL 2019	142/12933	148/12938		5.03%	0.96[0.76,1.21]
Total (95% CI)	**59102**	**58735**		**100%**	**0.93[0.88,0.97]**
Total events: 2724 (Higher omega 3), 2934 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=35.85, df=28(P=0.15); I^2=21.89%					
Test for overall effect: Z=3.08(P=0)					



Favours higher omega 3 — Favours lower omega 3

Analysis 1.15. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 15 CVD mortality - LCn3 - SA by summary risk of bias.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.15.1 Low risk of bias					
AlphaOmega - EPA+DHA 2010	80/2404	82/2433		6.98%	0.99[0.73,1.34]
AREDS2 2014	14/2147	13/2056		1.13%	1.03[0.49,2.19]
ASCEND 2018	196/7740	240/7740		18.49%	0.82[0.68,0.98]
Derosa 2016	2/138	3/143		0.2%	0.69[0.12,4.07]
DREAM Asbell 2018	1/349	0/186		0.06%	1.6[0.07,39.15]
FOSTAR 2016	0/101	1/101		0.06%	0.33[0.01,8.09]
OMEGA 2009	67/1919	51/1885		4.98%	1.29[0.9,1.85]
ORIGIN 2012	574/6281	581/6255		52.98%	0.98[0.88,1.1]
SCIMO 1999	0/112	1/111		0.06%	0.33[0.01,8.02]
SOFA 2006	6/273	13/273		0.71%	0.46[0.18,1.2]
SU.FOL.OM3 2010	23/1253	28/1248		2.15%	0.82[0.47,1.41]
VITAL 2019	142/12933	148/12938		12.21%	0.96[0.76,1.21]
Subtotal (95% CI)	**35650**	**35369**		**100%**	**0.95[0.88,1.03]**



Favours higher omega 3 — Favours lower omega 3

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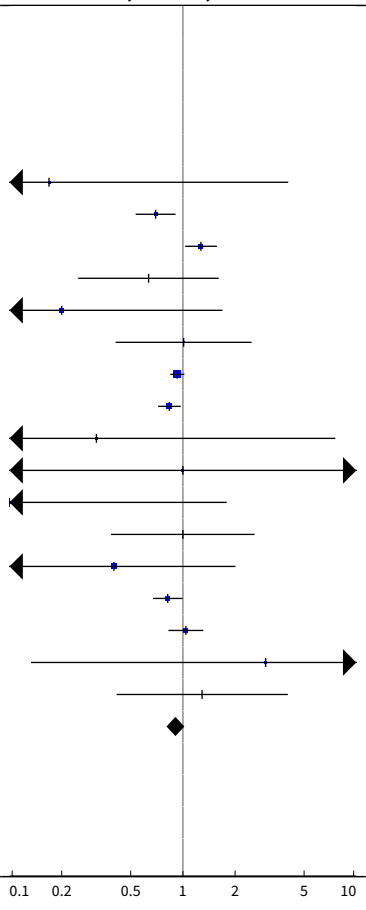
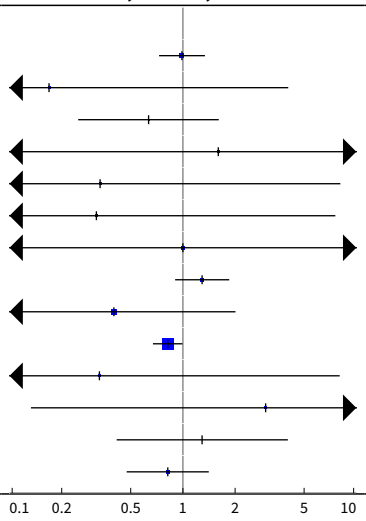
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 1105 (Higher omega 3), 1161 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=9.4, df=11(P=0.58); I²=0%					
Test for overall effect: Z=1.24(P=0.22)					
1.15.2 Moderate/high risk of bias					
Brox 2001	0/80	1/40		0.14%	0.17[0.01,4.05]
DART 1989	84/1015	121/1018		11.15%	0.7[0.53,0.91]
DART2 2003	180/1571	139/1543		14.06%	1.27[1.03,1.57]
DO IT 2010	7/282	11/281		1.5%	0.63[0.25,1.61]
Doi 2014	1/119	5/119		0.3%	0.2[0.02,1.69]
FAAT 2005	9/200	9/202		1.6%	1.01[0.41,2.49]
GISSI-HF 2008	712/3494	765/3481		22.02%	0.93[0.85,1.02]
GISSI-P 1999	291/5665	348/5658		17.88%	0.84[0.72,0.97]
HARP 1995	0/41	1/39		0.14%	0.32[0.01,7.57]
Kumar 2013	1/39	1/39		0.18%	1[0.06,15.43]
Nutristroke 2009	0/38	4/34		0.17%	0.1[0.01,1.79]
OFAMI 2001	8/150	8/150		1.44%	1[0.39,2.59]
Raitt 2005	2/100	5/100		0.52%	0.4[0.08,2.01]
REDUCE-IT 2019	174/4089	213/4090		14.93%	0.82[0.67,0.99]
Risk & Prevention 2013	142/6239	137/6266		12.79%	1.04[0.83,1.31]
Shinto 2014	1/13	0/13		0.14%	3[0.13,67.51]
SHOT 1996	7/317	5/293		1.03%	1.29[0.42,4.03]
Subtotal (95% CI)	**23452**	**23366**		**100%**	**0.9[0.8,1.02]**
Total events: 1619 (Higher omega 3), 1773 (Lower omega 3)					
Heterogeneity: Tau²=0.01; Chi²=25.87, df=16(P=0.06); I²=38.14%					
Test for overall effect: Z=1.67(P=0.1)					
Test for subgroup differences: Chi²=0.47, df=1 (P=0.49), I²=0%					



Analysis 1.16. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 16 CVD mortality - LCn3 - SA by compliance and study size.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.16.1 SA - low risk of compliance bias					
AlphaOmega - EPA+DHA 2010	80/2404	82/2433		15.51%	0.99[0.73,1.34]
Brox 2001	0/80	1/40		0.14%	0.17[0.01,4.05]
DO IT 2010	7/282	11/281		1.63%	0.63[0.25,1.61]
DREAM Asbell 2018	1/349	0/186		0.14%	1.6[0.07,39.15]
FOSTAR 2016	0/101	1/101		0.14%	0.33[0.01,8.09]
HARP 1995	0/41	1/39		0.14%	0.32[0.01,7.57]
Kumar 2013	1/39	1/39		0.19%	1[0.06,15.43]
OMEGA 2009	67/1919	51/1885		11.06%	1.29[0.9,1.85]
Raitt 2005	2/100	5/100		0.54%	0.4[0.08,2.01]
REDUCE-IT 2019	174/4089	213/4090		37.2%	0.82[0.67,0.99]
SCIMO 1999	0/112	1/111		0.14%	0.33[0.01,8.02]
Shinto 2014	1/13	0/13		0.15%	3[0.13,67.51]
SHOT 1996	7/317	5/293		1.1%	1.29[0.42,4.03]
SU.FOL.OM3 2010	23/1253	28/1248		4.77%	0.82[0.47,1.41]



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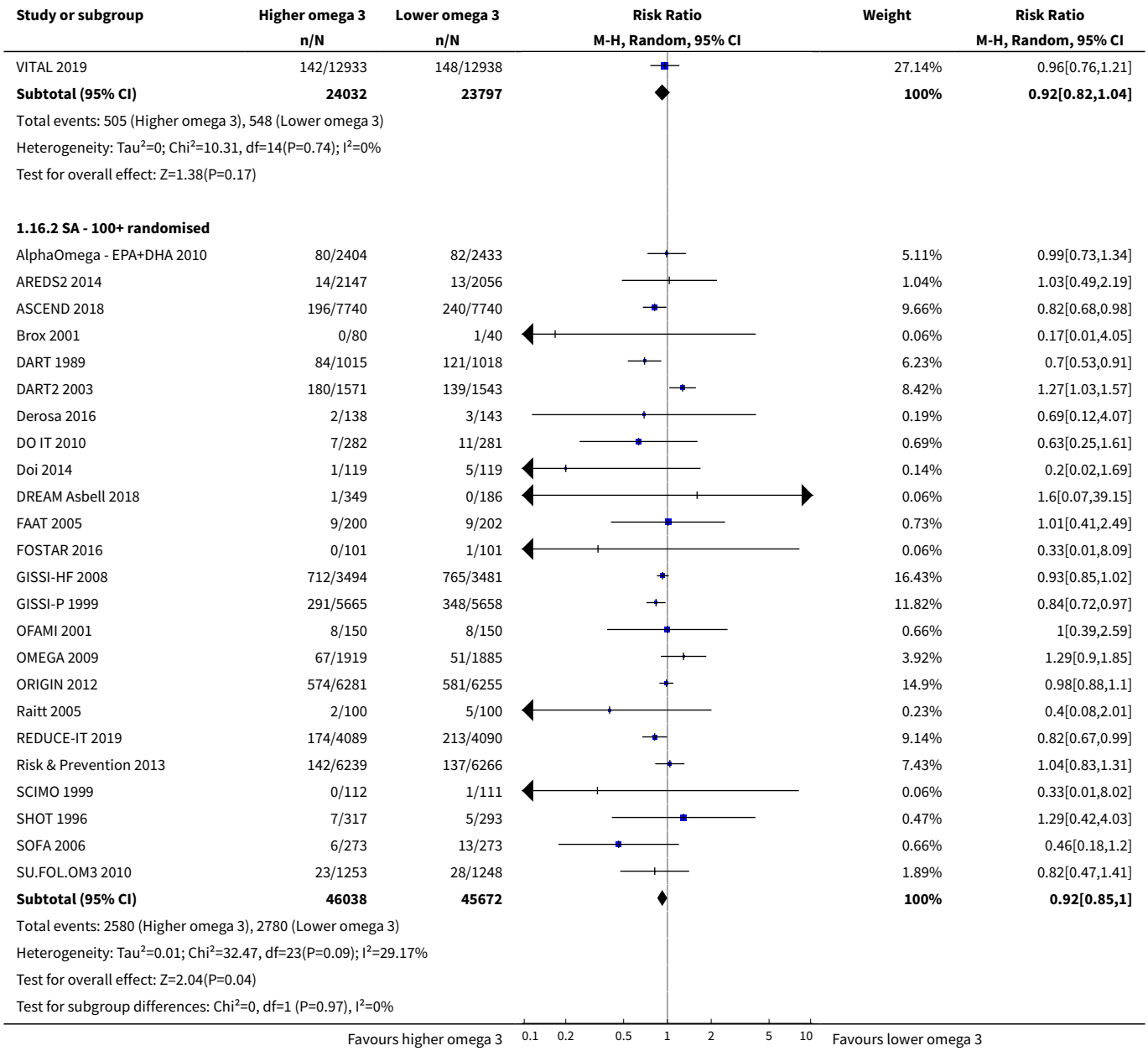
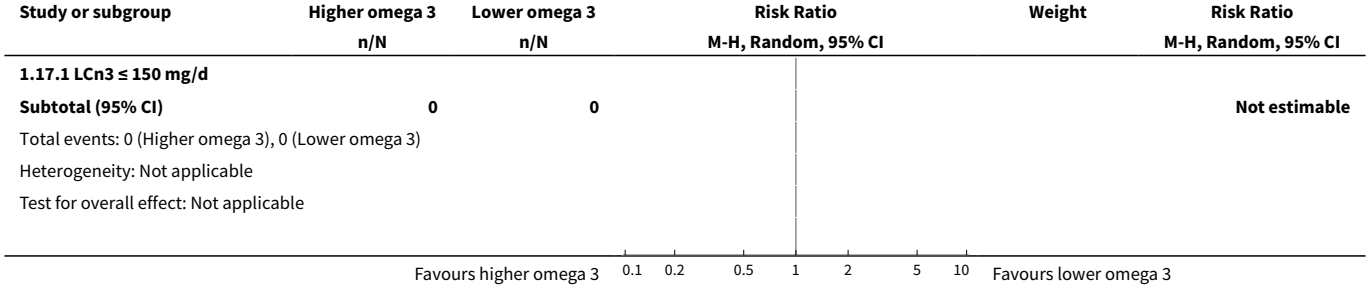


Analysis 1.17. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 17 CVD mortality - LCn3 - subgroup by dose.



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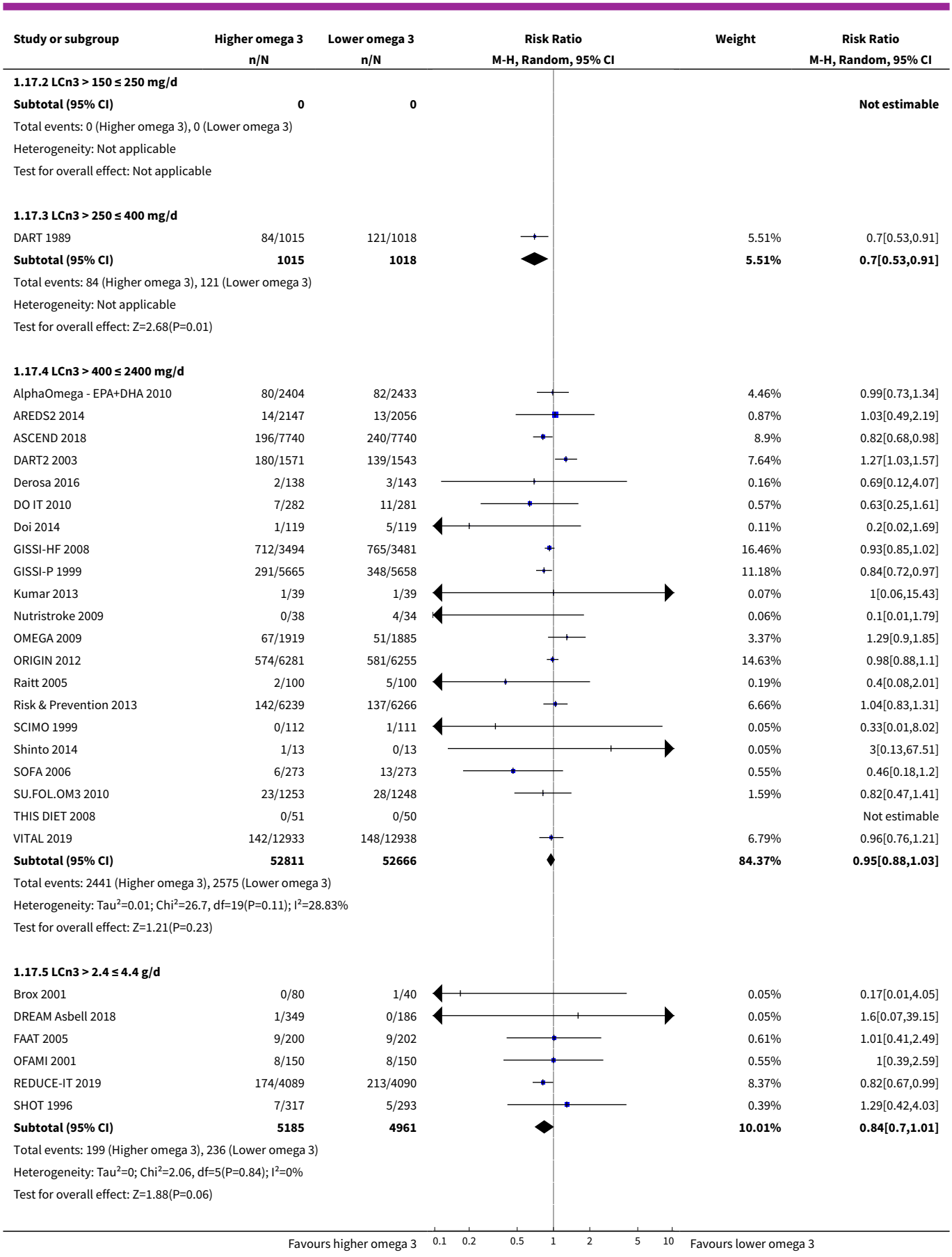

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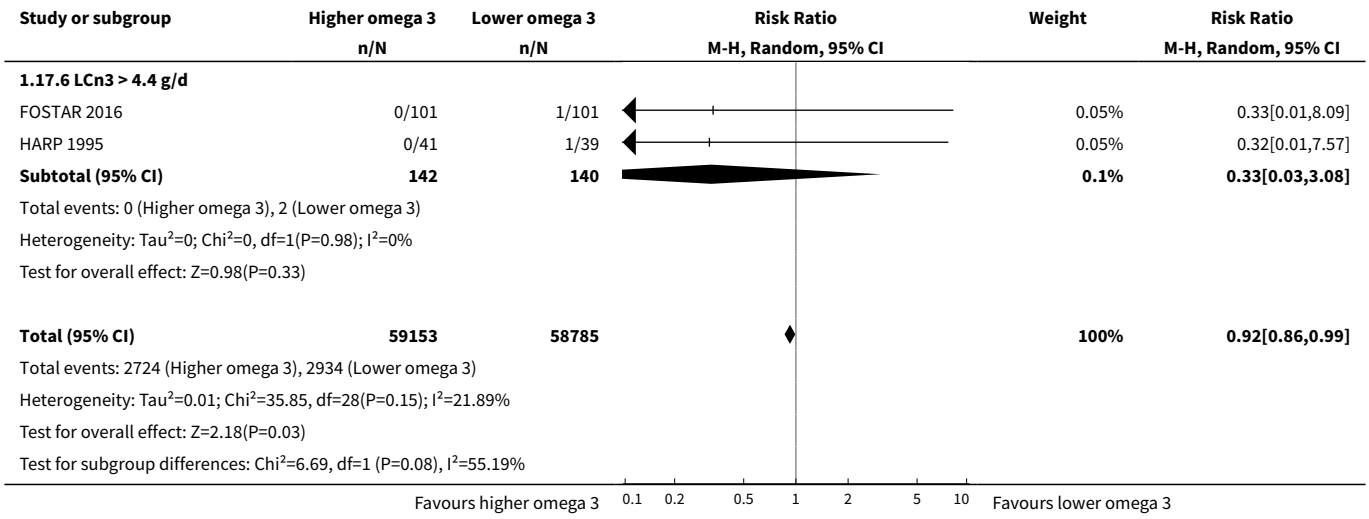
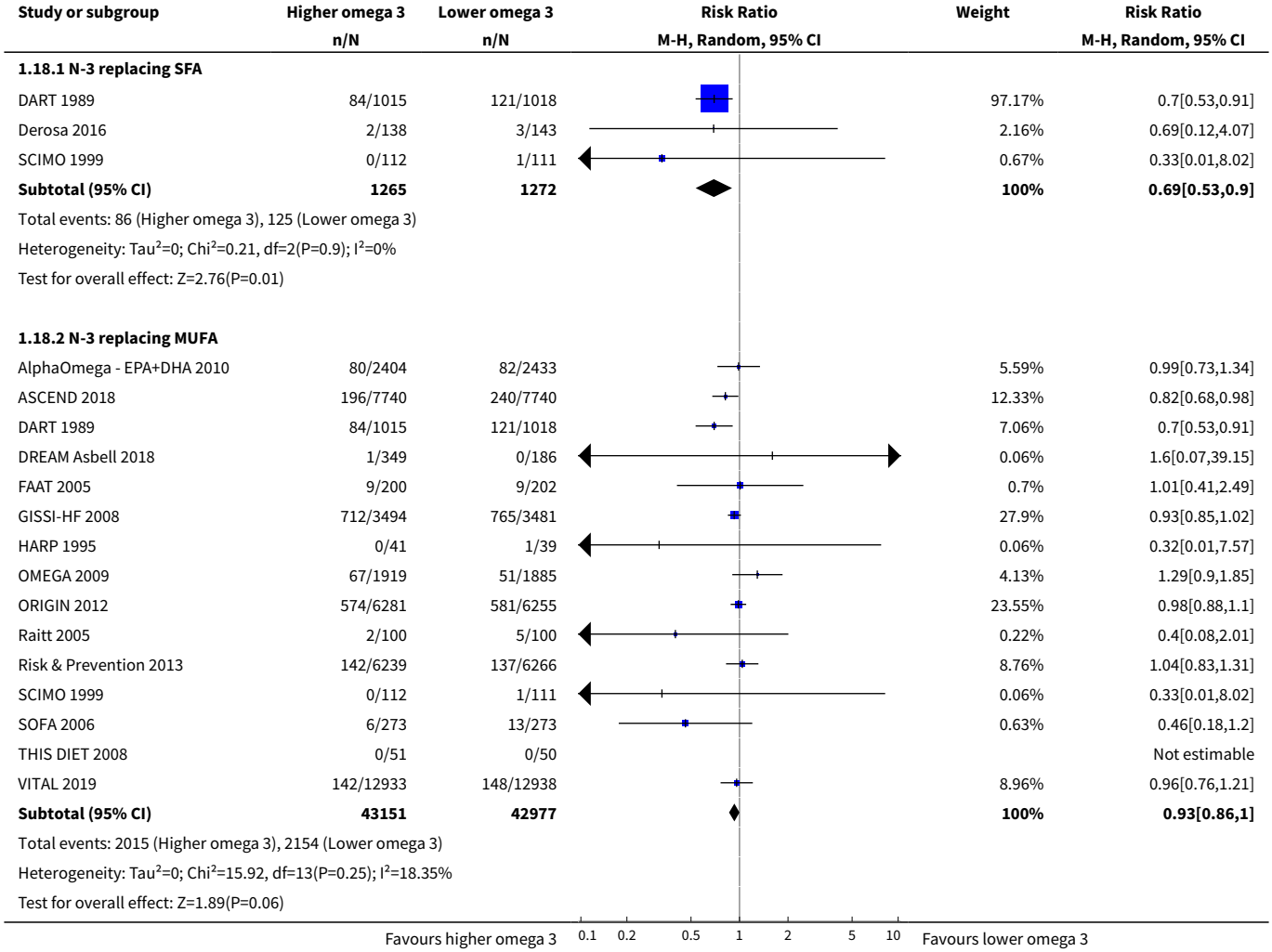


Analysis 1.18. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 18 CVD mortality - LCn3 - subgroup by replacement.



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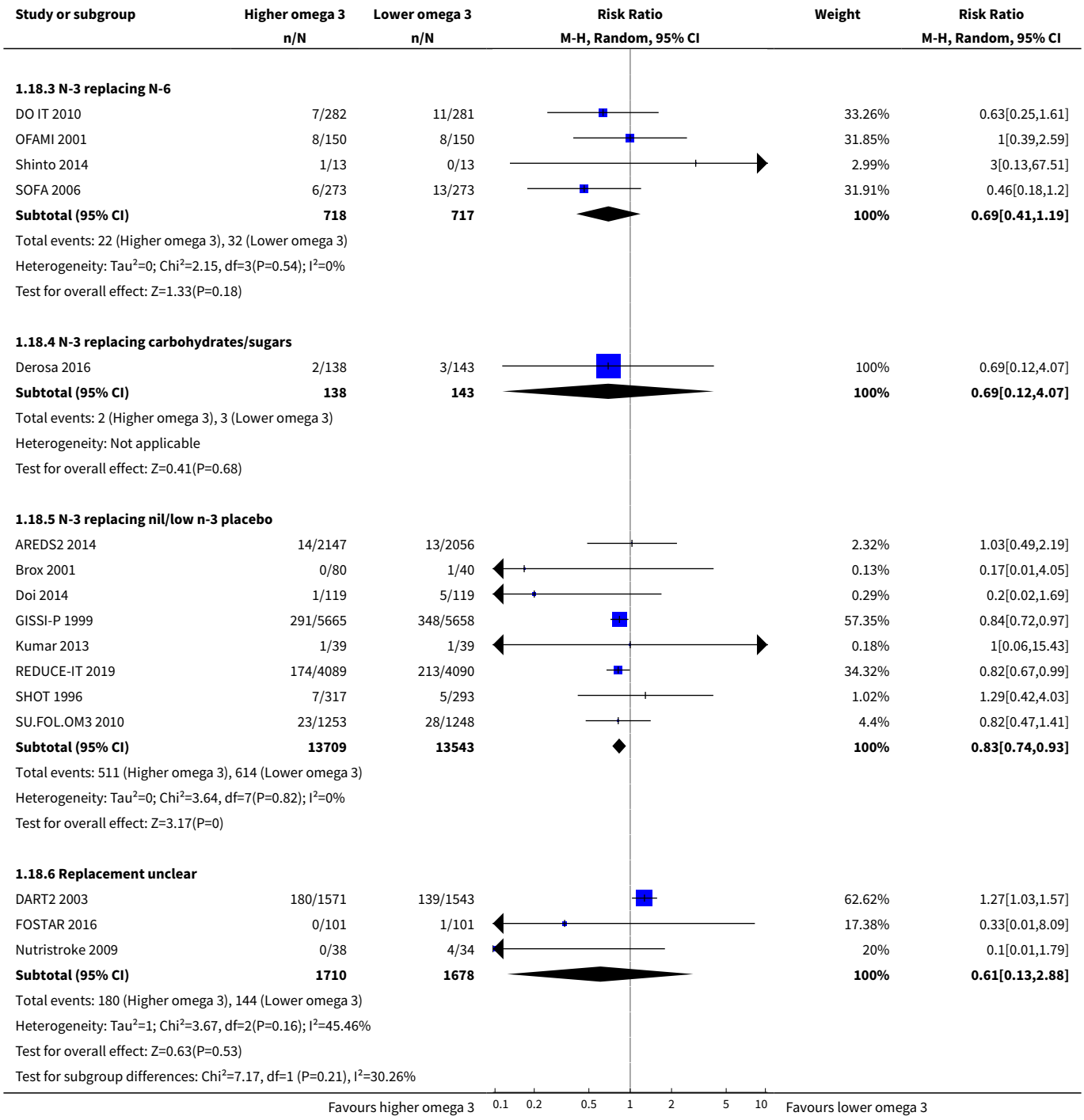
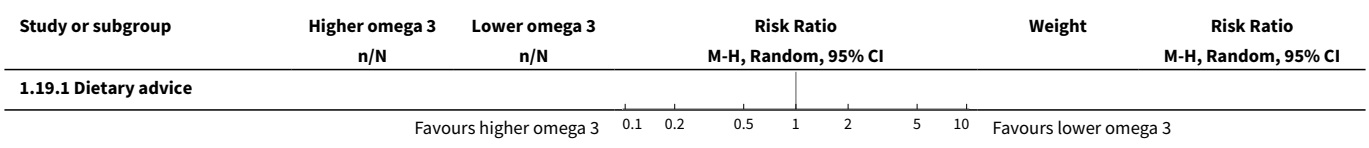


Analysis 1.19. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 19 CVD mortality - LCn3 - subgroup by intervention type.



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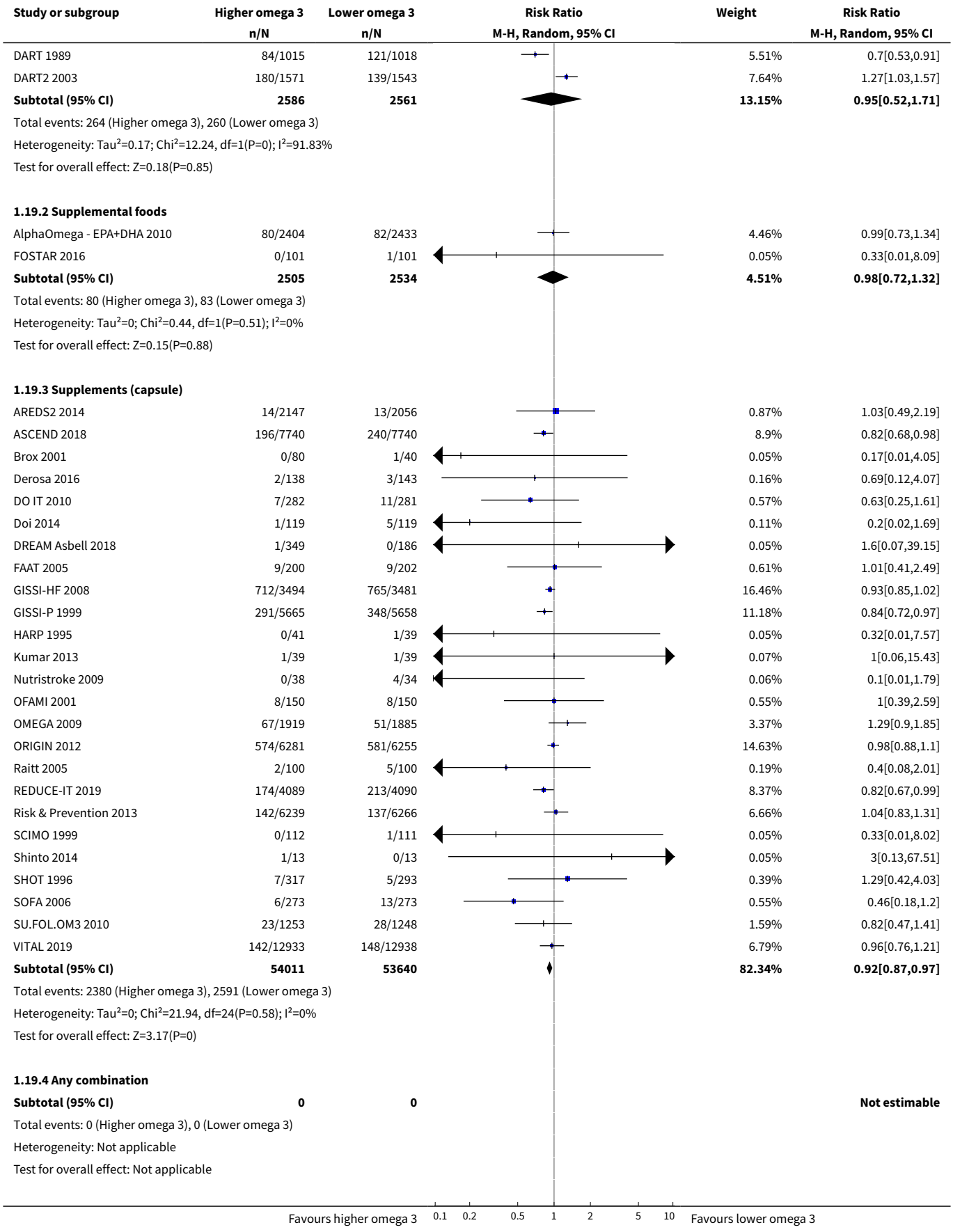

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	84/1015	121/1018		5.51%	0.7[0.53,0.91]
DART2 2003	180/1571	139/1543		7.64%	1.27[1.03,1.57]
Subtotal (95% CI)	**2586**	**2561**		**13.15%**	**0.95[0.52,1.71]**
Total events: 264 (Higher omega 3), 260 (Lower omega 3)					
Heterogeneity: Tau²=0.17; Chi²=12.24, df=1(P=0); I²=91.83%					
Test for overall effect: Z=0.18(P=0.85)					
1.19.2 Supplemental foods					
AlphaOmega - EPA+DHA 2010	80/2404	82/2433		4.46%	0.99[0.73,1.34]
FOSTAR 2016	0/101	1/101		0.05%	0.33[0.01,8.09]
Subtotal (95% CI)	**2505**	**2534**		**4.51%**	**0.98[0.72,1.32]**
Total events: 80 (Higher omega 3), 83 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=0.44, df=1(P=0.51); I²=0%					
Test for overall effect: Z=0.15(P=0.88)					
1.19.3 Supplements (capsule)					
AREDS2 2014	14/2147	13/2056		0.87%	1.03[0.49,2.19]
ASCEND 2018	196/7740	240/7740		8.9%	0.82[0.68,0.98]
Brox 2001	0/80	1/40		0.05%	0.17[0.01,4.05]
Derosa 2016	2/138	3/143		0.16%	0.69[0.12,4.07]
DO IT 2010	7/282	11/281		0.57%	0.63[0.25,1.61]
Doi 2014	1/119	5/119		0.11%	0.2[0.02,1.69]
DREAM Asbell 2018	1/349	0/186		0.05%	1.6[0.07,39.15]
FAAT 2005	9/200	9/202		0.61%	1.01[0.41,2.49]
GISSI-HF 2008	712/3494	765/3481		16.46%	0.93[0.85,1.02]
GISSI-P 1999	291/5665	348/5658		11.18%	0.84[0.72,0.97]
HARP 1995	0/41	1/39		0.05%	0.32[0.01,7.57]
Kumar 2013	1/39	1/39		0.07%	1[0.06,15.43]
Nutristroke 2009	0/38	4/34		0.06%	0.1[0.01,1.79]
OFAMI 2001	8/150	8/150		0.55%	1[0.39,2.59]
OMEGA 2009	67/1919	51/1885		3.37%	1.29[0.9,1.85]
ORIGIN 2012	574/6281	581/6255		14.63%	0.98[0.88,1.1]
Raitt 2005	2/100	5/100		0.19%	0.4[0.08,2.01]
REDUCE-IT 2019	174/4089	213/4090		8.37%	0.82[0.67,0.99]
Risk & Prevention 2013	142/6239	137/6266		6.66%	1.04[0.83,1.31]
SCIMO 1999	0/112	1/111		0.05%	0.33[0.01,8.02]
Shinto 2014	1/13	0/13		0.05%	3[0.13,67.51]
SHOT 1996	7/317	5/293		0.39%	1.29[0.42,4.03]
SOFA 2006	6/273	13/273		0.55%	0.46[0.18,1.2]
SU.FOL.OM3 2010	23/1253	28/1248		1.59%	0.82[0.47,1.41]
VITAL 2019	142/12933	148/12938		6.79%	0.96[0.76,1.21]
Subtotal (95% CI)	**54011**	**53640**		**82.34%**	**0.92[0.87,0.97]**
Total events: 2380 (Higher omega 3), 2591 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=21.94, df=24(P=0.58); I²=0%					
Test for overall effect: Z=3.17(P=0)					
1.19.4 Any combination					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 3), 0 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

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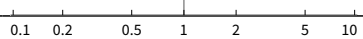
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total (95% CI)	**59102**	**58735**		**100%**	**0.92[0.86,0.99]**
Total events: 2724 (Higher omega 3), 2934 (Lower omega 3)					
Heterogeneity: Tau²=0.01; Chi²=35.85, df=28(P=0.15); I²=21.89%					
Test for overall effect: Z=2.18(P=0.03)					
Test for subgroup differences: Chi²=0.17, df=1 (P=0.92), I²=0%					

Favours higher omega 3 — Favours lower omega 3

Analysis 1.20. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 20 CVD mortality - LCn3 - subgroup by duration.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.20.1 Medium duration 1 to < 2 years in study					
Brox 2001	0/80	1/40		0.05%	0.17[0.01,4.05]
Derosa 2016	2/138	3/143		0.16%	0.69[0.12,4.07]
Doi 2014	1/119	5/119		0.11%	0.2[0.02,1.69]
DREAM Asbell 2018	1/349	0/186		0.05%	1.6[0.07,39.15]
FAAT 2005	9/200	9/202		0.61%	1.01[0.41,2.49]
Kumar 2013	1/39	1/39		0.07%	1[0.06,15.43]
Nutristroke 2009	0/38	4/34		0.06%	0.1[0.01,1.79]
OMEGA 2009	67/1919	51/1885		3.37%	1.29[0.9,1.85]
Shinto 2014	1/13	0/13		0.05%	3[0.13,67.51]
SHOT 1996	7/317	5/293		0.39%	1.29[0.42,4.03]
SOFA 2006	6/273	13/273		0.55%	0.46[0.18,1.2]
Subtotal (95% CI)	**3485**	**3227**		**5.48%**	**0.94[0.64,1.37]**
Total events: 95 (Higher omega 3), 92 (Lower omega 3)					
Heterogeneity: Tau²=0.05; Chi²=11.24, df=10(P=0.34); I²=11.02%					
Test for overall effect: Z=0.34(P=0.73)					
1.20.2 Medium-long duration: 2 to < 4 years in study					
AlphaOmega - EPA+DHA 2010	80/2404	82/2433		4.46%	0.99[0.73,1.34]
DART 1989	84/1015	121/1018		5.51%	0.7[0.53,0.91]
DO IT 2010	7/282	11/281		0.57%	0.63[0.25,1.61]
FOSTAR 2016	0/101	1/101		0.05%	0.33[0.01,8.09]
GISSI-HF 2008	712/3494	765/3481		16.46%	0.93[0.85,1.02]
GISSI-P 1999	291/5665	348/5658		11.18%	0.84[0.72,0.97]
HARP 1995	0/41	1/39		0.05%	0.32[0.01,7.57]
OFAMI 2001	8/150	8/150		0.55%	1[0.39,2.59]
Raitt 2005	2/100	5/100		0.19%	0.4[0.08,2.01]
SCIMO 1999	0/112	1/111		0.05%	0.33[0.01,8.02]
Subtotal (95% CI)	**13364**	**13372**		**39.07%**	**0.89[0.82,0.95]**
Total events: 1184 (Higher omega 3), 1343 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=7.88, df=9(P=0.55); I²=0%					
Test for overall effect: Z=3.32(P=0)					
1.20.3 Long duration: ≥ 4 years in study					
AREDS2 2014	14/2147	13/2056		0.87%	1.03[0.49,2.19]
ASCEND 2018	196/7740	240/7740		8.9%	0.82[0.68,0.98]
DART2 2003	180/1571	139/1543		7.64%	1.27[1.03,1.57]



Favours higher omega 3 — Favours lower omega 3

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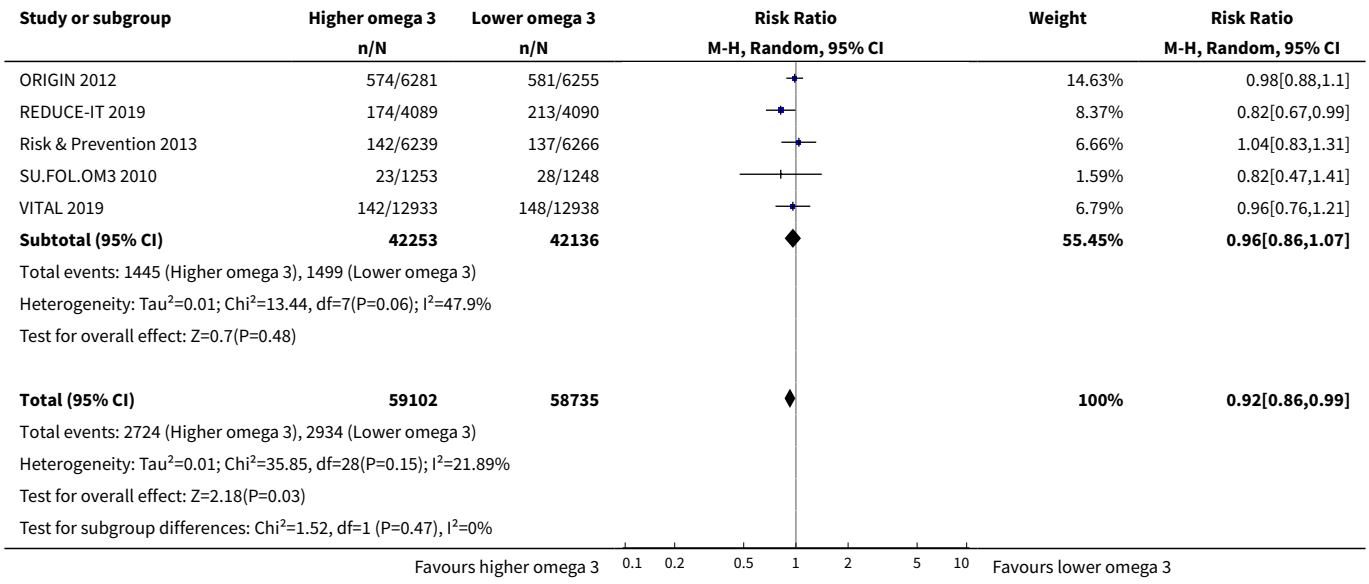
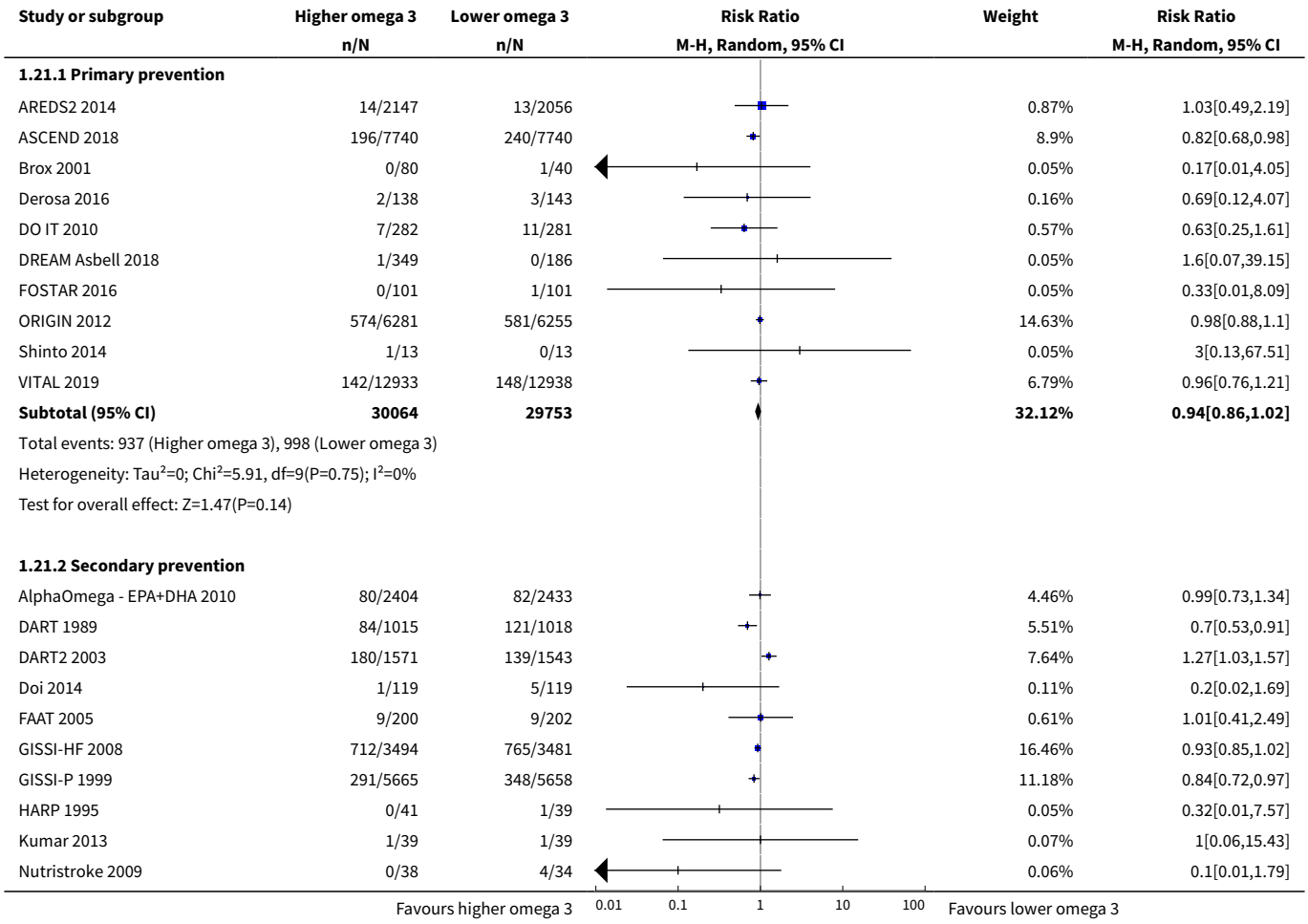


Analysis 1.21. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 21 CVD mortality - LCn3 - subgroup by primary or secondary prevention.



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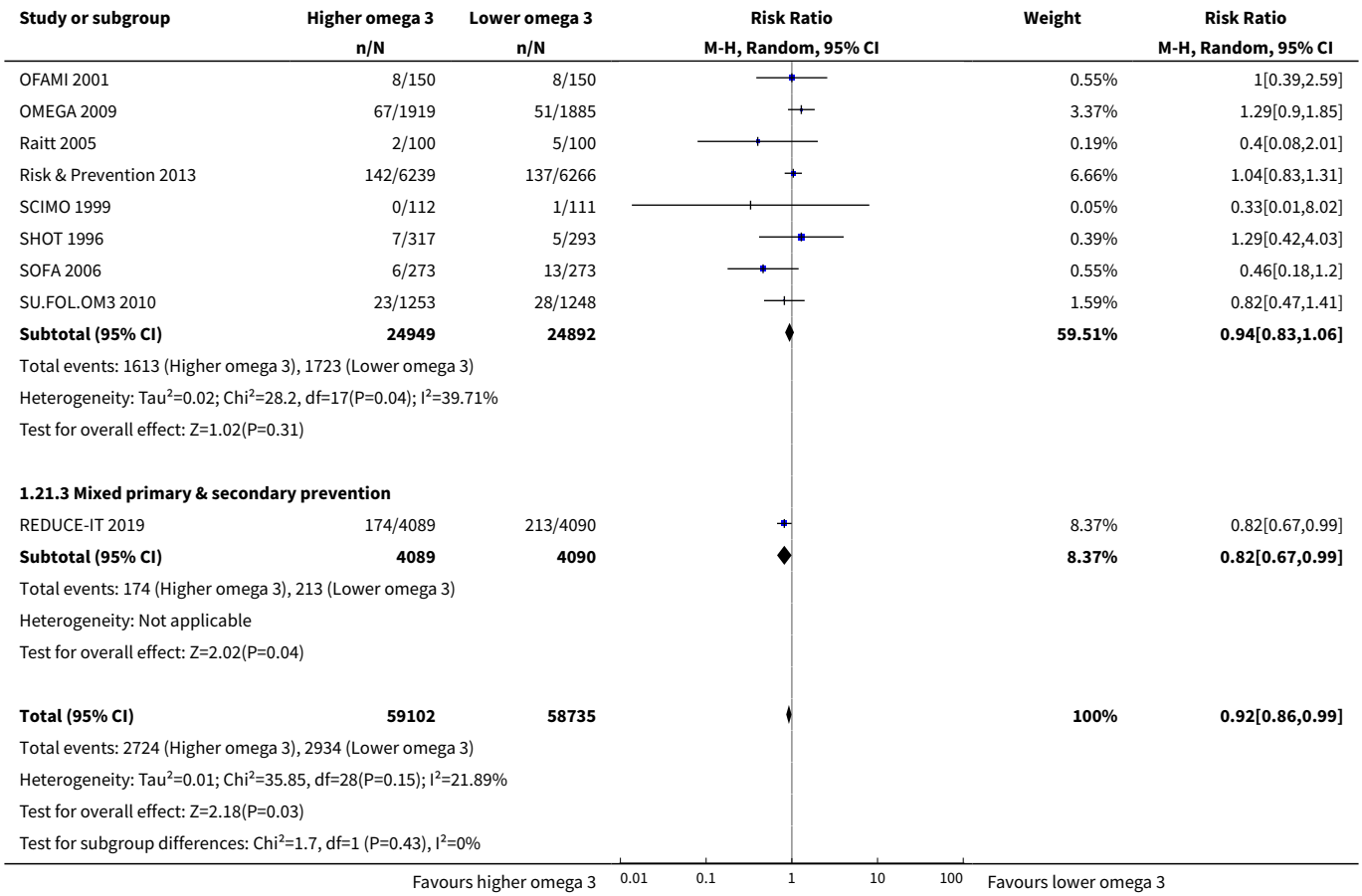
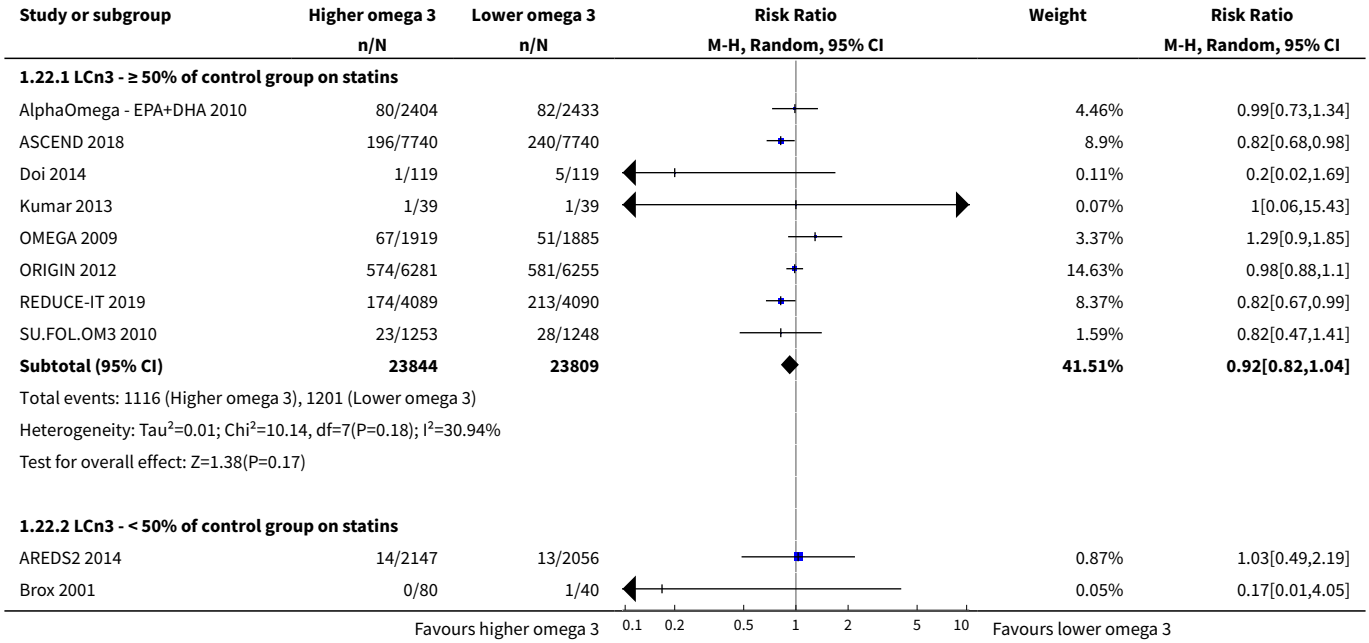


Analysis 1.22. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 22 CVD mortality - LCn3 - subgroup by statin uses.



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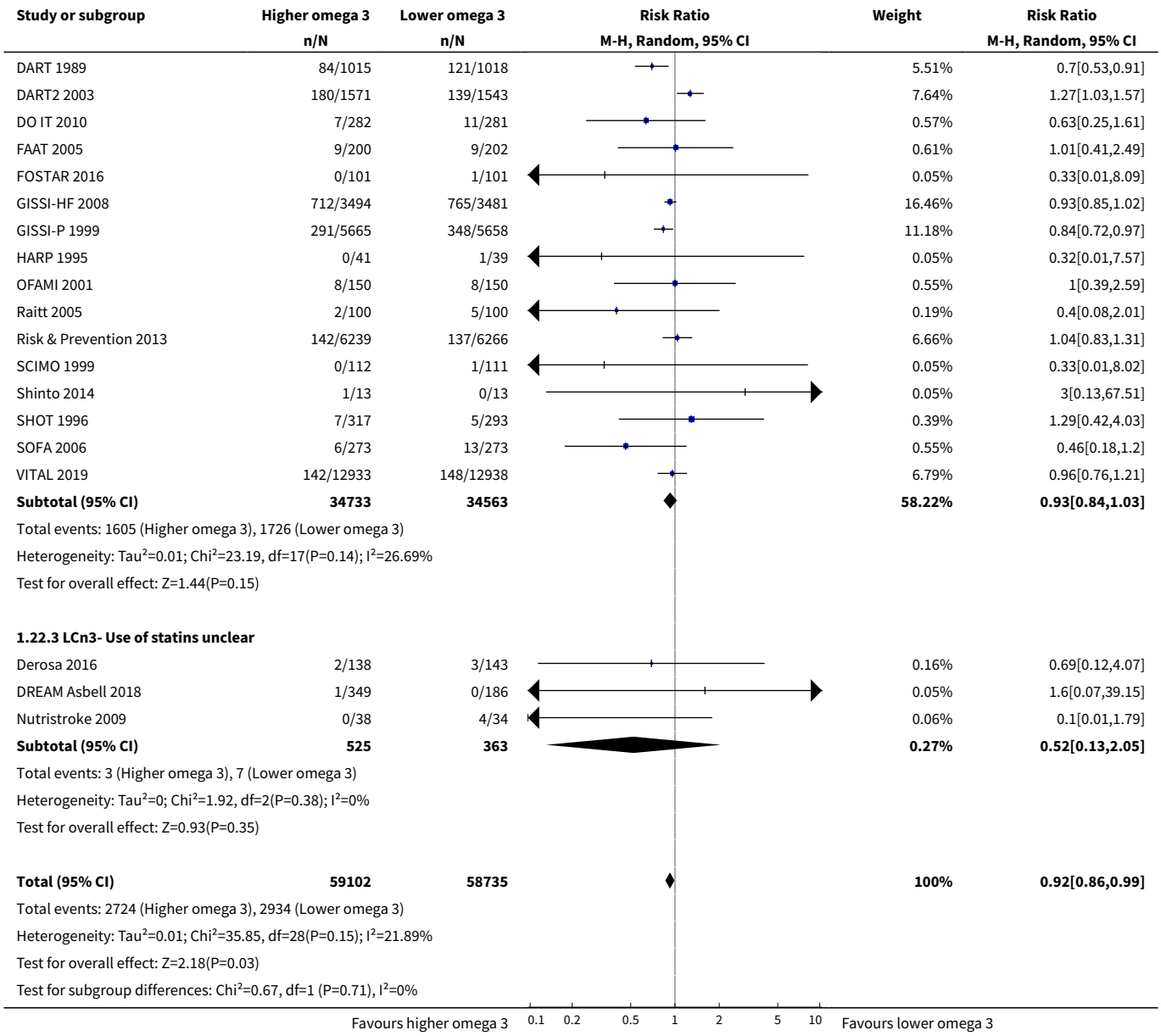
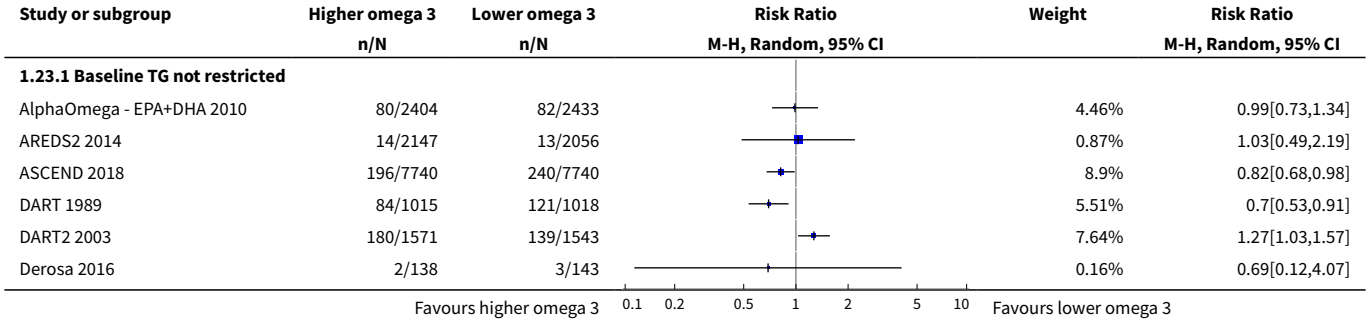


Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	84/1015	121/1018		5.51%	0.7[0.53,0.91]
DART2 2003	180/1571	139/1543		7.64%	1.27[1.03,1.57]
DO IT 2010	7/282	11/281		0.57%	0.63[0.25,1.61]
FAAT 2005	9/200	9/202		0.61%	1.01[0.41,2.49]
FOSTAR 2016	0/101	1/101		0.05%	0.33[0.01,8.09]
GISSI-HF 2008	712/3494	765/3481		16.46%	0.93[0.85,1.02]
GISSI-P 1999	291/5665	348/5658		11.18%	0.84[0.72,0.97]
HARP 1995	0/41	1/39		0.05%	0.32[0.01,7.57]
OFAMI 2001	8/150	8/150		0.55%	1[0.39,2.59]
Raitt 2005	2/100	5/100		0.19%	0.4[0.08,2.01]
Risk & Prevention 2013	142/6239	137/6266		6.66%	1.04[0.83,1.31]
SCIMO 1999	0/112	1/111		0.05%	0.33[0.01,8.02]
Shinto 2014	1/13	0/13		0.05%	3[0.13,67.51]
SHOT 1996	7/317	5/293		0.39%	1.29[0.42,4.03]
SOFA 2006	6/273	13/273		0.55%	0.46[0.18,1.2]
VITAL 2019	142/12933	148/12938		6.79%	0.96[0.76,1.21]
Subtotal (95% CI)	**34733**	**34563**		**58.22%**	**0.93[0.84,1.03]**
Total events: 1605 (Higher omega 3), 1726 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=23.19, df=17(P=0.14); I^2=26.69%					
Test for overall effect: Z=1.44(P=0.15)					
1.22.3 LCn3- Use of statins unclear					
Derosa 2016	2/138	3/143		0.16%	0.69[0.12,4.07]
DREAM Asbell 2018	1/349	0/186		0.05%	1.6[0.07,39.15]
Nutristroke 2009	0/38	4/34		0.06%	0.1[0.01,1.79]
Subtotal (95% CI)	**525**	**363**		**0.27%**	**0.52[0.13,2.05]**
Total events: 3 (Higher omega 3), 7 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=1.92, df=2(P=0.38); I^2=0%					
Test for overall effect: Z=0.93(P=0.35)					
Total (95% CI)	**59102**	**58735**		**100%**	**0.92[0.86,0.99]**
Total events: 2724 (Higher omega 3), 2934 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=35.85, df=28(P=0.15); I^2=21.89%					
Test for overall effect: Z=2.18(P=0.03)					
Test for subgroup differences: Chi^2=0.67, df=1 (P=0.71), I^2=0%					

Analysis 1.23. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 23 CVD mortality - LCn3 - subgroup by baseline TG.



Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.23.1 Baseline TG not restricted					
AlphaOmega - EPA+DHA 2010	80/2404	82/2433		4.46%	0.99[0.73,1.34]
AREDS2 2014	14/2147	13/2056		0.87%	1.03[0.49,2.19]
ASCEND 2018	196/7740	240/7740		8.9%	0.82[0.68,0.98]
DART 1989	84/1015	121/1018		5.51%	0.7[0.53,0.91]
DART2 2003	180/1571	139/1543		7.64%	1.27[1.03,1.57]
Derosa 2016	2/138	3/143		0.16%	0.69[0.12,4.07]

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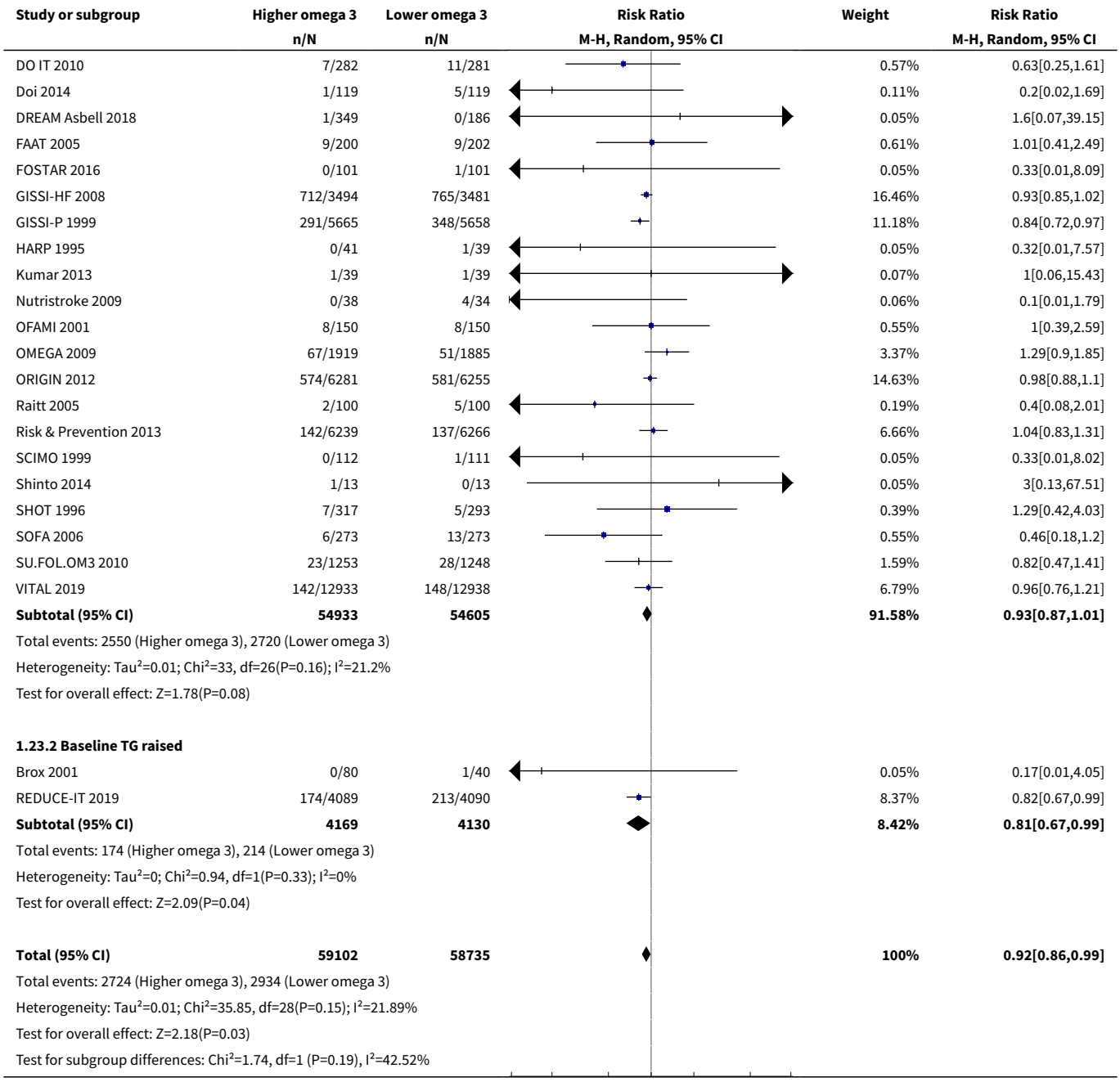
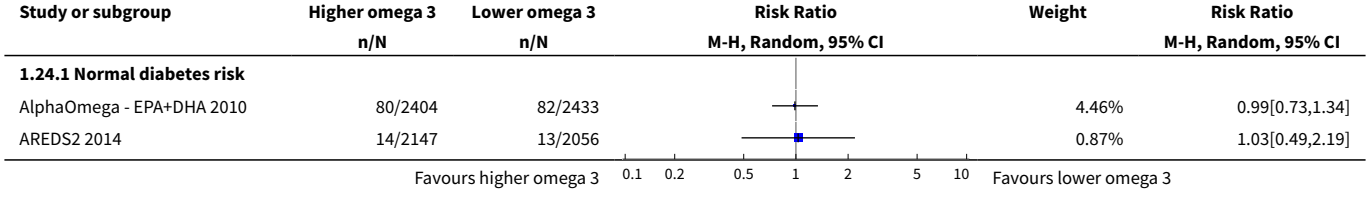


Analysis 1.24. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 24 CVD mortality - LCn3 - subgroup by baseline DM.



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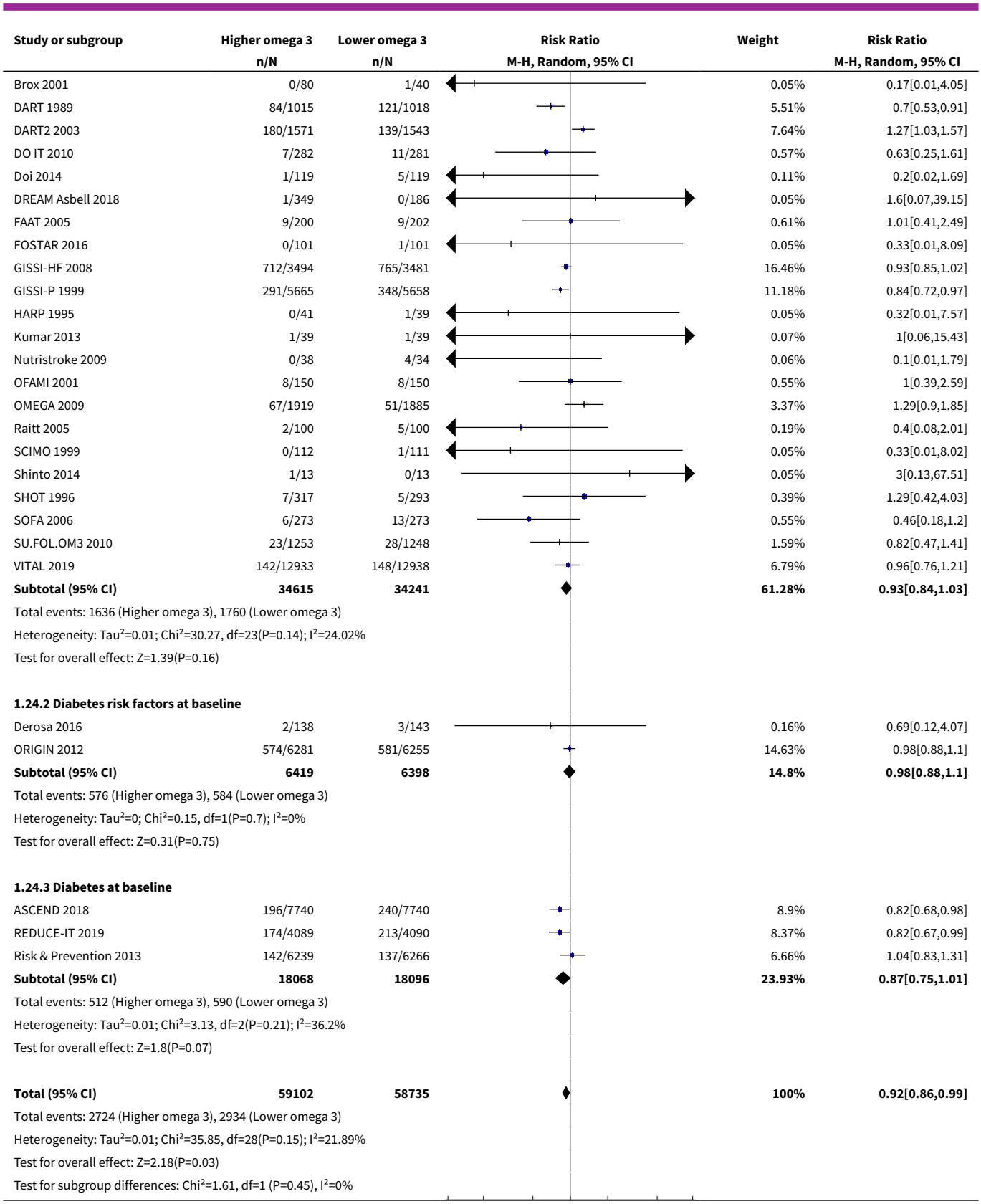

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Brox 2001	0/80	1/40		0.05%	0.17[0.01,4.05]
DART 1989	84/1015	121/1018		5.51%	0.7[0.53,0.91]
DART2 2003	180/1571	139/1543		7.64%	1.27[1.03,1.57]
DO IT 2010	7/282	11/281		0.57%	0.63[0.25,1.61]
Doi 2014	1/119	5/119		0.11%	0.2[0.02,1.69]
DREAM Asbell 2018	1/349	0/186		0.05%	1.6[0.07,39.15]
FAAT 2005	9/200	9/202		0.61%	1.01[0.41,2.49]
FOSTAR 2016	0/101	1/101		0.05%	0.33[0.01,8.09]
GISSI-HF 2008	712/3494	765/3481		16.46%	0.93[0.85,1.02]
GISSI-P 1999	291/5665	348/5658		11.18%	0.84[0.72,0.97]
HARP 1995	0/41	1/39		0.05%	0.32[0.01,7.57]
Kumar 2013	1/39	1/39		0.07%	1[0.06,15.43]
Nutristroke 2009	0/38	4/34		0.06%	0.1[0.01,1.79]
OFAMI 2001	8/150	8/150		0.55%	1[0.39,2.59]
OMEGA 2009	67/1919	51/1885		3.37%	1.29[0.9,1.85]
Raitt 2005	2/100	5/100		0.19%	0.4[0.08,2.01]
SCIMO 1999	0/112	1/111		0.05%	0.33[0.01,8.02]
Shinto 2014	1/13	0/13		0.05%	3[0.13,67.51]
SHOT 1996	7/317	5/293		0.39%	1.29[0.42,4.03]
SOFA 2006	6/273	13/273		0.55%	0.46[0.18,1.2]
SU.FOL.OM3 2010	23/1253	28/1248		1.59%	0.82[0.47,1.41]
VITAL 2019	142/12933	148/12938		6.79%	0.96[0.76,1.21]
Subtotal (95% CI)	**34615**	**34241**		**61.28%**	**0.93[0.84,1.03]**
Total events: 1636 (Higher omega 3), 1760 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=30.27, df=23(P=0.14); I^2=24.02%					
Test for overall effect: Z=1.39(P=0.16)					
1.24.2 Diabetes risk factors at baseline					
Derosa 2016	2/138	3/143		0.16%	0.69[0.12,4.07]
ORIGIN 2012	574/6281	581/6255		14.63%	0.98[0.88,1.1]
Subtotal (95% CI)	**6419**	**6398**		**14.8%**	**0.98[0.88,1.1]**
Total events: 576 (Higher omega 3), 584 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.15, df=1(P=0.7); I^2=0%					
Test for overall effect: Z=0.31(P=0.75)					
1.24.3 Diabetes at baseline					
ASCEND 2018	196/7740	240/7740		8.9%	0.82[0.68,0.98]
REDUCE-IT 2019	174/4089	213/4090		8.37%	0.82[0.67,0.99]
Risk & Prevention 2013	142/6239	137/6266		6.66%	1.04[0.83,1.31]
Subtotal (95% CI)	**18068**	**18096**		**23.93%**	**0.87[0.75,1.01]**
Total events: 512 (Higher omega 3), 590 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=3.13, df=2(P=0.21); I^2=36.2%					
Test for overall effect: Z=1.8(P=0.07)					
Total (95% CI)	**59102**	**58735**		**100%**	**0.92[0.86,0.99]**
Total events: 2724 (Higher omega 3), 2934 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=35.85, df=28(P=0.15); I^2=21.89%					
Test for overall effect: Z=2.18(P=0.03)					
Test for subgroup differences: Chi^2=1.61, df=1 (P=0.45), I^2=0%					

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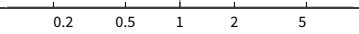
Analysis 1.25. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 25 Cardiovascular events (overall) - LCn3.

Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 fats n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
AFFORD 2013	20/153	11/163		0.46%	1.94[0.96,3.91]
AlphaOmega - EPA+DHA 2010	332/2404	331/2433		5.22%	1.02[0.88,1.17]
AREDS2 2014	213/2147	208/2056		4.06%	0.98[0.82,1.18]
ASCEND 2018	689/7740	712/7740		6.7%	0.97[0.88,1.07]
Baldassarre 2006	1/32	0/32		0.02%	3[0.13,71]
Brox 2001	0/80	1/40		0.02%	0.17[0.01,4.05]
DART 1989	467/1015	487/1018		6.98%	0.96[0.88,1.05]
DART2 2003	206/1571	155/1543		3.7%	1.31[1.07,1.59]
Derosa 2016	2/128	3/130		0.07%	0.68[0.12,3.98]
DO IT 2010	29/282	35/281		0.98%	0.83[0.52,1.31]
Doi 2014	11/119	24/119		0.5%	0.46[0.24,0.89]
ENRGISE 2018	5/148	9/141		0.2%	0.53[0.18,1.54]
EPE-A 2014	5/168	6/75		0.17%	0.37[0.12,1.18]
EPIC-1 2008	1/188	0/186		0.02%	2.97[0.12,72.4]
EPOCH 2014	8/195	5/196		0.19%	1.61[0.54,4.83]
FAAT 2005	31/200	39/202		1.13%	0.8[0.52,1.23]
FORWARD 2013	4/289	4/297		0.12%	1.03[0.26,4.07]
FOSTAR 2016	18/101	16/101		0.59%	1.13[0.61,2.08]
GISSI-HF 2008	783/3494	831/3481		7.24%	0.94[0.86,1.02]
GISSI-P 1999	1552/5666	1550/5658		8.18%	1[0.94,1.06]
HARP 1995	7/41	7/39		0.25%	0.95[0.37,2.46]
HEARTS 2017	45/143	39/142		1.52%	1.15[0.8,1.64]
JELIS 2007	262/9326	324/9319		4.63%	0.81[0.69,0.95]
Kumar 2013	1/39	1/39		0.03%	1[0.06,15.43]
MAPT 2017	192/820	164/832		3.97%	1.19[0.99,1.43]
Nodari 2011 HF	10/67	26/66		0.53%	0.38[0.2,0.72]
Nutristroke 2009	0/38	4/34		0.03%	0.1[0.01,1.79]
OFAMI 2001	42/150	36/150		1.37%	1.17[0.8,1.71]
OMEGA 2009	534/1752	541/1701		6.72%	0.96[0.87,1.06]
ORIGIN 2012	1276/6281	1295/6255		7.86%	0.98[0.92,1.05]
Proudman 2015	1/87	0/53		0.02%	1.84[0.08,44.38]
Puri 2005	1/60	0/61		0.02%	3.05[0.13,73.4]
Raitt 2005	2/100	5/100		0.09%	0.4[0.08,2.01]
REDUCE-IT 2019	459/4089	606/4090		6.2%	0.76[0.68,0.85]
Risk & Prevention 2013	733/6239	745/6266		6.86%	0.99[0.9,1.09]
Sandhu 2016	2/107	1/106		0.04%	1.98[0.18,21.52]
SCIMO 1999	17/112	26/111		0.72%	0.65[0.37,1.13]
Shinto 2014	1/13	0/13		0.02%	3[0.13,67.51]
SHOT 1996	15/317	12/293		0.41%	1.16[0.55,2.43]
SOFA 2006	65/273	62/273		2%	1.05[0.77,1.42]
SU.FOL.OM3 2010	216/1253	211/1248		4.28%	1.02[0.86,1.21]
THIS DIET 2008	14/51	10/50		0.44%	1.37[0.67,2.8]
VITAL 2019	386/12933	419/12938		5.39%	0.92[0.8,1.06]
Total (95% CI)	**70411**	**70071**		**100%**	**0.96[0.92,1.01]**

Total events: 8658 (Favours higher omega 3), 8961 (Lower omega 3 fats)

Heterogeneity: Tau^2=0.01; Chi^2=75.11, df=42(P=0); I^2=44.08%

Test for overall effect: Z=1.5(P=0.13)



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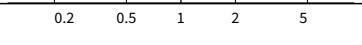
Analysis 1.26. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 26 CVD events - LCn3 - SA fixed effect.

Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 fats n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
AFFORD 2013	20/153	11/163		0.12%	1.94[0.96,3.91]
AlphaOmega - EPA+DHA 2010	332/2404	331/2433		3.66%	1.02[0.88,1.17]
AREDS2 2014	213/2147	208/2056		2.37%	0.98[0.82,1.18]
ASCEND 2018	689/7740	712/7740		7.93%	0.97[0.88,1.07]
Baldassarre 2006	1/32	0/32		0.01%	3[0.13,71]
Brox 2001	0/80	1/40		0.02%	0.17[0.01,4.05]
DART 1989	467/1015	487/1018		5.41%	0.96[0.88,1.05]
DART2 2003	206/1571	155/1543		1.74%	1.31[1.07,1.59]
Derosa 2016	2/128	3/130		0.03%	0.68[0.12,3.98]
DO IT 2010	29/282	35/281		0.39%	0.83[0.52,1.31]
Doi 2014	11/119	24/119		0.27%	0.46[0.24,0.89]
ENRGISE 2018	5/148	9/141		0.1%	0.53[0.18,1.54]
EPE-A 2014	5/168	6/75		0.09%	0.37[0.12,1.18]
EPIC-1 2008	1/188	0/186		0.01%	2.97[0.12,72.4]
EPOCH 2014	8/195	5/196		0.06%	1.61[0.54,4.83]
FAAT 2005	31/200	39/202		0.43%	0.8[0.52,1.23]
FORWARD 2013	4/289	4/297		0.04%	1.03[0.26,4.07]
FOSTAR 2016	18/101	16/101		0.18%	1.13[0.61,2.08]
GISSI-HF 2008	783/3494	831/3481		9.27%	0.94[0.86,1.02]
GISSI-P 1999	1552/5666	1550/5658		17.27%	1[0.94,1.06]
HARP 1995	7/41	7/39		0.08%	0.95[0.37,2.46]
HEARTS 2017	45/143	39/142		0.44%	1.15[0.8,1.64]
JELIS 2007	262/9326	324/9319		3.61%	0.81[0.69,0.95]
Kumar 2013	1/39	1/39		0.01%	1[0.06,15.43]
MAPT 2017	192/820	164/832		1.81%	1.19[0.99,1.43]
Nodari 2011 HF	10/67	26/66		0.29%	0.38[0.2,0.72]
Nutristroke 2009	0/38	4/34		0.05%	0.1[0.01,1.79]
OFAMI 2001	42/150	36/150		0.4%	1.17[0.8,1.71]
OMEGA 2009	534/1752	541/1701		6.11%	0.96[0.87,1.06]
ORIGIN 2012	1276/6281	1295/6255		14.45%	0.98[0.92,1.05]
Proudman 2015	1/87	0/53		0.01%	1.84[0.08,44.38]
Puri 2005	1/60	0/61		0.01%	3.05[0.13,73.4]
Raitt 2005	2/100	5/100		0.06%	0.4[0.08,2.01]
REDUCE-IT 2019	459/4089	606/4090		6.75%	0.76[0.68,0.85]
Risk & Prevention 2013	733/6239	745/6266		8.28%	0.99[0.9,1.09]
Sandhu 2016	2/107	1/106		0.01%	1.98[0.18,21.52]
SCIMO 1999	17/112	26/111		0.29%	0.65[0.37,1.13]
Shinto 2014	1/13	0/13		0.01%	3[0.13,67.51]
SHOT 1996	15/317	12/293		0.14%	1.16[0.55,2.43]
SOFA 2006	65/273	62/273		0.69%	1.05[0.77,1.42]
SU.FOL.OM3 2010	216/1253	211/1248		2.35%	1.02[0.86,1.21]
THIS DIET 2008	14/51	10/50		0.11%	1.37[0.67,2.8]
VITAL 2019	386/12933	419/12938		4.66%	0.92[0.8,1.06]
Total (95% CI)	**70411**	**70071**		**100%**	**0.96[0.94,0.99]**
Total events: 8658 (Favours higher omega 3), 8961 (Lower omega 3 fats)					



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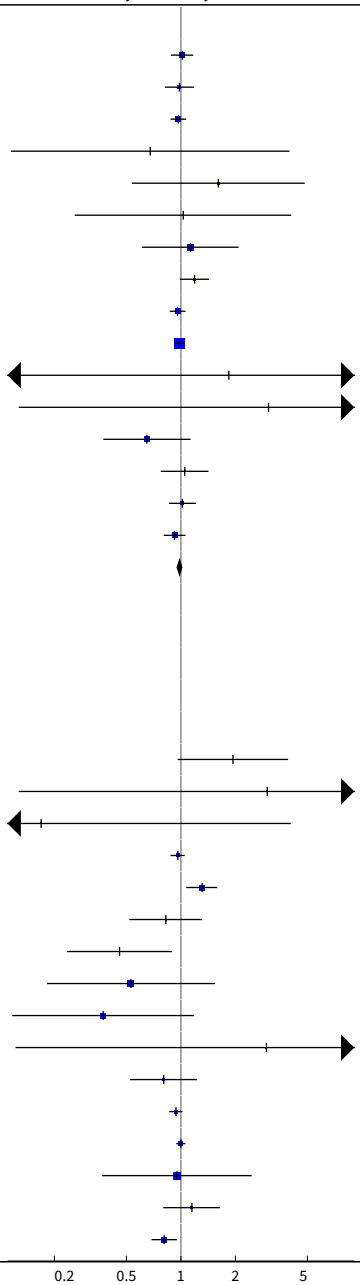
Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 fats n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=75.11, df=42(P=0); I²=44.08%					
Test for overall effect: Z=2.84(P=0)					

Favours higher omega 3 — Favours lower omega 3

Analysis 1.27. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 27 CVD events - LCn3 - SA by summary risk of bias.

Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 fats n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.27.1 Low summary risk of bias					
AlphaOmega - EPA+DHA 2010	332/2404	331/2433		7.96%	1.02[0.88,1.17]
AREDS2 2014	213/2147	208/2056		4.85%	0.98[0.82,1.18]
ASCEND 2018	689/7740	712/7740		15.96%	0.97[0.88,1.07]
Derosa 2016	2/128	3/130		0.05%	0.68[0.12,3.98]
EPOCH 2014	8/195	5/196		0.13%	1.61[0.54,4.83]
FORWARD 2013	4/289	4/297		0.08%	1.03[0.26,4.07]
FOSTAR 2016	18/101	16/101		0.42%	1.13[0.61,2.08]
MAPT 2017	192/820	164/832		4.67%	1.19[0.99,1.43]
OMEGA 2009	534/1752	541/1701		16.17%	0.96[0.87,1.06]
ORIGIN 2012	1276/6281	1295/6255		33.51%	0.98[0.92,1.05]
Proudman 2015	1/87	0/53		0.02%	1.84[0.08,44.38]
Puri 2005	1/60	0/61		0.02%	3.05[0.13,73.4]
SCIMO 1999	17/112	26/111		0.52%	0.65[0.37,1.13]
SOFA 2006	65/273	62/273		1.71%	1.05[0.77,1.42]
SU.FOL.OM3 2010	216/1253	211/1248		5.33%	1.02[0.86,1.21]
VITAL 2019	386/12933	419/12938		8.59%	0.92[0.8,1.06]
Subtotal (95% CI)	**36575**	**36425**		**100%**	**0.98[0.95,1.02]**
Total events: 3954 (Favours higher omega 3), 3997 (Lower omega 3 fats)					
Heterogeneity: Tau²=0; Chi²=9.74, df=15(P=0.84); I²=0%					
Test for overall effect: Z=0.81(P=0.42)					
1.27.2 Moderate or high summary risk of bias					
AFFORD 2013	20/153	11/163		1.39%	1.94[0.96,3.91]
Baldassarre 2006	1/32	0/32		0.08%	3[0.13,71]
Brox 2001	0/80	1/40		0.08%	0.17[0.01,4.05]
DART 1989	467/1015	487/1018		11.69%	0.96[0.88,1.05]
DART2 2003	206/1571	155/1543		8.02%	1.31[1.07,1.59]
DO IT 2010	29/282	35/281		2.82%	0.83[0.52,1.31]
Doi 2014	11/119	24/119		1.53%	0.46[0.24,0.89]
ENRGISE 2018	5/148	9/141		0.64%	0.53[0.18,1.54]
EPE-A 2014	5/168	6/75		0.55%	0.37[0.12,1.18]
EPIC-1 2008	1/188	0/186		0.07%	2.97[0.12,72.4]
FAAT 2005	31/200	39/202		3.18%	0.8[0.52,1.23]
GISSI-HF 2008	783/3494	831/3481		11.91%	0.94[0.86,1.02]
GISSI-P 1999	1552/5666	1550/5658		12.64%	1[0.94,1.06]
HARP 1995	7/41	7/39		0.8%	0.95[0.37,2.46]
HEARTS 2017	45/143	39/142		4.1%	1.15[0.8,1.64]
JELIS 2007	262/9326	324/9319		9.27%	0.81[0.69,0.95]



Favours higher omega 3 — Favours lower omega 3

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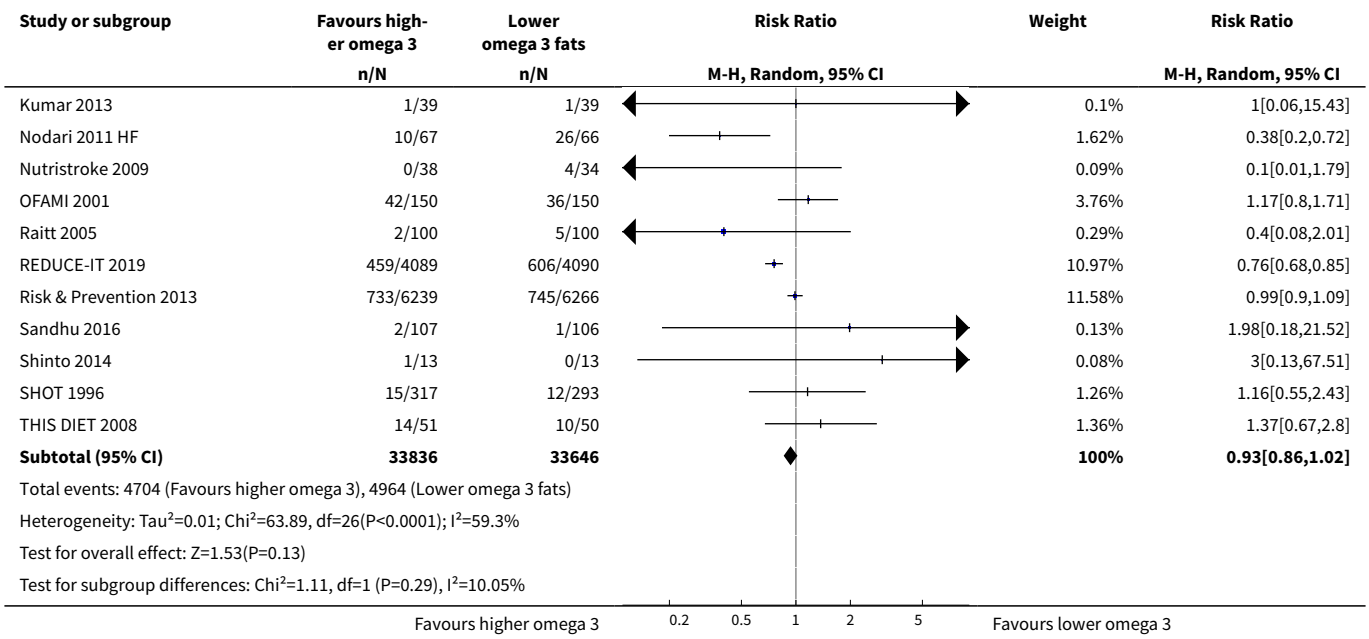
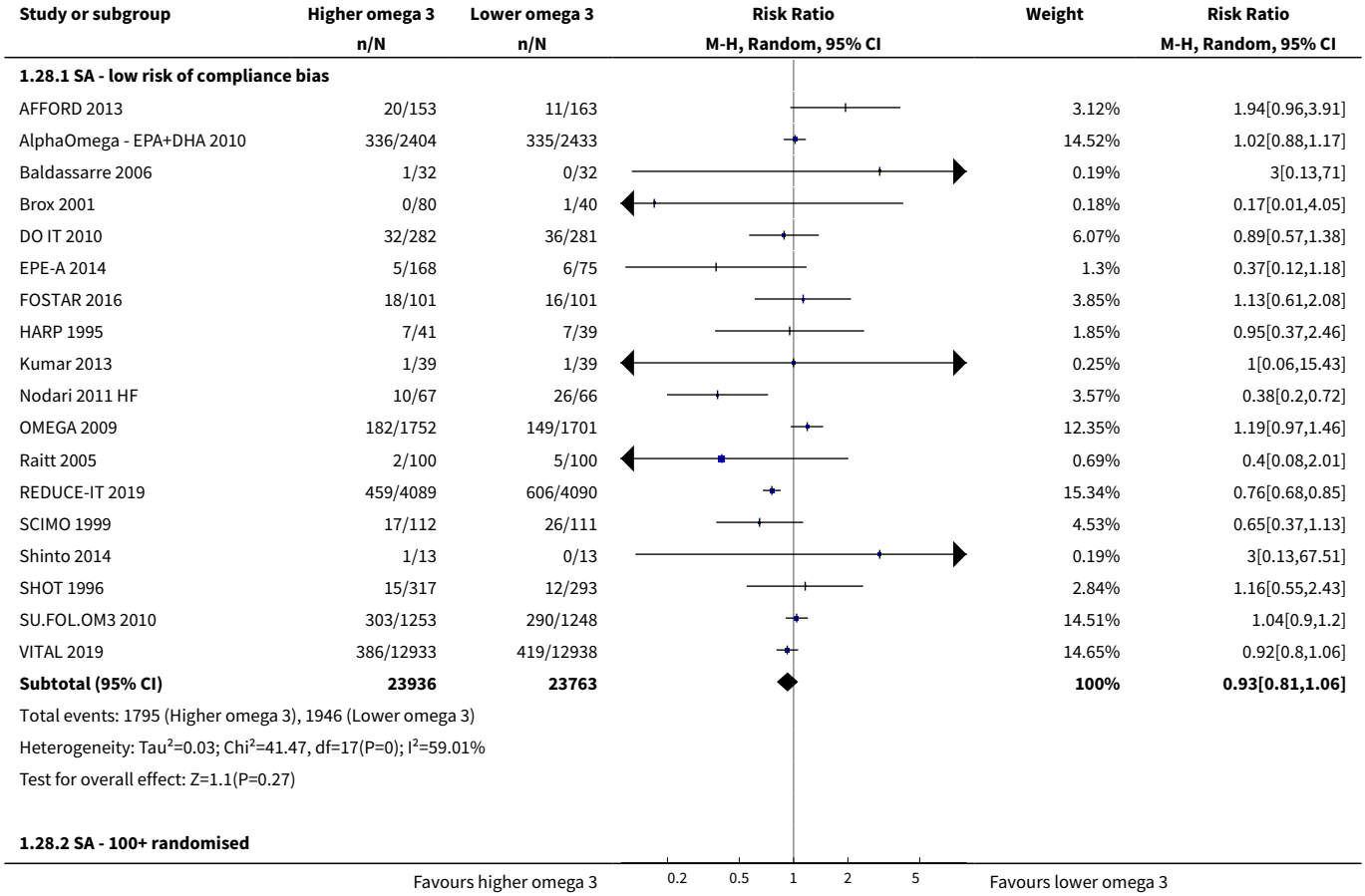


Analysis 1.28. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 28 CVD events - LCn3 - SA by compliance and study size.



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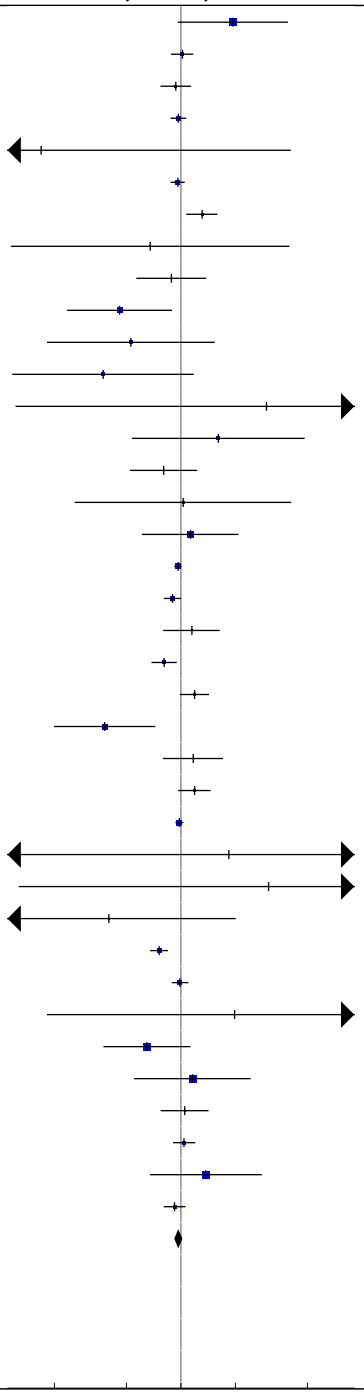
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
AFFORD 2013	20/153	11/163		0.5%	1.94[0.96,3.91]
AlphaOmega - EPA+DHA 2010	336/2404	335/2433		5.43%	1.02[0.88,1.17]
AREDS2 2014	183/2147	187/2056		3.93%	0.94[0.77,1.14]
ASCEND 2018	689/7740	712/7740		6.83%	0.97[0.88,1.07]
Brox 2001	0/80	1/40		0.03%	0.17[0.01,4.05]
DART 1989	467/1015	487/1018		7.09%	0.96[0.88,1.05]
DART2 2003	206/1571	155/1543		3.89%	1.31[1.07,1.59]
Derosa 2016	2/128	3/130		0.08%	0.68[0.12,3.98]
DO IT 2010	32/282	36/281		1.14%	0.89[0.57,1.38]
Doi 2014	11/119	24/119		0.55%	0.46[0.24,0.89]
ENRGISE 2018	5/148	9/141		0.22%	0.53[0.18,1.54]
EPE-A 2014	5/168	6/75		0.19%	0.37[0.12,1.18]
EPIC-1 2008	1/188	0/186		0.03%	2.97[0.12,72.4]
EPOCH 2014	8/195	5/196		0.21%	1.61[0.54,4.83]
FAAT 2005	31/200	39/202		1.22%	0.8[0.52,1.23]
FORWARD 2013	4/289	4/297		0.13%	1.03[0.26,4.07]
FOSTAR 2016	18/101	16/101		0.64%	1.13[0.61,2.08]
GISSI-HF 2008	1635/3494	1687/3481		8.53%	0.97[0.92,1.01]
GISSI-P 1999	547/5666	608/5658		6.48%	0.9[0.81,1]
HEARTS 2017	45/143	39/142		1.64%	1.15[0.8,1.64]
JELIS 2007	262/9326	324/9319		4.82%	0.81[0.69,0.95]
MAPT 2017	192/820	164/832		4.17%	1.19[0.99,1.43]
Nodari 2011 HF	10/67	26/66		0.58%	0.38[0.2,0.72]
OFAMI 2001	42/150	36/150		1.48%	1.17[0.8,1.71]
OMEGA 2009	182/1752	149/1701		3.68%	1.19[0.97,1.46]
ORIGIN 2012	2055/6281	2087/6255		8.51%	0.98[0.93,1.03]
Proudman 2015	1/87	0/53		0.03%	1.84[0.08,44.38]
Puri 2005	1/60	0/61		0.03%	3.05[0.13,73.4]
Raitt 2005	2/100	5/100		0.1%	0.4[0.08,2.01]
REDUCE-IT 2019	459/4089	606/4090		6.35%	0.76[0.68,0.85]
Risk & Prevention 2013	620/6239	630/6266		6.64%	0.99[0.89,1.1]
Sandhu 2016	2/107	1/106		0.05%	1.98[0.18,21.52]
SCIMO 1999	17/112	26/111		0.78%	0.65[0.37,1.13]
SHOT 1996	15/317	12/293		0.45%	1.16[0.55,2.43]
SOFA 2006	65/273	62/273		2.14%	1.05[0.77,1.42]
SU.FOL.OM3 2010	303/1253	290/1248		5.42%	1.04[0.9,1.2]
THIS DIET 2008	14/51	10/50		0.48%	1.37[0.67,2.8]
VITAL 2019	386/12933	419/12938		5.57%	0.92[0.8,1.06]
Subtotal (95% CI)	**70248**	**69914**		**100%**	**0.97[0.92,1.02]**
Total events: 8873 (Higher omega 3), 9211 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=76.08, df=37(P=0); I^2=51.37%					
Test for overall effect: Z=1.31(P=0.19)					
Test for subgroup differences: Chi^2=0.33, df=1 (P=0.56), I^2=0%					



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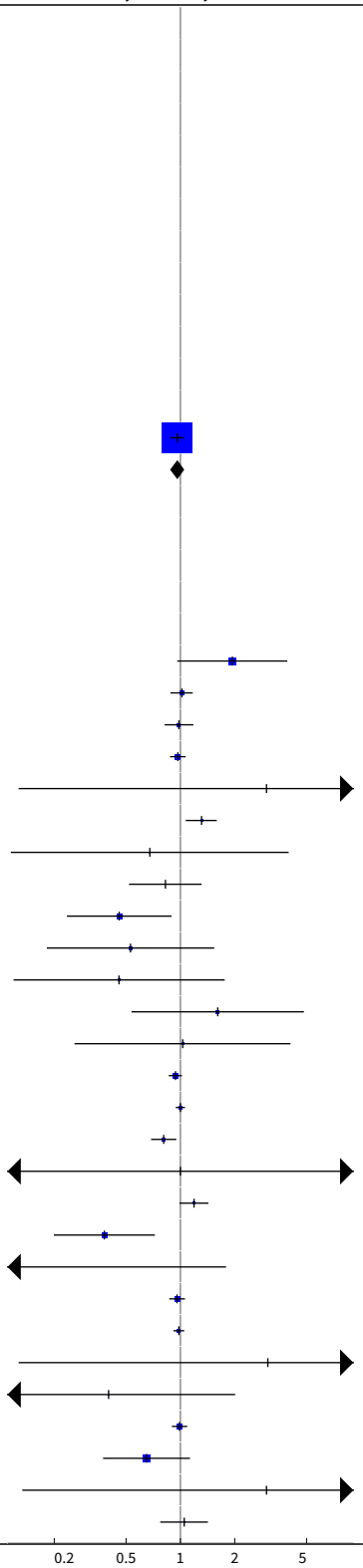
Analysis 1.29. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 29 CVD events - LCn3 - subgroup by dose.

Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.29.1 LCn3 ≤ 150 mg/d					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours higher omega 3), 0 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.29.2 LCn3 > 150 ≤ 250 mg/d					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours higher omega 3), 0 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.29.3 LCn3 > 250 ≤ 400 mg/d					
DART 1989	467/1015	487/1018		100%	0.96[0.88,1.05]
Subtotal (95% CI)	**1015**	**1018**		**100%**	**0.96[0.88,1.05]**
Total events: 467 (Favours higher omega 3), 487 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.83(P=0.41)					
1.29.4 LCn3 > 400 ≤ 2400 mg/d					
AFFORD 2013	20/153	11/163		0.47%	1.94[0.96,3.91]
AlphaOmega - EPA+DHA 2010	332/2404	331/2433		6.27%	1.02[0.88,1.17]
AREDS2 2014	213/2147	208/2056		4.7%	0.98[0.82,1.18]
ASCEND 2018	689/7740	712/7740		8.47%	0.97[0.88,1.07]
Baldassarre 2006	1/32	0/32		0.02%	3[0.13,71]
DART2 2003	206/1571	155/1543		4.24%	1.31[1.07,1.59]
Derosa 2016	2/128	3/130		0.08%	0.68[0.12,3.98]
DO IT 2010	29/282	35/281		1.03%	0.83[0.52,1.31]
Doi 2014	11/119	24/119		0.52%	0.46[0.24,0.89]
ENRGISE 2018	5/148	9/141		0.21%	0.53[0.18,1.54]
EPE-A 2014	3/82	6/75		0.13%	0.46[0.12,1.76]
EPOCH 2014	8/195	5/196		0.2%	1.61[0.54,4.83]
FORWARD 2013	4/289	4/297		0.13%	1.03[0.26,4.07]
GISSI-HF 2008	783/3494	831/3481		9.34%	0.94[0.86,1.02]
GISSI-P 1999	1552/5666	1550/5658		10.91%	1[0.94,1.06]
JELIS 2007	262/9326	324/9319		5.46%	0.81[0.69,0.95]
Kumar 2013	1/39	1/39		0.03%	1[0.06,15.43]
MAPT 2017	192/820	164/832		4.59%	1.19[0.99,1.43]
Nodari 2011 HF	10/67	26/66		0.56%	0.38[0.2,0.72]
Nutristroke 2009	0/38	4/34		0.03%	0.1[0.01,1.79]
OMEGA 2009	534/1752	541/1701		8.51%	0.96[0.87,1.06]
ORIGIN 2012	1276/6281	1295/6255		10.37%	0.98[0.92,1.05]
Puri 2005	1/60	0/61		0.02%	3.05[0.13,73.4]
Raitt 2005	2/100	5/100		0.09%	0.4[0.08,2.01]
Risk & Prevention 2013	733/6239	745/6266		8.72%	0.99[0.9,1.09]
SCIMO 1999	17/112	26/111		0.75%	0.65[0.37,1.13]
Shinto 2014	1/13	0/13		0.02%	3[0.13,67.51]
SOFA 2006	65/273	62/273		2.17%	1.05[0.77,1.42]



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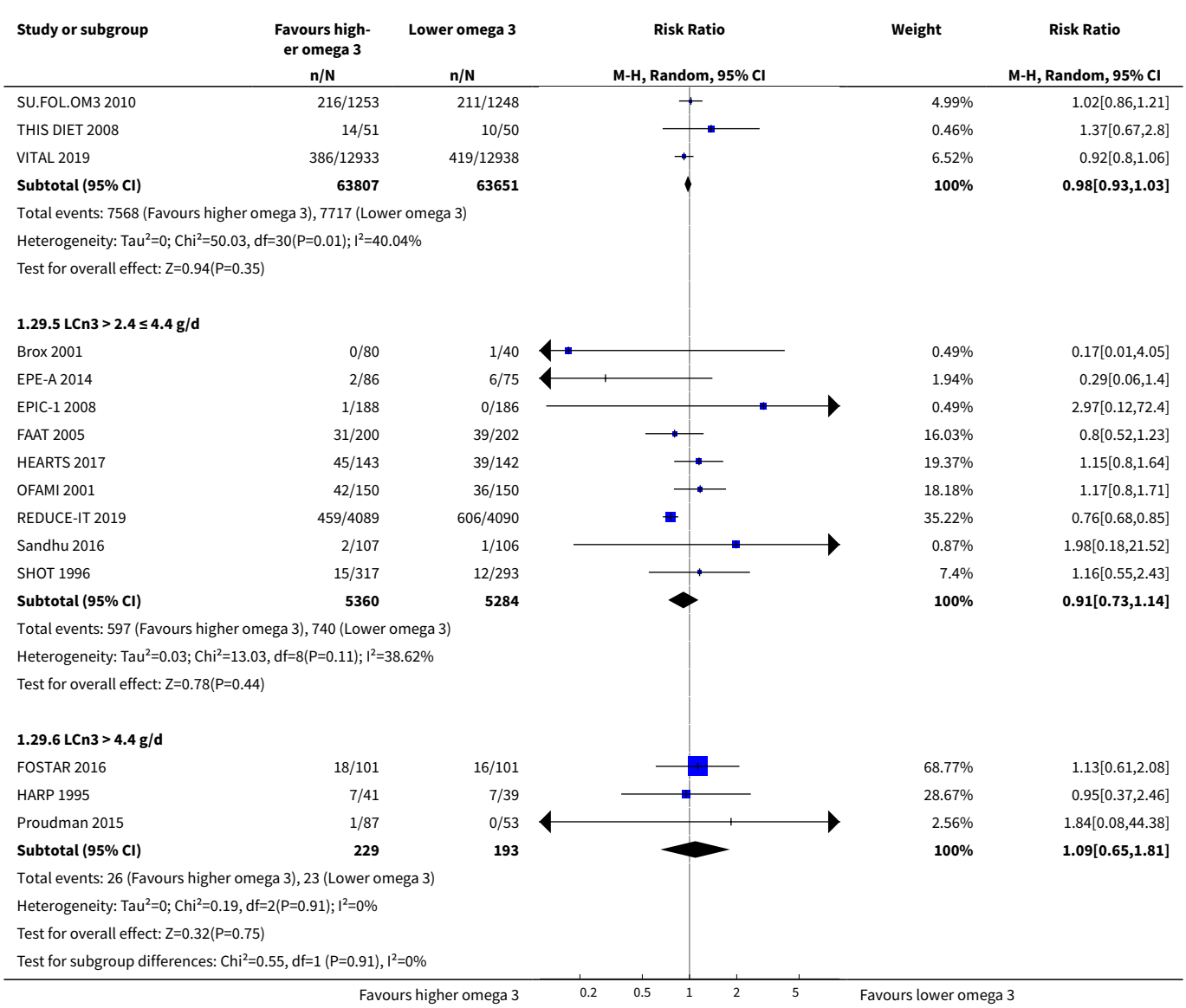
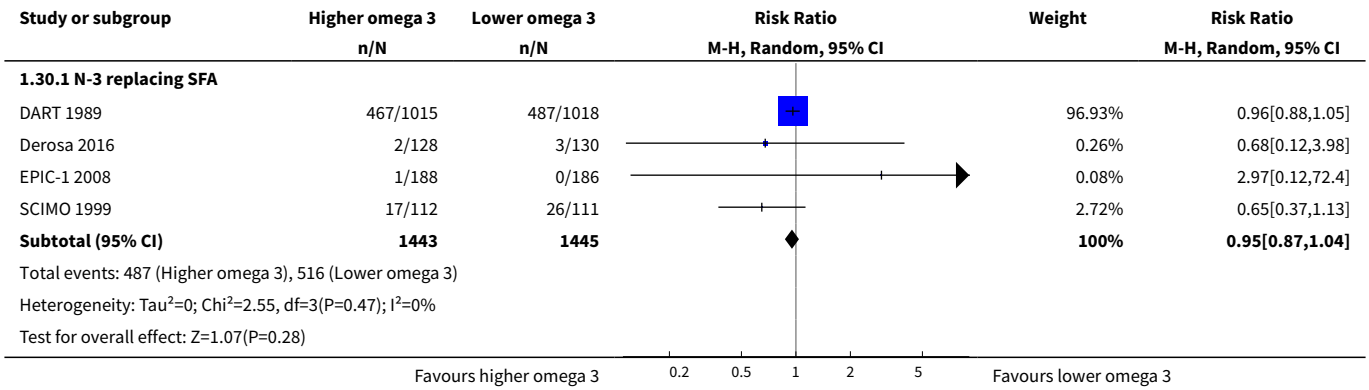


Analysis 1.30. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 30 CVD events - LCn3 - subgroup by replacement.



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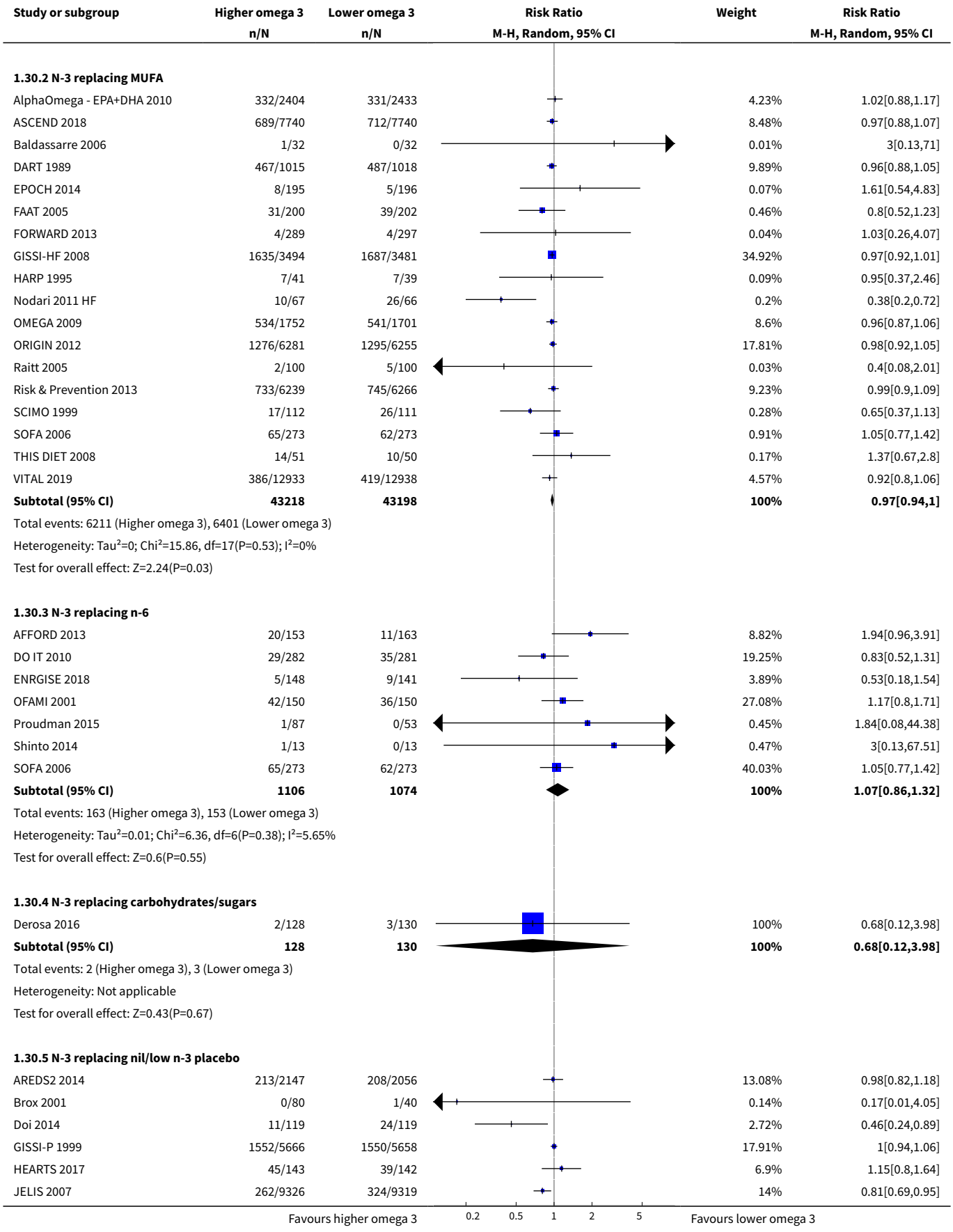

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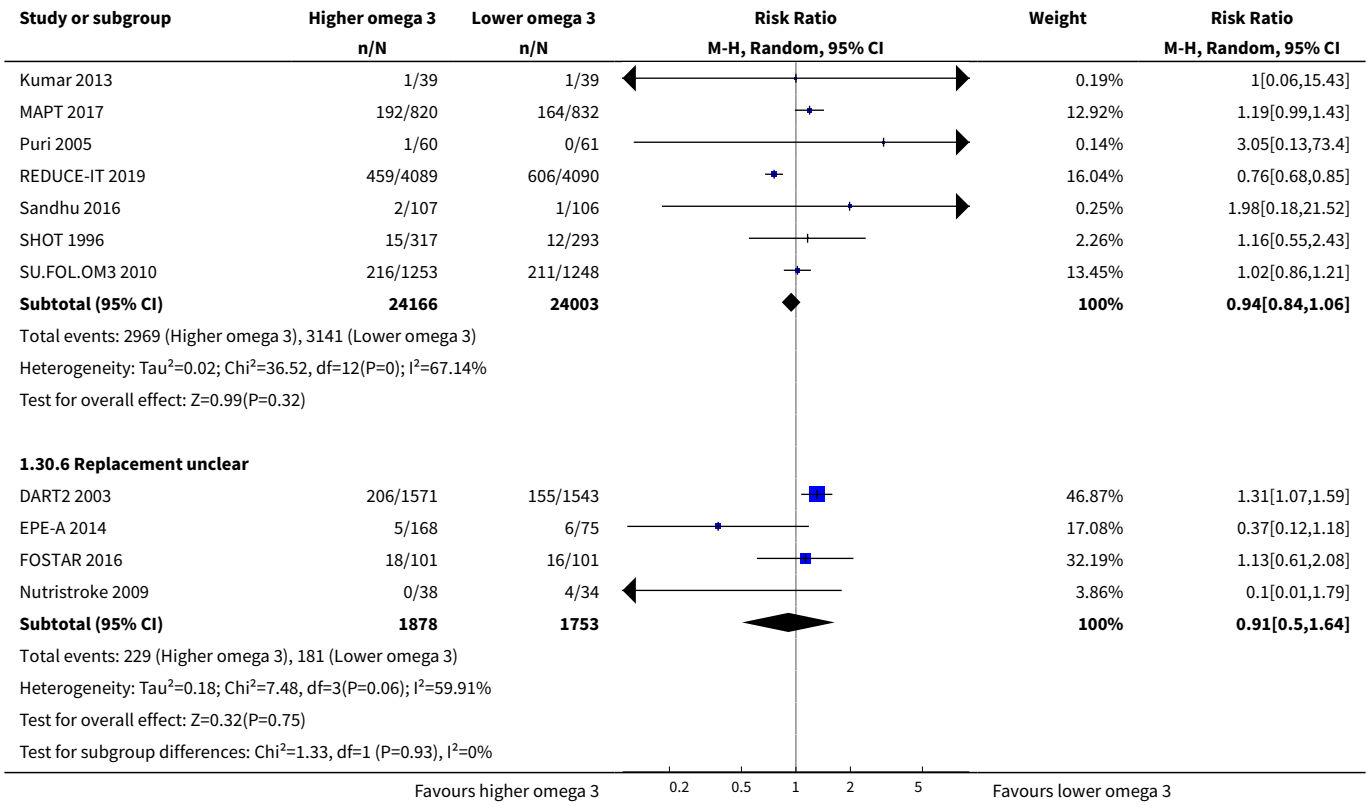
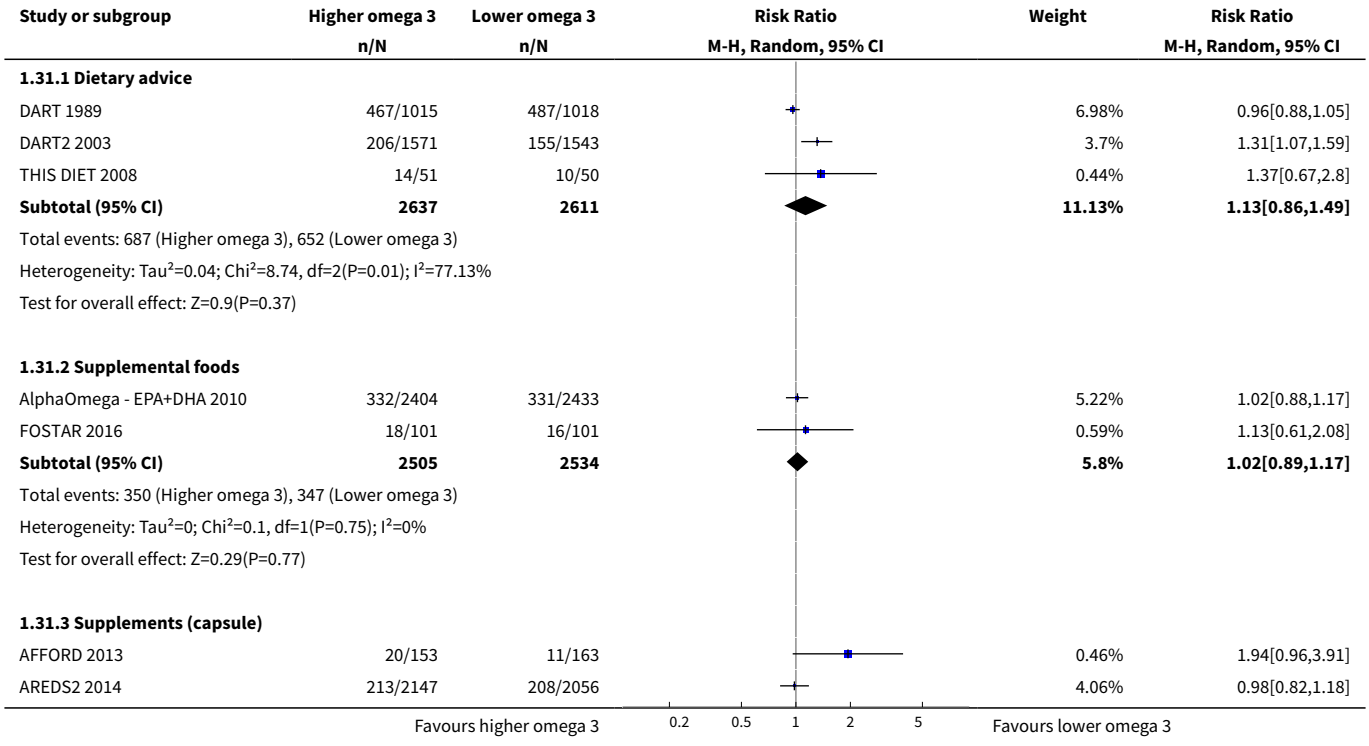


Analysis 1.31. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 31 CVD events - LCn3 - subgroup by intervention type.



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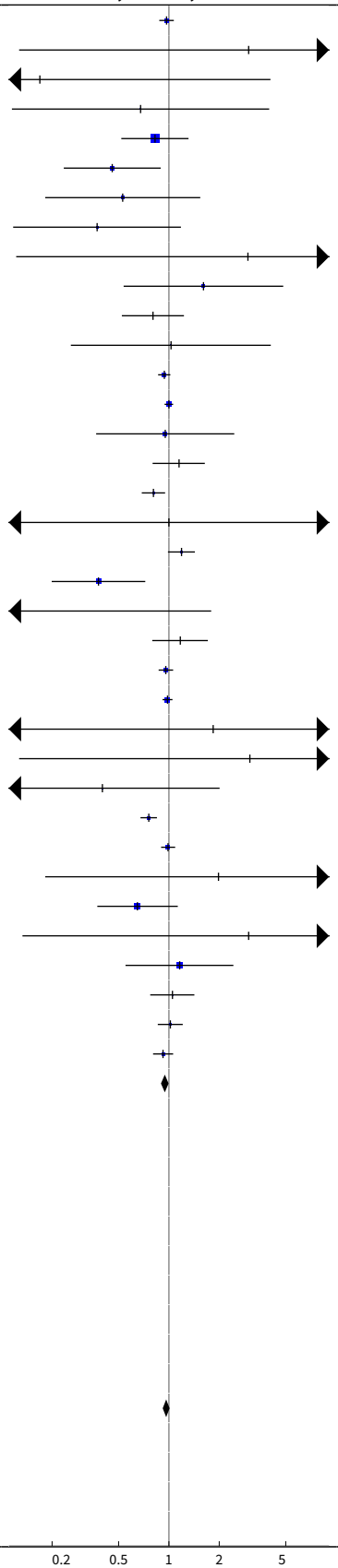
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ASCEND 2018	689/7740	712/7740		6.7%	0.97[0.88,1.07]
Baldassarre 2006	1/32	0/32		0.02%	3[0.13,71]
Brox 2001	0/80	1/40		0.02%	0.17[0.01,4.05]
Derosa 2016	2/128	3/130		0.07%	0.68[0.12,3.98]
DO IT 2010	29/282	35/281		0.98%	0.83[0.52,1.31]
Doi 2014	11/119	24/119		0.5%	0.46[0.24,0.89]
ENRGISE 2018	5/148	9/141		0.2%	0.53[0.18,1.54]
EPE-A 2014	5/168	6/75		0.17%	0.37[0.12,1.18]
EPIC-1 2008	1/188	0/186		0.02%	2.97[0.12,72.4]
EPOCH 2014	8/195	5/196		0.19%	1.61[0.54,4.83]
FAAT 2005	31/200	39/202		1.13%	0.8[0.52,1.23]
FORWARD 2013	4/289	4/297		0.12%	1.03[0.26,4.07]
GISSI-HF 2008	783/3494	831/3481		7.24%	0.94[0.86,1.02]
GISSI-P 1999	1552/5666	1550/5658		8.18%	1[0.94,1.06]
HARP 1995	7/41	7/39		0.25%	0.95[0.37,2.46]
HEARTS 2017	45/143	39/142		1.52%	1.15[0.8,1.64]
JELIS 2007	262/9326	324/9319		4.63%	0.81[0.69,0.95]
Kumar 2013	1/39	1/39		0.03%	1[0.06,15.43]
MAPT 2017	192/820	164/832		3.97%	1.19[0.99,1.43]
Nodari 2011 HF	10/67	26/66		0.53%	0.38[0.2,0.72]
Nutristroke 2009	0/38	4/34		0.03%	0.1[0.01,1.79]
OFAMI 2001	42/150	36/150		1.37%	1.17[0.8,1.71]
OMEGA 2009	534/1752	541/1701		6.72%	0.96[0.87,1.06]
ORIGIN 2012	1276/6281	1295/6255		7.86%	0.98[0.92,1.05]
Proudman 2015	1/87	0/53		0.02%	1.84[0.08,44.38]
Puri 2005	1/60	0/61		0.02%	3.05[0.13,73.4]
Raitt 2005	2/100	5/100		0.09%	0.4[0.08,2.01]
REDUCE-IT 2019	459/4089	606/4090		6.2%	0.76[0.68,0.85]
Risk & Prevention 2013	733/6239	745/6266		6.86%	0.99[0.9,1.09]
Sandhu 2016	2/107	1/106		0.04%	1.98[0.18,21.52]
SCIMO 1999	17/112	26/111		0.72%	0.65[0.37,1.13]
Shinto 2014	1/13	0/13		0.02%	3[0.13,67.51]
SHOT 1996	15/317	12/293		0.41%	1.16[0.55,2.43]
SOFA 2006	65/273	62/273		2%	1.05[0.77,1.42]
SU.FOL.OM3 2010	216/1253	211/1248		4.28%	1.02[0.86,1.21]
VITAL 2019	386/12933	419/12938		5.39%	0.92[0.8,1.06]
Subtotal (95% CI)	**65269**	**64926**		**83.07%**	**0.94[0.9,1]**
Total events: 7621 (Higher omega 3), 7962 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=64, df=37(P=0); I^2=42.19%					
Test for overall effect: Z=2.11(P=0.03)					
1.31.4 Any combination					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 3), 0 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**70411**	**70071**		**100%**	**0.96[0.92,1.01]**
Total events: 8658 (Higher omega 3), 8961 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=75.11, df=42(P=0); I^2=44.08%					
Test for overall effect: Z=1.5(P=0.13)					
Test for subgroup differences: Chi^2=2.52, df=1 (P=0.28), I^2=20.48%					



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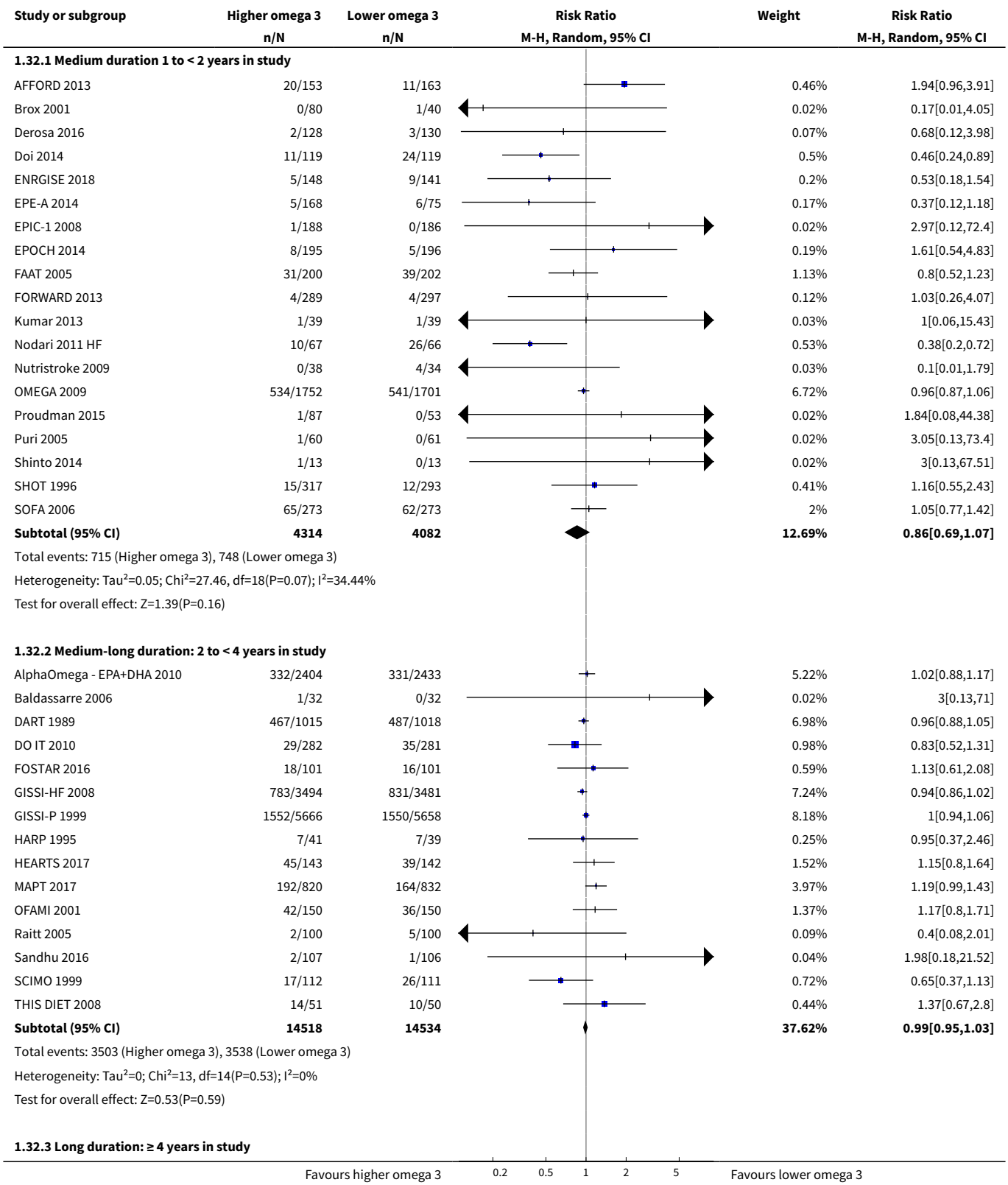
Analysis 1.32. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 32 CVD events - LCn3 - subgroup by duration.



Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.32.1 Medium duration 1 to < 2 years in study					
AFFORD 2013	20/153	11/163		0.46%	1.94[0.96,3.91]
Brox 2001	0/80	1/40		0.02%	0.17[0.01,4.05]
Derosa 2016	2/128	3/130		0.07%	0.68[0.12,3.98]
Doi 2014	11/119	24/119		0.5%	0.46[0.24,0.89]
ENRGISE 2018	5/148	9/141		0.2%	0.53[0.18,1.54]
EPE-A 2014	5/168	6/75		0.17%	0.37[0.12,1.18]
EPIC-1 2008	1/188	0/186		0.02%	2.97[0.12,72.4]
EPOCH 2014	8/195	5/196		0.19%	1.61[0.54,4.83]
FAAT 2005	31/200	39/202		1.13%	0.8[0.52,1.23]
FORWARD 2013	4/289	4/297		0.12%	1.03[0.26,4.07]
Kumar 2013	1/39	1/39		0.03%	1[0.06,15.43]
Nodari 2011 HF	10/67	26/66		0.53%	0.38[0.2,0.72]
Nutristroke 2009	0/38	4/34		0.03%	0.1[0.01,1.79]
OMEGA 2009	534/1752	541/1701		6.72%	0.96[0.87,1.06]
Proudman 2015	1/87	0/53		0.02%	1.84[0.08,44.38]
Puri 2005	1/60	0/61		0.02%	3.05[0.13,73.4]
Shinto 2014	1/13	0/13		0.02%	3[0.13,67.51]
SHOT 1996	15/317	12/293		0.41%	1.16[0.55,2.43]
SOFA 2006	65/273	62/273		2%	1.05[0.77,1.42]
Subtotal (95% CI)	**4314**	**4082**		**12.69%**	**0.86[0.69,1.07]**
Total events: 715 (Higher omega 3), 748 (Lower omega 3)					
Heterogeneity: Tau^2=0.05; Chi^2=27.46, df=18(P=0.07); I^2=34.44%					
Test for overall effect: Z=1.39(P=0.16)					
1.32.2 Medium-long duration: 2 to < 4 years in study					
AlphaOmega - EPA+DHA 2010	332/2404	331/2433		5.22%	1.02[0.88,1.17]
Baldassarre 2006	1/32	0/32		0.02%	3[0.13,71]
DART 1989	467/1015	487/1018		6.98%	0.96[0.88,1.05]
DO IT 2010	29/282	35/281		0.98%	0.83[0.52,1.31]
FOSTAR 2016	18/101	16/101		0.59%	1.13[0.61,2.08]
GISSI-HF 2008	783/3494	831/3481		7.24%	0.94[0.86,1.02]
GISSI-P 1999	1552/5666	1550/5658		8.18%	1[0.94,1.06]
HARP 1995	7/41	7/39		0.25%	0.95[0.37,2.46]
HEARTS 2017	45/143	39/142		1.52%	1.15[0.8,1.64]
MAPT 2017	192/820	164/832		3.97%	1.19[0.99,1.43]
OFAMI 2001	42/150	36/150		1.37%	1.17[0.8,1.71]
Raitt 2005	2/100	5/100		0.09%	0.4[0.08,2.01]
Sandhu 2016	2/107	1/106		0.04%	1.98[0.18,21.52]
SCIMO 1999	17/112	26/111		0.72%	0.65[0.37,1.13]
THIS DIET 2008	14/51	10/50		0.44%	1.37[0.67,2.8]
Subtotal (95% CI)	**14518**	**14534**		**37.62%**	**0.99[0.95,1.03]**
Total events: 3503 (Higher omega 3), 3538 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=13, df=14(P=0.53); I^2=0%					
Test for overall effect: Z=0.53(P=0.59)					
1.32.3 Long duration: ≥ 4 years in study					

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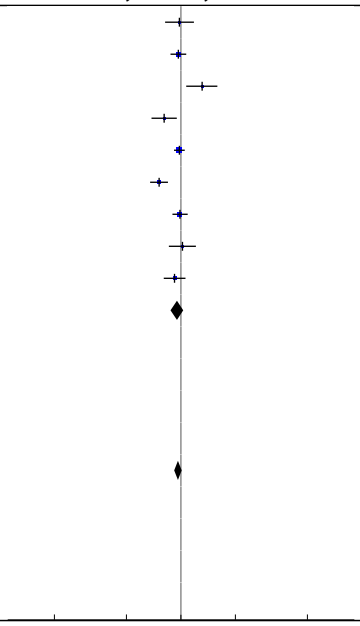
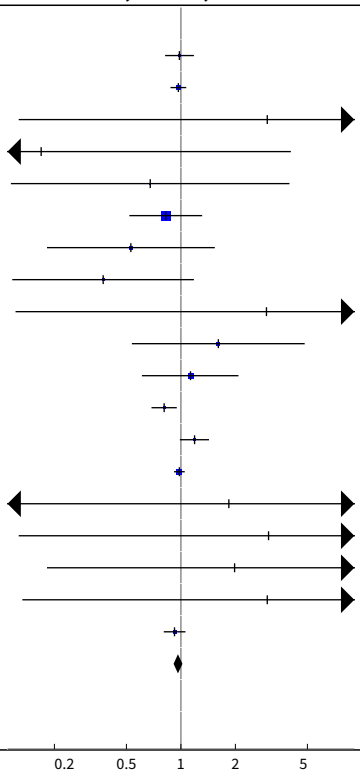
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
AREDS2 2014	213/2147	208/2056		4.06%	0.98[0.82,1.18]
ASCEND 2018	689/7740	712/7740		6.7%	0.97[0.88,1.07]
DART2 2003	206/1571	155/1543		3.7%	1.31[1.07,1.59]
JELIS 2007	262/9326	324/9319		4.63%	0.81[0.69,0.95]
ORIGIN 2012	1276/6281	1295/6255		7.86%	0.98[0.92,1.05]
REDUCE-IT 2019	459/4089	606/4090		6.2%	0.76[0.68,0.85]
Risk & Prevention 2013	733/6239	745/6266		6.86%	0.99[0.9,1.09]
SU.FOL.OM3 2010	216/1253	211/1248		4.28%	1.02[0.86,1.21]
VITAL 2019	386/12933	419/12938		5.39%	0.92[0.8,1.06]
Subtotal (95% CI)	**51579**	**51455**		**49.69%**	**0.95[0.88,1.03]**
Total events: 4440 (Higher omega 3), 4675 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=31.91, df=8(P<0.0001); I^2=74.93%					
Test for overall effect: Z=1.2(P=0.23)					
Total (95% CI)	**70411**	**70071**		**100%**	**0.96[0.92,1.01]**
Total events: 8658 (Higher omega 3), 8961 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=75.11, df=42(P=0); I^2=44.08%					
Test for overall effect: Z=1.5(P=0.13)					
Test for subgroup differences: Chi^2=2.2, df=1 (P=0.33), I^2=8.95%					



Analysis 1.33. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 33 CVD events - LCn3 - subgroup by primary or secondary prevention.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.33.1 Primary prevention of CVD					
AREDS2 2014	213/2147	208/2056		4.06%	0.98[0.82,1.18]
ASCEND 2018	689/7740	712/7740		6.7%	0.97[0.88,1.07]
Baldassarre 2006	1/32	0/32		0.02%	3[0.13,71]
Brox 2001	0/80	1/40		0.02%	0.17[0.01,4.05]
Derosa 2016	2/128	3/130		0.07%	0.68[0.12,3.98]
DO IT 2010	29/282	35/281		0.98%	0.83[0.52,1.31]
ENRGISE 2018	5/148	9/141		0.2%	0.53[0.18,1.54]
EPE-A 2014	5/168	6/75		0.17%	0.37[0.12,1.18]
EPIC-1 2008	1/188	0/186		0.02%	2.97[0.12,72.4]
EPOCH 2014	8/195	5/196		0.19%	1.61[0.54,4.83]
FOSTAR 2016	18/101	16/101		0.59%	1.13[0.61,2.08]
JELIS 2007	262/9326	324/9319		4.63%	0.81[0.69,0.95]
MAPT 2017	192/820	164/832		3.97%	1.19[0.99,1.43]
ORIGIN 2012	1276/6281	1295/6255		7.86%	0.98[0.92,1.05]
Proudman 2015	1/87	0/53		0.02%	1.84[0.08,44.38]
Puri 2005	1/60	0/61		0.02%	3.05[0.13,73.4]
Sandhu 2016	2/107	1/106		0.04%	1.98[0.18,21.52]
Shinto 2014	1/13	0/13		0.02%	3[0.13,67.51]
VITAL 2019	386/12933	419/12938		5.39%	0.92[0.8,1.06]
Subtotal (95% CI)	**40836**	**40555**		**35.02%**	**0.96[0.91,1.02]**
Total events: 3092 (Higher omega 3), 3198 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=19.43, df=18(P=0.37); I^2=7.36%					



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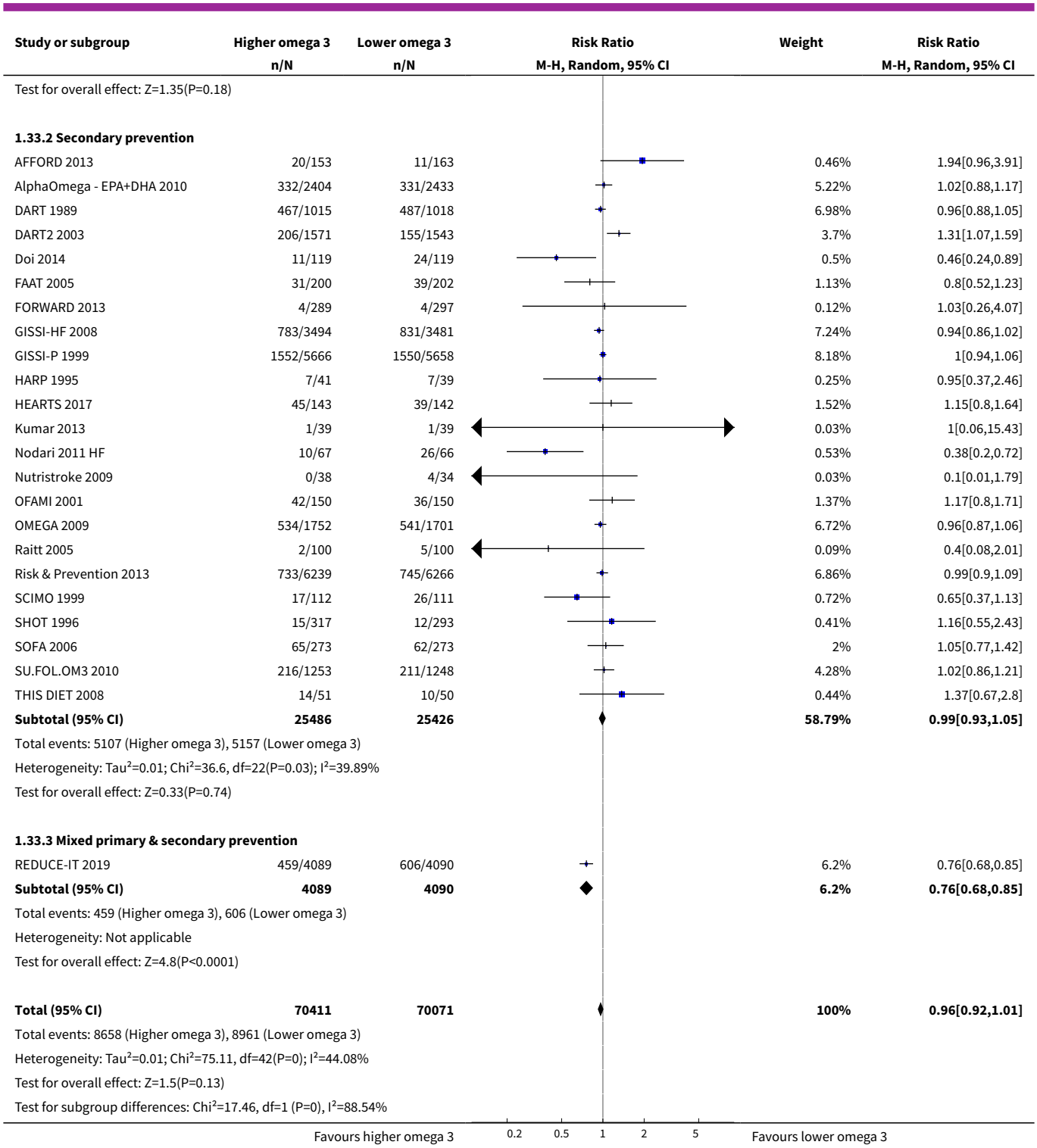

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=1.35(P=0.18)					
1.33.2 Secondary prevention					
AFFORD 2013	20/153	11/163		0.46%	1.94[0.96,3.91]
AlphaOmega - EPA+DHA 2010	332/2404	331/2433		5.22%	1.02[0.88,1.17]
DART 1989	467/1015	487/1018		6.98%	0.96[0.88,1.05]
DART2 2003	206/1571	155/1543		3.7%	1.31[1.07,1.59]
Doi 2014	11/119	24/119		0.5%	0.46[0.24,0.89]
FAAT 2005	31/200	39/202		1.13%	0.8[0.52,1.23]
FORWARD 2013	4/289	4/297		0.12%	1.03[0.26,4.07]
GISSI-HF 2008	783/3494	831/3481		7.24%	0.94[0.86,1.02]
GISSI-P 1999	1552/5666	1550/5658		8.18%	1[0.94,1.06]
HARP 1995	7/41	7/39		0.25%	0.95[0.37,2.46]
HEARTS 2017	45/143	39/142		1.52%	1.15[0.8,1.64]
Kumar 2013	1/39	1/39		0.03%	1[0.06,15.43]
Nodari 2011 HF	10/67	26/66		0.53%	0.38[0.2,0.72]
Nutristroke 2009	0/38	4/34		0.03%	0.1[0.01,1.79]
OFAMI 2001	42/150	36/150		1.37%	1.17[0.8,1.71]
OMEGA 2009	534/1752	541/1701		6.72%	0.96[0.87,1.06]
Raitt 2005	2/100	5/100		0.09%	0.4[0.08,2.01]
Risk & Prevention 2013	733/6239	745/6266		6.86%	0.99[0.9,1.09]
SCIMO 1999	17/112	26/111		0.72%	0.65[0.37,1.13]
SHOT 1996	15/317	12/293		0.41%	1.16[0.55,2.43]
SOFA 2006	65/273	62/273		2%	1.05[0.77,1.42]
SU.FOL.OM3 2010	216/1253	211/1248		4.28%	1.02[0.86,1.21]
THIS DIET 2008	14/51	10/50		0.44%	1.37[0.67,2.8]
Subtotal (95% CI)	**25486**	**25426**		**58.79%**	**0.99[0.93,1.05]**
Total events: 5107 (Higher omega 3), 5157 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=36.6, df=22(P=0.03); I^2=39.89%					
Test for overall effect: Z=0.33(P=0.74)					
1.33.3 Mixed primary & secondary prevention					
REDUCE-IT 2019	459/4089	606/4090		6.2%	0.76[0.68,0.85]
Subtotal (95% CI)	**4089**	**4090**		**6.2%**	**0.76[0.68,0.85]**
Total events: 459 (Higher omega 3), 606 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.8(P<0.0001)					
Total (95% CI)	**70411**	**70071**		**100%**	**0.96[0.92,1.01]**
Total events: 8658 (Higher omega 3), 8961 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=75.11, df=42(P=0); I^2=44.08%					
Test for overall effect: Z=1.5(P=0.13)					
Test for subgroup differences: Chi^2=17.46, df=1 (P=0), I^2=88.54%					

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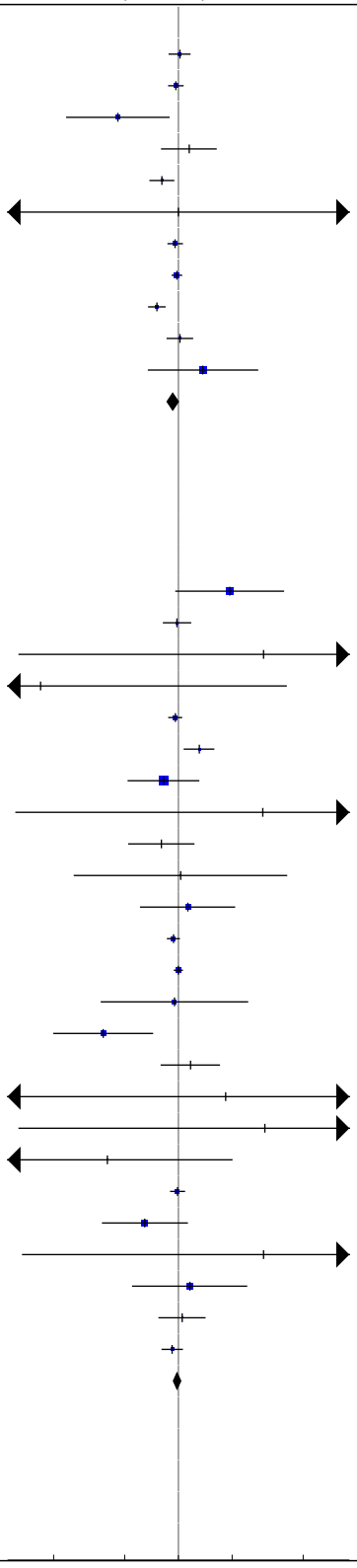
Analysis 1.34. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 34 CVD events - LCn3 - subgroup by statin use.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.34.1 LCn3 - ≥ 50% of control group on statins					
AlphaOmega - EPA+DHA 2010	332/2404	331/2433		5.22%	1.02[0.88,1.17]
ASCEND 2018	689/7740	712/7740		6.7%	0.97[0.88,1.07]
Doi 2014	11/119	24/119		0.5%	0.46[0.24,0.89]
HEARTS 2017	45/143	39/142		1.52%	1.15[0.8,1.64]
JELIS 2007	262/9326	324/9319		4.63%	0.81[0.69,0.95]
Kumar 2013	1/39	1/39		0.03%	1[0.06,15.43]
OMEGA 2009	534/1752	541/1701		6.72%	0.96[0.87,1.06]
ORIGIN 2012	1276/6281	1295/6255		7.86%	0.98[0.92,1.05]
REDUCE-IT 2019	459/4089	606/4090		6.2%	0.76[0.68,0.85]
SU.FOL.OM3 2010	216/1253	211/1248		4.28%	1.02[0.86,1.21]
THIS DIET 2008	14/51	10/50		0.44%	1.37[0.67,2.8]
Subtotal (95% CI)	**33197**	**33136**		**44.11%**	**0.93[0.86,1.01]**
Total events: 3839 (Higher omega 3), 4094 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=28.04, df=10(P=0); I^2=64.34%					
Test for overall effect: Z=1.76(P=0.08)					
1.34.2 LCn3 - < 50% of control group on statins					
AFFORD 2013	20/153	11/163		0.46%	1.94[0.96,3.91]
AREDS2 2014	213/2147	208/2056		4.06%	0.98[0.82,1.18]
Baldassarre 2006	1/32	0/32		0.02%	3[0.13,71]
Brox 2001	0/80	1/40		0.02%	0.17[0.01,4.05]
DART 1989	467/1015	487/1018		6.98%	0.96[0.88,1.05]
DART2 2003	206/1571	155/1543		3.7%	1.31[1.07,1.59]
DO IT 2010	29/282	35/281		0.98%	0.83[0.52,1.31]
EPIC-1 2008	1/188	0/186		0.02%	2.97[0.12,72.4]
FAAT 2005	31/200	39/202		1.13%	0.8[0.52,1.23]
FORWARD 2013	4/289	4/297		0.12%	1.03[0.26,4.07]
FOSTAR 2016	18/101	16/101		0.59%	1.13[0.61,2.08]
GISSI-HF 2008	783/3494	831/3481		7.24%	0.94[0.86,1.02]
GISSI-P 1999	1552/5666	1550/5658		8.18%	1[0.94,1.06]
HARP 1995	7/41	7/39		0.25%	0.95[0.37,2.46]
Nodari 2011 HF	10/67	26/66		0.53%	0.38[0.2,0.72]
OFAMI 2001	42/150	36/150		1.37%	1.17[0.8,1.71]
Proudman 2015	1/87	0/53		0.02%	1.84[0.08,44.38]
Puri 2005	1/60	0/61		0.02%	3.05[0.13,73.4]
Raitt 2005	2/100	5/100		0.09%	0.4[0.08,2.01]
Risk & Prevention 2013	733/6239	745/6266		6.86%	0.99[0.9,1.09]
SCIMO 1999	17/112	26/111		0.72%	0.65[0.37,1.13]
Shinto 2014	1/13	0/13		0.02%	3[0.13,67.51]
SHOT 1996	15/317	12/293		0.41%	1.16[0.55,2.43]
SOFA 2006	65/273	62/273		2%	1.05[0.77,1.42]
VITAL 2019	386/12933	419/12938		5.39%	0.92[0.8,1.06]
Subtotal (95% CI)	**35610**	**35421**		**51.2%**	**0.98[0.93,1.04]**
Total events: 4605 (Higher omega 3), 4675 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=31.84, df=24(P=0.13); I^2=24.63%					
Test for overall effect: Z=0.64(P=0.52)					
1.34.3 LCn3 - use of statins unclear					



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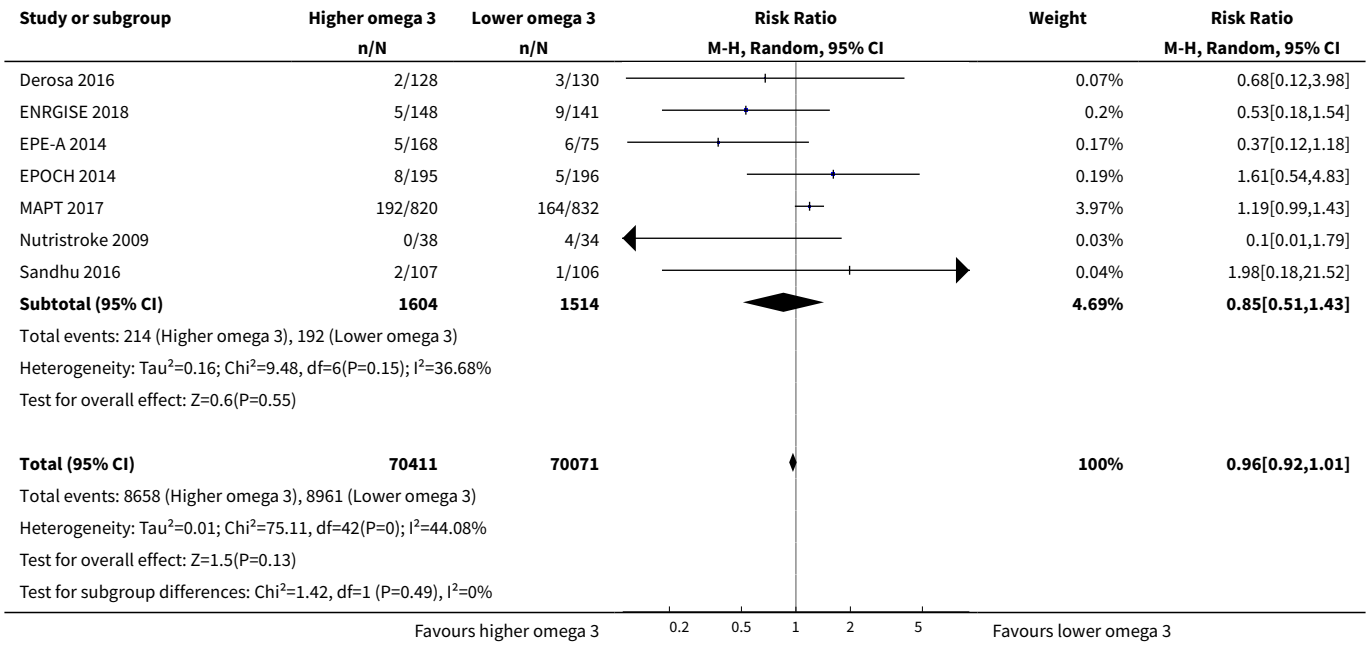
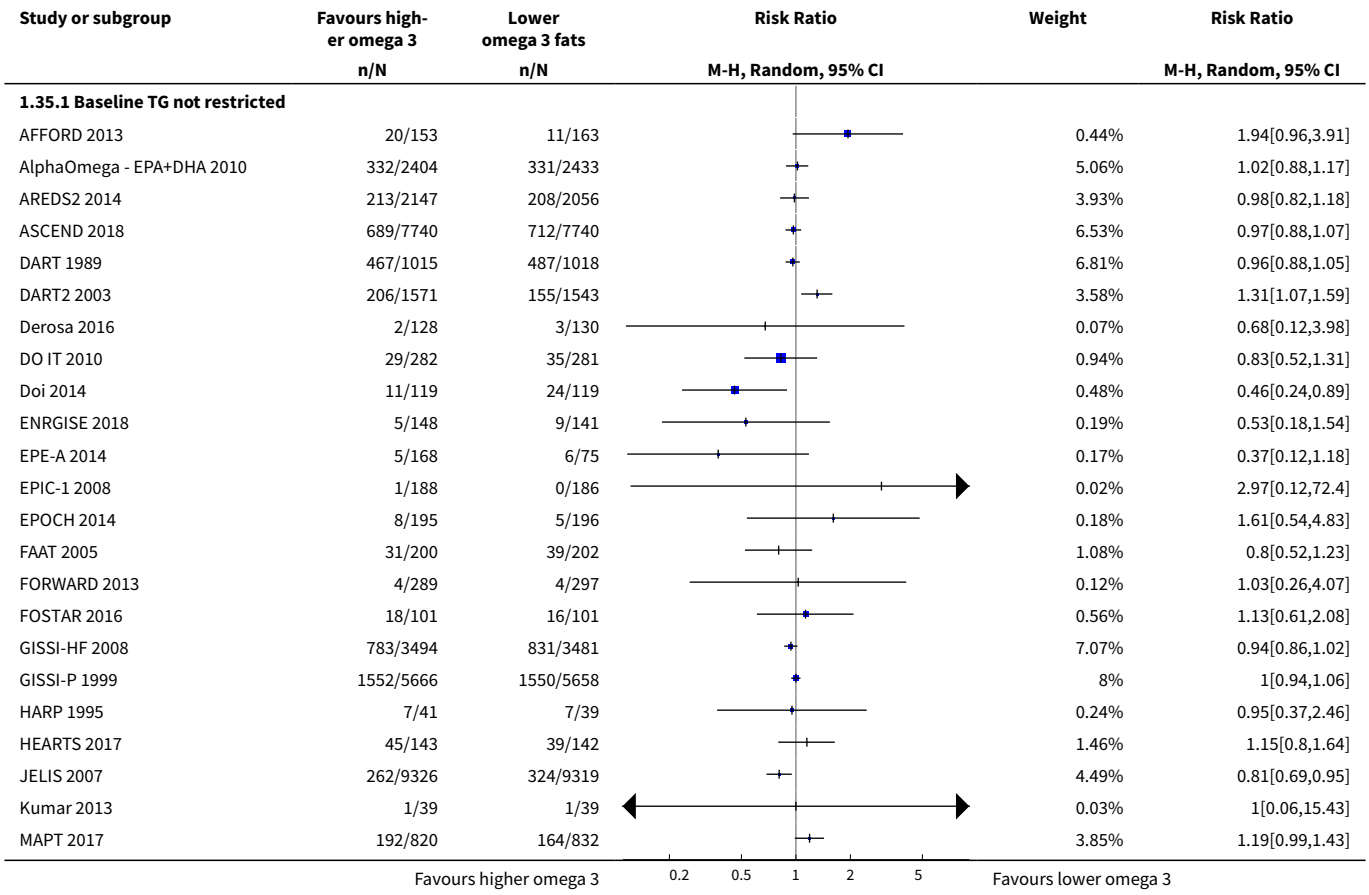


Analysis 1.35. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 35 CVD events - LCn3 - subgroup by baseline TG.



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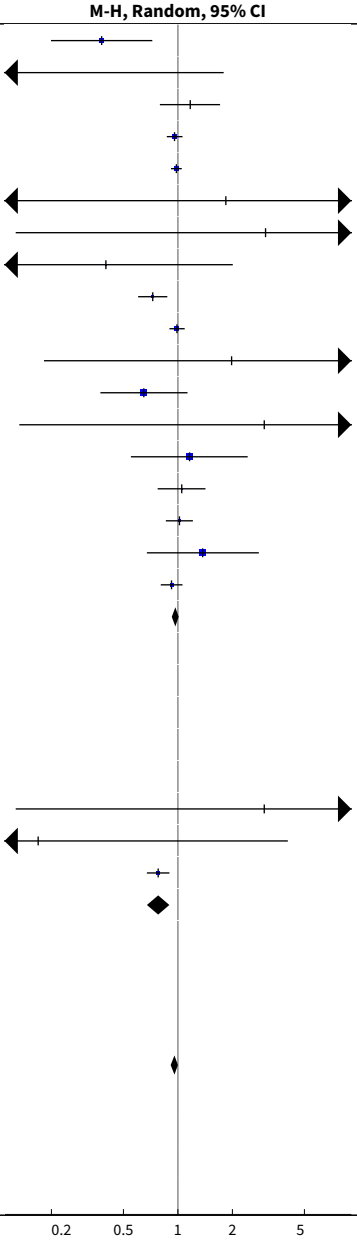
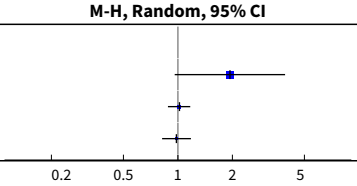
Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 fats n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Nodari 2011 HF	10/67	26/66		0.51%	0.38[0.2,0.72]
Nutristroke 2009	0/38	4/34		0.03%	0.1[0.01,1.79]
OFAMI 2001	42/150	36/150		1.32%	1.17[0.8,1.71]
OMEGA 2009	534/1752	541/1701		6.55%	0.96[0.87,1.06]
ORIGIN 2012	1276/6281	1295/6255		7.69%	0.98[0.92,1.05]
Proudman 2015	1/87	0/53		0.02%	1.84[0.08,44.38]
Puri 2005	1/60	0/61		0.02%	3.05[0.13,73.4]
Raitt 2005	2/100	5/100		0.09%	0.4[0.08,2.01]
REDUCE-IT 2019	169/1605	235/1620		3.83%	0.73[0.6,0.87]
Risk & Prevention 2013	733/6239	745/6266		6.68%	0.99[0.9,1.09]
Sandhu 2016	2/107	1/106		0.04%	1.98[0.18,21.52]
SCIMO 1999	17/112	26/111		0.69%	0.65[0.37,1.13]
Shinto 2014	1/13	0/13		0.02%	3[0.13,67.51]
SHOT 1996	15/317	12/293		0.39%	1.16[0.55,2.43]
SOFA 2006	65/273	62/273		1.92%	1.05[0.77,1.42]
SU.FOL.OM3 2010	216/1253	211/1248		4.15%	1.02[0.86,1.21]
THIS DIET 2008	14/51	10/50		0.43%	1.37[0.67,2.8]
VITAL 2019	386/12933	419/12938		5.24%	0.92[0.8,1.06]
Subtotal (95% CI)	**67815**	**67529**		**94.95%**	**0.97[0.92,1.01]**
Total events: 8367 (Favours higher omega 3), 8589 (Lower omega 3 fats)					
Heterogeneity: Tau^2=0.01; Chi^2=64.66, df=40(P=0.01); I^2=38.13%					
Test for overall effect: Z=1.41(P=0.16)					
1.35.2 Baseline TG raised					
Baldassarre 2006	1/32	0/32		0.02%	3[0.13,71]
Brox 2001	0/80	1/40		0.02%	0.17[0.01,4.05]
REDUCE-IT 2019	290/2481	371/2469		5.01%	0.78[0.67,0.9]
Subtotal (95% CI)	**2593**	**2541**		**5.05%**	**0.78[0.67,0.9]**
Total events: 291 (Favours higher omega 3), 372 (Lower omega 3 fats)					
Heterogeneity: Tau^2=0; Chi^2=1.59, df=2(P=0.45); I^2=0%					
Test for overall effect: Z=3.45(P=0)					
Total (95% CI)	**70408**	**70070**		**100%**	**0.96[0.91,1]**
Total events: 8658 (Favours higher omega 3), 8961 (Lower omega 3 fats)					
Heterogeneity: Tau^2=0.01; Chi^2=75.36, df=43(P=0); I^2=42.94%					
Test for overall effect: Z=1.83(P=0.07)					
Test for subgroup differences: Chi^2=8.17, df=1 (P=0), I^2=87.75%					



Analysis 1.36. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 36 CVD events - LCn3 - subgroup by baseline diabetes.

Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 fats n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.36.1 Normal diabetes risk					
AFFORD 2013	20/153	11/163		0.44%	1.94[0.96,3.91]
AlphaOmega - EPA+DHA 2010	332/2404	331/2433		5.07%	1.02[0.88,1.17]
AREDS2 2014	213/2147	208/2056		3.94%	0.98[0.82,1.18]



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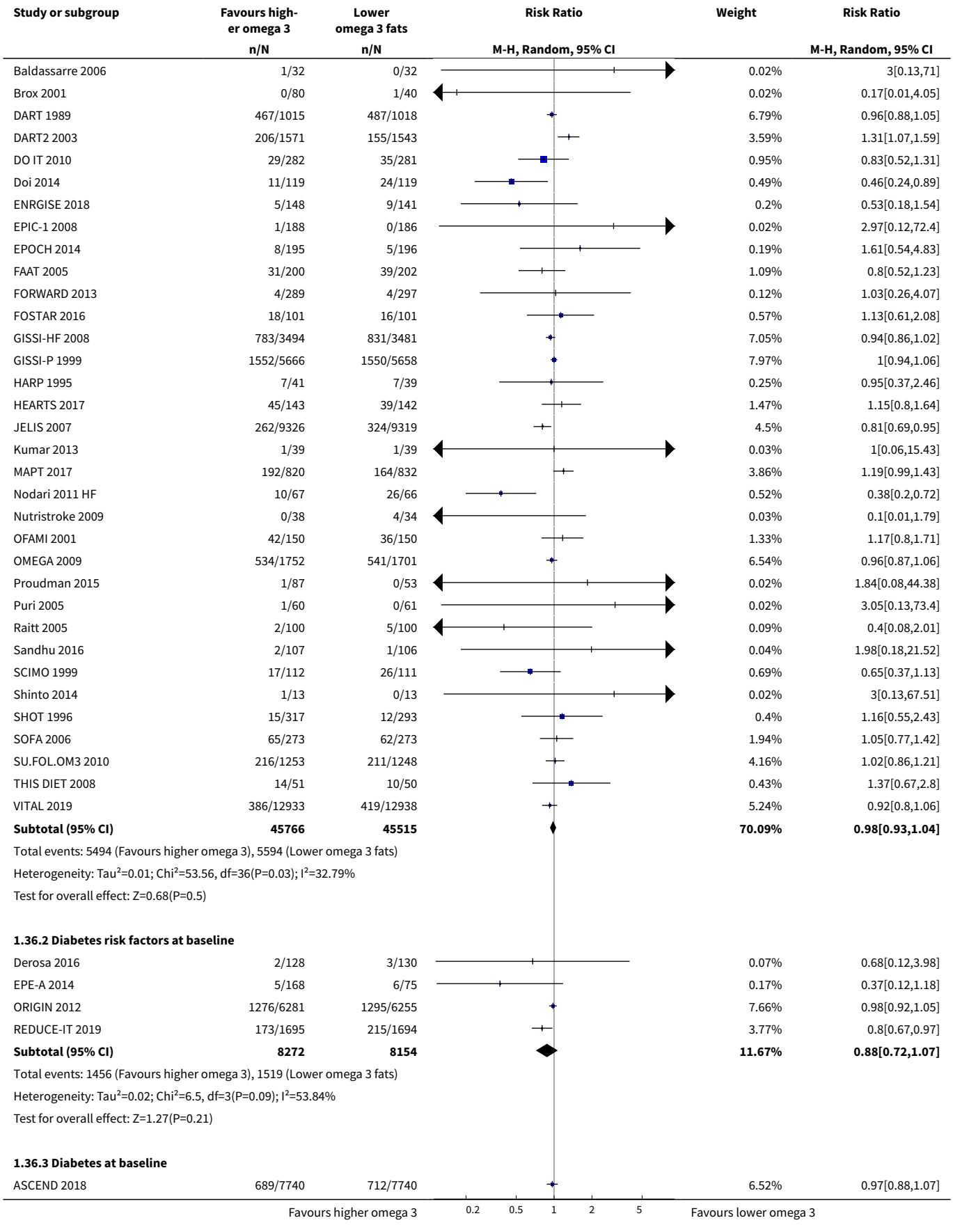

Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 fats n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Baldassarre 2006	1/32	0/32		0.02%	3[0.13,71]
Brox 2001	0/80	1/40		0.02%	0.17[0.01,4.05]
DART 1989	467/1015	487/1018		6.79%	0.96[0.88,1.05]
DART2 2003	206/1571	155/1543		3.59%	1.31[1.07,1.59]
DO IT 2010	29/282	35/281		0.95%	0.83[0.52,1.31]
Doi 2014	11/119	24/119		0.49%	0.46[0.24,0.89]
ENRGISE 2018	5/148	9/141		0.2%	0.53[0.18,1.54]
EPIC-1 2008	1/188	0/186		0.02%	2.97[0.12,72.4]
EPOCH 2014	8/195	5/196		0.19%	1.61[0.54,4.83]
FAAT 2005	31/200	39/202		1.09%	0.8[0.52,1.23]
FORWARD 2013	4/289	4/297		0.12%	1.03[0.26,4.07]
FOSTAR 2016	18/101	16/101		0.57%	1.13[0.61,2.08]
GISSI-HF 2008	783/3494	831/3481		7.05%	0.94[0.86,1.02]
GISSI-P 1999	1552/5666	1550/5658		7.97%	1[0.94,1.06]
HARP 1995	7/41	7/39		0.25%	0.95[0.37,2.46]
HEARTS 2017	45/143	39/142		1.47%	1.15[0.8,1.64]
JELIS 2007	262/9326	324/9319		4.5%	0.81[0.69,0.95]
Kumar 2013	1/39	1/39		0.03%	1[0.06,15.43]
MAPT 2017	192/820	164/832		3.86%	1.19[0.99,1.43]
Nodari 2011 HF	10/67	26/66		0.52%	0.38[0.2,0.72]
Nutristroke 2009	0/38	4/34		0.03%	0.1[0.01,1.79]
OFAMI 2001	42/150	36/150		1.33%	1.17[0.8,1.71]
OMEGA 2009	534/1752	541/1701		6.54%	0.96[0.87,1.06]
Proudman 2015	1/87	0/53		0.02%	1.84[0.08,44.38]
Puri 2005	1/60	0/61		0.02%	3.05[0.13,73.4]
Raitt 2005	2/100	5/100		0.09%	0.4[0.08,2.01]
Sandhu 2016	2/107	1/106		0.04%	1.98[0.18,21.52]
SCIMO 1999	17/112	26/111		0.69%	0.65[0.37,1.13]
Shinto 2014	1/13	0/13		0.02%	3[0.13,67.51]
SHOT 1996	15/317	12/293		0.4%	1.16[0.55,2.43]
SOFA 2006	65/273	62/273		1.94%	1.05[0.77,1.42]
SU.FOL.OM3 2010	216/1253	211/1248		4.16%	1.02[0.86,1.21]
THIS DIET 2008	14/51	10/50		0.43%	1.37[0.67,2.8]
VITAL 2019	386/12933	419/12938		5.24%	0.92[0.8,1.06]
Subtotal (95% CI)	**45766**	**45515**		**70.09%**	**0.98[0.93,1.04]**
Total events: 5494 (Favours higher omega 3), 5594 (Lower omega 3 fats)					
Heterogeneity: Tau^2=0.01; Chi^2=53.56, df=36(P=0.03); I^2=32.79%					
Test for overall effect: Z=0.68(P=0.5)					
1.36.2 Diabetes risk factors at baseline					
Derosa 2016	2/128	3/130		0.07%	0.68[0.12,3.98]
EPE-A 2014	5/168	6/75		0.17%	0.37[0.12,1.18]
ORIGIN 2012	1276/6281	1295/6255		7.66%	0.98[0.92,1.05]
REDUCE-IT 2019	173/1695	215/1694		3.77%	0.8[0.67,0.97]
Subtotal (95% CI)	**8272**	**8154**		**11.67%**	**0.88[0.72,1.07]**
Total events: 1456 (Favours higher omega 3), 1519 (Lower omega 3 fats)					
Heterogeneity: Tau^2=0.02; Chi^2=6.5, df=3(P=0.09); I^2=53.84%					
Test for overall effect: Z=1.27(P=0.21)					
1.36.3 Diabetes at baseline					
ASCEND 2018	689/7740	712/7740		6.52%	0.97[0.88,1.07]

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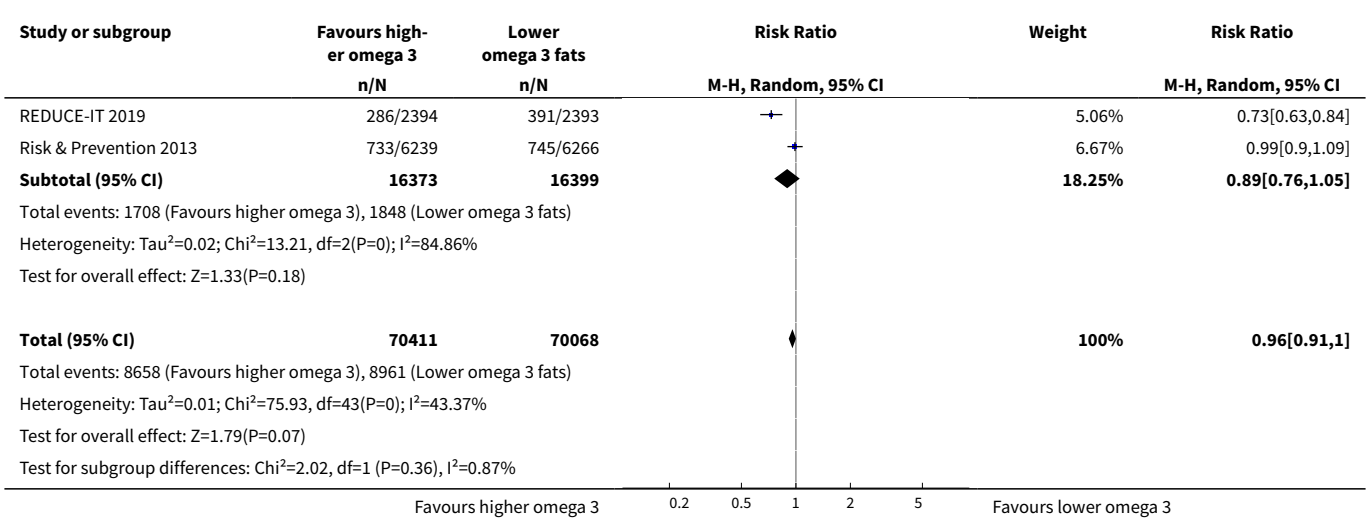
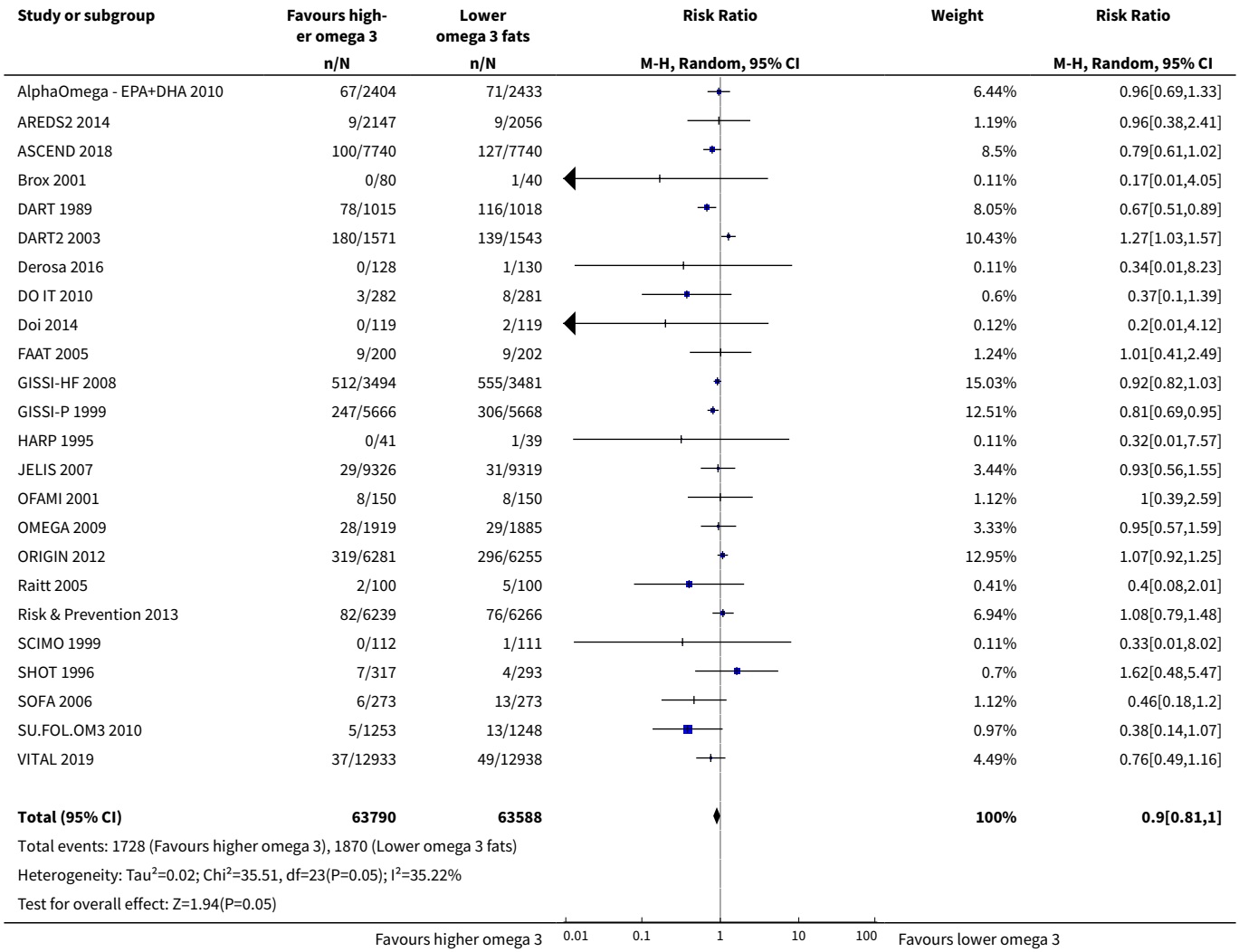


Analysis 1.37. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 37 Coronary heart disease mortality (overall) - LCn3.



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Analysis 1.38. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 38 CHD mortality - LCn3 - SA fixed effect.

Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 fats n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
AlphaOmega - EPA+DHA 2010	67/2404	71/2433		3.76%	0.96[0.69,1.33]
AREDS2 2014	9/2147	9/2056		0.49%	0.96[0.38,2.41]
ASCEND 2018	100/7740	127/7740		6.77%	0.79[0.61,1.02]
Brox 2001	0/80	1/40		0.11%	0.17[0.01,4.05]
DART 1989	78/1015	116/1018		6.18%	0.67[0.51,0.89]
DART2 2003	180/1571	139/1543		7.48%	1.27[1.03,1.57]
Derosa 2016	0/128	1/130		0.08%	0.34[0.01,8.23]
DO IT 2010	3/282	8/281		0.43%	0.37[0.1,1.39]
Doi 2014	0/119	2/119		0.13%	0.2[0.01,4.12]
FAAT 2005	9/200	9/202		0.48%	1.01[0.41,2.49]
GISSI-HF 2008	512/3494	555/3481		29.64%	0.92[0.82,1.03]
GISSI-P 1999	247/5666	306/5668		16.31%	0.81[0.69,0.95]
HARP 1995	0/41	1/39		0.08%	0.32[0.01,7.57]
JELIS 2007	29/9326	31/9319		1.65%	0.93[0.56,1.55]
OFAMI 2001	8/150	8/150		0.43%	1[0.39,2.59]
OMEGA 2009	28/1919	29/1885		1.56%	0.95[0.57,1.59]
ORIGIN 2012	319/6281	296/6255		15.81%	1.07[0.92,1.25]
Raitt 2005	2/100	5/100		0.27%	0.4[0.08,2.01]
Risk & Prevention 2013	82/6239	76/6266		4.04%	1.08[0.79,1.48]
SCIMO 1999	0/112	1/111		0.08%	0.33[0.01,8.02]
SHOT 1996	7/317	4/293		0.22%	1.62[0.48,5.47]
SOFA 2006	6/273	13/273		0.69%	0.46[0.18,1.2]
SU.FOL.OM3 2010	5/1253	13/1248		0.69%	0.38[0.14,1.07]
VITAL 2019	37/12933	49/12938		2.61%	0.76[0.49,1.16]
Total (95% CI)	**63790**	**63588**		**100%**	**0.92[0.86,0.98]**
Total events: 1728 (Favours higher omega 3), 1870 (Lower omega 3 fats)					
Heterogeneity: Tau^2=0; Chi^2=35.51, df=23(P=0.05); I^2=35.22%					
Test for overall effect: Z=2.58(P=0.01)					

Favours higher omega 3 — Favours lower omega 3

Analysis 1.39. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 39 CHD mortality - LCn3 - SA by summary risk of bias.

Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 fats n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.39.1 Low summary risk of bias					
AlphaOmega - EPA+DHA 2010	67/2404	71/2433		16.11%	0.96[0.69,1.33]
AREDS2 2014	9/2147	9/2056		2.82%	0.96[0.38,2.41]
ASCEND 2018	100/7740	127/7740		21.73%	0.79[0.61,1.02]
Derosa 2016	0/128	1/130		0.25%	0.34[0.01,8.23]
OMEGA 2009	28/1919	29/1885		8.05%	0.95[0.57,1.59]
ORIGIN 2012	319/6281	296/6255		34.88%	1.07[0.92,1.25]

Favours higher omega 3 — Favours lower omega 3

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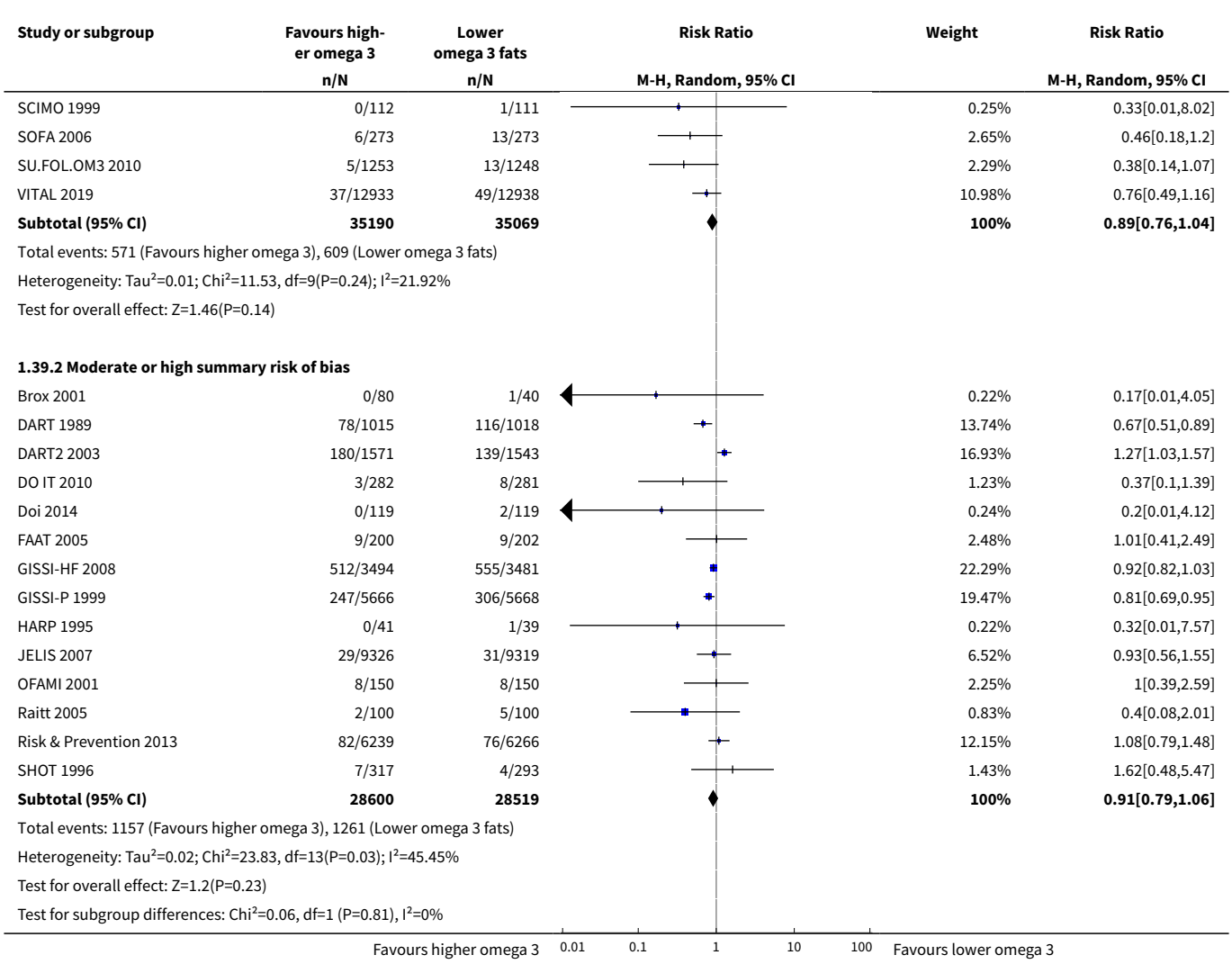
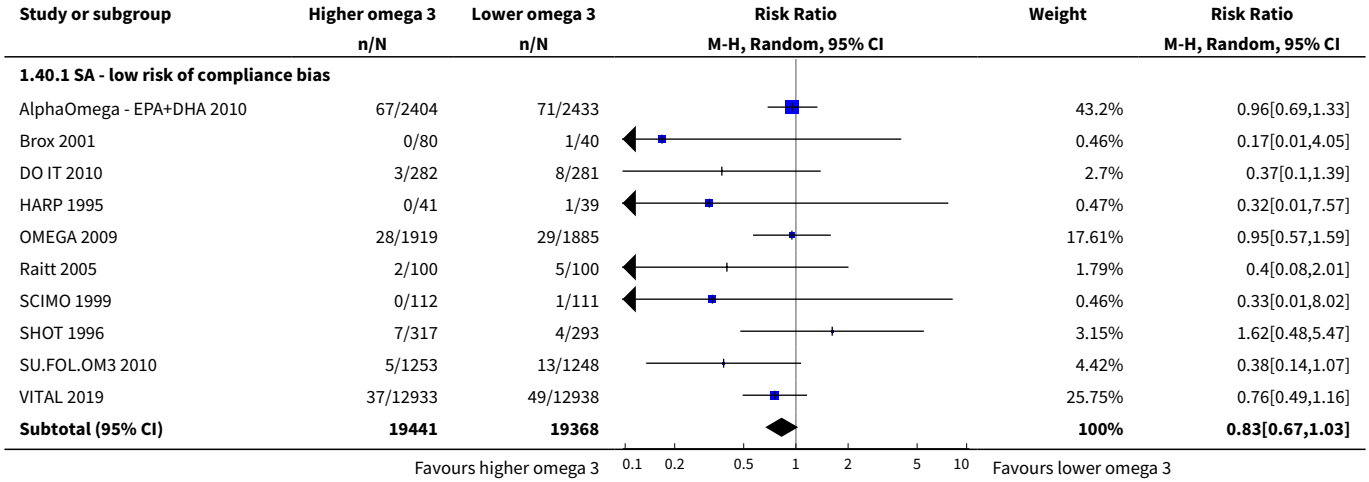


Analysis 1.40. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 40 CHD mortality - LCn3 - SA by compliance and study size.



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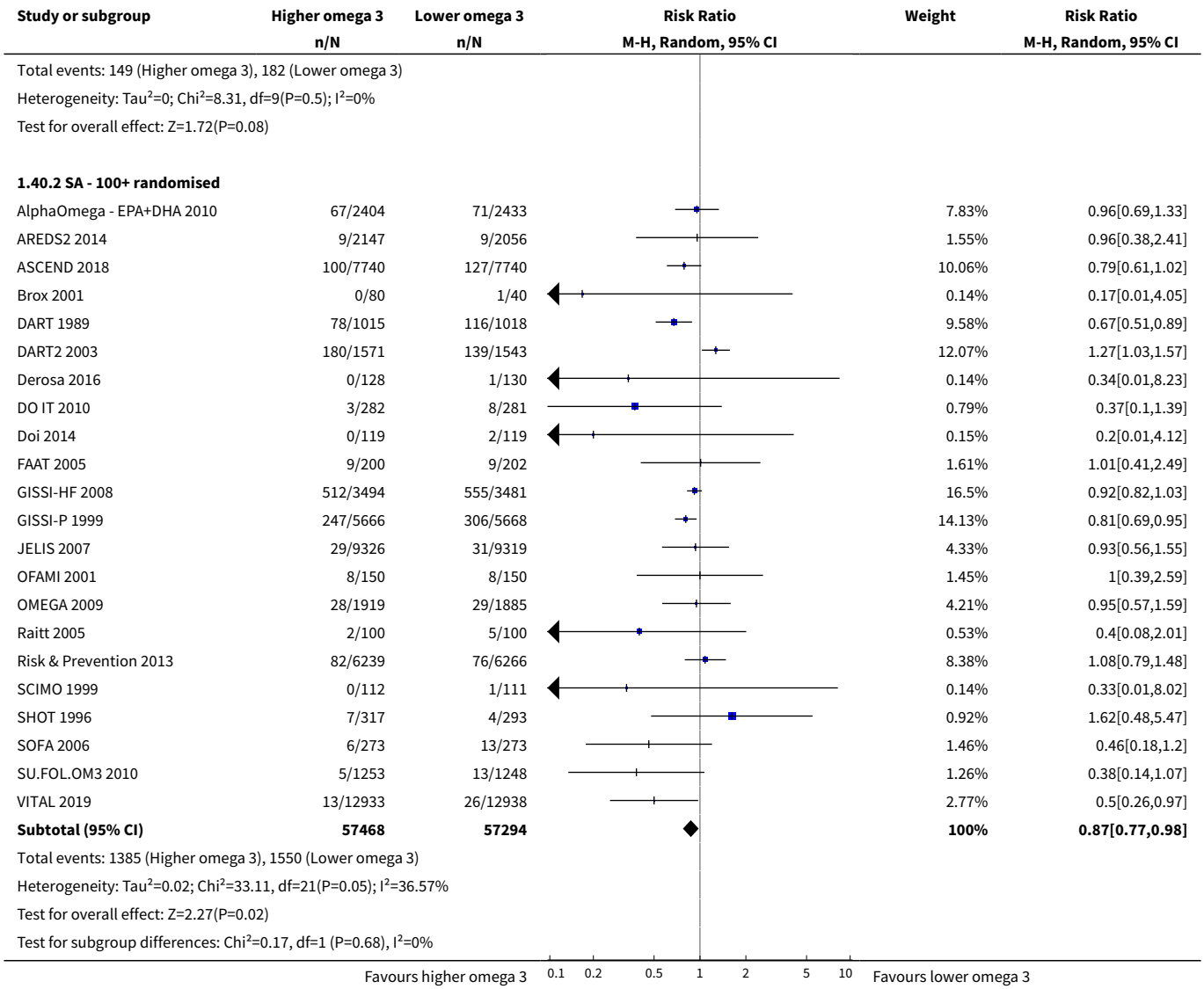
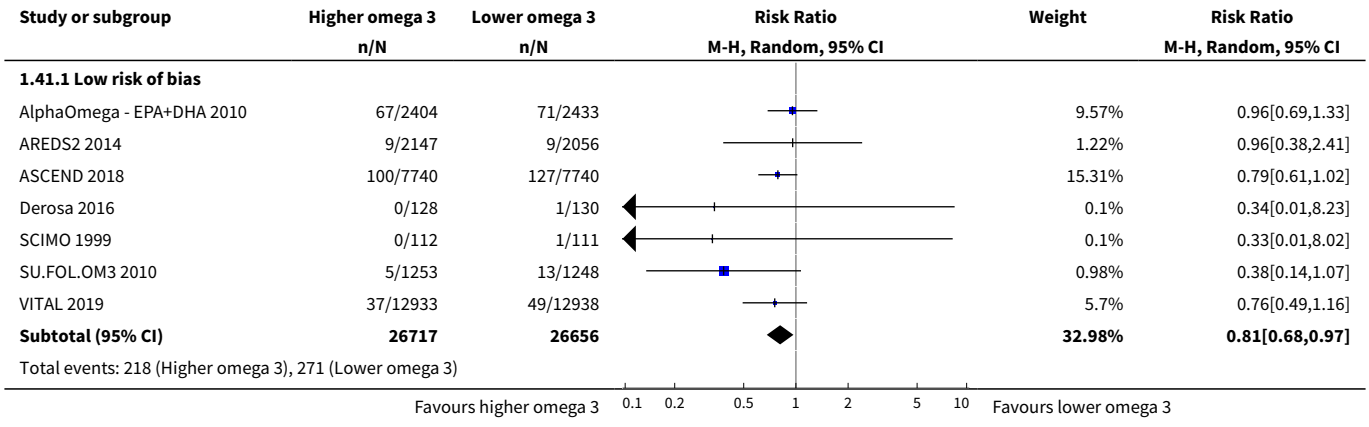


Analysis 1.41. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 41 CHD mortality - LCn3 - SA omitting cardiac death.



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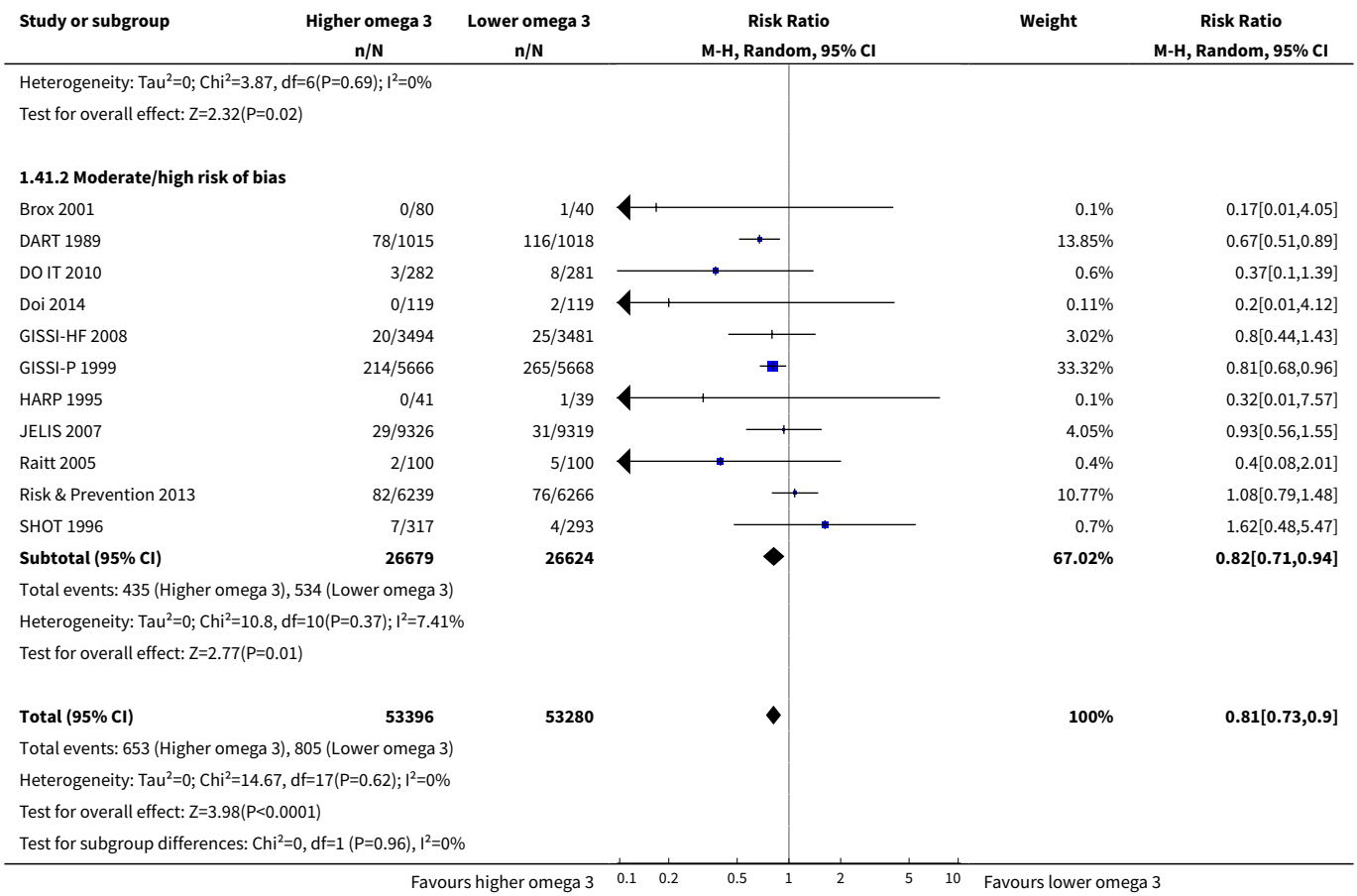
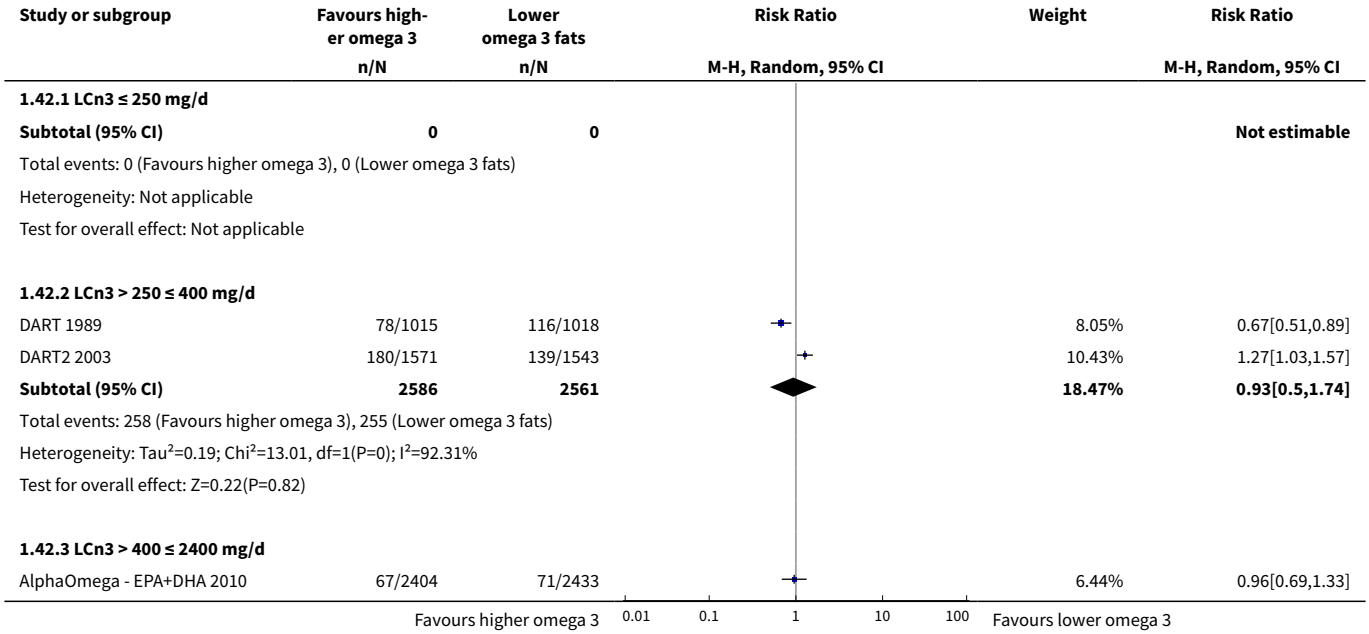


Analysis 1.42. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 42 CHD mortality - LCn3 - subgroup by dose.



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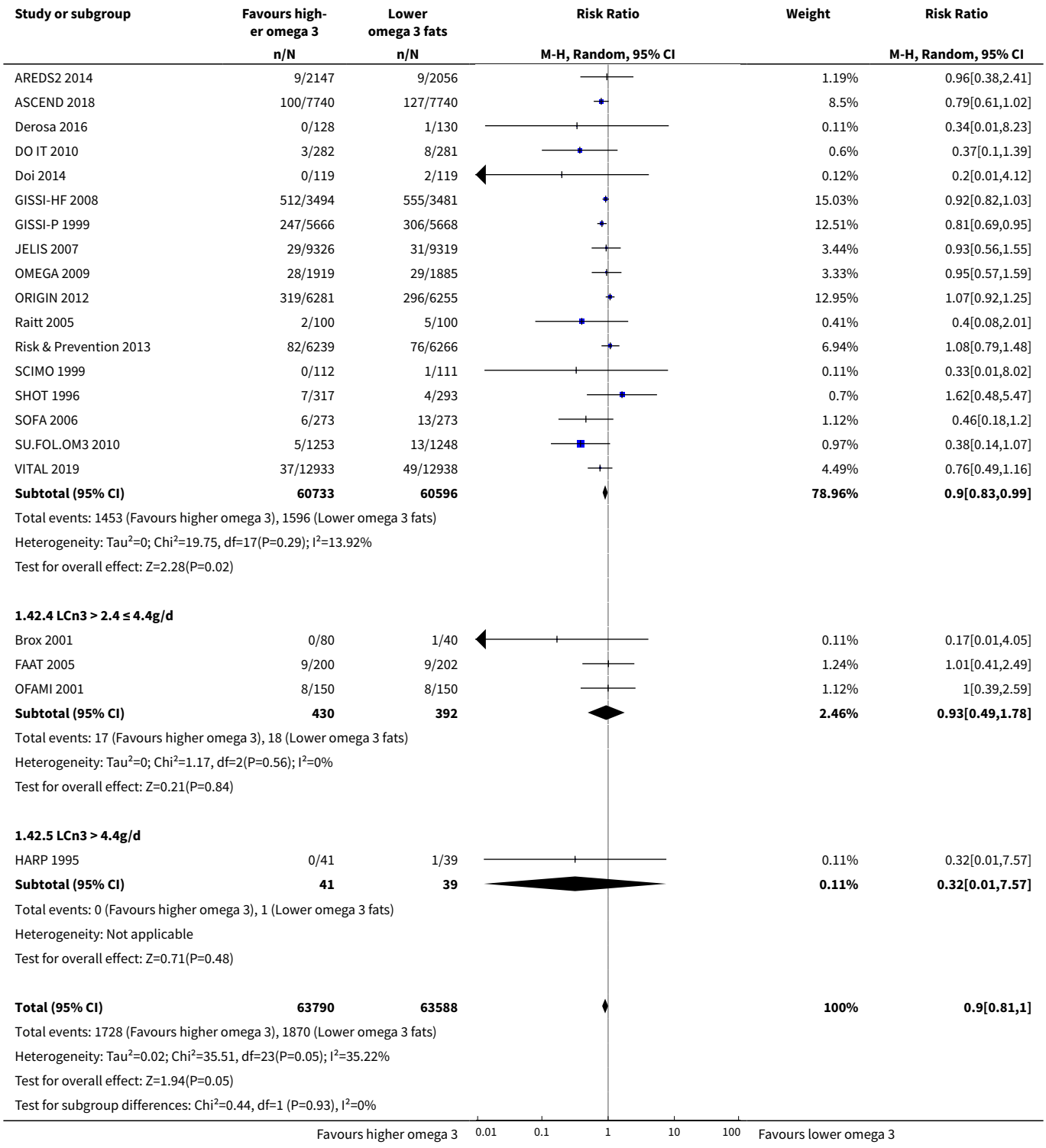

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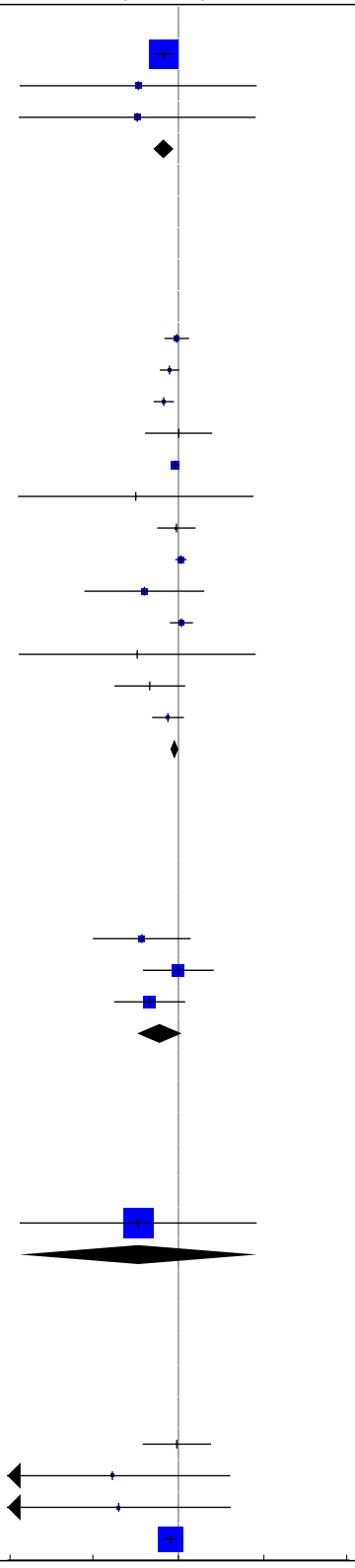
Analysis 1.43. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 43 CHD mortality - LCn3 - subgroup by replacement.

Study or subgroup	High omega 3 n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.43.1 N-3 replacing SFA					
DART 1989	78/1015	116/1018		98.55%	0.67[0.51,0.89]
Derosa 2016	0/128	1/130		0.72%	0.34[0.01,8.23]
SCIMO 1999	0/112	1/111		0.72%	0.33[0.01,8.02]
Subtotal (95% CI)	**1255**	**1259**		**100%**	**0.67[0.51,0.88]**
Total events: 78 (High omega 3), 118 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.37, df=2(P=0.83); I^2=0%					
Test for overall effect: Z=2.92(P=0)					
1.43.2 N-3 replacing MUFA					
AlphaOmega - EPA+DHA 2010	67/2404	71/2433		8.2%	0.96[0.69,1.33]
ASCEND 2018	100/7740	127/7740		11.61%	0.79[0.61,1.02]
DART 1989	78/1015	116/1018		10.82%	0.67[0.51,0.89]
FAAT 2005	9/200	9/202		1.34%	1.01[0.41,2.49]
GISSI-HF 2008	512/3494	555/3481		26.89%	0.92[0.82,1.03]
HARP 1995	0/41	1/39		0.11%	0.32[0.01,7.57]
OMEGA 2009	28/1919	29/1885		3.83%	0.95[0.57,1.59]
ORIGIN 2012	319/6281	296/6255		21.1%	1.07[0.92,1.25]
Raitt 2005	2/100	5/100		0.43%	0.4[0.08,2.01]
Risk & Prevention 2013	82/6239	76/6266		8.99%	1.08[0.79,1.48]
SCIMO 1999	0/112	1/111		0.11%	0.33[0.01,8.02]
SOFA 2006	6/273	13/273		1.21%	0.46[0.18,1.2]
VITAL 2019	37/12933	49/12938		5.36%	0.76[0.49,1.16]
Subtotal (95% CI)	**42751**	**42741**		**100%**	**0.9[0.81,1]**
Total events: 1240 (High omega 3), 1348 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=16.02, df=12(P=0.19); I^2=25.09%					
Test for overall effect: Z=1.98(P=0.05)					
1.43.3 N-3 replacing n-6					
DO IT 2010	3/282	8/281		20.76%	0.37[0.1,1.39]
OFAMI 2001	8/150	8/150		39.59%	1[0.39,2.59]
SOFA 2006	6/273	13/273		39.65%	0.46[0.18,1.2]
Subtotal (95% CI)	**705**	**704**		**100%**	**0.6[0.33,1.09]**
Total events: 17 (High omega 3), 29 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.9, df=2(P=0.39); I^2=0%					
Test for overall effect: Z=1.67(P=0.1)					
1.43.4 N-3 replacing carbohydrates/sugars					
Derosa 2016	0/128	1/130		100%	0.34[0.01,8.23]
Subtotal (95% CI)	**128**	**130**		**100%**	**0.34[0.01,8.23]**
Total events: 0 (High omega 3), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.67(P=0.51)					
1.43.5 N-3 replacing nil/low n-3 placebo					
AREDS2 2014	9/2147	9/2056		2.66%	0.96[0.38,2.41]
Brox 2001	0/80	1/40		0.22%	0.17[0.01,4.05]
Doi 2014	0/119	2/119		0.25%	0.2[0.01,4.12]
GISSI-P 1999	247/5666	306/5668		84.39%	0.81[0.69,0.95]



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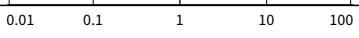
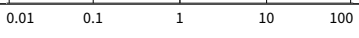
Study or subgroup	High omega 3 n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
JELIS 2007	29/9326	31/9319		8.83%	0.93[0.56,1.55]
SHOT 1996	7/317	4/293		1.52%	1.62[0.48,5.47]
SU.FOL.OM3 2010	5/1253	13/1248		2.13%	0.38[0.14,1.07]
Subtotal (95% CI)	**18908**	**18743**		**100%**	**0.81[0.7,0.94]**
Total events: 297 (High omega 3), 366 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.47, df=6(P=0.49); I^2=0%					
Test for overall effect: Z=2.72(P=0.01)					
Test for subgroup differences: Chi^2=5.99, df=1 (P=0.2), I^2=33.2%					



Favours high LCn3 — Favours low LCn3

Analysis 1.44. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 44 CHD mortality - LCn3 - subgroup by intervention type.

Study or subgroup	High omega 3 n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.44.1 Dietary advice					
DART 1989	78/1015	116/1018		8.05%	0.67[0.51,0.89]
DART2 2003	180/1571	139/1543		10.43%	1.27[1.03,1.57]
Subtotal (95% CI)	**2586**	**2561**		**18.47%**	**0.93[0.5,1.74]**
Total events: 258 (High omega 3), 255 (Control)					
Heterogeneity: Tau^2=0.19; Chi^2=13.01, df=1(P=0); I^2=92.31%					
Test for overall effect: Z=0.22(P=0.82)					
1.44.2 Supplemental foods					
AlphaOmega - EPA+DHA 2010	67/2404	71/2433		6.44%	0.96[0.69,1.33]
Subtotal (95% CI)	**2404**	**2433**		**6.44%**	**0.96[0.69,1.33]**
Total events: 67 (High omega 3), 71 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.27(P=0.78)					
1.44.3 Supplements (capsule)					
AREDS2 2014	9/2147	9/2056		1.19%	0.96[0.38,2.41]
ASCEND 2018	100/7740	127/7740		8.5%	0.79[0.61,1.02]
Brox 2001	0/80	1/40		0.11%	0.17[0.01,4.05]
Derosa 2016	0/128	1/130		0.11%	0.34[0.01,8.23]
DO IT 2010	3/282	8/281		0.6%	0.37[0.1,1.39]
Doi 2014	0/119	2/119		0.12%	0.2[0.01,4.12]
FAAT 2005	9/200	9/202		1.24%	1.01[0.41,2.49]
GISSI-HF 2008	512/3494	555/3481		15.03%	0.92[0.82,1.03]
GISSI-P 1999	247/5666	306/5668		12.51%	0.81[0.69,0.95]
HARP 1995	0/41	1/39		0.11%	0.32[0.01,7.57]
JELIS 2007	29/9326	31/9319		3.44%	0.93[0.56,1.55]
OFAMI 2001	8/150	8/150		1.12%	1[0.39,2.59]
OMEGA 2009	28/1919	29/1885		3.33%	0.95[0.57,1.59]
ORIGIN 2012	319/6281	296/6255		12.95%	1.07[0.92,1.25]
Raitt 2005	2/100	5/100		0.41%	0.4[0.08,2.01]
Risk & Prevention 2013	82/6239	76/6266		6.94%	1.08[0.79,1.48]
SCIMO 1999	0/112	1/111		0.11%	0.33[0.01,8.02]
SHOT 1996	7/317	4/293		0.7%	1.62[0.48,5.47]



Favours high ALA — Favours low ALA

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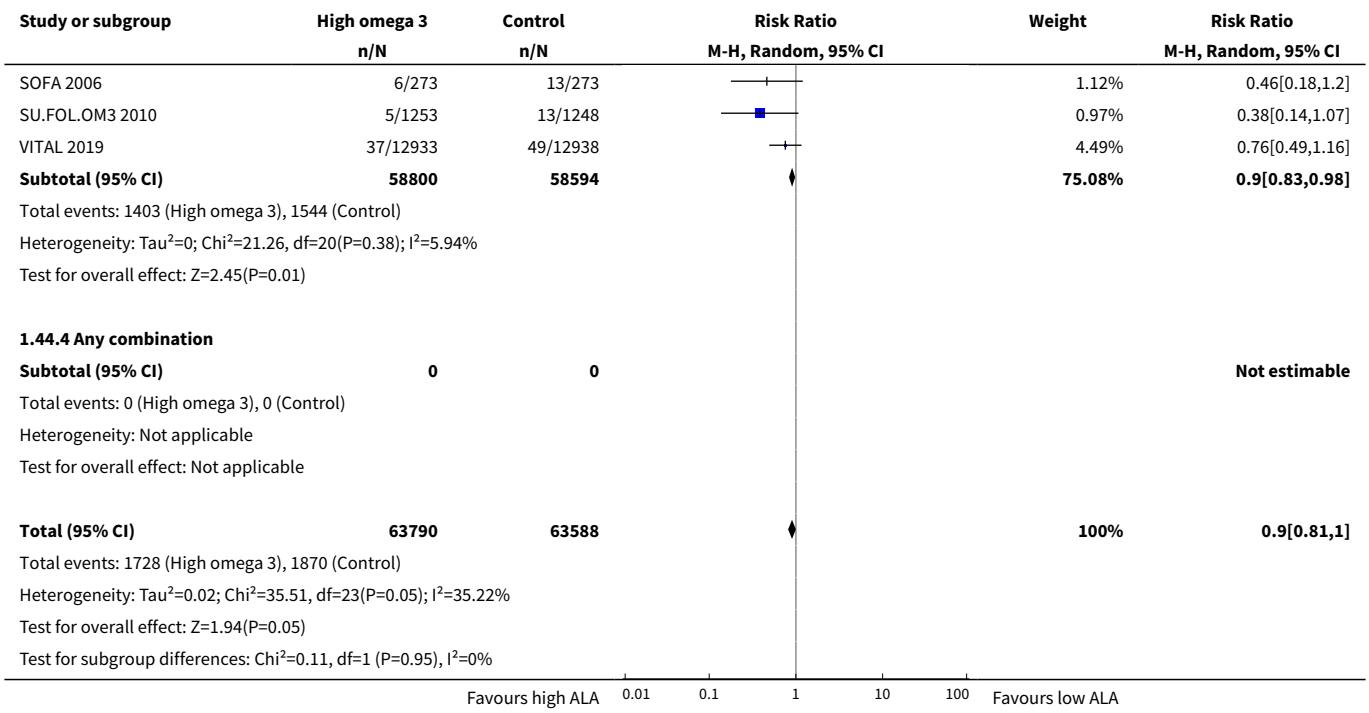
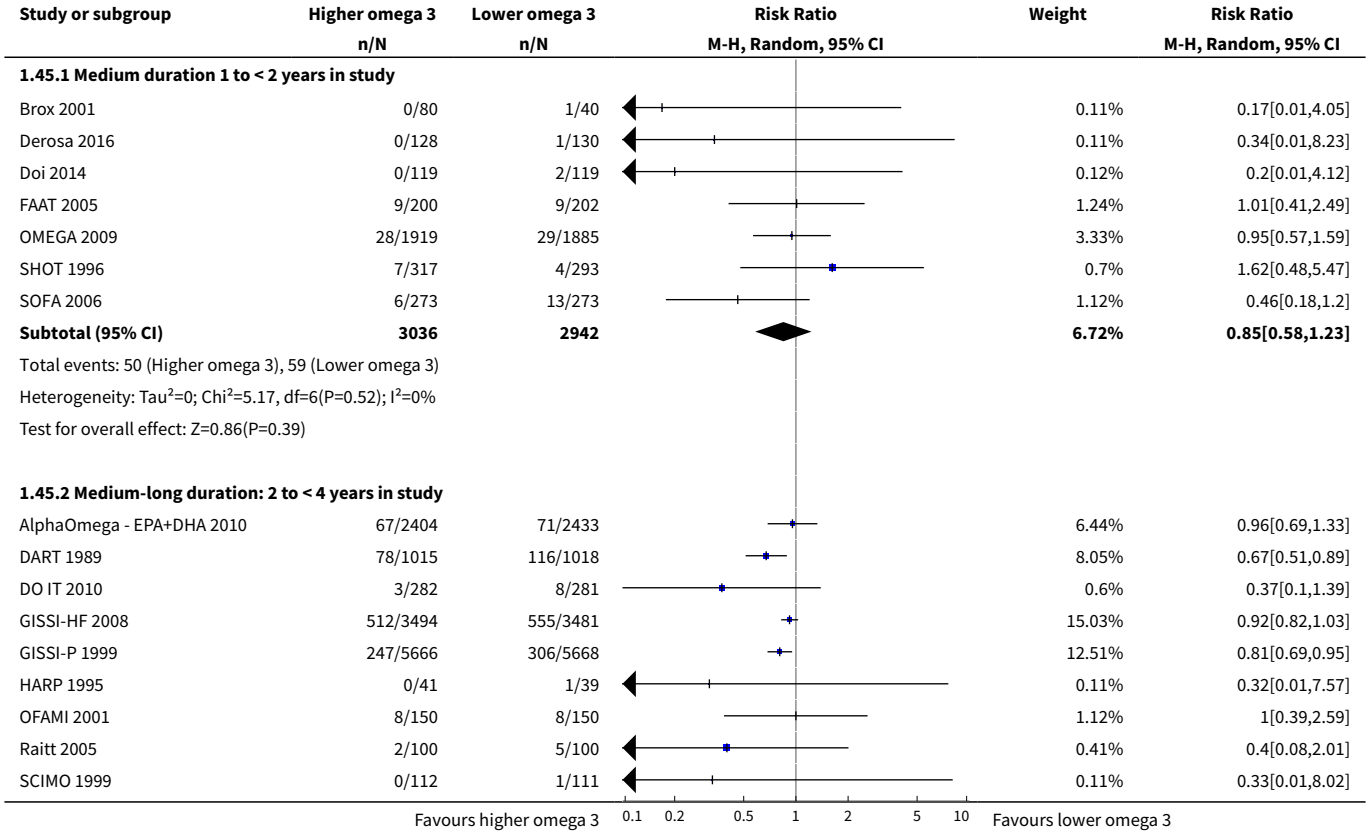


Analysis 1.45. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 45 CHD mortality - LCn3 - subgroup by duration.



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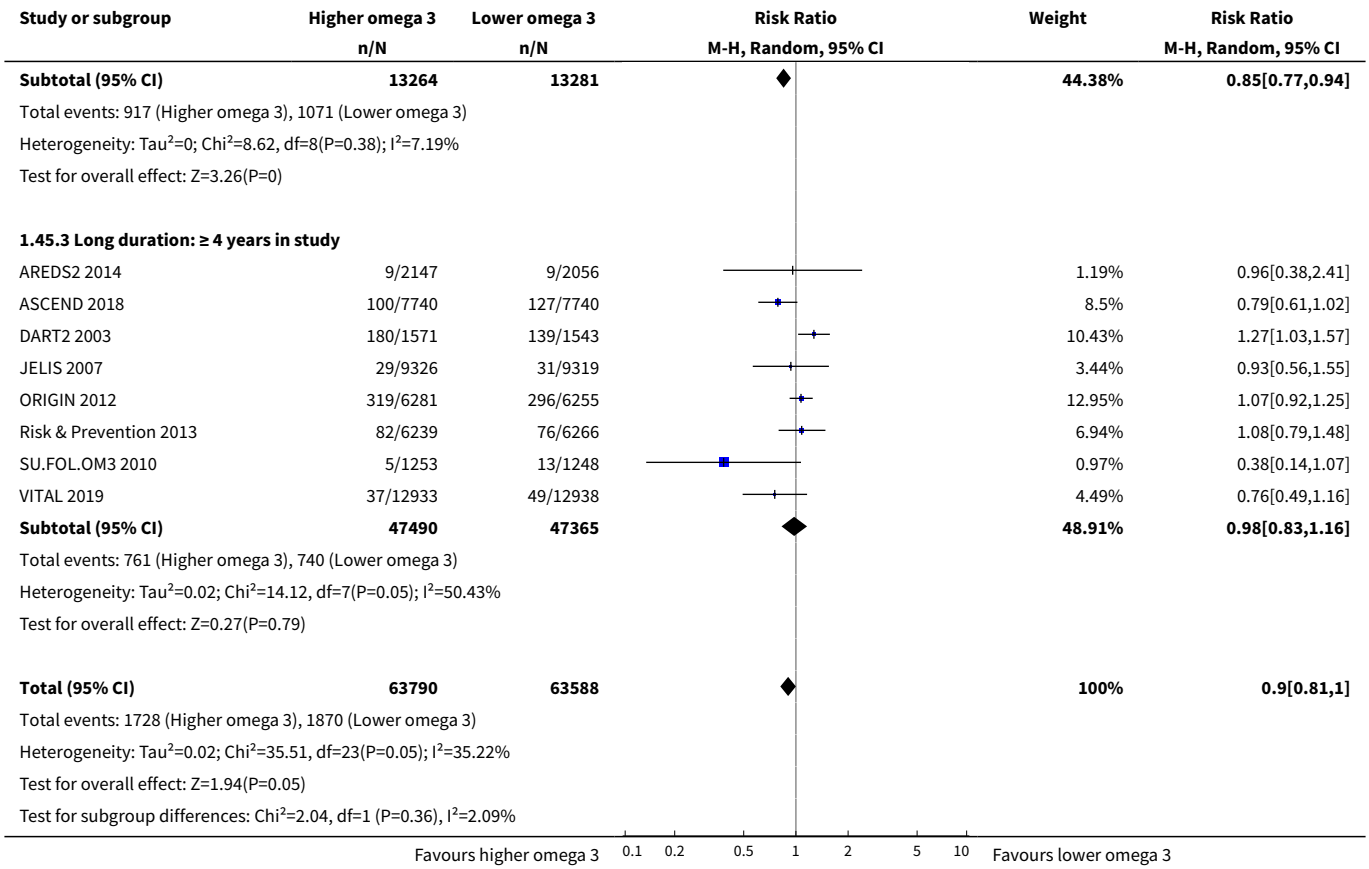
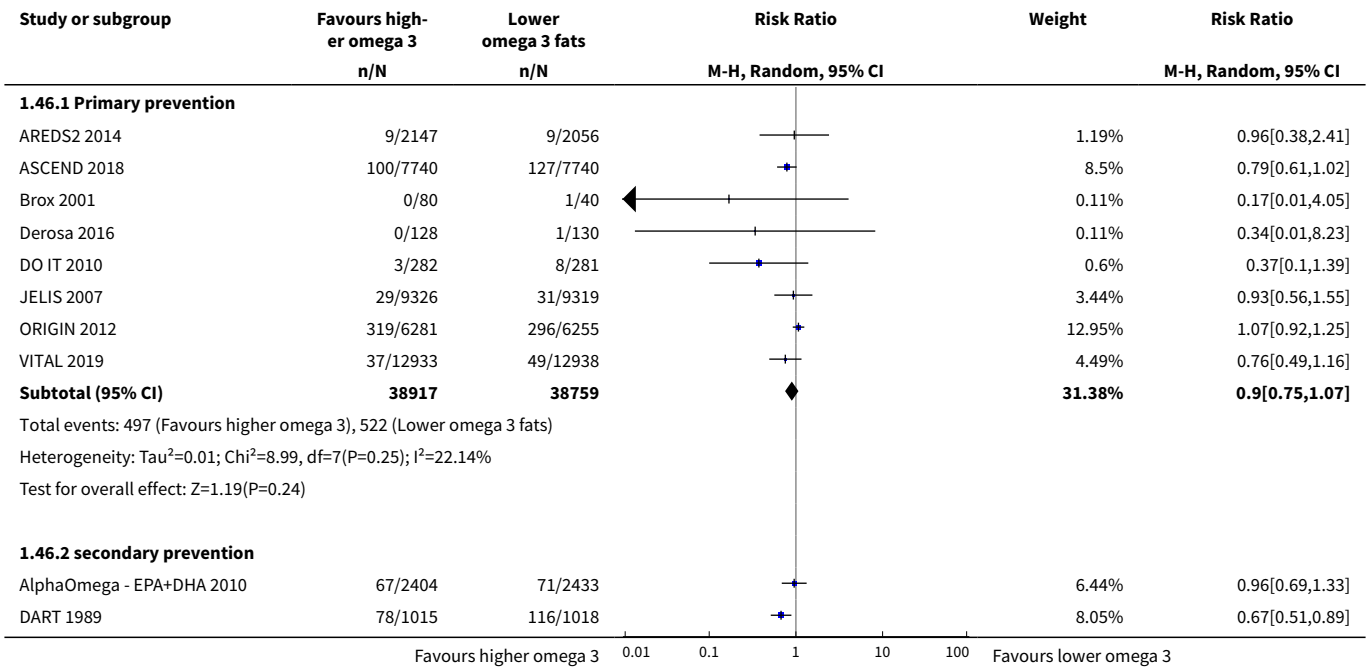


Analysis 1.46. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 46 CHD mortality - LCn3 - subgroup by primary or secondary prevention.



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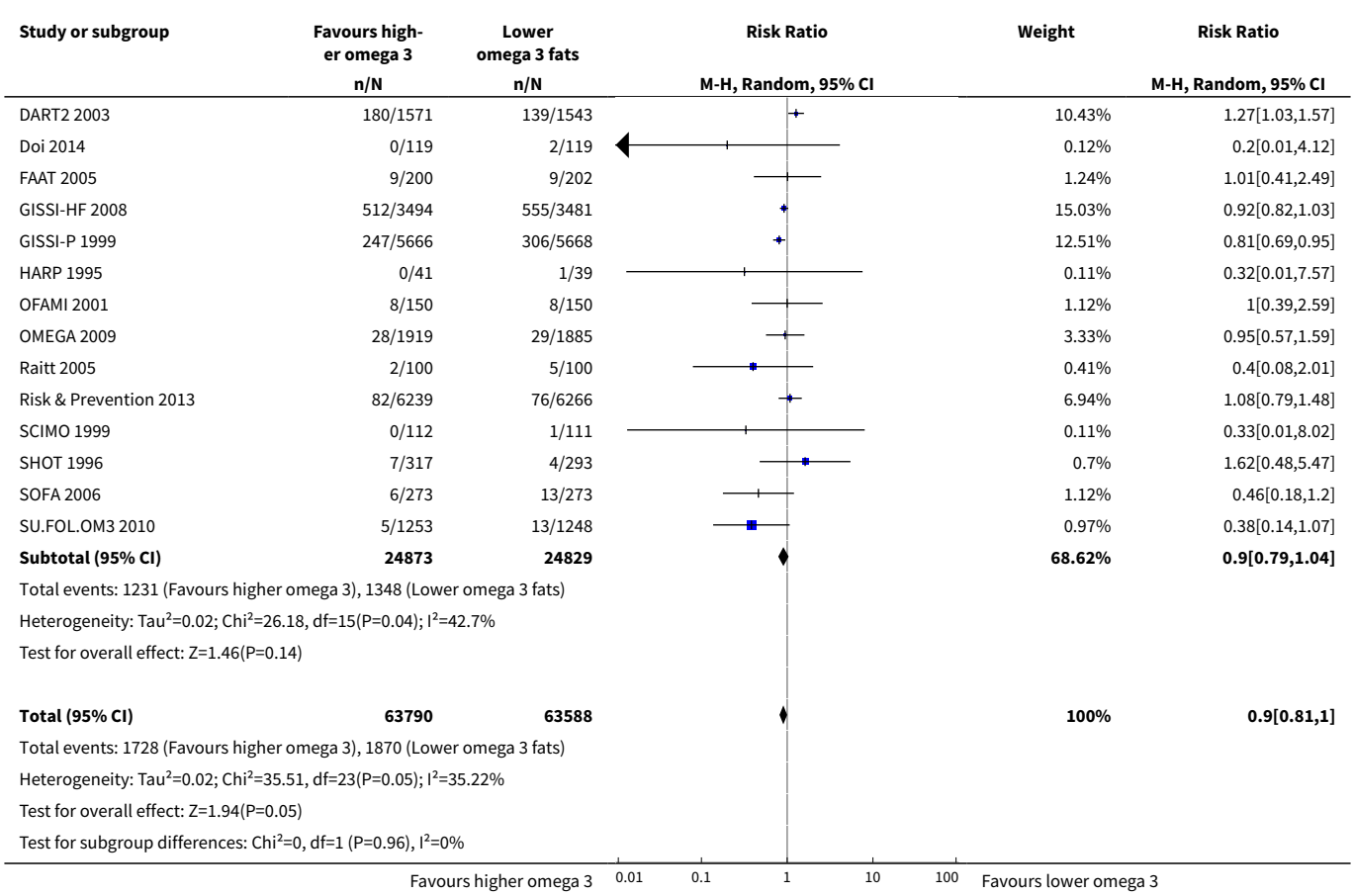
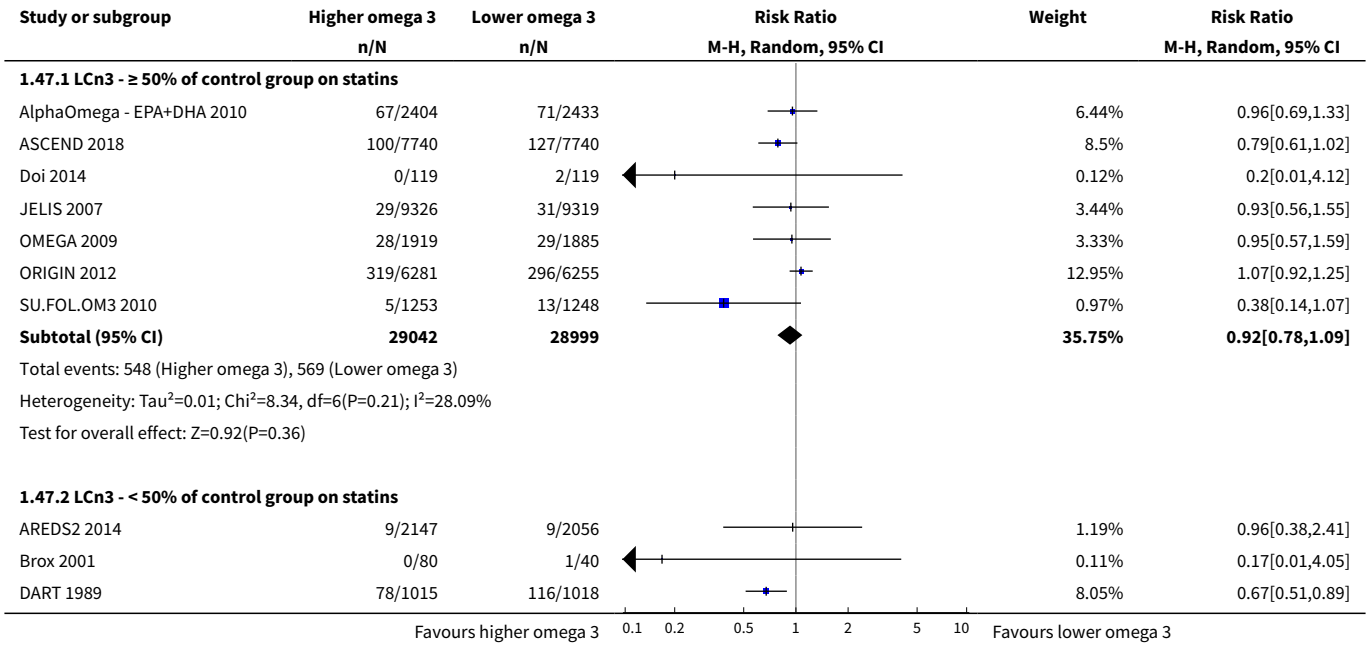


Analysis 1.47. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 47 CHD mortality - LCn3 - subgroup by statin use.



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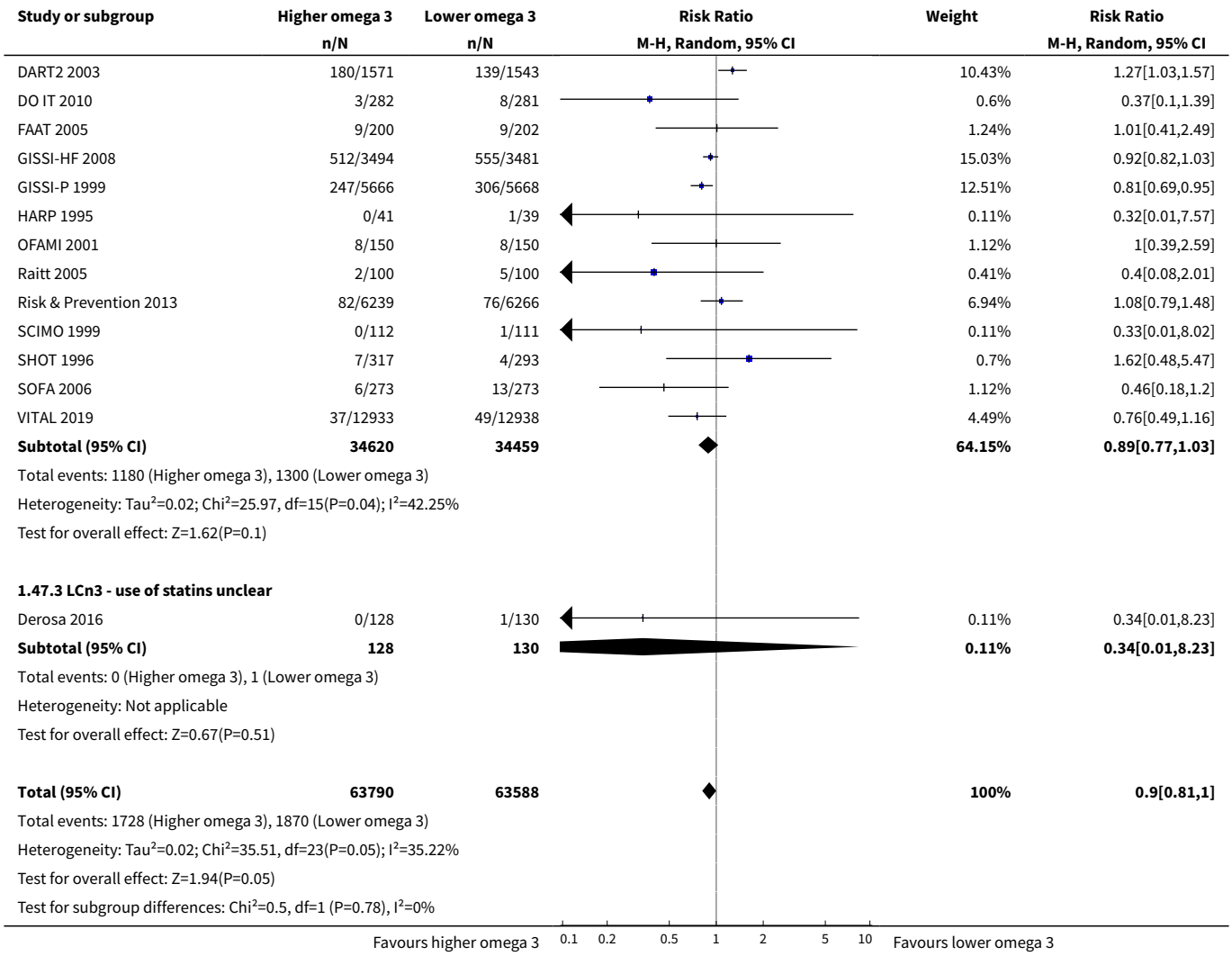
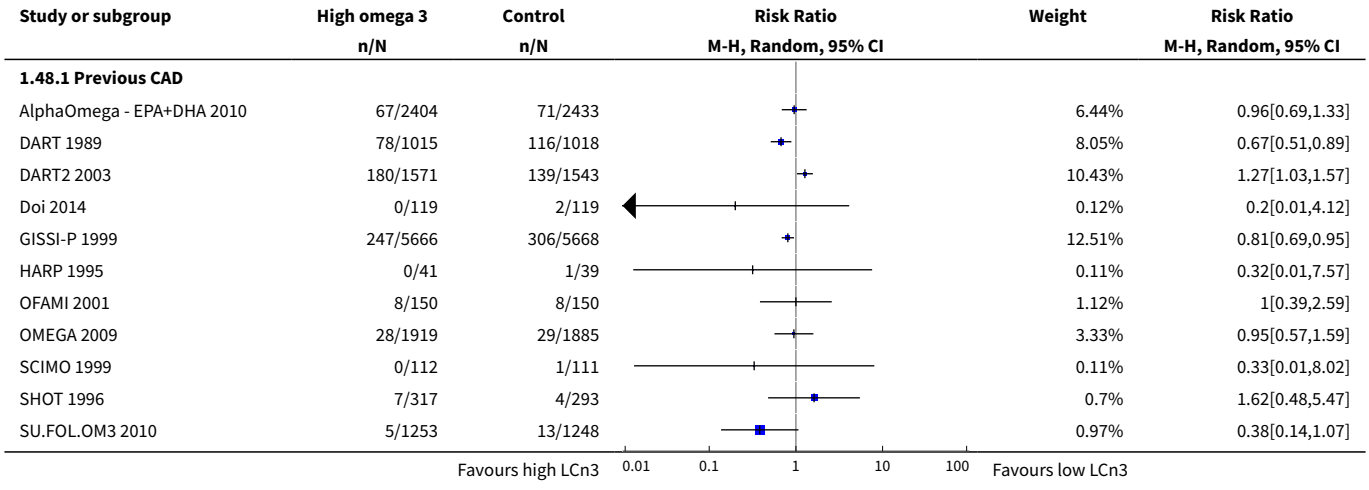


Analysis 1.48. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 48 CHD mortality - LCn3 - subgroup by CAD history.



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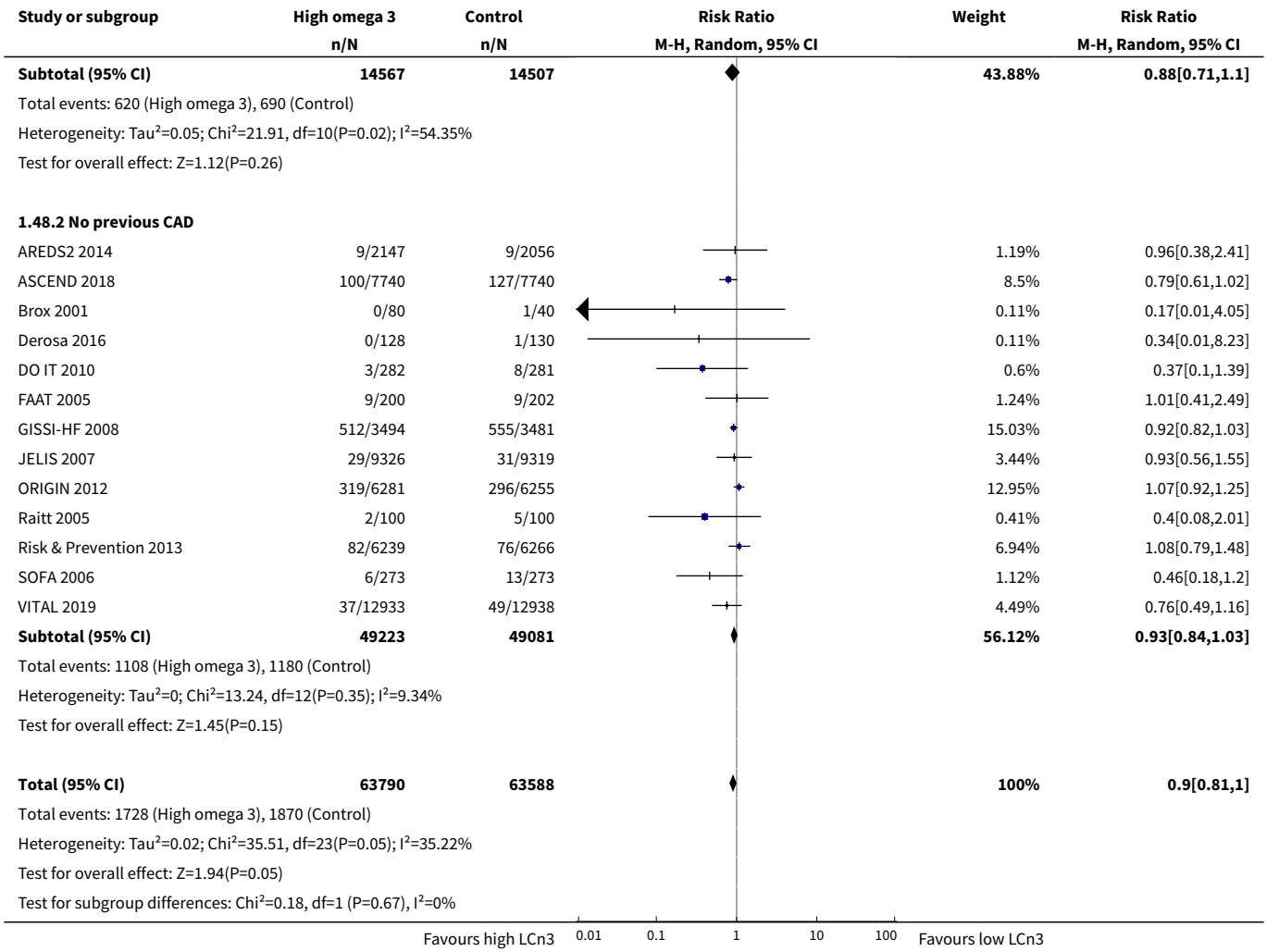
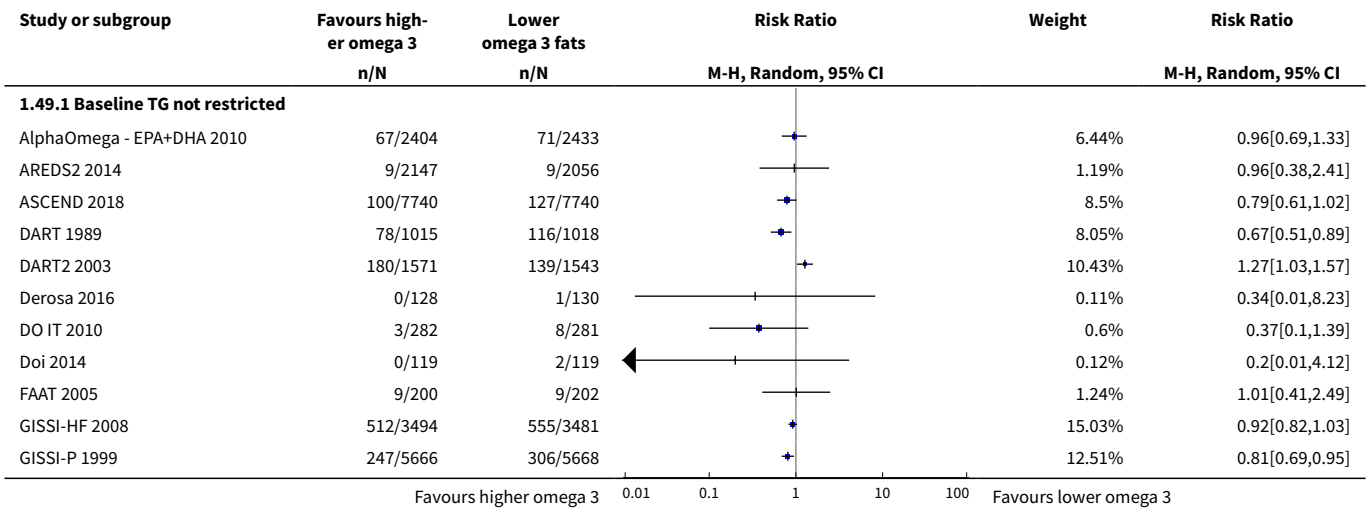


Analysis 1.49. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 49 CHD mortality - LCn3 - subgroup by baseline TG.



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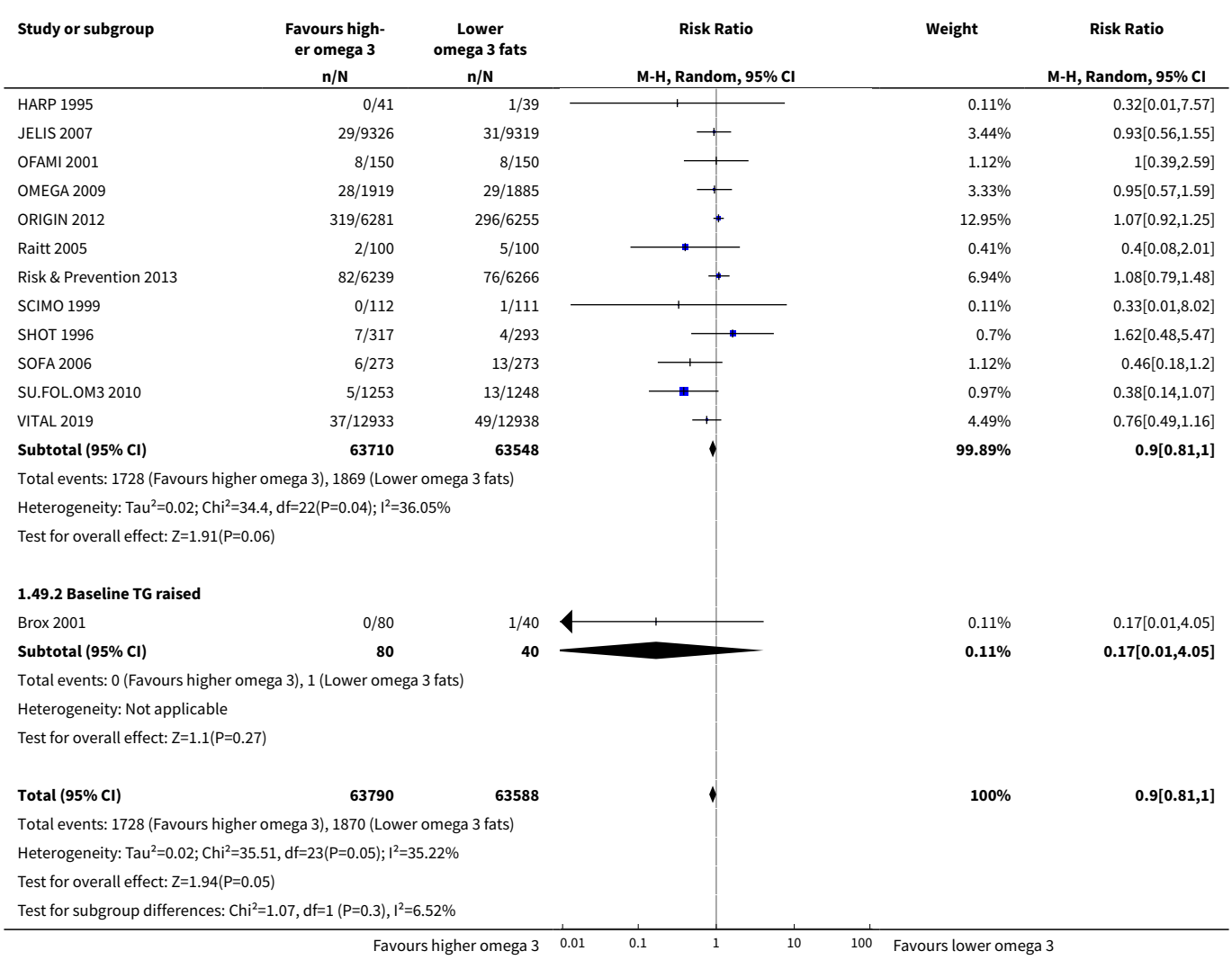
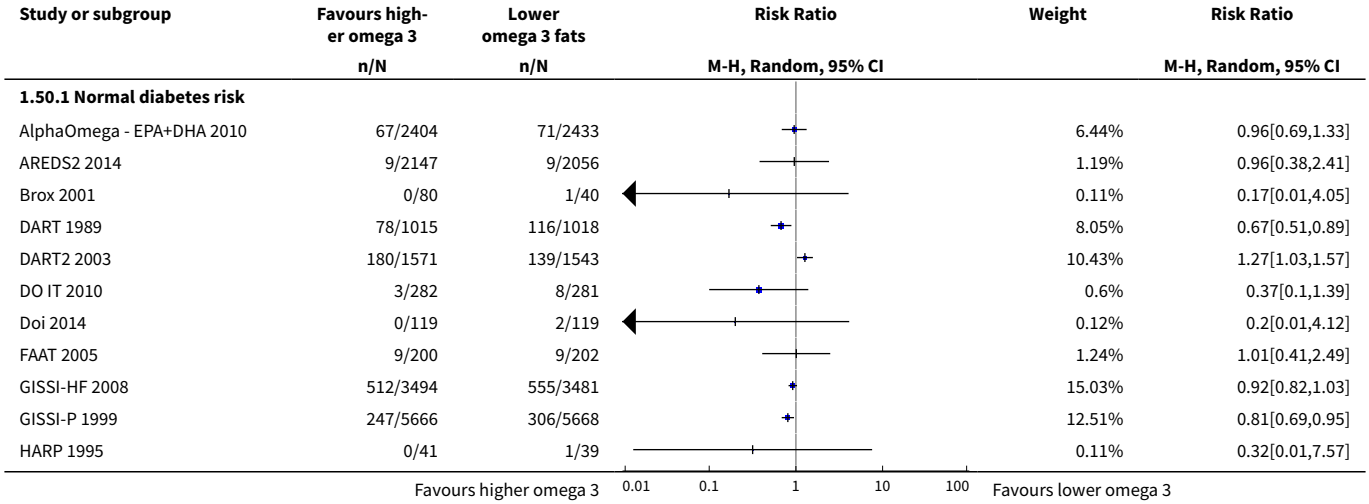


Analysis 1.50. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 50 CHD mortality - LCn3 - subgroup by baseline DM.



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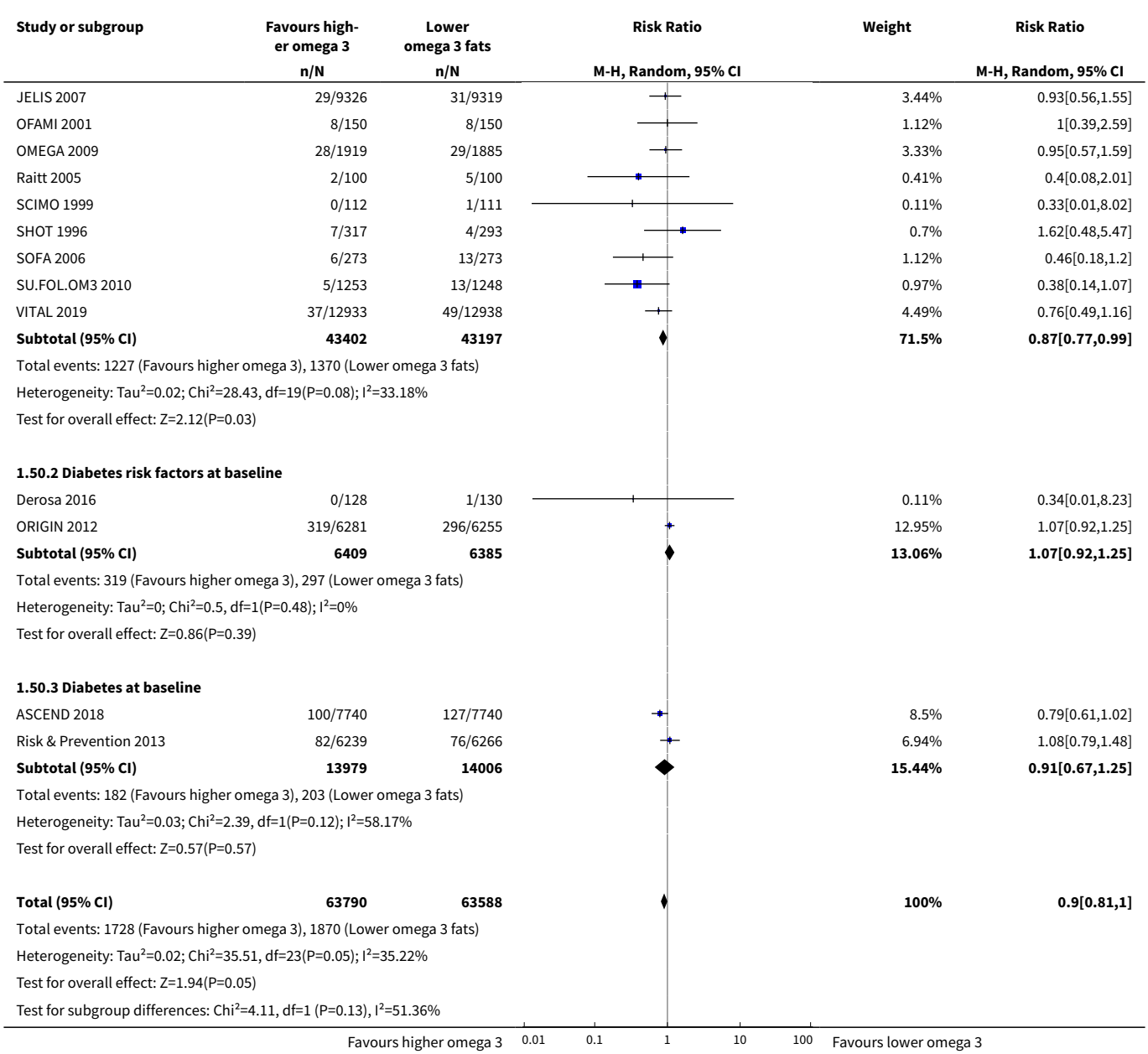
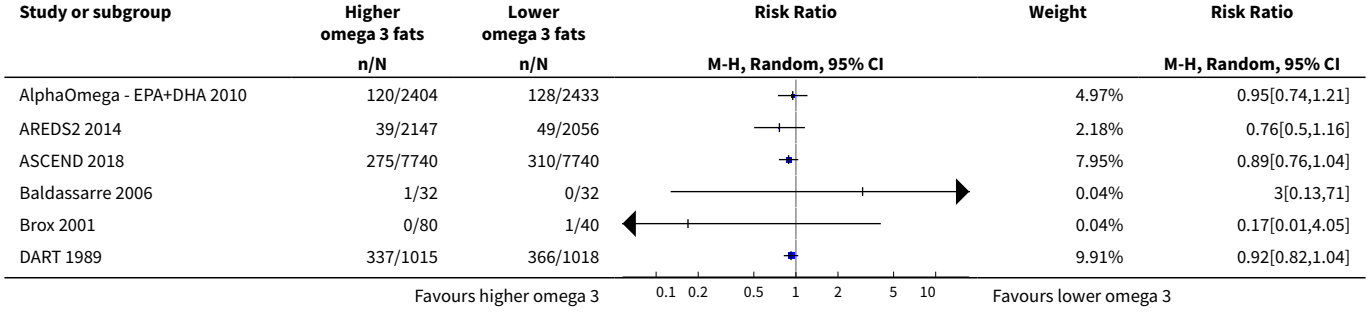


Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 fats n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
JELIS 2007	29/9326	31/9319		3.44%	0.93[0.56,1.55]
OFAMI 2001	8/150	8/150		1.12%	1[0.39,2.59]
OMEGA 2009	28/1919	29/1885		3.33%	0.95[0.57,1.59]
Raitt 2005	2/100	5/100		0.41%	0.4[0.08,2.01]
SCIMO 1999	0/112	1/111		0.11%	0.33[0.01,8.02]
SHOT 1996	7/317	4/293		0.7%	1.62[0.48,5.47]
SOFA 2006	6/273	13/273		1.12%	0.46[0.18,1.2]
SU.FOL.OM3 2010	5/1253	13/1248		0.97%	0.38[0.14,1.07]
VITAL 2019	37/12933	49/12938		4.49%	0.76[0.49,1.16]
Subtotal (95% CI)	**43402**	**43197**		**71.5%**	**0.87[0.77,0.99]**
Total events: 1227 (Favours higher omega 3), 1370 (Lower omega 3 fats)					
Heterogeneity: Tau^2=0.02; Chi^2=28.43, df=19(P=0.08); I^2=33.18%					
Test for overall effect: Z=2.12(P=0.03)					
1.50.2 Diabetes risk factors at baseline					
Derosa 2016	0/128	1/130		0.11%	0.34[0.01,8.23]
ORIGIN 2012	319/6281	296/6255		12.95%	1.07[0.92,1.25]
Subtotal (95% CI)	**6409**	**6385**		**13.06%**	**1.07[0.92,1.25]**
Total events: 319 (Favours higher omega 3), 297 (Lower omega 3 fats)					
Heterogeneity: Tau^2=0; Chi^2=0.5, df=1(P=0.48); I^2=0%					
Test for overall effect: Z=0.86(P=0.39)					
1.50.3 Diabetes at baseline					
ASCEND 2018	100/7740	127/7740		8.5%	0.79[0.61,1.02]
Risk & Prevention 2013	82/6239	76/6266		6.94%	1.08[0.79,1.48]
Subtotal (95% CI)	**13979**	**14006**		**15.44%**	**0.91[0.67,1.25]**
Total events: 182 (Favours higher omega 3), 203 (Lower omega 3 fats)					
Heterogeneity: Tau^2=0.03; Chi^2=2.39, df=1(P=0.12); I^2=58.17%					
Test for overall effect: Z=0.57(P=0.57)					
Total (95% CI)	**63790**	**63588**		**100%**	**0.9[0.81,1]**
Total events: 1728 (Favours higher omega 3), 1870 (Lower omega 3 fats)					
Heterogeneity: Tau^2=0.02; Chi^2=35.51, df=23(P=0.05); I^2=35.22%					
Test for overall effect: Z=1.94(P=0.05)					
Test for subgroup differences: Chi^2=4.11, df=1 (P=0.13), I^2=51.36%					

Analysis 1.51. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 51 Coronary heart disease events (overall) - LCn3.



Study or subgroup	Higher omega 3 fats n/N	Lower omega 3 fats n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
AlphaOmega - EPA+DHA 2010	120/2404	128/2433		4.97%	0.95[0.74,1.21]
AREDS2 2014	39/2147	49/2056		2.18%	0.76[0.5,1.16]
ASCEND 2018	275/7740	310/7740		7.95%	0.89[0.76,1.04]
Baldassarre 2006	1/32	0/32		0.04%	3[0.13,71]
Brox 2001	0/80	1/40		0.04%	0.17[0.01,4.05]
DART 1989	337/1015	366/1018		9.91%	0.92[0.82,1.04]

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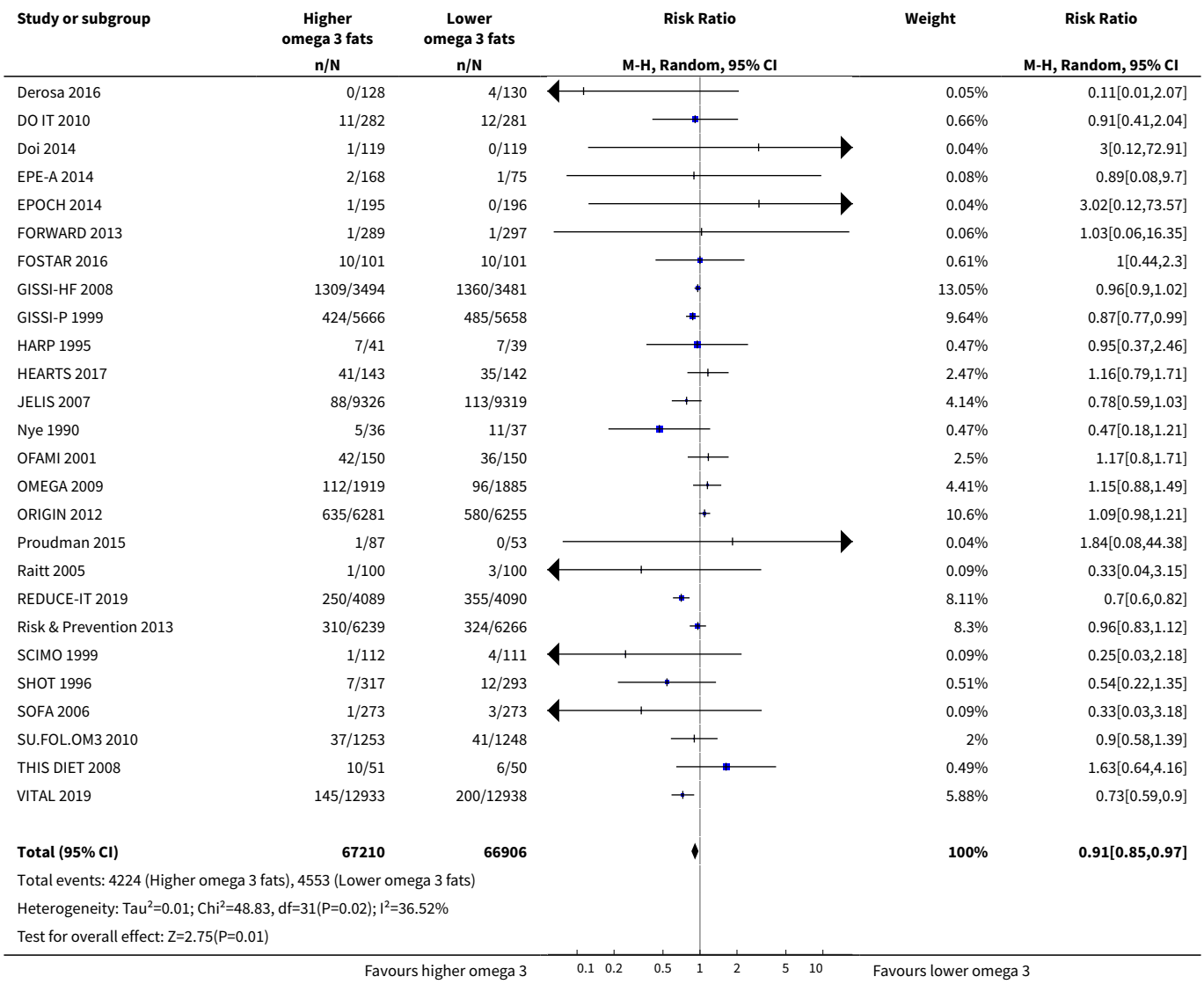
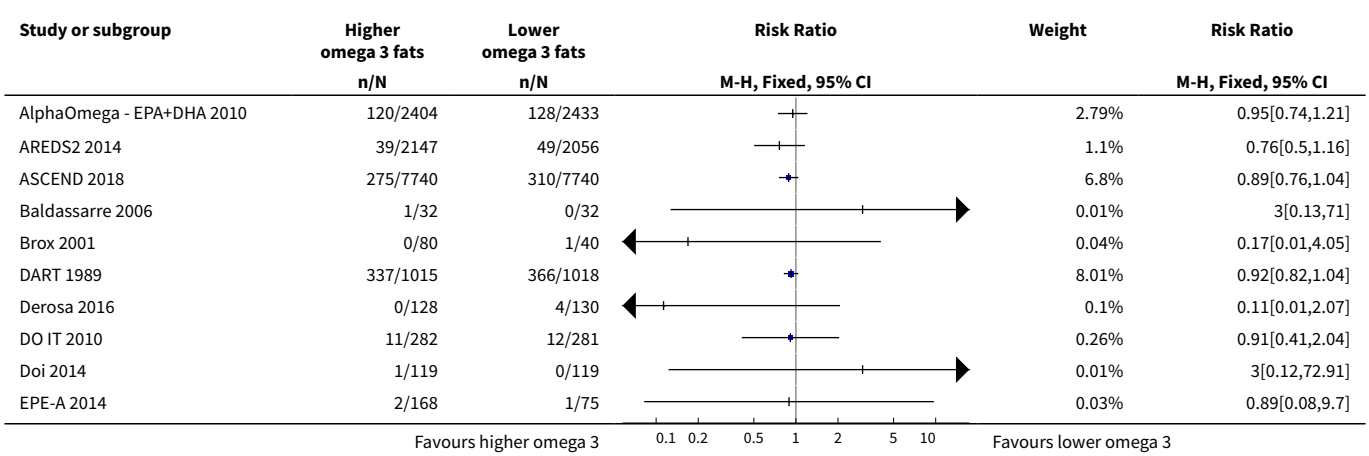


Analysis 1.52. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 52 CHD events - LCn3 - SA fixed effect.



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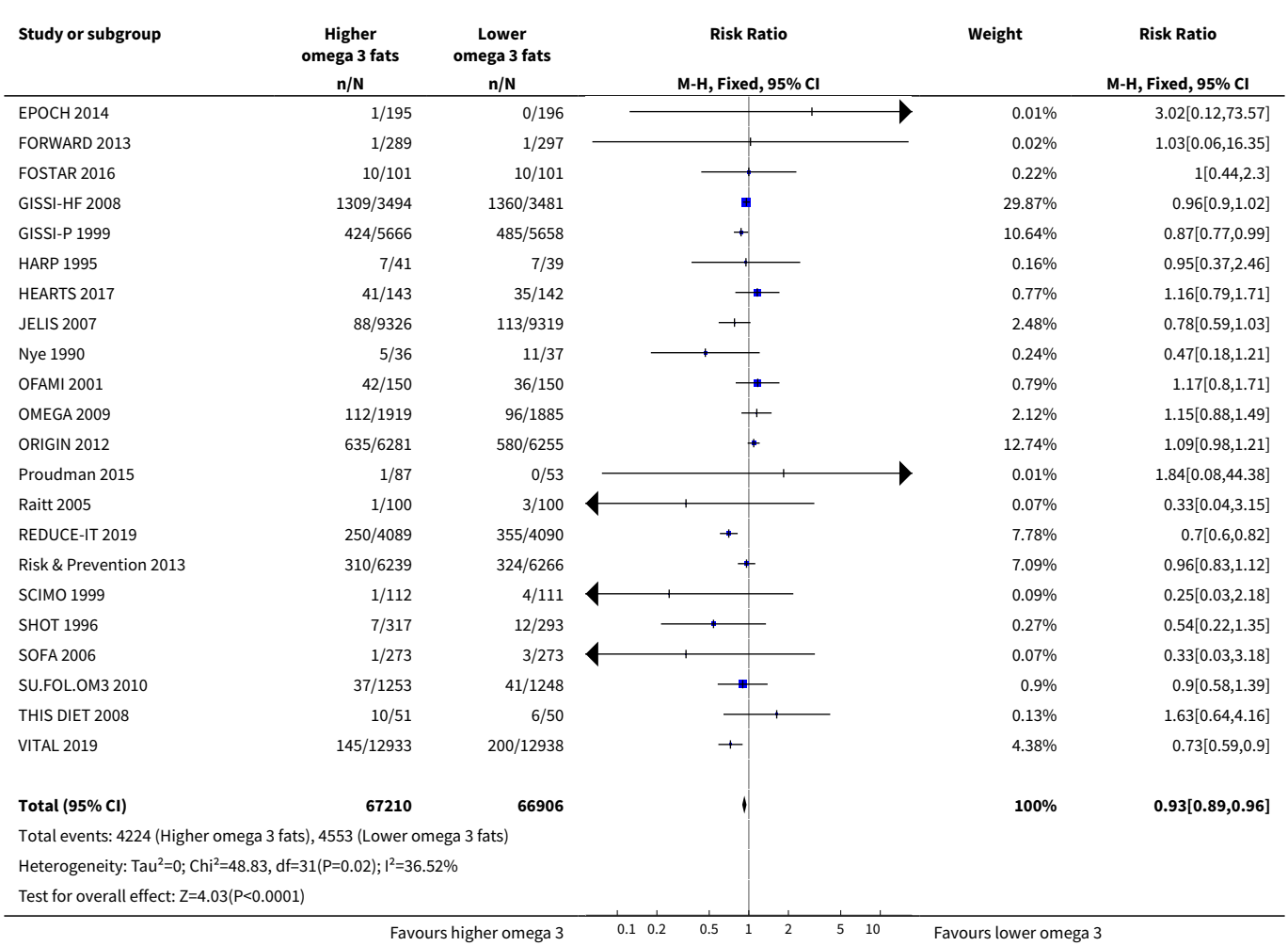
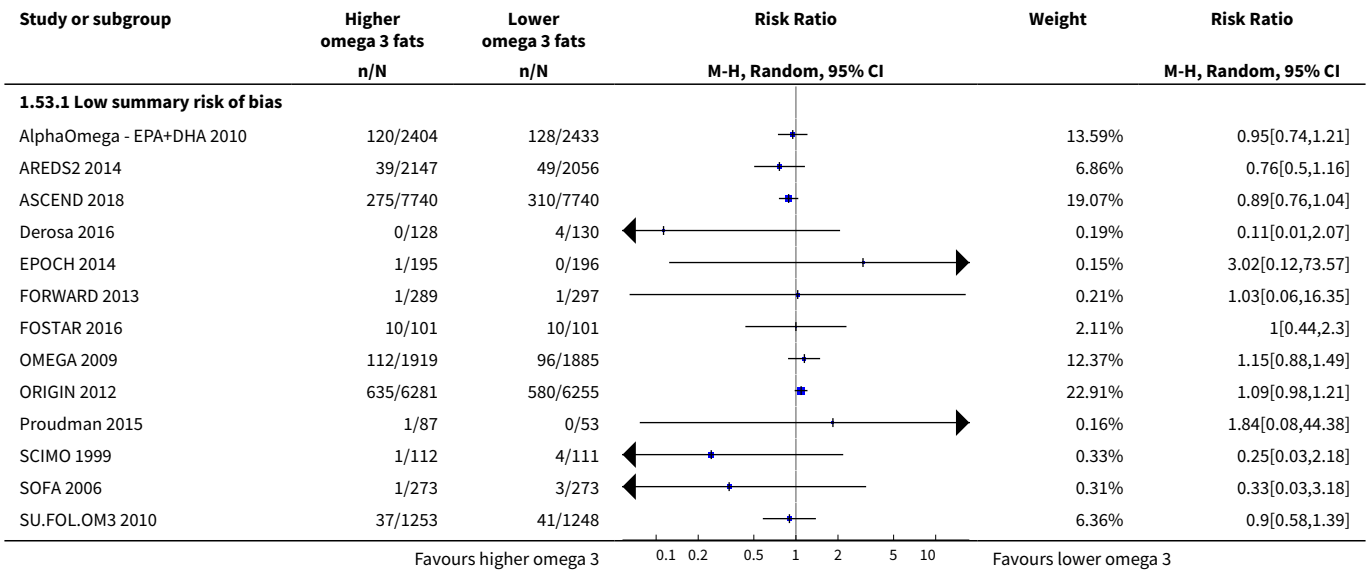


Analysis 1.53. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 53 CHD events - LCn3 - SA by summary risk of bias.



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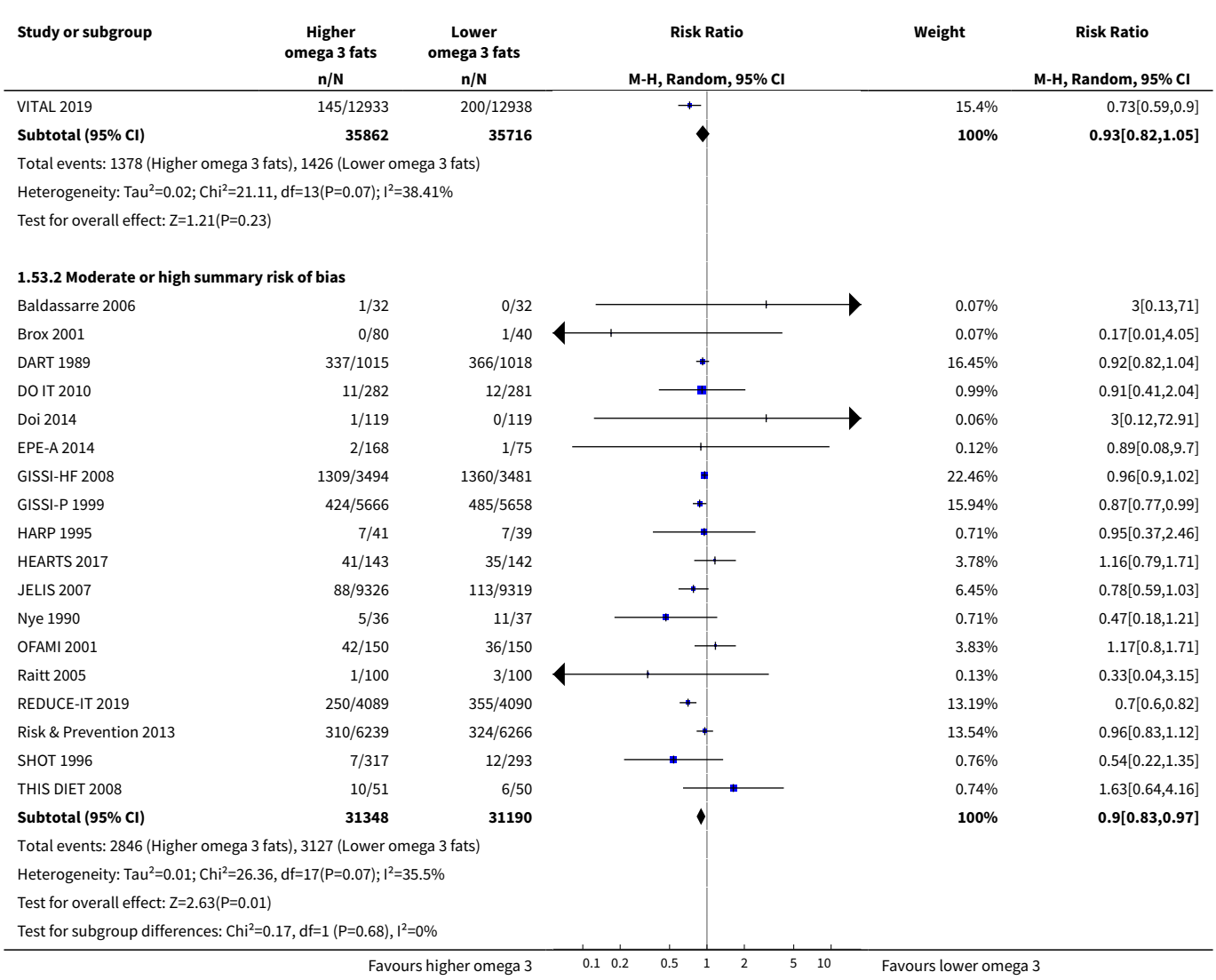
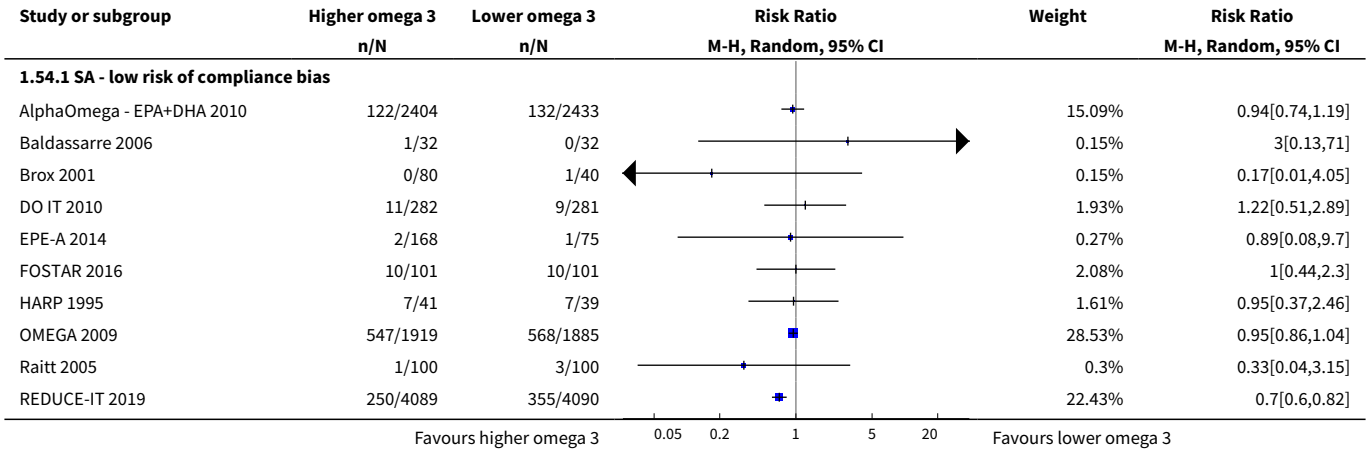


Analysis 1.54. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 54 CHD events - LCn3 - SA by compliance and study size.



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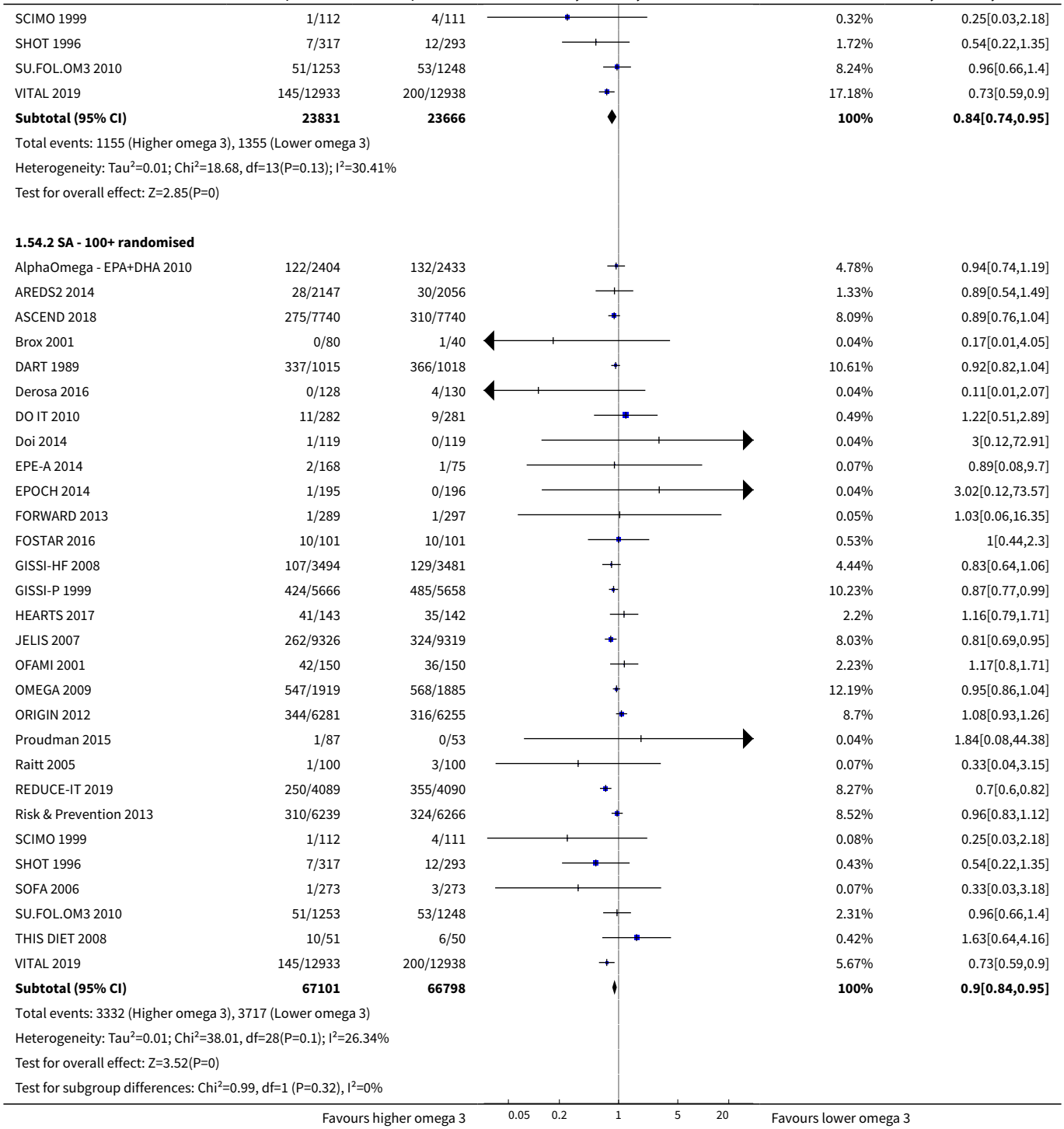

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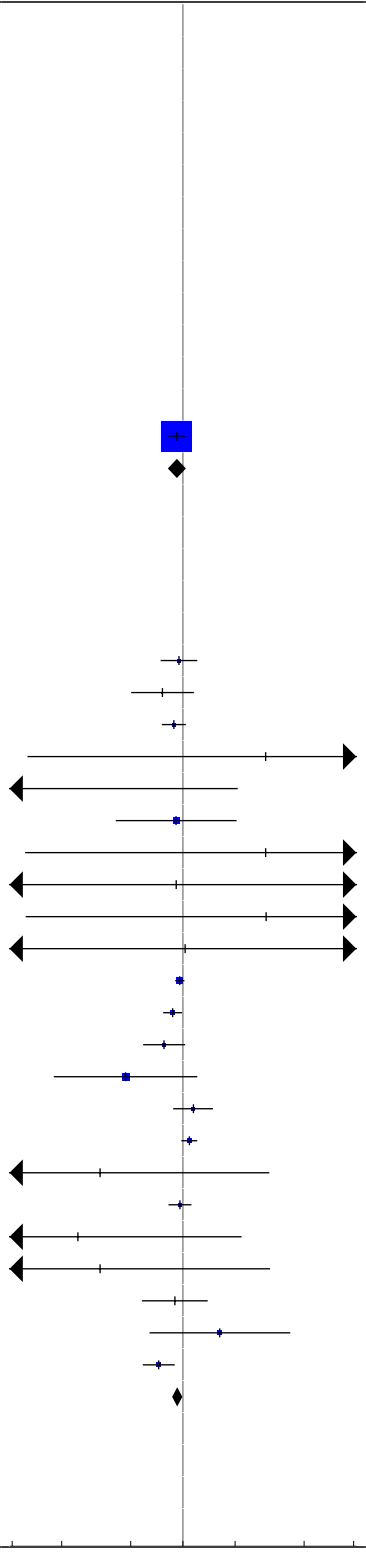
Analysis 1.55. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 55 CHD events - LCn3 - subgroup by dose.

Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.55.1 LCn3 ≤ 150 mg/d					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours higher omega 3), 0 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.55.2 LCn3 > 150 ≤ 250 mg/d					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours higher omega 3), 0 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.55.3 LCn3 > 250 ≤ 400 mg/d					
DART 1989	337/1015	366/1018		100%	0.92[0.82,1.04]
Subtotal (95% CI)	**1015**	**1018**		**100%**	**0.92[0.82,1.04]**
Total events: 337 (Favours higher omega 3), 366 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.3(P=0.19)					
1.55.4 LCn3 > 400 ≤ 2400 mg/d					
AlphaOmega - EPA+DHA 2010	120/2404	128/2433		5.92%	0.95[0.74,1.21]
AREDS2 2014	39/2147	49/2056		2.4%	0.76[0.5,1.16]
ASCEND 2018	275/7740	310/7740		10.37%	0.89[0.76,1.04]
Baldassarre 2006	1/32	0/32		0.05%	3[0.13,71]
Derosa 2016	0/128	4/130		0.05%	0.11[0.01,2.07]
DO IT 2010	11/282	12/281		0.7%	0.91[0.41,2.04]
Doi 2014	1/119	0/119		0.05%	3[0.12,72.91]
EPE-A 2014	1/82	1/75		0.06%	0.91[0.06,14.37]
EPOCH 2014	1/195	0/196		0.05%	3.02[0.12,73.57]
FORWARD 2013	1/289	1/297		0.06%	1.03[0.06,16.35]
GISSI-HF 2008	1309/3494	1360/3481		20.34%	0.96[0.9,1.02]
GISSI-P 1999	424/5666	485/5658		13.28%	0.87[0.77,0.99]
JELIS 2007	88/9326	113/9319		4.81%	0.78[0.59,1.03]
Nye 1990	5/36	11/37		0.5%	0.47[0.18,1.21]
OMEGA 2009	112/1919	96/1885		5.16%	1.15[0.88,1.49]
ORIGIN 2012	635/6281	580/6255		15.09%	1.09[0.98,1.21]
Raitt 2005	1/100	3/100		0.09%	0.33[0.04,3.15]
Risk & Prevention 2013	310/6239	324/6266		10.95%	0.96[0.83,1.12]
SCIMO 1999	1/112	4/111		0.1%	0.25[0.03,2.18]
SOFA 2006	1/273	3/273		0.09%	0.33[0.03,3.18]
SU.FOL.OM3 2010	37/1253	41/1248		2.19%	0.9[0.58,1.39]
THIS DIET 2008	10/51	6/50		0.52%	1.63[0.64,4.16]
VITAL 2019	145/12933	200/12938		7.19%	0.73[0.59,0.9]
Subtotal (95% CI)	**61101**	**60980**		**100%**	**0.93[0.87,0.99]**
Total events: 3528 (Favours higher omega 3), 3731 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=30.39, df=22(P=0.11); I²=27.61%					
Test for overall effect: Z=2.17(P=0.03)					



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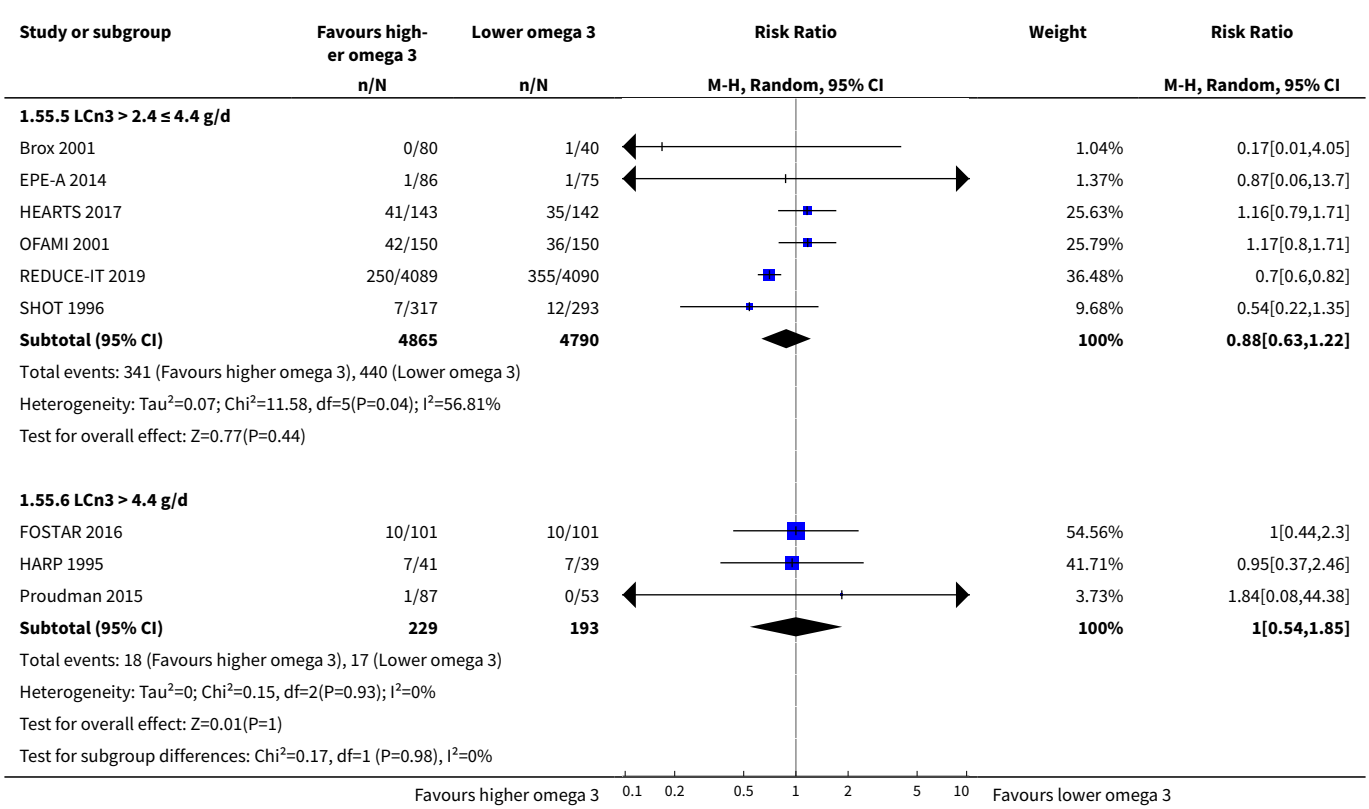
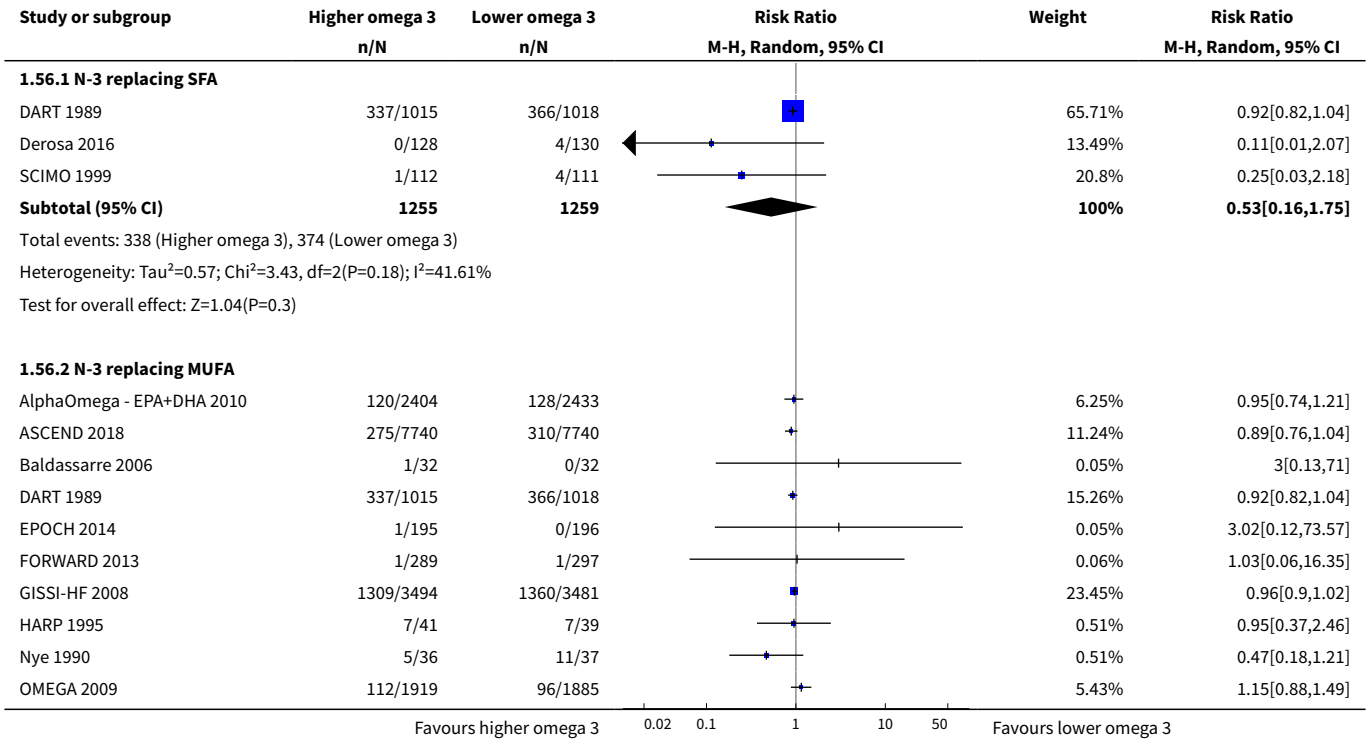


Analysis 1.56. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 56 CHD events - LCn3 - subgroup by replacement.



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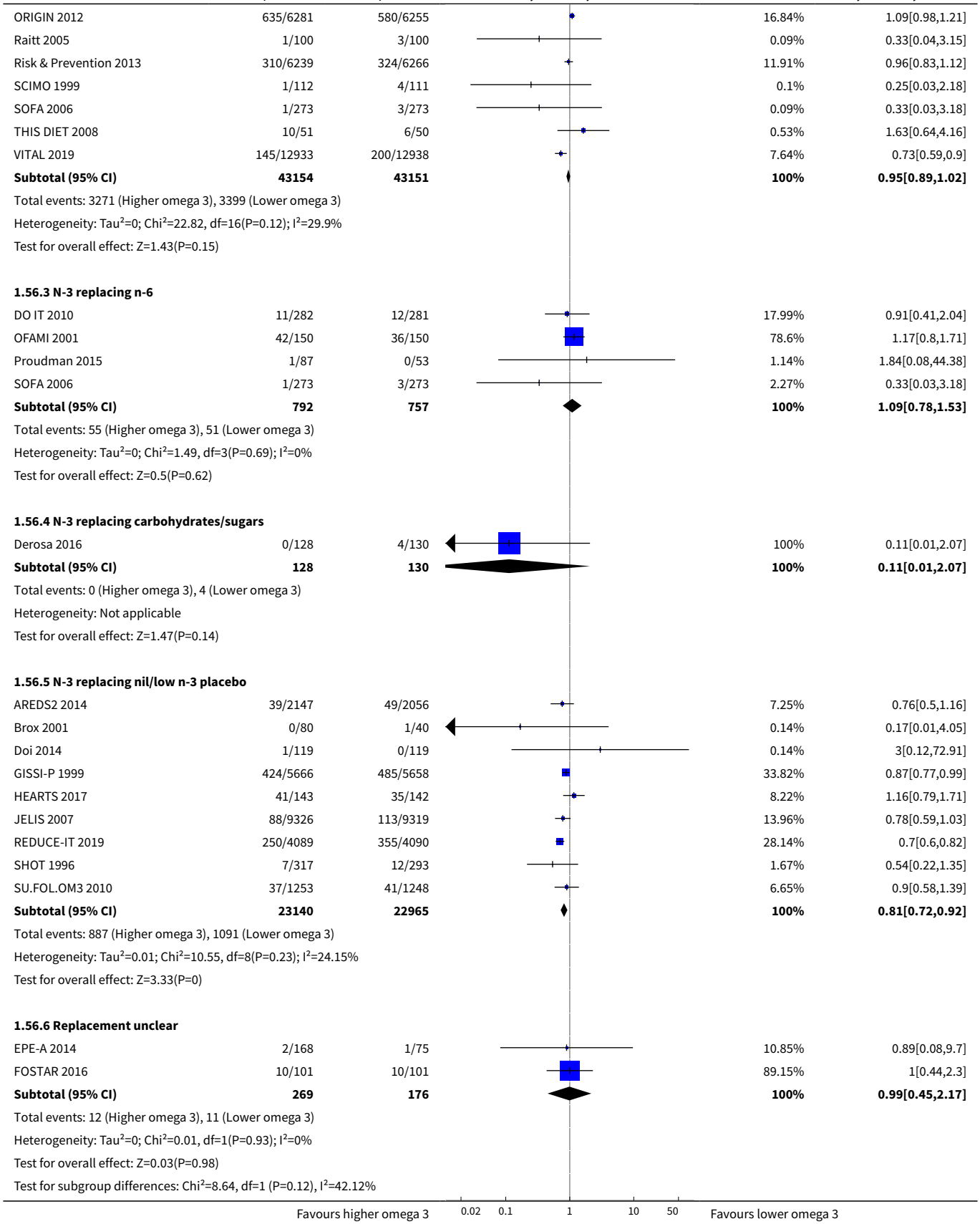

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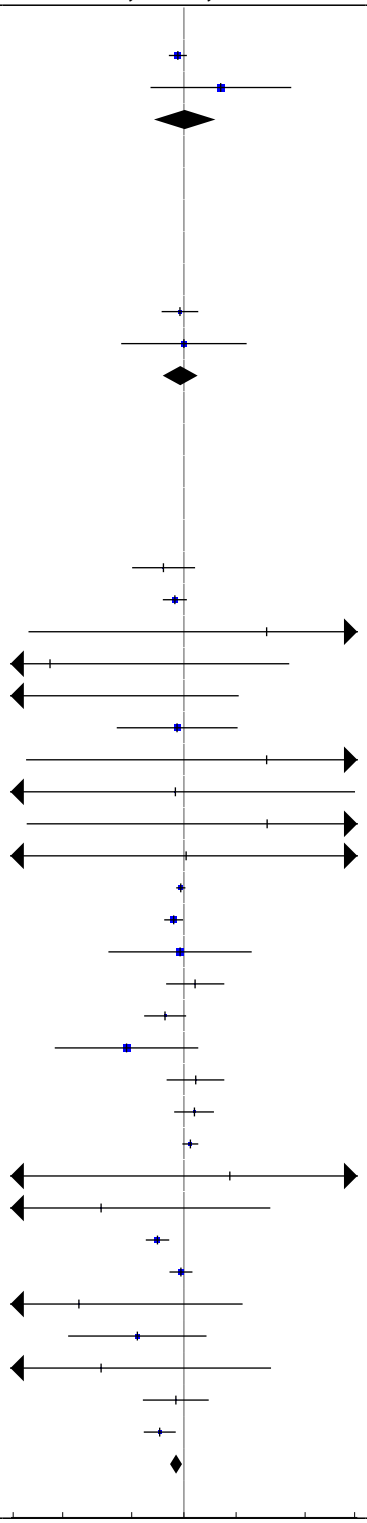
Analysis 1.57. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 57 CHD events - LCn3 - subgroup by intervention type.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.57.1 Dietary advice					
DART 1989	337/1015	366/1018		9.91%	0.92[0.82,1.04]
THIS DIET 2008	10/51	6/50		0.49%	1.63[0.64,4.16]
Subtotal (95% CI)	**1066**	**1068**		**10.4%**	**1.01[0.67,1.52]**
Total events: 347 (Higher omega 3), 372 (Lower omega 3)					
Heterogeneity: Tau^2=0.05; Chi^2=1.41, df=1(P=0.23); I^2=29.26%					
Test for overall effect: Z=0.05(P=0.96)					
1.57.2 Supplemental foods					
AlphaOmega - EPA+DHA 2010	120/2404	128/2433		4.97%	0.95[0.74,1.21]
FOSTAR 2016	10/101	10/101		0.61%	1[0.44,2.3]
Subtotal (95% CI)	**2505**	**2534**		**5.59%**	**0.95[0.75,1.2]**
Total events: 130 (Higher omega 3), 138 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.91); I^2=0%					
Test for overall effect: Z=0.41(P=0.68)					
1.57.3 Supplements (capsule)					
AREDS2 2014	39/2147	49/2056		2.18%	0.76[0.5,1.16]
ASCEND 2018	275/7740	310/7740		7.95%	0.89[0.76,1.04]
Baldassarre 2006	1/32	0/32		0.04%	3[0.13,71]
Brox 2001	0/80	1/40		0.04%	0.17[0.01,4.05]
Derosa 2016	0/128	4/130		0.05%	0.11[0.01,2.07]
DO IT 2010	11/282	12/281		0.66%	0.91[0.41,2.04]
Doi 2014	1/119	0/119		0.04%	3[0.12,72.91]
EPE-A 2014	2/168	1/75		0.08%	0.89[0.08,9.7]
EPOCH 2014	1/195	0/196		0.04%	3.02[0.12,73.57]
FORWARD 2013	1/289	1/297		0.06%	1.03[0.06,16.35]
GISSI-HF 2008	1309/3494	1360/3481		13.05%	0.96[0.9,1.02]
GISSI-P 1999	424/5666	485/5658		9.64%	0.87[0.77,0.99]
HARP 1995	7/41	7/39		0.47%	0.95[0.37,2.46]
HEARTS 2017	41/143	35/142		2.47%	1.16[0.79,1.71]
JELIS 2007	88/9326	113/9319		4.14%	0.78[0.59,1.03]
Nye 1990	5/36	11/37		0.47%	0.47[0.18,1.21]
OFAMI 2001	42/150	36/150		2.5%	1.17[0.8,1.71]
OMEGA 2009	112/1919	96/1885		4.41%	1.15[0.88,1.49]
ORIGIN 2012	635/6281	580/6255		10.6%	1.09[0.98,1.21]
Proudman 2015	1/87	0/53		0.04%	1.84[0.08,44.38]
Raitt 2005	1/100	3/100		0.09%	0.33[0.04,3.15]
REDUCE-IT 2019	250/4089	355/4090		8.11%	0.7[0.6,0.82]
Risk & Prevention 2013	310/6239	324/6266		8.3%	0.96[0.83,1.12]
SCIMO 1999	1/112	4/111		0.09%	0.25[0.03,2.18]
SHOT 1996	7/317	12/293		0.51%	0.54[0.22,1.35]
SOFA 2006	1/273	3/273		0.09%	0.33[0.03,3.18]
SU.FOL.OM3 2010	37/1253	41/1248		2%	0.9[0.58,1.39]
VITAL 2019	145/12933	200/12938		5.88%	0.73[0.59,0.9]
Subtotal (95% CI)	**63639**	**63304**		**84.01%**	**0.9[0.83,0.98]**
Total events: 3747 (Higher omega 3), 4043 (Lower omega 3)					



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Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0.01; Chi²=47.41, df=27(P=0.01); I²=43.05%					
Test for overall effect: Z=2.57(P=0.01)					
1.57.4 Any combination					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 3), 0 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**67210**	**66906**		**100%**	**0.91[0.85,0.97]**
Total events: 4224 (Higher omega 3), 4553 (Lower omega 3)					
Heterogeneity: Tau²=0.01; Chi²=48.83, df=31(P=0.02); I²=36.52%					
Test for overall effect: Z=2.75(P=0.01)					
Test for subgroup differences: Chi²=0.47, df=1 (P=0.79), I²=0%					

Favours higher omega 3 — 0.1 0.2 0.5 1 2 5 10 — Favours lower omega 3

Analysis 1.58. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 58 CHD events - LCn3 - subgroup by duration.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.58.1 Medium duration 1 to < 2 years in study					
Brox 2001	0/80	1/40		0.04%	0.17[0.01,4.05]
Derosa 2016	0/128	4/130		0.05%	0.11[0.01,2.07]
Doi 2014	1/119	0/119		0.04%	3[0.12,72.91]
EPE-A 2014	2/168	1/75		0.08%	0.89[0.08,9.7]
EPOCH 2014	1/195	0/196		0.04%	3.02[0.12,73.57]
FORWARD 2013	1/289	1/297		0.06%	1.03[0.06,16.35]
Nye 1990	5/36	11/37		0.47%	0.47[0.18,1.21]
OMEGA 2009	112/1919	96/1885		4.41%	1.15[0.88,1.49]
Proudman 2015	1/87	0/53		0.04%	1.84[0.08,44.38]
SHOT 1996	7/317	12/293		0.51%	0.54[0.22,1.35]
SOFA 2006	1/273	3/273		0.09%	0.33[0.03,3.18]
Subtotal (95% CI)	**3611**	**3398**		**5.84%**	**0.9[0.64,1.25]**
Total events: 131 (Higher omega 3), 129 (Lower omega 3)					
Heterogeneity: Tau²=0.03; Chi²=10.56, df=10(P=0.39); I²=5.34%					
Test for overall effect: Z=0.64(P=0.52)					
1.58.2 Medium-long duration: 2 to < 4 years in study					
AlphaOmega - EPA+DHA 2010	120/2404	128/2433		4.97%	0.95[0.74,1.21]
Baldassarre 2006	1/32	0/32		0.04%	3[0.13,71]
DART 1989	337/1015	366/1018		9.91%	0.92[0.82,1.04]
DO IT 2010	11/282	12/281		0.66%	0.91[0.41,2.04]
FOSTAR 2016	10/101	10/101		0.61%	1[0.44,2.3]
GISSI-HF 2008	1309/3494	1360/3481		13.05%	0.96[0.9,1.02]
GISSI-P 1999	424/5666	485/5658		9.64%	0.87[0.77,0.99]
HARP 1995	7/41	7/39		0.47%	0.95[0.37,2.46]
HEARTS 2017	41/143	35/142		2.47%	1.16[0.79,1.71]
OFAMI 2001	42/150	36/150		2.5%	1.17[0.8,1.71]

Favours higher omega 3 — 0.1 0.2 0.5 1 2 5 10 — Favours lower omega 3

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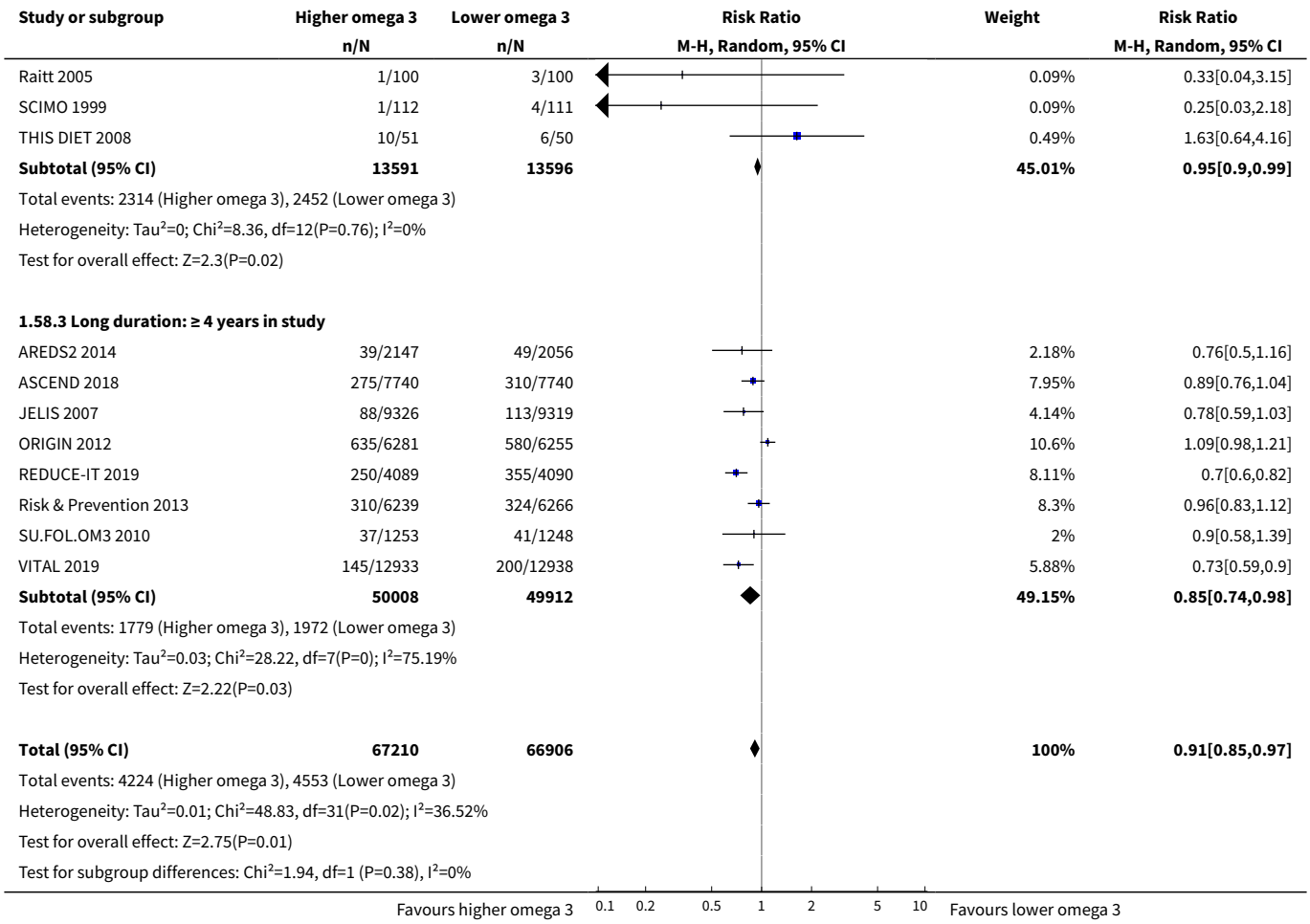
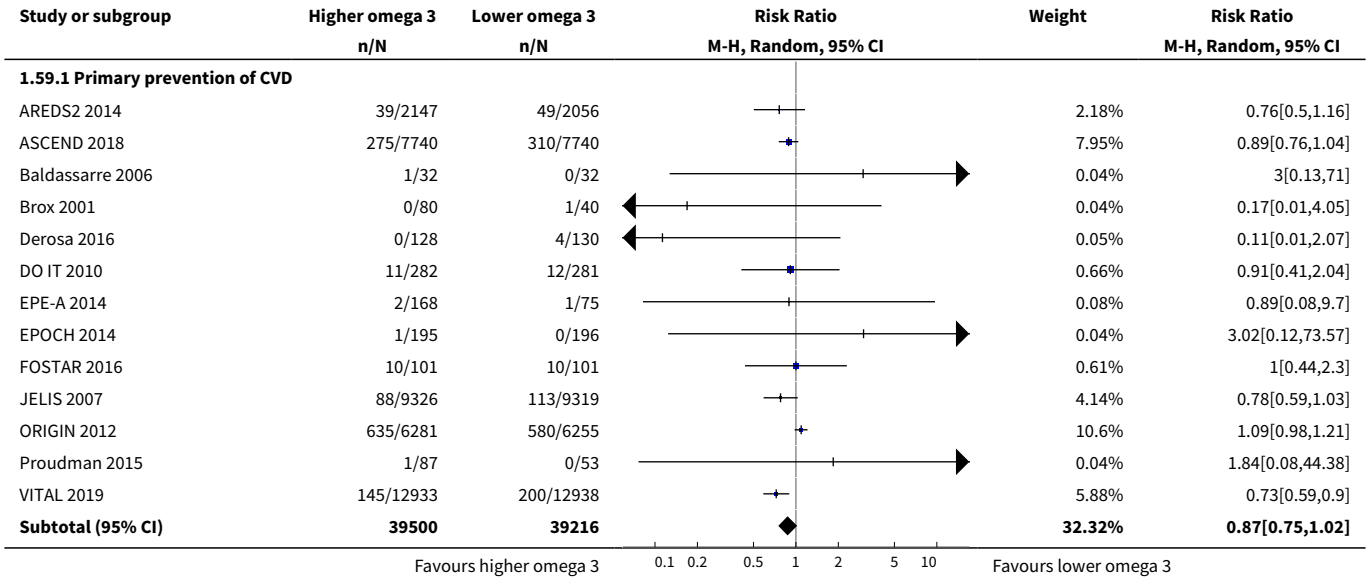


Analysis 1.59. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 59 CHD events - LCn3 - subgroup by primary or secondary prevention.



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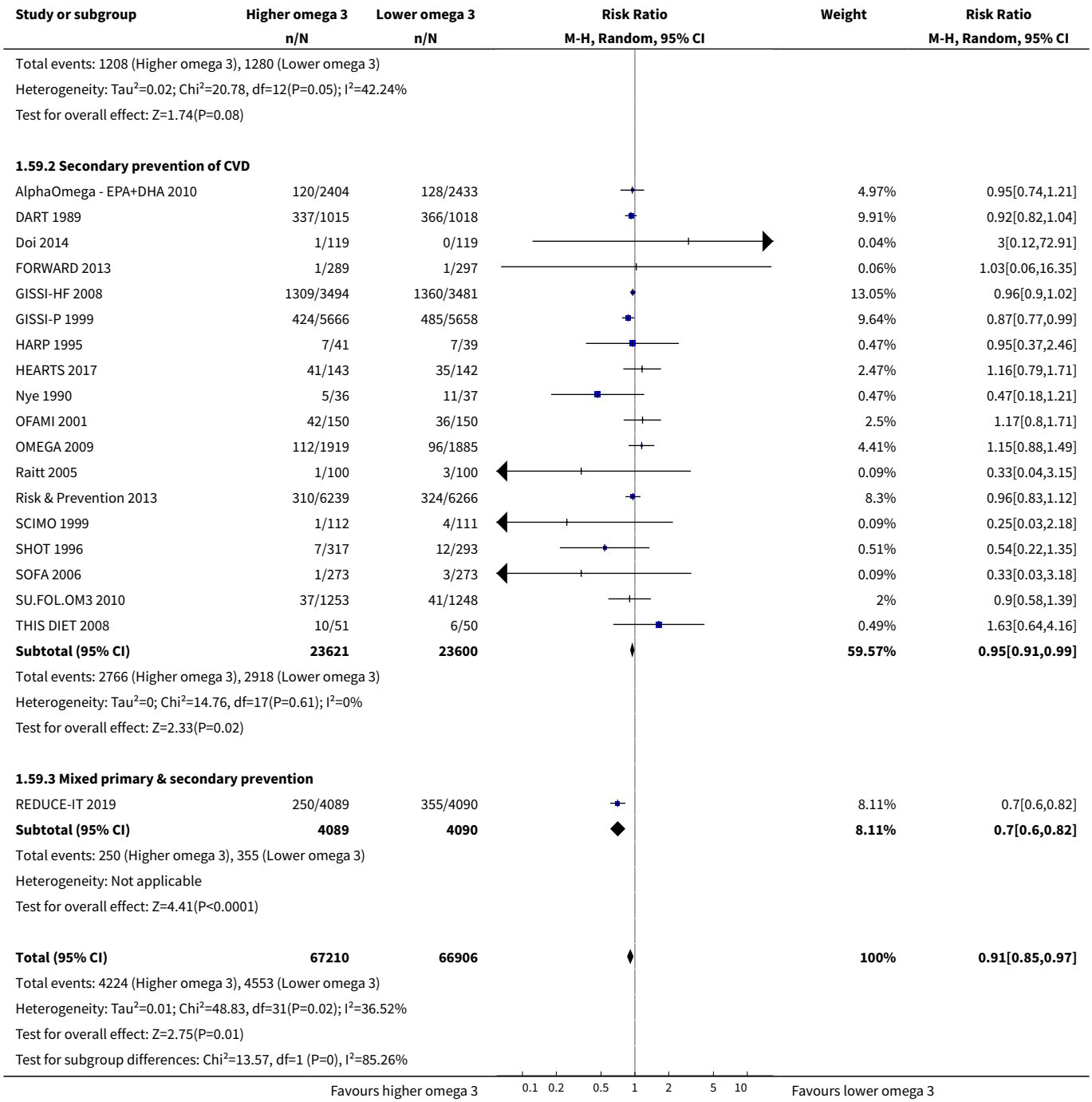
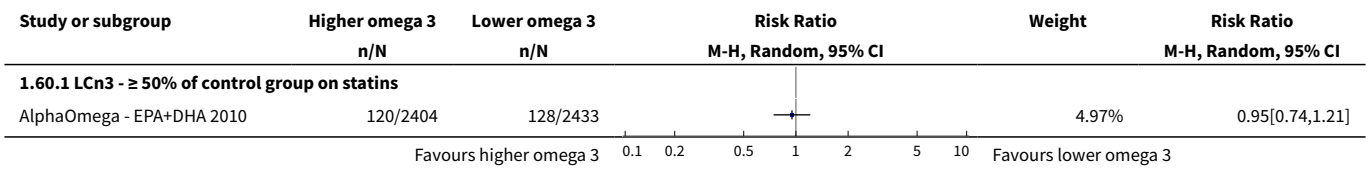


Analysis 1.60. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 60 CHD events - LCn3 - subgroup by statin use.



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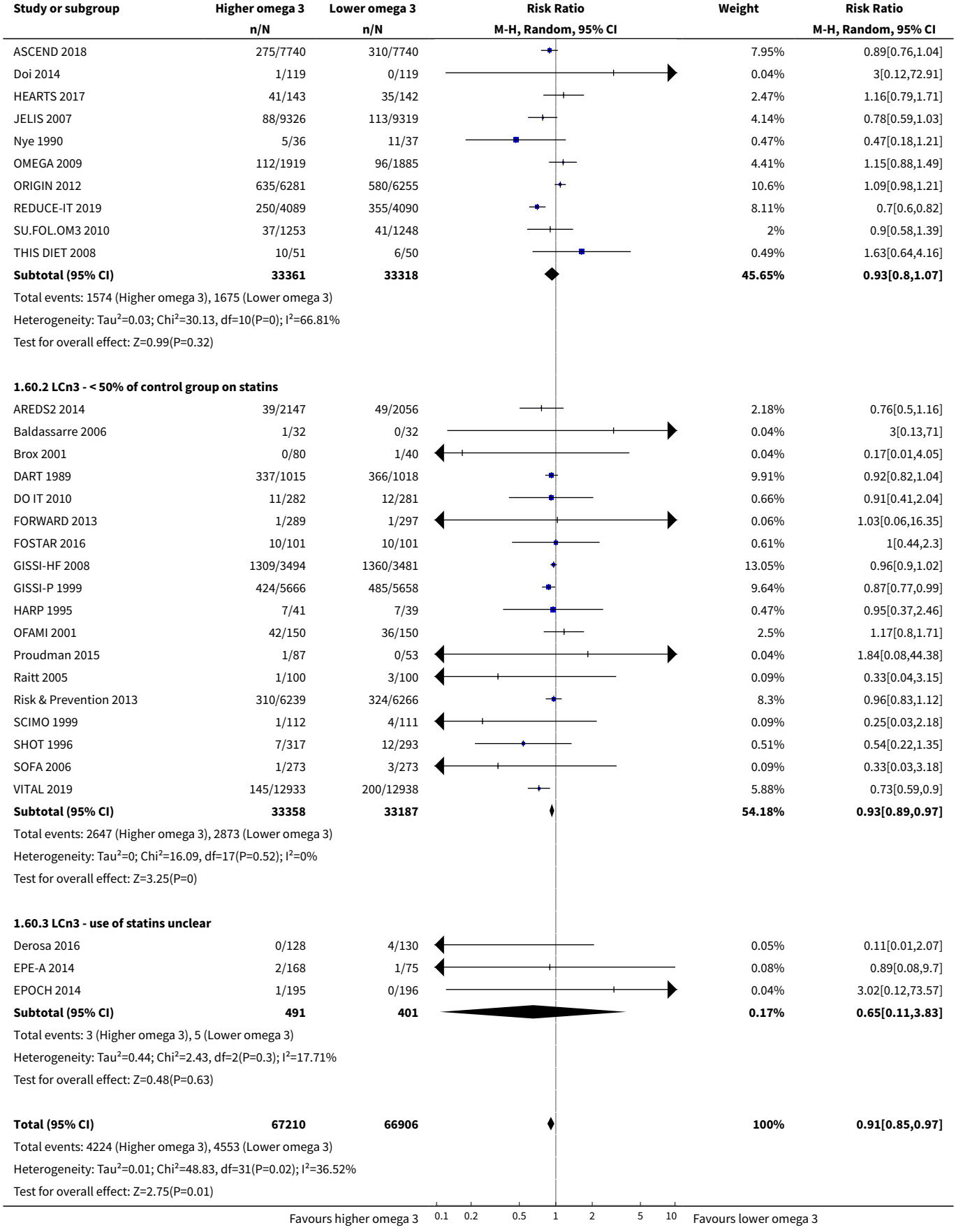

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ASCEND 2018	275/7740	310/7740		7.95%	0.89[0.76,1.04]
Doi 2014	1/119	0/119		0.04%	3[0.12,72.91]
HEARTS 2017	41/143	35/142		2.47%	1.16[0.79,1.71]
JELIS 2007	88/9326	113/9319		4.14%	0.78[0.59,1.03]
Nye 1990	5/36	11/37		0.47%	0.47[0.18,1.21]
OMEGA 2009	112/1919	96/1885		4.41%	1.15[0.88,1.49]
ORIGIN 2012	635/6281	580/6255		10.6%	1.09[0.98,1.21]
REDUCE-IT 2019	250/4089	355/4090		8.11%	0.7[0.6,0.82]
SU.FOL.OM3 2010	37/1253	41/1248		2%	0.9[0.58,1.39]
THIS DIET 2008	10/51	6/50		0.49%	1.63[0.64,4.16]
Subtotal (95% CI)	**33361**	**33318**		**45.65%**	**0.93[0.8,1.07]**
Total events: 1574 (Higher omega 3), 1675 (Lower omega 3)					
Heterogeneity: Tau²=0.03; Chi²=30.13, df=10(P=0); I²=66.81%					
Test for overall effect: Z=0.99(P=0.32)					
1.60.2 LCn3 - < 50% of control group on statins					
AREDS2 2014	39/2147	49/2056		2.18%	0.76[0.5,1.16]
Baldassarre 2006	1/32	0/32		0.04%	3[0.13,71]
Brox 2001	0/80	1/40		0.04%	0.17[0.01,4.05]
DART 1989	337/1015	366/1018		9.91%	0.92[0.82,1.04]
DO IT 2010	11/282	12/281		0.66%	0.91[0.41,2.04]
FORWARD 2013	1/289	1/297		0.06%	1.03[0.06,16.35]
FOSTAR 2016	10/101	10/101		0.61%	1[0.44,2.3]
GISSI-HF 2008	1309/3494	1360/3481		13.05%	0.96[0.9,1.02]
GISSI-P 1999	424/5666	485/5658		9.64%	0.87[0.77,0.99]
HARP 1995	7/41	7/39		0.47%	0.95[0.37,2.46]
OFAMI 2001	42/150	36/150		2.5%	1.17[0.8,1.71]
Proudman 2015	1/87	0/53		0.04%	1.84[0.08,44.38]
Raitt 2005	1/100	3/100		0.09%	0.33[0.04,3.15]
Risk & Prevention 2013	310/6239	324/6266		8.3%	0.96[0.83,1.12]
SCIMO 1999	1/112	4/111		0.09%	0.25[0.03,2.18]
SHOT 1996	7/317	12/293		0.51%	0.54[0.22,1.35]
SOFA 2006	1/273	3/273		0.09%	0.33[0.03,3.18]
VITAL 2019	145/12933	200/12938		5.88%	0.73[0.59,0.9]
Subtotal (95% CI)	**33358**	**33187**		**54.18%**	**0.93[0.89,0.97]**
Total events: 2647 (Higher omega 3), 2873 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=16.09, df=17(P=0.52); I²=0%					
Test for overall effect: Z=3.25(P=0)					
1.60.3 LCn3 - use of statins unclear					
Derosa 2016	0/128	4/130		0.05%	0.11[0.01,2.07]
EPE-A 2014	2/168	1/75		0.08%	0.89[0.08,9.7]
EPOCH 2014	1/195	0/196		0.04%	3.02[0.12,73.57]
Subtotal (95% CI)	**491**	**401**		**0.17%**	**0.65[0.11,3.83]**
Total events: 3 (Higher omega 3), 5 (Lower omega 3)					
Heterogeneity: Tau²=0.44; Chi²=2.43, df=2(P=0.3); I²=17.71%					
Test for overall effect: Z=0.48(P=0.63)					
Total (95% CI)	**67210**	**66906**		**100%**	**0.91[0.85,0.97]**
Total events: 4224 (Higher omega 3), 4553 (Lower omega 3)					
Heterogeneity: Tau²=0.01; Chi²=48.83, df=31(P=0.02); I²=36.52%					
Test for overall effect: Z=2.75(P=0.01)					

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Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for subgroup differences: Chi²=0.16, df=1 (P=0.93), I²=0%					

Favours higher omega 3 — 0.1 0.2 0.5 1 2 5 10 — Favours lower omega 3

Analysis 1.61. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 61 CHD events - LCn3 subgroup by CAD history.

Study or subgroup	High omega 3 n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.61.1 Previous CAD					
AlphaOmega - EPA+DHA 2010	120/2404	128/2433		4.97%	0.95[0.74,1.21]
DART 1989	337/1015	366/1018		9.91%	0.92[0.82,1.04]
Doi 2014	1/119	0/119		0.04%	3[0.12,72.91]
GISSI-P 1999	424/5666	485/5658		9.64%	0.87[0.77,0.99]
HARP 1995	7/41	7/39		0.47%	0.95[0.37,2.46]
HEARTS 2017	41/143	35/142		2.47%	1.16[0.79,1.71]
Nye 1990	5/36	11/37		0.47%	0.47[0.18,1.21]
OFAMI 2001	42/150	36/150		2.5%	1.17[0.8,1.71]
OMEGA 2009	112/1919	96/1885		4.41%	1.15[0.88,1.49]
SCIMO 1999	1/112	4/111		0.09%	0.25[0.03,2.18]
SHOT 1996	7/317	12/293		0.51%	0.54[0.22,1.35]
SU.FOL.OM3 2010	37/1253	41/1248		2%	0.9[0.58,1.39]
THIS DIET 2008	10/51	6/50		0.49%	1.63[0.64,4.16]
Subtotal (95% CI)	**13226**	**13183**		**37.98%**	**0.94[0.87,1.02]**
Total events: 1144 (High omega 3), 1227 (Control)					
Heterogeneity: Tau²=0; Chi²=12.75, df=12(P=0.39); I²=5.91%					
Test for overall effect: Z=1.49(P=0.14)					
1.61.2 No previous CAD					
AREDS2 2014	39/2147	49/2056		2.18%	0.76[0.5,1.16]
ASCEND 2018	275/7740	310/7740		7.95%	0.89[0.76,1.04]
Baldassarre 2006	1/32	0/32		0.04%	3[0.13,71]
Brox 2001	0/80	1/40		0.04%	0.17[0.01,4.05]
Derosa 2016	0/128	4/130		0.05%	0.11[0.01,2.07]
DO IT 2010	11/282	12/281		0.66%	0.91[0.41,2.04]
EPE-A 2014	2/168	1/75		0.08%	0.89[0.08,9.7]
EPOCH 2014	1/195	0/196		0.04%	3.02[0.12,73.57]
FORWARD 2013	1/289	1/297		0.06%	1.03[0.06,16.35]
FOSTAR 2016	10/101	10/101		0.61%	1[0.44,2.3]
GISSI-HF 2008	1309/3494	1360/3481		13.05%	0.96[0.9,1.02]
JELIS 2007	88/9326	113/9319		4.14%	0.78[0.59,1.03]
ORIGIN 2012	635/6281	580/6255		10.6%	1.09[0.98,1.21]
Proudman 2015	1/87	0/53		0.04%	1.84[0.08,44.38]
Raitt 2005	1/100	3/100		0.09%	0.33[0.04,3.15]
Risk & Prevention 2013	310/6239	324/6266		8.3%	0.96[0.83,1.12]
SOFA 2006	1/273	3/273		0.09%	0.33[0.03,3.18]
VITAL 2019	145/12933	200/12938		5.88%	0.73[0.59,0.9]
Subtotal (95% CI)	**49895**	**49633**		**53.91%**	**0.93[0.86,1]**
Total events: 2830 (High omega 3), 2971 (Control)					
Heterogeneity: Tau²=0; Chi²=22.54, df=17(P=0.16); I²=24.57%					

Favours high LCn3 — 0.01 0.1 1 10 100 — Favours low LCn3

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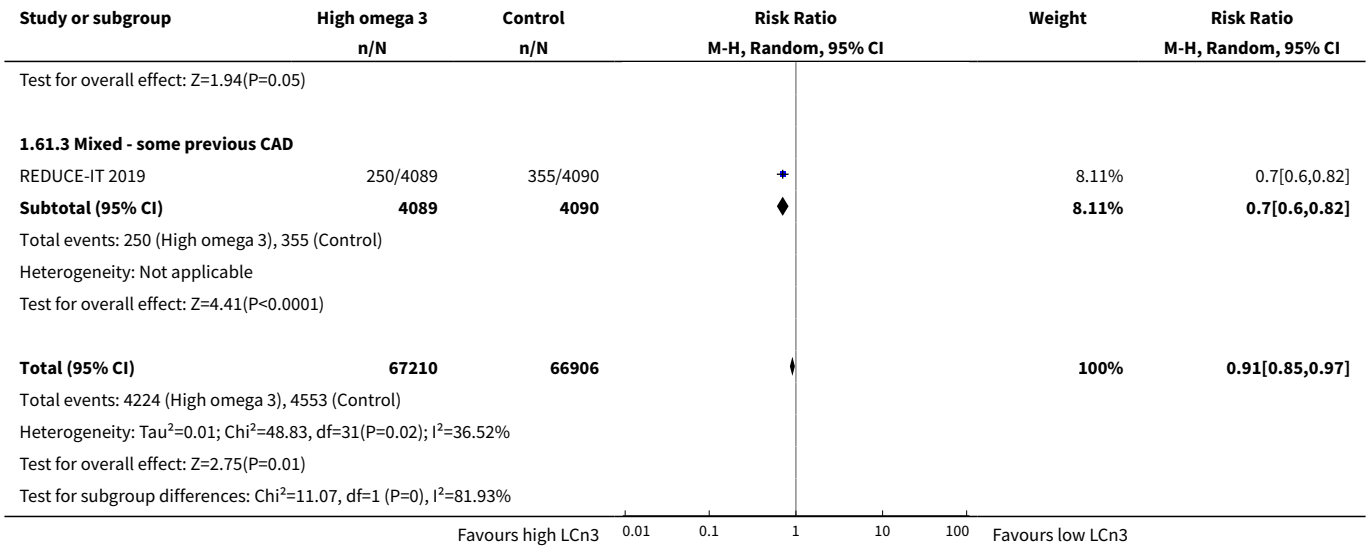
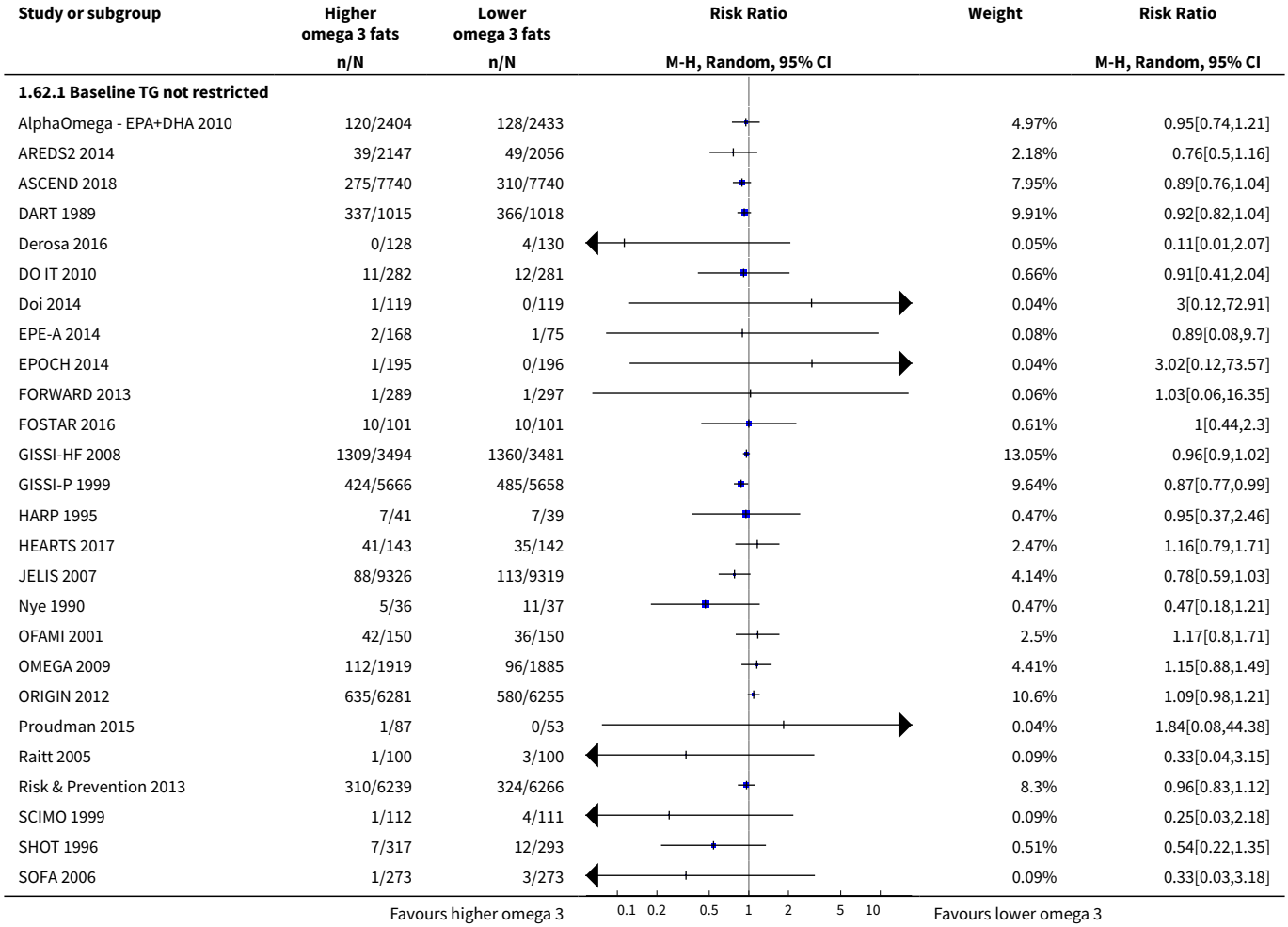


Analysis 1.62. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 62 CHD events - LCn3 - subgroup by baseline TG.



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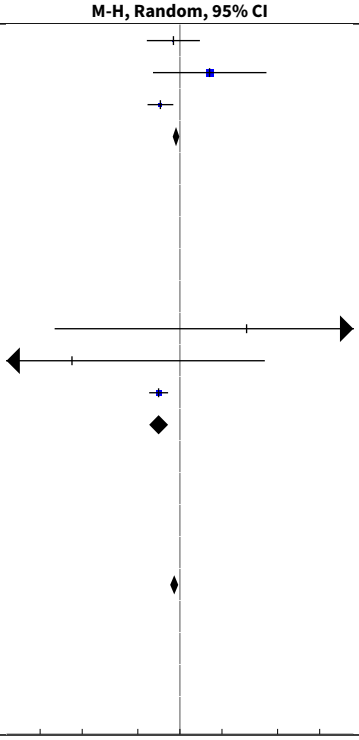
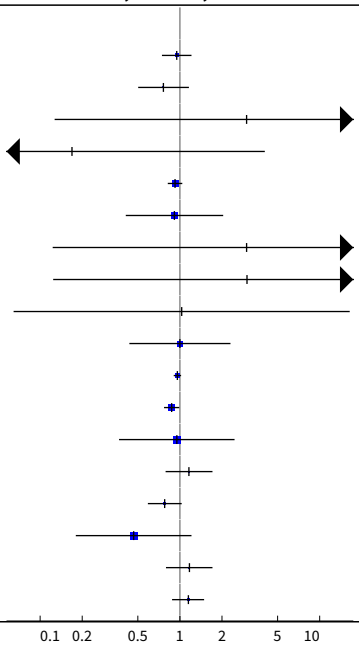
Study or subgroup	Higher omega 3 fats n/N	Lower omega 3 fats n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
SU.FOL.OM3 2010	37/1253	41/1248		2%	0.9[0.58,1.39]
THIS DIET 2008	10/51	6/50		0.49%	1.63[0.64,4.16]
VITAL 2019	145/12933	200/12938		5.88%	0.73[0.59,0.9]
Subtotal (95% CI)	**63009**	**62744**		**91.8%**	**0.94[0.89,0.99]**
Total events: 3973 (Higher omega 3 fats), 4197 (Lower omega 3 fats)					
Heterogeneity: Tau^2=0; Chi^2=33.9, df=28(P=0.2); I^2=17.4%					
Test for overall effect: Z=2.29(P=0.02)					
1.62.2 Baseline TG raised					
Baldassarre 2006	1/32	0/32		0.04%	3[0.13,71]
Brox 2001	0/80	1/40		0.04%	0.17[0.01,4.05]
REDUCE-IT 2019	250/4089	355/4090		8.11%	0.7[0.6,0.82]
Subtotal (95% CI)	**4201**	**4162**		**8.2%**	**0.7[0.6,0.82]**
Total events: 251 (Higher omega 3 fats), 356 (Lower omega 3 fats)					
Heterogeneity: Tau^2=0; Chi^2=1.58, df=2(P=0.45); I^2=0%					
Test for overall effect: Z=4.41(P<0.0001)					
Total (95% CI)	**67210**	**66906**		**100%**	**0.91[0.85,0.97]**
Total events: 4224 (Higher omega 3 fats), 4553 (Lower omega 3 fats)					
Heterogeneity: Tau^2=0.01; Chi^2=48.83, df=31(P=0.02); I^2=36.52%					
Test for overall effect: Z=2.75(P=0.01)					
Test for subgroup differences: Chi^2=11.6, df=1 (P=0), I^2=91.38%					



Favours higher omega 3 — Favours lower omega 3

Analysis 1.63. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 63 CHD events - LCn3 - subgroup by baseline DM.

Study or subgroup	Higher omega 3 fats n/N	Lower omega 3 fats n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.63.1 Normal diabetes risk					
AlphaOmega - EPA+DHA 2010	120/2404	128/2433		4.97%	0.95[0.74,1.21]
AREDS2 2014	39/2147	49/2056		2.18%	0.76[0.5,1.16]
Baldassarre 2006	1/32	0/32		0.04%	3[0.13,71]
Brox 2001	0/80	1/40		0.04%	0.17[0.01,4.05]
DART 1989	337/1015	366/1018		9.91%	0.92[0.82,1.04]
DO IT 2010	11/282	12/281		0.66%	0.91[0.41,2.04]
Doi 2014	1/119	0/119		0.04%	3[0.12,72.91]
EPOCH 2014	1/195	0/196		0.04%	3.02[0.12,73.57]
FORWARD 2013	1/289	1/297		0.06%	1.03[0.06,16.35]
FOSTAR 2016	10/101	10/101		0.61%	1[0.44,2.3]
GISSI-HF 2008	1309/3494	1360/3481		13.05%	0.96[0.9,1.02]
GISSI-P 1999	424/5666	485/5658		9.64%	0.87[0.77,0.99]
HARP 1995	7/41	7/39		0.47%	0.95[0.37,2.46]
HEARTS 2017	41/143	35/142		2.47%	1.16[0.79,1.71]
JELIS 2007	88/9326	113/9319		4.14%	0.78[0.59,1.03]
Nye 1990	5/36	11/37		0.47%	0.47[0.18,1.21]
OFAMI 2001	42/150	36/150		2.5%	1.17[0.8,1.71]
OMEGA 2009	112/1919	96/1885		4.41%	1.15[0.88,1.49]



Favours higher omega 3 — Favours lower omega 3

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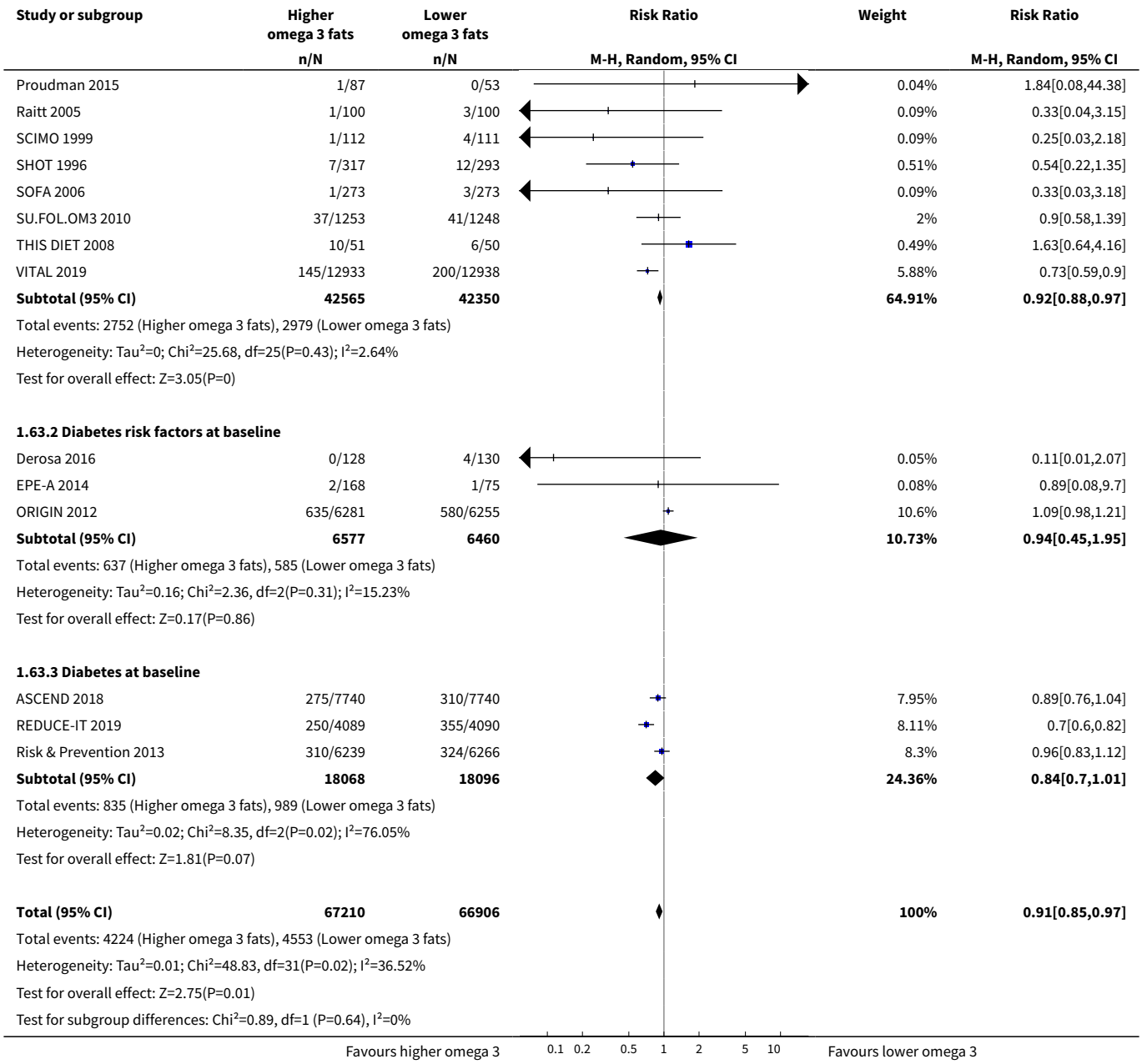
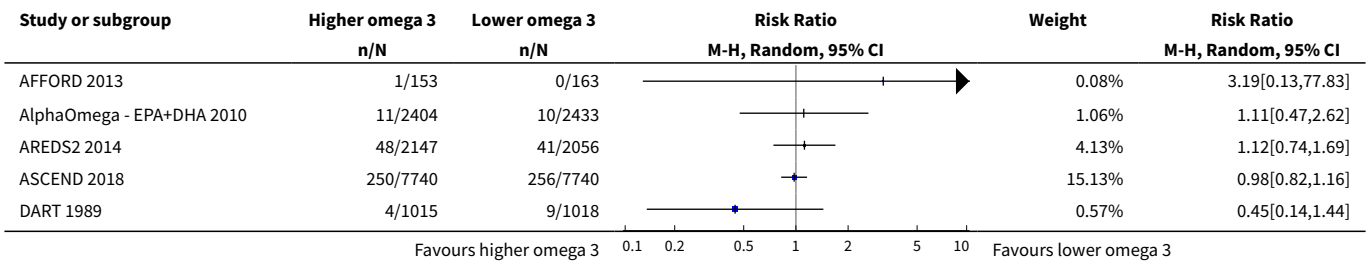


Analysis 1.64. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 64 Stroke (overall) - LCn3.



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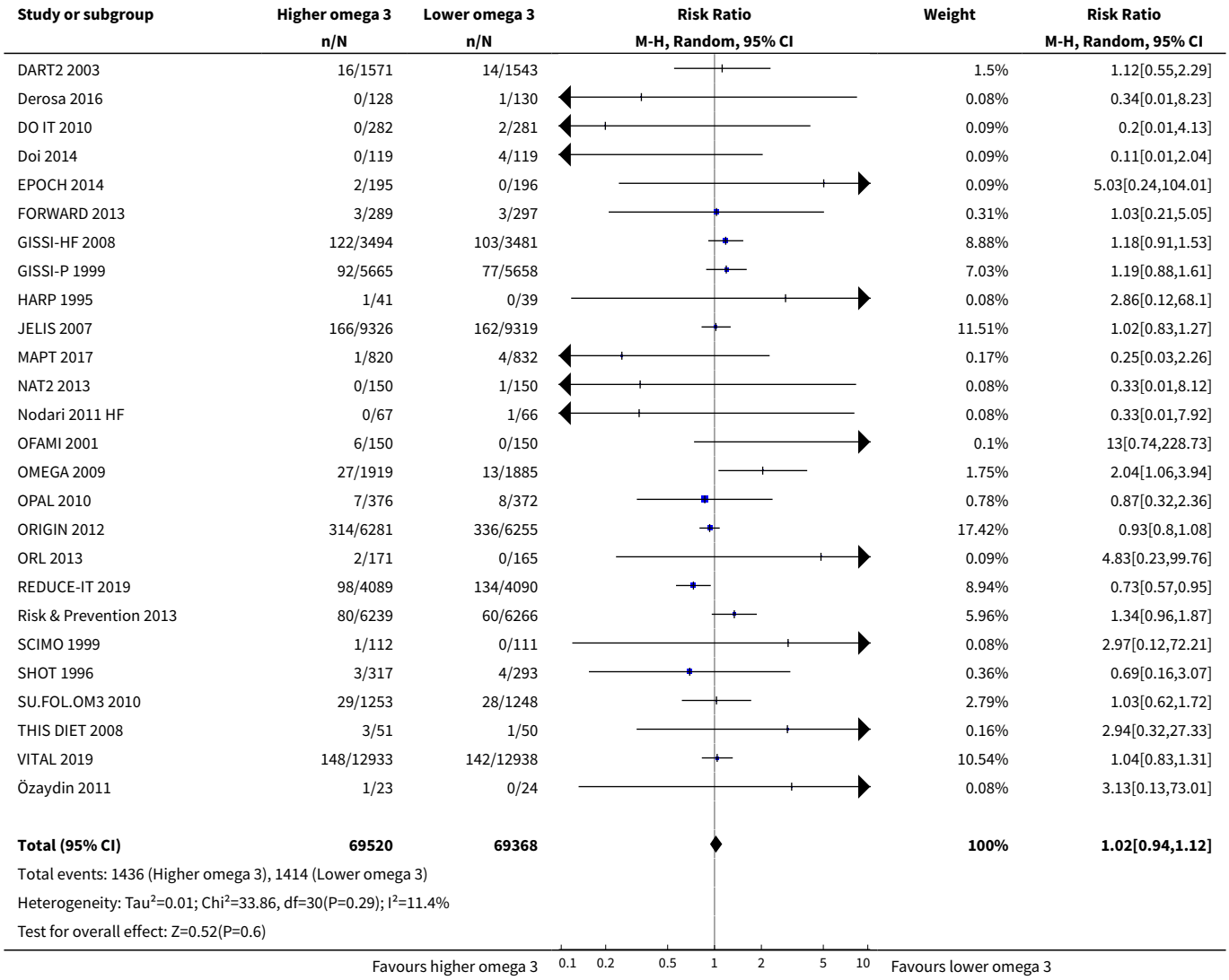
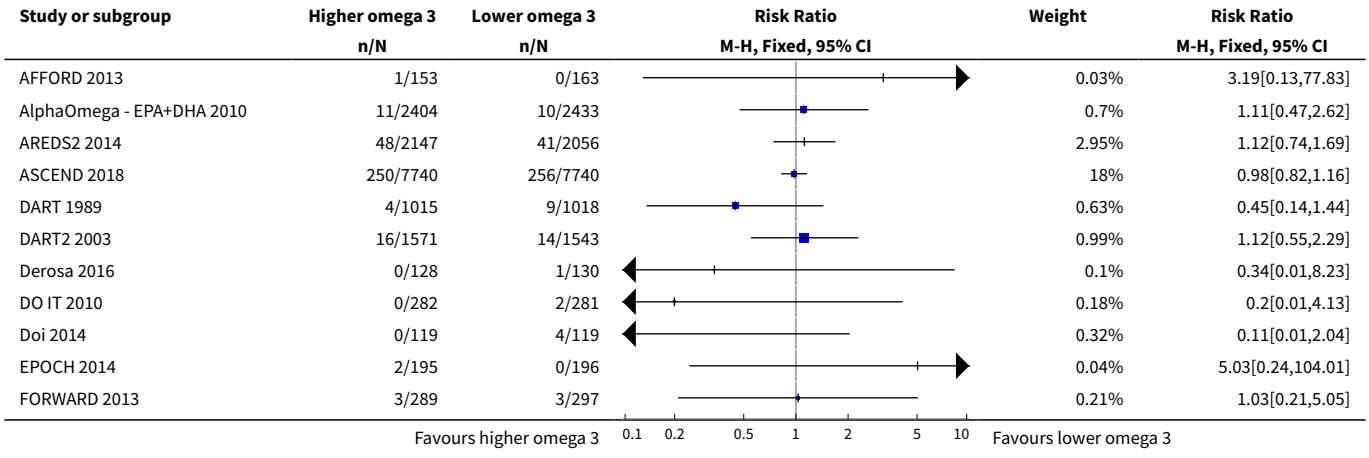


Analysis 1.65. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 65 Stroke - LCn3 - SA fixed effect.



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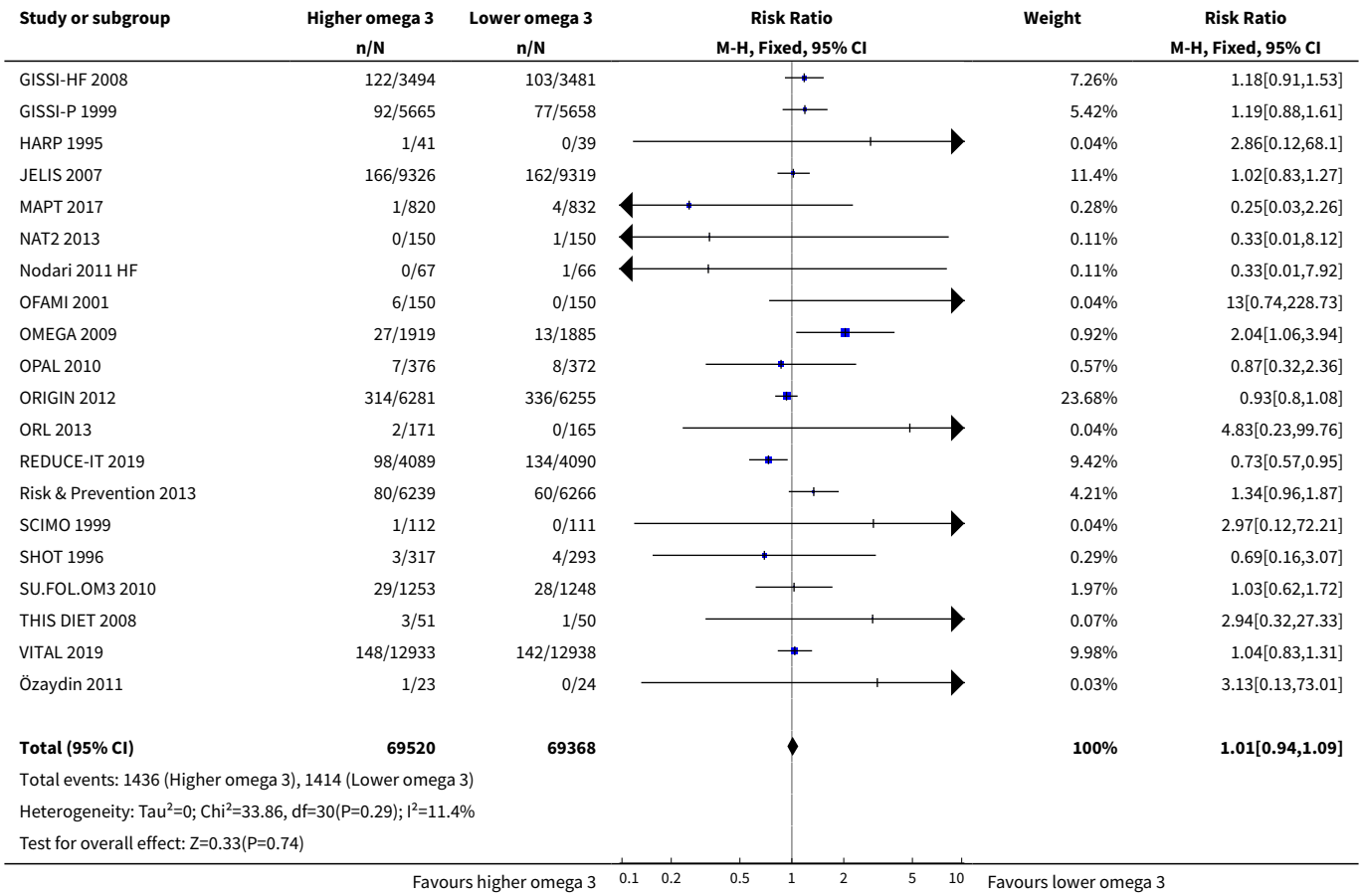
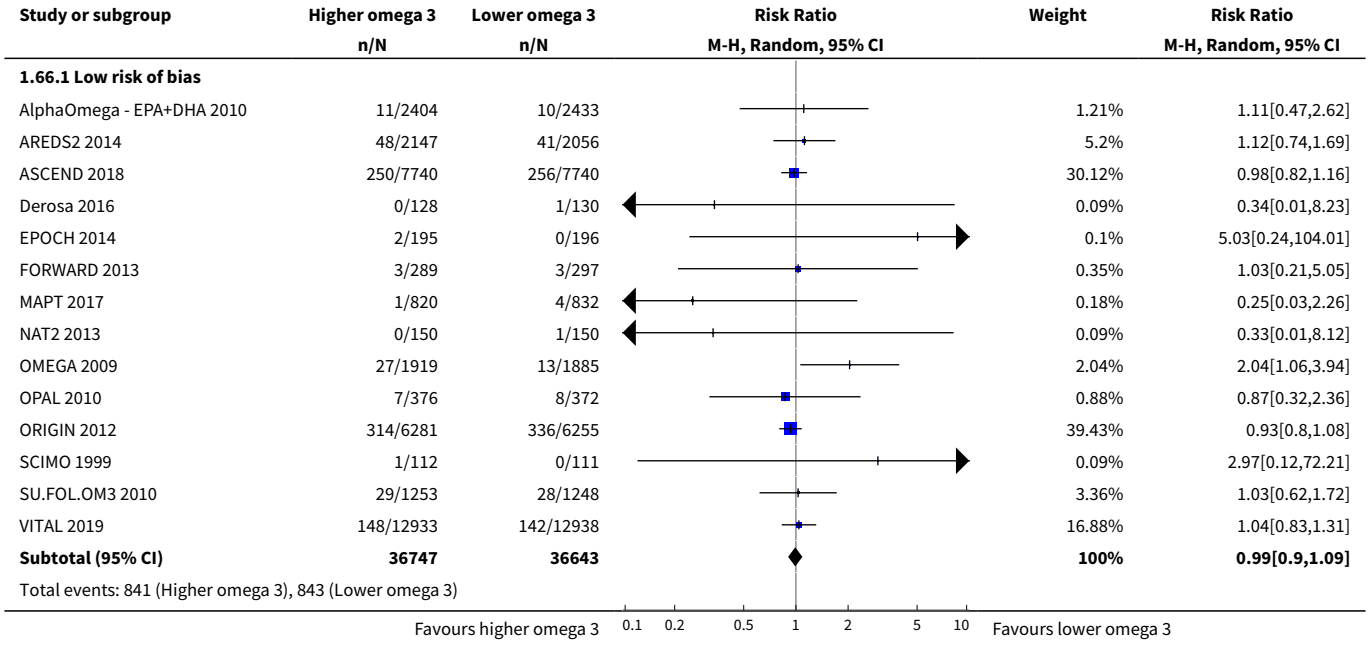


Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
GISSI-HF 2008	122/3494	103/3481		7.26%	1.18[0.91,1.53]
GISSI-P 1999	92/5665	77/5658		5.42%	1.19[0.88,1.61]
HARP 1995	1/41	0/39		0.04%	2.86[0.12,68.1]
JELIS 2007	166/9326	162/9319		11.4%	1.02[0.83,1.27]
MAPT 2017	1/820	4/832		0.28%	0.25[0.03,2.26]
NAT2 2013	0/150	1/150		0.11%	0.33[0.01,8.12]
Nodari 2011 HF	0/67	1/66		0.11%	0.33[0.01,7.92]
OFAMI 2001	6/150	0/150		0.04%	13[0.74,228.73]
OMEGA 2009	27/1919	13/1885		0.92%	2.04[1.06,3.94]
OPAL 2010	7/376	8/372		0.57%	0.87[0.32,2.36]
ORIGIN 2012	314/6281	336/6255		23.68%	0.93[0.8,1.08]
ORL 2013	2/171	0/165		0.04%	4.83[0.23,99.76]
REDUCE-IT 2019	98/4089	134/4090		9.42%	0.73[0.57,0.95]
Risk & Prevention 2013	80/6239	60/6266		4.21%	1.34[0.96,1.87]
SCIMO 1999	1/112	0/111		0.04%	2.97[0.12,72.21]
SHOT 1996	3/317	4/293		0.29%	0.69[0.16,3.07]
SU.FOL.OM3 2010	29/1253	28/1248		1.97%	1.03[0.62,1.72]
THIS DIET 2008	3/51	1/50		0.07%	2.94[0.32,27.33]
VITAL 2019	148/12933	142/12938		9.98%	1.04[0.83,1.31]
Özaydin 2011	1/23	0/24		0.03%	3.13[0.13,73.01]
Total (95% CI)	**69520**	**69368**		**100%**	**1.01[0.94,1.09]**
Total events: 1436 (Higher omega 3), 1414 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=33.86, df=30(P=0.29); I^2=11.4%					
Test for overall effect: Z=0.33(P=0.74)					

Analysis 1.66. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 66 Stroke - LCn3 - SA by summary risk of bias.



Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.66.1 Low risk of bias					
AlphaOmega - EPA+DHA 2010	11/2404	10/2433		1.21%	1.11[0.47,2.62]
AREDS2 2014	48/2147	41/2056		5.2%	1.12[0.74,1.69]
ASCEND 2018	250/7740	256/7740		30.12%	0.98[0.82,1.16]
Derosa 2016	0/128	1/130		0.09%	0.34[0.01,8.23]
EPOCH 2014	2/195	0/196		0.1%	5.03[0.24,104.01]
FORWARD 2013	3/289	3/297		0.35%	1.03[0.21,5.05]
MAPT 2017	1/820	4/832		0.18%	0.25[0.03,2.26]
NAT2 2013	0/150	1/150		0.09%	0.33[0.01,8.12]
OMEGA 2009	27/1919	13/1885		2.04%	2.04[1.06,3.94]
OPAL 2010	7/376	8/372		0.88%	0.87[0.32,2.36]
ORIGIN 2012	314/6281	336/6255		39.43%	0.93[0.8,1.08]
SCIMO 1999	1/112	0/111		0.09%	2.97[0.12,72.21]
SU.FOL.OM3 2010	29/1253	28/1248		3.36%	1.03[0.62,1.72]
VITAL 2019	148/12933	142/12938		16.88%	1.04[0.83,1.31]
Subtotal (95% CI)	**36747**	**36643**		**100%**	**0.99[0.9,1.09]**
Total events: 841 (Higher omega 3), 843 (Lower omega 3)					

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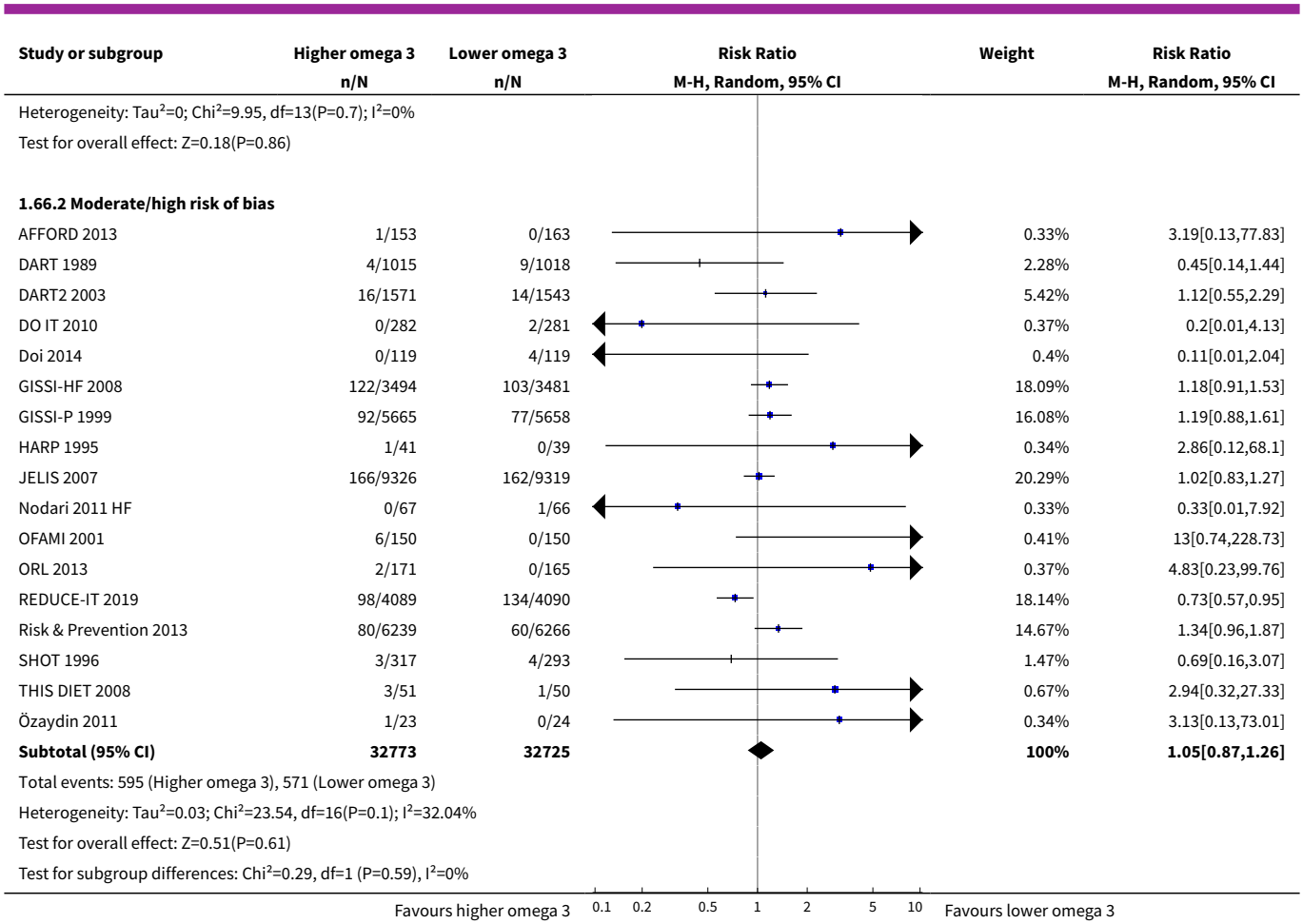
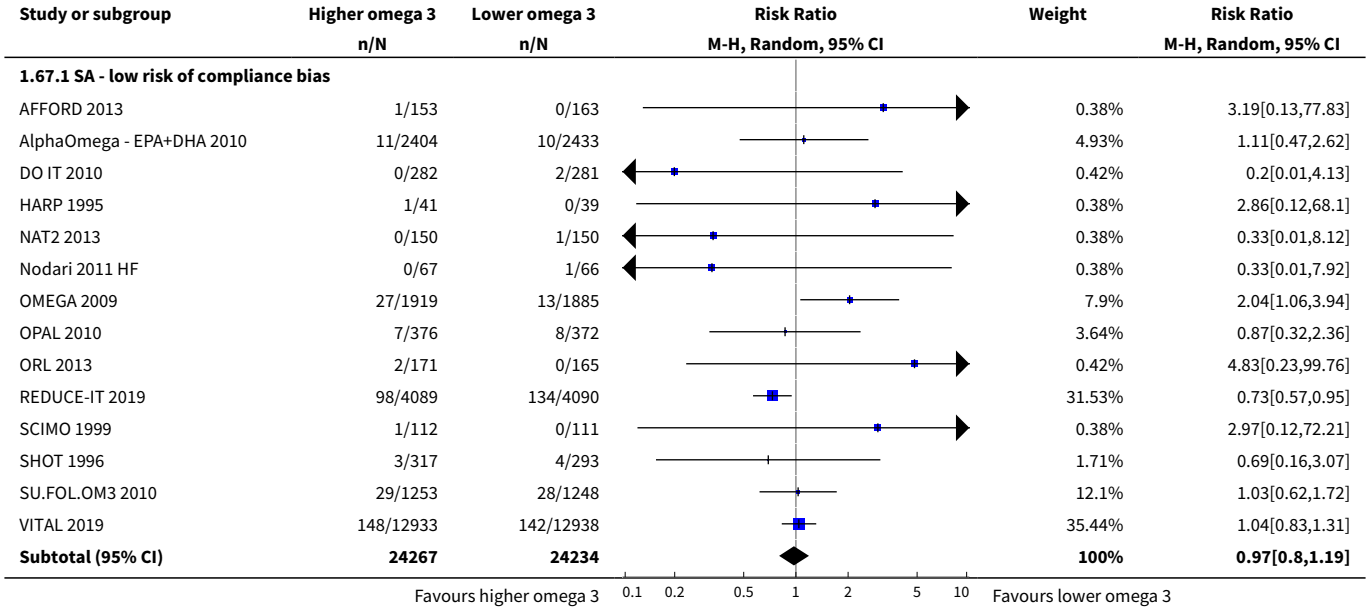


Analysis 1.67. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 67 Stroke - LCn3 - SA by compliance and study size.



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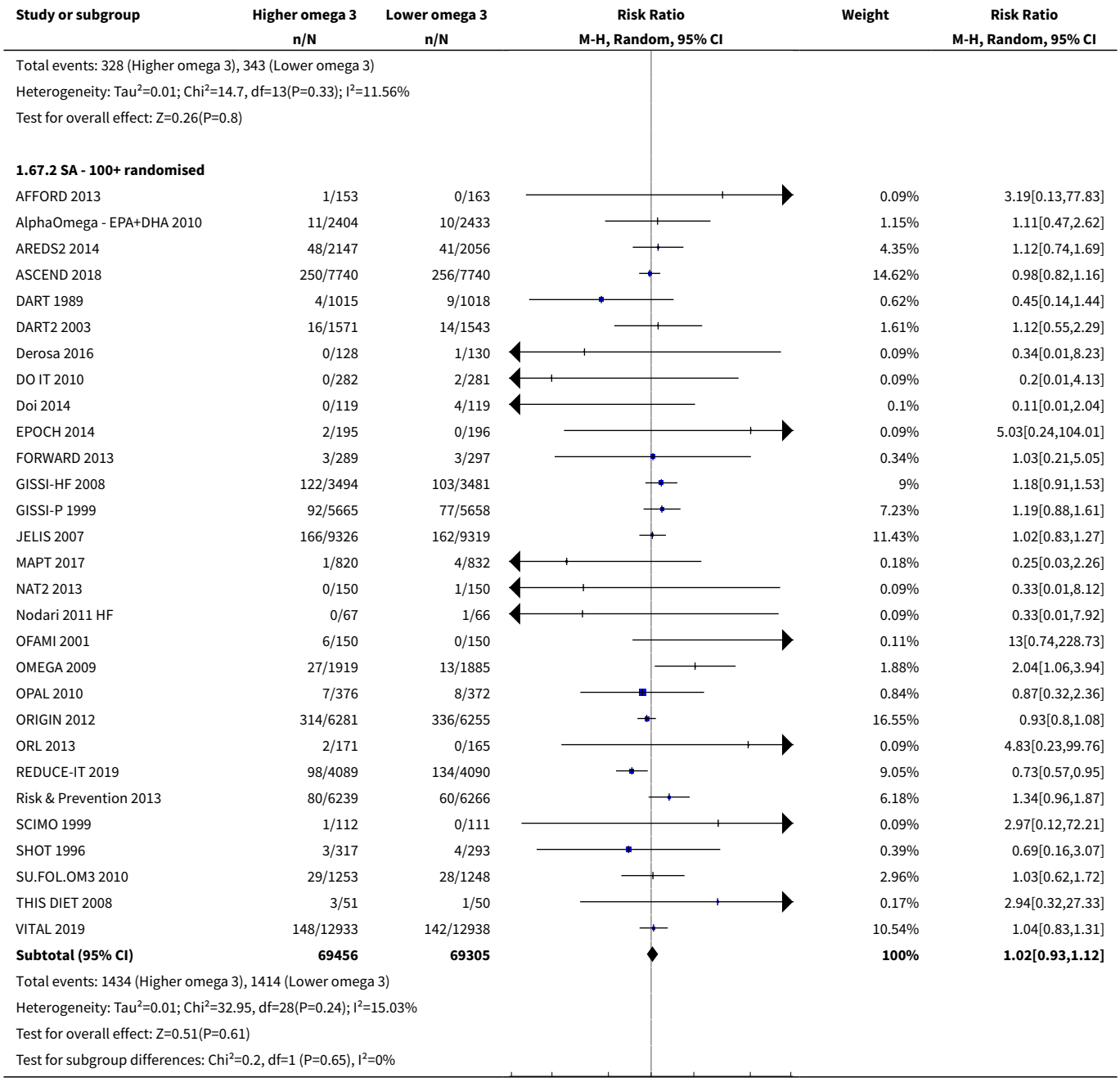
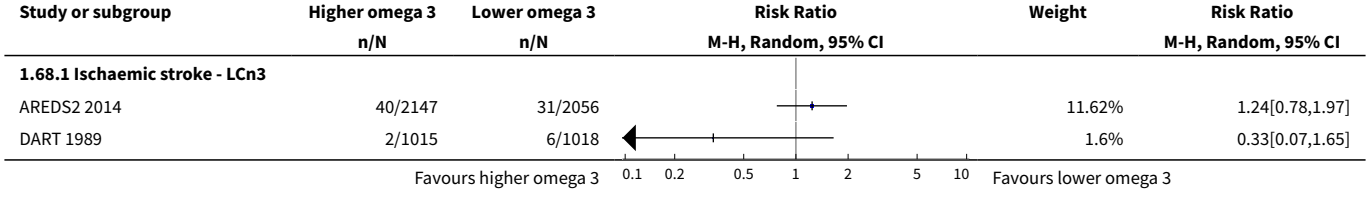


Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 328 (Higher omega 3), 343 (Lower omega 3)					
Heterogeneity: Tau²=0.01; Chi²=14.7, df=13(P=0.33); I²=11.56%					
Test for overall effect: Z=0.26(P=0.8)					
1.67.2 SA - 100+ randomised					
AFFORD 2013	1/153	0/163		0.09%	3.19[0.13,77.83]
AlphaOmega - EPA+DHA 2010	11/2404	10/2433		1.15%	1.11[0.47,2.62]
AREDS2 2014	48/2147	41/2056		4.35%	1.12[0.74,1.69]
ASCEND 2018	250/7740	256/7740		14.62%	0.98[0.82,1.16]
DART 1989	4/1015	9/1018		0.62%	0.45[0.14,1.44]
DART2 2003	16/1571	14/1543		1.61%	1.12[0.55,2.29]
Derosa 2016	0/128	1/130		0.09%	0.34[0.01,8.23]
DO IT 2010	0/282	2/281		0.09%	0.2[0.01,4.13]
Doi 2014	0/119	4/119		0.1%	0.11[0.01,2.04]
EPOCH 2014	2/195	0/196		0.09%	5.03[0.24,104.01]
FORWARD 2013	3/289	3/297		0.34%	1.03[0.21,5.05]
GISSI-HF 2008	122/3494	103/3481		9%	1.18[0.91,1.53]
GISSI-P 1999	92/5665	77/5658		7.23%	1.19[0.88,1.61]
JELIS 2007	166/9326	162/9319		11.43%	1.02[0.83,1.27]
MAPT 2017	1/820	4/832		0.18%	0.25[0.03,2.26]
NAT2 2013	0/150	1/150		0.09%	0.33[0.01,8.12]
Nodari 2011 HF	0/67	1/66		0.09%	0.33[0.01,7.92]
OFAMI 2001	6/150	0/150		0.11%	13[0.74,228.73]
OMEGA 2009	27/1919	13/1885		1.88%	2.04[1.06,3.94]
OPAL 2010	7/376	8/372		0.84%	0.87[0.32,2.36]
ORIGIN 2012	314/6281	336/6255		16.55%	0.93[0.8,1.08]
ORL 2013	2/171	0/165		0.09%	4.83[0.23,99.76]
REDUCE-IT 2019	98/4089	134/4090		9.05%	0.73[0.57,0.95]
Risk & Prevention 2013	80/6239	60/6266		6.18%	1.34[0.96,1.87]
SCIMO 1999	1/112	0/111		0.09%	2.97[0.12,72.21]
SHOT 1996	3/317	4/293		0.39%	0.69[0.16,3.07]
SU.FOL.OM3 2010	29/1253	28/1248		2.96%	1.03[0.62,1.72]
THIS DIET 2008	3/51	1/50		0.17%	2.94[0.32,27.33]
VITAL 2019	148/12933	142/12938		10.54%	1.04[0.83,1.31]
Subtotal (95% CI)	**69456**	**69305**		**100%**	**1.02[0.93,1.12]**
Total events: 1434 (Higher omega 3), 1414 (Lower omega 3)					
Heterogeneity: Tau²=0.01; Chi²=32.95, df=28(P=0.24); I²=15.03%					
Test for overall effect: Z=0.51(P=0.61)					
Test for subgroup differences: Chi²=0.2, df=1 (P=0.65), I²=0%					

Analysis 1.68. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 68 Stroke - LCn3 - subgroup by stroke type.



Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.68.1 Ischaemic stroke - LCn3					
AREDS2 2014	40/2147	31/2056		11.62%	1.24[0.78,1.97]
DART 1989	2/1015	6/1018		1.6%	0.33[0.07,1.65]

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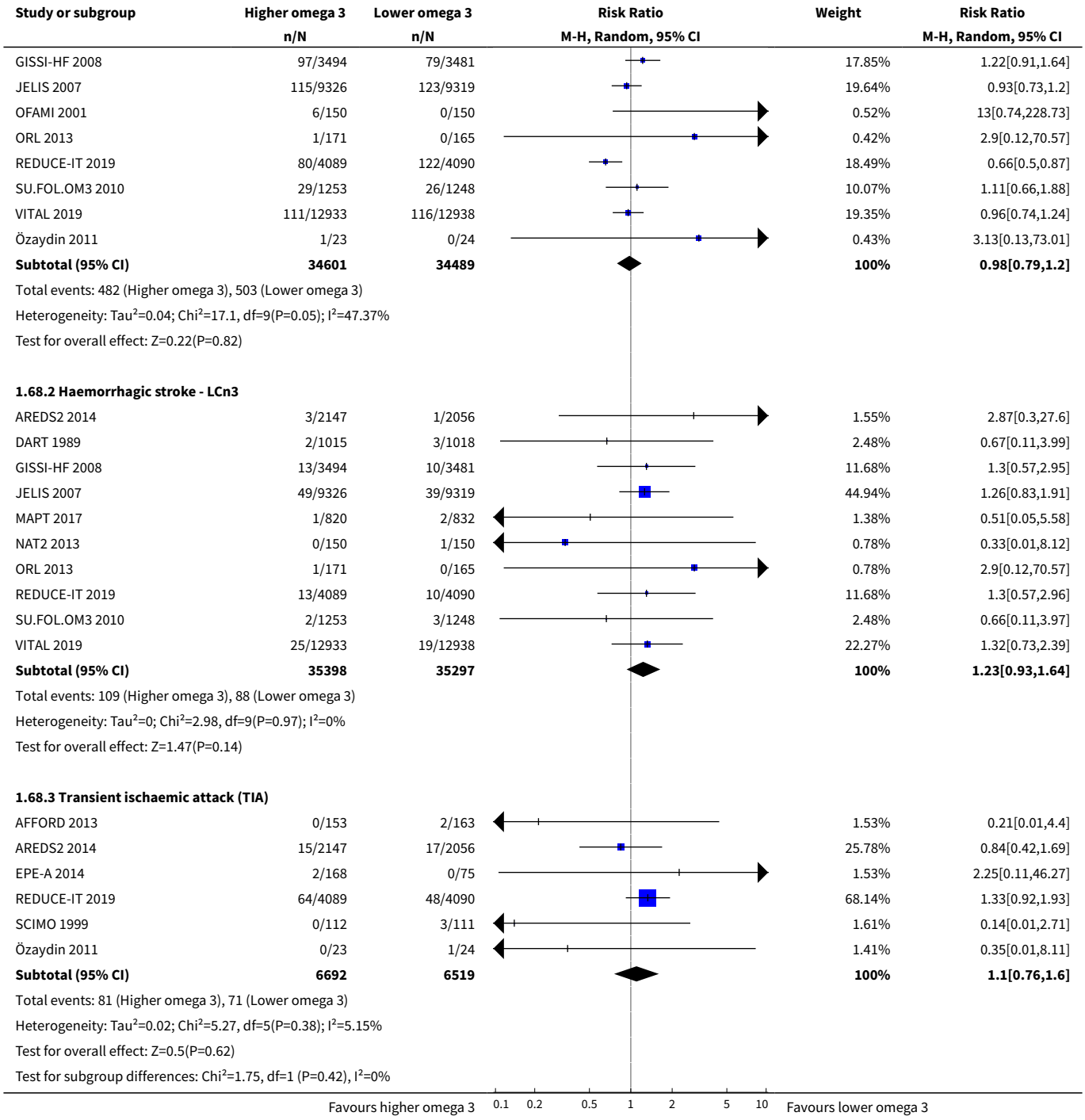
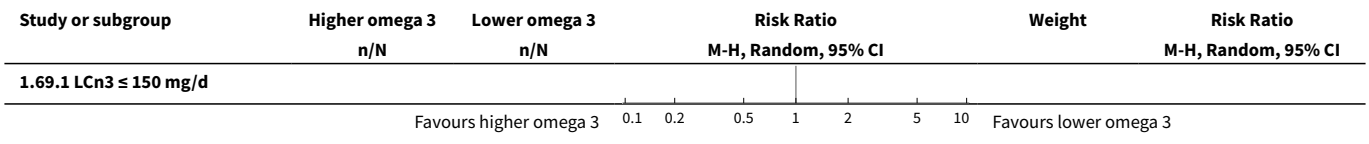


Analysis 1.69. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 69 Stroke - LCn3 - subgroup by dose.



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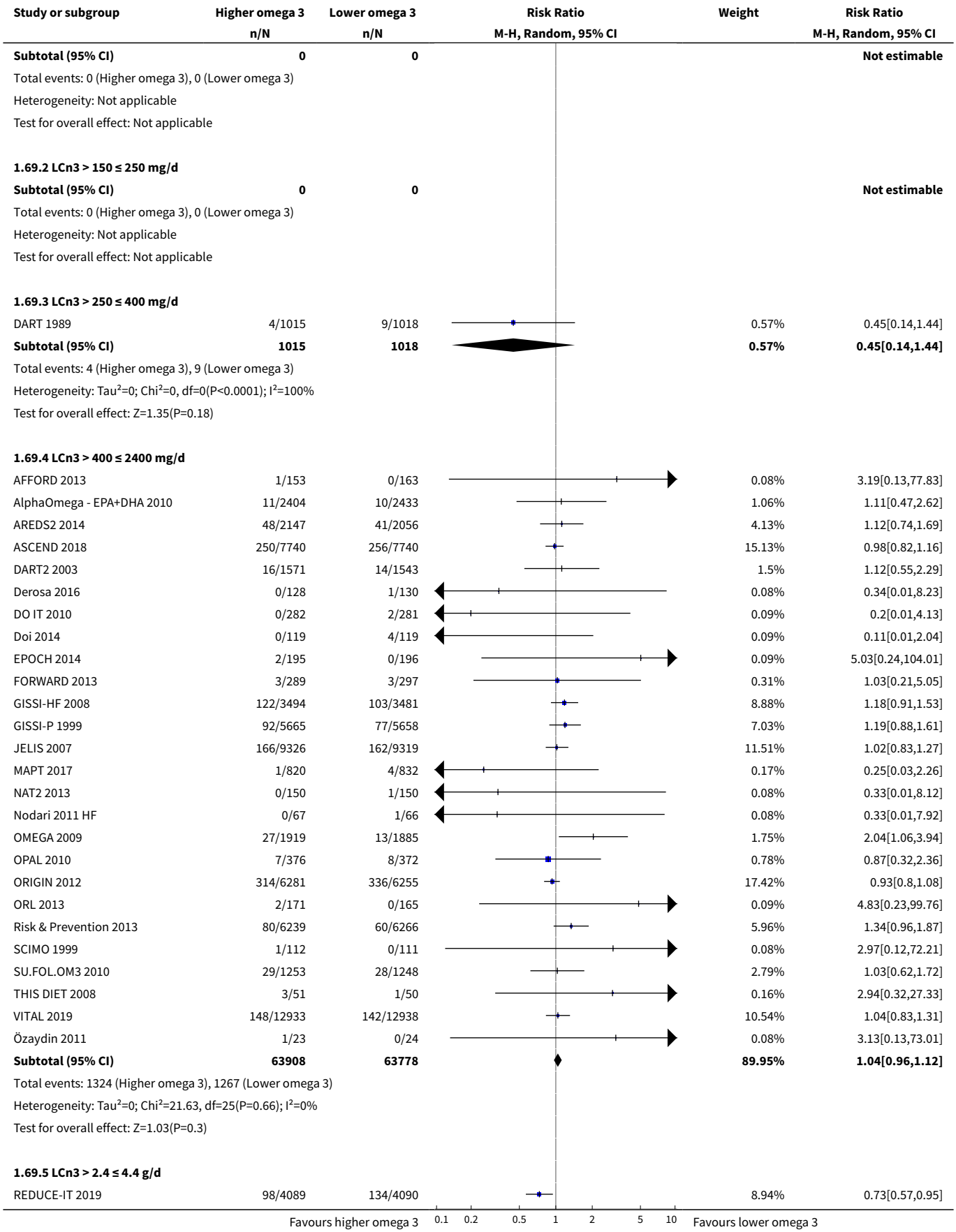

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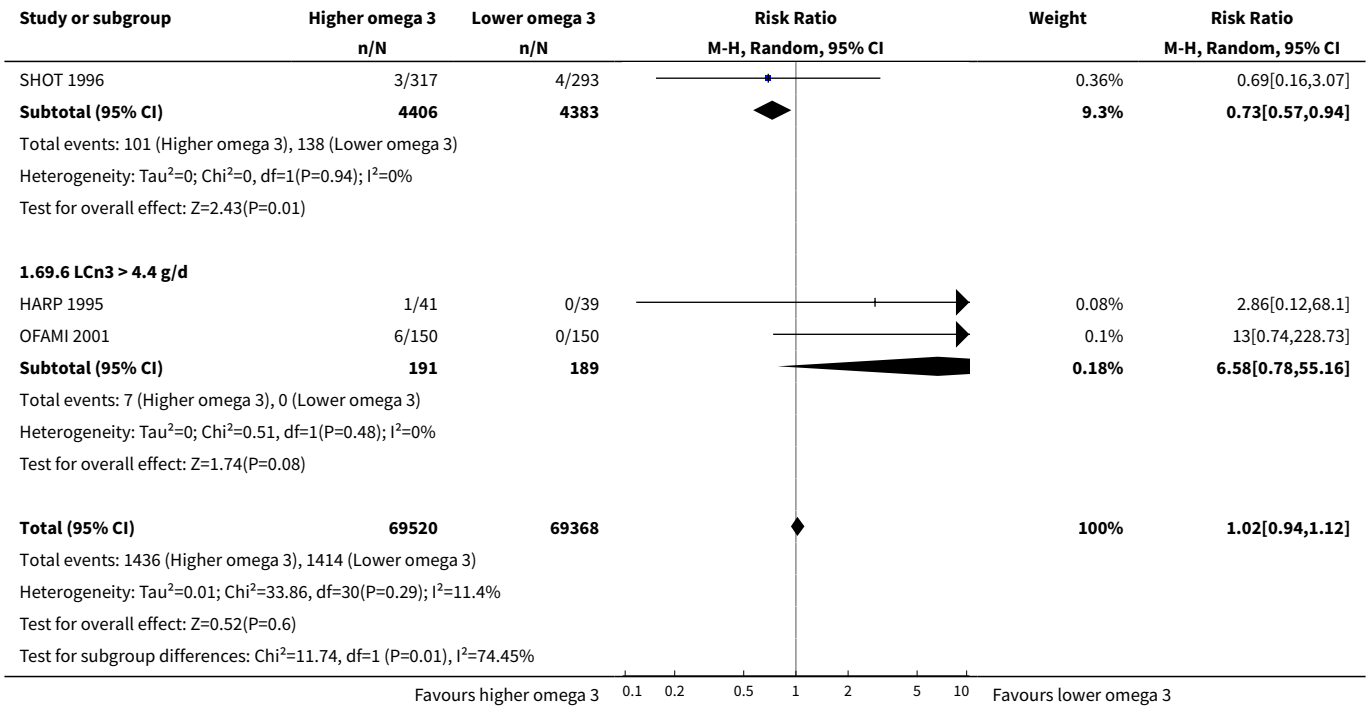
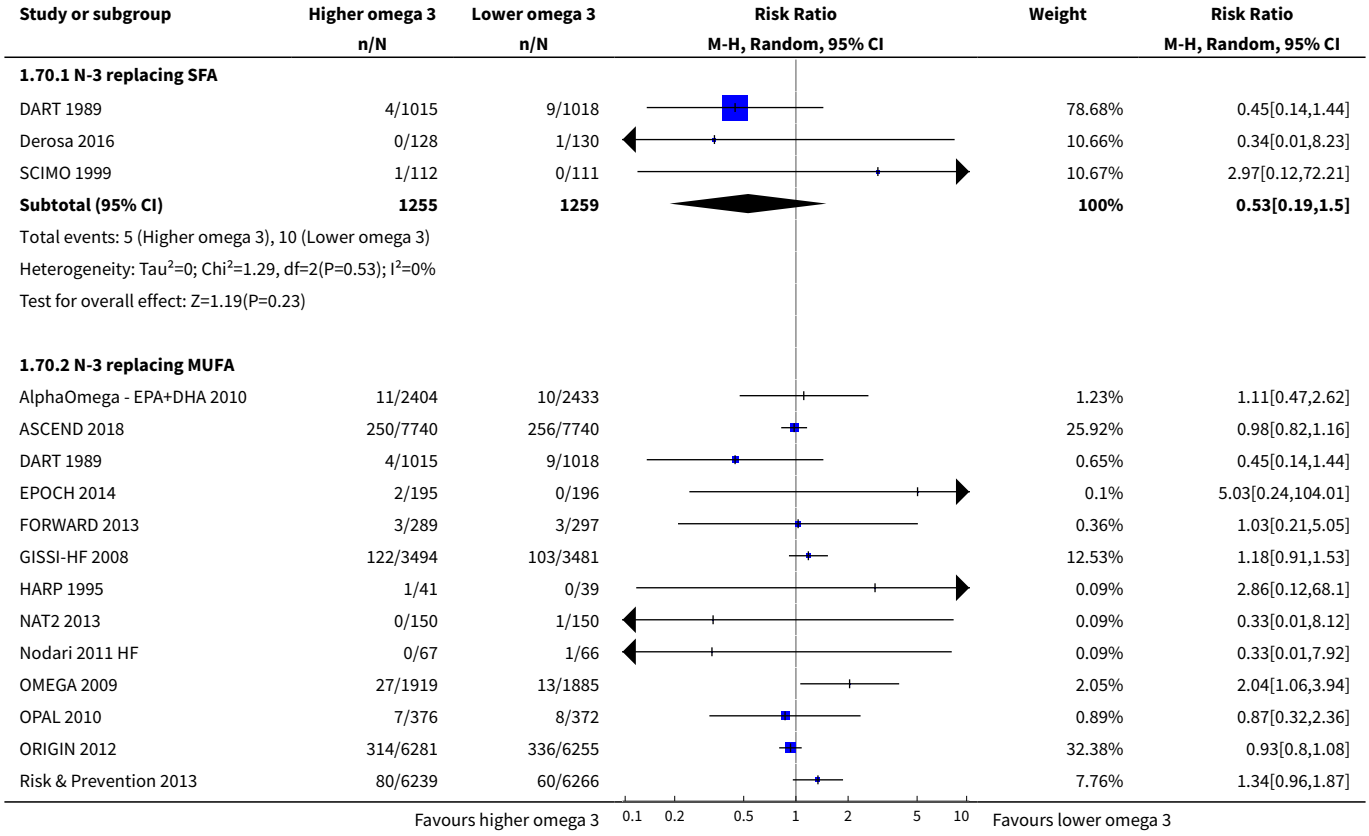


Analysis 1.70. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 70 Stroke - LCn3 - subgroup by replacement.



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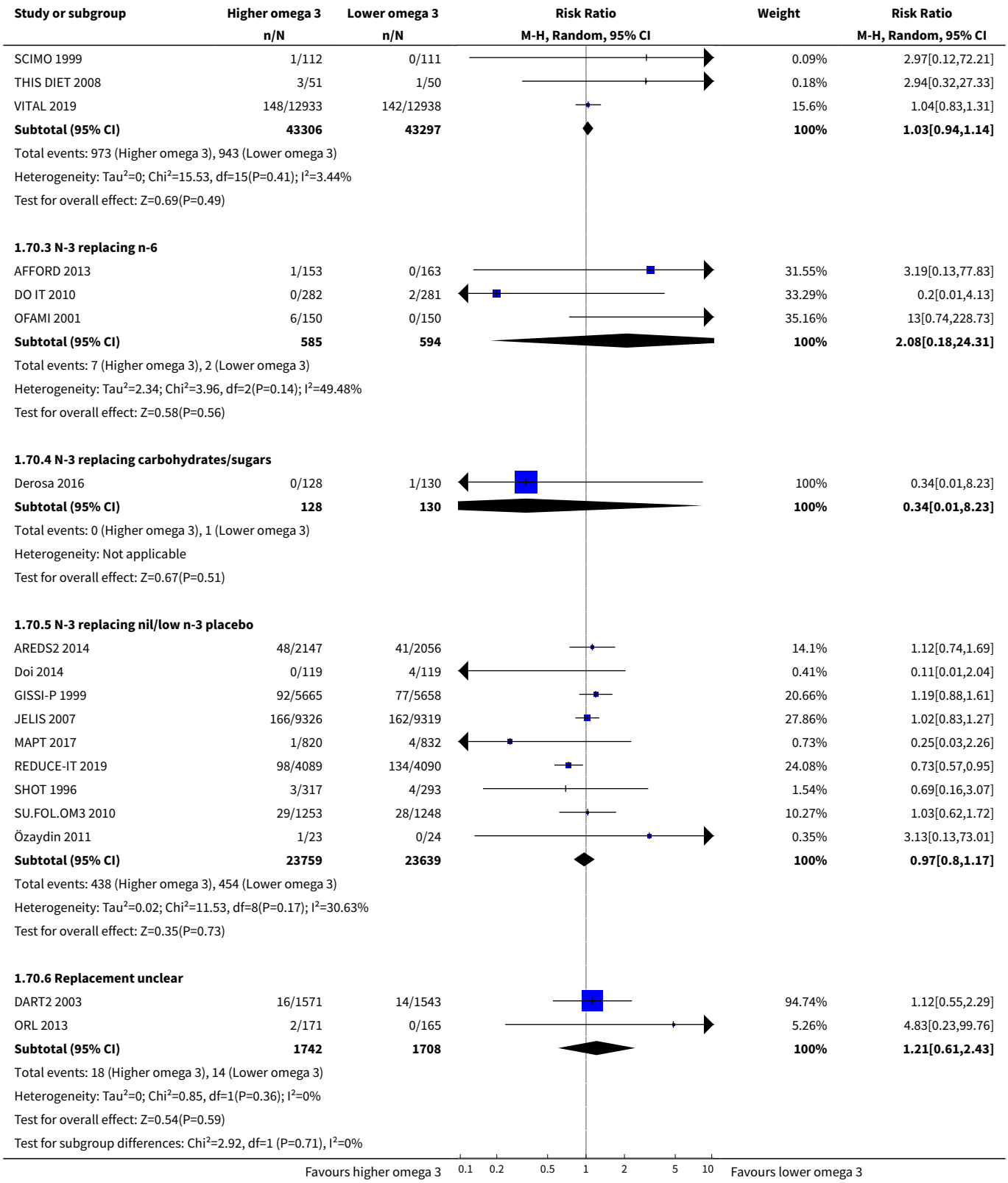

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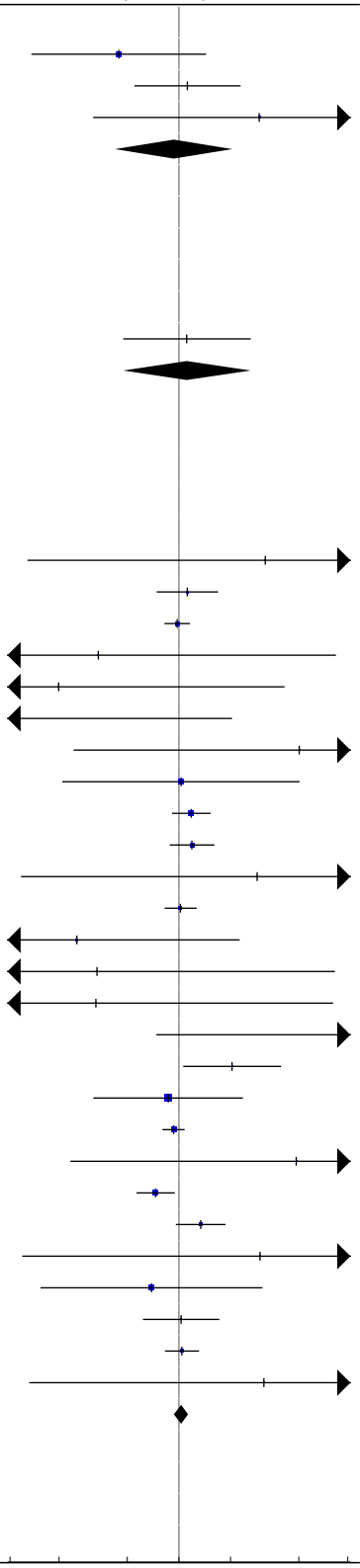
Analysis 1.71. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 71 Stroke - LCn3 - subgroup by intervention type.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.71.1 Dietary advice					
DART 1989	4/1015	9/1018		0.57%	0.45[0.14,1.44]
DART2 2003	16/1571	14/1543		1.5%	1.12[0.55,2.29]
THIS DIET 2008	3/51	1/50		0.16%	2.94[0.32,27.33]
Subtotal (95% CI)	**2637**	**2611**		**2.23%**	**0.93[0.42,2.05]**
Total events: 23 (Higher omega 3), 24 (Lower omega 3)					
Heterogeneity: Tau^2=0.15; Chi^2=2.79, df=2(P=0.25); I^2=28.36%					
Test for overall effect: Z=0.17(P=0.86)					
1.71.2 Supplemental foods					
AlphaOmega - EPA+DHA 2010	11/2404	10/2433		1.06%	1.11[0.47,2.62]
Subtotal (95% CI)	**2404**	**2433**		**1.06%**	**1.11[0.47,2.62]**
Total events: 11 (Higher omega 3), 10 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.25(P=0.81)					
1.71.3 Supplements (capsule)					
AFFORD 2013	1/153	0/163		0.08%	3.19[0.13,77.83]
AREDS2 2014	48/2147	41/2056		4.13%	1.12[0.74,1.69]
ASCEND 2018	250/7740	256/7740		15.13%	0.98[0.82,1.16]
Derosa 2016	0/128	1/130		0.08%	0.34[0.01,8.23]
DO IT 2010	0/282	2/281		0.09%	0.2[0.01,4.13]
Doi 2014	0/119	4/119		0.09%	0.11[0.01,2.04]
EPOCH 2014	2/195	0/196		0.09%	5.03[0.24,104.01]
FORWARD 2013	3/289	3/297		0.31%	1.03[0.21,5.05]
GISSI-HF 2008	122/3494	103/3481		8.88%	1.18[0.91,1.53]
GISSI-P 1999	92/5665	77/5658		7.03%	1.19[0.88,1.61]
HARP 1995	1/41	0/39		0.08%	2.86[0.12,68.1]
JELIS 2007	166/9326	162/9319		11.51%	1.02[0.83,1.27]
MAPT 2017	1/820	4/832		0.17%	0.25[0.03,2.26]
NAT2 2013	0/150	1/150		0.08%	0.33[0.01,8.12]
Nodari 2011 HF	0/67	1/66		0.08%	0.33[0.01,7.92]
OFAMI 2001	6/150	0/150		0.1%	13[0.74,228.73]
OMEGA 2009	27/1919	13/1885		1.75%	2.04[1.06,3.94]
OPAL 2010	7/376	8/372		0.78%	0.87[0.32,2.36]
ORIGIN 2012	314/6281	336/6255		17.42%	0.93[0.8,1.08]
ORL 2013	2/171	0/165		0.09%	4.83[0.23,99.76]
REDUCE-IT 2019	98/4089	134/4090		8.94%	0.73[0.57,0.95]
Risk & Prevention 2013	80/6239	60/6266		5.96%	1.34[0.96,1.87]
SCIMO 1999	1/112	0/111		0.08%	2.97[0.12,72.21]
SHOT 1996	3/317	4/293		0.36%	0.69[0.16,3.07]
SU.FOL.OM3 2010	29/1253	28/1248		2.79%	1.03[0.62,1.72]
VITAL 2019	148/12933	142/12938		10.54%	1.04[0.83,1.31]
Özaydin 2011	1/23	0/24		0.08%	3.13[0.13,73.01]
Subtotal (95% CI)	**64479**	**64324**		**96.71%**	**1.03[0.93,1.13]**
Total events: 1402 (Higher omega 3), 1380 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=30.98, df=26(P=0.23); I^2=16.08%					
Test for overall effect: Z=0.57(P=0.57)					



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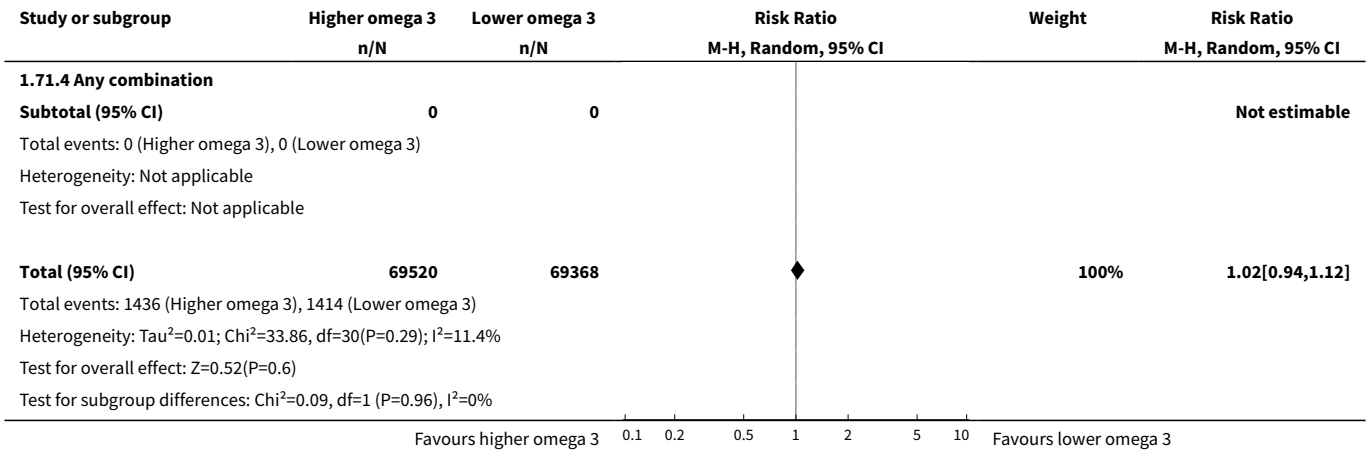
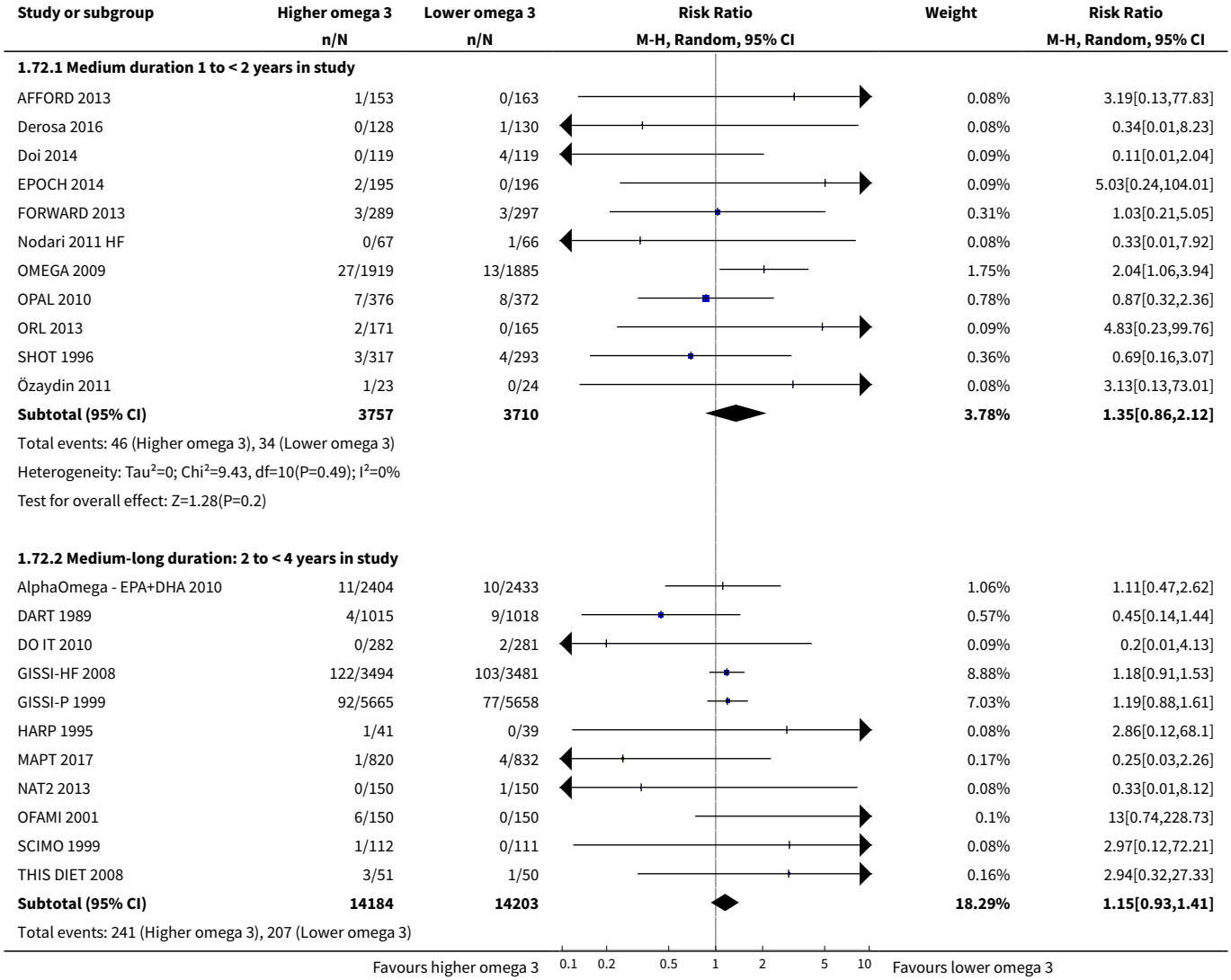


Analysis 1.72. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 72 Stroke - LCn3 - subgroup by duration.



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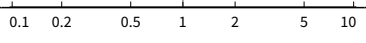
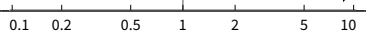
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0.01; Chi²=10.38, df=10(P=0.41); I²=3.7%					
Test for overall effect: Z=1.29(P=0.2)					
1.72.3 Long duration: ≥ 4 years in study					
AREDS2 2014	48/2147	41/2056		4.13%	1.12[0.74,1.69]
ASCEND 2018	250/7740	256/7740		15.13%	0.98[0.82,1.16]
DART2 2003	16/1571	14/1543		1.5%	1.12[0.55,2.29]
JELIS 2007	166/9326	162/9319		11.51%	1.02[0.83,1.27]
ORIGIN 2012	314/6281	336/6255		17.42%	0.93[0.8,1.08]
REDUCE-IT 2019	98/4089	134/4090		8.94%	0.73[0.57,0.95]
Risk & Prevention 2013	80/6239	60/6266		5.96%	1.34[0.96,1.87]
SU.FOL.OM3 2010	29/1253	28/1248		2.79%	1.03[0.62,1.72]
VITAL 2019	148/12933	142/12938		10.54%	1.04[0.83,1.31]
Subtotal (95% CI)	**51579**	**51455**		**77.93%**	**0.98[0.89,1.08]**
Total events: 1149 (Higher omega 3), 1173 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=9.83, df=8(P=0.28); I²=18.64%					
Test for overall effect: Z=0.38(P=0.7)					
Total (95% CI)	**69520**	**69368**		**100%**	**1.02[0.94,1.12]**
Total events: 1436 (Higher omega 3), 1414 (Lower omega 3)					
Heterogeneity: Tau²=0.01; Chi²=33.86, df=30(P=0.29); I²=11.4%					
Test for overall effect: Z=0.52(P=0.6)					
Test for subgroup differences: Chi²=3.29, df=1 (P=0.19), I²=39.18%					



Favours higher omega 3 — Favours lower omega 3

Analysis 1.73. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 73 Stroke - LCn3 - subgroup by primary or secondary prevention.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.73.1 Primary prevention of CVD					
AREDS2 2014	48/2147	41/2056		4.13%	1.12[0.74,1.69]
ASCEND 2018	250/7740	256/7740		15.13%	0.98[0.82,1.16]
Derosa 2016	0/128	1/130		0.08%	0.34[0.01,8.23]
DO IT 2010	0/282	2/281		0.09%	0.2[0.01,4.13]
EPOCH 2014	2/195	0/196		0.09%	5.03[0.24,104.01]
JELIS 2007	166/9326	162/9319		11.51%	1.02[0.83,1.27]
MAPT 2017	1/820	4/832		0.17%	0.25[0.03,2.26]
OPAL 2010	7/376	8/372		0.78%	0.87[0.32,2.36]
ORIGIN 2012	314/6281	336/6255		17.42%	0.93[0.8,1.08]
ORL 2013	2/171	0/165		0.09%	4.83[0.23,99.76]
VITAL 2019	148/12933	142/12938		10.54%	1.04[0.83,1.31]
Subtotal (95% CI)	**40399**	**40284**		**60.02%**	**0.98[0.9,1.07]**
Total events: 938 (Higher omega 3), 952 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=6.5, df=10(P=0.77); I²=0%					
Test for overall effect: Z=0.42(P=0.68)					
1.73.2 Secondary prevention of CVD					
AFFORD 2013	1/153	0/163		0.08%	3.19[0.13,77.83]



Favours higher omega 3 — Favours lower omega 3

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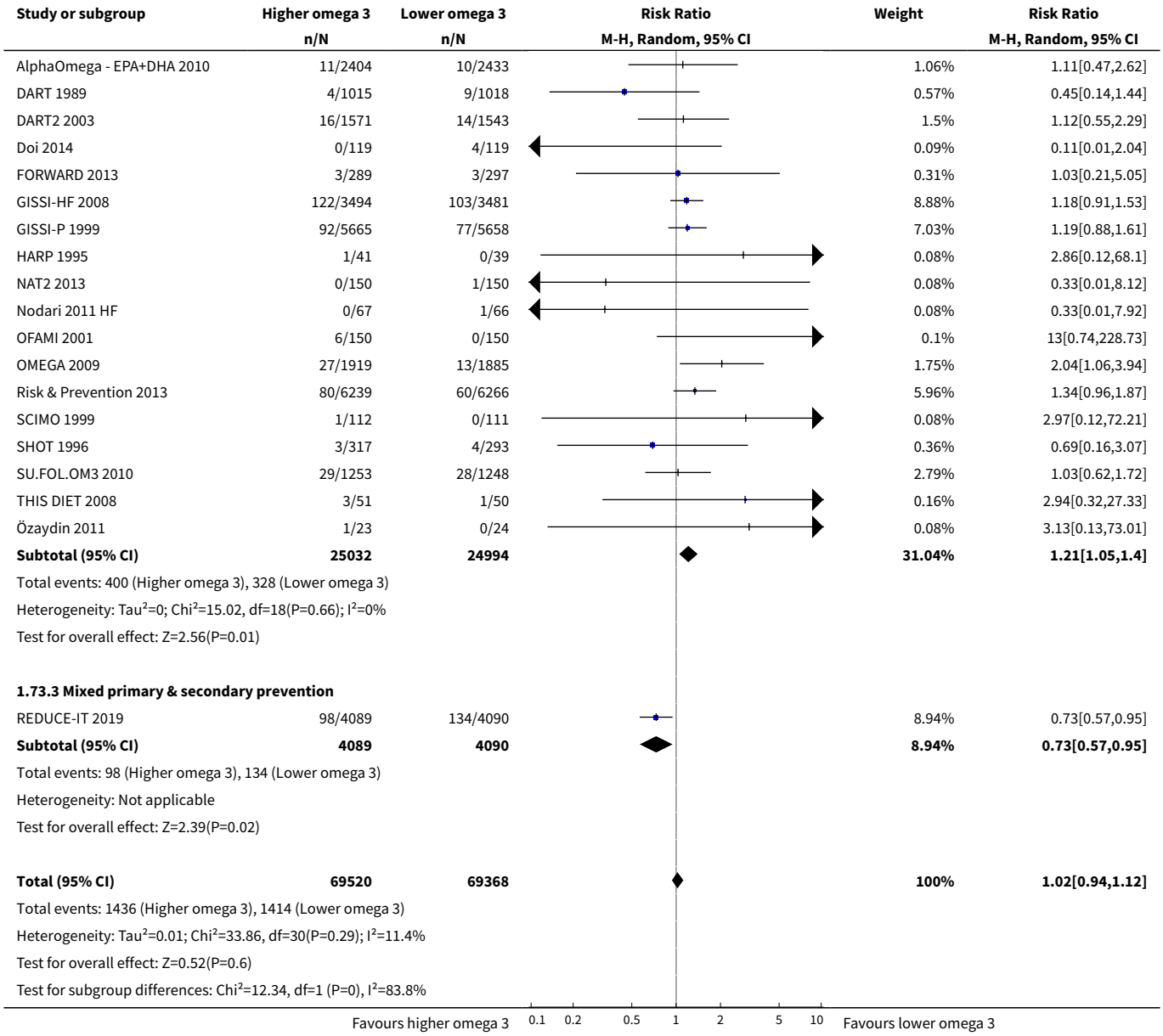
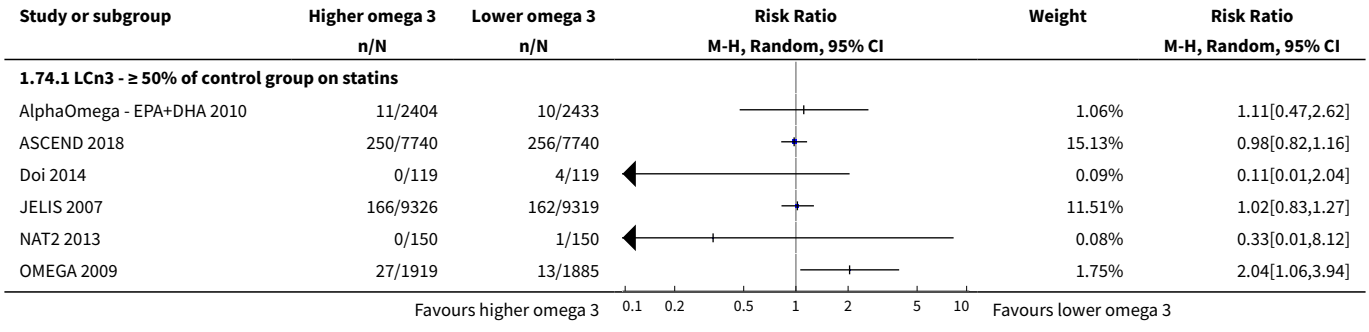


Analysis 1.74. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 74 Stroke - LCn3 - subgroup by statin use.



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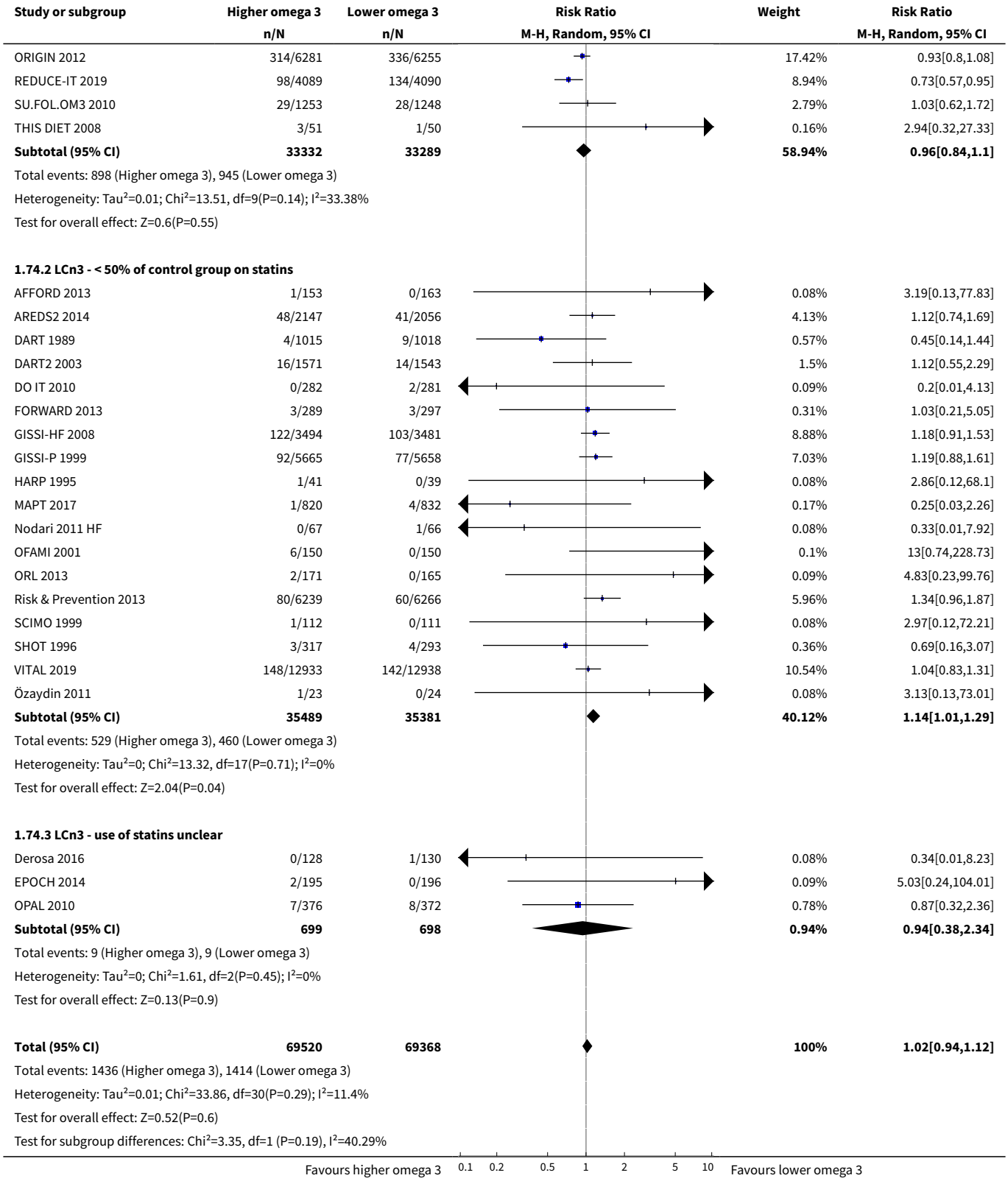

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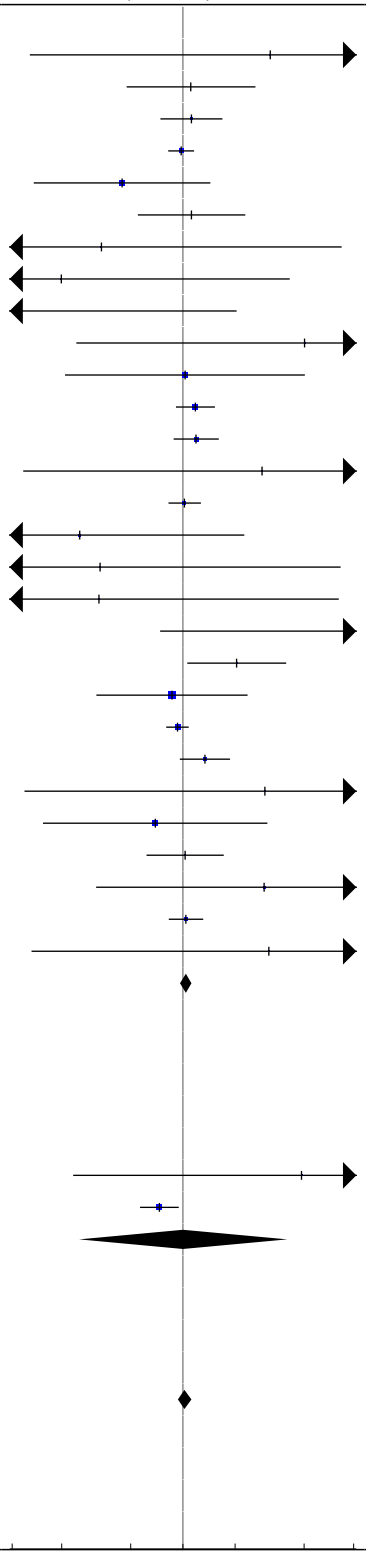
Analysis 1.75. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 75 Stroke - LCn3 - subgroup by baseline TG.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.75.1 Baseline TG not restricted					
AFFORD 2013	1/153	0/163		0.08%	3.19[0.13,77.83]
AlphaOmega - EPA+DHA 2010	11/2404	10/2433		1.06%	1.11[0.47,2.62]
AREDS2 2014	48/2147	41/2056		4.13%	1.12[0.74,1.69]
ASCEND 2018	250/7740	256/7740		15.13%	0.98[0.82,1.16]
DART 1989	4/1015	9/1018		0.57%	0.45[0.14,1.44]
DART2 2003	16/1571	14/1543		1.5%	1.12[0.55,2.29]
Derosa 2016	0/128	1/130		0.08%	0.34[0.01,8.23]
DO IT 2010	0/282	2/281		0.09%	0.2[0.01,4.13]
Doi 2014	0/119	4/119		0.09%	0.11[0.01,2.04]
EPOCH 2014	2/195	0/196		0.09%	5.03[0.24,104.01]
FORWARD 2013	3/289	3/297		0.31%	1.03[0.21,5.05]
GISSI-HF 2008	122/3494	103/3481		8.88%	1.18[0.91,1.53]
GISSI-P 1999	92/5665	77/5658		7.03%	1.19[0.88,1.61]
HARP 1995	1/41	0/39		0.08%	2.86[0.12,68.1]
JELIS 2007	166/9326	162/9319		11.51%	1.02[0.83,1.27]
MAPT 2017	1/820	4/832		0.17%	0.25[0.03,2.26]
NAT2 2013	0/150	1/150		0.08%	0.33[0.01,8.12]
Nodari 2011 HF	0/67	1/66		0.08%	0.33[0.01,7.92]
OFAMI 2001	6/150	0/150		0.1%	13[0.74,228.73]
OMEGA 2009	27/1919	13/1885		1.75%	2.04[1.06,3.94]
OPAL 2010	7/376	8/372		0.78%	0.87[0.32,2.36]
ORIGIN 2012	314/6281	336/6255		17.42%	0.93[0.8,1.08]
Risk & Prevention 2013	80/6239	60/6266		5.96%	1.34[0.96,1.87]
SCIMO 1999	1/112	0/111		0.08%	2.97[0.12,72.21]
SHOT 1996	3/317	4/293		0.36%	0.69[0.16,3.07]
SU.FOL.OM3 2010	29/1253	28/1248		2.79%	1.03[0.62,1.72]
THIS DIET 2008	3/51	1/50		0.16%	2.94[0.32,27.33]
VITAL 2019	148/12933	142/12938		10.54%	1.04[0.83,1.31]
Özaydin 2011	1/23	0/24		0.08%	3.13[0.13,73.01]
Subtotal (95% CI)	**65260**	**65113**		**90.97%**	**1.04[0.96,1.12]**
Total events: 1336 (Higher omega 3), 1280 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=26.3, df=28(P=0.56); I^2=0%					
Test for overall effect: Z=0.95(P=0.34)					
1.75.2 Baseline TG raised					
ORL 2013	2/171	0/165		0.09%	4.83[0.23,99.76]
REDUCE-IT 2019	98/4089	134/4090		8.94%	0.73[0.57,0.95]
Subtotal (95% CI)	**4260**	**4255**		**9.03%**	**1[0.25,4]**
Total events: 100 (Higher omega 3), 134 (Lower omega 3)					
Heterogeneity: Tau^2=0.58; Chi^2=1.48, df=1(P=0.22); I^2=32.57%					
Test for overall effect: Z=0.01(P=1)					
Total (95% CI)	**69520**	**69368**		**100%**	**1.02[0.94,1.12]**
Total events: 1436 (Higher omega 3), 1414 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=33.86, df=30(P=0.29); I^2=11.4%					
Test for overall effect: Z=0.52(P=0.6)					
Test for subgroup differences: Chi^2=0, df=1 (P=0.96), I^2=0%					



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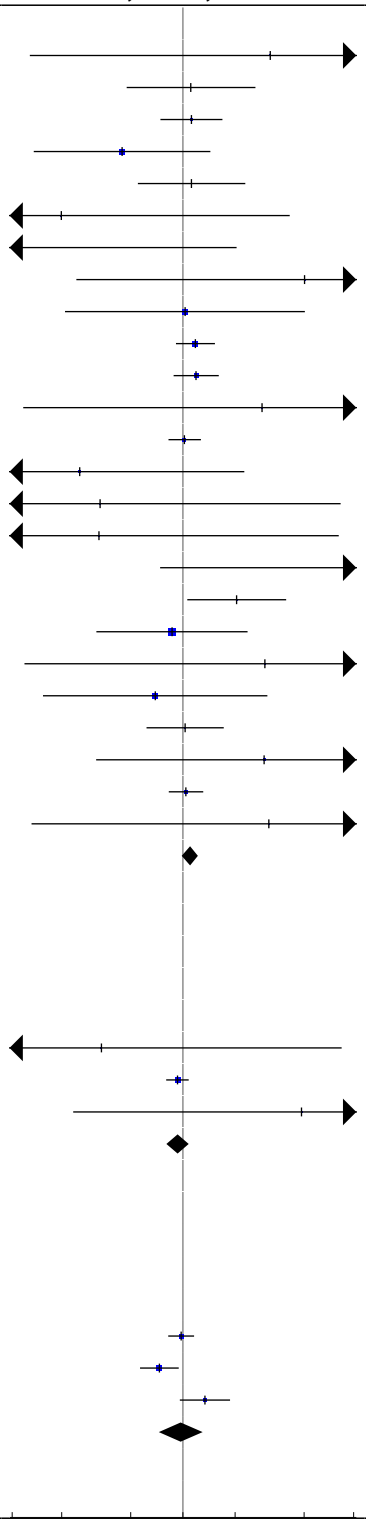
Analysis 1.76. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 76 Stroke - LCn3 - subgroup by baseline DM.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.76.1 Normal diabetes risk					
AFFORD 2013	1/153	0/163		0.08%	3.19[0.13,77.83]
AlphaOmega - EPA+DHA 2010	11/2404	10/2433		1.06%	1.11[0.47,2.62]
AREDS2 2014	48/2147	41/2056		4.13%	1.12[0.74,1.69]
DART 1989	4/1015	9/1018		0.57%	0.45[0.14,1.44]
DART2 2003	16/1571	14/1543		1.5%	1.12[0.55,2.29]
DO IT 2010	0/282	2/281		0.09%	0.2[0.01,4.13]
Doi 2014	0/119	4/119		0.09%	0.11[0.01,2.04]
EPOCH 2014	2/195	0/196		0.09%	5.03[0.24,104.01]
FORWARD 2013	3/289	3/297		0.31%	1.03[0.21,5.05]
GISSI-HF 2008	122/3494	103/3481		8.88%	1.18[0.91,1.53]
GISSI-P 1999	92/5665	77/5658		7.03%	1.19[0.88,1.61]
HARP 1995	1/41	0/39		0.08%	2.86[0.12,68.1]
JELIS 2007	166/9326	162/9319		11.51%	1.02[0.83,1.27]
MAPT 2017	1/820	4/832		0.17%	0.25[0.03,2.26]
NAT2 2013	0/150	1/150		0.08%	0.33[0.01,8.12]
Nodari 2011 HF	0/67	1/66		0.08%	0.33[0.01,7.92]
OFAMI 2001	6/150	0/150		0.1%	13[0.74,228.73]
OMEGA 2009	27/1919	13/1885		1.75%	2.04[1.06,3.94]
OPAL 2010	7/376	8/372		0.78%	0.87[0.32,2.36]
SCIMO 1999	1/112	0/111		0.08%	2.97[0.12,72.21]
SHOT 1996	3/317	4/293		0.36%	0.69[0.16,3.07]
SU.FOL.OM3 2010	29/1253	28/1248		2.79%	1.03[0.62,1.72]
THIS DIET 2008	3/51	1/50		0.16%	2.94[0.32,27.33]
VITAL 2019	148/12933	142/12938		10.54%	1.04[0.83,1.31]
Özaydin 2011	1/23	0/24		0.08%	3.13[0.13,73.01]
Subtotal (95% CI)	**44872**	**44722**		**52.38%**	**1.1[0.98,1.22]**
Total events: 692 (Higher omega 3), 627 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=20.07, df=24(P=0.69); I^2=0%					
Test for overall effect: Z=1.66(P=0.1)					
1.76.2 Diabetes risk factors at baseline					
Derosa 2016	0/128	1/130		0.08%	0.34[0.01,8.23]
ORIGIN 2012	314/6281	336/6255		17.42%	0.93[0.8,1.08]
ORL 2013	2/171	0/165		0.09%	4.83[0.23,99.76]
Subtotal (95% CI)	**6580**	**6550**		**17.58%**	**0.93[0.8,1.08]**
Total events: 316 (Higher omega 3), 337 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=1.52, df=2(P=0.47); I^2=0%					
Test for overall effect: Z=0.92(P=0.36)					
1.76.3 Diabetes at baseline					
ASCEND 2018	250/7740	256/7740		15.13%	0.98[0.82,1.16]
REDUCE-IT 2019	98/4089	134/4090		8.94%	0.73[0.57,0.95]
Risk & Prevention 2013	80/6239	60/6266		5.96%	1.34[0.96,1.87]
Subtotal (95% CI)	**18068**	**18096**		**30.03%**	**0.97[0.73,1.3]**
Total events: 428 (Higher omega 3), 450 (Lower omega 3)					
Heterogeneity: Tau^2=0.05; Chi^2=8.16, df=2(P=0.02); I^2=75.49%					



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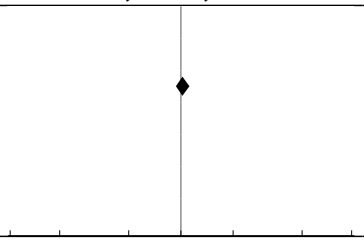
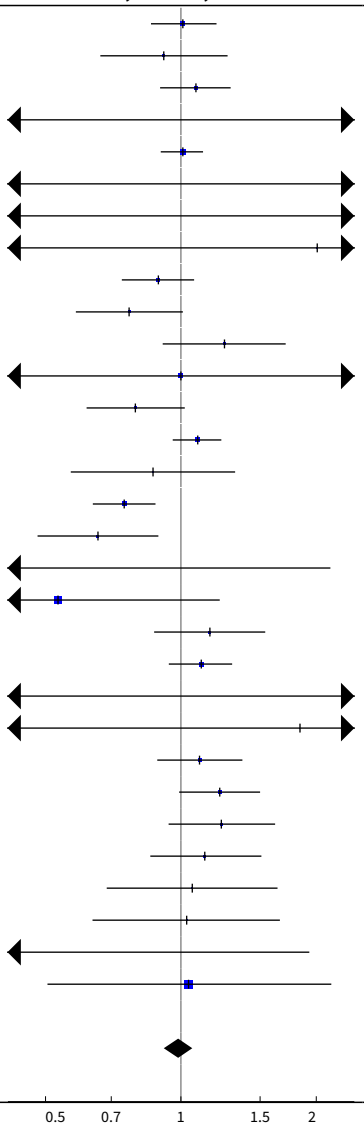
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=0.21(P=0.84)					
Total (95% CI)	**69520**	**69368**		**100%**	**1.02[0.94,1.12]**
Total events: 1436 (Higher omega 3), 1414 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=33.86, df=30(P=0.29); I^2=11.4%					
Test for overall effect: Z=0.52(P=0.6)					
Test for subgroup differences: Chi^2=3.14, df=1 (P=0.21), I^2=36.33%					



Analysis 1.77. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 77 Arrythmia (overall) - LCn3.

Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
AFFORD 2013	98/153	103/163		6.61%	1.01[0.86,1.2]
AlphaOmega - EPA+DHA 2010	67/2404	74/2433		3.38%	0.92[0.66,1.27]
ASCEND 2018	236/7740	219/7740		6.22%	1.08[0.9,1.29]
Derosa 2016	1/128	3/130		0.11%	0.34[0.04,3.21]
DISAF 2003	154/201	157/206		8.23%	1.01[0.9,1.12]
DREAM Asbell 2018	0/349	1/186		0.05%	0.18[0.01,4.35]
EPIC-1 2008	1/188	0/186		0.05%	2.97[0.12,72.4]
EPOCH 2014	2/195	1/196		0.09%	2.01[0.18,21.99]
Erdogan 2007	41/54	46/54		6.08%	0.89[0.74,1.07]
FAAT 2005	60/200	79/202		4.21%	0.77[0.58,1.01]
FORWARD 2013	68/289	56/297		3.54%	1.25[0.91,1.71]
FOSTAR 2016	4/101	4/101		0.28%	1[0.26,3.89]
GISSI-HF 2008	76/278	98/284		4.64%	0.79[0.62,1.02]
GISSI-HF 2008	444/2921	408/2914		7.78%	1.09[0.96,1.23]
GISSI-P 1999	40/2836	46/2828		2.34%	0.87[0.57,1.32]
Kumar 2012	61/91	78/87		6.77%	0.75[0.64,0.88]
Nodari 2011 AF	37/100	56/99		3.62%	0.65[0.48,0.89]
Nodari 2011 HF	1/67	4/66		0.11%	0.25[0.03,2.15]
OFAMI 2001	8/150	15/150		0.73%	0.53[0.23,1.22]
OMEGA 2009	99/1919	84/1885		4.02%	1.16[0.87,1.54]
ORIGIN 2012	288/6281	259/6255		6.68%	1.11[0.94,1.3]
ORL 2013	0/171	1/165		0.05%	0.32[0.01,7.84]
Proudman 2015	1/87	0/53		0.05%	1.84[0.08,44.38]
Raitt 2005	65/100	59/100		5.33%	1.1[0.89,1.37]
REDUCE-IT 2019	188/4089	154/4090		5.54%	1.22[0.99,1.5]
Risk & Prevention 2013	113/6239	92/6266		4.21%	1.23[0.94,1.62]
Sianni 2013	147/268	29/60		4.03%	1.13[0.85,1.51]
SOFA 2006	36/273	34/273		2.2%	1.06[0.68,1.64]
SU.FOL.OM3 2010	33/1253	32/1248		1.9%	1.03[0.64,1.66]
THIS DIET 2008	2/51	5/50		0.21%	0.39[0.08,1.93]
Özaydin 2011	9/23	9/24		0.93%	1.04[0.51,2.16]
Total (95% CI)	**39199**	**38791**		**100%**	**0.99[0.92,1.06]**
Total events: 2380 (Favours higher omega 3), 2206 (Lower omega 3)					



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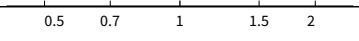
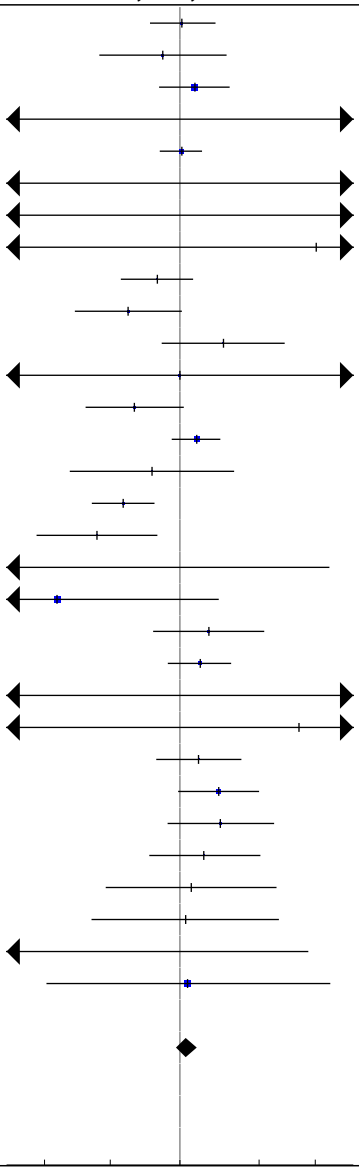
Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0.01; Chi²=53.93, df=30(P=0); I²=44.37%					
Test for overall effect: Z=0.38(P=0.7)					



Favours higher omega 3 — Favours lower omega 3

Analysis 1.78. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 78 Arrythmia - LCn3 - SA fixed effects.

Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
AFFORD 2013	98/153	103/163		4.49%	1.01[0.86,1.2]
AlphaOmega - EPA+DHA 2010	67/2404	74/2433		3.31%	0.92[0.66,1.27]
ASCEND 2018	236/7740	219/7740		9.85%	1.08[0.9,1.29]
Derosa 2016	1/128	3/130		0.13%	0.34[0.04,3.21]
DISAF 2003	154/201	157/206		6.98%	1.01[0.9,1.12]
DREAM Asbell 2018	0/349	1/186		0.09%	0.18[0.01,4.35]
EPIC-1 2008	1/188	0/186		0.02%	2.97[0.12,72.4]
EPOCH 2014	2/195	1/196		0.04%	2.01[0.18,21.99]
Erdogan 2007	41/54	46/54		2.07%	0.89[0.74,1.07]
FAAT 2005	60/200	79/202		3.54%	0.77[0.58,1.01]
FORWARD 2013	68/289	56/297		2.49%	1.25[0.91,1.71]
FOSTAR 2016	4/101	4/101		0.18%	1[0.26,3.89]
GISSI-HF 2008	76/278	98/284		4.36%	0.79[0.62,1.02]
GISSI-HF 2008	444/2921	408/2914		18.38%	1.09[0.96,1.23]
GISSI-P 1999	40/2836	46/2828		2.07%	0.87[0.57,1.32]
Kumar 2012	61/91	78/87		3.59%	0.75[0.64,0.88]
Nodari 2011 AF	37/100	56/99		2.53%	0.65[0.48,0.89]
Nodari 2011 HF	1/67	4/66		0.18%	0.25[0.03,2.15]
OFAMI 2001	8/150	15/150		0.67%	0.53[0.23,1.22]
OMEGA 2009	99/1919	84/1885		3.81%	1.16[0.87,1.54]
ORIGIN 2012	288/6281	259/6255		11.68%	1.11[0.94,1.3]
ORL 2013	0/171	1/165		0.07%	0.32[0.01,7.84]
Proudman 2015	1/87	0/53		0.03%	1.84[0.08,44.38]
Raitt 2005	65/100	59/100		2.65%	1.1[0.89,1.37]
REDUCE-IT 2019	188/4089	154/4090		6.93%	1.22[0.99,1.5]
Risk & Prevention 2013	113/6239	92/6266		4.13%	1.23[0.94,1.62]
Sianni 2013	147/268	29/60		2.13%	1.13[0.85,1.51]
SOFA 2006	36/273	34/273		1.53%	1.06[0.68,1.64]
SU.FOL.OM3 2010	33/1253	32/1248		1.44%	1.03[0.64,1.66]
THIS DIET 2008	2/51	5/50		0.23%	0.39[0.08,1.93]
Özaydin 2011	9/23	9/24		0.4%	1.04[0.51,2.16]
Total (95% CI)	**39199**	**38791**		**100%**	**1.03[0.98,1.09]**
Total events: 2380 (Favours higher omega 3), 2206 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=53.93, df=30(P=0); I²=44.37%					
Test for overall effect: Z=1.18(P=0.24)					



Favours higher omega 3 — Favours lower omega 3

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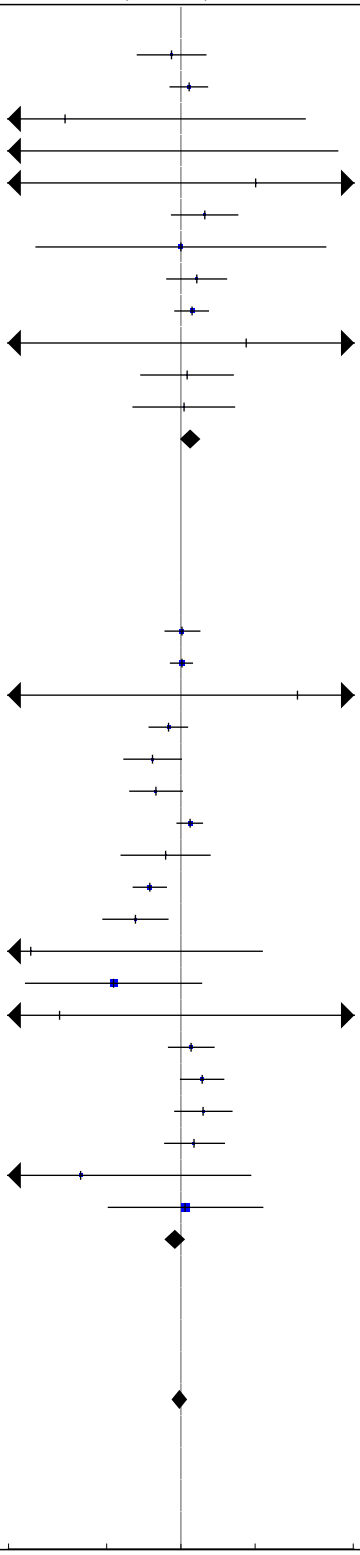
Analysis 1.79. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 79 Arrhythmia- LCn3 - SA by summary risk of bias.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.79.1 Low summary risk of bias					
AlphaOmega - EPA+DHA 2010	67/2404	74/2433		3.38%	0.92[0.66,1.27]
ASCEND 2018	236/7740	219/7740		6.22%	1.08[0.9,1.29]
Derosa 2016	1/128	3/130		0.11%	0.34[0.04,3.21]
DREAM Asbell 2018	0/349	1/186		0.05%	0.18[0.01,4.35]
EPOCH 2014	2/195	1/196		0.09%	2.01[0.18,21.99]
FORWARD 2013	68/289	56/297		3.54%	1.25[0.91,1.71]
FOSTAR 2016	4/101	4/101		0.28%	1[0.26,3.89]
OMEGA 2009	99/1919	84/1885		4.02%	1.16[0.87,1.54]
ORIGIN 2012	288/6281	259/6255		6.68%	1.11[0.94,1.3]
Proudman 2015	1/87	0/53		0.05%	1.84[0.08,44.38]
SOFA 2006	36/273	34/273		2.2%	1.06[0.68,1.64]
SU.FOL.OM3 2010	33/1253	32/1248		1.9%	1.03[0.64,1.66]
Subtotal (95% CI)	**21019**	**20797**		**28.52%**	**1.09[0.99,1.2]**
Total events: 835 (Higher omega 3), 767 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=4.75, df=11(P=0.94); I^2=0%					
Test for overall effect: Z=1.78(P=0.08)					
1.79.2 Moderate to high risk of bias					
AFFORD 2013	98/153	103/163		6.61%	1.01[0.86,1.2]
DISAF 2003	154/201	157/206		8.23%	1.01[0.9,1.12]
EPIC-1 2008	1/188	0/186		0.05%	2.97[0.12,72.4]
Erdogan 2007	41/54	46/54		6.08%	0.89[0.74,1.07]
FAAT 2005	60/200	79/202		4.21%	0.77[0.58,1.01]
GISSI-HF 2008	76/278	98/284		4.64%	0.79[0.62,1.02]
GISSI-HF 2008	444/2921	408/2914		7.78%	1.09[0.96,1.23]
GISSI-P 1999	40/2836	46/2828		2.34%	0.87[0.57,1.32]
Kumar 2012	61/91	78/87		6.77%	0.75[0.64,0.88]
Nodari 2011 AF	37/100	56/99		3.62%	0.65[0.48,0.89]
Nodari 2011 HF	1/67	4/66		0.11%	0.25[0.03,2.15]
OFAMI 2001	8/150	15/150		0.73%	0.53[0.23,1.22]
ORL 2013	0/171	1/165		0.05%	0.32[0.01,7.84]
Raitt 2005	65/100	59/100		5.33%	1.1[0.89,1.37]
REDUCE-IT 2019	188/4089	154/4090		5.54%	1.22[0.99,1.5]
Risk & Prevention 2013	113/6239	92/6266		4.21%	1.23[0.94,1.62]
Sianni 2013	147/268	29/60		4.03%	1.13[0.85,1.51]
THIS DIET 2008	2/51	5/50		0.21%	0.39[0.08,1.93]
Özaydin 2011	9/23	9/24		0.93%	1.04[0.51,2.16]
Subtotal (95% CI)	**18180**	**17994**		**71.48%**	**0.94[0.86,1.04]**
Total events: 1545 (Higher omega 3), 1439 (Lower omega 3)					
Heterogeneity: Tau^2=0.02; Chi^2=44.02, df=18(P=0); I^2=59.11%					
Test for overall effect: Z=1.14(P=0.26)					
Total (95% CI)	**39199**	**38791**		**100%**	**0.99[0.92,1.06]**
Total events: 2380 (Higher omega 3), 2206 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=53.93, df=30(P=0); I^2=44.37%					
Test for overall effect: Z=0.38(P=0.7)					
Test for subgroup differences: Chi^2=4.22, df=1 (P=0.04), I^2=76.28%					



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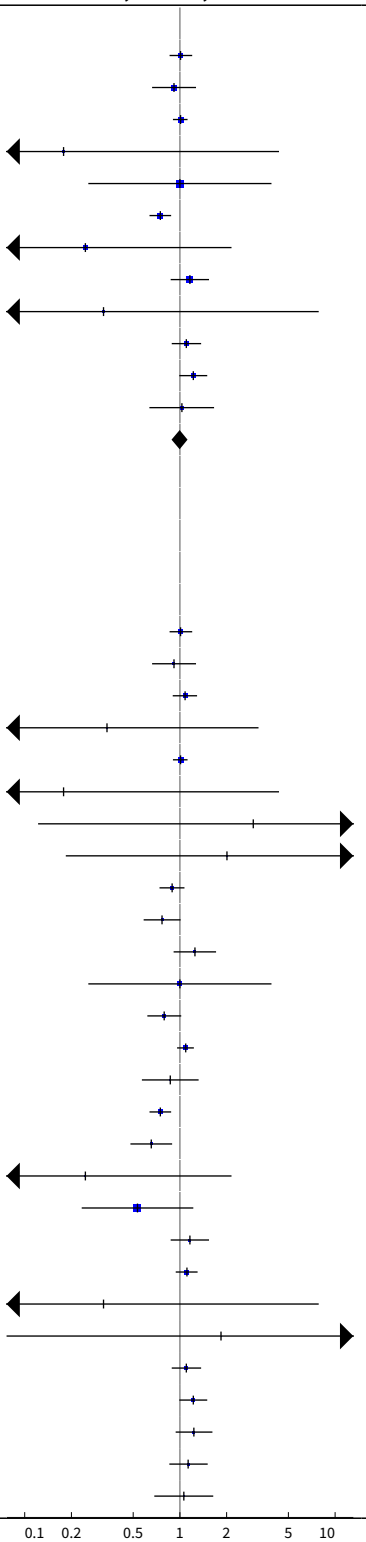
Analysis 1.80. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 80 Arrhythmia- LCn3 - SA by compliance and study size.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.80.1 SA - low risk of compliance bias					
AFFORD 2013	98/153	103/163		15.37%	1.01[0.86,1.2]
AlphaOmega - EPA+DHA 2010	67/2404	74/2433		8.39%	0.92[0.66,1.27]
DISAF 2003	154/201	157/206		18.56%	1.01[0.9,1.12]
DREAM Asbell 2018	0/349	1/186		0.14%	0.18[0.01,4.35]
FOSTAR 2016	4/101	4/101		0.76%	1[0.26,3.89]
Kumar 2012	61/91	78/87		15.7%	0.75[0.64,0.88]
Nodari 2011 HF	1/67	4/66		0.3%	0.25[0.03,2.15]
OMEGA 2009	99/1919	84/1885		9.86%	1.16[0.87,1.54]
ORL 2013	0/171	1/165		0.14%	0.32[0.01,7.84]
Raitt 2005	65/100	59/100		12.73%	1.1[0.89,1.37]
REDUCE-IT 2019	188/4089	154/4090		13.18%	1.22[0.99,1.5]
SU.FOL.OM3 2010	33/1253	32/1248		4.88%	1.03[0.64,1.66]
Subtotal (95% CI)	**10898**	**10730**		**100%**	**1[0.88,1.12]**
Total events: 770 (Higher omega 3), 751 (Lower omega 3)					
Heterogeneity: Tau^2=0.02; Chi^2=23.1, df=11(P=0.02); I^2=52.39%					
Test for overall effect: Z=0.06(P=0.95)					
1.80.2 SA - 100+ randomised					
AFFORD 2013	98/153	103/163		6.63%	1.01[0.86,1.2]
AlphaOmega - EPA+DHA 2010	67/2404	74/2433		3.44%	0.92[0.66,1.27]
ASCEND 2018	236/7740	219/7740		6.26%	1.08[0.9,1.29]
Derosa 2016	1/128	3/130		0.11%	0.34[0.04,3.21]
DISAF 2003	154/201	157/206		8.2%	1.01[0.9,1.12]
DREAM Asbell 2018	0/349	1/186		0.05%	0.18[0.01,4.35]
EPIC-1 2008	1/188	0/186		0.05%	2.97[0.12,72.4]
EPOCH 2014	2/195	1/196		0.1%	2.01[0.18,21.99]
Erdogan 2007	41/54	46/54		6.12%	0.89[0.74,1.07]
FAAT 2005	60/200	79/202		4.27%	0.77[0.58,1.01]
FORWARD 2013	68/289	56/297		3.6%	1.25[0.91,1.71]
FOSTAR 2016	4/101	4/101		0.29%	1[0.26,3.89]
GISSI-HF 2008	76/278	98/284		4.7%	0.79[0.62,1.02]
GISSI-HF 2008	444/2921	408/2914		7.77%	1.09[0.96,1.23]
GISSI-P 1999	40/2836	46/2828		2.4%	0.87[0.57,1.32]
Kumar 2012	61/91	78/87		6.79%	0.75[0.64,0.88]
Nodari 2011 AF	37/100	56/99		3.69%	0.65[0.48,0.89]
Nodari 2011 HF	1/67	4/66		0.12%	0.25[0.03,2.15]
OFAMI 2001	8/150	15/150		0.75%	0.53[0.23,1.22]
OMEGA 2009	99/1919	84/1885		4.08%	1.16[0.87,1.54]
ORIGIN 2012	288/6281	259/6255		6.7%	1.11[0.94,1.3]
ORL 2013	0/171	1/165		0.05%	0.32[0.01,7.84]
Proudman 2015	1/87	0/53		0.05%	1.84[0.08,44.38]
Raitt 2005	65/100	59/100		5.38%	1.1[0.89,1.37]
REDUCE-IT 2019	188/4089	154/4090		5.59%	1.22[0.99,1.5]
Risk & Prevention 2013	113/6239	92/6266		4.27%	1.23[0.94,1.62]
Sianni 2013	147/268	29/60		4.09%	1.13[0.85,1.51]
SOFA 2006	36/273	34/273		2.25%	1.06[0.68,1.64]



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Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
SU.FOL.OM3 2010	33/1253	32/1248		1.95%	1.03[0.64,1.66]
THIS DIET 2008	2/51	5/50		0.22%	0.39[0.08,1.93]
Subtotal (95% CI)	**39176**	**38767**		**100%**	**0.98[0.91,1.06]**
Total events: 2371 (Higher omega 3), 2197 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=53.92, df=29(P=0); I^2=46.22%					
Test for overall effect: Z=0.4(P=0.69)					
Test for subgroup differences: Chi^2=0.02, df=1 (P=0.88), I^2=0%					

Analysis 1.81. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 81 Arrhythmia - LCn3 - subgroup by new or recurrent.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.81.1 New arrhythmia					
AlphaOmega - EPA+DHA 2010	67/2404	74/2433		4.62%	0.92[0.66,1.27]
ASCEND 2018	236/7740	219/7740		14.93%	1.08[0.9,1.29]
Derosa 2016	1/128	3/130		0.1%	0.34[0.04,3.21]
DREAM Asbell 2018	0/349	1/186		0.05%	0.18[0.01,4.35]
EPIC-1 2008	1/188	0/186		0.05%	2.97[0.12,72.4]
EPOCH 2014	2/195	1/196		0.09%	2.01[0.18,21.99]
FOSTAR 2016	4/101	4/101		0.27%	1[0.26,3.89]
GISSI-HF 2008	444/2921	408/2914		31.76%	1.09[0.96,1.23]
GISSI-P 1999	40/2836	46/2828		2.77%	0.87[0.57,1.32]
Nodari 2011 HF	1/67	4/66		0.1%	0.25[0.03,2.15]
OFAMI 2001	8/150	15/150		0.72%	0.53[0.23,1.22]
OMEGA 2009	99/1919	84/1885		6.09%	1.16[0.87,1.54]
ORIGIN 2012	288/6281	259/6255		18.19%	1.11[0.94,1.3]
ORL 2013	0/171	1/165		0.05%	0.32[0.01,7.84]
Proudman 2015	1/87	0/53		0.05%	1.84[0.08,44.38]
REDUCE-IT 2019	188/4089	154/4090		11.27%	1.22[0.99,1.5]
Risk & Prevention 2013	113/6239	92/6266		6.58%	1.23[0.94,1.62]
SU.FOL.OM3 2010	33/1253	32/1248		2.13%	1.03[0.64,1.66]
THIS DIET 2008	2/51	5/50		0.19%	0.39[0.08,1.93]
Subtotal (95% CI)	**37169**	**36942**		**100%**	**1.09[1.01,1.17]**
Total events: 1528 (Higher omega 3), 1402 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=14.29, df=18(P=0.71); I^2=0%					
Test for overall effect: Z=2.38(P=0.02)					
1.81.2 Recurrent arrhythmia					
AFFORD 2013	98/153	103/163		11.11%	1.01[0.86,1.2]
DISAF 2003	154/201	157/206		13.53%	1.01[0.9,1.12]
Erdogan 2007	41/54	46/54		10.3%	0.89[0.74,1.07]
FAAT 2005	60/200	79/202		7.33%	0.77[0.58,1.01]
FORWARD 2013	68/289	56/297		6.22%	1.25[0.91,1.71]
GISSI-HF 2008	76/278	98/284		8.03%	0.79[0.62,1.02]
Kumar 2012	61/91	78/87		11.36%	0.75[0.64,0.88]
Nodari 2011 AF	37/100	56/99		6.36%	0.65[0.48,0.89]
Raitt 2005	65/100	59/100		9.13%	1.1[0.89,1.37]

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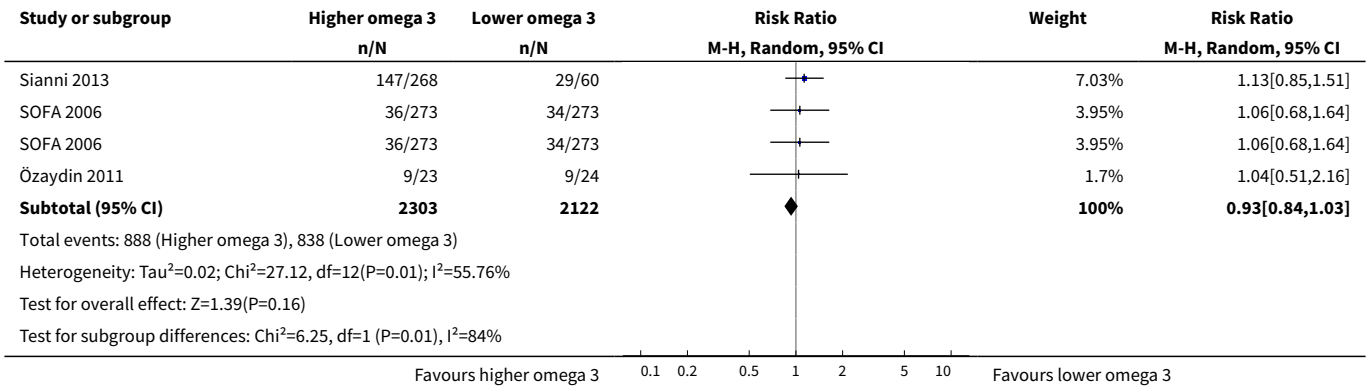
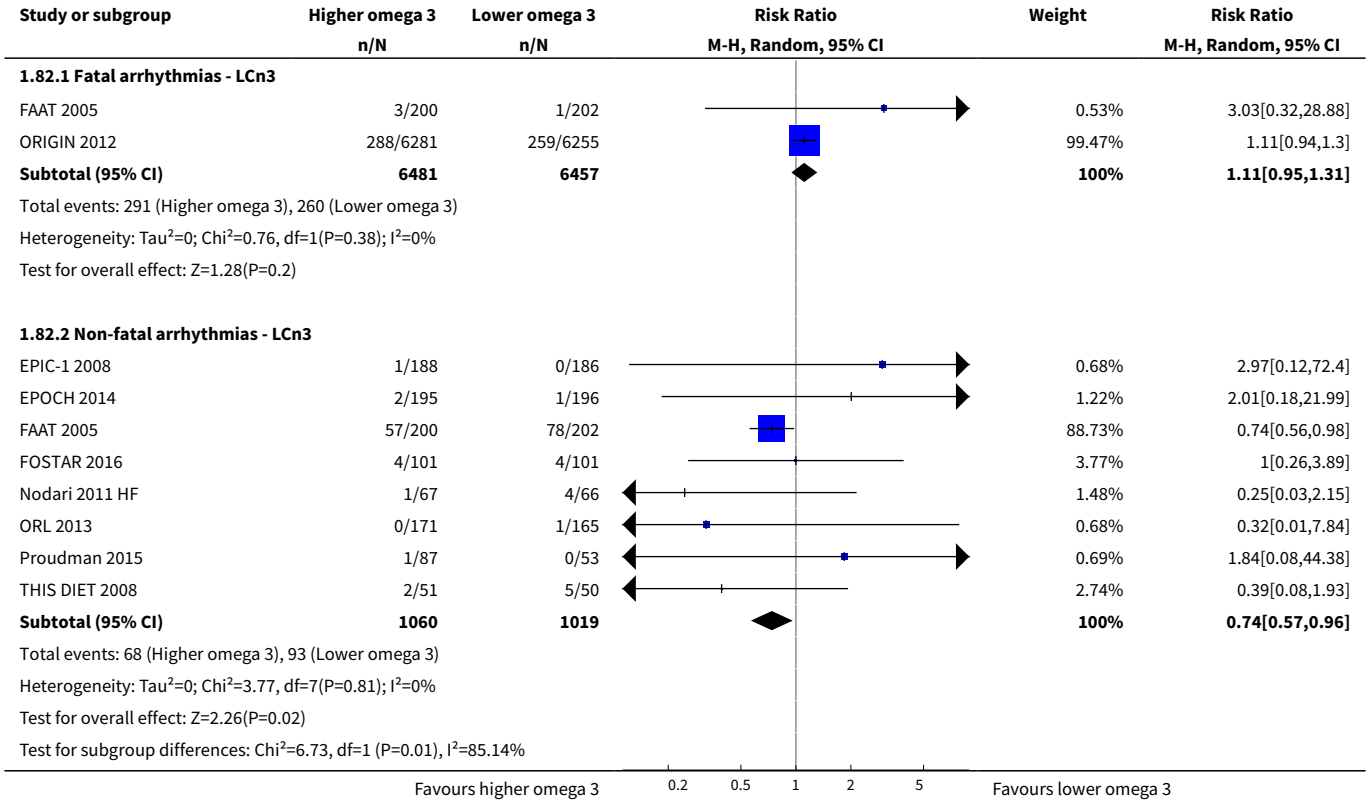
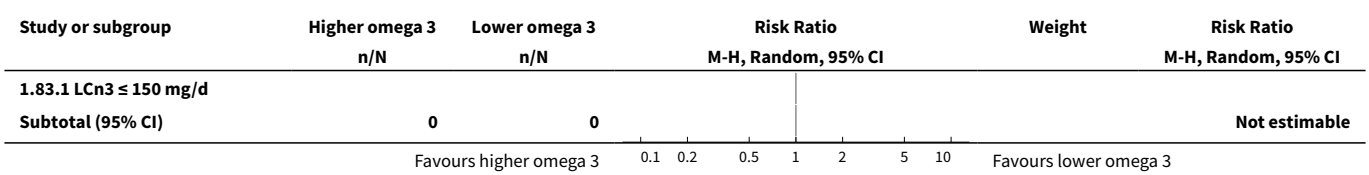


Analysis 1.82. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 82 Arrhythmia - LCn3 - subgroup by fatality.



Analysis 1.83. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 83 Arrhythmia - LCn3 - subgroup by dose.



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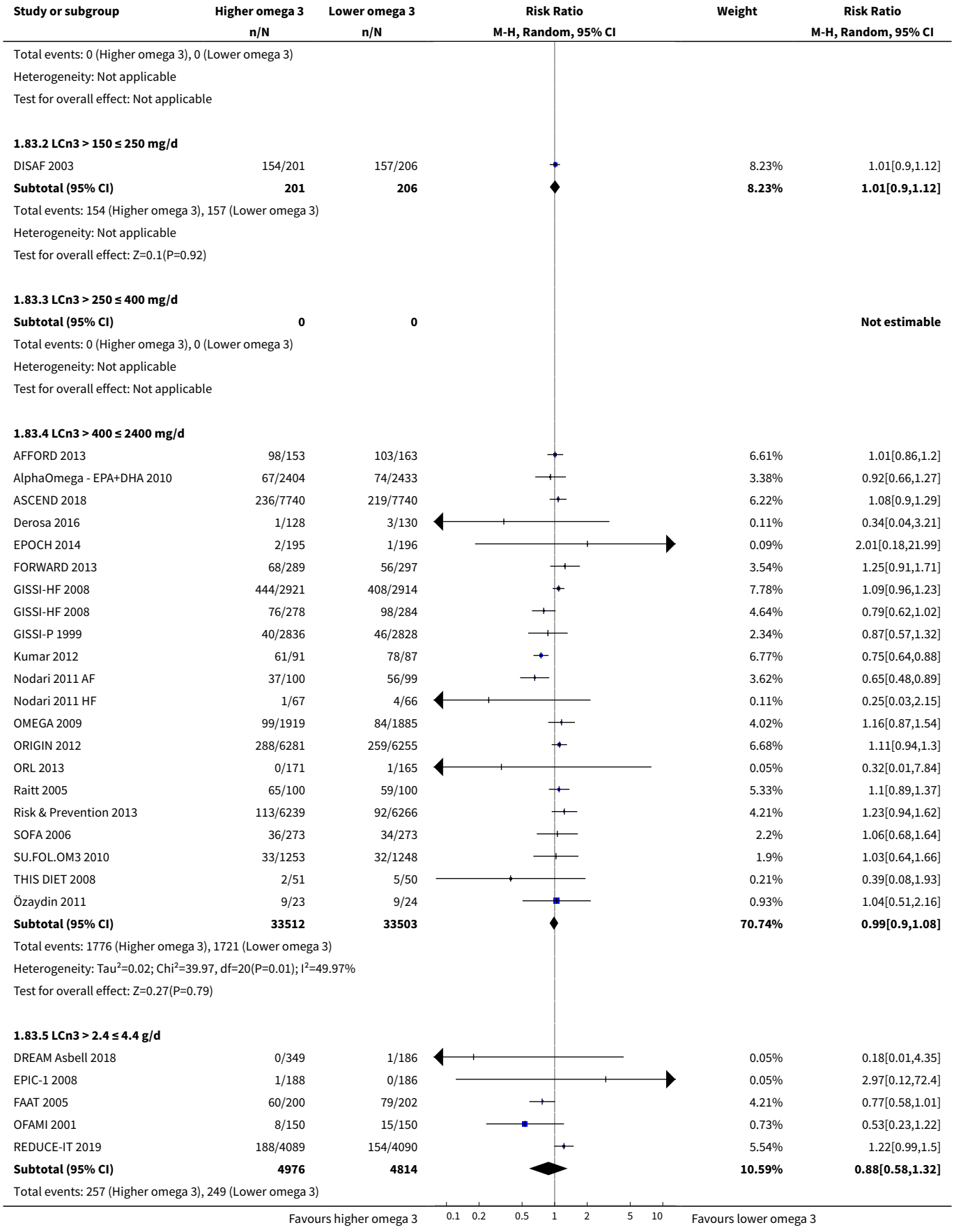

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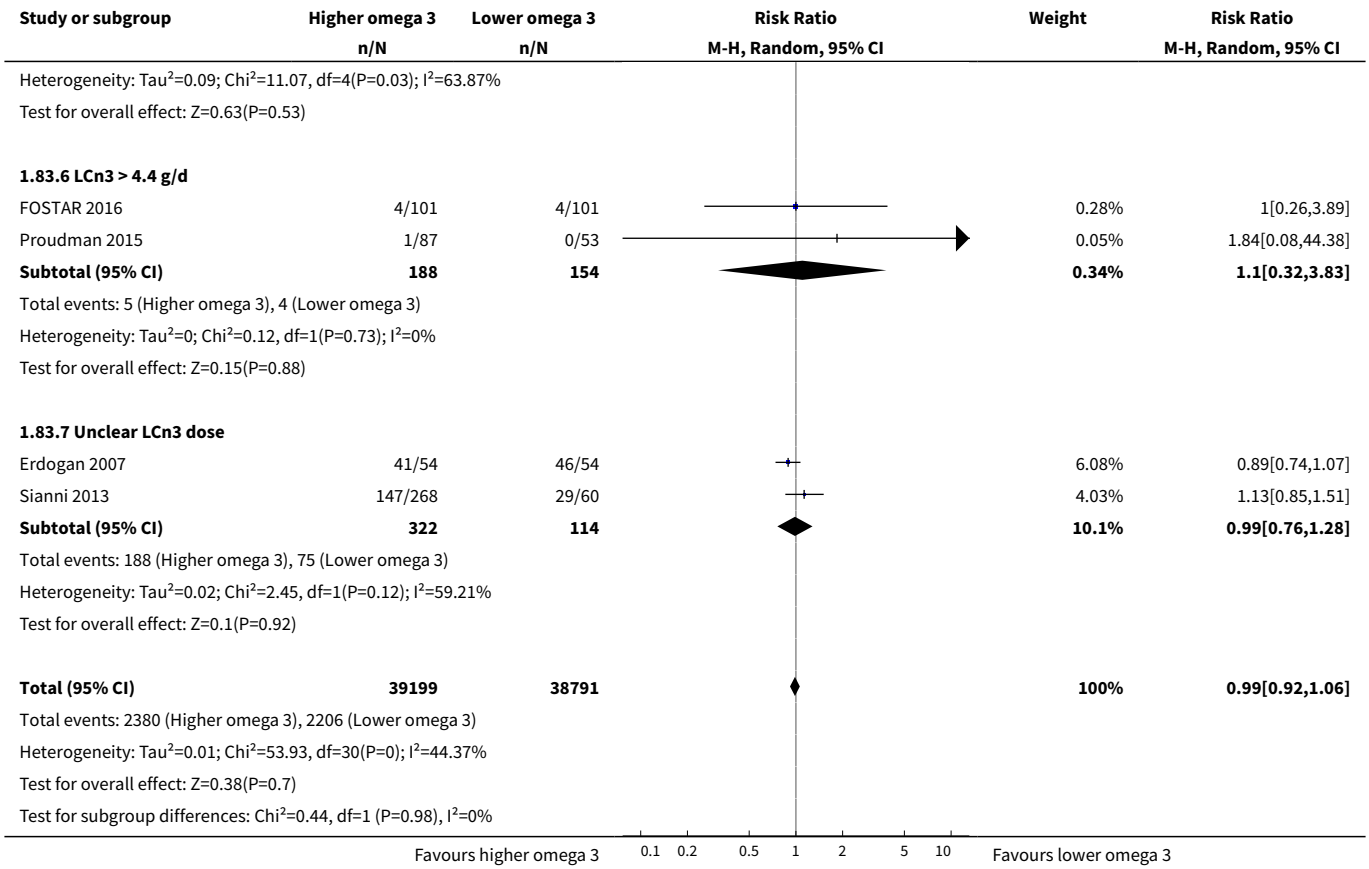
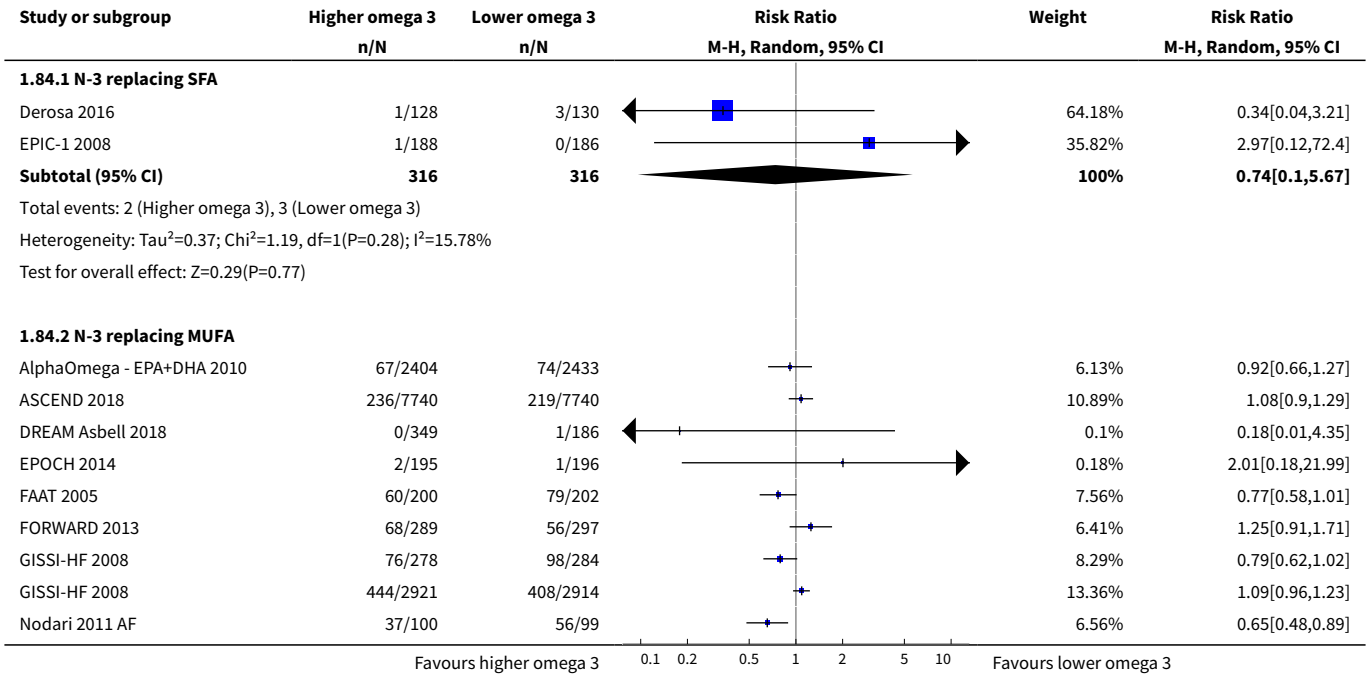


Analysis 1.84. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 84 Arrhythmia - LCn3 - subgroup by replacement.



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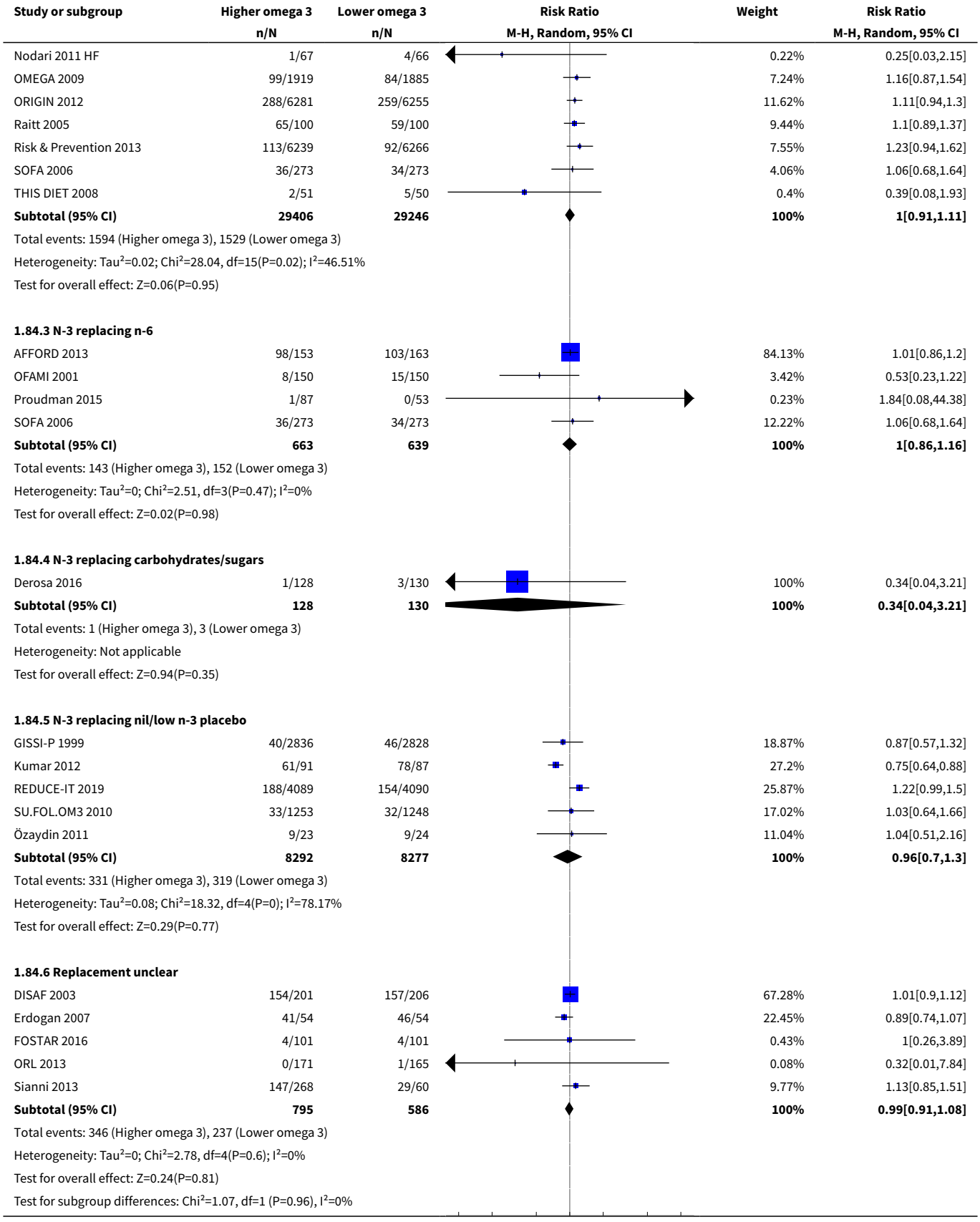

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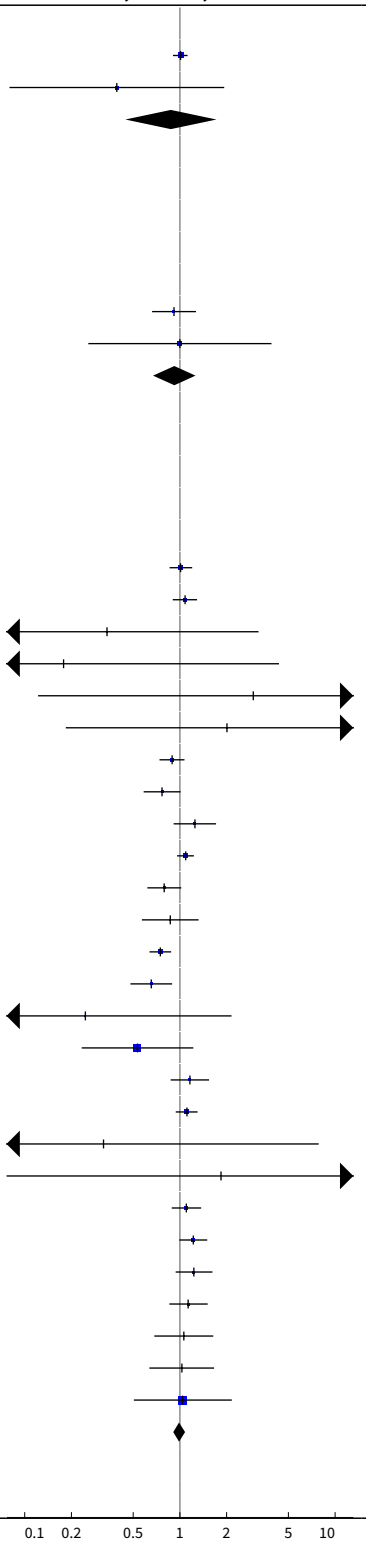
Analysis 1.85. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 85 Arrhythmia - LCn3 - subgroup by intervention type.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.85.1 Dietary advice					
DISAF 2003	154/201	157/206		8.23%	1.01[0.9,1.12]
THIS DIET 2008	2/51	5/50		0.21%	0.39[0.08,1.93]
Subtotal (95% CI)	**252**	**256**		**8.44%**	**0.87[0.44,1.72]**
Total events: 156 (Higher omega 3), 162 (Lower omega 3)					
Heterogeneity: Tau^2=0.14; Chi^2=1.41, df=1(P=0.23); I^2=29.15%					
Test for overall effect: Z=0.39(P=0.7)					
1.85.2 Supplemental foods					
AlphaOmega - EPA+DHA 2010	67/2404	74/2433		3.38%	0.92[0.66,1.27]
FOSTAR 2016	4/101	4/101		0.28%	1[0.26,3.89]
Subtotal (95% CI)	**2505**	**2534**		**3.66%**	**0.92[0.67,1.26]**
Total events: 71 (Higher omega 3), 78 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.9); I^2=0%					
Test for overall effect: Z=0.51(P=0.61)					
1.85.3 Supplements (capsule)					
AFFORD 2013	98/153	103/163		6.61%	1.01[0.86,1.2]
ASCEND 2018	236/7740	219/7740		6.22%	1.08[0.9,1.29]
Derosa 2016	1/128	3/130		0.11%	0.34[0.04,3.21]
DREAM Asbell 2018	0/349	1/186		0.05%	0.18[0.01,4.35]
EPIC-1 2008	1/188	0/186		0.05%	2.97[0.12,72.4]
EPOCH 2014	2/195	1/196		0.09%	2.01[0.18,21.99]
Erdogan 2007	41/54	46/54		6.08%	0.89[0.74,1.07]
FAAT 2005	60/200	79/202		4.21%	0.77[0.58,1.01]
FORWARD 2013	68/289	56/297		3.54%	1.25[0.91,1.71]
GISSI-HF 2008	444/2921	408/2914		7.78%	1.09[0.96,1.23]
GISSI-HF 2008	76/278	98/284		4.64%	0.79[0.62,1.02]
GISSI-P 1999	40/2836	46/2828		2.34%	0.87[0.57,1.32]
Kumar 2012	61/91	78/87		6.77%	0.75[0.64,0.88]
Nodari 2011 AF	37/100	56/99		3.62%	0.65[0.48,0.89]
Nodari 2011 HF	1/67	4/66		0.11%	0.25[0.03,2.15]
OFAMI 2001	8/150	15/150		0.73%	0.53[0.23,1.22]
OMEGA 2009	99/1919	84/1885		4.02%	1.16[0.87,1.54]
ORIGIN 2012	288/6281	259/6255		6.68%	1.11[0.94,1.3]
ORL 2013	0/171	1/165		0.05%	0.32[0.01,7.84]
Proudman 2015	1/87	0/53		0.05%	1.84[0.08,44.38]
Raitt 2005	65/100	59/100		5.33%	1.1[0.89,1.37]
REDUCE-IT 2019	188/4089	154/4090		5.54%	1.22[0.99,1.5]
Risk & Prevention 2013	113/6239	92/6266		4.21%	1.23[0.94,1.62]
Sianni 2013	147/268	29/60		4.03%	1.13[0.85,1.51]
SOFA 2006	36/273	34/273		2.2%	1.06[0.68,1.64]
SU.FOL.OM3 2010	33/1253	32/1248		1.9%	1.03[0.64,1.66]
Özaydin 2011	9/23	9/24		0.93%	1.04[0.51,2.16]
Subtotal (95% CI)	**36442**	**36001**		**87.9%**	**0.99[0.91,1.08]**
Total events: 2153 (Higher omega 3), 1966 (Lower omega 3)					
Heterogeneity: Tau^2=0.02; Chi^2=52.65, df=26(P=0); I^2=50.62%					



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Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=0.3(P=0.77)					
1.85.4 Any combination					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 3), 0 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**39199**	**38791**		**100%**	**0.99[0.92,1.06]**
Total events: 2380 (Higher omega 3), 2206 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=53.93, df=30(P=0); I^2=44.37%					
Test for overall effect: Z=0.38(P=0.7)					
Test for subgroup differences: Chi^2=0.29, df=1 (P=0.87), I^2=0%					

Favours higher omega 3 — 0.1 0.2 0.5 1 2 5 10 — Favours lower omega 3

Analysis 1.86. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 86 Arrhythmia - LCn3 - subgroup by duration.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.86.1 Medium duration 1 to < 2 years in study					
AFFORD 2013	98/153	103/163		6.61%	1.01[0.86,1.2]
Derosa 2016	1/128	3/130		0.11%	0.34[0.04,3.21]
DISAF 2003	154/201	157/206		8.23%	1.01[0.9,1.12]
DREAM Asbell 2018	0/349	1/186		0.05%	0.18[0.01,4.35]
EPIC-1 2008	1/188	0/186		0.05%	2.97[0.12,72.4]
EPOCH 2014	2/195	1/196		0.09%	2.01[0.18,21.99]
Erdogan 2007	41/54	46/54		6.08%	0.89[0.74,1.07]
FAAT 2005	60/200	79/202		4.21%	0.77[0.58,1.01]
FORWARD 2013	68/289	56/297		3.54%	1.25[0.91,1.71]
Kumar 2012	61/91	78/87		6.77%	0.75[0.64,0.88]
Nodari 2011 AF	37/100	56/99		3.62%	0.65[0.48,0.89]
Nodari 2011 HF	1/67	4/66		0.11%	0.25[0.03,2.15]
OMEGA 2009	99/1919	84/1885		4.02%	1.16[0.87,1.54]
ORL 2013	0/171	1/165		0.05%	0.32[0.01,7.84]
Proudman 2015	1/87	0/53		0.05%	1.84[0.08,44.38]
Sianni 2013	147/268	29/60		4.03%	1.13[0.85,1.51]
SOFA 2006	36/273	34/273		2.2%	1.06[0.68,1.64]
Özaydin 2011	9/23	9/24		0.93%	1.04[0.51,2.16]
Subtotal (95% CI)	**4756**	**4332**		**50.75%**	**0.94[0.84,1.04]**
Total events: 816 (Higher omega 3), 741 (Lower omega 3)					
Heterogeneity: Tau^2=0.02; Chi^2=30.35, df=17(P=0.02); I^2=43.99%					
Test for overall effect: Z=1.22(P=0.22)					
1.86.2 Medium-long duration: 2 to < 4 years in study					
AlphaOmega - EPA+DHA 2010	67/2404	74/2433		3.38%	0.92[0.66,1.27]
FOSTAR 2016	4/101	4/101		0.28%	1[0.26,3.89]
GISSI-HF 2008	444/2921	408/2914		7.78%	1.09[0.96,1.23]
GISSI-HF 2008	76/278	98/284		4.64%	0.79[0.62,1.02]

Favours higher omega 3 — 0.1 0.2 0.5 1 2 5 10 — Favours lower omega 3

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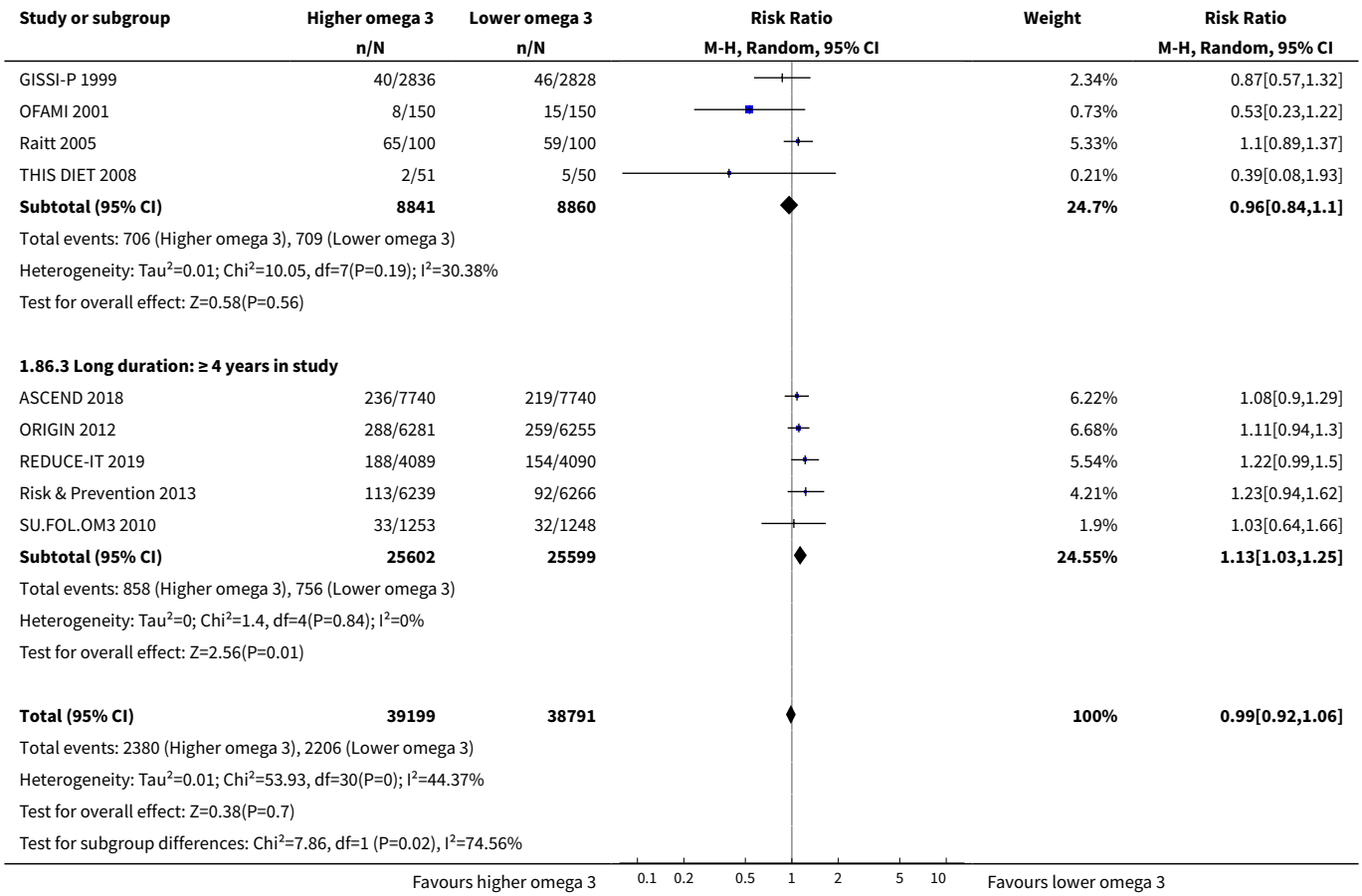
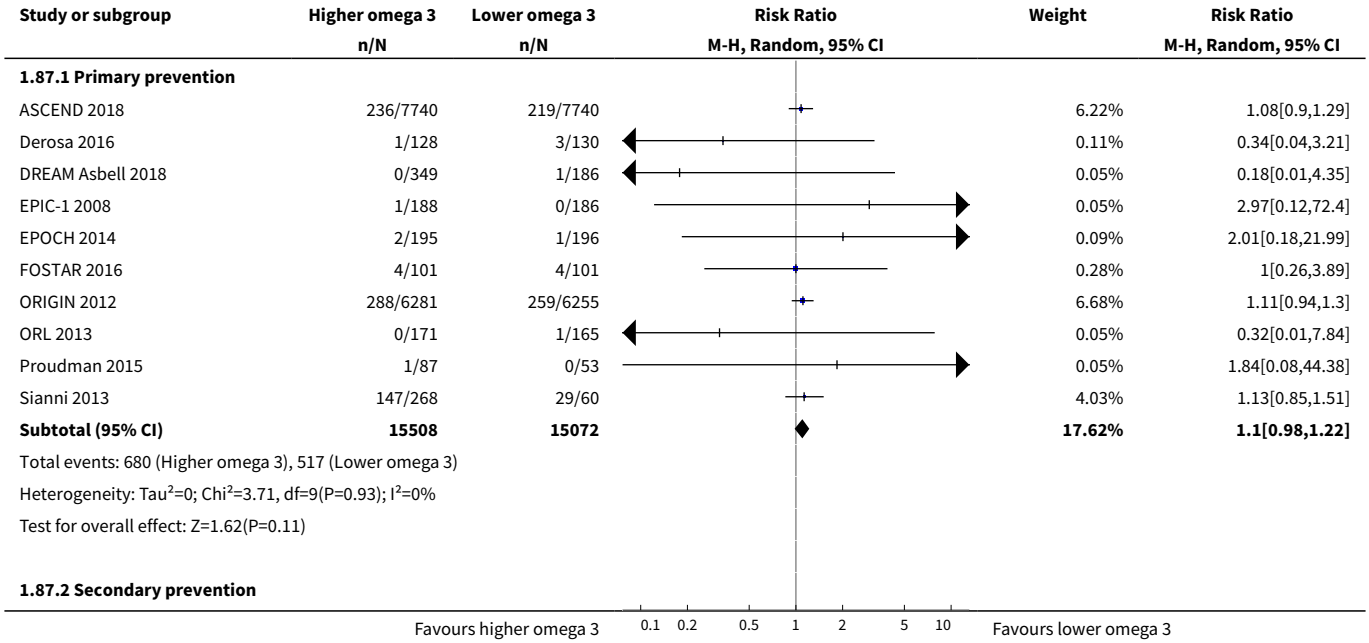


Analysis 1.87. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 87 Arrhythmia - LCn3 - subgroup by primary or secondary prevention3.



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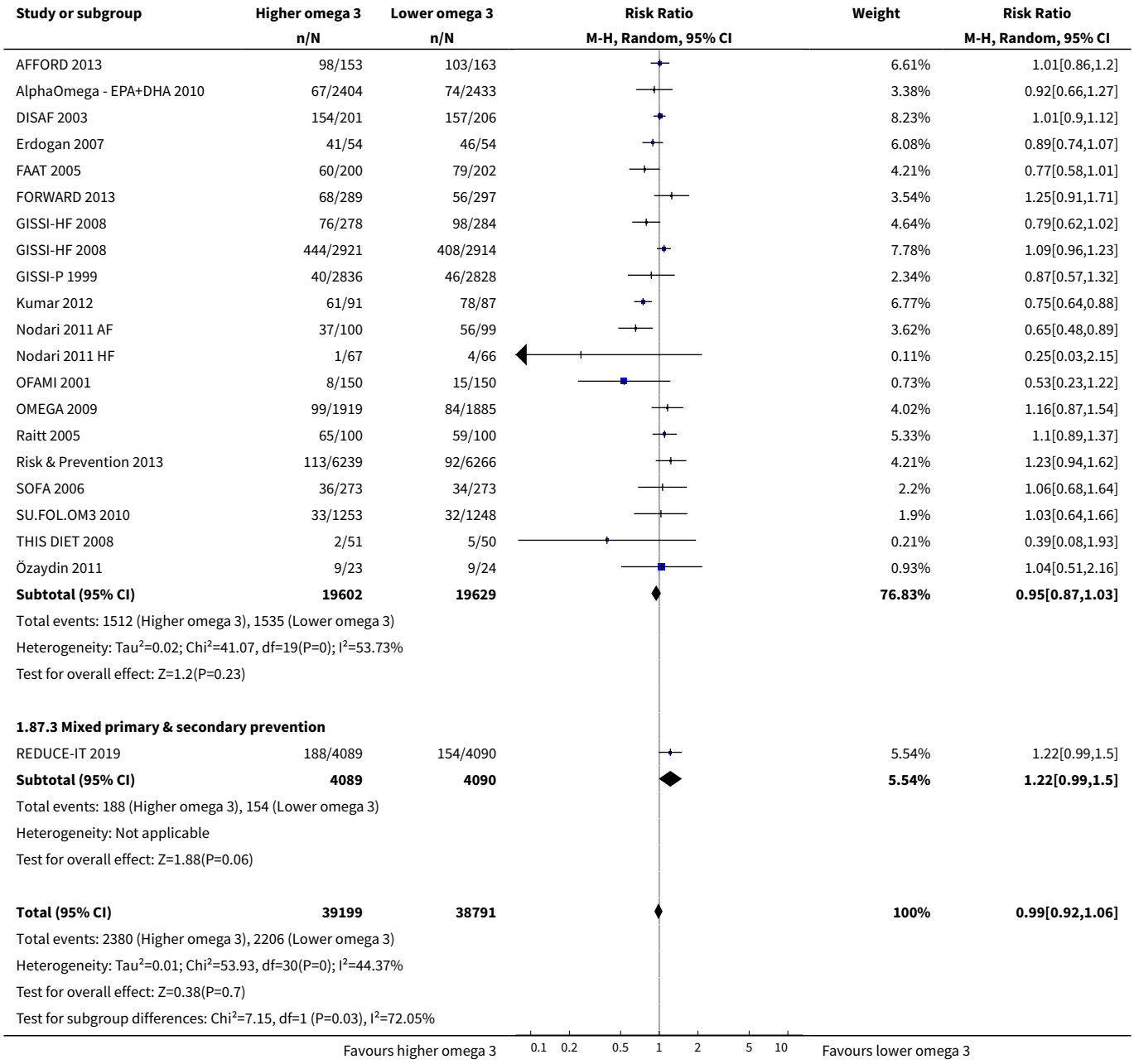
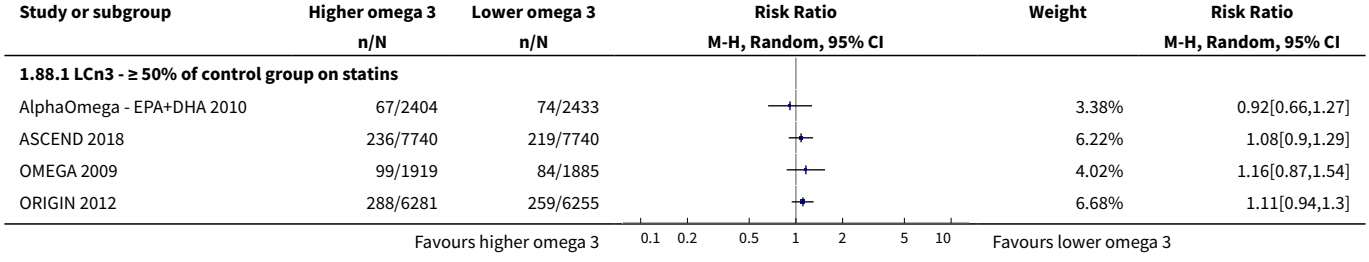


Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
AFFORD 2013	98/153	103/163		6.61%	1.01[0.86,1.2]
AlphaOmega - EPA+DHA 2010	67/2404	74/2433		3.38%	0.92[0.66,1.27]
DISAF 2003	154/201	157/206		8.23%	1.01[0.9,1.12]
Erdogan 2007	41/54	46/54		6.08%	0.89[0.74,1.07]
FAAT 2005	60/200	79/202		4.21%	0.77[0.58,1.01]
FORWARD 2013	68/289	56/297		3.54%	1.25[0.91,1.71]
GISSI-HF 2008	76/278	98/284		4.64%	0.79[0.62,1.02]
GISSI-HF 2008	444/2921	408/2914		7.78%	1.09[0.96,1.23]
GISSI-P 1999	40/2836	46/2828		2.34%	0.87[0.57,1.32]
Kumar 2012	61/91	78/87		6.77%	0.75[0.64,0.88]
Nodari 2011 AF	37/100	56/99		3.62%	0.65[0.48,0.89]
Nodari 2011 HF	1/67	4/66		0.11%	0.25[0.03,2.15]
OFAMI 2001	8/150	15/150		0.73%	0.53[0.23,1.22]
OMEGA 2009	99/1919	84/1885		4.02%	1.16[0.87,1.54]
Raitt 2005	65/100	59/100		5.33%	1.1[0.89,1.37]
Risk & Prevention 2013	113/6239	92/6266		4.21%	1.23[0.94,1.62]
SOFA 2006	36/273	34/273		2.2%	1.06[0.68,1.64]
SU.FOL.OM3 2010	33/1253	32/1248		1.9%	1.03[0.64,1.66]
THIS DIET 2008	2/51	5/50		0.21%	0.39[0.08,1.93]
Özaydin 2011	9/23	9/24		0.93%	1.04[0.51,2.16]
Subtotal (95% CI)	**19602**	**19629**		**76.83%**	**0.95[0.87,1.03]**
Total events: 1512 (Higher omega 3), 1535 (Lower omega 3)					
Heterogeneity: Tau^2=0.02; Chi^2=41.07, df=19(P=0); I^2=53.73%					
Test for overall effect: Z=1.2(P=0.23)					
1.87.3 Mixed primary & secondary prevention					
REDUCE-IT 2019	188/4089	154/4090		5.54%	1.22[0.99,1.5]
Subtotal (95% CI)	**4089**	**4090**		**5.54%**	**1.22[0.99,1.5]**
Total events: 188 (Higher omega 3), 154 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.88(P=0.06)					
Total (95% CI)	**39199**	**38791**		**100%**	**0.99[0.92,1.06]**
Total events: 2380 (Higher omega 3), 2206 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=53.93, df=30(P=0); I^2=44.37%					
Test for overall effect: Z=0.38(P=0.7)					
Test for subgroup differences: Chi^2=7.15, df=1 (P=0.03), I^2=72.05%					

Analysis 1.88. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 88 Arrhythmia - LCn3 - subgroup by statin use.



Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.88.1 LCn3 - ≥ 50% of control group on statins					
AlphaOmega - EPA+DHA 2010	67/2404	74/2433		3.38%	0.92[0.66,1.27]
ASCEND 2018	236/7740	219/7740		6.22%	1.08[0.9,1.29]
OMEGA 2009	99/1919	84/1885		4.02%	1.16[0.87,1.54]
ORIGIN 2012	288/6281	259/6255		6.68%	1.11[0.94,1.3]

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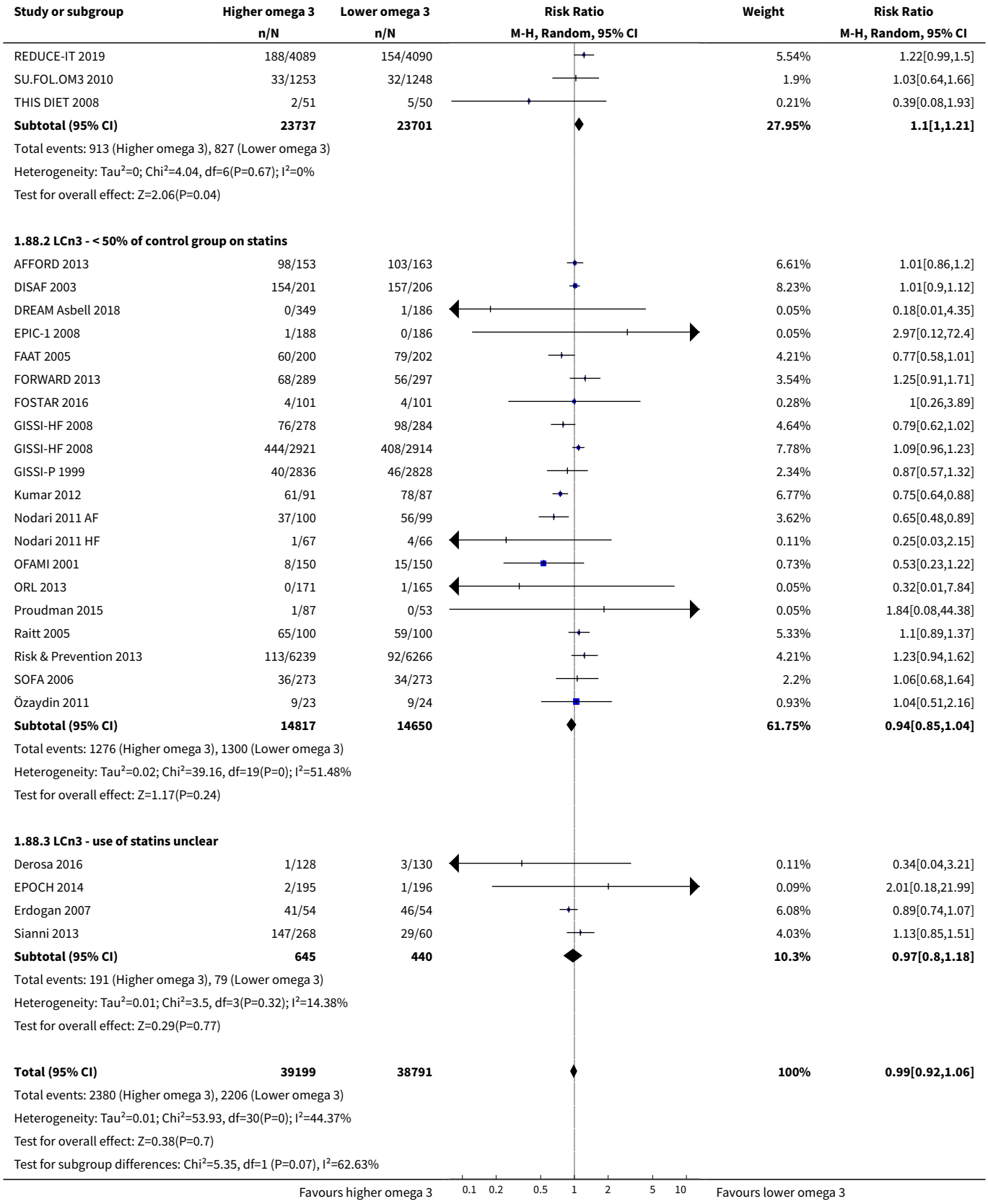

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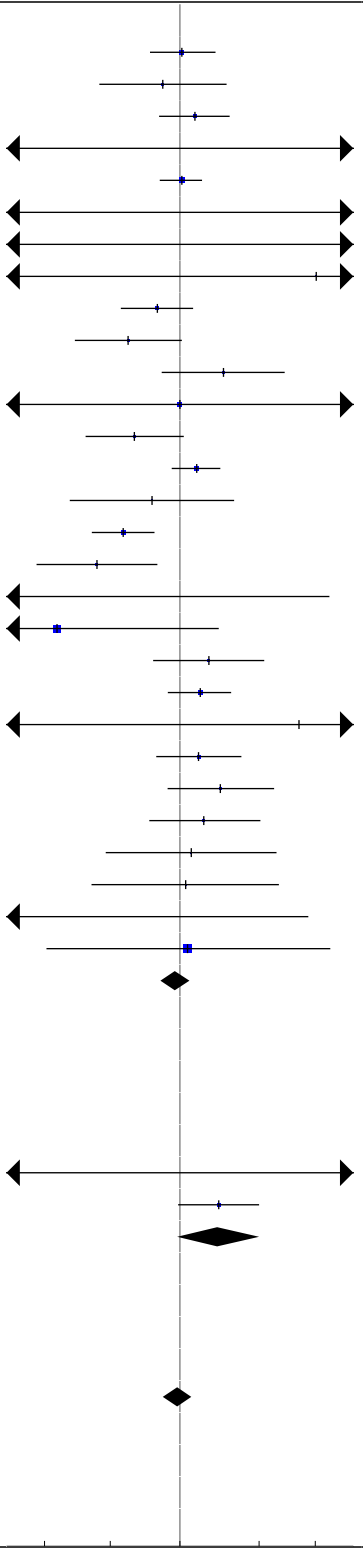
Analysis 1.89. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 89 Arrythmia - LCn3 - subgroup by baseline TG.

Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.89.1 Baseline TG not restricted					
AFFORD 2013	98/153	103/163		6.61%	1.01[0.86,1.2]
AlphaOmega - EPA+DHA 2010	67/2404	74/2433		3.38%	0.92[0.66,1.27]
ASCEND 2018	236/7740	219/7740		6.22%	1.08[0.9,1.29]
Derosa 2016	1/128	3/130		0.11%	0.34[0.04,3.21]
DISAF 2003	154/201	157/206		8.23%	1.01[0.9,1.12]
DREAM Asbell 2018	0/349	1/186		0.05%	0.18[0.01,4.35]
EPIC-1 2008	1/188	0/186		0.05%	2.97[0.12,72.4]
EPOCH 2014	2/195	1/196		0.09%	2.01[0.18,21.99]
Erdogan 2007	41/54	46/54		6.08%	0.89[0.74,1.07]
FAAT 2005	60/200	79/202		4.21%	0.77[0.58,1.01]
FORWARD 2013	68/289	56/297		3.54%	1.25[0.91,1.71]
FOSTAR 2016	4/101	4/101		0.28%	1[0.26,3.89]
GISSI-HF 2008	76/278	98/284		4.64%	0.79[0.62,1.02]
GISSI-HF 2008	444/2921	408/2914		7.78%	1.09[0.96,1.23]
GISSI-P 1999	40/2836	46/2828		2.34%	0.87[0.57,1.32]
Kumar 2012	61/91	78/87		6.77%	0.75[0.64,0.88]
Nodari 2011 AF	37/100	56/99		3.62%	0.65[0.48,0.89]
Nodari 2011 HF	1/67	4/66		0.11%	0.25[0.03,2.15]
OFAMI 2001	8/150	15/150		0.73%	0.53[0.23,1.22]
OMEGA 2009	99/1919	84/1885		4.02%	1.16[0.87,1.54]
ORIGIN 2012	288/6281	259/6255		6.68%	1.11[0.94,1.3]
Proudman 2015	1/87	0/53		0.05%	1.84[0.08,44.38]
Raitt 2005	65/100	59/100		5.33%	1.1[0.89,1.37]
Risk & Prevention 2013	113/6239	92/6266		4.21%	1.23[0.94,1.62]
Sianni 2013	147/268	29/60		4.03%	1.13[0.85,1.51]
SOFA 2006	36/273	34/273		2.2%	1.06[0.68,1.64]
SU.FOL.OM3 2010	33/1253	32/1248		1.9%	1.03[0.64,1.66]
THIS DIET 2008	2/51	5/50		0.21%	0.39[0.08,1.93]
Özaydin 2011	9/23	9/24		0.93%	1.04[0.51,2.16]
Subtotal (95% CI)	**34939**	**34536**		**94.4%**	**0.97[0.9,1.05]**
Total events: 2192 (Favours higher omega 3), 2051 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=49.12, df=28(P=0.01); I^2=42.99%					
Test for overall effect: Z=0.68(P=0.49)					
1.89.2 Baseline TG raised					
ORL 2013	0/171	1/165		0.05%	0.32[0.01,7.84]
REDUCE-IT 2019	188/4089	154/4090		5.54%	1.22[0.99,1.5]
Subtotal (95% CI)	**4260**	**4255**		**5.6%**	**1.21[0.99,1.5]**
Total events: 188 (Favours higher omega 3), 155 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.67, df=1(P=0.41); I^2=0%					
Test for overall effect: Z=1.83(P=0.07)					
Total (95% CI)	**39199**	**38791**		**100%**	**0.99[0.92,1.06]**
Total events: 2380 (Favours higher omega 3), 2206 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=53.93, df=30(P=0); I^2=44.37%					
Test for overall effect: Z=0.38(P=0.7)					
Test for subgroup differences: Chi^2=3.81, df=1 (P=0.05), I^2=73.72%					



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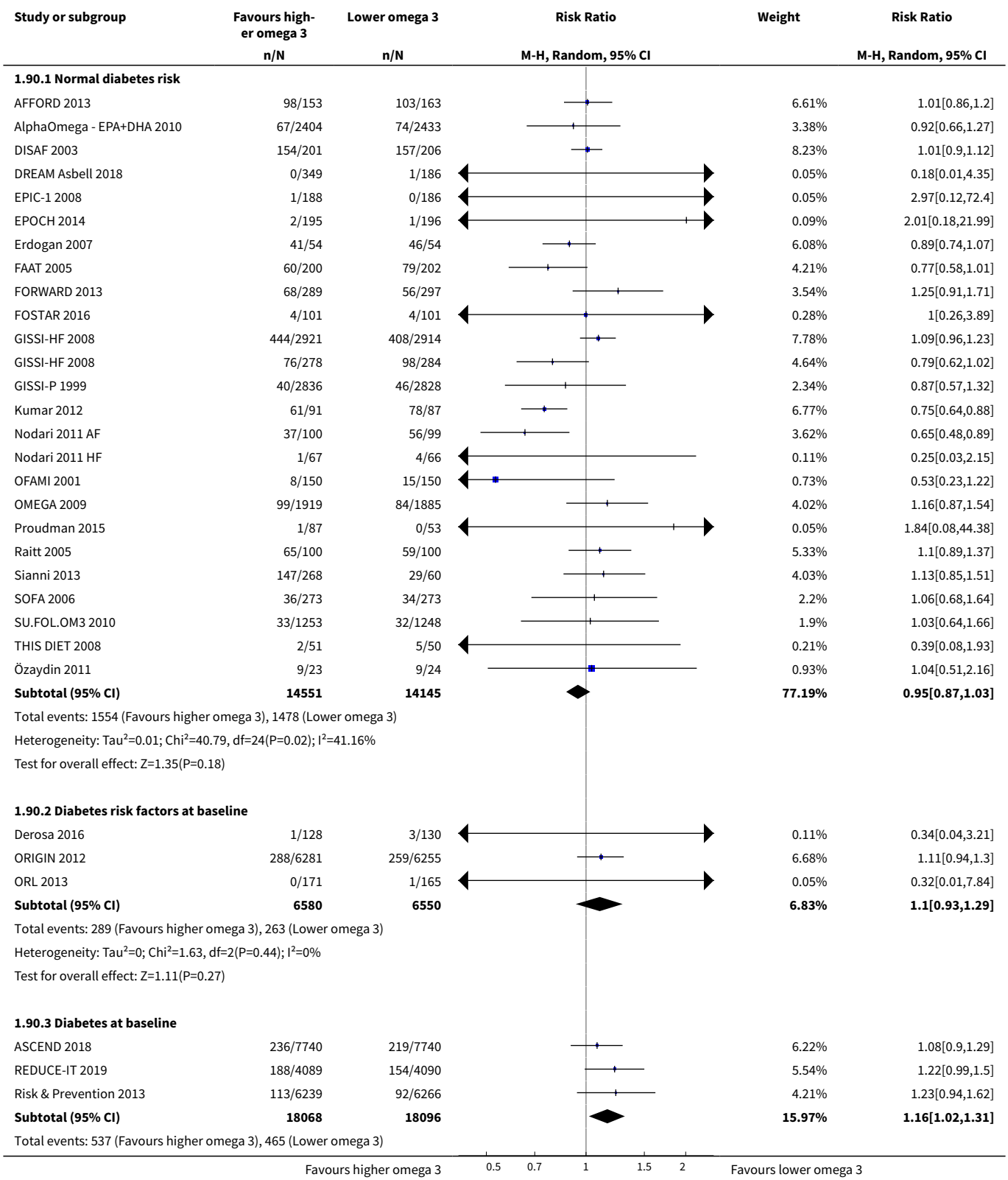
Analysis 1.90. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 90 Arrythmia - LCn3 - subgroup by baseline DM.



Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.90.1 Normal diabetes risk					
AFFORD 2013	98/153	103/163		6.61%	1.01[0.86,1.2]
AlphaOmega - EPA+DHA 2010	67/2404	74/2433		3.38%	0.92[0.66,1.27]
DISAF 2003	154/201	157/206		8.23%	1.01[0.9,1.12]
DREAM Asbell 2018	0/349	1/186		0.05%	0.18[0.01,4.35]
EPIC-1 2008	1/188	0/186		0.05%	2.97[0.12,72.4]
EPOCH 2014	2/195	1/196		0.09%	2.01[0.18,21.99]
Erdogan 2007	41/54	46/54		6.08%	0.89[0.74,1.07]
FAAT 2005	60/200	79/202		4.21%	0.77[0.58,1.01]
FORWARD 2013	68/289	56/297		3.54%	1.25[0.91,1.71]
FOSTAR 2016	4/101	4/101		0.28%	1[0.26,3.89]
GISSI-HF 2008	444/2921	408/2914		7.78%	1.09[0.96,1.23]
GISSI-HF 2008	76/278	98/284		4.64%	0.79[0.62,1.02]
GISSI-P 1999	40/2836	46/2828		2.34%	0.87[0.57,1.32]
Kumar 2012	61/91	78/87		6.77%	0.75[0.64,0.88]
Nodari 2011 AF	37/100	56/99		3.62%	0.65[0.48,0.89]
Nodari 2011 HF	1/67	4/66		0.11%	0.25[0.03,2.15]
OFAMI 2001	8/150	15/150		0.73%	0.53[0.23,1.22]
OMEGA 2009	99/1919	84/1885		4.02%	1.16[0.87,1.54]
Proudman 2015	1/87	0/53		0.05%	1.84[0.08,44.38]
Raitt 2005	65/100	59/100		5.33%	1.1[0.89,1.37]
Sianni 2013	147/268	29/60		4.03%	1.13[0.85,1.51]
SOFA 2006	36/273	34/273		2.2%	1.06[0.68,1.64]
SU.FOL.OM3 2010	33/1253	32/1248		1.9%	1.03[0.64,1.66]
THIS DIET 2008	2/51	5/50		0.21%	0.39[0.08,1.93]
Özaydin 2011	9/23	9/24		0.93%	1.04[0.51,2.16]
Subtotal (95% CI)	**14551**	**14145**		**77.19%**	**0.95[0.87,1.03]**
Total events: 1554 (Favours higher omega 3), 1478 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=40.79, df=24(P=0.02); I^2=41.16%					
Test for overall effect: Z=1.35(P=0.18)					
1.90.2 Diabetes risk factors at baseline					
Derosa 2016	1/128	3/130		0.11%	0.34[0.04,3.21]
ORIGIN 2012	288/6281	259/6255		6.68%	1.11[0.94,1.3]
ORL 2013	0/171	1/165		0.05%	0.32[0.01,7.84]
Subtotal (95% CI)	**6580**	**6550**		**6.83%**	**1.1[0.93,1.29]**
Total events: 289 (Favours higher omega 3), 263 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=1.63, df=2(P=0.44); I^2=0%					
Test for overall effect: Z=1.11(P=0.27)					
1.90.3 Diabetes at baseline					
ASCEND 2018	236/7740	219/7740		6.22%	1.08[0.9,1.29]
REDUCE-IT 2019	188/4089	154/4090		5.54%	1.22[0.99,1.5]
Risk & Prevention 2013	113/6239	92/6266		4.21%	1.23[0.94,1.62]
Subtotal (95% CI)	**18068**	**18096**		**15.97%**	**1.16[1.02,1.31]**
Total events: 537 (Favours higher omega 3), 465 (Lower omega 3)					

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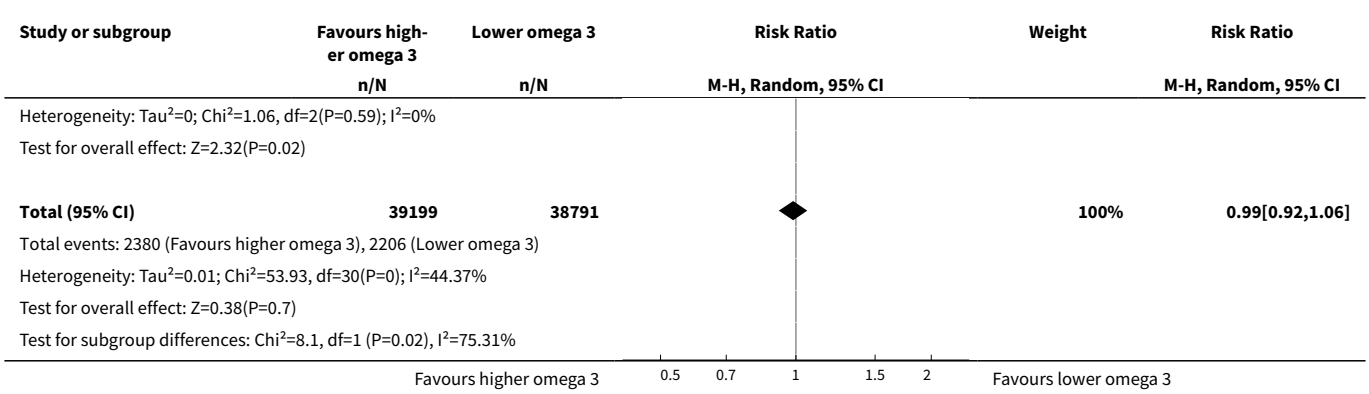

Comparison 2. High vs low LCn3 omega-3 fats (secondary outcomes)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 MACCEs - LCn3	5	34730	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.97, 1.09]
2 Myocardial infarction (overall) - LCn3	27	133012	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.81, 0.96]
3 Total MI - LCn3 - SA fixed effects	27	133012	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.83, 0.94]
4 Total MI - LCn3 - SA by summary risk of bias	27		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Low summary risk of bias	13	71376	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.83, 1.05]
4.2 Moderate or high summary risk of bias	14	61636	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.76, 0.94]
5 Total MI - LCn3 - SA by compliance and study size	26		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 SA - low risk of compliance bias	12	47052	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.70, 0.94]
5.2 SA - 100+ randomised	24	121545	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.80, 0.96]
6 Total MI - LCn3 - subgroup by fatality	27		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Fatal MI	16	86342	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.52, 1.03]
6.2 Non-fatal MI	25	132443	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.84, 1.02]
7 Sudden cardiac death (overall) - LCn3	15	73183	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.77, 1.11]
8 Angina - LCn3	13	48621	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.92, 1.06]
8.1 Low summary risk of bias	6	21355	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.90, 1.08]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.2 Moderate or high risk of bias	7	27266	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.88, 1.10]
9 Heart failure - LCn3	17	73303	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.87, 1.02]
9.1 Low summary risk of bias	7	39656	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.89, 1.05]
9.2 Moderate to high risk of bias	10	33647	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.69, 1.04]
10 Revascularisation - LCn3	24	129382	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.86, 1.00]
10.1 Low summary risk of bias	8	64545	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.91, 1.01]
10.2 Moderate to high risk of bias	16	64837	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.78, 1.00]
11 Peripheral arterial disease - LCn3	7	57214	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.76, 1.18]
12 PAD - LCn3 - SA fixed effects	7	57214	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.76, 1.18]
13 PAD - LCn3 - SA by summary risk of bias	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 Low summary risk of bias	2	12738	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.75, 1.62]
13.2 Moderate or high risk of bias	5	44476	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.68, 1.15]
14 PAD - LCn3 - SA compliance and study size	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 SA compliance	2	8381	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.58, 1.87]
14.2 SA study size 100+	7	57214	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.76, 1.18]
15 Acute coronary syndrome - LCn3	2	2703	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.71, 2.00]
15.1 LCn3	2	2703	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.71, 2.00]
16 Body weight, kg - LCn3	14	17000	Mean Difference (IV, Random, 95% CI)	0.00 [-0.69, 0.70]
17 Weight, kg - LCn3 - SA fixed effects	14	17000	Mean Difference (IV, Fixed, 95% CI)	0.19 [-0.19, 0.57]
18 Weight, kg - LCn3 - SA by summary risk of bias	14		Mean Difference (IV, Random, 95% CI)	Subtotals only
18.1 Low summary risk of bias	8	16406	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.94, 0.75]
18.2 Moderate or high risk of bias	6	594	Mean Difference (IV, Random, 95% CI)	0.27 [-1.08, 1.63]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19 Weight, kg - LCn3 - SA by compliance and study size	12		Mean Difference (IV, Random, 95% CI)	Subtotals only
19.1 SA - low risk of compliance bias	7	828	Mean Difference (IV, Random, 95% CI)	0.58 [-0.52, 1.69]
19.2 SA - 100+ randomised	9	16733	Mean Difference (IV, Random, 95% CI)	0.06 [-0.67, 0.79]
20 Weight, kg - LCn3 - subgroup by dose	14		Mean Difference (IV, Random, 95% CI)	Subtotals only
20.1 LCn3 ≤ 150 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
20.2 LCn3 > 150 ≤ 250 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
20.3 LCn3 > 250 ≤ 400 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
20.4 LCn3 > 400 ≤ 2400 mg/d	9	16368	Mean Difference (IV, Random, 95% CI)	-0.34 [-1.14, 0.46]
20.5 LCn3 > 2.4 ≤ 4.4 g/d	4	481	Mean Difference (IV, Random, 95% CI)	0.11 [-2.58, 2.80]
20.6 LCn3 > 4.4 g/d	2	261	Mean Difference (IV, Random, 95% CI)	1.51 [0.28, 2.75]
21 Weight, kg - LCn3 - subgroup by replacement	14		Mean Difference (IV, Random, 95% CI)	Subtotals only
21.1 N-3 replacing SFA	2	433	Mean Difference (IV, Random, 95% CI)	-2.51 [-4.30, -0.72]
21.2 N-3 replacing MUFA	8	16036	Mean Difference (IV, Random, 95% CI)	0.17 [-0.34, 0.68]
21.3 N-3 replacing n-6	1	41	Mean Difference (IV, Random, 95% CI)	-1.3 [-3.83, 1.23]
21.4 N-3 replacing carbs/sugars	1	258	Mean Difference (IV, Random, 95% CI)	-2.70 [-4.75, -0.65]
21.5 N-3 replacing nil/low n-3 placebo	1	240	Mean Difference (IV, Random, 95% CI)	0.44 [-1.11, 1.99]
21.6 Replacement unclear	3	425	Mean Difference (IV, Random, 95% CI)	1.46 [0.23, 2.68]
22 Weight, kg - LCn3 - subgroup by intervention type	14	17000	Mean Difference (IV, Random, 95% CI)	0.00 [-0.69, 0.70]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.1 Dietary advice	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
22.2 Supplemental foods	1	202	Mean Difference (IV, Random, 95% CI)	1.5 [0.25, 2.75]
22.3 Supplement (capsule)	11	16726	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.82, 0.53]
22.4 Any combination	2	72	Mean Difference (IV, Random, 95% CI)	-0.43 [-6.47, 5.61]
23 Weight, kg - LCn3 - subgroup by duration	14		Mean Difference (IV, Random, 95% CI)	Subtotals only
23.1 Medium duration 1 to < 2 years in study	8	840	Mean Difference (IV, Random, 95% CI)	-0.54 [-2.21, 1.12]
23.2 Medium-long duration: 2 to < 4 years in study	4	676	Mean Difference (IV, Random, 95% CI)	0.81 [-0.30, 1.92]
23.3 Long duration ≥ 4 years in study	2	15484	Mean Difference (IV, Random, 95% CI)	0.03 [-0.53, 0.59]
24 Weight, kg - LCn3 - subgroup by primary or secondary prevention	14		Mean Difference (IV, Random, 95% CI)	Subtotals only
24.1 Primary CVD prevention	11	16526	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.87, 0.78]
24.2 Secondary CVD prevention	3	474	Mean Difference (IV, Random, 95% CI)	0.16 [-1.24, 1.56]
25 Weight, kg - LCn3 - subgroup by statin use	14		Mean Difference (IV, Random, 95% CI)	Subtotals only
25.1 LCn3 - ≥ 50% of control group on statins	4	15819	Mean Difference (IV, Random, 95% CI)	0.11 [-0.42, 0.63]
25.2 LCn3 - < 50% of control group on statins	5	614	Mean Difference (IV, Random, 95% CI)	0.47 [-0.66, 1.60]
25.3 LCn3 - use of statins unclear	5	567	Mean Difference (IV, Random, 95% CI)	-1.51 [-3.30, 0.27]
26 Body mass index, kg/m^2 - LCn3	15	15474	Mean Difference (IV, Random, 95% CI)	0.06 [-0.14, 0.25]
27 BMI, kg/m^2 - LCn3 - SA fixed effects	15	15474	Mean Difference (IV, Random, 95% CI)	0.06 [-0.14, 0.25]
28 BMI, kg/m^2- LCn3 - SA by summary risk of bias	15		Mean Difference (IV, Random, 95% CI)	Subtotals only

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
28.1 Low risk of bias	5	14190	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.36, 0.33]
28.2 Moderate/high risk of bias	10	1284	Mean Difference (IV, Random, 95% CI)	0.05 [-0.12, 0.21]
29 BMI, kg/m^2- LCn3 - SA by compliance and study size	11		Mean Difference (IV, Random, 95% CI)	Subtotals only
29.1 SA - low risk of compliance bias	5	1848	Mean Difference (IV, Random, 95% CI)	0.09 [-0.21, 0.38]
29.2 SA - 100+ randomised	10	15222	Mean Difference (IV, Random, 95% CI)	0.01 [-0.12, 0.15]
30 BMI, kg/m^2 - LCn3 - subgroup by dose	15		Mean Difference (IV, Random, 95% CI)	Subtotals only
30.1 LCn3 > 150 ≤ 250 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
30.2 LCn3 ≤ 150 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
30.3 LCn3 > 250 ≤ 400 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
30.4 LCn3 > 400 ≤ 2400 mg/d	11	14789	Mean Difference (IV, Random, 95% CI)	0.01 [-0.11, 0.13]
30.5 LCn3 > 2.4 ≤ 4.4 g/d	4	685	Mean Difference (IV, Random, 95% CI)	1.08 [0.07, 2.10]
30.6 LCn3 > 4.4 g/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
31 BMI, kg/m^2 - LCn3 - subgroup by replacement	15		Mean Difference (IV, Random, 95% CI)	Subtotals only
31.1 N-3 replacing SFA	1	258	Mean Difference (IV, Random, 95% CI)	-0.60 [-1.14, -0.06]
31.2 N-3 replacing MUFA	7	14180	Mean Difference (IV, Random, 95% CI)	0.08 [-0.12, 0.28]
31.3 N-3 replacing n-6	3	513	Mean Difference (IV, Random, 95% CI)	0.18 [-0.46, 0.81]
31.4 N-3 replacing carbs/sugars	1	258	Mean Difference (IV, Random, 95% CI)	-0.60 [-1.14, -0.06]
31.5 N-3 replacing nil/low n-3 placebo	2	300	Mean Difference (IV, Random, 95% CI)	0.86 [-0.30, 2.01]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
31.6 Replacement unclear	2	223	Mean Difference (IV, Random, 95% CI)	0.58 [-1.17, 2.33]
32 BMI, kg/m² - LCn3 - subgroup by intervention type	15	15474	Mean Difference (IV, Random, 95% CI)	0.06 [-0.14, 0.25]
32.1 Dietary advice	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
32.2 Supplemental foods	1	1260	Mean Difference (IV, Random, 95% CI)	0.1 [-0.10, 0.30]
32.3 Supplement (capsule)	13	14169	Mean Difference (IV, Random, 95% CI)	0.04 [-0.22, 0.29]
32.4 Any combination	1	45	Mean Difference (IV, Random, 95% CI)	1.60 [-0.43, 3.63]
33 BMI, kg/m² - LCn3 - subgroup by duration	15		Mean Difference (IV, Random, 95% CI)	Subtotals only
33.1 Medium duration 1 to < 2 years in study	9	906	Mean Difference (IV, Random, 95% CI)	0.24 [-0.40, 0.88]
33.2 Medium-long duration: 2 to < 4 years in study	5	2032	Mean Difference (IV, Random, 95% CI)	0.13 [-0.06, 0.32]
33.3 Long duration ≥ 4 years in study	1	12536	Mean Difference (IV, Random, 95% CI)	0.0 [-0.20, 0.20]
34 BMI, kg/m² - LCn3 - subgroup by primary or secondary prevention	15		Mean Difference (IV, Random, 95% CI)	Subtotals only
34.1 Primary CVD prevention	11	13610	Mean Difference (IV, Random, 95% CI)	0.15 [-0.36, 0.66]
34.2 Secondary CVD prevention	4	1864	Mean Difference (IV, Random, 95% CI)	0.06 [-0.07, 0.20]
35 BMI, kg/m² - LCn3 - subgroup by statin use	15		Mean Difference (IV, Random, 95% CI)	Subtotals only
35.1 LCn3 - ≥ 50% of control group on statins	4	14131	Mean Difference (IV, Random, 95% CI)	0.17 [-0.17, 0.50]
35.2 LCn3 - < 50% of control group on statins	4	665	Mean Difference (IV, Random, 95% CI)	0.02 [-0.15, 0.19]
35.3 LCn3 - use of statins unclear	7	678	Mean Difference (IV, Random, 95% CI)	0.06 [-0.86, 0.97]
36 Other measures of adiposity - LCn3	7		Mean Difference (IV, Random, 95% CI)	Subtotals only

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
36.1 Percentage body fat	2	127	Mean Difference (IV, Random, 95% CI)	0.85 [-6.87, 8.57]
36.2 Percentage visceral fat	1	95	Mean Difference (IV, Random, 95% CI)	-1.80 [-15.03, 11.43]
36.3 Waist circumference, cm	4	916	Mean Difference (IV, Random, 95% CI)	0.72 [-0.17, 1.62]
36.4 Waist-hip ratio	1	100	Mean Difference (IV, Random, 95% CI)	0.0 [-0.01, 0.01]
36.5 Abdominal circumference, cm	1	256	Mean Difference (IV, Random, 95% CI)	-0.70 [-8.78, 7.38]
36.6 Hip circumference, cm	1	258	Mean Difference (IV, Random, 95% CI)	-2.40 [-9.80, 5.00]
37 Total cholesterol, serum, mmoL/L - LCn3	30	38469	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.05, 0.03]
38 TC, mmoL/L - LCn3 - SA fixed effects	30	38469	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.06, -0.02]
39 TC, mmoL/L - LCn3 - SA by summary risk of bias	30		Mean Difference (IV, Random, 95% CI)	Subtotals only
39.1 Low summary risk of bias	10	15878	Mean Difference (IV, Random, 95% CI)	0.01 [-0.04, 0.06]
39.2 Moderate or high risk of bias	20	22591	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.08, 0.02]
40 TC, mmoL/L - LCn3 - SA by compliance and study size	22		Mean Difference (IV, Random, 95% CI)	Subtotals only
40.1 SA - low risk of compliance bias	14	3341	Mean Difference (IV, Random, 95% CI)	0.02 [-0.05, 0.09]
40.2 SA - 100+ randomised	17	37810	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.05, 0.05]
41 TC, mmoL/L - LCn3 - subgroup by dose	30		Mean Difference (IV, Random, 95% CI)	Subtotals only
41.1 LCn3 ≤ 150 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
41.2 LCn3 > 150 ≤ 250 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
41.3 LCn3 > 250 ≤ 400 mg/d	1	1715	Mean Difference (IV, Random, 95% CI)	0.10 [-0.01, 0.21]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
41.4 LCn3 > 400 ≤ 2400 mg/d	19	35210	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.06, -0.01]
41.5 LCn3 > 2.4 ≤ 4.4 g/d	8	1456	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.22, 0.01]
41.6 LCn3 > 4.4 g/d	2	88	Mean Difference (IV, Random, 95% CI)	0.08 [-0.28, 0.45]
42 TC, mmoL/L - LCn3 - subgroup by replacement	30		Mean Difference (IV, Random, 95% CI)	Subtotals only
42.1 N-3 replacing SFA	3	2148	Mean Difference (IV, Random, 95% CI)	0.10 [-0.01, 0.20]
42.2 N-3 replacing MUFA	16	17452	Mean Difference (IV, Random, 95% CI)	0.01 [-0.04, 0.05]
42.3 N-3 replacing n-6	4	729	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.34, 0.31]
42.4 N-3 replacing carbs/sugars	1	258	Mean Difference (IV, Random, 95% CI)	-0.20 [-1.03, 0.63]
42.5 N-3 replacing nil/low n-3 placebo	7	19745	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.07, -0.03]
42.6 Replacement unclear	2	285	Mean Difference (IV, Random, 95% CI)	0.12 [-0.14, 0.38]
43 TC, mmoL/L - LCn3 - subgroup by intervention type	30		Mean Difference (IV, Random, 95% CI)	Subtotals only
43.1 Dietary advice	1	1715	Mean Difference (IV, Random, 95% CI)	0.10 [-0.01, 0.21]
43.2 Supplemental foods	1	1210	Mean Difference (IV, Random, 95% CI)	0.02 [-0.09, 0.13]
43.3 Supplement (capsule)	26	35333	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.07, -0.02]
43.4 Any combination	2	211	Mean Difference (IV, Random, 95% CI)	0.13 [-0.10, 0.37]
44 TC, mmoL/L - LCn3 - subgroup by duration	30		Mean Difference (IV, Random, 95% CI)	Subtotals only
44.1 Medium duration 1 to < 2 years in study	15	1661	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.16, 0.04]
44.2 Medium-long duration: 2 to < 4 years in study	11	4471	Mean Difference (IV, Random, 95% CI)	0.03 [-0.04, 0.09]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
44.3 Long duration ≥ 4 years in study	4	32337	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.08, 0.07]
45 TC, mmoL/L - LCn3 - subgroup by primary or secondary prevention	30		Mean Difference (IV, Random, 95% CI)	Subtotals only
45.1 Primary prevention	18	33744	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.06, -0.02]
45.2 Secondary prevention	12	4725	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.08, 0.07]
46 TC, mmoL/L - LCn3 - subgroup by statin use	30		Mean Difference (IV, Random, 95% CI)	Subtotals only
46.1 LCn3 - ≥ 50% of control group on statins	8	34011	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.06, -0.02]
46.2 LCn3 - < 50% of control group on statins	15	3871	Mean Difference (IV, Random, 95% CI)	0.01 [-0.08, 0.10]
46.3 LCn3 - use of statins unclear	7	587	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.27, 0.22]
47 Triglycerides, fasting, serum, mmoL/L - LCn3	27	43998	Mean Difference (IV, Random, 95% CI)	-0.24 [-0.31, -0.16]
48 TG, fasting, mmoL/L - LCn3 - SA fixed effects	27	43998	Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.26, -0.17]
49 TG, fasting, mmoL/L - LCn3 - SA by summary risk of bias	27		Mean Difference (IV, Random, 95% CI)	Subtotals only
49.1 Low summary risk of bias	8	14654	Mean Difference (IV, Random, 95% CI)	-0.19 [-0.28, -0.10]
49.2 Moderate or high risk of bias	19	29344	Mean Difference (IV, Random, 95% CI)	-0.25 [-0.35, -0.15]
50 TG, fasting, mmoL/L - LCn3 - SA by compliance and study size	20		Mean Difference (IV, Random, 95% CI)	Subtotals only
50.1 SA - low risk of compliance bias	13	11485	Mean Difference (IV, Random, 95% CI)	-0.26 [-0.36, -0.16]
50.2 SA - 100+ randomised	17	43484	Mean Difference (IV, Random, 95% CI)	-0.24 [-0.32, -0.15]
51 TG, fasting, mmoL/L - LCn3 - subgroup by dose	27		Mean Difference (IV, Random, 95% CI)	Subtotals only
51.1 LCn3 ≤ 150 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
51.2 LCn3 > 150 ≤ 250 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
51.3 LCn3 > 250 ≤ 400 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
51.4 LCn3 > 400 ≤ 2400 mg/d	18	34388	Mean Difference (IV, Random, 95% CI)	-0.18 [-0.25, -0.11]
51.5 LCn3 > 2.4 ≤ 4.4 g/d	7	9526	Mean Difference (IV, Random, 95% CI)	-0.36 [-0.53, -0.20]
51.6 LCn3 > 4.4 g/d	2	84	Mean Difference (IV, Random, 95% CI)	-0.41 [-0.68, -0.14]
52 TG, fasting, mmoL/L - LCn3 - subgroup by replacement	27		Mean Difference (IV, Random, 95% CI)	Subtotals only
52.1 N-3 replacing SFA	2	429	Mean Difference (IV, Random, 95% CI)	-0.27 [-0.59, 0.04]
52.2 N-3 replacing MUFA	13	14634	Mean Difference (IV, Random, 95% CI)	-0.18 [-0.25, -0.10]
52.3 N-3 replacing n-6	4	715	Mean Difference (IV, Random, 95% CI)	-0.33 [-0.50, -0.16]
52.4 N-3 replacing carbs/sugars	1	258	Mean Difference (IV, Random, 95% CI)	-0.5 [-1.49, 0.49]
52.5 N-3 replacing nil/low n-3 placebo	6	27776	Mean Difference (IV, Random, 95% CI)	-0.18 [-0.51, 0.14]
52.6 Replacement unclear	3	615	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.58, 0.18]
53 TG, fasting, mmoL/L - LCn3 - subgroup by intervention type	27		Mean Difference (IV, Random, 95% CI)	Subtotals only
53.1 Dietary advice	1	71	Mean Difference (IV, Random, 95% CI)	0.02 [-0.36, 0.40]
53.2 Supplemental foods	1	1210	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.15, 0.09]
53.3 Supplement (capsule)	24	42556	Mean Difference (IV, Random, 95% CI)	-0.19 [-0.38, -0.00]
53.4 Any combination	1	161	Mean Difference (IV, Random, 95% CI)	0.01 [-0.28, 0.30]
54 TG, fasting, mmoL/L - LCn3 - subgroup by duration	27		Mean Difference (IV, Random, 95% CI)	Subtotals only

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
54.1 Medium duration 1 to < 2 years in study	13	1880	Mean Difference (IV, Random, 95% CI)	-0.27 [-0.36, -0.19]
54.2 Medium-long duration: 2 to < 4 years in study	10	2550	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.31, -0.02]
54.3 Long duration ≥ 4 years in study	4	39568	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.32, -0.07]
55 TG, fasting, mmoL/L - LCn3 - subgroup by primary or secondary prevention	27		Mean Difference (IV, Random, 95% CI)	Subtotals only
55.1 Primary prevention	17	33114	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.26, -0.14]
55.2 Secondary prevention	9	2705	Mean Difference (IV, Random, 95% CI)	-0.27 [-0.44, -0.10]
55.3 Mixed primary & secondary prevention	1	8179	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
56 TG, fasting, mmoL/L - LCn3 - subgroup by statin use	27		Mean Difference (IV, Random, 95% CI)	Subtotals only
56.1 LCn3 - ≥ 50% of control group on statins	7	40976	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.21, -0.01]
56.2 LCn3 - < 50% of control group on statins	14	2414	Mean Difference (IV, Random, 95% CI)	-0.27 [-0.36, -0.18]
56.3 LCn3 - use of statins unclear	6	608	Mean Difference (IV, Random, 95% CI)	-0.23 [-0.38, -0.08]
57 High-density lipoprotein, serum, mmoL/L - LCn3	30	46604	Mean Difference (IV, Random, 95% CI)	0.03 [0.01, 0.05]
58 HDL, mmoL/L - LCn3 - SA fixed effects	30	46604	Mean Difference (IV, Fixed, 95% CI)	0.01 [0.00, 0.02]
59 HDL, mmoL/L - LCn3 - SA by summary risk of bias	30		Mean Difference (IV, Random, 95% CI)	Subtotals only
59.1 Low summary risk of bias	9	15840	Mean Difference (IV, Random, 95% CI)	0.02 [-0.01, 0.05]
59.2 Moderate or high risk of bias	21	30764	Mean Difference (IV, Random, 95% CI)	0.03 [0.00, 0.06]
60 HDL, mmoL/L - LCn3 - SA by compliance and study size	23		Mean Difference (IV, Random, 95% CI)	Subtotals only
60.1 SA - low risk of compliance bias	14	11381	Mean Difference (IV, Random, 95% CI)	0.05 [0.01, 0.10]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
60.2 SA - 100+ randomised	18	45940	Mean Difference (IV, Random, 95% CI)	0.03 [0.01, 0.05]
61 HDL, mmoL/L - LCn3 - subgroup by dose	30		Mean Difference (IV, Random, 95% CI)	Subtotals only
61.1 LCn3 ≤ 150 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
61.2 LCn3 > 150 ≤ 250 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
61.3 LCn3 > 250 ≤ 400 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
61.4 LCn3 > 400 ≤ 2400 mg/d	20	36920	Mean Difference (IV, Random, 95% CI)	0.02 [0.00, 0.04]
61.5 LCn3 > 2.4 ≤ 4.4 g/d	9	9625	Mean Difference (IV, Random, 95% CI)	0.06 [0.02, 0.10]
61.6 LCn3 > 4.4 g/d	1	59	Mean Difference (IV, Random, 95% CI)	0.0 [-0.16, 0.16]
62 HDL, mmoL/L - LCn3 - subgroup by replacement	30		Mean Difference (IV, Random, 95% CI)	Subtotals only
62.1 N-3 replacing SFA	3	2143	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.10, 0.07]
62.2 N-3 replacing MUFA	16	17453	Mean Difference (IV, Random, 95% CI)	0.03 [-0.00, 0.06]
62.3 N-3 replacing n-6	3	688	Mean Difference (IV, Random, 95% CI)	0.06 [0.00, 0.11]
62.4 N-3 replacing carbs/sugars	1	258	Mean Difference (IV, Random, 95% CI)	0.10 [-0.17, 0.37]
62.5 N-3 replacing nil/low n-3 placebo	8	27924	Mean Difference (IV, Random, 95% CI)	0.04 [-0.01, 0.09]
62.6 Replacement unclear	2	281	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.14, 0.08]
63 HDL, mmoL/L - LCn3 - subgroup by intervention type	30		Mean Difference (IV, Random, 95% CI)	Subtotals only
63.1 Dietary advice	2	1785	Mean Difference (IV, Random, 95% CI)	0.01 [-0.02, 0.04]
63.2 Supplemental foods	1	1210	Mean Difference (IV, Random, 95% CI)	0.03 [0.00, 0.06]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
63.3 Supplement (capsule)	24	43375	Mean Difference (IV, Random, 95% CI)	0.04 [0.01, 0.06]
63.4 Any combination	3	234	Mean Difference (IV, Random, 95% CI)	0.10 [-0.10, 0.31]
64 HDL, mmoL/L - LCn3 - subgroup by duration	30		Mean Difference (IV, Random, 95% CI)	Subtotals only
64.1 Medium duration 1 to < 2 years in study	13	1562	Mean Difference (IV, Random, 95% CI)	0.08 [0.01, 0.14]
64.2 Medium-long duration: 2 to < 4 years in study	12	4526	Mean Difference (IV, Random, 95% CI)	0.02 [-0.00, 0.04]
64.3 Long duration ≥ 4 years in study	5	40516	Mean Difference (IV, Random, 95% CI)	0.01 [-0.01, 0.04]
65 HDL, mmoL/L - LCn3 - subgroup by primary or secondary prevention	29		Mean Difference (IV, Random, 95% CI)	Subtotals only
65.1 Primary prevention	18	33804	Mean Difference (IV, Random, 95% CI)	0.03 [0.00, 0.06]
65.2 Secondary prevention	10	4547	Mean Difference (IV, Random, 95% CI)	0.03 [-0.00, 0.06]
65.3 Mixed primary & secondary prevention	1	8179	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
66 HDL, mmoL/L - LCn3 - subgroup by statin use	30		Mean Difference (IV, Random, 95% CI)	Subtotals only
66.1 LCn3 - ≥ 50% of control group on statins	10	42261	Mean Difference (IV, Random, 95% CI)	0.02 [0.00, 0.04]
66.2 LCn3 - < 50% of control group on statins	13	3690	Mean Difference (IV, Random, 95% CI)	0.04 [-0.00, 0.08]
66.3 LCn3 - use of statins unclear	7	653	Mean Difference (IV, Random, 95% CI)	0.07 [-0.07, 0.21]
67 Low-density lipoprotein, serum, mmoL/L - LCn3	25	43454	Mean Difference (IV, Random, 95% CI)	0.01 [-0.01, 0.03]
68 LDL, mmoL/L - LCn3 - SA fixed effects	25	43454	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.01, 0.03]
69 LDL, mmoL/L - LCn3 - SA by summary risk of bias	25		Mean Difference (IV, Random, 95% CI)	Subtotals only
69.1 Low summary risk of bias	9	14840	Mean Difference (IV, Random, 95% CI)	0.02 [-0.03, 0.07]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
69.2 Moderate or high risk of bias	16	28614	Mean Difference (IV, Random, 95% CI)	0.01 [-0.02, 0.03]
70 LDL, mmoL/L - LCn3 - SA by compliance and study size	19		Mean Difference (IV, Random, 95% CI)	Subtotals only
70.1 SA - low risk of compliance bias	14	11344	Mean Difference (IV, Random, 95% CI)	0.05 [-0.02, 0.11]
70.2 SA - 100+ randomised	14	42885	Mean Difference (IV, Random, 95% CI)	0.01 [-0.01, 0.03]
71 LDL, mmoL/L - LCn3 - subgroup by dose	25		Mean Difference (IV, Random, 95% CI)	Subtotals only
71.1 LCn3 ≤ 150 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
71.2 LCn3 > 150 ≤ 250 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
71.3 LCn3 > 250 ≤ 400 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
71.4 LCn3 > 400 ≤ 2400 mg/d	16	34054	Mean Difference (IV, Random, 95% CI)	0.01 [-0.01, 0.02]
71.5 LCn3 > 2.4 ≤ 4.4 g/d	7	9312	Mean Difference (IV, Random, 95% CI)	0.03 [-0.08, 0.15]
71.6 LCn3 > 4.4 g/d	2	88	Mean Difference (IV, Random, 95% CI)	0.22 [-0.09, 0.54]
72 LDL, mmoL/L - LCn3 - subgroup by replacement	25		Mean Difference (IV, Random, 95% CI)	Subtotals only
72.1 N-3 replacing SFA	2	429	Mean Difference (IV, Random, 95% CI)	0.17 [-0.14, 0.47]
72.2 N-3 replacing MUFA	14	14710	Mean Difference (IV, Random, 95% CI)	0.01 [-0.03, 0.05]
72.3 N-3 replacing n-6	2	242	Mean Difference (IV, Random, 95% CI)	0.14 [-0.26, 0.55]
72.4 N-3 replacing carbs/sugars	1	258	Mean Difference (IV, Random, 95% CI)	0.20 [-0.51, 0.91]
72.5 N-3 replacing nil/low n-3 placebo	6	27790	Mean Difference (IV, Random, 95% CI)	0.00 [-0.02, 0.02]
72.6 Replacement unclear	2	454	Mean Difference (IV, Random, 95% CI)	0.09 [-0.04, 0.23]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
73 LDL, mmoL/L - LCn3 - subgroup by intervention type	25		Mean Difference (IV, Random, 95% CI)	Subtotals only
73.1 Dietary advice	1	71	Mean Difference (IV, Random, 95% CI)	0.08 [-0.22, 0.38]
73.2 Supplemental foods	1	1124	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.10, 0.06]
73.3 Supplement (capsule)	21	42187	Mean Difference (IV, Random, 95% CI)	0.01 [-0.01, 0.03]
73.4 Any combination	2	72	Mean Difference (IV, Random, 95% CI)	0.08 [-0.44, 0.61]
74 LDL, mmoL/L - LCn3 - subgroup by duration	25		Mean Difference (IV, Random, 95% CI)	Subtotals only
74.1 Medium duration 1 to < 2 years in study	14	1862	Mean Difference (IV, Random, 95% CI)	0.06 [-0.03, 0.14]
74.2 Medium-long duration: 2 to < 4 years in study	7	2024	Mean Difference (IV, Random, 95% CI)	0.01 [-0.06, 0.07]
74.3 Long duration ≥ 4 years in study	4	39568	Mean Difference (IV, Random, 95% CI)	0.03 [-0.04, 0.10]
75 LDL, mmoL/L - LCn3 - subgroup by primary or secondary prevention	25		Mean Difference (IV, Random, 95% CI)	Subtotals only
75.1 Primary prevention	16	32717	Mean Difference (IV, Random, 95% CI)	0.01 [-0.01, 0.03]
75.2 Secondary prevention	8	2558	Mean Difference (IV, Random, 95% CI)	0.02 [-0.04, 0.09]
75.3 Mixed primary & secondary prevention	1	8179	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
76 LDL, mmoL/L - LCn3 - subgroup by statin use	25		Mean Difference (IV, Random, 95% CI)	Subtotals only
76.1 LCn3 - ≥ 50% of control group on statins	9	41227	Mean Difference (IV, Random, 95% CI)	0.00 [-0.02, 0.02]
76.2 LCn3 - < 50% of control group on statins	9	1564	Mean Difference (IV, Random, 95% CI)	0.12 [0.03, 0.21]
76.3 LCn3 - use of statins unclear	7	663	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.17, 0.14]

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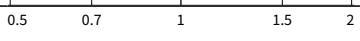
Analysis 2.1. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 1 MACCEs - LCn3.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
AREDS2 2014	116/2147	113/2056		4.76%	0.98[0.76,1.26]
DART 1989	338/1015	332/1018		19.65%	1.02[0.9,1.16]
OMEGA 2009	182/1752	149/1701		7.12%	1.19[0.97,1.46]
ORIGIN 2012	1034/6281	1017/6255		48.23%	1.01[0.94,1.1]
Risk & Prevention 2013	484/6239	467/6266		20.24%	1.04[0.92,1.18]
Total (95% CI)	**17434**	**17296**		**100%**	**1.03[0.97,1.09]**
Total events: 2154 (Higher omega 3), 2078 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=2.16, df=4(P=0.71); I²=0%					
Test for overall effect: Z=1.05(P=0.29)					



Favours higher omega 3 — Favours lower omega 3

Analysis 2.2. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 2 Myocardial infarction (overall) - LCn3.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
AlphaOmega - EPA+DHA 2010	89/2404	102/2433		6.12%	0.88[0.67,1.17]
AREDS2 2014	28/2147	30/2056		2.32%	0.89[0.54,1.49]
ASCEND 2018	186/7740	200/7740		9.34%	0.93[0.76,1.13]
Baldassarre 2006	1/32	0/32		0.07%	3[0.13,71]
Brox 2001	0/80	1/40		0.07%	0.17[0.01,4.05]
DART 1989	207/1015	215/1018		10.81%	0.97[0.81,1.14]
Derosa 2016	0/128	3/130		0.08%	0.15[0.01,2.78]
DO IT 2010	11/282	9/281		0.88%	1.22[0.51,2.89]
Doi 2014	1/119	0/119		0.07%	3[0.12,72.91]
EPOCH 2014	1/195	0/196		0.07%	3.02[0.12,73.57]
FORWARD 2013	1/289	1/297		0.09%	1.03[0.06,16.35]
GISSI-HF 2008	107/3494	129/3481		7%	0.83[0.64,1.06]
GISSI-P 1999	223/5665	233/5658		10.25%	0.96[0.8,1.14]
HARP 1995	1/41	3/39		0.14%	0.32[0.03,2.92]
JELIS 2007	71/9326	93/9319		5.31%	0.76[0.56,1.04]
OMEGA 2009	87/1919	78/1885		5.54%	1.1[0.81,1.48]
ORIGIN 2012	344/6281	316/6255		12.11%	1.08[0.93,1.26]
Proudman 2015	1/87	0/53		0.07%	1.84[0.08,44.38]
Raitt 2005	1/100	3/100		0.14%	0.33[0.04,3.15]
REDUCE-IT 2019	250/4089	355/4090		11.65%	0.7[0.6,0.82]
Risk & Prevention 2013	80/6239	90/6266		5.53%	0.89[0.66,1.2]
SCIMO 1999	1/112	4/111		0.14%	0.25[0.03,2.18]
SHOT 1996	7/317	12/293		0.78%	0.54[0.22,1.35]
SOFA 2006	1/273	3/273		0.13%	0.33[0.03,3.18]
SU.FOL.OM3 2010	32/1253	32/1248		2.56%	1[0.61,1.62]
THIS DIET 2008	1/51	3/50		0.14%	0.33[0.04,3.04]
VITAL 2019	145/12933	200/12938		8.61%	0.73[0.59,0.9]
Total (95% CI)	**66611**	**66401**		**100%**	**0.88[0.81,0.96]**
Total events: 1877 (Higher omega 3), 2115 (Lower omega 3)					
Heterogeneity: Tau²=0.01; Chi²=34.48, df=26(P=0.12); I²=24.6%					

Favours higher omega 3 — Favours lower omega 3

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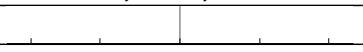
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=2.94(P=0)					



Favours higher omega 3 — Favours lower omega 3

Analysis 2.3. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 3 Total MI - LCn3 - SA fixed effects.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
AlphaOmega - EPA+DHA 2010	89/2404	102/2433		4.78%	0.88[0.67,1.17]
AREDS2 2014	28/2147	30/2056		1.45%	0.89[0.54,1.49]
ASCEND 2018	186/7740	200/7740		9.43%	0.93[0.76,1.13]
Baldassarre 2006	1/32	0/32		0.02%	3[0.13,71]
Brox 2001	0/80	1/40		0.09%	0.17[0.01,4.05]
DART 1989	207/1015	215/1018		10.12%	0.97[0.81,1.14]
Derosa 2016	0/128	3/130		0.16%	0.15[0.01,2.78]
DO IT 2010	11/282	9/281		0.43%	1.22[0.51,2.89]
Doi 2014	1/119	0/119		0.02%	3[0.12,72.91]
EPOCH 2014	1/195	0/196		0.02%	3.02[0.12,73.57]
FORWARD 2013	1/289	1/297		0.05%	1.03[0.06,16.35]
GISSI-HF 2008	107/3494	129/3481		6.09%	0.83[0.64,1.06]
GISSI-P 1999	223/5665	233/5658		10.99%	0.96[0.8,1.14]
HARP 1995	1/41	3/39		0.15%	0.32[0.03,2.92]
JELIS 2007	71/9326	93/9319		4.39%	0.76[0.56,1.04]
OMEGA 2009	87/1919	78/1885		3.71%	1.1[0.81,1.48]
ORIGIN 2012	344/6281	316/6255		14.93%	1.08[0.93,1.26]
Proudman 2015	1/87	0/53		0.03%	1.84[0.08,44.38]
Raitt 2005	1/100	3/100		0.14%	0.33[0.04,3.15]
REDUCE-IT 2019	250/4089	355/4090		16.74%	0.7[0.6,0.82]
Risk & Prevention 2013	80/6239	90/6266		4.24%	0.89[0.66,1.2]
SCIMO 1999	1/112	4/111		0.19%	0.25[0.03,2.18]
SHOT 1996	7/317	12/293		0.59%	0.54[0.22,1.35]
SOFA 2006	1/273	3/273		0.14%	0.33[0.03,3.18]
SU.FOL.OM3 2010	32/1253	32/1248		1.51%	1[0.61,1.62]
THIS DIET 2008	1/51	3/50		0.14%	0.33[0.04,3.04]
VITAL 2019	145/12933	200/12938		9.43%	0.73[0.59,0.9]
Total (95% CI)	**66611**	**66401**		**100%**	**0.89[0.83,0.94]**
Total events: 1877 (Higher omega 3), 2115 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=34.48, df=26(P=0.12); I^2=24.6%					
Test for overall effect: Z=3.95(P<0.0001)					

Favours higher omega 3 — Favours lower omega 3

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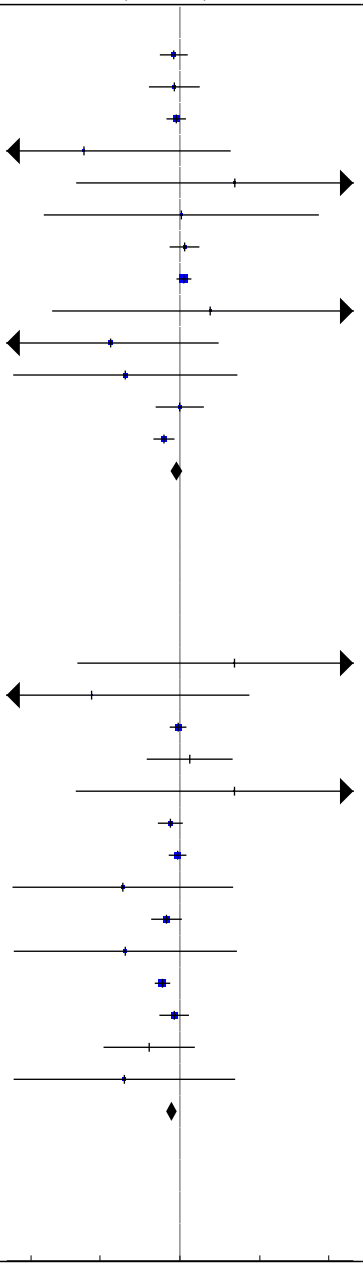
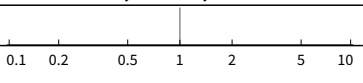
Analysis 2.4. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 4 Total MI - LCn3 - SA by summary risk of bias.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.4.1 Low summary risk of bias					
AlphaOmega - EPA+DHA 2010	89/2404	102/2433		12.81%	0.88[0.67,1.17]
AREDS2 2014	28/2147	30/2056		4.75%	0.89[0.54,1.49]
ASCEND 2018	186/7740	200/7740		19.93%	0.93[0.76,1.13]
Derosa 2016	0/128	3/130		0.16%	0.15[0.01,2.78]
EPOCH 2014	1/195	0/196		0.14%	3.02[0.12,73.57]
FORWARD 2013	1/289	1/297		0.18%	1.03[0.06,16.35]
OMEGA 2009	87/1919	78/1885		11.56%	1.1[0.81,1.48]
ORIGIN 2012	344/6281	316/6255		26.23%	1.08[0.93,1.26]
Proudman 2015	1/87	0/53		0.14%	1.84[0.08,44.38]
SCIMO 1999	1/112	4/111		0.29%	0.25[0.03,2.18]
SOFA 2006	1/273	3/273		0.27%	0.33[0.03,3.18]
SU.FOL.OM3 2010	32/1253	32/1248		5.25%	1[0.61,1.62]
VITAL 2019	145/12933	200/12938		18.29%	0.73[0.59,0.9]
Subtotal (95% CI)	**35761**	**35615**		**100%**	**0.93[0.83,1.05]**
Total events: 916 (Higher omega 3), 969 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=15.04, df=12(P=0.24); I^2=20.19%					
Test for overall effect: Z=1.17(P=0.24)					
2.4.2 Moderate or high summary risk of bias					
Baldassarre 2006	1/32	0/32		0.11%	3[0.13,71]
Brox 2001	0/80	1/40		0.11%	0.17[0.01,4.05]
DART 1989	207/1015	215/1018		21.11%	0.97[0.81,1.14]
DO IT 2010	11/282	9/281		1.46%	1.22[0.51,2.89]
Doi 2014	1/119	0/119		0.11%	3[0.12,72.91]
GISSI-HF 2008	107/3494	129/3481		12.83%	0.83[0.64,1.06]
GISSI-P 1999	223/5665	233/5658		19.82%	0.96[0.8,1.14]
HARP 1995	1/41	3/39		0.23%	0.32[0.03,2.92]
JELIS 2007	71/9326	93/9319		9.49%	0.76[0.56,1.04]
Raitt 2005	1/100	3/100		0.22%	0.33[0.04,3.15]
REDUCE-IT 2019	250/4089	355/4090		23.07%	0.7[0.6,0.82]
Risk & Prevention 2013	80/6239	90/6266		9.91%	0.89[0.66,1.2]
SHOT 1996	7/317	12/293		1.3%	0.54[0.22,1.35]
THIS DIET 2008	1/51	3/50		0.23%	0.33[0.04,3.04]
Subtotal (95% CI)	**30850**	**30786**		**100%**	**0.84[0.76,0.94]**
Total events: 961 (Higher omega 3), 1146 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=15.93, df=13(P=0.25); I^2=18.38%					
Test for overall effect: Z=3.15(P=0)					
Test for subgroup differences: Chi^2=1.53, df=1 (P=0.22), I^2=34.55%					



Analysis 2.5. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 5 Total MI - LCn3 - SA by compliance and study size.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 SA - low risk of compliance bias					



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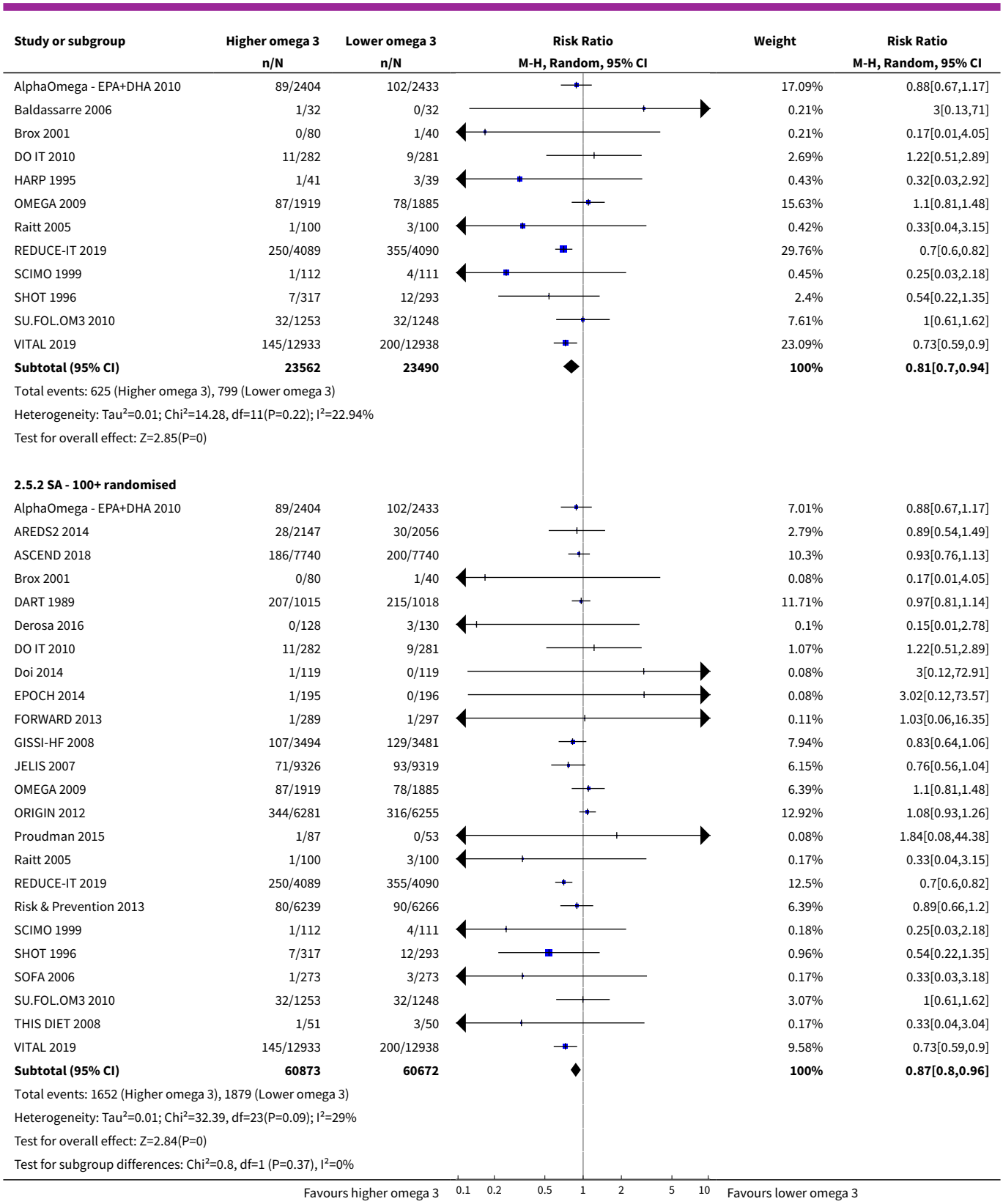

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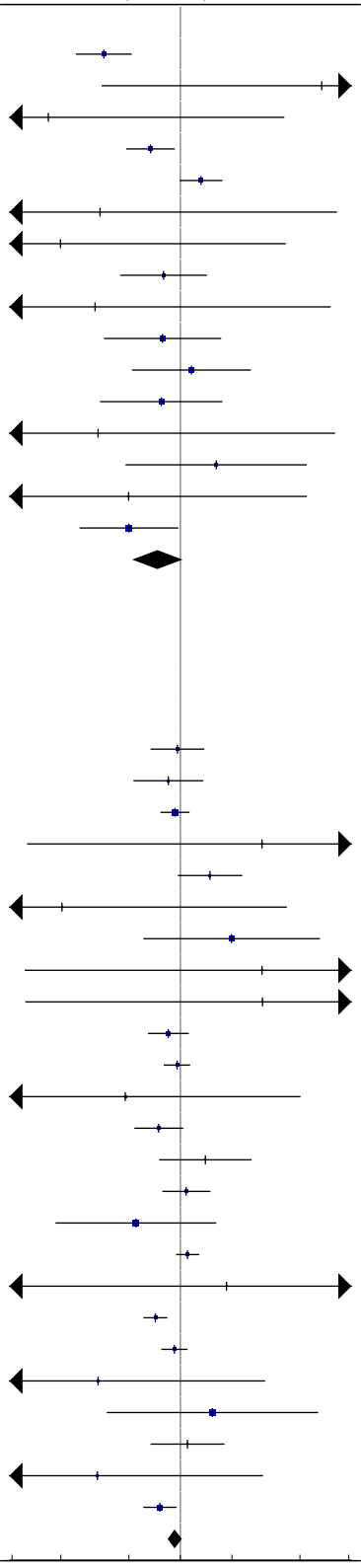
Analysis 2.6. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 6 Total MI - LCn3 - subgroup by fatality.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.6.1 Fatal MI					
AlphaOmega - EPA+DHA 2010	36/2404	102/2433		13.12%	0.36[0.25,0.52]
AREDS2 2014	3/2147	0/2056		1.22%	6.7[0.35,129.7]
Brox 2001	0/80	1/40		1.07%	0.17[0.01,4.05]
DART 1989	56/1015	84/1018		13.65%	0.67[0.48,0.93]
DART2 2003	102/1571	76/1543		14.04%	1.32[0.99,1.76]
Derosa 2016	0/128	1/130		1.06%	0.34[0.01,8.23]
DO IT 2010	0/282	2/281		1.17%	0.2[0.01,4.13]
GISSI-HF 2008	20/3494	25/3481		10.68%	0.8[0.44,1.43]
HARP 1995	0/41	1/39		1.08%	0.32[0.01,7.57]
JELIS 2007	11/9326	14/9319		8.5%	0.79[0.36,1.73]
OMEGA 2009	13/1919	11/1885		8.39%	1.16[0.52,2.58]
Risk & Prevention 2013	10/6239	13/6266		8.17%	0.77[0.34,1.76]
SCIMO 1999	0/112	1/111		1.06%	0.33[0.01,8.02]
SHOT 1996	7/317	4/293		5.21%	1.62[0.48,5.47]
SU.FOL.OM3 2010	1/1253	2/1248		1.79%	0.5[0.05,5.49]
VITAL 2019	13/12933	26/12938		9.79%	0.5[0.26,0.97]
Subtotal (95% CI)	**43261**	**43081**		**100%**	**0.73[0.52,1.03]**
Total events: 272 (Higher omega 3), 363 (Lower omega 3)					
Heterogeneity: Tau^2=0.19; Chi^2=38.87, df=15(P=0); I^2=61.41%					
Test for overall effect: Z=1.78(P=0.07)					
2.6.2 Non-fatal MI					
AlphaOmega - EPA+DHA 2010	56/2404	59/2433		4.83%	0.96[0.67,1.38]
AREDS2 2014	30/2147	40/2433		3.23%	0.85[0.53,1.36]
ASCEND 2018	186/7740	200/7740		9.74%	0.93[0.76,1.13]
Baldassarre 2006	1/32	0/32		0.09%	3[0.13,71]
DART 1989	49/1015	33/1018		3.69%	1.49[0.97,2.3]
Derosa 2016	0/128	2/130		0.1%	0.2[0.01,4.19]
DO IT 2010	8/282	4/281		0.6%	1.99[0.61,6.54]
Doi 2014	1/119	0/119		0.09%	3[0.12,72.91]
EPOCH 2014	1/195	0/196		0.09%	3.02[0.12,73.57]
GISSI-HF 2008	92/3494	108/3481		6.95%	0.85[0.65,1.12]
GISSI-P 1999	223/5665	233/5658		10.5%	0.96[0.8,1.14]
HARP 1995	1/41	2/39		0.16%	0.48[0.04,5.04]
JELIS 2007	62/9326	83/9319		5.54%	0.75[0.54,1.04]
OFAMI 2001	21/150	15/150		2%	1.4[0.75,2.61]
OMEGA 2009	74/1662	67/1631		5.64%	1.08[0.78,1.5]
OPAL 2010	5/376	9/372		0.72%	0.55[0.19,1.62]
ORIGIN 2012	316/6281	284/6225		11.59%	1.1[0.94,1.29]
Proudman 2015	1/86	0/53		0.09%	1.86[0.08,44.89]
REDUCE-IT 2019	237/4089	332/4090		11.37%	0.71[0.61,0.84]
Risk & Prevention 2013	228/6239	248/6266		10.65%	0.92[0.77,1.1]
SCIMO 1999	1/112	3/111		0.17%	0.33[0.03,3.13]
SHOT 1996	5/317	3/293		0.42%	1.54[0.37,6.39]
SU.FOL.OM3 2010	32/1253	29/1248		2.95%	1.1[0.67,1.81]
THIS DIET 2008	1/51	3/50		0.18%	0.33[0.04,3.04]
VITAL 2019	132/12933	174/12938		8.62%	0.76[0.61,0.95]
Subtotal (95% CI)	**66137**	**66306**		**100%**	**0.92[0.84,1.02]**



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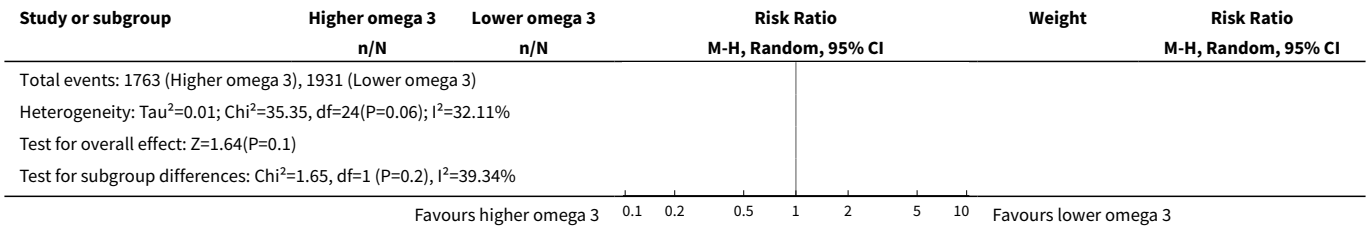
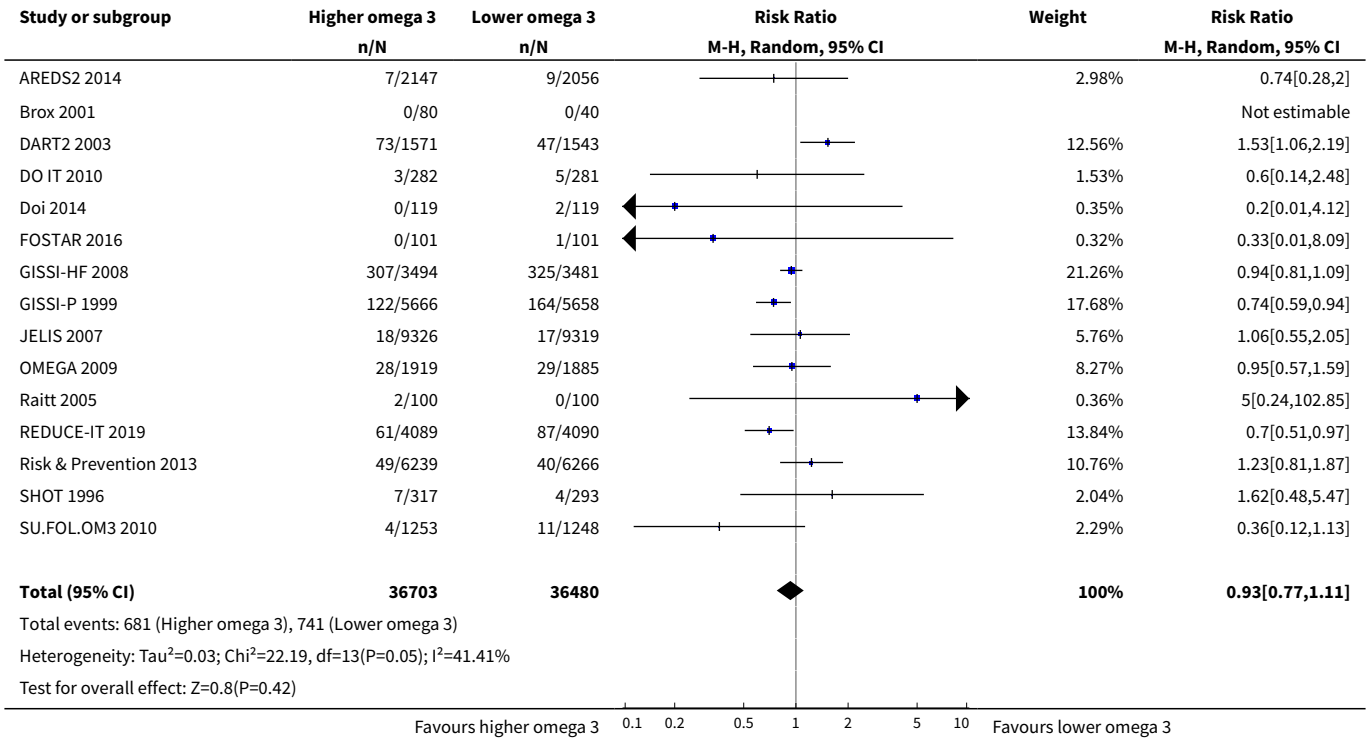
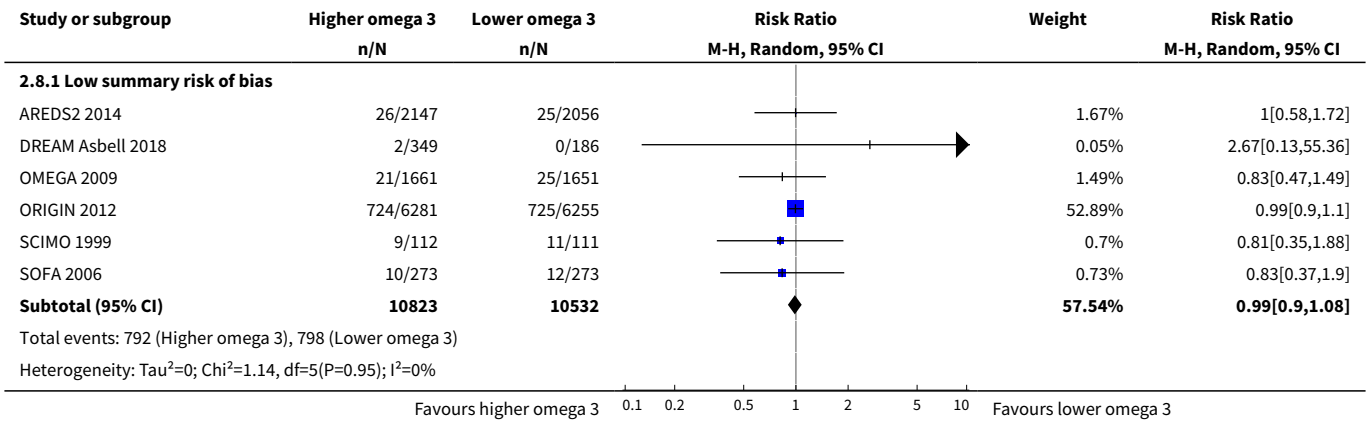


Analysis 2.7. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 7 Sudden cardiac death (overall) - LCn3.



Analysis 2.8. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 8 Angina - LCn3.



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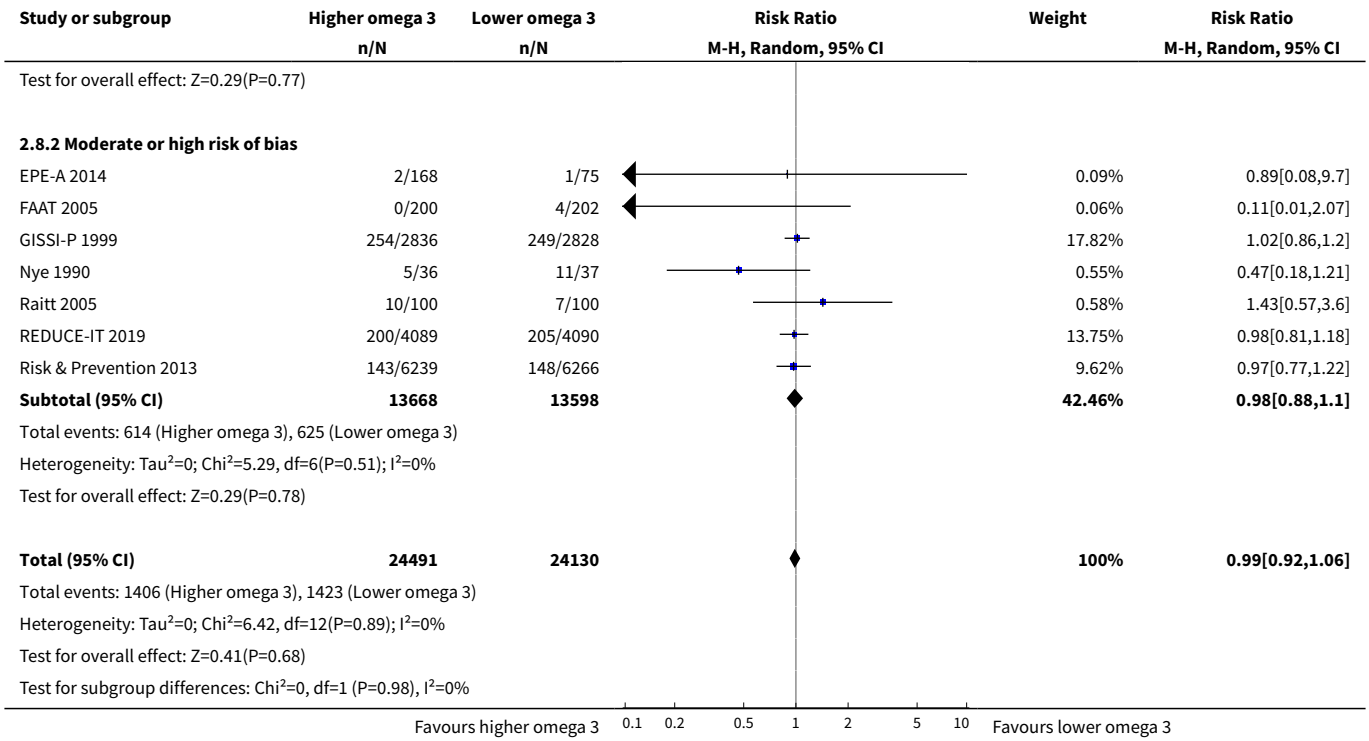
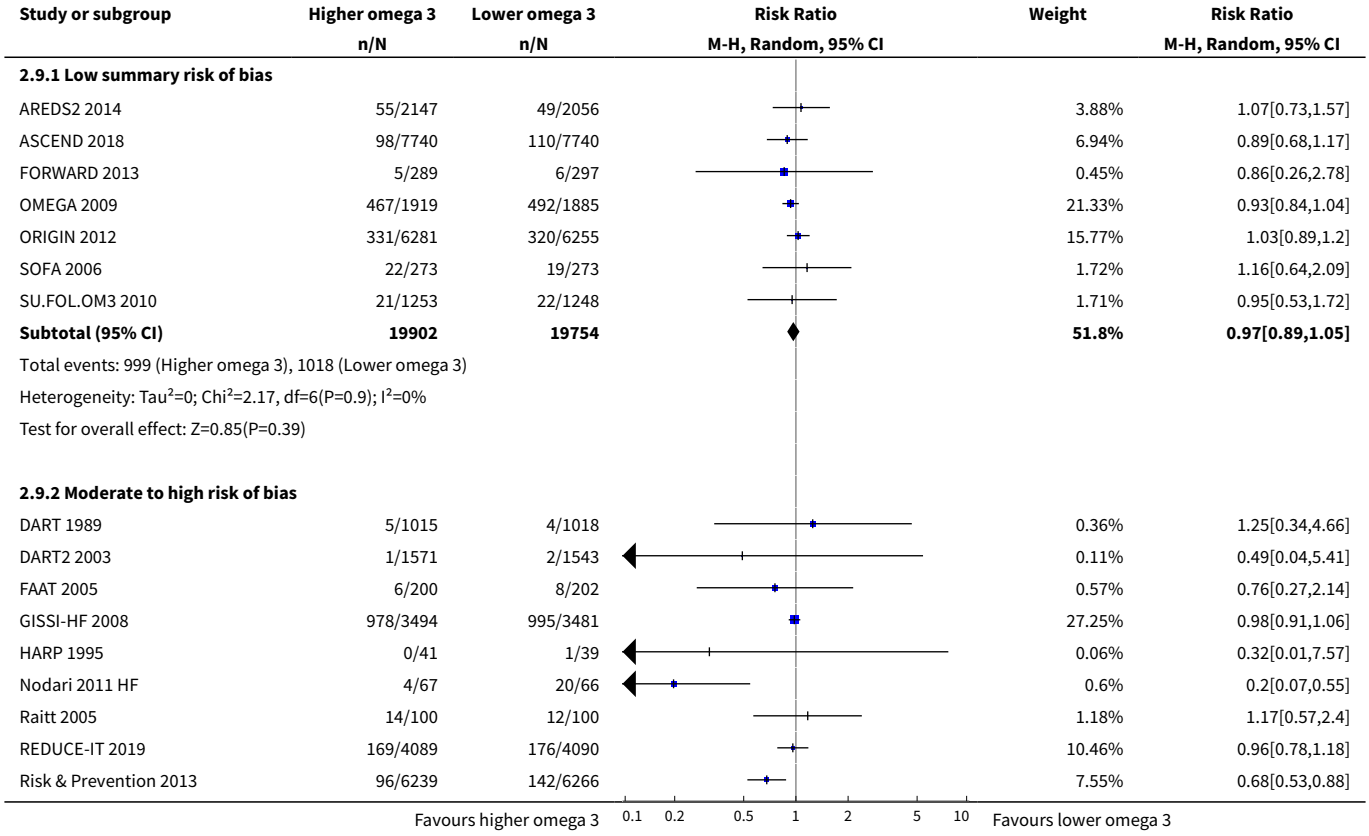


Analysis 2.9. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 9 Heart failure - LCn3.



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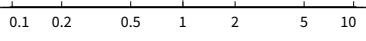
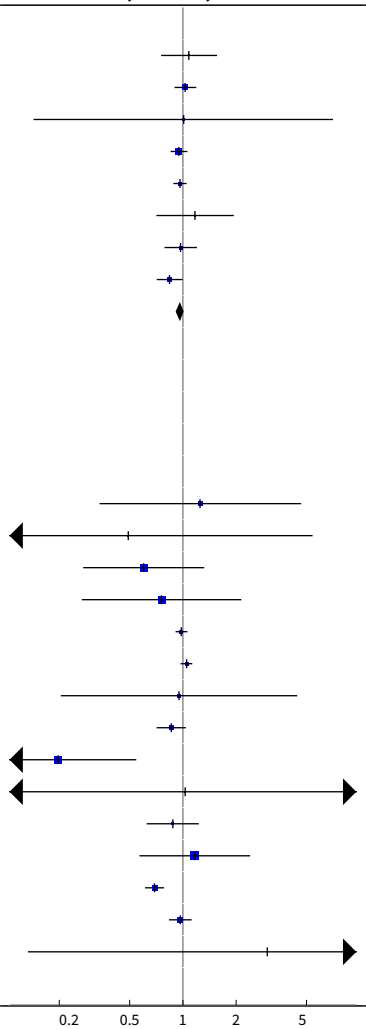
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Shinto 2014	1/13	0/13		0.06%	3[0.13,67.51]
Subtotal (95% CI)	**16829**	**16818**		**48.2%**	**0.85[0.69,1.04]**
Total events: 1274 (Higher omega 3), 1360 (Lower omega 3)					
Heterogeneity: Tau^2=0.03; Chi^2=18.48, df=9(P=0.03); I^2=51.3%					
Test for overall effect: Z=1.56(P=0.12)					
Total (95% CI)	**36731**	**36572**		**100%**	**0.94[0.87,1.02]**
Total events: 2273 (Higher omega 3), 2378 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=20.66, df=16(P=0.19); I^2=22.56%					
Test for overall effect: Z=1.56(P=0.12)					
Test for subgroup differences: Chi^2=1.32, df=1 (P=0.25), I^2=24.07%					



Favours higher omega 3 — Favours lower omega 3

Analysis 2.10. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 10 Revascularisation - LCn3.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.10.1 Low summary risk of bias					
AREDS2 2014	60/2147	53/2056		2.89%	1.08[0.75,1.56]
ASCEND 2018	368/7740	356/7740		8.42%	1.03[0.9,1.19]
EPOCH 2014	2/195	2/196		0.13%	1.01[0.14,7.06]
OMEGA 2009	466/1686	482/1654		9.86%	0.95[0.85,1.06]
ORIGIN 2012	866/6281	896/6255		10.74%	0.96[0.88,1.05]
SCIMO 1999	26/112	22/111		1.7%	1.17[0.71,1.94]
SU.FOL.OM3 2010	152/1253	156/1248		6.01%	0.97[0.79,1.2]
VITAL 2019	247/12933	294/12938		7.43%	0.84[0.71,0.99]
Subtotal (95% CI)	**32347**	**32198**		**47.18%**	**0.96[0.91,1.01]**
Total events: 2187 (Higher omega 3), 2261 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=4.55, df=7(P=0.71); I^2=0%					
Test for overall effect: Z=1.45(P=0.15)					
2.10.2 Moderate to high risk of bias					
DART 1989	5/1015	4/1018		0.28%	1.25[0.34,4.66]
DART2 2003	1/1571	2/1543		0.09%	0.49[0.04,5.41]
Doi 2014	9/119	15/119		0.75%	0.6[0.27,1.32]
FAAT 2005	6/200	8/202		0.44%	0.76[0.27,2.14]
GISSI-HF 2008	978/3494	995/3481		11.2%	0.98[0.91,1.06]
GISSI-P 1999	1104/5666	1053/5658		11.16%	1.05[0.97,1.13]
HARP 1995	3/41	3/39		0.21%	0.95[0.2,4.43]
JELIS 2007	191/9326	222/9319		6.59%	0.86[0.71,1.04]
Nodari 2011 HF	4/67	20/66		0.46%	0.2[0.07,0.55]
Nye 1990	1/36	1/37		0.07%	1.03[0.07,15.82]
OFAMI 2001	43/150	49/150		3.19%	0.88[0.62,1.23]
Raitt 2005	14/100	12/100		0.89%	1.17[0.57,2.4]
REDUCE-IT 2019	376/4089	544/4090		9.17%	0.69[0.61,0.78]
Risk & Prevention 2013	334/6239	347/6266		8.26%	0.97[0.84,1.12]
Shinto 2014	1/13	0/13		0.05%	3[0.13,67.51]
SHOT 1996	0/317	0/293			Not estimable



Favours higher omega 3 — Favours lower omega 3

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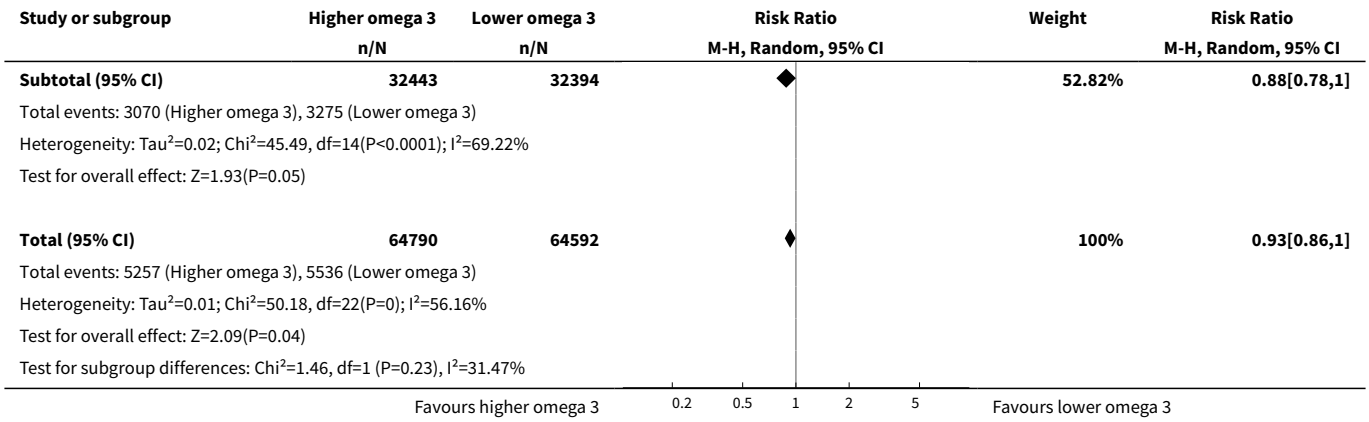
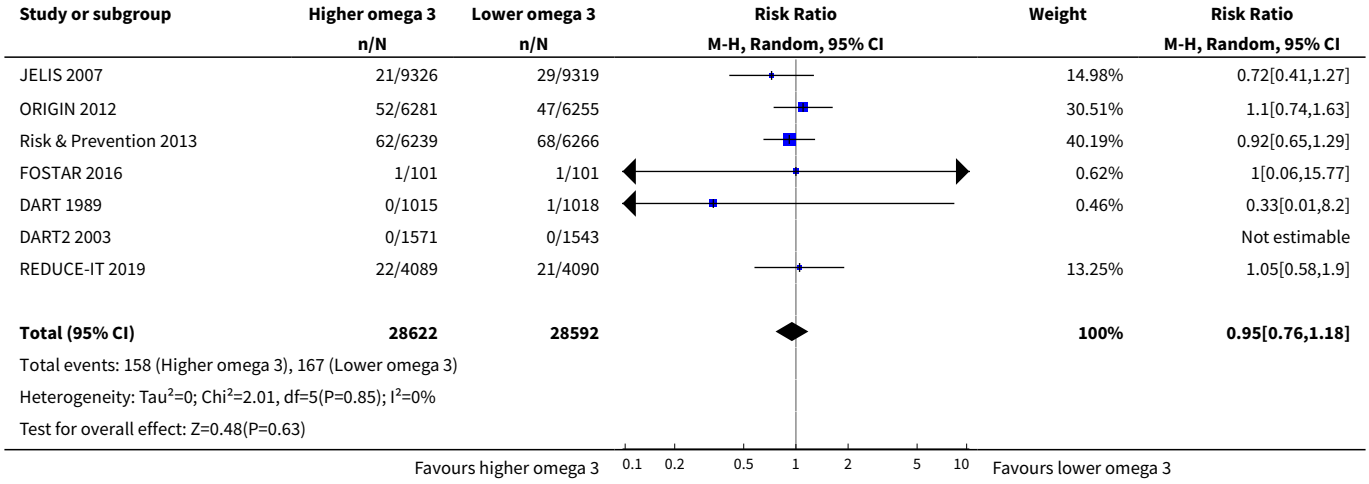
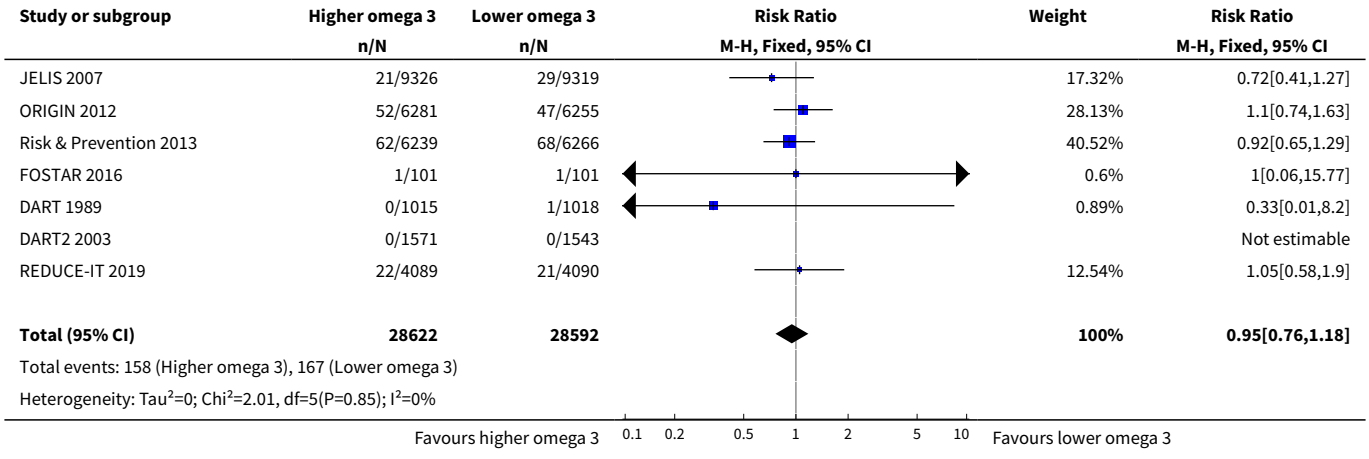


Analysis 2.11. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 11 Peripheral arterial disease - LCn3.



Analysis 2.12. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 12 PAD - LCn3 - SA fixed effects.



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Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=0.5(P=0.62)					

Favours higher omega 3 — Favours lower omega 3

Analysis 2.13. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 13 PAD - LCn3 - SA by summary risk of bias.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.13.1 Low summary risk of bias					
ORIGIN 2012	52/6281	47/6255		98.01%	1.1[0.74,1.63]
FOSTAR 2016	1/101	1/101		1.99%	1[0.06,15.77]
Subtotal (95% CI)	**6382**	**6356**		**100%**	**1.1[0.75,1.62]**
Total events: 53 (Higher omega 3), 48 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.95); I^2=0%					
Test for overall effect: Z=0.48(P=0.63)					
2.13.2 Moderate or high risk of bias					
JELIS 2007	21/9326	29/9319		21.75%	0.72[0.41,1.27]
Risk & Prevention 2013	62/6239	68/6266		58.35%	0.92[0.65,1.29]
DART 1989	0/1015	1/1018		0.67%	0.33[0.01,8.2]
DART2 2003	0/1571	0/1543			Not estimable
REDUCE-IT 2019	22/4089	21/4090		19.23%	1.05[0.58,1.9]
Subtotal (95% CI)	**22240**	**22236**		**100%**	**0.89[0.68,1.15]**
Total events: 105 (Higher omega 3), 119 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=1.2, df=3(P=0.75); I^2=0%					
Test for overall effect: Z=0.9(P=0.37)					
Test for subgroup differences: Chi^2=0.81, df=1 (P=0.37), I^2=0%					

Favours higher omega 3 — Favours lower omega 3

Analysis 2.14. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 14 PAD - LCn3 - SA compliance and study size.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.14.1 SA compliance					
FOSTAR 2016	1/101	1/101		4.47%	1[0.06,15.77]
REDUCE-IT 2019	22/4089	21/4090		95.53%	1.05[0.58,1.9]
Subtotal (95% CI)	**4190**	**4191**		**100%**	**1.05[0.58,1.87]**
Total events: 23 (Higher omega 3), 22 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.97); I^2=0%					
Test for overall effect: Z=0.15(P=0.88)					
2.14.2 SA study size 100+					
JELIS 2007	21/9326	29/9319		14.98%	0.72[0.41,1.27]
ORIGIN 2012	52/6281	47/6255		30.51%	1.1[0.74,1.63]
Risk & Prevention 2013	62/6239	68/6266		40.19%	0.92[0.65,1.29]
FOSTAR 2016	1/101	1/101		0.62%	1[0.06,15.77]

Favours higher omega 3 — Favours lower omega 3

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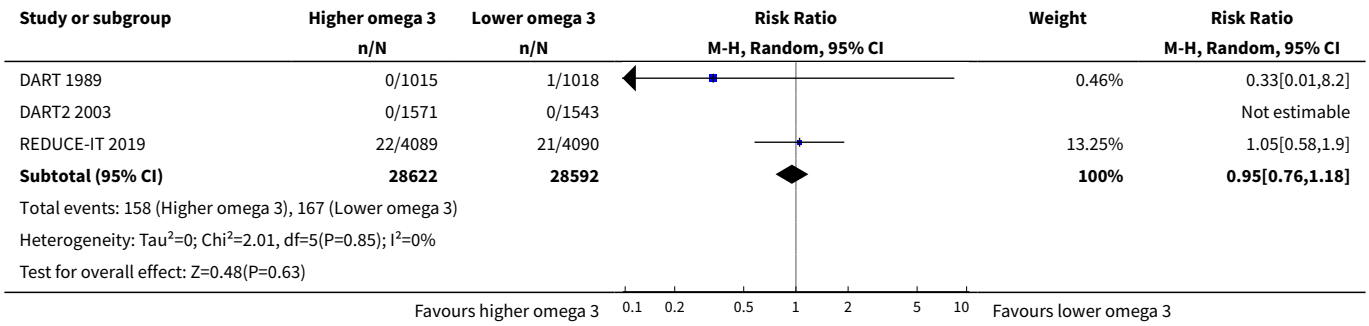
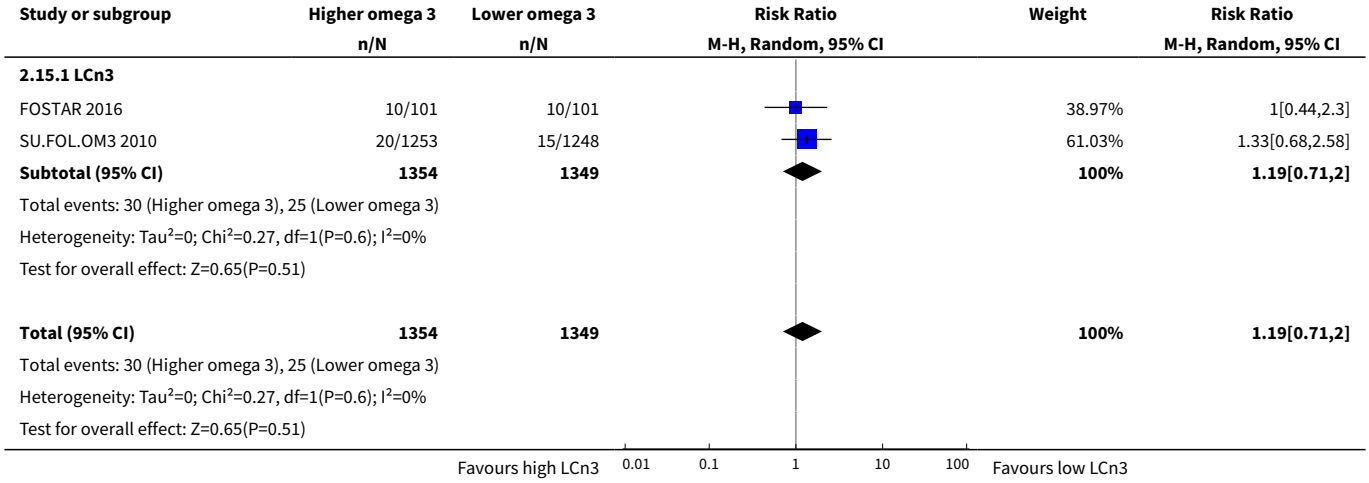
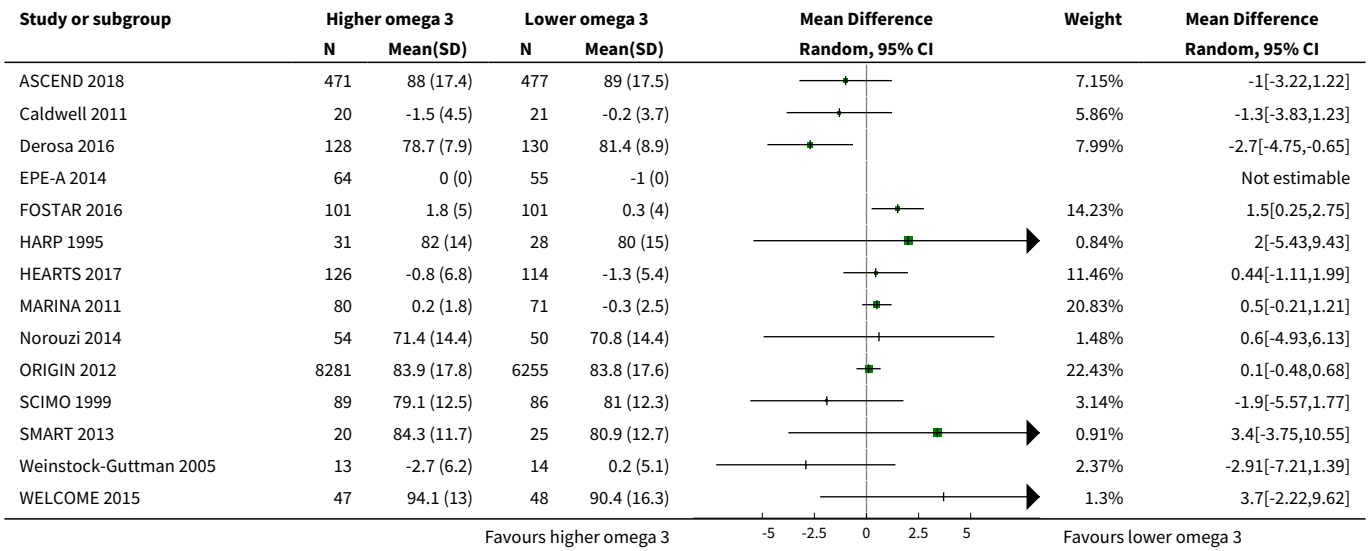


Analysis 2.15. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 15 Acute coronary syndrome - LCn3.



Analysis 2.16. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 16 Body weight, kg - LCn3.



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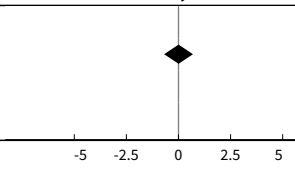
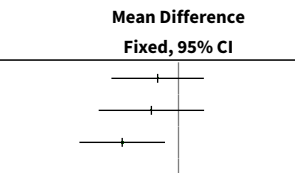
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Total ***	**9525**		**7475**			**100%**	**0[-0.69,0.7]**
Heterogeneity: Tau^2=0.47; Chi^2=20.79, df=12(P=0.05); I^2=42.27%							
Test for overall effect: Z=0.01(P=0.99)							



Favours higher omega 3 — Favours lower omega 3

Analysis 2.17. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 17 Weight, kg - LCn3 - SA fixed effects.

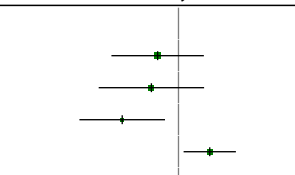
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
ASCEND 2018	471	88 (17.4)	477	89 (17.5)		2.98%	-1[-3.22,1.22]
Caldwell 2011	20	-1.5 (4.5)	21	-0.2 (3.7)		2.29%	-1.3[-3.83,1.23]
Derosa 2016	128	78.7 (7.9)	130	81.4 (8.9)		3.47%	-2.7[-4.75,-0.65]
EPE-A 2014	64	0 (0)	55	-1 (0)			Not estimable
FOSTAR 2016	101	1.8 (5)	101	0.3 (4)		9.3%	1.5[0.25,2.75]
HARP 1995	31	82 (14)	28	80 (15)		0.27%	2[-5.43,9.43]
HEARTS 2017	126	-0.8 (6.8)	114	-1.3 (5.4)		6.12%	0.44[-1.11,1.99]
MARINA 2011	80	0.2 (1.8)	71	-0.3 (2.5)		29.15%	0.5[-0.21,1.21]
Norouzi 2014	54	71.4 (14.4)	50	70.8 (14.4)		0.48%	0.6[-4.93,6.13]
ORIGIN 2012	8281	83.9 (17.8)	6255	83.8 (17.6)		43.38%	0.1[-0.48,0.68]
SCIMO 1999	89	79.1 (12.5)	86	81 (12.3)		1.08%	-1.9[-5.57,1.77]
SMART 2013	20	84.3 (11.7)	25	80.9 (12.7)		0.29%	3.4[-3.75,10.55]
Weinstock-Guttman 2005	13	-2.7 (6.2)	14	0.2 (5.1)		0.79%	-2.91[-7.21,1.39]
WELCOME 2015	47	94.1 (13)	48	90.4 (16.3)		0.42%	3.7[-2.22,9.62]
Total ***	**9525**		**7475**			**100%**	**0.19[-0.19,0.57]**
Heterogeneity: Tau^2=0; Chi^2=20.79, df=12(P=0.05); I^2=42.27%							
Test for overall effect: Z=0.98(P=0.33)							



Favours higher omega 3 — Favours lower omega 3

Analysis 2.18. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 18 Weight, kg - LCn3 - SA by summary risk of bias.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.18.1 Low summary risk of bias							
ASCEND 2018	471	88 (17.4)	477	89 (17.5)		9.57%	-1[-3.22,1.22]
Caldwell 2011	20	-1.5 (4.5)	21	-0.2 (3.7)		7.99%	-1.3[-3.83,1.23]
Derosa 2016	128	78.7 (7.9)	130	81.4 (8.9)		10.57%	-2.7[-4.75,-0.65]
FOSTAR 2016	101	1.8 (5)	101	0.3 (4)		17.34%	1.5[0.25,2.75]
MARINA 2011	80	0.2 (1.8)	71	-0.3 (2.5)		23.42%	0.5[-0.21,1.21]
ORIGIN 2012	8281	83.9 (17.8)	6255	83.8 (17.6)		24.75%	0.1[-0.48,0.68]
SCIMO 1999	89	79.1 (12.5)	86	81 (12.3)		4.45%	-1.9[-5.57,1.77]
WELCOME 2015	47	94.1 (13)	48	90.4 (16.3)		1.9%	3.7[-2.22,9.62]
Subtotal ***	**9217**		**7189**			**100%**	**-0.1[-0.94,0.75]**
Heterogeneity: Tau^2=0.66; Chi^2=17.66, df=7(P=0.01); I^2=60.37%							



Favours higher omega 3 — Favours lower omega 3

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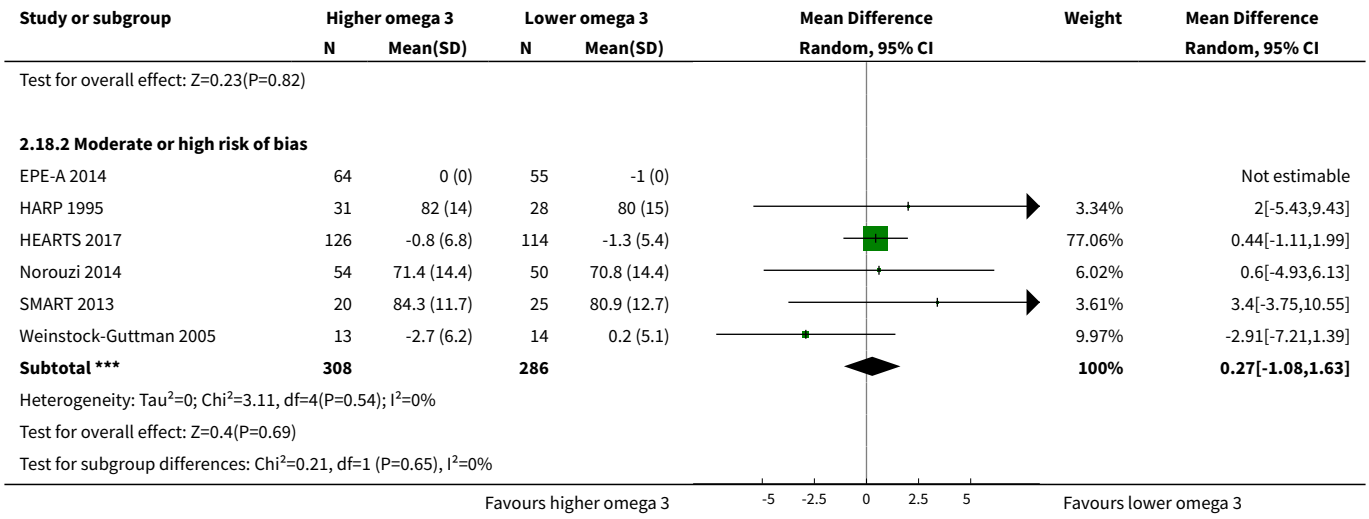
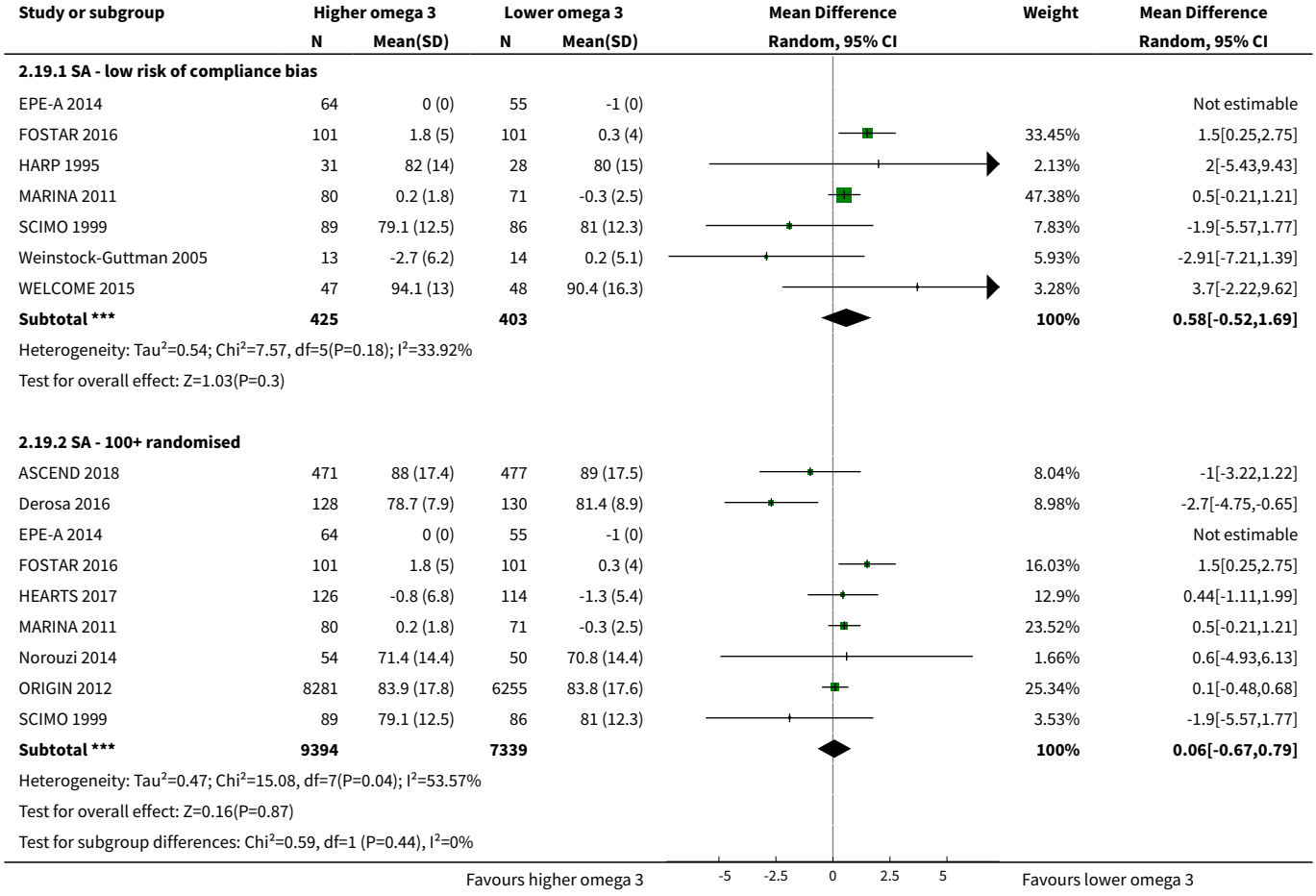


Analysis 2.19. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 19 Weight, kg - LCn3 - SA by compliance and study size.



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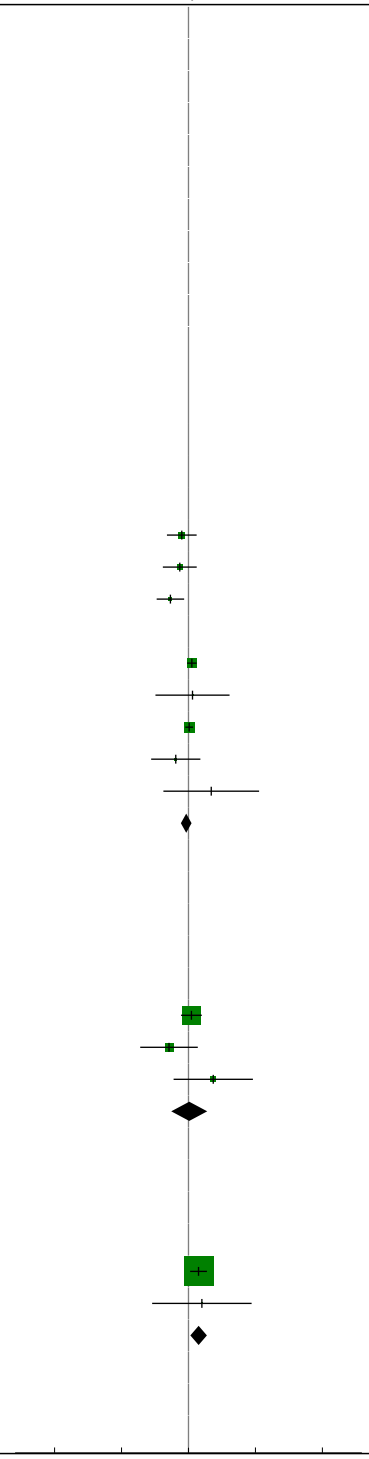
Analysis 2.20. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 20 Weight, kg - LCn3 - subgroup by dose.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.20.1 LCn3 ≤ 150 mg/d							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.20.2 LCn3 > 150 ≤ 250 mg/d							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.20.3 LCn3 > 250 ≤ 400 mg/d							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.20.4 LCn3 > 400 ≤ 2400 mg/d							
ASCEND 2018	471	88 (17.4)	477	89 (17.5)		9.8%	-1[-3.22,1.22]
Caldwell 2011	20	-1.5 (4.5)	21	-0.2 (3.7)		7.98%	-1.3[-3.83,1.23]
Derosa 2016	128	78.7 (7.9)	130	81.4 (8.9)		10.99%	-2.7[-4.75,-0.65]
EPE-A 2014	55	0.5 (0)	55	-1 (0)			Not estimable
MARINA 2011	80	0.2 (1.8)	71	-0.3 (2.5)		30.59%	0.5[-0.21,1.21]
Norouzi 2014	54	71.4 (14.4)	50	70.8 (14.4)		1.98%	0.6[-4.93,6.13]
ORIGIN 2012	8281	83.9 (17.8)	6255	83.8 (17.6)		33.22%	0.1[-0.48,0.68]
SCIMO 1999	89	79.1 (12.5)	86	81 (12.3)		4.22%	-1.9[-5.57,1.77]
SMART 2013	20	84.3 (11.7)	25	80.9 (12.7)		1.21%	3.4[-3.75,10.55]
Subtotal ***	**9198**		**7170**			**100%**	**-0.34[-1.14,0.46]**
Heterogeneity: Tau^2=0.41; Chi^2=12.39, df=7(P=0.09); I^2=43.49%							
Test for overall effect: Z=0.83(P=0.4)							
2.20.5 LCn3 > 2.4 ≤ 4.4 g/d							
EPE-A 2014	64	0 (0)	55	-1 (0)			Not estimable
HEARTS 2017	126	-0.8 (6.8)	114	-1.3 (5.4)		58.52%	0.44[-1.11,1.99]
Weinstock-Guttman 2005	13	-2.7 (6.2)	14	0.2 (5.1)		25.43%	-2.91[-7.21,1.39]
WELCOME 2015	47	94.1 (13)	48	90.4 (16.3)		16.06%	3.7[-2.22,9.62]
Subtotal ***	**250**		**231**			**100%**	**0.11[-2.58,2.8]**
Heterogeneity: Tau^2=2.6; Chi^2=3.44, df=2(P=0.18); I^2=41.81%							
Test for overall effect: Z=0.08(P=0.94)							
2.20.6 LCn3 > 4.4 g/d							
FOSTAR 2016	101	1.8 (5)	101	0.3 (4)		97.23%	1.5[0.25,2.75]
HARP 1995	31	82 (14)	28	80 (15)		2.77%	2[-5.43,9.43]
Subtotal ***	**132**		**129**			**100%**	**1.51[0.28,2.75]**
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.9); I^2=0%							
Test for overall effect: Z=2.4(P=0.02)							
Test for subgroup differences: Chi^2=6.1, df=1 (P=0.05), I^2=67.19%							



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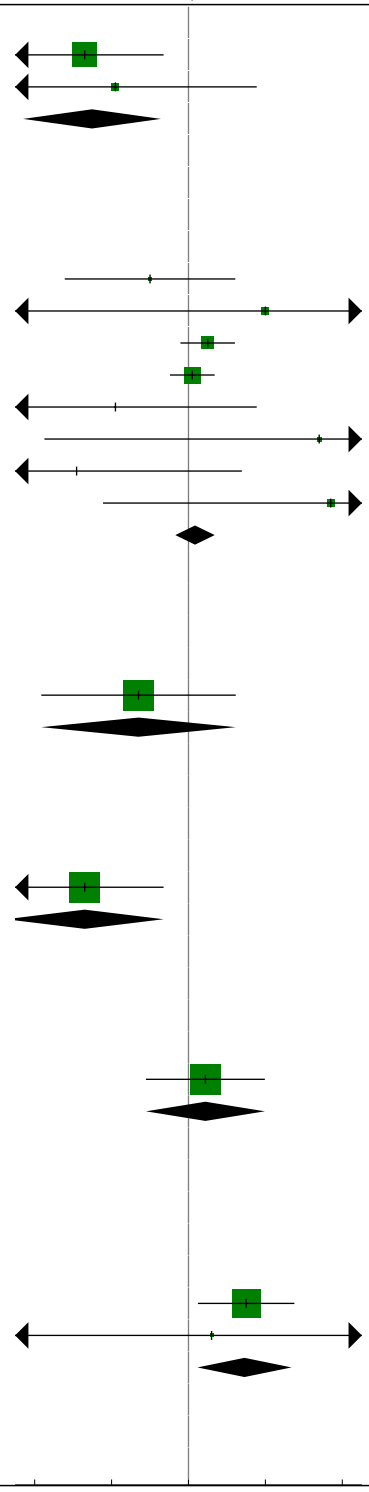
Analysis 2.21. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 21 Weight, kg - LCn3 - subgroup by replacement.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.21.1 N-3 replacing SFA							
Derosa 2016	128	78.7 (7.9)	130	81.4 (8.9)		76.22%	-2.7[-4.75,-0.65]
SCIMO 1999	89	79.1 (12.5)	86	81 (12.3)		23.78%	-1.9[-5.57,1.77]
Subtotal ***	**217**		**216**			**100%**	**-2.51[-4.3,-0.72]**
Heterogeneity: Tau^2=0; Chi^2=0.14, df=1(P=0.71); I^2=0%							
Test for overall effect: Z=2.74(P=0.01)							
2.21.2 N-3 replacing MUFA							
ASCEND 2018	471	88 (17.4)	477	89 (17.5)		5.16%	-1[-3.22,1.22]
HARP 1995	31	82 (14)	28	80 (15)		0.48%	2[-5.43,9.43]
MARINA 2011	80	0.2 (1.8)	71	-0.3 (2.5)		38.7%	0.5[-0.21,1.21]
ORIGIN 2012	8281	83.9 (17.8)	6255	83.8 (17.6)		51.07%	0.1[-0.48,0.68]
SCIMO 1999	89	79.1 (12.5)	86	81 (12.3)		1.92%	-1.9[-5.57,1.77]
SMART 2013	20	84.3 (11.7)	25	80.9 (12.7)		0.51%	3.4[-3.75,10.55]
Weinstock-Guttman 2005	13	-2.7 (6.2)	14	0.2 (5.1)		1.41%	-2.91[-7.21,1.39]
WELCOME 2015	47	94.1 (13)	48	90.4 (16.3)		0.75%	3.7[-2.22,9.62]
Subtotal ***	**9032**		**7004**			**100%**	**0.17[-0.34,0.68]**
Heterogeneity: Tau^2=0.05; Chi^2=7.53, df=7(P=0.38); I^2=7%							
Test for overall effect: Z=0.65(P=0.52)							
2.21.3 N-3 replacing n-6							
Caldwell 2011	20	-1.5 (4.5)	21	-0.2 (3.7)		100%	-1.3[-3.83,1.23]
Subtotal ***	**20**		**21**			**100%**	**-1.3[-3.83,1.23]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.01(P=0.31)							
2.21.4 N-3 replacing carbs/sugars							
Derosa 2016	128	78.7 (7.9)	130	81.4 (8.9)		100%	-2.7[-4.75,-0.65]
Subtotal ***	**128**		**130**			**100%**	**-2.7[-4.75,-0.65]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.58(P=0.01)							
2.21.5 N-3 replacing nil/low n-3 placebo							
HEARTS 2017	126	-0.8 (6.8)	114	-1.3 (5.4)		100%	0.44[-1.11,1.99]
Subtotal ***	**126**		**114**			**100%**	**0.44[-1.11,1.99]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.56(P=0.58)							
2.21.6 Replacement unclear							
EPE-A 2014	64	0 (0)	55	-1 (0)			Not estimable
FOSTAR 2016	101	1.8 (5)	101	0.3 (4)		95.11%	1.5[0.25,2.75]
Norouzi 2014	54	71.4 (14.4)	50	70.8 (14.4)		4.89%	0.6[-4.93,6.13]
Subtotal ***	**219**		**206**			**100%**	**1.46[0.23,2.68]**
Heterogeneity: Tau^2=0; Chi^2=0.1, df=1(P=0.76); I^2=0%							
Test for overall effect: Z=2.33(P=0.02)							
Test for subgroup differences: Chi^2=21.35, df=1 (P=0), I^2=76.58%							



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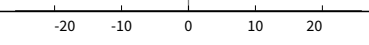
Analysis 2.22. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 22 Weight, kg - LCn3 - subgroup by intervention type.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.22.1 Dietary advice							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.22.2 Supplemental foods							
FOSTAR 2016	101	1.8 (5)	101	0.3 (4)		14.23%	1.5[0.25,2.75]
Subtotal ***	**101**		**101**			**14.23%**	**1.5[0.25,2.75]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.34(P=0.02)							
2.22.3 Supplement (capsule)							
ASCEND 2018	471	88 (17.4)	477	89 (17.5)		7.15%	-1[-3.22,1.22]
Caldwell 2011	20	-1.5 (4.5)	21	-0.2 (3.7)		5.86%	-1.3[-3.83,1.23]
Derosa 2016	128	78.7 (7.9)	130	81.4 (8.9)		7.99%	-2.7[-4.75,-0.65]
EPE-A 2014	64	0 (0)	55	-1 (0)			Not estimable
HARP 1995	31	82 (14)	28	80 (15)		0.84%	2[-5.43,9.43]
HEARTS 2017	126	-0.8 (6.8)	114	-1.3 (5.4)		11.46%	0.44[-1.11,1.99]
MARINA 2011	80	0.2 (1.8)	71	-0.3 (2.5)		20.83%	0.5[-0.21,1.21]
Norouzi 2014	54	71.4 (14.4)	50	70.8 (14.4)		1.48%	0.6[-4.93,6.13]
ORIGIN 2012	8281	83.9 (17.8)	6255	83.8 (17.6)		22.43%	0.1[-0.48,0.68]
SCIMO 1999	89	79.1 (12.5)	86	81 (12.3)		3.14%	-1.9[-5.57,1.77]
WELCOME 2015	47	94.1 (13)	48	90.4 (16.3)		1.3%	3.7[-2.22,9.62]
Subtotal ***	**9391**		**7335**			**82.49%**	**-0.14[-0.82,0.53]**
Heterogeneity: Tau^2=0.29; Chi^2=13.5, df=9(P=0.14); I^2=33.35%							
Test for overall effect: Z=0.42(P=0.68)							
2.22.4 Any combination							
SMART 2013	20	84.3 (11.7)	25	80.9 (12.7)		0.91%	3.4[-3.75,10.55]
Weinstock-Guttman 2005	13	-2.7 (6.2)	14	0.2 (5.1)		2.37%	-2.91[-7.21,1.39]
Subtotal ***	**33**		**39**			**3.28%**	**-0.43[-6.47,5.61]**
Heterogeneity: Tau^2=10.86; Chi^2=2.2, df=1(P=0.14); I^2=54.53%							
Test for overall effect: Z=0.14(P=0.89)							
Total ***	**9525**		**7475**			**100%**	**0[-0.69,0.7]**
Heterogeneity: Tau^2=0.47; Chi^2=20.79, df=12(P=0.05); I^2=42.27%							
Test for overall effect: Z=0.01(P=0.99)							
Test for subgroup differences: Chi^2=5.17, df=1 (P=0.08), I^2=61.29%							



Favours higher omega 3 — Favours lower omega 3

Analysis 2.23. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 23 Weight, kg - LCn3 - subgroup by duration.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.23.1 Medium duration 1 to < 2 years in study							
Caldwell 2011	20	-1.5 (4.5)	21	-0.2 (3.7)		18.68%	-1.3[-3.83,1.23]

Favours higher omega 3 — Favours lower omega 3

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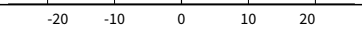
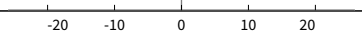
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Derosa 2016	128	78.7 (7.9)	130	81.4 (8.9)		21.9%	-2.7[-4.75,-0.65]
EPE-A 2014	64	0 (0)	55	-1 (0)			Not estimable
MARINA 2011	80	0.2 (1.8)	71	-0.3 (2.5)		31%	0.5[-0.21,1.21]
Norouzi 2014	54	71.4 (14.4)	50	70.8 (14.4)		7.1%	0.6[-4.93,6.13]
SMART 2013	20	84.3 (11.7)	25	80.9 (12.7)		4.66%	3.4[-3.75,10.55]
Weinstock-Guttman 2005	13	-2.7 (6.2)	14	0.2 (5.1)		10.3%	-2.91[-7.21,1.39]
WELCOME 2015	47	94.1 (13)	48	90.4 (16.3)		6.37%	3.7[-2.22,9.62]
Subtotal ***	**426**		**414**			**100%**	**-0.54[-2.21,1.12]**
Heterogeneity: Tau²=2.2; Chi²=13.7, df=6(P=0.03); I²=56.19%							
Test for overall effect: Z=0.64(P=0.52)							
2.23.2 Medium-long duration: 2 to < 4 years in study							
FOSTAR 2016	101	1.8 (5)	101	0.3 (4)		51.07%	1.5[0.25,2.75]
HARP 1995	31	82 (14)	28	80 (15)		2.2%	2[-5.43,9.43]
HEARTS 2017	126	-0.8 (6.8)	114	-1.3 (5.4)		38.14%	0.44[-1.11,1.99]
SCIMO 1999	89	79.1 (12.5)	86	81 (12.3)		8.59%	-1.9[-5.57,1.77]
Subtotal ***	**347**		**329**			**100%**	**0.81[-0.3,1.92]**
Heterogeneity: Tau²=0.22; Chi²=3.53, df=3(P=0.32); I²=15.11%							
Test for overall effect: Z=1.44(P=0.15)							
2.23.3 Long duration ≥ 4 years in study							
ASCEND 2018	471	88 (17.4)	477	89 (17.5)		6.42%	-1[-3.22,1.22]
ORIGIN 2012	8281	83.9 (17.8)	6255	83.8 (17.6)		93.58%	0.1[-0.48,0.68]
Subtotal ***	**8752**		**6732**			**100%**	**0.03[-0.53,0.59]**
Heterogeneity: Tau²=0; Chi²=0.88, df=1(P=0.35); I²=0%							
Test for overall effect: Z=0.1(P=0.92)							
Test for subgroup differences: Chi²=2.21, df=1 (P=0.33), I²=9.55%							



Favours higher omega 3 — Favours lower omega 3

Analysis 2.24. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 24 Weight, kg - LCn3 - subgroup by primary or secondary prevention.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.24.1 Primary CVD prevention							
ASCEND 2018	471	88 (17.4)	477	89 (17.5)		9.21%	-1[-3.22,1.22]
Caldwell 2011	20	-1.5 (4.5)	21	-0.2 (3.7)		7.67%	-1.3[-3.83,1.23]
Derosa 2016	128	78.7 (7.9)	130	81.4 (8.9)		10.19%	-2.7[-4.75,-0.65]
EPE-A 2014	64	0 (0)	55	-1 (0)			Not estimable
FOSTAR 2016	101	1.8 (5)	101	0.3 (4)		16.93%	1.5[0.25,2.75]
MARINA 2011	80	0.2 (1.8)	71	-0.3 (2.5)		23.14%	0.5[-0.21,1.21]
Norouzi 2014	54	71.4 (14.4)	50	70.8 (14.4)		2.05%	0.6[-4.93,6.13]
ORIGIN 2012	8281	83.9 (17.8)	6255	83.8 (17.6)		24.52%	0.1[-0.48,0.68]
SMART 2013	20	84.3 (11.7)	25	80.9 (12.7)		1.26%	3.4[-3.75,10.55]
Weinstock-Guttman 2005	13	-2.7 (6.2)	14	0.2 (5.1)		3.23%	-2.91[-7.21,1.39]
WELCOME 2015	47	94.1 (13)	48	90.4 (16.3)		1.8%	3.7[-2.22,9.62]
Subtotal ***	**9279**		**7247**			**100%**	**-0.04[-0.87,0.78]**
Heterogeneity: Tau²=0.63; Chi²=19.22, df=9(P=0.02); I²=53.16%							
Test for overall effect: Z=0.11(P=0.91)							



Favours higher omega 3 — Favours lower omega 3

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Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.24.2 Secondary CVD prevention							
HARP 1995	31	82 (14)	28	80 (15)		3.55%	2[-5.43,9.43]
HEARTS 2017	126	-0.8 (6.8)	114	-1.3 (5.4)		81.94%	0.44[-1.11,1.99]
SCIMO 1999	89	79.1 (12.5)	86	81 (12.3)		14.51%	-1.9[-5.57,1.77]
Subtotal ***	**246**		**228**			**100%**	**0.16[-1.24,1.56]**
Heterogeneity: Tau²=0; Chi²=1.57, df=2(P=0.46); I²=0%							
Test for overall effect: Z=0.22(P=0.83)							
Test for subgroup differences: Chi²=0.06, df=1 (P=0.81), I²=0%							

Favours higher omega 3 -20 -10 0 10 20 Favours lower omega 3

Analysis 2.25. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 25 Weight, kg - LCn3 - subgroup by statin use.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.25.1 LCn3 - ≥ 50% of control group on statins							
ASCEND 2018	471	88 (17.4)	477	89 (17.5)		5.62%	-1[-3.22,1.22]
HEARTS 2017	126	-0.8 (6.8)	114	-1.3 (5.4)		11.57%	0.44[-1.11,1.99]
ORIGIN 2012	8281	83.9 (17.8)	6255	83.8 (17.6)		82.02%	0.1[-0.48,0.68]
WELCOME 2015	47	94.1 (13)	48	90.4 (16.3)		0.79%	3.7[-2.22,9.62]
Subtotal ***	**8925**		**6894**			**100%**	**0.11[-0.42,0.63]**
Heterogeneity: Tau²=0; Chi²=2.55, df=3(P=0.47); I²=0%							
Test for overall effect: Z=0.39(P=0.69)							
2.25.2 LCn3 - < 50% of control group on statins							
FOSTAR 2016	101	1.8 (5)	101	0.3 (4)		34.62%	1.5[0.25,2.75]
HARP 1995	31	82 (14)	28	80 (15)		2.23%	2[-5.43,9.43]
MARINA 2011	80	0.2 (1.8)	71	-0.3 (2.5)		48.77%	0.5[-0.21,1.21]
SCIMO 1999	89	79.1 (12.5)	86	81 (12.3)		8.18%	-1.9[-5.57,1.77]
Weinstock-Guttman 2005	13	-2.7 (6.2)	14	0.2 (5.1)		6.2%	-2.91[-7.21,1.39]
Subtotal ***	**314**		**300**			**100%**	**0.47[-0.66,1.6]**
Heterogeneity: Tau²=0.55; Chi²=6.53, df=4(P=0.16); I²=38.74%							
Test for overall effect: Z=0.82(P=0.41)							
2.25.3 LCn3 - use of statins unclear							
Caldwell 2011	20	-1.5 (4.5)	21	-0.2 (3.7)		36.23%	-1.3[-3.83,1.23]
Derosa 2016	128	78.7 (7.9)	130	81.4 (8.9)		48.17%	-2.7[-4.75,-0.65]
EPE-A 2014	64	0 (0)	55	-1 (0)			Not estimable
Norouzi 2014	54	71.4 (14.4)	50	70.8 (14.4)		9.65%	0.6[-4.93,6.13]
SMART 2013	20	84.3 (11.7)	25	80.9 (12.7)		5.96%	3.4[-3.75,10.55]
Subtotal ***	**286**		**281**			**100%**	**-1.51[-3.3,0.27]**
Heterogeneity: Tau²=0.62; Chi²=3.63, df=3(P=0.3); I²=17.31%							
Test for overall effect: Z=1.66(P=0.1)							
Test for subgroup differences: Chi²=3.52, df=1 (P=0.17), I²=43.1%							

Favours higher omega 3 -20 -10 0 10 20 Favours lower omega 3

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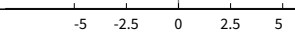
Analysis 2.26. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 26 Body mass index, kg/m² - LCn3.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
AlphaOmega - EPA+DHA 2010	630	0 (1.8)	630	-0.1 (1.8)		24.7%	0.1[-0.1,0.3]
Caldwell 2011	20	-0.5 (4.5)	21	-0.2 (3.7)		0.59%	-0.3[-2.83,2.23]
Derosa 2016	128	28.6 (2.1)	130	29.2 (2.3)		9.53%	-0.6[-1.14,-0.06]
DO IT 2010	124	26.8 (3.5)	117	27 (3.9)		3.88%	-0.2[-1.14,0.74]
EPE-A 2014	64	0 (0)	55	-0.3 (0)			Not estimable
HEARTS 2017	126	0.6 (7.5)	114	-0.2 (1.8)		1.97%	0.8[-0.56,2.16]
Mita 2007	30	25.1 (5.3)	30	24.1 (3)		0.79%	1[-1.18,3.18]
Nodari 2011 HF	67	26 (0.4)	66	26 (0.6)		26.28%	0[-0.17,0.17]
Norouzi 2014	54	24.8 (4.9)	50	24.2 (4.2)		1.21%	0.58[-1.17,2.33]
OFAMI 2001	115	26.6 (3.9)	116	26 (3.2)		4.01%	0.6[-0.32,1.52]
ORIGIN 2012	6281	30.3 (5.6)	6255	30.3 (5.6)		24.88%	0[-0.2,0.2]
SMART 2013	20	29.8 (3.5)	25	28.2 (3.4)		0.91%	1.6[-0.43,3.63]
Sofi 2010	6	-0.6 (0)	5	-0.1 (0)			Not estimable
Tande 2016	50	0.6 (9.7)	50	-0.4 (12.1)		0.21%	1[-3.3,5.3]
WELCOME 2015	47	33.4 (4.9)	48	30.8 (4.5)		1.04%	2.6[0.71,4.49]
Total ***	**7762**		**7712**			**100%**	**0.06[-0.14,0.25]**

Heterogeneity: Tau^2=0.03; Chi^2=19.67, df=12(P=0.07); I^2=39%

Test for overall effect: Z=0.56(P=0.57)



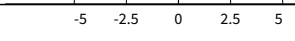
Favours higher omega 3 — Favours lower omega 3

Analysis 2.27. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 27 BMI, kg/m² - LCn3 - SA fixed effects.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
AlphaOmega - EPA+DHA 2010	630	0 (1.8)	630	-0.1 (1.8)		24.7%	0.1[-0.1,0.3]
Caldwell 2011	20	-0.5 (4.5)	21	-0.2 (3.7)		0.59%	-0.3[-2.83,2.23]
Derosa 2016	128	28.6 (2.1)	130	29.2 (2.3)		9.53%	-0.6[-1.14,-0.06]
DO IT 2010	124	26.8 (3.5)	117	27 (3.9)		3.88%	-0.2[-1.14,0.74]
EPE-A 2014	64	0 (0)	55	-0.3 (0)			Not estimable
HEARTS 2017	126	0.6 (7.5)	114	-0.2 (1.8)		1.97%	0.8[-0.56,2.16]
Mita 2007	30	25.1 (5.3)	30	24.1 (3)		0.79%	1[-1.18,3.18]
Nodari 2011 HF	67	26 (0.4)	66	26 (0.6)		26.28%	0[-0.17,0.17]
Norouzi 2014	54	24.8 (4.9)	50	24.2 (4.2)		1.21%	0.58[-1.17,2.33]
OFAMI 2001	115	26.6 (3.9)	116	26 (3.2)		4.01%	0.6[-0.32,1.52]
ORIGIN 2012	6281	30.3 (5.6)	6255	30.3 (5.6)		24.88%	0[-0.2,0.2]
SMART 2013	20	29.8 (3.5)	25	28.2 (3.4)		0.91%	1.6[-0.43,3.63]
Sofi 2010	6	-0.6 (0)	5	-0.1 (0)			Not estimable
Tande 2016	50	0.6 (9.7)	50	-0.4 (12.1)		0.21%	1[-3.3,5.3]
WELCOME 2015	47	33.4 (4.9)	48	30.8 (4.5)		1.04%	2.6[0.71,4.49]
Total ***	**7762**		**7712**			**100%**	**0.06[-0.14,0.25]**

Heterogeneity: Tau^2=0.03; Chi^2=19.67, df=12(P=0.07); I^2=39%

Test for overall effect: Z=0.56(P=0.57)



Favours higher omega 3 — Favours lower omega 3

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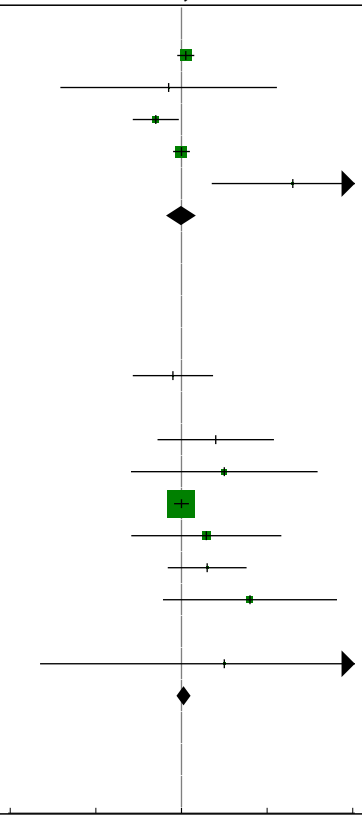
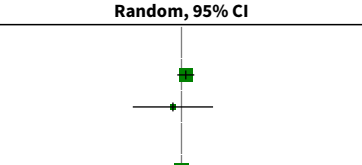
Analysis 2.28. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 28 BMI, kg/m²- LCn3 - SA by summary risk of bias.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.28.1 Low risk of bias							
AlphaOmega - EPA+DHA 2010	630	0 (1.8)	630	-0.1 (1.8)		36.97%	0.1[-0.1,0.3]
Caldwell 2011	20	-0.5 (4.5)	21	-0.2 (3.7)		1.81%	-0.3[-2.83,2.23]
Derosa 2016	128	28.6 (2.1)	130	29.2 (2.3)		21%	-0.6[-1.14,-0.06]
ORIGIN 2012	6281	30.3 (5.6)	6255	30.3 (5.6)		37.09%	0[-0.2,0.2]
WELCOME 2015	47	33.4 (4.9)	48	30.8 (4.5)		3.13%	2.6[0.71,4.49]
Subtotal ***	**7106**		**7084**			**100%**	**-0.01[-0.36,0.33]**
Heterogeneity: Tau²=0.08; Chi²=12.98, df=4(P=0.01); I²=69.17%							
Test for overall effect: Z=0.07(P=0.94)							
2.28.2 Moderate/high risk of bias							
DO IT 2010	124	26.8 (3.5)	117	27 (3.9)		3.08%	-0.2[-1.14,0.74]
EPE-A 2014	64	0 (0)	55	-0.3 (0)			Not estimable
HEARTS 2017	126	0.6 (7.5)	114	-0.2 (1.8)		1.47%	0.8[-0.56,2.16]
Mita 2007	30	25.1 (5.3)	30	24.1 (3)		0.57%	1[-1.18,3.18]
Nodari 2011 HF	67	26 (0.4)	66	26 (0.6)		89.99%	0[-0.17,0.17]
Norouzi 2014	54	24.8 (4.9)	50	24.2 (4.2)		0.88%	0.58[-1.17,2.33]
OFAMI 2001	115	26.6 (3.9)	116	26 (3.2)		3.2%	0.6[-0.32,1.52]
SMART 2013	20	29.8 (3.5)	25	28.2 (3.4)		0.66%	1.6[-0.43,3.63]
Sofi 2010	6	-0.6 (0)	5	-0.1 (0)			Not estimable
Tande 2016	50	0.6 (9.7)	50	-0.4 (12.1)		0.15%	1[-3.3,5.3]
Subtotal ***	**656**		**628**			**100%**	**0.05[-0.12,0.21]**
Heterogeneity: Tau²=0; Chi²=6.64, df=7(P=0.47); I²=0%							
Test for overall effect: Z=0.57(P=0.57)							
Test for subgroup differences: Chi²=0.1, df=1 (P=0.76), I²=0%							



Analysis 2.29. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 29 BMI, kg/m²- LCn3 - SA by compliance and study size.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.29.1 SA - low risk of compliance bias							
AlphaOmega - EPA+DHA 2010	630	0 (1.8)	630	-0.1 (1.8)		43.64%	0.1[-0.1,0.3]
DO IT 2010	124	26.8 (3.5)	117	27 (3.9)		8.24%	-0.2[-1.14,0.74]
EPE-A 2014	64	0 (0)	55	-0.3 (0)			Not estimable
Nodari 2011 HF	67	26 (0.4)	66	26 (0.6)		45.84%	0[-0.17,0.17]
WELCOME 2015	47	33.4 (4.9)	48	30.8 (4.5)		2.28%	2.6[0.71,4.49]
Subtotal ***	**932**		**916**			**100%**	**0.09[-0.21,0.38]**
Heterogeneity: Tau²=0.04; Chi²=7.81, df=3(P=0.05); I²=61.57%							
Test for overall effect: Z=0.58(P=0.56)							
2.29.2 SA - 100+ randomised							
AlphaOmega - EPA+DHA 2010	630	0 (1.8)	630	-0.1 (1.8)		27.85%	0.1[-0.1,0.3]
Derosa 2016	128	28.6 (2.1)	130	29.2 (2.3)		5.51%	-0.6[-1.14,-0.06]



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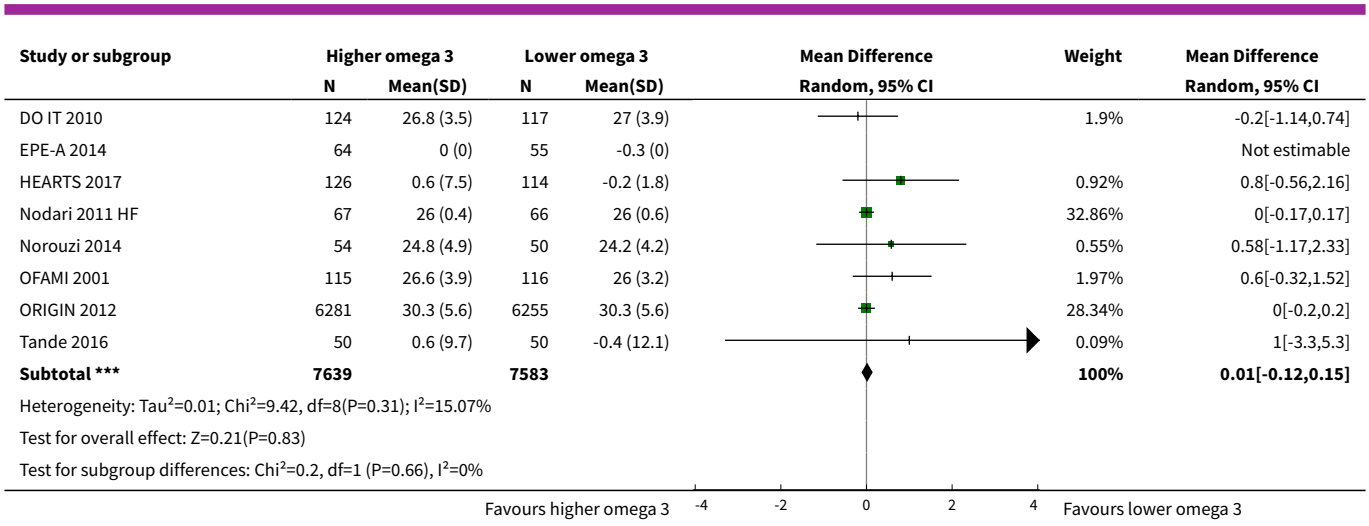


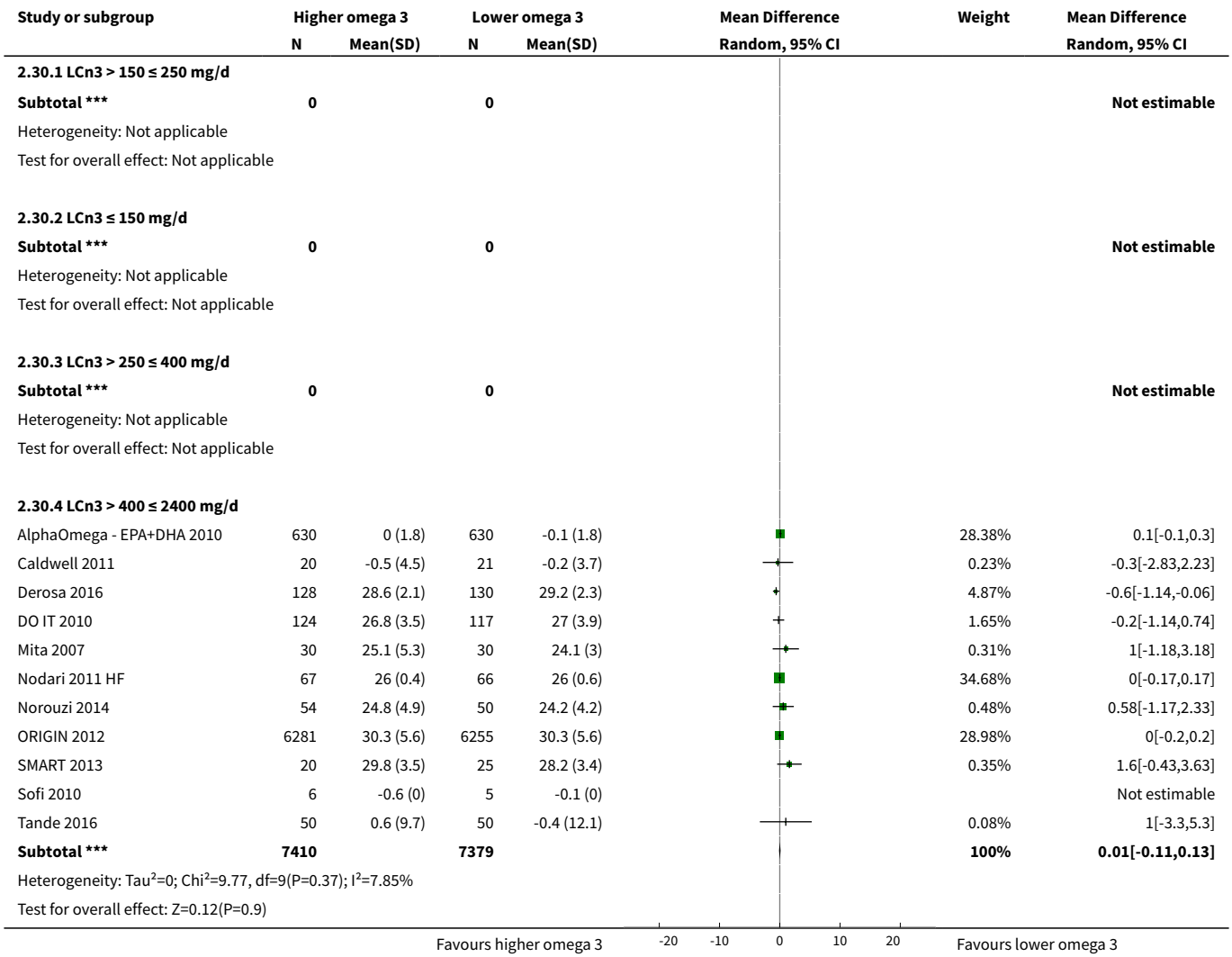
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
DO IT 2010	124	26.8 (3.5)	117	27 (3.9)		1.9%	-0.2[-1.14,0.74]
EPE-A 2014	64	0 (0)	55	-0.3 (0)			Not estimable
HEARTS 2017	126	0.6 (7.5)	114	-0.2 (1.8)		0.92%	0.8[-0.56,2.16]
Nodari 2011 HF	67	26 (0.4)	66	26 (0.6)		32.86%	0[-0.17,0.17]
Norouzi 2014	54	24.8 (4.9)	50	24.2 (4.2)		0.55%	0.58[-1.17,2.33]
OFAMI 2001	115	26.6 (3.9)	116	26 (3.2)		1.97%	0.6[-0.32,1.52]
ORIGIN 2012	6281	30.3 (5.6)	6255	30.3 (5.6)		28.34%	0[-0.2,0.2]
Tande 2016	50	0.6 (9.7)	50	-0.4 (12.1)		0.09%	1[-3.3,5.3]
Subtotal * **	**7639**		**7583**			**100%**	**0.01[-0.12,0.15]**

Heterogeneity: Tau²=0.01; Chi²=9.42, df=8(P=0.31); I²=15.07%

Test for overall effect: Z=0.21(P=0.83)

Test for subgroup differences: Chi²=0.2, df=1 (P=0.66), I²=0%

Analysis 2.30. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 30 BMI, kg/m² - LCn3 - subgroup by dose.



Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.30.1 LCn3 > 150 ≤ 250 mg/d							
Subtotal * **	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.30.2 LCn3 ≤ 150 mg/d							
Subtotal * **	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.30.3 LCn3 > 250 ≤ 400 mg/d							
Subtotal * **	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.30.4 LCn3 > 400 ≤ 2400 mg/d							
AlphaOmega - EPA+DHA 2010	630	0 (1.8)	630	-0.1 (1.8)		28.38%	0.1[-0.1,0.3]
Caldwell 2011	20	-0.5 (4.5)	21	-0.2 (3.7)		0.23%	-0.3[-2.83,2.23]
Derosa 2016	128	28.6 (2.1)	130	29.2 (2.3)		4.87%	-0.6[-1.14,-0.06]
DO IT 2010	124	26.8 (3.5)	117	27 (3.9)		1.65%	-0.2[-1.14,0.74]
Mita 2007	30	25.1 (5.3)	30	24.1 (3)		0.31%	1[-1.18,3.18]
Nodari 2011 HF	67	26 (0.4)	66	26 (0.6)		34.68%	0[-0.17,0.17]
Norouzi 2014	54	24.8 (4.9)	50	24.2 (4.2)		0.48%	0.58[-1.17,2.33]
ORIGIN 2012	6281	30.3 (5.6)	6255	30.3 (5.6)		28.98%	0[-0.2,0.2]
SMART 2013	20	29.8 (3.5)	25	28.2 (3.4)		0.35%	1.6[-0.43,3.63]
Sofi 2010	6	-0.6 (0)	5	-0.1 (0)			Not estimable
Tande 2016	50	0.6 (9.7)	50	-0.4 (12.1)		0.08%	1[-3.3,5.3]
Subtotal * **	**7410**		**7379**			**100%**	**0.01[-0.11,0.13]**

Heterogeneity: Tau²=0; Chi²=9.77, df=9(P=0.37); I²=7.85%

Test for overall effect: Z=0.12(P=0.9)

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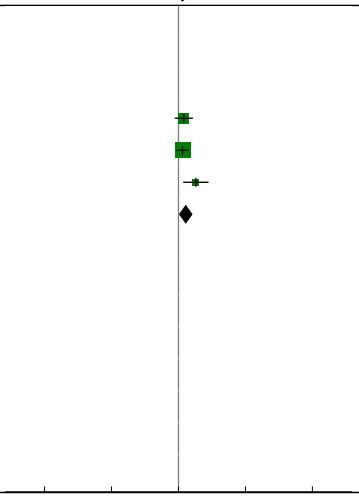
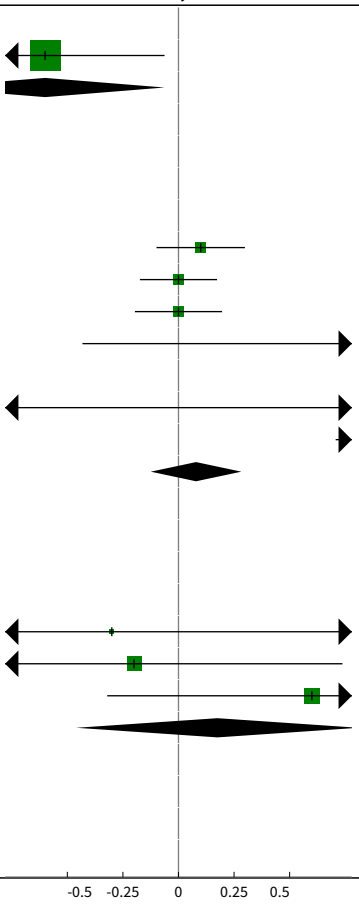
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.30.5 LCn3 > 2.4 ≤ 4.4 g/d							
EPE-A 2014	64	0 (0)	55	-0.3 (0)			Not estimable
HEARTS 2017	126	0.6 (7.5)	114	-0.2 (1.8)		32.23%	0.8[-0.56,2.16]
OFAMI 2001	115	26.6 (3.9)	116	26 (3.2)		46.86%	0.6[-0.32,1.52]
WELCOME 2015	47	33.4 (4.9)	48	30.8 (4.5)		20.91%	2.6[0.71,4.49]
Subtotal ***	**352**		**333**			**100%**	**1.08[0.07,2.1]**
Heterogeneity: Tau²=0.35; Chi²=3.52, df=2(P=0.17); I²=43.16%							
Test for overall effect: Z=2.09(P=0.04)							
2.30.6 LCn3 > 4.4 g/d							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Chi²=4.24, df=1 (P=0.04), I²=76.41%							



Analysis 2.31. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 31 BMI, kg/m² - LCn3 - subgroup by replacement.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.31.1 N-3 replacing SFA							
Derosa 2016	128	28.6 (2.1)	130	29.2 (2.3)		100%	-0.6[-1.14,-0.06]
Subtotal ***	**128**		**130**			**100%**	**-0.6[-1.14,-0.06]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.19(P=0.03)							
2.31.2 N-3 replacing MUFA							
AlphaOmega - EPA+DHA 2010	630	0 (1.8)	630	-0.1 (1.8)		31.65%	0.1[-0.1,0.3]
Nodari 2011 HF	67	26 (0.4)	66	26 (0.6)		34.09%	0[-0.17,0.17]
ORIGIN 2012	6281	30.3 (5.6)	6255	30.3 (5.6)		31.92%	0[-0.2,0.2]
SMART 2013	20	29.8 (3.5)	25	28.2 (3.4)		0.98%	1.6[-0.43,3.63]
Sofi 2010	6	-0.6 (0)	5	-0.1 (0)			Not estimable
Tande 2016	50	0.6 (9.7)	50	-0.4 (12.1)		0.22%	1[-3.3,5.3]
WELCOME 2015	47	33.4 (4.9)	48	30.8 (4.5)		1.13%	2.6[0.71,4.49]
Subtotal ***	**7101**		**7079**			**100%**	**0.08[-0.12,0.28]**
Heterogeneity: Tau²=0.02; Chi²=10.19, df=5(P=0.07); I²=50.94%							
Test for overall effect: Z=0.76(P=0.45)							
2.31.3 N-3 replacing n-6							
Caldwell 2011	20	-0.5 (4.5)	21	-0.2 (3.7)		6.32%	-0.3[-2.83,2.23]
DO IT 2010	124	26.8 (3.5)	117	27 (3.9)		45.98%	-0.2[-1.14,0.74]
OFAMI 2001	115	26.6 (3.9)	116	26 (3.2)		47.7%	0.6[-0.32,1.52]
Subtotal ***	**259**		**254**			**100%**	**0.18[-0.46,0.81]**
Heterogeneity: Tau²=0; Chi²=1.57, df=2(P=0.46); I²=0%							
Test for overall effect: Z=0.54(P=0.59)							
2.31.4 N-3 replacing carbs/sugars							



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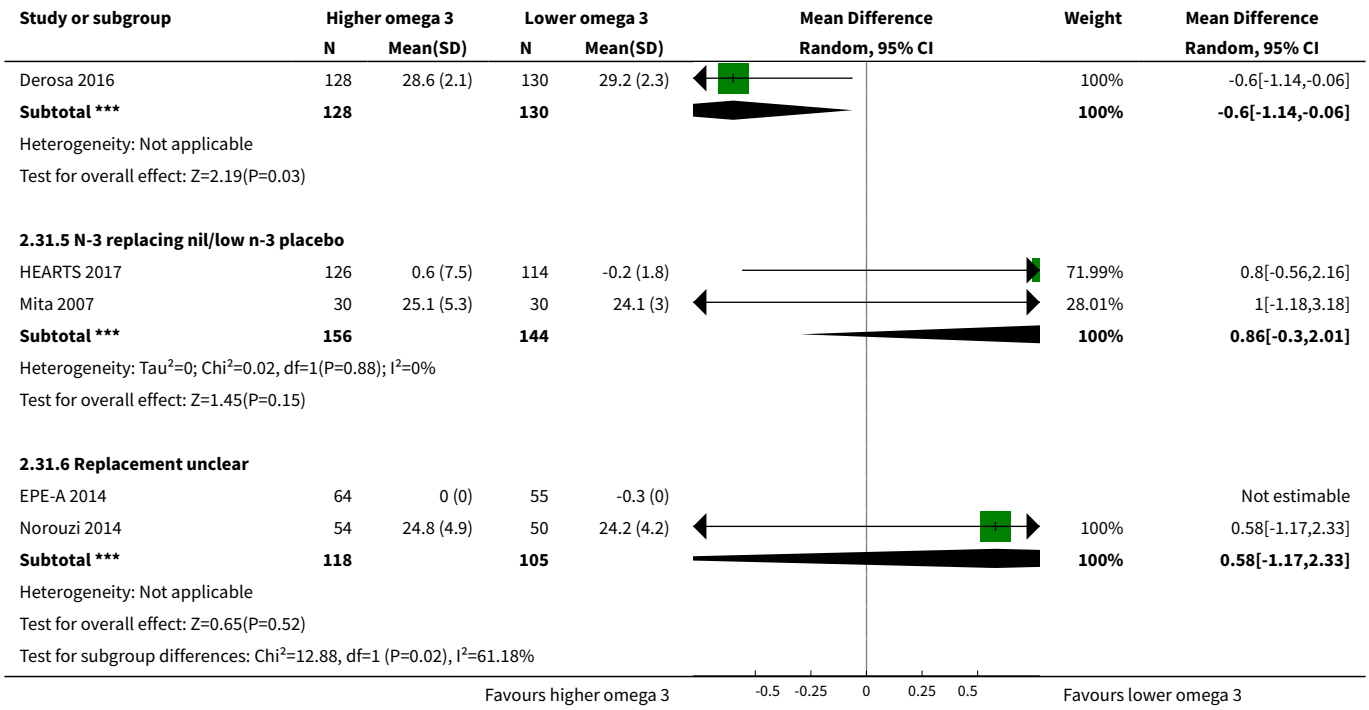
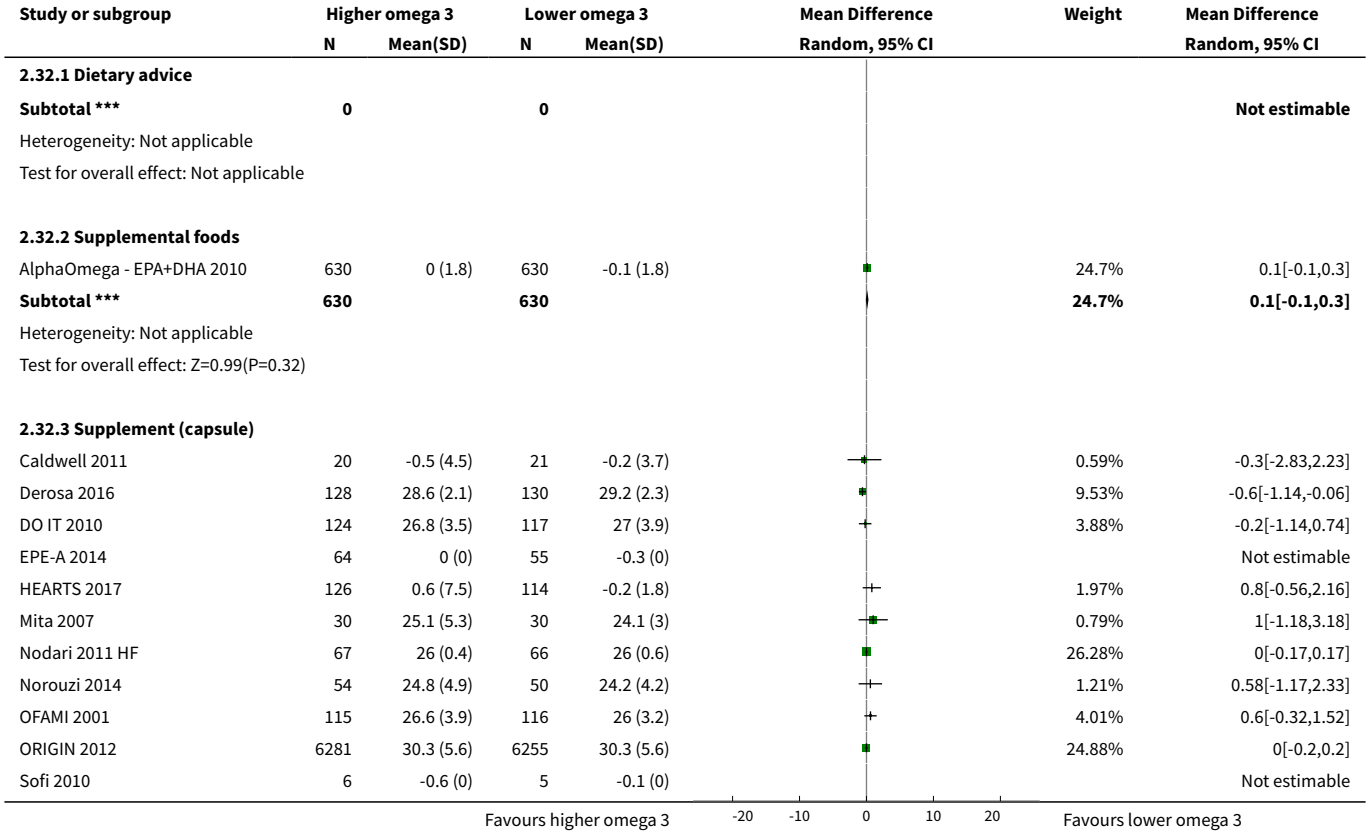


Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Derosa 2016	128	28.6 (2.1)	130	29.2 (2.3)		100%	-0.6[-1.14,-0.06]
Subtotal ***	**128**		**130**			**100%**	**-0.6[-1.14,-0.06]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.19(P=0.03)							
2.31.5 N-3 replacing nil/low n-3 placebo							
HEARTS 2017	126	0.6 (7.5)	114	-0.2 (1.8)		71.99%	0.8[-0.56,2.16]
Mita 2007	30	25.1 (5.3)	30	24.1 (3)		28.01%	1[-1.18,3.18]
Subtotal ***	**156**		**144**			**100%**	**0.86[-0.3,2.01]**
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.88); I^2=0%							
Test for overall effect: Z=1.45(P=0.15)							
2.31.6 Replacement unclear							
EPE-A 2014	64	0 (0)	55	-0.3 (0)			Not estimable
Norouzi 2014	54	24.8 (4.9)	50	24.2 (4.2)		100%	0.58[-1.17,2.33]
Subtotal ***	**118**		**105**			**100%**	**0.58[-1.17,2.33]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.65(P=0.52)							
Test for subgroup differences: Chi^2=12.88, df=1 (P=0.02), I^2=61.18%							

Analysis 2.32. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 32 BMI, kg/m² - LCn3 - subgroup by intervention type.



Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.32.1 Dietary advice							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.32.2 Supplemental foods							
AlphaOmega - EPA+DHA 2010	630	0 (1.8)	630	-0.1 (1.8)		24.7%	0.1[-0.1,0.3]
Subtotal ***	**630**		**630**			**24.7%**	**0.1[-0.1,0.3]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.99(P=0.32)							
2.32.3 Supplement (capsule)							
Caldwell 2011	20	-0.5 (4.5)	21	-0.2 (3.7)		0.59%	-0.3[-2.83,2.23]
Derosa 2016	128	28.6 (2.1)	130	29.2 (2.3)		9.53%	-0.6[-1.14,-0.06]
DO IT 2010	124	26.8 (3.5)	117	27 (3.9)		3.88%	-0.2[-1.14,0.74]
EPE-A 2014	64	0 (0)	55	-0.3 (0)			Not estimable
HEARTS 2017	126	0.6 (7.5)	114	-0.2 (1.8)		1.97%	0.8[-0.56,2.16]
Mita 2007	30	25.1 (5.3)	30	24.1 (3)		0.79%	1[-1.18,3.18]
Nodari 2011 HF	67	26 (0.4)	66	26 (0.6)		26.28%	0[-0.17,0.17]
Norouzi 2014	54	24.8 (4.9)	50	24.2 (4.2)		1.21%	0.58[-1.17,2.33]
OFAMI 2001	115	26.6 (3.9)	116	26 (3.2)		4.01%	0.6[-0.32,1.52]
ORIGIN 2012	6281	30.3 (5.6)	6255	30.3 (5.6)		24.88%	0[-0.2,0.2]
Sofi 2010	6	-0.6 (0)	5	-0.1 (0)			Not estimable

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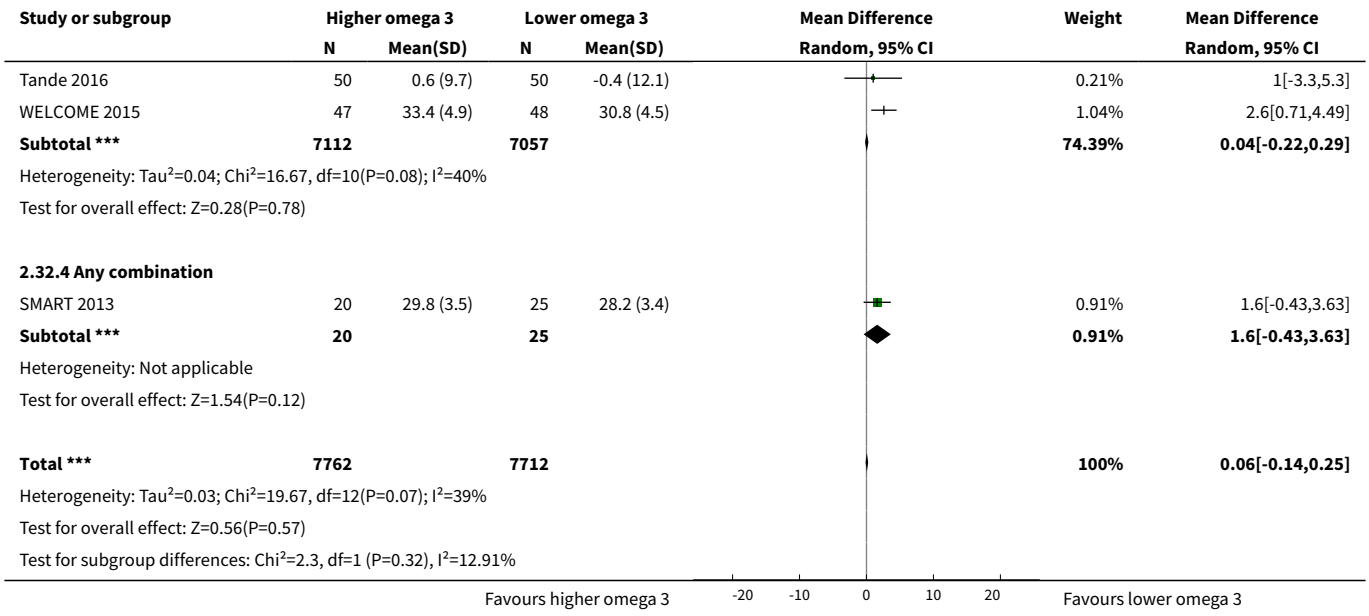
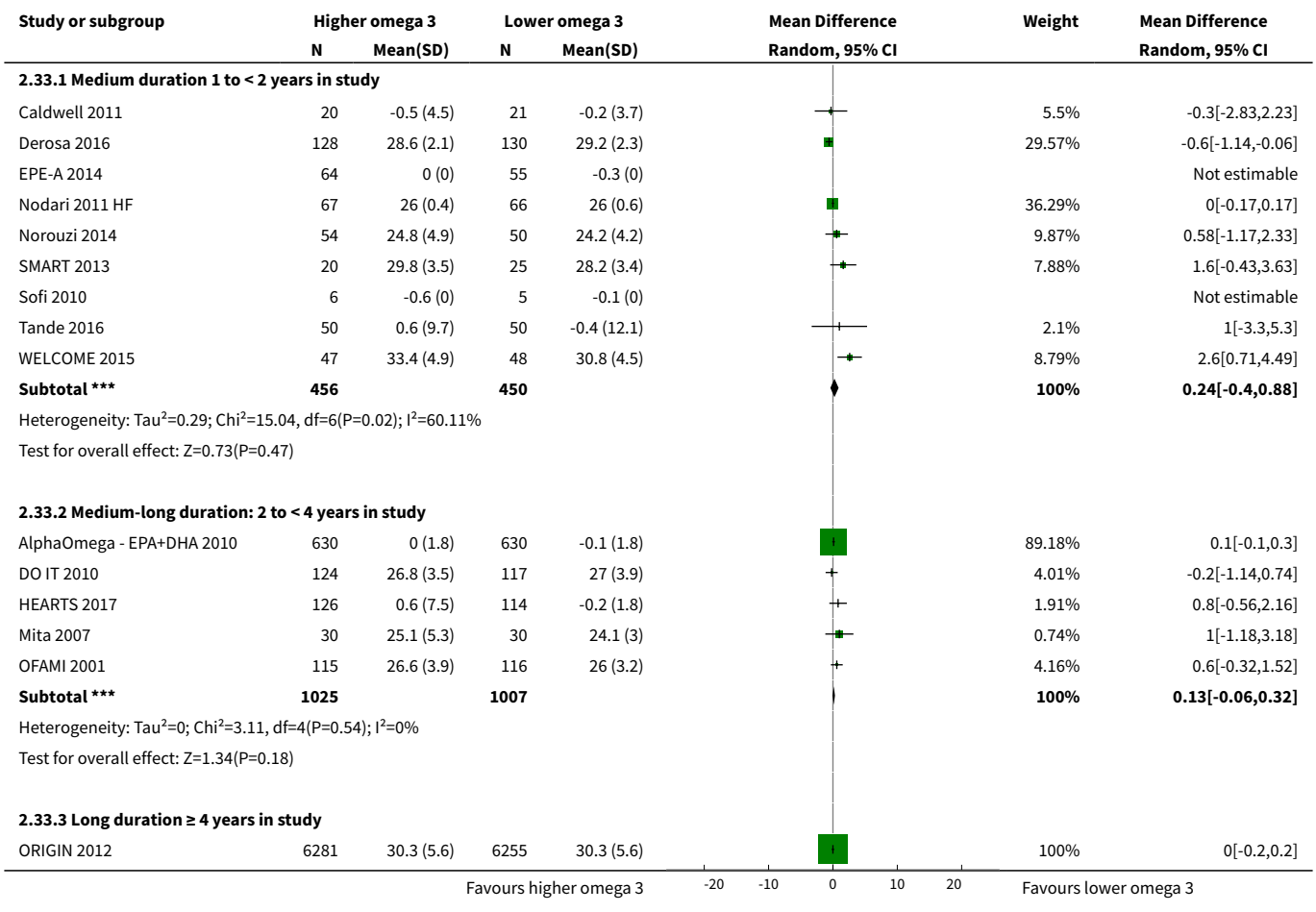


Analysis 2.33. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 33 BMI, kg/m² - LCn3 - subgroup by duration.



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Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Subtotal ***	**6281**		**6255**			**100%**	**0[-0.2,0.2]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Chi^2=1.13, df=1 (P=0.57), I^2=0%							

Favours higher omega 3 -20 -10 0 10 20 Favours lower omega 3

Analysis 2.34. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 34 BMI, kg/m² - LCn3 - subgroup by primary or secondary prevention.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.34.1 Primary CVD prevention							
Caldwell 2011	20	-0.5 (4.5)	21	-0.2 (3.7)		3.65%	-0.3[-2.83,2.23]
Derosa 2016	128	28.6 (2.1)	130	29.2 (2.3)		24.45%	-0.6[-1.14,-0.06]
DO IT 2010	124	26.8 (3.5)	117	27 (3.9)		15.77%	-0.2[-1.14,0.74]
EPE-A 2014	64	0 (0)	55	-0.3 (0)			Not estimable
Mita 2007	30	25.1 (5.3)	30	24.1 (3)		4.74%	1[-1.18,3.18]
Norouzi 2014	54	24.8 (4.9)	50	24.2 (4.2)		6.8%	0.58[-1.17,2.33]
ORIGIN 2012	6281	30.3 (5.6)	6255	30.3 (5.6)		31.9%	0[-0.2,0.2]
SMART 2013	20	29.8 (3.5)	25	28.2 (3.4)		5.33%	1.6[-0.43,3.63]
Sofi 2010	6	-0.6 (0)	5	-0.1 (0)			Not estimable
Tande 2016	50	0.6 (9.7)	50	-0.4 (12.1)		1.36%	1[-3.3,5.3]
WELCOME 2015	47	33.4 (4.9)	48	30.8 (4.5)		6%	2.6[0.71,4.49]
Subtotal ***	**6824**		**6786**			**100%**	**0.15[-0.36,0.66]**
Heterogeneity: Tau^2=0.2; Chi^2=16.01, df=8(P=0.04); I^2=50.04%							
Test for overall effect: Z=0.58(P=0.56)							
2.34.2 Secondary CVD prevention							
AlphaOmega - EPA+DHA 2010	630	0 (1.8)	630	-0.1 (1.8)		42.36%	0.1[-0.1,0.3]
HEARTS 2017	126	0.6 (7.5)	114	-0.2 (1.8)		0.96%	0.8[-0.56,2.16]
Nodari 2011 HF	67	26 (0.4)	66	26 (0.6)		54.59%	0[-0.17,0.17]
OFAMI 2001	115	26.6 (3.9)	116	26 (3.2)		2.09%	0.6[-0.32,1.52]
Subtotal ***	**938**		**926**			**100%**	**0.06[-0.07,0.2]**
Heterogeneity: Tau^2=0; Chi^2=3.07, df=3(P=0.38); I^2=2.44%							
Test for overall effect: Z=0.92(P=0.36)							
Test for subgroup differences: Chi^2=0.11, df=1 (P=0.74), I^2=0%							

Favours higher omega 3 -20 -10 0 10 20 Favours lower omega 3

Analysis 2.35. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 35 BMI, kg/m² - LCn3 - subgroup by statin use.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.35.1 LCn3 - ≥ 50% of control group on statins							
AlphaOmega - EPA+DHA 2010	630	0 (1.8)	630	-0.1 (1.8)		45.68%	0.1[-0.1,0.3]
HEARTS 2017	126	0.6 (7.5)	114	-0.2 (1.8)		5.47%	0.8[-0.56,2.16]
ORIGIN 2012	6281	30.3 (5.6)	6255	30.3 (5.6)		45.88%	0[-0.2,0.2]

Favours higher omega 3 -20 -10 0 10 20 Favours lower omega 3

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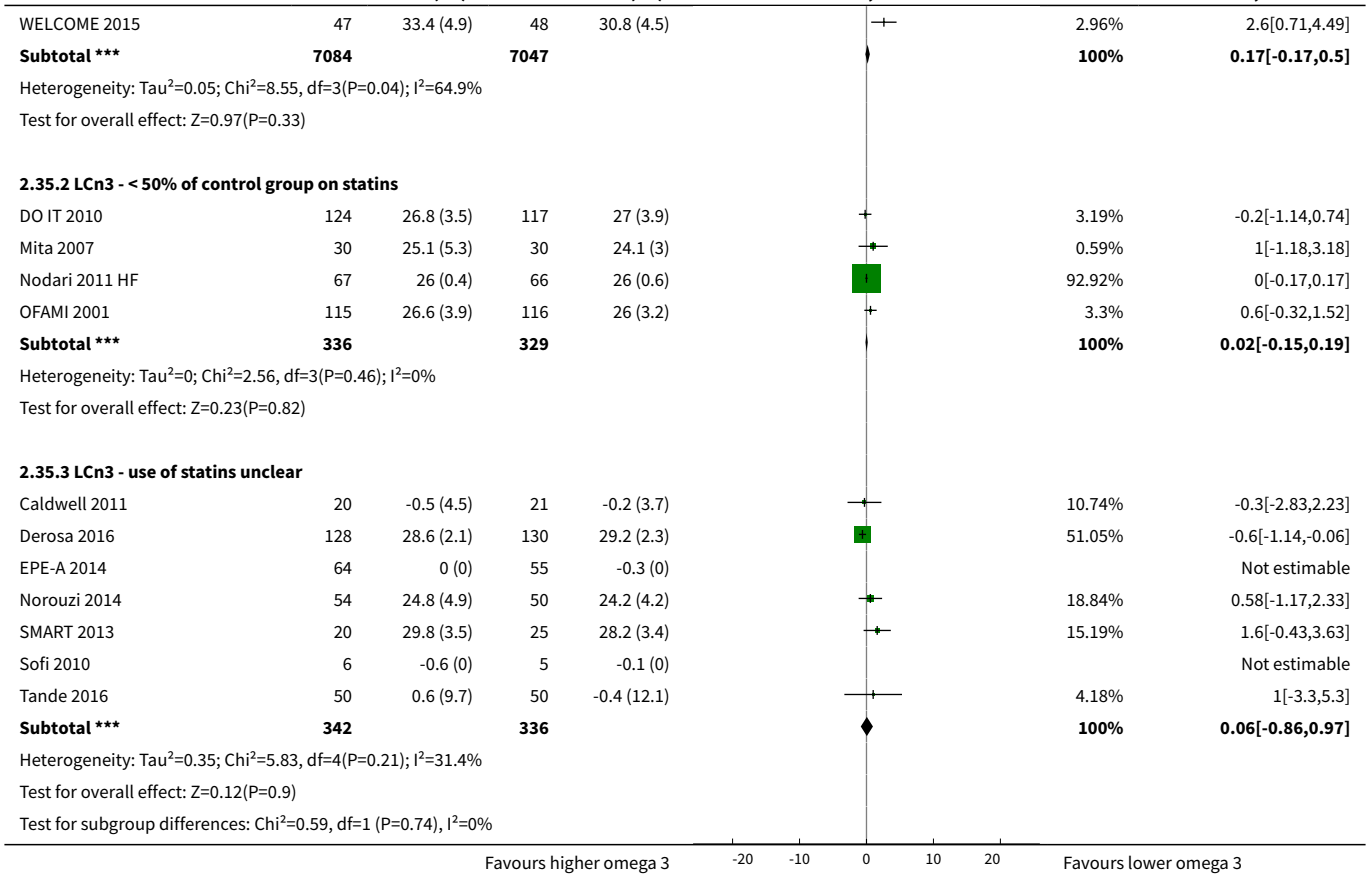
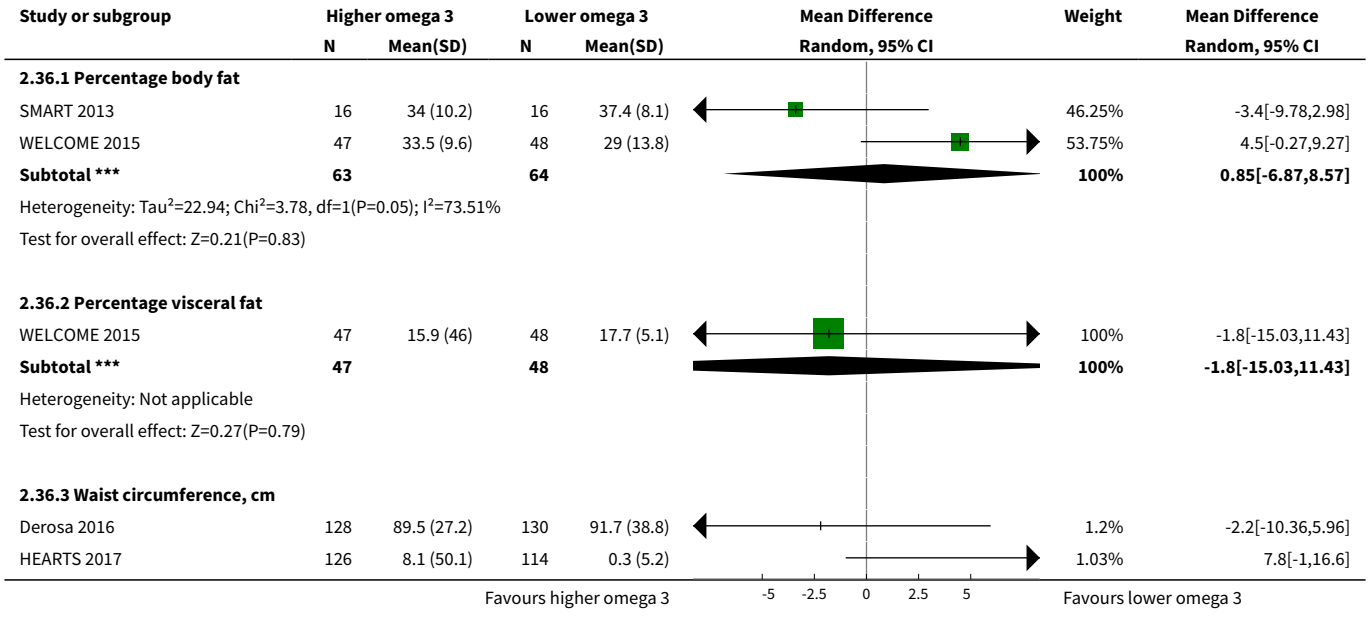


Analysis 2.36. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 36 Other measures of adiposity - LCn3.



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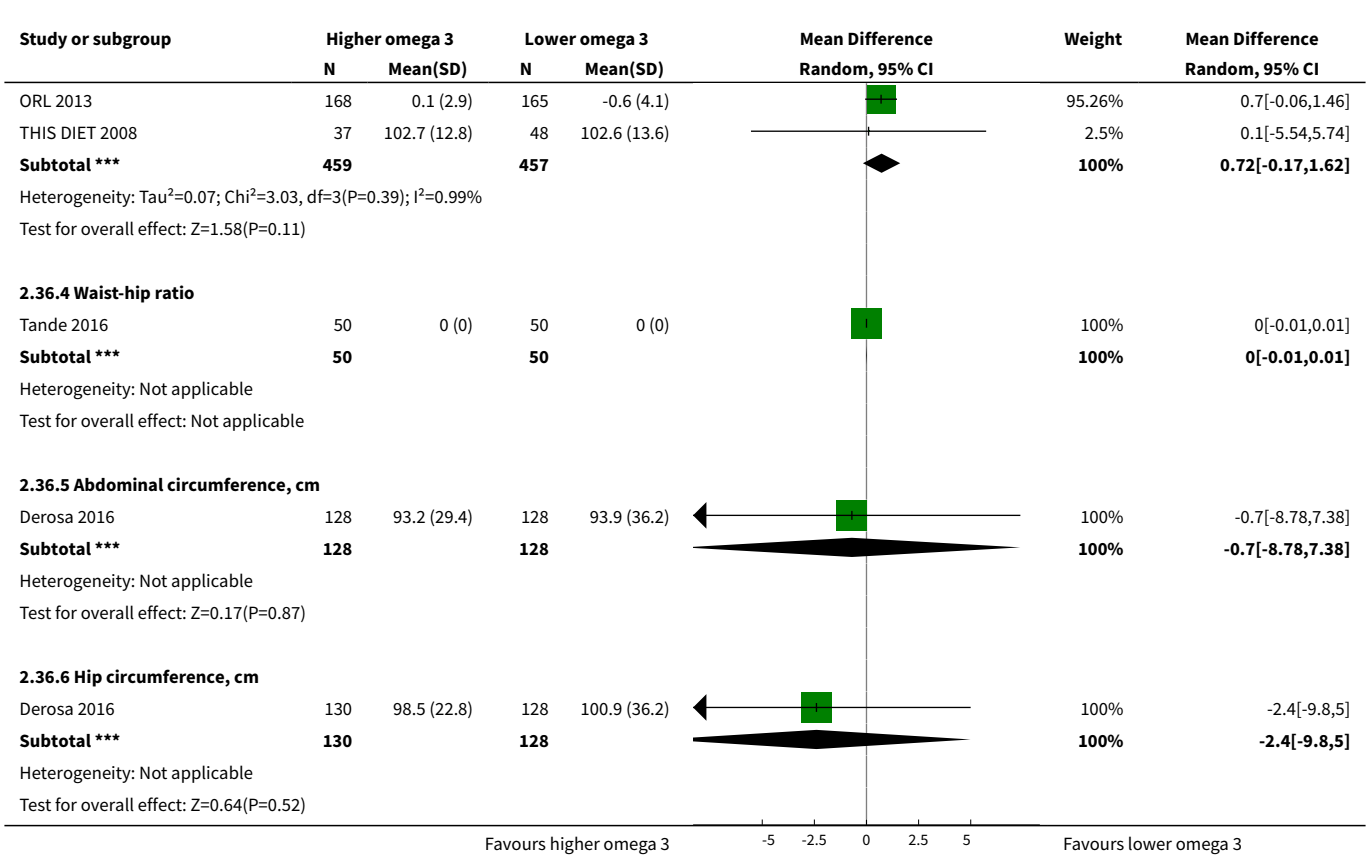
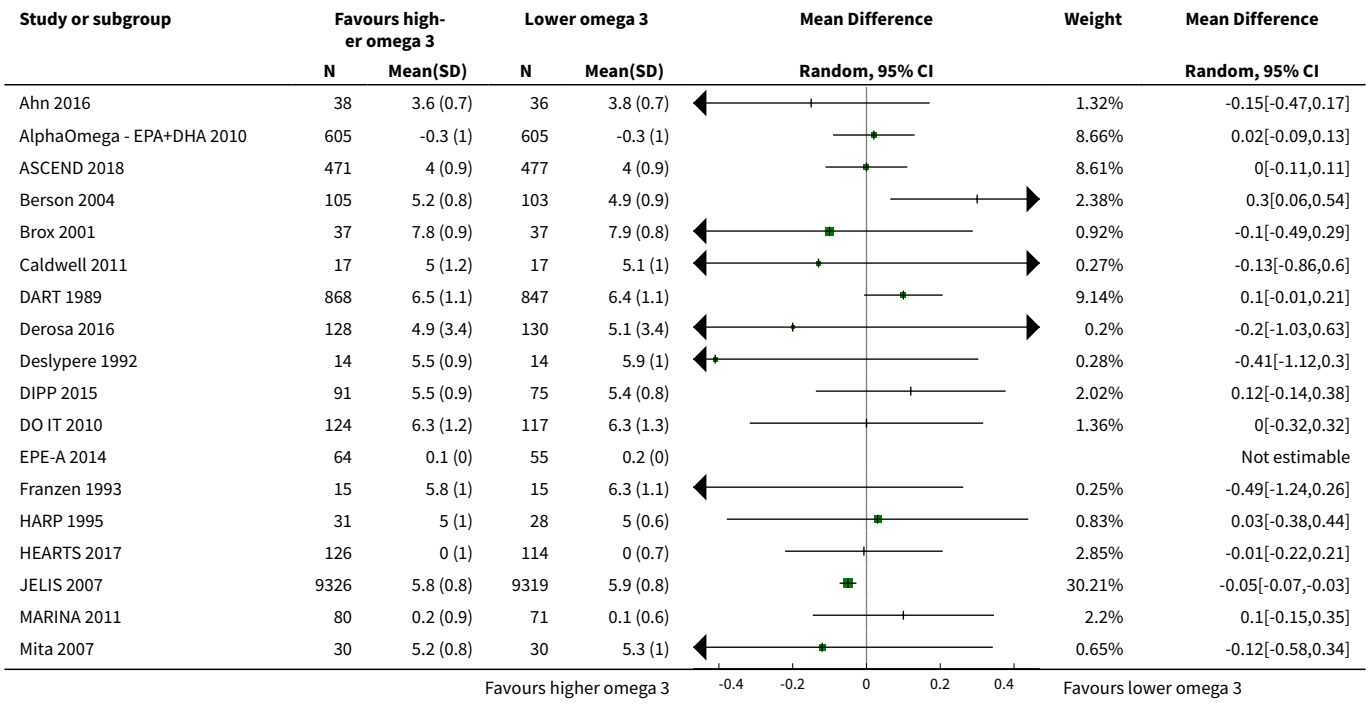


Analysis 2.37. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 37 Total cholesterol, serum, mmoL/L - LCn3.



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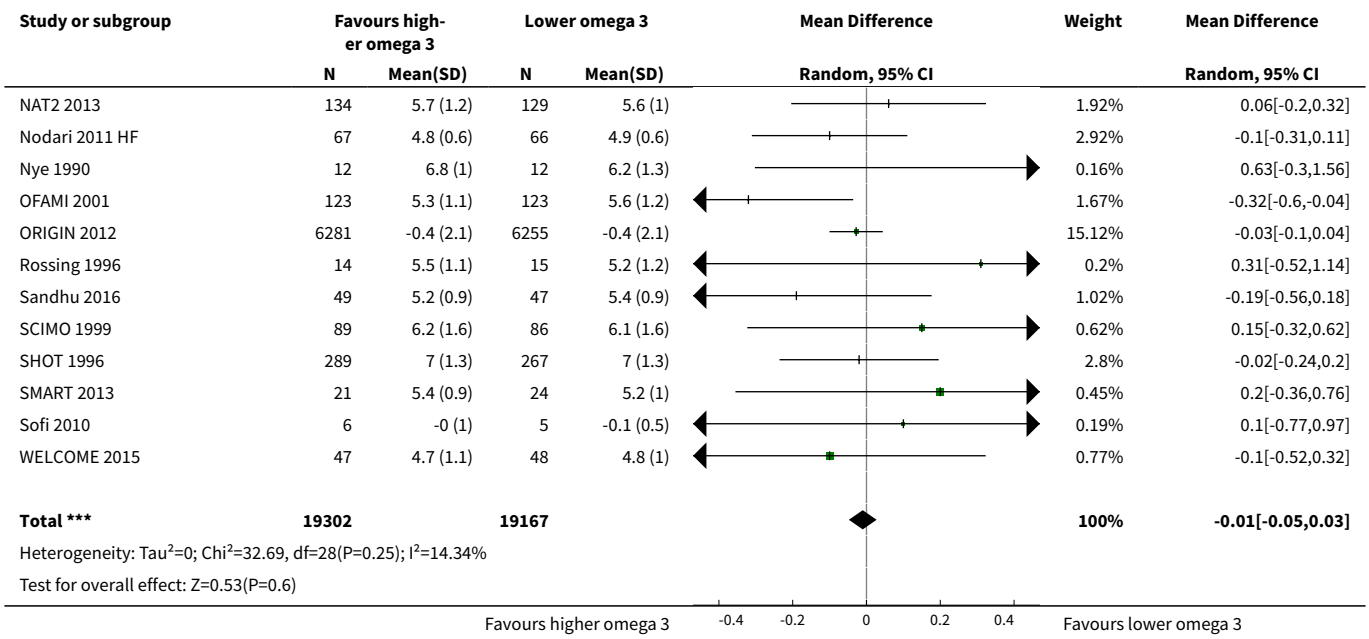
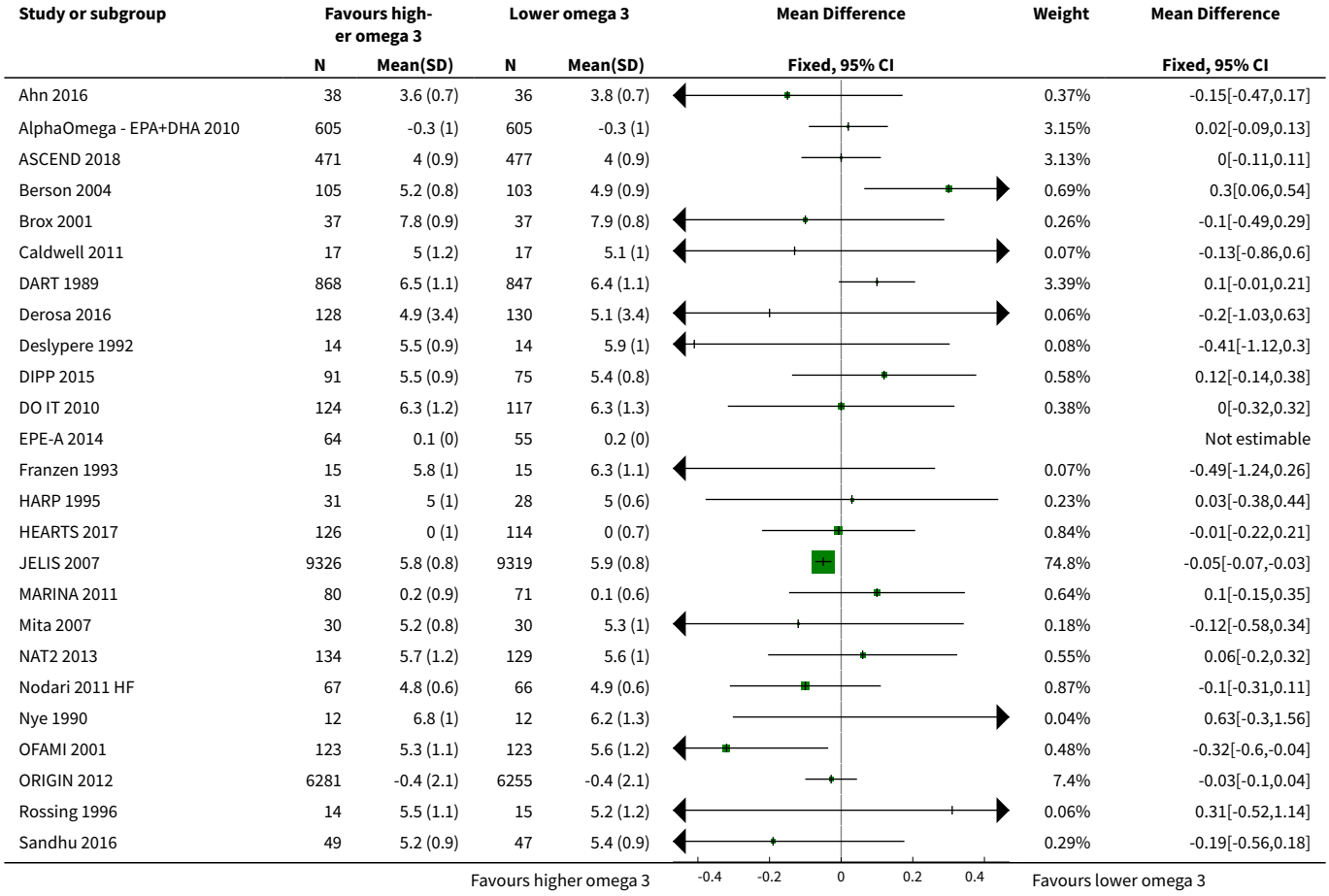


Analysis 2.38. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 38 TC, mmoL/L - LCn3 - SA fixed effects.



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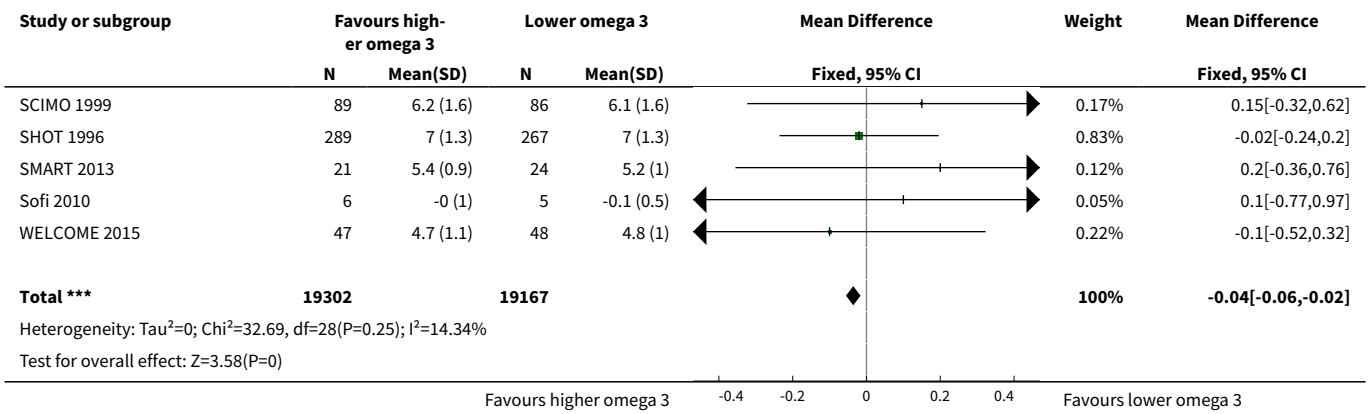
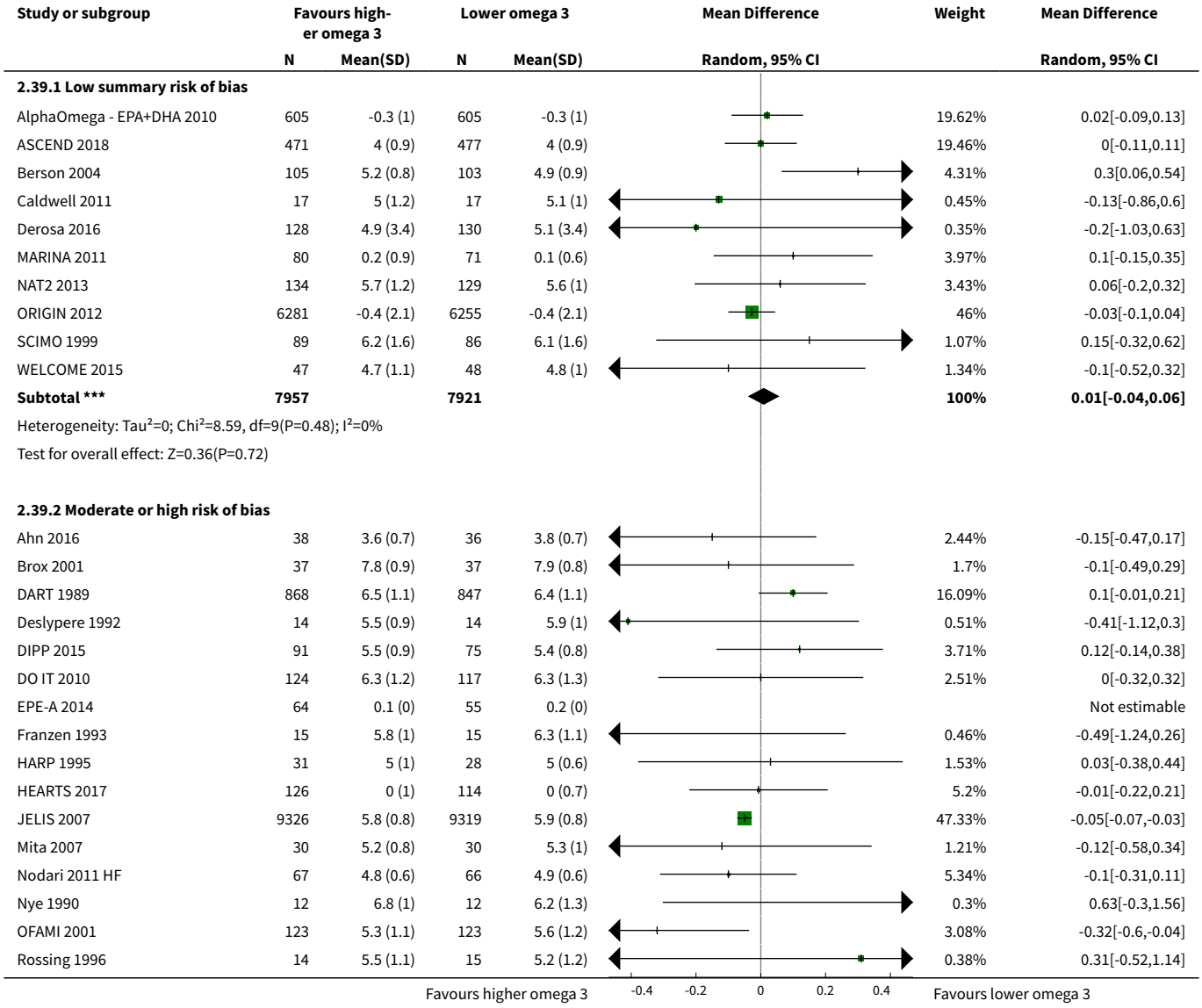


Analysis 2.39. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 39 TC, mmoL/L - LCn3 - SA by summary risk of bias.



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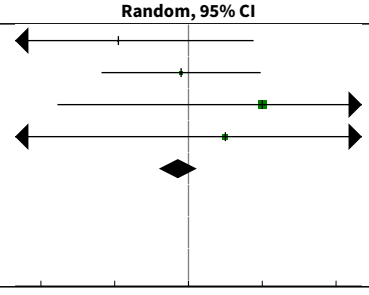
Study or subgroup	Favours higher omega 3 N	Mean(SD)	Lower omega 3 N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Sandhu 2016	49	5.2 (0.9)	47	5.4 (0.9)		1.89%	-0.19[-0.56,0.18]
SHOT 1996	289	7 (1.3)	267	7 (1.3)		5.12%	-0.02[-0.24,0.2]
SMART 2013	21	5.4 (0.9)	24	5.2 (1)		0.84%	0.2[-0.36,0.76]
Sofi 2010	6	-0 (1)	5	-0.1 (0.5)		0.35%	0.1[-0.77,0.97]
Subtotal * **	**11345**		**11246**			**100%**	**-0.03[-0.08,0.02]**

Heterogeneity: Tau²=0; Chi²=20.25, df=18(P=0.32); I²=11.1%

Test for overall effect: Z=1.1(P=0.27)

Test for subgroup differences: Chi²=1.1, df=1 (P=0.3), I²=8.77%



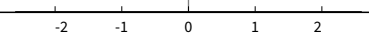
Analysis 2.40. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 40 TC, mmoL/L - LCn3 - SA by compliance and study size.

Study or subgroup	Higher omega 3 N	Mean(SD)	Lower omega 3 N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.40.1 SA - low risk of compliance bias							
AlphaOmega - EPA+DHA 2010	605	-0.3 (1)	605	-0.3 (1)		38.11%	0.02[-0.09,0.13]
Berson 2004	105	5.2 (0.8)	103	4.9 (0.9)		8.38%	0.3[0.06,0.54]
Brox 2001	37	7.8 (0.9)	37	7.9 (0.8)		3.09%	-0.1[-0.49,0.29]
Deslypere 1992	14	5.5 (0.9)	14	5.9 (1)		0.91%	-0.41[-1.12,0.3]
DO IT 2010	124	6.3 (1.2)	117	6.3 (1.3)		4.64%	0[-0.32,0.32]
EPE-A 2014	64	0.1 (0)	55	0.2 (0)			Not estimable
HARP 1995	31	5 (1)	28	5 (0.6)		2.78%	0.03[-0.38,0.44]
MARINA 2011	80	5.6 (0.9)	71	5.6 (0.4)		9.6%	0[-0.22,0.22]
NAT2 2013	134	5.7 (1.2)	129	5.6 (1)		6.67%	0.06[-0.2,0.32]
Nodari 2011 HF	67	4.8 (0.6)	66	4.9 (0.6)		10.47%	-0.1[-0.31,0.11]
Rossing 1996	14	5.5 (1.1)	15	5.2 (1.2)		0.67%	0.31[-0.52,1.14]
SCIMO 1999	89	6.2 (1.6)	86	6.1 (1.6)		2.08%	0.15[-0.32,0.62]
SHOT 1996	289	7 (1.3)	267	7 (1.3)		10%	-0.02[-0.24,0.2]
WELCOME 2015	47	4.7 (1.1)	48	4.8 (1)		2.6%	-0.1[-0.52,0.32]
Subtotal * **	**1700**		**1641**			**100%**	**0.02[-0.05,0.09]**

Heterogeneity: Tau²=0; Chi²=9.78, df=12(P=0.64); I²=0%

Test for overall effect: Z=0.6(P=0.55)

2.40.2 SA - 100+ randomised							
AlphaOmega - EPA+DHA 2010	605	-0.3 (1)	605	-0.3 (1)		10.26%	0.02[-0.09,0.13]
ASCEND 2018	471	4 (0.9)	477	4 (0.9)		10.21%	0[-0.11,0.11]
Berson 2004	105	5.2 (0.8)	103	4.9 (0.9)		3.34%	0.3[0.06,0.54]
DART 1989	868	6.5 (1.1)	847	6.4 (1.1)		10.7%	0.1[-0.01,0.21]
Derosa 2016	128	4.9 (3.4)	130	5.1 (3.4)		0.31%	-0.2[-1.03,0.63]
DIPP 2015	91	5.5 (0.9)	75	5.4 (0.8)		2.86%	0.12[-0.14,0.38]
DO IT 2010	124	6.3 (1.2)	117	6.3 (1.3)		1.97%	0[-0.32,0.32]
EPE-A 2014	64	0.1 (0)	55	0.2 (0)			Not estimable
HEARTS 2017	126	0 (1)	114	0 (0.7)		3.94%	-0.01[-0.22,0.21]
JELIS 2007	9326	5.8 (0.8)	9319	5.9 (0.8)		23.26%	-0.05[-0.07,-0.03]
MARINA 2011	80	5.6 (0.9)	71	5.6 (0.4)		3.75%	0[-0.22,0.22]
NAT2 2013	134	5.7 (1.2)	129	5.6 (1)		2.73%	0.06[-0.2,0.32]
Nodari 2011 HF	67	4.8 (0.6)	66	4.9 (0.6)		4.04%	-0.1[-0.31,0.11]



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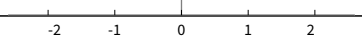
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
OFAMI 2001	123	5.3 (1.1)	123	5.6 (1.2)		2.4%	-0.32[-0.6,-0.04]
ORIGIN 2012	6281	-0.4 (2.1)	6255	-0.4 (2.1)		15.42%	-0.03[-0.1,0.04]
SCIMO 1999	89	6.2 (1.6)	86	6.1 (1.6)		0.92%	0.15[-0.32,0.62]
SHOT 1996	289	7 (1.3)	267	7 (1.3)		3.88%	-0.02[-0.24,0.2]
Subtotal * **	**18971**		**18839**			**100%**	**-0[-0.05,0.05]**
Heterogeneity: Tau²=0; Chi²=24.09, df=15(P=0.06); I²=37.74%							
Test for overall effect: Z=0(P=1)							
Test for subgroup differences: Chi²=0.25, df=1 (P=0.62), I²=0%							

Favours higher omega 3 — Favours lower omega 3

Analysis 2.41. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 41 TC, mmoL/L - LCn3 - subgroup by dose.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.41.1 LCn3 ≤ 150 mg/d							
Subtotal * **	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.41.2 LCn3 > 150 ≤ 250 mg/d							
Subtotal * **	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.41.3 LCn3 > 250 ≤ 400 mg/d							
DART 1989	868	6.5 (1.1)	847	6.4 (1.1)		100%	0.1[-0.01,0.21]
Subtotal * **	**868**		**847**			**100%**	**0.1[-0.01,0.21]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=1.84(P=0.07)							
2.41.4 LCn3 > 400 ≤ 2400 mg/d							
Ahn 2016	38	3.6 (0.7)	36	3.8 (0.7)		0.56%	-0.15[-0.47,0.17]
AlphaOmega - EPA+DHA 2010	605	-0.3 (1)	605	-0.3 (1)		4.68%	0.02[-0.09,0.13]
ASCEND 2018	471	4 (0.9)	477	4 (0.9)		4.64%	0[-0.11,0.11]
Berson 2004	105	5.2 (0.8)	103	4.9 (0.9)		1.05%	0.3[0.06,0.54]
Caldwell 2011	17	5 (1.2)	17	5.1 (1)		0.11%	-0.13[-0.86,0.6]
Derosa 2016	128	4.9 (3.4)	130	5.1 (3.4)		0.08%	-0.2[-1.03,0.63]
Deslypere 1992	14	5.5 (0.9)	14	5.9 (1)		0.11%	-0.41[-1.12,0.3]
DIPP 2015	91	5.5 (0.9)	75	5.4 (0.8)		0.88%	0.12[-0.14,0.38]
DO IT 2010	124	6.3 (1.2)	117	6.3 (1.3)		0.58%	0[-0.32,0.32]
JELIS 2007	9326	5.8 (0.8)	9319	5.9 (0.8)		72.46%	-0.05[-0.07,-0.03]
MARINA 2011	80	5.6 (0.9)	71	5.6 (0.4)		1.2%	0[-0.22,0.22]
Mita 2007	30	5.2 (0.8)	30	5.3 (1)		0.27%	-0.12[-0.58,0.34]
NAT2 2013	134	5.7 (1.2)	129	5.6 (1)		0.83%	0.06[-0.2,0.32]
Nodari 2011 HF	67	4.8 (0.6)	66	4.9 (0.6)		1.31%	-0.1[-0.31,0.11]
Nye 1990	12	6.8 (1)	12	6.2 (1.3)		0.07%	0.63[-0.3,1.56]
ORIGIN 2012	6281	-0.4 (2.1)	6255	-0.4 (2.1)		10.63%	-0.03[-0.1,0.04]
SCIMO 1999	89	6.2 (1.6)	86	6.1 (1.6)		0.26%	0.15[-0.32,0.62]



Favours higher omega 3 — Favours lower omega 3

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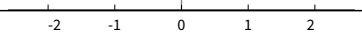
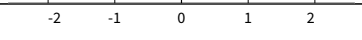
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
SMART 2013	21	5.4 (0.9)	24	5.2 (1)		0.19%	0.2[-0.36,0.76]
Sofi 2010	6	-0 (1)	5	-0.1 (0.5)		0.08%	0.1[-0.77,0.97]
Subtotal ***	**17639**		**17571**			**100%**	**-0.04[-0.06,-0.01]**
Heterogeneity: Tau^2=0; Chi^2=18.25, df=18(P=0.44); I^2=1.36%							
Test for overall effect: Z=2.88(P=0)							
2.41.5 LCn3 > 2.4 ≤ 4.4 g/d							
Brox 2001	37	7.8 (0.9)	37	7.9 (0.8)		8.6%	-0.1[-0.49,0.29]
EPE-A 2014	64	0.1 (0)	55	0.2 (0)			Not estimable
Franzen 1993	15	5.8 (1)	15	6.3 (1.1)		2.29%	-0.49[-1.24,0.26]
HEARTS 2017	126	0 (1)	114	0 (0.7)		28.34%	-0.01[-0.22,0.21]
OFAMI 2001	123	5.3 (1.1)	123	5.6 (1.2)		16.06%	-0.32[-0.6,-0.04]
Sandhu 2016	49	5.2 (0.9)	47	5.4 (0.9)		9.64%	-0.19[-0.56,0.18]
SHOT 1996	289	7 (1.3)	267	7 (1.3)		27.83%	-0.02[-0.24,0.2]
WELCOME 2015	47	4.7 (1.1)	48	4.8 (1)		7.23%	-0.1[-0.52,0.32]
Subtotal ***	**750**		**706**			**100%**	**-0.1[-0.22,0.01]**
Heterogeneity: Tau^2=0; Chi^2=4.82, df=6(P=0.57); I^2=0%							
Test for overall effect: Z=1.8(P=0.07)							
2.41.6 LCn3 > 4.4 g/d							
HARP 1995	31	5 (1)	28	5 (0.6)		80.49%	0.03[-0.38,0.44]
Rossing 1996	14	5.5 (1.1)	15	5.2 (1.2)		19.51%	0.31[-0.52,1.14]
Subtotal ***	**45**		**43**			**100%**	**0.08[-0.28,0.45]**
Heterogeneity: Tau^2=0; Chi^2=0.35, df=1(P=0.55); I^2=0%							
Test for overall effect: Z=0.45(P=0.65)							
Test for subgroup differences: Chi^2=7.93, df=1 (P=0.05), I^2=62.15%							



Favours higher omega 3 — Favours lower omega 3

Analysis 2.42. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 42 TC, mmoL/L - LCn3 - subgroup by replacement.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.42.1 N-3 replacing SFA							
DART 1989	868	6.5 (1.1)	847	6.4 (1.1)		93.71%	0.1[-0.01,0.21]
Derosa 2016	128	4.9 (3.4)	130	5.1 (3.4)		1.54%	-0.2[-1.03,0.63]
SCIMO 1999	89	6.2 (1.6)	86	6.1 (1.6)		4.75%	0.15[-0.32,0.62]
Subtotal ***	**1085**		**1063**			**100%**	**0.1[-0.01,0.2]**
Heterogeneity: Tau^2=0; Chi^2=0.54, df=2(P=0.76); I^2=0%							
Test for overall effect: Z=1.86(P=0.06)							
2.42.2 N-3 replacing MUFA							
AlphaOmega - EPA+DHA 2010	605	-0.3 (1)	605	-0.3 (1)		15.52%	0.02[-0.09,0.13]
ASCEND 2018	471	4 (0.9)	477	4 (0.9)		15.4%	0[-0.11,0.11]
DART 1989	868	6.5 (1.1)	847	6.4 (1.1)		16.69%	0.1[-0.01,0.21]
Deslypere 1992	14	5.5 (0.9)	14	5.9 (1)		0.37%	-0.41[-1.12,0.3]
Franzen 1993	15	5.8 (1)	15	6.3 (1.1)		0.33%	-0.49[-1.24,0.26]
HARP 1995	31	5 (1)	28	5 (0.6)		1.13%	0.03[-0.38,0.44]
MARINA 2011	80	5.6 (0.9)	71	5.6 (0.4)		3.91%	0[-0.22,0.22]



Favours higher omega 3 — Favours lower omega 3

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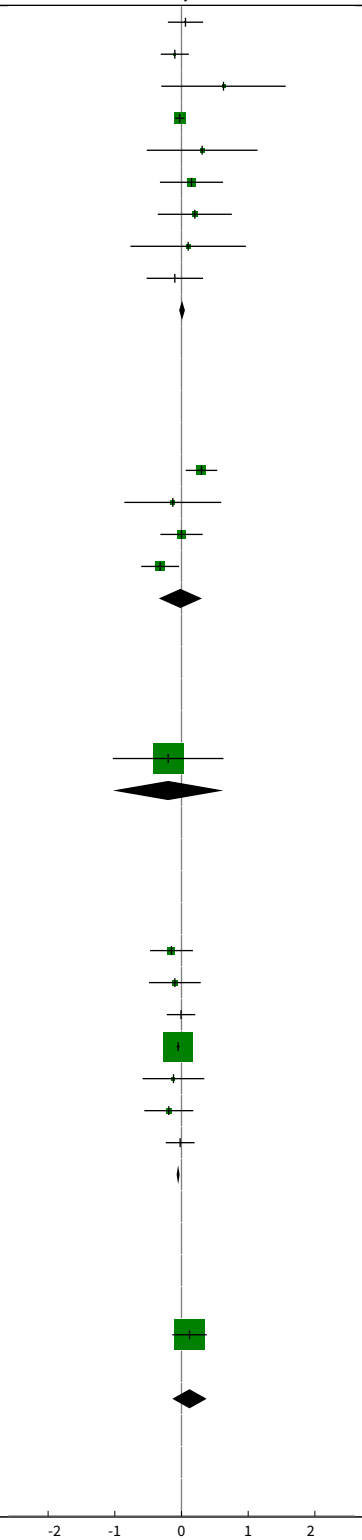
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
NAT2 2013	134	5.7 (1.2)	129	5.6 (1)		2.72%	0.06[-0.2,0.32]
Nodari 2011 HF	67	4.8 (0.6)	66	4.9 (0.6)		4.26%	-0.1[-0.31,0.11]
Nye 1990	12	6.8 (1)	12	6.2 (1.3)		0.22%	0.63[-0.3,1.56]
ORIGIN 2012	6281	-0.4 (2.1)	6255	-0.4 (2.1)		36.39%	-0.03[-0.1,0.04]
Rossing 1996	14	5.5 (1.1)	15	5.2 (1.2)		0.27%	0.31[-0.52,1.14]
SCIMO 1999	89	6.2 (1.6)	86	6.1 (1.6)		0.85%	0.15[-0.32,0.62]
SMART 2013	21	5.4 (0.9)	24	5.2 (1)		0.61%	0.2[-0.36,0.76]
Sofi 2010	6	-0 (1)	5	-0.1 (0.5)		0.25%	0.1[-0.77,0.97]
WELCOME 2015	47	4.7 (1.1)	48	4.8 (1)		1.06%	-0.1[-0.52,0.32]
Subtotal ***	**8755**		**8697**			**100%**	**0.01[-0.04,0.05]**
Heterogeneity: Tau^2=0; Chi^2=11.38, df=15(P=0.72); I^2=0%							
Test for overall effect: Z=0.36(P=0.72)							
2.42.3 N-3 replacing n-6							
Berson 2004	105	5.2 (0.8)	103	4.9 (0.9)		30.93%	0.3[0.06,0.54]
Caldwell 2011	17	5 (1.2)	17	5.1 (1)		12.94%	-0.13[-0.86,0.6]
DO IT 2010	124	6.3 (1.2)	117	6.3 (1.3)		27.33%	0[-0.32,0.32]
OFAMI 2001	123	5.3 (1.1)	123	5.6 (1.2)		28.8%	-0.32[-0.6,-0.04]
Subtotal ***	**369**		**360**			**100%**	**-0.02[-0.34,0.31]**
Heterogeneity: Tau^2=0.07; Chi^2=11.11, df=3(P=0.01); I^2=72.99%							
Test for overall effect: Z=0.1(P=0.92)							
2.42.4 N-3 replacing carbs/sugars							
Derosa 2016	128	4.9 (3.4)	130	5.1 (3.4)		100%	-0.2[-1.03,0.63]
Subtotal ***	**128**		**130**			**100%**	**-0.2[-1.03,0.63]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=0.47(P=0.64)							
2.42.5 N-3 replacing nil/low n-3 placebo							
Ahn 2016	38	3.6 (0.7)	36	3.8 (0.7)		0.48%	-0.15[-0.47,0.17]
Brox 2001	37	7.8 (0.9)	37	7.9 (0.8)		0.33%	-0.1[-0.49,0.29]
HEARTS 2017	126	0 (1)	114	0 (0.7)		1.09%	-0.01[-0.22,0.21]
JELIS 2007	9326	5.8 (0.8)	9319	5.9 (0.8)		96.44%	-0.05[-0.07,-0.03]
Mita 2007	30	5.2 (0.8)	30	5.3 (1)		0.23%	-0.12[-0.58,0.34]
Sandhu 2016	49	5.2 (0.9)	47	5.4 (0.9)		0.37%	-0.19[-0.56,0.18]
SHOT 1996	289	7 (1.3)	267	7 (1.3)		1.07%	-0.02[-0.24,0.2]
Subtotal ***	**9895**		**9850**			**100%**	**-0.05[-0.07,-0.03]**
Heterogeneity: Tau^2=0; Chi^2=1.31, df=6(P=0.97); I^2=0%							
Test for overall effect: Z=4.45(P<0.0001)							
2.42.6 Replacement unclear							
DIPP 2015	91	5.5 (0.9)	75	5.4 (0.8)		100%	0.12[-0.14,0.38]
EPE-A 2014	64	0.1 (0)	55	0.2 (0)			Not estimable
Subtotal ***	**155**		**130**			**100%**	**0.12[-0.14,0.38]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.91(P=0.36)							
Test for subgroup differences: Chi^2=13.51, df=1 (P=0.02), I^2=62.98%							



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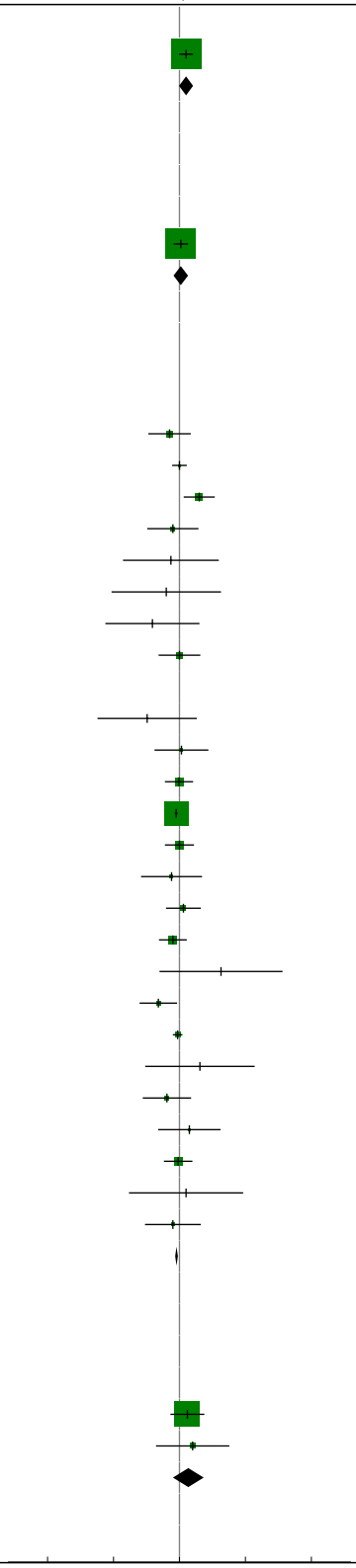
Analysis 2.43. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 43 TC, mmoL/L - LCn3 - subgroup by intervention type.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.43.1 Dietary advice							
DART 1989	868	6.5 (1.1)	847	6.4 (1.1)		100%	0.1[-0.01,0.21]
Subtotal ***	**868**		**847**			**100%**	**0.1[-0.01,0.21]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=1.84(P=0.07)							
2.43.2 Supplemental foods							
AlphaOmega - EPA+DHA 2010	605	-0.3 (1)	605	-0.3 (1)		100%	0.02[-0.09,0.13]
Subtotal ***	**605**		**605**			**100%**	**0.02[-0.09,0.13]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.35(P=0.72)							
2.43.3 Supplement (capsule)							
Ahn 2016	38	3.6 (0.7)	36	3.8 (0.7)		0.4%	-0.15[-0.47,0.17]
ASCEND 2018	471	4 (0.9)	477	4 (0.9)		3.37%	0[-0.11,0.11]
Berson 2004	105	5.2 (0.8)	103	4.9 (0.9)		0.75%	0.3[0.06,0.54]
Brox 2001	37	7.8 (0.9)	37	7.9 (0.8)		0.28%	-0.1[-0.49,0.29]
Caldwell 2011	17	5 (1.2)	17	5.1 (1)		0.08%	-0.13[-0.86,0.6]
Derosa 2016	128	4.9 (3.4)	130	5.1 (3.4)		0.06%	-0.2[-1.03,0.63]
Deslypere 1992	14	5.5 (0.9)	14	5.9 (1)		0.08%	-0.41[-1.12,0.3]
DO IT 2010	124	6.3 (1.2)	117	6.3 (1.3)		0.41%	0[-0.32,0.32]
EPE-A 2014	64	0.1 (0)	55	0.2 (0)			Not estimable
Franzen 1993	15	5.8 (1)	15	6.3 (1.1)		0.07%	-0.49[-1.24,0.26]
HARP 1995	31	5 (1)	28	5 (0.6)		0.25%	0.03[-0.38,0.44]
HEARTS 2017	126	0 (1)	114	0 (0.7)		0.91%	-0.01[-0.22,0.21]
JELIS 2007	9326	5.8 (0.8)	9319	5.9 (0.8)		80.52%	-0.05[-0.07,-0.03]
MARINA 2011	80	5.6 (0.9)	71	5.6 (0.4)		0.86%	0[-0.22,0.22]
Mita 2007	30	5.2 (0.8)	30	5.3 (1)		0.19%	-0.12[-0.58,0.34]
NAT2 2013	134	5.7 (1.2)	129	5.6 (1)		0.59%	0.06[-0.2,0.32]
Nodari 2011 HF	67	4.8 (0.6)	66	4.9 (0.6)		0.93%	-0.1[-0.31,0.11]
Nye 1990	12	6.8 (1)	12	6.2 (1.3)		0.05%	0.63[-0.3,1.56]
OFAMI 2001	123	5.3 (1.1)	123	5.6 (1.2)		0.51%	-0.32[-0.6,-0.04]
ORIGIN 2012	6281	-0.4 (2.1)	6255	-0.4 (2.1)		7.96%	-0.03[-0.1,0.04]
Rossing 1996	14	5.5 (1.1)	15	5.2 (1.2)		0.06%	0.31[-0.52,1.14]
Sandhu 2016	49	5.2 (0.9)	47	5.4 (0.9)		0.31%	-0.19[-0.56,0.18]
SCIMO 1999	89	6.2 (1.6)	86	6.1 (1.6)		0.19%	0.15[-0.32,0.62]
SHOT 1996	289	7 (1.3)	267	7 (1.3)		0.89%	-0.02[-0.24,0.2]
Sofi 2010	6	-0 (1)	5	-0.1 (0.5)		0.06%	0.1[-0.77,0.97]
WELCOME 2015	47	4.7 (1.1)	48	4.8 (1)		0.23%	-0.1[-0.52,0.32]
Subtotal ***	**17717**		**17616**			**100%**	**-0.04[-0.07,-0.02]**
Heterogeneity: Tau²=0; Chi²=21.56, df=24(P=0.61); I²=0%							
Test for overall effect: Z=4.3(P<0.0001)							
2.43.4 Any combination							
DIPP 2015	91	5.5 (0.9)	75	5.4 (0.8)		82.33%	0.12[-0.14,0.38]
SMART 2013	21	5.4 (0.9)	24	5.2 (1)		17.67%	0.2[-0.36,0.76]
Subtotal ***	**112**		**99**			**100%**	**0.13[-0.1,0.37]**
Heterogeneity: Tau²=0; Chi²=0.07, df=1(P=0.8); I²=0%							
Test for overall effect: Z=1.13(P=0.26)							



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Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for subgroup differences: Chi²=9.99, df=1 (P=0.02), I²=69.96%							

Favours higher omega 3 -2 -1 0 1 2 Favours lower omega 3

Analysis 2.44. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 44 TC, mmoL/L - LCn3 - subgroup by duration.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.44.1 Medium duration 1 to < 2 years in study							
Ahn 2016	38	3.6 (0.7)	36	3.8 (0.7)		9.6%	-0.15[-0.47,0.17]
Brox 2001	37	7.8 (0.9)	37	7.9 (0.8)		6.59%	-0.1[-0.49,0.29]
Caldwell 2011	17	5 (1.2)	17	5.1 (1)		1.88%	-0.13[-0.86,0.6]
Derosa 2016	128	4.9 (3.4)	130	5.1 (3.4)		1.44%	-0.2[-1.03,0.63]
Deslypere 1992	14	5.5 (0.9)	14	5.9 (1)		1.95%	-0.41[-1.12,0.3]
EPE-A 2014	64	0.1 (0)	55	0.2 (0)			Not estimable
Franzen 1993	15	5.8 (1)	15	6.3 (1.1)		1.75%	-0.49[-1.24,0.26]
MARINA 2011	80	5.6 (0.9)	71	5.6 (0.4)		20.47%	0[-0.22,0.22]
Nodari 2011 HF	67	4.8 (0.6)	66	4.9 (0.6)		22.33%	-0.1[-0.31,0.11]
Nye 1990	12	6.8 (1)	12	6.2 (1.3)		1.14%	0.63[-0.3,1.56]
Rossing 1996	14	5.5 (1.1)	15	5.2 (1.2)		1.44%	0.31[-0.52,1.14]
SHOT 1996	289	7 (1.3)	267	7 (1.3)		21.32%	-0.02[-0.24,0.2]
SMART 2013	21	5.4 (0.9)	24	5.2 (1)		3.22%	0.2[-0.36,0.76]
Sofi 2010	6	-0 (1)	5	-0.1 (0.5)		1.32%	0.1[-0.77,0.97]
WELCOME 2015	47	4.7 (1.1)	48	4.8 (1)		5.54%	-0.1[-0.52,0.32]
Subtotal ***	**849**		**812**			**100%**	**-0.06[-0.16,0.04]**
Heterogeneity: Tau²=0; Chi²=7.09, df=13(P=0.9); I²=0%							
Test for overall effect: Z=1.09(P=0.27)							
2.44.2 Medium-long duration: 2 to < 4 years in study							
AlphaOmega - EPA+DHA 2010	605	-0.3 (1)	605	-0.3 (1)		30%	0.02[-0.09,0.13]
DART 1989	868	6.5 (1.1)	847	6.4 (1.1)		32.06%	0.1[-0.01,0.21]
DIPP 2015	91	5.5 (0.9)	75	5.4 (0.8)		5.94%	0.12[-0.14,0.38]
DO IT 2010	124	6.3 (1.2)	117	6.3 (1.3)		3.95%	0[-0.32,0.32]
HARP 1995	31	5 (1)	28	5 (0.6)		2.38%	0.03[-0.38,0.44]
HEARTS 2017	126	0 (1)	114	0 (0.7)		8.54%	-0.01[-0.22,0.21]
Mita 2007	30	5.2 (0.8)	30	5.3 (1)		1.86%	-0.12[-0.58,0.34]
NAT2 2013	134	5.7 (1.2)	129	5.6 (1)		5.65%	0.06[-0.2,0.32]
OFAMI 2001	123	5.3 (1.1)	123	5.6 (1.2)		4.89%	-0.32[-0.6,-0.04]
Sandhu 2016	49	5.2 (0.9)	47	5.4 (0.9)		2.95%	-0.19[-0.56,0.18]
SCIMO 1999	89	6.2 (1.6)	86	6.1 (1.6)		1.78%	0.15[-0.32,0.62]
Subtotal ***	**2270**		**2201**			**100%**	**0.03[-0.04,0.09]**
Heterogeneity: Tau²=0; Chi²=10.24, df=10(P=0.42); I²=2.3%							
Test for overall effect: Z=0.86(P=0.39)							
2.44.3 Long duration ≥ 4 years in study							
ASCEND 2018	471	4 (0.9)	477	4 (0.9)		21.18%	0[-0.11,0.11]
Berson 2004	105	5.2 (0.8)	103	4.9 (0.9)		7.6%	0.3[0.06,0.54]
JELIS 2007	9326	5.8 (0.8)	9319	5.9 (0.8)		41.27%	-0.05[-0.07,-0.03]
ORIGIN 2012	6281	-0.4 (2.1)	6255	-0.4 (2.1)		29.96%	-0.03[-0.1,0.04]

Favours higher omega 3 -2 -1 0 1 2 Favours lower omega 3

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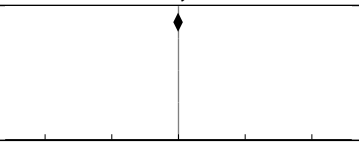
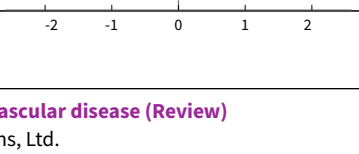
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Subtotal ***	**16183**		**16154**			**100%**	**-0.01[-0.08,0.07]**
Heterogeneity: Tau²=0; Chi²=9.25, df=3(P=0.03); I²=67.58%							
Test for overall effect: Z=0.17(P=0.86)							
Test for subgroup differences: Chi²=1.97, df=1 (P=0.37), I²=0%							



Favours higher omega 3 — Favours lower omega 3

Analysis 2.45. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 45 TC, mmoL/L - LCn3 - subgroup by primary or secondary prevention.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.45.1 Primary prevention							
ASCEND 2018	471	4 (0.9)	477	4 (0.9)		3.51%	0[-0.11,0.11]
Berson 2004	105	5.2 (0.8)	103	4.9 (0.9)		0.78%	0.3[0.06,0.54]
Brox 2001	37	7.8 (0.9)	37	7.9 (0.8)		0.29%	-0.1[-0.49,0.29]
Caldwell 2011	17	5 (1.2)	17	5.1 (1)		0.08%	-0.13[-0.86,0.6]
Derosa 2016	128	4.9 (3.4)	130	5.1 (3.4)		0.06%	-0.2[-1.03,0.63]
Deslypere 1992	14	5.5 (0.9)	14	5.9 (1)		0.08%	-0.41[-1.12,0.3]
DIPP 2015	91	5.5 (0.9)	75	5.4 (0.8)		0.65%	0.12[-0.14,0.38]
DO IT 2010	124	6.3 (1.2)	117	6.3 (1.3)		0.43%	0[-0.32,0.32]
EPE-A 2014	64	0.1 (0)	55	0.2 (0)			Not estimable
JELIS 2007	9326	5.8 (0.8)	9319	5.9 (0.8)		83.9%	-0.05[-0.07,-0.03]
MARINA 2011	80	5.6 (0.9)	71	5.6 (0.4)		0.89%	0[-0.22,0.22]
Mita 2007	30	5.2 (0.8)	30	5.3 (1)		0.2%	-0.12[-0.58,0.34]
ORIGIN 2012	6281	-0.4 (2.1)	6255	-0.4 (2.1)		8.3%	-0.03[-0.1,0.04]
Rossing 1996	14	5.5 (1.1)	15	5.2 (1.2)		0.06%	0.31[-0.52,1.14]
Sandhu 2016	49	5.2 (0.9)	47	5.4 (0.9)		0.32%	-0.19[-0.56,0.18]
SMART 2013	21	5.4 (0.9)	24	5.2 (1)		0.14%	0.2[-0.36,0.76]
Sofi 2010	6	-0 (1)	5	-0.1 (0.5)		0.06%	0.1[-0.77,0.97]
WELCOME 2015	47	4.7 (1.1)	48	4.8 (1)		0.24%	-0.1[-0.52,0.32]
Subtotal ***	**16905**		**16839**			**100%**	**-0.04[-0.06,-0.02]**
Heterogeneity: Tau²=0; Chi²=14.64, df=16(P=0.55); I²=0%							
Test for overall effect: Z=4.02(P<0.0001)							
2.45.2 Secondary prevention							
Ahn 2016	38	3.6 (0.7)	36	3.8 (0.7)		4.87%	-0.15[-0.47,0.17]
AlphaOmega - EPA+DHA 2010	605	-0.3 (1)	605	-0.3 (1)		22.59%	0.02[-0.09,0.13]
DART 1989	868	6.5 (1.1)	847	6.4 (1.1)		23.39%	0.1[-0.01,0.21]
Franzen 1993	15	5.8 (1)	15	6.3 (1.1)		0.98%	-0.49[-1.24,0.26]
HARP 1995	31	5 (1)	28	5 (0.6)		3.15%	0.03[-0.38,0.44]
HEARTS 2017	126	0 (1)	114	0 (0.7)		9.67%	-0.01[-0.22,0.21]
NAT2 2013	134	5.7 (1.2)	129	5.6 (1)		6.85%	0.06[-0.2,0.32]
Nodari 2011 HF	67	4.8 (0.6)	66	4.9 (0.6)		9.88%	-0.1[-0.31,0.11]
Nye 1990	12	6.8 (1)	12	6.2 (1.3)		0.64%	0.63[-0.3,1.56]
OFAMI 2001	123	5.3 (1.1)	123	5.6 (1.2)		6.05%	-0.32[-0.6,-0.04]
SCIMO 1999	89	6.2 (1.6)	86	6.1 (1.6)		2.39%	0.15[-0.32,0.62]
SHOT 1996	289	7 (1.3)	267	7 (1.3)		9.53%	-0.02[-0.24,0.2]
Subtotal ***	**2397**		**2328**			**100%**	**-0[-0.08,0.07]**
Heterogeneity: Tau²=0; Chi²=13.93, df=11(P=0.24); I²=21.04%							



Favours higher omega 3 — Favours lower omega 3

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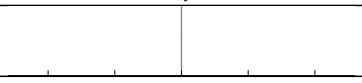
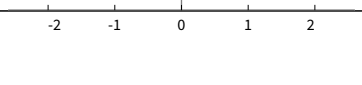
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for overall effect: Z=0.09(P=0.93)							
Test for subgroup differences: Chi²=0.97, df=1 (P=0.32), I²=0%							



Favours higher omega 3 — Favours lower omega 3

Analysis 2.46. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 46 TC, mmoL/L - LCn3 - subgroup by statin use.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.46.1 LCn3 - ≥ 50% of control group on statins							
Ahn 2016	38	3.6 (0.7)	36	3.8 (0.7)		0.41%	-0.15[-0.47,0.17]
AlphaOmega - EPA+DHA 2010	605	-0.3 (1)	605	-0.3 (1)		3.49%	0.02[-0.09,0.13]
ASCEND 2018	471	4 (0.9)	477	4 (0.9)		3.46%	0[-0.11,0.11]
HEARTS 2017	126	0 (1)	114	0 (0.7)		0.93%	-0.01[-0.22,0.21]
JELIS 2007	9326	5.8 (0.8)	9319	5.9 (0.8)		82.68%	-0.05[-0.07,-0.03]
NAT2 2013	134	5.7 (1.2)	129	5.6 (1)		0.61%	0.06[-0.2,0.32]
ORIGIN 2012	6281	-0.4 (2.1)	6255	-0.4 (2.1)		8.18%	-0.03[-0.1,0.04]
WELCOME 2015	47	4.7 (1.1)	48	4.8 (1)		0.24%	-0.1[-0.52,0.32]
Subtotal ***	**17028**		**16983**			**100%**	**-0.04[-0.06,-0.02]**
Heterogeneity: Tau²=0; Chi²=3.55, df=7(P=0.83); I²=0%							
Test for overall effect: Z=4.13(P<0.0001)							
2.46.2 LCn3 - < 50% of control group on statins							
Berson 2004	105	5.2 (0.8)	103	4.9 (0.9)		9.29%	0.3[0.06,0.54]
Brox 2001	37	7.8 (0.9)	37	7.9 (0.8)		4.37%	-0.1[-0.49,0.29]
DART 1989	868	6.5 (1.1)	847	6.4 (1.1)		19.42%	0.1[-0.01,0.21]
Deslypere 1992	14	5.5 (0.9)	14	5.9 (1)		1.46%	-0.41[-1.12,0.3]
DIPP 2015	91	5.5 (0.9)	75	5.4 (0.8)		8.25%	0.12[-0.14,0.38]
DO IT 2010	124	6.3 (1.2)	117	6.3 (1.3)		6.08%	0[-0.32,0.32]
Franzen 1993	15	5.8 (1)	15	6.3 (1.1)		1.32%	-0.49[-1.24,0.26]
HARP 1995	31	5 (1)	28	5 (0.6)		4.01%	0.03[-0.38,0.44]
MARINA 2011	80	5.6 (0.9)	71	5.6 (0.4)		10.13%	0[-0.22,0.22]
Mita 2007	30	5.2 (0.8)	30	5.3 (1)		3.24%	-0.12[-0.58,0.34]
Nodari 2011 HF	67	4.8 (0.6)	66	4.9 (0.6)		10.69%	-0.1[-0.31,0.11]
OFAMI 2001	123	5.3 (1.1)	123	5.6 (1.2)		7.16%	-0.32[-0.6,-0.04]
Rossing 1996	14	5.5 (1.1)	15	5.2 (1.2)		1.09%	0.31[-0.52,1.14]
SCIMO 1999	89	6.2 (1.6)	86	6.1 (1.6)		3.11%	0.15[-0.32,0.62]
SHOT 1996	289	7 (1.3)	267	7 (1.3)		10.39%	-0.02[-0.24,0.2]
Subtotal ***	**1977**		**1894**			**100%**	**0.01[-0.08,0.1]**
Heterogeneity: Tau²=0.01; Chi²=19.6, df=14(P=0.14); I²=28.57%							
Test for overall effect: Z=0.22(P=0.82)							
2.46.3 LCn3 - use of statins unclear							
Caldwell 2011	17	5 (1.2)	17	5.1 (1)		11.48%	-0.13[-0.86,0.6]
Derosa 2016	128	4.9 (3.4)	130	5.1 (3.4)		8.79%	-0.2[-1.03,0.63]
EPE-A 2014	64	0.1 (0)	55	0.2 (0)			Not estimable
Nye 1990	12	6.8 (1)	12	6.2 (1.3)		6.96%	0.63[-0.3,1.56]
Sandhu 2016	49	5.2 (0.9)	47	5.4 (0.9)		45.06%	-0.19[-0.56,0.18]
SMART 2013	21	5.4 (0.9)	24	5.2 (1)		19.64%	0.2[-0.36,0.76]



Favours higher omega 3 — Favours lower omega 3

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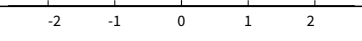
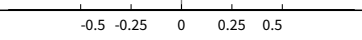
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Sofi 2010	6	-0 (1)	5	-0.1 (0.5)		8.08%	0.1[-0.77,0.97]
Subtotal ***	**297**		**290**			**100%**	**-0.03[-0.27,0.22]**
Heterogeneity: Tau²=0; Chi²=3.64, df=5(P=0.6); I²=0%							
Test for overall effect: Z=0.21(P=0.83)							
Test for subgroup differences: Chi²=1.34, df=1 (P=0.51), I²=0%							



Favours higher omega 3 — Favours lower omega 3

Analysis 2.47. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 47 Triglycerides, fasting, serum, mmoL/L - LCn3.

Study or subgroup	Favours higher omega 3 N	Favours higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
AlphaOmega - EPA+DHA 2010	605	-0.1 (1.2)	605	-0 (1)		8.47%	-0.03[-0.15,0.09]
Berson 2004	105	1.1 (0.7)	103	1.4 (1.2)		4.43%	-0.33[-0.6,-0.06]
Derosa 2016	128	1.4 (3.4)	130	1.9 (4.6)		0.54%	-0.5[-1.49,0.49]
Deslypere 1992	14	0.8 (0.4)	14	1.2 (0.8)		2.16%	-0.43[-0.88,0.02]
DIPP 2015	90	1.5 (1.1)	71	1.4 (0.8)		4.16%	0.01[-0.28,0.3]
DO IT 2010	124	1.4 (0.8)	117	1.6 (0.9)		5.72%	-0.16[-0.38,0.06]
EPE-A 2014	64	-0.1 (0)	55	0.1 (0)			Not estimable
HARP 1995	31	1.1 (0.6)	28	1.6 (0.8)		3.28%	-0.47[-0.81,-0.13]
HEARTS 2017	126	-0.2 (0)	114	-0 (0)			Not estimable
JELIS 2007	7023	1.4 (0)	7057	1.5 (0)			Not estimable
JELIS 2007	2303	1.6 (0)	2262	1.7 (0)			Not estimable
Lorenz-Meyer 1996	13	-0.4 (0.7)	12	-0.1 (0.5)		2.3%	-0.32[-0.76,0.12]
MARINA 2011	80	-0.2 (0.5)	71	0.1 (0.6)		6.8%	-0.3[-0.48,-0.12]
Mita 2007	30	1.8 (1.1)	30	1.5 (0.9)		1.83%	0.26[-0.24,0.76]
Nodari 2011 HF	67	1.6 (0.5)	66	1.8 (0.8)		5.5%	-0.14[-0.36,0.08]
Nye 1990	12	1.4 (0.6)	12	1.8 (0.6)		2.16%	-0.4[-0.85,0.05]
OFAMI 2001	120	1.3 (0.6)	121	1.8 (1.1)		5.72%	-0.51[-0.73,-0.29]
ORIGIN 2012	6281	-0.3 (2.7)	6255	-0.1 (2.7)		9.39%	-0.16[-0.26,-0.07]
ORL 2013	170	-0.8 (0.9)	165	-0.4 (0.9)		6.43%	-0.38[-0.57,-0.19]
REDUCE-IT 2019	4089	1.9 (0)	4090	2.3 (0)			Not estimable
Sandhu 2016	49	1.1 (0.6)	47	1.2 (0.5)		5.81%	-0.16[-0.37,0.05]
SCIMO 1999	87	-0.2 (1)	84	0.1 (1.2)		3.51%	-0.25[-0.58,0.08]
SHOT 1996	289	1.6 (1)	267	2.1 (1.2)		6.46%	-0.45[-0.64,-0.26]
SMART 2013	21	1.1 (0.6)	24	1.2 (0.5)		3.85%	-0.07[-0.38,0.24]
Sofi 2010	6	-0.4 (0.8)	5	0.2 (0.2)		1.2%	-0.59[-1.23,0.05]
Tande 2016	50	-0 (0.7)	50	0.2 (0.7)		4.59%	-0.21[-0.47,0.05]
THIS DIET 2008	37	1.5 (0.8)	34	1.4 (0.9)		2.88%	0.02[-0.36,0.4]
WELCOME 2015	47	1.5 (1.2)	48	1.8 (0.6)		2.8%	-0.3[-0.68,0.08]
Total ***	**22061**		**21937**			**100%**	**-0.24[-0.31,-0.16]**
Heterogeneity: Tau²=0.01; Chi²=42.25, df=22(P=0.01); I²=47.93%							
Test for overall effect: Z=6.24(P<0.0001)							



Favours higher omega 3 — Favours lower omega 3

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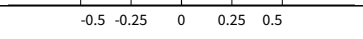
Analysis 2.48. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 48 TG, fasting, mmoL/L - LCn3 - SA fixed effects.

Study or subgroup	Favours higher omega 3 N	Favours higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
AlphaOmega - EPA+DHA 2010	605	-0.1 (1.2)	605	-0 (1)		14.38%	-0.03[-0.15,0.09]
Berson 2004	105	1.1 (0.7)	103	1.4 (1.2)		2.94%	-0.33[-0.6,-0.06]
Derosa 2016	128	1.4 (3.4)	130	1.9 (4.6)		0.23%	-0.5[-1.49,0.49]
Deslypere 1992	14	0.8 (0.4)	14	1.2 (0.8)		1.07%	-0.43[-0.88,0.02]
DIPP 2015	90	1.5 (1.1)	71	1.4 (0.8)		2.65%	0.01[-0.28,0.3]
DO IT 2010	124	1.4 (0.8)	117	1.6 (0.9)		4.72%	-0.16[-0.38,0.06]
EPE-A 2014	64	-0.1 (0)	55	0.1 (0)			Not estimable
HARP 1995	31	1.1 (0.6)	28	1.6 (0.8)		1.86%	-0.47[-0.81,-0.13]
HEARTS 2017	126	-0.2 (0)	114	-0 (0)			Not estimable
JELIS 2007	2303	1.6 (0)	2262	1.7 (0)			Not estimable
JELIS 2007	7023	1.4 (0)	7057	1.5 (0)			Not estimable
Lorenz-Meyer 1996	13	-0.4 (0.7)	12	-0.1 (0.5)		1.16%	-0.32[-0.76,0.12]
MARINA 2011	80	-0.2 (0.5)	71	0.1 (0.6)		7.02%	-0.3[-0.48,-0.12]
Mita 2007	30	1.8 (1.1)	30	1.5 (0.9)		0.88%	0.26[-0.24,0.76]
Nodari 2011 HF	67	1.6 (0.5)	66	1.8 (0.8)		4.35%	-0.14[-0.36,0.08]
Nye 1990	12	1.4 (0.6)	12	1.8 (0.6)		1.07%	-0.4[-0.85,0.05]
OFAMI 2001	120	1.3 (0.6)	121	1.8 (1.1)		4.71%	-0.51[-0.73,-0.29]
ORIGIN 2012	6281	-0.3 (2.7)	6255	-0.1 (2.7)		24.71%	-0.16[-0.26,-0.07]
ORL 2013	170	-0.8 (0.9)	165	-0.4 (0.9)		6.1%	-0.38[-0.57,-0.19]
REDUCE-IT 2019	4089	1.9 (0)	4090	2.3 (0)			Not estimable
Sandhu 2016	49	1.1 (0.6)	47	1.2 (0.5)		4.87%	-0.16[-0.37,0.05]
SCIMO 1999	87	-0.2 (1)	84	0.1 (1.2)		2.04%	-0.25[-0.58,0.08]
SHOT 1996	289	1.6 (1)	267	2.1 (1.2)		6.19%	-0.45[-0.64,-0.26]
SMART 2013	21	1.1 (0.6)	24	1.2 (0.5)		2.35%	-0.07[-0.38,0.24]
Sofi 2010	6	-0.4 (0.8)	5	0.2 (0.2)		0.54%	-0.59[-1.23,0.05]
Tande 2016	50	-0 (0.7)	50	0.2 (0.7)		3.13%	-0.21[-0.47,0.05]
THIS DIET 2008	37	1.5 (0.8)	34	1.4 (0.9)		1.55%	0.02[-0.36,0.4]
WELCOME 2015	47	1.5 (1.2)	48	1.8 (0.6)		1.5%	-0.3[-0.68,0.08]
Total ***	**22061**		**21937**			**100%**	**-0.21[-0.26,-0.17]**

Heterogeneity: $Tau^2=0$; $Chi^2=42.25$, df=22(P=0.01); $I^2=47.93\%$

Test for overall effect: Z=8.9(P<0.0001)



Analysis 2.49. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 49 TG, fasting, mmoL/L - LCn3 - SA by summary risk of bias.

Study or subgroup	Favours higher omega 3 N	Favours higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.49.1 Low summary risk of bias							
AlphaOmega - EPA+DHA 2010	605	-0.1 (1.2)	605	-0 (1)		25.56%	-0.03[-0.15,0.09]
Berson 2004	105	1.1 (0.7)	103	1.4 (1.2)		9%	-0.33[-0.6,-0.06]
Derosa 2016	128	1.4 (3.4)	130	1.9 (4.6)		0.83%	-0.5[-1.49,0.49]
Lorenz-Meyer 1996	13	-0.4 (0.7)	12	-0.1 (0.5)		3.98%	-0.32[-0.76,0.12]
MARINA 2011	80	-0.2 (0.5)	71	0.1 (0.6)		17.09%	-0.3[-0.48,-0.12]

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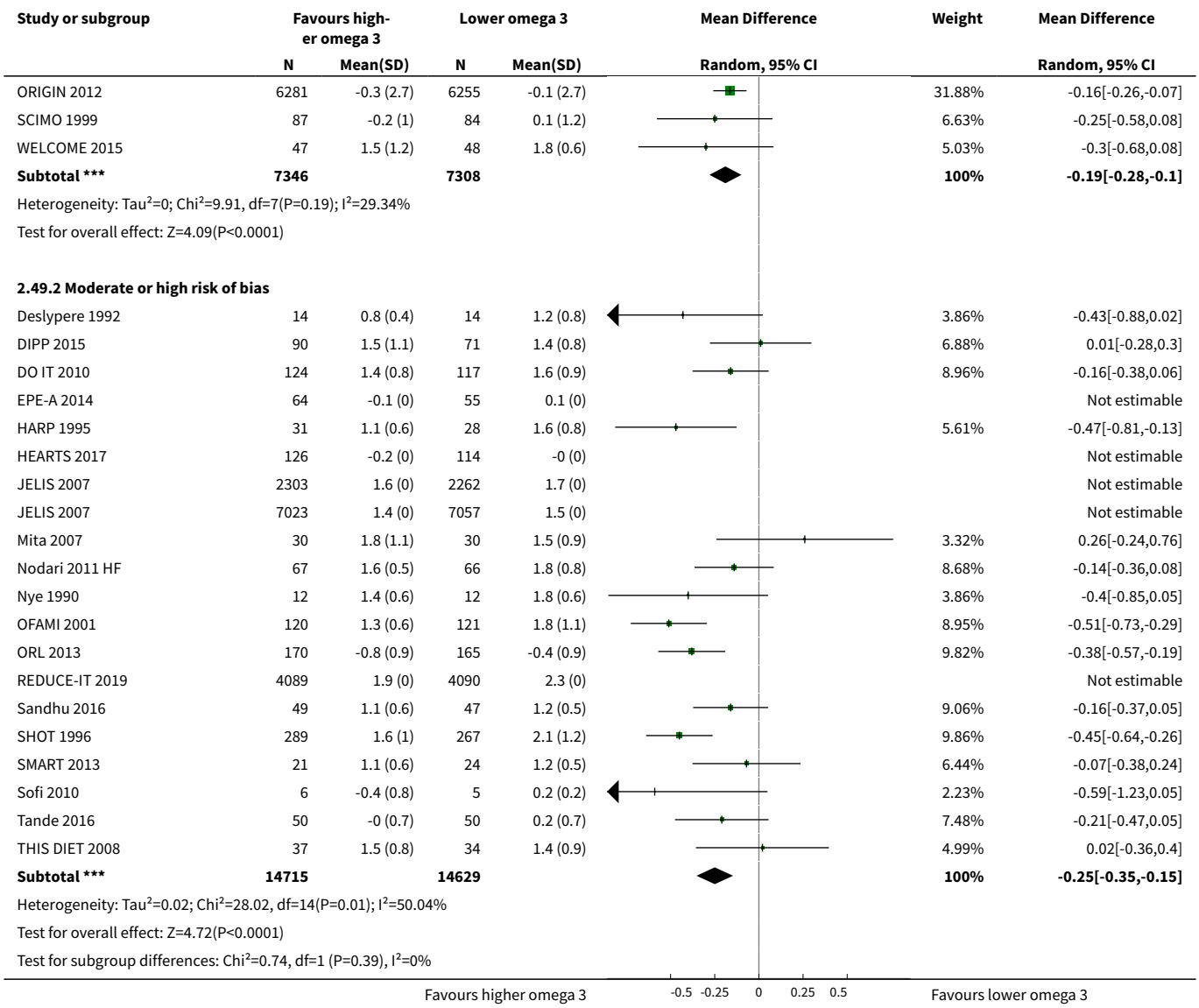
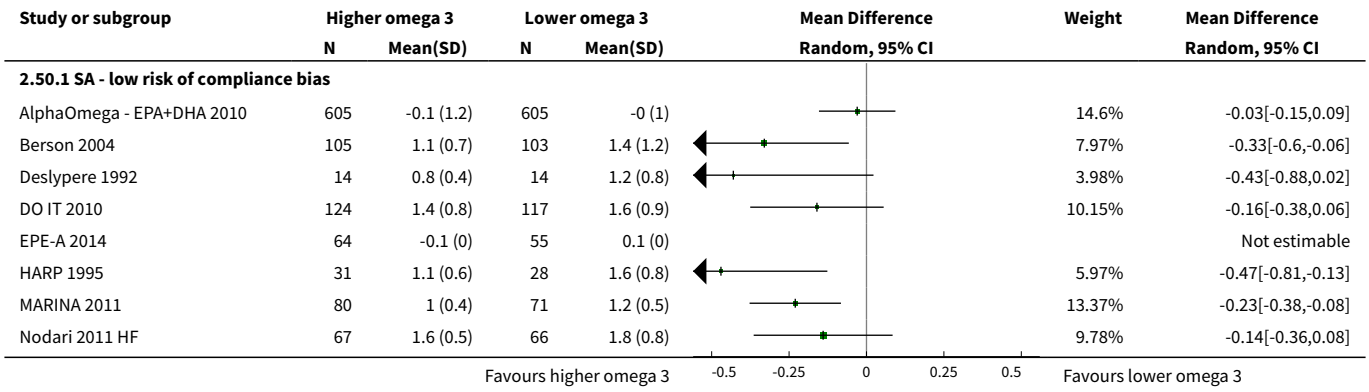


Analysis 2.50. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 50 TG, fasting, mmoL/L - LCn3 - SA by compliance and study size.



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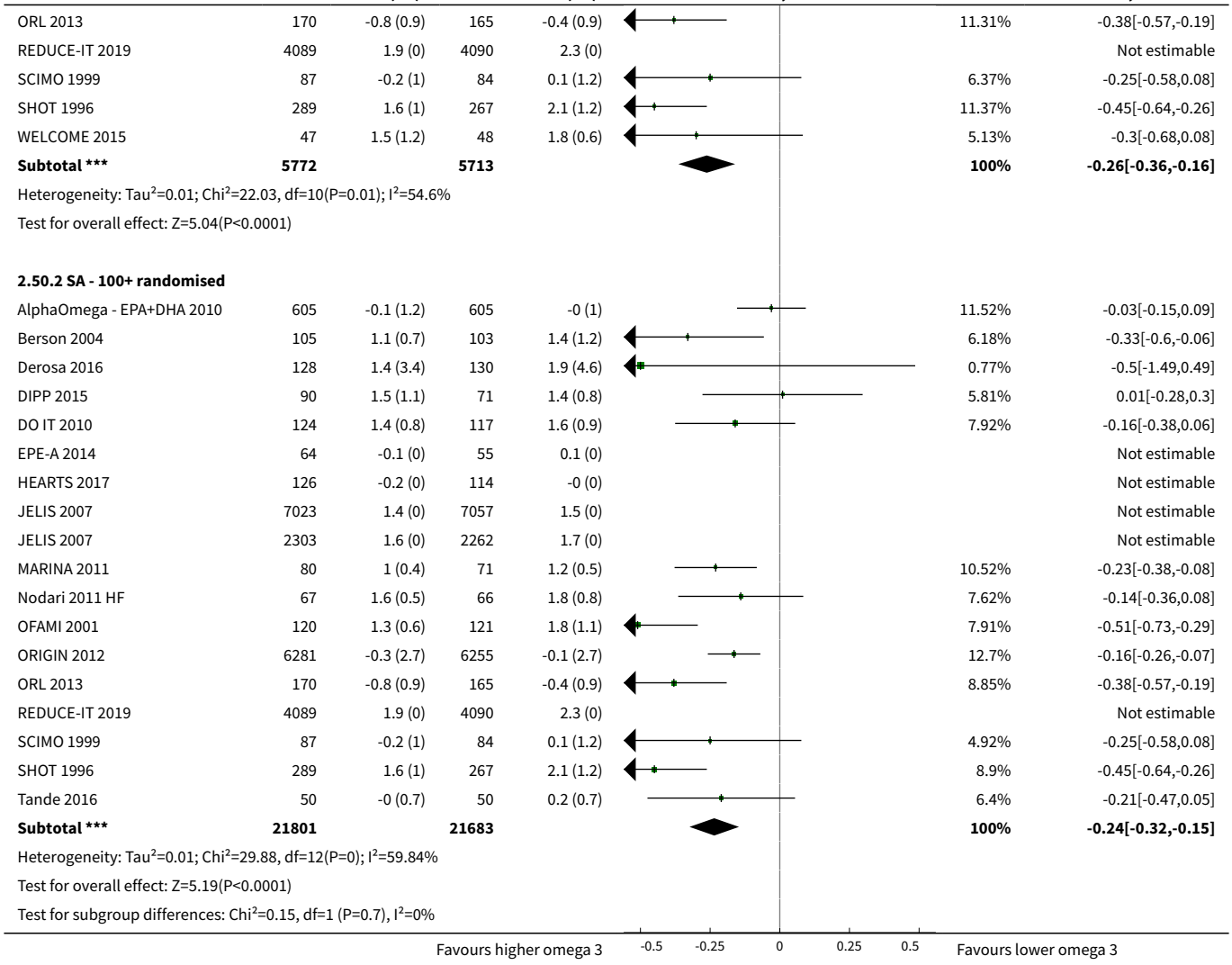
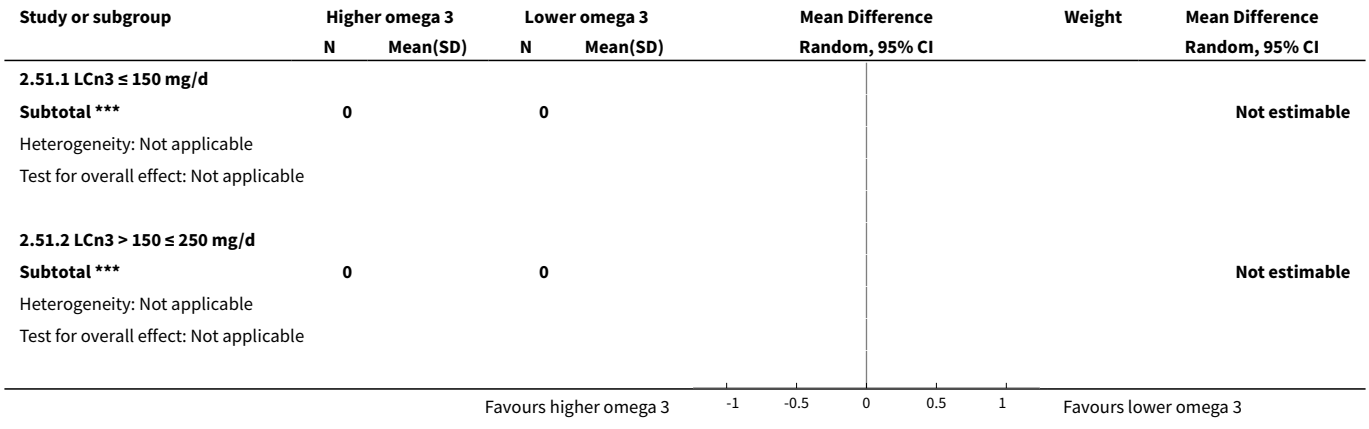


Analysis 2.51. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 51 TG, fasting, mmoL/L - LCn3 - subgroup by dose.



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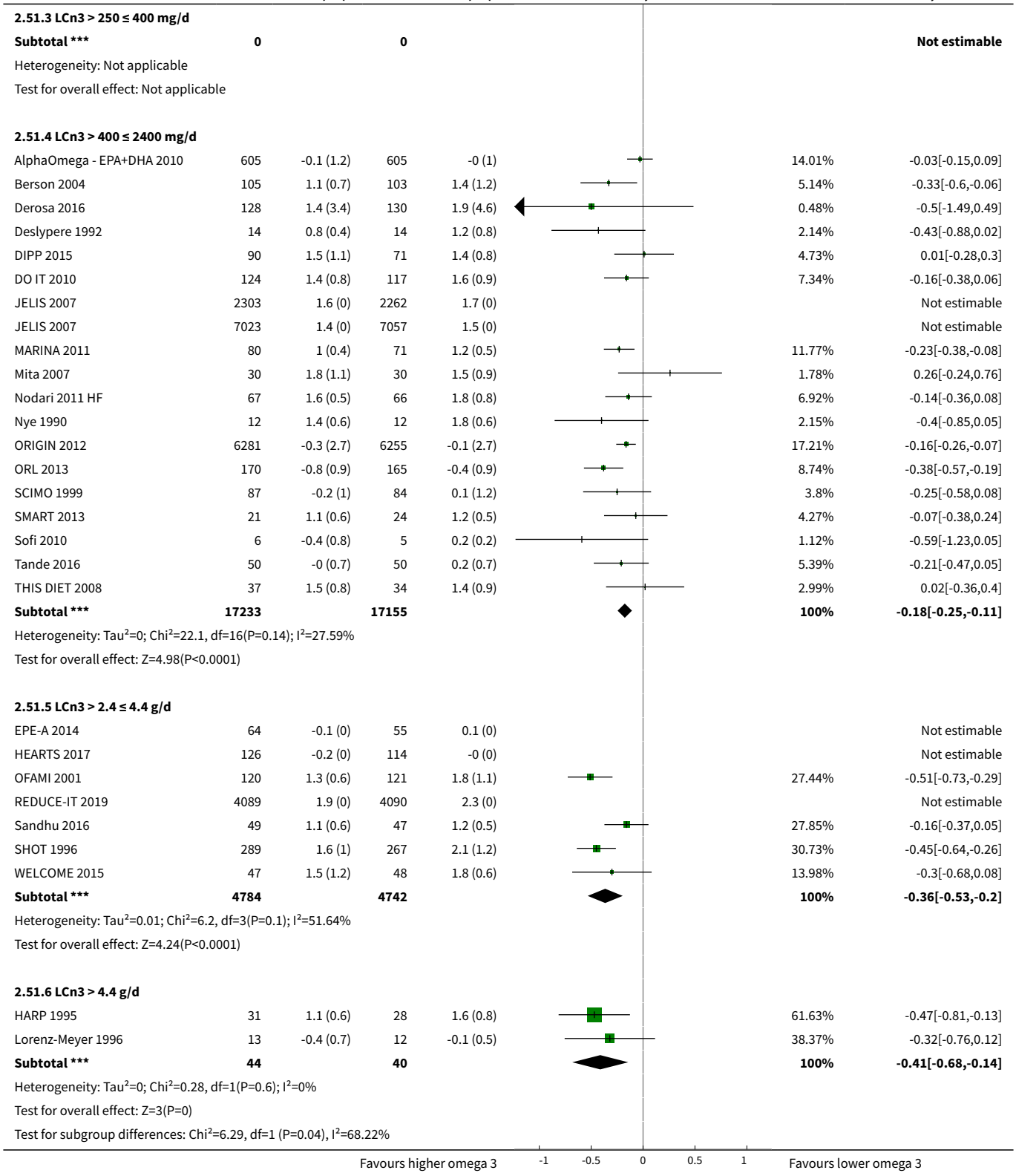

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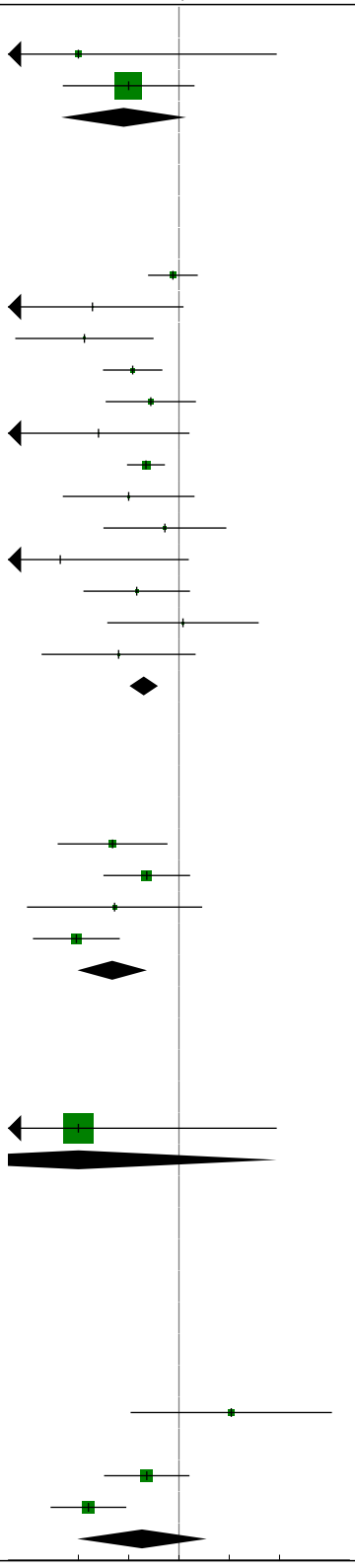
Analysis 2.52. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 52 TG, fasting, mmoL/L - LCn3 - subgroup by replacement.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.52.1 N-3 replacing SFA							
Derosa 2016	128	1.4 (3.4)	130	1.9 (4.6)		9.93%	-0.5[-1.49,0.49]
SCIMO 1999	87	-0.2 (1)	84	0.1 (1.2)		90.07%	-0.25[-0.58,0.08]
Subtotal ***	**215**		**214**			**100%**	**-0.27[-0.59,0.04]**
Heterogeneity: Tau²=0; Chi²=0.22, df=1(P=0.64); I²=0%							
Test for overall effect: Z=1.73(P=0.08)							
2.52.2 N-3 replacing MUFA							
AlphaOmega - EPA+DHA 2010	605	-0.1 (1.2)	605	-0 (1)		19.34%	-0.03[-0.15,0.09]
Deslypere 1992	14	0.8 (0.4)	14	1.2 (0.8)		2.31%	-0.43[-0.88,0.02]
HARP 1995	31	1.1 (0.6)	28	1.6 (0.8)		3.87%	-0.47[-0.81,-0.13]
MARINA 2011	80	1 (0.4)	71	1.2 (0.5)		15.43%	-0.23[-0.38,-0.08]
Nodari 2011 HF	67	1.6 (0.5)	66	1.8 (0.8)		8.19%	-0.14[-0.36,0.08]
Nye 1990	12	1.4 (0.6)	12	1.8 (0.6)		2.32%	-0.4[-0.85,0.05]
ORIGIN 2012	6281	-0.3 (2.7)	6255	-0.1 (2.7)		25.7%	-0.16[-0.26,-0.07]
SCIMO 1999	87	-0.2 (1)	84	0.1 (1.2)		4.23%	-0.25[-0.58,0.08]
SMART 2013	21	1.1 (0.6)	24	1.2 (0.5)		4.8%	-0.07[-0.38,0.24]
Sofi 2010	6	-0.4 (0.8)	5	0.2 (0.2)		1.19%	-0.59[-1.23,0.05]
Tande 2016	50	-0 (0.7)	50	0.2 (0.7)		6.18%	-0.21[-0.47,0.05]
THIS DIET 2008	37	1.5 (0.8)	34	1.4 (0.9)		3.27%	0.02[-0.36,0.4]
WELCOME 2015	47	1.5 (1.2)	48	1.8 (0.6)		3.17%	-0.3[-0.68,0.08]
Subtotal ***	**7338**		**7296**			**100%**	**-0.18[-0.25,-0.1]**
Heterogeneity: Tau²=0; Chi²=14.61, df=12(P=0.26); I²=17.89%							
Test for overall effect: Z=4.86(P<0.0001)							
2.52.3 N-3 replacing n-6							
Berson 2004	105	1.1 (0.7)	103	1.4 (1.2)		24.33%	-0.33[-0.6,-0.06]
DO IT 2010	124	1.4 (0.8)	117	1.6 (0.9)		31.59%	-0.16[-0.38,0.06]
Lorenz-Meyer 1996	13	-0.4 (0.7)	12	-0.1 (0.5)		12.52%	-0.32[-0.76,0.12]
OFAMI 2001	120	1.3 (0.6)	121	1.8 (1.1)		31.55%	-0.51[-0.73,-0.29]
Subtotal ***	**362**		**353**			**100%**	**-0.33[-0.5,-0.16]**
Heterogeneity: Tau²=0.01; Chi²=5.07, df=3(P=0.17); I²=40.8%							
Test for overall effect: Z=3.77(P=0)							
2.52.4 N-3 replacing carbs/sugars							
Derosa 2016	128	1.4 (3.4)	130	1.9 (4.6)		100%	-0.5[-1.49,0.49]
Subtotal ***	**128**		**130**			**100%**	**-0.5[-1.49,0.49]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.99(P=0.32)							
2.52.5 N-3 replacing nil/low n-3 placebo							
HEARTS 2017	126	-0.2 (0)	114	-0 (0)			Not estimable
JELIS 2007	2303	1.6 (0)	2262	1.7 (0)			Not estimable
JELIS 2007	7023	1.4 (0)	7057	1.5 (0)			Not estimable
Mita 2007	30	1.8 (1.1)	30	1.5 (0.9)		21.8%	0.26[-0.24,0.76]
REDUCE-IT 2019	4089	1.9 (0)	4090	2.3 (0)			Not estimable
Sandhu 2016	49	1.1 (0.6)	47	1.2 (0.5)		38.39%	-0.16[-0.37,0.05]
SHOT 1996	289	1.6 (1)	267	2.1 (1.2)		39.81%	-0.45[-0.64,-0.26]
Subtotal ***	**13909**		**13867**			**100%**	**-0.18[-0.51,0.14]**



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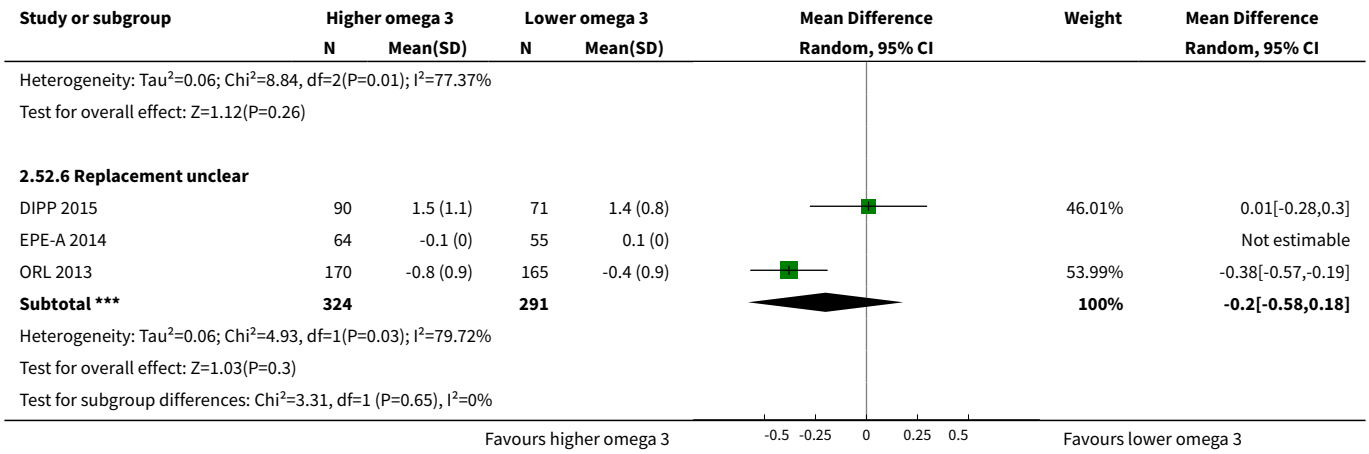
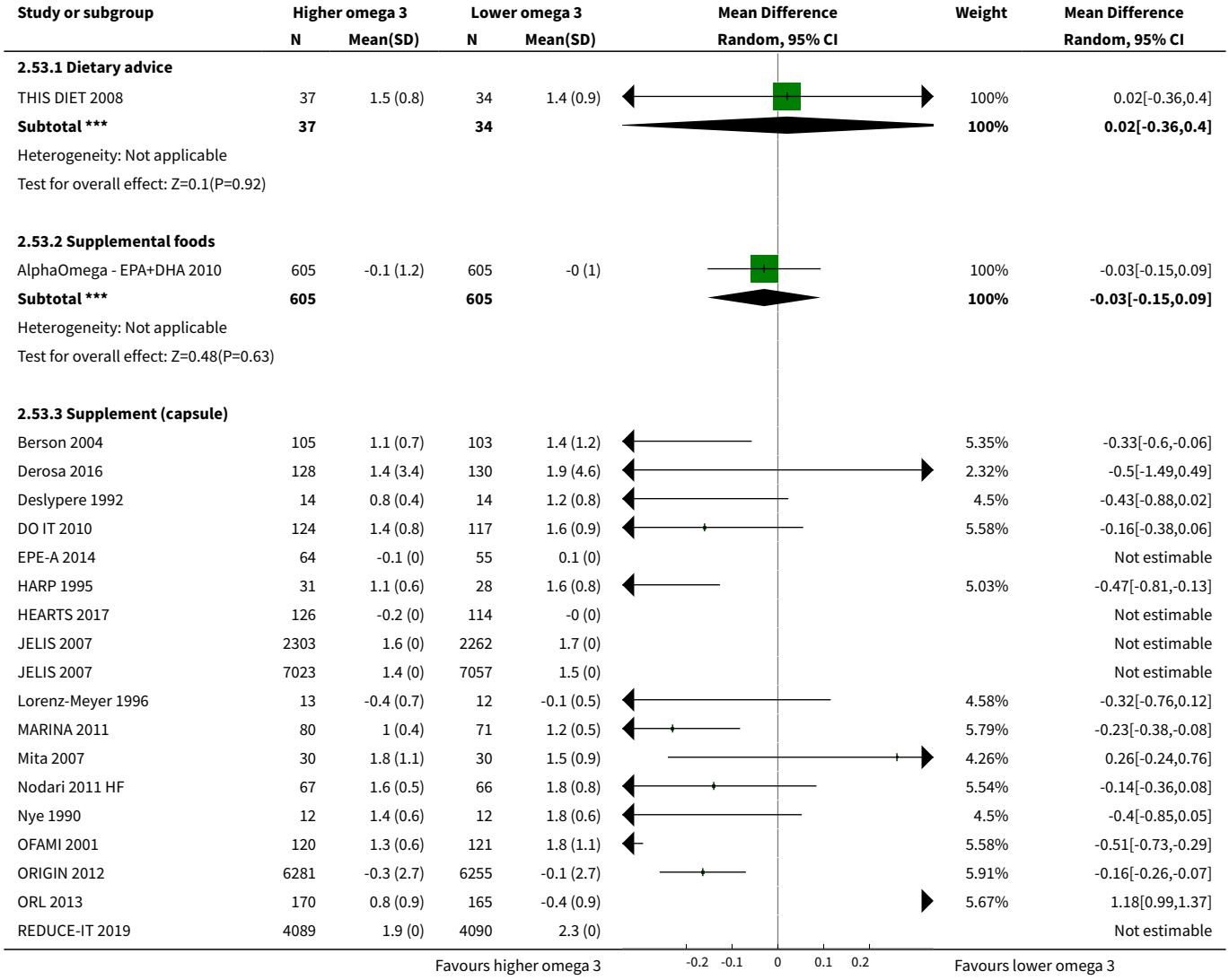


Analysis 2.53. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 53 TG, fasting, mmoL/L - LCn3 - subgroup by intervention type.



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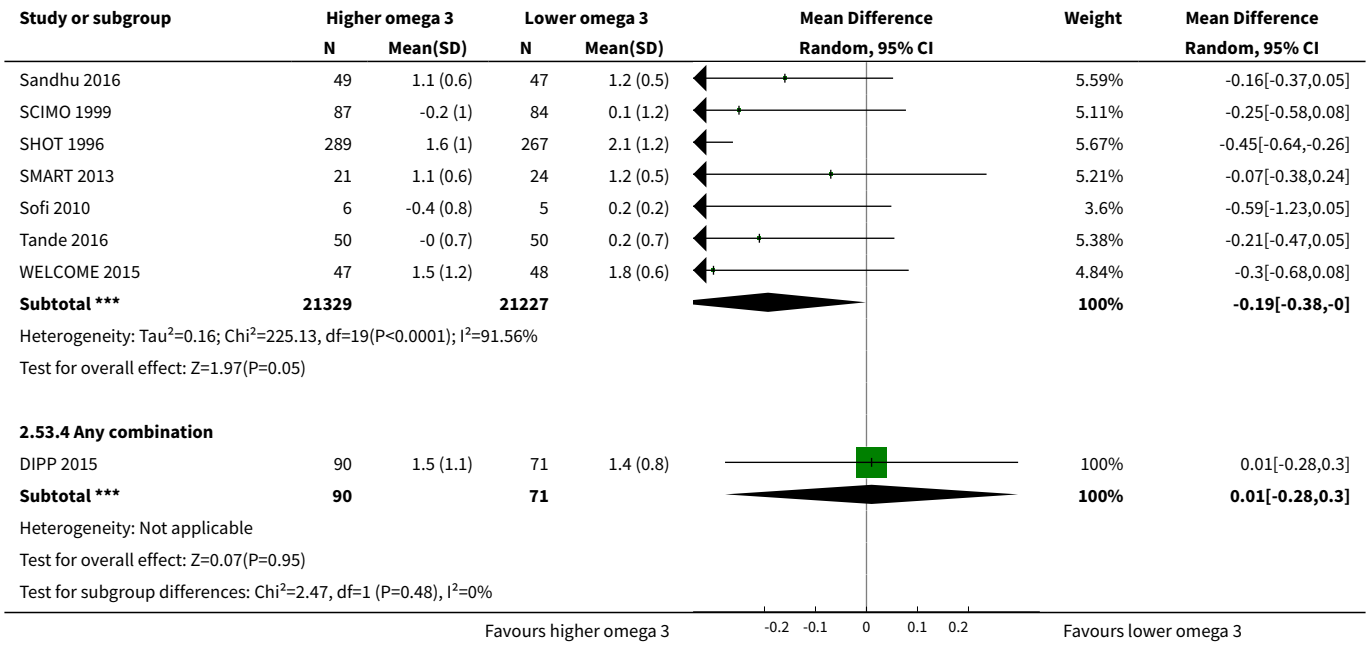
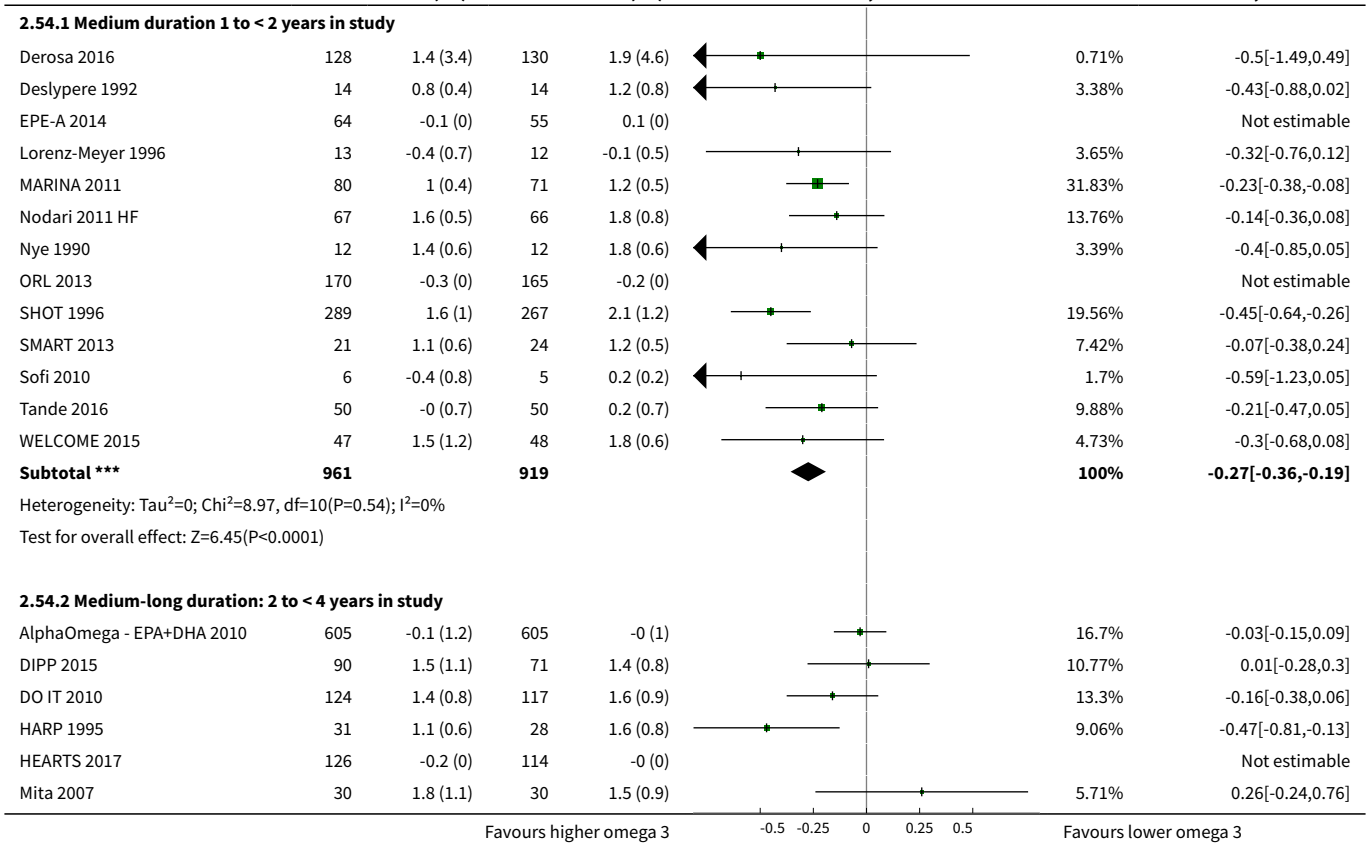


Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Sandhu 2016	49	1.1 (0.6)	47	1.2 (0.5)		5.59%	-0.16[-0.37,0.05]
SCIMO 1999	87	-0.2 (1)	84	0.1 (1.2)		5.11%	-0.25[-0.58,0.08]
SHOT 1996	289	1.6 (1)	267	2.1 (1.2)		5.67%	-0.45[-0.64,-0.26]
SMART 2013	21	1.1 (0.6)	24	1.2 (0.5)		5.21%	-0.07[-0.38,0.24]
Sofi 2010	6	-0.4 (0.8)	5	0.2 (0.2)		3.6%	-0.59[-1.23,0.05]
Tande 2016	50	-0 (0.7)	50	0.2 (0.7)		5.38%	-0.21[-0.47,0.05]
WELCOME 2015	47	1.5 (1.2)	48	1.8 (0.6)		4.84%	-0.3[-0.68,0.08]
Subtotal ***	**21329**		**21227**			**100%**	**-0.19[-0.38,-0]**
Heterogeneity: Tau²=0.16; Chi²=225.13, df=19(P<0.0001); I²=91.56%							
Test for overall effect: Z=1.97(P=0.05)							
2.53.4 Any combination							
DIPP 2015	90	1.5 (1.1)	71	1.4 (0.8)		100%	0.01[-0.28,0.3]
Subtotal ***	**90**		**71**			**100%**	**0.01[-0.28,0.3]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.07(P=0.95)							
Test for subgroup differences: Chi²=2.47, df=1 (P=0.48), I²=0%							

Analysis 2.54. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 54 TG, fasting, mmoL/L - LCn3 - subgroup by duration.



Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.54.1 Medium duration 1 to < 2 years in study							
Derosa 2016	128	1.4 (3.4)	130	1.9 (4.6)		0.71%	-0.5[-1.49,0.49]
Deslypere 1992	14	0.8 (0.4)	14	1.2 (0.8)		3.38%	-0.43[-0.88,0.02]
EPE-A 2014	64	-0.1 (0)	55	0.1 (0)			Not estimable
Lorenz-Meyer 1996	13	-0.4 (0.7)	12	-0.1 (0.5)		3.65%	-0.32[-0.76,0.12]
MARINA 2011	80	1 (0.4)	71	1.2 (0.5)		31.83%	-0.23[-0.38,-0.08]
Nodari 2011 HF	67	1.6 (0.5)	66	1.8 (0.8)		13.76%	-0.14[-0.36,0.08]
Nye 1990	12	1.4 (0.6)	12	1.8 (0.6)		3.39%	-0.4[-0.85,0.05]
ORL 2013	170	-0.3 (0)	165	-0.2 (0)			Not estimable
SHOT 1996	289	1.6 (1)	267	2.1 (1.2)		19.56%	-0.45[-0.64,-0.26]
SMART 2013	21	1.1 (0.6)	24	1.2 (0.5)		7.42%	-0.07[-0.38,0.24]
Sofi 2010	6	-0.4 (0.8)	5	0.2 (0.2)		1.7%	-0.59[-1.23,0.05]
Tande 2016	50	-0 (0.7)	50	0.2 (0.7)		9.88%	-0.21[-0.47,0.05]
WELCOME 2015	47	1.5 (1.2)	48	1.8 (0.6)		4.73%	-0.3[-0.68,0.08]
Subtotal ***	**961**		**919**			**100%**	**-0.27[-0.36,-0.19]**
Heterogeneity: Tau²=0; Chi²=8.97, df=10(P=0.54); I²=0%							
Test for overall effect: Z=6.45(P<0.0001)							
2.54.2 Medium-long duration: 2 to < 4 years in study							
AlphaOmega - EPA+DHA 2010	605	-0.1 (1.2)	605	-0 (1)		16.7%	-0.03[-0.15,0.09]
DIPP 2015	90	1.5 (1.1)	71	1.4 (0.8)		10.77%	0.01[-0.28,0.3]
DO IT 2010	124	1.4 (0.8)	117	1.6 (0.9)		13.3%	-0.16[-0.38,0.06]
HARP 1995	31	1.1 (0.6)	28	1.6 (0.8)		9.06%	-0.47[-0.81,-0.13]
HEARTS 2017	126	-0.2 (0)	114	-0 (0)			Not estimable
Mita 2007	30	1.8 (1.1)	30	1.5 (0.9)		5.71%	0.26[-0.24,0.76]

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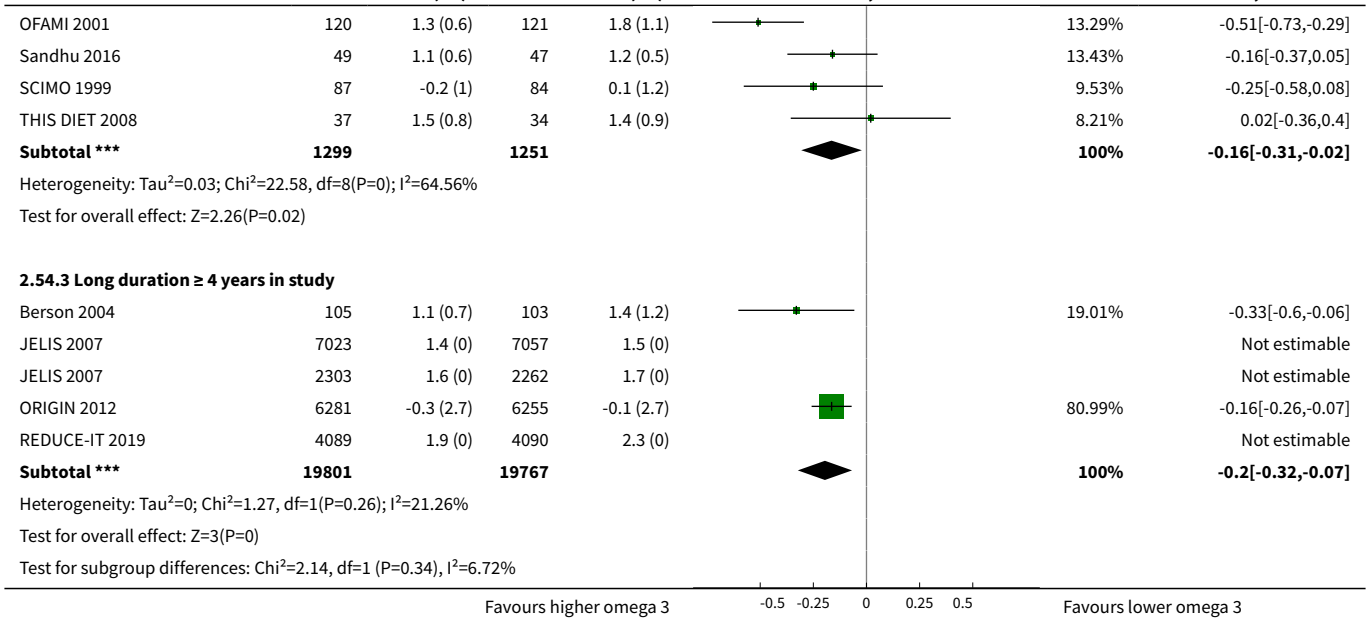
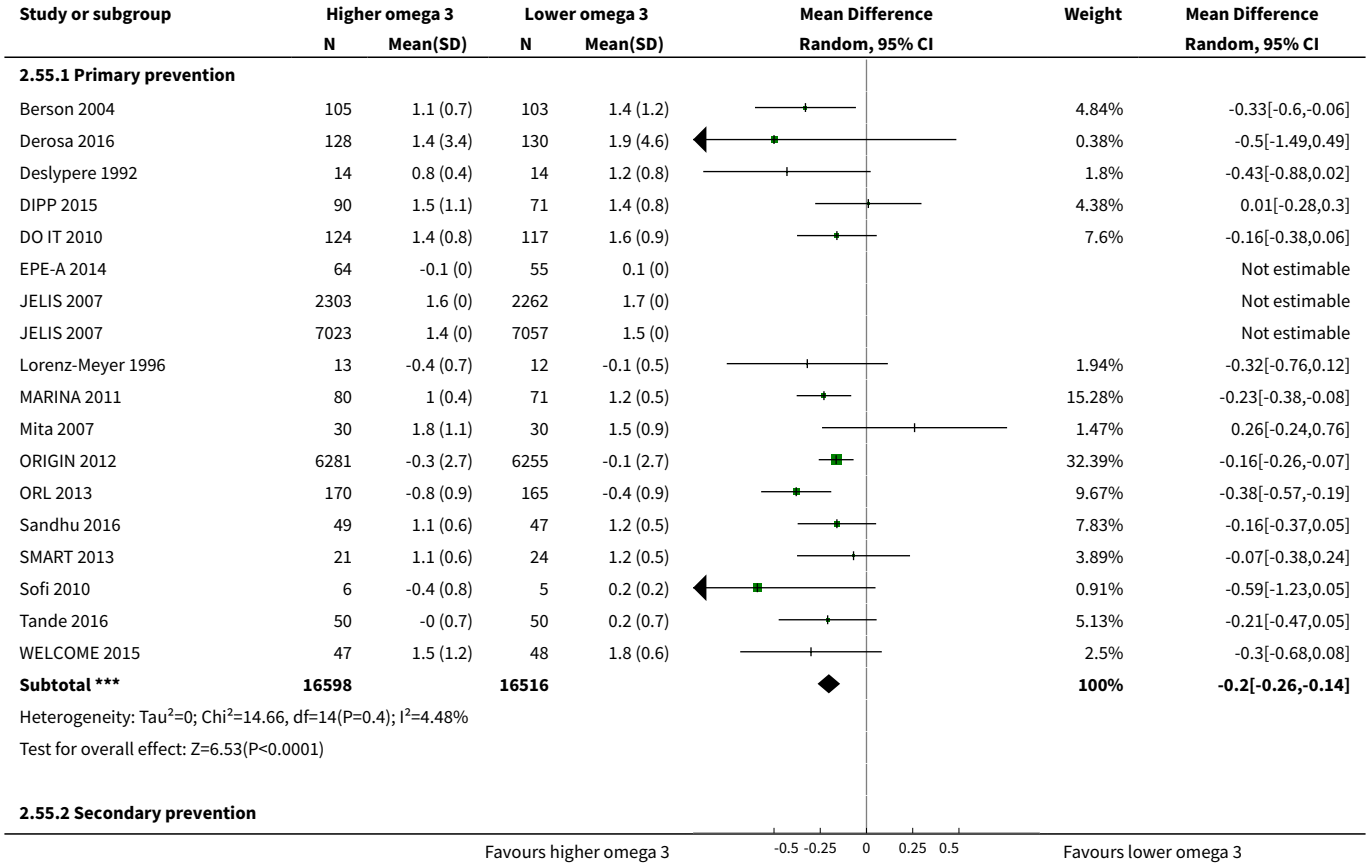


Analysis 2.55. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 55 TG, fasting, mmoL/L - LCn3 - subgroup by primary or secondary prevention.



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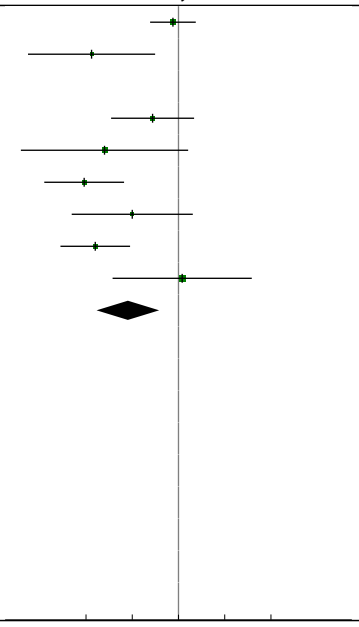
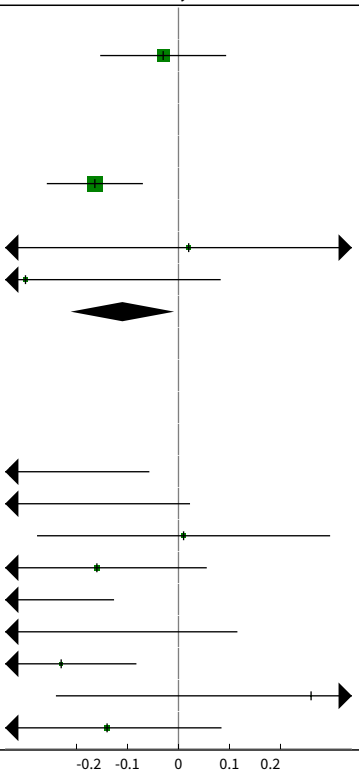
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
AlphaOmega - EPA+DHA 2010	605	-0.1 (1.2)	605	-0 (1)		17.03%	-0.03[-0.15,0.09]
HARP 1995	31	1.1 (0.6)	28	1.6 (0.8)		10.57%	-0.47[-0.81,-0.13]
HEARTS 2017	126	-0.2 (0)	114	-0 (0)			Not estimable
Nodari 2011 HF	67	1.6 (0.5)	66	1.8 (0.8)		14.09%	-0.14[-0.36,0.08]
Nye 1990	12	1.4 (0.6)	12	1.8 (0.6)		8.01%	-0.4[-0.85,0.05]
OFAMI 2001	120	1.3 (0.6)	121	1.8 (1.1)		14.36%	-0.51[-0.73,-0.29]
SCIMO 1999	87	-0.2 (1)	84	0.1 (1.2)		11.01%	-0.25[-0.58,0.08]
SHOT 1996	289	1.6 (1)	267	2.1 (1.2)		15.2%	-0.45[-0.64,-0.26]
THIS DIET 2008	37	1.5 (0.8)	34	1.4 (0.9)		9.73%	0.02[-0.36,0.4]
Subtotal * **	**1374**		**1331**			**100%**	**-0.27[-0.44,-0.1]**
Heterogeneity: Tau²=0.04; Chi²=26.5, df=7(P=0); I²=73.59%							
Test for overall effect: Z=3.17(P=0)							
2.55.3 Mixed primary & secondary prevention							
REDUCE-IT 2019	4089	1.9 (0)	4090	2.3 (0)			Not estimable
Subtotal * **	**4089**		**4090**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Chi²=0.58, df=1 (P=0.44), I²=0%							



Analysis 2.56. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 56 TG, fasting, mmoL/L - LCn3 - subgroup by statin use.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.56.1 LCn3 - ≥ 50% of control group on statins							
AlphaOmega - EPA+DHA 2010	605	-0.1 (1.2)	605	-0 (1)		37.68%	-0.03[-0.15,0.09]
HEARTS 2017	126	-0.2 (0)	114	-0 (0)			Not estimable
JELIS 2007	2303	1.6 (0)	2262	1.7 (0)			Not estimable
JELIS 2007	7023	1.4 (0)	7057	1.5 (0)			Not estimable
ORIGIN 2012	6281	-0.3 (2.7)	6255	-0.1 (2.7)		49.11%	-0.16[-0.26,-0.07]
REDUCE-IT 2019	4089	1.9 (0)	4090	2.3 (0)			Not estimable
THIS DIET 2008	37	1.5 (0.8)	34	1.4 (0.9)		6.71%	0.02[-0.36,0.4]
WELCOME 2015	47	1.5 (1.2)	48	1.8 (0.6)		6.5%	-0.3[-0.68,0.08]
Subtotal * **	**20511**		**20465**			**100%**	**-0.11[-0.21,-0.01]**
Heterogeneity: Tau²=0; Chi²=4.25, df=3(P=0.24); I²=29.43%							
Test for overall effect: Z=2.12(P=0.03)							
2.56.2 LCn3 - < 50% of control group on statins							
Berson 2004	105	1.1 (0.7)	103	1.4 (1.2)		7.04%	-0.33[-0.6,-0.06]
Deslypere 1992	14	0.8 (0.4)	14	1.2 (0.8)		3.46%	-0.43[-0.88,0.02]
DIPP 2015	90	1.5 (1.1)	71	1.4 (0.8)		6.62%	0.01[-0.28,0.3]
DO IT 2010	124	1.4 (0.8)	117	1.6 (0.9)		9.06%	-0.16[-0.38,0.06]
HARP 1995	31	1.1 (0.6)	28	1.6 (0.8)		5.23%	-0.47[-0.81,-0.13]
Lorenz-Meyer 1996	13	-0.4 (0.7)	12	-0.1 (0.5)		3.67%	-0.32[-0.76,0.12]
MARINA 2011	80	1 (0.4)	71	1.2 (0.5)		12.13%	-0.23[-0.38,-0.08]
Mita 2007	30	1.8 (1.1)	30	1.5 (0.9)		2.94%	0.26[-0.24,0.76]
Nodari 2011 HF	67	1.6 (0.5)	66	1.8 (0.8)		8.72%	-0.14[-0.36,0.08]



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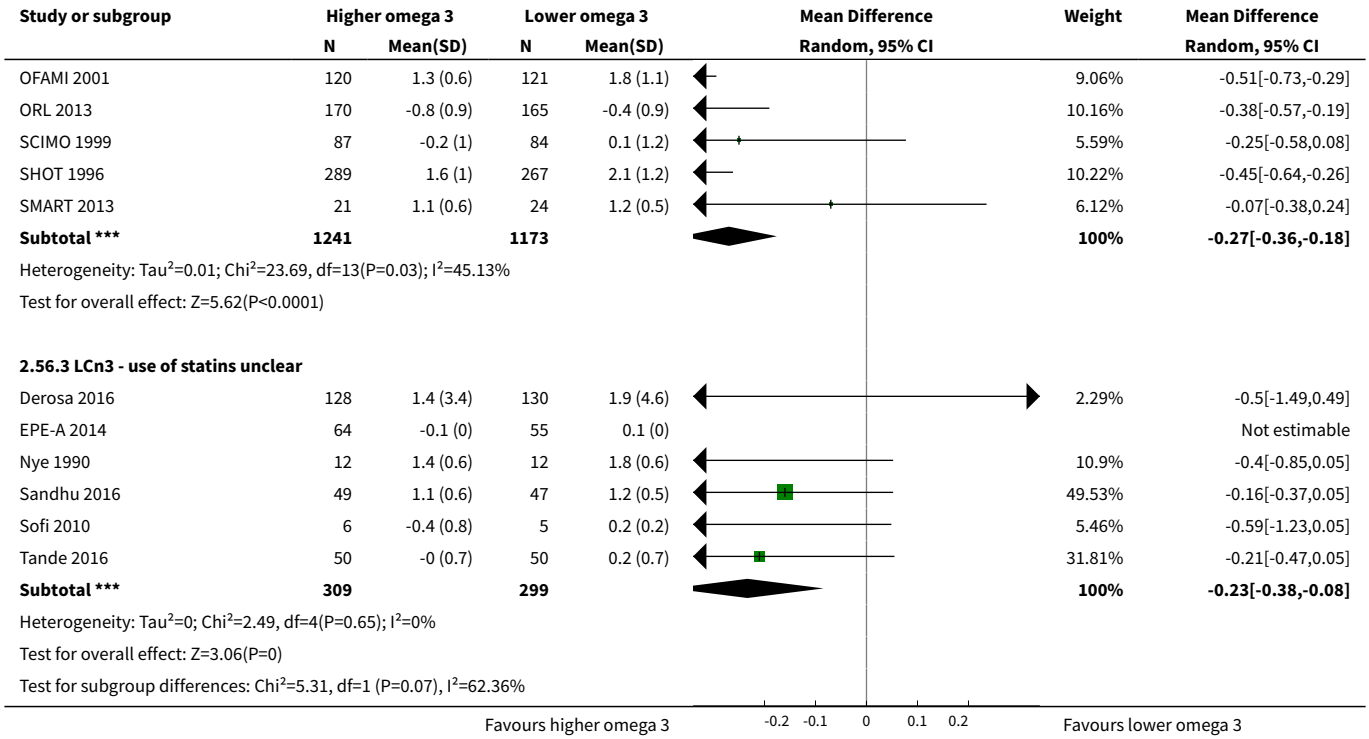
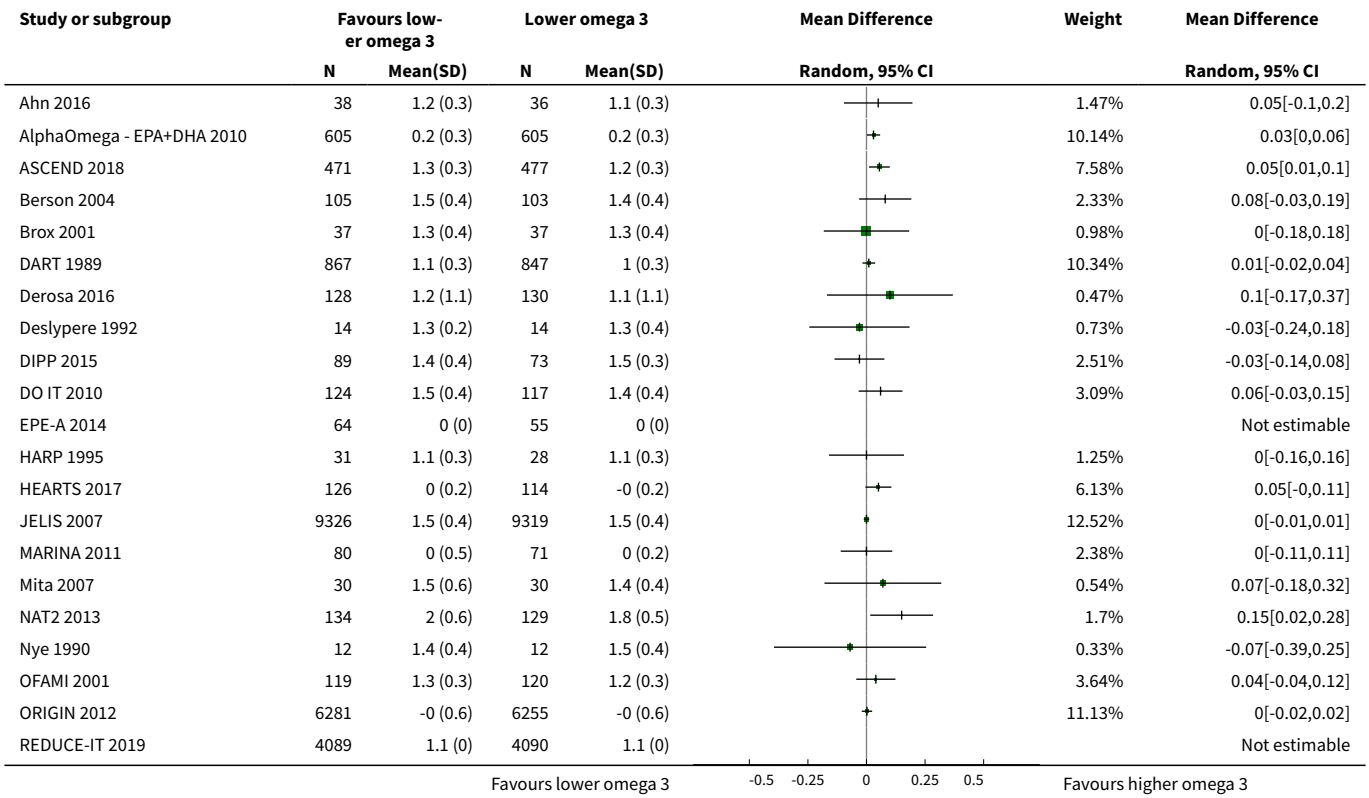


Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
OFAMI 2001	120	1.3 (0.6)	121	1.8 (1.1)		9.06%	-0.51[-0.73,-0.29]
ORL 2013	170	-0.8 (0.9)	165	-0.4 (0.9)		10.16%	-0.38[-0.57,-0.19]
SCIMO 1999	87	-0.2 (1)	84	0.1 (1.2)		5.59%	-0.25[-0.58,0.08]
SHOT 1996	289	1.6 (1)	267	2.1 (1.2)		10.22%	-0.45[-0.64,-0.26]
SMART 2013	21	1.1 (0.6)	24	1.2 (0.5)		6.12%	-0.07[-0.38,0.24]
Subtotal ***	**1241**		**1173**			**100%**	**-0.27[-0.36,-0.18]**
Heterogeneity: Tau²=0.01; Chi²=23.69, df=13(P=0.03); I²=45.13%							
Test for overall effect: Z=5.62(P<0.0001)							
2.56.3 LCn3 - use of statins unclear							
Derosa 2016	128	1.4 (3.4)	130	1.9 (4.6)		2.29%	-0.5[-1.49,0.49]
EPE-A 2014	64	-0.1 (0)	55	0.1 (0)			Not estimable
Nye 1990	12	1.4 (0.6)	12	1.8 (0.6)		10.9%	-0.4[-0.85,0.05]
Sandhu 2016	49	1.1 (0.6)	47	1.2 (0.5)		49.53%	-0.16[-0.37,0.05]
Sofi 2010	6	-0.4 (0.8)	5	0.2 (0.2)		5.46%	-0.59[-1.23,0.05]
Tande 2016	50	-0 (0.7)	50	0.2 (0.7)		31.81%	-0.21[-0.47,0.05]
Subtotal ***	**309**		**299**			**100%**	**-0.23[-0.38,-0.08]**
Heterogeneity: Tau²=0; Chi²=2.49, df=4(P=0.65); I²=0%							
Test for overall effect: Z=3.06(P=0)							
Test for subgroup differences: Chi²=5.31, df=1 (P=0.07), I²=62.36%							

Analysis 2.57. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 57 High-density lipoprotein, serum, mmoL/L - LCn3.



Study or subgroup	Favours lower omega 3 N	Favours lower omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Ahn 2016	38	1.2 (0.3)	36	1.1 (0.3)		1.47%	0.05[-0.1,0.2]
AlphaOmega - EPA+DHA 2010	605	0.2 (0.3)	605	0.2 (0.3)		10.14%	0.03[0,0.06]
ASCEND 2018	471	1.3 (0.3)	477	1.2 (0.3)		7.58%	0.05[0.01,0.1]
Berson 2004	105	1.5 (0.4)	103	1.4 (0.4)		2.33%	0.08[-0.03,0.19]
Brox 2001	37	1.3 (0.4)	37	1.3 (0.4)		0.98%	0[-0.18,0.18]
DART 1989	867	1.1 (0.3)	847	1 (0.3)		10.34%	0.01[-0.02,0.04]
Derosa 2016	128	1.2 (1.1)	130	1.1 (1.1)		0.47%	0.1[-0.17,0.37]
Deslypere 1992	14	1.3 (0.2)	14	1.3 (0.4)		0.73%	-0.03[-0.24,0.18]
DIPP 2015	89	1.4 (0.4)	73	1.5 (0.3)		2.51%	-0.03[-0.14,0.08]
DO IT 2010	124	1.5 (0.4)	117	1.4 (0.4)		3.09%	0.06[-0.03,0.15]
EPE-A 2014	64	0 (0)	55	0 (0)			Not estimable
HARP 1995	31	1.1 (0.3)	28	1.1 (0.3)		1.25%	0[-0.16,0.16]
HEARTS 2017	126	0 (0.2)	114	-0 (0.2)		6.13%	0.05[-0,0.11]
JELIS 2007	9326	1.5 (0.4)	9319	1.5 (0.4)		12.52%	0[-0.01,0.01]
MARINA 2011	80	0 (0.5)	71	0 (0.2)		2.38%	0[-0.11,0.11]
Mita 2007	30	1.5 (0.6)	30	1.4 (0.4)		0.54%	0.07[-0.18,0.32]
NAT2 2013	134	2 (0.6)	129	1.8 (0.5)		1.7%	0.15[0.02,0.28]
Nye 1990	12	1.4 (0.4)	12	1.5 (0.4)		0.33%	-0.07[-0.39,0.25]
OFAMI 2001	119	1.3 (0.3)	120	1.2 (0.3)		3.64%	0.04[-0.04,0.12]
ORIGIN 2012	6281	-0 (0.6)	6255	-0 (0.6)		11.13%	0[-0.02,0.02]
REDUCE-IT 2019	4089	1.1 (0)	4090	1.1 (0)			Not estimable

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Study or subgroup	Favours lower omega 3 N	Mean(SD)	Lower omega 3 N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Sandhu 2016	49	1.8 (0.5)	47	1.8 (0.5)		0.82%	0.01[-0.19,0.21]
SCIMO 1999	87	0 (0.3)	84	0.1 (0.3)		3.58%	-0.09[-0.17,-0.01]
SHOT 1996	289	1.2 (0.3)	267	1.1 (0.3)		6.93%	0.1[0.05,0.15]
SMART 2013	21	1.5 (0.4)	24	1.4 (0.4)		0.61%	0.1[-0.13,0.33]
Sofi 2010	6	0.4 (0.3)	5	-0.7 (0.7)		0.08%	1.08[0.42,1.74]
Tande 2016	50	0 (0.2)	50	0 (0.2)		3.7%	0.01[-0.07,0.09]
THIS DIET 2008	37	1 (0.2)	34	1 (0.3)		1.94%	0[-0.12,0.12]
Weinstock-Guttman 2005	13	0.1 (0.2)	14	-0.3 (0.5)		0.42%	0.34[0.05,0.63]
WELCOME 2015	47	1.1 (0.3)	48	1.1 (0.2)		2.66%	0[-0.1,0.1]
Total * **	**23369**		**23235**			**100%**	**0.03[0.01,0.05]**
Heterogeneity: Tau^2=0; Chi^2=54.45, df=27(P=0); I^2=50.41%							
Test for overall effect: Z=2.79(P=0.01)							

Favours lower omega 3 -0.5 -0.25 0 0.25 0.5 Favours higher omega 3

Analysis 2.58. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 58 HDL, mmoL/L - LCn3 - SA fixed effects.

Study or subgroup	Favours lower omega 3 N	Mean(SD)	Lower omega 3 N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Ahn 2016	38	1.2 (0.3)	36	1.1 (0.3)		0.32%	0.05[-0.1,0.2]
AlphaOmega - EPA+DHA 2010	605	0.2 (0.3)	605	0.2 (0.3)		8.65%	0.03[0,0.06]
ASCEND 2018	471	1.3 (0.3)	477	1.2 (0.3)		3.49%	0.05[0.01,0.1]
Berson 2004	105	1.5 (0.4)	103	1.4 (0.4)		0.55%	0.08[-0.03,0.19]
Brox 2001	37	1.3 (0.4)	37	1.3 (0.4)		0.21%	0[-0.18,0.18]
DART 1989	867	1.1 (0.3)	847	1 (0.3)		9.42%	0.01[-0.02,0.04]
Derosa 2016	128	1.2 (1.1)	130	1.1 (1.1)		0.1%	0.1[-0.17,0.37]
Deslypere 1992	14	1.3 (0.2)	14	1.3 (0.4)		0.15%	-0.03[-0.24,0.18]
DIPP 2015	89	1.4 (0.4)	73	1.5 (0.3)		0.61%	-0.03[-0.14,0.08]
DO IT 2010	124	1.5 (0.4)	117	1.4 (0.4)		0.79%	0.06[-0.03,0.15]
EPE-A 2014	64	0 (0)	55	0 (0)			Not estimable
HARP 1995	31	1.1 (0.3)	28	1.1 (0.3)		0.27%	0[-0.16,0.16]
HEARTS 2017	126	0 (0.2)	114	-0 (0.2)		2.24%	0.05[-0,0.11]
JELIS 2007	9326	1.5 (0.4)	9319	1.5 (0.4)		50.7%	0[-0.01,0.01]
MARINA 2011	80	0 (0.5)	71	0 (0.2)		0.57%	0[-0.11,0.11]
Mita 2007	30	1.5 (0.6)	30	1.4 (0.4)		0.11%	0.07[-0.18,0.32]
NAT2 2013	134	2 (0.6)	129	1.8 (0.5)		0.38%	0.15[0.02,0.28]
Nye 1990	12	1.4 (0.4)	12	1.5 (0.4)		0.07%	-0.07[-0.39,0.25]
OFAMI 2001	119	1.3 (0.3)	120	1.2 (0.3)		0.98%	0.04[-0.04,0.12]
ORIGIN 2012	6281	-0 (0.6)	6255	-0 (0.6)		14.11%	0[-0.02,0.02]
REDUCE-IT 2019	4089	1.1 (0)	4090	1.1 (0)			Not estimable
Sandhu 2016	49	1.8 (0.5)	47	1.8 (0.5)		0.17%	0.01[-0.19,0.21]
SCIMO 1999	87	0 (0.3)	84	0.1 (0.3)		0.96%	-0.09[-0.17,-0.01]
SHOT 1996	289	1.2 (0.3)	267	1.1 (0.3)		2.85%	0.1[0.05,0.15]
SMART 2013	21	1.5 (0.4)	24	1.4 (0.4)		0.13%	0.1[-0.13,0.33]
Sofi 2010	6	0.4 (0.3)	5	-0.7 (0.7)		0.02%	1.08[0.42,1.74]
Tande 2016	50	0 (0.2)	50	0 (0.2)		1%	0.01[-0.07,0.09]
THIS DIET 2008	37	1 (0.2)	34	1 (0.3)		0.44%	0[-0.12,0.12]

Favours lower omega 3 -0.5 -0.25 0 0.25 0.5 Favours higher omega 3

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Study or subgroup	Favours lower omega 3 N	Mean(SD)	Lower omega 3 N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Weinstock-Guttman 2005	13	0.1 (0.2)	14	-0.3 (0.5)		0.08%	0.34[0.05,0.63]
WELCOME 2015	47	1.1 (0.3)	48	1.1 (0.2)		0.65%	0[-0.1,0.1]
Total ***	**23369**		**23235**			**100%**	**0.01[0,0.02]**
Heterogeneity: Tau²=0; Chi²=54.45, df=27(P=0); I²=50.41%							
Test for overall effect: Z=2.72(P=0.01)							

Favours lower omega 3 -0.5 -0.25 0 0.25 0.5 Favours higher omega 3

Analysis 2.59. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 59 HDL, mmoL/L - LCn3 - SA by summary risk of bias.

Study or subgroup	Favours lower omega 3 N	Mean(SD)	Lower omega 3 N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.59.1 Low summary risk of bias							
AlphaOmega - EPA+DHA 2010	605	0.2 (0.3)	605	0.2 (0.3)		23.33%	0.03[0,0.06]
ASCEND 2018	471	1.3 (0.3)	477	1.2 (0.3)		18.02%	0.05[0.01,0.1]
Berson 2004	105	1.5 (0.4)	103	1.4 (0.4)		5.95%	0.08[-0.03,0.19]
Derosa 2016	128	1.2 (1.1)	130	1.1 (1.1)		1.23%	0.1[-0.17,0.37]
MARINA 2011	80	0 (0.5)	71	0 (0.2)		6.07%	0[-0.11,0.11]
NAT2 2013	134	2 (0.6)	129	1.8 (0.5)		4.38%	0.15[0.02,0.28]
ORIGIN 2012	6281	-0 (0.6)	6255	-0 (0.6)		25.28%	0[-0.02,0.02]
SCIMO 1999	87	0 (0.3)	84	0.1 (0.3)		8.98%	-0.09[-0.17,-0.01]
WELCOME 2015	47	1.1 (0.3)	48	1.1 (0.2)		6.76%	0[-0.1,0.1]
Subtotal ***	**7938**		**7902**			**100%**	**0.02[-0.01,0.05]**
Heterogeneity: Tau²=0; Chi²=17.13, df=8(P=0.03); I²=53.3%							
Test for overall effect: Z=1.41(P=0.16)							
2.59.2 Moderate or high risk of bias							
Ahn 2016	38	1.2 (0.3)	36	1.1 (0.3)		2.95%	0.05[-0.1,0.2]
Brox 2001	37	1.3 (0.4)	37	1.3 (0.4)		2%	0[-0.18,0.18]
DART 1989	867	1.1 (0.3)	847	1 (0.3)		16.04%	0.01[-0.02,0.04]
Deslypere 1992	14	1.3 (0.2)	14	1.3 (0.4)		1.5%	-0.03[-0.24,0.18]
DIPP 2015	89	1.4 (0.4)	73	1.5 (0.3)		4.88%	-0.03[-0.14,0.08]
DO IT 2010	124	1.5 (0.4)	117	1.4 (0.4)		5.88%	0.06[-0.03,0.15]
EPE-A 2014	64	0 (0)	55	0 (0)			Not estimable
HARP 1995	31	1.1 (0.3)	28	1.1 (0.3)		2.52%	0[-0.16,0.16]
HEARTS 2017	126	0 (0.2)	114	-0 (0.2)		10.66%	0.05[-0,0.11]
JELIS 2007	9326	1.5 (0.4)	9319	1.5 (0.4)		18.39%	0[-0.01,0.01]
Mita 2007	30	1.5 (0.6)	30	1.4 (0.4)		1.13%	0.07[-0.18,0.32]
Nye 1990	12	1.4 (0.4)	12	1.5 (0.4)		0.68%	-0.07[-0.39,0.25]
OFAMI 2001	119	1.3 (0.3)	120	1.2 (0.3)		6.82%	0.04[-0.04,0.12]
REDUCE-IT 2019	4089	1.1 (0)	4090	1.1 (0)			Not estimable
Sandhu 2016	49	1.8 (0.5)	47	1.8 (0.5)		1.69%	0.01[-0.19,0.21]
SHOT 1996	289	1.2 (0.3)	267	1.1 (0.3)		11.78%	0.1[0.05,0.15]
SMART 2013	21	1.5 (0.4)	24	1.4 (0.4)		1.27%	0.1[-0.13,0.33]
Sofi 2010	6	0.4 (0.3)	5	-0.7 (0.7)		0.17%	1.08[0.42,1.74]
Tande 2016	50	0 (0.2)	50	0 (0.2)		6.92%	0.01[-0.07,0.09]
THIS DIET 2008	37	1 (0.2)	34	1 (0.3)		3.85%	0[-0.12,0.12]

Favours lower omega 3 -0.5 -0.25 0 0.25 0.5 Favours higher omega 3

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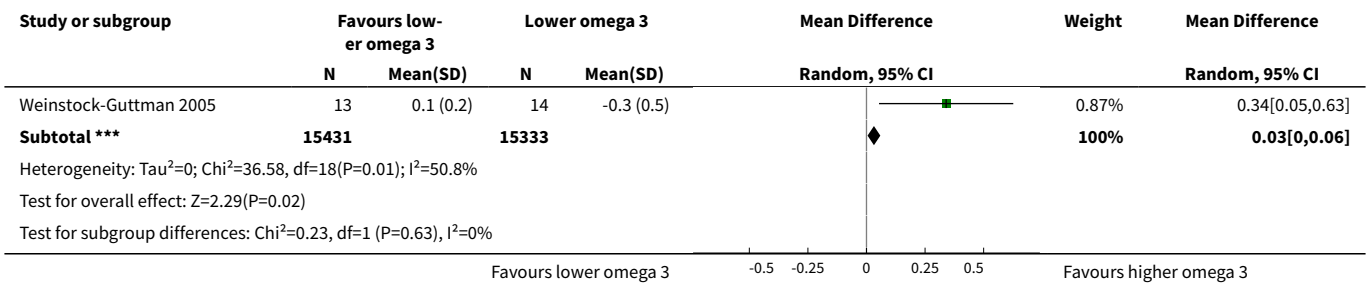
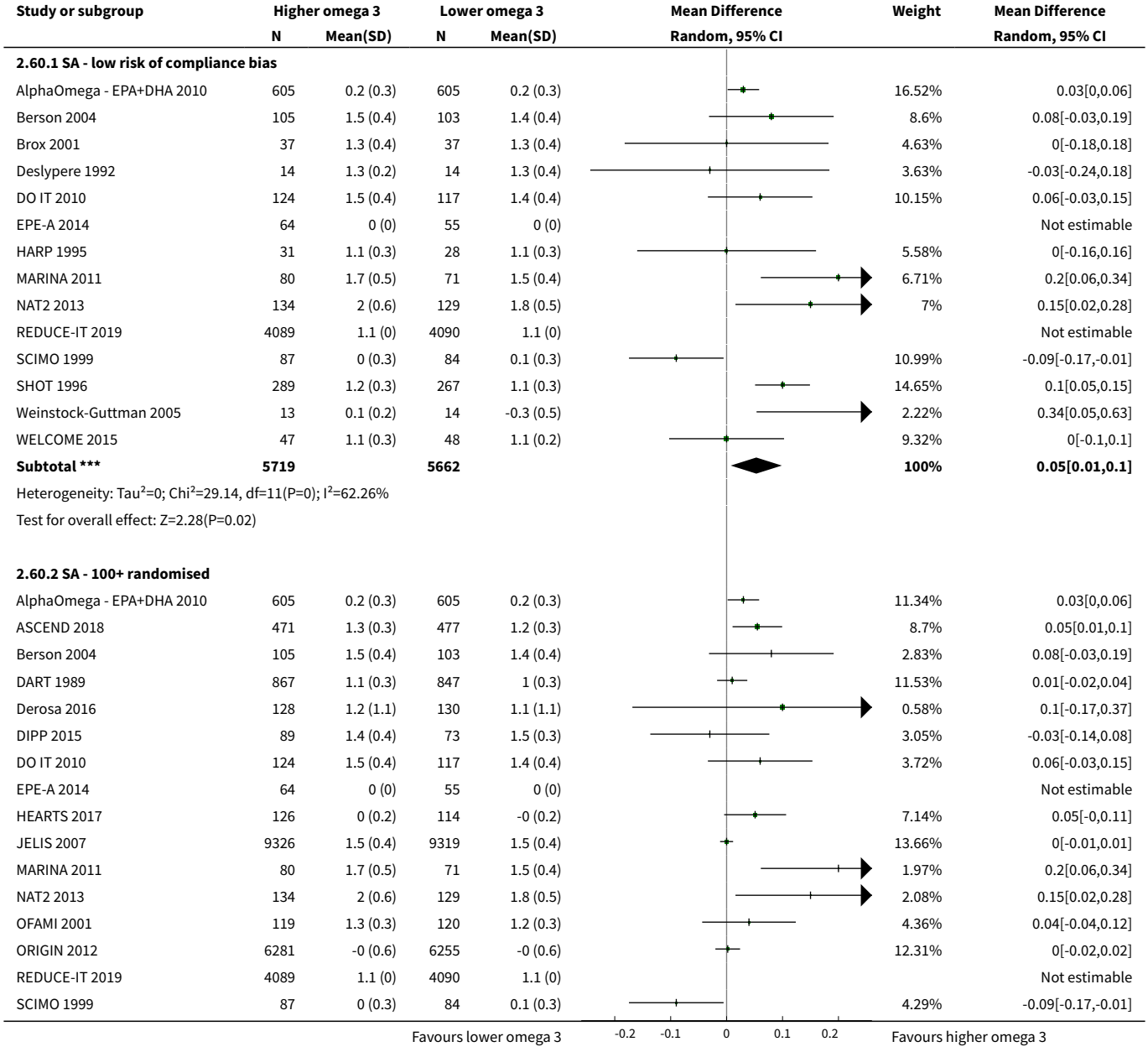


Analysis 2.60. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 60 HDL, mmoL/L - LCn3 - SA by compliance and study size.



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Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
SHOT 1996	289	1.2 (0.3)	267	1.1 (0.3)		8.01%	0.1[0.05,0.15]
Tande 2016	50	0 (0.2)	50	0 (0.2)		4.43%	0.01[-0.07,0.09]
Subtotal ***	**23034**		**22906**			**100%**	**0.03[0.01,0.05]**
Heterogeneity: Tau²=0; Chi²=44.93, df=15(P<0.0001); I²=66.62%							
Test for overall effect: Z=2.88(P=0)							
Test for subgroup differences: Chi²=0.76, df=1 (P=0.38), I²=0%							

Favours lower omega 3 -0.2 -0.1 0 0.1 0.2 Favours higher omega 3

Analysis 2.61. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 61 HDL, mmoL/L - LCn3 - subgroup by dose.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.61.1 LCn3 ≤ 150 mg/d							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.61.2 LCn3 > 150 ≤ 250 mg/d							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.61.3 LCn3 > 250 ≤ 400 mg/d							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.61.4 LCn3 > 400 ≤ 2400 mg/d							
Ahn 2016	38	1.2 (0.3)	36	1.1 (0.3)		1.85%	0.05[-0.1,0.2]
AlphaOmega - EPA+DHA 2010	605	0.2 (0.3)	605	0.2 (0.3)		13.44%	0.03[0,0.06]
ASCEND 2018	471	1.3 (0.3)	477	1.2 (0.3)		9.9%	0.05[0.01,0.1]
Berson 2004	105	1.5 (0.4)	103	1.4 (0.4)		2.96%	0.08[-0.03,0.19]
DART 1989	867	1.1 (0.3)	847	1 (0.3)		13.71%	0.01[-0.02,0.04]
Derosa 2016	128	1.2 (1.1)	130	1.1 (1.1)		0.59%	0.1[-0.17,0.37]
Deslypere 1992	14	1.3 (0.2)	14	1.3 (0.4)		0.91%	-0.03[-0.24,0.18]
DIPP 2015	89	1.4 (0.4)	73	1.5 (0.3)		3.19%	-0.03[-0.14,0.08]
DO IT 2010	124	1.5 (0.4)	117	1.4 (0.4)		3.93%	0.06[-0.03,0.15]
JELIS 2007	9326	1.5 (0.4)	9319	1.5 (0.4)		16.81%	0[-0.01,0.01]
MARINA 2011	80	1.7 (0.5)	71	1.5 (0.4)		2.03%	0.2[0.06,0.34]
Mita 2007	30	1.5 (0.6)	30	1.4 (0.4)		0.68%	0.07[-0.18,0.32]
NAT2 2013	134	2 (0.6)	129	1.8 (0.5)		2.15%	0.15[0.02,0.28]
Nye 1990	12	1.4 (0.4)	12	1.5 (0.4)		0.41%	-0.07[-0.39,0.25]
ORIGIN 2012	6281	-0 (0.6)	6255	-0 (0.6)		14.83%	0[-0.02,0.02]
SCIMO 1999	87	0 (0.3)	84	0.1 (0.3)		4.57%	-0.09[-0.17,-0.01]
SMART 2013	21	1.5 (0.4)	24	1.4 (0.4)		0.77%	0.1[-0.13,0.33]
Sofi 2010	6	0.4 (0.3)	5	-0.7 (0.7)		0.1%	1.08[0.42,1.74]
Tande 2016	50	0 (0.2)	50	0 (0.2)		4.73%	0.01[-0.07,0.09]
THIS DIET 2008	37	1 (0.2)	34	1 (0.3)		2.46%	0[-0.12,0.12]

Favours higher omega 3 -1 -0.5 0 0.5 1 Favours lower omega 3

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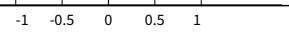
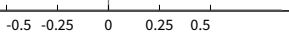
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Subtotal ***	**18505**		**18415**			**100%**	**0.02[0,0.04]**
Heterogeneity: Tau²=0; Chi²=40.87, df=19(P=0); I²=53.51%							
Test for overall effect: Z=2.04(P=0.04)							
2.61.5 LCn3 > 2.4 ≤ 4.4 g/d							
Brox 2001	37	1.3 (0.4)	37	1.3 (0.4)		4.81%	0[-0.18,0.18]
EPE-A 2014	64	0 (0)	55	0 (0)			Not estimable
HEARTS 2017	126	0 (0.2)	114	-0 (0.2)		27.93%	0.05[-0,0.11]
OFAMI 2001	119	1.3 (0.3)	120	1.2 (0.3)		17.17%	0.04[-0.04,0.12]
REDUCE-IT 2019	4089	1.1 (0)	4090	1.1 (0)			Not estimable
Sandhu 2016	49	1.8 (0.5)	47	1.8 (0.5)		4.05%	0.01[-0.19,0.21]
SHOT 1996	289	1.2 (0.3)	267	1.1 (0.3)		31.24%	0.1[0.05,0.15]
Weinstock-Guttman 2005	13	0.1 (0.2)	14	-0.3 (0.5)		2.06%	0.34[0.05,0.63]
WELCOME 2015	47	1.1 (0.3)	48	1.1 (0.2)		12.73%	0[-0.1,0.1]
Subtotal ***	**4833**		**4792**			**100%**	**0.06[0.02,0.1]**
Heterogeneity: Tau²=0; Chi²=8.4, df=6(P=0.21); I²=28.59%							
Test for overall effect: Z=2.8(P=0.01)							
2.61.6 LCn3 > 4.4 g/d							
HARP 1995	31	1.1 (0.3)	28	1.1 (0.3)		100%	0[-0.16,0.16]
Subtotal ***	**31**		**28**			**100%**	**0[-0.16,0.16]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Chi²=2.65, df=1 (P=0.27), I²=24.52%							



Favours higher omega 3 — Favours lower omega 3

Analysis 2.62. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 62 HDL, mmoL/L - LCn3 - subgroup by replacement.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.62.1 N-3 replacing SFA							
DART 1989	867	1.1 (0.3)	847	1 (0.3)		54.93%	0.01[-0.02,0.04]
Derosa 2016	128	1.2 (1.1)	130	1.1 (1.1)		8.41%	0.1[-0.17,0.37]
SCIMO 1999	87	0 (0.3)	84	0.1 (0.3)		36.66%	-0.09[-0.17,-0.01]
Subtotal ***	**1082**		**1061**			**100%**	**-0.02[-0.1,0.07]**
Heterogeneity: Tau²=0; Chi²=5.39, df=2(P=0.07); I²=62.92%							
Test for overall effect: Z=0.44(P=0.66)							
2.62.2 N-3 replacing MUFA							
AlphaOmega - EPA+DHA 2010	605	0.2 (0.3)	605	0.2 (0.3)		15.15%	0.03[0,0.06]
ASCEND 2018	471	1.3 (0.3)	477	1.2 (0.3)		12.66%	0.05[0.01,0.1]
DART 1989	867	1.1 (0.3)	847	1 (0.3)		15.32%	0.01[-0.02,0.04]
Deslypere 1992	14	1.3 (0.2)	14	1.3 (0.4)		1.78%	-0.03[-0.24,0.18]
HARP 1995	31	1.1 (0.3)	28	1.1 (0.3)		2.94%	0[-0.16,0.16]
MARINA 2011	80	1.7 (0.5)	71	1.5 (0.4)		3.7%	0.2[0.06,0.34]
NAT2 2013	134	2 (0.6)	129	1.8 (0.5)		3.9%	0.15[0.02,0.28]
Nye 1990	12	1.4 (0.4)	12	1.5 (0.4)		0.82%	-0.07[-0.39,0.25]
ORIGIN 2012	6281	-0 (0.6)	6255	-0 (0.6)		15.97%	0[-0.02,0.02]



Favours higher omega 3 — Favours lower omega 3

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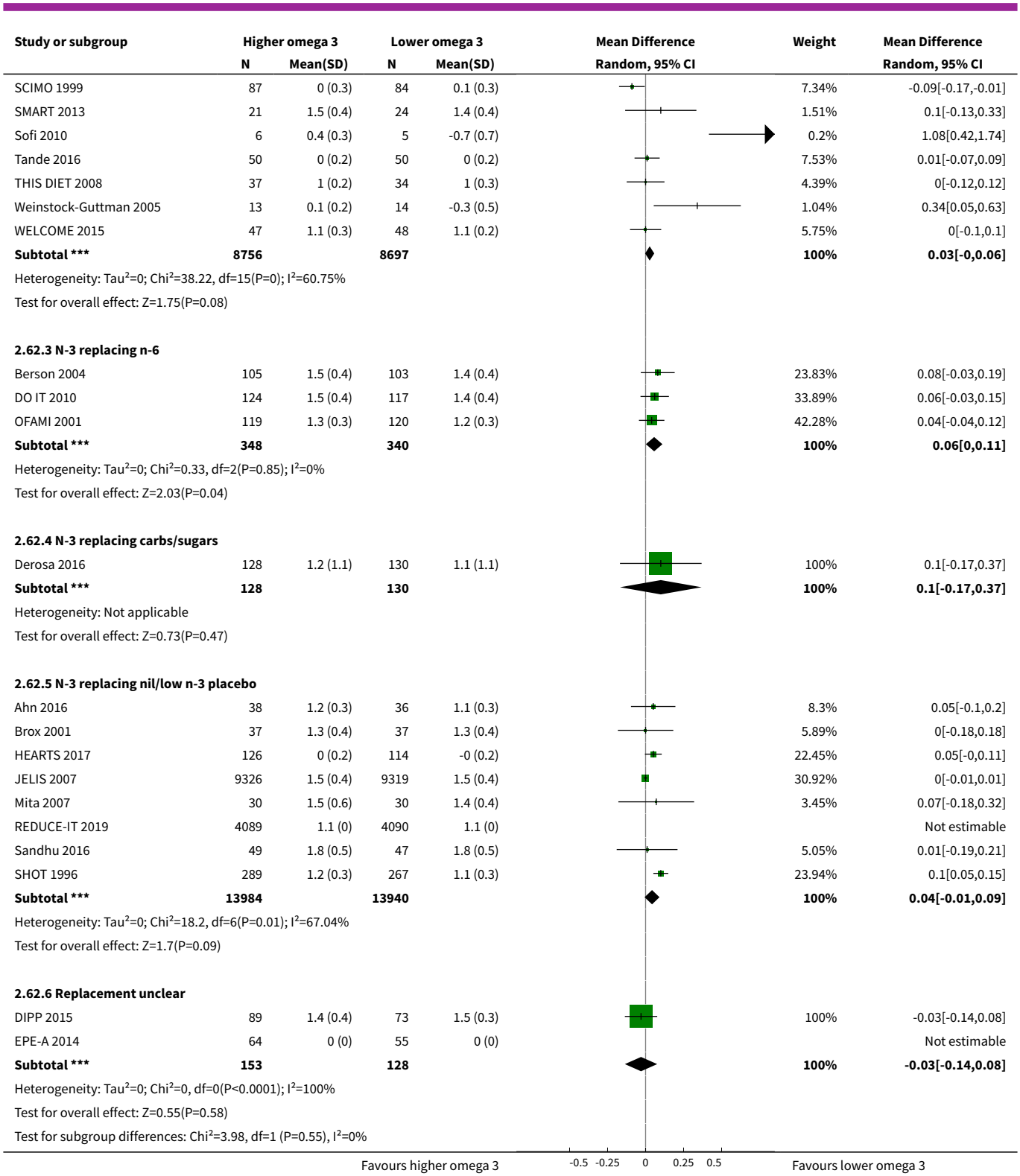

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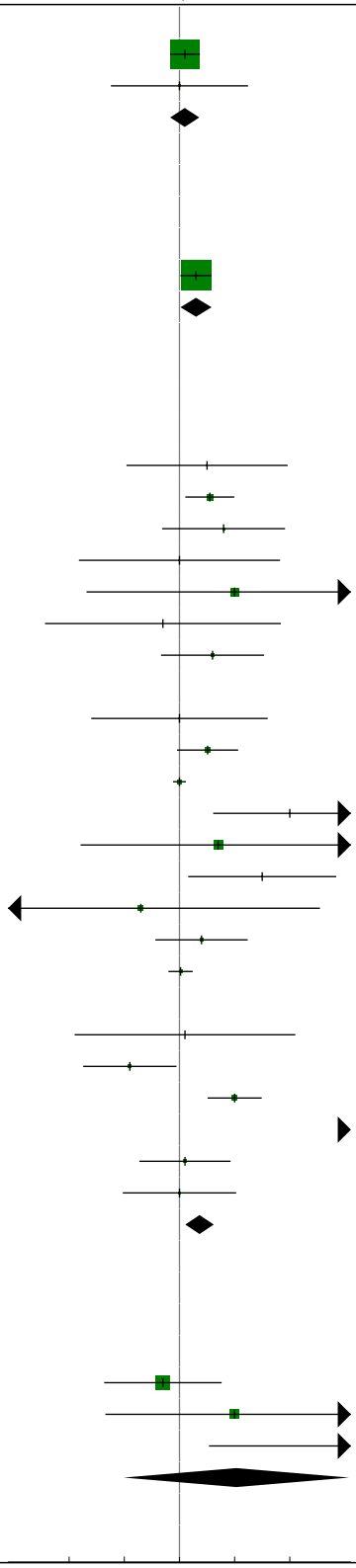
Analysis 2.63. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 63 HDL, mmoL/L - LCn3 - subgroup by intervention type.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.63.1 Dietary advice							
DART 1989	867	1.1 (0.3)	847	1 (0.3)		95.5%	0.01[-0.02,0.04]
THIS DIET 2008	37	1 (0.2)	34	1 (0.3)		4.5%	0[-0.12,0.12]
Subtotal ***	**904**		**881**			**100%**	**0.01[-0.02,0.04]**
Heterogeneity: Tau²=0; Chi²=0.02, df=1(P=0.88); I²=0%							
Test for overall effect: Z=0.71(P=0.48)							
2.63.2 Supplemental foods							
AlphaOmega - EPA+DHA 2010	605	0.2 (0.3)	605	0.2 (0.3)		100%	0.03[0,0.06]
Subtotal ***	**605**		**605**			**100%**	**0.03[0,0.06]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.09(P=0.04)							
2.63.3 Supplement (capsule)							
Ahn 2016	38	1.2 (0.3)	36	1.1 (0.3)		2.53%	0.05[-0.1,0.2]
ASCEND 2018	471	1.3 (0.3)	477	1.2 (0.3)		9.69%	0.05[0.01,0.1]
Berson 2004	105	1.5 (0.4)	103	1.4 (0.4)		3.84%	0.08[-0.03,0.19]
Brox 2001	37	1.3 (0.4)	37	1.3 (0.4)		1.74%	0[-0.18,0.18]
Derosa 2016	128	1.2 (1.1)	130	1.1 (1.1)		0.86%	0.1[-0.17,0.37]
Deslypere 1992	14	1.3 (0.2)	14	1.3 (0.4)		1.31%	-0.03[-0.24,0.18]
DO IT 2010	124	1.5 (0.4)	117	1.4 (0.4)		4.88%	0.06[-0.03,0.15]
EPE-A 2014	64	0 (0)	55	0 (0)			Not estimable
HARP 1995	31	1.1 (0.3)	28	1.1 (0.3)		2.18%	0[-0.16,0.16]
HEARTS 2017	126	0 (0.2)	114	-0 (0.2)		8.35%	0.05[-0,0.11]
JELIS 2007	9326	1.5 (0.4)	9319	1.5 (0.4)		13.21%	0[-0.01,0.01]
MARINA 2011	80	1.7 (0.5)	71	1.5 (0.4)		2.75%	0.2[0.06,0.34]
Mita 2007	30	1.5 (0.6)	30	1.4 (0.4)		0.99%	0.07[-0.18,0.32]
NAT2 2013	134	2 (0.6)	129	1.8 (0.5)		2.9%	0.15[0.02,0.28]
Nye 1990	12	1.4 (0.4)	12	1.5 (0.4)		0.6%	-0.07[-0.39,0.25]
OFAMI 2001	119	1.3 (0.3)	120	1.2 (0.3)		5.59%	0.04[-0.04,0.12]
ORIGIN 2012	6281	-0 (0.6)	6255	-0 (0.6)		12.35%	0[-0.02,0.02]
REDUCE-IT 2019	4089	1.1 (0)	4090	1.1 (0)			Not estimable
Sandhu 2016	49	1.8 (0.5)	47	1.8 (0.5)		1.48%	0.01[-0.19,0.21]
SCIMO 1999	87	0 (0.3)	84	0.1 (0.3)		5.52%	-0.09[-0.17,-0.01]
SHOT 1996	289	1.2 (0.3)	267	1.1 (0.3)		9.1%	0.1[0.05,0.15]
Sofi 2010	6	0.4 (0.3)	5	-0.7 (0.7)		0.15%	1.08[0.42,1.74]
Tande 2016	50	0 (0.2)	50	0 (0.2)		5.66%	0.01[-0.07,0.09]
WELCOME 2015	47	1.1 (0.3)	48	1.1 (0.2)		4.3%	0[-0.1,0.1]
Subtotal ***	**21737**		**21638**			**100%**	**0.04[0.01,0.06]**
Heterogeneity: Tau²=0; Chi²=53.56, df=21(P=0); I²=60.79%							
Test for overall effect: Z=2.77(P=0.01)							
2.63.4 Any combination							
DIPP 2015	89	1.4 (0.4)	73	1.5 (0.3)		44.34%	-0.03[-0.14,0.08]
SMART 2013	21	1.5 (0.4)	24	1.4 (0.4)		30.33%	0.1[-0.13,0.33]
Weinstock-Guttman 2005	13	0.1 (0.2)	14	-0.3 (0.5)		25.33%	0.34[0.05,0.63]
Subtotal ***	**123**		**111**			**100%**	**0.1[-0.1,0.31]**
Heterogeneity: Tau²=0.02; Chi²=6.06, df=2(P=0.05); I²=67.01%							
Test for overall effect: Z=0.99(P=0.32)							



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Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for subgroup differences: Chi²=2.74, df=1 (P=0.43), I²=0%							

Favours higher omega 3 -0.2 -0.1 0 0.1 0.2 Favours lower omega 3

Analysis 2.64. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 64 HDL, mmoL/L - LCn3 - subgroup by duration.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.64.1 Medium duration 1 to < 2 years in study							
Ahn 2016	38	1.2 (0.3)	36	1.1 (0.3)		9.97%	0.05[-0.1,0.2]
Brox 2001	37	1.3 (0.4)	37	1.3 (0.4)		7.72%	0[-0.18,0.18]
Derosa 2016	128	1.2 (1.1)	130	1.1 (1.1)		4.45%	0.1[-0.17,0.37]
Deslypere 1992	14	1.3 (0.2)	14	1.3 (0.4)		6.25%	-0.03[-0.24,0.18]
EPE-A 2014	64	0 (0)	55	0 (0)			Not estimable
MARINA 2011	80	1.7 (0.5)	71	1.5 (0.4)		10.49%	0.2[0.06,0.34]
Nye 1990	12	1.4 (0.4)	12	1.5 (0.4)		3.27%	-0.07[-0.39,0.25]
SHOT 1996	289	1.2 (0.3)	267	1.1 (0.3)		18.52%	0.1[0.05,0.15]
SMART 2013	21	1.5 (0.4)	24	1.4 (0.4)		5.48%	0.1[-0.13,0.33]
Sofi 2010	6	0.4 (0.3)	5	-0.7 (0.7)		0.89%	1.08[0.42,1.74]
Tande 2016	50	0 (0.2)	50	0 (0.2)		15.42%	0.01[-0.07,0.09]
Weinstock-Guttman 2005	13	0.1 (0.2)	14	-0.3 (0.5)		4.02%	0.34[0.05,0.63]
WELCOME 2015	47	1.1 (0.3)	48	1.1 (0.2)		13.52%	0[-0.1,0.1]
Subtotal ***	**799**		**763**			**100%**	**0.08[0.01,0.14]**
Heterogeneity: Tau²=0.01; Chi²=23.18, df=11(P=0.02); I²=52.54%							
Test for overall effect: Z=2.3(P=0.02)							
2.64.2 Medium-long duration: 2 to < 4 years in study							
AlphaOmega - EPA+DHA 2010	605	0.2 (0.3)	605	0.2 (0.3)		26.49%	0.03[0,0.06]
DART 1989	867	1.1 (0.3)	847	1 (0.3)		27.35%	0.01[-0.02,0.04]
DIPP 2015	89	1.4 (0.4)	73	1.5 (0.3)		4.37%	-0.03[-0.14,0.08]
DO IT 2010	124	1.5 (0.4)	117	1.4 (0.4)		5.51%	0.06[-0.03,0.15]
HARP 1995	31	1.1 (0.3)	28	1.1 (0.3)		2.05%	0[-0.16,0.16]
HEARTS 2017	126	0 (0.2)	114	-0 (0.2)		12.66%	0.05[-0,0.11]
Mita 2007	30	1.5 (0.6)	30	1.4 (0.4)		0.87%	0.07[-0.18,0.32]
NAT2 2013	134	2 (0.6)	129	1.8 (0.5)		2.86%	0.15[0.02,0.28]
OFAMI 2001	119	1.3 (0.3)	120	1.2 (0.3)		6.66%	0.04[-0.04,0.12]
Sandhu 2016	49	1.8 (0.5)	47	1.8 (0.5)		1.34%	0.01[-0.19,0.21]
SCIMO 1999	87	0 (0.3)	84	0.1 (0.3)		6.54%	-0.09[-0.17,-0.01]
THIS DIET 2008	37	1 (0.2)	34	1 (0.3)		3.3%	0[-0.12,0.12]
Subtotal ***	**2298**		**2228**			**100%**	**0.02[-0,0.04]**
Heterogeneity: Tau²=0; Chi²=14.41, df=11(P=0.21); I²=23.65%							
Test for overall effect: Z=1.75(P=0.08)							
2.64.3 Long duration ≥ 4 years in study							
ASCEND 2018	471	1.3 (0.3)	477	1.2 (0.3)		17.45%	0.05[0.01,0.1]
Berson 2004	105	1.5 (0.4)	103	1.4 (0.4)		3.91%	0.08[-0.03,0.19]
JELIS 2007	9326	1.5 (0.4)	9319	1.5 (0.4)		44.39%	0[-0.01,0.01]
ORIGIN 2012	6281	-0 (0.6)	6255	-0 (0.6)		34.25%	0[-0.02,0.02]
REDUCE-IT 2019	4089	1.1 (0)	4090	1.1 (0)			Not estimable

Favours higher omega 3 -1 -0.5 0 0.5 1 Favours lower omega 3

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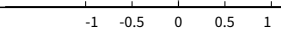
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Subtotal ***	**20272**		**20244**			**100%**	**0.01[-0.01,0.04]**
Heterogeneity: Tau²=0; Chi²=7.35, df=3(P=0.06); I²=59.2%							
Test for overall effect: Z=1.15(P=0.25)							
Test for subgroup differences: Chi²=3.17, df=1 (P=0.21), I²=36.89%							



Favours higher omega 3 — Favours lower omega 3

Analysis 2.65. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 65 HDL, mmoL/L - LCn3 - subgroup by primary or secondary prevention.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.65.1 Primary prevention							
ASCEND 2018	471	1.3 (0.3)	477	1.2 (0.3)		14.51%	0.05[0.01,0.1]
Berson 2004	105	1.5 (0.4)	103	1.4 (0.4)		4.94%	0.08[-0.03,0.19]
Brox 2001	37	1.3 (0.4)	37	1.3 (0.4)		2.13%	0[-0.18,0.18]
Derosa 2016	128	1.2 (1.1)	130	1.1 (1.1)		1.04%	0.1[-0.17,0.37]
Deslypere 1992	14	1.3 (0.2)	14	1.3 (0.4)		1.59%	-0.03[-0.24,0.18]
DIPP 2015	89	1.4 (0.4)	73	1.5 (0.3)		5.3%	-0.03[-0.14,0.08]
DO IT 2010	124	1.5 (0.4)	117	1.4 (0.4)		6.43%	0.06[-0.03,0.15]
EPE-A 2014	64	0 (0)	55	0 (0)			Not estimable
JELIS 2007	9326	1.5 (0.4)	9319	1.5 (0.4)		21.98%	0[-0.01,0.01]
MARINA 2011	80	1.7 (0.5)	71	1.5 (0.4)		3.45%	0.2[0.06,0.34]
Mita 2007	30	1.5 (0.6)	30	1.4 (0.4)		1.19%	0.07[-0.18,0.32]
ORIGIN 2012	6281	-0 (0.6)	6255	-0 (0.6)		20%	0[-0.02,0.02]
Sandhu 2016	49	1.8 (0.5)	47	1.8 (0.5)		1.8%	0.01[-0.19,0.21]
SMART 2013	21	1.5 (0.4)	24	1.4 (0.4)		1.34%	0.1[-0.13,0.33]
Sofi 2010	6	0.4 (0.3)	5	-0.7 (0.7)		0.18%	1.08[0.42,1.74]
Tande 2016	50	0 (0.2)	50	0 (0.2)		7.62%	0.01[-0.07,0.09]
Weinstock-Guttman 2005	13	0.1 (0.2)	14	-0.3 (0.5)		0.91%	0.34[0.05,0.63]
WELCOME 2015	47	1.1 (0.3)	48	1.1 (0.2)		5.59%	0[-0.1,0.1]
Subtotal ***	**16935**		**16869**			**100%**	**0.03[0,0.06]**
Heterogeneity: Tau²=0; Chi²=33.54, df=16(P=0.01); I²=52.29%							
Test for overall effect: Z=2.12(P=0.03)							
2.65.2 Secondary prevention							
AlphaOmega - EPA+DHA 2010	605	0.2 (0.3)	605	0.2 (0.3)		19.43%	0.03[0,0.06]
DART 1989	867	1.1 (0.3)	847	1 (0.3)		19.67%	0.01[-0.02,0.04]
HARP 1995	31	1.1 (0.3)	28	1.1 (0.3)		3.48%	0[-0.16,0.16]
HEARTS 2017	126	0 (0.2)	114	-0 (0.2)		13.67%	0.05[-0,0.11]
NAT2 2013	134	2 (0.6)	129	1.8 (0.5)		4.64%	0.15[0.02,0.28]
Nye 1990	12	1.4 (0.4)	12	1.5 (0.4)		0.95%	-0.07[-0.39,0.25]
OFAMI 2001	119	1.3 (0.3)	120	1.2 (0.3)		9.04%	0.04[-0.04,0.12]
SCIMO 1999	87	0 (0.3)	84	0.1 (0.3)		8.92%	-0.09[-0.17,-0.01]
SHOT 1996	289	1.2 (0.3)	267	1.1 (0.3)		14.96%	0.1[0.05,0.15]
THIS DIET 2008	37	1 (0.2)	34	1 (0.3)		5.24%	0[-0.12,0.12]
Subtotal ***	**2307**		**2240**			**100%**	**0.03[-0,0.06]**
Heterogeneity: Tau²=0; Chi²=22.05, df=9(P=0.01); I²=59.19%							
Test for overall effect: Z=1.91(P=0.06)							

Favours higher omega 3 — Favours lower omega 3

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Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.65.3 Mixed primary & secondary prevention							
REDUCE-IT 2019	4089	1.1 (0)	4090	1.1 (0)			Not estimable
Subtotal ***	**4089**		**4090**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Chi^2=0, df=1 (P=0.95), I^2=0%							

Favours higher omega 3 -0.5 -0.25 0 0.25 0.5 Favours lower omega 3

Analysis 2.66. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 66 HDL, mmoL/L - LCn3 - subgroup by statin use.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.66.1 LCn3 - ≥ 50% of control group on statins							
Ahn 2016	38	1.2 (0.3)	36	1.1 (0.3)		1.65%	0.05[-0.1,0.2]
AlphaOmega - EPA+DHA 2010	605	0.2 (0.3)	605	0.2 (0.3)		19.03%	0.03[0,0.06]
ASCEND 2018	471	1.3 (0.3)	477	1.2 (0.3)		11.9%	0.05[0.01,0.1]
HEARTS 2017	126	0 (0.2)	114	-0 (0.2)		8.8%	0.05[-0,0.11]
JELIS 2007	9326	1.5 (0.4)	9319	1.5 (0.4)		28.68%	0[-0.01,0.01]
NAT2 2013	134	2 (0.6)	129	1.8 (0.5)		1.94%	0.15[0.02,0.28]
ORIGIN 2012	6281	-0 (0.6)	6255	-0 (0.6)		22.58%	0[-0.02,0.02]
REDUCE-IT 2019	4089	1.1 (0)	4090	1.1 (0)			Not estimable
THIS DIET 2008	37	1 (0.2)	34	1 (0.3)		2.24%	0[-0.12,0.12]
WELCOME 2015	47	1.1 (0.3)	48	1.1 (0.2)		3.18%	0[-0.1,0.1]
Subtotal ***	**21154**		**21107**			**100%**	**0.02[0,0.04]**
Heterogeneity: Tau^2=0; Chi^2=15.73, df=8(P=0.05); I^2=49.14%							
Test for overall effect: Z=2.13(P=0.03)							
2.66.2 LCn3 - < 50% of control group on statins							
Berson 2004	105	1.5 (0.4)	103	1.4 (0.4)		8.02%	0.08[-0.03,0.19]
Brox 2001	37	1.3 (0.4)	37	1.3 (0.4)		4.28%	0[-0.18,0.18]
DART 1989	867	1.1 (0.3)	847	1 (0.3)		15.82%	0.01[-0.02,0.04]
Deslypere 1992	14	1.3 (0.2)	14	1.3 (0.4)		3.34%	-0.03[-0.24,0.18]
DIPP 2015	89	1.4 (0.4)	73	1.5 (0.3)		8.41%	-0.03[-0.14,0.08]
DO IT 2010	124	1.5 (0.4)	117	1.4 (0.4)		9.5%	0.06[-0.03,0.15]
HARP 1995	31	1.1 (0.3)	28	1.1 (0.3)		5.16%	0[-0.16,0.16]
MARINA 2011	80	1.7 (0.5)	71	1.5 (0.4)		6.23%	0.2[0.06,0.34]
Mita 2007	30	1.5 (0.6)	30	1.4 (0.4)		2.59%	0.07[-0.18,0.32]
OFAMI 2001	119	1.3 (0.3)	120	1.2 (0.3)		10.4%	0.04[-0.04,0.12]
SCIMO 1999	87	0 (0.3)	84	0.1 (0.3)		10.31%	-0.09[-0.17,-0.01]
SHOT 1996	289	1.2 (0.3)	267	1.1 (0.3)		13.89%	0.1[0.05,0.15]
Weinstock-Guttman 2005	13	0.1 (0.2)	14	-0.3 (0.5)		2.04%	0.34[0.05,0.63]
Subtotal ***	**1885**		**1805**			**100%**	**0.04[-0,0.08]**
Heterogeneity: Tau^2=0; Chi^2=31.01, df=12(P=0); I^2=61.3%							
Test for overall effect: Z=1.8(P=0.07)							
2.66.3 LCn3 - use of statins unclear							
Derosa 2016	128	1.2 (1.1)	130	1.1 (1.1)		15.08%	0.1[-0.17,0.37]
EPE-A 2014	64	0 (0)	55	0 (0)			Not estimable

Favours higher omega 3 -1 -0.5 0 0.5 1 Favours lower omega 3

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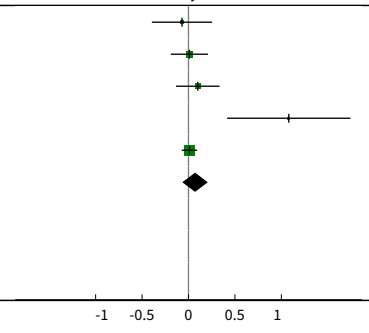
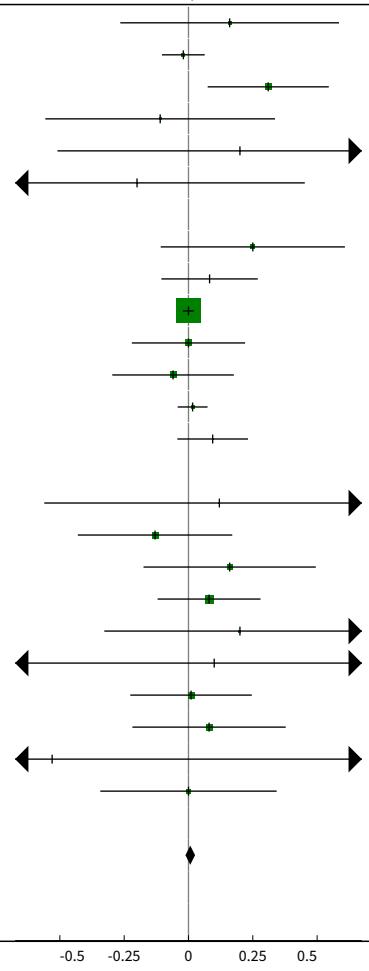
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Nye 1990	12	1.4 (0.4)	12	1.5 (0.4)		11.91%	-0.07[-0.39,0.25]
Sandhu 2016	49	1.8 (0.5)	47	1.8 (0.5)		20.26%	0.01[-0.19,0.21]
SMART 2013	21	1.5 (0.4)	24	1.4 (0.4)		17.48%	0.1[-0.13,0.33]
Sofi 2010	6	0.4 (0.3)	5	-0.7 (0.7)		3.84%	1.08[0.42,1.74]
Tande 2016	50	0 (0.2)	50	0 (0.2)		31.43%	0.01[-0.07,0.09]
Subtotal * **	**330**		**323**			**100%**	**0.07[-0.07,0.21]**
Heterogeneity: Tau²=0.01; Chi²=10.86, df=5(P=0.05); I²=53.96%							
Test for overall effect: Z=1.01(P=0.31)							
Test for subgroup differences: Chi²=1.06, df=1 (P=0.59), I²=0%							



Analysis 2.67. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 67 Low-density lipoprotein, serum, mmoL/L - LCn3.

Study or subgroup	Favours higher omega 3 N	Favours higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Ahn 2016	38	2.2 (1.3)	36	2.1 (0.1)		0.19%	0.16[-0.26,0.58]
AlphaOmega - EPA+DHA 2010	562	-0.4 (0.7)	562	-0.4 (0.7)		5.09%	-0.02[-0.1,0.06]
Berson 2004	105	3.2 (0.9)	103	2.9 (0.8)		0.63%	0.31[0.07,0.55]
Caldwell 2011	17	3.2 (0.9)	17	3.3 (0.1)		0.18%	-0.11[-0.56,0.34]
Derosa 2016	128	3.3 (3.4)	130	3.1 (2.3)		0.07%	0.2[-0.51,0.91]
Deslypere 1992	14	3.9 (0.9)	14	4.1 (0.9)		0.08%	-0.2[-0.85,0.45]
EPE-A 2014	64	0.2 (0)	55	0.1 (0)			Not estimable
HARP 1995	31	3.4 (0.8)	28	3.2 (0.6)		0.27%	0.25[-0.11,0.61]
HEARTS 2017	126	0.2 (0.9)	114	0.1 (0.6)		1%	0.08[-0.11,0.27]
JELIS 2007	9326	3.5 (0.8)	9319	3.5 (0.7)		75.69%	0[-0.02,0.02]
MARINA 2011	80	0.2 (0.9)	71	0.2 (0.4)		0.72%	0[-0.22,0.22]
NAT2 2013	134	3.7 (1.1)	129	3.7 (0.9)		0.63%	-0.06[-0.3,0.18]
ORIGIN 2012	6281	-0.3 (1.7)	6255	-0.3 (1.7)		10.4%	0.02[-0.04,0.07]
ORL 2013	170	0.1 (0.7)	165	-0 (0.6)		1.86%	0.09[-0.04,0.23]
REDUCE-IT 2019	4089	2.2 (0)	4090	2.4 (0)			Not estimable
Rossing 1996	14	3.5 (0.9)	15	3.4 (1)		0.08%	0.12[-0.56,0.8]
Sandhu 2016	49	2.8 (0.8)	47	3 (0.8)		0.39%	-0.13[-0.43,0.17]
SCIMO 1999	87	-0.2 (1.2)	84	-0.4 (1)		0.31%	0.16[-0.17,0.49]
SHOT 1996	289	5.1 (1.2)	267	5 (1.2)		0.88%	0.08[-0.12,0.28]
SMART 2013	21	3.4 (0.9)	24	3.2 (0.9)		0.13%	0.2[-0.33,0.73]
Sofi 2010	6	-0 (1)	5	-0.1 (0.4)		0.04%	0.1[-0.79,0.99]
Tande 2016	50	-0 (0.7)	50	-0 (0.5)		0.63%	0.01[-0.23,0.25]
THIS DIET 2008	37	2.6 (0.7)	34	2.5 (0.6)		0.4%	0.08[-0.22,0.38]
Weinstock-Guttman 2005	13	0.1 (0.6)	14	0.6 (2.4)		0.02%	-0.53[-1.82,0.76]
WELCOME 2015	47	2.8 (0.9)	48	2.8 (0.8)		0.3%	0[-0.34,0.34]
Total * **	**21778**		**21676**			**100%**	**0.01[-0.01,0.03]**
Heterogeneity: Tau²=0; Chi²=16.62, df=22(P=0.78); I²=0%							
Test for overall effect: Z=0.73(P=0.47)							



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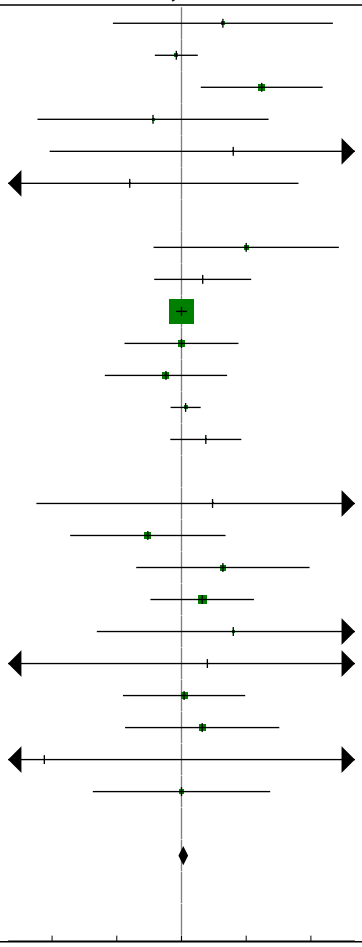
Analysis 2.68. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 68 LDL, mmoL/L - LCn3 - SA fixed effects.

Study or subgroup	Favours higher omega 3 N	Favours higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Ahn 2016	38	2.2 (1.3)	36	2.1 (0.1)		0.19%	0.16[-0.26,0.58]
AlphaOmega - EPA+DHA 2010	562	-0.4 (0.7)	562	-0.4 (0.7)		5.09%	-0.02[-0.1,0.06]
Berson 2004	105	3.2 (0.9)	103	2.9 (0.8)		0.63%	0.31[0.07,0.55]
Caldwell 2011	17	3.2 (0.9)	17	3.3 (0.1)		0.18%	-0.11[-0.56,0.34]
Derosa 2016	128	3.3 (3.4)	130	3.1 (2.3)		0.07%	0.2[-0.51,0.91]
Deslypere 1992	14	3.9 (0.9)	14	4.1 (0.9)		0.08%	-0.2[-0.85,0.45]
EPE-A 2014	64	0.2 (0)	55	0.1 (0)			Not estimable
HARP 1995	31	3.4 (0.8)	28	3.2 (0.6)		0.27%	0.25[-0.11,0.61]
HEARTS 2017	126	0.2 (0.9)	114	0.1 (0.6)		1%	0.08[-0.11,0.27]
JELIS 2007	9326	3.5 (0.8)	9319	3.5 (0.7)		75.69%	0[-0.02,0.02]
MARINA 2011	80	0.2 (0.9)	71	0.2 (0.4)		0.72%	0[-0.22,0.22]
NAT2 2013	134	3.7 (1.1)	129	3.7 (0.9)		0.63%	-0.06[-0.3,0.18]
ORIGIN 2012	6281	-0.3 (1.7)	6255	-0.3 (1.7)		10.4%	0.02[-0.04,0.07]
ORL 2013	170	0.1 (0.7)	165	-0 (0.6)		1.86%	0.09[-0.04,0.23]
REDUCE-IT 2019	4089	2.2 (0)	4090	2.4 (0)			Not estimable
Rossing 1996	14	3.5 (0.9)	15	3.4 (1)		0.08%	0.12[-0.56,0.8]
Sandhu 2016	49	2.8 (0.8)	47	3 (0.8)		0.39%	-0.13[-0.43,0.17]
SCIMO 1999	87	-0.2 (1.2)	84	-0.4 (1)		0.31%	0.16[-0.17,0.49]
SHOT 1996	289	5.1 (1.2)	267	5 (1.2)		0.88%	0.08[-0.12,0.28]
SMART 2013	21	3.4 (0.9)	24	3.2 (0.9)		0.13%	0.2[-0.33,0.73]
Sofi 2010	6	-0 (1)	5	-0.1 (0.4)		0.04%	0.1[-0.79,0.99]
Tande 2016	50	-0 (0.7)	50	-0 (0.5)		0.63%	0.01[-0.23,0.25]
THIS DIET 2008	37	2.6 (0.7)	34	2.5 (0.6)		0.4%	0.08[-0.22,0.38]
Weinstock-Guttman 2005	13	0.1 (0.6)	14	0.6 (2.4)		0.02%	-0.53[-1.82,0.76]
WELCOME 2015	47	2.8 (0.9)	48	2.8 (0.8)		0.3%	0[-0.34,0.34]
Total ***	**21778**		**21676**			**100%**	**0.01[-0.01,0.03]**

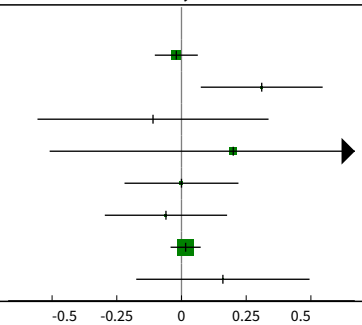
Heterogeneity: $Tau^2=0$; $Chi^2=16.62$, df=22(P=0.78); $I^2=0\%$

Test for overall effect: Z=0.73(P=0.47)



Analysis 2.69. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 69 LDL, mmoL/L - LCn3 - SA by summary risk of bias.

Study or subgroup	Favours higher omega 3 N	Favours higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.69.1 Low summary risk of bias							
AlphaOmega - EPA+DHA 2010	562	-0.4 (0.7)	562	-0.4 (0.7)		29.41%	-0.02[-0.1,0.06]
Berson 2004	105	3.2 (0.9)	103	2.9 (0.8)		4.25%	0.31[0.07,0.55]
Caldwell 2011	17	3.2 (0.9)	17	3.3 (0.1)		1.2%	-0.11[-0.56,0.34]
Derosa 2016	128	3.3 (3.4)	130	3.1 (2.3)		0.48%	0.2[-0.51,0.91]
MARINA 2011	80	0.2 (0.9)	71	0.2 (0.4)		4.85%	0[-0.22,0.22]
NAT2 2013	134	3.7 (1.1)	129	3.7 (0.9)		4.22%	-0.06[-0.3,0.18]
ORIGIN 2012	6281	-0.3 (1.7)	6255	-0.3 (1.7)		51.43%	0.02[-0.04,0.07]
SCIMO 1999	87	-0.2 (1.2)	84	-0.4 (1)		2.13%	0.16[-0.17,0.49]



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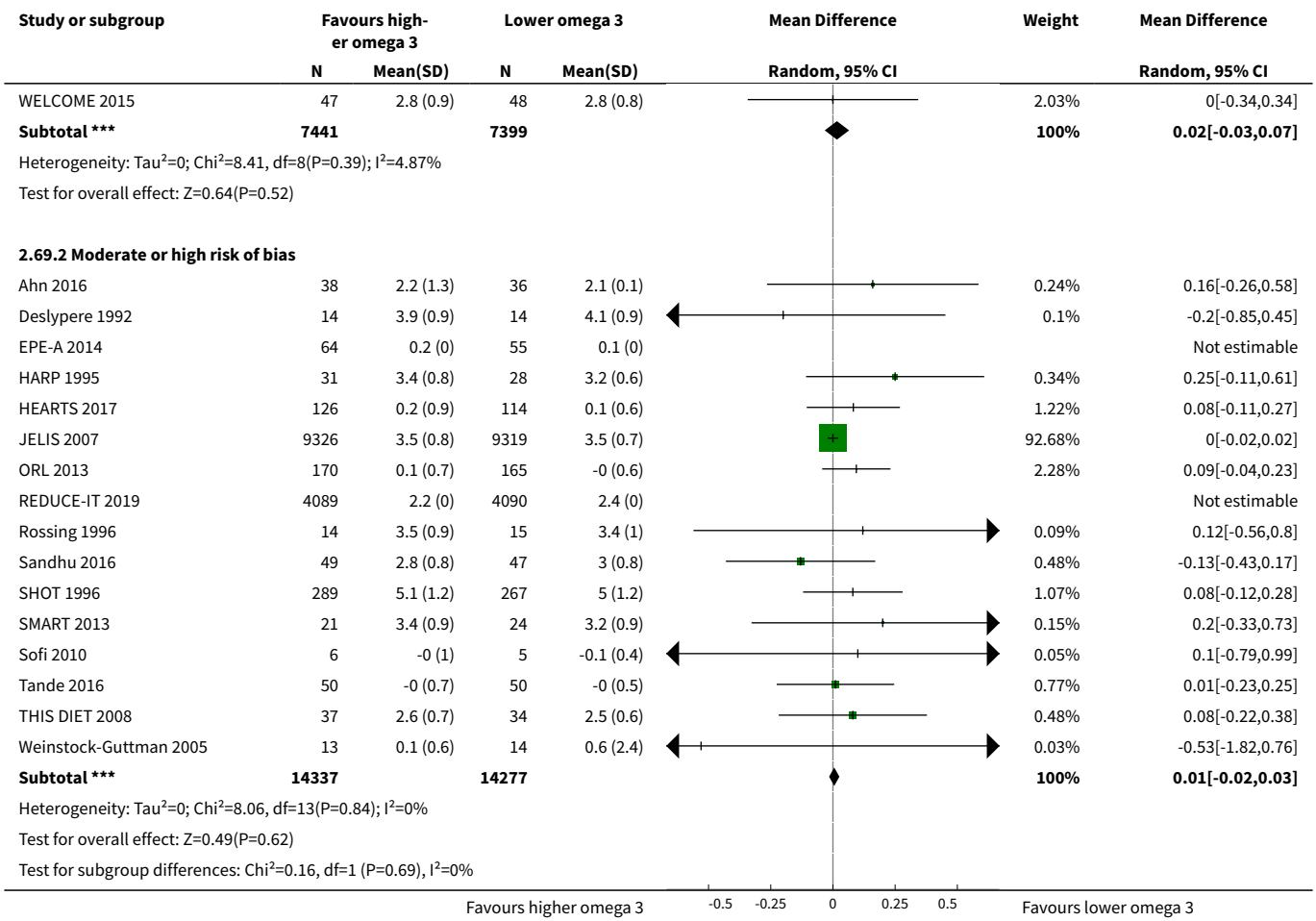
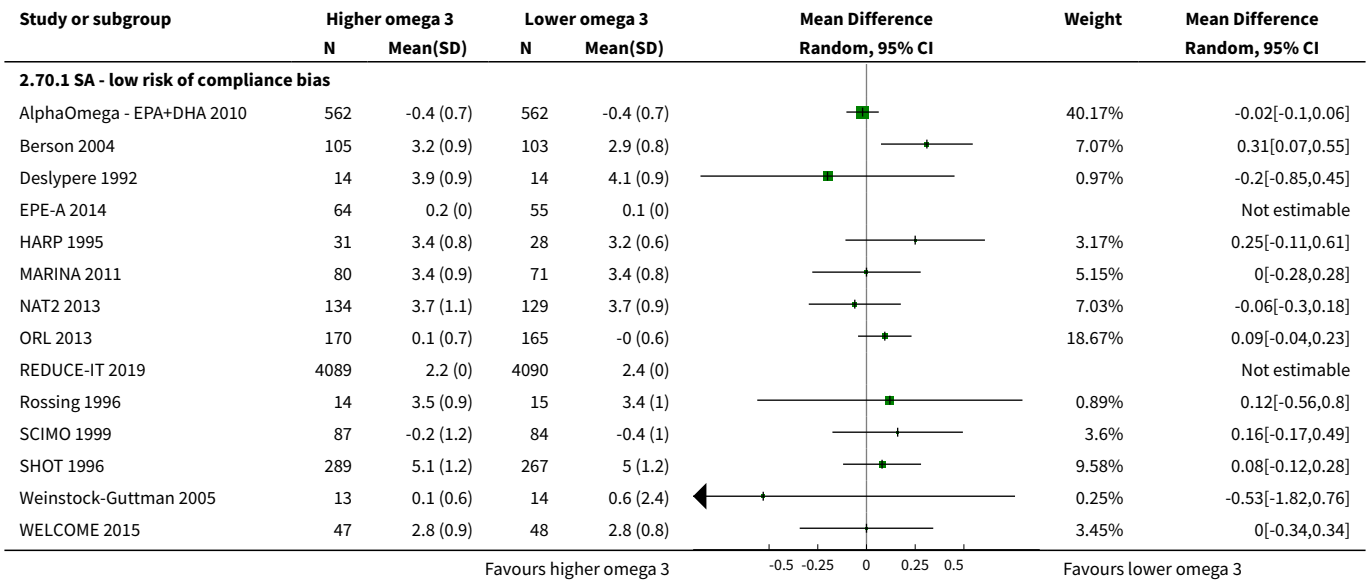


Analysis 2.70. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 70 LDL, mmoL/L - LCn3 - SA by compliance and study size.



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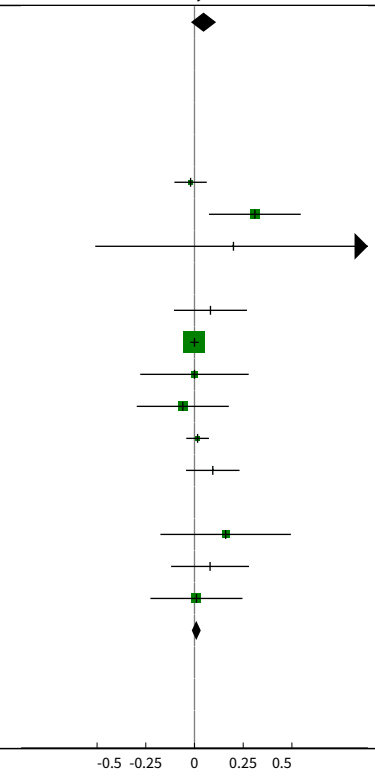
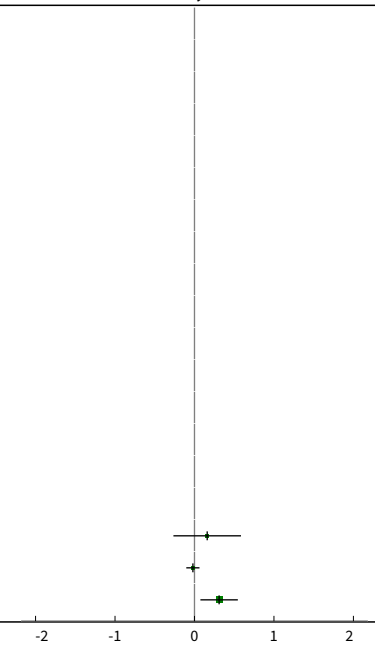
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Subtotal ***	**5699**		**5645**			**100%**	**0.05[-0.02,0.11]**
Heterogeneity: Tau²=0; Chi²=11.76, df=11(P=0.38); I²=6.45%							
Test for overall effect: Z=1.41(P=0.16)							
2.70.2 SA - 100+ randomised							
AlphaOmega - EPA+DHA 2010	562	-0.4 (0.7)	562	-0.4 (0.7)		7.37%	-0.02[-0.1,0.06]
Berson 2004	105	3.2 (0.9)	103	2.9 (0.8)		0.95%	0.31[0.07,0.55]
Derosa 2016	128	3.3 (3.4)	130	3.1 (2.3)		0.11%	0.2[-0.51,0.91]
EPE-A 2014	64	0.2 (0)	55	0.1 (0)			Not estimable
HEARTS 2017	126	0.2 (0.9)	114	0.1 (0.6)		1.5%	0.08[-0.11,0.27]
JELIS 2007	9326	3.5 (0.8)	9319	3.5 (0.7)		68.55%	0[-0.02,0.02]
MARINA 2011	80	3.4 (0.9)	71	3.4 (0.8)		0.68%	0[-0.28,0.28]
NAT2 2013	134	3.7 (1.1)	129	3.7 (0.9)		0.95%	-0.06[-0.3,0.18]
ORIGIN 2012	6281	-0.3 (1.7)	6255	-0.3 (1.7)		14.39%	0.02[-0.04,0.07]
ORL 2013	170	0.1 (0.7)	165	-0 (0.6)		2.77%	0.09[-0.04,0.23]
REDUCE-IT 2019	4089	2.2 (0)	4090	2.4 (0)			Not estimable
SCIMO 1999	87	-0.2 (1.2)	84	-0.4 (1)		0.47%	0.16[-0.17,0.49]
SHOT 1996	289	5.1 (1.2)	267	5 (1.2)		1.32%	0.08[-0.12,0.28]
Tande 2016	50	-0 (0.7)	50	-0 (0.5)		0.95%	0.01[-0.23,0.25]
Subtotal ***	**21491**		**21394**			**100%**	**0.01[-0.01,0.03]**
Heterogeneity: Tau²=0; Chi²=11.33, df=11(P=0.42); I²=2.93%							
Test for overall effect: Z=0.78(P=0.44)							
Test for subgroup differences: Chi²=1.13, df=1 (P=0.29), I²=11.7%							



Analysis 2.71. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 71 LDL, mmoL/L - LCn3 - subgroup by dose.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.71.1 LCn3 ≤ 150 mg/d							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.71.2 LCn3 > 150 ≤ 250 mg/d							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.71.3 LCn3 > 250 ≤ 400 mg/d							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.71.4 LCn3 > 400 ≤ 2400 mg/d							
Ahn 2016	38	2.2 (1.3)	36	2.1 (0.1)		0.2%	0.16[-0.26,0.58]
AlphaOmega - EPA+DHA 2010	562	-0.4 (0.7)	562	-0.4 (0.7)		5.26%	-0.02[-0.1,0.06]
Berson 2004	105	3.2 (0.9)	103	2.9 (0.8)		0.65%	0.31[0.07,0.55]



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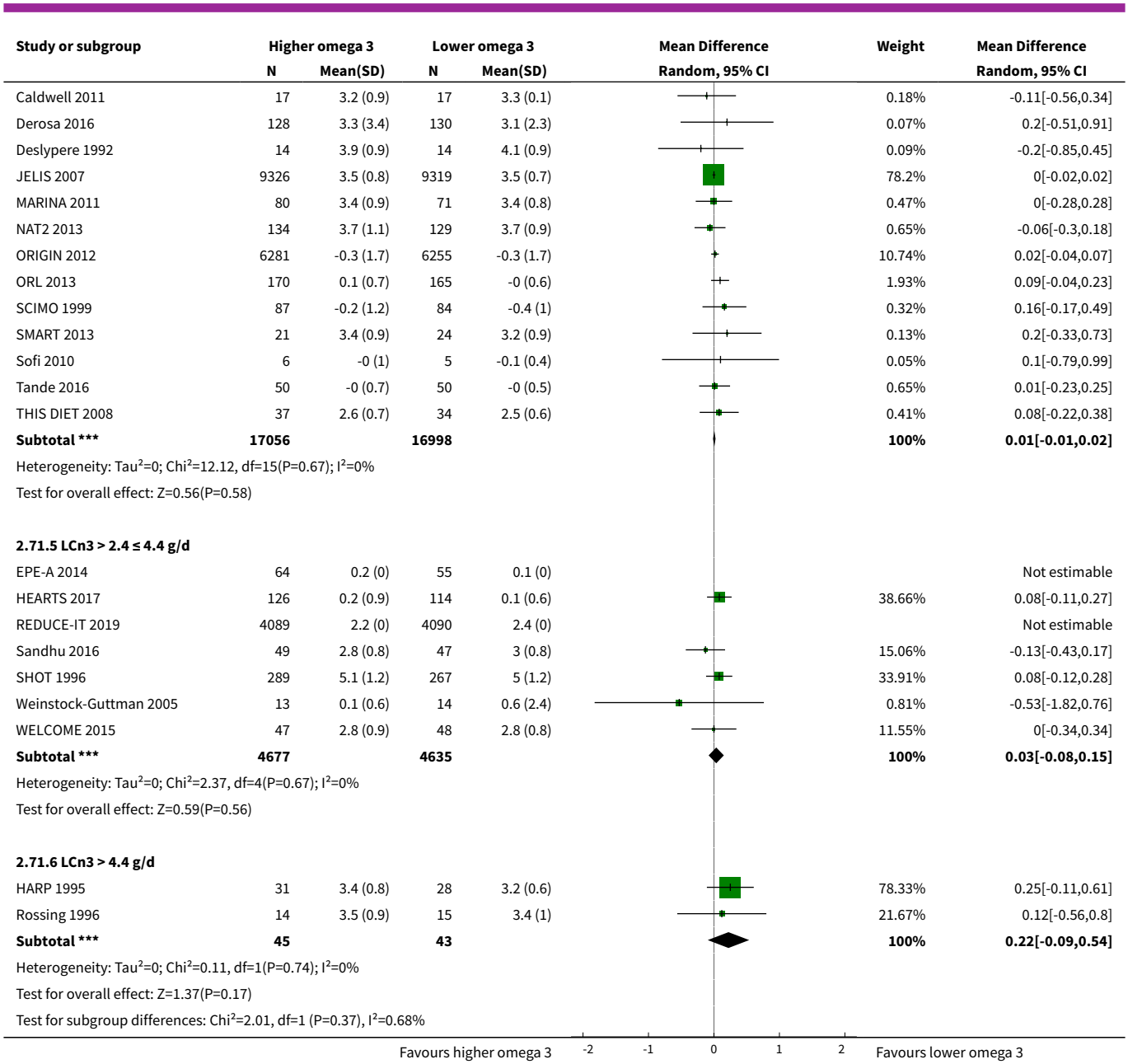
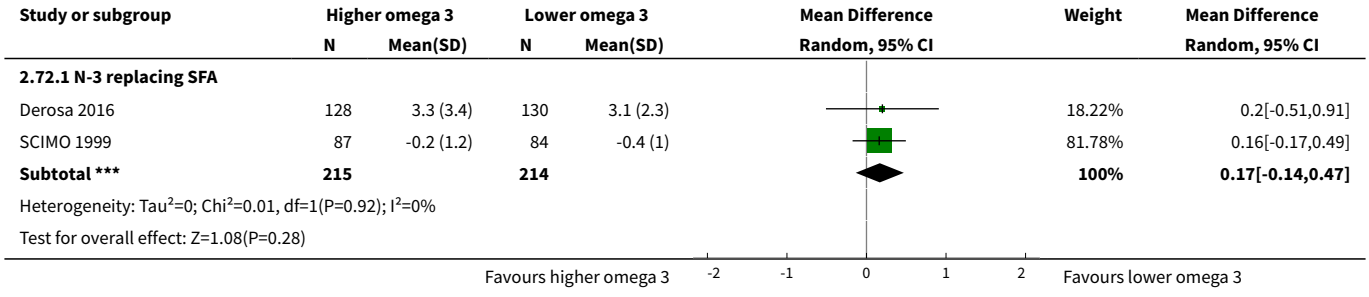


Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Caldwell 2011	17	3.2 (0.9)	17	3.3 (0.1)		0.18%	-0.11[-0.56,0.34]
Derosa 2016	128	3.3 (3.4)	130	3.1 (2.3)		0.07%	0.2[-0.51,0.91]
Deslypere 1992	14	3.9 (0.9)	14	4.1 (0.9)		0.09%	-0.2[-0.85,0.45]
JELIS 2007	9326	3.5 (0.8)	9319	3.5 (0.7)		78.2%	0[-0.02,0.02]
MARINA 2011	80	3.4 (0.9)	71	3.4 (0.8)		0.47%	0[-0.28,0.28]
NAT2 2013	134	3.7 (1.1)	129	3.7 (0.9)		0.65%	-0.06[-0.3,0.18]
ORIGIN 2012	6281	-0.3 (1.7)	6255	-0.3 (1.7)		10.74%	0.02[-0.04,0.07]
ORL 2013	170	0.1 (0.7)	165	-0 (0.6)		1.93%	0.09[-0.04,0.23]
SCIMO 1999	87	-0.2 (1.2)	84	-0.4 (1)		0.32%	0.16[-0.17,0.49]
SMART 2013	21	3.4 (0.9)	24	3.2 (0.9)		0.13%	0.2[-0.33,0.73]
Sofi 2010	6	-0 (1)	5	-0.1 (0.4)		0.05%	0.1[-0.79,0.99]
Tande 2016	50	-0 (0.7)	50	-0 (0.5)		0.65%	0.01[-0.23,0.25]
THIS DIET 2008	37	2.6 (0.7)	34	2.5 (0.6)		0.41%	0.08[-0.22,0.38]
Subtotal ***	**17056**		**16998**			**100%**	**0.01[-0.01,0.02]**
Heterogeneity: Tau²=0; Chi²=12.12, df=15(P=0.67); I²=0%							
Test for overall effect: Z=0.56(P=0.58)							
2.71.5 LCn3 > 2.4 ≤ 4.4 g/d							
EPE-A 2014	64	0.2 (0)	55	0.1 (0)			Not estimable
HEARTS 2017	126	0.2 (0.9)	114	0.1 (0.6)		38.66%	0.08[-0.11,0.27]
REDUCE-IT 2019	4089	2.2 (0)	4090	2.4 (0)			Not estimable
Sandhu 2016	49	2.8 (0.8)	47	3 (0.8)		15.06%	-0.13[-0.43,0.17]
SHOT 1996	289	5.1 (1.2)	267	5 (1.2)		33.91%	0.08[-0.12,0.28]
Weinstock-Guttman 2005	13	0.1 (0.6)	14	0.6 (2.4)		0.81%	-0.53[-1.82,0.76]
WELCOME 2015	47	2.8 (0.9)	48	2.8 (0.8)		11.55%	0[-0.34,0.34]
Subtotal ***	**4677**		**4635**			**100%**	**0.03[-0.08,0.15]**
Heterogeneity: Tau²=0; Chi²=2.37, df=4(P=0.67); I²=0%							
Test for overall effect: Z=0.59(P=0.56)							
2.71.6 LCn3 > 4.4 g/d							
HARP 1995	31	3.4 (0.8)	28	3.2 (0.6)		78.33%	0.25[-0.11,0.61]
Rossing 1996	14	3.5 (0.9)	15	3.4 (1)		21.67%	0.12[-0.56,0.8]
Subtotal ***	**45**		**43**			**100%**	**0.22[-0.09,0.54]**
Heterogeneity: Tau²=0; Chi²=0.11, df=1(P=0.74); I²=0%							
Test for overall effect: Z=1.37(P=0.17)							
Test for subgroup differences: Chi²=2.01, df=1 (P=0.37), I²=0.68%							

Analysis 2.72. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 72 LDL, mmoL/L - LCn3 - subgroup by replacement.



Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.72.1 N-3 replacing SFA							
Derosa 2016	128	3.3 (3.4)	130	3.1 (2.3)		18.22%	0.2[-0.51,0.91]
SCIMO 1999	87	-0.2 (1.2)	84	-0.4 (1)		81.78%	0.16[-0.17,0.49]
Subtotal ***	**215**		**214**			**100%**	**0.17[-0.14,0.47]**
Heterogeneity: Tau²=0; Chi²=0.01, df=1(P=0.92); I²=0%							
Test for overall effect: Z=1.08(P=0.28)							

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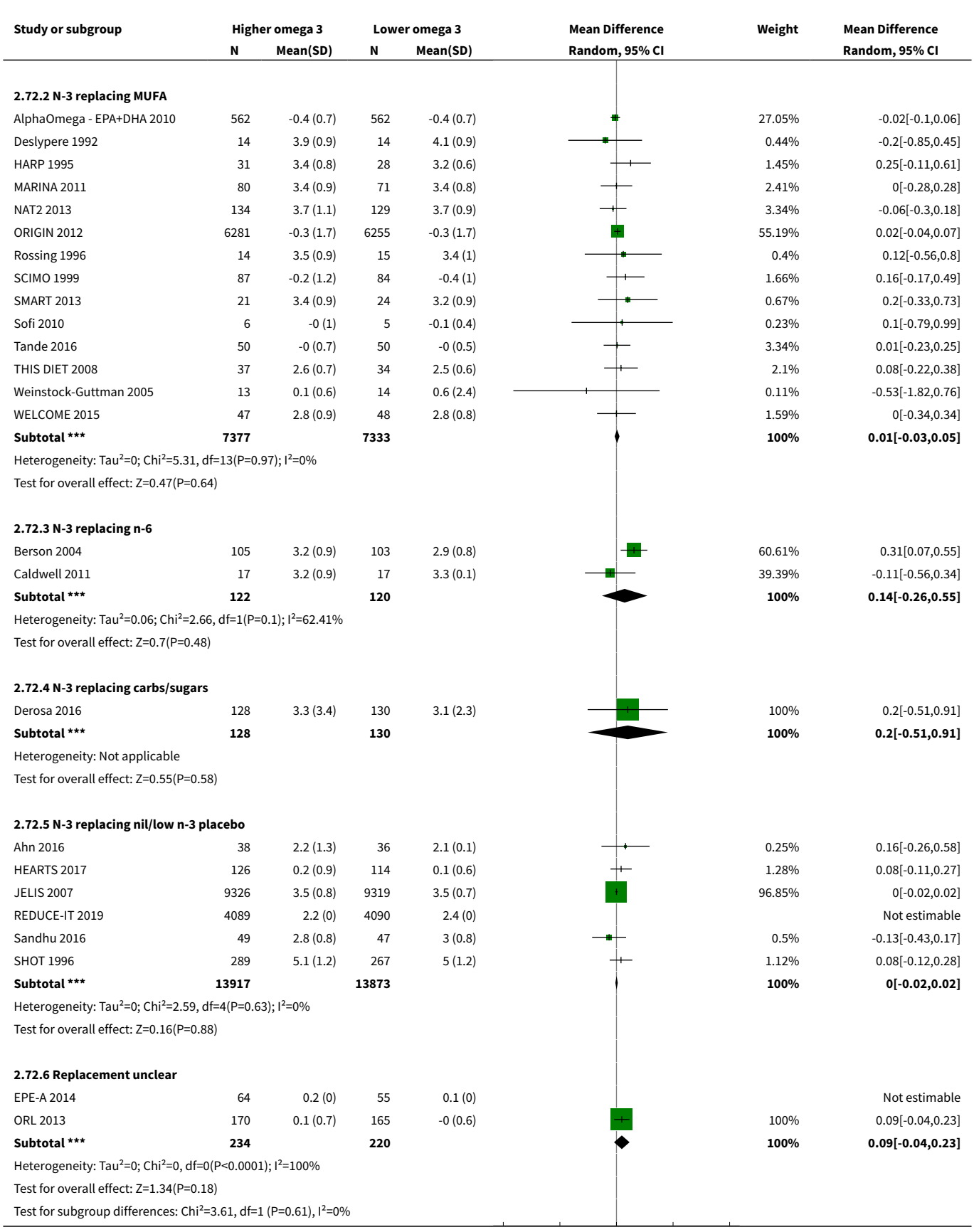

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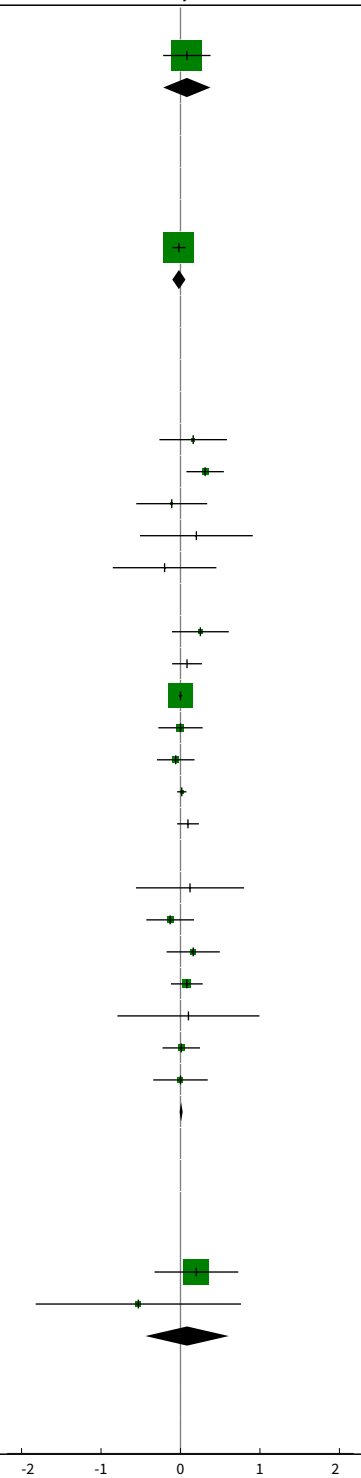
Analysis 2.73. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 73 LDL, mmoL/L - LCn3 - subgroup by intervention type.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.73.1 Dietary advice							
THIS DIET 2008	37	2.6 (0.7)	34	2.5 (0.6)		100%	0.08[-0.22,0.38]
Subtotal ***	**37**		**34**			**100%**	**0.08[-0.22,0.38]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.53(P=0.6)							
2.73.2 Supplemental foods							
AlphaOmega - EPA+DHA 2010	562	-0.4 (0.7)	562	-0.4 (0.7)		100%	-0.02[-0.1,0.06]
Subtotal ***	**562**		**562**			**100%**	**-0.02[-0.1,0.06]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.47(P=0.64)							
2.73.3 Supplement (capsule)							
Ahn 2016	38	2.2 (1.3)	36	2.1 (0.1)		0.21%	0.16[-0.26,0.58]
Berson 2004	105	3.2 (0.9)	103	2.9 (0.8)		0.67%	0.31[0.07,0.55]
Caldwell 2011	17	3.2 (0.9)	17	3.3 (0.1)		0.19%	-0.11[-0.56,0.34]
Derosa 2016	128	3.3 (3.4)	130	3.1 (2.3)		0.07%	0.2[-0.51,0.91]
Deslypere 1992	14	3.9 (0.9)	14	4.1 (0.9)		0.09%	-0.2[-0.85,0.45]
EPE-A 2014	64	0.2 (0)	55	0.1 (0)			Not estimable
HARP 1995	31	3.4 (0.8)	28	3.2 (0.6)		0.29%	0.25[-0.11,0.61]
HEARTS 2017	126	0.2 (0.9)	114	0.1 (0.6)		1.06%	0.08[-0.11,0.27]
JELIS 2007	9326	3.5 (0.8)	9319	3.5 (0.7)		80.44%	0[-0.02,0.02]
MARINA 2011	80	3.4 (0.9)	71	3.4 (0.8)		0.48%	0[-0.28,0.28]
NAT2 2013	134	3.7 (1.1)	129	3.7 (0.9)		0.67%	-0.06[-0.3,0.18]
ORIGIN 2012	6281	-0.3 (1.7)	6255	-0.3 (1.7)		11.05%	0.02[-0.04,0.07]
ORL 2013	170	0.1 (0.7)	165	-0 (0.6)		1.98%	0.09[-0.04,0.23]
REDUCE-IT 2019	4089	2.2 (0)	4090	2.4 (0)			Not estimable
Rossing 1996	14	3.5 (0.9)	15	3.4 (1)		0.08%	0.12[-0.56,0.8]
Sandhu 2016	49	2.8 (0.8)	47	3 (0.8)		0.41%	-0.13[-0.43,0.17]
SCIMO 1999	87	-0.2 (1.2)	84	-0.4 (1)		0.33%	0.16[-0.17,0.49]
SHOT 1996	289	5.1 (1.2)	267	5 (1.2)		0.93%	0.08[-0.12,0.28]
Sofi 2010	6	-0 (1)	5	-0.1 (0.4)		0.05%	0.1[-0.79,0.99]
Tande 2016	50	-0 (0.7)	50	-0 (0.5)		0.67%	0.01[-0.23,0.25]
WELCOME 2015	47	2.8 (0.9)	48	2.8 (0.8)		0.32%	0[-0.34,0.34]
Subtotal ***	**21145**		**21042**			**100%**	**0.01[-0.01,0.03]**
Heterogeneity: Tau^2=0; Chi^2=14.79, df=18(P=0.68); I^2=0%							
Test for overall effect: Z=0.81(P=0.42)							
2.73.4 Any combination							
SMART 2013	21	3.4 (0.9)	24	3.2 (0.9)		84.01%	0.2[-0.33,0.73]
Weinstock-Guttman 2005	13	0.1 (0.6)	14	0.6 (2.4)		15.99%	-0.53[-1.82,0.76]
Subtotal ***	**34**		**38**			**100%**	**0.08[-0.44,0.61]**
Heterogeneity: Tau^2=0.01; Chi^2=1.05, df=1(P=0.31); I^2=4.84%							
Test for overall effect: Z=0.31(P=0.76)							
Test for subgroup differences: Chi^2=0.73, df=1 (P=0.87), I^2=0%							



Favours higher omega 3 — Favours lower omega 3

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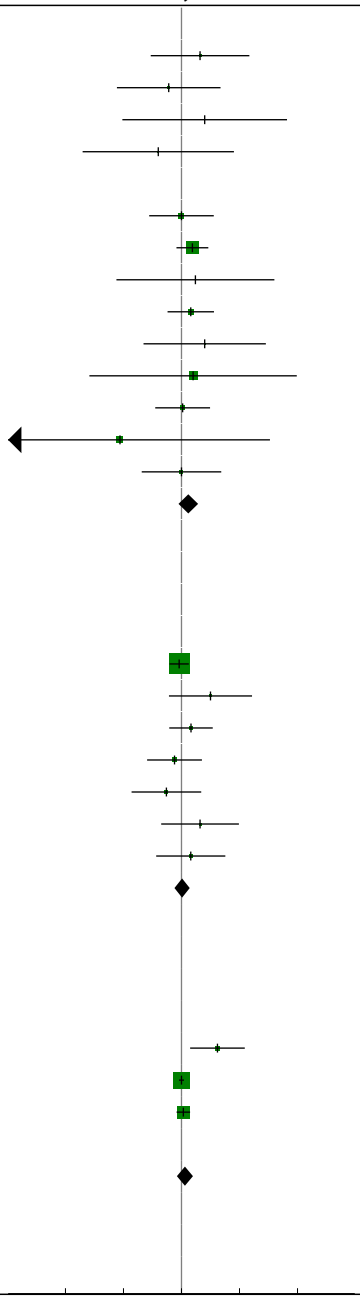
Analysis 2.74. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 74 LDL, mmoL/L - LCn3 - subgroup by duration.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.74.1 Medium duration 1 to < 2 years in study							
Ahn 2016	38	2.2 (1.3)	36	2.1 (0.1)		3.96%	0.16[-0.26,0.58]
Caldwell 2011	17	3.2 (0.9)	17	3.3 (0.1)		3.59%	-0.11[-0.56,0.34]
Derosa 2016	128	3.3 (3.4)	130	3.1 (2.3)		1.42%	0.2[-0.51,0.91]
Deslypere 1992	14	3.9 (0.9)	14	4.1 (0.9)		1.68%	-0.2[-0.85,0.45]
EPE-A 2014	64	0.2 (0)	55	0.1 (0)			Not estimable
MARINA 2011	80	3.4 (0.9)	71	3.4 (0.8)		9.23%	0[-0.28,0.28]
ORL 2013	170	0.1 (0.7)	165	-0 (0.6)		37.94%	0.09[-0.04,0.23]
Rossing 1996	14	3.5 (0.9)	15	3.4 (1)		1.54%	0.12[-0.56,0.8]
SHOT 1996	289	5.1 (1.2)	267	5 (1.2)		17.86%	0.08[-0.12,0.28]
SMART 2013	21	3.4 (0.9)	24	3.2 (0.9)		2.57%	0.2[-0.33,0.73]
Sofi 2010	6	-0 (1)	5	-0.1 (0.4)		0.89%	0.1[-0.79,0.99]
Tande 2016	50	-0 (0.7)	50	-0 (0.5)		12.81%	0.01[-0.23,0.25]
Weinstock-Guttman 2005	13	0.1 (0.6)	14	0.6 (2.4)		0.43%	-0.53[-1.82,0.76]
WELCOME 2015	47	2.8 (0.9)	48	2.8 (0.8)		6.08%	0[-0.34,0.34]
Subtotal ***	**951**		**911**			**100%**	**0.06[-0.03,0.14]**
Heterogeneity: Tau^2=0; Chi^2=3.38, df=12(P=0.99); I^2=0%							
Test for overall effect: Z=1.36(P=0.17)							
2.74.2 Medium-long duration: 2 to < 4 years in study							
AlphaOmega - EPA+DHA 2010	562	-0.4 (0.7)	562	-0.4 (0.7)		62.92%	-0.02[-0.1,0.06]
HARP 1995	31	3.4 (0.8)	28	3.2 (0.6)		3.38%	0.25[-0.11,0.61]
HEARTS 2017	126	0.2 (0.9)	114	0.1 (0.6)		12.35%	0.08[-0.11,0.27]
NAT2 2013	134	3.7 (1.1)	129	3.7 (0.9)		7.77%	-0.06[-0.3,0.18]
Sandhu 2016	49	2.8 (0.8)	47	3 (0.8)		4.81%	-0.13[-0.43,0.17]
SCIMO 1999	87	-0.2 (1.2)	84	-0.4 (1)		3.87%	0.16[-0.17,0.49]
THIS DIET 2008	37	2.6 (0.7)	34	2.5 (0.6)		4.89%	0.08[-0.22,0.38]
Subtotal ***	**1026**		**998**			**100%**	**0.01[-0.06,0.07]**
Heterogeneity: Tau^2=0; Chi^2=4.93, df=6(P=0.55); I^2=0%							
Test for overall effect: Z=0.15(P=0.88)							
2.74.3 Long duration ≥ 4 years in study							
Berson 2004	105	3.2 (0.9)	103	2.9 (0.8)		7.49%	0.31[0.07,0.55]
JELIS 2007	9326	3.5 (0.8)	9319	3.5 (0.7)		52.63%	0[-0.02,0.02]
ORIGIN 2012	6281	-0.3 (1.7)	6255	-0.3 (1.7)		39.88%	0.02[-0.04,0.07]
REDUCE-IT 2019	4089	2.2 (0)	4090	2.4 (0)			Not estimable
Subtotal ***	**19801**		**19767**			**100%**	**0.03[-0.04,0.1]**
Heterogeneity: Tau^2=0; Chi^2=6.78, df=2(P=0.03); I^2=70.52%							
Test for overall effect: Z=0.84(P=0.4)							
Test for subgroup differences: Chi^2=0.97, df=1 (P=0.62), I^2=0%							



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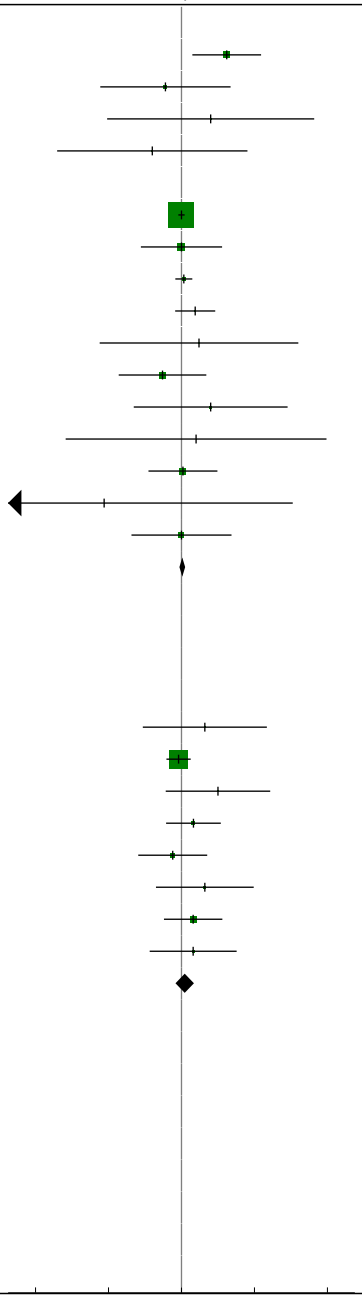
Analysis 2.75. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 75 LDL, mmoL/L - LCn3 - subgroup by primary or secondary prevention.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.75.1 Primary prevention							
Berson 2004	105	3.2 (0.9)	103	2.9 (0.8)		0.7%	0.31[0.07,0.55]
Caldwell 2011	17	3.2 (0.9)	17	3.3 (0.1)		0.19%	-0.11[-0.56,0.34]
Derosa 2016	128	3.3 (3.4)	130	3.1 (2.3)		0.08%	0.2[-0.51,0.91]
Deslypere 1992	14	3.9 (0.9)	14	4.1 (0.9)		0.09%	-0.2[-0.85,0.45]
EPE-A 2014	64	0.2 (0)	55	0.1 (0)			Not estimable
JELIS 2007	9326	3.5 (0.8)	9319	3.5 (0.7)		83.22%	0[-0.02,0.02]
MARINA 2011	80	3.4 (0.9)	71	3.4 (0.8)		0.5%	0[-0.28,0.28]
ORIGIN 2012	6281	-0.3 (1.7)	6255	-0.3 (1.7)		11.43%	0.02[-0.04,0.07]
ORL 2013	170	0.1 (0.7)	165	-0 (0.6)		2.05%	0.09[-0.04,0.23]
Rossing 1996	14	3.5 (0.9)	15	3.4 (1)		0.08%	0.12[-0.56,0.8]
Sandhu 2016	49	2.8 (0.8)	47	3 (0.8)		0.43%	-0.13[-0.43,0.17]
SMART 2013	21	3.4 (0.9)	24	3.2 (0.9)		0.14%	0.2[-0.33,0.73]
Sofi 2010	6	-0 (1)	5	-0.1 (0.4)		0.05%	0.1[-0.79,0.99]
Tande 2016	50	-0 (0.7)	50	-0 (0.5)		0.69%	0.01[-0.23,0.25]
Weinstock-Guttman 2005	13	0.1 (0.6)	14	0.6 (2.4)		0.02%	-0.53[-1.82,0.76]
WELCOME 2015	47	2.8 (0.9)	48	2.8 (0.8)		0.33%	0[-0.34,0.34]
Subtotal ***	**16385**		**16332**			**100%**	**0.01[-0.01,0.03]**
Heterogeneity: Tau^2=0; Chi^2=11.45, df=14(P=0.65); I^2=0%							
Test for overall effect: Z=0.55(P=0.58)							
2.75.2 Secondary prevention							
Ahn 2016	38	2.2 (1.3)	36	2.1 (0.1)		2.21%	0.16[-0.26,0.58]
AlphaOmega - EPA+DHA 2010	562	-0.4 (0.7)	562	-0.4 (0.7)		58.03%	-0.02[-0.1,0.06]
HARP 1995	31	3.4 (0.8)	28	3.2 (0.6)		3.12%	0.25[-0.11,0.61]
HEARTS 2017	126	0.2 (0.9)	114	0.1 (0.6)		11.39%	0.08[-0.11,0.27]
NAT2 2013	134	3.7 (1.1)	129	3.7 (0.9)		7.17%	-0.06[-0.3,0.18]
SCIMO 1999	87	-0.2 (1.2)	84	-0.4 (1)		3.57%	0.16[-0.17,0.49]
SHOT 1996	289	5.1 (1.2)	267	5 (1.2)		10%	0.08[-0.12,0.28]
THIS DIET 2008	37	2.6 (0.7)	34	2.5 (0.6)		4.51%	0.08[-0.22,0.38]
Subtotal ***	**1304**		**1254**			**100%**	**0.02[-0.04,0.09]**
Heterogeneity: Tau^2=0; Chi^2=4.92, df=7(P=0.67); I^2=0%							
Test for overall effect: Z=0.68(P=0.49)							
2.75.3 Mixed primary & secondary prevention							
REDUCE-IT 2019	4089	2.2 (0)	4090	2.4 (0)			Not estimable
Subtotal ***	**4089**		**4090**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Chi^2=0.24, df=1 (P=0.62), I^2=0%							



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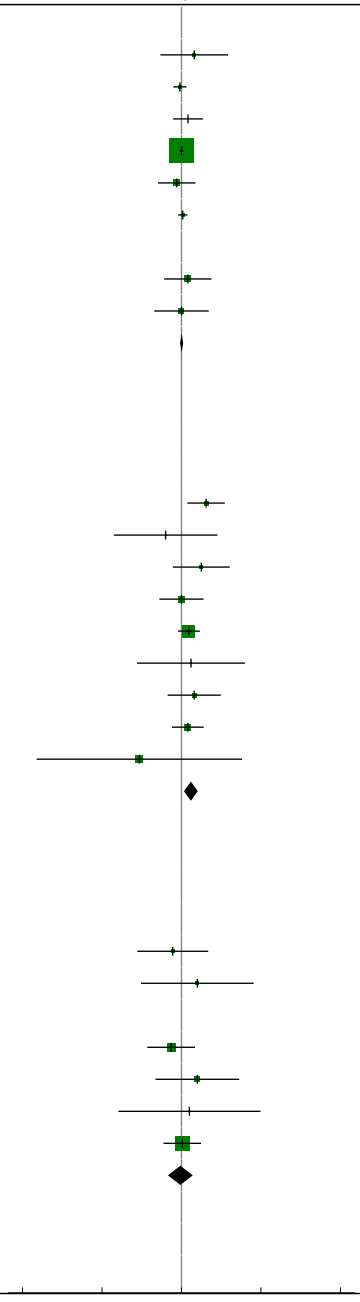
Analysis 2.76. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 76 LDL, mmoL/L - LCn3 - subgroup by statin use.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.76.1 LCn3 - ≥ 50% of control group on statins							
Ahn 2016	38	2.2 (1.3)	36	2.1 (0.1)		0.21%	0.16[-0.26,0.58]
AlphaOmega - EPA+DHA 2010	562	-0.4 (0.7)	562	-0.4 (0.7)		5.44%	-0.02[-0.1,0.06]
HEARTS 2017	126	0.2 (0.9)	114	0.1 (0.6)		1.07%	0.08[-0.11,0.27]
JELIS 2007	9326	3.5 (0.8)	9319	3.5 (0.7)		80.78%	0[-0.02,0.02]
NAT2 2013	134	3.7 (1.1)	129	3.7 (0.9)		0.67%	-0.06[-0.3,0.18]
ORIGIN 2012	6281	-0.3 (1.7)	6255	-0.3 (1.7)		11.09%	0.02[-0.04,0.07]
REDUCE-IT 2019	4089	2.2 (0)	4090	2.4 (0)			Not estimable
THIS DIET 2008	37	2.6 (0.7)	34	2.5 (0.6)		0.42%	0.08[-0.22,0.38]
WELCOME 2015	47	2.8 (0.9)	48	2.8 (0.8)		0.32%	0[-0.34,0.34]
Subtotal ***	**20640**		**20587**			**100%**	**0[-0.02,0.02]**
Heterogeneity: Tau^2=0; Chi^2=2.29, df=7(P=0.94); I^2=0%							
Test for overall effect: Z=0.19(P=0.85)							
2.76.2 LCn3 - < 50% of control group on statins							
Berson 2004	105	3.2 (0.9)	103	2.9 (0.8)		13.78%	0.31[0.07,0.55]
Deslypere 1992	14	3.9 (0.9)	14	4.1 (0.9)		1.8%	-0.2[-0.85,0.45]
HARP 1995	31	3.4 (0.8)	28	3.2 (0.6)		5.96%	0.25[-0.11,0.61]
MARINA 2011	80	3.4 (0.9)	71	3.4 (0.8)		9.87%	0[-0.28,0.28]
ORL 2013	170	0.1 (0.7)	165	-0 (0.6)		40.57%	0.09[-0.04,0.23]
Rossing 1996	14	3.5 (0.9)	15	3.4 (1)		1.65%	0.12[-0.56,0.8]
SCIMO 1999	87	-0.2 (1.2)	84	-0.4 (1)		6.82%	0.16[-0.17,0.49]
SHOT 1996	289	5.1 (1.2)	267	5 (1.2)		19.1%	0.08[-0.12,0.28]
Weinstock-Guttman 2005	13	0.1 (0.6)	14	0.6 (2.4)		0.46%	-0.53[-1.82,0.76]
Subtotal ***	**803**		**761**			**100%**	**0.12[0.03,0.21]**
Heterogeneity: Tau^2=0; Chi^2=5.96, df=8(P=0.65); I^2=0%							
Test for overall effect: Z=2.64(P=0.01)							
2.76.3 LCn3 - use of statins unclear							
Caldwell 2011	17	3.2 (0.9)	17	3.3 (0.1)		12.27%	-0.11[-0.56,0.34]
Derosa 2016	128	3.3 (3.4)	130	3.1 (2.3)		4.86%	0.2[-0.51,0.91]
EPE-A 2014	64	0.2 (0)	55	0.1 (0)			Not estimable
Sandhu 2016	49	2.8 (0.8)	47	3 (0.8)		27.15%	-0.13[-0.43,0.17]
SMART 2013	21	3.4 (0.9)	24	3.2 (0.9)		8.8%	0.2[-0.33,0.73]
Sofi 2010	6	-0 (1)	5	-0.1 (0.4)		3.06%	0.1[-0.79,0.99]
Tande 2016	50	-0 (0.7)	50	-0 (0.5)		43.84%	0.01[-0.23,0.25]
Subtotal ***	**335**		**328**			**100%**	**-0.01[-0.17,0.14]**
Heterogeneity: Tau^2=0; Chi^2=1.84, df=5(P=0.87); I^2=0%							
Test for overall effect: Z=0.18(P=0.86)							
Test for subgroup differences: Chi^2=6.53, df=1 (P=0.04), I^2=69.36%							



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Comparison 3. High vs low LCn3 omega-3 fats (tertiary outcomes)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Blood pressure, mmHg - LCn3	17		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Systolic BP - LCn3	17	35601	Mean Difference (IV, Random, 95% CI)	0.01 [-0.31, 0.34]
1.2 Diastolic BP - LCn3	15	35626	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.22, 0.17]
2 Serious adverse events - LCn3	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Any serious adverse events	3	9116	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.94, 1.06]
2.2 Bleeding	11	80147	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.91, 1.37]
2.3 Serious GI events	3	774	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.64, 2.80]
2.4 Pulmonary embolus or DVT - LCn3	5	3546	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.44, 2.98]
2.5 Progression to advanced AMD (age-related macular degeneration)	1	4203	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.90, 1.02]
3 Side effects - LCn3	38		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Dropouts due to side effects	23	16755	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.99, 1.36]
3.2 Abdominal pain or discomfort	9	41056	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.91, 1.20]
3.3 Diarrhoea	13	37013	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.87, 1.19]
3.4 Nausea	8	35819	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.96, 1.49]
3.5 Any gastrointestinal side effect - LCn3 fats	33	89668	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.97, 1.26]
3.6 Skin problems (itching, rashes)	9	36721	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.52, 2.37]
3.7 Headache or worsening migraine	4	1526	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.51, 1.40]
3.8 Reflux	3	8916	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.79, 1.91]
3.9 Pain (joint, lumbar, muscle pain)	3	27359	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.74, 1.23]
3.10 All side effects combined	14	39439	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.95, 1.08]

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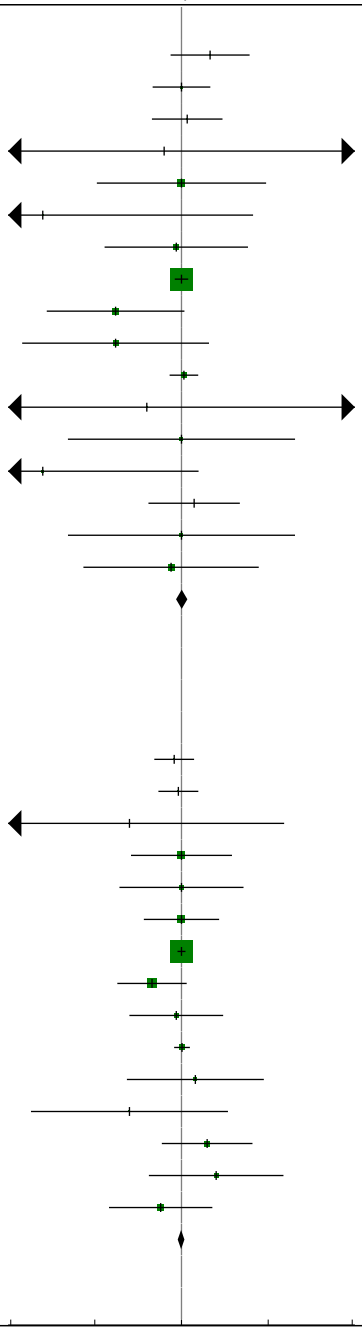
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Dropouts - LCn3	35	56089	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.90, 1.04]

Analysis 3.1. Comparison 3 High vs low LCn3 omega-3 fats (tertiary outcomes), Outcome 1 Blood pressure, mmHg - LCn3.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.1.1 Systolic BP - LCn3							
AlphaOmega - EPA+DHA 2010	632	-0.6 (20)	632	-2.3 (21.3)		2.06%	1.65[-0.63,3.93]
ASCEND 2018	471	137 (13)	477	137 (13.1)		3.86%	0[-1.66,1.66]
DART 1989	871	138.1 (21.9)	852	137.7 (21.2)		2.58%	0.33[-1.7,2.36]
Deslypere 1992	14	118 (21)	14	119 (18)		0.05%	-1[-15.49,13.49]
DO IT 2010	124	143 (16)	117	143 (22)		0.45%	0[-4.88,4.88]
HARP 1995	31	129 (16)	28	137 (29)		0.07%	-8[-20.13,4.13]
HEARTS 2017	126	-3.7 (15.9)	114	-3.4 (16.7)		0.62%	-0.3[-4.43,3.83]
JELIS 2007	9326	133.3 (14)	9319	133.3 (13)		70.93%	0[-0.39,0.39]
MARINA 2011	80	118.3 (12.1)	71	122.1 (12.7)		0.68%	-3.8[-7.77,0.17]
OFAMI 2001	127	132.2 (24.4)	130	136 (19.3)		0.37%	-3.8[-9.19,1.59]
ORIGIN 2012	6281	-4.4 (22.5)	5255	-4.5 (22.5)		15.69%	0.14[-0.68,0.96]
Rossing 1996	14	142 (18.7)	15	144 (15.5)		0.07%	-2[-14.55,10.55]
SCIMO 1999	87	8.3 (19.1)	84	8.3 (24.2)		0.25%	0[-6.55,6.55]
SMART 2013	20	120 (13)	23	128 (17)		0.13%	-8[-16.98,0.98]
Tande 2016	50	2.7 (6.3)	50	2 (7.1)		1.54%	0.73[-1.9,3.36]
THIS DIET 2008	37	123 (16)	34	123 (12)		0.25%	0[-6.55,6.55]
WELCOME 2015	47	133.3 (13.7)	48	133.9 (11.3)		0.42%	-0.6[-5.66,4.46]
Subtotal ***	**18338**		**17263**			**100%**	**0.01[-0.31,0.34]**
Heterogeneity: Tau^2=0; Chi^2=12.85, df=16(P=0.68); I^2=0%							
Test for overall effect: Z=0.08(P=0.94)							
3.1.2 Diastolic BP - LCn3							
AlphaOmega - EPA+DHA 2010	632	-3.2 (10.5)	632	-2.7 (10.3)		2.86%	-0.42[-1.57,0.73]
DART 1989	870	81.4 (12.5)	852	81.6 (11.9)		2.84%	-0.18[-1.33,0.97]
Deslypere 1992	14	72 (13)	14	75 (11)		0.05%	-3[-11.92,5.92]
DO IT 2010	124	79 (11)	117	79 (12)		0.44%	0[-2.91,2.91]
HARP 1995	31	77 (7)	28	77 (7)		0.29%	0[-3.58,3.58]
HEARTS 2017	126	-3.2 (8.5)	114	-3.2 (8.6)		0.8%	0[-2.17,2.17]
JELIS 2007	9326	78 (8)	9319	78 (8)		71.36%	0[-0.23,0.23]
MARINA 2011	80	71.2 (6.2)	71	72.9 (6.3)		0.94%	-1.7[-3.7,0.3]
OFAMI 2001	127	80.8 (9.3)	130	81.1 (12.6)		0.52%	-0.3[-3,2.4]
ORIGIN 2012	6281	-4.9 (12.8)	6255	-5 (13.1)		18.31%	0.03[-0.42,0.48]
SCIMO 1999	87	4.2 (11.5)	84	3.4 (14.6)		0.24%	0.8[-3.15,4.75]
SMART 2013	20	74 (9)	23	77 (10)		0.12%	-3[-8.68,2.68]
Tande 2016	50	-0.9 (7.2)	50	-2.4 (6)		0.55%	1.48[-1.13,4.09]
THIS DIET 2008	37	74 (9)	37	72 (8)		0.25%	2[-1.88,5.88]
WELCOME 2015	47	81.7 (8.2)	48	82.9 (6.5)		0.42%	-1.2[-4.18,1.78]
Subtotal ***	**17852**		**17774**			**100%**	**-0.02[-0.22,0.17]**
Heterogeneity: Tau^2=0; Chi^2=7.93, df=14(P=0.89); I^2=0%							
Test for overall effect: Z=0.24(P=0.81)							



Favours higher omega 3 — Favours lower omega 3

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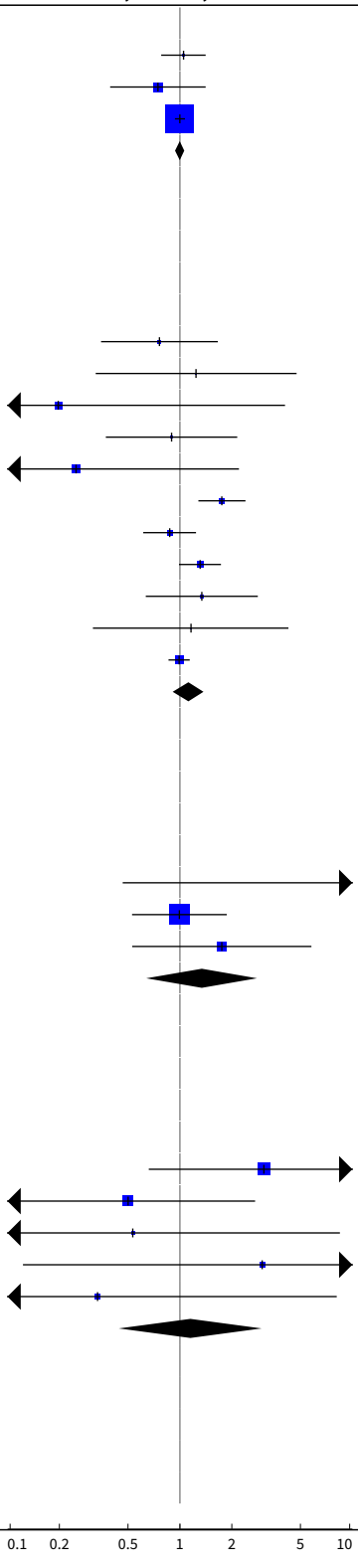
Analysis 3.2. Comparison 3 High vs low LCn3 omega-3 fats (tertiary outcomes), Outcome 2 Serious adverse events - LCn3.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Any serious adverse events					
ADCS 2010	76/238	50/164		4.57%	1.05[0.78,1.41]
DREAM Asbell 2018	21/349	15/186		0.99%	0.75[0.39,1.41]
REDUCE-IT 2019	1252/4089	1254/4090		94.44%	1[0.94,1.07]
Subtotal (95% CI)	**4676**	**4440**		**100%**	**1[0.94,1.06]**
Total events: 1349 (Higher omega 3), 1319 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.9, df=2(P=0.64); I^2=0%					
Test for overall effect: Z=0.06(P=0.95)					
3.2.2 Bleeding					
AFFORD 2013	10/153	14/163		5.61%	0.76[0.35,1.66]
DREAM Asbell 2018	7/349	3/186		2.18%	1.24[0.33,4.75]
EPIC-1 2008	0/187	2/184		0.45%	0.2[0.01,4.07]
EPIC-2 2008	9/189	10/188		4.63%	0.9[0.37,2.15]
FOSTAR 2016	1/101	4/101		0.87%	0.25[0.03,2.2]
JELIS 2007	105/9326	60/9319		17.36%	1.75[1.28,2.4]
ORIGIN 2012	57/6281	65/6255		15.72%	0.87[0.61,1.24]
REDUCE-IT 2019	111/4089	85/4090		19.07%	1.31[0.99,1.73]
Risk & Prevention 2013	16/6239	12/6266		6.02%	1.34[0.63,2.83]
SHOT 1996	5/317	4/293		2.29%	1.16[0.31,4.26]
VITAL 2019	370/12933	374/12938		25.8%	0.99[0.86,1.14]
Subtotal (95% CI)	**40164**	**39983**		**100%**	**1.12[0.91,1.37]**
Total events: 691 (Higher omega 3), 633 (Lower omega 3)					
Heterogeneity: Tau^2=0.04; Chi^2=17.83, df=10(P=0.06); I^2=43.92%					
Test for overall effect: Z=1.05(P=0.3)					
3.2.3 Serious GI events					
ENRGISE 2018	4/148	0/141		6.12%	8.58[0.47,157.87]
HEARTS 2017	17/143	17/142		64.79%	0.99[0.53,1.87]
Raitt 2005	7/100	4/100		29.09%	1.75[0.53,5.79]
Subtotal (95% CI)	**391**	**383**		**100%**	**1.34[0.64,2.8]**
Total events: 28 (Higher omega 3), 21 (Lower omega 3)					
Heterogeneity: Tau^2=0.12; Chi^2=2.57, df=2(P=0.28); I^2=22.18%					
Test for overall effect: Z=0.77(P=0.44)					
3.2.4 Pulmonary embolus or DVT - LCn3					
ADCS 2010	8/214	2/164		38.57%	3.07[0.66,14.24]
DART 1989	2/1015	4/1018		31.67%	0.5[0.09,2.73]
DREAM Asbell 2018	1/349	1/186		11.9%	0.53[0.03,8.47]
NAT2 2013	1/150	0/150		8.93%	3[0.12,73.06]
OFAMI 2001	0/150	1/150		8.93%	0.33[0.01,8.12]
Subtotal (95% CI)	**1878**	**1668**		**100%**	**1.15[0.44,2.98]**
Total events: 12 (Higher omega 3), 8 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=3.72, df=4(P=0.45); I^2=0%					
Test for overall effect: Z=0.28(P=0.78)					
3.2.5 Progression to advanced AMD (age-related macular degeneration)					



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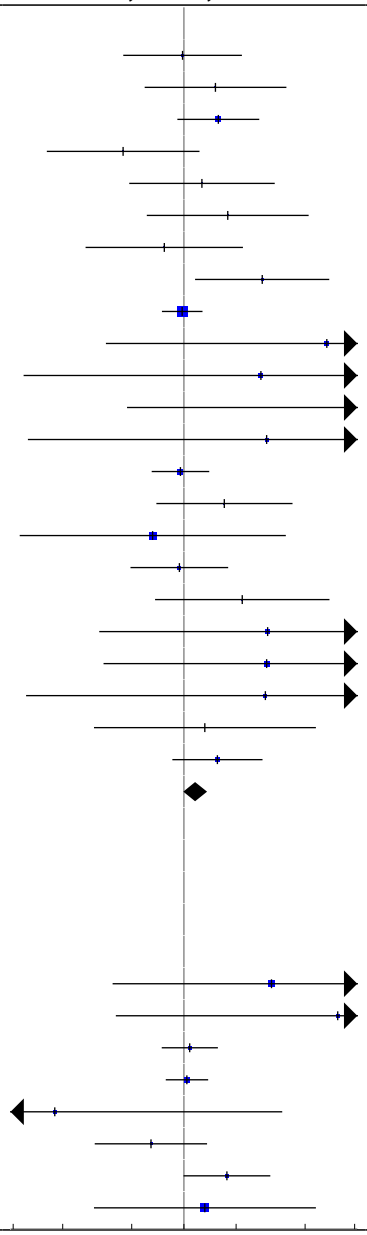
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
AREDS2 2014	1025/2147	1024/2056		100%	0.96[0.9,1.02]
Subtotal (95% CI)	**2147**	**2056**		**100%**	**0.96[0.9,1.02]**
Total events: 1025 (Higher omega 3), 1024 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.34(P=0.18)					

Favours higher omega 3 — Favours lower omega 3

Analysis 3.3. Comparison 3 High vs low LCn3 omega-3 fats (tertiary outcomes), Outcome 3 Side effects - LCn3.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.3.1 Dropouts due to side effects					
ADCS 2010	14/238	10/167		4.03%	0.98[0.45,2.16]
AFFORD 2013	10/153	7/163		2.83%	1.52[0.59,3.9]
AlphaOmega - EPA+DHA 2010	32/1192	21/1236		8.36%	1.58[0.92,2.72]
EPE-A 2014	7/168	7/75		2.44%	0.45[0.16,1.23]
EPIC-1 2008	9/187	7/185		2.68%	1.27[0.48,3.34]
EPIC-2 2008	9/189	5/188		2.17%	1.79[0.61,5.24]
FORWARD 2013	6/289	8/297		2.29%	0.77[0.27,2.19]
FOSTAR 2016	17/101	6/101		3.16%	2.83[1.16,6.89]
GISSI-HF 2008	102/3494	104/3481		33.14%	0.98[0.75,1.28]
HARP 1995	3/41	0/39		0.29%	6.67[0.36,125.02]
HERO 2009	1/26	0/24		0.25%	2.78[0.12,65.08]
Kumar 2012	4/91	0/87		0.3%	8.61[0.47,157.57]
Kumar 2013	1/39	0/39		0.25%	3[0.13,71.46]
MAPT 2017	48/820	51/832		16.8%	0.95[0.65,1.4]
NAT2 2013	12/150	7/150		3.06%	1.71[0.69,4.23]
Nodari 2011 AF	2/100	3/99		0.8%	0.66[0.11,3.87]
OPAL 2010	17/434	18/433		5.9%	0.94[0.49,1.8]
ORL 2013	9/171	4/165		1.87%	2.17[0.68,6.91]
Puri 2005	3/67	1/68		0.5%	3.04[0.32,28.54]
Rossing 1996	3/18	1/18		0.53%	3[0.34,26.19]
Sandhu 2016	1/54	0/53		0.25%	2.95[0.12,70.72]
SCIMO 1999	4/112	3/111		1.15%	1.32[0.3,5.77]
SHOT 1996	27/317	16/293		6.96%	1.56[0.86,2.84]
Subtotal (95% CI)	**8451**	**8304**		**100%**	**1.16[0.99,1.36]**
Total events: 341 (Higher omega 3), 279 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=22.11, df=22(P=0.45); I²=0.51%					
Test for overall effect: Z=1.86(P=0.06)					
3.3.2 Abdominal pain or discomfort					
DREAM Asbell 2018	6/349	1/186		0.43%	3.2[0.39,26.36]
EPE-A 2014	3/68	0/75		0.22%	7.71[0.41,146.61]
EPIC-1 2008	45/187	41/184		11.51%	1.08[0.75,1.57]
EPIC-2 2008	65/189	62/188		17.44%	1.04[0.79,1.38]
Lorenz-Meyer 1996	0/70	2/63		0.21%	0.18[0.01,3.69]
OPAL 2010	11/434	17/433		3.3%	0.65[0.31,1.36]
ORIGIN 2012	32/6281	18/6255		5.34%	1.77[0.99,3.15]
SCIMO 1999	4/112	3/111		0.88%	1.32[0.3,5.77]



Favours higher omega 3 — Favours lower omega 3

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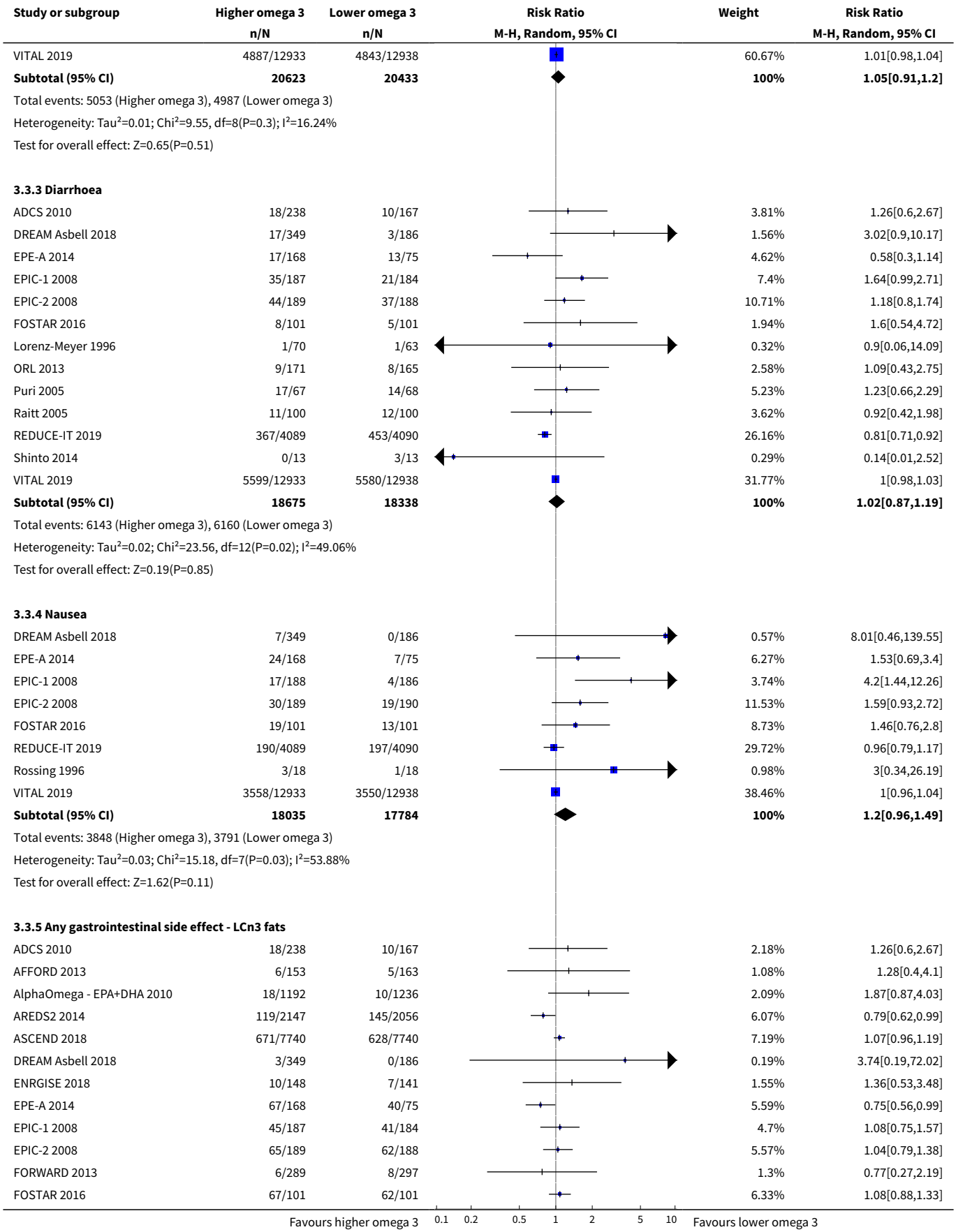

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
VITAL 2019	4887/12933	4843/12938		60.67%	1.01[0.98,1.04]
Subtotal (95% CI)	**20623**	**20433**		**100%**	**1.05[0.91,1.2]**
Total events: 5053 (Higher omega 3), 4987 (Lower omega 3)					
Heterogeneity: Tau²=0.01; Chi²=9.55, df=8(P=0.3); I²=16.24%					
Test for overall effect: Z=0.65(P=0.51)					
3.3.3 Diarrhoea					
ADCS 2010	18/238	10/167		3.81%	1.26[0.6,2.67]
DREAM Asbell 2018	17/349	3/186		1.56%	3.02[0.9,10.17]
EPE-A 2014	17/168	13/75		4.62%	0.58[0.3,1.14]
EPIC-1 2008	35/187	21/184		7.4%	1.64[0.99,2.71]
EPIC-2 2008	44/189	37/188		10.71%	1.18[0.8,1.74]
FOSTAR 2016	8/101	5/101		1.94%	1.6[0.54,4.72]
Lorenz-Meyer 1996	1/70	1/63		0.32%	0.9[0.06,14.09]
ORL 2013	9/171	8/165		2.58%	1.09[0.43,2.75]
Puri 2005	17/67	14/68		5.23%	1.23[0.66,2.29]
Raitt 2005	11/100	12/100		3.62%	0.92[0.42,1.98]
REDUCE-IT 2019	367/4089	453/4090		26.16%	0.81[0.71,0.92]
Shinto 2014	0/13	3/13		0.29%	0.14[0.01,2.52]
VITAL 2019	5599/12933	5580/12938		31.77%	1[0.98,1.03]
Subtotal (95% CI)	**18675**	**18338**		**100%**	**1.02[0.87,1.19]**
Total events: 6143 (Higher omega 3), 6160 (Lower omega 3)					
Heterogeneity: Tau²=0.02; Chi²=23.56, df=12(P=0.02); I²=49.06%					
Test for overall effect: Z=0.19(P=0.85)					
3.3.4 Nausea					
DREAM Asbell 2018	7/349	0/186		0.57%	8.01[0.46,139.55]
EPE-A 2014	24/168	7/75		6.27%	1.53[0.69,3.4]
EPIC-1 2008	17/188	4/186		3.74%	4.2[1.44,12.26]
EPIC-2 2008	30/189	19/190		11.53%	1.59[0.93,2.72]
FOSTAR 2016	19/101	13/101		8.73%	1.46[0.76,2.8]
REDUCE-IT 2019	190/4089	197/4090		29.72%	0.96[0.79,1.17]
Rossing 1996	3/18	1/18		0.98%	3[0.34,26.19]
VITAL 2019	3558/12933	3550/12938		38.46%	1[0.96,1.04]
Subtotal (95% CI)	**18035**	**17784**		**100%**	**1.2[0.96,1.49]**
Total events: 3848 (Higher omega 3), 3791 (Lower omega 3)					
Heterogeneity: Tau²=0.03; Chi²=15.18, df=7(P=0.03); I²=53.88%					
Test for overall effect: Z=1.62(P=0.11)					
3.3.5 Any gastrointestinal side effect - LCn3 fats					
ADCS 2010	18/238	10/167		2.18%	1.26[0.6,2.67]
AFFORD 2013	6/153	5/163		1.08%	1.28[0.4,4.1]
AlphaOmega - EPA+DHA 2010	18/1192	10/1236		2.09%	1.87[0.87,4.03]
AREDS2 2014	119/2147	145/2056		6.07%	0.79[0.62,0.99]
ASCEND 2018	671/7740	628/7740		7.19%	1.07[0.96,1.19]
DREAM Asbell 2018	3/349	0/186		0.19%	3.74[0.19,72.02]
ENRGISE 2018	10/148	7/141		1.55%	1.36[0.53,3.48]
EPE-A 2014	67/168	40/75		5.59%	0.75[0.56,0.99]
EPIC-1 2008	45/187	41/184		4.7%	1.08[0.75,1.57]
EPIC-2 2008	65/189	62/188		5.57%	1.04[0.79,1.38]
FORWARD 2013	6/289	8/297		1.3%	0.77[0.27,2.19]
FOSTAR 2016	67/101	62/101		6.33%	1.08[0.88,1.33]

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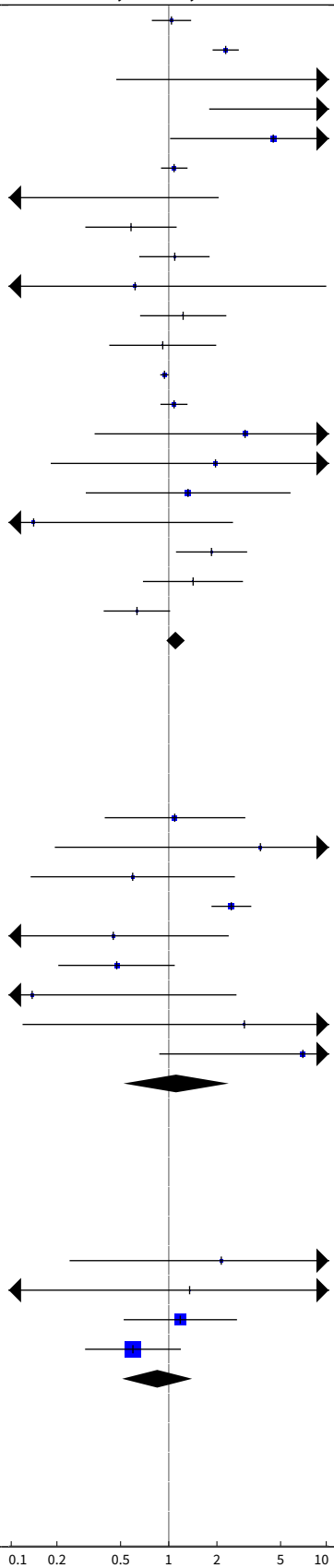
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
GISSI-HF 2008	96/3494	92/3481		5.58%	1.04[0.78,1.38]
JELIS 2007	352/9326	155/9319		6.54%	2.27[1.88,2.74]
Kumar 2012	4/91	0/87		0.2%	8.61[0.47,157.57]
Kumar 2013	14/39	0/39		0.21%	29[1.79,469.76]
Lorenz-Meyer 1996	10/70	2/63		0.71%	4.5[1.02,19.76]
MAPT 2017	175/820	164/832		6.51%	1.08[0.9,1.31]
OPAL 2010	0/434	4/433		0.2%	0.11[0.01,2.05]
ORIGIN 2012	14/6281	24/6255		2.6%	0.58[0.3,1.12]
ORL 2013	27/171	24/165		3.54%	1.09[0.65,1.8]
Proudman 2015	1/86	1/53		0.22%	0.62[0.04,9.65]
Puri 2005	17/67	14/68		2.79%	1.23[0.66,2.29]
Raitt 2005	11/100	12/100		2.09%	0.92[0.42,1.98]
REDUCE-IT 2019	1350/4089	1437/4090		7.42%	0.94[0.88,1]
Risk & Prevention 2013	200/6239	186/6266		6.44%	1.08[0.89,1.31]
Rossing 1996	3/18	1/18		0.35%	3[0.34,26.19]
Sandhu 2016	2/54	1/53		0.29%	1.96[0.18,21.01]
SCIMO 1999	4/112	3/111		0.71%	1.32[0.3,5.77]
Shinto 2014	0/13	3/13		0.2%	0.14[0.01,2.52]
SHOT 1996	40/317	20/293		3.5%	1.85[1.11,3.09]
SOFA 2006	17/273	12/273		2.3%	1.42[0.69,2.91]
Tande 2016	18/64	28/63		3.75%	0.63[0.39,1.02]
Subtotal (95% CI)	**45059**	**44609**		**100%**	**1.1[0.97,1.26]**
Total events: 3450 (Higher omega 3), 3201 (Lower omega 3)					
Heterogeneity: Tau^2=0.06; Chi^2=125.02, df=32(P<0.0001); I^2=74.4%					
Test for overall effect: Z=1.44(P=0.15)					
3.3.6 Skin problems (itching, rashes)					
AREDS2 2014	8/2147	7/2056		15.77%	1.09[0.4,3.01]
DREAM Asbell 2018	3/349	0/186		5.05%	3.74[0.19,72.02]
EPE-A 2014	4/168	3/75		12%	0.6[0.14,2.59]
JELIS 2007	160/9326	65/9319		21.29%	2.46[1.85,3.28]
Lorenz-Meyer 1996	2/70	4/63		10.67%	0.45[0.09,2.37]
Risk & Prevention 2013	8/6239	17/6266		17.3%	0.47[0.2,1.09]
Sandhu 2016	0/54	3/53		5.1%	0.14[0.01,2.65]
SCIMO 1999	1/112	0/111		4.49%	2.97[0.12,72.21]
Tande 2016	7/64	1/63		8.34%	6.89[0.87,54.4]
Subtotal (95% CI)	**18529**	**18192**		**100%**	**1.11[0.52,2.37]**
Total events: 193 (Higher omega 3), 100 (Lower omega 3)					
Heterogeneity: Tau^2=0.68; Chi^2=24.84, df=8(P=0); I^2=67.79%					
Test for overall effect: Z=0.27(P=0.79)					
3.3.7 Headache or worsening migraine					
DREAM Asbell 2018	4/349	1/186		5.32%	2.13[0.24,18.94]
EPE-A 2014	1/168	0/75		2.5%	1.35[0.06,32.74]
EPIC-1 2008	12/187	10/184		38.31%	1.18[0.52,2.67]
EPIC-2 2008	12/189	20/188		53.87%	0.6[0.3,1.19]
Subtotal (95% CI)	**893**	**633**		**100%**	**0.85[0.51,1.4]**
Total events: 29 (Higher omega 3), 31 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=2.41, df=3(P=0.49); I^2=0%					
Test for overall effect: Z=0.65(P=0.52)					
3.3.8 Reflux					



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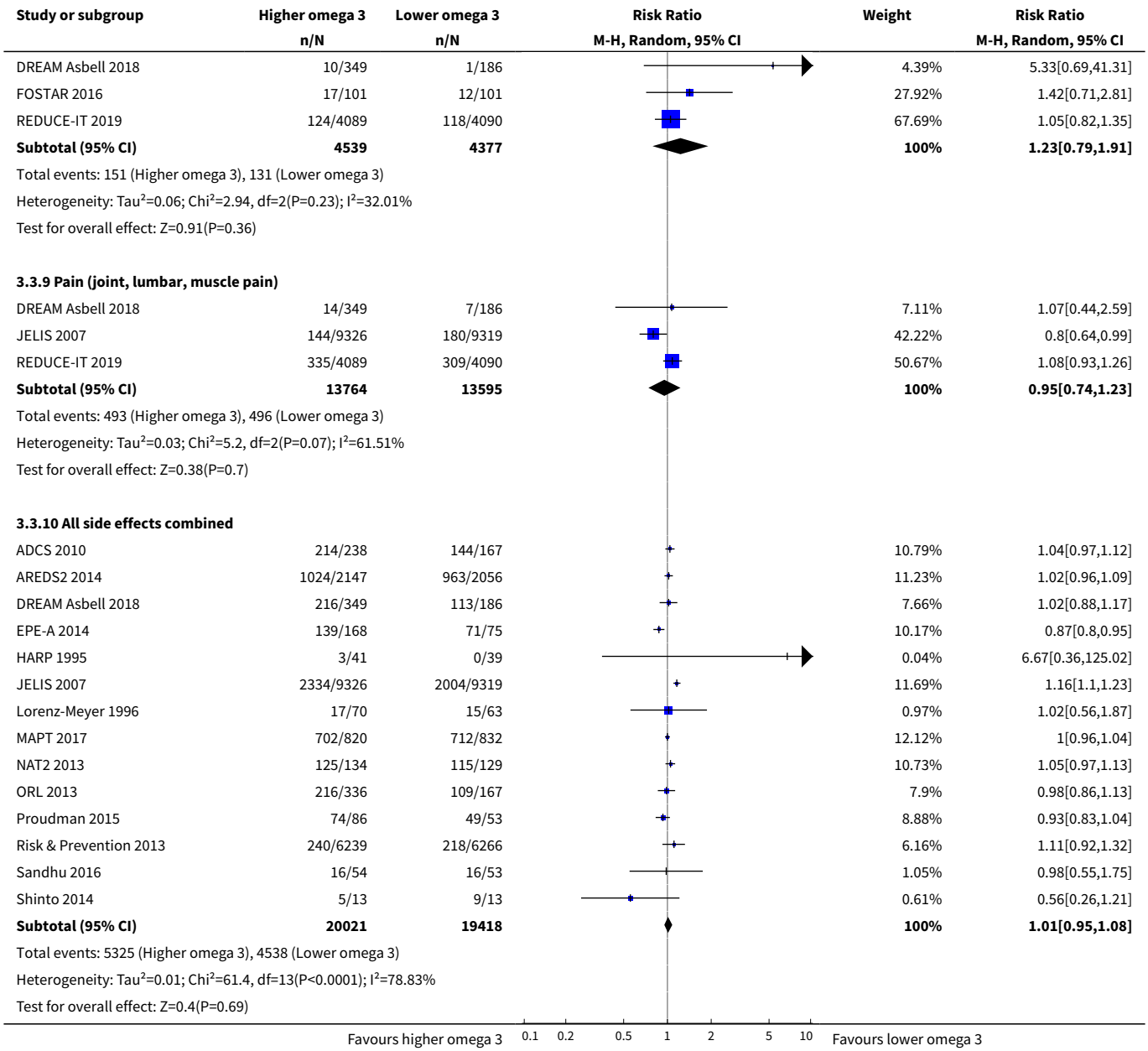
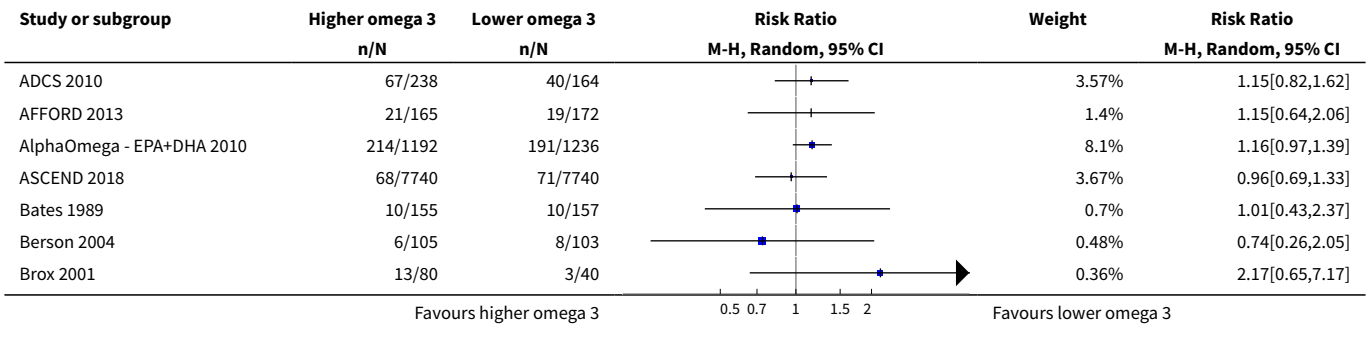


Analysis 3.4. Comparison 3 High vs low LCn3 omega-3 fats (tertiary outcomes), Outcome 4 Dropouts - LCn3.



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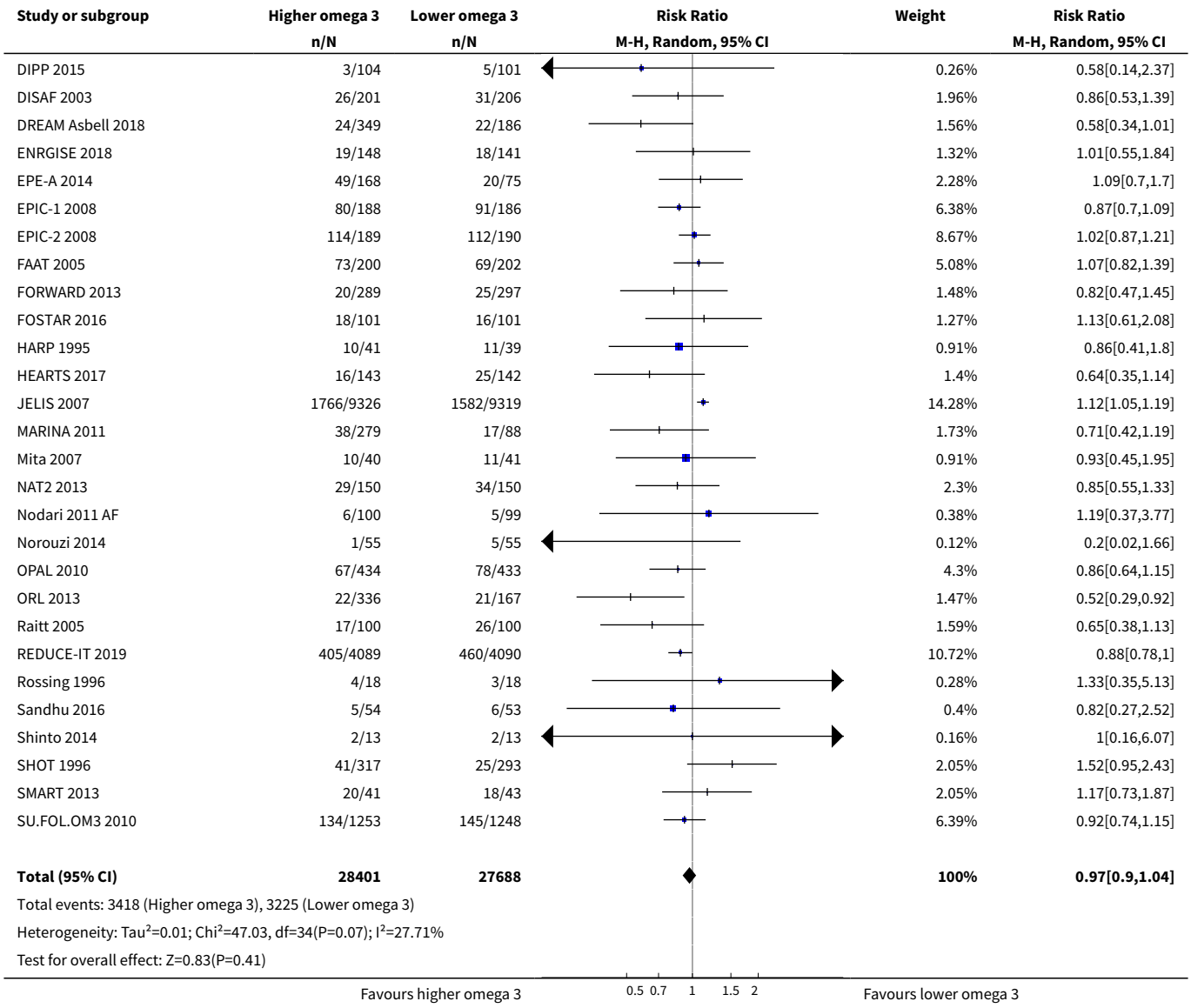

Comparison 4. High vs low ALA omega-3 fat (primary outcomes)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality (overall) - ALA	5	19327	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.84, 1.20]
2 All-cause mortality - ALA - sensitivity analysis (SA) fixed-effect	5	19327	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.85, 1.21]
3 All-cause mortality - ALA - SA by summary risk of bias	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Low risk of bias	3	5213	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.72, 1.45]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 Moderate/high risk of bias	2	14114	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.71, 1.67]
4 All-cause mortality - ALA - SA by compliance and study size	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 SA - low risk of compliance bias	3	5811	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.68, 1.63]
4.2 SA - 100+ randomised	5	19327	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.84, 1.20]
5 All-cause mortality - ALA - subgroup by dose	5	19327	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.84, 1.20]
5.1 ALA low < 5 g/d	1	4837	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.80, 1.19]
5.2 ALA high ≥ 5 g/d	4	14490	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.77, 1.75]
6 All-cause mortality - ALA - subgroup by replacement	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 ALA replacing SFA	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 ALA replacing MUFA	1	4837	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.80, 1.19]
6.3 ALA replacing n-6	2	13672	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.48, 3.86]
6.4 ALA replacing CHO	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.5 ALA replacing nil/low n-3 placebo	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.6 ALA replacement unclear	2	818	Risk Ratio (M-H, Random, 95% CI)	2.78 [0.29, 26.49]
7 All cause mortality - ALA - subgroup by intervention type	5	19327	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.84, 1.20]
7.1 Dietary advice	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 Supplemental foods	4	5921	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.82, 1.21]
7.3 Supplements (capsule)	1	13406	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.70, 1.64]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.4 Any combination	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8 All-cause mortality - ALA - subgroup by duration	5	19327	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.84, 1.20]
8.1 Medium duration 1 to < 2 years in study	2	13516	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.71, 1.67]
8.2 Medium-long duration: 2 to < 4 years in study	3	5811	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.68, 1.63]
8.3 Long duration: ≥ 4 years in study	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9 All-cause mortality - ALA - subgroup by primary or secondary prevention	5	19327	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.84, 1.20]
9.1 Primary CVD prevention	3	14380	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.75, 1.74]
9.2 Secondary CVD prevention	2	4947	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.81, 1.19]
10 All-cause mortality - ALA - subgroup by statin use	5	19327	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.84, 1.20]
10.1 ALA - ≥ 50% of control group on statins	2	4947	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.81, 1.19]
10.2 ALA - < 50% of control group on statins	3	14380	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.75, 1.74]
11 Cardiovascular mortality (overall) - ALA	4	18619	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.74, 1.25]
12 CVD mortality - ALA - SA fixed-effect	4	18619	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.74, 1.25]
13 CVD mortality - ALA - SA by summary risk of bias	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 Low risk of bias	3	5213	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.70, 1.28]
13.2 Moderate/high risk of bias	1	13406	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.58, 1.70]
14 CVD mortality - ALA - SA by compliance and study size	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 SA - low risk of compliance bias	2	5103	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.70, 1.27]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.2 SA - 100+ randomised	4	18619	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.74, 1.25]
15 CVD mortality - ALA - subgroup by dose	4	18619	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.74, 1.25]
15.1 ALA low < 5 g/d	1	4837	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.69, 1.27]
15.2 ALA high ≥ 5 g/d	3	13782	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.62, 1.73]
16 CVD mortality - ALA - subgroup by replacement	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
16.1 N-3 replacing SFA	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.2 N-3 replacing MUFA	1	4837	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.69, 1.27]
16.3 N-3 replacing n-6	2	13672	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.60, 1.70]
16.4 N-3 replacing carbohydrates/sugars	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.5 N-3 replacing nil/low n-3 placebo	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.6 Replacement unclear	1	110	Risk Ratio (M-H, Random, 95% CI)	2.69 [0.11, 64.74]
17 CVD mortality - ALA - subgroup by intervention type	4	18619	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.74, 1.25]
17.1 Dietary advice	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.2 Supplemental foods	3	5213	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.70, 1.28]
17.3 Supplements (capsule)	1	13406	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.58, 1.70]
17.4 Any combination	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
18 CVD mortality - ALA - subgroup by duration	4	18619	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.74, 1.25]
18.1 Medium duration 1 to < 2 years in study	2	13516	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.61, 1.73]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.2 Medium-long duration: 2 to < 4 years in study	2	5103	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.70, 1.27]
18.3 Long duration: ≥ 4 years in study	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
19 CVD mortality - ALA - subgroup by primary or secondary prevention	4	18619	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.74, 1.25]
19.1 Primary prevention	1	13406	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.58, 1.70]
19.2 Secondary prevention	3	5213	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.70, 1.28]
20 CVD mortality - ALA - subgroup by statin uses	4	18619	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.74, 1.25]
20.1 ALA - ≥ 50% of control group on statins	2	4947	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.70, 1.28]
20.2 ALA - < 50% of control group on statins	2	13672	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.60, 1.70]
21 Cardiovascular events (overall) - ALA	5	19327	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.83, 1.07]
22 CVD events - ALA - SA fixed-effect	5	19327	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.84, 1.07]
23 CVD events - ALA - SA by summary risk of bias	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
23.1 Low risk of bias	3	5213	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.79, 1.04]
23.2 Moderate/high risk of bias	2	14114	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.84, 1.48]
24 CVD events - ALA - SA by compliance and study size	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
24.1 SA - low risk of compliance bias	3	5811	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.79, 1.04]
24.2 SA - 100+ randomised	5	19327	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.83, 1.07]
25 CVD events - ALA - subgroup by dose	5	19327	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.83, 1.07]
25.1 ALA low < 5 g/d	1	4837	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.79, 1.05]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
25.2 ALA high ≥ 5 g/d	4	14490	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.82, 1.40]
26 CVD events - ALA - subgroup by replacement	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
26.1 N-3 replacing SFA	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
26.2 N-3 replacing MUFA	1	4837	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.79, 1.05]
26.3 N-3 replacing n-6	2	13672	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.24, 2.41]
26.4 N-3 replacing carbohydrates/sugars	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
26.5 N-3 replacing nil/low n-3 placebo	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
26.6 Replacement unclear	2	818	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.36, 2.43]
27 CVD events - ALA - subgroup by intervention type	5	19327	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.83, 1.07]
27.1 Dietary advice	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
27.2 Supplemental foods	4	5921	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.79, 1.04]
27.3 Supplements (capsule)	1	13406	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.85, 1.51]
27.4 Any combination	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
28 CVD events - ALA - subgroup by duration	5	19327	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.83, 1.07]
28.1 Medium duration 1 to < 2 years in study	2	13516	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.86, 1.50]
28.2 Medium-long duration: 2 to < 4 years in study	3	5811	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.79, 1.04]
28.3 Long duration: ≥ 4 years in study	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
29 CVD events - ALA - subgroup by primary or secondary prevention	5	19327	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.83, 1.07]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
29.1 Primary prevention	3	14380	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.46, 1.67]
29.2 Secondary prevention	2	4947	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.80, 1.05]
30 CVD events - ALA - subgroup by statin use	5	19327	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.83, 1.07]
30.1 ALA - ≥ 50% of control group on statins	2	4947	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.80, 1.05]
30.2 ALA - < 50% of control group on statins	3	14380	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.46, 1.67]
31 Coronary heart disease mortality (overall) - ALA	3	18353	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.72, 1.26]
32 CHD mortality - ALA - SA fixed-effect	3	18353	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.72, 1.26]
33 CHD mortality - ALA - SA by summary risk of bias	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
33.1 Low risk of bias	2	4947	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.67, 1.30]
33.2 Moderate/high risk of bias	1	13406	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.58, 1.70]
34 CHD mortality - ALA - SA by compliance and study size	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
34.1 SA - low risk of compliance bias	1	4837	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.66, 1.28]
34.2 SA - 100+ randomised	3	18353	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.72, 1.26]
35 CHD mortality - ALA - subgroup by dose	3	18353	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.72, 1.26]
35.1 ALA low < 5 g/d	1	4837	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.66, 1.28]
35.2 ALA high ≥ 5 g/d	2	13516	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.61, 1.73]
36 CHD mortality - ALA - subgroup by replacement	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
36.1 N-3 replacing SFA	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
36.2 Coronary heart mortality-ALA	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
36.3 N-3 replacing MUFA	1	4837	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.66, 1.28]
36.4 N-3 replacing n-6	1	13406	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.58, 1.70]
36.5 N-3 replacing carbohydrates/sugars	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
36.6 N-3 replacing nil/low n-3 placebo	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
36.7 Replacement unclear	1	110	Risk Ratio (M-H, Random, 95% CI)	2.69 [0.11, 64.74]
37 CHD mortality - ALA - subgroup by intervention type	3	18353	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.72, 1.26]
37.1 Dietary advice	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
37.2 Supplemental foods	2	4947	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.67, 1.30]
37.3 Supplements (capsule)	1	13406	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.58, 1.70]
37.4 Any combination	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
38 CHD mortality - ALA - subgroup by duration	3	18353	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.72, 1.26]
38.1 Medium duration 1 to < 2 years in study	2	13516	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.61, 1.73]
38.2 Medium-long duration: 2 to < 4 years in study	1	4837	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.66, 1.28]
38.3 Long duration: ≥ 4 years in study	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
39 CHD mortality - ALA - subgroup by primary or secondary prevention	3	18353	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.72, 1.26]
39.1 Primary prevention of CVD	1	13406	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.58, 1.70]
39.2 Secondary prevention of CVD	2	4947	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.67, 1.30]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
40 CHD mortality - ALA - subgroup by statin use	3	18353	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.72, 1.26]
40.1 ALA - ≥ 50% of control group on statins	2	4947	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.67, 1.30]
40.2 ALA - < 50% of control group on statins	1	13406	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.58, 1.70]
41 CHD mortality - ALA - subgroup by CAD history	3	18353	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.72, 1.26]
41.1 Previous CAD	1	4837	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.66, 1.28]
41.2 No previous CAD	2	13516	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.61, 1.73]
42 Coronary heart disease events (overall) - ALA	4	19061	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.82, 1.22]
43 CHD events - ALA - SA fixed-effect	4	19061	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.82, 1.21]
44 CHD events - ALA - SA by summary risk of bias	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
44.1 Low risk of bias	2	4947	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.71, 1.15]
44.2 Moderate/high risk of bias	2	14114	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.86, 1.67]
45 CHD events - ALA - SA by compliance and study size	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
45.1 SA - low risk of compliance bias	2	5545	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.73, 1.17]
45.2 SA - 100+ randomised	4	19061	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.82, 1.22]
46 CHD events - ALA - subgroup by dose	4	19061	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.82, 1.22]
46.1 ALA low < 5 g/d	1	4837	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.72, 1.17]
46.2 ALA high ≥ 5 g/d	3	14224	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.84, 1.61]
47 CHD events - ALA - subgroup by replacement	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
47.1 N-3 replacing SFA	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
47.2 N-3 replacing MUFA	1	4837	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.72, 1.17]
47.3 N-3 replacing n-6	1	13406	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.85, 1.65]
47.4 N-3 replacing carbohydrates/sugars	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
47.5 N-3 replacing nil/low n-3 placebo	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
47.6 Replacement unclear	2	818	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.08, 5.81]
48 CHD events - ALA - subgroup by intervention type	4	19061	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.82, 1.22]
48.1 Dietary advice	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
48.2 Supplemental foods	3	5655	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.72, 1.16]
48.3 Supplements (capsule)	1	13406	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.85, 1.65]
48.4 Any combination	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
49 CHD events - ALA - subgroup by duration	4	19061	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.82, 1.22]
49.1 Medium duration 1 to < 2 years in study	2	13516	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.34, 2.58]
49.2 Medium-long duration: 2 to < 4 years in study	2	5545	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.73, 1.17]
49.3 Long duration: ≥ 4 years in study	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
50 CHD events - ALA - subgroup by primary or secondary prevention	4	19061	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.82, 1.22]
50.1 Primary prevention	2	14114	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.86, 1.67]
50.2 Secondary prevention	2	4947	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.71, 1.15]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
51 CHD events - ALA - subgroup by statin use	4	19061	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.82, 1.22]
51.1 ALA - ≥ 50% of control group on statins	2	4947	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.71, 1.15]
51.2 ALA - < 50% of control group on statins	2	14114	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.86, 1.67]
52 CHD events - ALA - subgroup by CAD history	4	19061	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.82, 1.22]
52.1 Previous CAD	1	4837	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.72, 1.17]
52.2 No previous CAD	3	14224	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.84, 1.61]
53 Stroke (overall) - ALA	5	19327	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.66, 2.01]
54 Stroke - ALA - SA fixed-effect	5	19327	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.71, 2.13]
55 Stroke - ALA - SA by summary risk of bias	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
55.1 Low risk of bias	3	5213	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.45, 2.09]
55.2 Moderate/high risk of bias	2	14114	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.62, 3.13]
56 Stroke - ALA - SA by compliance and study size	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
56.1 SA - low risk of compliance bias	3	5811	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.39, 1.87]
56.2 SA - 100+ randomised	5	19327	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.66, 2.01]
57 Stroke - ALA - subgroup by dose	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
57.1 ALA low < 5 g/d	1	4837	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.39, 2.15]
57.2 ALA high ≥ 5 g/d	4	14490	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.65, 2.85]
58 Stroke - ALA - subgroup by replacement	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
58.1 N-3 replacing SFA	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
58.2 N-3 replacing MUFA	1	4837	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.39, 2.15]
58.3 N-3 replacing n-6	2	13672	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.53, 3.01]
58.4 N-3 replacing carbohydrates/sugars	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
58.5 N-3 replacing nil/low n-3 placebo	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
58.6 Replacement unclear	2	818	Risk Ratio (M-H, Random, 95% CI)	1.79 [0.31, 10.17]
59 Stroke - ALA - subgroup by intervention type	5	19327	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.66, 2.01]
59.1 Dietary advice	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
59.2 Supplemental foods	4	5921	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.46, 2.03]
59.3 Supplements (capsule)	1	13406	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.62, 3.36]
59.4 Any combination	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
60 Stroke - ALA - subgroup by duration	5	19327	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.66, 2.01]
60.1 Medium duration 1 to < 2 years in study	2	13516	Risk Ratio (M-H, Random, 95% CI)	1.56 [0.70, 3.44]
60.2 Medium-long duration: 2 to < 4 years in study	3	5811	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.39, 1.87]
60.3 Long duration: ≥ 4 years in study	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
61 Stroke - ALA - subgroup by primary or secondary prevention	5	19327	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.66, 2.01]
61.1 Primary prevention	3	14380	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.57, 2.74]
61.2 Secondary prevention	2	4947	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.47, 2.34]
62 Stroke - ALA - subgroup by statin use	5	19327	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.71, 2.18]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
62.1 ALA - ≥ 50% of control group on statins	2	4947	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.56, 2.77]
62.2 ALA - < 50% of control group on statins	3	14380	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.57, 2.74]
63 Stroke - ALA - subgroup by stroke type	3	13782	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.65, 3.01]
63.1 Ischaemic stroke - ALA	3	13782	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.65, 3.01]
63.2 Haemorrhagic stroke - ALA	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
64 Arrythmia (overall) - ALA	2	4912	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.55, 0.97]
64.1 ALA - new arrhythmias	1	4837	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.57, 1.10]
64.2 ALA - recurrent arrhythmias	1	75	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.35, 1.03]
65 Arrythmia - ALA - SA fixed-effect	2	4912	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.57, 1.00]
66 Arrhythmia - ALA - SA by summary risk of bias	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
66.1 Low risk of bias	1	4837	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.57, 1.10]
66.2 Moderate/high risk of bias	1	75	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.35, 1.03]
67 Arrythmia - ALA - SA by compliance and study size	1	9674	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.63, 1.00]
67.1 SA - low risk of compliance bias	1	4837	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.57, 1.10]
67.2 SA - 100+ randomised	1	4837	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.57, 1.10]

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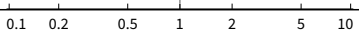
Analysis 4.1. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 1 All-cause mortality (overall) - ALA.

Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 fats n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
AlphaOmega - ALA 2010	182/2409	188/2428		81.74%	0.98[0.8,1.19]
FLAX-PAD 2013	1/58	0/52		0.31%	2.69[0.11,64.74]
MARGARIN 2002	3/109	1/157		0.62%	4.32[0.46,41]
Norwegian 1968	43/6716	40/6690		17.02%	1.07[0.7,1.64]
WAHA 2016	1/362	0/346		0.31%	2.87[0.12,70.16]
Total (95% CI)	**9654**	**9673**		**100%**	**1.01[0.84,1.2]**
Total events: 230 (Favours higher omega 3), 229 (Lower omega 3 fats)					
Heterogeneity: Tau^2=0; Chi^2=2.57, df=4(P=0.63); I^2=0%					
Test for overall effect: Z=0.08(P=0.94)					

Favours higher omega 3 — Favours lower omega 3

Analysis 4.2. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 2 All-cause mortality - ALA - sensitivity analysis (SA) fixed-effect.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
AlphaOmega - ALA 2010	182/2409	188/2428		81.7%	0.98[0.8,1.19]
FLAX-PAD 2013	1/58	0/52		0.23%	2.69[0.11,64.74]
MARGARIN 2002	3/109	1/157		0.36%	4.32[0.46,41]
Norwegian 1968	43/6716	40/6690		17.49%	1.07[0.7,1.64]
WAHA 2016	1/362	0/346		0.22%	2.87[0.12,70.16]
Total (95% CI)	**9654**	**9673**		**100%**	**1.01[0.85,1.21]**
Total events: 230 (Higher omega 3), 229 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=2.57, df=4(P=0.63); I^2=0%					
Test for overall effect: Z=0.14(P=0.89)					



Favours higher omega 3 — Favours lower omega 3

Analysis 4.3. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 3 All-cause mortality - ALA - SA by summary risk of bias.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.3.1 Low risk of bias					
AlphaOmega - ALA 2010	182/2409	188/2428		96.41%	0.98[0.8,1.19]
FLAX-PAD 2013	1/58	0/52		1.2%	2.69[0.11,64.74]
MARGARIN 2002	3/109	1/157		2.38%	4.32[0.46,41]
Subtotal (95% CI)	**2576**	**2637**		**100%**	**1.02[0.72,1.45]**
Total events: 186 (Higher omega 3), 189 (Lower omega 3)					
Heterogeneity: Tau^2=0.02; Chi^2=2.05, df=2(P=0.36); I^2=2.55%					
Test for overall effect: Z=0.13(P=0.9)					

Favours high ALA — Favours low ALA

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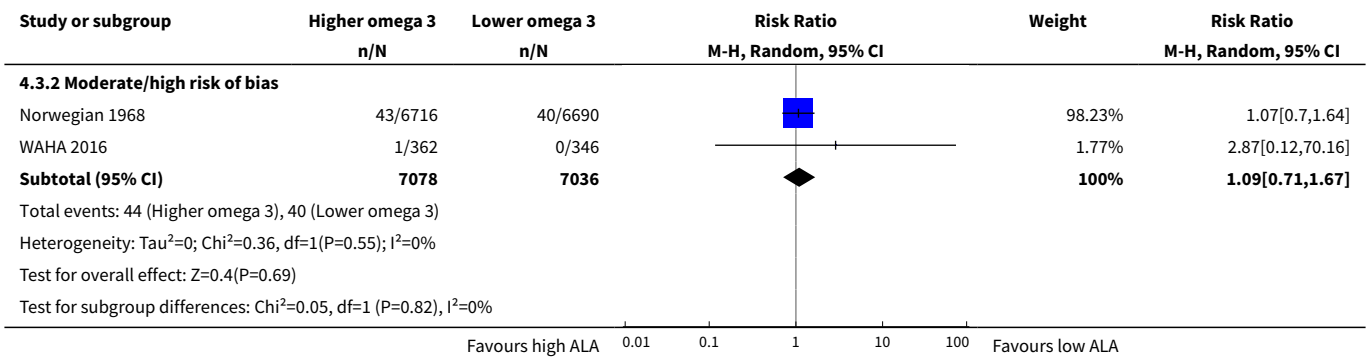
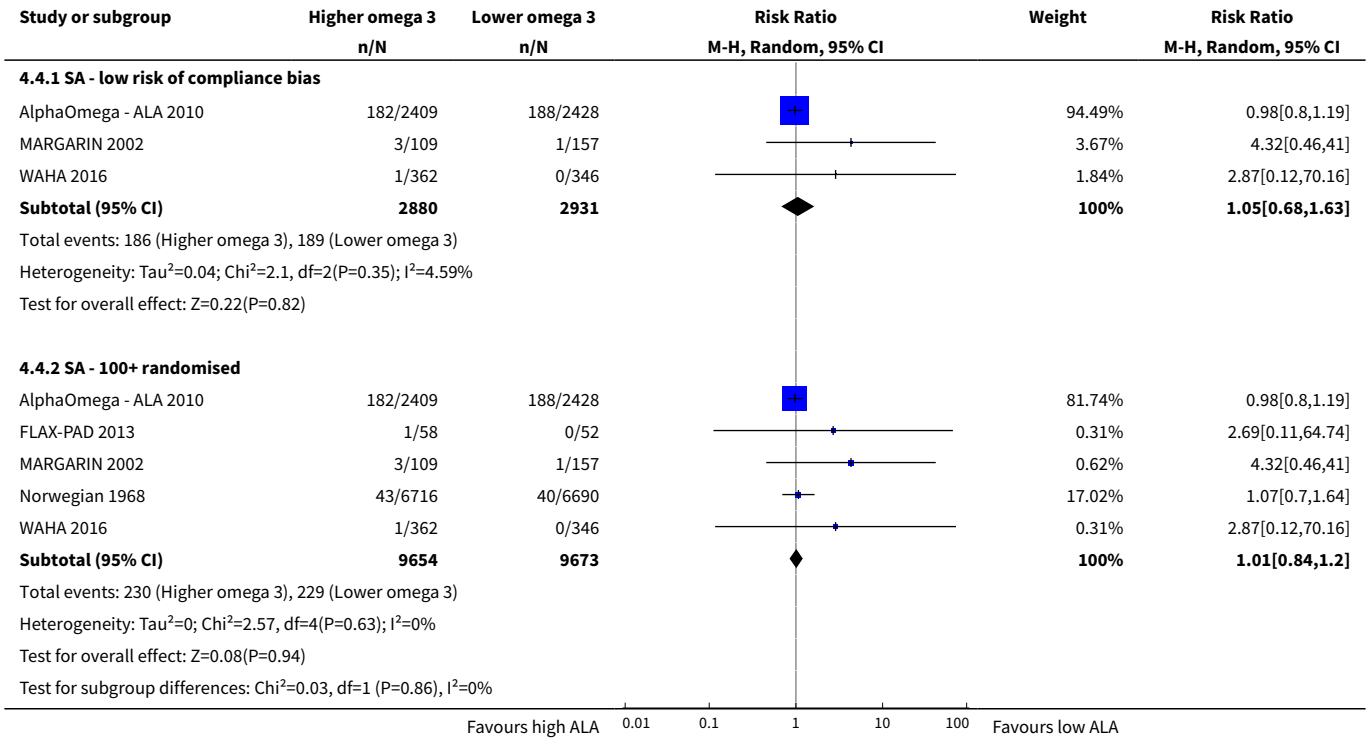
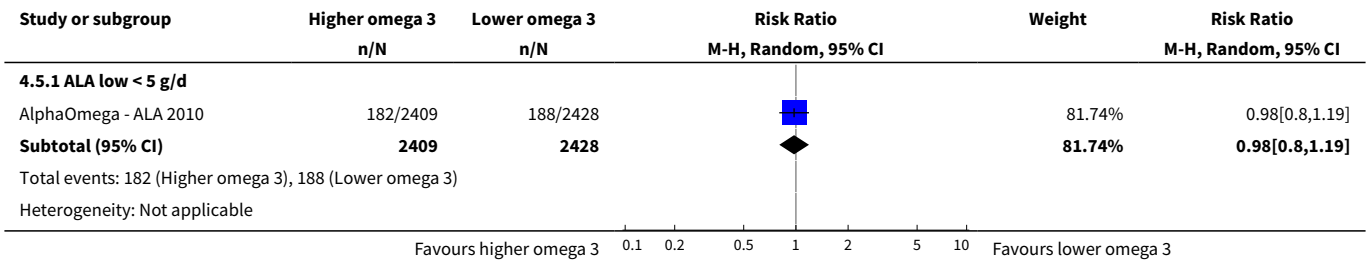


Analysis 4.4. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 4 All-cause mortality - ALA - SA by compliance and study size.



Analysis 4.5. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 5 All-cause mortality - ALA - subgroup by dose.



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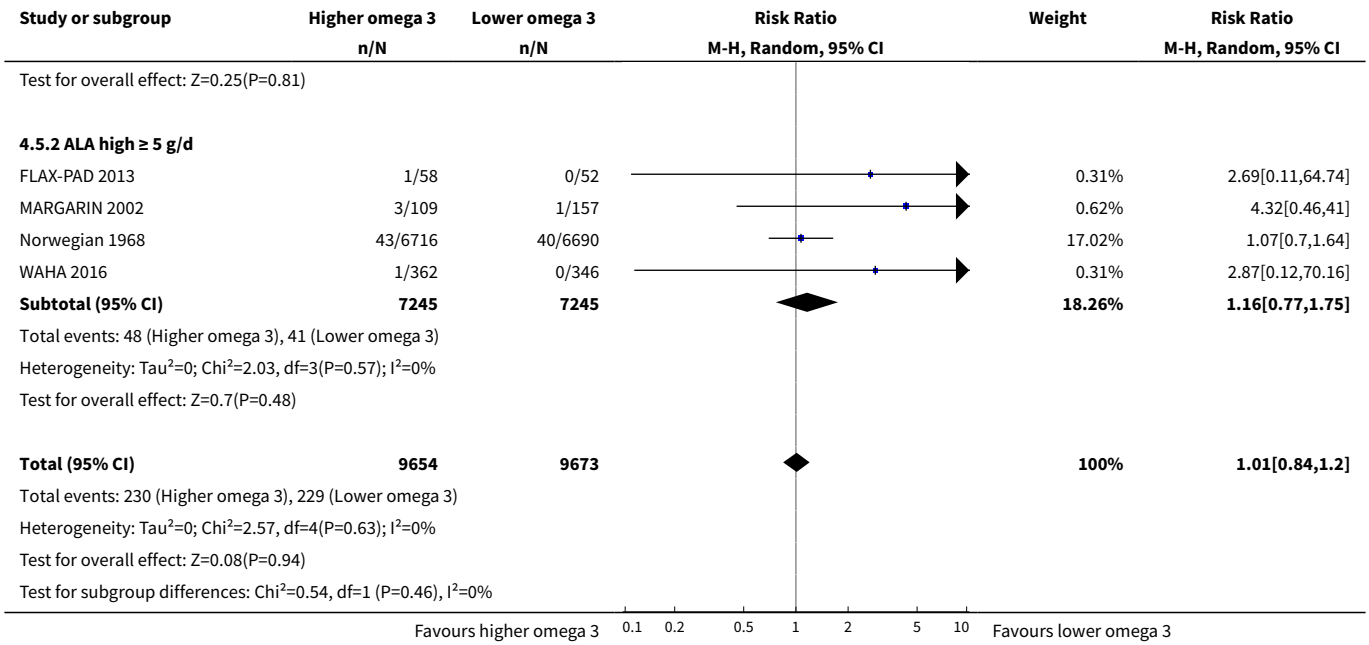
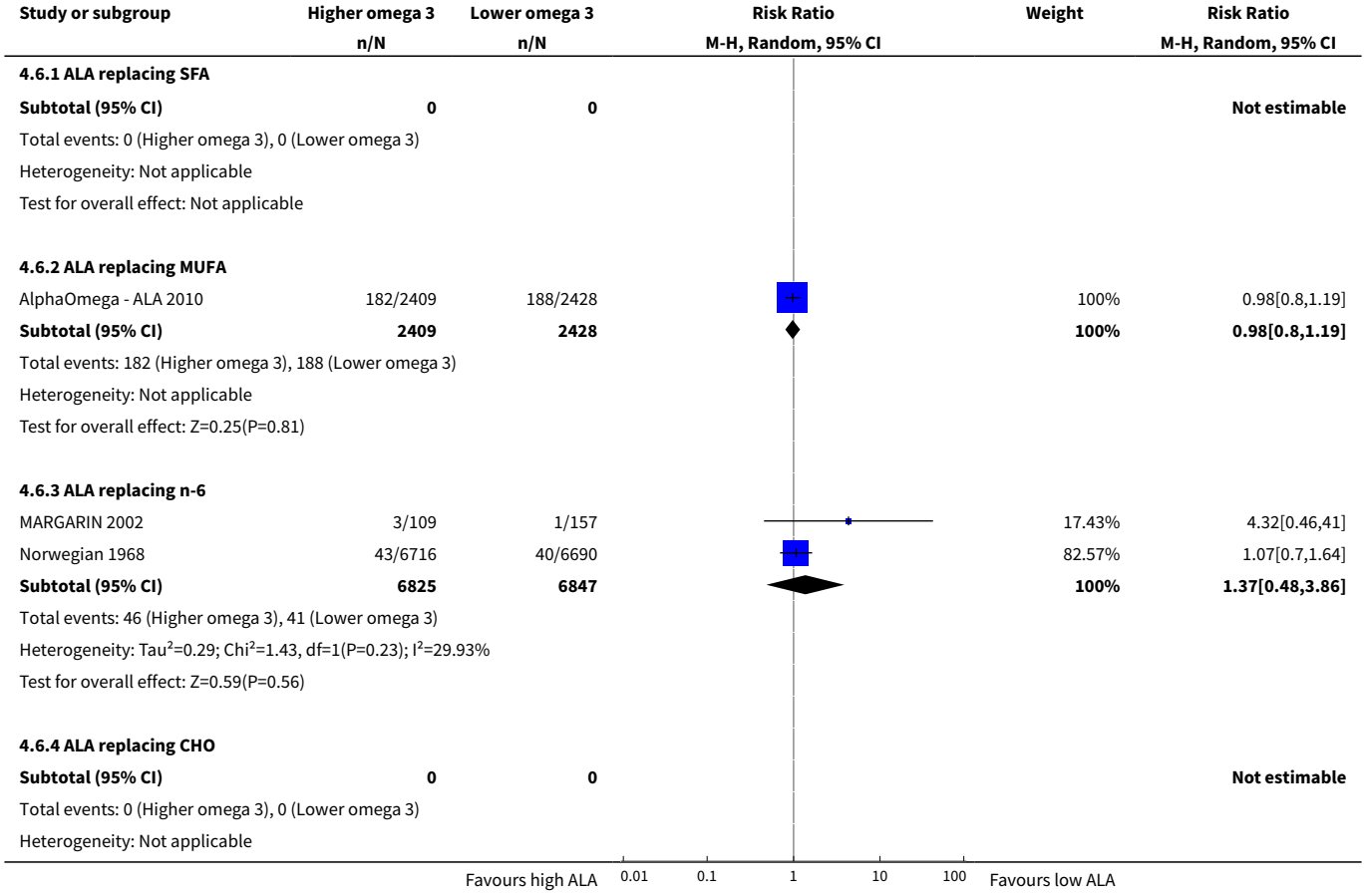


Analysis 4.6. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 6 All-cause mortality - ALA - subgroup by replacement.



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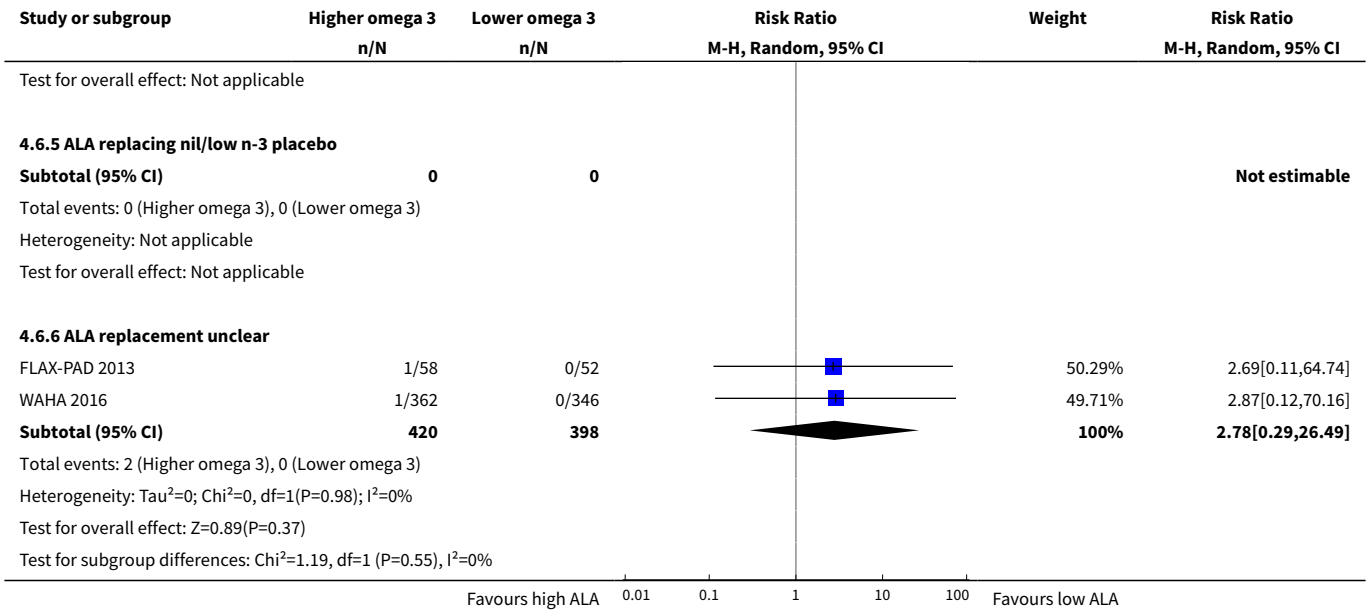
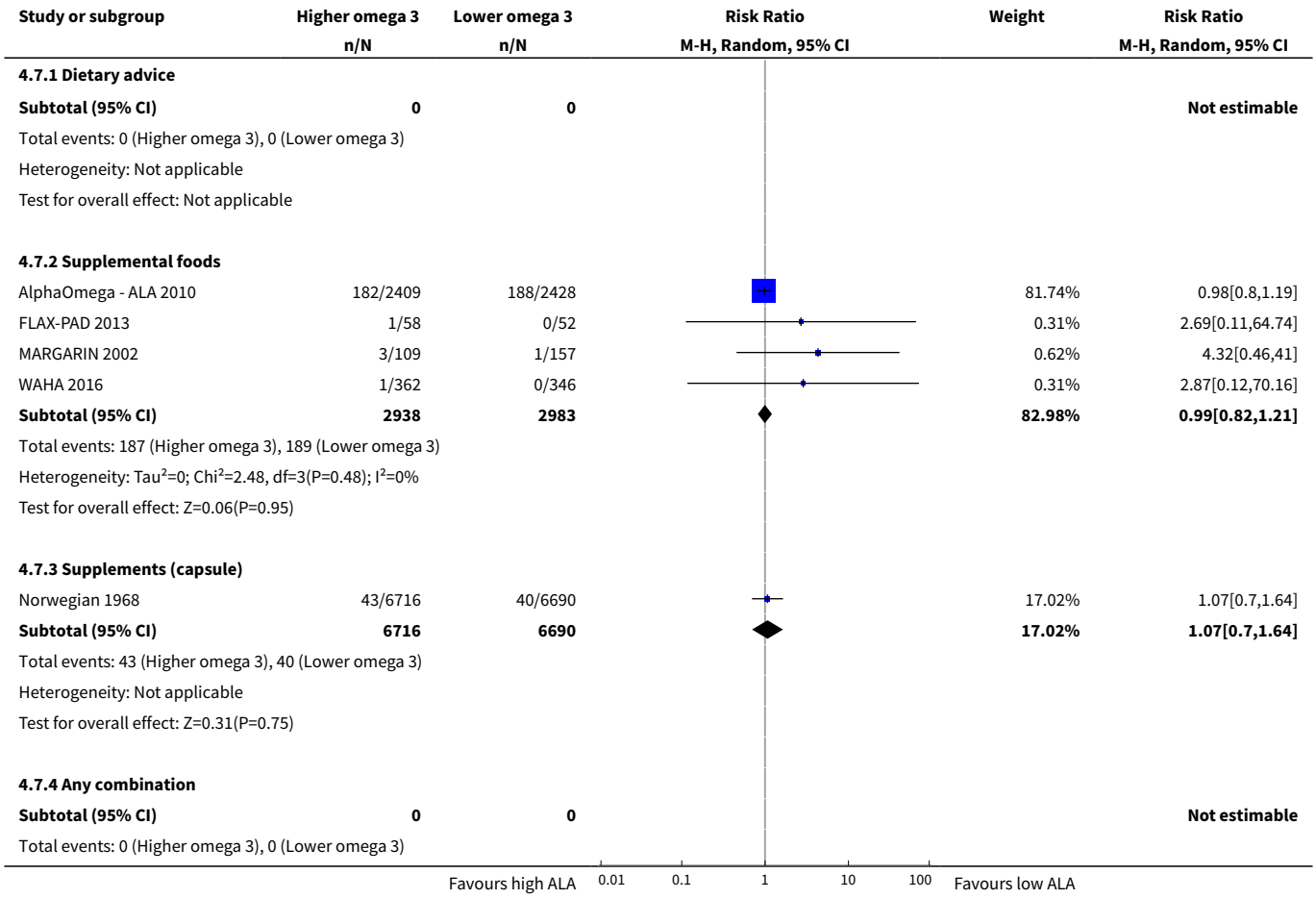


Analysis 4.7. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 7 All cause mortality - ALA - subgroup by intervention type.



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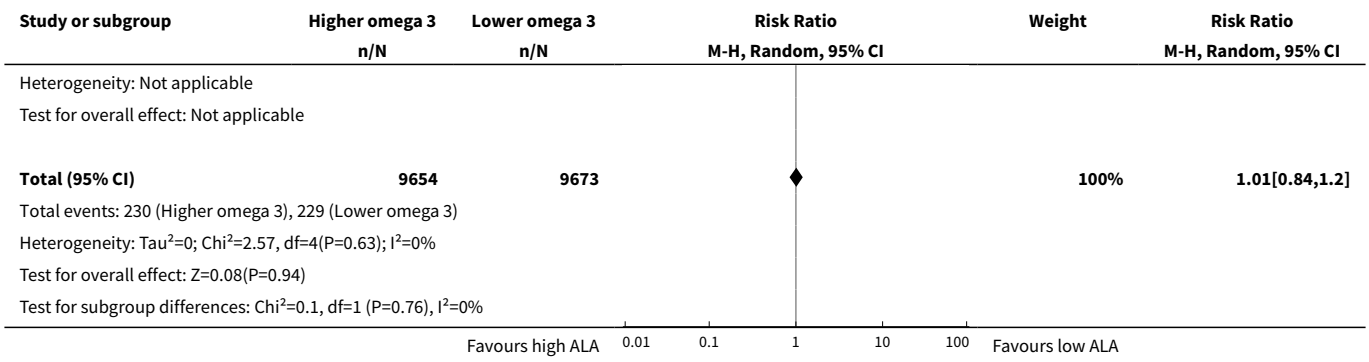
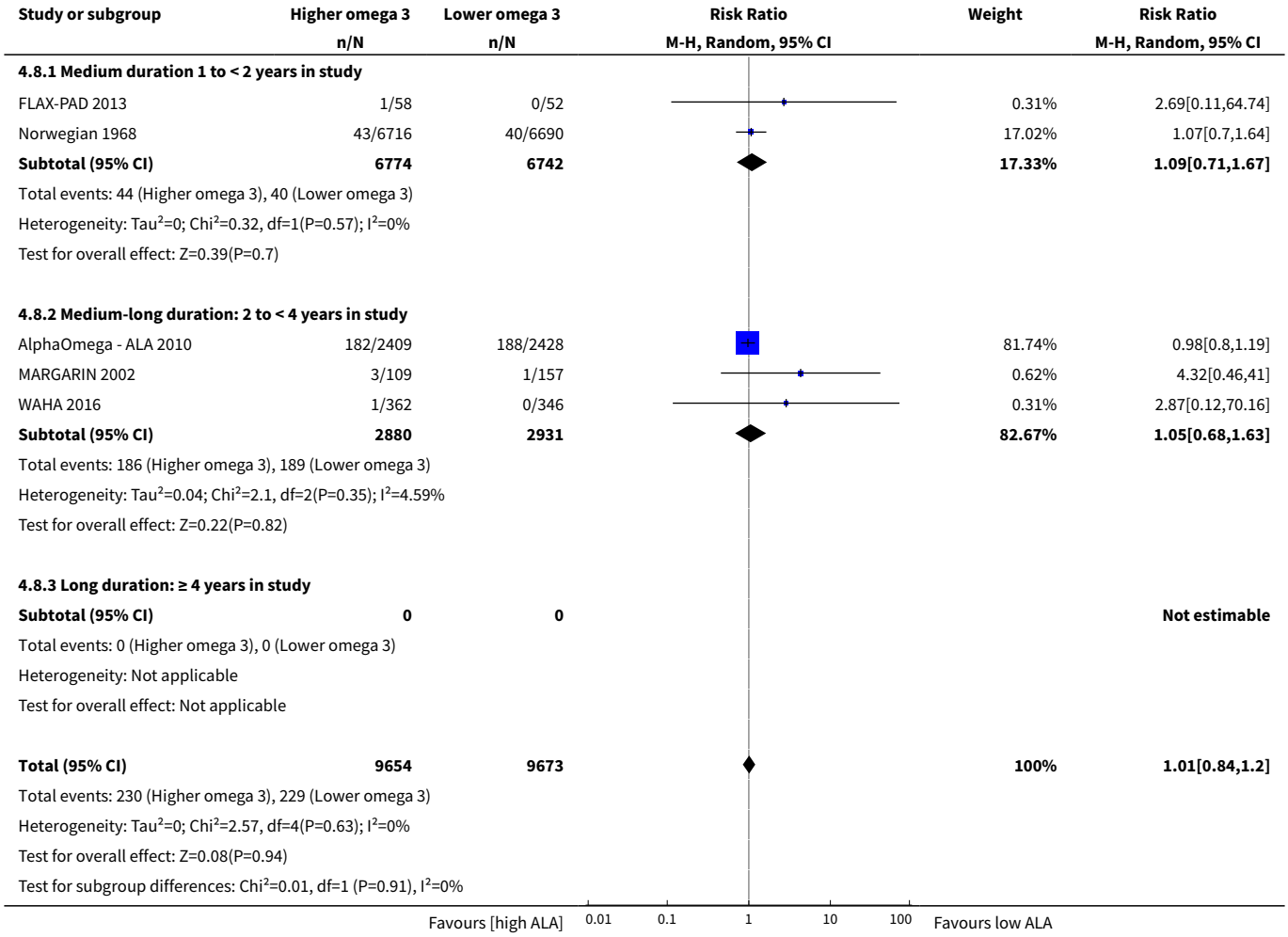


Analysis 4.8. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 8 All-cause mortality - ALA - subgroup by duration.



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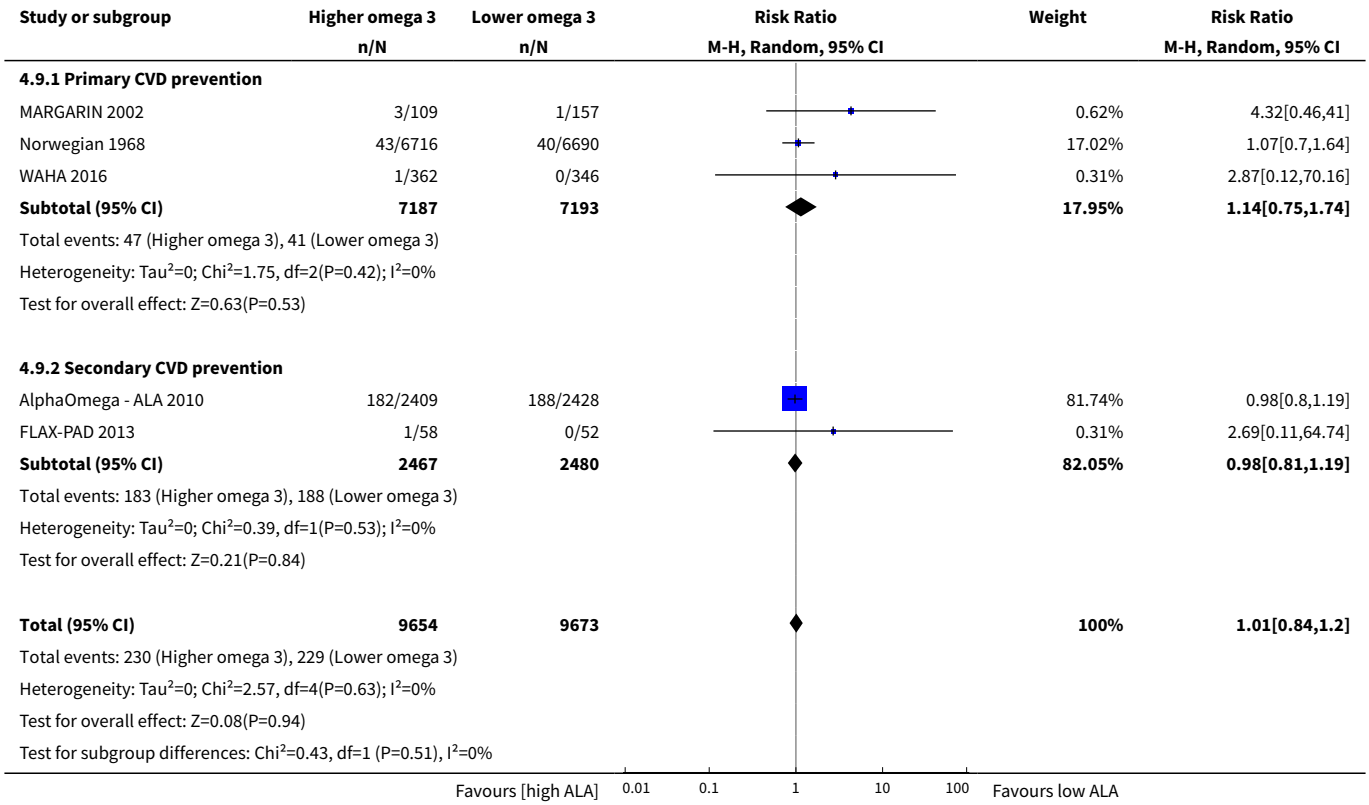
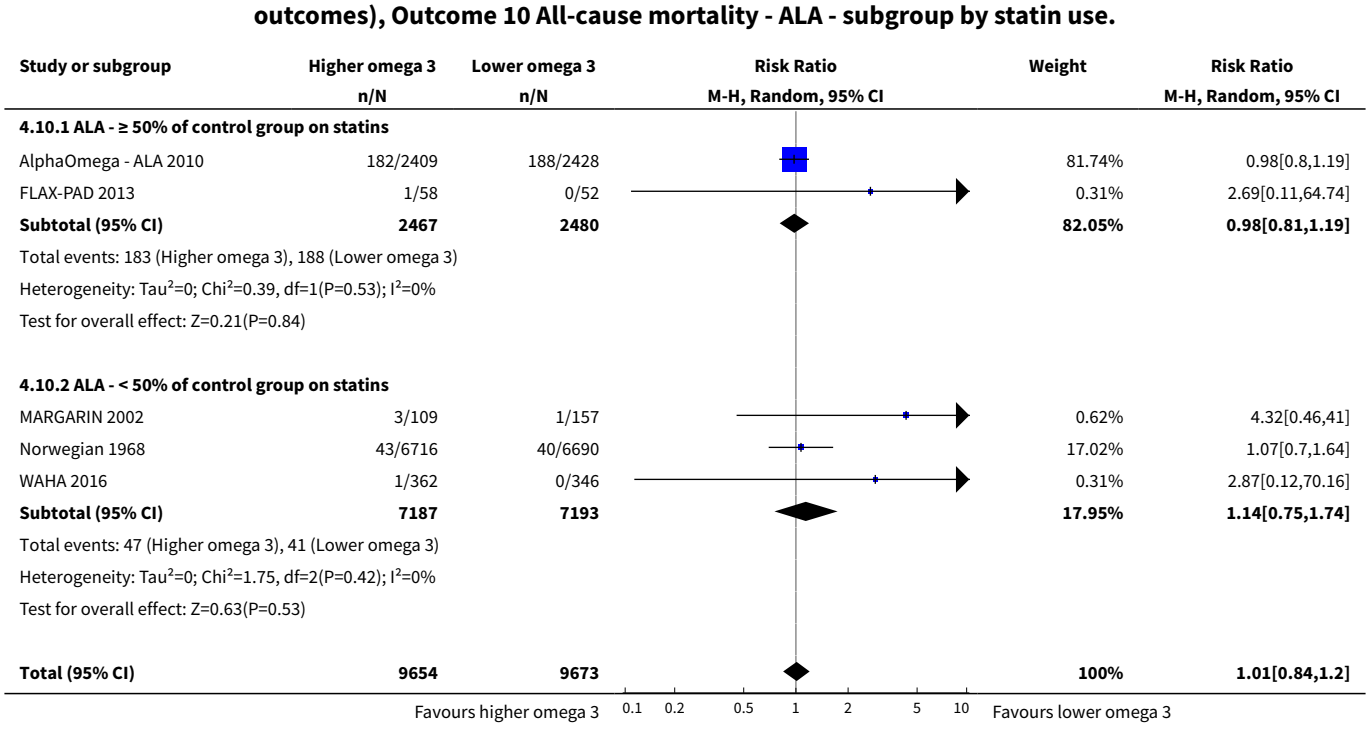
Analysis 4.9. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 9 All-cause mortality - ALA - subgroup by primary or secondary prevention.



Analysis 4.10. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 10 All-cause mortality - ALA - subgroup by statin use.



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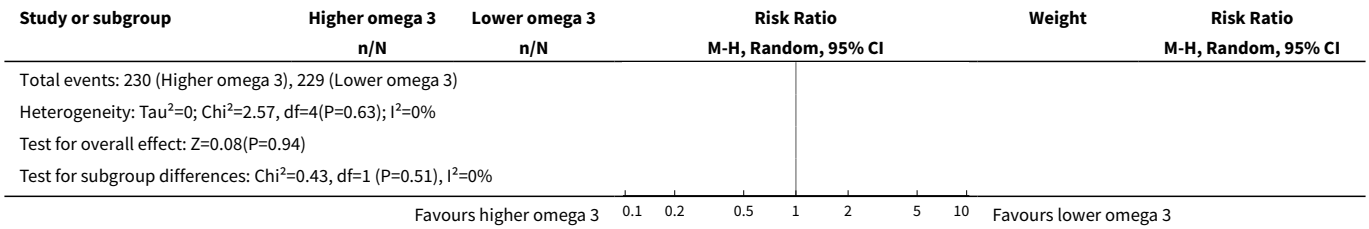
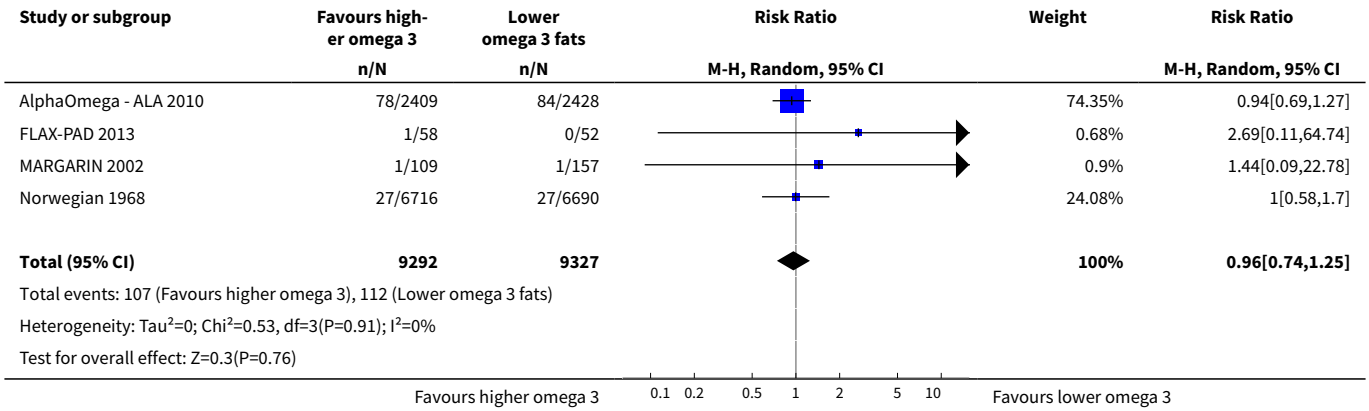
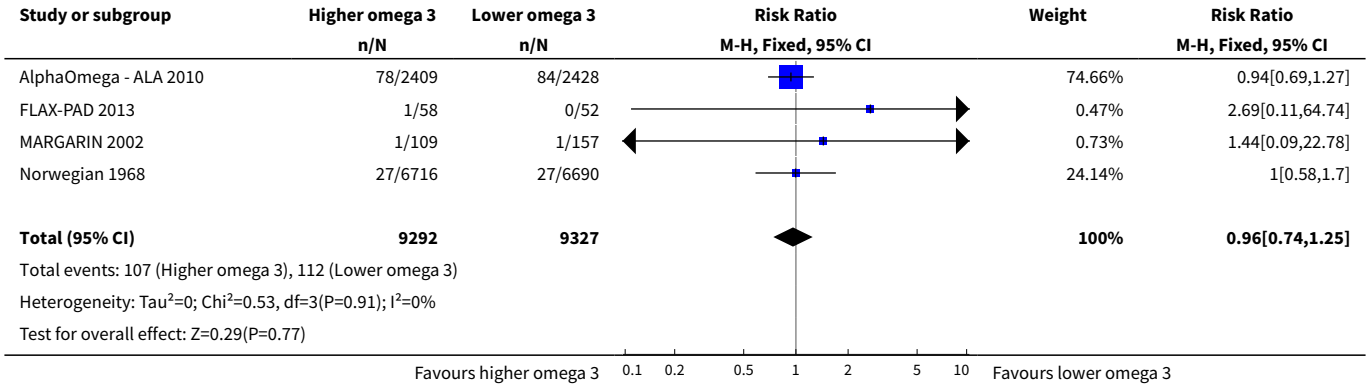


Analysis 4.11. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 11 Cardiovascular mortality (overall) - ALA.



Analysis 4.12. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 12 CVD mortality - ALA - SA fixed-effect.



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Analysis 4.13. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 13 CVD mortality - ALA - SA by summary risk of bias.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.13.1 Low risk of bias					
AlphaOmega - ALA 2010	78/2409	84/2428		97.93%	0.94[0.69,1.27]
FLAX-PAD 2013	1/58	0/52		0.89%	2.69[0.11,64.74]
MARGARIN 2002	1/109	1/157		1.18%	1.44[0.09,22.78]
Subtotal (95% CI)	**2576**	**2637**		**100%**	**0.95[0.7,1.28]**
Total events: 80 (Higher omega 3), 85 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.51, df=2(P=0.77); I^2=0%					
Test for overall effect: Z=0.34(P=0.74)					
4.13.2 Moderate/high risk of bias					
Norwegian 1968	27/6716	27/6690		100%	1[0.58,1.7]
Subtotal (95% CI)	**6716**	**6690**		**100%**	**1[0.58,1.7]**
Total events: 27 (Higher omega 3), 27 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.01(P=0.99)					
Test for subgroup differences: Chi^2=0.02, df=1 (P=0.88), I^2=0%					

Analysis 4.14. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 14 CVD mortality - ALA - SA by compliance and study size.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.14.1 SA - low risk of compliance bias					
AlphaOmega - ALA 2010	78/2409	84/2428		98.81%	0.94[0.69,1.27]
MARGARIN 2002	1/109	1/157		1.19%	1.44[0.09,22.78]
Subtotal (95% CI)	**2518**	**2585**		**100%**	**0.94[0.7,1.27]**
Total events: 79 (Higher omega 3), 85 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.09, df=1(P=0.76); I^2=0%					
Test for overall effect: Z=0.4(P=0.69)					
4.14.2 SA - 100+ randomised					
AlphaOmega - ALA 2010	78/2409	84/2428		74.35%	0.94[0.69,1.27]
FLAX-PAD 2013	1/58	0/52		0.68%	2.69[0.11,64.74]
MARGARIN 2002	1/109	1/157		0.9%	1.44[0.09,22.78]
Norwegian 1968	27/6716	27/6690		24.08%	1[0.58,1.7]
Subtotal (95% CI)	**9292**	**9327**		**100%**	**0.96[0.74,1.25]**
Total events: 107 (Higher omega 3), 112 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.53, df=3(P=0.91); I^2=0%					
Test for overall effect: Z=0.3(P=0.76)					
Test for subgroup differences: Chi^2=0.01, df=1 (P=0.92), I^2=0%					

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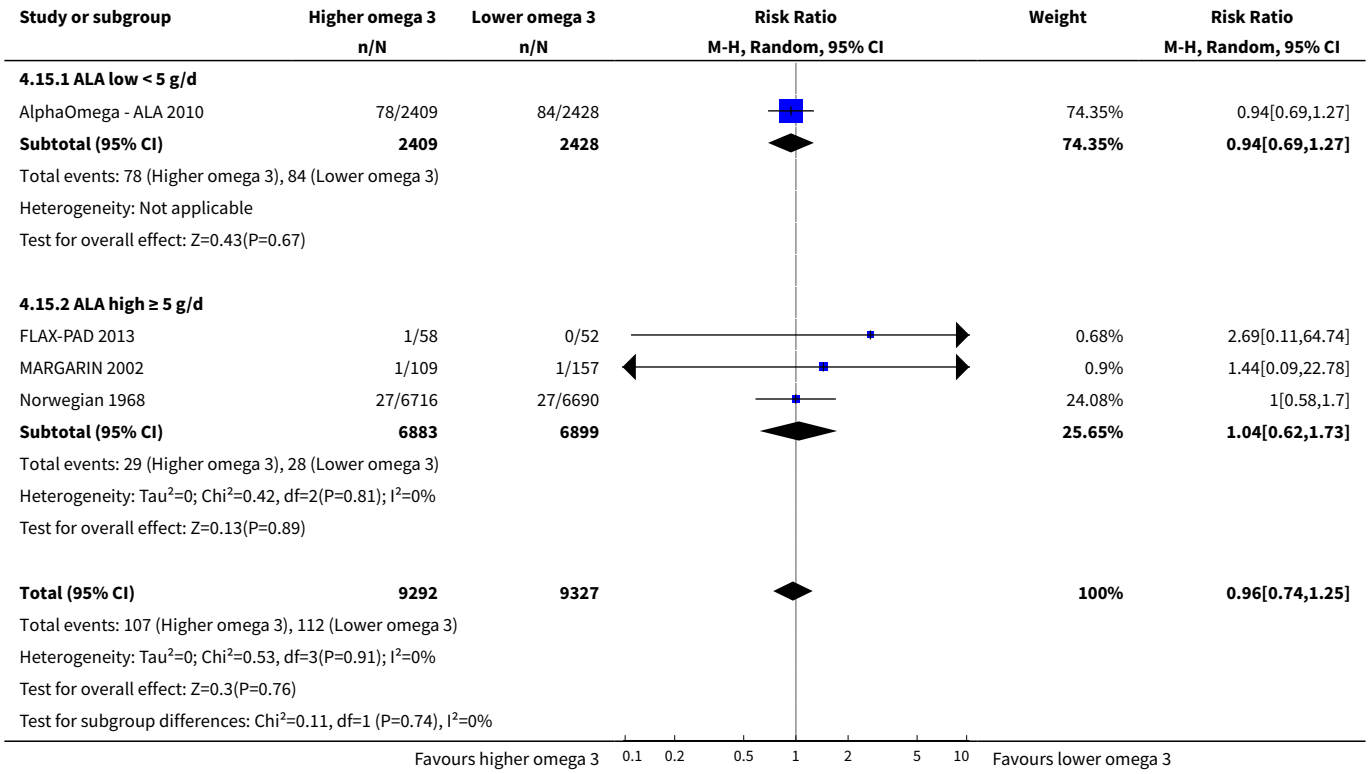
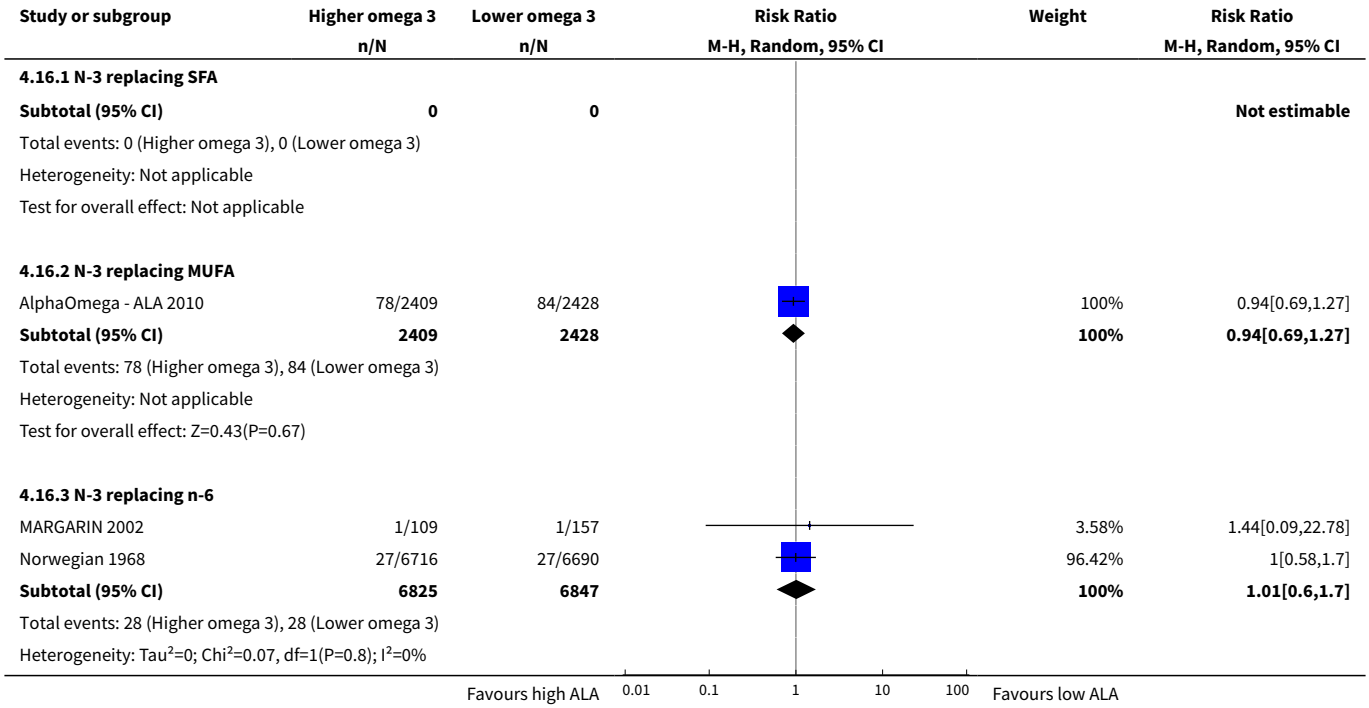
Analysis 4.15. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 15 CVD mortality - ALA - subgroup by dose.



Analysis 4.16. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 16 CVD mortality - ALA - subgroup by replacement.



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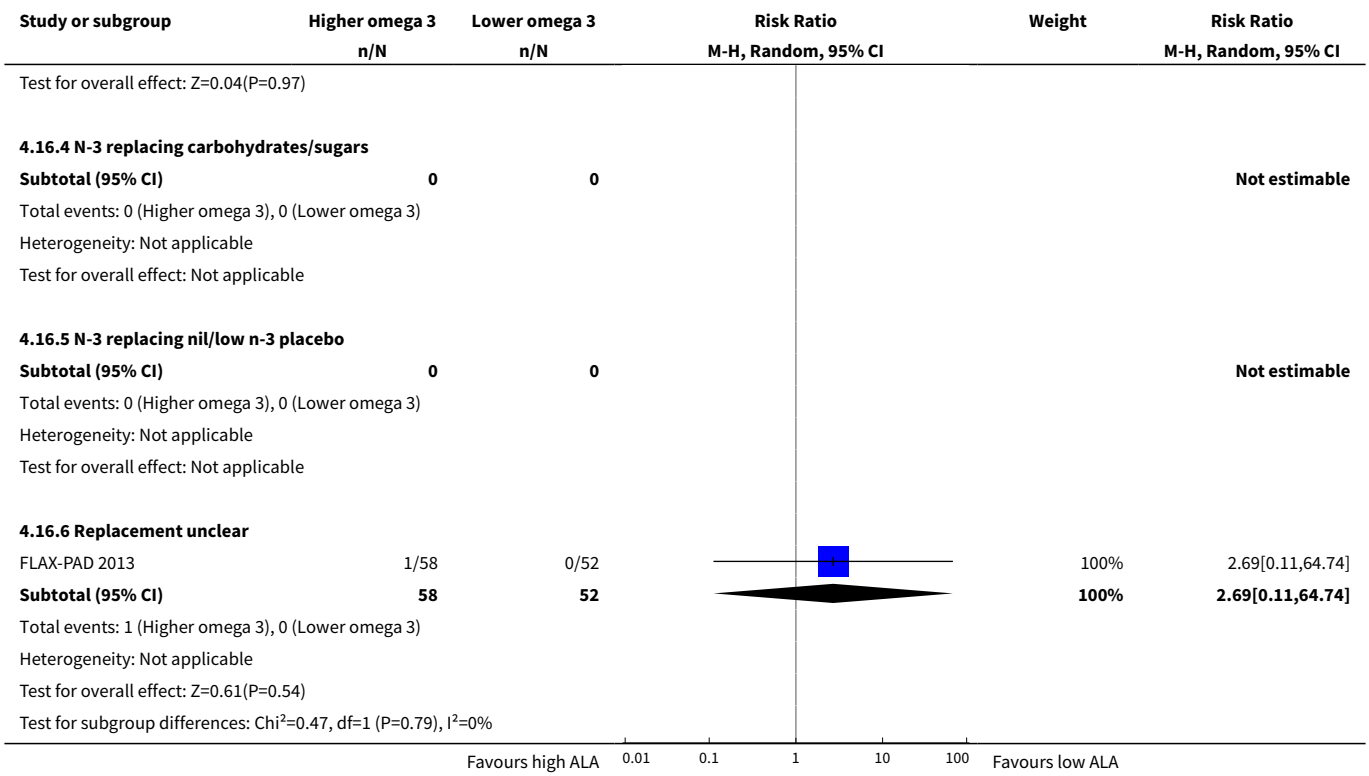
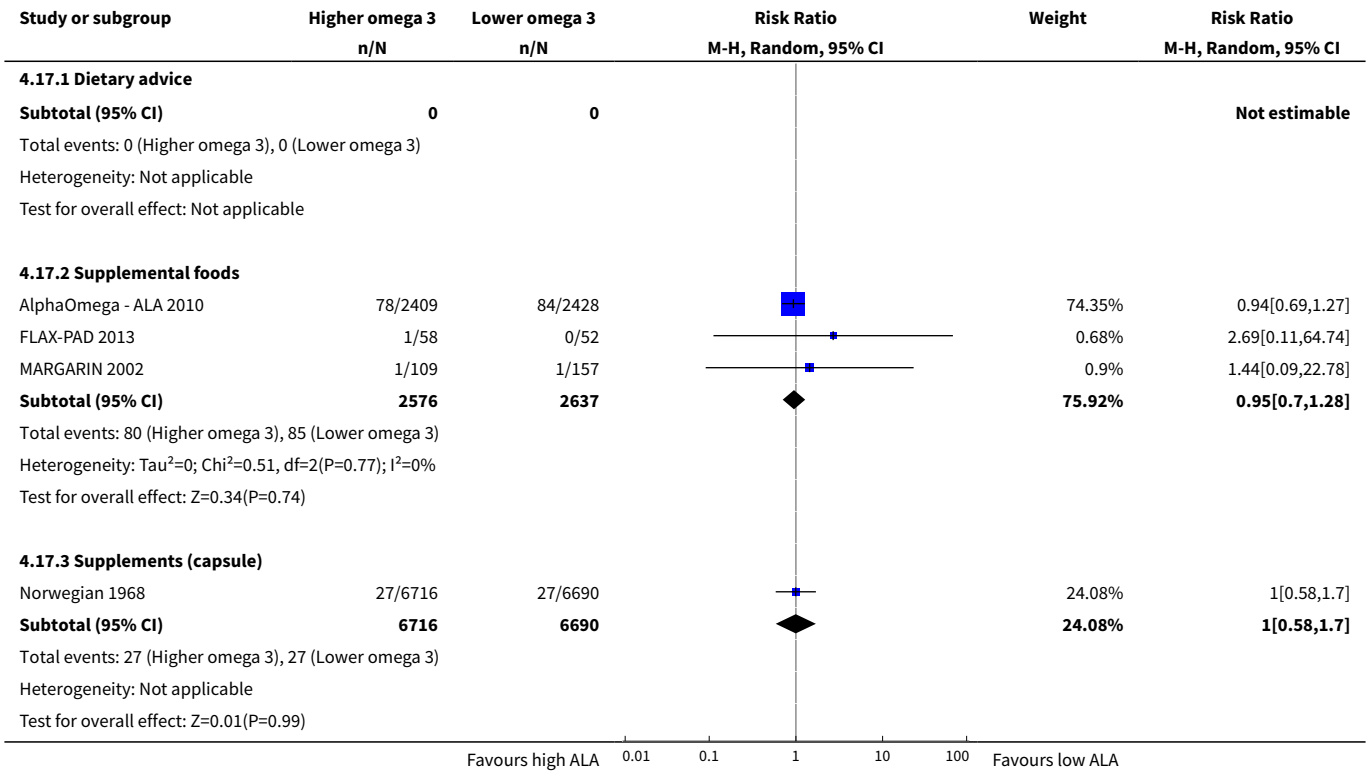


Analysis 4.17. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 17 CVD mortality - ALA - subgroup by intervention type.



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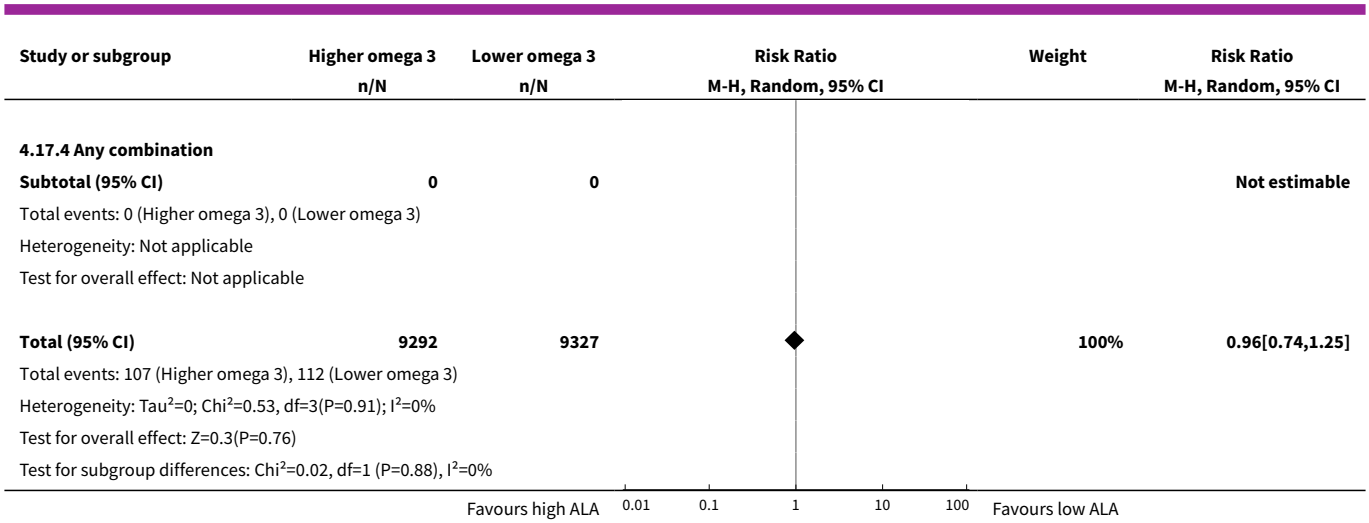
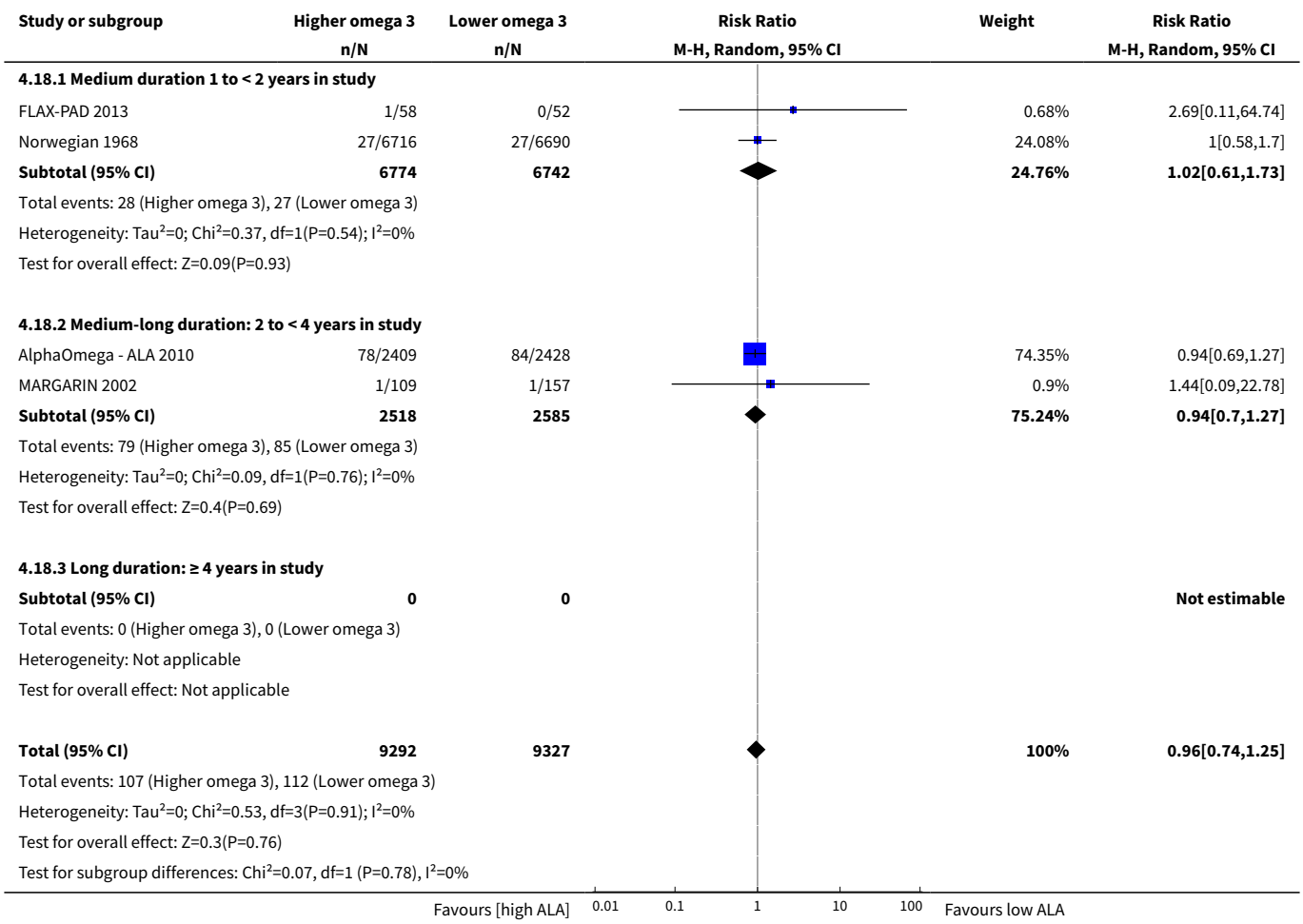


Analysis 4.18. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 18 CVD mortality - ALA - subgroup by duration.



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Analysis 4.19. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 19 CVD mortality - ALA - subgroup by primary or secondary prevention.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.19.1 Primary prevention					
Norwegian 1968	27/6716	27/6690		24.08%	1[0.58,1.7]
Subtotal (95% CI)	**6716**	**6690**		**24.08%**	**1[0.58,1.7]**
Total events: 27 (Higher omega 3), 27 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.01(P=0.99)					
4.19.2 Secondary prevention					
AlphaOmega - ALA 2010	78/2409	84/2428		74.35%	0.94[0.69,1.27]
FLAX-PAD 2013	1/58	0/52		0.68%	2.69[0.11,64.74]
MARGARIN 2002	1/109	1/157		0.9%	1.44[0.09,22.78]
Subtotal (95% CI)	**2576**	**2637**		**75.92%**	**0.95[0.7,1.28]**
Total events: 80 (Higher omega 3), 85 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.51, df=2(P=0.77); I^2=0%					
Test for overall effect: Z=0.34(P=0.74)					
Total (95% CI)	**9292**	**9327**		**100%**	**0.96[0.74,1.25]**
Total events: 107 (Higher omega 3), 112 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.53, df=3(P=0.91); I^2=0%					
Test for overall effect: Z=0.3(P=0.76)					
Test for subgroup differences: Chi^2=0.02, df=1 (P=0.88), I^2=0%					

Analysis 4.20. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 20 CVD mortality - ALA - subgroup by statin uses.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.20.1 ALA - ≥ 50% of control group on statins					
AlphaOmega - ALA 2010	78/2409	84/2428		74.35%	0.94[0.69,1.27]
FLAX-PAD 2013	1/58	0/52		0.68%	2.69[0.11,64.74]
Subtotal (95% CI)	**2467**	**2480**		**75.02%**	**0.94[0.7,1.28]**
Total events: 79 (Higher omega 3), 84 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.42, df=1(P=0.52); I^2=0%					
Test for overall effect: Z=0.37(P=0.71)					
4.20.2 ALA - < 50% of control group on statins					
MARGARIN 2002	1/109	1/157		0.9%	1.44[0.09,22.78]
Norwegian 1968	27/6716	27/6690		24.08%	1[0.58,1.7]
Subtotal (95% CI)	**6825**	**6847**		**24.98%**	**1.01[0.6,1.7]**
Total events: 28 (Higher omega 3), 28 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.07, df=1(P=0.8); I^2=0%					
Test for overall effect: Z=0.04(P=0.97)					
Total (95% CI)	**9292**	**9327**		**100%**	**0.96[0.74,1.25]**
Total events: 107 (Higher omega 3), 112 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.53, df=3(P=0.91); I^2=0%					

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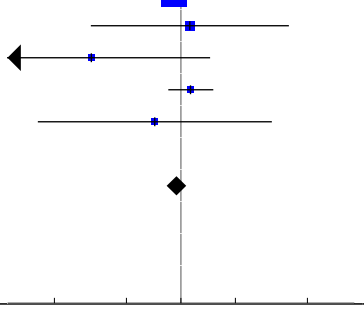
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=0.3(P=0.76)					
Test for subgroup differences: Chi²=0.05, df=1 (P=0.83), I²=0%					

Favours higher omega 3 — Favours lower omega 3

Analysis 4.21. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 21 Cardiovascular events (overall) - ALA.

Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 fats n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
AlphaOmega - ALA 2010	319/2409	352/2428		78.63%	0.91[0.79,1.05]
FLAX-PAD 2013	5/58	4/52		0.98%	1.12[0.32,3.95]
MARGARIN 2002	2/109	9/157		0.68%	0.32[0.07,1.45]
Norwegian 1968	99/6716	87/6690		19.01%	1.13[0.85,1.51]
WAHA 2016	3/362	4/346		0.7%	0.72[0.16,3.18]
Total (95% CI)	**9654**	**9673**		**100%**	**0.95[0.83,1.07]**
Total events: 428 (Favours higher omega 3), 456 (Lower omega 3 fats)					
Heterogeneity: Tau²=0; Chi²=3.95, df=4(P=0.41); I²=0%					
Test for overall effect: Z=0.89(P=0.38)					



Favours higher omega 3 — Favours lower omega 3

Analysis 4.22. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 22 CVD events - ALA - SA fixed-effect.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
AlphaOmega - ALA 2010	319/2409	352/2428		77.32%	0.91[0.79,1.05]
FLAX-PAD 2013	5/58	4/52		0.93%	1.12[0.32,3.95]
MARGARIN 2002	2/109	9/157		1.63%	0.32[0.07,1.45]
Norwegian 1968	99/6716	87/6690		19.22%	1.13[0.85,1.51]
WAHA 2016	3/362	4/346		0.9%	0.72[0.16,3.18]
Total (95% CI)	**9654**	**9673**		**100%**	**0.95[0.84,1.07]**
Total events: 428 (Higher omega 3), 456 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=3.95, df=4(P=0.41); I²=0%					
Test for overall effect: Z=0.87(P=0.38)					

Favours [high ALA] — Favours low ALA

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Analysis 4.23. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 23 CVD events - ALA - SA by summary risk of bias.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.23.1 Low risk of bias					
AlphaOmega - ALA 2010	319/2409	352/2428		97.93%	0.91[0.79,1.05]
FLAX-PAD 2013	5/58	4/52		1.22%	1.12[0.32,3.95]
MARGARIN 2002	2/109	9/157		0.85%	0.32[0.07,1.45]
Subtotal (95% CI)	**2576**	**2637**		**100%**	**0.91[0.79,1.04]**
Total events: 326 (Higher omega 3), 365 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=1.94, df=2(P=0.38); I^2=0%					
Test for overall effect: Z=1.37(P=0.17)					
4.23.2 Moderate/high risk of bias					
Norwegian 1968	99/6716	87/6690		96.44%	1.13[0.85,1.51]
WAHA 2016	3/362	4/346		3.56%	0.72[0.16,3.18]
Subtotal (95% CI)	**7078**	**7036**		**100%**	**1.12[0.84,1.48]**
Total events: 102 (Higher omega 3), 91 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.35, df=1(P=0.55); I^2=0%					
Test for overall effect: Z=0.76(P=0.45)					
Test for subgroup differences: Chi^2=1.66, df=1 (P=0.2), I^2=39.72%					

Analysis 4.24. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 24 CVD events - ALA - SA by compliance and study size.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.24.1 SA - low risk of compliance bias					
AlphaOmega - ALA 2010	319/2409	352/2428		98.27%	0.91[0.79,1.05]
MARGARIN 2002	2/109	9/157		0.85%	0.32[0.07,1.45]
WAHA 2016	3/362	4/346		0.88%	0.72[0.16,3.18]
Subtotal (95% CI)	**2880**	**2931**		**100%**	**0.9[0.79,1.04]**
Total events: 324 (Higher omega 3), 365 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=1.93, df=2(P=0.38); I^2=0%					
Test for overall effect: Z=1.43(P=0.15)					
4.24.2 SA - 100+ randomised					
AlphaOmega - ALA 2010	319/2409	352/2428		78.63%	0.91[0.79,1.05]
FLAX-PAD 2013	5/58	4/52		0.98%	1.12[0.32,3.95]
MARGARIN 2002	2/109	9/157		0.68%	0.32[0.07,1.45]
Norwegian 1968	99/6716	87/6690		19.01%	1.13[0.85,1.51]
WAHA 2016	3/362	4/346		0.7%	0.72[0.16,3.18]
Subtotal (95% CI)	**9654**	**9673**		**100%**	**0.95[0.83,1.07]**
Total events: 428 (Higher omega 3), 456 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=3.95, df=4(P=0.41); I^2=0%					
Test for overall effect: Z=0.89(P=0.38)					
Test for subgroup differences: Chi^2=0.22, df=1 (P=0.64), I^2=0%					

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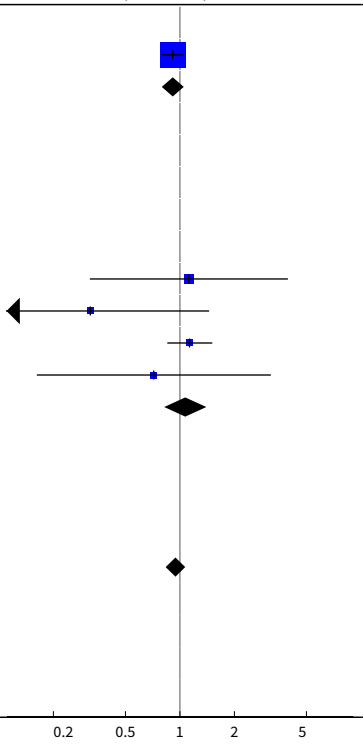
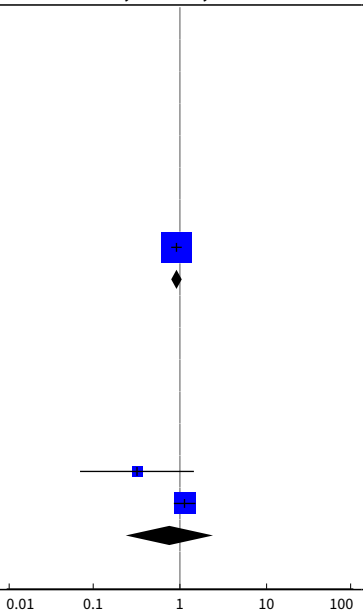
Analysis 4.25. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 25 CVD events - ALA - subgroup by dose.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.25.1 ALA low < 5 g/d					
AlphaOmega - ALA 2010	319/2409	352/2428		78.63%	0.91[0.79,1.05]
Subtotal (95% CI)	**2409**	**2428**		**78.63%**	**0.91[0.79,1.05]**
Total events: 319 (Higher omega 3), 352 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.26(P=0.21)					
4.25.2 ALA high ≥ 5 g/d					
FLAX-PAD 2013	5/58	4/52		0.98%	1.12[0.32,3.95]
MARGARIN 2002	2/109	9/157		0.68%	0.32[0.07,1.45]
Norwegian 1968	99/6716	87/6690		19.01%	1.13[0.85,1.51]
WAHA 2016	3/362	4/346		0.7%	0.72[0.16,3.18]
Subtotal (95% CI)	**7245**	**7245**		**21.37%**	**1.07[0.82,1.4]**
Total events: 109 (Higher omega 3), 104 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=2.89, df=3(P=0.41); I^2=0%					
Test for overall effect: Z=0.51(P=0.61)					
Total (95% CI)	**9654**	**9673**		**100%**	**0.95[0.83,1.07]**
Total events: 428 (Higher omega 3), 456 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=3.95, df=4(P=0.41); I^2=0%					
Test for overall effect: Z=0.89(P=0.38)					
Test for subgroup differences: Chi^2=1.06, df=1 (P=0.3), I^2=6.05%					



Analysis 4.26. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 26 CVD events - ALA - subgroup by replacement.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.26.1 N-3 replacing SFA					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 3), 0 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
4.26.2 N-3 replacing MUFA					
AlphaOmega - ALA 2010	319/2409	352/2428		100%	0.91[0.79,1.05]
Subtotal (95% CI)	**2409**	**2428**		**100%**	**0.91[0.79,1.05]**
Total events: 319 (Higher omega 3), 352 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.26(P=0.21)					
4.26.3 N-3 replacing n-6					
MARGARIN 2002	2/109	9/157		32.11%	0.32[0.07,1.45]
Norwegian 1968	99/6716	87/6690		67.89%	1.13[0.85,1.51]
Subtotal (95% CI)	**6825**	**6847**		**100%**	**0.76[0.24,2.41]**
Total events: 101 (Higher omega 3), 96 (Lower omega 3)					



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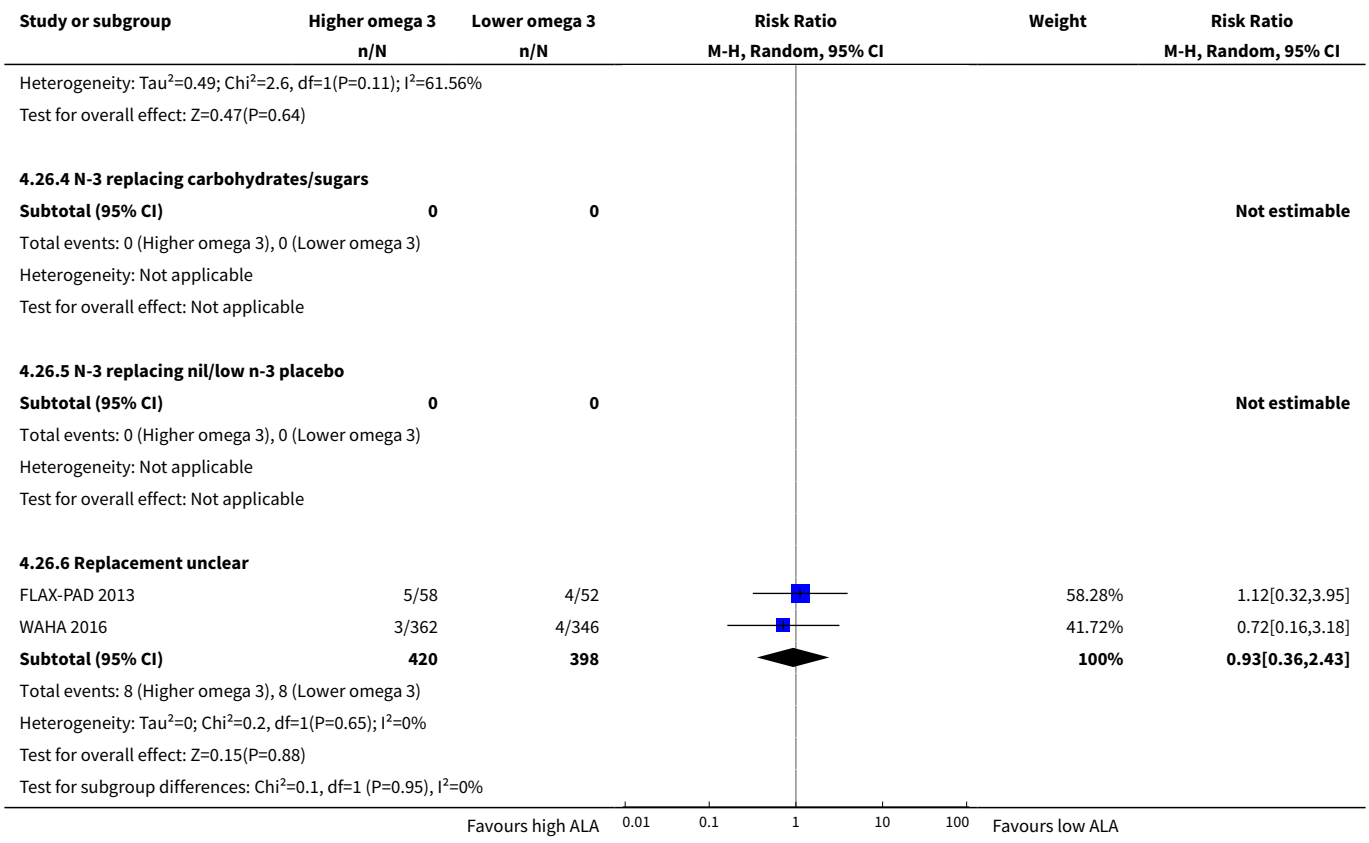
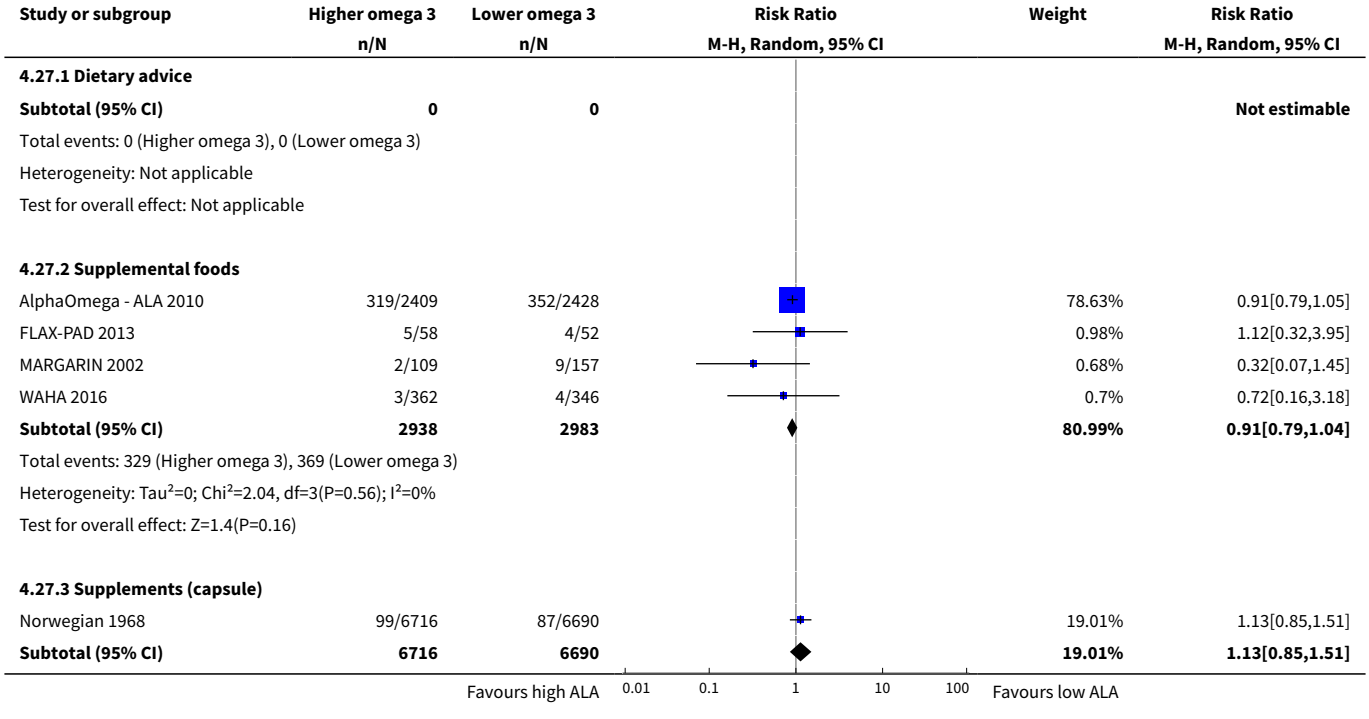


Analysis 4.27. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 27 CVD events - ALA - subgroup by intervention type.



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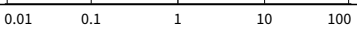
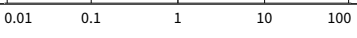
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 99 (Higher omega 3), 87 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.86(P=0.39)					
4.27.4 Any combination					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 3), 0 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**9654**	**9673**		**100%**	**0.95[0.83,1.07]**
Total events: 428 (Higher omega 3), 456 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=3.95, df=4(P=0.41); I^2=0%					
Test for overall effect: Z=0.89(P=0.38)					
Test for subgroup differences: Chi^2=1.91, df=1 (P=0.17), I^2=47.75%					



Analysis 4.28. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 28 CVD events - ALA - subgroup by duration.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.28.1 Medium duration 1 to < 2 years in study					
FLAX-PAD 2013	5/58	4/52		0.98%	1.12[0.32,3.95]
Norwegian 1968	99/6716	87/6690		19.01%	1.13[0.85,1.51]
Subtotal (95% CI)	**6774**	**6742**		**19.99%**	**1.13[0.86,1.5]**
Total events: 104 (Higher omega 3), 91 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.99); I^2=0%					
Test for overall effect: Z=0.88(P=0.38)					
4.28.2 Medium-long duration: 2 to < 4 years in study					
AlphaOmega - ALA 2010	319/2409	352/2428		78.63%	0.91[0.79,1.05]
MARGARIN 2002	2/109	9/157		0.68%	0.32[0.07,1.45]
WAHA 2016	3/362	4/346		0.7%	0.72[0.16,3.18]
Subtotal (95% CI)	**2880**	**2931**		**80.01%**	**0.9[0.79,1.04]**
Total events: 324 (Higher omega 3), 365 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=1.93, df=2(P=0.38); I^2=0%					
Test for overall effect: Z=1.43(P=0.15)					
4.28.3 Long duration: ≥ 4 years in study					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 3), 0 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**9654**	**9673**		**100%**	**0.95[0.83,1.07]**
Total events: 428 (Higher omega 3), 456 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=3.95, df=4(P=0.41); I^2=0%					
Test for overall effect: Z=0.89(P=0.38)					



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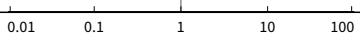
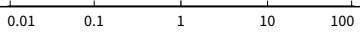
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for subgroup differences: Chi²=2.02, df=1 (P=0.15), I²=50.61%					



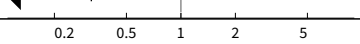
Analysis 4.29. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 29 CVD events - ALA - subgroup by primary or secondary prevention.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.29.1 Primary prevention					
MARGARIN 2002	2/109	9/157		0.68%	0.32[0.07,1.45]
Norwegian 1968	99/6716	87/6690		19.01%	1.13[0.85,1.51]
WAHA 2016	3/362	4/346		0.7%	0.72[0.16,3.18]
Subtotal (95% CI)	**7187**	**7193**		**20.39%**	**0.87[0.46,1.67]**
Total events: 104 (Higher omega 3), 100 (Lower omega 3)					
Heterogeneity: Tau²=0.14; Chi²=2.89, df=2(P=0.24); I²=30.76%					
Test for overall effect: Z=0.41(P=0.68)					
4.29.2 Secondary prevention					
AlphaOmega - ALA 2010	319/2409	352/2428		78.63%	0.91[0.79,1.05]
FLAX-PAD 2013	5/58	4/52		0.98%	1.12[0.32,3.95]
Subtotal (95% CI)	**2467**	**2480**		**79.61%**	**0.92[0.8,1.05]**
Total events: 324 (Higher omega 3), 356 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=0.1, df=1(P=0.75); I²=0%					
Test for overall effect: Z=1.23(P=0.22)					
Total (95% CI)	**9654**	**9673**		**100%**	**0.95[0.83,1.07]**
Total events: 428 (Higher omega 3), 456 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=3.95, df=4(P=0.41); I²=0%					
Test for overall effect: Z=0.89(P=0.38)					
Test for subgroup differences: Chi²=0.02, df=1 (P=0.89), I²=0%					



Analysis 4.30. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 30 CVD events - ALA - subgroup by statin use.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.30.1 ALA - ≥ 50% of control group on statins					
AlphaOmega - ALA 2010	319/2409	352/2428		78.63%	0.91[0.79,1.05]
FLAX-PAD 2013	5/58	4/52		0.98%	1.12[0.32,3.95]
Subtotal (95% CI)	**2467**	**2480**		**79.61%**	**0.92[0.8,1.05]**
Total events: 324 (Higher omega 3), 356 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=0.1, df=1(P=0.75); I²=0%					
Test for overall effect: Z=1.23(P=0.22)					
4.30.2 ALA - < 50% of control group on statins					
MARGARIN 2002	2/109	9/157		0.68%	0.32[0.07,1.45]



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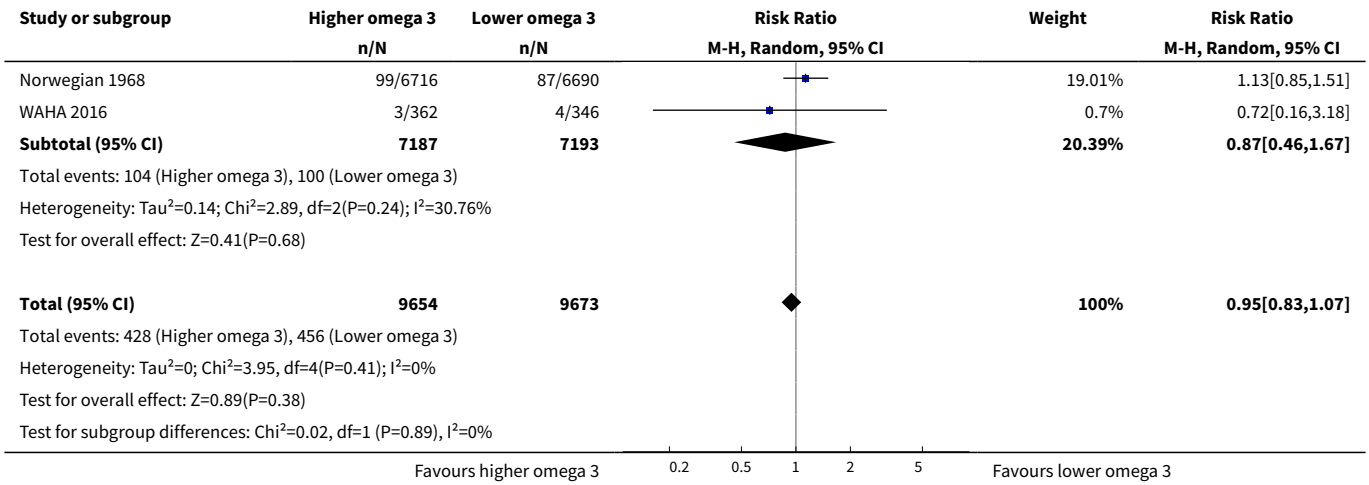
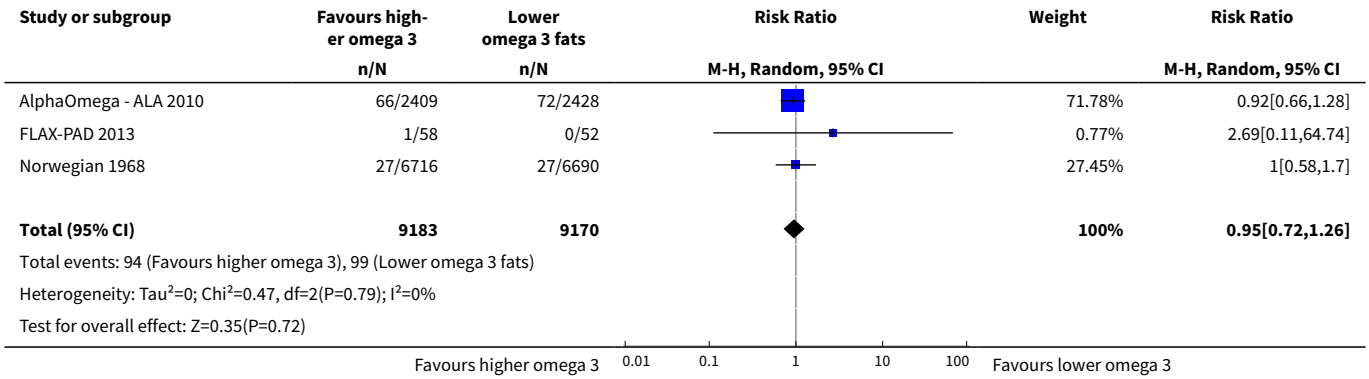
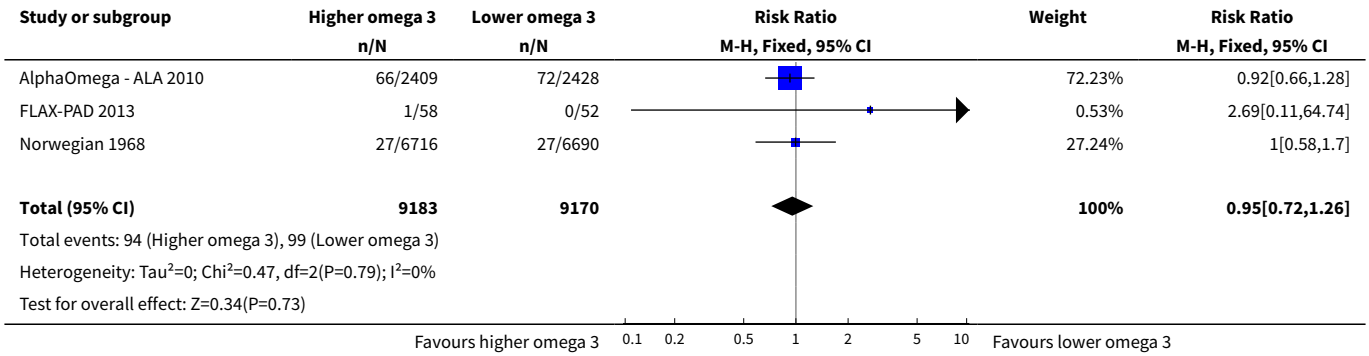


Analysis 4.31. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 31 Coronary heart disease mortality (overall) - ALA.



Analysis 4.32. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 32 CHD mortality - ALA - SA fixed-effect.



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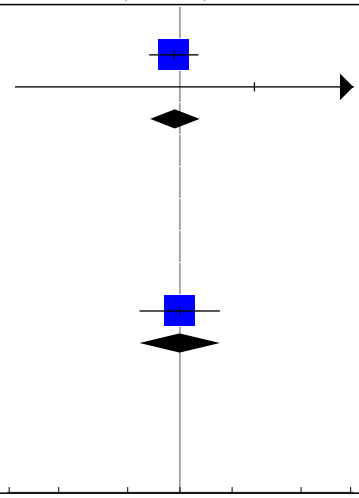
Analysis 4.33. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 33 CHD mortality - ALA - SA by summary risk of bias.

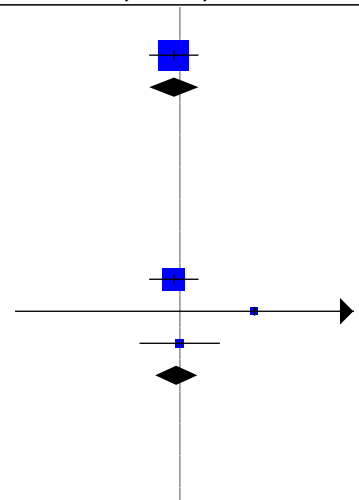
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.33.1 Low risk of bias					
AlphaOmega - ALA 2010	66/2409	72/2428		98.94%	0.92[0.66,1.28]
FLAX-PAD 2013	1/58	0/52		1.06%	2.69[0.11,64.74]
Subtotal (95% CI)	**2467**	**2480**		**100%**	**0.93[0.67,1.3]**
Total events: 67 (Higher omega 3), 72 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.43, df=1(P=0.51); I^2=0%					
Test for overall effect: Z=0.41(P=0.68)					
4.33.2 Moderate/high risk of bias					
Norwegian 1968	27/6716	27/6690		100%	1[0.58,1.7]
Subtotal (95% CI)	**6716**	**6690**		**100%**	**1[0.58,1.7]**
Total events: 27 (Higher omega 3), 27 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.01(P=0.99)					
Test for subgroup differences: Chi^2=0.04, df=1 (P=0.84), I^2=0%					



Favours higher omega 3 — Favours lower omega 3

Analysis 4.34. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 34 CHD mortality - ALA - SA by compliance and study size.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.34.1 SA - low risk of compliance bias					
AlphaOmega - ALA 2010	66/2409	72/2428		100%	0.92[0.66,1.28]
Subtotal (95% CI)	**2409**	**2428**		**100%**	**0.92[0.66,1.28]**
Total events: 66 (Higher omega 3), 72 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.47(P=0.64)					
4.34.2 SA - 100+ randomised					
AlphaOmega - ALA 2010	66/2409	72/2428		71.78%	0.92[0.66,1.28]
FLAX-PAD 2013	1/58	0/52		0.77%	2.69[0.11,64.74]
Norwegian 1968	27/6716	27/6690		27.45%	1[0.58,1.7]
Subtotal (95% CI)	**9183**	**9170**		**100%**	**0.95[0.72,1.26]**
Total events: 94 (Higher omega 3), 99 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.47, df=2(P=0.79); I^2=0%					
Test for overall effect: Z=0.35(P=0.72)					
Test for subgroup differences: Chi^2=0.02, df=1 (P=0.9), I^2=0%					



Favours higher omega 3 — Favours lower omega 3

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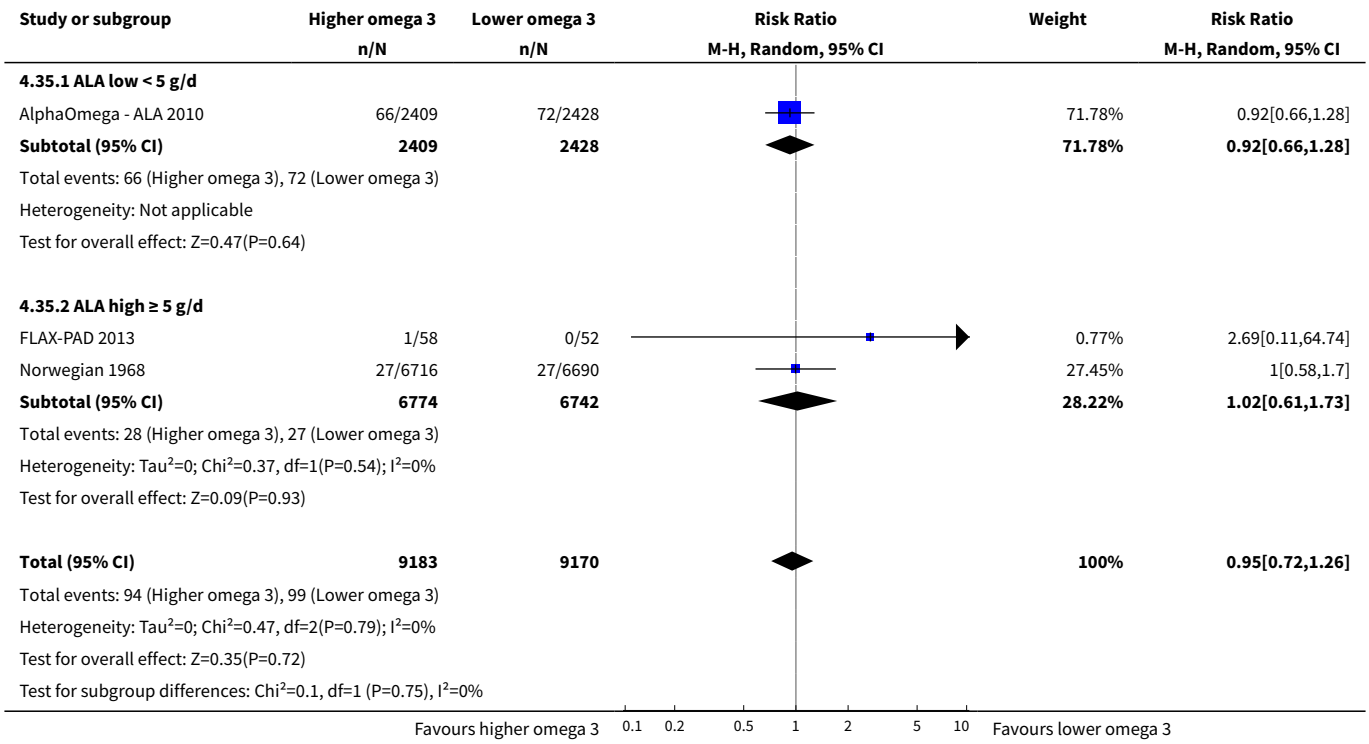
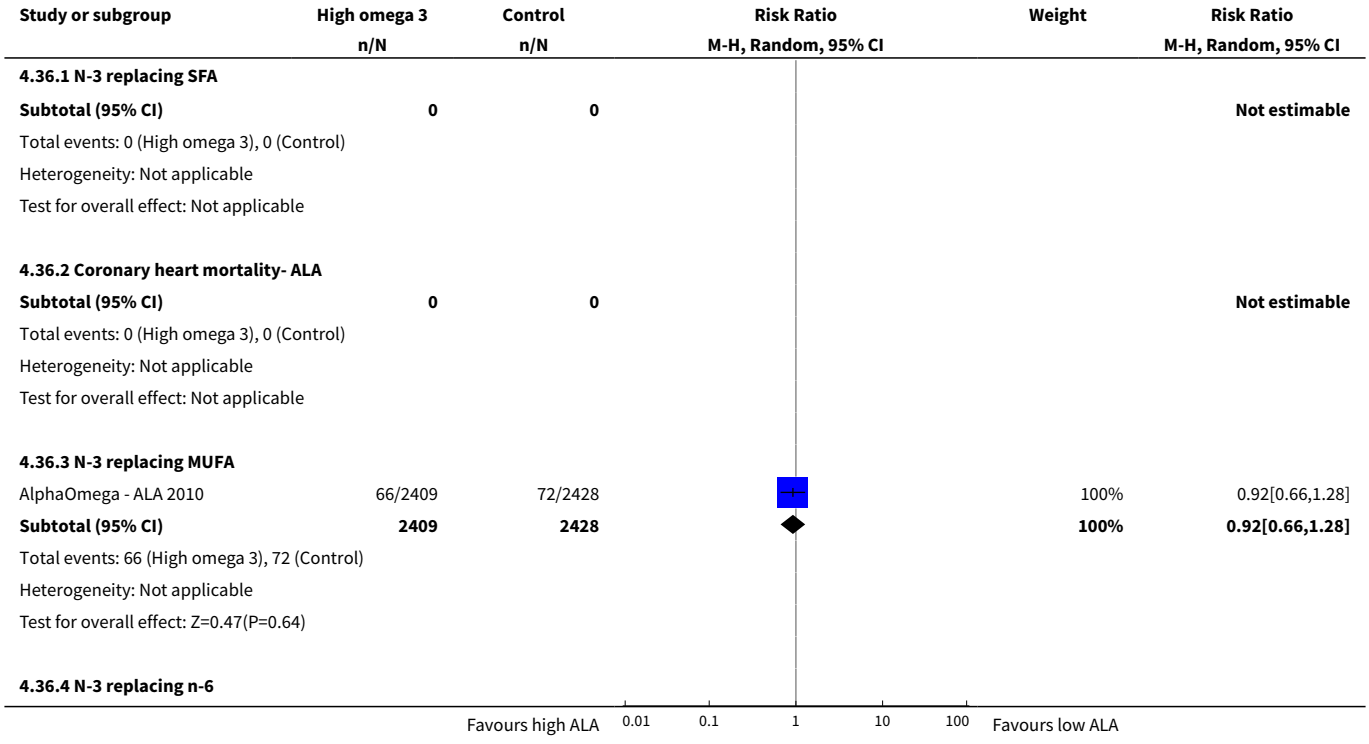
Analysis 4.35. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 35 CHD mortality - ALA - subgroup by dose.



Analysis 4.36. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 36 CHD mortality - ALA - subgroup by replacement.



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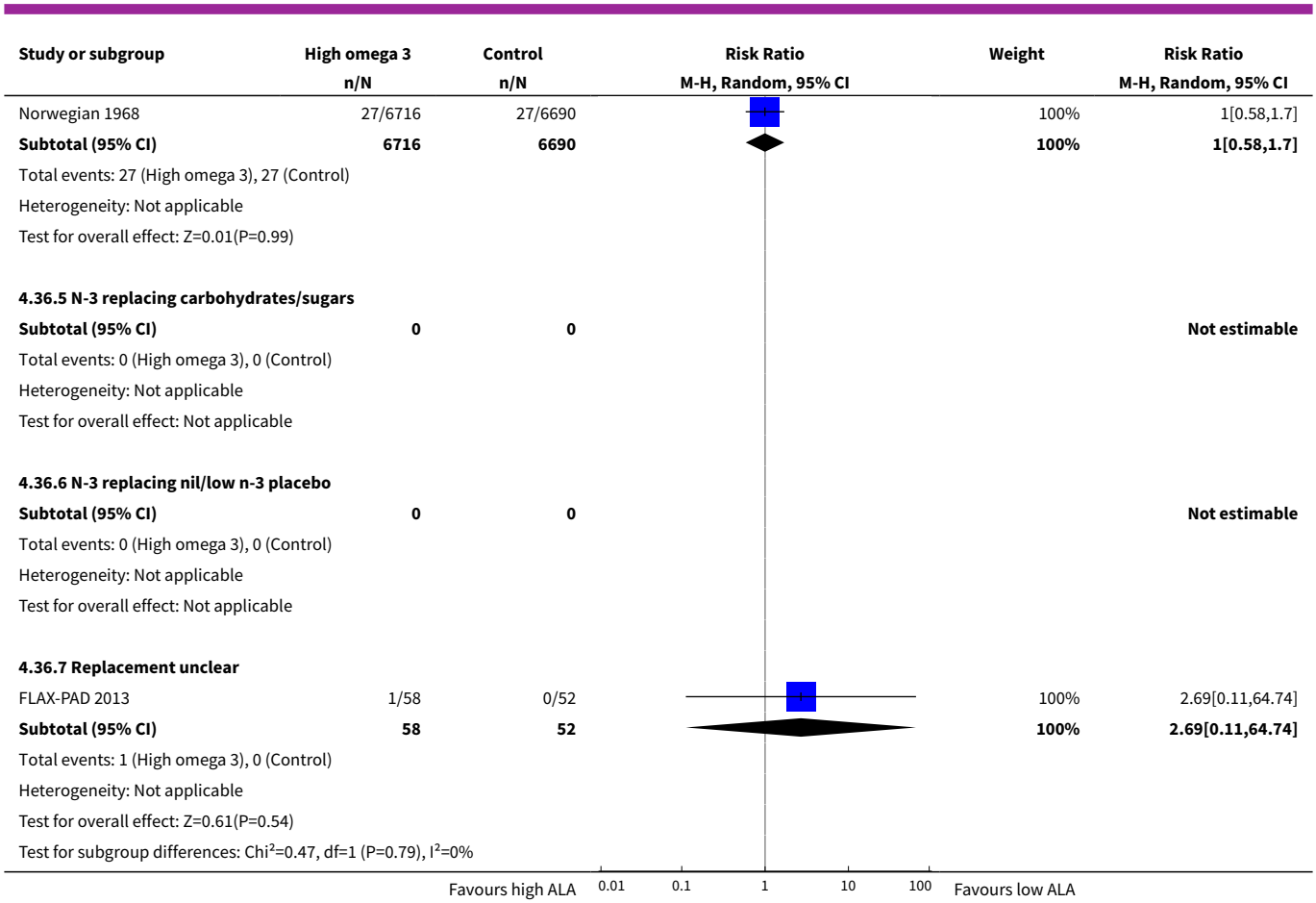
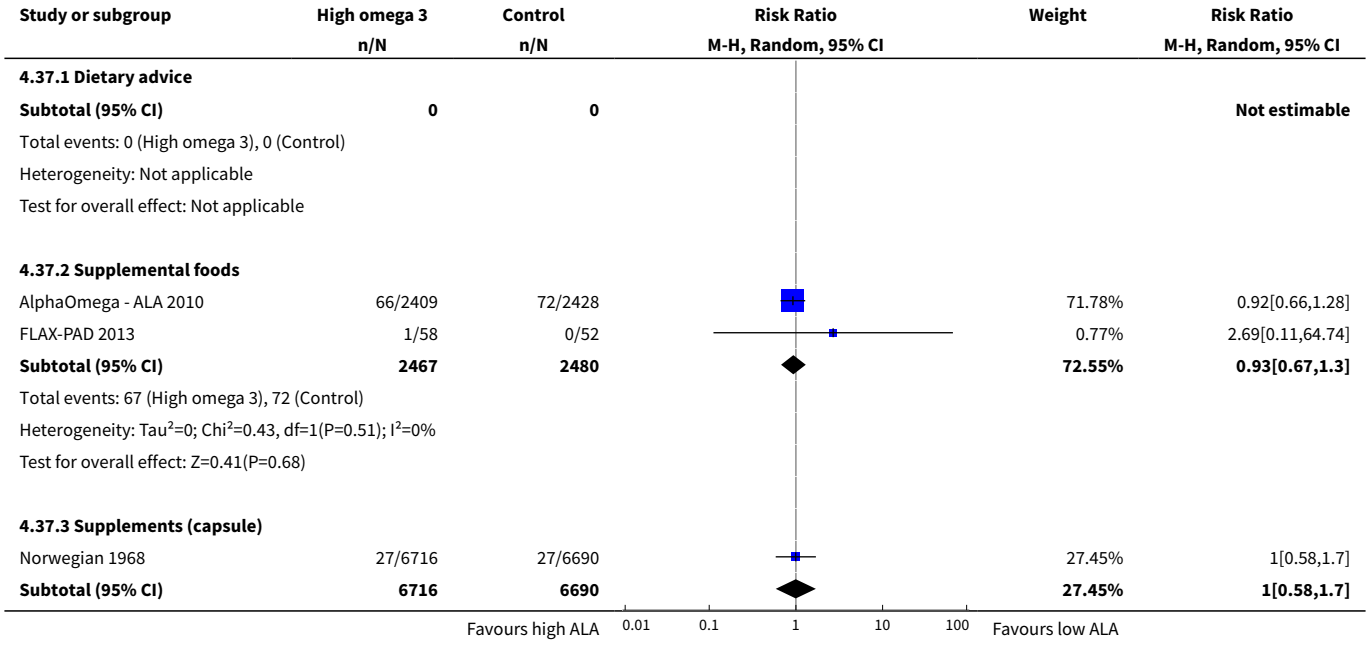


Analysis 4.37. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 37 CHD mortality - ALA - subgroup by intervention type.



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Study or subgroup	High omega 3 n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 27 (High omega 3), 27 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.01(P=0.99)					
4.37.4 Any combination					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (High omega 3), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**9183**	**9170**		**100%**	**0.95[0.72,1.26]**
Total events: 94 (High omega 3), 99 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.47, df=2(P=0.79); I^2=0%					
Test for overall effect: Z=0.35(P=0.72)					
Test for subgroup differences: Chi^2=0.04, df=1 (P=0.84), I^2=0%					

Analysis 4.38. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 38 CHD mortality - ALA - subgroup by duration.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.38.1 Medium duration 1 to < 2 years in study					
FLAX-PAD 2013	1/58	0/52		0.77%	2.69[0.11,64.74]
Norwegian 1968	27/6716	27/6690		27.45%	1[0.58,1.7]
Subtotal (95% CI)	**6774**	**6742**		**28.22%**	**1.02[0.61,1.73]**
Total events: 28 (Higher omega 3), 27 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.37, df=1(P=0.54); I^2=0%					
Test for overall effect: Z=0.09(P=0.93)					
4.38.2 Medium-long duration: 2 to < 4 years in study					
AlphaOmega - ALA 2010	66/2409	72/2428		71.78%	0.92[0.66,1.28]
Subtotal (95% CI)	**2409**	**2428**		**71.78%**	**0.92[0.66,1.28]**
Total events: 66 (Higher omega 3), 72 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.47(P=0.64)					
4.38.3 Long duration: ≥ 4 years in study					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 3), 0 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**9183**	**9170**		**100%**	**0.95[0.72,1.26]**
Total events: 94 (Higher omega 3), 99 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.47, df=2(P=0.79); I^2=0%					
Test for overall effect: Z=0.35(P=0.72)					
Test for subgroup differences: Chi^2=0.1, df=1 (P=0.75), I^2=0%					

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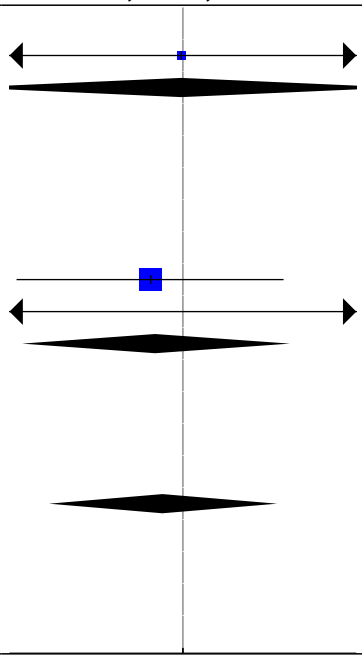
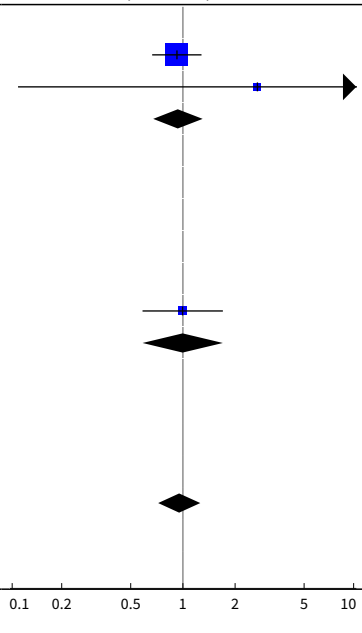
Analysis 4.39. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 39 CHD mortality - ALA - subgroup by primary or secondary prevention.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.39.1 Primary prevention of CVD					
Norwegian 1968	27/6716	27/6690		27.45%	1[0.58,1.7]
Subtotal (95% CI)	**6716**	**6690**		**27.45%**	**1[0.58,1.7]**
Total events: 27 (Higher omega 3), 27 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.01(P=0.99)					
4.39.2 Secondary prevention of CVD					
AlphaOmega - ALA 2010	66/2409	72/2428		71.78%	0.92[0.66,1.28]
FLAX-PAD 2013	1/58	0/52		0.77%	2.69[0.11,64.74]
Subtotal (95% CI)	**2467**	**2480**		**72.55%**	**0.93[0.67,1.3]**
Total events: 67 (Higher omega 3), 72 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.43, df=1(P=0.51); I^2=0%					
Test for overall effect: Z=0.41(P=0.68)					
Total (95% CI)	**9183**	**9170**		**100%**	**0.95[0.72,1.26]**
Total events: 94 (Higher omega 3), 99 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.47, df=2(P=0.79); I^2=0%					
Test for overall effect: Z=0.35(P=0.72)					
Test for subgroup differences: Chi^2=0.04, df=1 (P=0.84), I^2=0%					



Analysis 4.40. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 40 CHD mortality - ALA - subgroup by statin use.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.40.1 ALA - ≥ 50% of control group on statins					
AlphaOmega - ALA 2010	66/2409	72/2428		71.78%	0.92[0.66,1.28]
FLAX-PAD 2013	1/58	0/52		0.77%	2.69[0.11,64.74]
Subtotal (95% CI)	**2467**	**2480**		**72.55%**	**0.93[0.67,1.3]**
Total events: 67 (Higher omega 3), 72 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.43, df=1(P=0.51); I^2=0%					
Test for overall effect: Z=0.41(P=0.68)					
4.40.2 ALA - < 50% of control group on statins					
Norwegian 1968	27/6716	27/6690		27.45%	1[0.58,1.7]
Subtotal (95% CI)	**6716**	**6690**		**27.45%**	**1[0.58,1.7]**
Total events: 27 (Higher omega 3), 27 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.01(P=0.99)					
Total (95% CI)	**9183**	**9170**		**100%**	**0.95[0.72,1.26]**
Total events: 94 (Higher omega 3), 99 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.47, df=2(P=0.79); I^2=0%					



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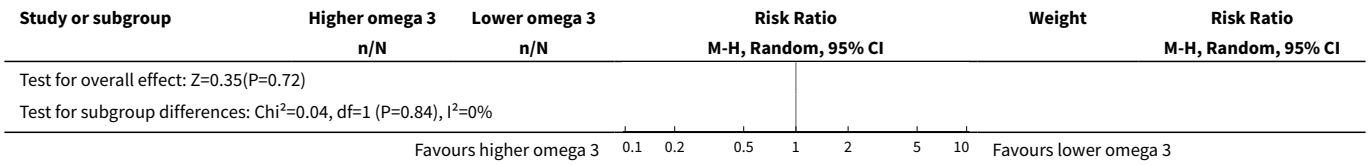
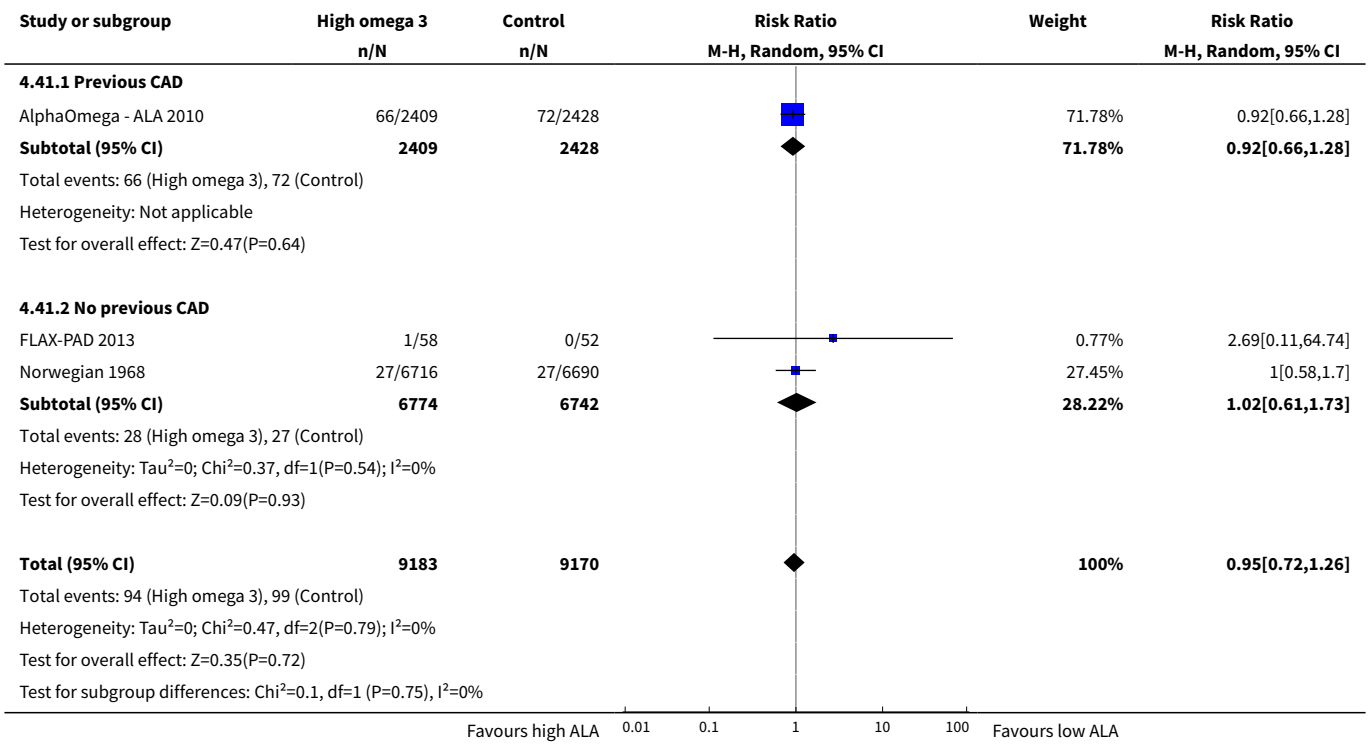
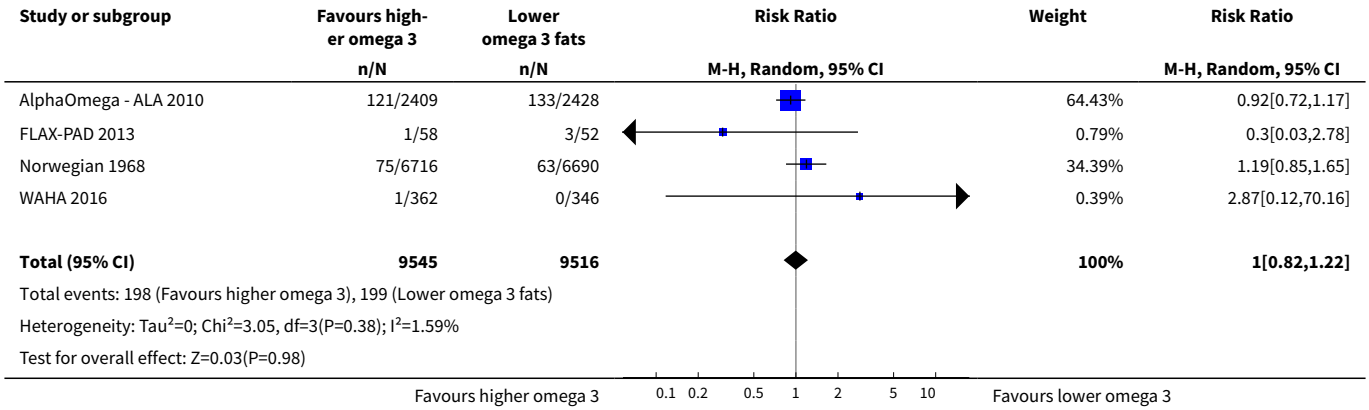


Analysis 4.41. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 41 CHD mortality - ALA - subgroup by CAD history.



Analysis 4.42. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 42 Coronary heart disease events (overall) - ALA.



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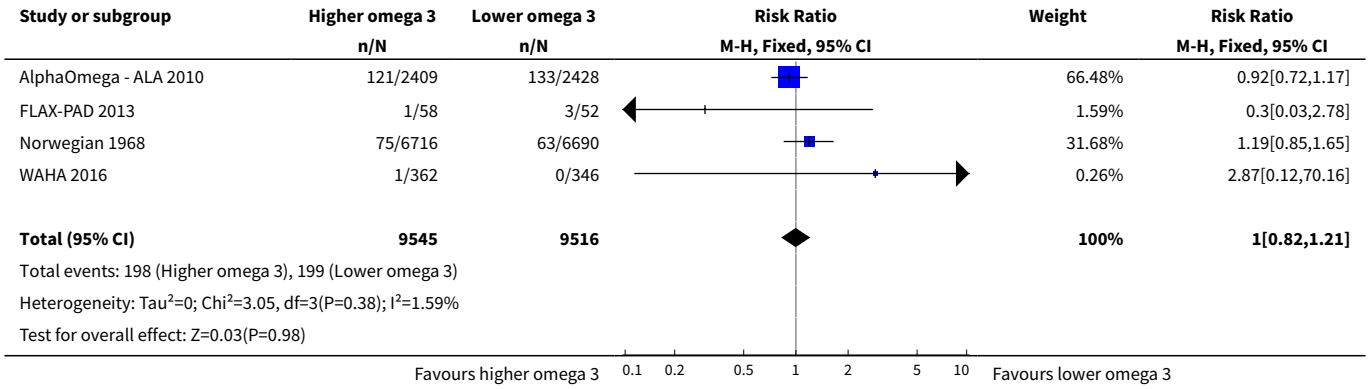
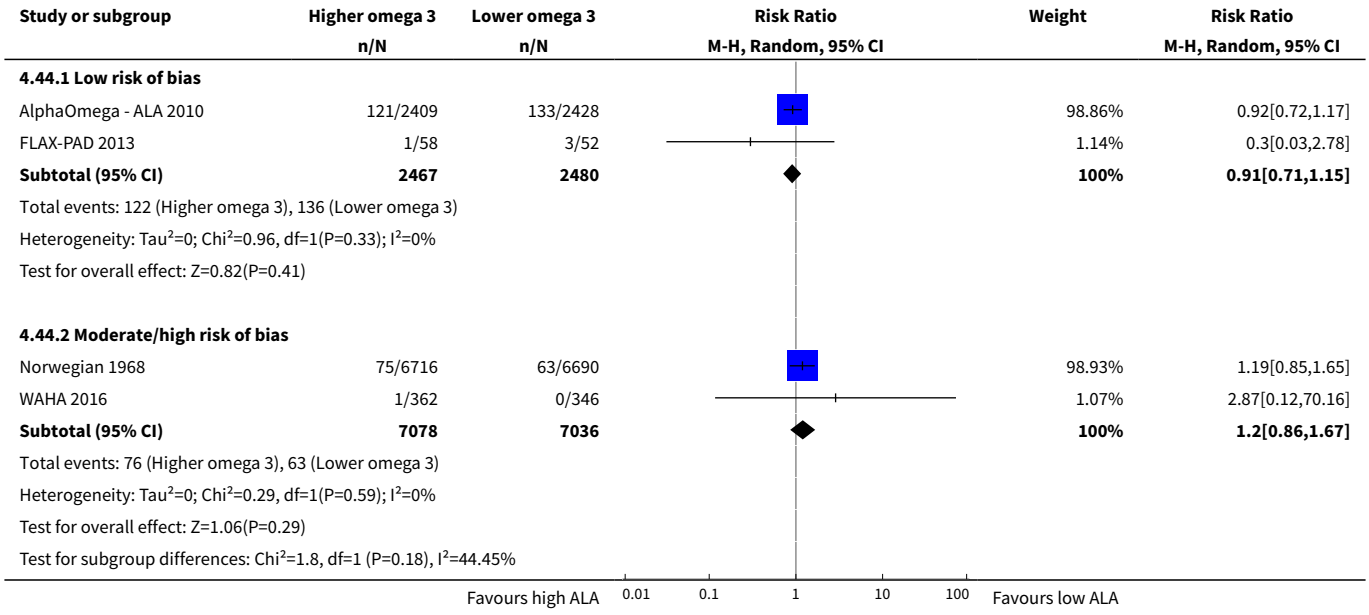
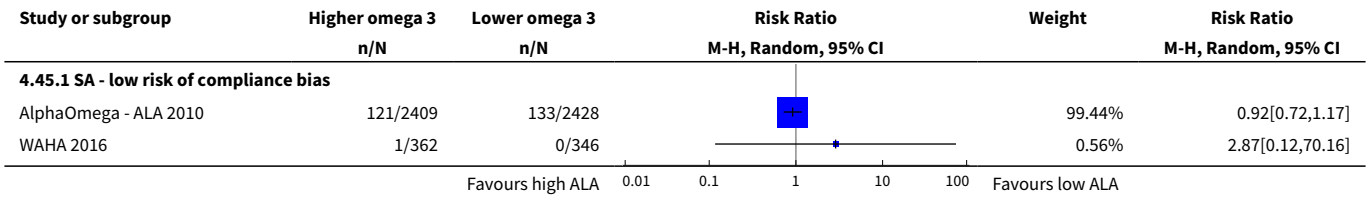
Analysis 4.43. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 43 CHD events - ALA - SA fixed-effect.



Analysis 4.44. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 44 CHD events - ALA - SA by summary risk of bias.



Analysis 4.45. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 45 CHD events - ALA - SA by compliance and study size.



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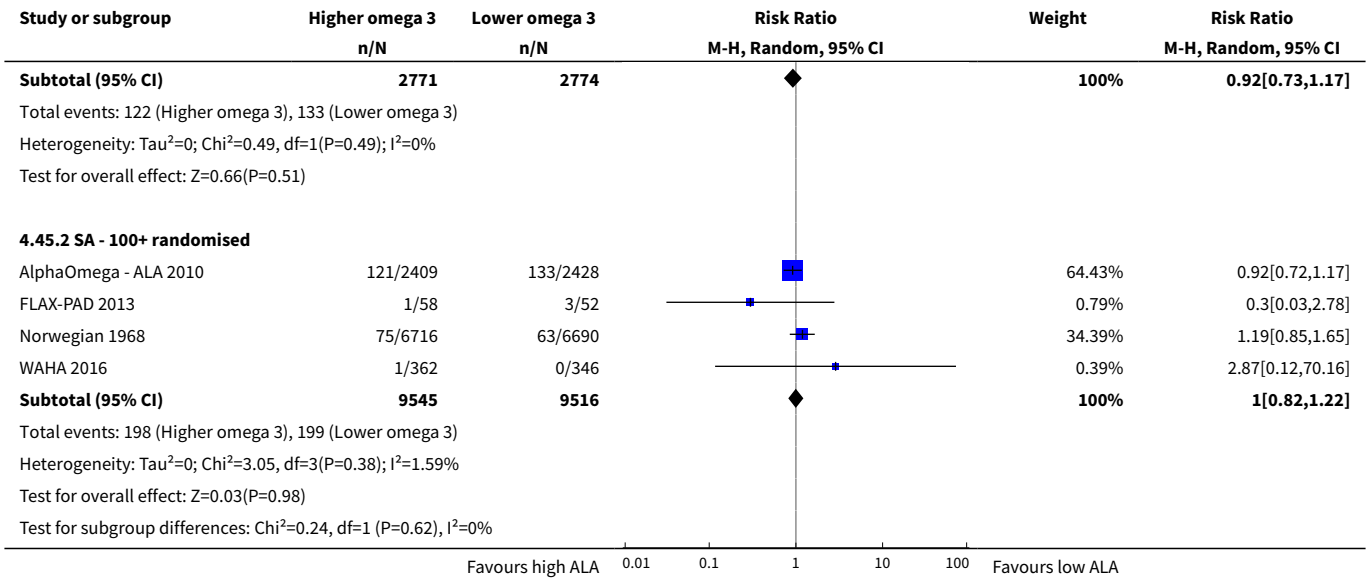
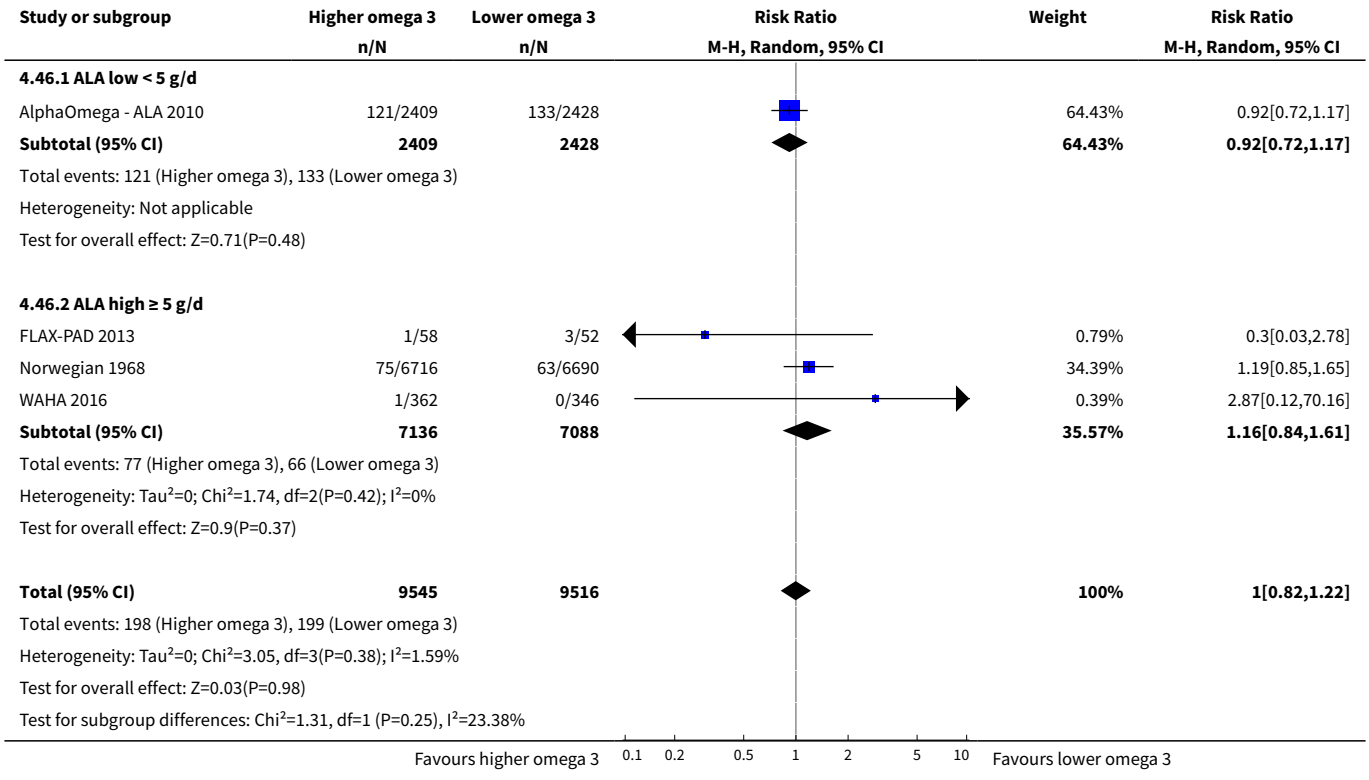


Analysis 4.46. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 46 CHD events - ALA - subgroup by dose.



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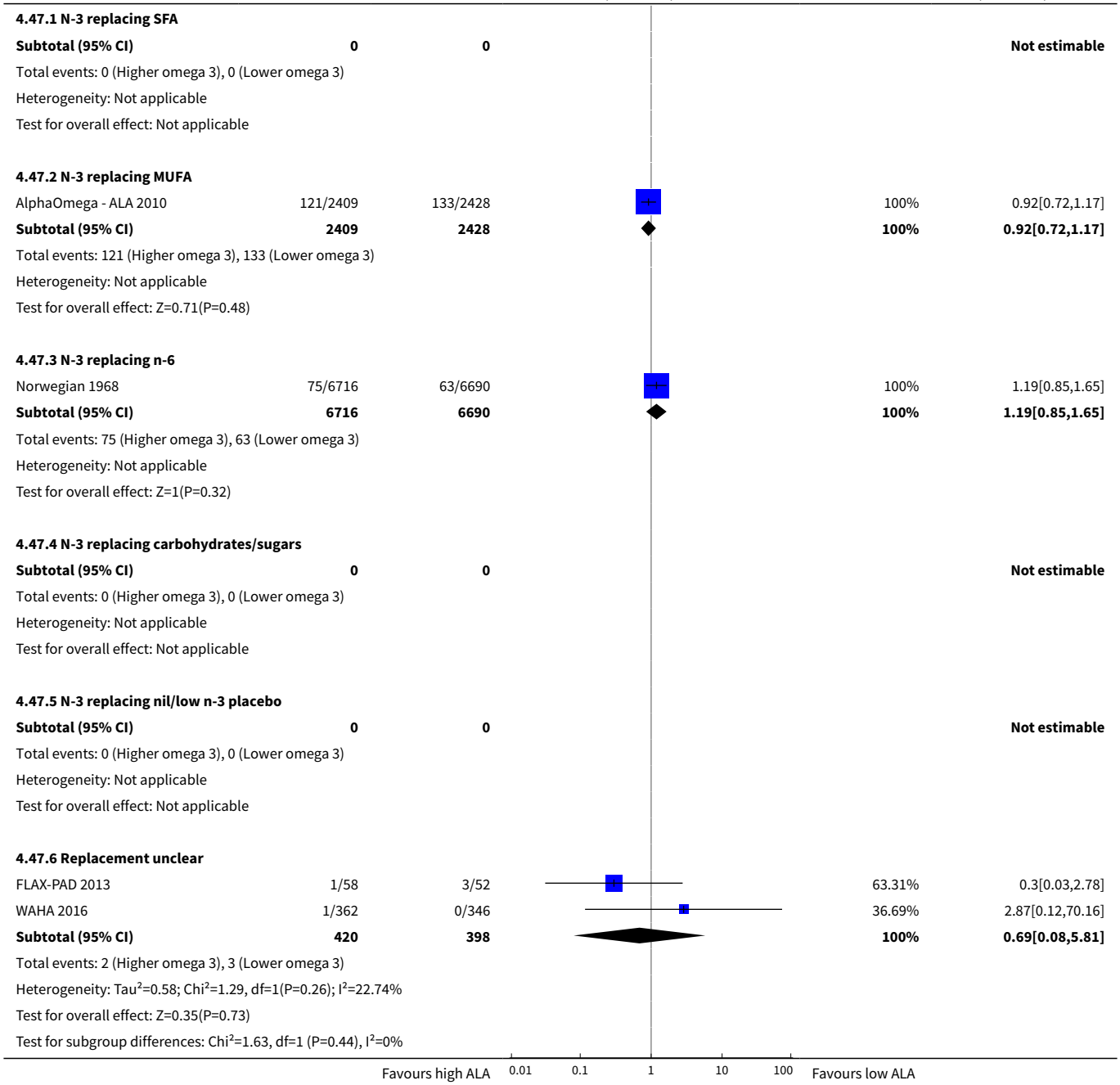
Analysis 4.47. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 47 CHD events - ALA - subgroup by replacement.



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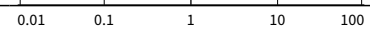
Analysis 4.48. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 48 CHD events - ALA - subgroup by intervention type.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.48.1 Dietary advice					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 3), 0 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
4.48.2 Supplemental foods					
AlphaOmega - ALA 2010	121/2409	133/2428		64.43%	0.92[0.72,1.17]
FLAX-PAD 2013	1/58	3/52		0.79%	0.3[0.03,2.78]
WAHA 2016	1/362	0/346		0.39%	2.87[0.12,70.16]
Subtotal (95% CI)	**2829**	**2826**		**65.61%**	**0.91[0.72,1.16]**
Total events: 123 (Higher omega 3), 136 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=1.46, df=2(P=0.48); I^2=0%					
Test for overall effect: Z=0.77(P=0.44)					
4.48.3 Supplements (capsule)					
Norwegian 1968	75/6716	63/6690		34.39%	1.19[0.85,1.65]
Subtotal (95% CI)	**6716**	**6690**		**34.39%**	**1.19[0.85,1.65]**
Total events: 75 (Higher omega 3), 63 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1(P=0.32)					
4.48.4 Any combination					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 3), 0 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**9545**	**9516**		**100%**	**1[0.82,1.22]**
Total events: 198 (Higher omega 3), 199 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=3.05, df=3(P=0.38); I^2=1.59%					
Test for overall effect: Z=0.03(P=0.98)					
Test for subgroup differences: Chi^2=1.59, df=1 (P=0.21), I^2=37.23%					

Analysis 4.49. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 49 CHD events - ALA - subgroup by duration.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.49.1 Medium duration 1 to < 2 years in study					
FLAX-PAD 2013	1/58	3/52		0.79%	0.3[0.03,2.78]
Norwegian 1968	75/6716	63/6690		34.39%	1.19[0.85,1.65]
Subtotal (95% CI)	**6774**	**6742**		**35.19%**	**0.94[0.34,2.58]**
Total events: 76 (Higher omega 3), 66 (Lower omega 3)					
Heterogeneity: Tau^2=0.29; Chi^2=1.43, df=1(P=0.23); I^2=30.28%					
Test for overall effect: Z=0.12(P=0.91)					



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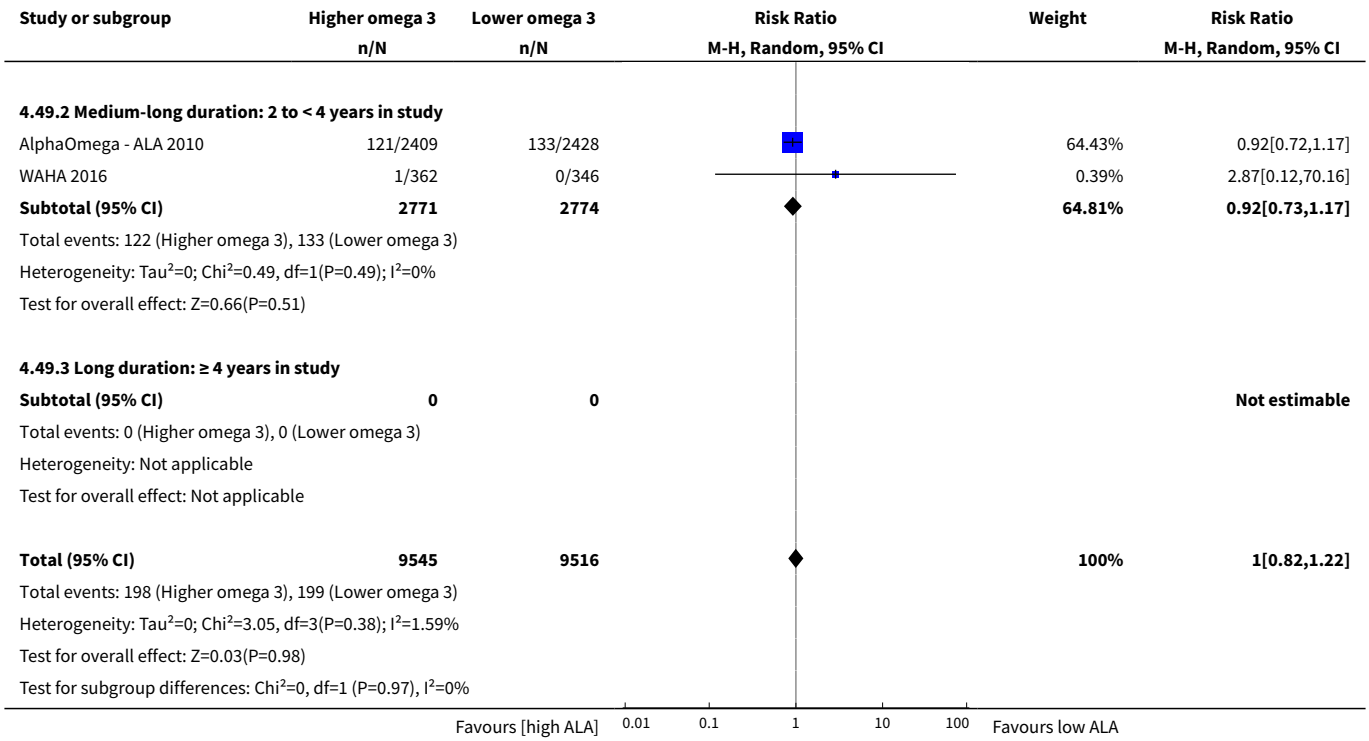
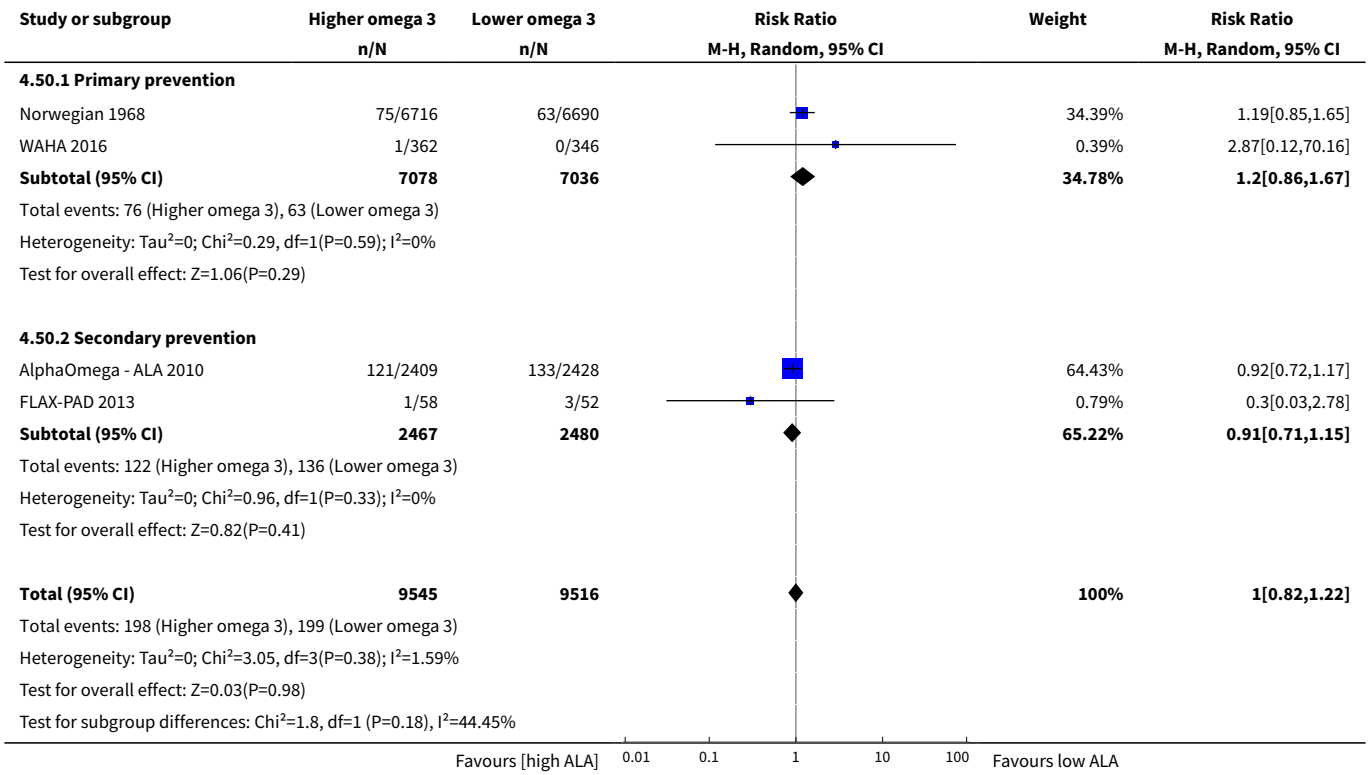


Analysis 4.50. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 50 CHD events - ALA - subgroup by primary or secondary prevention.



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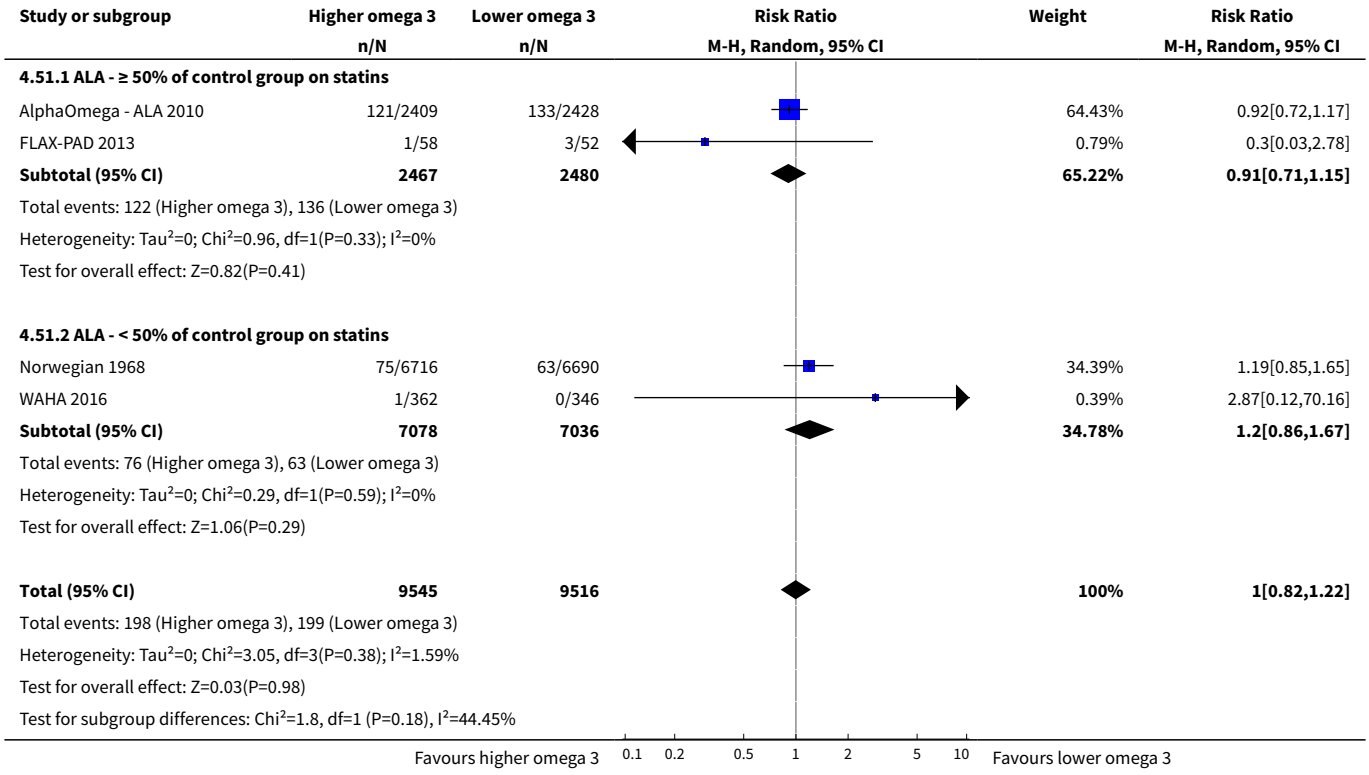
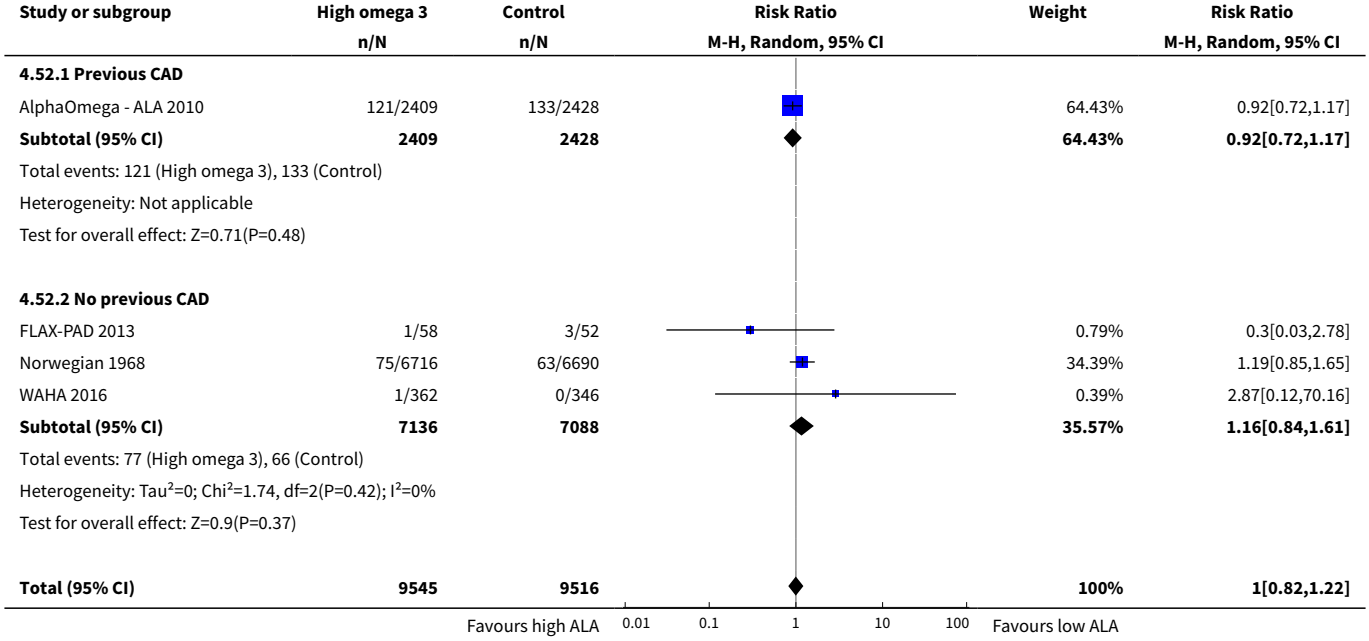
Analysis 4.51. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 51 CHD events - ALA - subgroup by statin use.



Analysis 4.52. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 52 CHD events - ALA - subgroup by CAD history.



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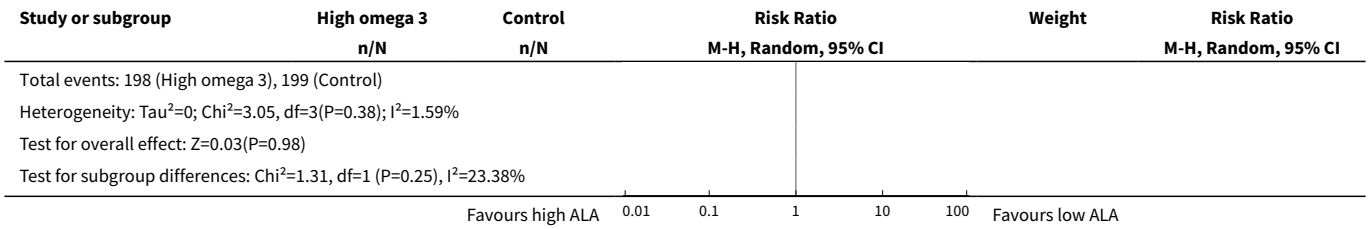
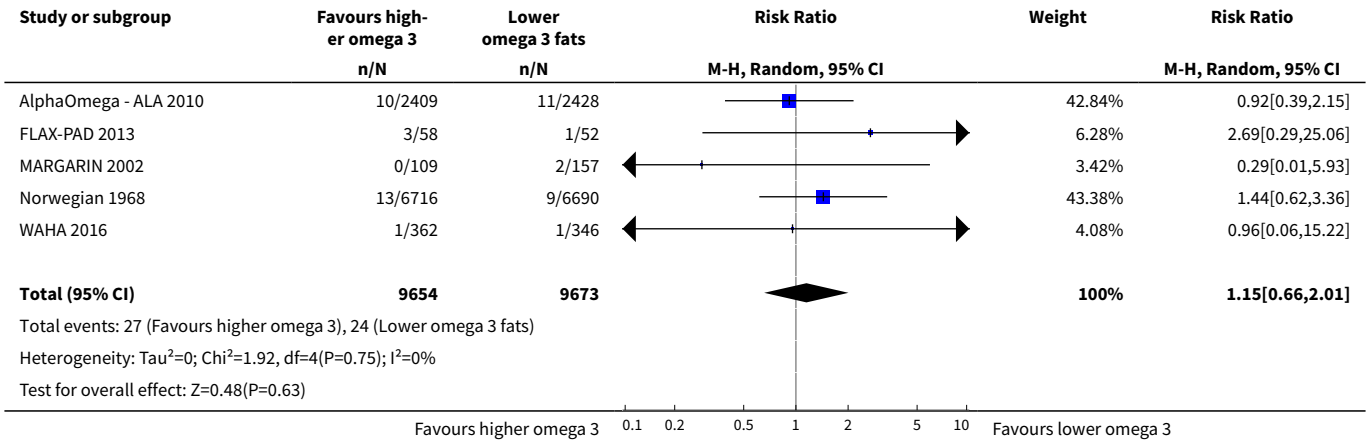
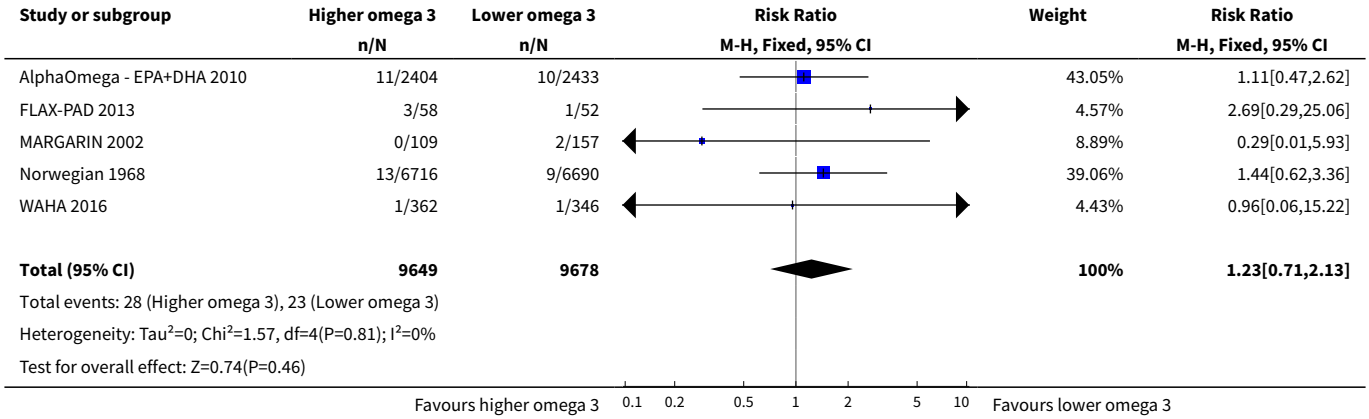


Analysis 4.53. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 53 Stroke (overall) - ALA.



Analysis 4.54. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 54 Stroke - ALA - SA fixed-effect.



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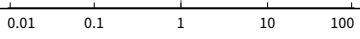
Analysis 4.55. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 55 Stroke - ALA - SA by summary risk of bias.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.55.1 Low risk of bias					
AlphaOmega - ALA 2010	10/2409	11/2428		81.55%	0.92[0.39,2.15]
FLAX-PAD 2013	3/58	1/52		11.95%	2.69[0.29,25.06]
MARGARIN 2002	0/109	2/157		6.5%	0.29[0.01,5.93]
Subtotal (95% CI)	**2576**	**2637**		**100%**	**0.97[0.45,2.09]**
Total events: 13 (Higher omega 3), 14 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=1.44, df=2(P=0.49); I^2=0%					
Test for overall effect: Z=0.09(P=0.93)					
4.55.2 Moderate/high risk of bias					
Norwegian 1968	13/6716	9/6690		91.4%	1.44[0.62,3.36]
WAHA 2016	1/362	1/346		8.6%	0.96[0.06,15.22]
Subtotal (95% CI)	**7078**	**7036**		**100%**	**1.39[0.62,3.13]**
Total events: 14 (Higher omega 3), 10 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.08, df=1(P=0.78); I^2=0%					
Test for overall effect: Z=0.79(P=0.43)					
Test for subgroup differences: Chi^2=0.4, df=1 (P=0.53), I^2=0%					

Analysis 4.56. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 56 Stroke - ALA - SA by compliance and study size.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.56.1 SA - low risk of compliance bias					
AlphaOmega - ALA 2010	10/2409	11/2428		85.1%	0.92[0.39,2.15]
MARGARIN 2002	0/109	2/157		6.78%	0.29[0.01,5.93]
WAHA 2016	1/362	1/346		8.11%	0.96[0.06,15.22]
Subtotal (95% CI)	**2880**	**2931**		**100%**	**0.85[0.39,1.87]**
Total events: 11 (Higher omega 3), 14 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.53, df=2(P=0.77); I^2=0%					
Test for overall effect: Z=0.4(P=0.69)					
4.56.2 SA - 100+ randomised					
AlphaOmega - ALA 2010	10/2409	11/2428		42.84%	0.92[0.39,2.15]
FLAX-PAD 2013	3/58	1/52		6.28%	2.69[0.29,25.06]
MARGARIN 2002	0/109	2/157		3.42%	0.29[0.01,5.93]
Norwegian 1968	13/6716	9/6690		43.38%	1.44[0.62,3.36]
WAHA 2016	1/362	1/346		4.08%	0.96[0.06,15.22]
Subtotal (95% CI)	**9654**	**9673**		**100%**	**1.15[0.66,2.01]**
Total events: 27 (Higher omega 3), 24 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=1.92, df=4(P=0.75); I^2=0%					
Test for overall effect: Z=0.48(P=0.63)					
Test for subgroup differences: Chi^2=0.37, df=1 (P=0.54), I^2=0%					



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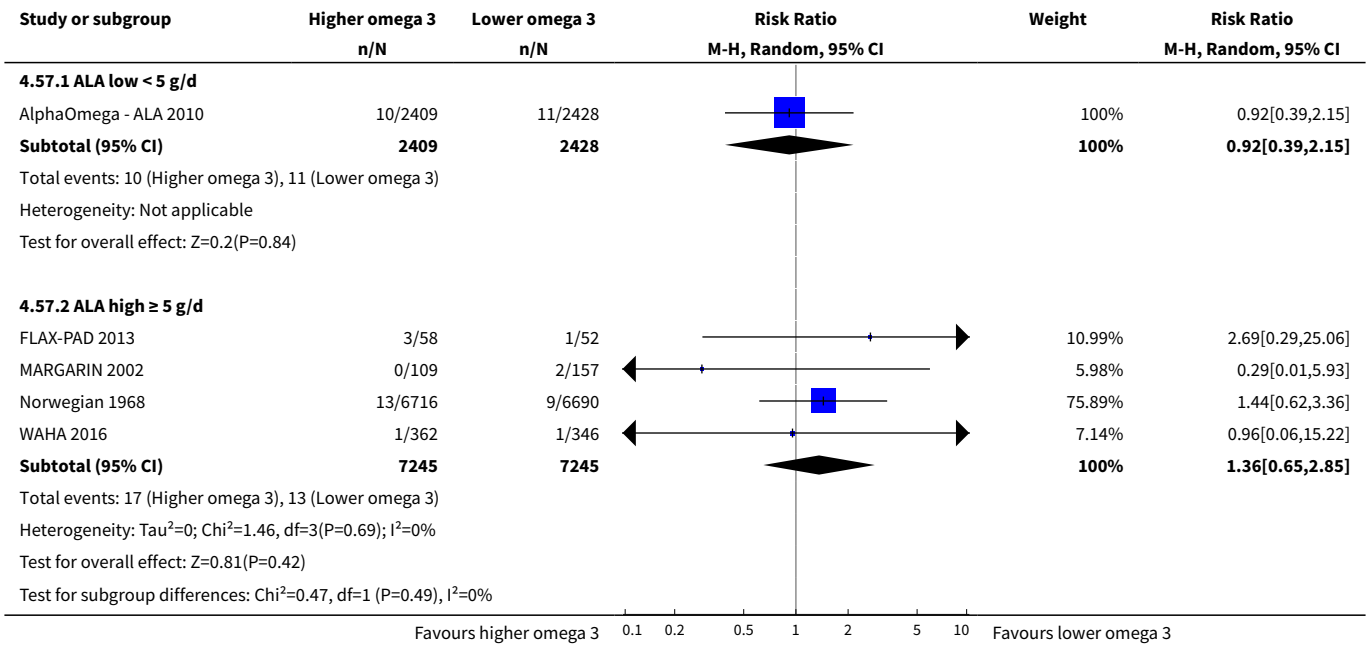
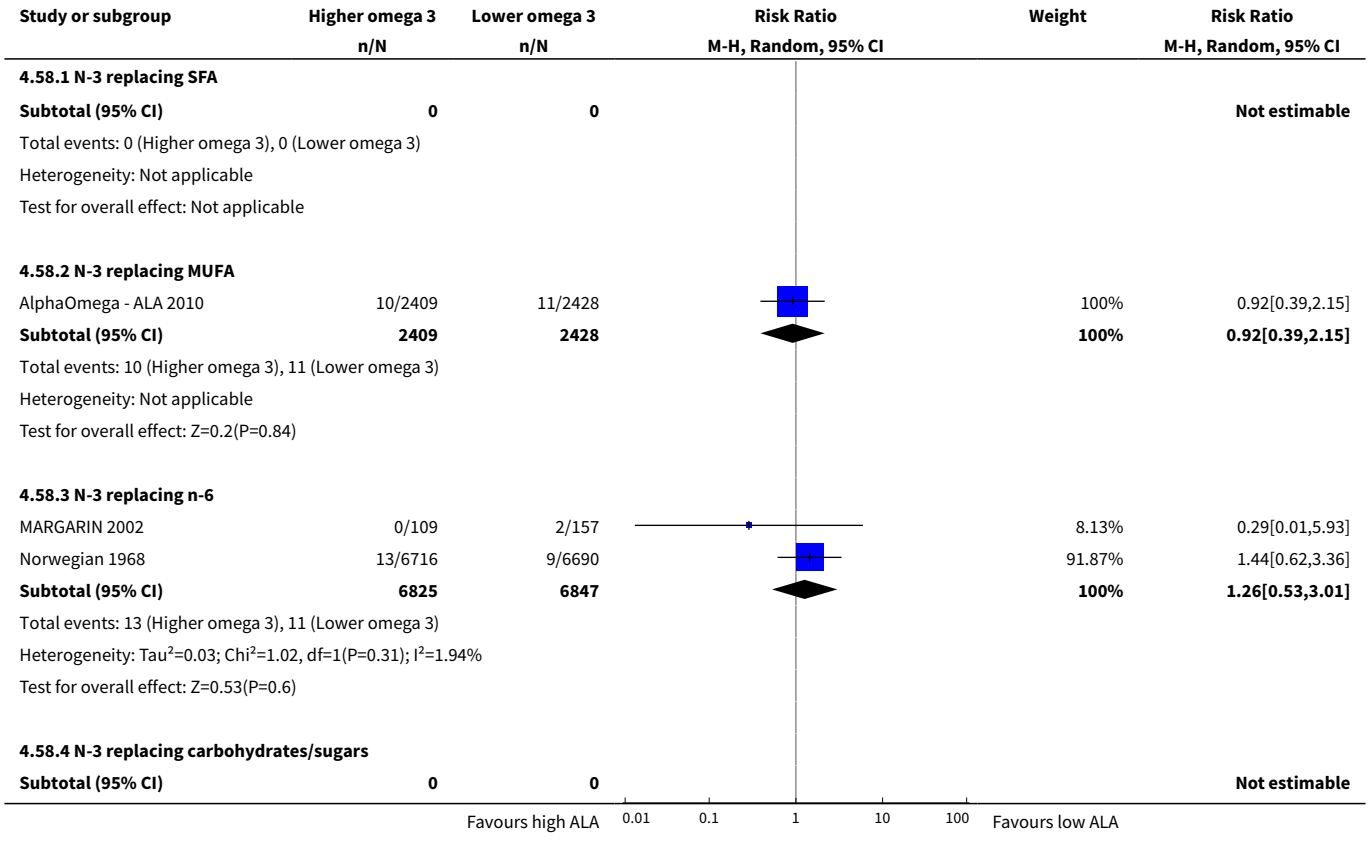
Analysis 4.57. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 57 Stroke - ALA - subgroup by dose.



Analysis 4.58. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 58 Stroke - ALA - subgroup by replacement.



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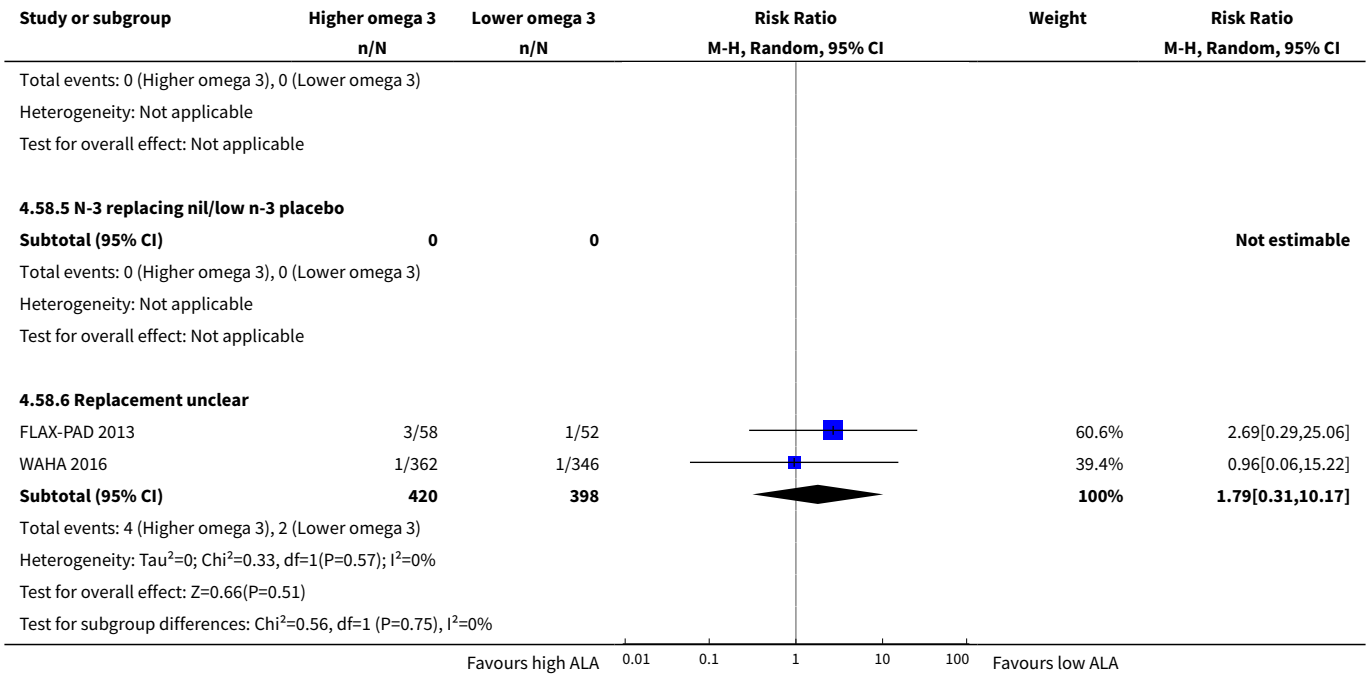
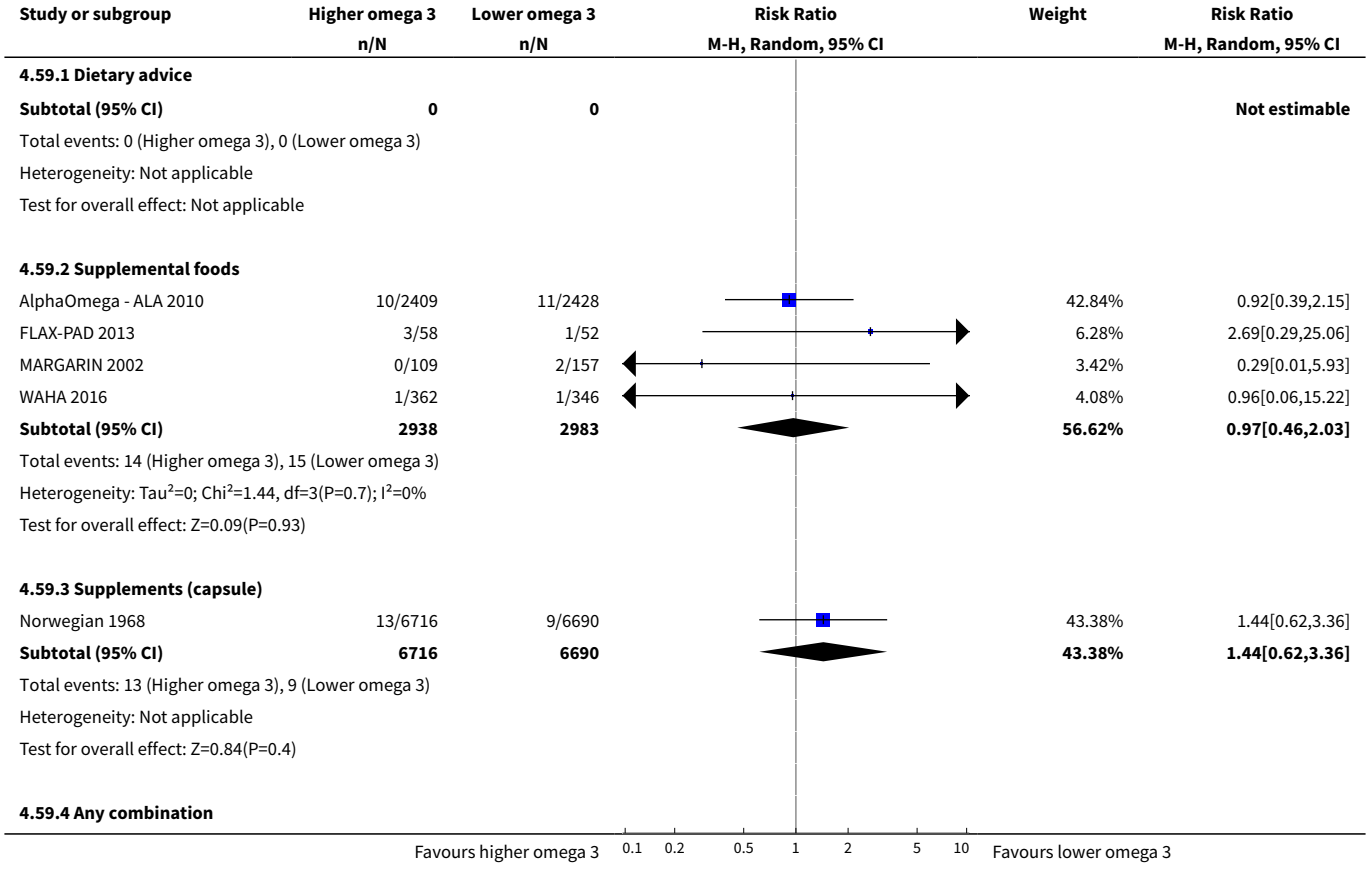


Analysis 4.59. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 59 Stroke - ALA - subgroup by intervention type.



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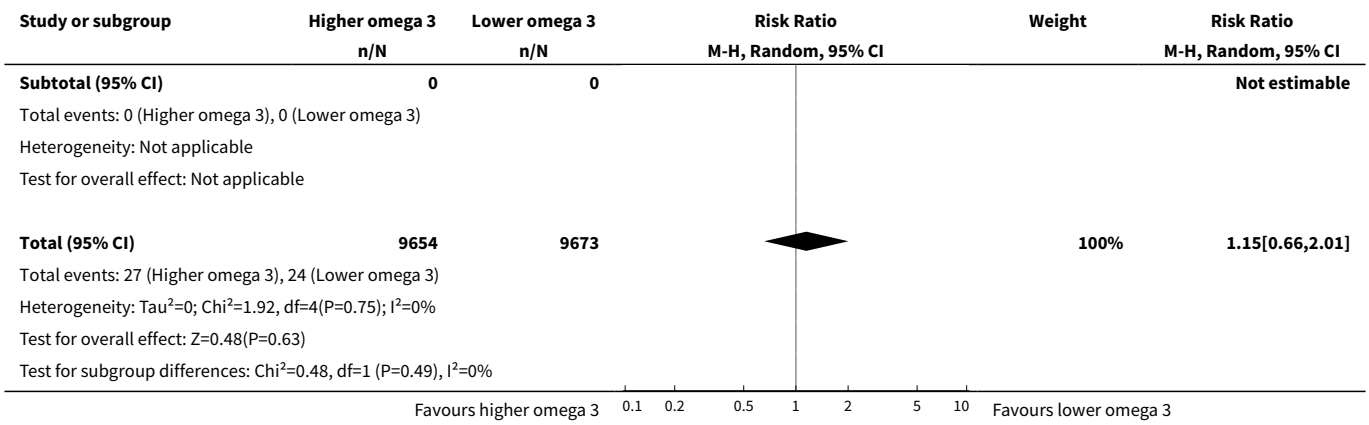
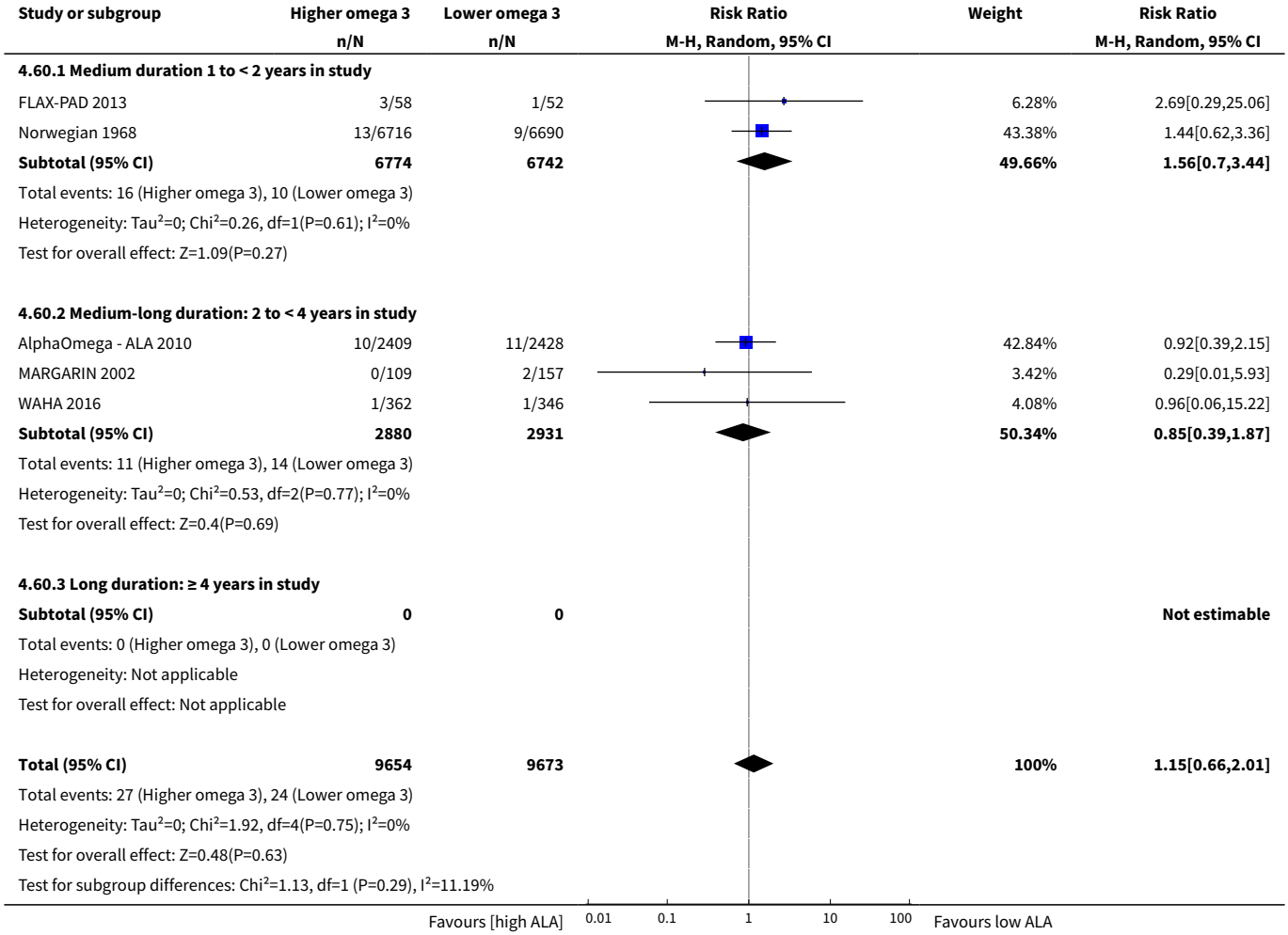


Analysis 4.60. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 60 Stroke - ALA - subgroup by duration.



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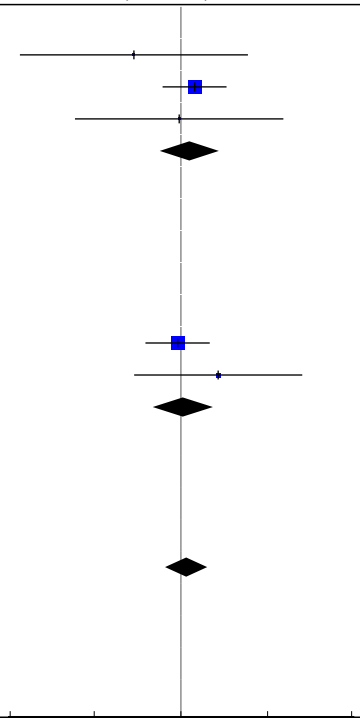
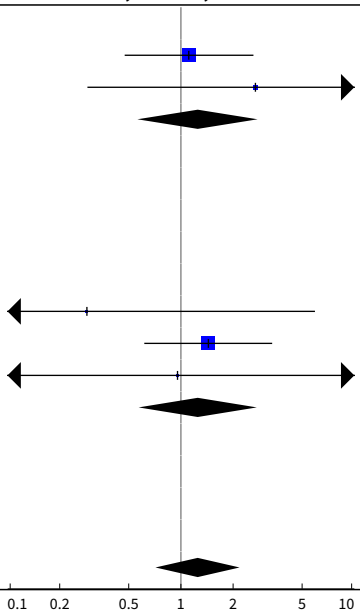
Analysis 4.61. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 61 Stroke - ALA - subgroup by primary or secondary prevention.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.61.1 Primary prevention					
MARGARIN 2002	0/109	2/157		3.42%	0.29[0.01,5.93]
Norwegian 1968	13/6716	9/6690		43.38%	1.44[0.62,3.36]
WAHA 2016	1/362	1/346		4.08%	0.96[0.06,15.22]
Subtotal (95% CI)	**7187**	**7193**		**50.88%**	**1.25[0.57,2.74]**
Total events: 14 (Higher omega 3), 12 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=1.06, df=2(P=0.59); I^2=0%					
Test for overall effect: Z=0.56(P=0.58)					
4.61.2 Secondary prevention					
AlphaOmega - ALA 2010	10/2409	11/2428		42.84%	0.92[0.39,2.15]
FLAX-PAD 2013	3/58	1/52		6.28%	2.69[0.29,25.06]
Subtotal (95% CI)	**2467**	**2480**		**49.12%**	**1.05[0.47,2.34]**
Total events: 13 (Higher omega 3), 12 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.78, df=1(P=0.38); I^2=0%					
Test for overall effect: Z=0.12(P=0.9)					
Total (95% CI)	**9654**	**9673**		**100%**	**1.15[0.66,2.01]**
Total events: 27 (Higher omega 3), 24 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=1.92, df=4(P=0.75); I^2=0%					
Test for overall effect: Z=0.48(P=0.63)					
Test for subgroup differences: Chi^2=0.09, df=1 (P=0.76), I^2=0%					



Analysis 4.62. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 62 Stroke - ALA - subgroup by statin use.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.62.1 ALA - ≥ 50% of control group on statins					
AlphaOmega - EPA+DHA 2010	11/2404	10/2433		42.84%	1.11[0.47,2.62]
FLAX-PAD 2013	3/58	1/52		6.28%	2.69[0.29,25.06]
Subtotal (95% CI)	**2462**	**2485**		**49.12%**	**1.25[0.56,2.77]**
Total events: 14 (Higher omega 3), 11 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.52, df=1(P=0.47); I^2=0%					
Test for overall effect: Z=0.54(P=0.59)					
4.62.2 ALA - < 50% of control group on statins					
MARGARIN 2002	0/109	2/157		3.42%	0.29[0.01,5.93]
Norwegian 1968	13/6716	9/6690		43.38%	1.44[0.62,3.36]
WAHA 2016	1/362	1/346		4.08%	0.96[0.06,15.22]
Subtotal (95% CI)	**7187**	**7193**		**50.88%**	**1.25[0.57,2.74]**
Total events: 14 (Higher omega 3), 12 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=1.06, df=2(P=0.59); I^2=0%					
Test for overall effect: Z=0.56(P=0.58)					
Total (95% CI)	**9649**	**9678**		**100%**	**1.25[0.71,2.18]**



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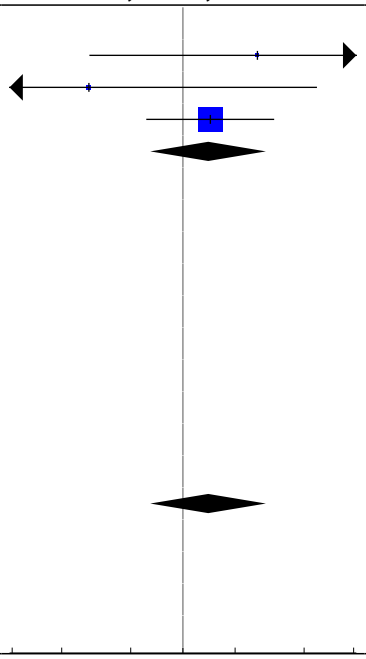
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 28 (Higher omega 3), 23 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=1.57, df=4(P=0.81); I²=0%					
Test for overall effect: Z=0.78(P=0.44)					
Test for subgroup differences: Chi²=0, df=1 (P=1), I²=0%					

Favours higher omega 3 — Favours lower omega 3

Analysis 4.63. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 63 Stroke - ALA - subgroup by stroke type.

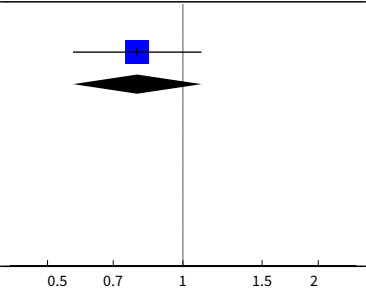
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.63.1 Ischaemic stroke - ALA					
FLAX-PAD 2013	3/58	1/52		11.83%	2.69[0.29,25.06]
MARGARIN 2002	0/109	2/157		6.43%	0.29[0.01,5.93]
Norwegian 1968	13/6716	9/6690		81.73%	1.44[0.62,3.36]
Subtotal (95% CI)	**6883**	**6899**		**100%**	**1.4[0.65,3.01]**
Total events: 16 (Higher omega 3), 12 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=1.39, df=2(P=0.5); I²=0%					
Test for overall effect: Z=0.85(P=0.39)					
4.63.2 Haemorrhagic stroke - ALA					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 3), 0 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**6883**	**6899**		**100%**	**1.4[0.65,3.01]**
Total events: 16 (Higher omega 3), 12 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=1.39, df=2(P=0.5); I²=0%					
Test for overall effect: Z=0.85(P=0.39)					
Test for subgroup differences: Not applicable					



Favours higher omega 3 — Favours lower omega 3

Analysis 4.64. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 64 Arrythmia (overall) - ALA.

Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.64.1 ALA - new arrhythmias					
AlphaOmega - ALA 2010	62/2409	79/2428		73.1%	0.79[0.57,1.1]
Subtotal (95% CI)	**2409**	**2428**		**73.1%**	**0.79[0.57,1.1]**
Total events: 62 (Favours higher omega 3), 79 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.4(P=0.16)					
4.64.2 ALA - recurrent arrhythmias					



Favours higher omega 3 — Favours lower omega 3

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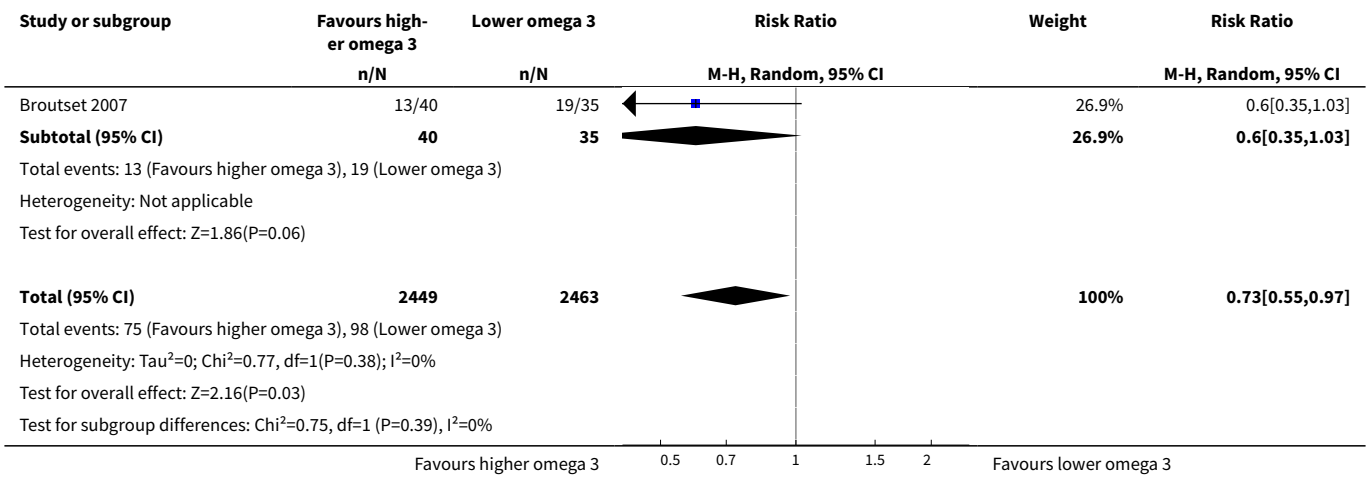
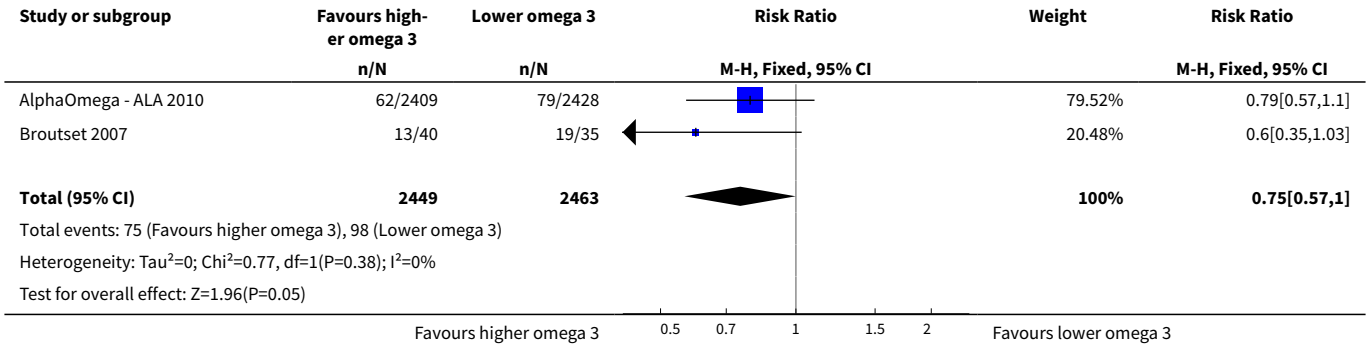
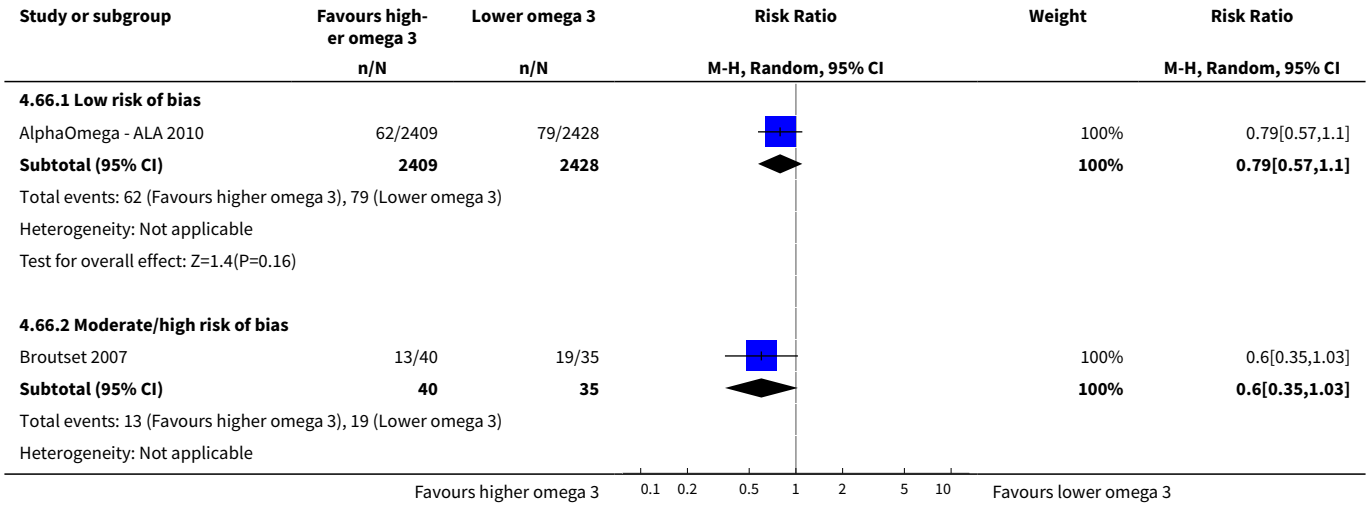


Analysis 4.65. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 65 Arrythmia - ALA - SA fixed-effect.



Analysis 4.66. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 66 Arrhythmia - ALA - SA by summary risk of bias.



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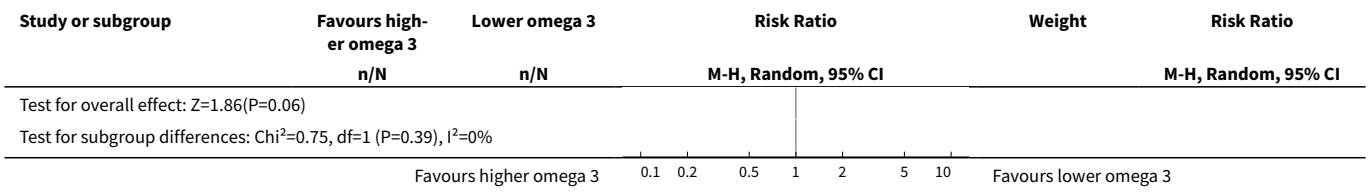
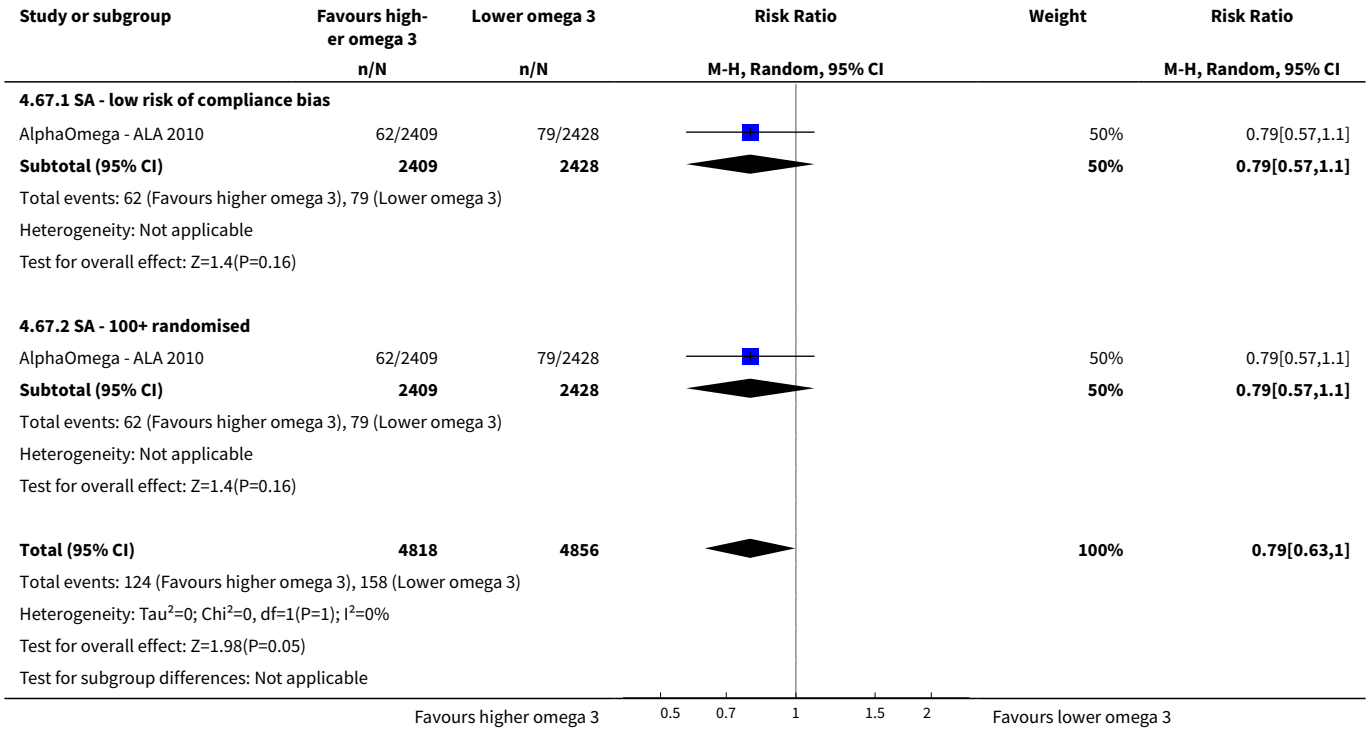


Analysis 4.67. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 67 Arrythmia - ALA - SA by compliance and study size.



Comparison 5. High vs low ALA omega-3 fat (secondary outcomes)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 MACCEs - ALA	1	110	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.32, 3.95]
2 Myocardial infarction (overall) - ALA	3	18353	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.76, 1.32]
3 Total MI - ALA - subgroup by fatality	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Fatal MI	2	4947	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.62, 1.46]
3.2 Non-fatal MI	3	5213	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.15, 1.77]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Angina - ALA	2	13516	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.75, 2.64]
5 Revascularisation - ALA	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 CABG - ALA	1	266	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.01, 5.93]
5.2 Angioplasty - ALA	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.3 Any revascularisation - ALA	1	266	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.07, 7.84]
6 Peripheral arterial disease - ALA	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7 Body weight, kg - ALA	4	664	Mean Difference (IV, Random, 95% CI)	-1.49 [-4.17, 1.18]
8 Weight, kg - ALA - sensitivity analysis (SA) fixed-effect	4	664	Mean Difference (IV, Fixed, 95% CI)	0.17 [-0.61, 0.96]
9 Weight, kg - ALA - SA by summary risk of bias	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 Low risk of bias	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9.2 Moderate/high risk of bias	4	664	Mean Difference (IV, Random, 95% CI)	-1.49 [-4.17, 1.18]
10 Weight, kg - ALA - SA by compliance and study size	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
10.1 SA - low risk of compliance bias	3	629	Mean Difference (IV, Random, 95% CI)	-1.59 [-4.47, 1.30]
10.2 SA - 100+ randomised	3	629	Mean Difference (IV, Random, 95% CI)	-1.59 [-4.47, 1.30]
11 Weight, kg - ALA - subgroup by dose	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
11.1 ALA low < 5 g/d	3	485	Mean Difference (IV, Random, 95% CI)	-0.71 [-3.31, 1.90]
11.2 ALA high > 5 g/d	1	179	Mean Difference (IV, Random, 95% CI)	-4.20 [-7.61, -0.79]
12 Weight, kg - ALA - subgroup by intervention type	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
12.1 Dietary advice	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12.2 Supplemental foods	3	526	Mean Difference (IV, Random, 95% CI)	-1.23 [-5.27, 2.80]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.3 Supplement (capsule)	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12.4 Any combination	1	138	Mean Difference (IV, Random, 95% CI)	-1.98 [-5.89, 1.92]
13 Weight, kg - ALA - subgroup by replacement	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
13.1 ALA replacing SFA	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
13.2 ALA replacing MUFA	1	138	Mean Difference (IV, Random, 95% CI)	-1.98 [-5.89, 1.92]
13.3 ALA replacing n-6	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
13.4 ALA replacing carbs/sugars	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
13.5 ALA replacing nil/low n-3 placebo	1	35	Mean Difference (IV, Random, 95% CI)	-0.30 [-10.57, 9.97]
13.6 Replacement unclear	2	491	Mean Difference (IV, Random, 95% CI)	-1.43 [-6.26, 3.39]
14 Weight, kg - ALA - subgroup by duration	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
14.1 Medium duration 1 to < 2 years in study	4	664	Mean Difference (IV, Random, 95% CI)	-1.49 [-4.17, 1.18]
14.2 Medium-long duration: 2 to < 4 years in study	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
14.3 Long duration ≥ 4 years in study	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
15 Weight, kg - ALA - subgroup by statin use	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
15.1 ALA - ≥ 50% of control group on statins	1	35	Mean Difference (IV, Random, 95% CI)	-0.30 [-10.57, 9.97]
15.2 ALA - < 50% of control group on statins	1	138	Mean Difference (IV, Random, 95% CI)	-1.98 [-5.89, 1.92]
15.3 ALA - use of statins unclear	2	491	Mean Difference (IV, Random, 95% CI)	-1.43 [-6.26, 3.39]
16 Weight, kg - ALA - subgroup by primary or secondary prevention	4		Mean Difference (IV, Random, 95% CI)	Subtotals only

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.1 Low CVD risk	3	629	Mean Difference (IV, Random, 95% CI)	-1.59 [-4.47, 1.30]
16.2 Moderate CVD risk	1	35	Mean Difference (IV, Random, 95% CI)	-0.30 [-10.57, 9.97]
16.3 High CVD risk	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
17 Body mass index, kg/m² - ALA	3	1581	Mean Difference (IV, Random, 95% CI)	-0.42 [-1.53, 0.69]
18 BMI, kg/m² - ALA - SA fixed-effect	3	1581	Mean Difference (IV, Fixed, 95% CI)	0.12 [-0.06, 0.30]
19 BMI, kg/m² - ALA - SA by summary risk of bias	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
19.1 Low risk of bias	2	1402	Mean Difference (IV, Random, 95% CI)	0.15 [-0.04, 0.33]
19.2 Moderate/high risk of bias	1	179	Mean Difference (IV, Random, 95% CI)	-1.5 [-2.86, -0.14]
20 BMI, kg/m² - ALA - SA by compliance and study size	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
20.1 SA - low risk of compliance bias	3	1581	Mean Difference (IV, Random, 95% CI)	-0.42 [-1.53, 0.69]
20.2 SA - 100+ randomised	3	1581	Mean Difference (IV, Random, 95% CI)	-0.42 [-1.53, 0.69]
21 BMI, kg/m² - ALA - subgroup by dose	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
21.1 ALA low < 5 g/d	1	1260	Mean Difference (IV, Random, 95% CI)	0.15 [-0.03, 0.33]
21.2 ALA high > 5 g/d	2	321	Mean Difference (IV, Random, 95% CI)	-1.12 [-2.24, 0.01]
22 BMI, kg/m² - ALA - subgroup by intervention type	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
22.1 Dietary advice	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
22.2 Supplemental foods	3	1581	Mean Difference (IV, Random, 95% CI)	-0.42 [-1.53, 0.69]
22.3 Supplement (capsule)	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.4 Any combination	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
23 BMI, kg/m² - ALA - subgroup by replacement	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
23.1 ALA replacing SFA	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
23.2 ALA replacing MUFA	1	1260	Mean Difference (IV, Random, 95% CI)	0.15 [-0.03, 0.33]
23.3 ALA replacing n-6	1	142	Mean Difference (IV, Random, 95% CI)	-0.3 [-2.29, 1.69]
23.4 ALA replacing carbs/sugars	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
23.5 ALA replacing nil/low n-3 placebo	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
23.6 Replacement unclear	1	179	Mean Difference (IV, Random, 95% CI)	-1.5 [-2.86, -0.14]
24 BMI, kg/m² - ALA - subgroup by duration	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
24.1 Medium duration 1 to < 2 years in study	1	179	Mean Difference (IV, Random, 95% CI)	-1.5 [-2.86, -0.14]
24.2 Medium-long duration: 2 to < 4 years in study	2	1402	Mean Difference (IV, Random, 95% CI)	0.15 [-0.04, 0.33]
24.3 Long duration ≥ 4 years in study	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
25 BMI, kg/m² - ALA - subgroup by statin use	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
25.1 ALA - ≥ 50% of control group on statins	1	1260	Mean Difference (IV, Random, 95% CI)	0.15 [-0.03, 0.33]
25.2 ALA - < 50% of control group on statins	1	142	Mean Difference (IV, Random, 95% CI)	-0.3 [-2.29, 1.69]
25.3 ALA - use of statins unclear	1	179	Mean Difference (IV, Random, 95% CI)	-1.5 [-2.86, -0.14]
26 BMI, kg/m² - ALA - subgroup by primary or secondary preventionA	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
26.1 Primary prevention of CVD	2	321	Mean Difference (IV, Random, 95% CI)	-1.12 [-2.24, 0.01]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
26.2 Secondary prevention of CVD	1	1260	Mean Difference (IV, Random, 95% CI)	0.15 [-0.03, 0.33]
27 Other measures of adiposity - ALA	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
27.1 Visceral adipose tissue, cm^2	1	35	Mean Difference (IV, Fixed, 95% CI)	27.0 [-21.28, 75.28]
27.2 Subcutaneous adipose tissue, cm^2	1	35	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
27.3 Waist circumference, cm	3	629	Mean Difference (IV, Fixed, 95% CI)	-1.59 [-3.10, -0.07]
28 Total cholesterol, serum, mmoL/L - ALA	6	2164	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.23, 0.05]
29 TC, mmoL/L - ALA - SA fixed-effect	6	2164	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.17, -0.03]
30 TC, mmoL/L - ALA - SA by summary risk of bias	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
30.1 Low risk of bias	3	1436	Mean Difference (IV, Random, 95% CI)	0.00 [-0.13, 0.14]
30.2 Moderate/high risk of bias	3	728	Mean Difference (IV, Random, 95% CI)	-0.19 [-0.36, -0.01]
31 TC, mmoL/L - ALA - SA by compliance and study size	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
31.1 SA - low risk of compliance bias	4	2045	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.25, 0.05]
31.2 SA - 100+ randomised	4	2045	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.25, 0.05]
32 TC, mmoL/L - ALA - subgroup by dose	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
32.1 ALA low < 5 g/d	3	1759	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.24, 0.09]
32.2 ALA high > 5 g/d	3	405	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.47, 0.21]
33 TC, mmoL/L - ALA - subgroup by intervention type	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
33.1 Dietary advice	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
33.2 Supplemental foods	6	2164	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.23, 0.05]
33.3 Supplement (capsule)	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
33.4 Any combination	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
34 TC, mmoL/L - ALA - subgroup by replacement	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
34.1 ALA replacing SFA	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
34.2 ALA replacing MUFA	1	1210	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.13, 0.09]
34.3 ALA replacing n-6	1	142	Mean Difference (IV, Random, 95% CI)	0.14 [-0.10, 0.38]
34.4 ALA replacing carbs/sugars	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
34.5 ALA replacing nil/low n-3 placebo	1	35	Mean Difference (IV, Random, 95% CI)	0.30 [-0.30, 0.90]
34.6 Replacement unclear	3	777	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.31, -0.11]
35 TC, mmoL/L - ALA - subgroup by duration	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
35.1 Medium duration 1 to < 2 years in study	4	812	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.33, -0.07]
35.2 Medium-long duration: 2 to < 4 years in study	2	1352	Mean Difference (IV, Random, 95% CI)	0.02 [-0.12, 0.16]
35.3 Long duration ≥ 4 years in study	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
36 TC, mmoL/L - ALA - subgroup by statin use	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
36.1 ALA - ≥ 50% of control group on statins	3	1329	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.15, 0.11]
36.2 ALA - < 50% of control group on statins	1	142	Mean Difference (IV, Random, 95% CI)	0.14 [-0.10, 0.38]
36.3 ALA - use of statins unclear	2	693	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.30, -0.11]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
37 TC, mmoL/L - ALA - subgroup by primary or secondary prevention	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
37.1 Primary prevention of CVD	4	870	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.30, 0.12]
37.2 Secondary prevention of CVD	2	1294	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.14, 0.08]
38 Triglycerides, fasting, serum, mmoL/L - ALA	6	1776	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.11, 0.05]
39 TG, fasting, mmoL/L - ALA - SA fixed-effect	6	1776	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.11, 0.05]
40 TG, fasting, mmoL/L- ALA - SA by summary risk of bias	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
40.1 Low risk of bias	3	1436	Mean Difference (IV, Random, 95% CI)	0.03 [-0.13, 0.19]
40.2 Moderate/high risk of bias	3	340	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.18, 0.09]
41 TG, fasting, mmoL/L- ALA - SA by compliance and study size	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
41.1 SA - low risk of compliance bias	4	1657	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.13, 0.04]
41.2 SA - 100+ randomised	4	1657	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.13, 0.04]
42 TG, fasting, mmoL/L - ALA - subgroup by dose	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
42.1 ALA low < 5 g/d	3	1371	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.16, 0.03]
42.2 ALA high > 5 g/d	3	405	Mean Difference (IV, Random, 95% CI)	0.05 [-0.09, 0.19]
43 TG, fasting, mmoL/L- ALA - subgroup by intervention type	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
43.1 Dietary advice	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
43.2 Supplemental foods	5	1650	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.10, 0.07]
43.3 Supplement (capsule)	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
43.4 Any combination	1	126	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.33, 0.09]
44 TG, fasting, mmoL/L-AL - subgroup by replacement	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
44.1 ALA replacing SFA	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
44.2 ALA replacing MUFA	2	1336	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.17, 0.02]
44.3 ALA replacing n-6	1	142	Mean Difference (IV, Random, 95% CI)	0.13 [-0.16, 0.42]
44.4 ALA replacing carbs/sugars	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
44.5 ALA replacing nil/low n-3 placebo	1	35	Mean Difference (IV, Random, 95% CI)	0.30 [-0.39, 0.99]
44.6 Replacement unclear	2	263	Mean Difference (IV, Random, 95% CI)	0.04 [-0.15, 0.23]
45 TG, fasting, mmoL/L- ALA - subgroup by duration	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
45.1 Medium duration 1 to < 2 years in study	4	424	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.15, 0.12]
45.2 Medium-long duration: 2 to < 4 years in study	2	1352	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.17, 0.15]
45.3 Long duration ≥ 4 years in study	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
46 TG, fasting, mmoL/L - ALA - subgroup by statin use	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
46.1 ALA - ≥ 50% of control group on statins	3	1329	Mean Difference (IV, Random, 95% CI)	0.03 [-0.17, 0.23]
46.2 ALA - < 50% of control group on statins	2	268	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.26, 0.23]
46.3 ALA - use of statins unclear	1	179	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.20, 0.16]
47 TG, fasting, mmoL/L- ALA - subgroup by primary or secondary prevention	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
47.1 Primary prevention	4	482	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.14, 0.11]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
47.2 Secondary prevention	2	1294	Mean Difference (IV, Random, 95% CI)	0.02 [-0.22, 0.25]
48 High-density lipoprotein, serum, mmoL/L - ALA	6	1776	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.08, 0.03]
49 HDL, mmoL/L - ALA - SA fixed-effect	6	1776	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.05, 0.00]
50 HDL, mmoL/L - ALA - SA by summary risk of bias	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
50.1 Low risk of bias	3	1436	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.06, 0.00]
50.2 Moderate/high risk of bias	3	340	Mean Difference (IV, Random, 95% CI)	0.04 [-0.14, 0.22]
51 HDL, mmoL/L - ALA - SA by compliance and study size	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
51.1 SA - low risk of compliance bias	4	1657	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.08, 0.04]
51.2 SA - 100+ randomised	4	1657	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.08, 0.04]
52 HDL, mmoL/L - ALA - subgroup by dose	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
52.1 ALA low < 5 g/d	3	1371	Mean Difference (IV, Random, 95% CI)	0.06 [-0.08, 0.19]
52.2 ALA high > 5 g/d	3	405	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.12, -0.01]
53 HDL, mmoL/L - ALA - subgroup by intervention type	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
53.1 Dietary advice	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
53.2 Supplemental foods	5	1650	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.06, -0.00]
53.3 Supplement (capsule)	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
53.4 Any combination	1	126	Mean Difference (IV, Random, 95% CI)	0.15 [0.01, 0.29]
54 HDL, mmoL/L - ALA - subgroup by replacement	6		Mean Difference (IV, Random, 95% CI)	Subtotals only

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
54.1 ALA replacing SFA	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
54.2 ALA replacing MUFA	2	1336	Mean Difference (IV, Random, 95% CI)	0.05 [-0.11, 0.22]
54.3 ALA replacing n-6	1	142	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.11, 0.03]
54.4 ALA replacing carbs/sugars	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
54.5 ALA replacing nil/low n-3 placebo	1	35	Mean Difference (IV, Random, 95% CI)	0.10 [-0.17, 0.37]
54.6 Replacement unclear	2	263	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.17, -0.02]
55 HDL, mmoL/L - ALA - subgroup by duration	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
55.1 Medium duration 1 to < 2 years in study	4	424	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.13, 0.13]
55.2 Medium-long duration: 2 to < 4 years in study	2	1352	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.05, 0.00]
55.3 Long duration ≥ 4 years in study	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
56 HDL, mmoL/L - ALA - subgroup by statin use	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
56.1 ALA - ≥ 50% of control group on statins	3	1329	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.09, 0.03]
56.2 ALA - < 50% of control group on statins	2	268	Mean Difference (IV, Random, 95% CI)	0.05 [-0.14, 0.23]
56.3 ALA - use of statins unclear	1	179	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.20, 0.02]
57 HDL, mmoL/L - ALA - subgroup by primary or secondary prevention	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
57.1 Low CVD risk	2	305	Mean Difference (IV, Random, 95% CI)	0.03 [-0.21, 0.26]
57.2 Moderate CVD risk	2	177	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.10, 0.04]
57.3 High CVD risk	2	1294	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.11, 0.03]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
58 Low-density lipoprotein, serum, mmoL/L - ALA	7	2201	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.15, 0.04]
59 LDL, mmoL/L - ALA - SA fixed-effect	7	2201	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.11, 0.00]
60 LDL, mmoL/L - ALA - SA by summary risk of bias	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
60.1 Low risk of bias	3	1350	Mean Difference (IV, Random, 95% CI)	0.02 [-0.05, 0.10]
60.2 Moderate/high risk of bias	4	851	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.22, -0.06]
61 LDL, mmoL/L - ALA - SA by compliance and study size	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
61.1 SA - low risk of compliance bias	5	2085	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.16, 0.06]
61.2 SA - 100+ randomised	5	2085	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.16, 0.06]
62 LDL, mmoL/L - ALA - subgroup by dose	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
62.1 ALA low < 5 g/d	4	1796	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.17, 0.05]
62.2 ALA high > 5 g/d	3	405	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.28, 0.19]
63 LDL, mmoL/L - ALA - subgroup by intervention type	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
63.1 Dietary advice	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
63.2 Supplemental foods	6	2075	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.17, 0.05]
63.3 Supplement (capsule)	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
63.4 Any combination	1	126	Mean Difference (IV, Random, 95% CI)	0.0 [-0.25, 0.25]
64 LDL, mmoL/L - ALA - subgroup by replacement	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
64.1 ALA replacing SFA	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

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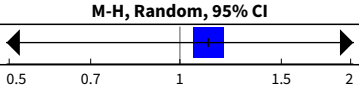
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
64.2 ALA replacing MUFA	2	1250	Mean Difference (IV, Random, 95% CI)	0.01 [-0.07, 0.09]
64.3 ALA replacing n-6	1	142	Mean Difference (IV, Random, 95% CI)	0.14 [-0.08, 0.36]
64.4 ALA replacing carbs/sugars	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
64.5 ALA replacing nil/low n-3 placebo	1	32	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.59, 0.39]
65 LDL, mmoL/L - ALA - subgroup by duration	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
65.1 Medium duration 1 to < 2 years in study	5	935	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.22, -0.06]
65.2 Medium-long duration: 2 to < 4 years in study	2	1266	Mean Difference (IV, Random, 95% CI)	0.03 [-0.06, 0.13]
65.3 Long duration ≥ 4 years in study	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
66 LDL, mmoL/L - ALA - subgroup by statin use	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
66.1 ALA - ≥ 50% of control group on statins	3	1240	Mean Difference (IV, Random, 95% CI)	0.00 [-0.08, 0.08]
66.2 ALA - < 50% of control group on statins	2	268	Mean Difference (IV, Random, 95% CI)	0.08 [-0.09, 0.24]
66.3 ALA - use of statins unclear	2	693	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.25, -0.07]
67 LDL, mmoL/L - ALA - subgroup by primary or secondary prevention	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
67.1 Primary prevention of CVD	5	993	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.20, 0.05]
67.2 Secondary prevention of CVD	2	1208	Mean Difference (IV, Random, 95% CI)	0.01 [-0.08, 0.09]

Analysis 5.1. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 1 MACCEs - ALA.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
FLAX-PAD 2013	5/58	4/52		100%	1.12[0.32,3.95]



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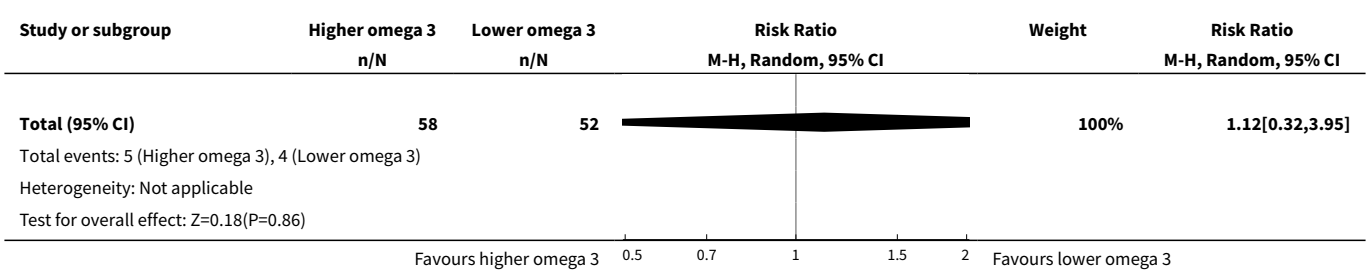
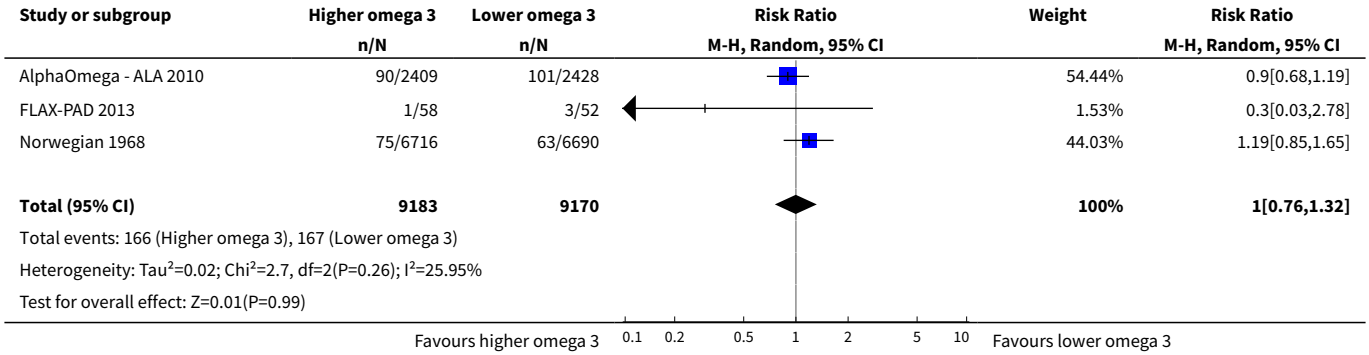
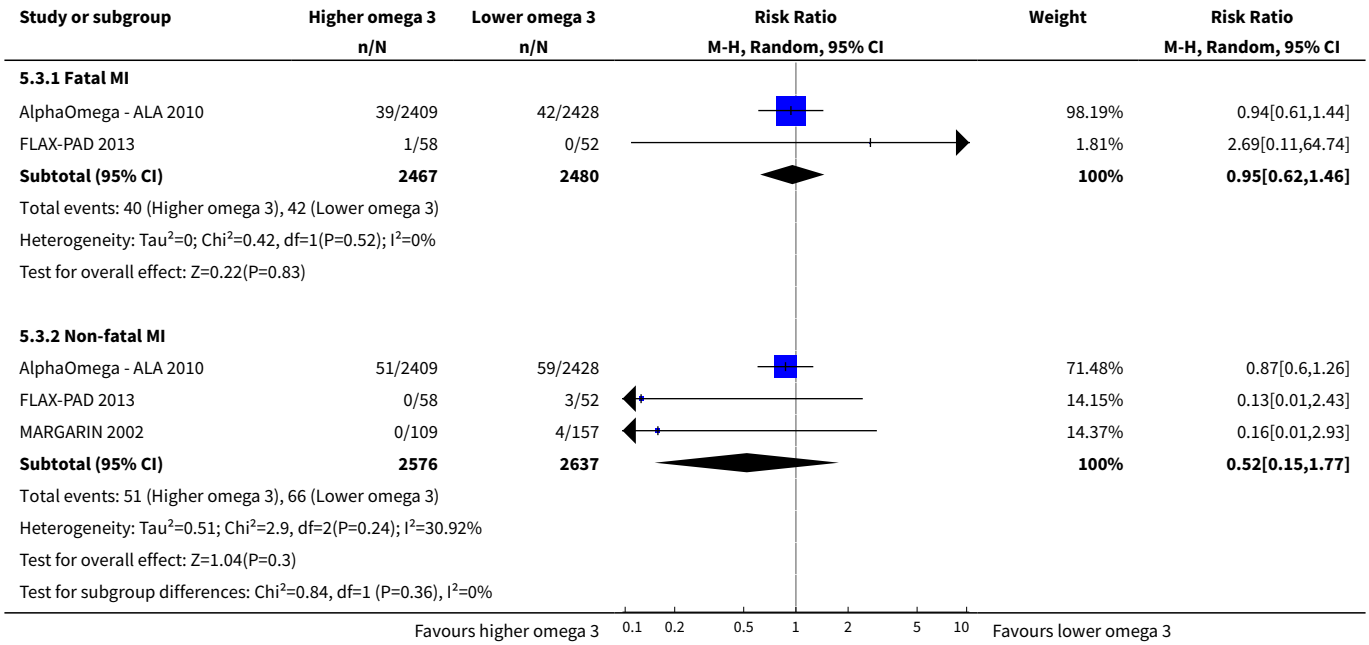


Analysis 5.2. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 2 Myocardial infarction (overall) - ALA.



Analysis 5.3. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 3 Total MI - ALA - subgroup by fatality.



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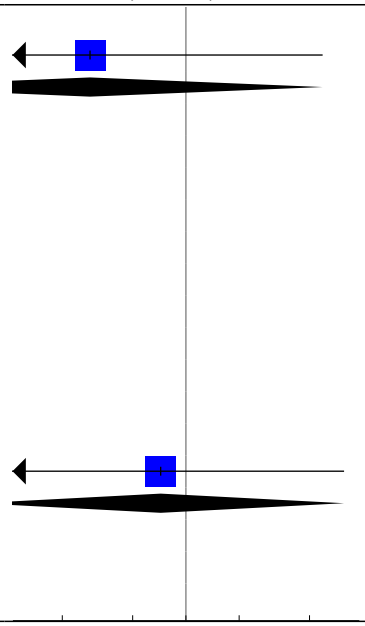
Analysis 5.4. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 4 Angina - ALA.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
FLAX-PAD 2013	1/58	0/52		3.93%	2.69[0.11,64.74]
Norwegian 1968	22/6716	16/6690		96.07%	1.37[0.72,2.61]
Total (95% CI)	**6774**	**6742**		**100%**	**1.41[0.75,2.64]**
Total events: 23 (Higher omega 3), 16 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.17, df=1(P=0.68); I^2=0%					
Test for overall effect: Z=1.06(P=0.29)					

Favours higher omega 3 — Favours lower omega 3

Analysis 5.5. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 5 Revascularisation - ALA.

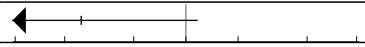
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.5.1 CABG - ALA					
MARGARIN 2002	0/109	2/157		100%	0.29[0.01,5.93]
Subtotal (95% CI)	**109**	**157**		**100%**	**0.29[0.01,5.93]**
Total events: 0 (Higher omega 3), 2 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.81(P=0.42)					
5.5.2 Angioplasty - ALA					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 3), 0 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
5.5.3 Any revascularisation - ALA					
MARGARIN 2002	1/109	2/157		100%	0.72[0.07,7.84]
Subtotal (95% CI)	**109**	**157**		**100%**	**0.72[0.07,7.84]**
Total events: 1 (Higher omega 3), 2 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.27(P=0.79)					



Favours higher omega 3 — Favours lower omega 3

Analysis 5.6. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 6 Peripheral arterial disease - ALA.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Norwegian 1968	2/6716	8/6690		0%	0.25[0.05,1.17]



Favours higher omega 3 — Favours lower omega 3

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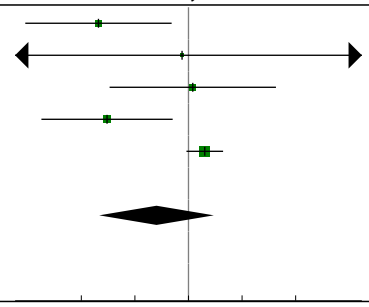
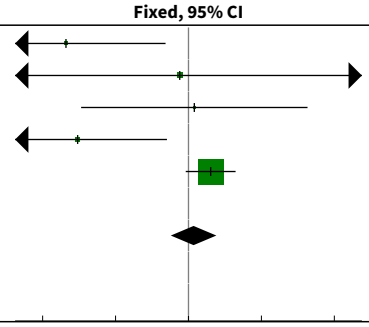
Analysis 5.7. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 7 Body weight, kg - ALA.

Study or subgroup	Favours higher omega 3 N	Mean(SD)	Lower omega 3 N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Dodin 2005	85	65.3 (11.2)	94	69.5 (12.1)		21.17%	-4.2[-7.61,-0.79]
HERO 2009	18	92 (17.1)	17	92.3 (13.8)		5.61%	-0.3[-10.57,9.97]
MENU 2016	34	-6.8 (8.2)	32	-7 (7.9)		19.23%	0.2[-3.68,4.08]
MENU 2016	35	-8.1 (7.1)	37	-4.3 (6.1)		22.7%	-3.8[-6.86,-0.74]
WAHA 2016	156	-0.3 (3.9)	156	-1 (3.9)		31.28%	0.76[-0.09,1.61]
Total ***	**328**		**336**			**100%**	**-1.49[-4.17,1.18]**
Heterogeneity: Tau^2=5.76; Chi^2=14.6, df=4(P=0.01); I^2=72.59%							
Test for overall effect: Z=1.09(P=0.27)							



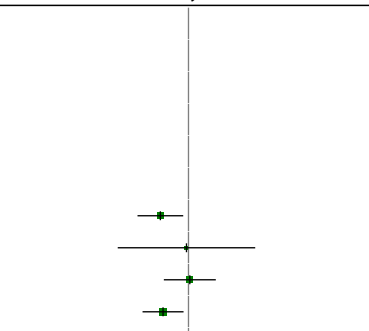
Analysis 5.8. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 8 Weight, kg - ALA - sensitivity analysis (SA) fixed-effect.

Study or subgroup	Higher omega 3 N	Mean(SD)	Lower omega 3 N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Dodin 2005	85	65.3 (11.2)	94	69.5 (12.1)		5.24%	-4.2[-7.61,-0.79]
HERO 2009	18	92 (17.1)	17	92.3 (13.8)		0.58%	-0.3[-10.57,9.97]
MENU 2016	34	-6.8 (8.2)	32	-7 (7.9)		4.05%	0.2[-3.68,4.08]
MENU 2016	35	-8.1 (7.1)	37	-4.3 (6.1)		6.51%	-3.8[-6.86,-0.74]
WAHA 2016	156	-0.3 (3.9)	156	-1 (3.9)		83.62%	0.76[-0.09,1.61]
Total ***	**328**		**336**			**100%**	**0.17[-0.61,0.96]**
Heterogeneity: Tau^2=0; Chi^2=14.6, df=4(P=0.01); I^2=72.59%							
Test for overall effect: Z=0.44(P=0.66)							



Analysis 5.9. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 9 Weight, kg - ALA - SA by summary risk of bias.

Study or subgroup	Higher omega 3 N	Mean(SD)	Lower omega 3 N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.9.1 Low risk of bias							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.9.2 Moderate/high risk of bias							
Dodin 2005	85	65.3 (11.2)	94	69.5 (12.1)		21.17%	-4.2[-7.61,-0.79]
HERO 2009	18	92 (17.1)	17	92.3 (13.8)		5.61%	-0.3[-10.57,9.97]
MENU 2016	34	-6.8 (8.2)	32	-7 (7.9)		19.23%	0.2[-3.68,4.08]
MENU 2016	35	-8.1 (7.1)	37	-4.3 (6.1)		22.7%	-3.8[-6.86,-0.74]
WAHA 2016	156	-0.3 (3.9)	156	-1 (3.9)		31.28%	0.76[-0.09,1.61]
Subtotal ***	**328**		**336**			**100%**	**-1.49[-4.17,1.18]**



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Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Heterogeneity: Tau²=5.76; Chi²=14.6, df=4(P=0.01); I²=72.59%							
Test for overall effect: Z=1.09(P=0.27)							

Favours higher omega 3 -20 -10 0 10 20 Favours lower omega 3

Analysis 5.10. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 10 Weight, kg - ALA - SA by compliance and study size.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.10.1 SA - low risk of compliance bias							
Dodin 2005	85	65.3 (11.2)	94	69.5 (12.1)		22.7%	-4.2[-7.61,-0.79]
MENU 2016	34	-6.8 (8.2)	32	-7 (7.9)		20.77%	0.2[-3.68,4.08]
MENU 2016	35	-8.1 (7.1)	37	-4.3 (6.1)		24.2%	-3.8[-6.86,-0.74]
WAHA 2016	156	-0.3 (3.9)	156	-1 (3.9)		32.32%	0.76[-0.09,1.61]
Subtotal ***	**310**		**319**			**100%**	**-1.59[-4.47,1.3]**
Heterogeneity: Tau²=6.52; Chi²=14.59, df=3(P=0); I²=79.43%							
Test for overall effect: Z=1.08(P=0.28)							
5.10.2 SA - 100+ randomised							
Dodin 2005	85	65.3 (11.2)	94	69.5 (12.1)		22.7%	-4.2[-7.61,-0.79]
MENU 2016	34	-6.8 (8.2)	32	-7 (7.9)		20.77%	0.2[-3.68,4.08]
MENU 2016	35	-8.1 (7.1)	37	-4.3 (6.1)		24.2%	-3.8[-6.86,-0.74]
WAHA 2016	156	-0.3 (3.9)	156	-1 (3.9)		32.32%	0.76[-0.09,1.61]
Subtotal ***	**310**		**319**			**100%**	**-1.59[-4.47,1.3]**
Heterogeneity: Tau²=6.52; Chi²=14.59, df=3(P=0); I²=79.43%							
Test for overall effect: Z=1.08(P=0.28)							

Favours higher omega 3 -20 -10 0 10 20 Favours lower omega 3

Analysis 5.11. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 11 Weight, kg - ALA - subgroup by dose.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.11.1 ALA low < 5 g/d							
HERO 2009	18	92 (17.1)	17	92.3 (13.8)		5.64%	-0.3[-10.57,9.97]
MENU 2016	35	-8.1 (7.1)	37	-4.3 (6.1)		28.03%	-3.8[-6.86,-0.74]
MENU 2016	34	-6.8 (8.2)	32	-7 (7.9)		22.7%	0.2[-3.68,4.08]
WAHA 2016	156	-0.3 (3.9)	156	-1 (3.9)		43.63%	0.76[-0.09,1.61]
Subtotal ***	**243**		**242**			**100%**	**-0.71[-3.31,1.9]**
Heterogeneity: Tau²=3.85; Chi²=7.94, df=3(P=0.05); I²=62.21%							
Test for overall effect: Z=0.53(P=0.6)							
5.11.2 ALA high > 5 g/d							
Dodin 2005	85	65.3 (11.2)	94	69.5 (12.1)		100%	-4.2[-7.61,-0.79]
Subtotal ***	**85**		**94**			**100%**	**-4.2[-7.61,-0.79]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.41(P=0.02)							

Favours higher omega 3 -20 -10 0 10 20 Favours lower omega 3

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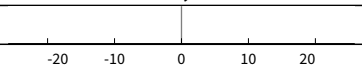
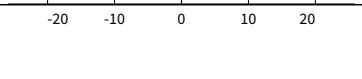
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for subgroup differences: Chi²=2.55, df=1 (P=0.11), I²=60.71%							



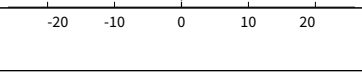
Analysis 5.12. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 12 Weight, kg - ALA - subgroup by intervention type.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.12.1 Dietary advice							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.12.2 Supplemental foods							
Dodin 2005	85	65.3 (11.2)	94	69.5 (12.1)		37.68%	-4.2[-7.61,-0.79]
HERO 2009	18	92 (17.1)	17	92.3 (13.8)		11.88%	-0.3[-10.57,9.97]
WAHA 2016	156	-0.3 (3.9)	156	-1 (3.9)		50.44%	0.76[-0.09,1.61]
Subtotal ***	**259**		**267**			**100%**	**-1.23[-5.27,2.8]**
Heterogeneity: Tau²=8.21; Chi²=7.65, df=2(P=0.02); I²=73.87%							
Test for overall effect: Z=0.6(P=0.55)							
5.12.3 Supplement (capsule)							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.12.4 Any combination							
MENU 2016	35	-8.1 (7.1)	37	-4.3 (6.1)		54.62%	-3.8[-6.86,-0.74]
MENU 2016	34	-6.8 (8.2)	32	-7 (7.9)		45.38%	0.2[-3.68,4.08]
Subtotal ***	**69**		**69**			**100%**	**-1.98[-5.89,1.92]**
Heterogeneity: Tau²=4.82; Chi²=2.52, df=1(P=0.11); I²=60.25%							
Test for overall effect: Z=1(P=0.32)							
Test for subgroup differences: Chi²=0.07, df=1 (P=0.79), I²=0%							



Analysis 5.13. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 13 Weight, kg - ALA - subgroup by replacement.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.13.1 ALA replacing SFA							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.13.2 ALA replacing MUFA							
MENU 2016	34	-6.8 (8.2)	32	-7 (7.9)		45.38%	0.2[-3.68,4.08]



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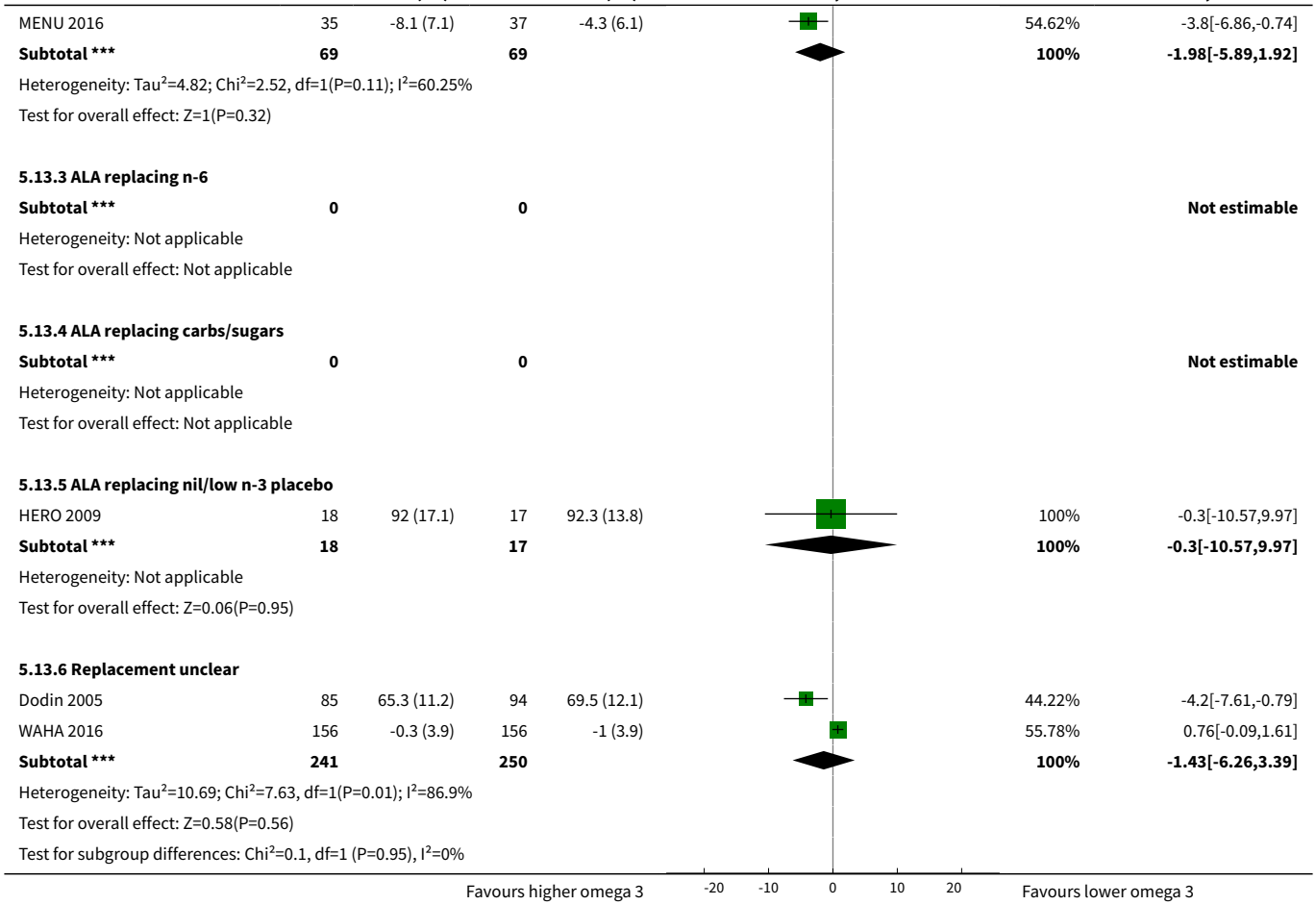
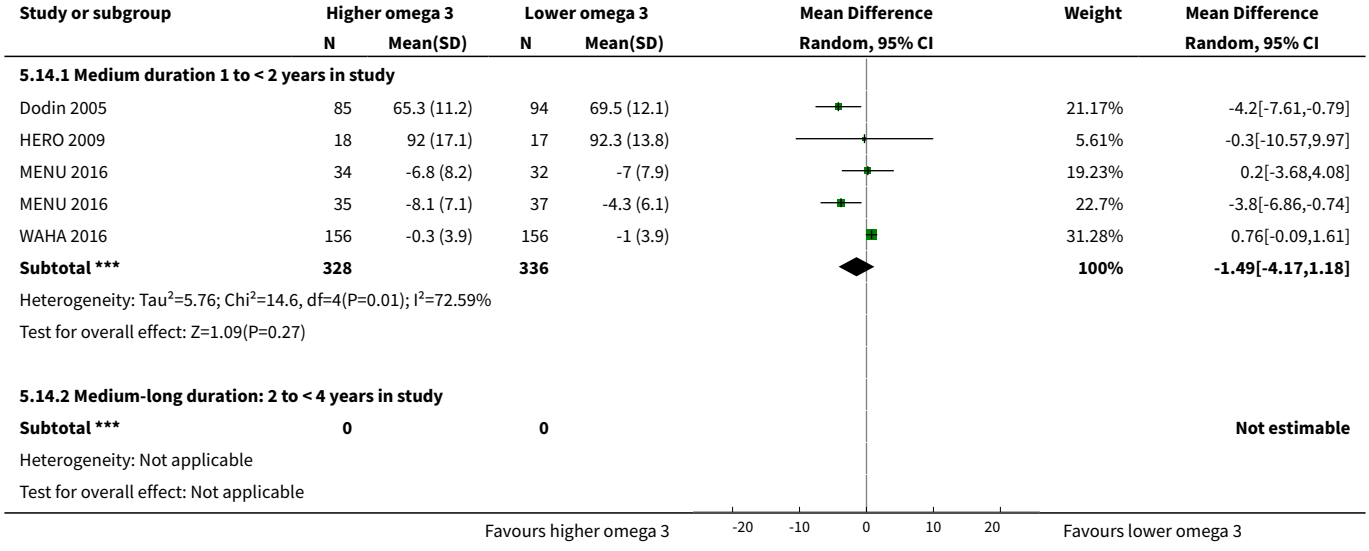


Analysis 5.14. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 14 Weight, kg - ALA - subgroup by duration.



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Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.14.3 Long duration ≥ 4 years in study							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							

Favours higher omega 3 -20 -10 0 10 20 Favours lower omega 3

Analysis 5.15. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 15 Weight, kg - ALA - subgroup by statin use.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.15.1 ALA - ≥ 50% of control group on statins							
HERO 2009	18	92 (17.1)	17	92.3 (13.8)		100%	-0.3[-10.57,9.97]
Subtotal ***	**18**		**17**			**100%**	**-0.3[-10.57,9.97]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.06(P=0.95)							
5.15.2 ALA - < 50% of control group on statins							
MENU 2016	34	-6.8 (8.2)	32	-7 (7.9)		45.38%	0.2[-3.68,4.08]
MENU 2016	35	-8.1 (7.1)	37	-4.3 (6.1)		54.62%	-3.8[-6.86,-0.74]
Subtotal ***	**69**		**69**			**100%**	**-1.98[-5.89,1.92]**
Heterogeneity: Tau^2=4.82; Chi^2=2.52, df=1(P=0.11); I^2=60.25%							
Test for overall effect: Z=1(P=0.32)							
5.15.3 ALA - use of statins unclear							
Dodin 2005	85	65.3 (11.2)	94	69.5 (12.1)		44.22%	-4.2[-7.61,-0.79]
WAHA 2016	156	-0.3 (3.9)	156	-1 (3.9)		55.78%	0.76[-0.09,1.61]
Subtotal ***	**241**		**250**			**100%**	**-1.43[-6.26,3.39]**
Heterogeneity: Tau^2=10.69; Chi^2=7.63, df=1(P=0.01); I^2=86.9%							
Test for overall effect: Z=0.58(P=0.56)							
Test for subgroup differences: Chi^2=0.1, df=1 (P=0.95), I^2=0%							

Favours higher omega 3 -20 -10 0 10 20 Favours lower omega 3

Analysis 5.16. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 16 Weight, kg - ALA - subgroup by primary or secondary prevention.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.16.1 Low CVD risk							
Dodin 2005	85	65.3 (11.2)	94	69.5 (12.1)		22.7%	-4.2[-7.61,-0.79]
MENU 2016	34	-6.8 (8.2)	32	-7 (7.9)		20.77%	0.2[-3.68,4.08]
MENU 2016	35	-8.1 (7.1)	37	-4.3 (6.1)		24.2%	-3.8[-6.86,-0.74]
WAHA 2016	156	-0.3 (3.9)	156	-1 (3.9)		32.32%	0.76[-0.09,1.61]
Subtotal ***	**310**		**319**			**100%**	**-1.59[-4.47,1.3]**
Heterogeneity: Tau^2=6.52; Chi^2=14.59, df=3(P=0); I^2=79.43%							

Favours higher omega 3 -20 -10 0 10 20 Favours lower omega 3

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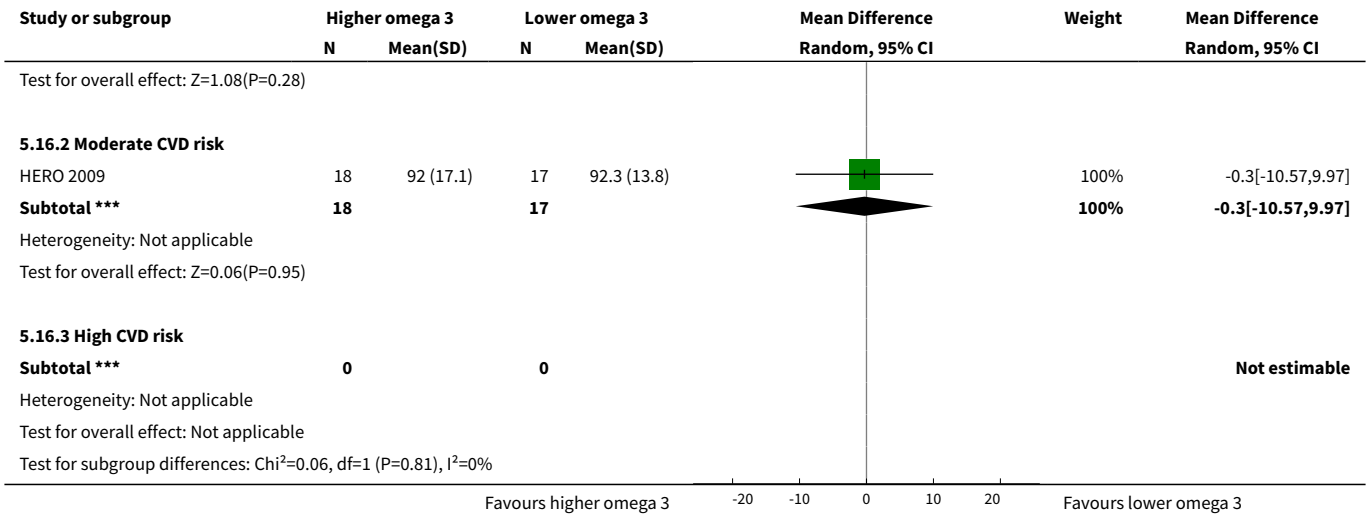
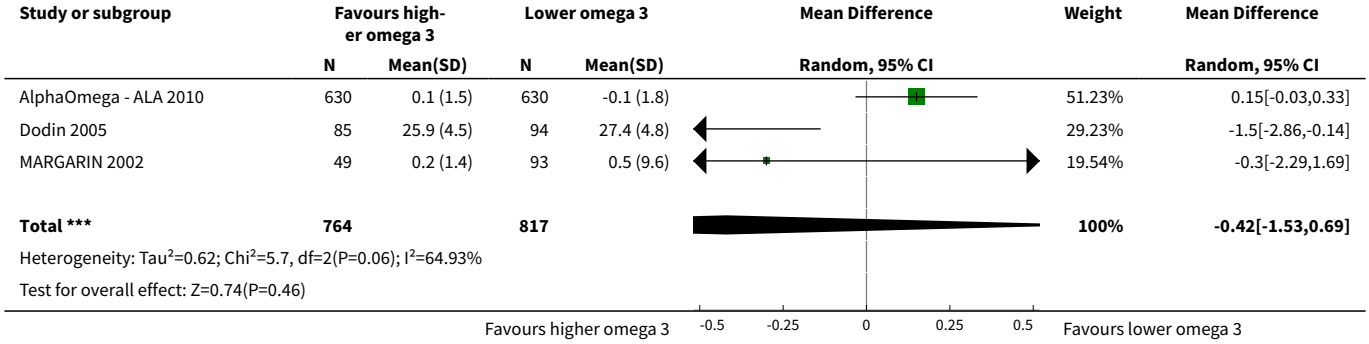
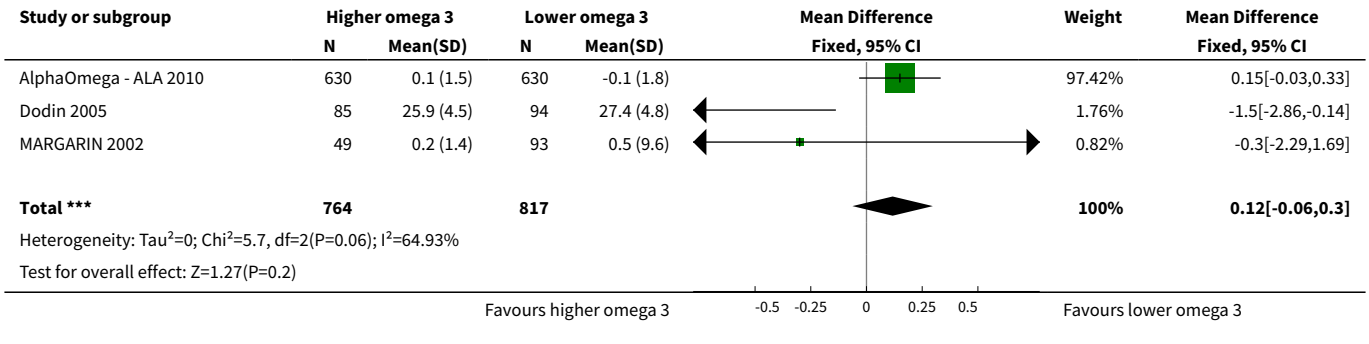


Analysis 5.17. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 17 Body mass index, kg/m² - ALA.



Analysis 5.18. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 18 BMI, kg/m² - ALA - SA fixed-effect.



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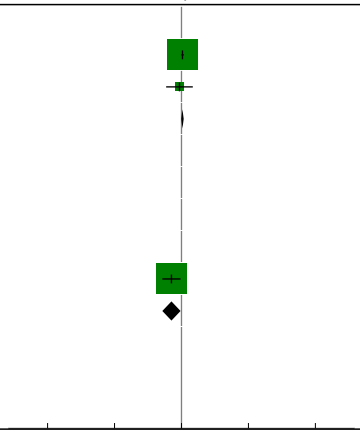
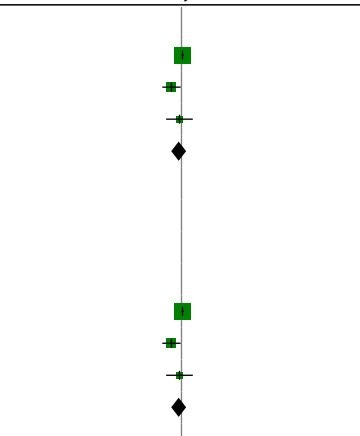
Analysis 5.19. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 19 BMI, kg/m² - ALA - SA by summary risk of bias.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.19.1 Low risk of bias							
AlphaOmega - ALA 2010	630	0.1 (1.5)	630	-0.1 (1.8)		99.16%	0.15[-0.03,0.33]
MARGARIN 2002	49	0.2 (1.4)	93	0.5 (9.6)		0.84%	-0.3[-2.29,1.69]
Subtotal ***	**679**		**723**			**100%**	**0.15[-0.04,0.33]**
Heterogeneity: Tau^2=0; Chi^2=0.19, df=1(P=0.66); I^2=0%							
Test for overall effect: Z=1.57(P=0.12)							
5.19.2 Moderate/high risk of bias							
Dodin 2005	85	25.9 (4.5)	94	27.4 (4.8)		100%	-1.5[-2.86,-0.14]
Subtotal ***	**85**		**94**			**100%**	**-1.5[-2.86,-0.14]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.16(P=0.03)							
Test for subgroup differences: Chi^2=5.51, df=1 (P=0.02), I^2=81.85%							



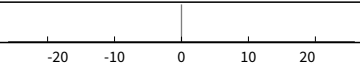
Analysis 5.20. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 20 BMI, kg/m² - ALA - SA by compliance and study size.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.20.1 SA - low risk of compliance bias							
AlphaOmega - ALA 2010	630	0.1 (1.5)	630	-0.1 (1.8)		51.23%	0.15[-0.03,0.33]
Dodin 2005	85	25.9 (4.5)	94	27.4 (4.8)		29.23%	-1.5[-2.86,-0.14]
MARGARIN 2002	49	0.2 (1.4)	93	0.5 (9.6)		19.54%	-0.3[-2.29,1.69]
Subtotal ***	**764**		**817**			**100%**	**-0.42[-1.53,0.69]**
Heterogeneity: Tau^2=0.62; Chi^2=5.7, df=2(P=0.06); I^2=64.93%							
Test for overall effect: Z=0.74(P=0.46)							
5.20.2 SA - 100+ randomised							
AlphaOmega - ALA 2010	630	0.1 (1.5)	630	-0.1 (1.8)		51.23%	0.15[-0.03,0.33]
Dodin 2005	85	25.9 (4.5)	94	27.4 (4.8)		29.23%	-1.5[-2.86,-0.14]
MARGARIN 2002	49	0.2 (1.4)	93	0.5 (9.6)		19.54%	-0.3[-2.29,1.69]
Subtotal ***	**764**		**817**			**100%**	**-0.42[-1.53,0.69]**
Heterogeneity: Tau^2=0.62; Chi^2=5.7, df=2(P=0.06); I^2=64.93%							
Test for overall effect: Z=0.74(P=0.46)							
Test for subgroup differences: Not applicable							



Analysis 5.21. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 21 BMI, kg/m² - ALA - subgroup by dose.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.21.1 ALA low < 5 g/d							



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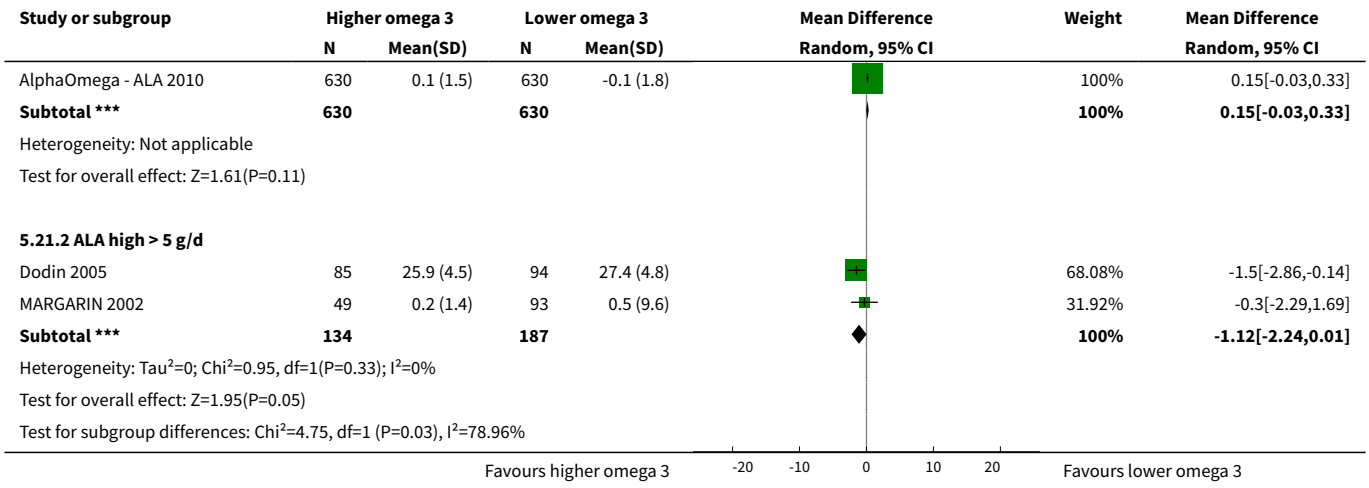
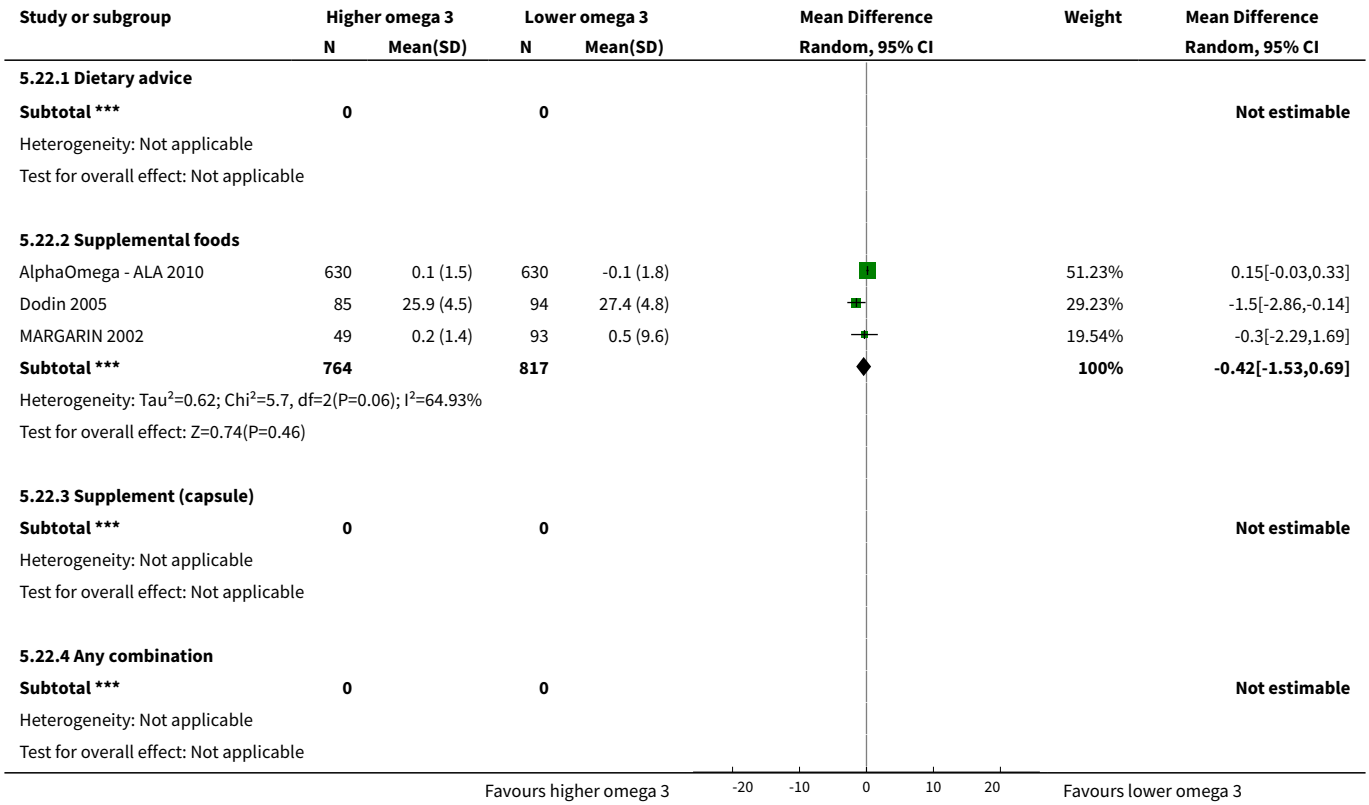


Analysis 5.22. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 22 BMI, kg/m² - ALA - subgroup by intervention type.



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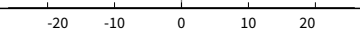
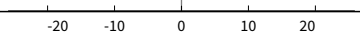
Analysis 5.23. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 23 BMI, kg/m² - ALA - subgroup by replacement.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.23.1 ALA replacing SFA							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.23.2 ALA replacing MUFA							
AlphaOmega - ALA 2010	630	0.1 (1.5)	630	-0.1 (1.8)		100%	0.15[-0.03,0.33]
Subtotal ***	**630**		**630**			**100%**	**0.15[-0.03,0.33]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.61(P=0.11)							
5.23.3 ALA replacing n-6							
MARGARIN 2002	49	0.2 (1.4)	93	0.5 (9.6)		100%	-0.3[-2.29,1.69]
Subtotal ***	**49**		**93**			**100%**	**-0.3[-2.29,1.69]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.3(P=0.77)							
5.23.4 ALA replacing carbs/sugars							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.23.5 ALA replacing nil/low n-3 placebo							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.23.6 Replacement unclear							
Dodin 2005	85	25.9 (4.5)	94	27.4 (4.8)		100%	-1.5[-2.86,-0.14]
Subtotal ***	**85**		**94**			**100%**	**-1.5[-2.86,-0.14]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.16(P=0.03)							
Test for subgroup differences: Chi²=5.7, df=1 (P=0.06), I²=64.93%							



Analysis 5.24. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 24 BMI, kg/m² - ALA - subgroup by duration.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.24.1 Medium duration 1 to < 2 years in study							
Dodin 2005	85	25.9 (4.5)	94	27.4 (4.8)		100%	-1.5[-2.86,-0.14]
Subtotal ***	**85**		**94**			**100%**	**-1.5[-2.86,-0.14]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.16(P=0.03)							
5.24.2 Medium-long duration: 2 to < 4 years in study							



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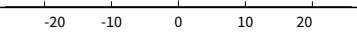
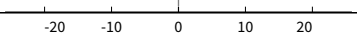
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
AlphaOmega - ALA 2010	630	0.1 (1.5)	630	-0.1 (1.8)		99.16%	0.15[-0.03,0.33]
MARGARIN 2002	49	0.2 (1.4)	93	0.5 (9.6)		0.84%	-0.3[-2.29,1.69]
Subtotal ***	**679**		**723**			**100%**	**0.15[-0.04,0.33]**
Heterogeneity: Tau²=0; Chi²=0.19, df=1(P=0.66); I²=0%							
Test for overall effect: Z=1.57(P=0.12)							
5.24.3 Long duration ≥ 4 years in study							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Chi²=5.51, df=1 (P=0.02), I²=81.85%							



Favours higher omega 3 — Favours lower omega 3

Analysis 5.25. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 25 BMI, kg/m² - ALA - subgroup by statin use.

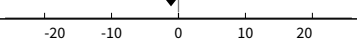
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.25.1 ALA - ≥ 50% of control group on statins							
AlphaOmega - ALA 2010	630	0.1 (1.5)	630	-0.1 (1.8)		100%	0.15[-0.03,0.33]
Subtotal ***	**630**		**630**			**100%**	**0.15[-0.03,0.33]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.61(P=0.11)							
5.25.2 ALA - < 50% of control group on statins							
MARGARIN 2002	49	0.2 (1.4)	93	0.5 (9.6)		100%	-0.3[-2.29,1.69]
Subtotal ***	**49**		**93**			**100%**	**-0.3[-2.29,1.69]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.3(P=0.77)							
5.25.3 ALA - use of statins unclear							
Dodin 2005	85	25.9 (4.5)	94	27.4 (4.8)		100%	-1.5[-2.86,-0.14]
Subtotal ***	**85**		**94**			**100%**	**-1.5[-2.86,-0.14]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.16(P=0.03)							
Test for subgroup differences: Chi²=5.7, df=1 (P=0.06), I²=64.93%							



Favours higher omega 3 — Favours lower omega 3

Analysis 5.26. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 26 BMI, kg/m² - ALA - subgroup by primary or secondary preventionA.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.26.1 Primary prevention of CVD							
Dodin 2005	85	25.9 (4.5)	94	27.4 (4.8)		68.08%	-1.5[-2.86,-0.14]
MARGARIN 2002	49	0.2 (1.4)	93	0.5 (9.6)		31.92%	-0.3[-2.29,1.69]
Subtotal ***	**134**		**187**			**100%**	**-1.12[-2.24,0.01]**



Favours higher omega 3 — Favours lower omega 3

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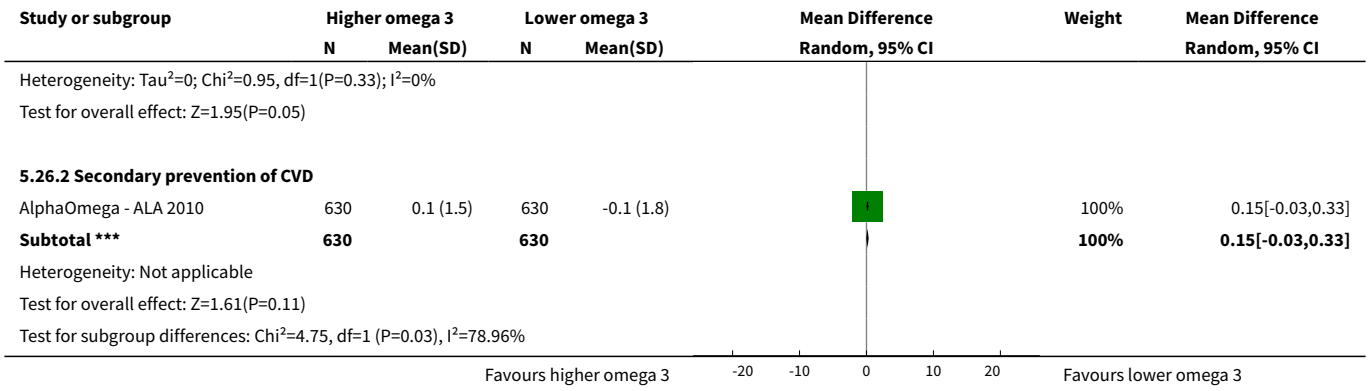
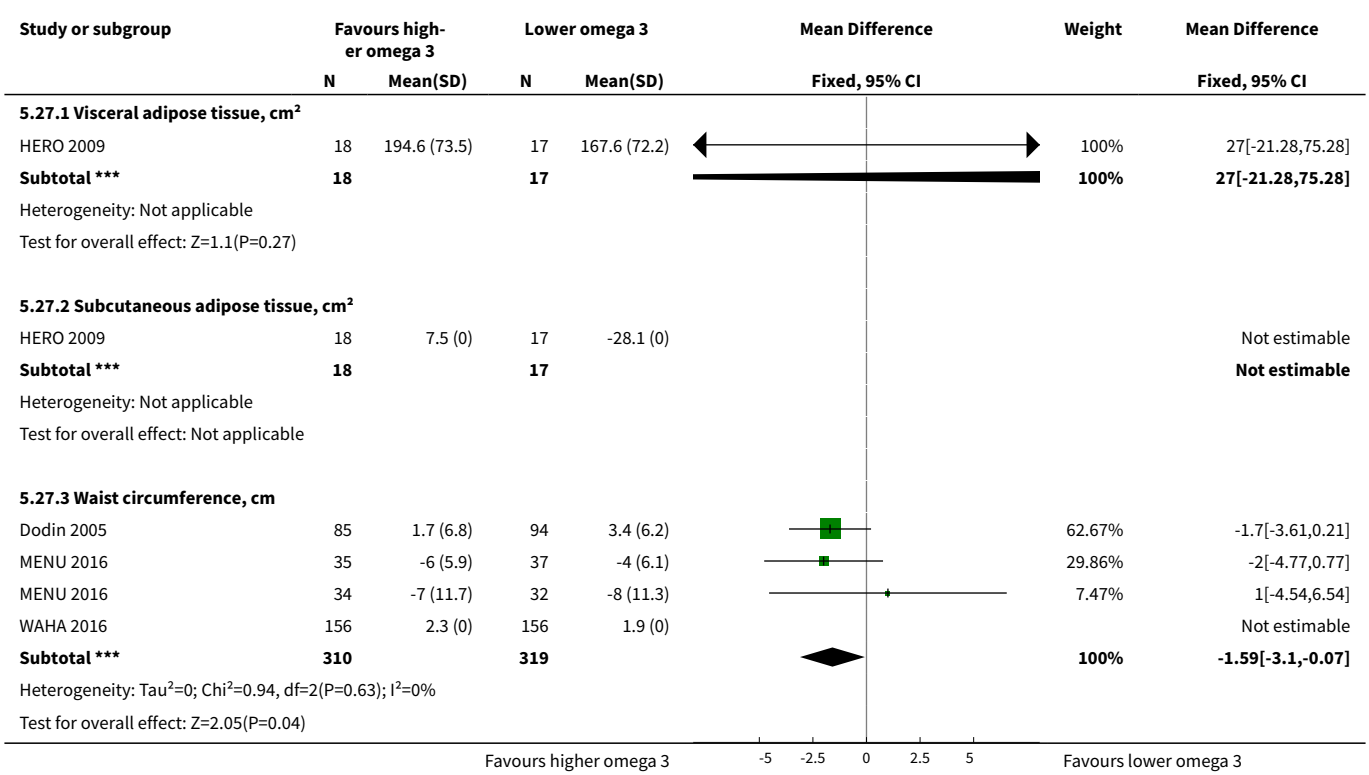
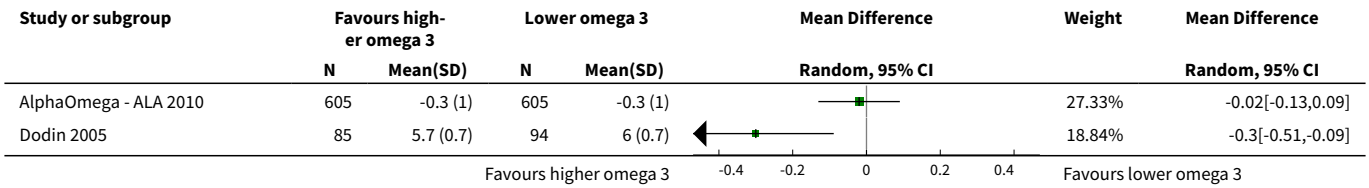


Analysis 5.27. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 27 Other measures of adiposity - ALA.



Analysis 5.28. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 28 Total cholesterol, serum, mmoL/L - ALA.



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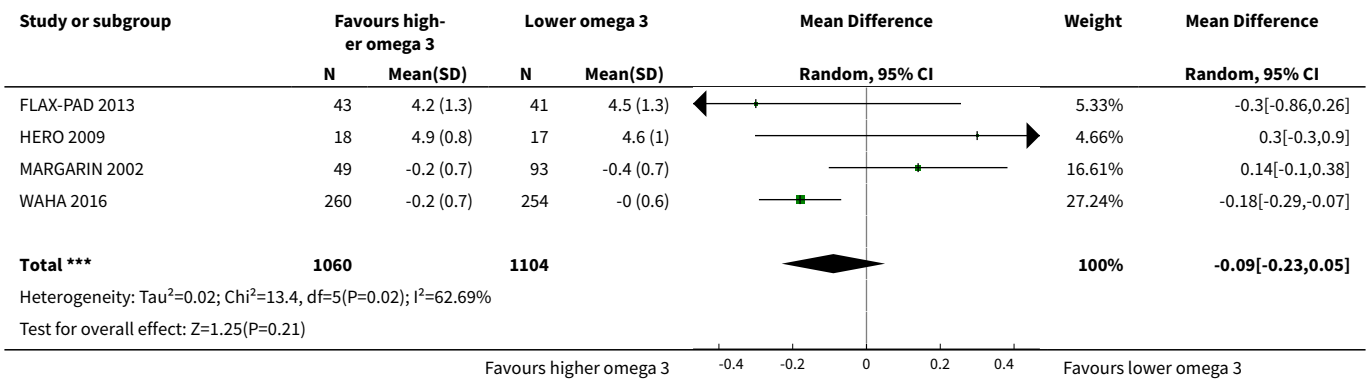
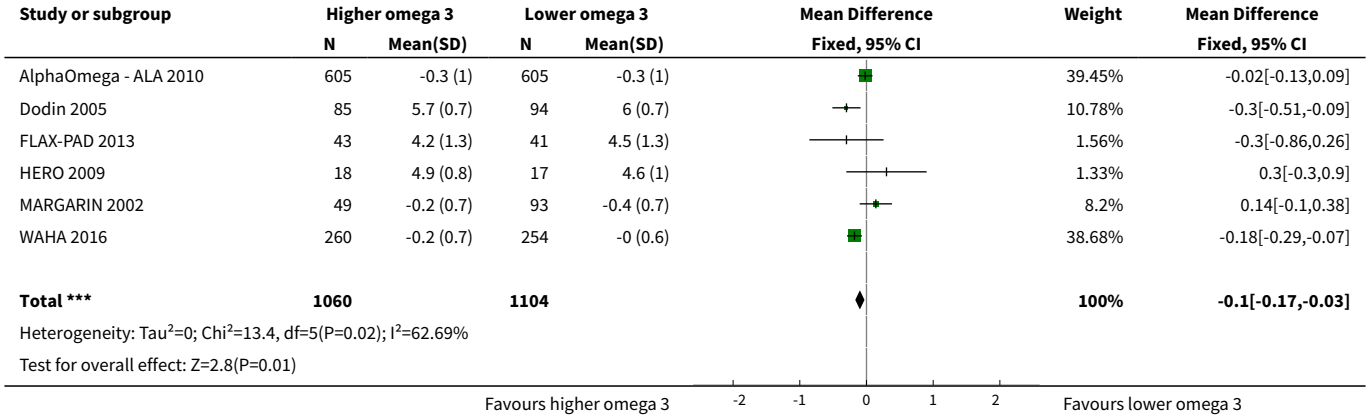
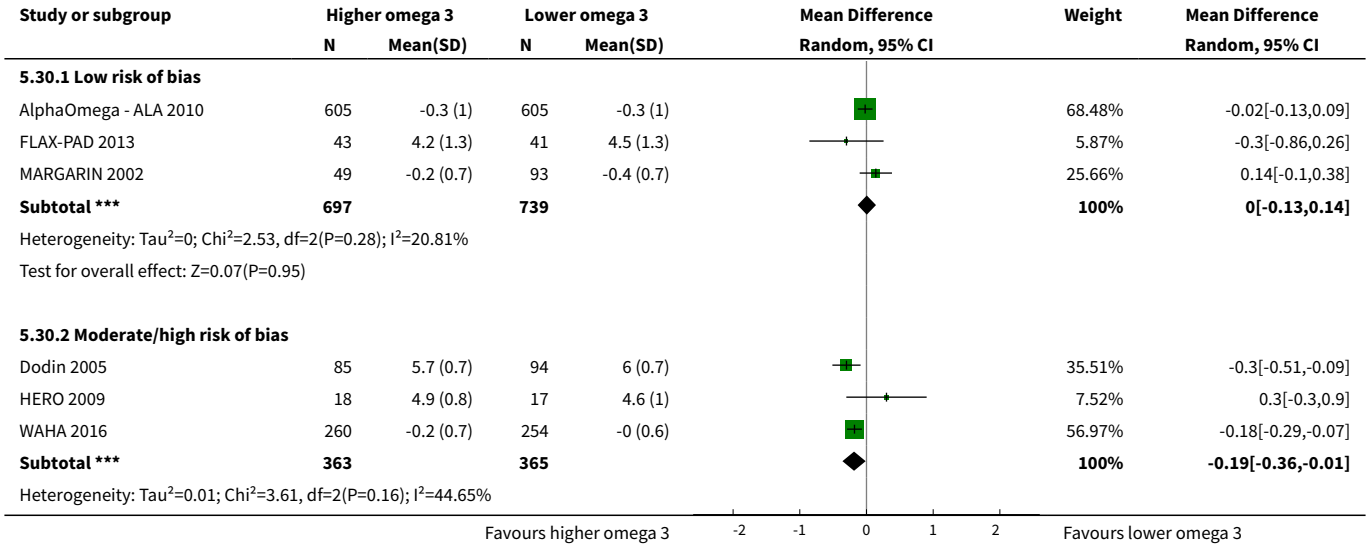


Analysis 5.29. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 29 TC, mmoL/L - ALA - SA fixed-effect.



Analysis 5.30. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 30 TC, mmoL/L - ALA - SA by summary risk of bias.



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Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for overall effect: Z=2.1(P=0.04)							
Test for subgroup differences: Chi²=2.84, df=1 (P=0.09), I²=64.8%							

Favours higher omega 3 -2 -1 0 1 2 Favours lower omega 3

Analysis 5.31. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 31 TC, mmoL/L - ALA - SA by compliance and study size.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.31.1 SA - low risk of compliance bias							
AlphaOmega - ALA 2010	605	-0.3 (1)	605	-0.3 (1)		30.24%	-0.02[-0.13,0.09]
Dodin 2005	85	5.7 (0.7)	94	6 (0.7)		21.04%	-0.3[-0.51,-0.09]
MARGARIN 2002	49	-0.2 (0.7)	93	-0.4 (0.7)		18.59%	0.14[-0.1,0.38]
WAHA 2016	260	-0.2 (0.7)	254	-0 (0.6)		30.14%	-0.18[-0.29,-0.07]
Subtotal ***	**999**		**1046**			**100%**	**-0.1[-0.25,0.05]**
Heterogeneity: Tau²=0.02; Chi²=11.21, df=3(P=0.01); I²=73.23%							
Test for overall effect: Z=1.28(P=0.2)							
5.31.2 SA - 100+ randomised							
AlphaOmega - ALA 2010	605	-0.3 (1)	605	-0.3 (1)		30.24%	-0.02[-0.13,0.09]
Dodin 2005	85	5.7 (0.7)	94	6 (0.7)		21.04%	-0.3[-0.51,-0.09]
MARGARIN 2002	49	-0.2 (0.7)	93	-0.4 (0.7)		18.59%	0.14[-0.1,0.38]
WAHA 2016	260	-0.2 (0.7)	254	-0 (0.6)		30.14%	-0.18[-0.29,-0.07]
Subtotal ***	**999**		**1046**			**100%**	**-0.1[-0.25,0.05]**
Heterogeneity: Tau²=0.02; Chi²=11.21, df=3(P=0.01); I²=73.23%							
Test for overall effect: Z=1.28(P=0.2)							
Test for subgroup differences: Not applicable							

Favours higher omega 3 -2 -1 0 1 2 Favours lower omega 3

Analysis 5.32. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 32 TC, mmoL/L - ALA - subgroup by dose.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.32.1 ALA low < 5 g/d							
AlphaOmega - ALA 2010	605	-0.3 (1)	605	-0.3 (1)		46.92%	-0.02[-0.13,0.09]
HERO 2009	18	4.9 (0.8)	17	4.6 (1)		6.37%	0.3[-0.3,0.9]
WAHA 2016	260	-0.2 (0.7)	254	-0 (0.6)		46.71%	-0.18[-0.29,-0.07]
Subtotal ***	**883**		**876**			**100%**	**-0.07[-0.24,0.09]**
Heterogeneity: Tau²=0.01; Chi²=5.65, df=2(P=0.06); I²=64.62%							
Test for overall effect: Z=0.91(P=0.36)							
5.32.2 ALA high > 5 g/d							
Dodin 2005	85	5.7 (0.7)	94	6 (0.7)		40.55%	-0.3[-0.51,-0.09]
FLAX-PAD 2013	43	4.2 (1.3)	41	4.5 (1.3)		20.84%	-0.3[-0.86,0.26]
MARGARIN 2002	49	-0.2 (0.7)	93	-0.4 (0.7)		38.61%	0.14[-0.1,0.38]
Subtotal ***	**177**		**228**			**100%**	**-0.13[-0.47,0.21]**

Favours higher omega 3 -2 -1 0 1 2 Favours lower omega 3

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Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Heterogeneity: Tau²=0.06; Chi²=7.62, df=2(P=0.02); I²=73.74%							
Test for overall effect: Z=0.76(P=0.45)							
Test for subgroup differences: Chi²=0.09, df=1 (P=0.77), I²=0%							

Analysis 5.33. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 33 TC, mmoL/L - ALA - subgroup by intervention type.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.33.1 Dietary advice							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.33.2 Supplemental foods							
AlphaOmega - ALA 2010	605	-0.3 (1)	605	-0.3 (1)		27.33%	-0.02[-0.13,0.09]
Dodin 2005	85	5.7 (0.7)	94	6 (0.7)		18.84%	-0.3[-0.51,-0.09]
FLAX-PAD 2013	43	4.2 (1.3)	41	4.5 (1.3)		5.33%	-0.3[-0.86,0.26]
HERO 2009	18	4.9 (0.8)	17	4.6 (1)		4.66%	0.3[-0.3,0.9]
MARGARIN 2002	49	-0.2 (0.7)	93	-0.4 (0.7)		16.61%	0.14[-0.1,0.38]
WAHA 2016	260	-0.2 (0.7)	254	-0 (0.6)		27.24%	-0.18[-0.29,-0.07]
Subtotal ***	**1060**		**1104**			**100%**	**-0.09[-0.23,0.05]**
Heterogeneity: Tau²=0.02; Chi²=13.4, df=5(P=0.02); I²=62.69%							
Test for overall effect: Z=1.25(P=0.21)							
5.33.3 Supplement (capsule)							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.33.4 Any combination							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							

Analysis 5.34. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 34 TC, mmoL/L - ALA - subgroup by replacement.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.34.1 ALA replacing SFA							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							

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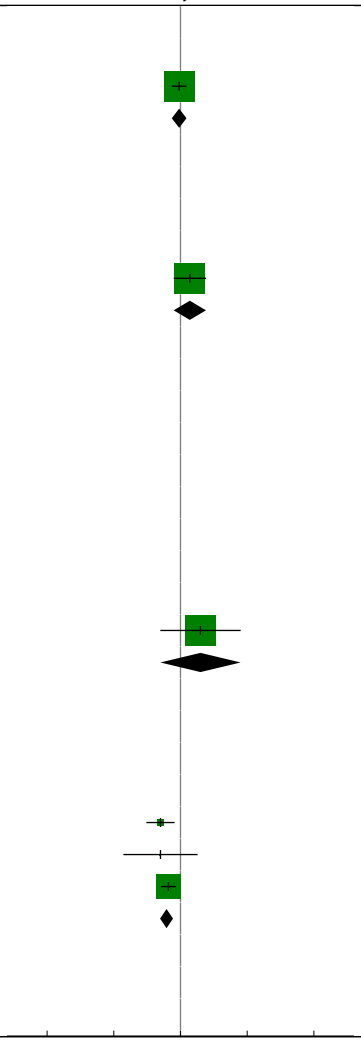
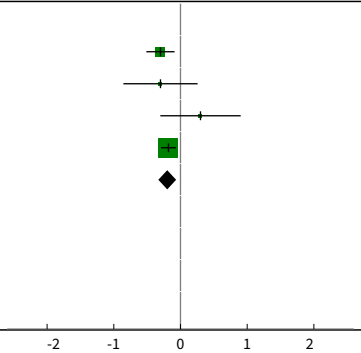
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.34.2 ALA replacing MUFA							
AlphaOmega - ALA 2010	605	-0.3 (1)	605	-0.3 (1)		100%	-0.02[-0.13,0.09]
Subtotal ***	**605**		**605**			**100%**	**-0.02[-0.13,0.09]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.35(P=0.72)							
5.34.3 ALA replacing n-6							
MARGARIN 2002	49	-0.2 (0.7)	93	-0.4 (0.7)		100%	0.14[-0.1,0.38]
Subtotal ***	**49**		**93**			**100%**	**0.14[-0.1,0.38]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.13(P=0.26)							
5.34.4 ALA replacing carbs/sugars							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.34.5 ALA replacing nil/low n-3 placebo							
HERO 2009	18	4.9 (0.8)	17	4.6 (1)		100%	0.3[-0.3,0.9]
Subtotal ***	**18**		**17**			**100%**	**0.3[-0.3,0.9]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.98(P=0.33)							
5.34.6 Replacement unclear							
Dodin 2005	85	5.7 (0.7)	94	6 (0.7)		21.14%	-0.3[-0.51,-0.09]
FLAX-PAD 2013	43	4.2 (1.3)	41	4.5 (1.3)		3.05%	-0.3[-0.86,0.26]
WAHA 2016	260	-0.2 (0.7)	254	-0 (0.6)		75.82%	-0.18[-0.29,-0.07]
Subtotal ***	**388**		**389**			**100%**	**-0.21[-0.31,-0.11]**
Heterogeneity: Tau^2=0; Chi^2=1.08, df=2(P=0.58); I^2=0%							
Test for overall effect: Z=4.22(P<0.0001)							
Test for subgroup differences: Chi^2=12.32, df=1 (P=0.01), I^2=75.66%							



Analysis 5.35. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 35 TC, mmoL/L - ALA - subgroup by duration.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.35.1 Medium duration 1 to < 2 years in study							
Dodin 2005	85	5.7 (0.7)	94	6 (0.7)		28.99%	-0.3[-0.51,-0.09]
FLAX-PAD 2013	43	4.2 (1.3)	41	4.5 (1.3)		5.46%	-0.3[-0.86,0.26]
HERO 2009	18	4.9 (0.8)	17	4.6 (1)		4.7%	0.3[-0.3,0.9]
WAHA 2016	260	-0.2 (0.7)	254	-0 (0.6)		60.85%	-0.18[-0.29,-0.07]
Subtotal ***	**406**		**406**			**100%**	**-0.2[-0.33,-0.07]**
Heterogeneity: Tau^2=0; Chi^2=3.75, df=3(P=0.29); I^2=20.03%							
Test for overall effect: Z=2.92(P=0)							
5.35.2 Medium-long duration: 2 to < 4 years in study							



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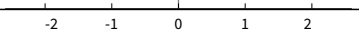
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
AlphaOmega - ALA 2010	605	-0.3 (1)	605	-0.3 (1)		73.62%	-0.02[-0.13,0.09]
MARGARIN 2002	49	-0.2 (0.7)	93	-0.4 (0.7)		26.38%	0.14[-0.1,0.38]
Subtotal ***	**654**		**698**			**100%**	**0.02[-0.12,0.16]**
Heterogeneity: Tau²=0; Chi²=1.39, df=1(P=0.24); I²=27.95%							
Test for overall effect: Z=0.31(P=0.75)							
5.35.3 Long duration ≥ 4 years in study							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Chi²=5.08, df=1 (P=0.02), I²=80.33%							



Favours higher omega 3 — Favours lower omega 3

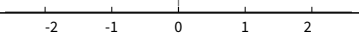
Analysis 5.36. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 36 TC, mmoL/L - ALA - subgroup by statin use.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.36.1 ALA - ≥ 50% of control group on statins							
AlphaOmega - ALA 2010	605	-0.3 (1)	605	-0.3 (1)		90.71%	-0.02[-0.13,0.09]
FLAX-PAD 2013	43	4.2 (1.3)	41	4.5 (1.3)		5.01%	-0.3[-0.86,0.26]
HERO 2009	18	4.9 (0.8)	17	4.6 (1)		4.28%	0.3[-0.3,0.9]
Subtotal ***	**666**		**663**			**100%**	**-0.02[-0.15,0.11]**
Heterogeneity: Tau²=0; Chi²=2.06, df=2(P=0.36); I²=2.85%							
Test for overall effect: Z=0.32(P=0.75)							
5.36.2 ALA - < 50% of control group on statins							
MARGARIN 2002	49	-0.2 (0.7)	93	-0.4 (0.7)		100%	0.14[-0.1,0.38]
Subtotal ***	**49**		**93**			**100%**	**0.14[-0.1,0.38]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.13(P=0.26)							
5.36.3 ALA - use of statins unclear							
Dodin 2005	85	5.7 (0.7)	94	6 (0.7)		21.8%	-0.3[-0.51,-0.09]
WAHA 2016	260	-0.2 (0.7)	254	-0 (0.6)		78.2%	-0.18[-0.29,-0.07]
Subtotal ***	**345**		**348**			**100%**	**-0.21[-0.3,-0.11]**
Heterogeneity: Tau²=0; Chi²=0.97, df=1(P=0.32); I²=0%							
Test for overall effect: Z=4.1(P<0.0001)							
Test for subgroup differences: Chi²=9.71, df=1 (P=0.01), I²=79.4%							

Favours higher omega 3 — Favours lower omega 3

Analysis 5.37. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 37 TC, mmoL/L - ALA - subgroup by primary or secondary prevention.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.37.1 Primary prevention of CVD							



Favours higher omega 3 — Favours lower omega 3

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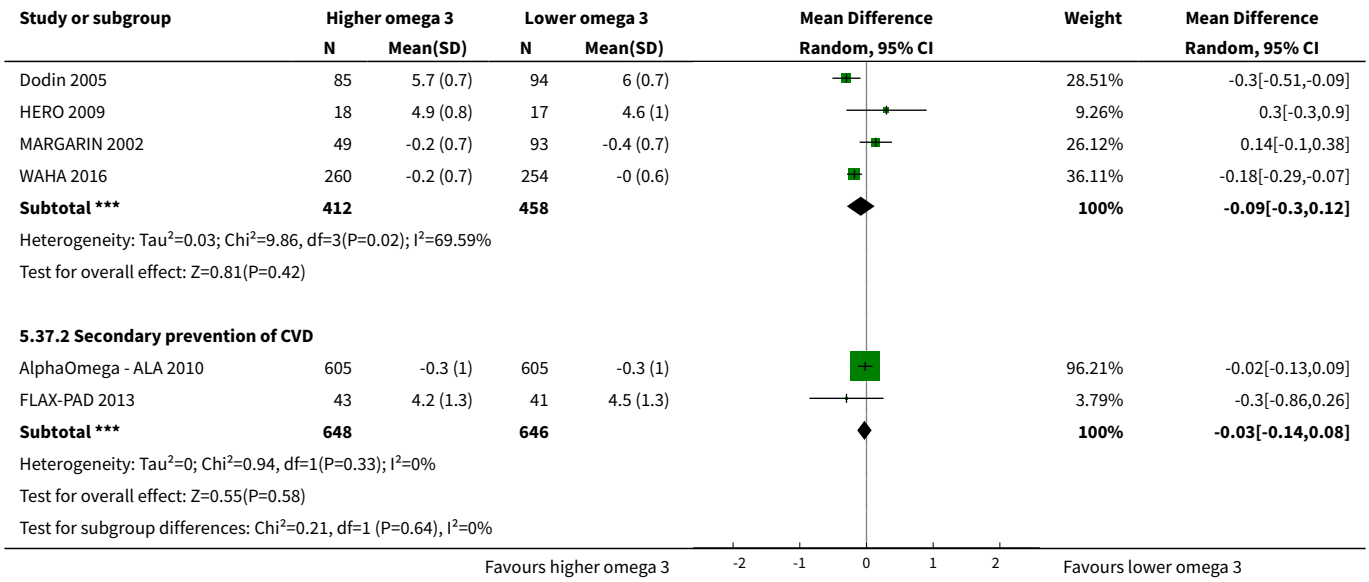
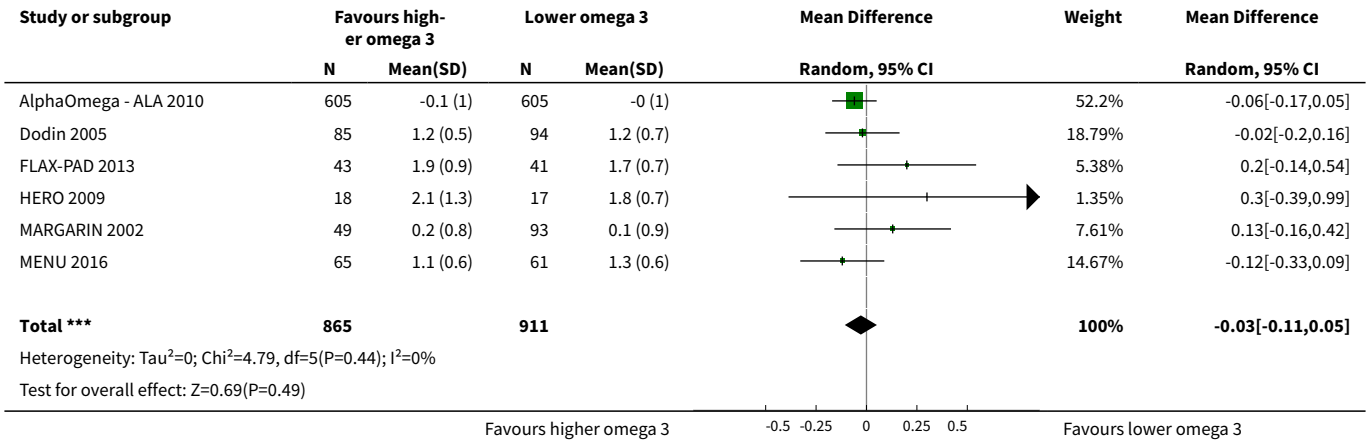
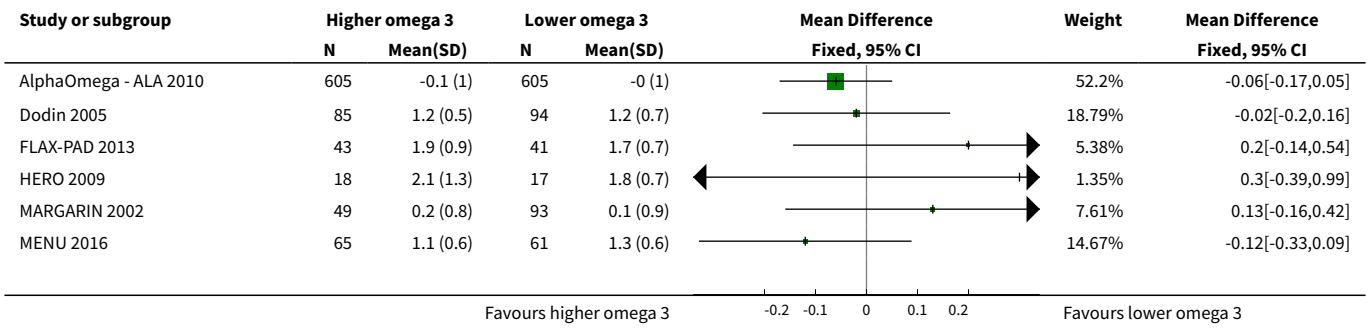


Analysis 5.38. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 38 Triglycerides, fasting, serum, mmoL/L - ALA.



Analysis 5.39. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 39 TG, fasting, mmoL/L - ALA - SA fixed-effect.



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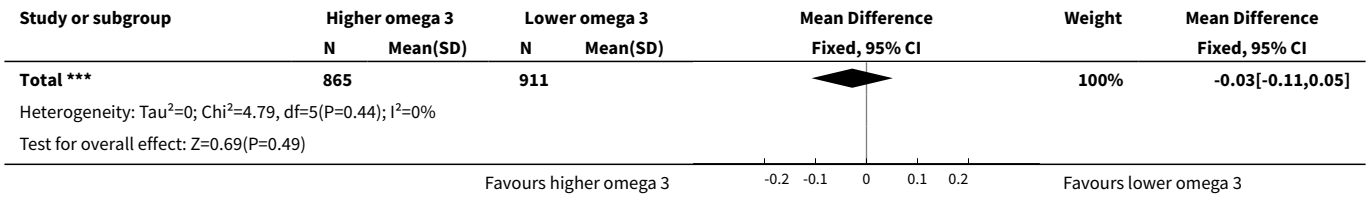
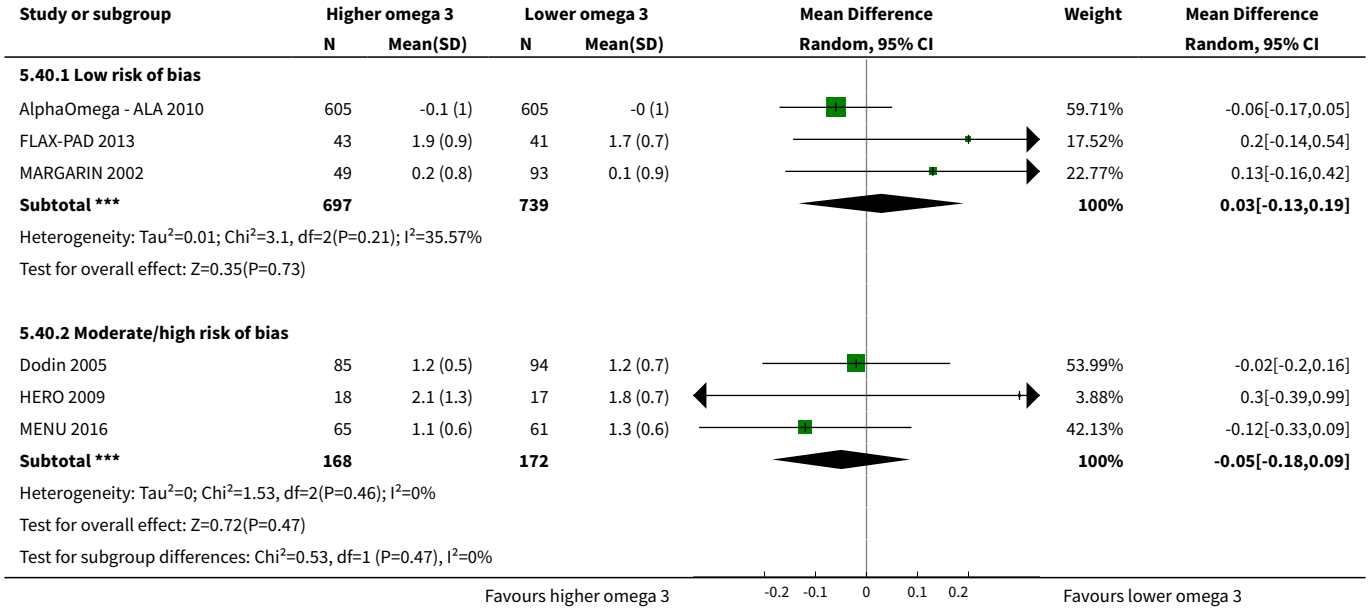
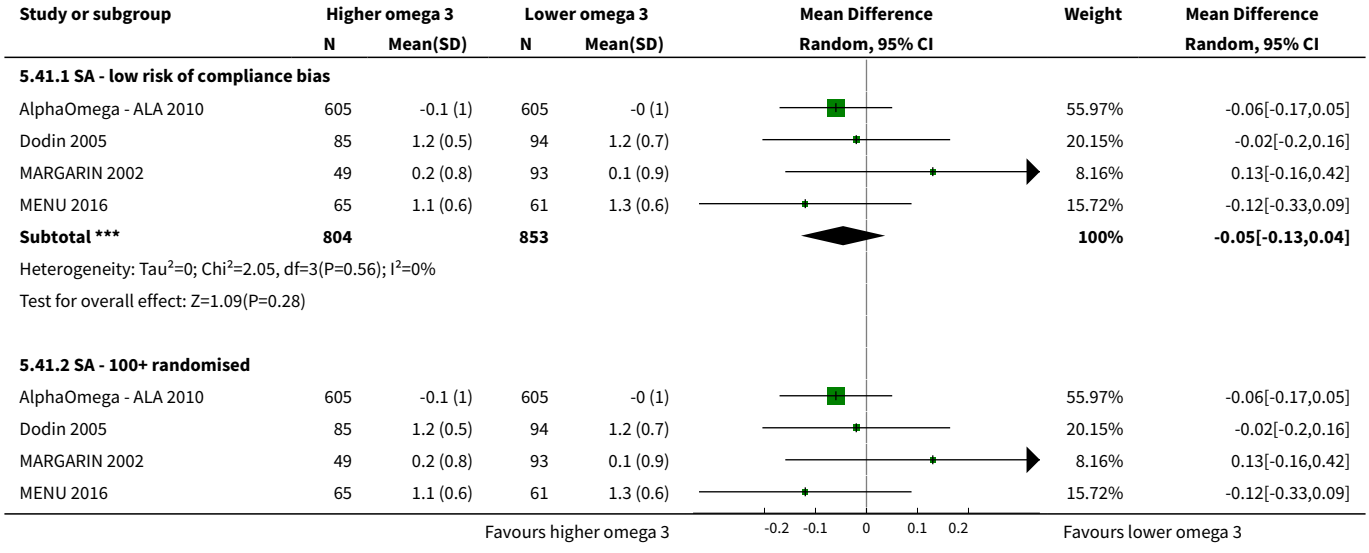


Analysis 5.40. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 40 TG, fasting, mmoL/L- ALA - SA by summary risk of bias.



Analysis 5.41. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 41 TG, fasting, mmoL/L- ALA - SA by compliance and study size.



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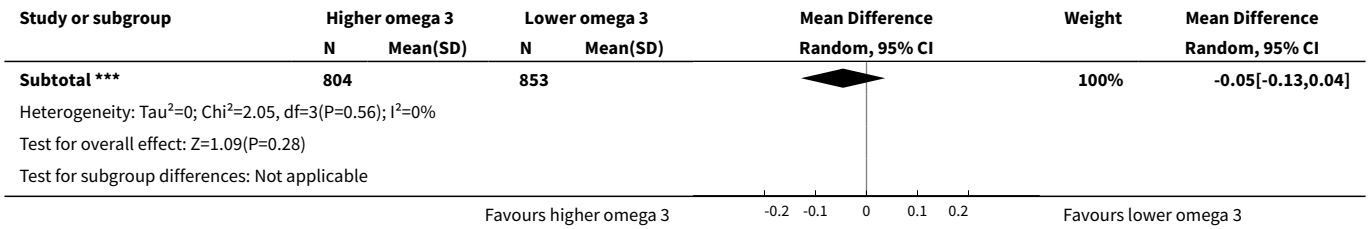
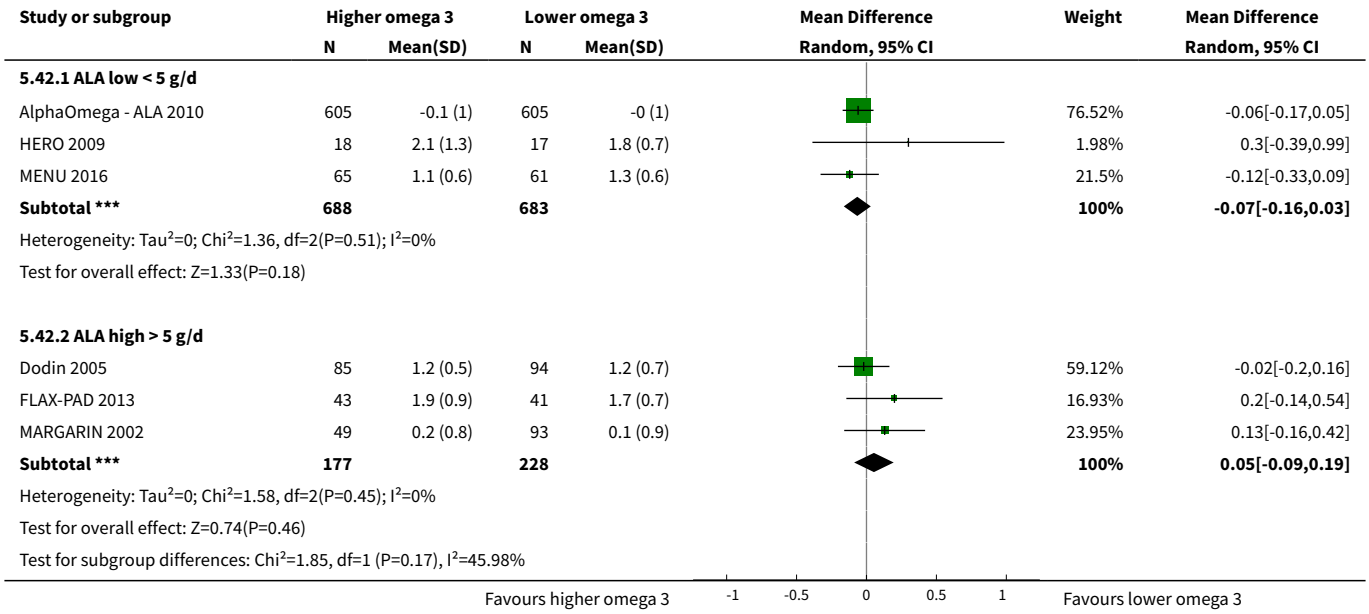
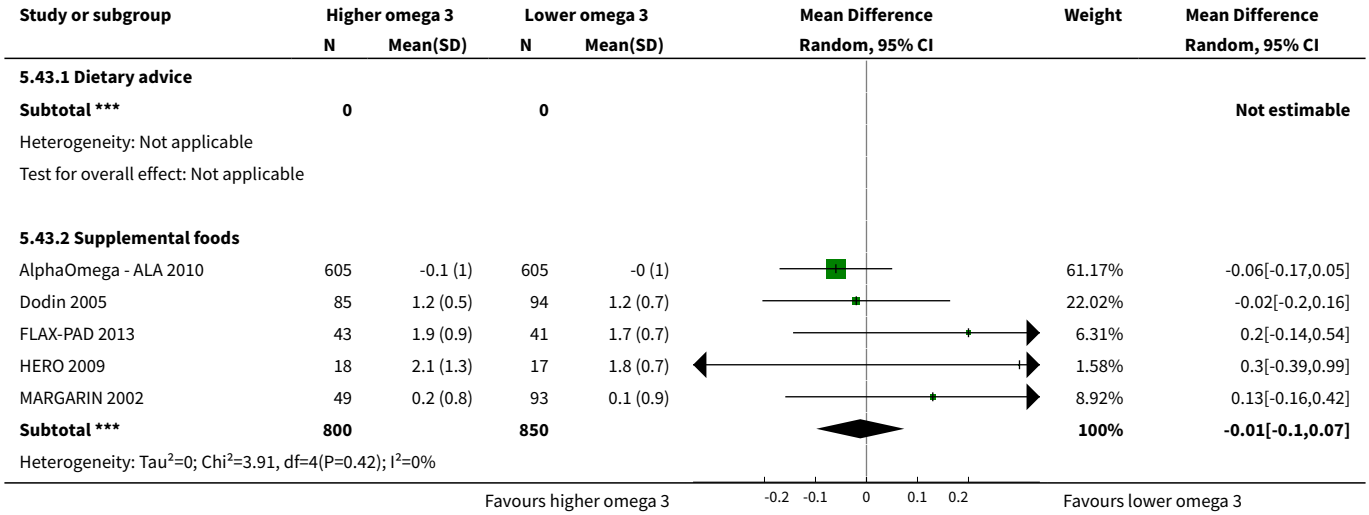


Analysis 5.42. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 42 TG, fasting, mmoL/L - ALA - subgroup by dose.



Analysis 5.43. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 43 TG, fasting, mmoL/L- ALA - subgroup by intervention type.



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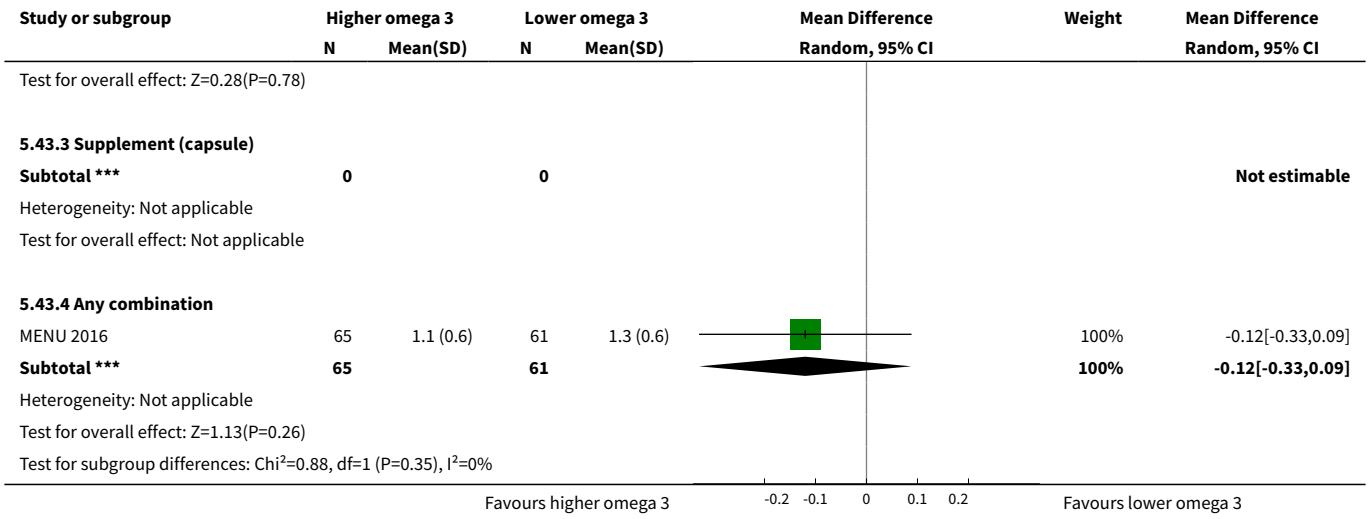
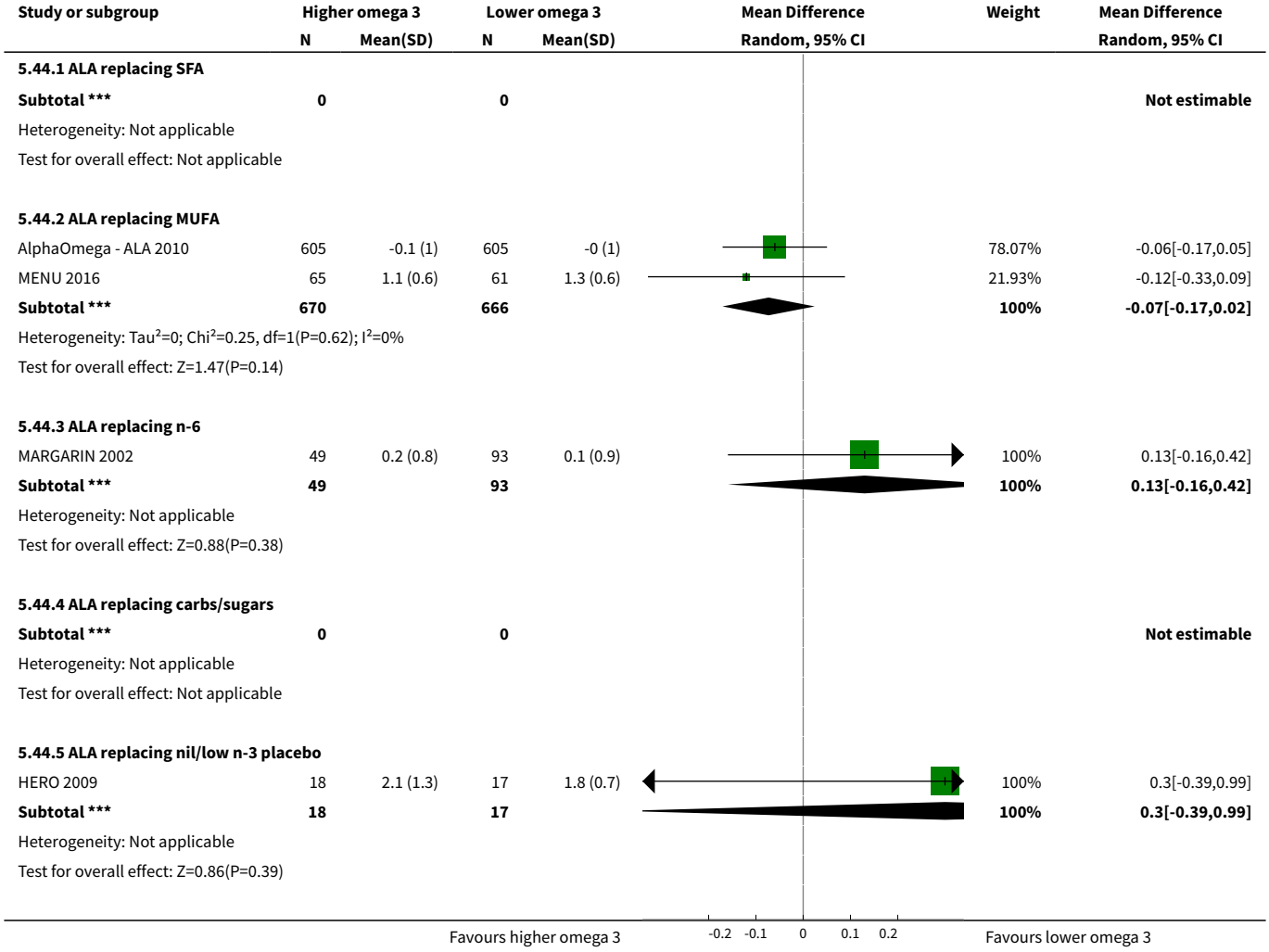


Analysis 5.44. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 44 TG, fasting, mmoL/L-AL - subgroup by replacement.



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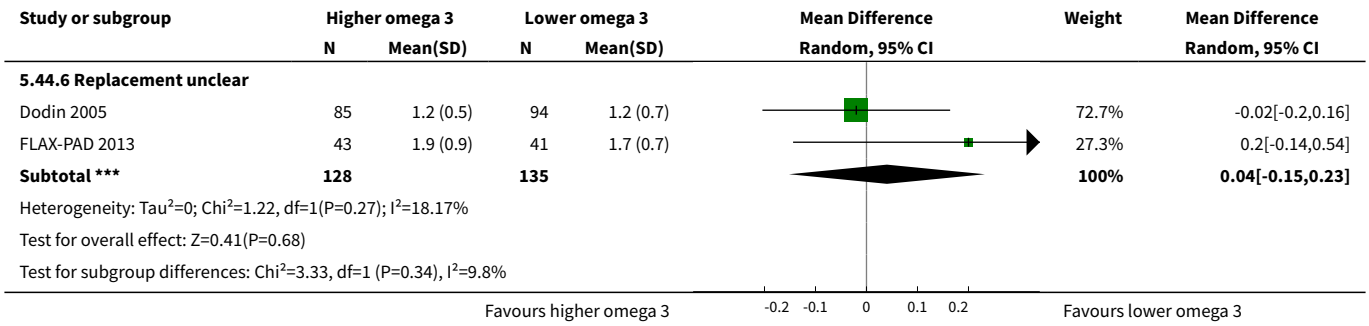
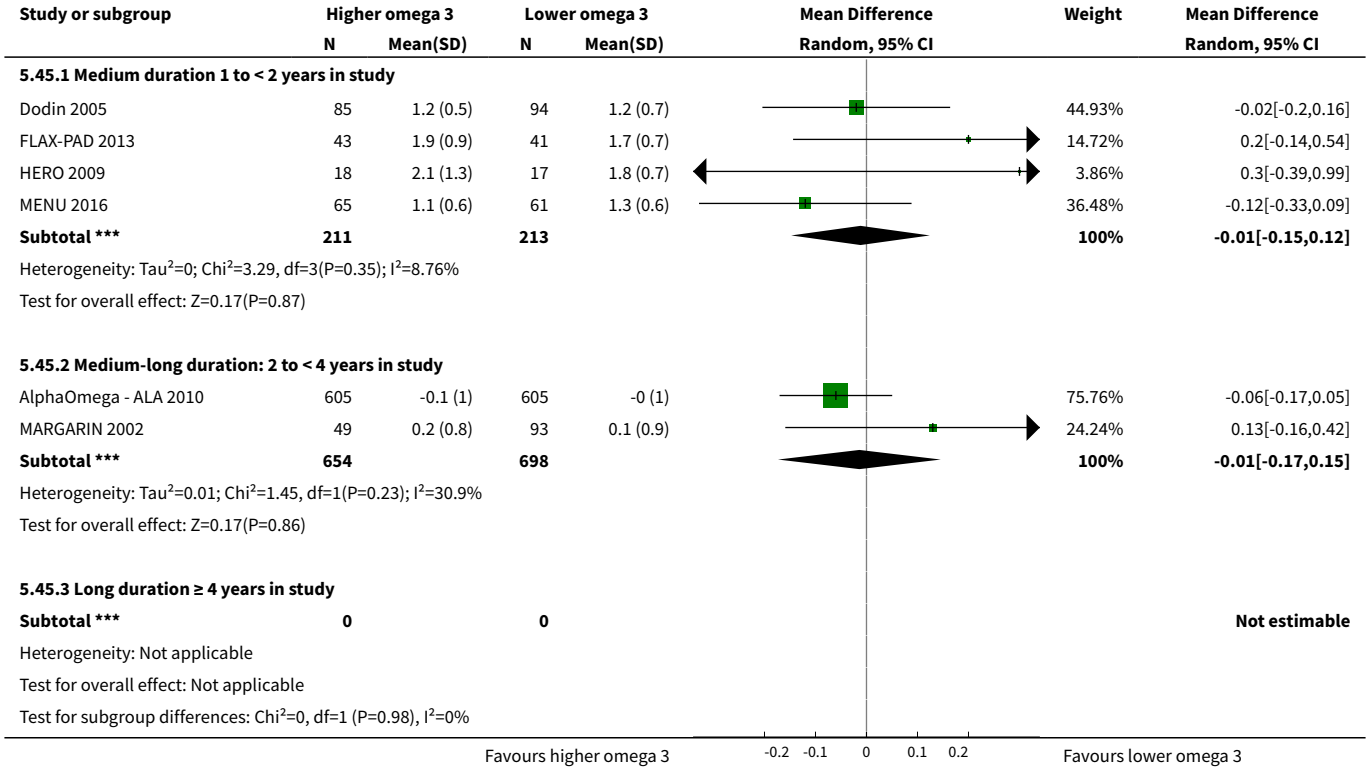
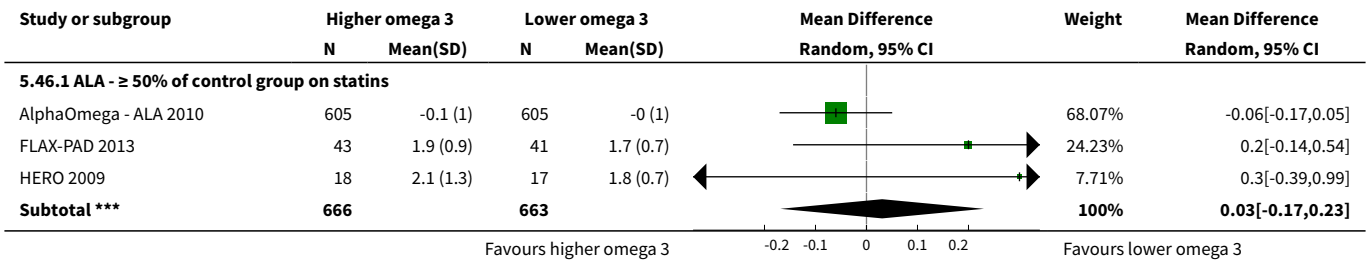


Analysis 5.45. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 45 TG, fasting, mmoL/L- ALA - subgroup by duration.



Analysis 5.46. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 46 TG, fasting, mmoL/L - ALA - subgroup by statin use.



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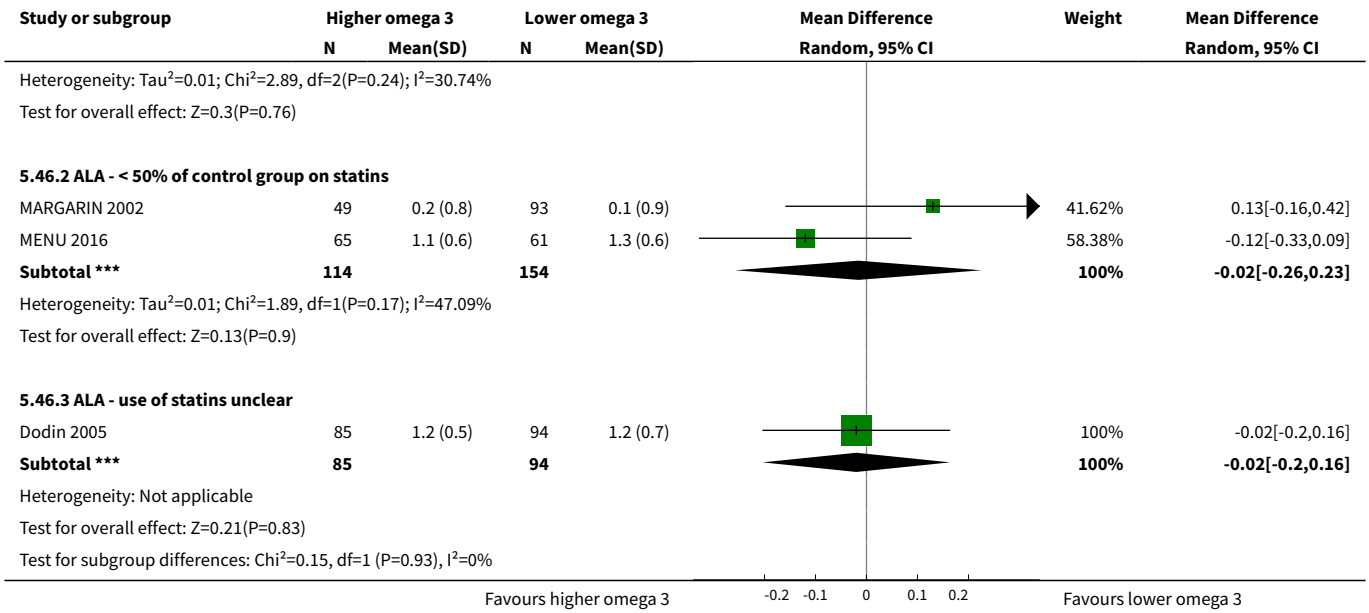
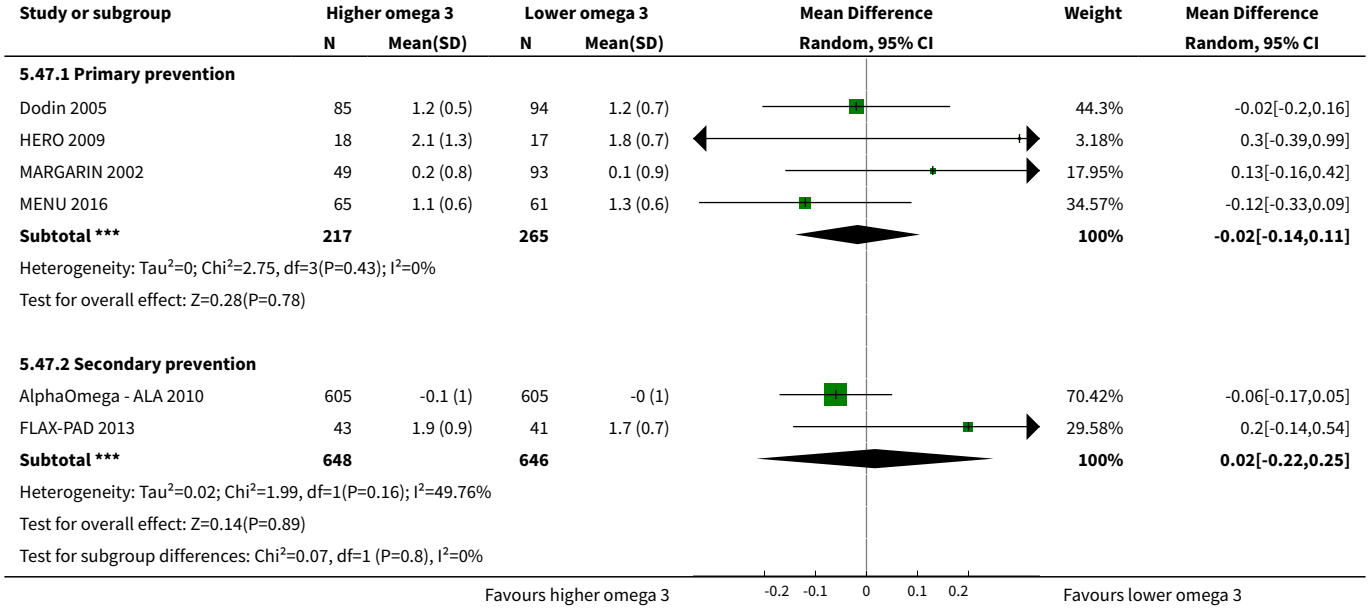


Analysis 5.47. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 47 TG, fasting, mmoL/L- ALA - subgroup by primary or secondary prevention.



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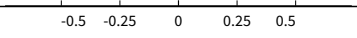
Analysis 5.48. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 48 High-density lipoprotein, serum, mmoL/L - ALA.

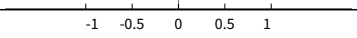
Study or subgroup	Favours lower omega 3 N	Favours lower omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
AlphaOmega - ALA 2010	605	0.1 (0.3)	605	0.2 (0.3)		33.71%	-0.02[-0.05,0.01]
Dodin 2005	85	1.7 (0.4)	94	1.8 (0.4)		14.75%	-0.09[-0.2,0.02]
FLAX-PAD 2013	43	1.1 (0.3)	41	1.2 (0.3)		14.75%	-0.1[-0.21,0.01]
HERO 2009	18	1.5 (0.4)	17	1.4 (0.4)		3.59%	0.1[-0.17,0.37]
MARGARIN 2002	49	0.1 (0.2)	93	0.1 (0.2)		22.74%	-0.04[-0.11,0.03]
MENU 2016	65	1.7 (0.4)	61	1.6 (0.4)		10.46%	0.15[0.01,0.29]
Total ***	**865**		**911**			**100%**	**-0.02[-0.08,0.03]**
Heterogeneity: Tau^2=0; Chi^2=10.58, df=5(P=0.06); I^2=52.75%							
Test for overall effect: Z=0.91(P=0.36)							



Favours lower omega 3 — Favours higher omega 3

Analysis 5.49. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 49 HDL, mmoL/L - ALA - SA fixed-effect.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
AlphaOmega - ALA 2010	605	0.1 (0.3)	605	0.2 (0.3)		73.68%	-0.02[-0.05,0.01]
Dodin 2005	85	1.7 (0.4)	94	1.8 (0.4)		5.11%	-0.09[-0.2,0.02]
FLAX-PAD 2013	43	1.1 (0.3)	41	1.2 (0.3)		5.11%	-0.1[-0.21,0.01]
HERO 2009	18	1.5 (0.4)	17	1.4 (0.4)		0.83%	0.1[-0.17,0.37]
MARGARIN 2002	49	0.1 (0.2)	93	0.1 (0.2)		12.21%	-0.04[-0.11,0.03]
MENU 2016	65	1.7 (0.4)	61	1.6 (0.4)		3.04%	0.15[0.01,0.29]
Total ***	**865**		**911**			**100%**	**-0.02[-0.05,0]**
Heterogeneity: Tau^2=0; Chi^2=10.58, df=5(P=0.06); I^2=52.75%							
Test for overall effect: Z=1.94(P=0.05)							



Favours higher omega 3 — Favours lower omega 3

Analysis 5.50. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 50 HDL, mmoL/L - ALA - SA by summary risk of bias.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.50.1 Low risk of bias							
AlphaOmega - ALA 2010	605	0.1 (0.3)	605	0.2 (0.3)		76.15%	-0.02[-0.05,0.01]
FLAX-PAD 2013	43	1.1 (0.3)	41	1.2 (0.3)		7.22%	-0.1[-0.21,0.01]
MARGARIN 2002	49	0.1 (0.2)	93	0.1 (0.2)		16.63%	-0.04[-0.11,0.03]
Subtotal ***	**697**		**739**			**100%**	**-0.03[-0.06,0]**
Heterogeneity: Tau^2=0; Chi^2=2.16, df=2(P=0.34); I^2=7.5%							
Test for overall effect: Z=1.96(P=0.05)							
5.50.2 Moderate/high risk of bias							

Favours higher omega 3 — Favours lower omega 3

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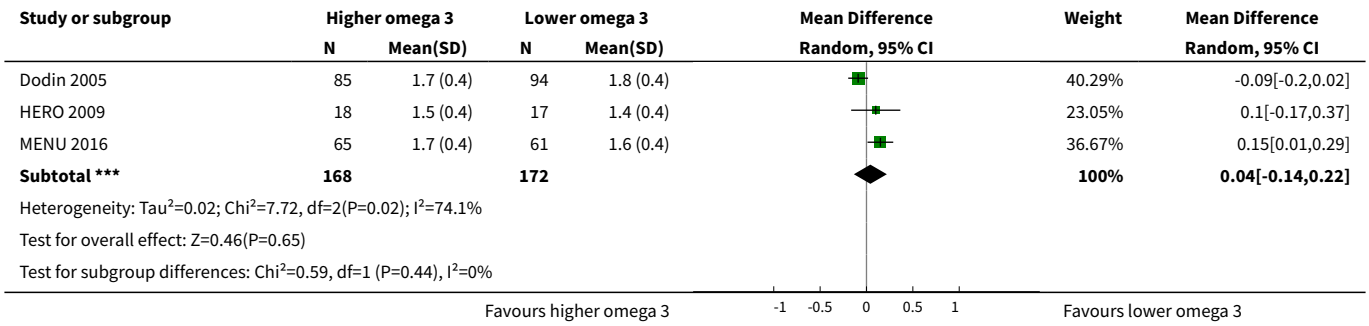
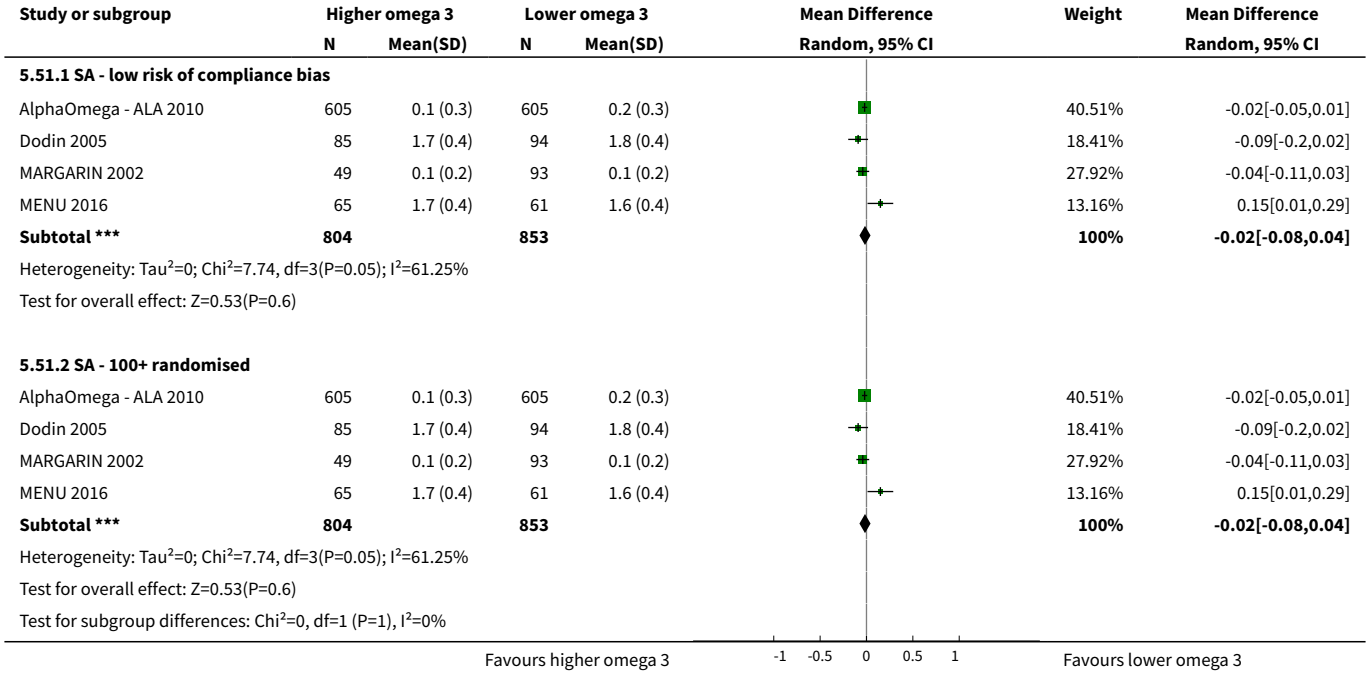
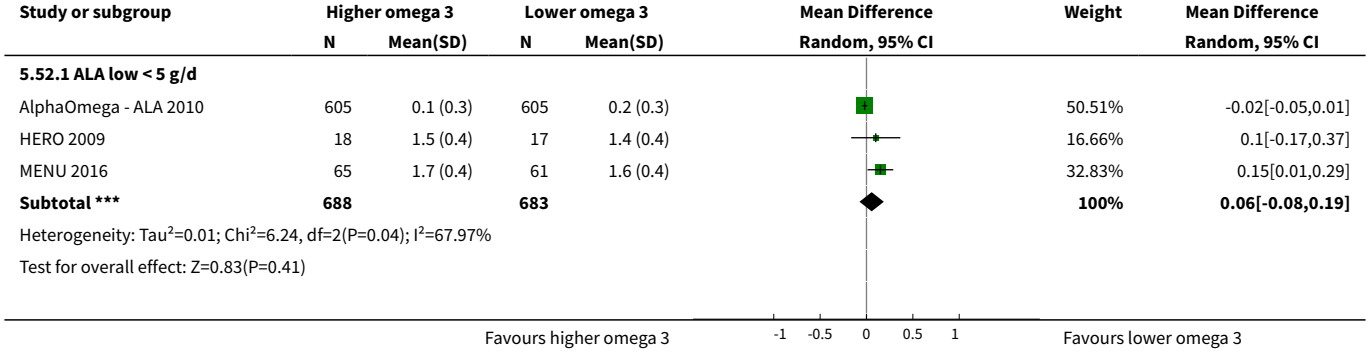


Analysis 5.51. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 51 HDL, mmoL/L - ALA - SA by compliance and study size.



Analysis 5.52. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 52 HDL, mmoL/L - ALA - subgroup by dose.



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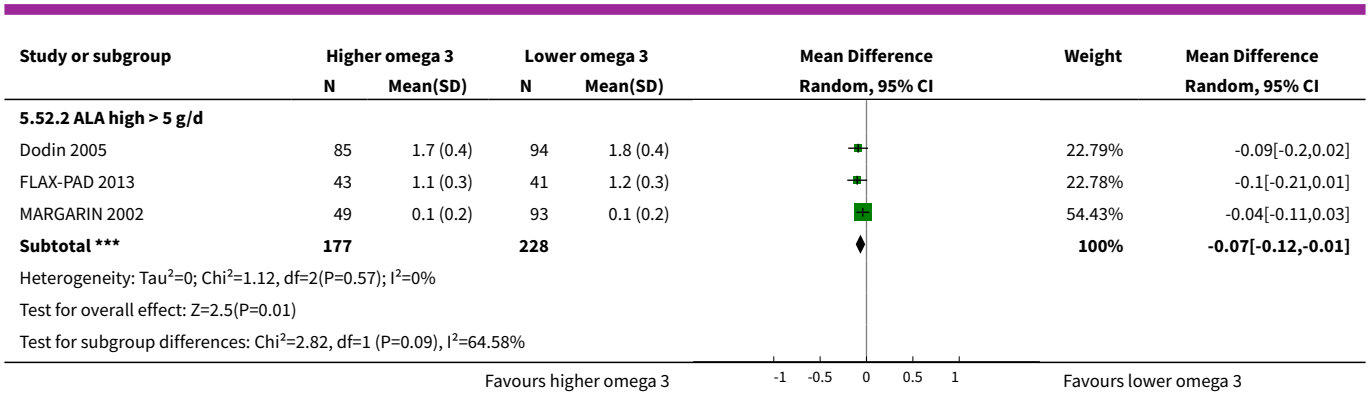
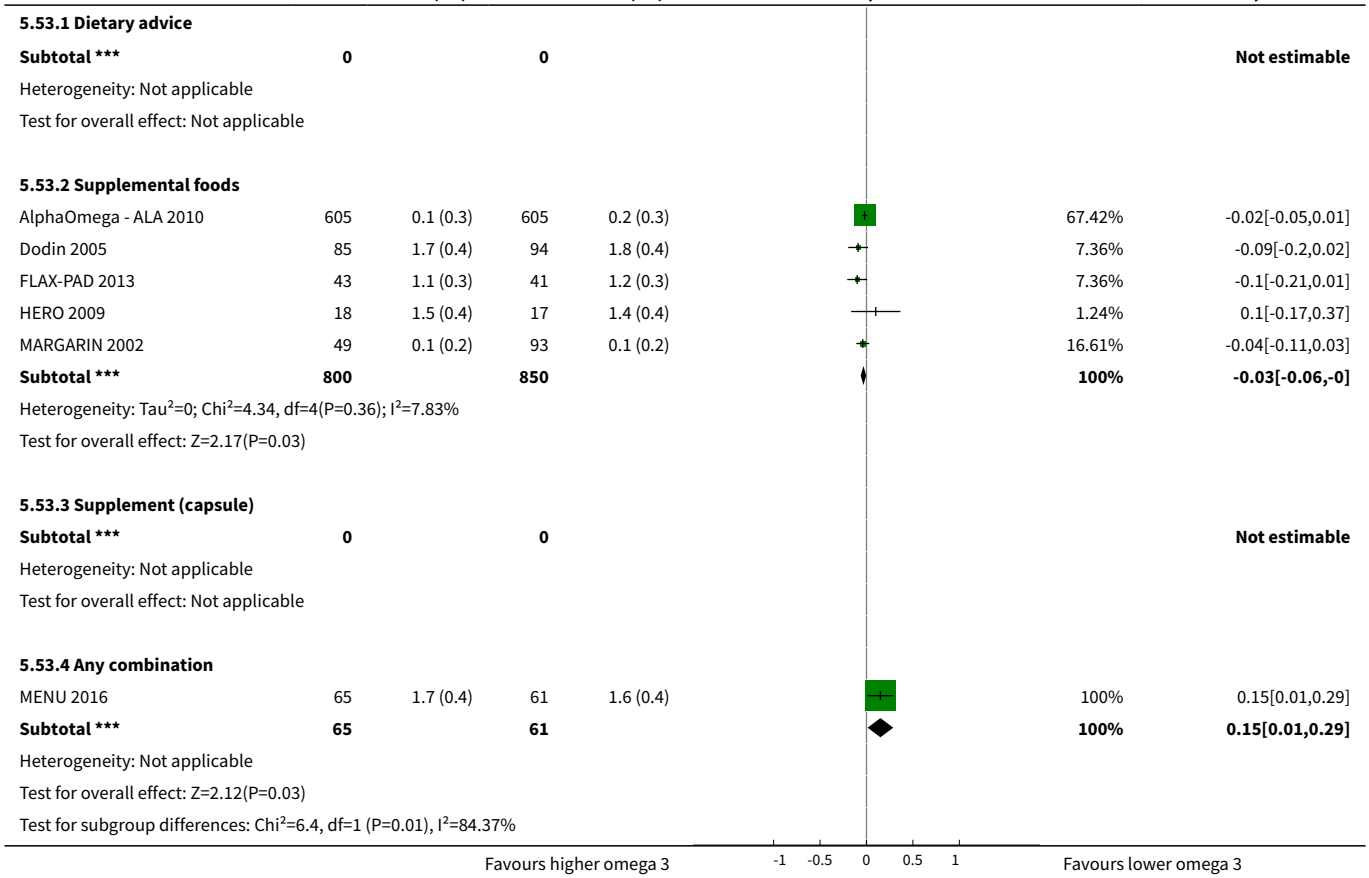


Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.52.2 ALA high > 5 g/d							
Dodin 2005	85	1.7 (0.4)	94	1.8 (0.4)		22.79%	-0.09[-0.2,0.02]
FLAX-PAD 2013	43	1.1 (0.3)	41	1.2 (0.3)		22.78%	-0.1[-0.21,0.01]
MARGARIN 2002	49	0.1 (0.2)	93	0.1 (0.2)		54.43%	-0.04[-0.11,0.03]
Subtotal ***	**177**		**228**			**100%**	**-0.07[-0.12,-0.01]**
Heterogeneity: Tau^2=0; Chi^2=1.12, df=2(P=0.57); I^2=0%							
Test for overall effect: Z=2.5(P=0.01)							
Test for subgroup differences: Chi^2=2.82, df=1 (P=0.09), I^2=64.58%							

Analysis 5.53. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 53 HDL, mmoL/L - ALA - subgroup by intervention type.



Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.53.1 Dietary advice							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.53.2 Supplemental foods							
AlphaOmega - ALA 2010	605	0.1 (0.3)	605	0.2 (0.3)		67.42%	-0.02[-0.05,0.01]
Dodin 2005	85	1.7 (0.4)	94	1.8 (0.4)		7.36%	-0.09[-0.2,0.02]
FLAX-PAD 2013	43	1.1 (0.3)	41	1.2 (0.3)		7.36%	-0.1[-0.21,0.01]
HERO 2009	18	1.5 (0.4)	17	1.4 (0.4)		1.24%	0.1[-0.17,0.37]
MARGARIN 2002	49	0.1 (0.2)	93	0.1 (0.2)		16.61%	-0.04[-0.11,0.03]
Subtotal ***	**800**		**850**			**100%**	**-0.03[-0.06,-0]**
Heterogeneity: Tau^2=0; Chi^2=4.34, df=4(P=0.36); I^2=7.83%							
Test for overall effect: Z=2.17(P=0.03)							
5.53.3 Supplement (capsule)							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.53.4 Any combination							
MENU 2016	65	1.7 (0.4)	61	1.6 (0.4)		100%	0.15[0.01,0.29]
Subtotal ***	**65**		**61**			**100%**	**0.15[0.01,0.29]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.12(P=0.03)							
Test for subgroup differences: Chi^2=6.4, df=1 (P=0.01), I^2=84.37%							

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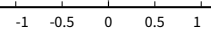
Analysis 5.54. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 54 HDL, mmoL/L - ALA - subgroup by replacement.

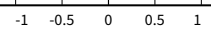
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.54.1 ALA replacing SFA							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.54.2 ALA replacing MUFA							
AlphaOmega - ALA 2010	605	0.1 (0.3)	605	0.2 (0.3)		58.29%	-0.02[-0.05,0.01]
MENU 2016	65	1.7 (0.4)	61	1.6 (0.4)		41.71%	0.15[0.01,0.29]
Subtotal ***	**670**		**666**			**100%**	**0.05[-0.11,0.22]**
Heterogeneity: Tau^2=0.01; Chi^2=5.55, df=1(P=0.02); I^2=81.99%							
Test for overall effect: Z=0.61(P=0.54)							
5.54.3 ALA replacing n-6							
MARGARIN 2002	49	0.1 (0.2)	93	0.1 (0.2)		100%	-0.04[-0.11,0.03]
Subtotal ***	**49**		**93**			**100%**	**-0.04[-0.11,0.03]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.13(P=0.26)							
5.54.4 ALA replacing carbs/sugars							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.54.5 ALA replacing nil/low n-3 placebo							
HERO 2009	18	1.5 (0.4)	17	1.4 (0.4)		100%	0.1[-0.17,0.37]
Subtotal ***	**18**		**17**			**100%**	**0.1[-0.17,0.37]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.74(P=0.46)							
5.54.6 Replacement unclear							
Dodin 2005	85	1.7 (0.4)	94	1.8 (0.4)		50%	-0.09[-0.2,0.02]
FLAX-PAD 2013	43	1.1 (0.3)	41	1.2 (0.3)		50%	-0.1[-0.21,0.01]
Subtotal ***	**128**		**135**			**100%**	**-0.09[-0.17,-0.02]**
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.9); I^2=0%							
Test for overall effect: Z=2.46(P=0.01)							
Test for subgroup differences: Chi^2=4.12, df=1 (P=0.25), I^2=27.16%							



Favours higher omega 3 — Favours lower omega 3

Analysis 5.55. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 55 HDL, mmoL/L - ALA - subgroup by duration.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.55.1 Medium duration 1 to < 2 years in study							
Dodin 2005	85	1.7 (0.4)	94	1.8 (0.4)		29.75%	-0.09[-0.2,0.02]
FLAX-PAD 2013	43	1.1 (0.3)	41	1.2 (0.3)		29.75%	-0.1[-0.21,0.01]
HERO 2009	18	1.5 (0.4)	17	1.4 (0.4)		14.41%	0.1[-0.17,0.37]



Favours higher omega 3 — Favours lower omega 3

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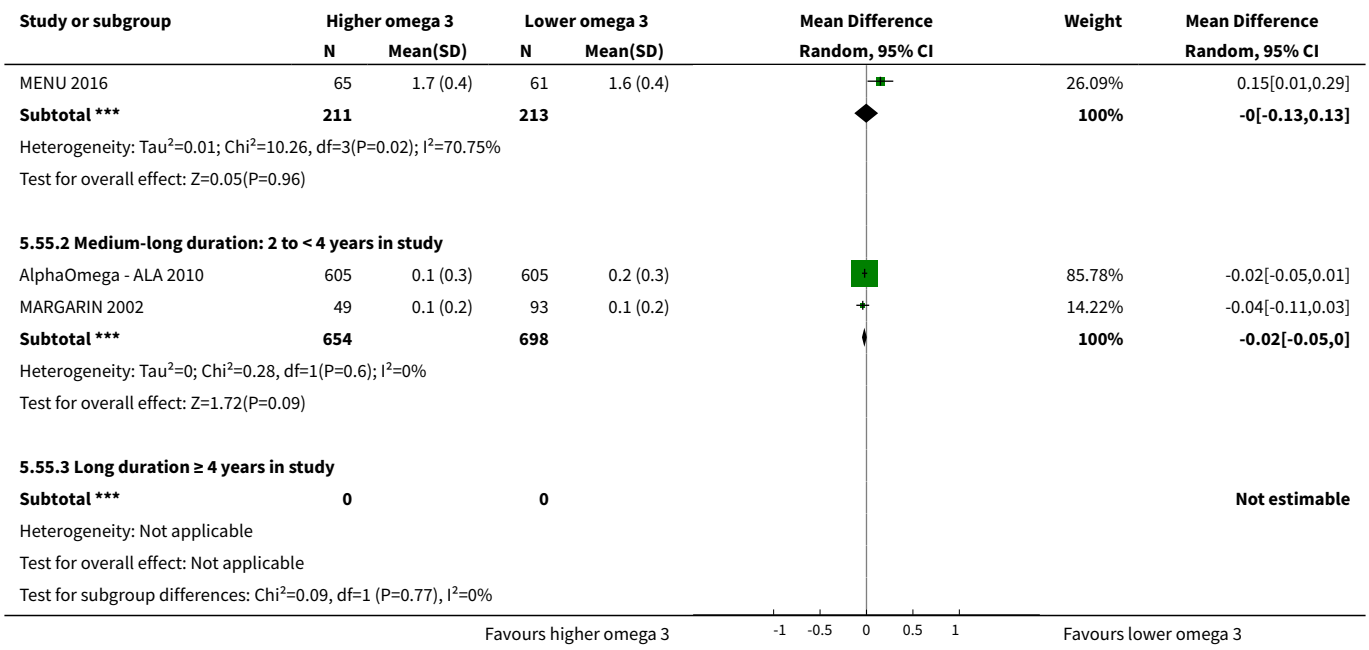
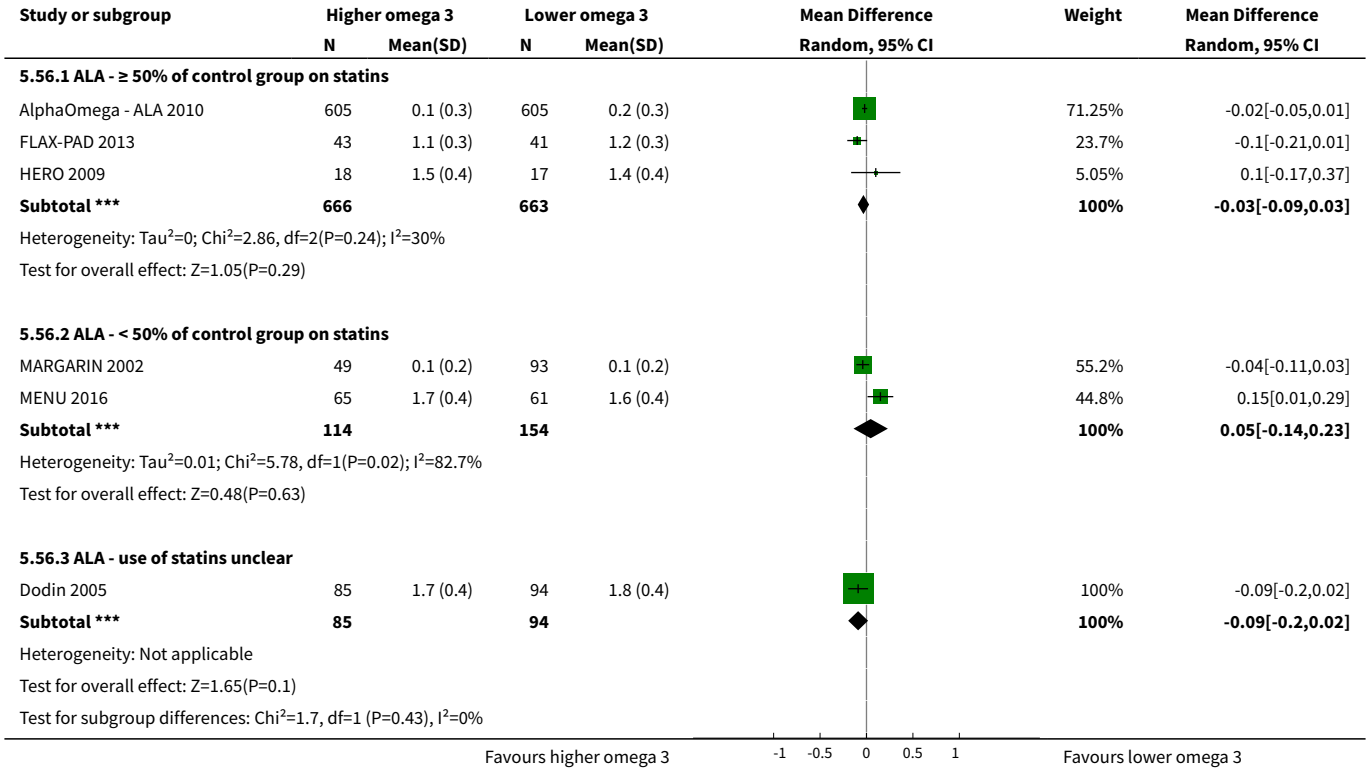


Analysis 5.56. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 56 HDL, mmoL/L - ALA - subgroup by statin use.



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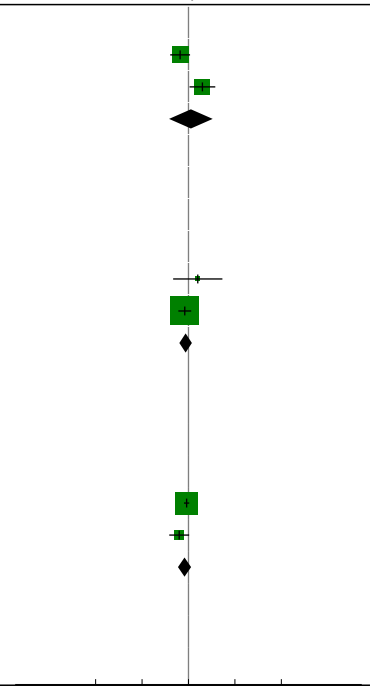
Analysis 5.57. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 57 HDL, mmoL/L - ALA - subgroup by primary or secondary prevention.

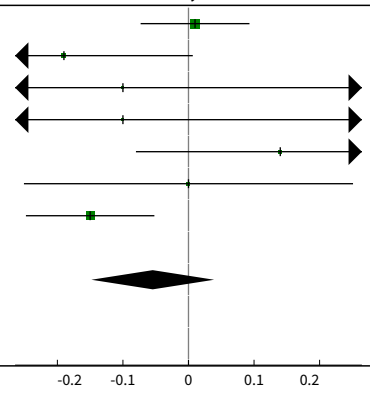
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.57.1 Low CVD risk							
Dodin 2005	85	1.7 (0.4)	94	1.8 (0.4)		51.76%	-0.09[-0.2,0.02]
MENU 2016	65	1.7 (0.4)	61	1.6 (0.4)		48.24%	0.15[0.01,0.29]
Subtotal ***	**150**		**155**			**100%**	**0.03[-0.21,0.26]**
Heterogeneity: Tau^2=0.02; Chi^2=7.22, df=1(P=0.01); I^2=86.15%							
Test for overall effect: Z=0.22(P=0.83)							
5.57.2 Moderate CVD risk							
HERO 2009	18	1.5 (0.4)	17	1.4 (0.4)		6.49%	0.1[-0.17,0.37]
MARGARIN 2002	49	0.1 (0.2)	93	0.1 (0.2)		93.51%	-0.04[-0.11,0.03]
Subtotal ***	**67**		**110**			**100%**	**-0.03[-0.1,0.04]**
Heterogeneity: Tau^2=0; Chi^2=1, df=1(P=0.32); I^2=0.27%							
Test for overall effect: Z=0.9(P=0.37)							
5.57.3 High CVD risk							
AlphaOmega - ALA 2010	605	0.1 (0.3)	605	0.2 (0.3)		71.65%	-0.02[-0.05,0.01]
FLAX-PAD 2013	43	1.1 (0.3)	41	1.2 (0.3)		28.35%	-0.1[-0.21,0.01]
Subtotal ***	**648**		**646**			**100%**	**-0.04[-0.11,0.03]**
Heterogeneity: Tau^2=0; Chi^2=2.01, df=1(P=0.16); I^2=50.24%							
Test for overall effect: Z=1.18(P=0.24)							
Test for subgroup differences: Chi^2=0.31, df=1 (P=0.85), I^2=0%							



Favours higher omega 3 — Favours lower omega 3

Analysis 5.58. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 58 Low-density lipoprotein, serum, mmoL/L - ALA.

Study or subgroup	Favours higher omega 3 N	Favours higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
AlphaOmega - ALA 2010	562	-0.4 (0.7)	562	-0.4 (0.7)		29.13%	0.01[-0.07,0.09]
Dodin 2005	85	3.5 (0.7)	94	3.6 (0.7)		14.18%	-0.19[-0.39,0.01]
FLAX-PAD 2013	43	2.3 (1.1)	41	2.4 (0.9)		4.23%	-0.1[-0.53,0.33]
HERO 2009	16	2.4 (0.6)	16	2.5 (0.8)		3.33%	-0.1[-0.59,0.39]
MARGARIN 2002	49	-0.4 (0.6)	93	-0.5 (0.7)		12.23%	0.14[-0.08,0.36]
MENU 2016	65	3 (0.8)	61	3 (0.6)		10.17%	0[-0.25,0.25]
WAHA 2016	260	-0.2 (0.5)	254	-0 (0.6)		26.73%	-0.15[-0.25,-0.05]
Total ***	**1080**		**1121**			**100%**	**-0.05[-0.15,0.04]**
Heterogeneity: Tau^2=0.01; Chi^2=11.05, df=6(P=0.09); I^2=45.7%							
Test for overall effect: Z=1.14(P=0.25)							



Favours higher omega 3 — Favours lower omega 3

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Analysis 5.59. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 59 LDL, mmoL/L - ALA - SA fixed-effect.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
AlphaOmega - ALA 2010	562	-0.4 (0.7)	562	-0.4 (0.7)		45.17%	0.01[-0.07,0.09]
Dodin 2005	85	3.5 (0.7)	94	3.6 (0.7)		8.06%	-0.19[-0.39,0.01]
FLAX-PAD 2013	43	2.3 (1.1)	41	2.4 (0.9)		1.69%	-0.1[-0.53,0.33]
HERO 2009	16	2.4 (0.6)	16	2.5 (0.8)		1.3%	-0.1[-0.59,0.39]
MARGARIN 2002	49	-0.4 (0.6)	93	-0.5 (0.7)		6.42%	0.14[-0.08,0.36]
MENU 2016	65	3 (0.8)	61	3 (0.6)		4.94%	0[-0.25,0.25]
WAHA 2016	260	-0.2 (0.5)	254	-0 (0.6)		32.43%	-0.15[-0.25,-0.05]
Total ***	**1080**		**1121**			**100%**	**-0.05[-0.11,0]**

Heterogeneity: $Tau^2=0$; $Chi^2=11.05$, df=6(P=0.09); $I^2=45.7\%$

Test for overall effect: Z=1.88(P=0.06)

Favours higher omega 3 — Favours lower omega 3

Analysis 5.60. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 60 LDL, mmoL/L - ALA - SA by summary risk of bias.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.60.1 Low risk of bias							
AlphaOmega - ALA 2010	562	-0.4 (0.7)	562	-0.4 (0.7)		84.77%	0.01[-0.07,0.09]
FLAX-PAD 2013	43	2.3 (1.1)	41	2.4 (0.9)		3.18%	-0.1[-0.53,0.33]
MARGARIN 2002	49	-0.4 (0.6)	93	-0.5 (0.7)		12.05%	0.14[-0.08,0.36]
Subtotal ***	**654**		**696**			**100%**	**0.02[-0.05,0.1]**
Heterogeneity: $Tau^2=0$; $Chi^2=1.49$, df=2(P=0.47); $I^2=0\%$							
Test for overall effect: Z=0.57(P=0.57)							
5.60.2 Moderate/high risk of bias							
Dodin 2005	85	3.5 (0.7)	94	3.6 (0.7)		17.24%	-0.19[-0.39,0.01]
HERO 2009	16	2.4 (0.6)	16	2.5 (0.8)		2.77%	-0.1[-0.59,0.39]
MENU 2016	65	3 (0.8)	61	3 (0.6)		10.58%	0[-0.25,0.25]
WAHA 2016	260	-0.2 (0.5)	254	-0 (0.6)		69.4%	-0.15[-0.25,-0.05]
Subtotal ***	**426**		**425**			**100%**	**-0.14[-0.22,-0.06]**
Heterogeneity: $Tau^2=0$; $Chi^2=1.51$, df=3(P=0.68); $I^2=0\%$							
Test for overall effect: Z=3.35(P=0)							
Test for subgroup differences: $Chi^2=8.05$, df=1 (P=0), $I^2=87.57\%$							

Favours higher omega 3 — Favours lower omega 3

Analysis 5.61. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 61 LDL, mmoL/L - ALA - SA by compliance and study size.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.61.1 SA - low risk of compliance bias							
AlphaOmega - ALA 2010	562	-0.4 (0.7)	562	-0.4 (0.7)		29.26%	0.01[-0.07,0.09]

Favours higher omega 3 — Favours lower omega 3

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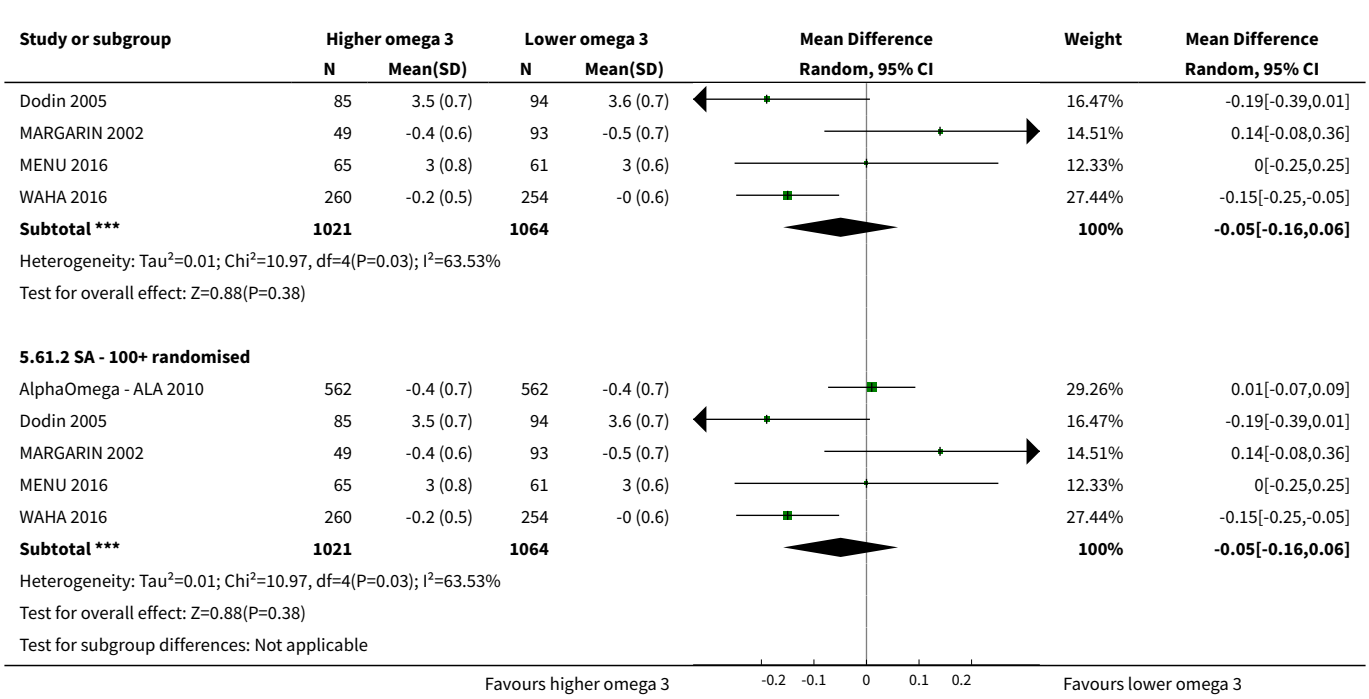
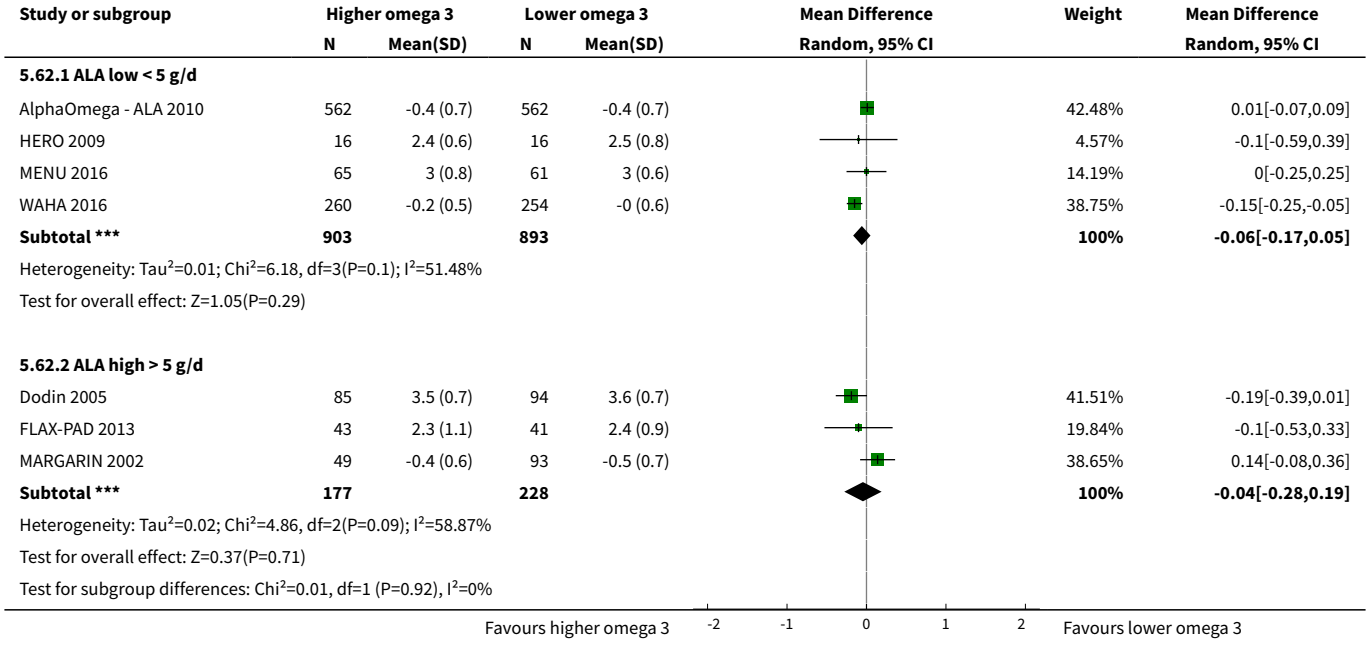


Analysis 5.62. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 62 LDL, mmoL/L - ALA - subgroup by dose.



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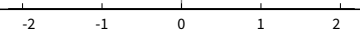
Analysis 5.63. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 63 LDL, mmoL/L - ALA - subgroup by intervention type.

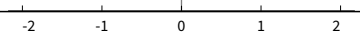
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.63.1 Dietary advice							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.63.2 Supplemental foods							
AlphaOmega - ALA 2010	562	-0.4 (0.7)	562	-0.4 (0.7)		30.84%	0.01[-0.07,0.09]
Dodin 2005	85	3.5 (0.7)	94	3.6 (0.7)		16.52%	-0.19[-0.39,0.01]
FLAX-PAD 2013	43	2.3 (1.1)	41	2.4 (0.9)		5.29%	-0.1[-0.53,0.33]
HERO 2009	16	2.4 (0.6)	16	2.5 (0.8)		4.19%	-0.1[-0.59,0.39]
MARGARIN 2002	49	-0.4 (0.6)	93	-0.5 (0.7)		14.45%	0.14[-0.08,0.36]
WAHA 2016	260	-0.2 (0.5)	254	-0 (0.6)		28.72%	-0.15[-0.25,-0.05]
Subtotal ***	**1015**		**1060**			**100%**	**-0.06[-0.17,0.05]**
Heterogeneity: Tau^2=0.01; Chi^2=10.87, df=5(P=0.05); I^2=53.99%							
Test for overall effect: Z=1.12(P=0.26)							
5.63.3 Supplement (capsule)							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.63.4 Any combination							
MENU 2016	65	3 (0.8)	61	3 (0.6)		100%	0[-0.25,0.25]
Subtotal ***	**65**		**61**			**100%**	**0[-0.25,0.25]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Chi^2=0.19, df=1 (P=0.66), I^2=0%							



Favours higher omega 3 — Favours lower omega 3

Analysis 5.64. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 64 LDL, mmoL/L - ALA - subgroup by replacement.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.64.1 ALA replacing SFA							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.64.2 ALA replacing MUFA							
AlphaOmega - ALA 2010	562	-0.4 (0.7)	562	-0.4 (0.7)		90.14%	0.01[-0.07,0.09]
MENU 2016	65	3 (0.8)	61	3 (0.6)		9.86%	0[-0.25,0.25]
Subtotal ***	**627**		**623**			**100%**	**0.01[-0.07,0.09]**
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.94); I^2=0%							
Test for overall effect: Z=0.22(P=0.82)							
5.64.3 ALA replacing n-6							



Favours higher omega 3 — Favours lower omega 3

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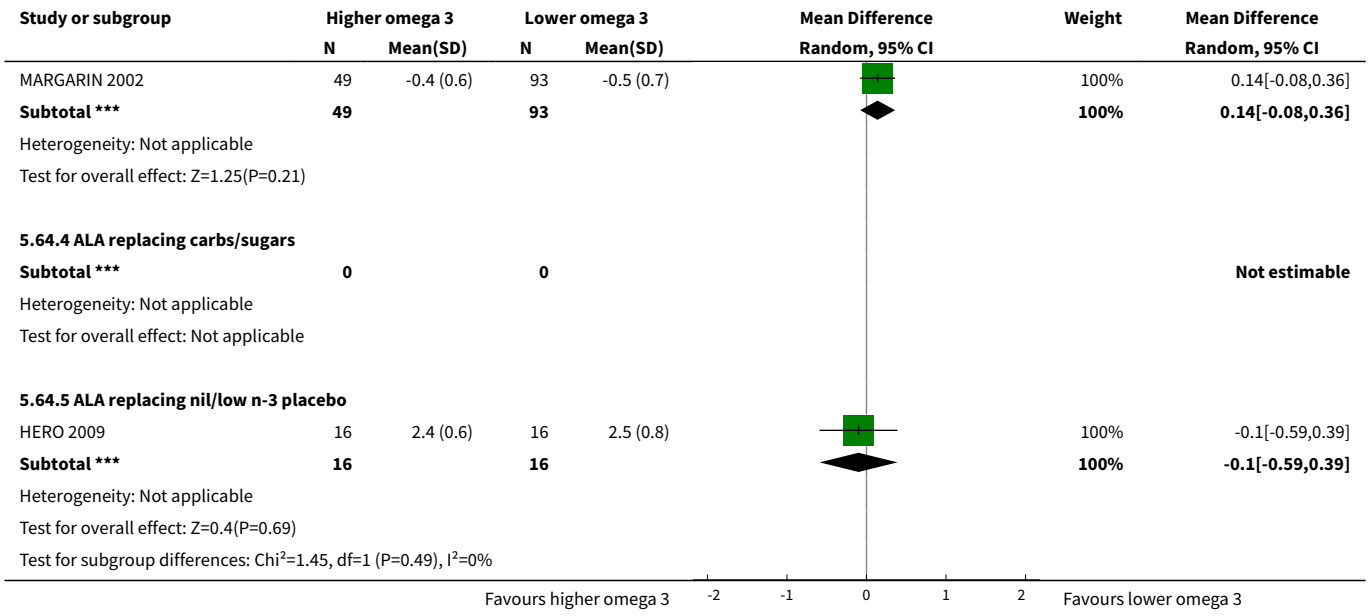
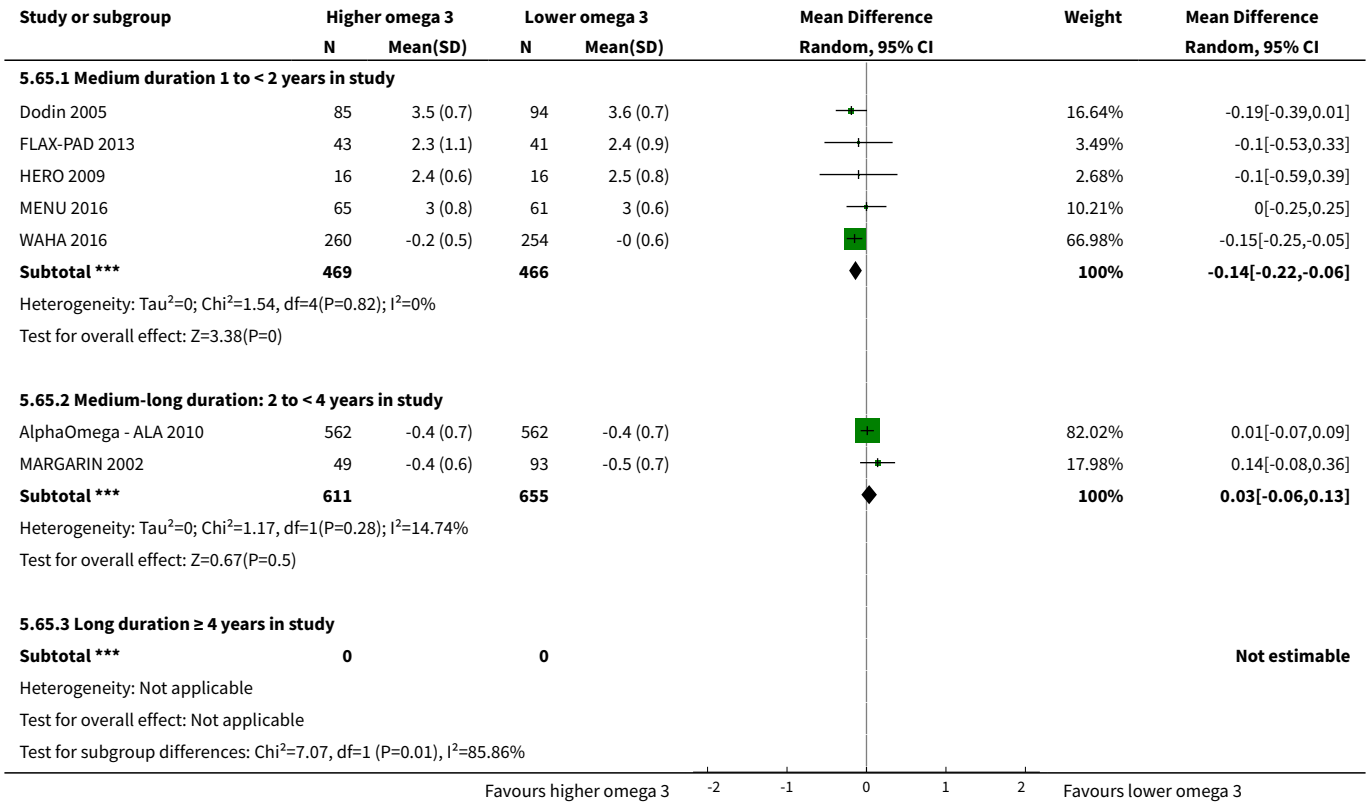


Analysis 5.65. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 65 LDL, mmoL/L - ALA - subgroup by duration.



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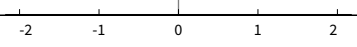
Analysis 5.66. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 66 LDL, mmoL/L - ALA - subgroup by statin use.

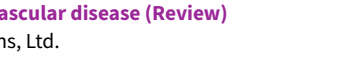
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.66.1 ALA - ≥ 50% of control group on statins							
AlphaOmega - ALA 2010	562	-0.4 (0.7)	562	-0.4 (0.7)		93.79%	0.01[-0.07,0.09]
FLAX-PAD 2013	43	2.3 (1.1)	41	2.4 (0.9)		3.51%	-0.1[-0.53,0.33]
HERO 2009	16	2.4 (0.6)	16	2.5 (0.8)		2.69%	-0.1[-0.59,0.39]
Subtotal ***	**621**		**619**			**100%**	**0[-0.08,0.08]**
Heterogeneity: Tau²=0; Chi²=0.42, df=2(P=0.81); I²=0%							
Test for overall effect: Z=0.08(P=0.94)							
5.66.2 ALA - < 50% of control group on statins							
MARGARIN 2002	49	-0.4 (0.6)	93	-0.5 (0.7)		56.52%	0.14[-0.08,0.36]
MENU 2016	65	3 (0.8)	61	3 (0.6)		43.48%	0[-0.25,0.25]
Subtotal ***	**114**		**154**			**100%**	**0.08[-0.09,0.24]**
Heterogeneity: Tau²=0; Chi²=0.68, df=1(P=0.41); I²=0%							
Test for overall effect: Z=0.94(P=0.35)							
5.66.3 ALA - use of statins unclear							
Dodin 2005	85	3.5 (0.7)	94	3.6 (0.7)		19.9%	-0.19[-0.39,0.01]
WAHA 2016	260	-0.2 (0.5)	254	-0 (0.6)		80.1%	-0.15[-0.25,-0.05]
Subtotal ***	**345**		**348**			**100%**	**-0.16[-0.25,-0.07]**
Heterogeneity: Tau²=0; Chi²=0.13, df=1(P=0.72); I²=0%							
Test for overall effect: Z=3.53(P=0)							
Test for subgroup differences: Chi²=9.83, df=1 (P=0.01), I²=79.65%							



Favours higher omega 3 — Favours lower omega 3

Analysis 5.67. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 67 LDL, mmoL/L - ALA - subgroup by primary or secondary prevention.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.67.1 Primary prevention of CVD							
Dodin 2005	85	3.5 (0.7)	94	3.6 (0.7)		21.73%	-0.19[-0.39,0.01]
HERO 2009	16	2.4 (0.6)	16	2.5 (0.8)		5.51%	-0.1[-0.59,0.39]
MARGARIN 2002	49	-0.4 (0.6)	93	-0.5 (0.7)		19%	0.14[-0.08,0.36]
MENU 2016	65	3 (0.8)	61	3 (0.6)		16.03%	0[-0.25,0.25]
WAHA 2016	260	-0.2 (0.5)	254	-0 (0.6)		37.73%	-0.15[-0.25,-0.05]
Subtotal ***	**475**		**518**			**100%**	**-0.08[-0.2,0.05]**
Heterogeneity: Tau²=0.01; Chi²=6.96, df=4(P=0.14); I²=42.52%							
Test for overall effect: Z=1.23(P=0.22)							
5.67.2 Secondary prevention of CVD							
AlphaOmega - ALA 2010	562	-0.4 (0.7)	562	-0.4 (0.7)		96.39%	0.01[-0.07,0.09]
FLAX-PAD 2013	43	2.3 (1.1)	41	2.4 (0.9)		3.61%	-0.1[-0.53,0.33]
Subtotal ***	**605**		**603**			**100%**	**0.01[-0.08,0.09]**
Heterogeneity: Tau²=0; Chi²=0.24, df=1(P=0.62); I²=0%							
Test for overall effect: Z=0.14(P=0.88)							
Test for subgroup differences: Chi²=1.22, df=1 (P=0.27), I²=18.32%							



Favours higher omega 3 — Favours lower omega 3

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Comparison 6. High vs low ALA omega-3 fats (tertiary outcomes)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Blood pressure, mmHg - ALA	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Systolic BP - ALA	4	1671	Mean Difference (IV, Random, 95% CI)	-0.87 [-4.48, 2.75]
1.2 Diastolic BP - ALA	4	1671	Mean Difference (IV, Random, 95% CI)	-1.42 [-4.40, 1.57]
2 Serious adverse events - ALA	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Any serious adverse events	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Bleeding	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Serious GI effects	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 Pulmonary embolus or DVT	1	708	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.80]
2.5 Thrombophleibitis	1	13406	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.72, 3.51]
2.6 Urolithiasis	1	13406	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.47, 1.36]
3 Side effects - ALA	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Dropouts due to side effects	5	3480	Risk Ratio (M-H, Random, 95% CI)	2.10 [0.66, 6.71]
3.2 Abdominal pain or discomfort	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Diarrhoea	1	708	Risk Ratio (M-H, Random, 95% CI)	3.82 [0.82, 17.88]
3.4 Nausea	1	110	Risk Ratio (M-H, Random, 95% CI)	6.29 [0.33, 118.93]
3.5 Any gastrointestinal side effect - ALA	4	3450	Risk Ratio (M-H, Random, 95% CI)	2.06 [0.62, 6.80]
3.6 Pain (joint, lumbar, muscle pain)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.7 All side effects combined	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Dropouts - ALA	6	3663	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.92, 1.25]

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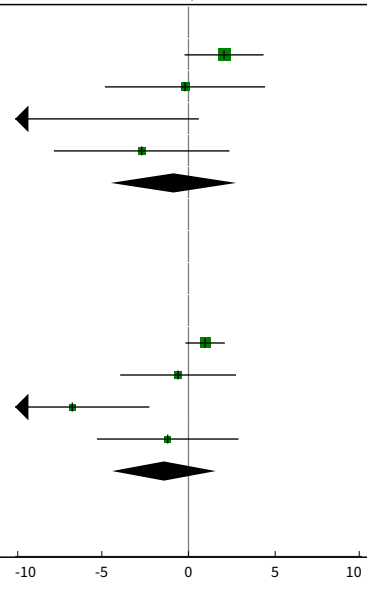
Analysis 6.1. Comparison 6 High vs low ALA omega-3 fats (tertiary outcomes), Outcome 1 Blood pressure, mmHg - ALA.

Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
6.1.1 Systolic BP - ALA							
AlphaOmega - ALA 2010	632	-0.2 (20)	632	-2.3 (21.3)		39.11%	2.05[-0.23,4.33]
Dodin 2005	85	120.6 (14.4)	94	120.8 (17.1)		26.39%	-0.2[-4.82,4.42]
FLAX-PAD 2013	45	136.2 (25.5)	41	145.6 (21.8)		10.21%	-9.4[-19.39,0.59]
MARGARIN 2002	49	-2.9 (14.7)	93	-0.2 (14.5)		24.28%	-2.7[-7.76,2.36]
Subtotal ***	**811**		**860**			**100%**	**-0.87[-4.48,2.75]**
Heterogeneity: Tau^2=7.36; Chi^2=7.15, df=3(P=0.07); I^2=58.03%							
Test for overall effect: Z=0.47(P=0.64)							
6.1.2 Diastolic BP - ALA							
AlphaOmega - ALA 2010	632	-1.8 (10.3)	632	-2.7 (10.3)		33.94%	0.96[-0.18,2.1]
Dodin 2005	85	75.5 (10.9)	94	76.1 (11.9)		24.68%	-0.6[-3.94,2.74]
FLAX-PAD 2013	45	71.8 (11.4)	41	78.5 (9.6)		19.95%	-6.7[-11.14,-2.26]
MARGARIN 2002	49	0.7 (11.9)	93	1.9 (11.6)		21.42%	-1.2[-5.28,2.88]
Subtotal ***	**811**		**860**			**100%**	**-1.42[-4.4,1.57]**
Heterogeneity: Tau^2=6.51; Chi^2=11.63, df=3(P=0.01); I^2=74.2%							
Test for overall effect: Z=0.93(P=0.35)							



Favours higher omega 3 — Favours lower omega 3

Analysis 6.2. Comparison 6 High vs low ALA omega-3 fats (tertiary outcomes), Outcome 2 Serious adverse events - ALA.

Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.2.1 Any serious adverse events					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 3), 0 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
6.2.2 Bleeding					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 3), 0 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
6.2.3 Serious GI effects					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 3), 0 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
6.2.4 Pulmonary embolus or DVT					
WAHA 2016	0/362	1/346		100%	0.32[0.01,7.8]
Subtotal (95% CI)	**362**	**346**		**100%**	**0.32[0.01,7.8]**
Total events: 0 (Higher omega 3), 1 (Lower omega 3)					
Heterogeneity: Not applicable					

Favours higher omega 3 — Favours lower omega 3

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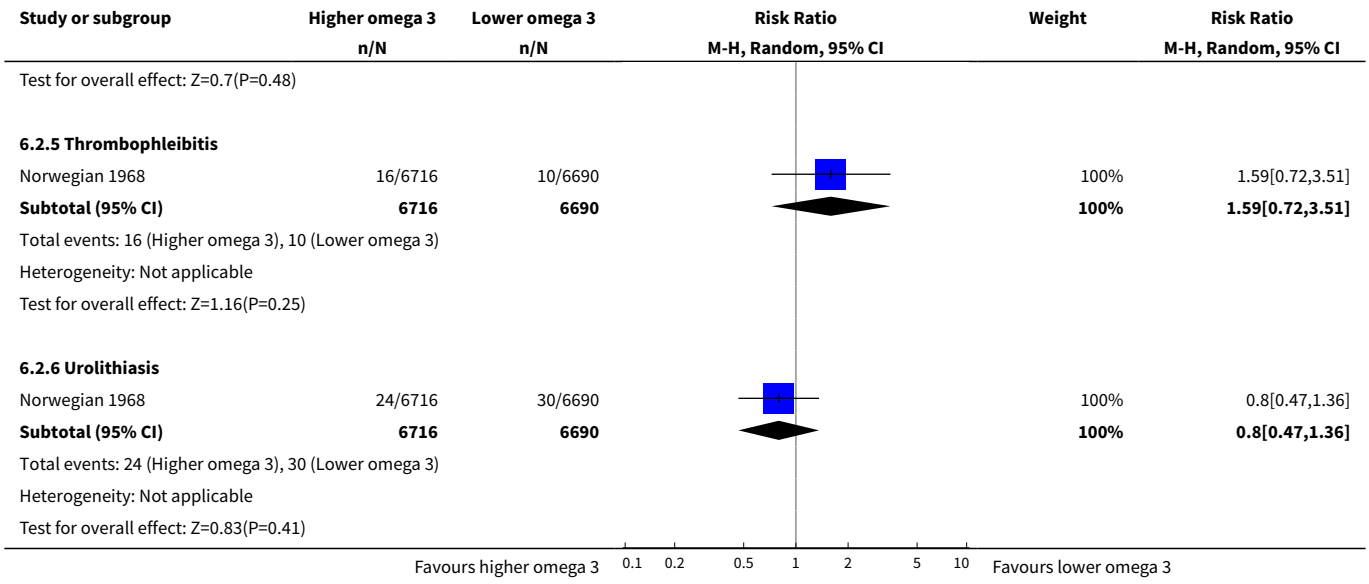
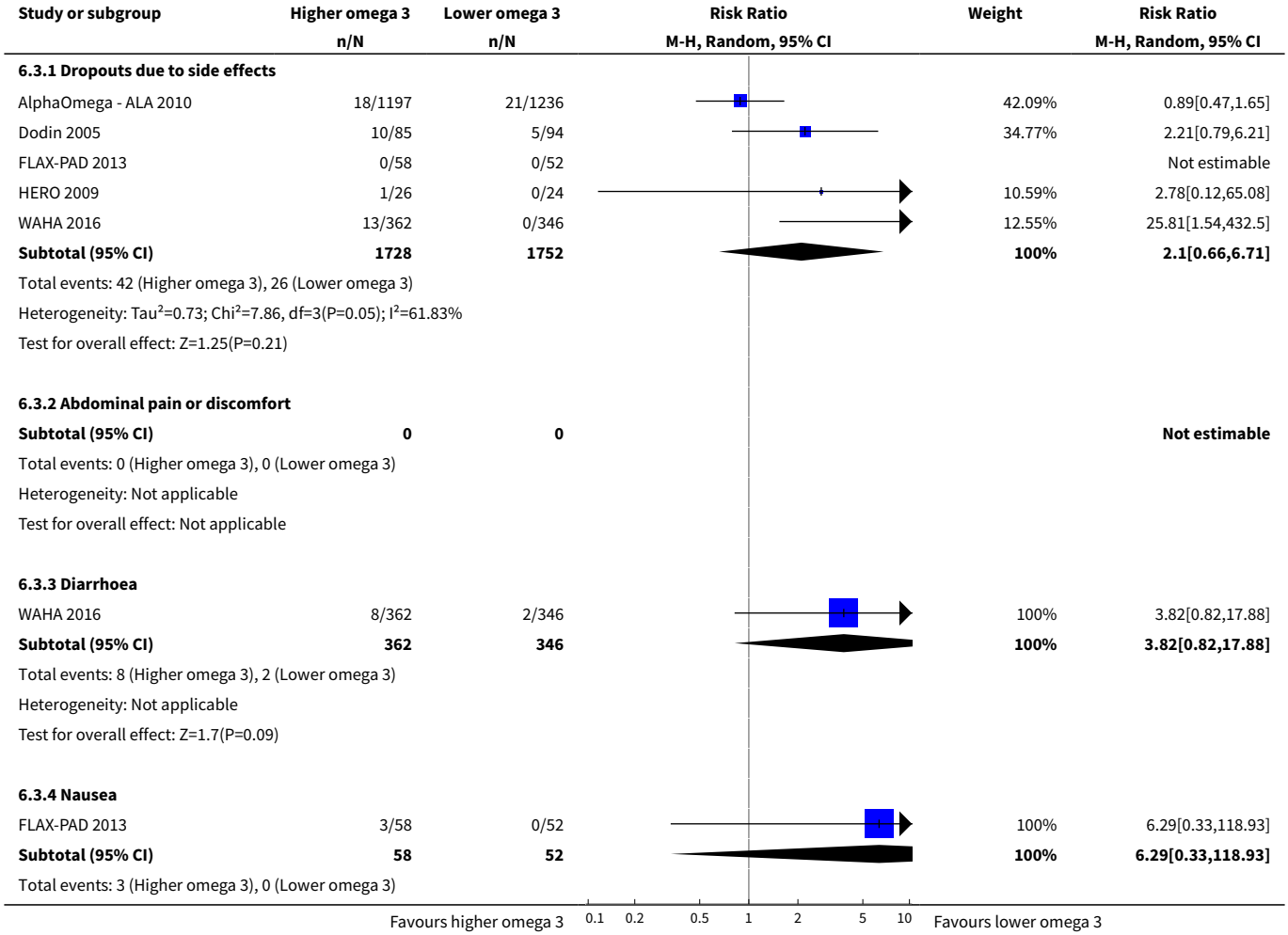


Analysis 6.3. Comparison 6 High vs low ALA omega-3 fats (tertiary outcomes), Outcome 3 Side effects - ALA.



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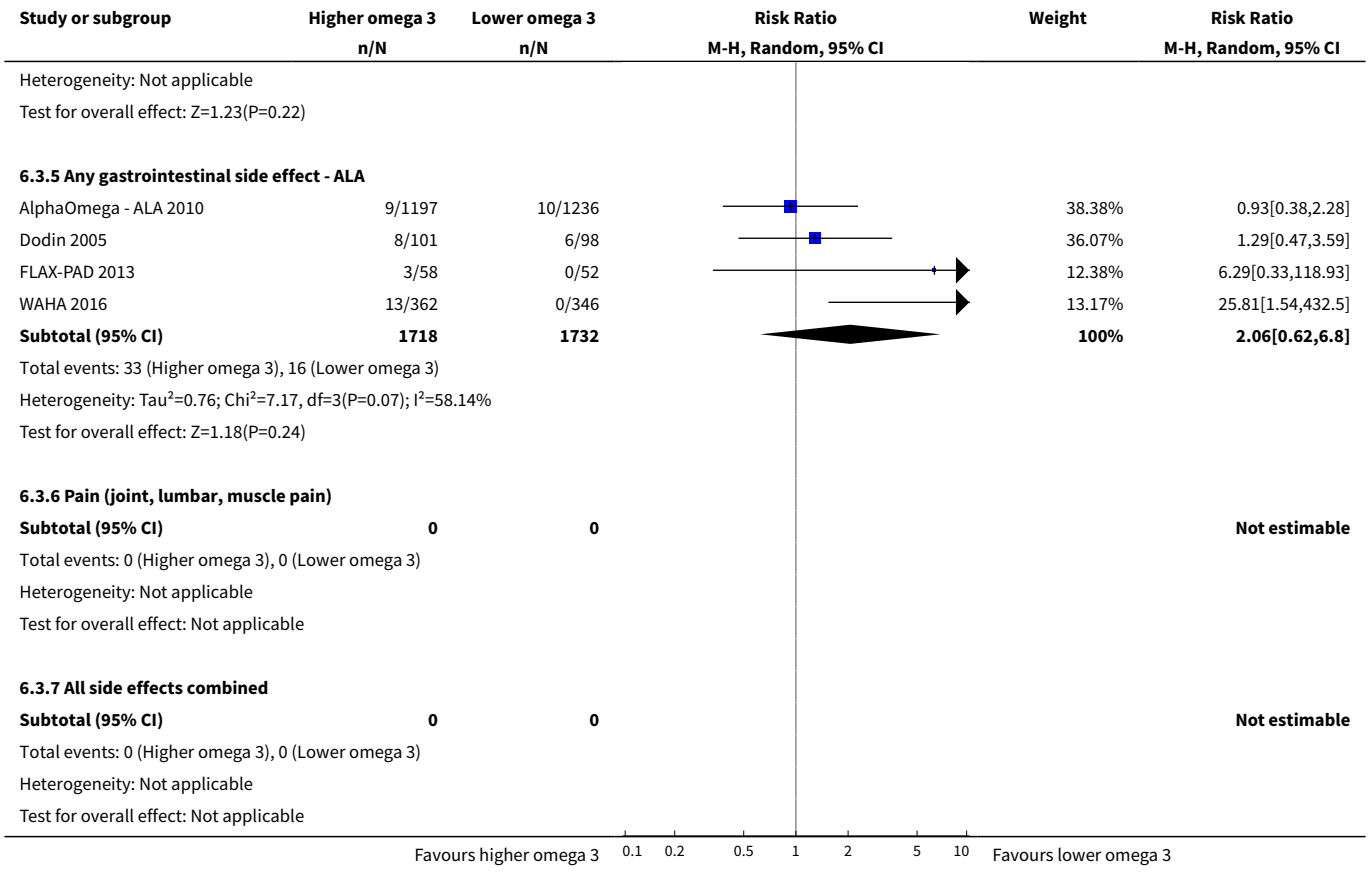
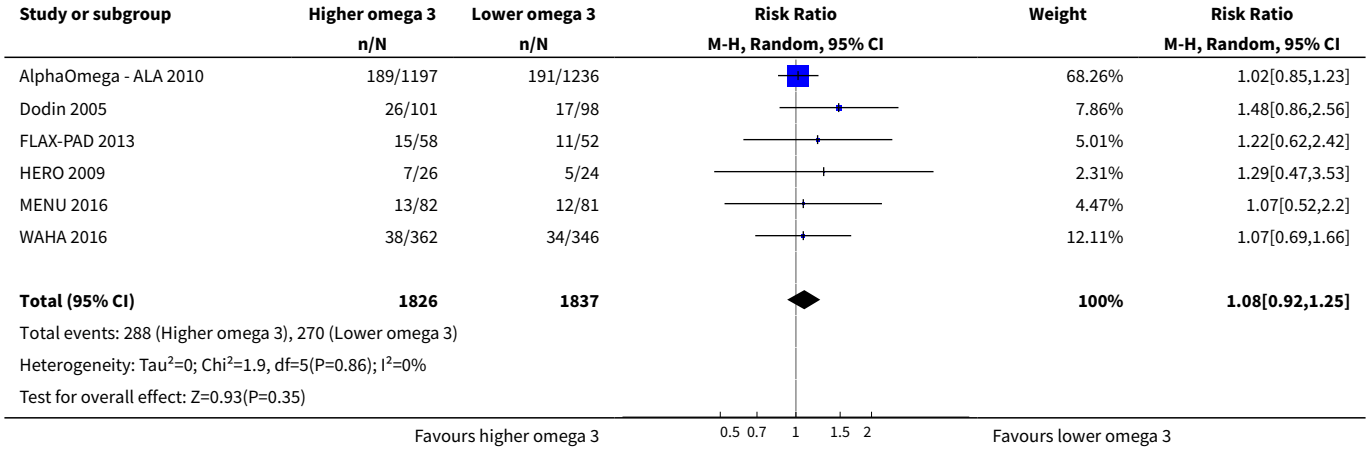


Analysis 6.4. Comparison 6 High vs low ALA omega-3 fats (tertiary outcomes), Outcome 4 Dropouts - ALA.



ADDITIONAL TABLES

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Table 1. Risk of bias assessment methods in greater detail

Risk of bias element	Criteria for low risk of bias	Criteria for unclear	Criteria for high risk of bias
Selection bias: random sequence generation	The trial authors needed to have described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. For example "the randomisation sequence was computer generated". We allowed that a good method of randomisation was strongly implied if the authors discussed stratification and/or blocking. Therefore, if the authors were not explicit about their randomisation method but did describe stratification or blocking we assessed this as corresponding to low risk.	The trial authors have not described their method in sufficient detail for the assessment of whether it would produce comparable groups. For example, the authors state "the trial was randomised" and provide no further information.	The randomisation method was assessed as not truly random, and may not produce comparable groups.
Selection bias: allocation concealment	The trial authors needed to have described the method used to conceal allocation sequence in sufficient detail to determine whether the allocations could have been foreseen in advance of, or during, enrolment. Good methods included putting allocation codes in opaque sealed envelopes (ideally prepared by someone outside the treatment or assessment teams and sequentially numbered), using a telephone allocation system after the participants had consented to participate or providing a random number that links to a specific set of capsules prepared and distributed centrally or by an arms-length pharmacist.	The trial authors gave insufficient detail as to method.	The allocation was known in advance of participants consenting to take part in the trial.
Performance bias: blinding of participants and personnel	The trial authors needed to have described all measures used, if any, to blind trial participants and personnel from knowledge of which intervention a participant received. Ideally, they should also have provided information relating to whether the intended blinding was effective. For example, the authors could say "both the intervention and placebo capsules looked and tasted the same." However, if the trial authors did not provide information on whether the blinding was effective, but sufficient detail was given on a good method of blinding, then we assumed that the blinding was effective and the risk of bias was low.	Insufficient methodological details were provided e.g. "the trial was blinded."	The trial was unblinded or where blinding was broken, e.g. "the capsules were visually identical but the participants reported a strong fishy flavour in the intervention group only."
Detection bias: blinding of outcome assessment	Trial authors needed to have described measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Ideally, they should also have provided information relating to whether the intended blinding was effective. For example, the authors could say "the outcome assessors had no knowledge of the group allocation, and both the intervention and placebo capsules looked and tasted the same so the self-assessment scales were also blinded." However if the trial authors did not provide information on whether the blinding was effective, but sufficient detail was given on a good method of blinding of the assessors, then we assumed that the blinding was effective and the risk of bias is low. All biochemical assessment (lipids, glucose, CRP, insulin, PSA, etc.) were	Insufficient methodological details were provided e.g. "the trial was blinded."	The trial was unblinded or blinding was broken, e.g. for a self-assessment measure "the capsules were visually identical but the participants reported a strong fishy flavour in the intervention group only." Because the level of blinding could vary by outcome, assessment of risk of bias was based on blinding of the review's primary outcome(s). Where primary outcomes had different assessments we opted for the

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Table 1. Risk of bias assessment methods in greater detail *(Continued)*

	considered at low risk of detection bias if outcome assessor blinding or double-blinding was stated.		higher risk of bias but noted that risk of bias was lower for other outcomes.
Attrition bias: incomplete outcome data	The trial authors needed to describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. They needed to report the number of attrition/exclusions, the numbers in each group at each time point, reasons for attrition/exclusion and any re-inclusions in analyses. Ideally, they would report how they imputed any missing data e.g. last observation carried forward. There needed to be a reasonable balance of attrition/exclusions between trial arms and ≤ 20% of the sample should be lost over a year.	The authors didn't state reasons for attrition/exclusion, or were unclear about the numbers lost to attrition/exclusion in each trial arm.	The authors demonstrated a substantial difference in the rates of attrition/exclusions between the trial arms and/or > 20% of the baseline sample was lost over a year (> 10% over 6 months).
Reporting bias: selective outcome reporting	The trial authors needed to have published their trial protocol or trials registry entry before the end of the trial's recruitment period, i.e. prospectively. They needed to have reported on all of the primary and secondary outcomes listed in the protocol/registry entry. We deemed reporting additional secondary outcomes in the results paper(s), although not ideal, to still be low risk.	No trial protocol or trials registry entry was found, it was registered retrospectively, or the dates of registration and participant recruitment were unclear.	The trial authors did not report at least one primary or secondary outcome listed in the protocol/registry entry or the results paper(s) reported a primary outcome that was not listed at all in the protocol or not listed as a primary outcome in the protocol.
Other sources of bias: attention bias	The trial authors needed to have reported that participants in all trial arms received the same amount of attention and time from researchers and clinical teams. For example, "All participants attended the clinic for a baseline assessment which took 2 hours. They were then followed with monthly telephone calls, and finally attended for a 6 month assessment at the clinic which took 1 hour." If the trial only differed by the content of the capsules, and the assessment schedule was not stated to differ between the two arms, we assumed it to be at low risk.	The authors did not state the attention each arm received.	Participants in different arms received different amounts of attention. For example "the intervention group only attended for additional assessments at months 2, 4, and 6" or "the rates of relapse differed substantially between the groups which led to differing amounts of treatment time and attention," or "the intervention group received a 40 minute dietary education session."
Other sources of bias: limited compliance	The trial authors needed to have reported on the level of compliance in all arms in sufficient detail to determine whether the trial results were robust. We followed a flow chart to make this determination. A statistically significant difference between the intervention and control groups in a body measure of at least 50% of the test fatty acids. Where no body measures were reported then estimated compliance needed to be greater than 64% (proportion complying multiplied by compliance threshold).	Compliance not reported or not in a way that could be interpreted.	Measures of compliance were reported but fell below the appropriate thresholds.
Other sources of bias: other	In the absence of any additional issues this item was coded "low risk of bias"	—	If fraud concerns had been raised and the paper had been withdrawn, or the author had been found guilty of fraud by a legal or medical entity the paper was

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Table 1. Risk of bias assessment methods in greater detail *(Continued)*

	excluded from the review. However if fraud concerns were raised, but the journal had not withdrawn the paper, and the author had not been formally sanctioned; then the trial was included in the review, but concerns were raised here, and the risk of bias for this item was high.

CRP: C-reactive protein; **PSA**: prostate specific antigen

Table 2. Meta-regression results for cardiovascular mortality[a]

Variable assessed	P value
LCn3 dose	0.21
ALA dose	0.88
Omega-6 dose	0.71
Total PUFA dose	0.78
Duration, months	0.78
Primary or secondary CVD prevention	0.82
Food or capsule	0.27
Risk of bias	0.91
Food or capsule	0.72
+ LCn3 dose	0.37
+ n6 dose	0.99

ALA: alpha-linolenic acid; **CVD**: cardiovascular disease; **LCn3**: long-chain omega-3 fatty acids; **PUFA**: polyunsaturated fatty acids

[a]Random-effects meta-regression exploring effects of LCn3 dose, ALA dose, omega-6 dose, total PUFA dose, trial duration, primary or secondary prevention, food or capsule intervention, and summary risk of bias (low or moderate to high) on cardiovascular mortality. We ran the meta-regression using all included trials that reported this outcome in this review, and its sister reviews (Hooper 2018 and Abdelhamid 2018b). For each variable the P value presented represents probability that the relationship was due to chance (as we had limited power we assumed a true relationship when P < 0.10). Meta-regression was of each variable singly, plus a multivariate meta-regression of the 3 single variables with lowest P values. See methods for further information.

Table 3. Meta-regression results for cardiovascular events[a]

Variable assessed	P value	Coefficient sign where P < 0.10

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Table 3. Meta-regression results for cardiovascular events[a] *(Continued)*

LCn3 dose	0.02	Negative (lower CVD event risk with higher LCn3 dose)
ALA dose	0.67	
Omega-6 dose	0.38	
Total PUFA dose	0.29	
Duration, months	0.16	
Primary or secondary CVD prevention	0.76	
Food or capsule	0.30	
Risk of bias	0.17	
Risk of bias + LCn3 dose + duration	0.19 0.07 0.19	Negative (lower CVD event risk with higher LCn3 dose)
LCn3 dose - analysis omitting REDUCE-IT 2019 data	0.99	

ALA: alpha-linolenic acid; **CVD**: cardiovascular disease; **LCn3**: long-chain omega-3 fatty acids; **PUFA**: polyunsaturated fatty acids

[a]Random-effects meta-regression exploring effects of LCn3 dose, ALA dose, omega-6 dose, total PUFA dose, trial duration, primary or secondary prevention, food or capsule intervention, and summary risk of bias (low or moderate to high) on cardiovascular events. We ran the meta-regression using all included trials that reported this outcome in this review, and its sister reviews (Hooper 2018 and Abdelhamid 2018b). For each variable the P value presented represents probability that the relationship was due to chance (as we had limited power we assumed a true relationship when P < 0.10). Meta-regression was of each variable singly, plus a multivariate meta-regression of the 3 single variables with lowest P values. See methods for further information.

Table 4. Meta-regression results for coronary heart disease deaths[a]

Variable assessed	P value
LCn3 dose	0.89
ALA dose	0.94
Omega-6 dose	0.61
Total PUFA dose	0.59
Duration, months	0.79
Primary or secondary CVD prevention	0.97
Food or capsule	0.59
Risk of bias	0.41
Risk of bias	0.60

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Table 4. Meta-regression results for coronary heart disease deaths[a] *(Continued)*

+ Food or capsule	0.81
+ PUFA dose	0.68

ALA: alpha-linolenic acid; **CVD**: cardiovascular disease; **LCn3**: long-chain omega-3 fatty acids; **PUFA**: polyunsaturated fatty acids

[a]Random-effects meta-regression exploring effects of LCn3 dose, ALA dose, omega-6 dose, total PUFA dose, trial duration, primary or secondary prevention, food or capsule intervention, and summary risk of bias (low or moderate to high) on coronary heart disease mortality. We ran the meta-regression using all included trials that reported this outcome in this review, and its sister reviews (Hooper 2018 and Abdelhamid 2018b). For each variable the P value presented represents probability that the relationship was due to chance (as we had limited power we assumed a true relationship when P < 0.10). Meta-regression was of each variable singly, plus a multivariate meta-regression of the 3 single variables with lowest P values. See methods for further information.

Table 5. Metaregression results for coronary heart disease events[a]

Variable assessed	P value	Coefficient sign where P < 0.10
LCn3 dose	0.02	Negative (risk of CHD events falls as LCn3 dose increases)
ALA dose	0.18	
Omega-6 dose	0.51	
Total PUFA dose	0.57	
Duration, months	0.16	
Primary or secondary CVD prevention	0.82	
Food or capsule	0.22	
Risk of bias	0.71	
ALA dose	0.36	Negative (risk of CHD events falls as LCn3 dose increases)
+ duration	0.35	
+ LCn3 dose	0.06	
LCn3 dose - analysis omitting REDUCE-IT data	0.81	

ALA: alpha-linolenic acid; **CHD:** coronary heart disease; **CVD**: cardiovascular disease; **LCn3**: long-chain omega-3 fatty acids; **PUFA**: polyunsaturated fatty acids

[a]Random-effects meta-regression exploring effects of LCn3 dose, ALA dose, omega-6 dose, total PUFA dose, trial duration, primary or secondary prevention, food or capsule intervention, and summary risk of bias (low or moderate to high) on CHD events. We ran the meta-regression using all included trials that reported this outcome in this review, and its sister reviews (Hooper 2018 and Abdelhamid 2018b). For each variable the P value presented represents probability that the relationship was due to chance (as we had limited power we assumed a true relationship when P < 0.10). Meta-regression was of each variable singly, plus a multivariate meta-regression of the 3 single variables with lowest P values. See methods for further information.

Table 6. Metaregression results for stroke[a]

Variable assessed	P value	Coefficient sign where P < 0.10

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Table 6. Metaregression results for stroke[a] *(Continued)*

LCn3 dose	0.12	—
ALA dose	0.73	—
Omega-6 dose	0.23	—
Total PUFA dose	0.09	Negative (lower risk with higher dose)
Duration, months	0.03	Negative (smaller risk with longer duration)
Primary or secondary CVD prevention	0.44	-
Food or capsule	0.36	—
Risk of bias	0.26	—
Duration	0.03	—
+ LCn3 dose	0.06	
+ total PUFA dose	0.15	

ALA: alpha-linolenic acid; **CVD**: cardiovascular disease; **LCn3**: long-chain omega-3 fatty acids; **PUFA**: polyunsaturated fatty acids

[a]Random-effects meta-regression exploring effects of LCn3 dose, ALA dose, omega-6 dose, total PUFA dose, trial duration, primary or secondary prevention, food or capsule intervention, and summary risk of bias (low or moderate to high) on stroke. We ran the meta-regression using all included trials that reported this outcome in this review, and its sister reviews (Hooper 2018 and Abdelhamid 2018b). For each variable the P value presented represents probability that the relationship was due to chance (as we had limited power we assumed a true relationship when P < 0.10). Meta-regression was of each variable singly, plus a multivariate meta-regression of the 3 single variables with lowest P values. See methods for further information.

Table 7. Meta-regression results for arrhythmia[a]

Variable assessed	P value	Coefficient sign where P < 0.10
LCn3 dose	0.52	-
ALA dose	0.45	—
Omega-6 dose	0.56	—
Total PUFA dose	0.99	—
Duration, months	0.03	Positive (higher risk with longer duration)
Primary or secondary CVD prevention	0.03	Negative (greater effect with primary prevention)
Food or capsule	1.00	—
Risk of bias	0.65	—
ALA dose	0.33	—
+ Primary secondary prevention	0.42	

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Table 7. Meta-regression results for arrhythmia[a] *(Continued)*

+ duration	0.42

ALA: alpha-linolenic acid; **CVD**: cardiovascular disease; **LCn3**: long-chain omega-3 fatty acids; **PUFA**: polyunsaturated fatty acids

[a]Random-effects meta-regression exploring effects of LCn3 dose, ALA dose, omega-6 dose, total PUFA dose, trial duration, primary or secondary prevention, food or capsule intervention, and summary risk of bias (low or moderate to high) on arrhythmia. We ran the meta-regression using all included trials that reported this outcome in this review, and its sister reviews (Hooper 2018 and Abdelhamid 2018b). For each variable the P value presented represents probability that the relationship was due to chance (as we had limited power we assumed a true relationship when $P < 0.10$). Meta-regression was of each variable singly, plus a multivariate meta-regression of the 3 single variables with lowest P values. See methods for further information.

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Table 8. Comparison of the results of long-chain omega-3 interventions in this review with other major recent reviews[a]

Systematic review	Balk 2016		Aung 2018		Hu 2019		This review	
Outcome	**Number of people experiencing events**	**RR (95% CI)**	**Number of people experiencing events**	**RR (95% CI)**	**Number of people experiencing events**	**RR (95% CI)**	**Number of people experiencing events**	**RR (95% CI)**
All-cause mortality	8480	0.97 (0.92 to 1.03)	-	Not assessed	-	Not assessed	11,297	0.97 (0.93 to 1.01)
Cardiovascular deaths	3799	0.92 (0.82 to 1.02)	-	Not assessed	4630	0.93 (0.88 to 0.99)	5658	0.92 (0.86 to 0.99)
CVD events (MACCEs in Balk 2016)	8085	0.96 (0.91 to 1.02)	12,001	0.97 (0.93 to 1.01)	14,694	0.97 (0.94 to 0.99)	17,619	0.96 (0.92 to 1.01)
CHD deaths	-	Not pooled	2695	0.93, (0.83 to 1.03)	2934	0.92 (0.86 to 0.98)	3598	0.90 (0.81 to 1.00)
CHD events	-	Not assessed	6273	0.96, (0.90 to 1.01)	7536	0.95 (0.91 to 0.99)	8791	0.91 (0.85 to 0.97)
Stroke	1467	0.98 (0.88 to 1.09)	1713	1.03 (0.93 to 1.13)	2459	1.05 (0.98 to 1.14)	2850	1.02 (0.94, 1.12)
Arrhythmia	-	Not pooled	-	Not assessed	-	Not assessed	4586	0.99 (0.92 to 1.06)

CHD: coronary heart disease; **CI:** confidence interval; **CVD:** cardiovascular disease; **MACCE:** major adverse cerebrovascular or cardiovascular event; **RCT:** randomised controlled trial; **RR:** risk ratio

[a]Meta-analysis of effects of long-chain omega-3 in three recent systematic reviews, Balk 2016, Aung 2018 and Hu 2019, comparing their findings with our findings for our primary outcomes.

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APPENDICES

Appendix 1. Search strategy 2019

CENTRAL

#1 MeSH descriptor: [Fish Oils] explode all trees

#2 MeSH descriptor: [Linseed Oil] this term only

#3 MeSH descriptor: [Linolenic Acids] this term only

#4 MeSH descriptor: [Fatty Acids, Omega-3] explode all trees

#5 (fish near/3 oil*)

#6 (oil* near/3 (cod* or marin*))

#7 (omega-3 or omega3 or (omega* near/5 fat*))

#8 eicosapentaen*

#9 docosahexaen*

#10 (oil* near/3 (flax* or rapeseed* or canola*))

#11 (Linolen* or alpha-linolen* or alphalinolen*)

#12 (perilla* or linseed* or maxepa*)

#13 (oil* near/3 (rape or colza))

#14 (marin* near/3 lipid*)

#15 (naudicelle* or herring* or sild)

#16 (clupe* near/3 hareng*)

#17 (whitebait or sardine* or sardina* or pilchard* or sprat* or brisling*)

#18 (salmo* near/3 trut*)

#19 (trout or bloater or kipper* or salmon or mackerel* or scomb* or conger* or tuna or tunny or tunafish or tuna-fish)

#20 (thunnus* or swordfish* or xiphias* or dogfish or scyliorrhinus*)

#21 (crab or crabs or (cancer pagarus))

#22 (DHA or EPA)

#23 MeSH descriptor: [Salmoniformes] explode all trees

#24 MeSH descriptor: [Tuna] this term only

#25 MeSH descriptor: [alpha-Linolenic Acid] this term only

#26 MeSH descriptor: [Flax] this term only

#27 (fish near/3 (diet* or capsul* or nutrit* or supplement*))

#28 (icosapentaen* or docosapentaen*)

#29 (oil* near/3 (purslane or mustard* or candlenut* or stillingia or walnut*))

#30 (laks or lax)

#31 (ALA or DPA)

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#32 (algal near oil*)

#33 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 Publication Year from 2017 to 2019

MEDLINE Ovid

1. exp Fish Oils/

2. Linseed Oil/

3. linolenic acids/ or alpha-linolenic acid/

4. Flax/

5. exp Fatty Acids, Omega-3/

6. (fish adj3 (diet* or nutrit* or oil* or supplement*)).ti,ab.

7. (oil* adj3 (cod* or marin*)).ti,ab.

8. (omega-3 or omega3 or (omega* adj5 fat*)).ti,ab.

9. eicosapentaen*.ti,ab.

10. docosahexaen*.ti,ab.

11. (oil* adj3 (flax* or rapeseed* or canola*)).ti,ab.

12. (Linolen* or alpha-linolen* or alphalinolen*).ti,ab.

13. (perilla* or linseed* or maxepa*).ti,ab.

14. (oil* adj3 (rape or colza)).ti,ab.

15. (marin* adj3 lipid*).ti,ab.

16. (naudicelle* or herring* or sild).ti,ab.

17. (clupe* adj3 hareng*).ti,ab.

18. (whitebait or sardine* or sardina* or pilchard* or sprat* or brisling*).ti,ab.

19. (salmo* adj3 trut*).ti,ab.

20. (trout or bloater or kipper* or salmon or mackerel* or scomb* or conger* or tuna or tunny or tunafish or tuna-fish).ti,ab.

21. (thunnus* or swordfish* or xiphias* or dogfish or scyliorrhinus* or laks or lax).ti,ab.

22. (crab or crabs or cancer pagarus).ti,ab.

23. exp salmoniformes/ or tuna/

24. (fish adj3 capsul*).ti,ab.

25. icosapentaen*.ti,ab.

26. docosapentaen*.ti,ab.

27. (oil* adj3 (purslane or mustard* or candlenut* or stillingia or walnut*)).ti,ab.

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

29. randomized controlled trial.pt.

30. controlled clinical trial.pt.

31. randomized.ab.

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32. placebo.ab.

33. clinical trials as topic.sh.

34. randomly.ab.

35. trial.ti.

36. 29 or 30 or 31 or 32 or 33 or 34 or 35

37. exp animals/ not humans.sh.

38. 36 not 37

39. 28 and 38

40. limit 39 to ed=20170427-20190213

41. 39 not (1* or 2*).ed.

42. 40 or 41

Embase Ovid

1. exp salmoniformes/ or tuna/

2. fish oil/

3. linseed oil/

4. linolenic acid/

5. Flax/

6. omega 3 fatty acid/

7. (fish adj3 (diet* or nutrit* or oil* or supplement*)).ti,ab.

8. (oil* adj3 (cod* or marin*)).ti,ab.

9. (omega-3 or omega3 or (omega* adj5 fat*)).ti,ab.

10. (eicosapentaen* or icosapentaen*).ti,ab.

11. docosahexaen*.ti,ab.

12. (oil* adj3 (flax* or rapeseed* or canola*)).ti,ab.

13. (Linolen* or alpha-linolen* or alphalinolen*).ti,ab.

14. (perilla* or linseed* or maxepa*).ti,ab.

15. (marin* adj3 lipid*).ti,ab.

16. (naudicelle* or herring* or sild).ti,ab.

17. (clupe* adj3 hareng*).ti,ab.

18. (whitebait or sardine* or sardina* or pilchard* or sprat* or brisling*).ti,ab.

19. (salmo* adj3 trut*).ti,ab.

20. (trout or bloater or kipper* or salmon or mackerel* or scomb* or conger* or tuna or tunny or tunafish or tuna-fish).ti,ab.

21. (thunnus* or swordfish* or xiphias* or dogfish or scyliorrhinus* or laks or lax).ti,ab.

22. (crab or crabs or (cancer adj3 pagarus)).ti,ab.

23. exp salmonine/

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24. (fish adj3 capsul*).ti,ab.

25. docosapentaen*.ti,ab.

26. (ALA or DHA or DPA or EPA).ti,ab.

27. (algal adj oil*).ti,ab.

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

29. random$.tw.

30. factorial$.tw.

31. crossover$.tw.

32. cross over$.tw.

33. cross-over$.tw.

34. placebo$.tw.

35. (doubl$ adj blind$).tw.

36. (singl$ adj blind$).tw.

37. assign$.tw.

38. allocat$.tw.

39. volunteer$.tw.

40. crossover procedure/

41. double blind procedure/

42. randomized controlled trial/

43. single blind procedure/

44. 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43

45. (animal/ or nonhuman/) not human/

46. 44 not 45

47. 28 and 46

48. limit 47 to dd=20160721-20170427

ClinicalTrials.com

1. Recruiting, Not yet recruiting, Active, not recruiting, Completed, Enrolling by invitation, Suspended, Terminated, Withdrawn, Unknown status Studies | Interventional Studies | omega-3 or "omega 3" OR EPA OR DHA OR eicosapentaen* OR docosahexaen* OR docosapentaen* | Adult, Older Adult | Studies that accept healthy volunteers | Phase 1, 2, 3, 4 | First posted from 09/20/2016 to 08/01/2019.

2. This search was re-run using the term "eicosapentaenoic" in place of the omega-3 string.

3. This search was re-run using the term "fish oil*" in place of the omega-3 string.

ICTRP

(omega-3 or "omega 3" OR EPA OR DHA OR eicosapentaen* OR docosahexaen* OR docosapentaen* OR fish oil*) for intervention (title and condition not limited, including any recruitment status, all phases though run separately, limited to date of registration 20th Sept 2016 to 1st August 2019).

Appendix 2. Medline search strategy 2002 (for the previous version of this review)

1 exp Fish Oils/

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2 exp Linseed Oil/
3 linolenic acids/ or exp alpha-linolenic acid/
4 exp Fatty Acids, Omega-3/
5 (fish adj5 (diet$ or nutrit$ or oil$ or supplement$)).tw.
6 (oil$ adj3 (cod$ or marin$ or rapeseed$ or canola$)).tw.
7 (omega-3 or omega3).tw.
8 (eicosapentaen$ or icosapentaen$).tw.
9 docosahexaen$.tw.
10 (Linolen$ or alpha-linolen$ or alphalinolen$).tw.
11 (maxepa$ or omacor$).tw.
12 (trout or kipper$ or salmon or mackerel$ or tuna or tunafish or sardine$ or pilchard$ or herring$).tw.
13 flax$.tw.
14 rapeseed$.tw.
15 canola$.tw.
16 alphalinolen$.tw.
17 perilla$.tw.
18 linolen$.tw.
19 linseed$.tw.
20 maxepa$.tw.
21 (oil$ adj3 colza).tw.
22 (marin$ adj3 (lipid$ or oil$)).tw.
23 naudicelle$.tw.
24 sild.tw.
25 (clupe$ adj3 hareng$).tw.
26 whitebait$.tw.
27 sprat$.tw.
28 brisling$.tw.
29 (salmo adj3 trut$).tw.
30 bloater.tw.
31 scomb$.tw.
32 conger$.tw.
33 tunny.tw.
34 tuna-fish.tw.
35 thunnus$.tw.
36 swordfish$.tw.
37 xiphias$.tw.
38 dogfish.tw.
39 scyliorhinus$.tw.
40 (crab or crabs).tw.
41 (cancer adj3 pagurus).tw.
42 (laks or lax).tw.
43 exp Flax/
44 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
45 randomized controlled trial.pt.
46 controlled clinical trial.pt.
47 randomized.ab.
48 placebo.ab.
49 clinical trials as topic.sh.
50 randomly.ab.
51 trial.ti.
52 50 or 47 or 51 or 46 or 45 or 48 or 49
53 (animals not (human and animals)).sh.
54 52 not 53
55 44 and 54
56 (20$ not (2000$ or 2001$)).ed.
57 55 and 56

Appendix 3. Search strategy 2016 (to update the omega-3 review)

CENTRAL

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#1 MeSH descriptor: [Fish Oils] explode all trees

#2 MeSH descriptor: [Linseed Oil] this term only

#3 MeSH descriptor: [Linolenic Acids] this term only

#4 MeSH descriptor: [Fatty Acids, Omega-3] explode all trees

#5 (fish near/3 oil*)

#6 (oil* near/3 (cod* or marin*))

#7 (omega-3 or omega3 or (omega* near/5 fat*))

#8 eicosapentaen*

#9 docosahexaen*

#10 (oil* near/3 (flax* or rapeseed* or canola*))

#11 (Linolen* or alpha-linolen* or alphalinolen*)

#12 (perilla* or linseed* or maxepa*)

#13 (oil* near/3 (rape or colza))

#14 (marin* near/3 lipid*)

#15 (naudicelle* or herring* or sild)

#16 (clupe* near/3 hareng*)

#17 (whitebait or sardine* or sardina* or pilchard* or sprat* or brisling*)

#18 (salmo* near/3 trut*)

#19 (trout or bloater or kipper* or salmon or mackerel* or scomb* or conger* or tuna or tunny or tunafish or tuna-fish)

#20 (thunnus* or swordfish* or xiphias* or dogfish or scyliorrhinus*)

#21 (crab or crabs or (cancer pagarus))

#22 (DHA or EPA)

#23 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 Publication Year from 2002 to 2016

#24 MeSH descriptor: [Salmoniformes] explode all trees

#25 MeSH descriptor: [Tuna] this term only

#26 MeSH descriptor: [alpha-Linolenic Acid] this term only

#27 MeSH descriptor: [Flax] this term only

#28 (fish near/3 (diet* or capsul* or nutrit* or supplement*))

#29 (icosapentaen* or docosapentaen*)

#30 (oil* near/3 (purslane or mustard* or candlenut* or stillingia or walnut*))

#31 (laks or lax)

#32 (ALA or DPA)

#33 (algal near oil*)

#34 #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33

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#35 #23 or #34

MEDLINE Ovid

1. exp Fish Oils/

2. Linseed Oil/

3. linolenic acids/ or alpha-linolenic acid/

4. Flax/

5. exp Fatty Acids, Omega-3/

6. (fish adj3 (diet* or nutrit* or oil* or supplement*)).ti,ab.

7. (oil* adj3 (cod* or marin*)).ti,ab.

8. (omega-3 or omega3 or (omega* adj5 fat*)).ti,ab.

9. eicosapentaen*.ti,ab.

10. docosahexaen*.ti,ab.

11. (oil* adj3 (flax* or rapeseed* or canola*)).ti,ab.

12. (Linolen* or alpha-linolen* or alphalinolen*).ti,ab.

13. (perilla* or linseed* or maxepa*).ti,ab.

14. (oil* adj3 (rape or colza)).ti,ab.

15. (marin* adj3 lipid*).ti,ab.

16. (naudicelle* or herring* or sild).ti,ab.

17. (clupe* adj3 hareng*).ti,ab.

18. (whitebait or sardine* or sardina* or pilchard* or sprat* or brisling*).ti,ab.

19. (salmo* adj3 trut*).ti,ab.

20. (trout or bloater or kipper* or salmon or mackerel* or scomb* or conger* or tuna or tunny or tunafish or tuna-fish).ti,ab.

21. (thunnus* or swordfish* or xiphias* or dogfish or scyliorrhinus* or laks or lax).ti,ab.

22. (crab or crabs or cancer pagarus).ti,ab.

23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22

24. randomized controlled trial.pt.

25. controlled clinical trial.pt.

26. randomized.ab.

27. placebo.ab.

28. clinical trials as topic.sh.

29. randomly.ab.

30. trial.ti.

31. 24 or 25 or 26 or 27 or 28 or 29 or 30

32. exp animals/ not humans.sh.

33. 31 not 32

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34. 23 and 33

35. limit 34 to ed=20020201-20160721

36. exp salmoniformes/ or tuna/

37. (fish adj3 capsul*).ti,ab.

38. icosapentaen*.ti,ab.

39. docosapentaen*.ti,ab.

40. (oil* adj3 (purslane or mustard* or candlenut* or stillingia or walnut*)).ti,ab.

41. 36 or 37 or 38 or 39 or 40

42. 33 and 41

43. 35 or 42

Embase Ovid

1. exp salmoniformes/ or tuna/

2. fish oil/

3. linseed oil/

4. linolenic acid/

5. Flax/

6. omega 3 fatty acid/

7. (fish adj3 (diet* or nutrit* or oil* or supplement*)).ti,ab.

8. (oil* adj3 (cod* or marin*)).ti,ab.

9. (omega-3 or omega3 or (omega* adj5 fat*)).ti,ab.

10. (eicosapentaen* or icosapentaen*).ti,ab.

11. docosahexaen*.ti,ab.

12. (oil* adj3 (flax* or rapeseed* or canola*)).ti,ab.

13. (Linolen* or alpha-linolen* or alphalinolen*).ti,ab.

14. (perilla* or linseed* or maxepa*).ti,ab.

15. (marin* adj3 lipid*).ti,ab.

16. (naudicelle* or herring* or sild).ti,ab.

17. (clupe* adj3 hareng*).ti,ab.

18. (whitebait or sardine* or sardina* or pilchard* or sprat* or brisling*).ti,ab.

19. (salmo* adj3 trut*).ti,ab.

20. (trout or bloater or kipper* or salmon or mackerel* or scomb* or conger* or tuna or tunny or tunafish or tuna-fish).ti,ab.

21. (thunnus* or swordfish* or xiphias* or dogfish or scyliorrhinus* or laks or lax).ti,ab.

22. (crab or crabs or (cancer adj3 pagarus)).ti,ab.

23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22

24. random$.tw.

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25. placebo$.tw.

26. (doubl$ adj blind$).tw.

27. (singl$ adj blind$).tw.

28. double blind procedure/

29. randomized controlled trial/

30. single blind procedure/

31. 24 or 25 or 26 or 27 or 28 or 29 or 30

32. (animal/ or nonhuman/) not human/

33. 31 not 32

34. 23 and 33

35. (2002* or 2003* or 2004* or 2005* or 2006* or 2007* or 2008* or 2009* or 2010* or 2011* or 2012* or 2013* or 2014* or 2015* or 2016*).dd,em.

36. 34 and 35

37. exp salmonine/

38. (fish adj3 capsul*).ti,ab.

39. docosapentaen*.ti,ab.

40. (ALA or DHA or DPA or EPA).ti,ab.

41. (algal adj oil*).ti,ab.

42. 37 or 38 or 39 or 40 or 41

43. 33 and 42

44. 36 or 43

Appendix 4. Search strategy 2017 (for allied reviews)

These searches were developed and run to collect relevant trials for the systematic reviews on omega-6 fats (the update of Hooper 2018) and on total polyunsaturated fatty acid (PUFA) fats (Abdelhamid 2018b) on health. They are shown here as these searches were run with the searches for this review, the identified titles and abstracts de-duplicated and combined, so that we assessed titles and abstracts for all three reviews together. These searches were each run from database inception, due to the widening of the inclusion criteria, then de-duplicated with each other. The RCT filter for MEDLINE is the Cochrane sensitivity and precision-maximising RCT filter, and for Embase, we applied terms as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011).

CENTRAL

#1 MeSH descriptor: [Fatty Acids, Essential] explode all trees

#2 MeSH descriptor: [Fatty Acids, Unsaturated] this term only

#3 ((polyunsaturat* or poly-unsaturat*) near/3 fat*)

#4 (poly* adj4 unsat* near/4 fatty acid*)

#5 PUFA

#6 MeSH descriptor: [Fatty Acids, Omega-6] explode all trees

#7 omega-6

#8 (n-6 near/4 acid*) or ("n 6" near/4 acid*)

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#9 linoleic acid*

#10 MeSH descriptor: [Corn Oil] this term only

#11 MeSH descriptor: [Cottonseed Oil] this term only

#12 MeSH descriptor: [Olive Oil] this term only

#13 MeSH descriptor: [Safflower Oil] this term only

#14 MeSH descriptor: [Sesame Oil] this term only

#15 MeSH descriptor: [Soybean Oil] this term only

#16 ((corn or maize or mazola) near/4 oil*)

#17 (cottonseed* or (cotton next seed*))

#18 (olive near/4 oil*)

#19 (safflower near/4 oil*)

#20 (sesame near/4 oil*)

#21 ((soy bean or soybean) near/4 (oil* or fat*))

#22 (so?a near/4 oil*)

#23 so?aoil*

#24 (soy near/4 oil*)

#25 (sunflower near/4 oil*)

#26 helianth*

#27 (grapeseed near/4 oil*)

#28 (canola near/4 oil*)

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

MEDLINE Ovid

1. exp fatty acids, essential/

2. fatty acids, unsaturated/

3. ((polyunsaturat* or poly-unsaturat*) adj3 fat*).ti,ab.

4. (poly* adj4 unsat* adj4 fatty acid*).ti,ab.

5. PUFA.ti,ab.

6. exp fatty acids, omega-6/

7. omega-6.ti,ab.

8. (n-6 adj4 acid*).ti,ab.

9. linoleic acid*.ti,ab.

10. corn oil/ or cottonseed oil/ or olive oil/ or safflower oil/ or sesame oil/ or soybean oil/

11. ((corn or maize or mazola) adj4 oil*).ti,ab.

12. (cottonseed* or (cotton adj seed*)).ti,ab.

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13. (olive adj4 oil*).ti,ab.

14. (safflower adj4 oil*).ti,ab.

15. (sesame adj4 oil*).ti,ab.

16. ((soy bean or soybean) adj4 (oil* or fat*)).ti,ab.

17. (so?a adj4 oil*).ti,ab.

18. so?aoil*.ti,ab.

19. (soy adj4 oil*).ti,ab.

20. (sunflower adj4 oil*).ti,ab.

21. helianth*.ti,ab.

22. (grapeseed adj4 oil*).ti,ab.

23. (canola adj4 oil*).ti,ab.

24. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23

25. randomized controlled trial.pt.

26. controlled clinical trial.pt.

27. randomized.ab.

28. placebo.ab.

29. clinical trials as topic.sh.

30. randomly.ab.

31. trial.ti.

32. 25 or 26 or 27 or 28 or 29 or 30 or 31

33. exp animals/ not humans.sh.

34. 32 not 33

35. 24 and 34

Embase Ovid

1. exp essential fatty acid/

2. unsaturated fatty acid/ or docosapentaenoic acid/ or omega 6 fatty acid/ or polyunsaturated fatty acid/

3. ((polyunsaturat* or poly-unsaturat*) adj3 fat*).ti,ab.

4. (poly* adj4 unsat* adj4 fatty acid*).ti,ab.

5. PUFA.ti,ab.

6. omega-6.ti,ab.

7. (n-6 adj4 acid*).ti,ab.

8. linoleic acid*.ti,ab.

9. edible oil/ or canola oil/ or corn oil/ or cotton seed oil/ or olive oil/ or safflower oil/ or safflower oil plus soybean oil/ or sesame seed oil/ or soybean oil/ or sunflower oil/

10. ((corn or maize or mazola) adj4 oil*).ti,ab.

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11. (cottonseed* or (cotton adj seed*)).ti,ab.

12. (olive adj4 oil*).ti,ab.

13. (safflower adj4 oil*).ti,ab.

14. (sesame adj4 oil*).ti,ab.

15. ((soy bean or soybean) adj4 (oil* or fat*)).ti,ab.

16. (so?a adj4 oil*).ti,ab.

17. so?aoil*.ti,ab.

18. (soy adj4 oil*).ti,ab.

19. (sunflower adj4 oil*).ti,ab.

20. helianth*.ti,ab.

21. (grapeseed adj4 oil*).ti,ab.

22. (canola adj4 oil*).ti,ab.

23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22

24. double blind procedure/

25. single blind procedure/

26. randomized controlled trial/

27. ((double* or single*) adj blind*).ti,ab.

28. (random* or placebo*).ti,ab.

29. 24 or 25 or 26 or 27 or 28

30. (animal/ or nonhuman/) not human/

31. 29 not 30

32. 23 and 31

F E E D B A C K

Interpretation of effect estimates, 18 July 2018

Summary

I am not clear how the quoted RRs and CIs in the abstract support statements of no effect in one part but statements of effect in another part. It seems that throughout the CIs comprehensively span unity. For example, how is a statement of 'probably reduces risk of CHD mortality' supported by the metrics '(1.1% to 1.0%, RR 0.95, 95% CI 0.72 to 1.26, 18,353 participants; 193 CHD deaths, 3 RCTs'? That seems like an entirely null result.

Reply

Thank you for your query.

We described the process of deciding whether there was “little or no effect”, or a positive or negative effect, in the methods section of the review (under “Summary of findings table”).

It was agreed with the World Health Organization (WHO) Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health, who commissioned this review as part of a wider set that an effect size of 8% (either way, so RR > 1.08 or < 0.92) in the point estimate of the risk ratio would suggest benefit or harm. Presence or absence of effect is decided on the basis of the pre-stated outcome measure, here RR. This certainty of this finding was assessed through the GRADE process (which is represented in the Summary of Findings tables).

- Wide confidence intervals lead to downgrading for imprecision,

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- changes in results in sensitivity analyses lead to downgrading for risk of bias,
- skewed funnel plots or knowledge of quantities of missing data lead to downgrading for publication bias,
- heterogeneity of results (high I^2) lead to downgrading for inconsistency, and
- limited representativeness of included populations lead to downgrading for indirectness.

We used absolute risk or NNTB to describe the scale of effect where an effect was suggested – this could be large or small (all in this review were very small).

You are absolutely correct in pointing out that this means that ALA intake probably makes little or no difference to CHD mortality. We apologise for this confusion, which resulted from us using an earlier cut-off of 7% to consider effectiveness. The effect for CV events is still "ALA intake may reduce the risk of cardiovascular events but by a very small amount (from 4.8 to 4.7%)" even though the effect is RR 0.95 (95% CI 0.83 to 1.07) as the sensitivity analysis limiting to studies at low summary risk of bias suggested a 9% reduction in risk (RR 0.91, 95% CI 0.79 to 1.04, I^2 = 0%). Effects of ALA on arrhythmia are clearer (main analysis suggests RR 0.79, 95% CI 0.57 to 1.10, moderate-certainty evidence).

This finding has now been corrected in the review.

Thank you for your keen eye! We hope this clarifies how decisions were made and effects expressed within the review (and the review series).

Contributors

Feedback submitted by: Bruce Neal

Response by Lee Hooper, contact author of review, and Bill Cayley, feedback editor of Cochrane Heart

Dosing and conclusions, 19 July 2018

Summary

Most of the CVD OR ranges listed for lcN3 data showed zones of significant OR benefit. No dosing information was included. I question the study's "conclusions", and believe that a more sensitive analysis of the data could easily show benefit in terms of CVD risk reduction.

Reply

Thank you for your comments, and your attention to the question of dosing. While with any intervention it certainly might seem plausible that a higher dose would be more likely to show benefit than a lower dose, this was not borne out in the studies that met inclusion criteria for this Review. As outlined in the Summary of Findings Tables, and summarized in the Abstract, the authors "found no evidence of dose-response or duration effects for any primary outcome, but there was a suggestion of greater protection in participants with lower baseline omega-6 intake across outcomes."

Contributors

Feedback submitted by: TR Morris

Response by Lee Hooper, contact author of review, and Bill Cayley, feedback editor of Cochrane Heart

Effect of study duration, 26 November 2019

Summary

I think it's incorrect to determine mortality as the percentage of patients who died during the considered studies (e.g., 9% for patients taking long chain omega 3, according to the article). Since those studies have different lengths (from 12 to 72 months), patients from long studies are expected to die with much higher rate, than patients from short studies. Long studies will contribute toward increasing the mortality metric, while short studies will decrease it. Instead, I suggest normalizing mortality by study duration. For example, let's take 1 month as a unit of duration. Then, if a study lasted 24 months and had mortality rate 3%, that is living rate of 97%, or 0.97, you calculate average living rate per month as 0.97^(1/24) ≈ 0.99875 = 99.875%, and you use 100% - 99.875% = 0.125% as average mortality rate per month in this study.

Reply

Thank you for your comments on the duration of our included trials. Outcome risk does differ between included trials and depends on baseline risk as well as trial duration, but this is not necessarily true of relative risk, our outcome measure. To assess duration effects, as well as effects of dose, baseline risk, intervention type, replacement, statin use, baseline triglyceride levels or diabetic status, we carried out extensive sub-grouping and meta-regression. We found no suggestion of consistent duration effects in either sub-grouping or meta-regression for either LCn3 or ALA except for effects of LCn3 on stroke, where longer trials suggested a smaller effect size in meta-regression (this was not clear in sub-grouping), and longer trials showed increased risk of arrhythmia with increased LCn3 in sub-grouping and meta-

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regression. These sub-grouping and meta-regression results are all discussed in the results section of the review. We believe that this accounts appropriately and fully for duration effects within the systematic review.

Contributors

Feedback submitted by: Philip Blagoveschensky, Data Science Masters student, Skoltech

Response by Lee Hooper, contact author of review, and Bill Cayley, feedback editor of Cochrane Heart

WHAT'S NEW

Date	Event	Description
11 October 2019	New citation required and conclusions have changed	Seven new trials (six of LCn3, one of ALA) added to included trials (of which six were moved from ongoing trials), and seven new ongoing trials added. Addition of these included trials boosts numbers of included participants by over 30%. The 86 included RCTs randomised 162,796 participants to trials of at least 12 months' duration. The updated evidence suggests that increasing LCn3 slightly reduces CHD mortality and CHD events (previously the evidence suggested little or no effect). Our understanding of effects of LCn3 on other outcomes, and of ALA on all outcomes, has not altered.
21 September 2019	New search has been performed	Electronic searches updated to February 2019, trials registry searches to July 2019.

HISTORY

Protocol first published: Issue 2, 1999
Review first published: Issue 4, 2004

Date	Event	Description
28 November 2018	New citation required but conclusions have not changed	The amendments did not change our conclusions.
28 November 2018	Feedback has been incorporated	We have responded to feedback by two parties.
28 November 2018	Amended	Effects of alpha-linolenic acid on coronary heart disease mortality now correctly interpreted as "little or no effect" as effect size was < 8%. Effects of long-chain omega-3 and alpha-linolenic acid on serum high-density lipoprotein reinterpreted as "little or no effect" as changes were < 5% of baseline. Study flow corrected.
13 March 2018	New citation required and conclusions have changed	This update now reports arrhythmia (atrial fibrillation) and cardiovascular mortality data. Data now included from 79 RCTs (112,059 participants) lasting at least one year, of which 25 were at low summary risk of bias. We added the following outcomes to the list of primary outcomes upon the request of World Health Organization (WHO) Nu-

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Date	Event	Description
		trition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health. 1. Cardiovascular mortality. 2. Arrhyhtmia (new and recurrent). We altered inclusion criteria to include only RCTs of at least 12 months' duration (rather than 6 months as previously), and we excluded cohort studies. We are assessing effects of long-chain omega-3 fats separately from effects of alpha-linolenic acid (as planned in the previously published version).
27 April 2017	New search has been performed	Electronic searches updated to 27 April 2017
14 March 2012	Amended	Additional tables re-numbered
16 October 2011	New search has been performed	Searches updated to July 2011. Cohort studies not included in this update, and previously included cohort studies and related text have been removed. Previously included trials where we know that no deaths or primary or secondary health events occurred were removed. New secondary outcomes added (fatal and non-fatal arrhythmias, and diabetes) Cardiovascular mortality added as a primary outcome.
9 September 2008	Amended	Converted to new review format.
1 August 2004	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

LH and CDS conceived and led the original version of this review; LH, CDS, HM and HVW were authors of the original version of this review. LH designed the searches, and CB developed, refined, ran and de-duplicated them. ASA, TJB, JSB, PB, GCT, KHOD, HVW, FS and LH screened titles and abstracts; ASA, JSB, PB, GCT and LH assessed full-text papers for inclusion; LH, PB and JSB searched trials registers and assessed entries for inclusion; LH and ASA located full texts, managed assessment and collection of titles, abstracts and full texts, data extraction and 'Risk of bias' assessment. All authors carried out data extraction and assessed risk of bias. LH, KHOD and JSB designed 'Risk of bias' assessment; JSB, KHOD, TJB, ASA and LH wrote to trial authors; LH, KHOD, JSB, TJB and ASA carried out data checks; JSB, TJB, LH and ASA tabulated intake and status data. FS, KHOD, JSB, HVW, CDS and LH provided methodological support. ASA, FKA and LH entered data into Review Manager 5 and ran meta-analyses, ASA and LH carried out sensitivity and subgroup analyses, and LH the meta-regression. ASA wrote the first draft of the review and LH the WHO NUGAG Subgroup on Diet and Health report; both carried out GRADE assessment and interpretation. All authors critically read and commented on the final draft and agreed on it for submission.

DECLARATIONS OF INTEREST

ASA: none known
TJB: none known
JSB: none known
PB: none known
GCT: none known
HJM: none known
KHOD: none known
FKA: none known

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CDS: none known
HVW: none known
FS: none known
LH: none known

SOURCES OF SUPPORT

Internal sources

- University of East Anglia, UK.

External sources

- World Health Organization Nutrition Guidance Expert Advisory Group (NUGAG), Other.

  WHO NUGAG Subgroup on Diet and Health requested and funded the update and extension of this review.
- This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to Cochrane Heart. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health and Social Care, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The differences between the protocol and this update were detailed in the previous update (Abdelhamid 2018a).

We have also added two sets of post-hoc subgroups recently requested by the World Health Organization (WHO), assessing whether baseline triglyceride or baseline diabetes status affect the primary outcomes. This is in response to a current debate (following publication of REDUCE-IT 2019) on whether beneficial effects are specifically seen in participants with raised triglycerides. We carried out these new subgroups for effects of long-chain omega-3 on primary outcomes, and we would have carried them out for effects of alpha-linolenic acid on primary outcomes, except that no included trials of alpha-linolenic acid were of people with raised triglycerides or with diabetes or risk factors.

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; *Primary Prevention; *Secondary Prevention; Adiposity; Arrhythmias, Cardiac [epidemiology]; Cardiovascular Diseases [diet therapy] [mortality] [*prevention & control]; Cause of Death; Coronary Disease [mortality]; Docosahexaenoic Acids [therapeutic use]; Eicosapentaenoic Acid [therapeutic use]; Fatty Acids, Omega-3 [adverse effects] [*therapeutic use]; Hemorrhage [epidemiology]; Pulmonary Embolism [epidemiology]; Randomized Controlled Trials as Topic; Regression Analysis; Stroke [epidemiology]; Treatment Outcome; alpha-Linolenic Acid [therapeutic use]

MeSH check words

Adult; Humans

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