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

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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

Researchers have suggested that 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)) benefit cardiovascular health. Guidelines recommend increasing omega-3-rich foods, and sometimes supplementation, but recent trials have not confirmed this.

Objectives

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

Search methods

We searched CENTRAL, MEDLINE and Embase to April 2017, plus ClinicalTrials.gov and World Health Organization International Clinical Trials Registry to September 2016, with no language restrictions. We handsearched systematic review references and bibliographies and contacted authors.

Selection criteria

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

Data collection and analysis

Two review authors independently assessed studies 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 79 RCTs (112,059 participants) in this review update and found that 25 were at low summary risk of bias. Trials were of 12 to 72 months' duration and included adults at varying cardiovascular risk, mainly in high-income countries. Most studies assessed LCn3

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 0.5g/d LCn3 to > 5 g/d (16 RCTs gave at least 3g/d LCn3).

Meta-analysis and sensitivity analyses suggested **little or no effect of increasing LCn3** on **all-cause mortality** (RR 0.98, 95% CI 0.90 to 1.03, 92,653 participants; 8189 deaths in 39 trials, high-quality evidence), **cardiovascular mortality** (RR 0.95, 95% CI 0.87 to 1.03, 67,772 participants; 4544 CVD deaths in 25 RCTs), **cardiovascular events** (RR 0.99, 95% CI 0.94 to 1.04, 90,378 participants; 14,737 people experienced events in 38 trials, high-quality evidence), **coronary heart disease (CHD) mortality** (RR 0.93, 95% CI 0.79 to 1.09, 73,491 participants; 1596 CHD deaths in 21 RCTs), **stroke** (RR 1.06, 95% CI 0.96 to 1.16, 89,358 participants; 1822 strokes in 28 trials) or **arrhythmia** (RR 0.97, 95% CI 0.90 to 1.05, 53,796 participants; 3788 people experienced arrhythmia in 28 RCTs). There was a suggestion that LCn3 reduced **CHD events** (RR 0.93, 95% CI 0.88 to 0.97, 84,301 participants; 5469 people experienced CHD events in 28 RCTs); however, this was not maintained in sensitivity analyses – LCn3 probably makes little or no difference to CHD event risk. All evidence was of moderate GRADE quality, except as noted.

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, 5 RCTs),**cardiovascular mortality** (RR 0.96, 95% CI 0.74 to 1.25, 18,619 participants; 219 cardiovascular deaths, 4 RCTs), and **CHD mortality** (1.1% to 1.0%, RR 0.95, 95% CI 0.72 to 1.26, 18,353 participants; 193 CHD deaths, 3 RCTs) and ALA may make **little or no difference to CHD events** (RR 1.00, 95% CI 0.80 to 1.22, 19,061 participants, 397 CHD events, 4 RCTs, low-quality evidence). However, increased ALA may slightly **reduce risk of cardiovascular events** (from 4.8% to 4.7%, RR 0.95, 95% CI 0.83 to 1.07, 19,327 participants; 884 CVD events, 5 RCTs, low-quality evidence with greater effects in trials at low summary risk of bias), and probably reduces risk of **arrhythmia** (3.3% to 2.6%, RR 0.79, 95% CI 0.57 to 1.10, 4,837 participants; 141 events, 1 RCT). Effects on **stroke are unclear**.

Sensitivity analysis retaining only trials at low summary risk of bias moved effect sizes towards the null (RR 1.0) for all LCn3 primary outcomes except arrhythmias, but for most ALA outcomes, effect sizes moved to suggest protection. LCn3 funnel plots suggested that adding in missing studies/results would move effect sizes towards null for most primary outcomes. There were no dose or duration effects in subgrouping or meta-regression.

There was no evidence that increasing LCn3 or ALA altered serious adverse events, adiposity or lipids, except LCn3 reduced triglycerides by ˜15% in a dose-dependant way (high-quality evidence).

Authors' conclusions

This is the most extensive systematic assessment of effects of omega-3 fats on cardiovascular health to date. Moderate- and high-quality evidence suggests that increasing EPA and DHA has little or no effect on mortality or cardiovascular health (evidence mainly from supplement trials). Previous suggestions of benefits from EPA and DHA supplements appear to spring from trials with higher risk of bias. Low-quality evidence suggests ALA may slightly reduce CVD event and arrhythmia risk.

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, CVD, 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

Omega-3 fats are essential – to stay healthy we must obtain some from food. The main types of omega-3 fats are alpha-linolenic acid (ALA), a fat found in plant foods, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), both found in fish. There is a common belief that eating more fish or taking omega-3 supplements reduces our risk of heart disease, stroke and death.

Study characteristics

The evidence is current to April 2017. The review included 79 trials involving over 112,000 people. These studies assessed effects of greater omega-3 intake versus lower or no omega-3 intake for heart and circulatory disease. Twenty-five studies 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. Participants increased omega-3 fats, or maintained their usual fats for at least a year. Most EPA and DHA trials provided capsules, few gave oily fish.

Key results

Increasing EPA and DHA has little or no effect on all-cause deaths and cardiovascular events (high-quality evidence) and probably makes little or no difference to cardiovascular death, coronary deaths or events, stroke, or heart irregularities (moderate-quality evidence,

coronary events are illnesses of the arteries which supply the heart). EPA and DHA slightly reduce serum triglycerides and raise HDL (high-quality evidence).

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/low-quality evidence). Effects of ALA on stroke are unclear as the evidence was of very low quality.

There is evidence that taking omega-3 capsules does not reduce heart disease, stroke or death. There is little evidence of effects of eating fish. Although EPA and DHA reduce triglycerides, supplementary omega-3 fats are probably not useful for preventing or treating heart and circulatory diseases. However, increasing plant-based ALA may be slightly protective for some heart and circulatory diseases.

Summary of findings for the main comparison. High versus low LCn3 for preventing cardiovascular disease and mortality (primary outcomes)

High versus low LCn3 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 studies were carried out in high-income economies (World Bank 2018), but four trials were carried out in upper-middle income countries (Argentina, Iran, Turkey and China). No studies took place in low- or low-middle income countries.
Intervention: higher intake of long-chain omega-3 fats
Comparison: lower intake of long-chain omega-3 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 (studies)	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 to 72 months	90 per 1,000	88 per 1,000 (83 to 92)	RR 0.98 (0.93 to 1.03)	92,653 (39 RCTs)	⊕⊕⊕⊕ High[a]	Meta-analysis and indications of bias suggest risk reduction of less than 2%. Long-chain omega-3 fat intake makes little or no difference to all-cause mortality.
Cardiovascular mortality – cardiovascular deaths Assessed with: deaths from any cardiovascular cause. Where this was not available, cardiac death was used instead where known.	69 per 1,000	66 per 1,000 (60 to 71)	RR 0.95 (0.87 to 1.03)	67,772 (25 RCTs)	⊕⊕⊕⊖ Moderate[b]	Meta-analysis and indications of bias suggest risk reduction of less than 5%. Long-chain omega-3 fat intake probably makes little or no difference to cardiovascular deaths.

Duration: range 12 to 72 months						
Cardiovascular events – cardiovascular events Assessed with: number of participants experiencing any cardiovascular event Duration: range 12 to 72 months	165 per 1,000	164 per 1,000 (155 to 172)	RR 0.99 (0.94 to 1.04)	90,378 (38 RCTs)	⊕⊕⊕⊕ High[c]	Meta-analysis and indications of bias suggest risk reduction of less than 1%. Long-chain omega-3 fat intake makes little or no difference to risk of cardiovascular events.
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 to 72 months	22 per 1,000	21 per 1,000 (18 to 24)	RR 0.93 (0.79 to 1.09)	73,491 (21 RCTs)	⊕⊕⊕⊖ Moderate[d]	Meta-analysis and indications of bias suggest risk reduction of less than 7%. Long-chain omega-3 fat intake probably makes little or no difference to coronary heart mortality.
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 to 72 months	68 per 1,000	63 per 1,000 (59 to 65)	RR 0.93 (0.88 to 0.97)	84,301 (28 RCTs)	⊕⊕⊕⊖ Moderate[e]	Meta-analysis and indications of bias suggest risk reduction of less than 7%. Long-chain omega-3 fat intake probably makes little or no difference to risk of coronary heart events.

Stroke Assessed with: number of participants experiencing at least one fatal or non-fatal, ischaemic or haemorrhagic stroke Duration: range 12 to 72 months	20 per 1,000	21 per 1,000 (19 to 23)	RR 1.06 (0.96 to 1.16)	89,358 (28 RCTs)	⊕⊕⊕⊖ Moderate[f]	Meta-analysis and indications of bias suggest increased risk of less than 6%. Long-chain omega-3 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 to 72 months	68 per 1,000	66 per 1,000 (62 to 72)	RR 0.97 (0.90 to 1.05)	53,796 (28 RCTs)	⊕⊕⊕⊖ Moderate[g]	Meta-analysis and indications of bias suggest risk reduction of less than 3%. Long-chain omega-3 fat intake probably makes little or no difference to risk of arrhythmia.
Harms: bleeding Assessed with: number of participants experiencing bleeding events. Duration: range 12 to 72 months	8 per 1,000	**8 per** 1,000 (5 to 11)	**RR 1.06** (0.73 to 1.52)	45,562 (8 RCTs)	⊕⊖⊖⊖ Very low[h]	The effect of long-chain omega-3 fat intake on bleeding is unclear as the evidence is of very low quality.
Harms: pulmonary embolus or DVT Assessed with: number of participants experiencing pulmonary embolus or deep vein thrombosis	5 per 1,000	**6 per** 1,000 (2 to 18)	**RR 1.25** (0.41 to 3.78)	3,011 (4 RCTs)	⊕⊖⊖⊖ Very low[i]	The effect of long-chain omega-3 fat intake on pulmonary embolus or DVT is unclear as the evidence is of very low quality.

Duration: range 18 to 36 months				

*__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; **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, LCn3**

- **Risk of bias**: effect size moved closer to no effect (RR 1.0) when analysis was limited to studies 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 studies. 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 was < 60% and I^2 reduced when analysis was limited to studies 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**: tight confidence intervals, very large numbers of participants have taken part in RCTs in long-term studies 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 studies with higher numbers of events in the intervention group might be missing. If such missing studies 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 studies 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 studies. 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 was < 60% and I^2 reduced when analysis was limited to studies 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 studies were conducted in high-income countries. Not downgraded.
- **Imprecision**: Although very large numbers of participants have taken part in RCTs in long-term studies, with consistent results, the 95% CI includes the null. 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 benefits or harms. Downgraded once.
- **Publication bias**: the funnel plot suggested that some small studies with higher numbers of events in the intervention group might be missing. If such missing studies were added back in, the RR would rise. This adds weight to the suggestion of little or no effect. Not downgraded.

[c]**Cardiovascular events, LCn3**

- **Risk of bias**: effect size moved closer to no effect (RR 1.0) when analysis was limited to studies 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 studies. 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 was < 60% and I^2 reduced when analysis was limited to studies 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 have taken part in RCTs in long-term studies 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. However, as 95% confidence intervals do not exclude important benefits or harms, we downgraded once.
- **Publication bias**: the funnel plot suggested that some small studies with higher numbers of events in the intervention group might be missing. If such missing studies 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 moved closer to no effect (RR 1.0) when analysis was limited to studies 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 studies. 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 was < 60% and I^2 reduced when analysis was limited to studies 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 studies were conducted in high-income countries. Not downgraded.
- **Imprecision**: very large numbers of participants have taken part in RCTs in long-term studies 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 benefits or harms we downgraded once.
- **Publication bias**: the funnel plot suggested that some small studies with higher numbers of events in the intervention group might be missing. If such missing studies were added back in the RR would rise. This adds weight to the suggestion of little or no effect. Not downgraded.

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

- **Risk of bias**: effect size moved closer to no effect (RR 1.0) when was analysis limited to studies at low summary risk of bias. This adds weight to the suggestion of little or no effect. However, effect size did not alter with fixed-effect meta-analysis or limiting to studies at low risk of compliance bias or larger trials. It was further noted by the WHO NUGAG Subgroup on Diet and Health that there was a significant effect observed in main analysis but the effect moved closer to a non-significant, null effect when analysis was limited to studies at low summary risk of bias. Downgraded once.
- **Inconsistency**: I^2 was < 60% and I^2 reduced when analysis was limited to studies 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**: 95% CI did not include the null. Not downgraded.
- **Publication bias**: the funnel plot suggested that some small studies with higher numbers of events in the intervention group might be missing. If such missing studies were added back in, the RR would rise. This adds weight to the suggestion of little or no effect. Not downgraded.

[f] **Stroke, LCn3**

- **Risk of bias**: effect size moved closer to no effect (RR 1.0) when analysis limited to studies 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 limiting to larger studies. Limiting to studies at low risk of compliance problems resulted in the suggestion of greater harm. 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 was < 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 have taken part in RCTs in long-term studies 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 benefits or harms, we downgraded once.
- **Publication bias**: the funnel plot did not suggest any small study bias. Not downgraded.

g **Arrhythmias, LCn3**
- **Risk of bias**: effect size remained similar in most sensitivity analyses, but moved closer to no effect (RR 1.01) when analysis used fixed-effect meta-analysis (adding weight to the suggestion of little or no effect) and suggested harm when limited to studies at low summary risk of bias. Not downgraded.
- **Inconsistency**: I^2 was < 60% and I^2 reduced when analysis was limited to studies 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**: As 95% confidence intervals do not exclude important benefits we downgraded once.
- **Publication bias**: funnel plot not interpretable as studies 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 studies at low summary risk of bias. Downgraded once.
- **Inconsistency**: I^2 was < 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 studies for funnel plot. Not downgraded.

i **Pulmonary embolus or DVD, LCn3**
- **Risk of bias**: effect size suggested greater harm when analysis limited to studies at low summary risk of bias. Downgraded once.
- **Inconsistency**: I^2 was < 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 studies for funnel plot. Not downgraded.

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

High versus low ALA 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 studies were carried out in high-income economies (World Bank 2018), but four trials were carried out in upper-middle income countries (Argentina, Iran, Turkey and China). No studies took place in low- or low-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 (studies)	Certainty of the evidence (GRADE)	Comments
	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 to 40 months	25 per 1000	25 per 1000 (21 to 29)	RR 1.01 (0.84 to 1.20)	19327 (5 RCTs)	⊕⊕⊕⊖ Moderate[a]	Meta-analysis and sensitivity analyses suggest risk increase of less than 1%. ALA intake probably makes little or no difference to all-cause mortality.
Cardiovascular mortality – cardiovascular deaths Assessed with: deaths from any cardiovascular cause. Where this was not available cardiac death was used instead where known. Duration: range 12 to 40 months	12 per 1000	12 per 1000 (9 to 15)	RR 0.96 (0.74 to 1.25)	18619 (4 RCTs)	⊕⊕⊕⊖ Moderate[b]	Meta-analysis and sensitivity analyses suggest risk reduction of less than 5%. ALA intake probably makes little or no difference to cardiovascular mortality.
Cardiovascular events – cardiovascular events Assessed with: number of partic-	48 per 1000	47 per 1000 (39 to 57)	RR 0.95 (0.83 to 1.07)	19327 (5 RCTs)	⊕⊕⊖⊖ Low[c]	Meta-analysis and sensitivity analyses suggest risk reduction of 5% to 10% (9% reduction in trials of low summary risk of bias, 10% in trials at low risk of compliance problems). ALA intake may reduce the risk of cardiovascular events but by a very small amount (from 4.8 to 4.7%). One thousand people would

ipants experiencing any cardiovascular event Duration: range 12 to 40 months						need to consume more ALA to prevent a single person experiencing a CVD event (NNT=1000).
Coronary heart 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 to 40 months	11 per 1000	10 per 1000 (8 to 14)	RR 0.95 (0.72 to 1.26)	18353 (3 RCTs)	⊕⊕⊕⊖ Moderate[d]	Meta-analysis and sensitivity analyses suggest risk reduction of 5% to 8%. ALA intake probably has little or no effect on risk of CHD mortality.
Coronary Heart Disease – 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 to 40 months	22 per 1000	22 per 1000 (17 to 28)	RR 1.00 (0.82 to 1.22)	19061 (4 RCTs)	⊕⊕⊖⊖ Low[e]	Meta-analysis and sensitivity analyses suggest risk reduction of 0% to 9%. ALA intake may make little or no difference to CHD events.
Stroke Assessed with: number of participants experiencing at least	2 per 1000	3 per 1000 (2 to 5)	RR 1.15 (0.66 to 2.01)	19327 (5 RCTs)	⊕⊖⊖⊖ Very low[f]	Meta-analysis and sensitivity analyses suggest risk increase of −15% to 23%. The effect of ALA intake on stroke is unclear as the evidence is of very low quality.

one fatal or non-fatal, ischaemic or haemorrhagic stroke Duration: range 12 to 40 months						
Arrhythmias – AF, VT, VF Assessed with: number of participants experiencing fatal or nonfatal, new or recurrent arrhythmia, including atrial fibrillation, ventricular tachycardia and ventricular fibrillation Duration: 1 trial of 40 months	33 per 1000	26 per 1000 (19 to 36)	RR 0.79 (0.57 to 1.10)	4837 (1 RCT)	⊕⊕⊕⊖ Moderate[g]	Meta-analysis and sensitivity analyses suggest risk reduction of 21%. ALA intake probably reduces the risk of arrhythmias a small amount (from 3.3 to 2.6%). 143 people would need to consume more ALA to prevent a single person experiencing an arrhythmic event (NNT=143).
Harms: bleeding Assessed with: number of participants experiencing bleeding events	The effect of ALA intake on bleeding is unclear as no studies reported this outcome.					
Harms: pulmonary embolus or DVT Assessed with: number of participants experiencing pulmonary embolus or deep vein thrombosis Duration: range 24 months	3 per 1000	**1 per** 1000 (0 to 23)	**RR 0.32** (0.01 to 7.80)	708 (1 study)	⊕⊖⊖⊖ Very low[h]	The effect of ALA intake on pulmonary embolus or DVT is unclear as the evidence is of very low quality.

*__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, ALA**
- **Risk of bias**: there was little or no effect in the main meta-analysis or when data were limited to RCTs at low summary risk of bias, low risk of compliance problems or larger trials, though a suggestion of increased risk of death with fixed-effect meta-analyses. Not downgraded.
- **Inconsistency**: I^2 was < 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 studies were conducted in high-income countries. Not downgraded.
- **Imprecision**: large numbers of participants have taken part in RCTs in long-term studies with consistent results. However, as 95% confidence intervals do not exclude important benefits or harms we downgraded once.
- **Publication bias**: funnel plot not useful as fewer than 10 trials included. Not downgraded.

[b] **Cardiovascular mortality, ALA**
- **Risk of bias**: there was little or no effect in the main analysis, or when data were limited to RCTs at low summary risk of bias, larger trials or fixed-effect meta-analysis, though a small benefit was suggested when studies were limited to trials with low risk of compliance bias. Not downgraded.
- **Inconsistency**: I^2 was < 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 studies were conducted in high-income countries. Not downgraded.
- **Imprecision**: large numbers of participants have taken part in RCTs in long-term studies with consistent results. However, as 95% confidence intervals do not exclude important benefits or harms we downgraded once.
- **Publication bias**: funnel plot not useful as fewer than 10 trials included. Not downgraded.

[c] **Cardiovascular events, ALA**
- **Risk of bias**: there was a small effect in the main analysis, with larger trials and in fixed-effect analysis, and a larger effect when data were limited to RCTs at low summary risk of bias or at low risk from compliance problems. Downgraded once.
- **Inconsistency**: I^2 was <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 studies were conducted in high-income countries. Not downgraded.
- **Imprecision**: large numbers of participants have taken part in RCTs in long-term studies with consistent results. However, as 95% confidence intervals do not exclude important benefits or harms we downgraded once.
- **Publication bias**: funnel plot not useful as fewer than 10 trials included. Not downgraded.

[d] **Coronary heart disease mortality, ALA**
- **Risk of bias**: while ALA reduced CHD mortality by 5% in the main analysis, fixed-effect analysis and in larger trials, limiting data to RCTs at low summary risk of bias and low risk of compliance problems resulted in 7%-8% reductions. Not downgraded.

- **Inconsistency**: I^2 was < 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 studies were conducted in high-income countries. Not downgraded.
- **Imprecision**: large numbers of participants have taken part in RCTs in long-term studies with consistent results. However, as 95% confidence intervals do not exclude important benefits or harms we downgraded. Downgraded once.
- **Publication bias**: funnel plot not useful as fewer than 10 trials included. 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, or in larger studies, but some risk reduction (8 to 9%) when data were limited to RCTs at low summary risk of bias or low risk of compliance bias. Downgraded once.
- **Inconsistency**: I^2 was < 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 studies were conducted in high-income countries. Not downgraded.
- **Imprecision**: large numbers of participants have taken part in RCTs in long-term studies with consistent results. However, as 95% confidence intervals do not exclude important benefits or harms we downgraded. Downgraded once.
- **Publication bias**: funnel plot not useful as fewer than 10 trials included. 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 was < 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 studies were conducted in high-income countries. Not downgraded.
- **Imprecision**: large numbers of participants have taken part in RCTs in long-term studies, but only 49 participants experienced strokes. 95% confidence intervals do not exclude important benefits or harms, downgraded once.
- **Publication bias**: funnel plot not useful as fewer than 10 trials included. Not downgraded.

[g] **Arrhythmias, ALA**
- **Risk of bias**: there was a 21% reduction in risk of arrhythmia in the main analysis, when data were limited to RCTs at low summary risk of bias, in larger trials and when data were limited to trials at low risk from compliance. Not downgraded.
- **Inconsistency**: only one trial, no inconsistency. Not downgraded.
- **Indirectness**: a single trial, which included adults with previous MI in a high-income country and only assessed new arrhythmia. Not downgraded.
- **Imprecision**: large numbers of participants have taken part in this long term study. However, as 95% confidence intervals do not exclude important benefits or harms we downgraded once.
- **Publication bias**: funnel plot not useful as fewer than 10 trials included. 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 studies for funnel plot. Not downgraded.

Summary of findings 3. High versus low omega-3 fats for modification of CVD 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 studies were carried out in high-income economies (World Bank 2018), but four trials were carried out in upper-middle income countries. No studies 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 alpha-linolenic acids, 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 (studies)	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 0.01 kg lower (0.84 lower to 0.82 higher)	15812 (12 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 0.04 higher (0.16 lower to 0.24 higher)	15234 (14 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 0.04 higher)	37281 (28 RCTs)	⊕⊕⊕⊖ Moderate[c]	LCn3 intake probably makes little or no difference to serum total cholesterol.
Serum triglyceride, fasting – LCn3 – TG, mmol/L	Mean TG was 1.59 mmol/L	MD 0.24 lower (0.32 lower to 0.17 lower)	35534 (24 RCTs)	⊕⊕⊕⊕ High[d]	Increasing LCn3 intake reduces serum triglyceride.
Serum high density lipoprotein – LCn3 – HDL, mmol/L	Mean HDL was 1.32 mmol/L	MD 0.02 higher (0 to 0.04 higher)	37237 (27 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)	35035 (23 RCTs)	⊕⊕⊕⊖ Moderate[f]	LCn3 intake probably makes little or no difference to serum LDL.
Measures of adiposity – ALA – Weight, kg	Mean weight was 80.9 kg	MD 0.17 higher (0.61 lower to 0.96 higher)	664 (4 RCTs)	⊕⊖⊖⊖ Very low[g]	The effect of ALA intake on body weight is unclear as the evidence is of very low quality.

Measures of adiposity – ALA – BMI, kg/m^2	Mean BMI was 27.4 kg/m^2	MD 0.12 higher (0.06 lower to 0.3 higher)	1581 (3 RCTs)	⊕⊕⊝⊝ Low[h]	ALA intake may make little or no difference to BMI.
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 total cholesterol (low-quality/certainty evidence).
Serum Triglyceride, fasting – ALA – 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 triglycerides (moderate-quality/certainty evidence).
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)	⊕⊕⊝⊝ Low[l]	ALA intake may make little or no difference to 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).
__BMI__: body mass index; __CI__: confidence interval; __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, LCn3**
- **Risk of bias**: there was little or no effect in the main analysis or in any sensitivity analysis. Not downgraded.
- **Inconsistency**: I^2 was < 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 have taken part in RCTs in long-term studies with consistent results. 95% confidence intervals exclude important benefits or harms. Not downgraded.
- **Publication bias**: funnel plot was not interpretable, no clear small study bias. However, we are aware of several studies whose data could not be included; not downgraded.

[b] **Measures of adiposity, 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 was < 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 have taken part in RCTs in long-term studies with consistent results. 95% confidence intervals exclude important benefits or harms. Not downgraded.
- **Publication bias**: funnel plot was not interpretable, no clear small study bias. However, we are aware of several studies 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 was < 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**: when we ran fixed-effect analysis, a statistically significant effect was suggested. The 95% CI included null but excluded important benefits or harms. Downgraded once..
- **Publication bias**: funnel plot was not interpretable, no clear small study bias. However, we are aware of several studies whose data could not be included; not downgraded.

[d] **Lipids, serum triglycerides, LCn3**
- **Risk of bias**: there was a 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 was < 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 have taken part in RCTs in long-term studies with consistent results. 95% confidence intervals exclude harms. Not downgraded.
- **Publication bias**: funnel plot was not interpretable, no clear small study bias. However, we are aware of several studies whose data could not be included; not downgraded.

[e] **Lipids, HDL, LCn3**
- **Risk of bias**: the suggested increase in HDL with increased LCn3 was apparent in all sensitivity analyses. Not downgraded.
- **Inconsistency**: I^2 was < 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 have taken part in RCTs in long-term studies with consistent results. 95% confidence intervals exclude harms. Not downgraded.
- **Publication bias**: funnel plot was not interpretable, no clear small study bias. However, we are aware of several studies whose data could not be included; not downgraded.

[f] **Lipids, 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 was < 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 have taken part in RCTs in long-term studies with consistent results. 95% confidence intervals included the null but excluded important benefits or harms. Downgraded once.
- **Publication bias**: funnel plot was not interpretable, no clear small study bias. However, we are aware of several studies whose data could not be included; not downgraded.

[g] **Measures of adiposity, weight, ALA**
- **Risk of bias**: no included trials were at low summary risk of bias. Downgraded once.
- **Inconsistency**: I^2 was > 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**: large numbers of participants have taken part in RCTs in long-term studies with consistent results. 95% confidence intervals include some benefits or harms. Downgraded once.

- **Publication bias**: funnel plot was not interpretable, no clear small study bias. However, we are aware of several studies whose data could not be included; not downgraded.

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

- **Risk of bias**: there was little or no effect in the main analysis or in any sensitivity analysis. Not downgraded.
- **Inconsistency**: I^2 was > 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**: large numbers of participants have taken part in RCTs in long-term studies with consistent results. 95% confidence intervals include some benefits and harms. Downgraded once.
- **Publication bias**: funnel plot was not interpretable, no clear small study bias. However, we are aware of several studies whose data could not be included; not downgraded.

[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 was > 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**: when we ran fixed-effect analysis a statistically significant effect was suggested, but main analysis includes some benefits and harms. Downgraded once.
- **Publication bias**: funnel plot was not interpretable, no clear small study bias. However, we are aware of several studies 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 was < 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 have taken part in RCTs in long-term studies with consistent results. 95% include benefits and harms. Downgraded once.
- **Publication bias**: funnel plot was not interpretable, no clear small study bias. However, we are aware of several studies whose data could not be included; not downgraded.

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

- **Risk of bias**: there was a statistically significant effect with fixed effects analysis and when data were limited to RCTs at low summary risk of bias, but the main analysis and other sensitivity analyses also suggested reductions om HDL. Not downgraded.
- **Inconsistency**: I^2 was < 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 have taken part in RCTs in long-term studies with consistent results. 95% CI includes benefits and harms. Downgraded once.
- **Publication bias**: funnel plot was not interpretable, no clear small study bias. However, we are aware of several studies whose data could not be included; not downgraded.

[l] **Lipids, LDL, ALA**

- **Risk of bias**: apparent effect altered from slight benefit to slight harm when data were limited to RCTs at low summary risk of bias. Downgraded once.
- **Inconsistency**: I^2 was < 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**: when we ran fixed-effect analysis a statistically significant effect was suggested. For main analysis 95% CI included benefits and harms. Downgraded once.
- **Publication bias**: funnel plot was not interpretable, no clear small study bias. However, we are aware of several studies whose data could not be included; not downgraded.

BACKGROUND

Description of the condition

Cardiovascular diseases (CVDs) are disorders of the heart and blood vessels. They include 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 global deaths are due to CVD, more than from any other cause (WHO 2017). Of the 17.7 million people who died from CVDs in 2015, 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 CVDs (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), the longer chain omega-3 fats (LCn3). Alpha-linolenic acid (ALA or α-linolenic, 18:3) is the shorter chain omega-3 fat found in plants and grass-fed, which is partially converted to longer chain omega-3 fatty acids within our bodies. There is some debate about the effectiveness of this conversion, which may differ depending on 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 longer chain omega-3 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 omega-3 fatty acids, including chia seed, flax (linseed) and rapeseed (canola) oils (Nettleton 1991), their derivatives (e.g. margarines), purslane leaves (Simopoulos 1992), and nuts (especially walnuts).

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 (FSA 2000; Liem 1997; MAFF 1998A; USFDA 1995). These are all fat soluble and accumulate over time in the body, so harms may be exhibited only after long-term fish consumption or supplementation with fish oils. Animal intervention studies and human cohorts who have suffered accidental exposure to dioxins and PCBs suggest that pre-natal exposure may cause sub-fertility problems, and adult exposures may lead to an excess of total cancers (JECFA 2001). Human cohorts exposed to high levels of mercury exhibit neurological problems (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 CVD 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 long-chain omega-3 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 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" (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, the AHA 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. And for those with high triglycerides, even larger doses could help" (AHA 2016). These recommendations are balanced with a warning about potential excessive bleeding in those taking doses of > 3 g/d omega-3 fatty acids (presumably long-chain omega-3 fats). Such recommendations, and resulting increased fish consumption, have potentially negative long-term consequences for our marine ecosystems (Brunner 2009).

Epidemiological studies have supported the relationship between high omega-3 intake and lower cardiovascular disease (CVD) rates (Ballard-Barbash 1987; Burr 1993; Kris-Etherton 2002). However, these associations could be due to some other characteristic 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 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% 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 RCTs alone, rather than cohort studies 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 randomised controlled trials (RCTs) have had various findings. An earlier version of this review found no effects for omega-3 fats on all-cause mortality or cardiovascular outcomes in trials of at least six months' duration (which included > 36,000 participants) (Hooper 2004). Since Hooper 2004 was published, several other systematic reviews have suggested a lack of effect for omega-3 fats on all-cause mortality or a variety of CVDs (Campbell 2013; Chowdhury 2012; Khoueiry 2013; Kotwal 2012; Kwak 2012; Mariani 2013; Rizos 2012; Zheng 2014). However, others have highlighted particular outcomes or circumstances in which CVD prevention was evident: after heart surgery (He 2013), for preventing sudden cardiac death (Zhao 2009), for reducing CVD mortality and sudden cardiac death (although with no effect on all-cause mortality) (Trikalinos 2012), for CVD 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 CVD outcomes (Balk 2016).

This systematic review and meta-analysis aimed to assess the evidence on the effects of omega-3 fats (long-chain and ALA separately) on all-cause mortality and CVDs. It also aimed to assess potentially harmful effects of omega-3 fats or compounds associated with consuming long-chain omega-3 fats such as excessive bleeding. A related review has formally systematically reviewed potential harms such as excessive cancers, rather than simply examining studies included in this review for cancer outcomes (Hanson 2017b). 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 CVD events occurred or were reported. Sister systematic reviews have assessed anti-inflammatory effects and effects on inflammatory bowel disease (Thorpe 2017), as well as effects on insulin sensitivity and glucose metabolism (Brown 2017).

The World Health Organization (WHO) is currently updating its guidance on polyunsaturated fatty acid intake in adults and children. The update and expansion of this review was commissioned by WHO in order to inform and contribute to the development of updated WHO recommendations. 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 (CVD) events, adiposity and lipids.

The primary review question was, 'Do long-chain omega-3 (LCn3, fish-based omega-3 fats) or ALA (plant-based omega-3 fats) 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 study summary risk of bias?
- Is protection or harm stronger with longer trial duration?

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 authors), and trials had to follow participants for at least 12 months (52 weeks or 360 days) for mortality and cardiovascular outcomes. 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 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 polyunsaturated fatty acids (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

Studies in adults (18 years or older, men and/or 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 alpha-linolenic acids, 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 studies 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.

Studies 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 (CHD deaths);
- coronary heart disease events (CHD events);
- stroke; and
- arrhythmia (atrial fibrillation).

We analysed coronary heart disease using the first of the following to be reported: number of participants experiencing CHD or coronary events, total myocardial infarction (MI), acute coronary syndrome or angina (stable and unstable). This meant that if trialists reported CHD events, we used these in analysis and ignored the other outcomes; where trials did not report CHD events but did report total MI, 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 CHD mortality post hoc as a primary outcome. Data used were the first of the following list reported: coronary death, ischaemic heart disease (IHD) death, fatal MI, 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 CHD, 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 CHD mortality did not encompass.

Secondary outcomes

Secondary outcomes included:

- major adverse cerebrovascular or cardiovascular events (MACCEs) or individual cardiovascular events (total, fatal or non-fatal MI, 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 MI, unstable angina, stroke or death. We did not consider studies that did not provide data on all these health events for this outcome.

The review included studies 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 study 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 study participant (so ALL trials assess 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 studies.

- 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 studies. 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 2017), cancers including breast cancer (Hanson 2017b), neurocognitive outcomes such as dementia (Jimoh 2017), irritable bowel disease (IBD) and inflammatory factors (Thorpe 2017), depression and anxiety (Hanson 2017a), and functional outcomes (Abdelhamid 2017), 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) Nutrition Guidance Expert Advisory Group (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.
- CVD mortality.
- CVD events.
- CHD mortality.
- CHD events.
- Stroke.
- Arrhythmia (atrial fibrillation).
- Serum lipids including total cholesterol (TC), fasting triglycerides (TG), high-density lipoprotein (HDL) and low-density lipoprotein (LDL).
- Measures of adiposity (body weight and body mass index).

We were not able to make all of these outcomes into primary outcomes. 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 quality 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 27 April 2017 to identify reports of relevant randomised clinical trials.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2017; Issue 3) in the Cochrane Library.
- Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE (Ovid, 1946 to 27 April 2017).
- Embase Classic and Embase (Ovid, 1947 to 2017 week 17).

We applied date limits to the terms from the original strategies so that the search included only new records, but we did not apply any date limits to newly added terms. Appendix 1 shows the MEDLINE search strategy for the original version of this review, and Appendix 2 shows the updated searches. We de-duplicated the results against each other. 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).

As we were also running searches for a new systematic review of the effects of polyunsaturated fats on cardiovascular disease (Abdelhamid 2018), as well as updating and extending a Cochrane Review of the effects of omega-6 polyunsaturated fats on health outcomes (Hooper 2018), we also ran searches for these reviews using the same RCT filters (Appendix 3). 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 dataset of RCTs that lasted at least six months and compared higher versus lower omega-6, omega-3 or total polyunsaturated fatty acids (PUFA) in adults. We used this dataset as the wider study pool from which we selected included studies for all reviews (Abdelhamid 2018; Abdelhamid 2017; Hooper 2018; Brown 2017; Hanson 2017a; Hanson 2017b; Jimoh 2017; Thorpe 2017; Hooper 2004).

We searched two trials registers, ClinicalTrials.gov (clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP, www.who.int/ictrp/en) on 23 September 2016 for registry entries for relevant completed and ongoing studies.

Searching other resources

We assessed titles and abstracts retrieved during these electronic searches for relevant RCTs and also relevant systematic reviews. We handsearched the included studies in all relevant systematic reviews for new trials and additional publications of included trials.

We contacted authors of all large included studies (at least 100 participants) and some smaller trials for further study data, methodological details and references to studies not yet identified, including published, unpublished or ongoing studies.

Data collection and analysis

Selection of studies

At least two reviewers independently assessed titles and abstracts resulting from the electronic and bibliographic searches. We combined the search results for this review and two others, Abdelhamid 2018and Hooper 2018, de-duplicating and assessing them at the same time. We rejected titles and abstracts on initial screen only if the reviewer could determine from the title and abstract that the article was not a report of a randomised controlled trial; did not address omega-3 intake (or total polyunsaturated fat or omega-6 fat for the other two reviews); 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 studies 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/abstract with certainty, we obtained the full text of the article for further evaluation. We made attempts to obtain full-text translations and/or evaluations of all potentially relevant non-English articles.

We used an in/out form to assess full-text papers and studies 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 assessors independently decided on inclusion of full-text RCTs, resolving any differences by discussion and, when necessary, in consultation with the review team.

Data extraction and management

We designed a data extraction form for this review, which each of the reviewers tested on a common 'training' study (SCIMO 1999), and we adapted it as appropriate. We extracted data concerning participants, interventions, and outcomes, as described above in the selection criteria section. We extracted dichotomous data from dietary advice studies at the latest point available in the trial (regardless of the amount of reinforcement of the original dietary message), while for supplement studies, 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 studies 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), long-chain omega-3 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 study 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 reviewers independently extracted original reports of trial results. We resolved differences between reviewers' results by discussion and, when necessary, in consultation with a third reviewer or the review team.

Assessment of risk of bias in included studies

Two reviewers independently assessed risk of bias for each included study, using Cochrane criteria (Higgins 2011), 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.

We considered a study to be at low risk of attention bias when participants were given the same amount of time and attention from study staff and health professionals whether they were in the intervention or control arms, and at low risk of compliance bias when 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 studies 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 this review, the omega-3 review and the total PUFA review (Abdelhamid 2018; Hooper 2018; Hooper 2004), we adopted a different approach after discussing the different nature 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 studies, we combined them using standardised mean difference (SMD).

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 studies, but only where we could be certain that we were not counting individual participants more than once within any one of our review outcome categories.

For studies with intervention arms providing different omega-3 doses, we combined data for the intervention groups for binary outcomes and used data on 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 study protocols to help us assess which studies measured each outcome. Where trials appeared to have collected – but did not report – data, we wrote to study authors to ask for information. We wrote to authors of all studies that randomised at least 100 participants as well as to those of many smaller studies (although not to all due to limited resources), prioritising our efforts on larger studies that would tend to provide more information to the review. For larger studies where we found no trials registry entry or protocol, we wrote to study authors to ask whether they had collected information on any outcomes of interest that we had not yet located. Where it was clear that data existed but could not be located to use within the review, we noted this and assessed the potential effect of this missing data on effect sizes narratively.

Assessment of heterogeneity

We assessed heterogeneity using the I^2 test and assumed it to be important when I^2 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 studies contributed to the meta-analysis (Egger 1997).

Data synthesis

Primary measures of interest were effects of dietary advice or supplementation of fish-based (long-chain, LCn3) omega-3 fats, and alpha linolenic acid (ALA), on primary outcomes. We separated out effects of LCn3 and ALA in all analyses and thus present two separate sets of results: one for ALA and one for LCn3.

We combined treatment/control differences in the outcomes across studies using relative risks (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 studies, but only where we were certain that we were not counting individual participants more than once within any one of our review outcome categories. However, individuals may have been counted for more than one of the review outcomes (in separate forest plots).

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 studies by subgrouping. The planned subgroup analyses were:

- 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 study, supplements (capsules or oils) provided to take as medicine or any combination;
- replacement of saturated fatty acids (SFA), 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 CVD;
- 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 long-chain omega-3 fats,
- ALA dose: higher versus lower levels of intake (≥ 5 g/d versus < 5 g/d);
- trial duration – studies 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 long-chain omega-3 intake, and baseline ALA intake.

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

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), 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 command metareg (Berkley 1995; Sharp 1998): log(e) relative risk 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) relative risk. 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 the update of Hooper 2018, and total PUFA trials from Abdelhamid 2018). 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 around 35 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);
- study size (retaining only trials that randomised at least 100 participants across all study 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 studies and designs.

'Summary of findings' tables

Outcome data were interpreted 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 < 8% (RR < 0.92 or > 1.08) for the highest quality 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.
2. For continuous outcomes increasing ALA or LCn3 was considered 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. Quality of evidence was assessed 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 quality of the body of evidence as it related to the studies that contributed data to the meta-analyses for the prespecified outcomes. We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), plus GRADEpro GDT software (GRADEpro GDT 2015). We justified all decisions to downgrade the quality of studies using footnotes and made comments to aid reader's understanding of the review.
4. Where there was a suggested effect the size of effect was assessed using the NNT or ARR.

We included three 'Summary of findings' tables: for effects of LCn3 on primary outcomes, effects of ALA on primary outcomes, and for key outcomes that were not included in the review primary outcomes (measures of adiposity and serum lipids).

RESULTS

Description of studies

Results of the search

The electronic searches for the full set of reviews (populating the dataset of all trials that assessed effects of higher versus lower omega-6, omega-3 or PUFA over at least 6 months) generated 37,810 titles and abstracts, which we de-duplicated to 19,772 hits. We assessed these along with 53 studies previously included from Hooper 2018 and Hooper 2004, to reassess for inclusion; 986 potentially relevant trials registry entries; and 35 new references gained from systematic review reference lists. In total, we assessed 20,846 titles and abstracts in duplicate to decide whether to retrieve full texts. We ultimately assessed 2155 full-text reports, of which 226 were systematic reviews. Two review authors independently assessed the remaining 1929 papers for inclusion and grouped them into studies. Of these, we included 364 RCTs in a wider set of trials that underpinned the full set of reviews (this review and several others including Abdelhamid 2018; Abdelhamid 2017; Hooper 2018; Brown 2017; Hanson 2017a; Hanson 2017b; Jimoh 2017; Thorpe 2017). This wider set of trials included RCTs of omega-3, omega-6 or total polyunsaturated fatty acids (PUFA) interventions with a duration of at least six months and regardless of outcomes reported (Figure 1). This database of 364 trials comprised 1020 documents (papers, abstracts and trials registry entries), plus additional data from 121 authors.

Figure 1. Study flow diagram.

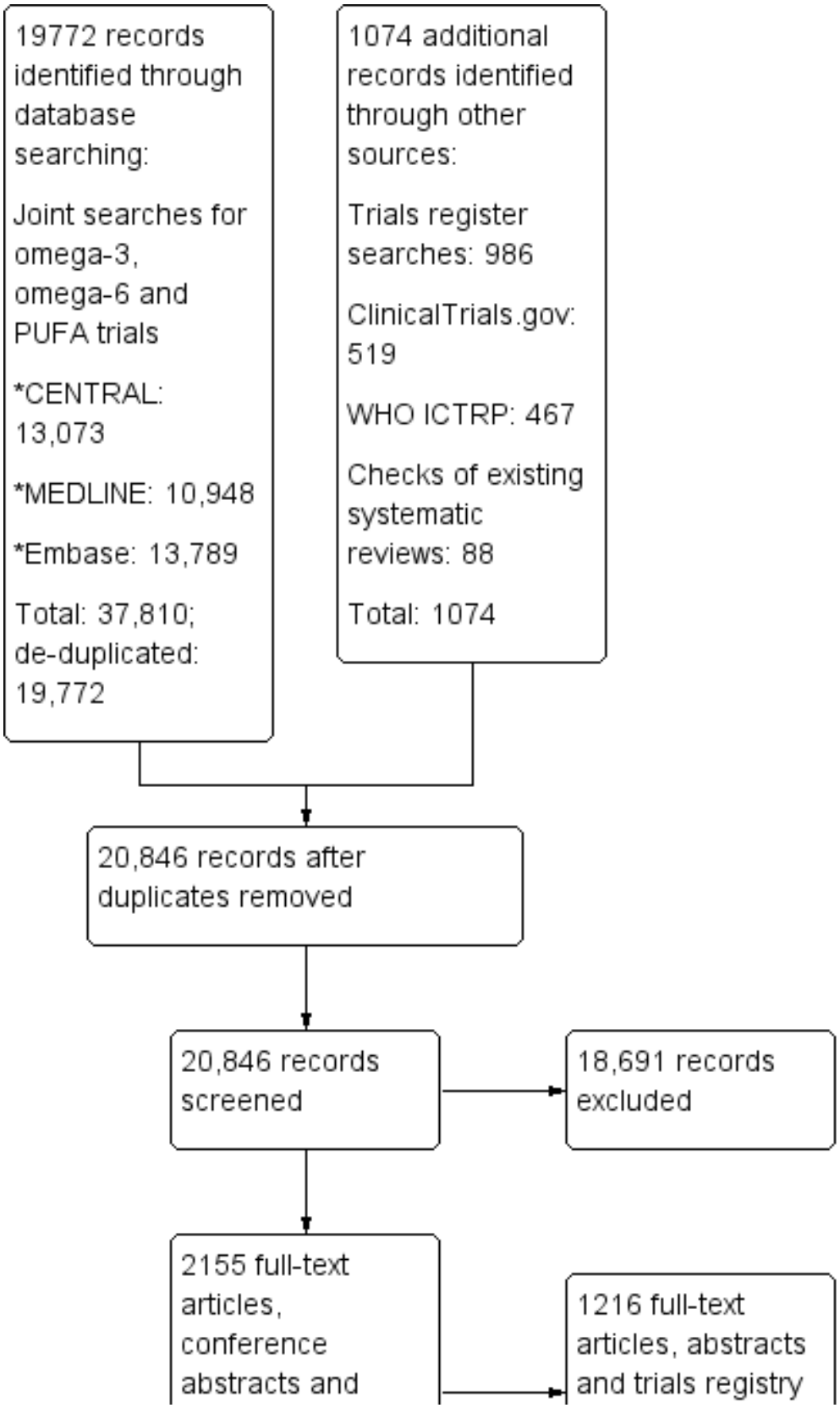


Figure 1. (Continued)

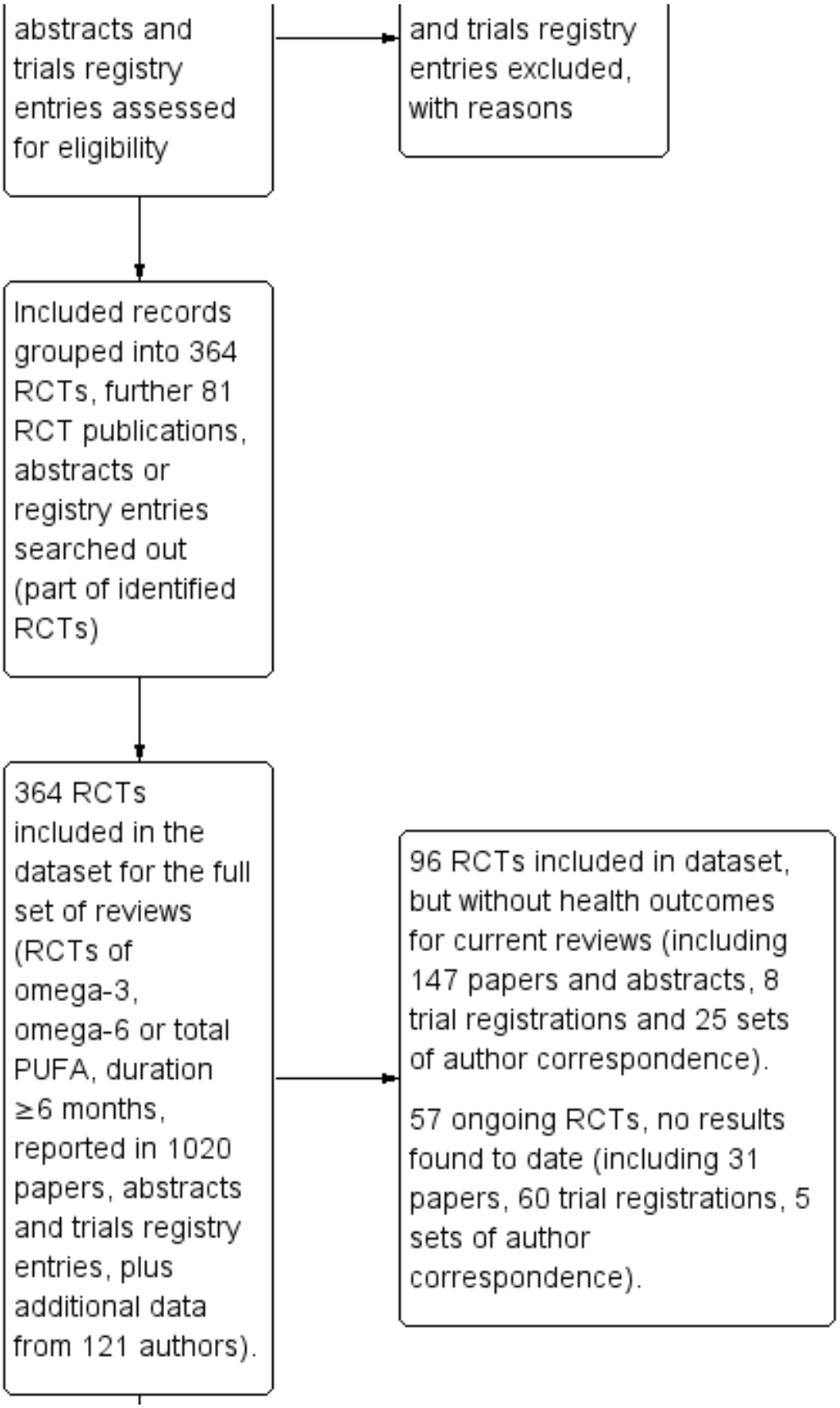
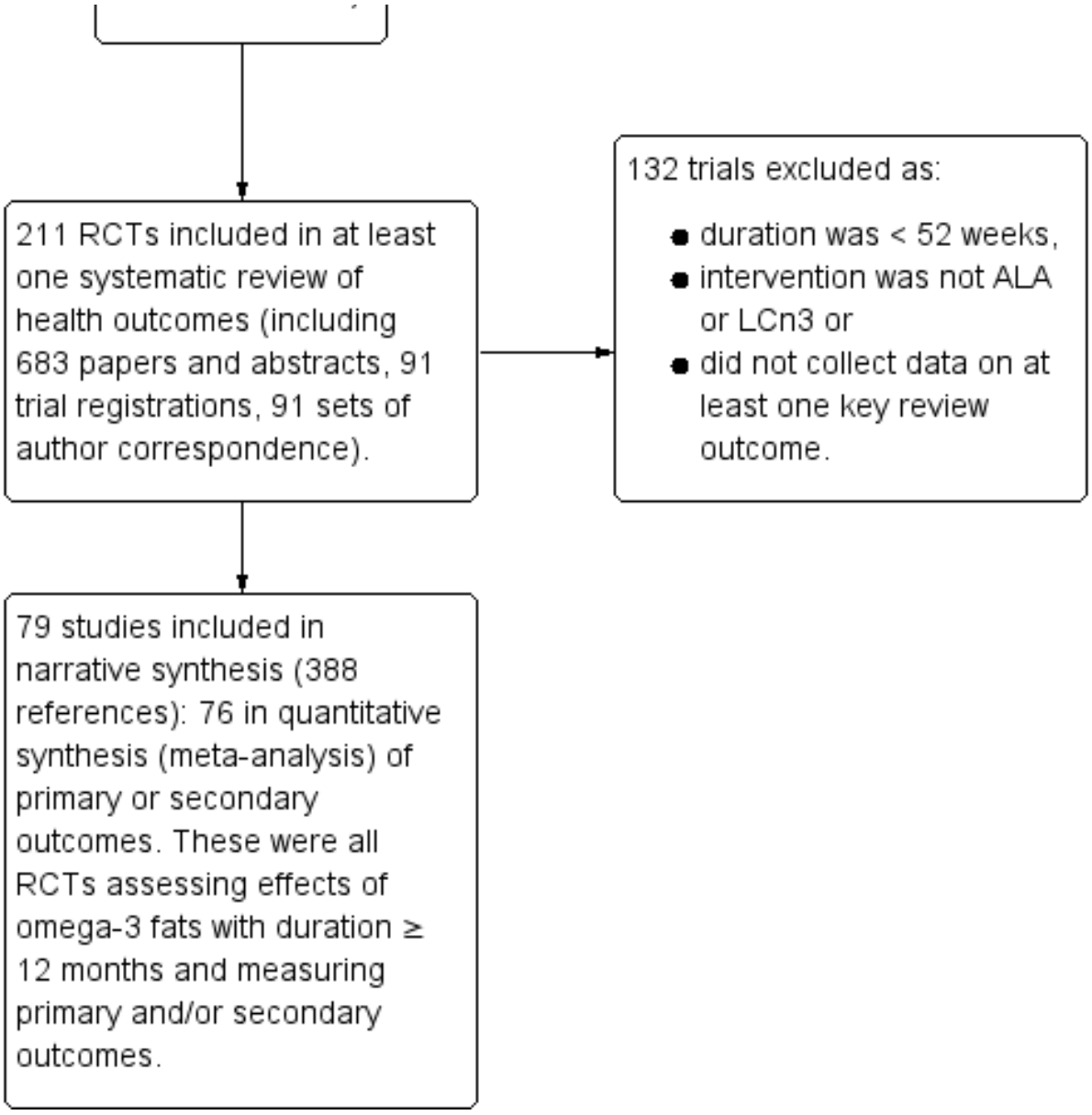


Figure 1. (Continued)



Of these 364 RCTs in the main dataset:

- 27 RCTs (51 documents) assessed effects of omega-3 fats over at least one year but were ongoing (without published outcome data);
- 258 RCTs (581 documents) did not assess effects of omega-3 fats or had a duration of less than one year or had not assessed relevant outcomes for this review, so we excluded them from this review; and
- 79 RCTs (388 documents) were eligible for inclusion in this review.

Of these 79 RCTs, 76 were included in meta-analyses. Three trials clearly collected relevant data but did not report them in a format that could be used in meta-analyses (Gill 2012; Ramirez-Ramirez 2013; Reed 2014; Figure 1).

Included studies

The 79 included RCTs randomised 112,059 participants, tripling the number of participants in the original version of this review (36,913 participants, some of whom were followed for only six months). The number of participants in included studies ranged from 11 to 18,645. Twelve trials randomised at least 1000 participants (AlphaOmega - ALA 2010; AlphaOmega - EPA+DHA 2010; AREDS2 2014; DART2 2003; DART 1989; GISSI-HF 2008; GISSI-P 1999; JELIS 2007; Norwegian 1968; OMEGA 2009; ORIGIN 2012; Risk & Prevention 2013; SU.FOL.OM3 2010), of which one was a 2 × 2 factorial trial where both interventions were included (AlphaOmega - ALA 2010; AlphaOmega - EPA+DHA 2010). Most of these larger trials assessed effects of longer chain omega-3 fats, but two studies/arms assessed effects of ALA (AlphaOmega - ALA 2010; Norwegian 1968).

Participants had cardiovascular disease at baseline in 33 of the trials (secondary prevention), and the remaining 46 trials were of primary prevention.

Most studies assessed effects of long-chain omega-3 fats.

- Sixty-two studies increased LCn3 intake using supplementary capsules or medicinal oils (ADCS 2010; AFFORD 2013; Ahn 2016; AREDS2 2014; Baldassarre 2006; Bates 1989; Berson 2004; Brox 2001; Caldwell 2011; Derosa 2016; Deslypere 1992; Doi 2014; DO IT 2010; 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; 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; Reed 2014; Risk & Prevention 2013; Rossing 1996; Sandhu 2016; SCIMO 1999; Shinto 2014; SHOT 1996; Sianni 2013; SOFA 2006; Sofi 2010; SU.FOL.OM3 2010; Tande 2016; WELCOME 2015; Zhang 2017).
- Two trials used supplemented or supplemental foods, such as enriched margarine or juice to increase LCn3 (AlphaOmega - EPA +DHA 2010; FOSTAR 2016).
- Four increased LCn3 fats using dietary advice (DART2 2003; DART 1989; 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 0.5g/d of EPA and DHA to > 5 g/d (17 RCTs had a dose of LCn3 < 1 g/d, 26 a dose of 1 to < 2 g/d, 11 of 2 to < 3 g/d, 16 RCTs had a dose of 3 or more g/d LCn3, 1 did not clearly state their dose).

Fewer studies assessed the effects of ALA on health outcomes.

- One trial used supplementary capsules or medicinal oils to increase ALA (Norwegian 1968).
- Six increased ALA using supplemented or supplemental foods, such as enriched margarine, bread, walnuts or other enriched food products (AlphaOmega - ALA 2010; 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, trialists did not state the ALA dose, so we treated the study 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.

The main study outcome was cardiovascular in 48 studies. Eighteen studies (19 comparisons) aimed to measure death or cardiovascular events (AlphaOmega - ALA 2010; AlphaOmega - EPA+DHA 2010; DART2 2003; DART 1989; 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; Risk & Prevention 2013; SOFA 2006; SU.FOL.OM3 2010; THIS DIET 2008).

Thirty studies aimed to measure various cardiovascular risk factors or progression of cardiovascular health.

- Atrial fibrillation recurrence or sinus rhythm (AFFORD 2013; 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; SCIMO 1999).
- Left ventricular function (Nodari 2011 HF).
- CABG graft patency (SHOT 1996).
- Lipids and other CVD 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 (IMT) (Baldassarre 2006; Gill 2012; MARINA 2011; Mita 2007).
- Body weight and adiposity (HERO 2009; MENU 2016; SMART 2013).

Thirty-one 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; NAT2 2013).
- Multiple sclerosis outcomes (Bates 1989; Weinstock-Guttman 2005).
- Cancer or pre-cancer outcomes (DIPP 2015).
- 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 (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).

Most studies 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 China (Zhang 2017). No studies took place in low- or low-middle income countries.

We identified a further 27 ongoing trials, which we describe in the table of Characteristics of ongoing studies. At the time of writing this review, all of these trials were unpublished, and some were recruiting or delivering interventions or had recently been completed, and trialists 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 full texts of over 1000 papers, so the full list of excluded studies 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 studies into our wider data set (Singh 1992; Singh 1997a; Singh 1997b; Singh 2002), but we later excluded them 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 studies and questioned the veracity of data behind several studies published by RB Singh. Another trial was retracted and so not included (Matsuyama 2005).

Risk of bias in included studies

We assessed summary risk of bias as low in 25 RCTs (26 comparisons: ADCS 2010; AlphaOmega - ALA 2010; AlphaOmega - EPA+DHA 2010; AREDS2 2014; Berson 2004; Caldwell 2011; Derosa 2016; 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; 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 study.

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

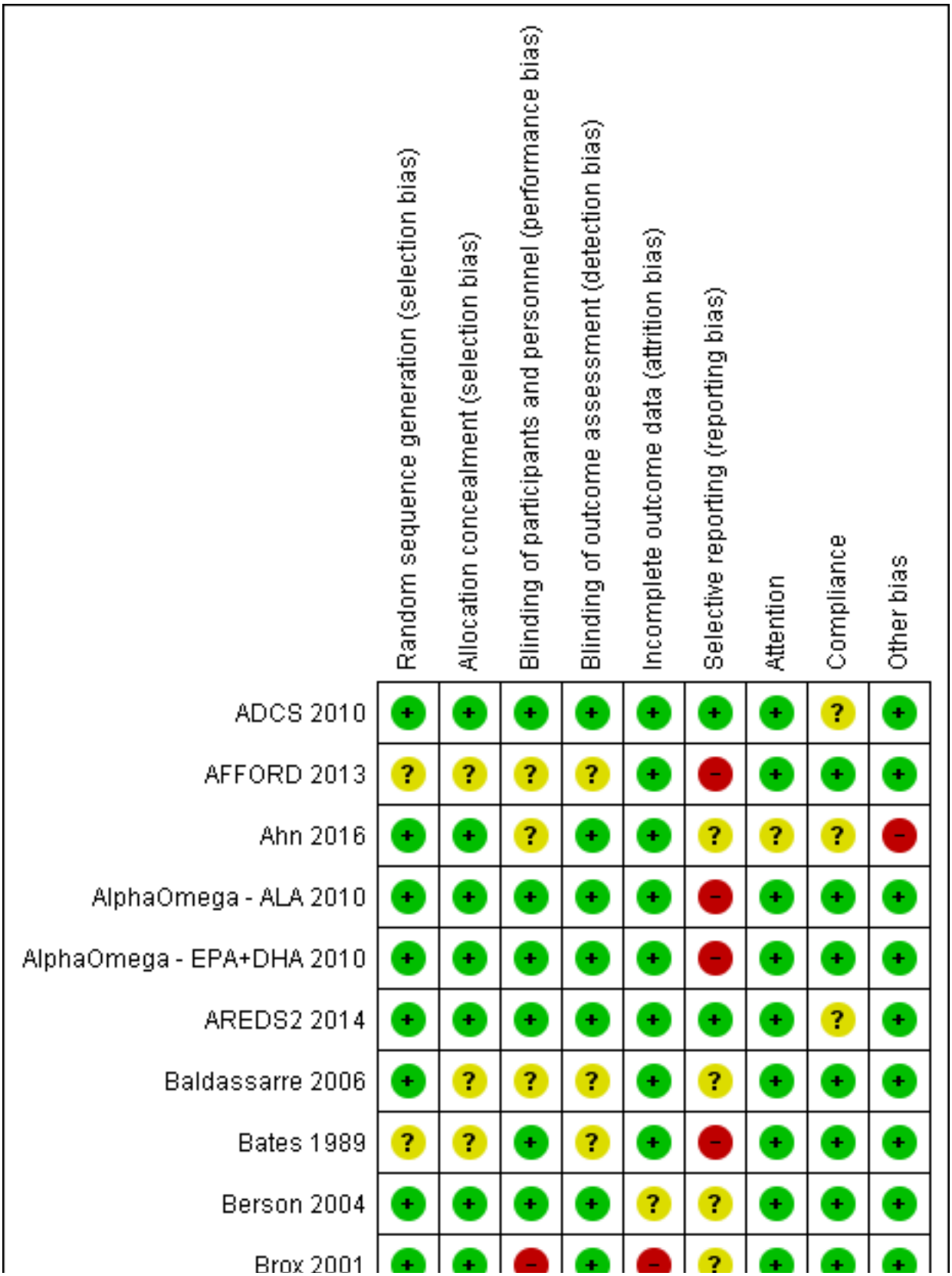
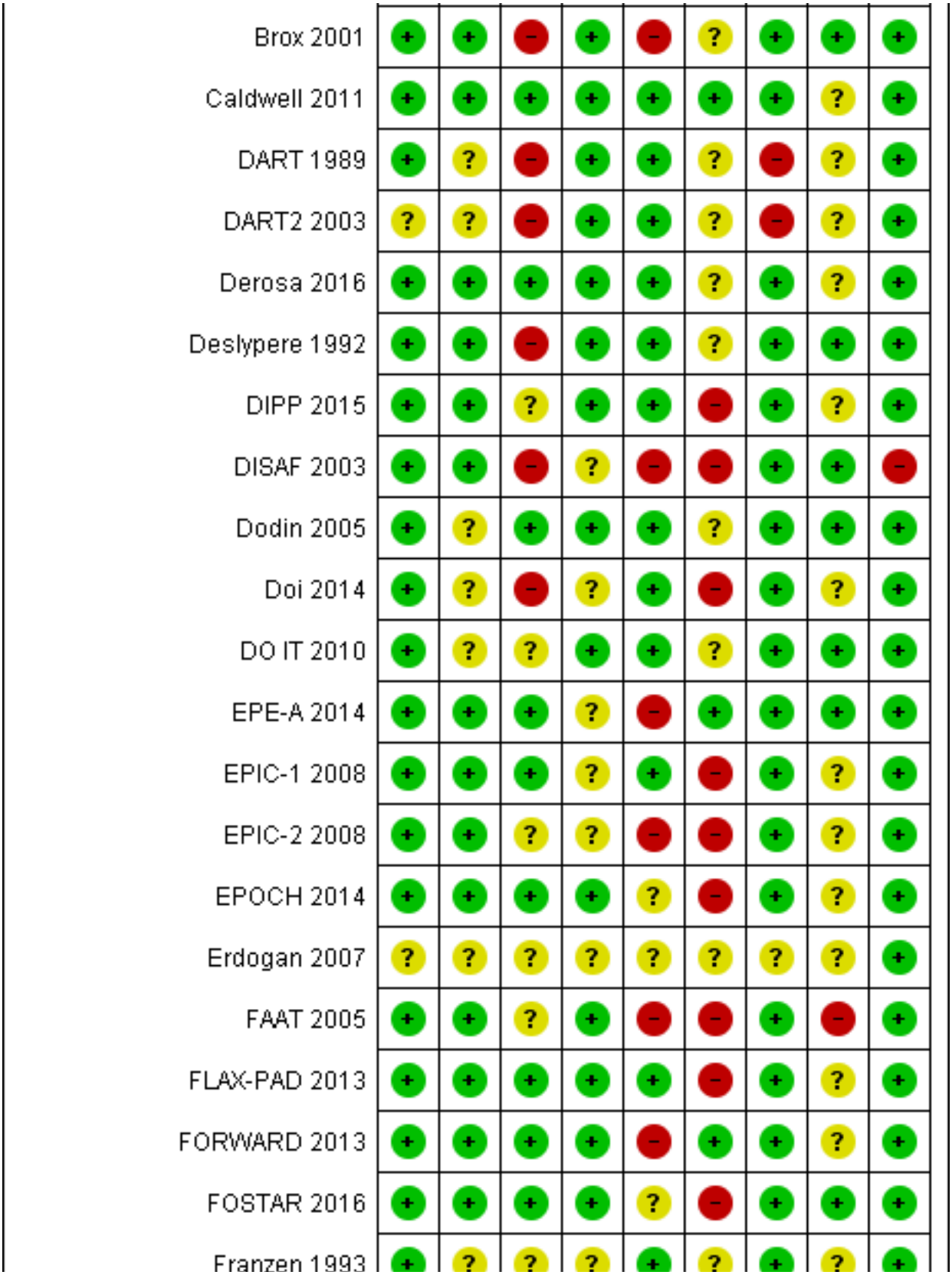


Figure 2. (Continued)



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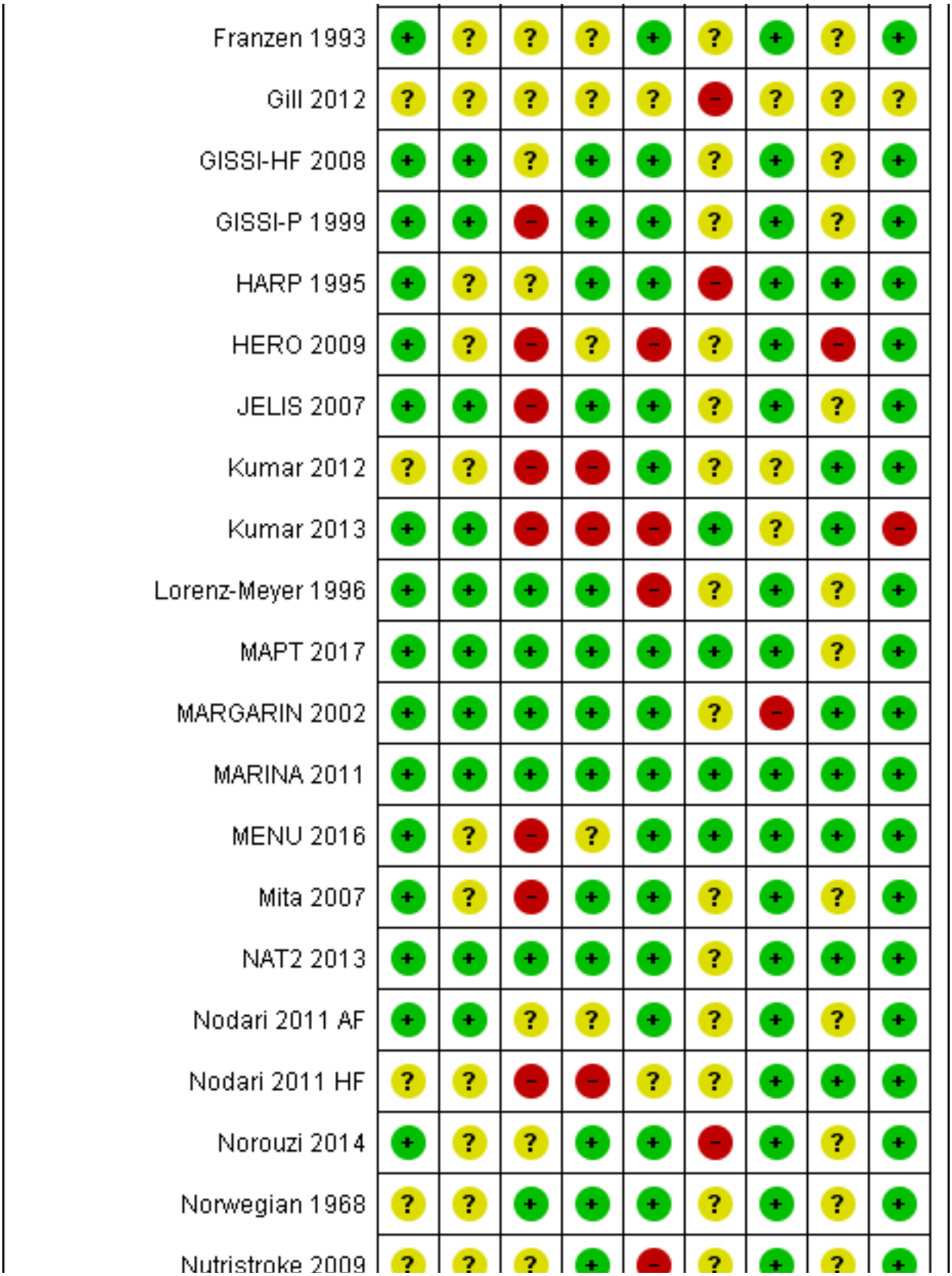

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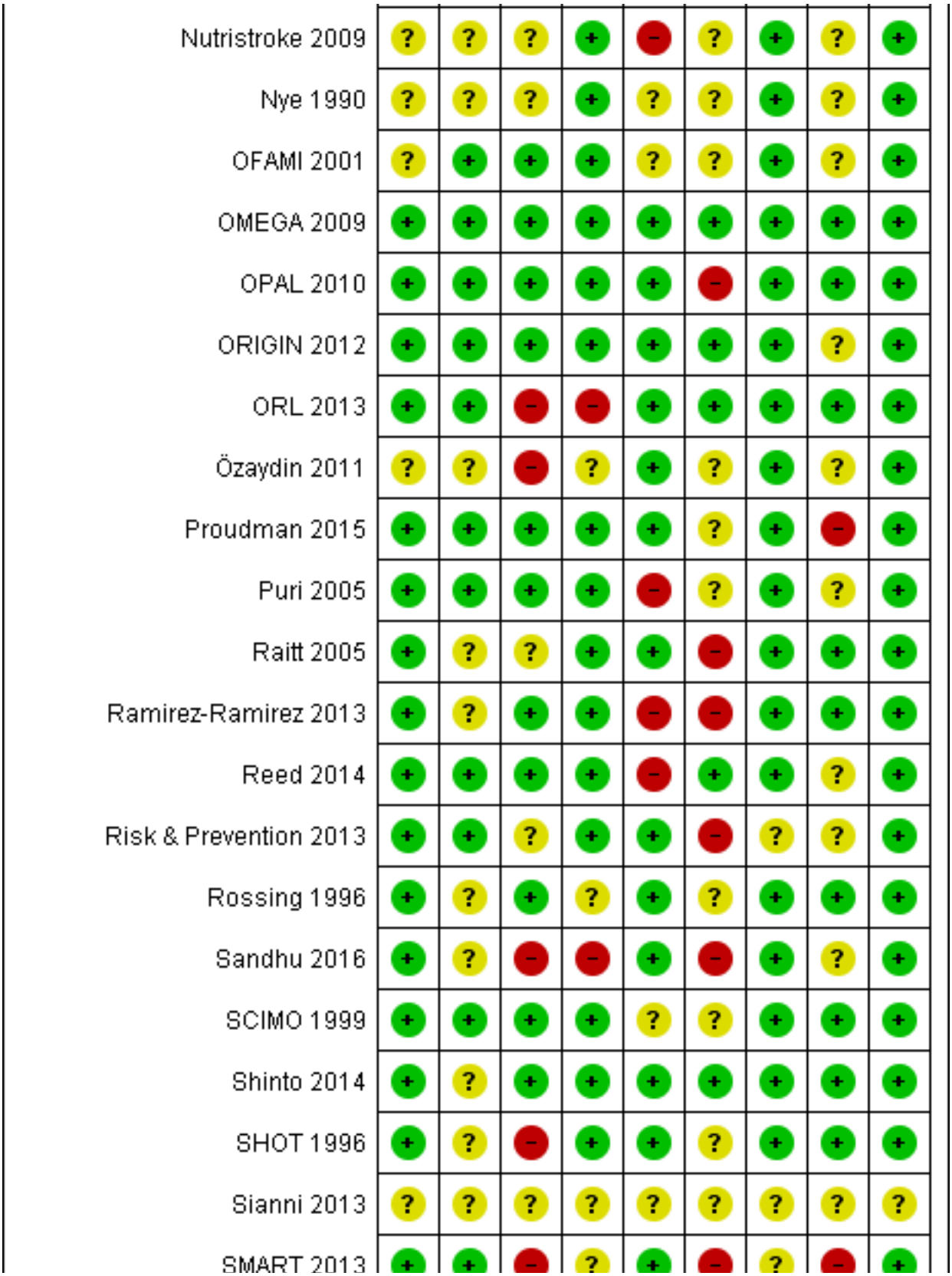

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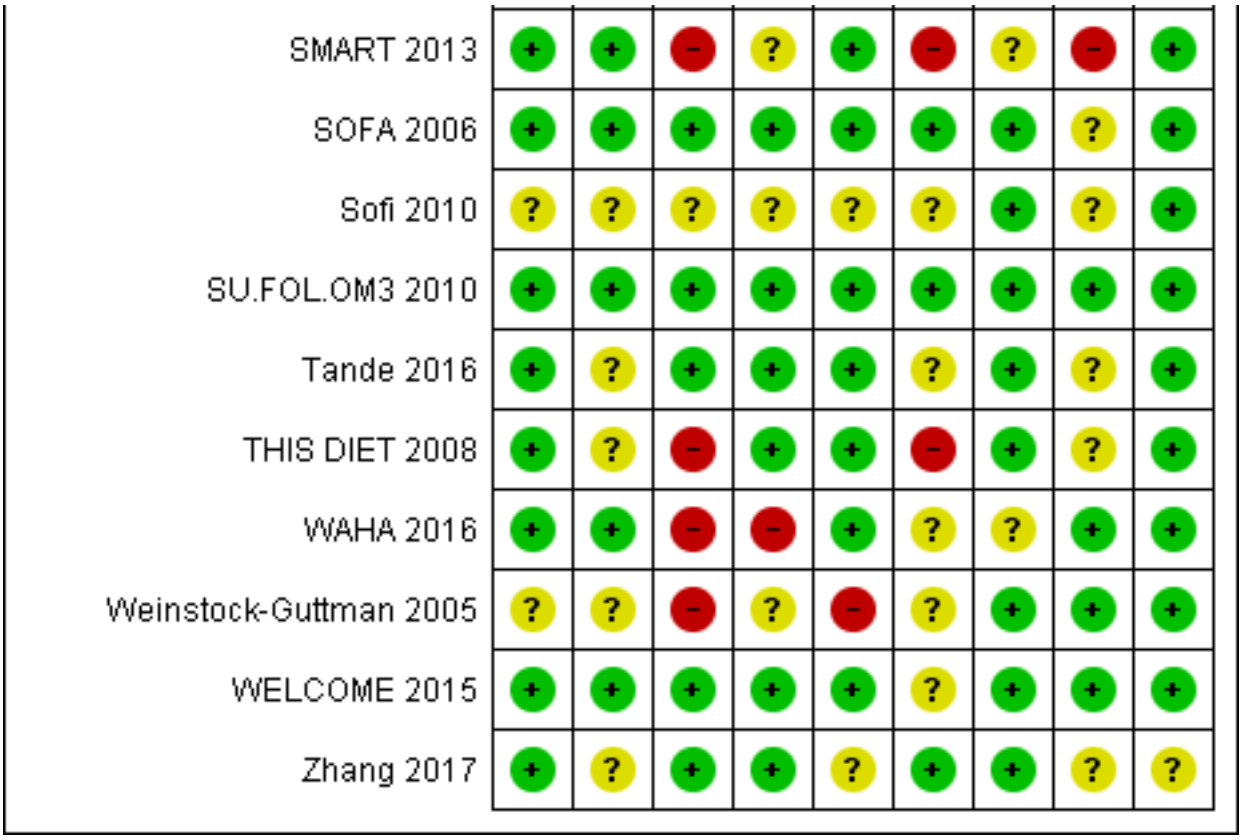


Allocation

Of the 79 RCT arms described in the 'Risk of bias' summary (Figure 2), 64 studies described randomisation well enough to merit an assessment of low risk (the remainder were unclear), and 45 study arms described adequate allocation concealment (the remaining 34 were unclear).

Blinding

We considered blinding of participants and personnel to be at low risk of bias in 37 of the 79 comparisons (Figure 2). Lack of blinding of participants put 22 trials at high risk of bias while the remaining 20 arms were at unclear risk. Blinding of outcome assessors put trials at low risk of detection bias in 53 studies and at high risk in 6 trials; this aspect was unclear in the remainder. We found that 33 studies were at low risk of both performance and detection bias.

Incomplete outcome data

We found that 53 trials were at low risk of attrition bias, 14 at high risk, and the remaining 12 at unclear risk.

Selective reporting

We determined that 17 trials had a pre-published trials registry entry or protocol and reported all planned outcomes appropriately so were considered at low risk of selective reporting. Twenty-three trials 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 from lack of compliance and attention bias and also noted other sources of bias. We found four studies to be at high risk of compliance bias (FAAT 2005; HERO 2009; Proudman 2015; SMART 2013), while 34 studies provided evidence of good compliance, and the remaining 41 studies were unclear. We noted a high risk of attention bias in three studies where intervention participants potentially had more dedicated time for dietary advice or follow-up (DART2 2003; DART 1989; MARGARIN 2002). Nine trials did not provide enough details to assess so we considered them to be at unclear risk of attention bias (Ahn 2016; Erdogan 2007; Gill 2012; Kumar 2012; Kumar 2013; Risk & Prevention 2013; Sianni 2013; SMART 2013; WAHA 2016), while we thought the remaining 67 were at low risk of attention bias. We judged three studies 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 study stopped early, and Kumar 2013 due to concerns over design. Three studies were at unclear risk due to insufficient methodological detail being provided (Gill 2012; Sianni 2013; Zhang 2017).

Effects of interventions

See: **Summary of findings for the main comparison** High versus low LCn3 for preventing cardiovascular disease and mortality (primary outcomes); **Summary of findings 2** High versus low ALA omega-3 fats for preventing cardiovascular disease (primary

outcomes); **Summary of findings 3** High versus low omega-3 fats for modification of CVD 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.

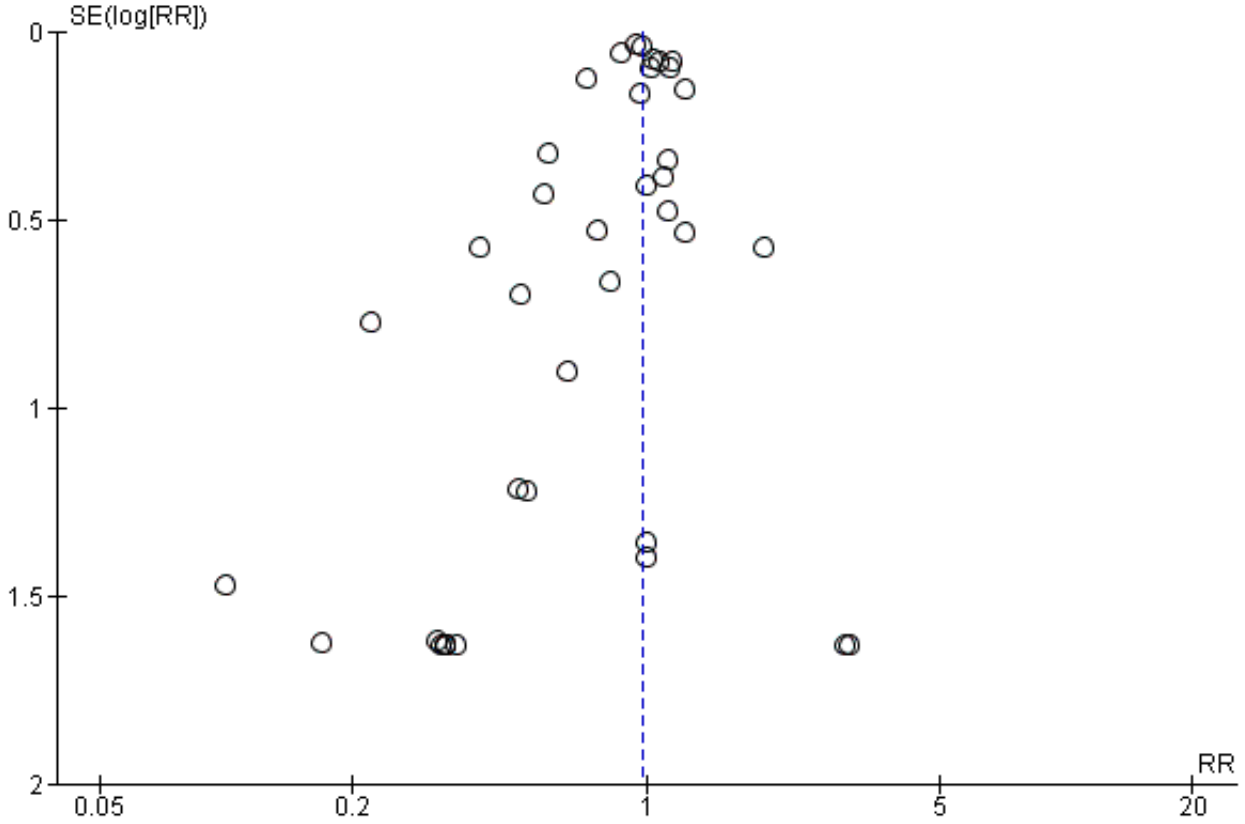
Effects of long-chain omega-3 fats on primary health outcomes

All-cause mortality (LCn3)

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

There was little or no effect of increasing long-chain omega-3 fats on all-cause mortality, despite 8189 deaths in > 92,000 participants (RR 0.98, 95% CI 0.93 to 1.03, I^2 = 12%, Analysis 1.1). The funnel plot suggested that some small studies with higher numbers of deaths in the intervention group might be missing (Figure 3), indicating small study bias. If such missing studies were added back in the RR would rise (towards the null value of 1.0).

Figure 3. Funnel plot of comparison: 1 High vs low LCn3 omega-3 fats (primary outcomes), outcome: 1.1 Aall-cause mortality (overall) – LCn3.



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 1.01, Analysis 1.2). Removing RCTs not at low summary risk of bias left us with 15 RCTs involving over 33,000 participants, 3059 of whom died, suggesting no effect of LCn3 on mortality (RR 1.01, 95% CI 0.94 to 1.08, I^2 = 0%, Analysis 1.3). This lack of effect was also evident in sensitivity analyses limited to studies at low risk of compliance bias and to larger studies (Analysis 1.4).

The lack of effect for LCn3 on mortality did not differ by replacement with mono-unsaturated fatty acids (MUFA), omega-3 fats or other types of placebo compounds (Analysis 1.6). There was no suggestion of any dose effect for long-chain omega-3 fats on mortality (Analysis 1.5), and subgroups with RRs further away from 1.00 had wider 95% confidence intervals. The lack of effect did not differ by primary versus secondary prevention (Analysis 1.9) or mode of intervention (dietary advice, supplemental foods, or capsules, Analysis 1.7). While there was some suggestion of a small risk reduction in total mortality with LCn3 in studies 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 = 0.007), the effect was not evident in shorter (1 to < 2 years) or longer studies (≥ 4 years, RR 1.03, 95% CI 0.98 to 1.09). Because of the lack of effect in longer studies, 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.

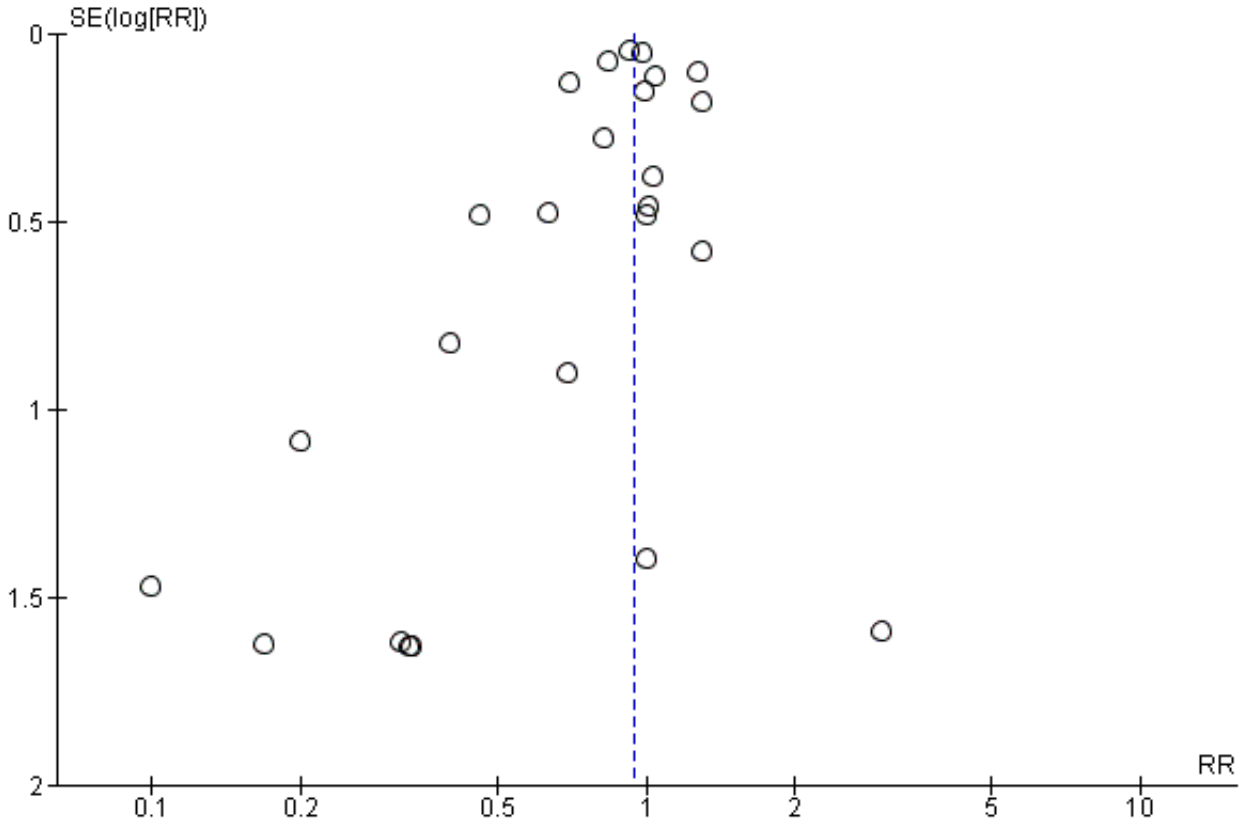
GRADE assessment suggested that the finding of little or no effect of LCn3 on all-cause mortality was supported by high-quality evidence (not downgraded, Summary of findings for the main comparison).

Cardiovascular mortality (LCn3)

Moderate-quality evidence suggests that long-chain omega-3 fat intake probably makes little or no difference to cardiovascular deaths.

Twenty-five trials in at least 67,000 participants, 4544 of whom died of CVD, reported on cardiovascular mortality (RR 0.95, 95% CI 0.87 to 1.03, I^2 = 24%, Analysis 1.11). The funnel plot suggested that some smaller studies 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 studies would increase the relative risk towards the null (no effect).

Figure 4. Funnel plot of comparison: 1 High vs low LCn3 omega-3 fats (primary outcomes), outcome: 1.11 Cardiovascular mortality (overall) – LCn3.



Fixed-effect meta-analysis suggested a 6% reduction in CVD mortality risk (RR 0.94, 95% CI 0.89 to 1.00, Analysis 1.12). However, sensitivity analyses removing RCTs not at low summary risk of bias left nine RCTs in over 29,000 participants, 1539 of whom died, suggesting little or no effect of LCn3 on CVD mortality (RR 0.99, 95% CI 0.90 to 1.09, I^2 = 0%, Analysis 1.13). Removing trials not at low risk of compliance bias had a similar effect (Analysis 1.14).

There were no statistically significant differences between subgroups and no differential effects by replacement (Analysis 1.16), mode of intervention (Analysis 1.17), duration (marginally significant difference between subgroups, P = 0.06; effects seen only in medium- to long-term trials and not in shorter or longer studies, Analysis 1.18), primary or secondary prevention (Analysis 1.19), statin use (Analysis 1.20) or omega-3 dose (Analysis 1.15). There was no suggestion of a dose-response effect.

Meta-regression to assess effects of LCn3 dose (or alpha-linolenic acid (ALA), omega-6 or total poly-unsaturated fatty acid (PUFA) dose), 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 value) showed no association between these factors and risk of cardiovascular mortality (all P values were > 0.60, Table 2). We saw no suggestion of dose-response or duration effects.

The suggestion of a protective effect disappeared in studies at low summary risk of bias and at low risk of compliance problems. The funnel plot suggests that the true risk ratio is 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 CVD mortality. GRADE assessment suggested moderate-quality evidence that long-chain omega-3 fat intake probably makes little or no difference to cardiovascular deaths (moderate-quality/certainty evidence, downgraded once for imprecision).

Combined cardiovascular events (LCn3)

High-quality 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 0.99, 95% CI 0.94 to 1.04, I^2 = 37%, Analysis 1.21). Analyses included 14,737 participants with cardiovascular events in more than 90,000 participants in 38 trials. The funnel plot suggested that some smaller studies with more participants experiencing cardiovascular events in the intervention group were missing (some small study bias, not shown) – if this were the case then adding the missing studies would increase the relative risk.

Sensitivity analyses removing trials at moderate to high risk of bias left 14 trials, including more than 31,000 participants, 6695 of whom had CVD events, with no suggestion of any effect of LCn3 fats (RR 1.00, 95% CI 0.96 to 1.05, I^2 = 0%, Analysis 1.23). Sensitivity analyses including studies 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 CVD events (Analysis 1.22; Analysis 1.24).

In subgroup analysis, there was no suggestion of a dose-response effect (Analysis 1.25). Effects did not differ by replacement (Analysis 1.26), baseline CVD risk (Analysis 1.29), type of intervention (Analysis 1.27), statin use (Analysis 1.30), LCn3 dose (Analysis 1.25) or study duration (Analysis 1.28), and there were no important differences between subgroups.

Meta-regression to assess effects of LCn3 dose (or doses of ALA, omega-6 and total PUFA), 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 value) showed no association between these factors and risk of cardiovascular events (all P values were ≥ 0.24, Table 3). We saw no suggestion of dose or duration effects.

GRADE assessment suggested high-quality evidence that LCn3 intake makes little or no difference to risk of cardiovascular events (high-quality/certainty evidence).

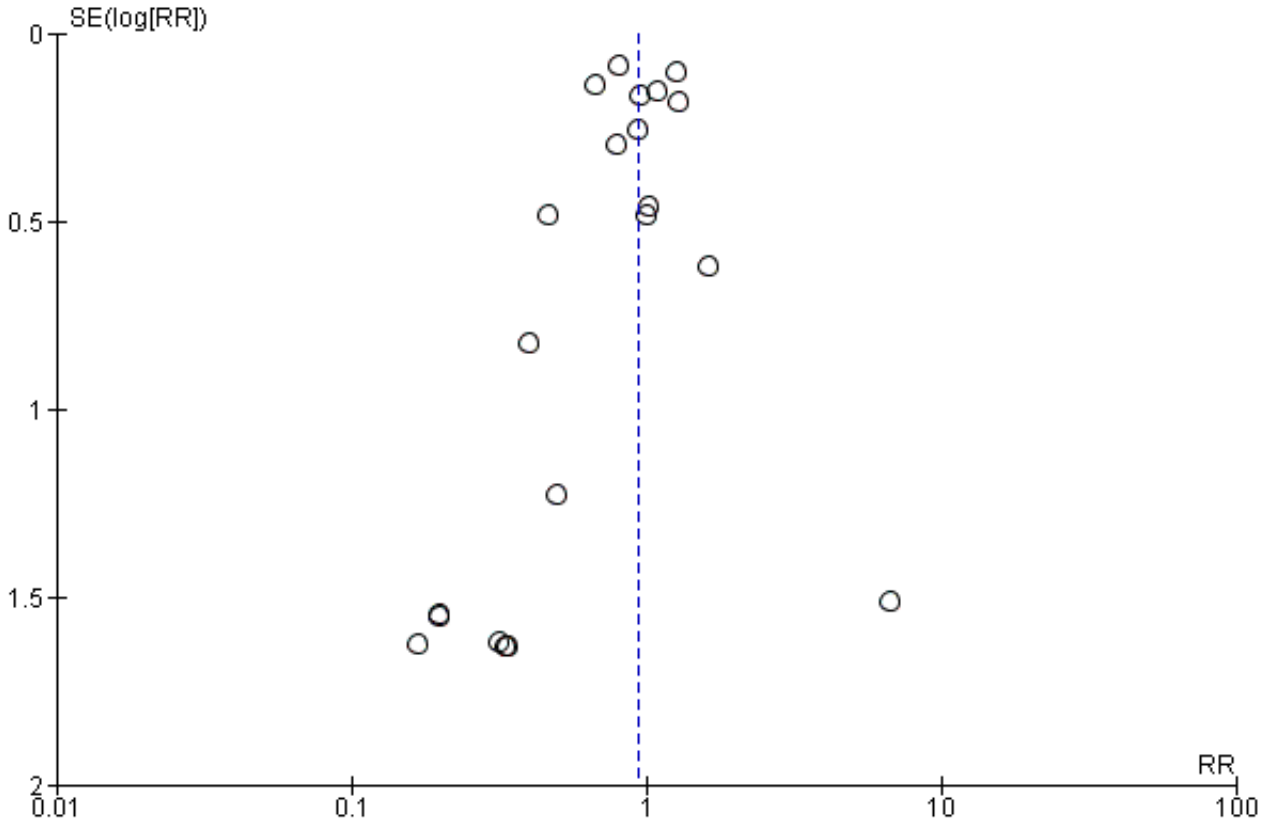
Coronary heart mortality (LCn3)

Moderate-quality evidence suggests that long-chain omega-3 fat intake probably makes little or no difference to coronary heart mortality.

There was a suggestion that increasing LCn3 fats reduced the risk of coronary heart mortality by 7% (RR 0.93, 95% CI 0.79 to 1.09, I^2 = 35%) in 21 trials reporting 1596 events in more than 73,000 participants (Analysis 1.31). Sensitivity analyses using a fixed-effect model suggested a 6% reduction in CHD mortality (Analysis 1.32).

However, retaining only RCTs at low summary risk of bias, meta-analysis of seven trials with more than 16,000 participants and 283 CHD deaths suggested no effect of LCn3 fats on CHD deaths (RR 1.00, 95% CI 0.72 to 1.37, I^2 = 18%, Analysis 1.33). Sensitivity analyses retaining only trials with low risk of compliance bias suggested a 5% increase in risk with LCn3, but retaining only larger trials suggested a 7% reduction (Analysis 1.34). The funnel plot suggested that some smaller studies with higher RRs were missing (Figure 5), and if added back these would increase the RR.

Figure 5. Funnel plot of comparison: 1 High vs low LCn3 omega-3 fats (primary outcomes), outcome: 1.31 Coronary heart disease mortality (overall) – LCn3.



When we added this outcome we had pre-specified that we would use the first of the following list reported in any trial: coronary death, ischaemic heart disease (IHD) death, fatal MI 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 CHD, such as cardiomyopathies and congenital and valvular heart diseases (though numbers are likely to be small). Omitting cardiac death resulted in a 17% reduction in CHD deaths with LCn3 (RR 0.83, 95% CI 0.74 to 0.94, I^2 = 0%, 16 trials including 65,325 participants, Analysis 1.35).

There were no statistically significant differences between subgroups for type of intervention (Analysis 1.38), dose (Analysis 1.36), baseline CVD risk (Analysis 1.40), statin use (Analysis 1.41) or baseline coronary artery disease status (Analysis 1.42). There were important differences between subgroups for study duration, with no effect in shorter trials (1 to < 2 years), a significant protective effect of LCn3 fats in medium- to long-term trials (2 to < 4 years) and an almost statistically significant harmful effect in long trials (≥ 4 years, Analysis 1.39), so we did not assume any differential effect by duration. The differences between subgroups for replacement disappeared when we omitted the 'replacement unclear' category (altering the test for subgroup differences to P = 0.46, Analysis 1.37).

Meta-regression to assess effects of LCn3 dose on CHD mortality found no relationship (P = 0.94, 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 CHD 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 CHD deaths. We saw no suggestion of dose or duration effects.

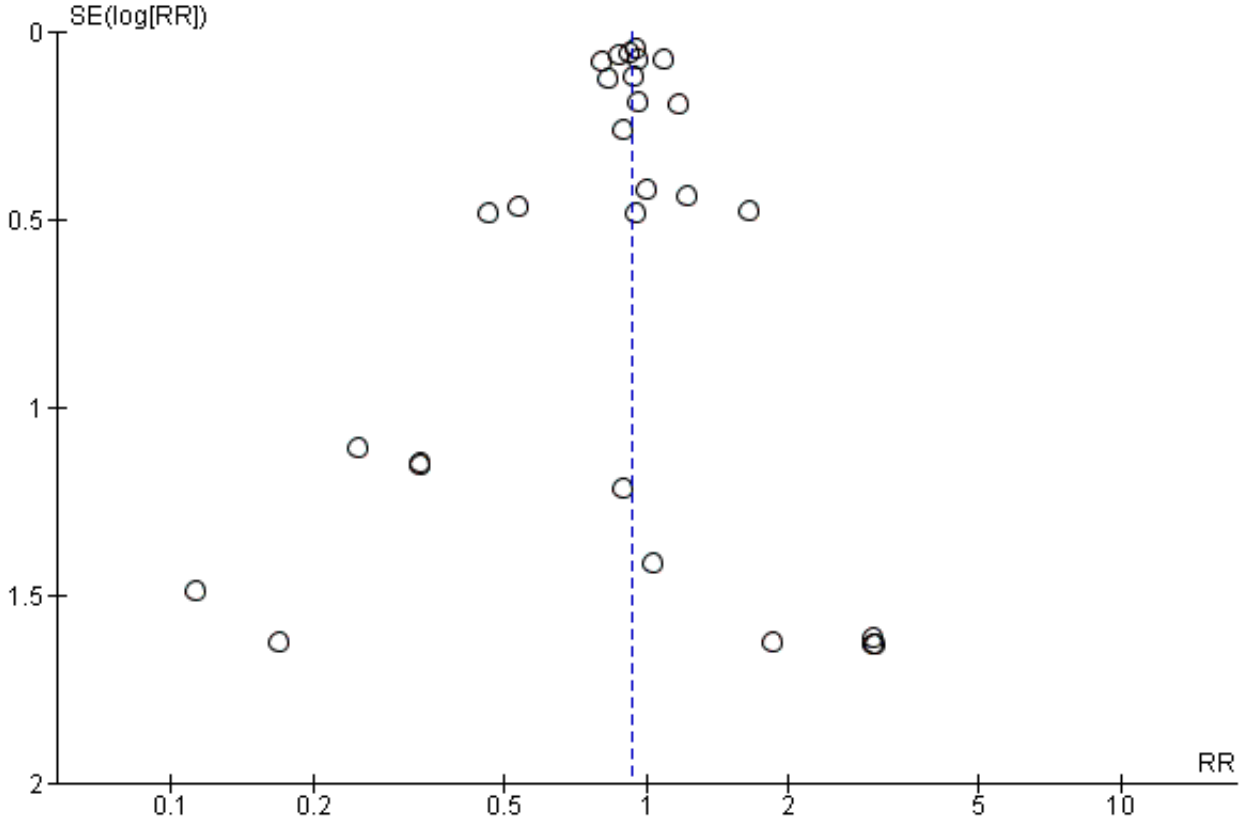
The suggestion of a protective effect disappeared in studies at low summary risk of bias, the funnel plot suggests that the true risk ratio is higher than the main estimate, and there was no suggestion of dose or duration effects, so we summarised the evidence by assuming little or no effect of LCn3 on CHD mortality. GRADE assessment suggested moderate-quality evidence that long-chain omega-3 fat intake probably makes little or no difference to coronary heart mortality (moderate-quality/certainty evidence, downgraded once for imprecision).

Coronary heart disease events (LCn3)

Moderate-quality evidence suggests that long-chain omega-3 fat intake probably makes little or no difference to risk of coronary heart events.

The main meta-analysis suggested a 7% reduction in people experiencing CHD events with higher intake of LCn3 fats (RR 0.93, 95% CI 0.88 to 0.97, I^2 = 0%, 5469 events, > 84,000 participants, Analysis 1.43). The funnel plot suggested that some smaller studies with more cardiovascular deaths in the intervention group were missing (some small study bias, Figure 6) – if this were the case then adding the missing studies would increase the relative risk.

Figure 6. Funnel plot of comparison: 1 High vs low LCn3 omega-3 fats (primary outcomes), outcome: 1.43 Coronary heart disease events (overall) – LCn3.



Sensitivity analyses using a fixed-effect model did not alter the results (RR 0.92, 95% CI 0.88 to 0.97, Analysis 1.44). The protective effect was lost in studies at low summary risk of bias (Analysis 1.45), and the effect was smaller when studies were limited to those with good compliance and to larger studies (Analysis 1.46). Removing RCTs not at low summary risk of bias left 12 trials with more than 30,000 participants, 2228 of whom developed CHD (RR 0.97, 95% CI 0.90 to 1.05, I^2 = 0%, Analysis 1.45).

There were no statistically significant differences between subgroups (Analysis 1.47; Analysis 1.48; Analysis 1.49; Analysis 1.50; Analysis 1.51; Analysis 1.52; Analysis 1.53).

Meta-regression to assess effects of LCn3, ALA, omega-6, total PUFA dose and 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 value) showed no association between these factors and the risk of CHD events (all P values were > 0.20, Table 5). We saw no suggestion of dose-response or duration effects.

Because a protective effect was only apparent in studies at higher risk of bias, we were concerned that the reduction in CHD events is residual and arises from methodological weaknesses in some of the studies (there was a marginally significant difference between the group of studies at low risk of bias, and those at moderate to high risk of bias, P = 0.09, Analysis 1.45). GRADE assessment suggested moderate-quality evidence that long-chain omega-3 fat intake probably makes little or no difference to risk of coronary heart events (moderate-quality/certainty evidence, downgraded once for risk of bias).

Stroke (LCn3)

Moderate-quality evidence suggests that long-chain omega-3 fat intake probably makes little or no difference to risk of experiencing a stroke.

There was a suggestion that increasing intake of LCn3 results in a 6% higher risk of stroke (RR 1.06, 95% CI 0.96 to 1.16, I^2 = 0%, 1822 reported strokes, Analysis 1.54), and the funnel plot did not suggest any small study bias (not shown).

Sensitivity analyses removing trials not at low summary risk of bias left 12 trials with 888 participants experiencing strokes, suggesting little or no effect of LCn3 fats on stroke (RR 0.98, 95% CI 0.86 to 1.12, I^2 = 0%, Analysis 1.56). Using fixed-effect meta-analysis also suggested a 6% increase in risk (Analysis 1.55), while sensitivity analysis removing trials with risk from poor compliance and smaller trials suggested there may be harm from increased LCn3 (Analysis 1.57).

When studies reported stroke type separately, the risk of both haemorrhagic (RR 1.20, 95% CI 0.85 to 1.69, I^2 = 0%, 130 participants with events) and ischaemic stroke were increased (RR 1.09, 95%

CI 0.89 to 1.33, I^2 = 13%, 556 people with events, in 8 trials each, Analysis 1.58). Five trials reported only 40 participants experiencing transient ischaemic attack (TIA), suggesting a 26% reduction in risk but with very wide confidence intervals (TIAs were not included in any other stroke categories, Analysis 1.58). Subgrouping did not suggest important differences by intervention type, replacement, statin use, trial duration or dose (Analysis 1.59; Analysis 1.60; Analysis 1.61; Analysis 1.62; Analysis 1.64). There was a suggestion of increased stroke risk in people with CVD 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 = 0.02, Analysis 1.63).

Meta-regression to assess effects of LCn3 dose did not find any clear dose response on risk of stroke (P = 0.42, Table 6). Univariate meta-regression suggested that trials of shorter duration showed a greater effect on reducing stroke (P = 0.012) and that LCn3 fats may be more protective against stroke in secondary prevention than primary (P = 0.04, Table 6). There were no clear relationships between dose of any PUFA type, risk of bias, or use of food or capsules, and no significant relationships in multivariate meta-regression.

Given that studies at low summary risk of bias suggested little or no effect of LCn3 on stroke risk, and there were no dose-response or duration relationships, we assumed little or no true effect. GRADE assessment suggests moderate-quality evidence that long-chain omega-3 fat intake probably makes little or no difference to risk of experiencing a stroke (moderate-quality/certainty evidence, downgraded once for imprecision).

Arrhythmia (LCn3)

Moderate-quality evidence suggests that long-chain omega-3 fat intake probably makes little or no difference to risk of arrhythmia.

There was no effect of LCn3 fats on incidence of new or recurrent (fatal and non-fatal) arrhythmias (RR 0.97, 95% CI 0.90 to 1.05, I^2 = 43%, 3788 events in > 53,000 participants, Analysis 1.65). The funnel plot was not interpretable as studies were clustered (not shown).

Sensitivity analyses removing trials not at low summary risk of bias left 10 trials with 1146 events (> 25,000 participants), suggesting a 10% increase in risk of arrhythmia with increased LCn3 (RR 1.10, 95% CI 0.98 to 1.23, I^2 = 0%, Analysis 1.67). Restricting the analysis to studies 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 = 0.03, Analysis 1.67). Using fixed-effect methodology did not alter the apparent lack of effect of LCn3 on arrhythmia (Analysis 1.66), and sensitivity analysis by compliance and study size also suggested little or no effect of LCn3 on arrhythmia (Analysis 1.68).

Subgrouping by new or recurrent arrhythmias suggested differences between subgroups, with LCn3 increasing the risk of new arrhythmias and reducing the risk of recurrent arrhythmia (Analysis 1.69). There were also statistically significant differences between subgroups by fatality, with a suggestion that LCn3 increased the risk of fatal arrhythmias but reduced the risk of non-fatal arrhythmias (Analysis 1.70). Subgroup analyses by type of intervention, replacement, baseline CVD risk, statin use, dose and study duration did not suggest any statistically significant differences between subgroups (Analysis 1.71; Analysis 1.72; Analysis 1.73; Analysis 1.74; Analysis 1.75; Analysis 1.76).

Meta-regression suggested a marginally significant negative dose-response relationship with LCn3 fats, such that lower dose was associated with lower risk of arrhythmia (P = 0.06, Table 7). The effect remained marginally significant when we controlled for primary or secondary prevention and study duration (P = 0.09). Because of the negative direction of this apparent dose-response relationship, we assumed it was likely to be a chance occurrence resulting from running a large number of statistical tests. There was also a marginally significant relationship for arrhythmia with primary versus secondary prevention, suggesting greater reduction in arrhythmia risk in primary prevention (P = 0.07, Table 7). There were no other suggested relationships.

GRADE assessment suggested moderate-quality evidence that long-chain omega-3 fat intake probably makes little or no difference to risk of arrhythmia (moderate-quality/certainty evidence, downgraded once for imprecision).

Effects of 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 studies for all ALA analyses we did not use 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 studies to carry out meta-regression with any reliability).

All-cause mortality (ALA)

Moderate-quality 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 458 deaths in more than 18,000 participants involved in four studies (RR 1.01, 95% CI 0.84 to 1.20, I^2 = 0%, Analysis 4.1).

Sensitivity analyses removing RCTs 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). Using fixed-effect meta-analysis suggested a 6% increase in risk of all-cause mortality with increased ALA (RR 1.06, 95% CI 0.84 to 1.34, Analysis 4.2), while limiting the analysis to studies at low risk of compliance problems showed a 5% increase, and including only larger trials showed little or no effect (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-quality/certainty evidence, downgraded once for imprecision).

Cardiovascular mortality (ALA)

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

Four studies 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 CVD deaths in > 18,000 participants.

Sensitivity analyses using fixed-effect meta-analysis did alter the lack of effect (RR 0.96, 95% CI 0.74 to 1.25, Analysis 4.12). Removing studies not at low risk of bias left three trials with 165 cardiovascular deaths, suggesting a 5% reduction of cardiovascular death risk with higher ALA (RR 0.95, 95% CI 0.70 to 1.28, Analysis 4.13). Sensitivity analysis by compliance or study size again suggested 6% and 4% reductions, respectively, in CVD mortality risk (Analysis 4.14).

Subgrouping by ALA dose, study duration, replacement, intervention type, statin use or primary/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 = 0.91, Table 2).

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

Cardiovascular events (ALA)

GRADE assessment suggested that increasing ALA intake may reduce the risk of cardiovascular events by a small amount.

There was a 5% reduction in 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 studies at moderate to high risk of bias left three trials in which 691 of > 5,000 enrolled participants experienced at least one cardiovascular event, suggesting a 9% reduction in risk of CVD events with higher ALA (RR 0.91, 95% CI 0.79 to 1.04, I^2 = 0%, Analysis 4.23). Fixed-effect analysis suggested a 5% reduction in risk (Analysis 4.22), while studies at low risk of compliance bias suggested a 10% reduction in risk, and larger studies a 5% reduction (Analysis 4.24).

Subgrouping by ALA dose, study duration, replacement, intervention type, statin use or primary/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 any dose effects (P = 0.70, Table 3).

GRADE assessment suggested that increasing ALA intake may reduce the risk of cardiovascular events by a small amount (low-quality/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 CHD mortality.

Three studies reported 193 CHD deaths in > 18,000 participants, suggesting a 5% reduction in CHD mortality with increased ALA (RR 0.95, 95% CI 0.72 to 1.26, I^2 = 0%, Analysis 4.31).

Sensitivity analyses using fixed-effect meta-analysis did not alter the effect (RR 0.95, 95% CI 0.72 to 1.26, Analysis 4.32). Studies at low summary risk of bias suggested a 7% reduction in risk of CHD mortality (including 2 trials with 4947 participants, RR 0.93, 95% CI 0.67 to 1.30, I^2 = 0%, Analysis 4.33), with similar effects in studies at low risk of compliance bias, or low risk of small study bias (Analysis 4.34).

Subgrouping by ALA dose, study duration, replacement, intervention type, statin use, primary/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). Meta-regression to assess for effects of ALA dose on CHD deaths did not suggest any dose effects (P = 0.93, Table 4).

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

Coronary heart disease events (ALA)

Low-quality evidence suggests that ALA intake may make little or no difference to CHD events.

Three studies contributed data to this outcome, with 396 out of over 18,000 participants experiencing at least one CHD event. There was little or no effect on CHD 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 studies not at low summary risk of bias left two studies with almost 5000 participants, suggesting a 9% reduction in risk of a CHD event (RR 0.91, 95% CI 0.71 to 1.15, Analysis 4.44), similar to sensitivity analysis omitting studies with potential compliance problems (Analysis 4.45), though no effects were seen when restricting analysis to larger trials (Analysis 4.45).

Subgrouping by ALA dose, study duration, replacement, intervention type, statin use, primary/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 4.52). Meta-regression did not suggest that there was a direct relationship between ALA dose and CHD events (Table 5).

Given the differences in sensitivity analyses, GRADE assessment suggested that ALA intake may make little or no difference to CHD events (low-quality/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 quality.

Five RCTs involved 51 people out of more than 18,000 participants experiencing a stroke, suggesting a 15% increase in stroke risk with increased ALA (RR1.15, 95% CI 0.66 to 2.01, I^2 = 0%, Analysis 4.53). Sensitivity analyses removing studies not at low summary risk of bias left three studies 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 studies at high risk of bias due to compliance suggested a 15% reduction in stroke risk, while larger studies suggested a 15% greater stroke risk (Analysis 4.56).

Subgrouping by ALA dose, study duration, replacement, intervention type, statin use or primary/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 studies reported on 28 ischaemic strokes, with no clear effects, and no studies reported on haemorrhagic stroke (Analysis 4.63). Meta-regression did not suggest any relationship between ALA dose and risk of stroke (Table 6).

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

Arrhythmia (ALA)

Moderate-quality evidence suggested that ALA intake probably reduces the risk of arrhythmias.

Only one study reported effects of ALA on arrhythmia, with 141 new arrhythmias in 4837 participants, suggesting a 21% reduction in arrhythmia but with wide confidence intervals (RR 0.79, 95% CI 0.57 to 1.10, Analysis 4.64). The results were identical when sensitivity analysis retained only studies at low summary risk of bias (as we judged the single included study to be at low risk of bias, Analysis 4.65). As there was only one trial, we did not carry out further sensitivity analyses or subgrouping. There was no suggestion of a dose-response relationship between ALA and arrhythmia risk in meta-regression (P = 0.67, Table 7).

GRADE assessment suggested that ALA intake probably reduces the risk of arrhythmias (moderate-quality/certainty evidence, downgraded once for imprecision).

Secondary outcomes

See Summary of findings 3 for a summary of our evidence on effects of long-chain omega-3 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 MI, 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-three studies (> 72,000 participants) reported on total (fatal and non-fatal) myocardial infarction (MI). Meta-analyses suggested that increasing LCn3 fats resulted in a small reduction in total MI (RR 0.95, 95% CI 0.88 to 1.03, I^2 = 0%, 2200 MI events, Analysis 2.2). This was confirmed in sensitivity analyses limited to studies without compliance problems and to studies that randomised at least 100 participants (Analysis 2.4), but analyses limited to studies at low summary risk of bias suggest little or no effect of LCn3 on MI (RR 1.03, 95% CI 0.92 to 1.15, I^2 = 0%, > 30,000 participants in 11 trials, and reporting on 1154 people experiencing at least one MI, Analysis 2.3). This suggests little or no true effect of LCn3 on MI.

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 MI subgroups (P = 0.23, Analysis 2.5).

Sudden cardiac death (LCn3)

There was little or no effect of LCn3 fats on sudden cardiac death (RR 0.97, 95% CI 0.80 to 1.18, I^2 = 38%, 1274 deaths, 14 studies in > 65,000 people, Analysis 2.6).

Angina (LCn3)

Meta-analysis of 11 studies involving more than 39,000 participants, 2418 of whom reported new or worsening angina, suggested little or no effect of increasing LCn3 fats (RR 0.99, 95% CI 0.92 to 1.07, I^2 = 0%, Analysis 2.7).

Heart failure (LCn3)

Meta-analysis suggested a small effect for LCn3 fatty acids on heart failure diagnosis in 15 trials with 4098 people experiencing events (RR 0.93, 95% CI 0.85 to 1.03, I^2 = 31%, Analysis 2.8). Because of this suggested effectiveness, we ran a sensitivity analysis limited to the six studies at low summary risk of bias, which suggested little effect (RR 0.97, 95% CI 0.89 to 1.06, I^2 = 0%, 1809 participants experiencing heart failure). For this reason 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 0.98, 95% CI 0.94 to 1.03, 6558 participants experiencing revascularisation, I^2 = 0%, Analysis 2.9). Data on angioplasty alone were similar (RR 0.96, 95% CI 0.74 to 1.24, 215 events), and there were insufficient reported CABGs to give meaningful results (9 events, Analysis 2.9).

Peripheral arterial disease (LCn3)

Meta-analysis suggested that LCn3 reduced the risk of peripheral arterial disease (PAD) by 7% (RR 0.93, 95% CI 0.74 to 1.18, I^2 = 0%, 282 events in > 49,000 participants, 7 trials, Analysis 2.10). All relevant studies had randomised at least 100 participants, so this sensitivity analysis did not alter the effect, but limiting the analysis to studies at low risk of compliance bias suggested little or no effect of LCn3 on PAD, and limiting analyses to studies at low summary risk of bias suggested an increase in PAD with increased LCn3 (Analysis 2.11; Analysis 2.12). The effect of LCn3 on peripheral

arterial disease is unclear – there may be increased, decreased or no effect.

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%, 55 events in > 2000 participants, 2 trials, Analysis 2.13).

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

Body weight

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

Twelve studies, 11 of which were included in meta-analysis, reported on the effect of increasing LCn3 on body weight, suggesting little or no effect in > 15,000 participants (mean difference (MD) −0.01 kg, 95% CI −0.84 to 0.82, I^2 = 49%, Analysis 2.14). Sensitivity analysis limited to studies 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 2.15; Analysis 2.16).

Subgroup analysis by intervention type, primary or secondary prevention, statin use and trial duration did not suggest important differences between subgroups (Analysis 2.19; Analysis 2.20; Analysis 2.21; Analysis 2.22). There was a marginally significant difference between dose subgroups (P = 0.06, Analysis 2.17) 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 including 261 participants, Analysis 2.17). Subgrouping by replacement suggested differences between subgroups (P < 0.001, Analysis 2.18, with reduced body weight when LCn3 replaced saturated fatty acids (SFA) or carbohydrates but increased weight when LCn3 replaced nil or low LCn3 (Analysis 2.18).

Several studies 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 these.

GRADE evidence suggests high-quality evidence that LCn3 intake makes little or no difference to body weight (high-quality/certainty evidence).

BMI

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

Fourteen trials, 12 of which were included in meta-analysis, reported on BMI, suggesting little or no effect of LCn3 on BMI (MD 0.04 kg/m^2, 95% CI −0.16 to 0.24, I^2 = 40%, > 15,000 participants, Analysis 2.23). This lack of effect was also apparent in sensitivity analyses limited to studies at low summary risk of bias (Analysis 2.24), with good compliance or with large study size (Analysis 2.25), as well as fixed-effect analysis (not shown). Subgroup analyses by primary or secondary prevention, LCn3 dose, intervention type, statin use and trial duration did not suggest important differences between subgroups (Analysis 2.26; Analysis 2.28; Analysis 2.29; Analysis 2.30; Analysis 2.31). There were significant differences between subgroups when subgrouped by replacement, suggesting lower BMI when LCn3 was replaced by SFA and carbohydrate, but increased BMI with LCn3 in other replacements (P = 0.04, Analysis 2.27).

Several studies 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.

GRADE evidence suggests high-quality evidence that LCn3 intake makes little or no difference to BMI (high-quality/certainty evidence).

Other measures of adiposity

Few studies 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 2.32).

Serum lipids (LCn3)

Several studies clearly measured lipids but did not report them in a way that we could include in our meta-analyses. These generally included Baldassarre 2006, Gill 2012, Ramirez-Ramirez 2013 and Reed 2014, plus Ahn 2016, Caldwell 2011, Franzen 1993 and Rossing 1996, which assessed but did not report triglycerides, and Franzen 1993, which measured but did not provide useable data for HDL and LDL cholesterol. For this reason missing data may potentially bias these outcomes.

Serum total cholesterol

Moderate-quality evidence shows that LCn3 intake probably makes little or no difference to serum total cholesterol.

Twenty-eight trials provided data on long-term effects of LCn3 fats on serum total cholesterol, suggesting little or no effect in more than 37,000 participants (MD −0.01 mmol/L, 95% CI −0.5 to 0.04, I^2 = 19%, Analysis 2.33). Sensitivity analyses 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 2.34; Analysis 2.35), but fixed-effect meta-analysis suggested that LCn3 reduced serum total cholesterol (MD −0.04 mmol/L, 95% CI −0.06 to −0.02, I^2 = 19%, not shown). Subgrouping by duration did not suggest any differential effects of LCn3 (Analysis 2.39). There were significant differences between subgroups by dose but no logical sequence suggesting a true dose-response effect (P = 0.03, Analysis 2.36). There were also subgroup differences for replacement and intervention type (Analysis 2.37; Analysis 2.38), with reductions in serum total cholesterol when supplemental capsules were used and when LCn3 replaced carbohydrates (Analysis 2.36; Analysis 2.37; Analysis 2.38).

GRADE assessment suggests moderate-quality evidence that LCn3 intake probably makes little or no difference to serum total cholesterol (moderate-quality/certainty evidence, downgraded once for imprecision).

Serum triglycerides

High-quality evidence suggests that LCn3 intake reduces serum triglycerides in a dose-dependent manner.

LCn3 fats significantly reduced serum triglycerides in > 35,000 participants in 23 trials (MD −0.24 mmol/L, 95% CI −0.31 to −0.16, I^2 = 48%, Analysis 2.42). This effect was not lost in sensitivity analysis excluding studies at moderate to high risk of bias, those without clear compliance or small studies (Analysis 2.43; Analysis 2.44), or using fixed-effect analysis (not shown). 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 2.46; Analysis 2.47; Analysis 2.48; Analysis 2.49; Analysis 2.50). 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 2.45).

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

HDL cholesterol

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

Twenty-seven trials including more than 37,000 participants suggested a small increase of less than 5% in serum HDL cholesterol with increased LCn3 (MD 0.02 mmol/L, 95% CI 0.00 to 0.04, P = 0.03, I^2 = 48%, Analysis 2.51). There was still a suggestion of a small HDL increase when we limited analysis to the eight studies at low summary risk of bias (MD 0.03 mmol/L, 95% CI −0.01 to 0.07, I^2 = 66%, > 14,000 participants, Analysis 2.52) where heterogeneity was very high. Limiting analyses by compliance and study size (Analysis 2.53) and in fixed-effect analysis (not shown), results suggested increases in HDL with LCn3. There were no significant differences between subgroups in any analysis except by duration, where shorter trials suggested HDL increases, with no effect in longer trials (P = 0.05, Analysis 2.57). There were no important differences between other subgroups and no suggestion of a dose-response relationship (Analysis 2.54; Analysis 2.55; Analysis 2.56; Analysis 2.58; Analysis 2.59).

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

LDL cholesterol

GRADE assessment suggests moderate-quality evidence that LCn3 intake probably makes little or no difference to LDL cholesterol.

There was little or no effect of increasing LCn3 on serum LDL cholesterol in over 35,000 participants from 23 trials (MD 0.01 mmol/L, 95% CI −0.01 to 0.03, I^2 = 0%, Analysis 2.60). This lack of effect did not alter in sensitivity analyses limited to trials at low summary risk of bias, to trials with good evidence of compliance (Analysis 2.61) , larger studies (Analysis 2.62) or in fixed-effect meta-analysis (not shown). We saw no statistically significant differences between subgroups except for with regard to statin use, where there was an increase in LDL cholesterol in nine trials where statin use was low (Analysis 2.63; Analysis 2.64; Analysis 2.65; Analysis 2.66; Analysis 2.67; Analysis 2.68).

GRADE assessment suggests moderate-quality evidence that LCn3 intake probably makes little or no difference to LDL cholesterol (moderate-quality/certainty evidence, downgraded once for imprecision).

Effects of ALA on secondary health outcomes

We did not plan any sensitivity or subgroup analyses on secondary outcomes, except for adiposity and lipids (key outcomes). 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, 9 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 studies reported that 333 out of more than 18,000 participants experienced a fatal or non-fatal MI, suggesting little or no effect of ALA on MI (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 MI subgroups (P = 0.36, Analysis 5.3).

Sudden cardiac death (ALA)

No studies 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 (RR1.41, 95% CI 0.75 to 2.64, I^2 = 0%, Analysis 5.4).

Heart failure (ALA)

No studies 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 PAD in a single study (RR 0.25, 95% CI 0.05 to 1.17, 10 of the > 13,000 participants experienced PAD, Analysis 5.6). There were insufficient data to suggest any effect of ALA on the outcome.

Acute coronary syndrome (ALA)

There were no trials assessing effects of ALA on acute coronary syndrome.

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

Low-quality evidence suggests that ALA intake may make little or no difference to BMI, but the effect of LCn3 intake on body weight is unclear as the evidence is of very low quality.

Four studies 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 fixed-effect meta-analysis suggested a slight increase in body weight with ALA (Analysis 5.8), while no studies 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 CVD (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 quality (downgraded once each for risk of bias, inconsistency 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 studies at low summary risk of bias suggested a small increase in BMI with ALA (Analysis 5.18; Analysis 5.19), while limiting to studies at low risk of compliance bias or eliminating smaller studies 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 studies giving more ALA (P = 0.03, Analysis 5.21). All included studies gave supplemental foods (Analysis 5.22). There were greater reductions in BMI in shorter studies (P = 0.02, Analysis 5.24) and in primary prevention studies (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 low-quality evidence that ALA intake may make little or no difference to BMI (low-quality/certainty evidence, downgraded once each for imprecision and inconsistency).

One study reported on visceral adipose tissue, suggesting no clear effect, but 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 studies at low summary risk of bias, not shown) removed all trials.

Serum lipids (ALA)

Serum total cholesterol

Low-quality 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 leads to a small reduction in total cholesterol, but with high heterogeneity (MD −0.09 mmol/L, 95% CI −0.23 to 0.05, I^2 = 63%, in > 2000 participants, Analysis 5.28). Restricting analyses to studies at low summary risk of bias suggested no effect of ALA (Analysis 5.30), but fixed-effect analysis suggested that the intervention led to a reduction (Analysis 5.29), as did sensitivity analyses limited to studies at low risk of compliance bias or larger studies (Analysis 5.31). All studies provided food supplements (Analysis 5.33), but subgroup analyses suggested greater reductions in total cholesterol in shorter duration studies (P = 0.02, Analysis 5.35). Other differences between subgroups resulted from effects 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-quality evidence that ALA intake may make little or no difference to serum total cholesterol (downgraded once each for imprecision and inconsistency).

Serum triglycerides

Moderate-quality evidence suggests that 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 study 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-quality evidence that ALA intake probably makes little or no difference to serum triglycerides (downgraded once for imprecision).

HDL cholesterol

Moderate-quality 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 6 trials (MD −0.02 mmol/L, 95% CI −0.08 to 0.03, I^2 = 53%, Analysis 5.48), although there were small reductions of HDL in both analyses by risk of bias and using fixed-effect meta-analysis (Analysis 5.49; Analysis 5.50) with similar effects in studies with good compliance and in larger trials (Analysis 5.51). A further trial, WAHA 2016, also measured HDL but did not provide data in a useable format for meta-analysis. There was a suggestion of greater HDL reduction with greater ALA dose (P = 0.09, Analysis 5.52), but no other subgrouping effects were evident (Analysis 5.53; Analysis 5.54; Analysis 5.55; Analysis 5.56; Analysis 5.57). GRADE assessment suggests moderate-quality evidence that ALA probably has little or no effect on HDL cholesterol (downgraded for imprecision).

LDL cholesterol

Low-quality evidence suggests that ALA intake may make little or no difference to LDL cholesterol.

There was a small reduction of LDL cholesterol with ALA in 2201 participants of 7 trials (MD −0.05 mmol/L, 95% CI −0.15 to 0.04, I^2 = 46%, Analysis 5.58), with similar effects in studies with good compliance and in larger trials (Analysis 5.61). While fixed-effect analysis suggested marginal statistical significance of this reduction (P = 0.06, Analysis 5.59), there were no effects when we limited analyses to studies at low summary risk of bias (MD 0.02 mmol/L, 95% CI −0.05 to 0.10, I^2 = 0%, Analysis 5.60). Subgrouping suggested no differences in effect by ALA dose or primary or secondary prevention (Analysis 5.62; Analysis 5.67), but shorter studies, those with unclear replacement and unclear statin use suggested reductions in LDL with ALA (Analysis 5.64; Analysis 5.65; Analysis 5.66). All studies provided supplemental foods

(Analysis 5.63). GRADE assessment suggests low-quality evidence that ALA intake may make little or no difference to LDL cholesterol (downgraded once each for risk of bias and imprecision).

Tertiary outcomes

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

We extracted these outcomes from studies 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.

Blood pressure (LCn3)

Fifteen included trials (> 34,000 participants) contributed data on effects of LCn3 fats on blood pressure. Meta-analysis suggested little or no effect of LCn3 on systolic (MD 0.02 mmHg, 95% CI −0.32 to 0.35, 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 2017), cancers including breast cancer (Hanson 2017b), neurocognitive outcomes such as dementia (Jimoh 2017), irritable bowel disease (IBD) and inflammatory factors (Thorpe 2017), depression and anxiety (Hanson 2017a), and functional outcomes (Abdelhamid 2017), so we do not present these outcomes here.

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

- Any serious adverse event (RR 1.05, 95% CI 0.78 to 1.41, I^2 NA, 126 events in > 400 participants in 1 trial).
- Bleeding (RR 1.06, 95% CI 0.73 to 1.52, I^2 = 49%, 374 events in > 45,000 participants in 8 trials).
- Gastrointestinal hospitalisation (RR 1.75, 95% CI 0.53 to 5.79, I^2 NA, 11 events in 200 participants in 1 trial).
- Pulmonary embolus or DVT (RR 1.25, 95% CI 0.41 to 3.78, I^2 = 11%, 18 events in > 3000 participants in 4 trials).
- Progression to advanced age-related macular degeneration (RR 0.96, 95% CI 0.90 to 1.02, I^2 NA, 2049 events in > 4000 participants in 1 trial).
- 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: 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%, 620 dropouts in > 16,000 participants, 23 trials).
- Increased abdominal pain or discomfort: data suggest an association with higher LCn3 (RR 1.10, 95% CI 0.84 to 1.45, I^2 = 24%, 303 events in > 14,000 participants, 7 trials).
- Diarrhoea: the data suggested an increased risk with increased LCn3 (RR 1.15, 95% CI 0.92 to 1.43, I^2 = 0%, 284 events in > 2000 participants, 10 trials).
- Nausea: risk increased with LCn3 (RR 1.76, 95% CI 1.25 to 2.48, I^2 = 0%, 140 events in > 1000 participants, 6 trials).
- Any gastrointestinal side effect: risk also appeared to increase with LCn3, albeit with very high heterogeneity (RR 1.12, 95% CI 0.94 to 1.34, I^2 = 74%, 2545 events in > 65,000 participants, 29 trials).
- Skin problems, including itching or rashes: these were not affected by LCn3 in a meta-analysis with high heterogeneity (RR 1.04, 95% CI 0.47 to 2.30, I^2 = 72%, 290 events in > 36,000 participants, 8 trials).
- Headache or worsening migraine: there were limited data on this outcome (RR 0.81, 95% CI 0.48 to 1.36, I^2 = 0%, 55 events in 996 participants, 3 trials).
- Reflux: there were limited data (RR 1.42, 95% CI 0.71 to 2.81, I^2 NA, 29 events in 202 participants, 1 trial).
- Joint lumbar and muscle pain: one study provided data suggesting that LCn3 reduced the risk of such pain (RR 0.80, 95% CI 0.64 to 0.99, 324 out of > 18,000 participants experiencing pain).
- All adverse 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 = 81%, 9534 people with at least one side effect in > 38,000 participants, 13 trials).

Dropouts (LCn3)

Included studies reported 5515 dropouts over > 31,000 participants in 30 trials, suggesting no difference in dropout rates between intervention and control arms (RR 1.02, 95% CI 0.95 to 1.09, I^2 = 11%, 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 studies 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 2017), cancers including breast cancer (Hanson 2017b), neurocognitive outcomes

such as dementia (Jimoh 2017), irritable bowel disease (IBD) and inflammatory factors (Thorpe 2017), depression and anxiety (Hanson 2017a), and functional outcomes (Abdelhamid 2017), so we do not present these outcomes here.

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

- Any serious adverse event: no data identified.
- Bleeding: no data identified.
- Gastrointestinal hospitalisation: no data identified.
- Pulmonary embolus or DVT: only one event was identified in a single study, so there were insufficient data to assess effects
- 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, I^2 NA, 26 events, > 13,000 participants, 1 trial).
- Urolithiasis: there were insufficient data to assess effects (RR 0.80, 95% CI 0.47 to 1.36, I^2 NA, 54 events, > 13,000 participants, 1 trial).

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%, 68 events, > 3000 participants, 5 trials).
- Abdominal pain or discomfort: no data identified.
- Diarrhoea: a single study 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, I^2 NA, 3 events, 110 participants, 1 trial).
- Any gastrointestinal side effect: there were insufficient data to assess effects of ALA (RR 1.79, 95% CI 0.48 to 6.69, I^2 = 69%, 46 events, > 3000 participants, 3 trials). The very 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 studies reported 558 dropouts over > 3000 participants in 6 trials, suggesting slightly higher dropout rates in participants taking higher 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 79 randomised controlled trials (112,059 participants), of which 25 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). Trials of 12 to 72 months' duration included adults at varying levels of cardiovascular risk, mainly in high-income countries. Most studies 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 long-chain omega-3 fats on risk of our primary outcomes: all-cause mortality, cardiovascular deaths, cardiovascular events, coronary heart disease deaths, coronary heart disease events, stroke or arrhythmias (moderate and high-quality evidence). For all of these outcomes except arrhythmia, limiting LCn3 analyses to trials at low summary risk of bias moved the effect size towards 1.0 (the null value) whether initial analyses suggested a protective effect (for example, for CHD mortality, whose effect size moved from RR 0.93 to RR 1.00) or a harmful effect (for example, stroke, whose effect size moved from RR 1.06 to RR 0.98). We found no suggestion of dose response (in subgrouping or meta-regression), or important effects regardless of sensitivity analysis, subgrouping or meta-regression. 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.

On the other hand we found moderate-quality evidence that increasing ALA probably reduces risk of arrhythmia (from 3.3% to 2.6%), and low-quality evidence that increasing ALA may reduce risk of CVD events a little (from 4.8% to 4.7%). However, there is probably little or no effect on all-cause or cardiovascular mortality, coronary heart disease mortality or events (low and moderate-quality evidence), and effects on stroke are unclear. For ALA, limiting analyses to studies at low summary risk of bias tended to reduce the RR, or increase the suggested protection. Data were more limited than for LCn3, and there were too few studies for informative funnel plots or subgroup analyses. These suggested benefits of ALA need to be considered with caution, as effects were small, and few trials (though often at low summary risk of bias) addressed the outcomes.

Meta-analyses suggested little or no effect of long-chain omega-3 fats or ALA intake on secondary outcomes: major adverse cerebrovascular or cardiovascular events, fatal and/or non-fatal myocardial infarction, sudden cardiac death, new or worsening angina, heart failure, revascularisation, peripheral arterial disease or acute coronary syndrome.

There was no evidence for effects of LCn3 or ALA on measures of adiposity, but LCn3 did reduce serum triglycerides by ~15% in a dose-dependant manner. We did not see this effect in trials of ALA, and no omega-3 fats altered total, HDL or LDL cholesterol in these long-term trials. Within the included studies 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 thrombotic tendency and anti-arrhythmic effects are not apparent in adult humans, but LCn3 does lower serum triglyceride levels a little.

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 CVD prevention.
  - 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, where there was a statistically significant difference between different dose subgroups and greater effects with higher 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 study summary risk of bias? Some analyses suggested a protective effect of LCn3 fats, but these effects disappeared when analyses were limited to studies at low summary risk of bias. The stronger studies with higher internal validity suggested few or no effects of LCn3 on mortality or CVD outcomes. On the other hand, for most primary cardiovascular outcomes, 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.

Overall completeness and applicability of evidence

We searched very carefully to find all studies relevant to this review and located 79 trials randomising 112,059 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. If trialists had assessed any of our outcomes, we requested data and included the study. 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 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 79 included studies (all except Baldassarre 2006; HERO 2009; Mita 2007; Nutristroke 2009; Özaydin 2011; Shinto 2014; Sofi 2010). 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.

We identified 27 trials that appeared 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 studies, and some stated that publications are forthcoming; others did not reply. We suspect that if trialists have not published outcomes, it is likely that any protective health effects did not reach statistical significance. Given that existing studies 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.

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 five provided data on EPA only (Doi 2014; JELIS 2007; Mita 2007; Nye 1990; Puri 2005). 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 studies. Of the 79 RCTs, 25 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. When sensitivity analyses removed LCn3 trials at moderate to high summary risk of bias, effect sizes moved closer to no effect (RR 1.0) for all primary outcomes except arrhythmias, where the RR rose to 1.10. Funnel plots for LCn3 trials suggested that there may be missing studies for all primary outcomes except stroke and arrhythmia, and in all cases adding such studies back in would move effect sizes closer to no effect (RR 1.0). This lack of effect in the studies at lowest risk of bias (with suggestions of effect in studies at moderate to high risk of bias) was an important finding from this review and supported our interpretation of lack of effect of long-chain omega-3 fats on our primary outcomes.

As there were fewer ALA trials, funnel plots were not useful, but sensitivity analyses retaining only trials at low summary risk of bias were more variable, often suggesting lower risk of a cardiovascular outcome.

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). Any data on bleeds, including haemorrhagic stroke, have been collated in this review, though we did not ask 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 and neurological problems within this review but have formally systematically reviewed them elsewhere (Hanson 2017b; Jimoh 2017). This approach is preferable to including data on these outcomes from within included studies, which would be incomplete and potentially underpowered to show important effects.

One problem with CVD outcomes is that they are collected together in a variety of ways, depending on the study. For example, in assessing CHD mortality, we pre-specified 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 includes 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 use individual patient data, as in one recent meta-analysis that included fewer trials than this review but was able to formulate their outcome data to match precisely between trials (Aung 2018). The next section discusses similarities and differences between this review and Aung 2018, but their findings were highly similar. For CHD mortality, our meta-analytic estimate of effect of LCn3 was RR 0.93, (95% CI 0.79 to 1.09, I^2 = 35%) in 21 trials reporting 1596 CHD deaths, while theirs was RR 0.93 (95% CI 0.83 to 1.03) in 10 trials reporting 2695 CHD 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 studies showing increased risk of CVD outcomes with omega-3 fats may be missing from some of the meta-analyses. If these studies were replaced they would tend to increase risk ratios. This suggests that there is some underlying small study bias within the review.

Given that the many LCn3 studies at moderate to high risk of bias appear to be inflating any protective effects, and that small study bias is also inflating any protective effects, it is justified to view with skepticism the occasional suggestion of a protective effect. 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.

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 studies). 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 studies 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 – the fact that we did not see them suggests that any such effects may not be important in the populations included in this review.

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 studies at low summary risk of bias. This clarified the lack of effect of LCn3 fats on CHD mortality, CHD events and heart failure, which otherwise appeared slightly protective, and on stroke, which otherwise appeared slightly harmful. On the other hand, these sensitivity analyses suggested some protective effects for ALA (on CVD events and arrhythmia), though effects were small and evidence limited.

The effect of LCn3 on arrhythmias was unclear. There was a suggestion that LCn3 was harmful regarding development of new arrhythmia (where trials were not set up with arrhythmia as a primary outcome), but protective of recurrent arrhythmia. However, trials at low summary risk of bias suggested harm, and other trials (at moderate to high risk of bias) suggested benefit. Eight of the 10 included studies at low summary risk of bias were trials assessing new arrhythmia. It is possible that the apparent difference between effects on new and recurrent arrhythmia are related to summary risk of bias.

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 adult humans, though LCn3 does appear to lower serum triglyceride levels. We did not systematically review blood pressure data so may have missed a few long-term studies (though not many) – missing data from included studies is likely to be a bigger issues. 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 2.6).

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 79 RCTs randomising more than 112,000 participants, who experienced over 8000 deaths and upwards of 4000 CVD 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 outcomes" (Balk 2016). This appears to be because the Balk review excluded RCTs of people with non-CVD and non-diabetes related diseases at baseline, while we included them. While Balk 2016 excluded some studies we included, it did not include any studies 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 112,059 participants randomised to high or low LCn3 or ALA experiencing 8648 deaths. Balk 2016 excluded studies 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 CVD, as these people tend to be elderly but there is no clear reason why omega-3 fats would affect CVD differently in this population than in other older adults at usual CVD 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 0.98 (95% CI 0.93 to 1.03, $I^2 = 6\%$), 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 CVD found no associations of LCn3 with CHD mortality (RR 0.93, 99% CI 0.83 to 1.03), nonfatal MI (RR 0.97, 99% CI 0.87 to 1.08), CHD 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 their 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, but the disadvantage of missing all the data from many large LCn3 trials such as DART2 2003 DART 1989 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 results of this review and Aung 2018 are also very similar (Table 8). LCn3 has little or no effect on major cardiovascular outcomes. This review, Balk 2016 and Aung 2018 addressed the analysis of the data in slightly different ways, creating sensitivity analyses for each other. The fact that they came to the same conclusions reassures us that our conclusions are solidly based.

Our results, suggesting high-quality evidence of no clinically useful cardiovascular health effects of either LCn3 or ALA, are consistent with many further high-quality recent systematic reviews (Campbell 2013; Chowdhury 2012; Enns 2014; He 2013; Khoueiry 2013; Kotwal 2012; Kwak 2012; Mariani 2013; Rizos 2012; Zheng 2014), and they confirm and expand on the findings of earlier versions of this review (Hooper 2004; Hooper 2006).

AUTHORS' CONCLUSIONS

Implications for practice

We found high-quality evidence that long-chain omega-3 fats do not have important positive or negative effects on mortality or CVD events and moderate-quality evidence that they have little or no effect on other measures of cardiovascular health in primary or secondary prevention. Most evidence on long-chain omega-3 fats came from trials of capsules of fish oil or EPA/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.

We found moderate-quality evidence that increasing ALA probably slightly reduces risk of CHD mortality and arrhythmia, and may slightly reduce risk of CVD events. However, there is probably little or no effect on all-cause or cardiovascular mortality or coronary heart disease events (low and moderate-quality evidence). Effects of ALA were very small - 143 people would need to increase their ALA intake to prevent one person developing arrhythmia, and 1000 would need to take more ALA to prevent one person experiencing a CVD event or dying from CHD. Trials of ALA gave ALA-rich or enriched foods such as walnuts or enriched margarine.

Supplemental long-chain omega-3 fats are probably not useful for preventing or treating cardiovascular disease, although long-chain omega-3 fats can help to reduce serum triglycerides and raise HDL a little. 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.

ALA is an essential fatty acid, an important part of a mixed diet, and increasing intakes may be very slightly beneficial for prevention or treatment of cardiovascular disease.

Implications for research

There are several large ongoing trials of supplemental long-chain omega-3 fats (see Characteristics of ongoing studies). We suggest that given the lack of convincing 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. Further large and high-quality 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

ADCS 2010 *(Continued)*

	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 less than 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) per day for a total daily dose of 2 g, each capsule contain 45% to 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 per day (made up of corn or soy oil) Compliance: measured by pill counts at every visit Length of intervention: 18 months
Outcomes	Main study 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) Available outcomes: mortality, measures of cognition, baseline & change in plasma DHA, adverse events Response to contact: no data provided
Notes	Study 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 fatty acids, 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, study coordinators, and site physicians.

ADCS 2010 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	The adequacy of blinding was assessed by questionnaires completed by caregivers, study coordinators, 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	Intention-to-treat analysis. At 12 months data were available for > 80% (ITT analysis)
Selective reporting (reporting bias)	Low risk	Prospectively registered February 2007, study 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 study 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-center study to evaluate the effect of n-3 fatty acids on arrhythmia recurrence in atrial fibrillation (AFFORD) 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, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers Medications taken by some, but < 20%: none Location: Canada Ethnicity: not reported
Interventions	Type: supplement (fish oil)

AFFORD 2013 *(Continued)*

	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 study Duration of intervention: 6 to 16 months
Outcomes	Main study 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	Authors contacted about QoL, resource use and dietary habits Study 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
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, transient ischemic attacks, 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 quality of life, 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

Ahn 2016 *(Continued)*

	Summary risk of bias: moderate to high
Participants	Statin treated CAD patients undergoing PCI 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 less than 20% of the control group: rosuvastatin, nitrates, calcium antagonists Location: South Korea Ethnicity: not reported
Interventions	Type: supplement (capsule) Comparison: EPA + DHA vs unclear (nil) Intervention: 3 g of ω-3 PUFA containing 1395 mg of EPA and 1125 mg of DHA per day. No further details. 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 study 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	Study funding: the study 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

Ahn 2016 *(Continued)*

Allocation concealment (selection bias)	Low risk	Participants were assigned randomisation numbers sequentially on recruitment to the study, and the randomisation codes were retained by the clinical research coordinator.
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 fatty acid levels reported
Other bias	High risk	It's unclear whether the study 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 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 less than 20% of the control group: antiarrythmic drugs, antidiabetic drugs Location: the Netherlands

AlphaOmega - ALA 2010 *(Continued)*

	Ethnicity: not reported
Interventions	Type: supplementary margarine Comparsion: ALA vs MUFA Intervention 20 g of enriched margarine per day incorporating: 2 g ALA. 8 × 250 g margarine tubs delivered every 12 weeks. Dose: average achieved +1.9 g/d ALA Control: 20 g of margarine per day. No additional n-3 PUFAs. Identical margarine (oleic acid) placebo. Compliance: unused margarine tubs were returned- daily intakes of margarine and n-3 fatty acids were calculated on the basis of the amount unused. Adherence was measured by levels of fatty acids in plasma cholesteryl esters, margarine and questionnaires. 90.5% of patients adhered to the protocol and consumed 20.6 (SD 2.8) g of margarine/d. Length of intervention: 40 months
Outcomes	Main study outcome: cardiovascular disease events Dropouts: 91 died, 98 discontinued intervention, 93 died, 93 discontinued control Available outcomes: deaths, MI, cardiovascular events, ventricular arrhythmia, Incident cardiovascular disease Response to contact: yes (data provided)
Notes	The study has 3 intervention arms (ALA margarine, EPA/DHA margarine, mixture of the two interventions). This table represents the ALA only intervention. Outcome data is used for the ALA group where reported separately or for the combined (ALA arm, ALA + EPA/DHA arm) Study funding: Netherlands Heart Foundation, National Institutes of Health and Unilever R&D (latter provided unrestricted grant for distribution of trial margarines)

Risk of bias

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 patients were followed up for events computerised linkage with municipal registries. 2531 patients were only followed up for baseline anthropometric and medical measurements.
Selective reporting (reporting bias)	High risk	Sudden cardiac death endpoint omitted. Registered in August 2005, recruitment was from 2002 to 2006. Outcomes papers published in 2010

AlphaOmega - ALA 2010 *(Continued)*

Attention	Low risk	All participants appear to have had similar frequency and quantity of attention and follow-up
Compliance	Low risk	Unused margarine tubs were returned; daily intakes of margarine and n-3 fatty acids were calculated on the basis of the amount unused. Adherence was measured by levels of fatty acids in plasma cholesteryl esters, margarine and questionnaires. 90.5% of patients adhered to the protocol and consumed 20.6 (SD 2.8) g of margarine/d
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 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 less than 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 of enriched margarine per day incorporating 400 mg EPA-DHA (240 mg EPA and 160 mg DHA). Dose: average achieved 376 mg/d EPA + DHA Control: 20 g of margarine per day. No additional n-3 PUFAs. Identical margarine (oleic acid) placebo Compliance: unused margarine tubs were returned; daily intakes of margarine and n-3 fatty acids were calculated on the basis of the amount unused. Adherence was measured by levels of fatty acids in plasma cholesteryl esters, margarine and questionnaires. 90.5% of patients adhered to the protocol. Length of intervention: 40 months
Outcomes	Main study outcome: cardiovascular disease events Dropouts: 95 died, 119 discontinued intervention, 93 died, 93 discontinued control

AlphaOmega - EPA+DHA 2010 *(Continued)*

	Available outcomes: deaths, MI, cardiovascular events, ventricular arrhythmia, incident cardiovascular disease Response to contact: yes (data provided)
Notes	The study has three intervention arms (ALA margarine, EPA/DHA margarine, mixture of the two 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) Study funding: Netherlands Heart Foundation, National Institutes of Health and Unilever R&D (latter provided unrestricted grant for distribution of trial margarines)

Risk of bias

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 patients were followed up for events computerised linkage with municipal registries. 2531 patients were only followed up for baseline anthropometric and medical measurements.
Selective reporting (reporting bias)	High risk	Sudden cardiac death endpoint omitted. Registered from August 2005, recruitment was from 2002 to 2006. Outcomes papers published in 2010
Attention	Low risk	All participants appear to have had similar frequency and quantity of attention and follow-up
Compliance	Low risk	Unused margarine tubs were returned; daily intakes of margarine and n-3 fatty acids were calculated on the basis of the amount unused. Adherence was measured by levels of fatty acids in plasma cholesteryl esters, margarine and questionnaires. 90.5% of patients adhered to the protocol and consumed 20.6 (SD 2.8) g of margarine/d
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

AREDS2 2014 *(Continued)*

	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 less than 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). Compliance: assessed by pill count – 84% of participants in each group took at least 75% of study medications Length of intervention: 60 months
Outcomes	Main study outcome: development of advanced AMD Dropouts: 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, cardiovascular death, MI, stroke, angina, heart failure, revascularisation, cognition, eye health, (authors provided data on diabetes diagnosis, depression diagnosis, breast cancer) Response to contact: yes (data provided)
Notes	Study funding: National Eye Institute/National Institutes of Health, Department of Health and Human Services

Risk of bias

Bias	Authors' judgement	Support for judgement

AREDS2 2014 *(Continued)*

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 study eligibility was verified. The assigned bottle number was used to distribute the study treatment(s). AREDS2 Coordinating centre personnel involved in creating the randomisation system had access to the bottle number/treatment assignments.
Blinding of participants and personnel (performance bias) 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 coordinating centre randomly assigned the event to a study adjudicator, who made the final determination of these study endpoints through review of the medical records and applying the endpoint criterion defined a priori. All adjudicators were masked to study 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, study coordinators, and all other study personnel are masked to treatment assignment, so attention bias not feasible
Compliance	Unclear risk	Assessed by pill count – 84% of participants in each group took at least 75% of study medications
Other bias	Low risk	None noted

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 N: 32 intervention, 32 control Level of risk for CVD: moderate 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

Baldassarre 2006 *(Continued)*

	Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but less than 20% of the control group: not reported (patients 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 fatty acid 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 three 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 study 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	Study 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) All outcomes	Unclear risk	Double-blind and placebo capsules were opaque and identical looking to intervention. However no information provided on capsules taste or smell
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 be-

Baldassarre 2006 *(Continued)*

		cause 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 multiple sclerosis 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 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)

Bates 1989 *(Continued)*

Outcomes	Main study outcome: multiple sclerosis 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	Study 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 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

Berson 2004 *(Continued)*

	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 less than 20% of the control group: not reported Location: USA Ethnicity: unclear (6% of the study 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 study 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	Study 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 patients were masked to group assignment
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 study 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)	Unclear risk	Numbers of dropouts and reasons for dropouts not stated. 221 participants randomised, data presented on 208 participants

Berson 2004 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	No trials registry entry or protocol found.
Attention	Low risk	Staff in contact with patients 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

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	Subjects with moderate hypercholesterolaemia N: 40 seal oil (SO), 40 cod liver oil (CLO), 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 less than 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): CLO dose: EPA + DHA 3.3 g/d Control: nil, no supplement Compliance: serum omega-3 fatty acids, rose from around 1 mmoL/L to 2.4 (seal oil), 2.1 (cod liver oil) and 1.2 mmoL/L (control) Length of intervention: 14 months
Outcomes	Main study outcome: serum lipids

Brox 2001 *(Continued)*

	Dropouts: 8 seal oil, 2 cod liver oil, 1 control Available outcomes: total and cardiovascular deaths, MI, combined CV events, lipids, adverse events Response to contact: yes (author provided methodological details)
Notes	Data of two intervention groups combined for dichotomous outcomes and CLO vs control data used for continuous outcomes Study funding: the study 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 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 study protocol or trials register entry was found
Attention	Low risk	No suggestion of differential attention
Compliance	Low risk	Serum omega-3 fatty acids, rose from around 1 mmoL/L to 2.4 (seal oil), 2.1 (cod liver oil) and 1.2 mmoL/L (control)
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 (non-alcoholic steatohepatitis) 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 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 less than 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 identical placebo (soybean) capsules per day 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 study 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, cardiovascular 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. Study funding: study was supported by NIH NCCAM Grant 5R21AT2901–2 and 5 M01 RR00847. Study medication and identical appearing placebo was provided at no charge by Nordic Natural. RBC phospholipid profile was performed by Metametrix (www.metametrix.com). M30, M65, adiponectin, and IGF-

Caldwell 2011 *(Continued)*

BP-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 subjects were blinded to therapy assignment throughout the study period. Both capsules were identical. However no information provided on capsules taste or smell
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 myocardial infarction 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

DART 1989 *(Continued)*

	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 Control: No such dietary advice or capsules Compliance: 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 **Dietary achievements** Total fat intake, %E (through study): 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 study): control 15 (SD 3), intervention 11 (SD 3), (MD −4.00, 95% CI −4.26 to −3.74); significant reduction PUFA intake (through study), %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 study), %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 study), %E: control 44 (SD 6),intervention 46 (SD 7) (MD 2.00, 95% CI 1.43 to 2.57); significant increase Protein intake (through study), %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 study outcome: total mortality, reinfarction, CHD death Dropouts: none for mortality Available outcomes: total and CV deaths, MI, CHD events, lipids, blood pressure, cancer deaths 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.

DART 1989 *(Continued)*

	Study funding: by the Welsh Scheme for the Development of Health and Social Research, the Welsh Heart Foundation and the Health Promotion, Research Trust. Seven Seas Health Care and Duncan Flockhart provided Maxepa capsules

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomised" confirmed by 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) All outcomes	High risk	Blinding of dietary advice (or lack of it) is not possible
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were not aware of study 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 study protocol or trials register entry was found
Attention	High risk	More attention was paid to those given dietary advice
Compliance	Unclear risk	7 day weighed food diary of a random sub-sample indicated intake of 2.5 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 capsulesn-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

DART2 2003 *(Continued)*

	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 less than 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) 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: none 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 to 108 months
Outcomes	Main study outcome: total mortality Dropouts: none for mortality Available outcomes: total and CV deaths, sudden death, stroke, heart failure, cancer deaths 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. Study funding: probably British Heart Foundation, Seven Seas Ltd, Novex Pharma Ltd and the Fish Foundation (these were acknowledged)

DART2 2003 *(Continued)*

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
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were not aware of study 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 study protocol was found, or trials registry entry
Attention	High risk	More attention was paid to those given dietary advice
Compliance	Unclear risk	Postal dietary questionnaire suggested dietary EPA intake increased by 2.4 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 patients with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) 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

Derosa 2016 *(Continued)*

	Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but less than 20% of the control group: not reported Location: Italy Ethnicity: white
Interventions	Type: capsule (n-3 PUFA) Comparison: EPA + DHA vs CHO + SFA Intervention: 3 ×1 g capsule/ day n-3 PUFAs (ethylic esters, each 1-g capsule of n-3 PUFAs contains highly concentrated ethyl esters of omega-3 fatty acids, primarily 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) Both groups were given diet advice to follow a controlled-energy diet based on AHA recommendations (50% of calories from carbohydrates, 30% from fat (6% saturated), and 20% from proteins, with a maximum cholesterol content of 300 mg/day and 35 g/day of fibre). Individuals were also encouraged to increase their physical activity by walking briskly for 20 to 30 min, 3 to 5 times per week, or by cycling Compliance: measured by counting the number of pills returned at the time of specified clinic visits Length of intervention: 18 months
Outcomes	Main study outcome: insulin resistance Dropouts: 23 across arms (no details on groups but stated that there were no difference between groups) Available outcomes: mortality, CV mortality, CHD event, stroke, combined CVD events, MI, AF, weight, BMI, lipids, diabetes mellitus Response to contact: yes (data provided)
Notes	Study funding: "The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties"

Risk of bias

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	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 study. 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

Derosa 2016 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	An intention-to-treat analysis was conducted for patients who received 1 dose of study medication
Selective reporting (reporting bias)	Unclear risk	No trial registry or protocol found
Attention	Low risk	No difference reported
Compliance	Unclear risk	Measured by counting the number of pills returned at the time of specified clinic visits
Other bias	Low risk	None noted

Deslypere 1992

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 less than 20% of the control group: not reported (no medications influencing lipid metabolism or non-steroidal anti-inflammatory drugs were allowed) Location: the Netherlands Ethnicity: not reported
Interventions	Type: capsules Comparsion: LCn3 vs MUFA Intervention 9 capsules (9 g vol.) per day, 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

Deslypere 1992 *(Continued)*

	Length of intervention: 12 months
Outcomes	Main study outcome: effect on coronary risk factors Dropouts: none Available outcomes: deaths (nil), CVD events (nil), lipids, BP, HbA1c, weight (measured but only text suggests "no significant changes in the anthropometric parameters (weight, length, waist, hip and thigh circumferences) during the study"), 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	Study funding: capsules supplied by Labaz (Brussels Belgium). The placebo capsules contained olive oil (Puget) and palm oil (Loders-Kroklaan, Wormerveer). Financial support by Sanofi-Labaz. Data entered for high fish oil versus placebo groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (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 (author states that the fishy taste was clear in the intervention capsules)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	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 nil), 24 months

DIPP 2015 *(Continued)*

	Summary risk of bias: moderate or high
Participants	Patients 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 Medications taken by 20%-49% of those in the control group: none Medications taken by some, but less than 20% of the control group: oral contraceptive pills Location: Japan Ethnicity: not reported
Interventions	Type: advice + supplement (fish oil capsules) Comparison: EPA + DHA + ALA vs omega-6 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/day (equivalent to 96 mg/day of EPA and 360 mg/day of DHA). Dose: 456mg/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 fatty acid concentrations, fatty acid 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 study outcome: number and size of colorectal tumours Dropouts: 3 intervention, 5 control Available outcomes: all cause mortality, dietary intake, plasma fatty acids, lipids, side effects, glucose Response to contact: yes (methodological details provided)
Notes	Study funding: all were either government or charity grants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly allocated using random digit number for allocation of participants

DIPP 2015 *(Continued)*

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
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 nil), 12 months Summary risk of bias: moderate or high
Participants	People presenting for first treatment of acute/persistent atrial fibrillation or flutter, confirmed by ECG N: intervention 201, control 206 Level of risk for CVD: high (patients with atrial fibrillation) 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: antiarrythmics, antithrombotics

DISAF 2003 *(Continued)*

	Medications taken by some, but less than 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 to 3 portions of oily fish per week (providing up to 10 g LCn3/ week), plus 2 to 3 portions of fruit and vegetables per day. Dose: 1.4 g/d EPA + DHA. Control: dietary assistants gave advice and support to eat 2 to 3 portions of fruit and vegetables per day. No other health/lifestyle given as part of the trial Compliance: assessed red blood cell fatty acids and found some increases in EPA and DHA in intervention compared to control (no further intake data) Length of intervention: 12 months
Outcomes	Main study outcome: sinus rhythm after 12 months Dropouts: unclear Available outcomes: deaths, AF recurrence Response to contact: yes (data provided)
Notes	Study 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 to 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.

DISAF 2003 *(Continued)*

Compliance	Low risk	Assessed red blood cell fatty acids 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 study) 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 less than 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 incl 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 inc 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 study outcome: atherosclerosis progression. Dropouts: intervention 14 died, 20 others discontinued, control 24 died, 18 others discontinued Available outcomes: mortality, cardiovascular deaths, CHD events, CV events, MI, stroke, diabetes, glucose, lipids, cancer diagnosis, cancer deaths, sudden death, BMI (waist circumference reported as median, IQR)

DO IT 2010 *(Continued)*

	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. Study funding: Norwegian Cardiovascular Council, Norwegian retail company RIMI, vegetable oil and margarine supplied by the Norwegian food company Mills DA and placebo capsules by LUBE

Risk of bias

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
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 n-6 LA), 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

Dodin 2005 *(Continued)*

	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 less than 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) 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: first morning urine collection was performed at randomisation and at month 12 to measure urinary lignin levels. In addition, study participants recorded their daily intake of seeds on diary cards and were asked to return unused bread and packages of seeds at each visit. Good compliance reported Duration of intervention: 12 months
Outcomes	Main study outcome: bone mineral density Dropouts: 26 intervention, 17 control (but 13/17 had an endpoint evaluation) Available outcomes: weight, BMI, QoL, blood pressure, lipids, glucose, adverse events, dietary intake, plasma fatty acids Response to contact: yes
Notes	Auhors replied to tell us that there were no deaths or CV events during the study Study 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 study. 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

Dodin 2005 *(Continued)*

		seeds were provided on a 3-month basis. The foods that both groups received was similar in appearance and packaging and was kept frozen until consumption to avoid essential fatty acid
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, investigators, staff, and statisticians were blinded to dietary assignments for the duration of the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis. Loss to follow-up 10%, reasons given
Selective reporting (reporting bias)	Unclear risk	No protocol or clinical trial registry entry found
Attention	Low risk	All participants had same number of visits
Compliance	Low risk	First morning urine collection was performed at randomisation and at month 12 to measure urinary lignin levels. In addition, study participants recorded their daily intake of seeds on diary cards and were asked to return unused bread and packages of seeds at each visit. Good compliance reported
Other bias	Low risk	None noted

Doi 2014

Methods	RCT, parallel, (n-3 EPA vs nil), 12 months Summary risk of bias: moderate or high
Participants	Patients having PCI 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 less than 20% of the control group: none Location: Japan Ethnicity: not reported
Interventions	Type: supplement (EPA) Comparison: EPA vs nil

Doi 2014 *(Continued)*

	Intervention: purified EPA ethyl esters (> 98%) 1800 mg EPA/day within 24 hours after PCI plus statins. Dose: 1.8 g/d EPA Control: statins with no EPA Compliance: not reported Length of intervention: 12 months
Outcomes	Main study outcome: cardiovascular events Dropouts: 1 intervention, 2 control Available outcomes: mortality, stroke, MI, sudden death, CV death, revascularisation Response to contact: no
Notes	Study funding: trial registry state "self-funded". The 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

EPE-A 2014

Methods	EPE-A RCT, parallel, 3 arms (n-3 EPA, low dose vs high dose vs unclear placebo), 12 months

EPE-A 2014 *(Continued)*

	Summary risk of bias: moderate or high
Participants	People with non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD) N: 86 intervention-high, 82 int low, 75 control (analysed 64, 55, 55 respectively, ITT analysis for primary outcomes) Level of risk for CVD: low (although 35% had type II diabetes) 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 less than 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) 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 study 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

EPE-A 2014 *(Continued)*

Study 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 study 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. 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, study 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 first version of clinicaltrials.gov entry)
Attention	Low risk	All participants had same follow-up visits.
Compliance	Low risk	Compliance was estimated by pill count and measuring the ratio of serum EPA to arachidonic acid. Compliance rates for the 3 groups (placebo vs EPA-E 1800 mg/d vs EPA-E 2700 mg/d) were 89.5% (6.8%), 90.3% (5.7%) and 89.5% (5.3%) respectively
Other bias	Low risk	None noted

EPIC-1 2008

Methods	EPANOVA in Crohn's disease, study 1 (EPIC-1) RCT, parallel, 2-arm (omega 3 vs MCT), 52 weeks Summary risk of bias: moderate or high
Participants	Adults with quiescent Crohn's disease (CDAI) score < 150 N: 188 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

EPIC-1 2008 *(Continued)*

	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 less than 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 (medium chain triglycerides of short SFAs) Intervention: 2 × 2 1 g gelatin capsules omega-3 free fatty acids (Epanova- 2.2 g EPA, 0.8 g DHA). Dose: 3 g/d EPA + DHA Control: 4 x1 g capsules medium chain triglycerides Compliance: pill counts, 79.2% adhered intervention, 75.6% adhered control Length of intervention: mean 52 weeks
Outcomes	Main study outcome: Crohns 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	Study funding: Tillotts Pharma, 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	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	Study 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.

EPIC-1 2008 *(Continued)*

Selective reporting (reporting bias)	High risk	Trials registration (NCT00613197) first received in 2008, but study 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 MCT), 58 weeks Summary risk of bias: moderate or high
Participants	Adults with a confirmed diagnosis of Crohn's Disease and a Crohn's Disease Activity Index (CDAI) score < 150 who are responding to steroid induction therapy N: 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 Medications taken by at least 50% of those in the control group: systemic corticosteroids – prednisolone, budesonide (but tapered and discontinued during the study) Medications taken by 20%-49% of those in the control group: only reported for prior 12 months Medications taken by some, but less than 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 (medium chain triglycerides of short SFAs) Intervention: 2 × 2 1 g gelatin capsules omega-3 free fatty acids (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 medium chain triglyceride 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 study outcome: maintain Crohns symptomatic remission Dropouts: 114 intervention, 112 control Available outcomes: mortality, CV events (nil), cancer diagnoses, adverse events Response to contact: yes (data provided)

EPIC-2 2008 *(Continued)*

Notes	Study funding: Tillotts Pharma, 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	Study 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, study start 2002. Published 2008. Some outcomes, such as quality of life, 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 patient interviews and pill counts, 75.4% adhered intervention, 81.4% adhered control
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 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

EPOCH 2014 *(Continued)*

	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 less than 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 three-monthly intervals, plus self-report calendars, mailed back on a monthly basis. If compliance fell below 85% (re calendars), they were contacted by a researcher who noted the reasons. Compliance also assessed by erythrocyte membrane n-3 LC PUFA status Length of intervention: 18 months
Outcomes	Main study outcome: change in cognitive performance Dropouts: not reported Available outcomes: mortality (nil), MI, stroke, revascularisation, arrhythmias, CV events Response to contact: yes (data provided)
Notes	Authors reported some events, but don't appear to be published. Study funding: EPAX donated the Omega-3 concentrate and Blackmores Pty Ltd donated the placebo and packaging of the Omega-3 concentrate. The trial was supported by the Brailsford Robertson Award 2007-2008 (University of Adelaide and CSIRO Food and Nutritional Sciences), and is funded by a National Health and Medical Research Project Grant (#578800).

Risk of bias

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 study investigators), 1:1 allocation. Computer-generated randomisation schedule
Allocation concealment (selection bias)	Low risk	An independent researcher prepared allocation to treatment
Blinding of participants and personnel (performance bias) 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

EPOCH 2014 *(Continued)*

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; blood pressure; 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 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 less than 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

Erdogan 2007 *(Continued)*

	Control: described only as "placebo"
	Compliance: not reported
	Length of intervention: 12 months
Outcomes	Main study outcome: atrial fibrillation 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
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 (ICDs)

FAAT 2005 *(Continued)*

	N: intervention 200, control 202 Level of risk for CVD: high (patients with ICDs). 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 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 study outcome: fatal ventricular arrhythmias Dropouts: intervention 13 deaths, unclear no. of dropouts, control 12 deaths, dropouts unclear Available outcomes: deaths, cardiovascular deaths, CVD events, deaths from heart failure, fatal arrhythmias, MI, angina Response to contact: yes (data provided)
Notes	Study funding: the study 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	Author confirmed allocation was concealed from investigators

FAAT 2005 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study 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. Author confirmed that investigators and patients 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 study 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 mixed fat), 12 months 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 less than 20% of the control group: insulin or blood sugar-lowering drugs Location: Canada

FLAX-PAD 2013 *(Continued)*

	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 fatty acid ALA were used as markers of dietary compliancy Length of intervention: 12 months
Outcomes	Main study outcome: all-cause mortality, cardiovascular mortality, stroke, and myocardial infarctions Dropouts: 15 intervention, 11 control Available outcomes: blood pressure, lipids, adverse events, plasma ALA Response to contact: yes (but no data provided)
Notes	Different intervention dropout figures reported in two publications (13 or 15) Study 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
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, of which group the subject 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, study 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

FLAX-PAD 2013 *(Continued)*

Other bias	Low risk	None noted

FORWARD 2013

Methods	Randomized trial to assess efficacy of PUFA for the maintenance of sinus rhythm in persistent atrial fibrillation (FORWARD) RCT, parallel, (n-3 EPA + DHA vs MUFA), 12 months Summary risk of bias: low
Participants	Patients with paroxysmal atrial fibrillation 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 less than 20% of the control group: none reported Location: Argentina Ethnicity: not reported
Interventions	Type: supplement (capsule) Comparison: EPA + DHA vs MUFA Intervention: one capsule/ day containing 1 g of n-3 PUFA (Societá Prodotti Antibiotici and SigmaTau, Italy) (provided 850 mg to 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 study outcome: survival free of atrial fibrillation Dropouts: 20 intervention, 25 control Available outcomes: mortality, MI, AF, heart failure, stroke, hospitalisation, side effects. Authors supplied further info on CVD events and methodology Response to contact: yes

FORWARD 2013 *(Continued)*

Notes	Study funding: through unrestricted grants provided by companies that supplied study 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 study location
Allocation concealment (selection bias)	Low risk	As above, centrally allocated. Communication from 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, study start January 2008, completion August 2011. All outcomes in trials registry appear to have been reported.
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

FOSTAR 2016 *(Continued)*

	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 Vit. D ~ 32% Medications taken by some, but less than 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 study oil Length of intervention: 24 months
Outcomes	Main study outcome: change in pain scale of WOMAC index Dropouts: 18 intervention, 16 control Available outcomes: mortality, CVD events, adverse events, analgesic use, bone marrow density, weight gain and serum fatty acids Response to contact: yes
Notes	Data on quality of life and pain score are presented in a figure and not in a usable format Study 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 one pharmacy and then used to allocate and administer the oil at each site

FOSTAR 2016 *(Continued)*

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 study, 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 study.
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 quality of life 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 study 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 coronary heart disease 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 less than 20% of the control group: not reported Lipid lowering medications were not allowed Location: Germany

Franzen 1993 *(Continued)*

	Ethnicity: not reported
Interventions	Type: fish oil capsules Comparison: EPA + DHA vs MUFA Intervention: 9 × 1 g capsules/day of fish oils (20% EPA, 15% DHA, 3.15 g/day total omega 3). Dose: 3.15 g/d EPA + DHA Control: 9 × 1 g capsules/day 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 study 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 fatty acids Response to contact: yes
Notes	Study 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) All outcomes	Unclear risk	No further details beyond stating "double blind"
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 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 less than 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 Length of intervention: 12 months
Outcomes	Main study outcome: change in carotid IMT Dropouts: unclear Available outcomes: lipids, insulin and glucose are stated as secondary outcomes but no usable data published Response to contact: no
Notes	Results cannot be used as numbers are not reported by study arm. Study funding: unclear, but mentions that Pfizer, NIH and "Northwest Lipids Clinic" are partners

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details

Gill 2012 *(Continued)*

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 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
Participants	Patients 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, statin Medications taken by some, but less than 20% of the control group: ARBs, other antiplatelets, calcium channel blockers, amiodarone

GISSI-HF 2008 *(Continued)*

	Location: Italy Ethnicity: unclear
Interventions	Type: supplement (capsule) Comparison: EPA + DHA vs MUFA Intervention:1 capsule per day 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 study outcome: time to death or admission to hospital for cardiovascular reasons Dropouts: 34 intervention, 46 control (1004 intervention and 1029 control stopped study treatment) Available outcomes: mortality, CV mortality, MI, stroke, new heart failure, incident AF, resumed arrhythmia gatalitis Response to contact: yes (no data provided)
Notes	Study 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
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) 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

GISSI-HF 2008 *(Continued)*

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) myocardial infarction N: 5666 intervention, 5658 control (99.9% follow-up at study 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 less than 20% of the control group: lipid lowering Location: Italy Ethnicity: not reported
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 study Duration of intervention: median follow-up 40 months
Outcomes	Main study outcome: all cause mortality, CV mortality, stroke, MI Dropouts: unclear (however, all randomised were included in analyses) Available outcomes: total, sudden and CV deaths, MI, stroke, angioplasty or CABG, angina, CHD, cancer diagnosis, cancer death, combined CV events, side effects Response to contact: no

GISSI-P 1999 *(Continued)*

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. Study 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 coordinating 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 study protocol or trials registry entry was found
Attention	Low risk	Slight as no placebo, otherwise similar
Compliance	Unclear risk	Capsule counts, 11.6% had stopped taking Omacor by 12 months, 28.5% by the end of the study
Other bias	Low risk	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	Patients with coronary heart disease N: 41 intervention, 39 control (99.9% follow-up at study 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

HARP 1995 *(Continued)*

	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 less than 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/day (Promega, Parke-Davis) in divided doses, preferably after meals. Each fish oil capsule contained 500 mg of n-3 polyunsaturated fatty acids composed of EPA (240 mg), DHA (160 mg) and other (100 mg) (mainly DPA) providing total daily dose of 6 g of n-3 fatty acids. 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 fatty acids in the fish oil group. Duration of intervention: average 28 months
Outcomes	Main study 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	Study 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

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

HARP 1995 *(Continued)*

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

HERO 2009

Methods	Healthy Eating to Reduce Overweight in people with type 2 diabetes (HERO) RCT, parallel, (n-3 ALA vs low n-3), 12 months Summary risk of bias: moderate or high
Participants	Overweight adults with non-insulin treated diabetes 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 less than 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 fatty acid levels which were similar in both groups Duration of intervention: 12 months

HERO 2009 *(Continued)*

Outcomes	Main study 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 Study 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

JELIS 2007 *(Continued)*

	N: intervention, 9326, control 9319 (analysed intervention 9326, control 9319)
	Level of risk for CVD: moderate (Patients 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 less than 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 patients in both groups were on statins.
	Compliance: monitored by local physicians and measuring plasma fatty acids concentrations. Study 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 study 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	Study 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 coordinating centre (see above)

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 to 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 fatty acids concentrations. Study 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	Patients with persistent atrial fibrillation (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 less than 20% of the control group: not reported Location: Australia

Kumar 2012 *(Continued)*

	Ethnicity: not reported
Interventions	Type: fish oil capsule Comparison: EPA + DHA vs nil Intervention: 6 capsules/day of a fish oil preparation containing a total dose of 1.02 g of EPA and 0.72 g DHA. Participants in the omega-3 group were asked to continue fish oils till a maximum of 1 year or till return of persistent AF. Dose: 1.7 g/d EPA + DHA Control: no supplements. Patients were advised not to take any fish oil supplements. All patients underwent cardioversion following randomisation. Compliance: was monitored on a weekly basis via telephone and during follow-up by using a pill count plus serum EPA and DHA levels which were significantly increased Duration of intervention: 1 year (or AF recurrence)
Outcomes	Main study outcome: atrial fibrillation 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	Study funding: the study 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	Patients 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.

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	Patients > 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: statin, renin-angiotensin system inhibitors Medications taken by 20%-49% of those in the control group: anti-arrhythmic drugs Medications taken by some, but less than 20% of the control group: not reported Location: Australia Ethnicity: not reported
Interventions	Type: omega 3 capsule Comparison: EPA + DHA vs nil Intervention: a triglyceride preparation containing a total of 6 g/day of omega-3 polyunsaturated fatty acids of which 1.8 g/day were n-3 (1.02 g EPA and 0.72 g DHA). Dose: 1.8 g/d EPA + DHA Control: no supplements Compliance: measured by weekly dietary history and pill count. Fatty acid status measured at randomisation and between 1-3 months post randomisation (blood samples). Duration of intervention: median 378 days
Outcomes	Main study outcome: atrial fibrillation 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	Study funding: unclear

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 patients.
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

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 patients, among compliant patients, 18 were censored (for not using the medication for 3 continuous weeks) Duration of intervention: 12 months
Outcomes	Main study outcome: Crohn's disease duration of remission Dropouts: unclear Available outcomes: mortality (nil), Crohn's disease activity and relapses, serum triglycerides Response to contact: yes (methodological details provided)
Notes	There was a third arm of dietary advice (for low CHO diet) Study 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 six (block size blinded to the centres)
Allocation concealment (selection bias)	Low risk	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". 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 study (relapses), however 20% omitted from analyses and numbers confusing

Lorenz-Meyer 1996 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No trials registry entry or protocol found
Attention	Low risk	All patients 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 patients, among compliant patients, 18 were censored (for not using the medication for three 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 ± multidomain intervention), 36 months Summary risk of bias: low
Participants	Population: people aged at least 70 years without dementia but with memory complaint, IADL limitation or slow gait speed N: 840 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 less than 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 caps). 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 caps) plus multi-domain intervention (nutrition, physical exercise, cognitive stimulation, social activities)

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 study interventions was assessed every 6 months. For supplementation, adherence was assessed by counting the number of capsules returned by participants (or based on treatment dates if the number of capsules was missing). Furthermore, biological samples were obtained at baseline and after 12 months to assess concentrations of DHA and EPA in red blood cell membranes. Duration of intervention: 36 months
Outcomes	Main study 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	Study funding: Gérontopôle of Toulouse, the French Ministry of Health (PHRC 2008, 2009), the Pierre Fabre Research Institute (manufacturer of the polyunsaturated fatty acid 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 polyunsaturated fatty acids), the multidomain intervention plus placebo, polyunsaturated fatty acids 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 study staff were blinded to polyunsaturated fatty acid or placebo assignment – both sets of capsules looked and tasted identical. In view of the nature of the multidomain intervention, the study 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 study staff were blinded to polyunsaturated fatty acid or placebo assignment—both sets of capsules looked and tasted identical. In view of the nature of the multidomain intervention, the study 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 two data managers, one statistician (CC) and two 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 intention-to-treat population (N = 1525), i.e. 155 excluded (9% over 3 years)

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 study 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 study (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 or more CVD risk factors N: total 282 randomised; 114 intervention (51 with nutrition education, 58 without NE) 157 control (52 with NE, 105 without NE) Level of risk for CVD: moderate (multiple cardiovascular risk factors, 10-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 ad libitum. Dose: average intake 6.3 g/d ALA (was also 1 g/d ALA in the control group).

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 vit E/g, 9 micro-g vit A/g and 0.023 micro-g vit D/g Comparison: ALA vs omega 6 Compliance: serum fatty acids used to assess, ALA rose by 0.47 mol % (SD 0.04) and 0.36 mol% (SD 0.04) intervention arms (with and without NE) and fell by 0.06 mol % (SD 0.04) and 0.11 mol % (SD 0.03) control arms (with and without NE), significantly different. Duration of intervention: 24 months
Outcomes	Main study outcome: cardiovascular 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	Study 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 coordination centre that organised masked distribution of margarines
Allocation concealment (selection bias)	Low risk	Allocated by an independent trial coordination centre which 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 one publication clarifies (55 randomised to each arm, 51 intervention and 52 control analysed).
Selective reporting (reporting bias)	Unclear risk	No study 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 study staff than the control group, and some (not quite randomly allocated) were sent individual motivational letters (Siero 2000).
Compliance	Low risk	Serum fatty acids used to assess, ALA rose by 0.47 mol% (SD 0.04) and 0.36 mol % (SD 0.04) intervention arms (with and without NE) and fell by 0.06 mol % (SD 0.04) and 0.11 mol % (SD 0.03) control arms (with and without NE), Significantly different
Other bias	Low risk	No further bias noted

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 less than 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/day 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 per day (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 @ base-line, 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 study outcome: endothelial function, arterial stiffness Dropouts: 38 intervention (13,13,12), 17 control

MARINA 2011 *(Continued)*

	Available outcomes: lipids, dietary intake, CRP, BP (supine and ambulatory – numeric data not provided, but study states that there were no significant differences between arms). Weight data not used as 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 authors: yes (many outcomes above provided in end of study report from authors)
Notes	Outcome data used G3 (highest dose) vs placebo for continuous outcomes and combined the 3 intervention groups vs placebo for dichotomous outcomes Study 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)

MENU 2016 *(Continued)*

	RCT, parallel, (walnut rich moderate fat diet vs moderate fat diet), 12 months Summary risk of bias: moderate or high
Participants	Overweight and obese women, of whom half were insulin resistant 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 (NR) intervention, 50 (NR) 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 less than 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 study), 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 study outcome: body weight Dropouts: 13 of 82 intervention, 12 of 81 control Available outcomes: weight, waist circumference, HDL and LDL cholesterol, triglycerides, insulin, glucose, HOMA-IR, HOMA-beta, CRP and IL-6 (estradiol, SHBG, nutrient gene interactions, physical activity and heart rate also presented) Response to contact: no reply received to date
Notes	Study funding: National Cancer Institute and California Walnut Commission
Risk of bias	

MENU 2016 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation stratified by age and insulin resistance
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study, 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 type 2 diabetics 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 less than 20% of the control group: antithrombotics

Mita 2007 *(Continued)*

	Location: Japan 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 study 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	Blood pressure data not used as groups are different at baseline Study funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients 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 study 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

Mita 2007 *(Continued)*

Other bias	Low risk	None noted

NAT2 2013

Methods	Nutritional AMD Treatment-2 (NAT2) RCT, parallel, (EPA + DHA vs MUFA), 36 months Summary risk of bias: low
Participants	Patients with early age related macular degeneration 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 study arm) Medications taken by at least 50% of those in the control group: lipid-lowering medication Medications taken by 20%-49% of those in the control group: agents acting on renin-angiotensin system, anti-inflammatory and anti-rheumatic products Medications taken by some, but less than 20% of the control group: insulin or blood sugar lowering drugs Location: France Ethnicity: unclear
Interventions	Type: supplement (fish oil capsule) Comparison: EPA + DHA vs MUFA Intervention: 3 daily fish oil capsules containing 1110 total n-3 FAs (EPA: 270 mg/day DHA: 840 mg/day) and vit E: 6 mg/day. Dose: 1.1 g/d EPA + DHA Control: 3 × 602 mg olive oil capsules a day containing 0.2 g total PUFA and vit 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 study outcome: time to occurrence of choroidal new vessels (CNV) in the study 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)

NAT2 2013 *(Continued)*

Study funding: Laboratoire Chauvin, Bausch & Lomb Inc

Risk of bias

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. The patients and the study personnel both 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	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 study protocol. Discontinuation for more than 5 months was considered to be a major deviation from the study protocol. Participants who dropped out were taken in account in the survival analysis and occurrence of CNV 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 spend with both study 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	Patients with persistent atrial fibrillation 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

Nodari 2011 AF *(Continued)*

	Hypertension: 47% intervention, 40% control Medications taken by at least 50% of those in the control group: beta-blockers, ACE inhibitors, anticoagulant therapy, amiodarone Medications taken by 20%-49% of those in the control group: diuretics, antiplatelet, statins Medications taken by some, but less than 20% of the control group: calcium channel blockers Location: Italy Ethnicity: 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 to 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 study 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	Study 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 patient 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 were accounted for. ITT analysis for main outcomes

Nodari 2011 AF *(Continued)*

Selective reporting (reporting bias)	Unclear risk	NCT01198275. Registered retrospectively in September 2010, study started January 2006, completed May 2008, main publication 2011
Attention	Low risk	No difference between groups
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 less than 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 to 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). Fatty acid EPA + DHA 0.83% in intervention group, 0.41% in control group. Duration of intervention: 12 months
Outcomes	Main study outcome: left ventricular function and functional capacity Dropouts: 0 intervention, 0 control

Nodari 2011 HF *(Continued)*

	Available outcomes: mortality (nil death), combined CVD events, AF, BMI, hospitalisation for cardiovascular reasons, hospitalisation for worsening heart failure, lipids, blood glucose (but too different at baseline to use), serum cytokine Response to contact: yes
Notes	Study funding: Centro per lo Studio ed il Trattamento dello Scompenso Cardiaco, one author was a consultant for 8 pharmaceutical companies

Risk of bias

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 study was double blind, but blinding of participants not checked. Author confirmed investigators not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	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 – study registration October 2010, recruitment November 2007 to 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	Patients 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

Norouzi 2014 *(Continued)*

	Age range: 15-74 years intervention, 30-74 years control Smokers: 0% (exclusion criteria) 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 less than 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) per day. Dose: 1 g/d DHA + EPA Control: 2 placebo capsules per day. Both capsules were similar in colour, shape, and taste. Both groups received one calcium capsules per day consisting of 1000 mg calcium and 400 IU vitamin D. Compliance: pill counts – compliance averaged 80% in both groups Duration of intervention: 14 months
Outcomes	Main study outcome: professionals evaluation of neurological function Dropouts: 1 intervention, 5 control Available outcomes: functional measures (total and sub-scales), BMI, leptin and adiponectin concentration. Response to contact: no
Notes	Study 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 study 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

Norouzi 2014 *(Continued)*

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"
Selective reporting (reporting bias)	High risk	Some of the outcomes stated in the trial register are not reported. Registered March 2011, study 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 less than 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 study outcome: morbidity and mortality

Norwegian 1968 *(Continued)*

	Dropouts: survival status was traced for all but 4 included men, health status was missing for about 80 men in total or 0.6%. Available outcomes: total and CV deaths, MI, angina, stroke, peripheral vascular disease, combined CV events, total cholesterol (subgroup) Response to contact: no
Notes	Study 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 study were followed up for survival and morbidity via the main health system
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registration found
Attention	Low risk	As company physicians administered oils and assessed outcomes but were blind to treatment arm there could not be attention bias
Compliance	Unclear risk	73% were still taking the linseed oil at 1 year, 72% were still taking their sunflower oil at 1 year (unclear how this was ascertained)
Other bias	Low risk	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

Nutristroke 2009 *(Continued)*

	Men: 74% intervention, 56% control 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 less than 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 study outcome: functional status in stroke survivors Dropouts: 6 intervention, 14 control Available outcomes: mortality and cardiovascular 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 study that also had an antioxidant supplementary focus (supplementary vitamins C and E, beta carotene and polyphenols) Study 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

Nutristroke 2009 *(Continued)*

		supplements during the study". However, only one placebo discussed and unclear whether it was a placebo capsule (for omega 3) or pill (for antioxidants)
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 less than 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

Nye 1990 *(Continued)*

	Compliance: no data Length of intervention: 12 months
Outcomes	Main study outcome: angina, restenosis Dropouts: none Available outcomes: angina, interventions, lipids (Nil death) Response to contact: no
Notes	Study 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 patients 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	Patients recruited 4-8 days after confirmed MI

OFAMI 2001 *(Continued)*

	N: 150 intervention, 150 control 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: b-blockers, aspirin Medications taken by 20%-49% of those in the control group: statins, ACE inhibitors Medications taken by some, but less than 20% of the control group: diuretics, warfarin Location: Norway Ethnicity: unclear
Interventions	Type: supplement (capsules) Comparison: EPA + DHA vs omega 6 Intervention: 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 study outcome: CV events Dropouts: unclear Available outcomes: total and CV deaths, MI, unstable angina, interventions, combined CV events, BMI, lipids, BP (authors provided additional data on glucose, AF, stroke) Response to contact: yes
Notes	Study funding: Pharmacia-Upjohn and Pronova

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned" – Pharmacia was responsible for randomisation. Author response: participants were randomised in blocks of 4
Allocation concealment (selection bias)	Low risk	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

OFAMI 2001 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	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 fatty acids 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 have had an acute myocardial infarction 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, vit 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

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 study 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, authors supplied information on angina, depression, cancers, AF Response to contact: yes
Notes	Study 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 patients and physicians to deduce the study 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 pre-specified 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 study arms.
Selective reporting (reporting bias)	Low risk	NCT00251134 registered in 2005. Study start date: 2003, Completed: 2008, study 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 polyunsaturated fatty acid (OPAL) 2 arm, parallel, RCT, 12 months Summary risk of bias: low

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 fatty acids, 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) • α-linoleic: intervention 21.5 (0.8); control 22.0 (0.9) Length of intervention: 24 months
Outcomes	Main study outcome: delayed onset of cognitive decline Dropouts: control: 78 (8 died, 53 withdrew, 17 discontinued intervention but provided data); 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	Study funding: UK Food Standards Agency, NHS R&D provided support costs
Risk of bias	

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 study. 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 study began. Protocol published 2006. Publication of first results 2010. Many outcomes, such as depression and BP were stated in trials registry entry but not reported.
Attention	Low risk	All participants had the same review schedule, and staff were unaware of assignments
Compliance	Low risk	Count returned capsules. Capsules not returned (intervention - median: 0.95; IQR: 0.82, 1.00; control - median: 0.95; IQR: 0.81, 1.00). Fasting serum fatty acids, 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). α-linoleic: 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, (capsule of n-3 fatty acids or placebo), 72 months
	Summary risk of bias: low
Participants	People at high risk of CV events with impaired fasting glucose, impaired glucose tolerance or diabetes
	N: 6319 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

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 less than 20%: thiazide diuretics, anticoagulant Location: 40 study locations in Europe and the Americas Ethnicity: unclear
Interventions	Type: supplement capsule (Omacor) Comparison: EPA + DHA vs MUFA Intervention: 1 gelatin capsule/d Omacor containing at least 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 study outcome: composite of the First Occurrence of Cardiovascular (CV) Death, Nonfatal Myocardial Infarction (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 versus standard care, and is not discussed here. Results are reported here for the trial duration and not the follow-up post trial (the ORIGIN and Legacy Effects, ORIGINALE). Study funding: 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	Study described as "double blind" and placebo described as identical. Blinding of patients, investigators, local and central trials personnel described. However, no information provided as to the capsule's smell and taste

ORIGIN 2012 *(Continued)*

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"
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, study started August 2003, final data collection December 2011. Most outcomes appear to have been reported in various publications (cardiovascular events only reported by glargine randomisation).
Attention	Low risk	No suggestion of differences between groups
Compliance	Unclear risk	Methods of assessment unclear, but reported that "rates of adherence to the study-drug regimen were similar in the two groups with 96% of patients continuing to receive the study drug at 1 year ... and 88% at the end of the study"
Other bias	Low risk	None noted

ORL 2013

Methods	Omega-3 fatty acids randomised long-term (ORL) RCT- parallel, 3 arms (TAK-085 2 g, TAK-085 4 g, and EPA-E 1.8 g), 12 months Summary risk of bias: moderate or high
Participants	Population: Japanese adults with hypertriglyceridaemia 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 less than 20%: not reported Location: Japan Ethnicity: unclear
Interventions	Type: supplement (TAK-085 capsules) Comparison: EPA + DHA higher vs lower dose

ORL 2013 *(Continued)*

	Intervention: 1 × 2/d capsule each containing 2 g of TAK-085 (1 g of fatty acid 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 fatty acid 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 Compliance: monitored every 4 weeks, mean rate of compliance reported as > 96% in each group Length of intervention: 12 months
Outcomes	Main study outcome: safety outcomes and adverse events Dropouts: group 1: 8, group 2: 14, group 3 (not analysed): 21 Available outcomes: adverse events (including CVD events, cancers), CRP, waist circumference, weight, blood pressure (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 third arm of EPA-E 1.8 g supplementation is not used here. Outcome data used TAK-4 vs TAK-2 Study 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, study start date November 2009, completion November 2011, so partially retrospective. However, entry appears to reflect reported outcomes.
Attention	Low risk	Capsules, appears 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
Participants	Patients with rheumatoid arthritis < 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 per week) Medications taken by 20%-49% of those in the control group: NSAIDS Medications taken by some, but less than 20% of the control group: oral or parenteral steroids Location: Australia Ethnicity: 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 study outcome: disease-modifying anti-rheumatic drugs (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 Study funding: National Health Medical Research Council of Australia and Royal Adelaide Hospital Research Committee. Melrose Health provided support for ongoing studies. The oil was made by the Royal Adelaide Hospital Pharmacy

Proudman 2015 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
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 study 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 study was retrospectively registered – registered in 2013, recruitment began in 2001
Attention	Low risk	No difference between groups
Compliance	High risk	Consumption checked at each visit. 100% compliance would be consumption of 3650 mL oil at 12 months. The fish oil group was less compliant than the control group with median intakes of 2482 mL (68%) and 3248 mL (89%), respectively (P = 0.015, Mann-Whitney U test). This provided an average daily intake of EPA + DHA of 3.7 g and 0.36 g in the fish oil and control groups, respectively
Other bias	Low risk	None noted

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

Puri 2005 *(Continued)*

	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: antidepressants Medications taken by some, but < 20%: neuroleptics Location: UK, USA, Canada, Australia 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/day 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 study 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	Study 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)	High risk	Clearly reported and complete, however > 20% attrition

Puri 2005 *(Continued)*
All outcomes

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 ventricular tachycardia or ventricular fibrillation (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 less than 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 study outcome: time to first episode of VT/VF

Raitt 2005 *(Continued)*

	Dropouts: 17 intervention, 26 control Available outcomes: deaths, CV death, MI, angina, revascularisation, arrhythmias, sudden cardiac death, cancer Response to contact: yes but no data provided
Notes	Study 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	ICD 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, study carried out from February 1999 to January 2004. Most outcomes stated in registry entry reported, but quality of life 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 multiple sclerosis 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)

Ramirez-Ramirez 2013 *(Continued)*

	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 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 less than 20% of the control group: not reported Location: Mexico Ethnicity: not reported
Interventions	Type: supplement Comparison: DHA + EPA vs sunflower oil 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 study 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	Study 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.

Ramirez-Ramirez 2013 *(Continued)*

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"
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

Reed 2014

Methods	RCT, parallel, 3 arms (fish oil or borage oil), 18 months Summary risk of bias: low
Participants	Adults with rheumatoid arthritis 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: methotrexate, DMARDs, and TNF blockers Medications taken by 20%-49% of those in the control group: corticosteroids and TNF blockers Medications taken by some, but less than 20% of the control group: 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 gm EPA:1.4 gm 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

Reed 2014 *(Continued)*

	Compliance: assessed by capsule counts and patient report. Patient report, indicates that 45% of patients reported ever missing a dose (borage: 42%, fish 48%). Median total capsules missed (excluding those with 0) were 182 (borage: 164, fish 169) Duration of intervention: 18 months
Outcomes	Main study outcome: RA modified disease activity score Dropouts: 25 intervention, 28 control Available outcomes: mortality (nil death), CVD events (nil), DAS score, CDAI score. 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 diastolic BP 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 author response, so not useable Response to contact: yes, authors supplied details of methodology but no usable outcome data
Notes	A third arm (45 participants) were given a combination of both oils but not discussed here. Study funding: National Institutes of Health Grant RO1-AT000309 from the National Center for Complementary and Alternative Medicine

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	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 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	Author confirmed outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Authors mention intention-to-treat analysis but shows completers analysis. Numbers of participants are not provided for all outcomes measured. Provide 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	Study prospectively registered in 2003, estimated study completion November 2008, published in 2014. Both outcomes reported in registry are reported in the publication.
Attention	Low risk	All patients were evaluated at 3-month intervals, by the same examiner.
Compliance	Unclear risk	Assessed by capsule counts and patient report. Patient report, indicates that 45% of patients reported ever missing a dose (borage: 42%, fish 48%). Median total capsules missed (excluding those with 0) were 182 (borage: 164, fish 169)
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 cardiovascular risk factors 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 Medications taken by 20%-49% of those in the control group: ACE inhibitor; ARB; diuretic agent; calcium-channel blocker; beta-blocker; oral hypoglycaemic drug; statin; antiplatelet agent Medications taken by some, but less than 20% of the control group: insulin Location: Italy Ethnicity: not reported
Interventions	Type: supplement (n-3 capsules) Comparison: EPA + DHA vs MUFA Intervention: 1 g/d n-3 capsules polyunsaturated fatty acid ethyl esters (EPA and DHA content 850-882 mg with an average ratio of 1.0 to 1.2). 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 study outcome: composite of time to death from cardiovascular causes or hospital admission for cardiovascular 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. 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.

Risk & Prevention 2013 *(Continued)*

	Study 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.
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 gastrointestinal) 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 study. Differences in groupings of cardiovascular events in tables 2; S4 and S5. For hospital admissions notes each patient could have more than one cardiovascular cause
Attention	Unclear risk	Does not state attention differs or is the same between groups- regularly see GP for follow-up 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

Rossing 1996 *(Continued)*

	Summary risk of bias: moderate or high
Participants	Adults with insulin-dependant diabetes mellitus, diabetic nephropathy and normal BP 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 less than 20% of the control group: not reported 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/day. 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 study 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 diastolic BP too different at baseline to include, GFR, PAI1, TPA, fibrinogen, etc. not relevant) Response to contact: yes
Notes	Study 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."

Rossing 1996 *(Continued)*

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. Intention-to-treat analysis appears to have been given for albuminuria only
Selective reporting (reporting bias)	Unclear risk	No trials registry entry or protocol found
Attention	Low risk	Time and attention appear to be the same. All patients were given dietary advice.
Compliance	Low risk	Reports significantly higher omega 3 levels in platelets at 12 months for the intervention group
Other bias	Low risk	None noted

Sandhu 2016

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 less than 20% of the control group: not reported Location: USA

Sandhu 2016 *(Continued)*

	Ethnicity: not reported
Interventions	Type: supplement (n-3 capsules) Comparison: EPA + DHA vs nil Intervention: group 4, Lovaza 4 g per day. 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 fatty acids 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 study outcome: change in breast density Dropouts: 5 intervention, 6 control Available outcomes: cardiovascular events, breast cancer, lipids, dietary intake, plasma FAs, adverse events (including one incidence of hyperglycaemia) Response to contact: yes
Notes	The study had 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 is combined for groups 4 and 5 vs 1 and 3 for binary outcomes and group 1 vs 4 used for continuous outcomes Study 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

Sandhu 2016 *(Continued)*

Selective reporting (reporting bias)	High risk	Biomarkers of oxidative stress (Urinary 8-(isoprostane) F-2α and 8OHdG, Lymphocyte 8-OHdG, DNA etheno adducts), Urinary 2-OHE1, 4-OHE1, and 16α-OHE1, Serum level of C-reactive protein and IL-6, Serum level of IGF-I and IGF-BP-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 fatty acids 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 fatty acids (SCIMO) 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 blood pressure) Medications taken by at least 50% of those in the control group: platelet inhibitors, beta-blockers Medications taken by 20%-49% of those in the control group: long-term nitrate therapy, lipid-lowering agents, ACE inhibitors, diuretics, calcium antagonists, other antihypertensive agents and digitalis. Medications taken by some, but less than 20% of the control group: nitrates only on demand Location: Germany Ethnicity: not reported
Interventions	Type: supplement (capsule) Comparison: EPA + DHA vs SFA + MUFA (average European fat composition) Intervention: concentrated fish oil capsules, 6x 1 g capsules/d for first 3 months, 3 × 1 g/d for rest of study (4 g/d EPA +DHA + DPA + ALA for first 3 months, then 2 g/d). Dose: ˜2 g/d LCn3 Control: capsules containing fat which replicated the fat composition of the average European diet, 6/d for first 3 months, 3/d for rest of study, opaque soft gelatin capsules identical to fish capsules in identical screw-top containers

SCIMO 1999 *(Continued)*

	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 study 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 Study funding: Pronova provided capsules and funds for study monitoring but it was stated that the funders played no part in analysis or publication

Risk of bias

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. Patients 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 cardiovascular 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 study trials register entry or protocol was found
Attention	Low risk	As study 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

Shinto 2014

Methods	RCT, parallel (fish oil capsule vs soybean oil capsule), 12 months Summary risk of bias: moderate to high
Participants	Patients aged 55 or more 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 less than 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/day of fish oils (975 mg EPA, 675 mg DHA per day). Dose: 1.65 g/d EPA + DHA Control: 3 × 1 g capsules/day soybean oil (which contains 5% fish oil) Both groups had a placebo lipoic acid tablet and lemon-flavoured capsules Compliance: assessed by pill counts and FA in red blood cell membranes. Results showed increased EPA + DHA levels in the intervention group. Length of intervention: 12 months
Outcomes	Main study outcome: F2-isoprostane levels (oxidative stress measure) Dropouts: 2 intervention, 2 control Available outcomes: mortality, CVD events, adverse events, serum fatty acids, measures of cognition (ADAS Cog and MMSE), ADL, IADL (also F2 isoprostane) Response to contact: not attempted
Notes	Study 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

Shinto 2014 *(Continued)*

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, study 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
Participants	People admitted for coronary bypass grafting 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 less than 20% of the control group: not reported Location: Norway

SHOT 1996 *(Continued)*

	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 to 257 mg/L at 9 months) and fell in the control group (170 to 169 mg/L at 9 months) Length of intervention: 12 months
Outcomes	Main study outcome: CABG graft patency Dropouts: 15 intervention, 14 control Available outcomes: deaths, CV deaths, MI, stroke, repeat CABG, combined CV events, lipids, side effects Response to contact: yes
Notes	The study had 4 arms; aspirin; warfarin; fish oil + aspirin; and warfarin + fish oil. The first 2 groups are combined as the control and the last two combined as intervention. Dietary assessment suggested total diet plus supplement intakes as follows: 2.7 g/d EPA + DHA at baseline, 5.5 g/d at 9 months intervention, 2.5 g/d at baseline, 2.2 g/d at 9 months control group Study 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
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 study personnel were aware of assignments. However, author suggested in personal communication that participants were not aware of their assignments.
Blinding of outcome assessment (detection bias) 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 study protocol or trials register entry was found
Attention	Low risk	Appeared equivalent between arms

SHOT 1996 *(Continued)*

Compliance	Low risk	Capsule count, 88% taken, serum EPA + DHA rose in the intervention group (176 to 257 mg/L at 9 months) and fell in the control group (170 to 169 mg/L at 9 months)
Other bias	Low risk	No further bias noted

Sianni 2013

Methods	RCT, parallel, (fish oil vs placebo), 12 months Summary risk of bias: moderate or high
Participants	Patients with hypertension and paroxysmal or persistent atrial fibrillation (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 less than 20% of the control group: not reported Location: Greece Ethnicity: not reported
Interventions	Type: supplement Comparison: fish oil vs unclear placebo Intervention: omega-3 fatty acids with no further details. Dose: 4 g/d omega Control: placebo, no further details Compliance: no details Duration of intervention: 12 months
Outcomes	Main study outcome: AF recurrence and BP Dropouts: no details Available outcomes: new AF episodes, BP (not in a usable format) Response to contact: no
Notes	Study funding: unclear The study's only publication was a conference abstract.

Sianni 2013 *(Continued)*

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

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 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

SMART 2013 *(Continued)*

	Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but less than 20% of the control group: 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 fatty acid supplements (capsules), but results not reported Duration of intervention: 12 months
Outcomes	Main study 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 cardiovascular events occurred (authors report) Response to contact: authors provided data on CVD events (none) and mean/SD data for TGs and fasting insulin
Notes	To assess effects of omega 3 fats the best comparison in this study is fish + S vs fish, so numerical data reflect this comparison. Study funding: Australian National Health and Medical Research Council, fish and olive oil capsules were provided free by Blackmores Australia

Risk of bias

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"

SMART 2013 *(Continued)*

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 intention-to-treat analyses carried out
Selective reporting (reporting bias)	High risk	We were unable to find data on 24 hour energy expenditure, oxidation or heart rate which were stated as primary and secondary outcomes in the trials registry.
Attention	Unclear risk	While dietary education was for 1 hour then 6 further half hour follow-ups plus written materials and monthly newsletters plus dietary interviews it is not clear whether this was in all arms or only some of them.
Compliance	High risk	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 fatty acids × 100 was significantly different for the fish oil supplemented group compared to the two others – but it was only measured in around half of the participants as the others dropped out, so presumably were non-compliant.
Other bias	Low risk	None noted

SOFA 2006

Methods	Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA) 2 arm, parallel RCT (n-3 EPA + DHA vs MUFA), 12 months Summary risk of bias: low
Participants	People with previous ventricular arrhythmias and implantable cardioverter defibrillators 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 and older) Smokers: 16% intervention, 8% control Hypertension: 53% intervention, 49% control Medications taken by at least 50% of those in the control group: beta-blockers

SOFA 2006 *(Continued)*

	Medications taken by 20%-49% of those in the control group: lipid lowering, antiarrythmic medications (combined) Medications taken by some, but less than 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 patients in the fish oil group and 218 in the placebo took more than 80% of their capsules. N-3 fatty acid composition in serum cholesterol levels was measured at baseline and the end of the trial. The EPA concentration in serum cholesterol esters increased in the expected range. No data provided Length of intervention: 12 months
Outcomes	Main study outcome: spontaneous ventricular tachyarrhythmias 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, cardiovascular events, side effects Response to contact: yes but no data provided
Notes	Study funding: Wageningen Centre for Food Sciences (alliance of major Dutch food industries and others)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients using beta-blockers were separately randomised in blocks of 2. A computer randomisation programme randomly took the first treatment of a block. The second patient 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 containing capsules labelled with medication numbers that are unidentifiable for patients as well as investigators. Fish oil and placebo capsules have identical appearance. Difference can't 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 patients who dropped out due to non-compliance.

SOFA 2006 *(Continued)*

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 patients in the fish oil group and 218 in the placebo took more than 80% of their capsules. N-3 fatty acid composition in serum cholesterol levels was measured at baseline and the end of the trial. The EPA concentration in serum cholesterol esters increased in the expected range. No data provided
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	Non-alcoholic fatty liver disease patients 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 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 less than 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 study outcome: fatty liver status

Sofi 2010 *(Continued)*

	Dropouts: unclear Available outcomes: lipids, glucose, insulin, HOMA, (BMI not in usable format, also LFTs, oxidative markers, adiponectin, fatty liver and steatosis outcomes) Response to contact: not yet attempted
Notes	Study 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
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 placebo, also B vitamin comparison), 4 years Summary risk of bias: low
Participants	People with a history of MI, unstable angina or ischemic 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

SU.FOL.OM3 2010 *(Continued)*

	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 study outcome: composite of myocardial infarction, cerebral vascular ischemic accident or cardiovascular 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, cardiovascular death, non fatal MI, stroke, CV events, coronary events, cancer events, Geriatric Depression Scale score, 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-terahydrofolate, 3 mg B-6, 20 µg B12) vs placebo Study 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 coordinating 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.

SU.FOL.OM3 2010 *(Continued)*

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 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 Age range: unclear (18 years and older) 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 less than 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

Tande 2016 *(Continued)*

	Control: identical capsules of olive oil. Compositional analysis indicated that the fatty acid content of the olive oil was primarily oleic acid (76.9%), palmitic acid (10.2%), and linoleic acid (7.7%). Compliance: assessed through the return of unused capsules. Compliance rate reported for both intervention and placebo groups was good (86-88%) Length of intervention: 12 months
Outcomes	Main study outcome: safety of Calanus oil consumption Dropouts: 14 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 author reply) Response to contact: author replied with methodological and event information
Notes	Study 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 as the intervention group. However, no information provided as to their smell and taste. Also unclear if investigators were blinded. Author reply stated "Each study subject was given a randomization number, which carried the name of the person, date of birth and treatment information (intervention or control). The randomization number was the only information made available to the study personnel, and the code was managed by personnel outside the research department. This code was broken after the completion of all analysis with all primary data processed." Blinding of 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

Tande 2016 *(Continued)*

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, 24 months Summary risk of bias: moderate or high
Participants	Recent survivors of first myocardial infarction (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 angiotensin receptor blockers. 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) Intervention: Mediterranean style diet high in n-3. Dietary counselling group sessions; two in first month then at months 3, 6, 12 and 24. Sessions focused on behaviour modification and practical aspects of assigned diet including recipes, shopping and dining out. 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/day); the Mediterranean-style diet was distinguished by greater omega-3 fat intake (> 0.75% kcal). Compliance: participants were required to attend six sessions and only invited but not required to attend extra sessions. 3-day food diaries were reviewed with dietitians. Compliance results not stated. **Dietary achievements:** Total fat intake, % E (at 24 months): control 29.7 (SD 9.3), intervention 29.1 (SD 8.6)

THIS DIET 2008 *(Continued)*

	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 study 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 diabetes mellitus, BMI and weight (different at baseline hence not used), waist circum, lipids, blood pressure, albuminuria, CRP, creatinine and dietary intake (authors supplied further data on newly diagnosed DM, glucose and insulin data, cancers, depression, atrial fibrillation) Response to contact: yes further data supplied as above
Notes	The study compared the 2 intervention groups to a non-randomised usual care control group (not reported here) Study funding: no funding details is provided but some reported conflict of interests for an 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 coordinator. Assignment was stratified by diabetes mellitus status using 10-envelope blocks. Envelopes were selected in the prepared order from a locked drawer by a study dietitian to assign interventions
Allocation concealment (selection bias)	Unclear risk	As above but opacity of envelopes is not stated.
Blinding of participants and personnel (performance bias) 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),

THIS DIET 2008 *(Continued)*

		publication 2008. A number of the outcomes from the registration were not reported e.g. cardiovascular 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

WAHA 2016

Methods	The Walnut and Healthy Aging Study (WAHA) 2-arm, parallel RCT (usual diet plus walnuts vs usual diet), 2 years Summary risk of bias: moderate to high
Participants	Middle-aged healthy adults N: 362 intervention, 346 control (only preliminary data on 312 participants from one of the two 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 less than 20% of the control group: not reported Location: Spain and USA Ethnicity: not reported
Interventions	Type: supplement (food) Comparison: ALA vs unclear 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

WAHA 2016 *(Continued)*

	Compliance: assessed by dietitians through FFQs, recount of empty packages, and changes in FAs concentrations. 95% consumed at least 30 g/d. The proportion of α-linolenic acid 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 study 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"). 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: authors provided additional outcome and methodology data.
Notes	Study 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 one centre (USA)

Risk of bias

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 study were treated as one number and were randomized into the same group".
Allocation concealment (selection bias)	Low risk	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	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

WAHA 2016 *(Continued)*

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 multiple sclerosis 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 Hypertension: not reported Medications taken by at least 50% of those in the control group: all patients received 400 units of vitamin E, one multivitamin tablet (not containing any PUFA) and at least 500 mg calcium per day Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but less than 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 daily, moderate fat diet (< 30% total calories) (American Heart Association 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 fatty acid 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 study outcome: physical component scale (PCS) Dropouts: 3 intervention, 7 control

Weinstock-Guttman 2005 *(Continued)*

	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	Study 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
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, (Omacor or placebo), 15-18 months Summary risk of bias: low
Participants	Patients with NAFLD N: 51 intervention, 52 control (analysed, 47 intervention, 48 control) Level of risk for CVD: moderate

WELCOME 2015 *(Continued)*

	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 less than 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 per day (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/ day (providing; ALA1%, oleic acid 67%, palmitic acid 15%, stearic acid 2%, n-6 fat: 15%) Compliance: was assessed by recording the returned unused capsules and quantification of erthrocyte EPA + DHA enrichment (a prespecified threshold of 2% for DHA & threshold of 0.7% for EPA enrichment) Duration of intervention: 15-18 months
Outcomes	Main study outcome: changes in mean liver fat %, changes in 2 liver fibrosis scores, change in serum biomarkers Dropouts: 4 intervention, 4 control Available outcomes: weight, BMI, lipids, blood pressure, glucose, insulin sensitivity, body fat measures, liver enzymes, HbA1c, serum n-3 FAs, authors provided details of diabetes diagnoses, % body fat, BP and carotid intima media thickness Response to contact: yes
Notes	Study 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 fatty acid 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).

WELCOME 2015 *(Continued)*

		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)
Allocation concealment (selection bias)	Low risk	Participants were block randomised by an independent clinical trials pharmacist to treatment with identical capsules by mouth of either n-3 fatty acid ethyl esters (4 g/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 study members throughout the trial. (McCormick-2015, p 2).
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 study members throughout the trial. However, the trial register record states "single blind (investigator)". Although the capsules were identical, no information provided as to their smell and taste
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	The ITT analysis included all patients randomised who had complete data (baseline and end-of-study measurements), regardless of whether they were later found to be ineligible, a protocol violator, given the wrong treatment allocation, or never treated) (Scorletti 2014, p 4)
Selective reporting (reporting bias)	Unclear risk	Prospectively registered September 2008, study start September 2009, end February 2017. Outcome data for cardiac function not yet published, though other cardiovascular 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 study 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 study 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)

Zhang 2017 *(Continued)*

	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 less than 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 Control: corn oil, orange-flavoured and orange colour to protect the study blind Compliance: participants were asked to return any remaining tablets. Compliance was defined as a ratio (actually taken/should have taken). Achieved 97% for intervention, 95% for control. Serum levels of DHA also measured, DHA at 6 months barely higher in intervention than in controls Duration of intervention: 12 months
Outcomes	Main study 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	Study 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 study 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 study blind . Packaged into identical pots, each containing 180 capsules, and labelled by staff who were not involved in the study. A blinding key linked each participant to his or her assigned treatment. This key was kept by an investigator not involved in any

Zhang 2017 *(Continued)*

		data collection or analyses, in a secure electronic file. The code was revealed at the completion of the trial following analyses of the main study 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 patients, 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
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	Patients with persistent atrial fibrillation (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 patients 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 less than 20% of the control group: calcium antagonists

Özaydin 2011 *(Continued)*

	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 study 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	Study funding: unclear

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; **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; **CDAI**: Clinical Disease Activity Index; **CHD**: coronary heart disease; **CHO**: carbohydrate; **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; **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; **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; **IBD**: inflammatory bowel disease; **IADL**: instrumental activities of daily living; **ICAM-1**: intercellular adhesion molecule 1; **IL**: interleukin;**IMT**: immune-mediated thrombocytopenia; **IQR**: interquartile range; **LCn3**: long-chain omega-3 fatty acids; **LDL**: low-density lipoprotein; **MD**: mean difference; **MDA**: malondialdehyde; **MI**: myocardial infarction; **MMSE**: Mini–Mental State Examination; **MS**: multiple sclerosis; **MUFA**: mono-unsaturated fatty acids; **MXT**: methotrexate;**n-3**: omega-3; **NASH**: non-alcoholic steatohepatitis; **NSAID**: non-steroidal anti-inflammatory drug; **PAI1**: plasminogen activator inhibitor-1; **PI**: principal investigator;**PUFA**: poly-unsaturated fatty acids; **PTCA**: percutaneous transluminal coronary angioplasty; **P/S**: poly-unsaturated/saturated fat ratio; **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; **RCT**: randomised controlled trial; **SFA**: saturated fatty acids; **SSZ**: sulfasalazine; **TAG**: triacylglycerol; **TG**: serum triglycerides; **TIA**: transient ischaemic attack; **TNF**: tumour necrosis factor; **VCAM-1**: vascular cell adhesion molecule 1; **WHO**: World Health Organization.

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

Study	Reason for exclusion
Alekseeva 2000	Study not randomised
Baleztena 2015	No relevant outcomes measured
Belch 1988	No relevant outcomes measured
Belluzzi 1996	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 to 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

Study	Reason for exclusion
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	Study 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
Franzen 1989	Study not randomised
Galarraga 2008	9-month intervention period
Gapparova 2000	Study 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	Study not randomised
Griffin 1999	Study 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	Authors confirmed no relevant outcomes measured
HEARTS 2015	Intervention included intensive behavioural changes including exercise and nutrition counselling geared towards weight loss
Hogg 1995	Participants not adult humans, or participants unwell at baseline
HOPE epilepsy 2012	Trial recruitment was suspended due to lack of funding

Study	Reason for exclusion
Huang 1996	No relevant outcomes measured
Huang 2008	Intervention was 9 months and no relevant outcomes
ISRCTN38354847	The proposed one-year study 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 & perindopril (group 2), sotalol, perindopril & 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
Konya 2000	Study not randomised
Kremer 1995	< 1 year duration
Kruger 1998	No relevant outcomes measured
Kurabayashi 2000	< 1 year duration
Lau 1993	Authors confirmed no relevant outcomes
Leaf 1995	Study not randomised
Lee 2010	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

Study	Reason for exclusion
Mate-Jimenez 1991	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
NU-AGE 2014	Multifactorial dietary intervention
NutriMEMO 2014	Mutlisupplement intervention
OFAMS 2012	No relevant outcomes measured
Okuda 1996	No appropriate control group
OLIVE 1998	Study 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	Study not randomised
Pogozheva 2000	Study not randomised
Puri 2008	Authors confirmed no relevant outcomes
Quazi 1994	Study not randomised, < 1 year intervention
Sacks 1994	< 1 year intervention
Saynor 1988	Study not randomised
Saynor 1992	No appropriate control group
Selvais 1995	Intervention was < 1 year
Shimizu 1995	Authors confirmed no relevant outcomes
Singh 1992	Expressions of concern issued by the *BMJ* and *The Lancet* regarding research by this first author (BMJ 2005; Horton 2005)
Singh 1997a	Expressions of concern issued by the*BMJ* and *The Lancet* regarding research by this first author (BMJ 2005; Horton 2005)
Singh 1997b	Expressions of concern issued by the *BMJ* and *The Lancet* regarding research by this first author (BMJ 2005; Horton 2005)
Singh 2002	Expressions of concern issued by the *BMJ* and *The Lancet* regarding research by this first author (BMJ 2005; Horton 2005)

Study	Reason for exclusion
Tariq 1989	Participants not adult humans, or participants unwell at baseline and intervention is < 1 year
Terano 1999	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, Vit 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	Study not randomised

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

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: triglycerides, 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 Study start date: 1 October 2014 Estimated study completion date: unclear
Contact information	Alex Brown (PI), Wardliparingga Aboriginal Unit, Adelaide, Australia, alex.brown@sahmri.com
Notes	ACTRN12614000732684 Alex Brown contacted in 2016: confirmed study is actively recruiting

AFORRD 2010

Trial name or title	Atorvastatin in Factorial with Omega-3 fatty acid Risk Reduction in Diabetes (AFORRD)
Methods	RCT
Participants	Patients 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) 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 Study start date: 1 November 2004 Estimated study 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

ASCEND 2012

Trial name or title	A Study of Cardiovascular Events iN Diabetes (ASCEND)
Methods	RCT
Participants	Patients with diabetes, without vascular disease
Interventions	Each for 7 years: Arm 1: omega-3 (1 g/d: 0.41 g EPA, 0.34 g DHA) and placebo tablets for aspirin Arm 2: aspirin (100 mg/d) and olive oil placebo capsule Arm 3: omega-3 (1 g/d) and aspirin (100 mg/d) Arm 4: olive oil placebo and placebo tablets for aspirin
Outcomes	Primary: cardiovascular events Secondary: mortality, hospitalisations, cancer

ASCEND 2012 *(Continued)*

Starting date	Registered on trials registry: 24 August 2005 Study start date: March 2005 Estimated study completion date: September 2017
Contact information	Jane Armitage (PI), University of Oxford Clinical Trial Service Unit
Notes	NCT00135226 Trial website: ascend.medsci.ox.ac.uk; rum.ctsu.ox.ac.uk/ascend

Bartold 2010

Trial name or title	Clinical efficacy of fish oil as adjunct therapy for patients with chronic periodontitis
Methods	RCT
Participants	Patients (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, C-reactive protein
Starting date	Registered on trials registry: 23 July 2010 Study start date: July 2010 Estimated study 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 study N = 33 participants Mark Bartold written to in 2016. Confirmed preparing full publications for submission

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

Beyond Aging Project 2015 *(Continued)*

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 Study start date: June 2011 Estimated study 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

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, impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), 201 participants discussed in one abstract, 134 in a later abstract
Interventions	Each for 3 years: Arm 1: reduced fat diet (fat content at or below 20% total energy, ratio of PUFA/SFA 0.8 to 1.0) Arm 2: normal/control diet
Outcomes	Incidence of diabetes, BMI, lipids, insulin, plasma glucose, HbA1c, blood pressure, nutritional intake
Starting date	Registered on trials registry: no registration found Study start date: not stated Estimated study completion date: not stated
Contact information	Chandrakala Galla, chandrakala.galla@gmail.com; Arpana Gaddam, dr.arpanag@gmail.com
Notes	Authors written to 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

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	Fatty acids, lipids, cytokines (IL-6, IL-1a)
Starting date	Registered on trials registry: 13 March 2012 Study start date: unclear Estimated study 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

DO HEALTH

Trial name or title	Vitamin D3- omega3- home exercise- healthy ageing and longevity trial (DO-HEALTH)
Methods	RCT
Participants	Community dwelling adults 70 years and older, 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)

DO HEALTH *(Continued)*

	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, blood pressure, cognitive decline, rate of any infection Secondary: other fractures, falls, pain in knee osteoarthritis, musculoskeletal changes, gastro-intestinal symptoms, mental and oral health, quality of life, life-expectancy, cardiovascular events, cancer, glucose measures, cost-benefit. All endpoints supported by a DO-HEALTH biomarker study
Starting date	Registered on trials registry: 6 December 2012 Study start date: December 2012 Estimated study completion date: November 2017
Contact information	Heike Bischoff-Ferrari (PI), Centre on Aging and Mobility, University of Zurich
Notes	NCT01745263 EudraCT: 2012−001249-41 www.do-health.eu

DREAM 2014

Trial name or title	DRy Eye Assessment and Management study (DREAM)
Methods	RCT
Participants	Adults with dry eye
Interventions	Each for 2 years Arm 1: omega-3 supplements (2000 mg EPA + 1000 mgDHA/d as 5 gel caps) Arm 2: olive oil supplements (5 gel caps)
Outcomes	Primary: OSDI score (ocular surface disease index) Secondary: other eye health measures, SF-36, healthcare utilisation costs, cost-effectiveness
Starting date	Registered on Trials Registry 28 April 2014 Study start date: November 2014 Estimated study completion date: July 2017
Contact information	Penny Asbell, Mount Sinai Icahn School of Medicine (Study Chair), Maureen Maguire, University of Pennsylvania (PI)
Notes	NCT02128763

ENRGISE 2016

Trial name or title	ENabling Reduction of low-Grade Inflammation in SEniors (ENRGISE)
Methods	RCT
Participants	People aged 70+ years with self-reported walking or stair-climbing difficulty
Interventions	Each for 1 year Arm 1: omega-3 fish oil (1.4 g/d for 6 months, possibly increasing to 2.8 g/d) Arm 2: losartan 25 mg/d Arm 3: placebo corn oil (for omega-3) plus placebo cellulose (for losartan) Arm 4: omega-3 plus losartan Arm 5: placebo corn oil (for omega-3) Arm 6: placebo cellulose (for losartan)
Outcomes	Primary: IL-6, 400 meter walk test Secondary: short physical performance battery, frailty, hand grip strength, knee dynamometry, SF-36
Starting date	Registered on Trials Registry 3 February 2016 Study start date: February 2016 Estimated study completion date: March 2018
Contact information	Jane Lu janelu@ufl.edu Michael Stancil mstancil@ufl.edu
Notes	NCT02676466

InTrePad 2013

Trial name or title	Intervention of testosterone and fish oil for the prevention of Alzheimer's Disease: InTrePad
Methods	RCT
Participants	PiB-PET (Pittsburgh compound B) positive men aged 60 years and over with subjective memory complaints
Interventions	Each for 56 weeks: Arm 1: DHA capsules (1720 mg/d) and testosterone undecanoate (intramuscular injection 1000 mg/4 mL every 8 weeks) Arm 2: placebo DHA and testosterone undecanoate (intramuscular injection 1000 mg/4 mL every 8 weeks) Arm 3: placebo DHA and placebo testosterone
Outcomes	Primary: PiB score

InTrePad 2013 *(Continued)*

	Secondary: neuropsychological, mood and daily functioning questionnaires, beta amyloid levels, fluorodeoxyglucose to assess brain glucose metabolism, inflammatory and oxidative biomarkers, hippocampal volume, quality of life, safety and tolerability of treatment
Starting date	Registered on trials registry: 14 January 2013 Study start date: 28 February 2013 Estimated study completion date: not stated
Contact information	Ralph Martins (PI), Sir James McCusker Alzheimer's Disease Research Unit, Hollywood Medical Centre, Nedlands, Australia, r.martins@ecu.edu.au
Notes	ACTRN12613000034730 Ralph Martins written to in 2016- no response

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 patients 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 Study start date: December 2011 Estimated study completion date: November 2016
Contact information	Bruno Vellas (PI), University Hospital, Toulouse, vellas.b@chu-toulouse.fr
Notes	NCT01513252 Bruno Vellas written to in 2016- no response

NCT00010868

Trial name or title	Omega 3 fatty acids in bipolar disorder prophylaxis
Methods	RCT
Participants	People aged 18 to 65 with bipolar disorder
Interventions	Each for 12 months: Arm 1: omega-3

NCT00010868 *(Continued)*

	Arm 2: placebo
Outcomes	Prophylactic efficacy
Starting date	Trial Registration entry: 2 February 2001 Trial start date: July 2000 Estimated study 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

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, atrial fibrillation
Starting date	Registered on trials registry: 29 March 2006 Study start date: unclear Estimated study completion date: unclear
Contact information	David Jenkins, University of Toronnto, nutritionproject@smh.toronto.on.ca
Notes	NCT00309439 David Jenkins written to in 2016: confirmed not published in full and data incomplete

NCT00410020

Trial name or title	Arrhythmia prevention with an alpha-linolenic enriched diet
Methods	RCT, parallel, 2 arm, 12 months
Participants	98 people with successful atrial fibrillation electrical cardioversion
Interventions	Canola margarine and oil, rich in ALA, versus a conventional diet (control), for 1 year

NCT00410020 *(Continued)*

Outcomes	Length of time to first recurrence of AF
Starting date	June 1999, expected finish date June 2003, registered December 2006 so appears to have been carried out
Contact information	Principal Investigator: Jean-Paul Broustet, MD, PhD, Universitary Hospital Haut-Lévêque Bordeaux France
Notes	NCT00410020, registered December 2006, no publication found

NCT01784042

Trial name or title	Dietary energy restriction and omega-3 fatty acids on mammary tissue
Methods	RCT
Participants	Overweight women (30-55 years) with increased breast cancer risk
Interventions	For 1 year: Arm 1: lovaza (omega-3-acid ethyl esters) Arm 2: lovaza and dietary energy restriction Arm 3: placebo Arm 4: placebo and dietary energy restriction
Outcomes	Ki67 expression at 1 year
Starting date	Registered on trials registry: 31 January 2013 Study start date: March 2013 Estimated study completion date: March 2018
Contact information	Andrea Manni, Hershey Medical Centre, amanni@hmc.psu.edu (PI) or Cynthia DuBrock, cdubrock@hmc.psu.edu
Notes	NCT01784042. Trials register states "Withdrawn (no funding)"

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

NCT02211560 *(Continued)*

Outcomes	Primary: selective reminding test (SRT) Secondary: mini mental state examination (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 Study start date: September 2014 Estimated study completion date: September 2019
Contact information	Nadia Niemerzyanski, nadiaN@enzymotec.com; Yael Richter, yaelr@enzymotec.com
Notes	NCT02211560

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 to 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) 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 Study start date: August 2014 Estimated study completion date: January 2019
Contact information	Anitra Sumbry, anitra.sumbry@osumc.edu; Lisa Yee (PI), Ohio State University
Notes	NCT02295059

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 to 70 years whose parents had AD
Interventions	Each for 18 months:

NCT02719327 *(Continued)*

	Arm 1: Icosapent ethyl EPA (Vascepa) 4 g/d gel cap Arm 2: matching gel cap placebo
Outcomes	Primary: cerebral blood flow by MRI (magnetic resonance imaging) Secondary: CSF biomarkers of AD, cognitive performance (preclinical Alzheimer's cognitive composite, PACC)
Starting date	Registered on trials registry: 21 March 2016 Study start date: December 2016 Estimated study completion date: November 2021
Contact information	Cynthia Carlsson, cynthia.carlsson@va.gov; Elena Beckman, elena.beckman@va.gov
Notes	NCT02719327

OMEMI 2014

Trial name or title	OMega-3 fatty acids in Elderly patients with Myocardial Infarction study (OMEMI)
Methods	RCT
Participants	Elderly patients (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 AMI, stroke and revascularisation Secondary: new onset atrial fibrillation, adipose tissue, serum fatty acids, makers of endothelial function, inflammation, coagulation and fibrinolytic activity, genes associated with atherothrombosis
Starting date	Registered on trials registry: 16 April 2013 Study start date: November 2012 Estimated study completion date: November 2019
Contact information	Svein Solheim, Center for Clinical Heart Research, Oslo University Hospital, arnljot.tveit@vestre-viken.no
Notes	NCT01841944

REDUCE-IT 2011

Trial name or title	Reduction of cardiovascular events with EPA-intervention trial (REDUCE-IT)
Methods	RCT

REDUCE-IT 2011 *(Continued)*

Participants	Patients (45 years or over) with hypertriglyceridaemia, with cardiovascular disease or at high risk for cardiovascular disease, and on statin
Interventions	Each for 4-6 years: Arm 1: EPA ethyl ester (AMR101 4 g/d) Arm 2: placebo
Outcomes	Primary: composite of cardiovascular death, MI, stroke, coronary revascularisation and hospitalisation for unstable angina Secondary: incidence of additional cardiovascular events, lipid and lipoprotein levels
Starting date	Registered on trials registry: 13 December 2011 Study start date: November 2011 Estimated study completion date: December 2017
Contact information	Deepak Bhatt (PI), Brigham and Women's Hospital
Notes	NCT01492361

seAFOOD 2013

Trial name or title	The seAFOod (systematic evaluation of Aspirin and Fish Oil) Polyp Prevention Trial
Methods	RCT
Participants	NHS Bowel Cancer Screening Programme patients (55-73 years) identified as "high risk" (5 or more small adenomas; or 3 or more adenomas with at least one being 10 mm or more in diameter) after their 1st screening colonoscopy
Interventions	Each for 12 months: Arm 1: EPA (ALFA capsules: 2 × 500 mg twice daily = 2 g/d) and aspirin placebo (1/d) Arm 2: EPA placebo (capric and capryllic acid triglycerides: 2/d) and aspirin (1/d = 300 mg/d) Arm 3: EPA (ALFA capsules: 2 × 500 mg twice daily = 2 g/d) and aspirin (1/d = 300 mg/d) Arm 4: EPA placebo (cparic and capryllic acid triglycerides: 2/d) and aspirin placebo (1/d)
Outcomes	Primary: number of patients with one or more adenomas at 12 months Secondary: adverse events, number of "advanced" adenomas per patients, number of "high risk" patients re-classified as "intermediate risk", number patients with one or more advanced adenomas, adenoma region in the colorectum, total number of adenomas per patient, number of patients with colorectal cancer, levels of bioactive lipid mediators e.g. omega-3
Starting date	Trial Registration entry: 6 May 2011 Trial start date: 30 May 2011 Estimated study completion: 31 July 2017
Contact information	Mark Hull, Leeds Institute of Molecular Medicine, m.a.hull@leeds.ac.uk

seAFOOD 2013 *(Continued)*

Notes	ISRCTN05926847 EudraCT 2010−020943−10 www.seafood-trial.co.uk

Shinto 2015

Trial name or title	N-3 PUFA for vascular cognitive aging
Methods	RCT
Participants	Older adults (80 years and older) 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 Study start date: May 2014 Estimated study completion date: March 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

STRENGTH 2015

Trial name or title	A long-term outcomes study to assess statin residual risk reduction with EpaNova in high cardiovascular risk patients with hypertriglyceridemia (STRENGTH)
Methods	RCT
Participants	Adult patients 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 less than 800 mg/g) and statin (once daily) Arm 2: corn oil placebo capsule and statin (once daily)
Outcomes	Primary: time to first occurrence of any component of the composite MACE (cardiovascular death, nonfatal MI, nonfatal stroke, emergent/elective coronary revascularisation, hospitalisation for unstable angina)

STRENGTH 2015 *(Continued)*

	Secondary: composite measure of cardiovascular events that include the first occurrence of cardiovascular death, nonfatal 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 cardiovascular death. Other measures include: all cause mortality, new atrial fibrillation, thrombotic events, heart failure events
Starting date	Trial Registration entry: 2 April 2014 Trial start date: October 2014 Estimated study completion: November 2019
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

SUPERIORSVG 2010

Trial name or title	Improving the results of heart bypass surgery using new approaches to surgery and medication (SUPERIORSVG)
Methods	RCT
Participants	Adults having coronary artery bypass graft (CABG) using saphenous vein graft (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 Study start date: July 2011 Estimated study completion date: December 2016
Contact information	Stephen Fremes, Sunnybrook Health Sciences Centre (PI)
Notes	NCT01047449

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 (optical coherence tomography-guided percutaneous coronary intervention)
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 cardiovascular events
Starting date	Registered on trials registry: 1 February 2014 Study start date: 1 February 2014 Estimated study completion date: 30 June 2019
Contact information	Shiro Uemura (PI), Nara Medical University, Japan, suemura@naramed-u.ac.jp
Notes	UMIN000012825

VITAL 2018

Trial name or title	VITamin D and omegA-3 triaL (VITAL)
Methods	RCT
Participants	Multi-ethnic population of > 25,000 apparently healthy adults (men 50 years plus, women 55 years plus) without cancer or CVD at baseline
Interventions	Each for mean 5 years: Arm 1: omega-3 (Omacor fish oil, EPA + DHA 1 g/d: 465 mg EPA; 375 mg DHA) and placebo Arm 2: placebo and vitamin D3 (1/d, 2,000IU) Arm 3: omega-3 (Omacor fish oil, EPA + DHA 1 g/d: 465 mg EPA; 375 mg DHA) and vitamin D3 (1/d, 2000 IU) Arm 4: placebo and placebo
Outcomes	Primary: reduction in risk for total cancer and CVD events (a composite of MI, stroke, and cardiovascular mortality) Secondary: lowered risk for expanded composite cardiovascular endpoint (MI, stroke, cardiovascular mortality, coronary revascularisation), the individual components of the primary endpoint, site specific cancers, mortality, 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

VITAL 2018 *(Continued)*

Starting date	Registered on trials registry: 13 January 2010 Study start date: July 2010 Estimated study completion date: December 2017
Contact information	JoAnn Manson or Julie Buring (PIs), Brigham and Women's Hospital, Boston and Harvard School of Public Health, Boston, vitalstudy@rics.bwh.harvard.edu
Notes	NCT01169259 www.vitalstudy.org

ACS: acute coronary syndrome; **AD**: Alzheimer's disease; **AF**: atrial fibrillation; **BMI**: body mass index; **BMI**: body mass index; **CABG**: coronary artery bypass graft; **CETP**: cholesteryl ester transfer protein; **CHD**: coronary heart disease; **CVD**: cardiovascular disease; **DHA**: docosahexaenoic acid; **EPA**: eicosapentaenoic acid; **GAD-7**: generalised anxiety disorder 7; **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; **MRI**: magentic 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**: poly-unsaturated fatty acids; **RCT**: randomised controlled trial; **RCT**: randomised controlled trial; **SFA**: saturated fatty acids; **SVG**: saphenous vein graft.

DATA AND ANALYSES

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

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 All-cause mortality (overall) - LCn3	39	92653	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.93, 1.03]
2 All-cause mortality - LCn3 - sensitivity analysis (SA) fixed-effect	39	90244	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.93, 1.01]
3 All-cause mortality - LCn3 - SA by summary risk of bias	39	92653	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.93, 1.03]
3.1 Low risk of bias	15	33146	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.94, 1.08]
3.2 Moderate/high risk of bias	24	59507	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.86, 1.03]
4 All-cause mortality - LCn3 - SA by compliance and study size	38		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 SA - low risk of compliance bias	18	15654	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.86, 1.14]
4.2 SA - 100+ randomised	35	92397	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.93, 1.03]
5 All-cause mortality - LCn3 - subgroup by dose	39	92653	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.93, 1.03]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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	28	87445	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.93, 1.05]
5.5 LCn3 > 2.4 ≤ 4.4 g/d	7	2486	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.67, 1.70]
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	39		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 LCn3 replacing SFA	5	3279	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.56, 0.92]
6.2 LCn3 replacing MUFA	15	46176	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.90, 1.02]
6.3 LCn3 replacing N-6	9	2806	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.51, 1.09]
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	10	39601	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.86, 1.14]
6.6 LCn3 replacement unclear	3	3593	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.46, 1.79]
7 All-cause mortality - LCn3 - subgroup by intervention type	39	92653	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.93, 1.03]
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)	33	81855	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.92, 1.01]
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	39	92653	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.93, 1.03]
8.1 Medium duration 1 to < 2 years in study	18	9737	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.82, 1.30]
8.2 Medium-long duration: 2 to < 4 years in study	14	29234	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.86, 0.96]
8.3 Long duration: ≥ 4 years in study	7	53682	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.98, 1.09]
9 All-cause mortality - LCn3 - subgroup by primary or secondary prevention	39	92653	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.93, 1.03]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Primary CVD prevention	17	41202	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.94, 1.08]
9.2 Secondary CVD prevention	22	51451	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.88, 1.04]
10 All-cause mortality - LCn3 - subgroup by statin use	39	90244	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.92, 1.03]
10.1 LCn3 - ≥50% of control group on statins	8	40500	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.93, 1.11]
10.2 LCn3 - < 50% of control group on statins	26	46604	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.88, 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 Cardiovascular mortality (overall) - LCn3	25	67772	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.87, 1.03]
12 CVD mortality - LCn3 - SA fixed-effect	25	67772	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.89, 1.00]
13 CVD mortality - LCn3 - SA by summary risk of bias	25	67772	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.87, 1.03]
13.1 Low risk of bias	9	29133	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.90, 1.09]
13.2 Moderate/high risk of bias	16	38639	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.80, 1.05]
14 CVD mortality - LCn3 - SA by compliance and study size	24		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 SA - low risk of compliance bias	12	13244	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.82, 1.23]
14.2 SA - 100+ randomised	21	67516	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.87, 1.04]
15 CVD mortality - LCn3 - subgroup by dose	26	67873	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.87, 1.03]
15.1 LCn3 ≤ 150 mg/d	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.2 LCn3 > 150 ≤ 250 mg/d	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.3 LCn3 > 250 ≤ 400 mg/d	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.53, 0.91]
15.4 LCn3 > 400 ≤ 2400 mg/d	19	64126	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.89, 1.06]
15.5 LCn3 > 2.4 ≤ 4.4 g/d	4	1432	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.58, 1.77]
15.6 LCn3 > 4.4 g/d	2	282	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.03, 3.08]
16 CVD mortality - LCn3 - subgroup by replacement	26		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.1 N-3 replacing SFA	3	2537	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.53, 0.90]
16.2 N-3 replacing MUFA	12	44242	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.86, 1.04]
16.3 N-3 replacing N-6	4	1435	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.41, 1.19]
16.4 N-3 replacing carbohydrates/sugars	1	281	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.12, 4.07]
16.5 N-3 replacing nil/low n-3 placebo	8	19275	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.73, 0.96]
16.6 Replacement unclear	2	3186	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.05, 5.77]
17 CVD mortality - LCn3 - subgroup by intervention type	25	67772	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.87, 1.03]
17.1 Dietary advice	2	5147	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.52, 1.71]
17.2 Supplemental foods	2	5039	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.72, 1.32]
17.3 Supplements (capsule)	21	57586	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.88, 0.99]
17.4 Any combination	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
18 CVD mortality - LCn3 - subgroup by duration	25	67772	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.87, 1.03]
18.1 Medium duration 1 to < 2 years in study	10	6177	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.57, 1.36]
18.2 Medium-long duration: 2 to < 4 years in study	10	26736	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.82, 0.95]
18.3 Long duration: ≥ 4 years in study	5	34859	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.93, 1.18]
19 CVD mortality - LCn3 - subgroup by primary or secondary prevention	25	67772	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.87, 1.03]
19.1 Primary prevention	7	17931	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.88, 1.09]
19.2 Secondary prevention	18	49841	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.83, 1.06]
20 CVD mortality - LCn3 - subgroup by statin uses	25	67772	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.87, 1.03]
20.1 LCn3 - ≥ 50% of control group on statins	6	23994	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.90, 1.10]
20.2 LCn3 - < 50% of control group on statins	17	43425	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.82, 1.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.3 LCn3- Use of statins unclear	2	353	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.06, 2.30]
21 Cardiovascular events (overall) - LCn3	38	90378	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.94, 1.04]
22 CVD events - LCn3 - SA fixed-effect	38	90378	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.95, 1.00]
23 CVD events - LCn3 - SA by summary risk of bias	38	90378	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.94, 1.04]
23.1 Low risk of bias	14	31649	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.96, 1.05]
23.2 Moderate/high risk of bias	24	58729	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.87, 1.03]
24 CVD events - LCn3 - SA by compliance and study size	37		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
24.1 SA - low risk of compliance bias	16	13649	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.84, 1.14]
24.2 SA - 100+ randomised	33	90058	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.94, 1.04]
25 CVD events - LCn3 - subgroup by dose	38	90453	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.94, 1.04]
25.1 LCn3 ≤ 150 mg/d	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
25.2 LCn3 > 150 ≤ 250 mg/d	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
25.3 LCn3 > 250 ≤ 400 mg/d	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.88, 1.05]
25.4 LCn3 > 400 ≤ 2400 mg/d	28	85818	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.93, 1.05]
25.5 LCn3 > 2.4 ≤ 4.4 g/d	7	2180	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.75, 1.28]
25.6 LCn3 > 4.4 g/d	3	422	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.65, 1.81]
26 CVD events - LCn3 - subgroup by replacement	38		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
26.1 N-3 replacing SFA	4	2888	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.87, 1.04]
26.2 N-3 replacing MUFA	16	45065	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.94, 1.02]
26.3 N-3 replacing n-6	6	1891	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.90, 1.35]
26.4 N-3 replacing carbohydrates/sugars	1	258	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.12, 3.98]
26.5 N-3 replacing nil/low n-3 placebo	12	39907	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.85, 1.07]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
26.6 Replacement unclear	3	3429	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.16, 2.07]
27 CVD events - LCn3 - subgroup by intervention type	38	90378	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.94, 1.04]
27.1 Dietary advice	3	5248	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.86, 1.49]
27.2 Supplemental foods	2	5039	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.89, 1.17]
27.3 Supplements (capsule)	33	80091	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.91, 1.02]
27.4 Any combination	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
28 CVD events - LCn3 - subgroup by duration	38	90378	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.94, 1.04]
28.1 Medium duration 1 to < 2 years in study	18	8107	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.68, 1.16]
28.2 Medium-long duration: 2 to < 4 years in study	14	28767	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.93, 1.01]
28.3 Long duration: ≥ 4 years in study	6	53504	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.91, 1.08]
29 CVD events - LCn3 - subgroup by primary or secondary prevention	38	90378	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.94, 1.04]
29.1 Primary prevention of CVD	16	39751	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.89, 1.05]
29.2 Secondary prevention	22	50627	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.93, 1.07]
30 CVD events - LCn3 - subgroup by statin use	38	90378	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.94, 1.04]
30.1 LCn3 - ≥ 50% of control group on statins	8	42389	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.08]
30.2 LCn3 - < 50% of control group on statins	24	45160	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.91, 1.04]
30.3 LCn3 - use of statins unclear	6	2829	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.53, 1.63]
31 Coronary heart disease mortality (overall) - LCn3	21	73491	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.79, 1.09]
32 CHD mortality - LCn3 - SA fixed-effect	21	73491	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.85, 1.03]
33 CHD mortality - LCn3 - SA by summary risk of bias	21	73491	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.79, 1.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
33.1 Low risk of bias	7	16372	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.72, 1.37]
33.2 Moderate/high risk of bias	14	57119	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.75, 1.10]
34 CHD mortality - LCn3 - SA by compliance and study size	21		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
34.1 SA - low risk of compliance bias	9	12938	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.83, 1.32]
34.2 SA - 100+ randomised	20	73411	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.79, 1.09]
35 CHD mortality - LCn3 - SA omitting cardiac death	16	65325	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.74, 0.94]
35.1 Low risk of bias	5	12022	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.69, 1.30]
35.2 Moderate/high risk of bias	11	53303	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.72, 0.94]
36 CHD mortality - LCn3 - subgroup by dose	21	73491	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.79, 1.09]
36.1 LCn3 ≤ 150 mg/d	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
36.2 LCn3 > 150 ≤ 250 mg/d	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
36.3 LCn3 > 250 ≤ 400 mg/d	2	5147	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.50, 1.74]
36.4 LCn3 > 400 ≤ 2400 mg/d	15	67442	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.80, 1.07]
36.5 LCn3 > 2.4 ≤ 4.4 g/d	3	822	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.49, 1.78]
36.6 LCn3 > 4.4 g/d	1	80	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.57]
37 CHD mortality - LCn3 - subgroup by replacement	21		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
37.1 N-3 replacing SFA	3	2514	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.51, 0.88]
37.2 N-3 replacing MUFA	10	31605	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.72, 1.10]
37.3 N-3 replacing n-6	3	1409	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.33, 1.24]
37.4 N-3 replacing carbohydrates/sugars	1	258	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.23]
37.5 N-3 replacing nil/low n-3 placebo	7	37651	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.70, 0.97]
37.6 Replacement unclear	1	3114	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.03, 1.57]
38 CHD mortality - LCn3 - subgroup by intervention type	21	73491	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.79, 1.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
38.1 Dietary advice	2	5147	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.50, 1.74]
38.2 Supplemental foods	1	4837	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.69, 1.33]
38.3 Supplements (capsule)	18	63507	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.79, 1.02]
38.4 Any combination	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
39 CHD mortality - LCn3 - subgroup by duration	21	73491	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.79, 1.09]
39.1 Medium duration 1 to < 2 years in study	7	5978	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.62, 1.50]
39.2 Medium-long duration: 2 to < 4 years in study	9	26545	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.69, 0.90]
39.3 Long duration: ≥ 4 years in study	5	40968	Risk Ratio (M-H, Random, 95% CI)	1.18 [1.00, 1.39]
40 CHD mortality - LCn3 - subgroup by primary or secondary prevention	21	73491	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.79, 1.09]
40.1 Primary prevention of CVD	5	23789	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.46, 1.61]
40.2 Secondary prevention of CVD	16	49702	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.79, 1.11]
41 CHD mortality - LCn3 - subgroup by statin use	21	73491	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.79, 1.09]
41.1 LCn3 - ≥ 50% of control group on statins	5	30025	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.84, 1.30]
41.2 LCn3 - < 50% of control group on statins	15	43208	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.72, 1.10]
41.3 LCn3 - use of statins unclear	1	258	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.23]
42 CHD mortality - LCn3 - subgroup by CAD history	21	73491	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.80, 1.09]
42.1 Previous CAD	11	29074	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.77, 1.20]
42.2 No previous CAD	10	44417	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.74, 1.16]
43 Coronary heart disease events (overall) - LCn3	28	84301	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.88, 0.97]
44 CHD events - LCn3 - SA fixed-effect	28	84301	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.88, 0.97]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
45 CHD events - LCn3 - SA by summary risk of bias	28	84301	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.88, 0.97]
45.1 Low risk of bias	12	30227	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.90, 1.05]
45.2 Moderate/high risk of bias	16	54074	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.84, 0.95]
46 CHD events - LCn3 - SA by compliance and study size	27		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
46.1 SA - low risk of compliance bias	12	13447	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.86, 1.02]
46.2 SA - 100+ randomised	25	84084	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.88, 0.98]
47 CHD events - LCn3 - subgroup by dose	28	84376	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.89, 0.98]
47.1 LCn3 ≤ 150 mg/d	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
47.2 LCn3 > 150 ≤ 250 mg/d	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
47.3 LCn3 > 250 ≤ 400 mg/d	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.82, 1.04]
47.4 LCn3 > 400 ≤ 2400 mg/d	21	80730	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.88, 0.98]
47.5 LCn3 > 2.4 ≤ 4.4 g/d	4	1191	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.53, 1.53]
47.6 LCn3 > 4.4 g/d	3	422	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.54, 1.85]
48 CHD events - LCn3 - subgroup by replacement	28		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
48.1 N-3 replacing SFA	3	2514	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.16, 1.75]
48.2 N-3 replacing MUFA	15	44954	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.90, 1.01]
48.3 N-3 replacing n-6	4	1549	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.88, 1.39]
48.4 N-3 replacing carbohydrates/sugars	1	258	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 2.07]
48.5 N-3 replacing nil/low n-3 placebo	8	37843	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.78, 0.94]
48.6 Replacement unclear	1	243	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.08, 9.70]
49 CHD events - LCn3 - subgroup by intervention type	28	84301	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.89, 0.98]
49.1 Dietary advice	2	2134	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.67, 1.52]
49.2 Supplemental foods	2	5039	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.75, 1.18]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
49.3 Supplements (capsule)	24	77128	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.88, 0.98]
49.4 Any combination	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
50 CHD events - LCn3 - subgroup by duration	28	84301	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.89, 0.98]
50.1 Medium duration 1 to < 2 years in study	11	7009	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.86, 1.03]
50.2 Medium-long duration: 2 to < 4 years in study	12	26902	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.84, 0.98]
50.3 Long duration: ≥ 4 years in study	5	50390	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.83, 1.07]
51 CHD events - LCn3 - subgroup by primary or secondary prevention	28	84301	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.89, 0.98]
51.1 Primary prevention of CVD	11	37365	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.81, 1.10]
51.2 Secondary prevention of CVD	17	46936	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.88, 0.98]
52 CHD events - LCn3 - subgroup by statin use	28	84301	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.89, 0.98]
52.1 LCn3 - ≥ 50% of control group on statins	8	42735	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.85, 1.05]
52.2 LCn3 - < 50% of control group on statins	17	40674	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.86, 0.98]
52.3 LCn3 - use of statins unclear	3	892	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.11, 3.83]
53 CHD events - LCn3 subgroup by CAD history	28	84301	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.88, 0.97]
53.1 Previous CAD	12	26124	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.87, 0.98]
53.2 No previous CAD	16	58177	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.86, 1.01]
54 Stroke (overall) - LCn3	28	89358	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.96, 1.16]
55 Stroke - LCn3 - SA fixed-effect	28	89358	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.97, 1.16]
56 Stroke - LCn3 - SA by summary risk of bias	28	89358	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.96, 1.16]
56.1 Low risk of bias	12	32039	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.86, 1.12]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
56.2 Moderate/high risk of bias	16	57319	Risk Ratio (M-H, Random, 95% CI)	1.13 [1.00, 1.29]
57 Stroke - LCn3 - SA by compliance and study size	27		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
57.1 SA - low risk of compliance bias	12	14451	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.86, 1.65]
57.2 SA - 100+ randomised	26	89231	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.97, 1.18]
58 Stroke - LCn3 - subgroup by stroke type	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
58.1 Ischaemic stroke - LCn3	8	35040	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.89, 1.33]
58.2 Haemorrhagic stroke - LCn3	8	36645	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.85, 1.69]
58.3 Transient ischaemic attack (TIA)	5	5032	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.39, 1.39]
59 Stroke - LCn3 - subgroup by dose	28		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
59.1 LCn3 ≤ 150 mg/d	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
59.2 LCn3 > 150 ≤ 250 mg/d	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
59.3 LCn3 > 250 ≤ 400 mg/d	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.14, 1.44]
59.4 LCn3 > 400 ≤ 2400 mg/d	24	86335	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.97, 1.16]
59.5 LCn3 > 2.4 ≤ 4.4 g/d	1	610	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.16, 3.07]
59.6 LCn3 > 4.4 g/d	2	380	Risk Ratio (M-H, Random, 95% CI)	6.58 [0.78, 55.16]
60 Stroke - LCn3 - subgroup by replacement	28		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
60.1 N-3 replacing SFA	3	2514	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.19, 1.50]
60.2 N-3 replacing MUFA	14	45252	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.94, 1.31]
60.3 N-3 replacing n-6	3	1179	Risk Ratio (M-H, Random, 95% CI)	2.08 [0.18, 24.31]
60.4 N-3 replacing carbohydrates/sugars	1	258	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.23]
60.5 N-3 replacing nil/low n-3 placebo	9	39555	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.92, 1.24]
60.6 Replacement unclear	1	3114	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.55, 2.29]

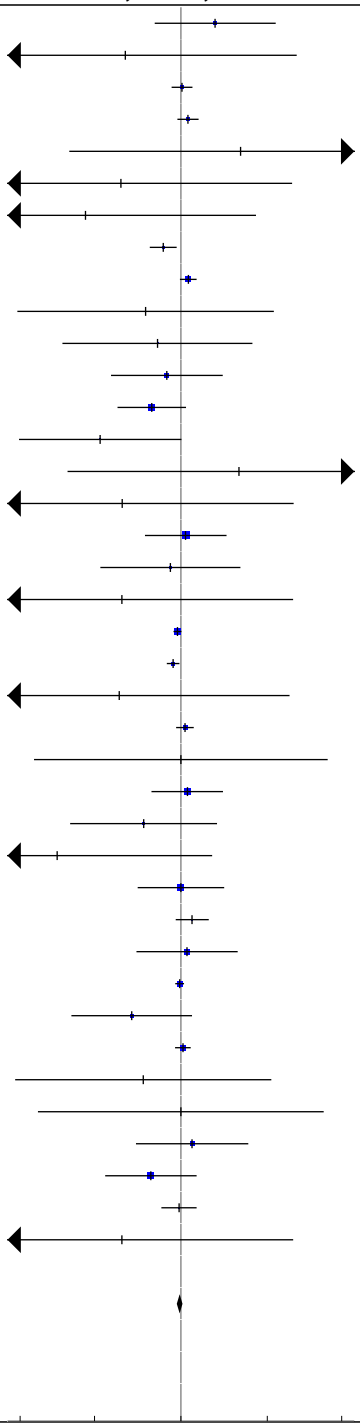
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
61 Stroke - LCn3 - subgroup by intervention type	28	89358	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.96, 1.16]
61.1 Dietary advice	3	5248	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.42, 2.05]
61.2 Supplemental foods	1	4837	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.47, 2.62]
61.3 Supplements (capsule)	24	79273	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.97, 1.18]
61.4 Any combination	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
62 Stroke - LCn3 - subgroup by duration	28	89358	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.96, 1.16]
62.1 Medium duration 1 to < 2 years in study	11	7467	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.86, 2.12]
62.2 Medium-long duration: 2 to < 4 years in study	11	28387	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.93, 1.41]
62.3 Long duration: ≥ 4 years in study	6	53504	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.91, 1.13]
63 Stroke - LCn3 - subgroup by primary or secondary prevention	28	89358	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.96, 1.16]
63.1 Primary prevention of CVD	9	39332	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.86, 1.09]
63.2 Secondary prevention of CVD	19	50026	Risk Ratio (M-H, Random, 95% CI)	1.21 [1.05, 1.40]
64 Stroke - LCn3 - subgroup by statin use	28	89358	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.96, 1.16]
64.1 LCn3 - ≥ 50% of control group on statins	8	42962	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.86, 1.23]
64.2 LCn3 - < 50% of control group on statins	17	44999	Risk Ratio (M-H, Random, 95% CI)	1.18 [1.02, 1.37]
64.3 LCn3 - use of statins unclear	3	1397	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.38, 2.34]
65 Arrythmia (overall) - LCn3	27	53796	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.90, 1.05]
66 Arrhythmia- LCn3 - SA fixed-effect	27	53796	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.96, 1.07]
67 Arrhythmia- LCn3 - SA by summary risk of bias	27	53796	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.90, 1.05]
67.1 Low risk of bias	10	25801	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.98, 1.23]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
67.2 Moderate/high risk of bias	17	27995	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.84, 1.02]
68 Arrhythmia- LCn3 - SA by compliance and study size	26		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
68.1 SA - low risk of compliance bias	10	12914	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.86, 1.09]
68.2 SA - 100+ randomised	26	53749	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.89, 1.05]
69 Arrhythmia - LCn3 - subgroup by new or recurrent	27		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
69.1 New arrhythmia	16	50175	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.99, 1.16]
69.2 Recurrent arrhythmia	12	4425	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.84, 1.03]
70 Arrhythmia - LCn3 - subgroup by fatality	17		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
70.1 Fatal arrhythmias - LCn3	2	12938	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.95, 1.31]
70.2 Non-fatal arrhythmias - LCn3	8	2079	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.57, 0.96]
70.3 Fatal and non-fatal arrhythmias combined - LCn3	10	36007	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.97, 1.17]
71 Arrhythmia - LCn3 - subgroup by dose	27	53796	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.89, 1.04]
71.1 LCn3 ≤ 150 mg/d	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
71.2 LCn3 > 150 ≤ 250 mg/d	1	407	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.90, 1.12]
71.3 LCn3 > 250 ≤ 400 mg/d	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
71.4 LCn3 > 400 ≤ 2400 mg/d	19	51535	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.88, 1.08]
71.5 LCn3 > 2.4 ≤ 4.4 g/d	3	1076	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.55, 0.94]
71.6 LCn3 > 4.4 g/d	2	342	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.32, 3.83]
71.7 Unclear LCn3 dose	2	436	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.76, 1.28]
72 Arrhythmia - LCn3 - subgroup by replacement	27		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
72.1 N-3 replacing SFA	2	632	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.10, 5.67]
72.2 N-3 replacing MUFA	12	42246	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.88, 1.11]
72.3 N-3 replacing n-6	4	1302	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.86, 1.16]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
72.4 N-3 replacing carbohydrates/sugars	1	258	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.04, 3.21]
72.5 N-3 replacing nil/low n-3 placebo	6	8983	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.69, 0.91]
72.6 Replacement unclear	4	1179	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.91, 1.08]
73 Arrhythmia - LCn3 - subgroup by intervention type	27	53796	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.90, 1.05]
73.1 Dietary advice	2	508	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.44, 1.72]
73.2 Supplemental foods	2	5039	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.67, 1.26]
73.3 Supplements (capsule)	23	48249	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.88, 1.06]
73.4 Any combination	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
74 Arrhythmia - LCn3 - subgroup by duration	27	53796	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.89, 1.04]
74.1 Medium duration 1 to < 2 years in study	17	8553	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.84, 1.04]
74.2 Medium-long duration: 2 to < 4 years in study	7	17701	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.84, 1.10]
74.3 Long duration: ≥ 4 years in study	3	27542	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.99, 1.29]
75 Arrhythmia - LCn3 - subgroup by primary or secondary prevention3	27		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
75.1 Primary prevention	8	14565	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.97, 1.28]
75.2 Secondary prevention	19	39231	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.86, 1.03]
76 Arrhythmia - LCn3 - subgroup by statin use	27		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
76.1 LCn3 - ≥ 50% of control group on statins	5	23779	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.95, 1.22]
76.2 LCn3 - < 50% of control group on statins	18	28932	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.85, 1.04]
76.3 LCn3 - use of statins unclear	4	1085	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.80, 1.18]

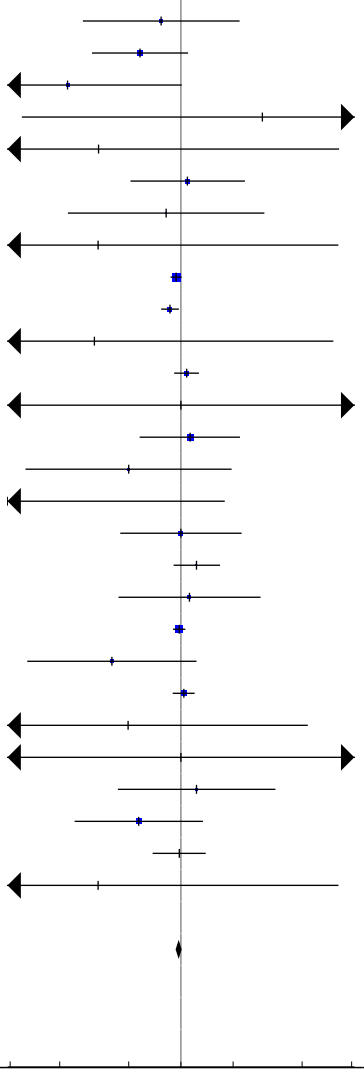
Analysis 1.1. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 1 All-cause mortality (overall) - LCn3.

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		0.22%	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		5.97%	1.02[0.84,1.24]
AREDS2 2014	200/2147	168/2056		5.96%	1.14[0.94,1.39]
Bates 1989	1/155	0/157		0.03%	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		3.96%	0.72[0.56,0.92]
DART2 2003	283/1571	242/1543		8.39%	1.15[0.98,1.34]
Derosa 2016	1/138	2/143		0.05%	0.52[0.05,5.65]
DIPP 2015	2/104	3/101		0.09%	0.65[0.11,3.79]
DISAF 2003	6/201	8/206		0.26%	0.77[0.27,2.18]
DO IT 2010	14/282	24/281		0.69%	0.58[0.31,1.1]
Doi 2014	2/119	9/119		0.12%	0.22[0.05,1.01]
EPIC-1 2008	1/183	0/180		0.03%	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		0.49%	1.09[0.51,2.34]
FORWARD 2013	4/289	5/297		0.17%	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		18.85%	0.94[0.87,1.01]
GISSI-P 1999	472/5666	545/5658		12.22%	0.86[0.77,0.97]
HARP 1995	0/41	1/39		0.03%	0.32[0.01,7.57]
JELIS 2007	286/9326	265/9319		7.8%	1.08[0.91,1.27]
Kumar 2013	1/39	1/39		0.04%	1[0.06,15.43]
MAPT 2017	18/840	16/840		0.63%	1.13[0.58,2.19]
NAT2 2013	3/150	6/150		0.15%	0.5[0.13,1.96]
Nutristroke 2009	0/38	4/34		0.03%	0.1[0.01,1.79]
OFAMI 2001	11/150	11/150		0.44%	1[0.45,2.24]
OMEGA 2009	88/1919	70/1885		2.75%	1.23[0.91,1.68]
OPAL 2010	9/434	8/433		0.32%	1.12[0.44,2.88]
ORIGIN 2012	951/6281	964/6225		17.48%	0.98[0.9,1.06]
Raitt 2005	4/100	10/100		0.22%	0.4[0.13,1.23]
Risk & Prevention 2013	348/6239	337/6266		9.29%	1.04[0.9,1.2]
SCIMO 1999	1/112	2/111		0.05%	0.5[0.05,5.39]
Shinto 2014	1/13	1/13		0.04%	1[0.07,14.34]
SHOT 1996	8/317	6/293		0.26%	1.23[0.43,3.51]
SOFA 2006	8/273	14/273		0.39%	0.57[0.24,1.34]
SU.FOL.OM3 2010	66/1253	68/1248		2.42%	0.97[0.7,1.34]
Zhang 2017	0/120	1/120		0.03%	0.33[0.01,8.1]
Total (95% CI)	**46479**	**46174**		**100%**	**0.98[0.93,1.03]**
Total events: 4048 (Favours higher omega 3), 4141 (Lower omega 3 fats)					
Heterogeneity: $Tau^2=0$; $Chi^2=43.01$, df=38(P=0.27); $I^2=11.64\%$					
Test for overall effect: Z=0.87(P=0.39)					



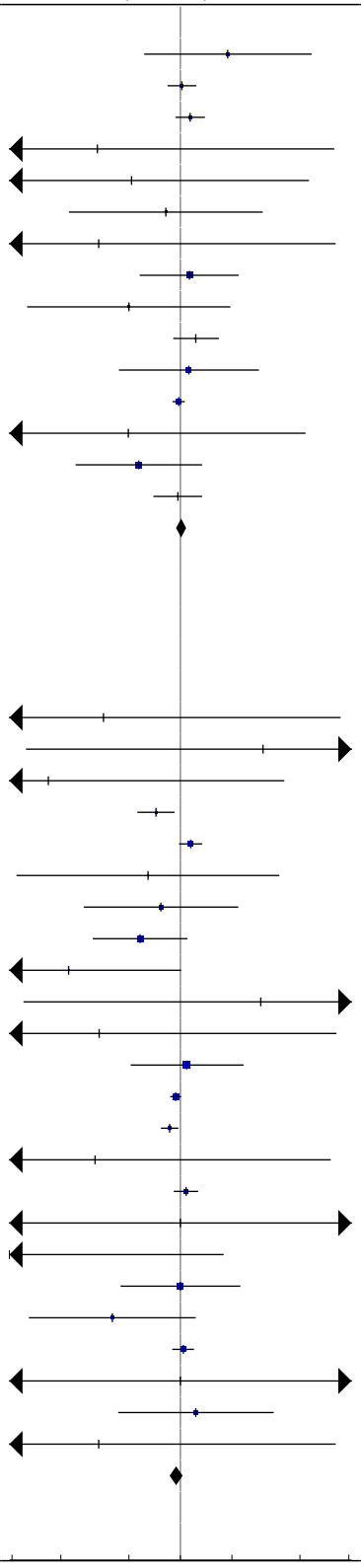
Analysis 1.2. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 2 All-cause mortality - LCn3 - sensitivity analysis (SA) fixed-effect.

Study or subgroup	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
ADCS 2010	11/238	4/164		0.12%	1.89[0.61,5.85]
AFFORD 2013	0/153	1/163		0.04%	0.35[0.01,8.65]
AlphaOmega - EPA+DHA 2010	95/1192	93/1236		2.25%	1.06[0.8,1.39]
AREDS2 2014	200/2147	168/2056		4.23%	1.14[0.94,1.39]
Bates 1989	1/155	0/157		0.01%	3.04[0.12,74.02]
Berson 2004	0/105	1/103		0.04%	0.33[0.01,7.94]
Brox 2001	0/80	1/40		0.05%	0.17[0.01,4.05]
DART 1989	94/1015	131/1018		3.22%	0.72[0.56,0.92]
DART2 2003	283/1571	242/1543		6.02%	1.15[0.98,1.34]
Derosa 2016	1/138	2/143		0.05%	0.52[0.05,5.65]
DIPP 2015	2/104	3/101		0.08%	0.65[0.11,3.79]
DISAF 2003	6/201	8/206		0.19%	0.77[0.27,2.18]
DO IT 2010	14/282	24/281		0.59%	0.58[0.31,1.1]
Doi 2014	2/119	9/119		0.22%	0.22[0.05,1.01]
EPIC-1 2008	1/183	0/180		0.01%	2.95[0.12,71.97]
EPIC-2 2008	0/189	1/190		0.04%	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		0.12%	0.82[0.22,3.03]
FOSTAR 2016	0/101	1/101		0.04%	0.33[0.01,8.09]
GISSI-HF 2008	955/3494	1014/3481		25.03%	0.94[0.87,1.01]
GISSI-P 1999	472/5666	545/5658		13.44%	0.86[0.77,0.97]
HARP 1995	0/41	1/39		0.04%	0.32[0.01,7.57]
JELIS 2007	286/9326	265/9319		6.53%	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		0.39%	1.13[0.58,2.19]
NAT2 2013	3/150	6/150		0.15%	0.5[0.13,1.96]
Nutristroke 2009	0/38	4/34		0.12%	0.1[0.01,1.79]
OFAMI 2001	11/150	11/150		0.27%	1[0.45,2.24]
OMEGA 2009	88/1919	70/1885		1.74%	1.23[0.91,1.68]
OPAL 2010	9/434	8/433		0.2%	1.12[0.44,2.88]
ORIGIN 2012	951/6281	964/6225		23.86%	0.98[0.9,1.06]
Raitt 2005	4/100	10/100		0.25%	0.4[0.13,1.23]
Risk & Prevention 2013	348/6239	337/6266		8.29%	1.04[0.9,1.2]
SCIMO 1999	1/112	2/111		0.05%	0.5[0.05,5.39]
Shinto 2014	1/13	1/13		0.02%	1[0.07,14.34]
SHOT 1996	8/317	6/293		0.15%	1.23[0.43,3.51]
SOFA 2006	8/273	14/273		0.34%	0.57[0.24,1.34]
SU.FOL.OM3 2010	58/1253	59/1248		1.46%	0.98[0.69,1.39]
Zhang 2017	0/120	1/120		0.04%	0.33[0.01,8.1]
Total (95% CI)	**45267**	**44977**		**100%**	**0.97[0.93,1.01]**
Total events: 3949 (Higher omega 3), 4041 (Lower omega 3)					
Heterogeneity: $Tau^2=0$; $Chi^2=43.12$, df=38(P=0.26); $I^2=11.87\%$					
Test for overall effect: Z=1.43(P=0.15)					



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	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
1.3.1 Low risk of bias					
ADCS 2010	11/238	4/164		0.22%	1.89[0.61,5.85]
AlphaOmega - EPA+DHA 2010	186/2404	184/2433		5.97%	1.02[0.84,1.24]
AREDS2 2014	200/2147	168/2056		5.96%	1.14[0.94,1.39]
Berson 2004	0/105	1/103		0.03%	0.33[0.01,7.94]
Derosa 2016	1/138	2/143		0.05%	0.52[0.05,5.65]
FORWARD 2013	4/289	5/297		0.17%	0.82[0.22,3.03]
FOSTAR 2016	0/101	1/101		0.03%	0.33[0.01,8.09]
MAPT 2017	18/840	16/840		0.63%	1.13[0.58,2.19]
NAT2 2013	3/150	6/150		0.15%	0.5[0.13,1.96]
OMEGA 2009	88/1919	70/1885		2.75%	1.23[0.91,1.68]
OPAL 2010	9/434	8/433		0.32%	1.12[0.44,2.88]
ORIGIN 2012	951/6281	964/6225		17.48%	0.98[0.9,1.06]
SCIMO 1999	1/112	2/111		0.05%	0.5[0.05,5.39]
SOFA 2006	8/273	14/273		0.39%	0.57[0.24,1.34]
SU.FOL.OM3 2010	66/1253	68/1248		2.42%	0.97[0.7,1.34]
Subtotal (95% CI)	**16684**	**16462**		**36.61%**	**1.01[0.94,1.08]**
Total events: 1546 (Higher omega 3), 1513 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=9.55, df=14(P=0.79); I^2=0%					
Test for overall effect: Z=0.23(P=0.81)					
1.3.2 Moderate/high risk of bias					
AFFORD 2013	0/153	1/163		0.03%	0.35[0.01,8.65]
Bates 1989	1/155	0/157		0.03%	3.04[0.12,74.02]
Brox 2001	0/80	1/40		0.03%	0.17[0.01,4.05]
DART 1989	94/1015	131/1018		3.96%	0.72[0.56,0.92]
DART2 2003	283/1571	242/1543		8.39%	1.15[0.98,1.34]
DIPP 2015	2/104	3/101		0.09%	0.65[0.11,3.79]
DISAF 2003	6/201	8/206		0.26%	0.77[0.27,2.18]
DO IT 2010	14/282	24/281		0.69%	0.58[0.31,1.1]
Doi 2014	2/119	9/119		0.12%	0.22[0.05,1.01]
EPIC-1 2008	1/183	0/180		0.03%	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		0.49%	1.09[0.51,2.34]
GISSI-HF 2008	955/3494	1014/3481		18.85%	0.94[0.87,1.01]
GISSI-P 1999	472/5666	545/5658		12.22%	0.86[0.77,0.97]
HARP 1995	0/41	1/39		0.03%	0.32[0.01,7.57]
JELIS 2007	286/9326	265/9319		7.8%	1.08[0.91,1.27]
Kumar 2013	1/39	1/39		0.04%	1[0.06,15.43]
Nutristroke 2009	0/38	4/34		0.03%	0.1[0.01,1.79]
OFAMI 2001	11/150	11/150		0.44%	1[0.45,2.24]
Raitt 2005	4/100	10/100		0.22%	0.4[0.13,1.23]
Risk & Prevention 2013	348/6239	337/6266		9.29%	1.04[0.9,1.2]
Shinto 2014	1/13	1/13		0.04%	1[0.07,14.34]
SHOT 1996	8/317	6/293		0.26%	1.23[0.43,3.51]
Zhang 2017	0/120	1/120		0.03%	0.33[0.01,8.1]
Subtotal (95% CI)	**29795**	**29712**		**63.39%**	**0.94[0.86,1.03]**
Total events: 2502 (Higher omega 3), 2628 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=31.55, df=23(P=0.11); I^2=27.1%					



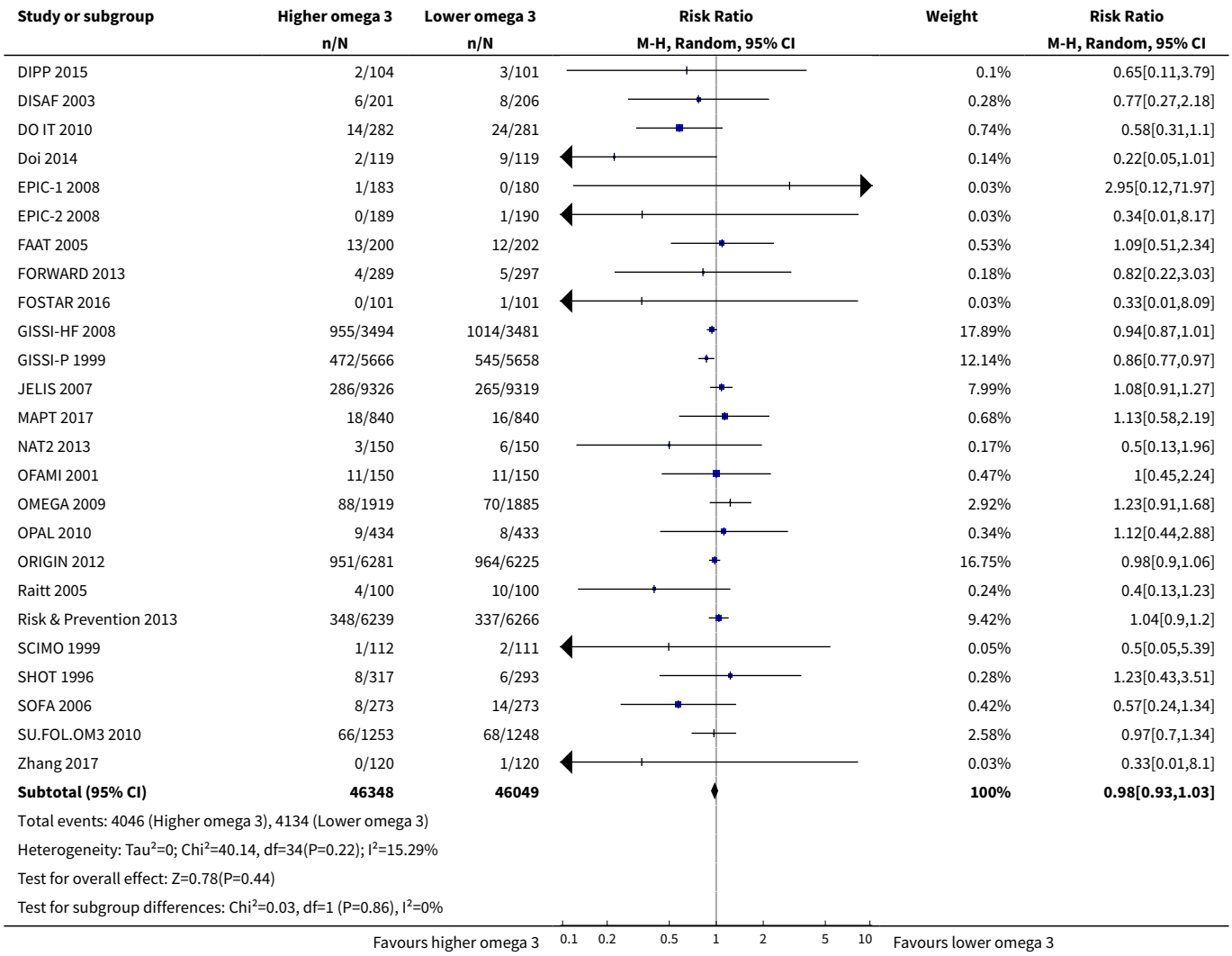
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=1.29(P=0.2)					
Total (95% CI)	**46479**	**46174**		**100%**	**0.98[0.93,1.03]**
Total events: 4048 (Higher omega 3), 4141 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=43.01, df=38(P=0.27); I^2=11.64%					
Test for overall effect: Z=0.87(P=0.39)					
Test for subgroup differences: Chi^2=1.36, df=1 (P=0.24), I^2=26.63%					

Favours higher omega 3 — 0.1 0.2 0.5 1 2 5 10 — Favours lower omega 3

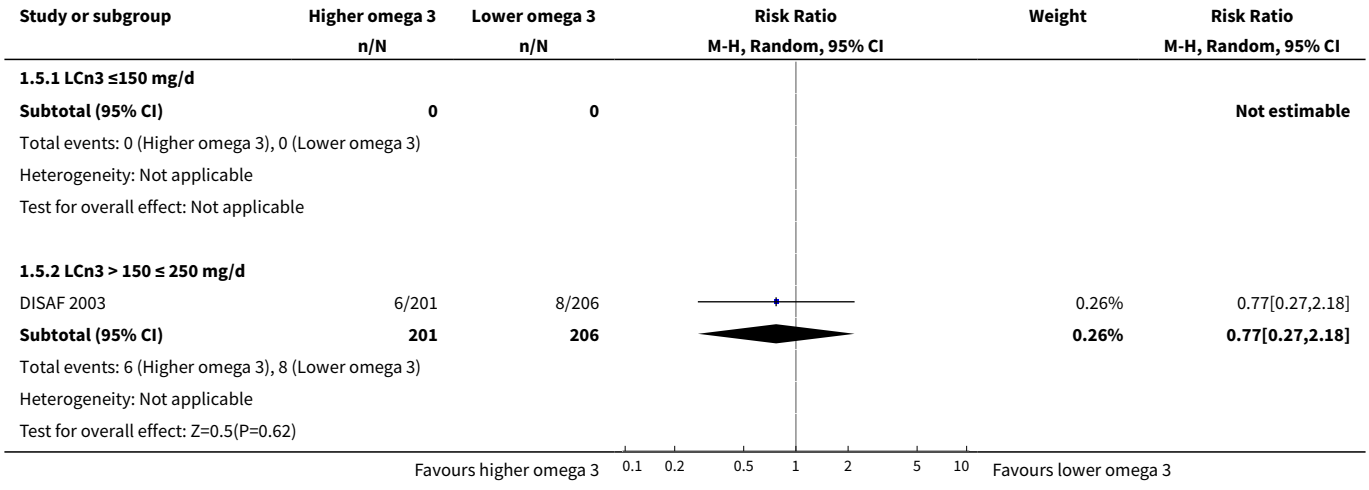
Analysis 1.4. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 4 All-cause mortality - LCn3 - SA by compliance and study size.

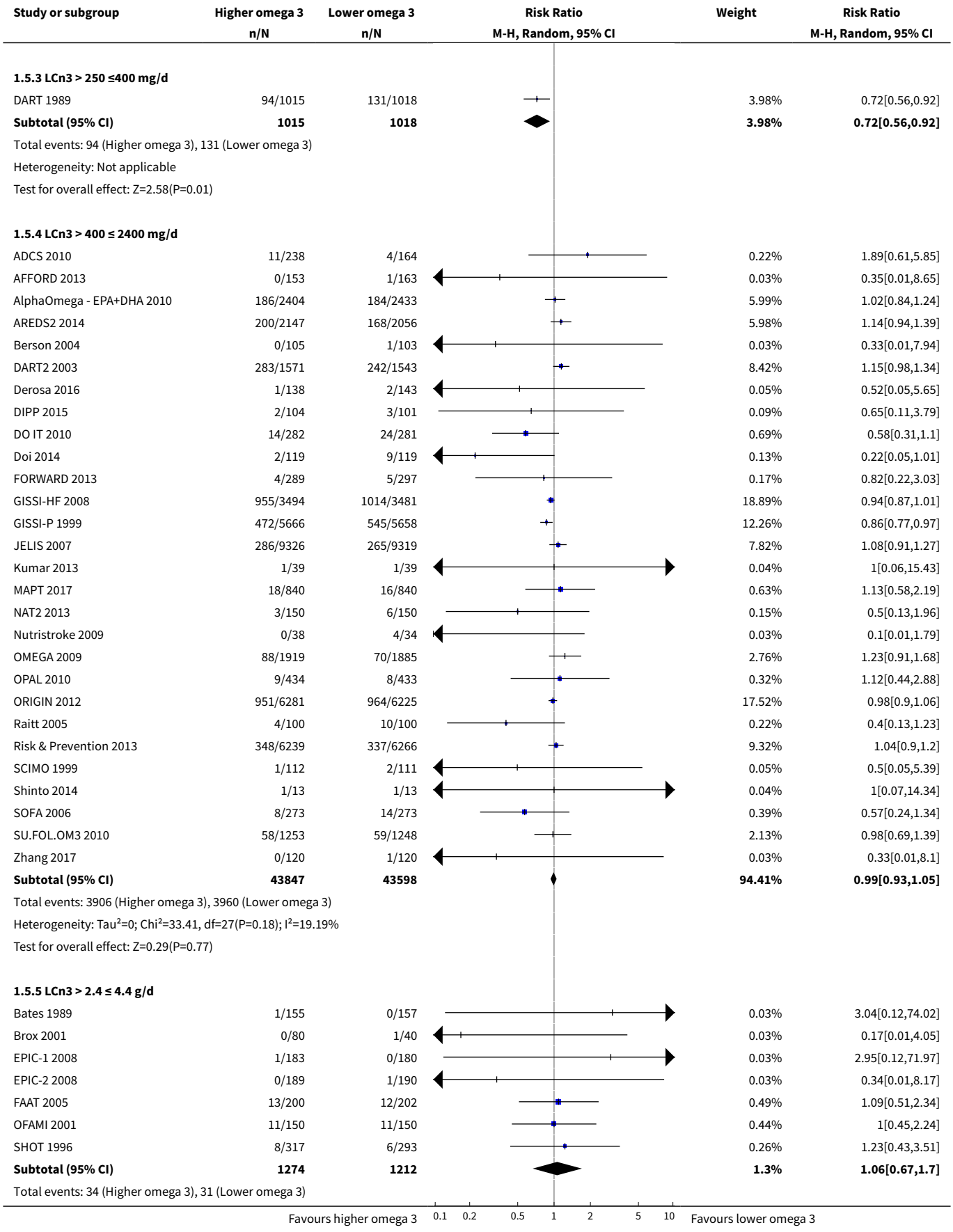
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 SA - low risk of compliance bias					
AFFORD 2013	0/153	1/163		0.18%	0.35[0.01,8.65]
AlphaOmega - EPA+DHA 2010	186/2404	184/2433		48.6%	1.02[0.84,1.24]
Bates 1989	1/155	0/157		0.18%	3.04[0.12,74.02]
Berson 2004	0/105	1/103		0.18%	0.33[0.01,7.94]
Brox 2001	0/80	1/40		0.18%	0.17[0.01,4.05]
DISAF 2003	6/201	8/206		1.72%	0.77[0.27,2.18]
DO IT 2010	14/282	24/281		4.58%	0.58[0.31,1.1]
FOSTAR 2016	0/101	1/101		0.18%	0.33[0.01,8.09]
HARP 1995	0/41	1/39		0.19%	0.32[0.01,7.57]
Kumar 2013	1/39	1/39		0.25%	1[0.06,15.43]
NAT2 2013	3/150	6/150		1%	0.5[0.13,1.96]
OMEGA 2009	88/1919	70/1885		19.73%	1.23[0.91,1.68]
OPAL 2010	9/434	8/433		2.1%	1.12[0.44,2.88]
Raitt 2005	4/100	10/100		1.47%	0.4[0.13,1.23]
SCIMO 1999	1/112	2/111		0.33%	0.5[0.05,5.39]
Shinto 2014	1/13	1/13		0.26%	1[0.07,14.34]
SHOT 1996	8/317	6/293		1.7%	1.23[0.43,3.51]
SU.FOL.OM3 2010	66/1253	68/1248		17.17%	0.97[0.7,1.34]
Subtotal (95% CI)	**7859**	**7795**		**100%**	**0.99[0.86,1.14]**
Total events: 388 (Higher omega 3), 393 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=12.5, df=17(P=0.77); I^2=0%					
Test for overall effect: Z=0.12(P=0.9)					
1.4.2 SA - 100+ randomised					
ADCS 2010	11/238	4/164		0.24%	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		6.2%	1.02[0.84,1.24]
AREDS2 2014	200/2147	168/2056		6.19%	1.14[0.94,1.39]
Bates 1989	1/155	0/157		0.03%	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		4.18%	0.72[0.56,0.92]
DART2 2003	283/1571	242/1543		8.56%	1.15[0.98,1.34]
Derosa 2016	1/138	2/143		0.05%	0.52[0.05,5.65]

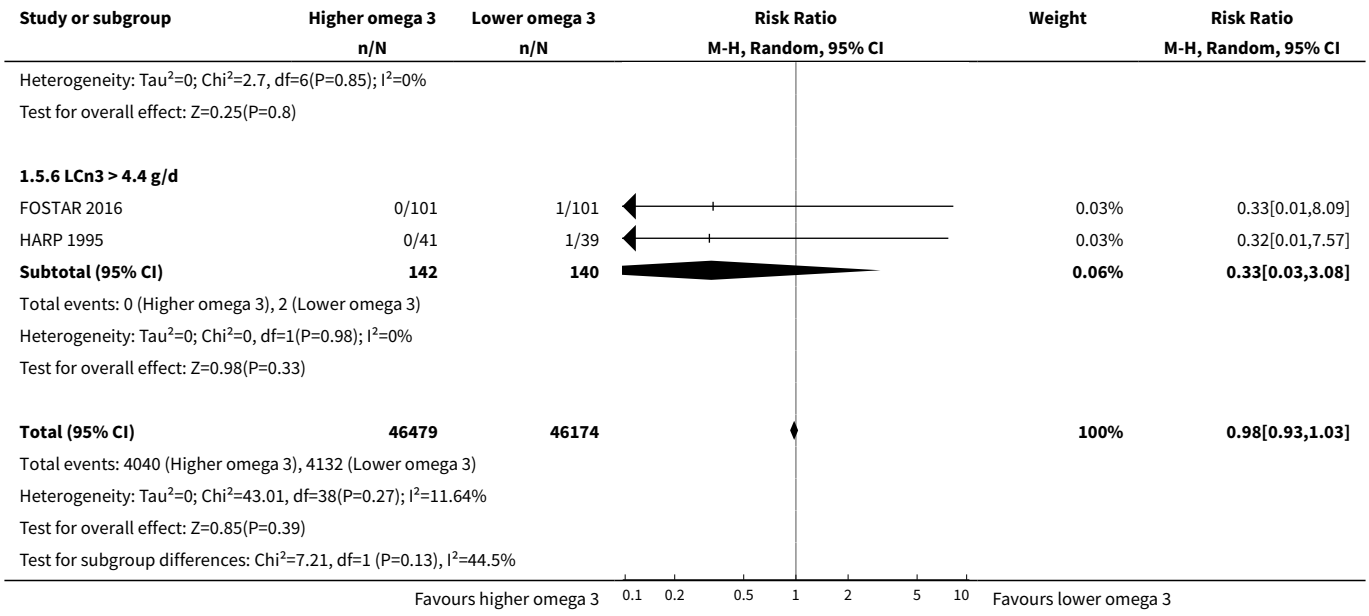
Favours higher omega 3 — 0.1 0.2 0.5 1 2 5 10 — Favours lower omega 3



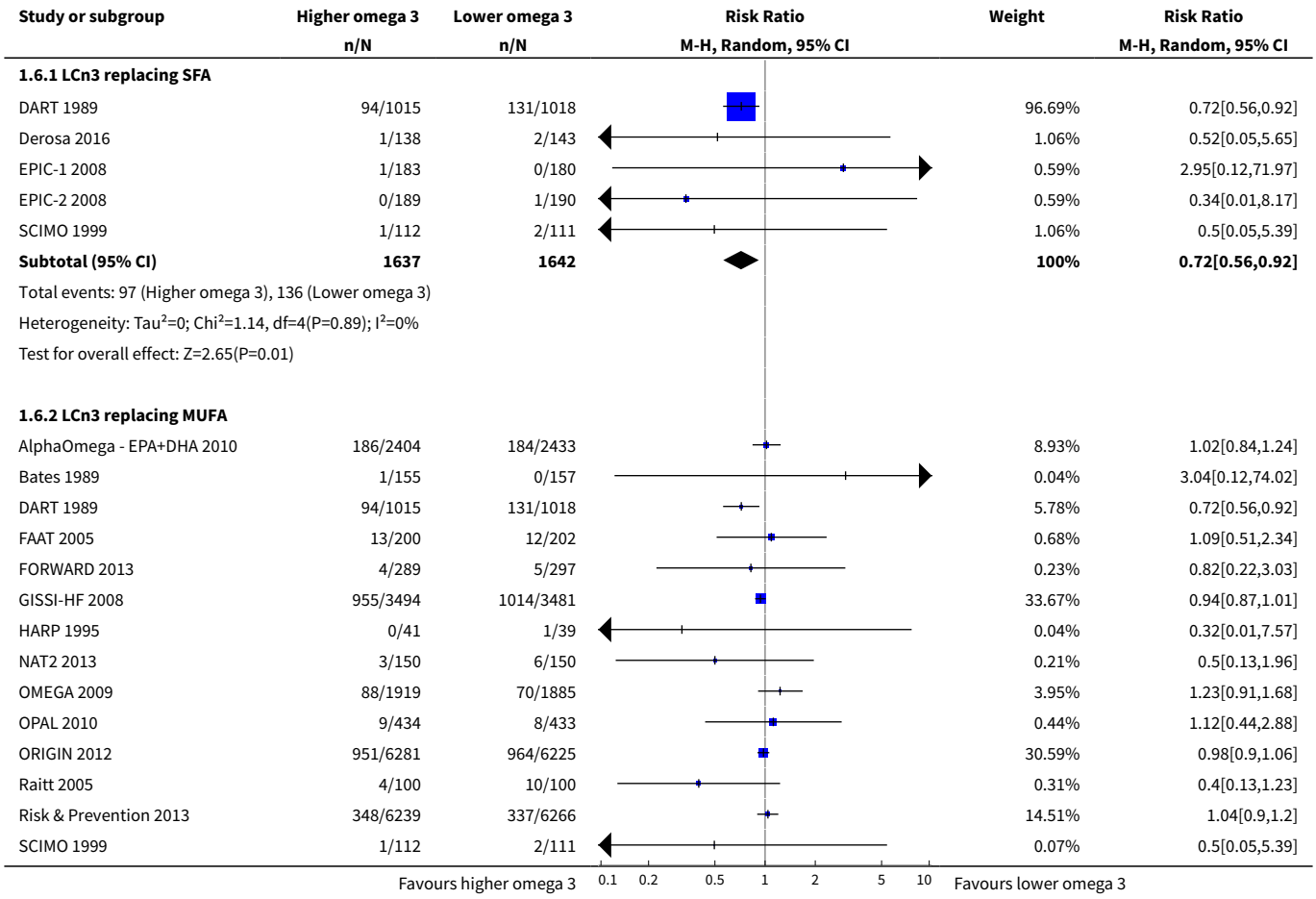
Analysis 1.5. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 5 All-cause mortality - LCn3 - subgroup by dose.

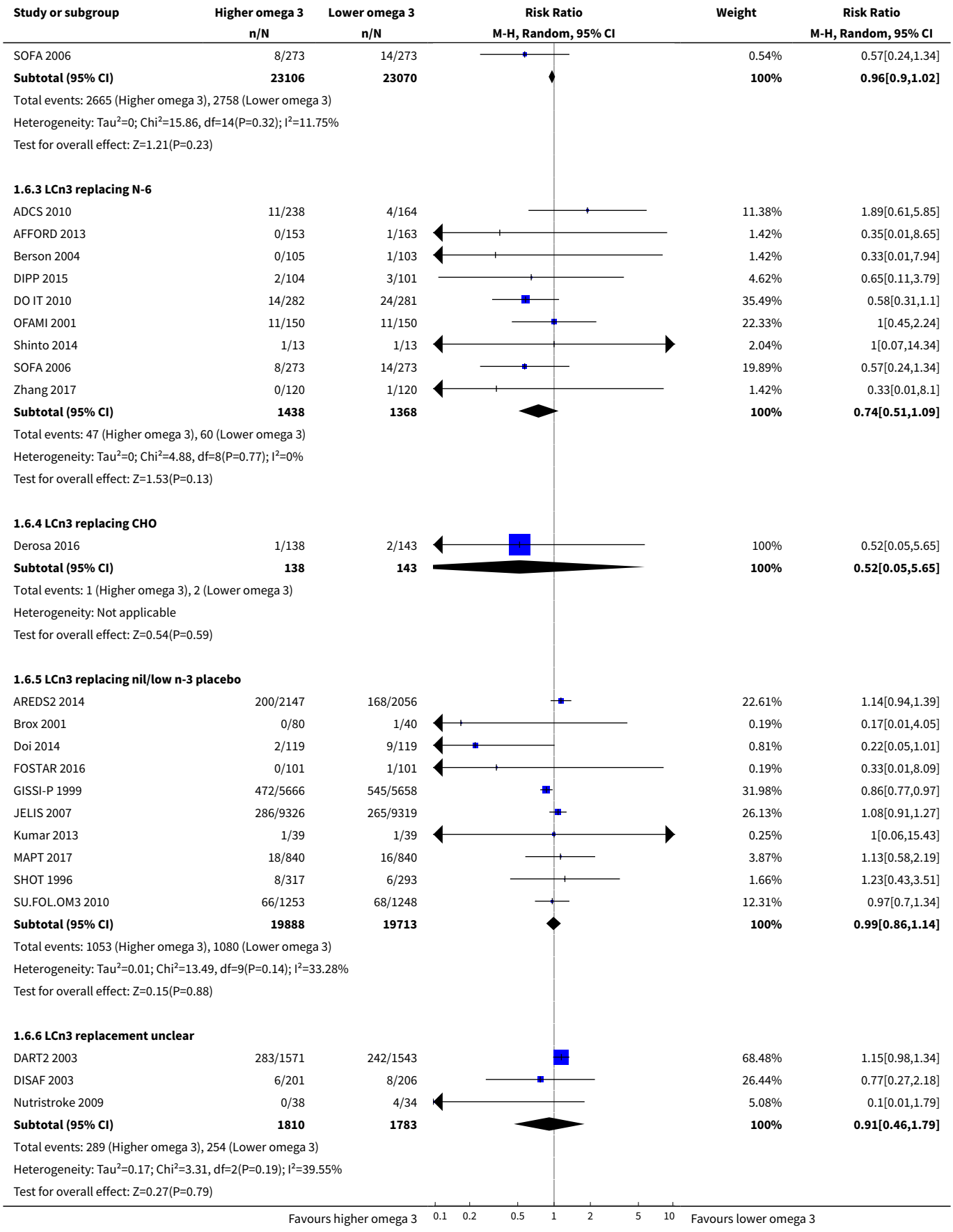






Analysis 1.6. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 6 All-cause mortality - LCn3 - subgroup by replacement.





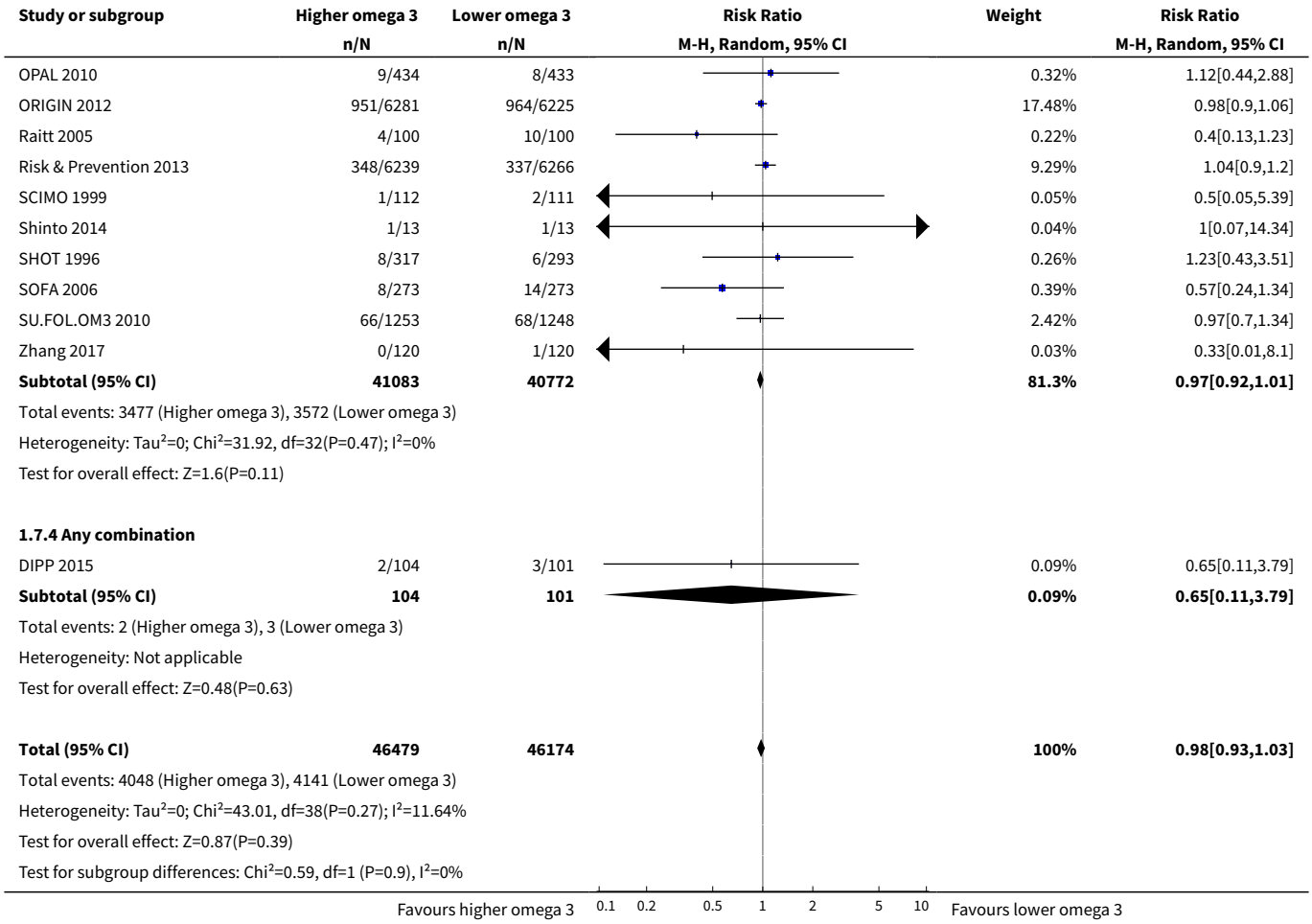
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for subgroup differences: Chi²=7.35, df=1 (P=0.2), I²=31.98%					

Favours higher omega 3 — Favours lower omega 3

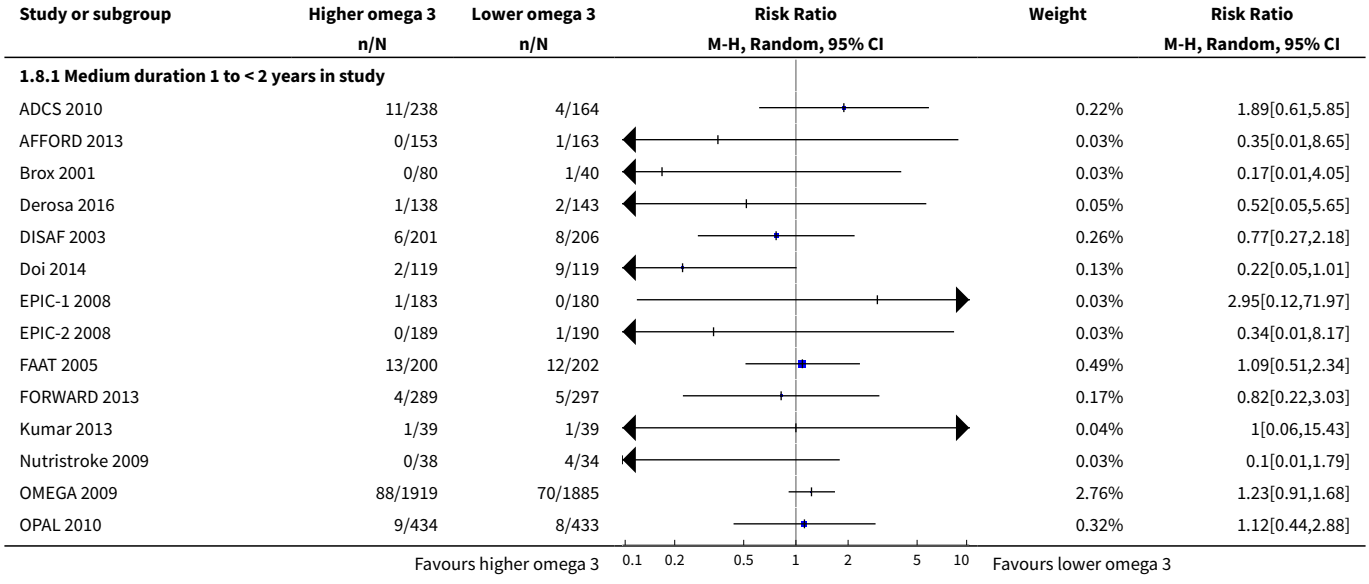
Analysis 1.7. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 7 All-cause mortality - LCn3 - subgroup by intervention type.

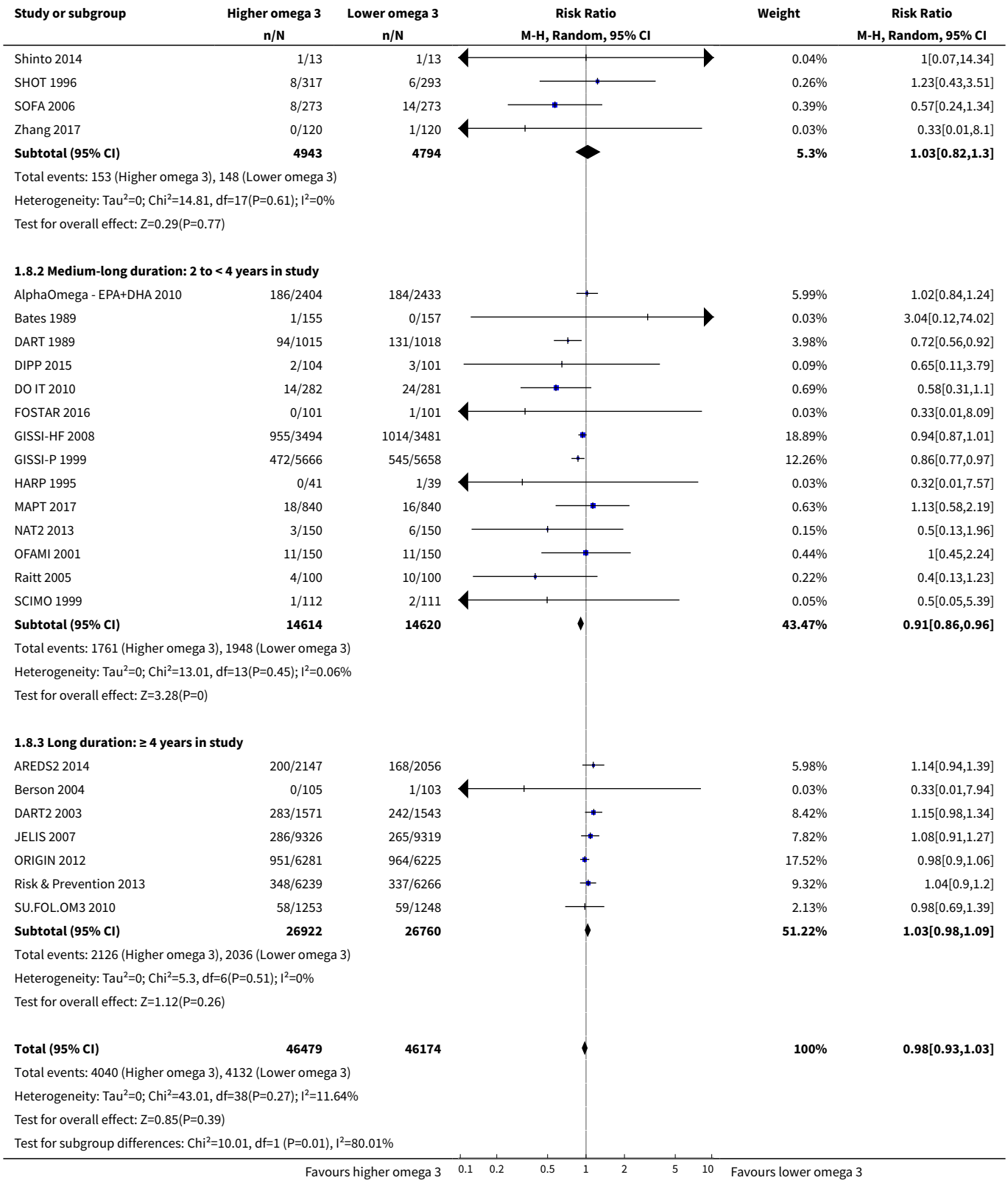
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 Dietary advice					
DART 1989	94/1015	131/1018		3.96%	0.72[0.56,0.92]
DART2 2003	283/1571	242/1543		8.39%	1.15[0.98,1.34]
DISAF 2003	6/201	8/206		0.26%	0.77[0.27,2.18]
Subtotal (95% CI)	**2787**	**2767**		**12.61%**	**0.9[0.6,1.35]**
Total events: 383 (Higher omega 3), 381 (Lower omega 3)					
Heterogeneity: Tau²=0.08; Chi²=9.9, df=2(P=0.01); I²=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		5.97%	1.02[0.84,1.24]
FOSTAR 2016	0/101	1/101		0.03%	0.33[0.01,8.09]
Subtotal (95% CI)	**2505**	**2534**		**6%**	**1.02[0.84,1.24]**
Total events: 186 (Higher omega 3), 185 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=0.47, df=1(P=0.49); I²=0%					
Test for overall effect: Z=0.19(P=0.85)					
1.7.3 Supplements (capsule)					
ADCS 2010	11/238	4/164		0.22%	1.89[0.61,5.85]
AFFORD 2013	0/153	1/163		0.03%	0.35[0.01,8.65]
AREDS2 2014	200/2147	168/2056		5.96%	1.14[0.94,1.39]
Bates 1989	1/155	0/157		0.03%	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]
Derosa 2016	1/138	2/143		0.05%	0.52[0.05,5.65]
DO IT 2010	14/282	24/281		0.69%	0.58[0.31,1.1]
Doi 2014	2/119	9/119		0.12%	0.22[0.05,1.01]
EPIC-1 2008	1/183	0/180		0.03%	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		0.49%	1.09[0.51,2.34]
FORWARD 2013	4/289	5/297		0.17%	0.82[0.22,3.03]
GISSI-HF 2008	955/3494	1014/3481		18.85%	0.94[0.87,1.01]
GISSI-P 1999	472/5666	545/5658		12.22%	0.86[0.77,0.97]
HARP 1995	0/41	1/39		0.03%	0.32[0.01,7.57]
JELIS 2007	286/9326	265/9319		7.8%	1.08[0.91,1.27]
Kumar 2013	1/39	1/39		0.04%	1[0.06,15.43]
MAPT 2017	18/840	16/840		0.63%	1.13[0.58,2.19]
NAT2 2013	3/150	6/150		0.15%	0.5[0.13,1.96]
Nutristroke 2009	0/38	4/34		0.03%	0.1[0.01,1.79]
OFAMI 2001	11/150	11/150		0.44%	1[0.45,2.24]
OMEGA 2009	88/1919	70/1885		2.75%	1.23[0.91,1.68]

Favours higher omega 3 — Favours lower omega 3



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



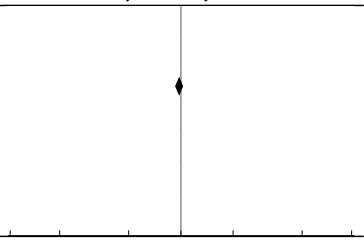


Analysis 1.9. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 9 All-cause mortality - LCn3 - subgroup by primary or secondary prevention.

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		0.22%	1.89[0.61,5.85]
AREDS2 2014	200/2147	168/2056		5.98%	1.14[0.94,1.39]
Bates 1989	1/155	0/157		0.03%	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]
Derosa 2016	1/138	2/143		0.05%	0.52[0.05,5.65]
DIPP 2015	2/104	3/101		0.09%	0.65[0.11,3.79]
DO IT 2010	14/282	24/281		0.69%	0.58[0.31,1.1]
EPIC-1 2008	1/183	0/180		0.03%	2.95[0.12,71.97]
EPIC-2 2008	0/189	1/190		0.03%	0.34[0.01,8.17]
FOSTAR 2016	0/101	1/101		0.03%	0.33[0.01,8.09]
JELIS 2007	286/9326	265/9319		7.82%	1.08[0.91,1.27]
MAPT 2017	18/840	16/840		0.63%	1.13[0.58,2.19]
OPAL 2010	9/434	8/433		0.32%	1.12[0.44,2.88]
ORIGIN 2012	951/6281	964/6225		17.52%	0.98[0.9,1.06]
Shinto 2014	1/13	1/13		0.04%	1[0.07,14.34]
Zhang 2017	0/120	1/120		0.03%	0.33[0.01,8.1]
Subtotal (95% CI)	**20736**	**20466**		**33.57%**	**1.01[0.94,1.08]**
Total events: 1495 (Higher omega 3), 1460 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=11.42, df=16(P=0.78); I^2=0%					
Test for overall effect: Z=0.24(P=0.81)					
1.9.2 Secondary CVD prevention					
AFFORD 2013	0/153	1/163		0.03%	0.35[0.01,8.65]
AlphaOmega - EPA+DHA 2010	186/2404	184/2433		5.99%	1.02[0.84,1.24]
DART 1989	94/1015	131/1018		3.98%	0.72[0.56,0.92]
DART2 2003	283/1571	242/1543		8.42%	1.15[0.98,1.34]
DISAF 2003	6/201	8/206		0.26%	0.77[0.27,2.18]
Doi 2014	2/119	9/119		0.13%	0.22[0.05,1.01]
FAAT 2005	13/200	12/202		0.49%	1.09[0.51,2.34]
FORWARD 2013	4/289	5/297		0.17%	0.82[0.22,3.03]
GISSI-HF 2008	955/3494	1014/3481		18.89%	0.94[0.87,1.01]
GISSI-P 1999	472/5666	545/5658		12.26%	0.86[0.77,0.97]
HARP 1995	0/41	1/39		0.03%	0.32[0.01,7.57]
Kumar 2013	1/39	1/39		0.04%	1[0.06,15.43]
NAT2 2013	3/150	6/150		0.15%	0.5[0.13,1.96]
Nutristroke 2009	0/38	4/34		0.03%	0.1[0.01,1.79]
OFAMI 2001	11/150	11/150		0.44%	1[0.45,2.24]
OMEGA 2009	88/1919	70/1885		2.76%	1.23[0.91,1.68]
Raitt 2005	4/100	10/100		0.22%	0.4[0.13,1.23]
Risk & Prevention 2013	348/6239	337/6266		9.32%	1.04[0.9,1.2]
SCIMO 1999	1/112	2/111		0.05%	0.5[0.05,5.39]
SHOT 1996	8/317	6/293		0.26%	1.23[0.43,3.51]
SOFA 2006	8/273	14/273		0.39%	0.57[0.24,1.34]
SU.FOL.OM3 2010	58/1253	59/1248		2.13%	0.98[0.69,1.39]
Subtotal (95% CI)	**25743**	**25708**		**66.43%**	**0.95[0.88,1.04]**
Total events: 2545 (Higher omega 3), 2672 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=29.78, df=21(P=0.1); I^2=29.48%					

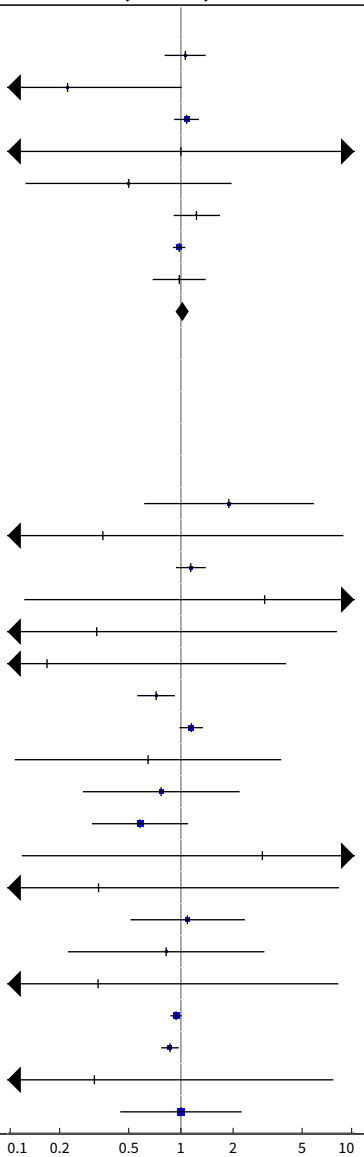
Favours higher omega 3 — Favours lower omega 3

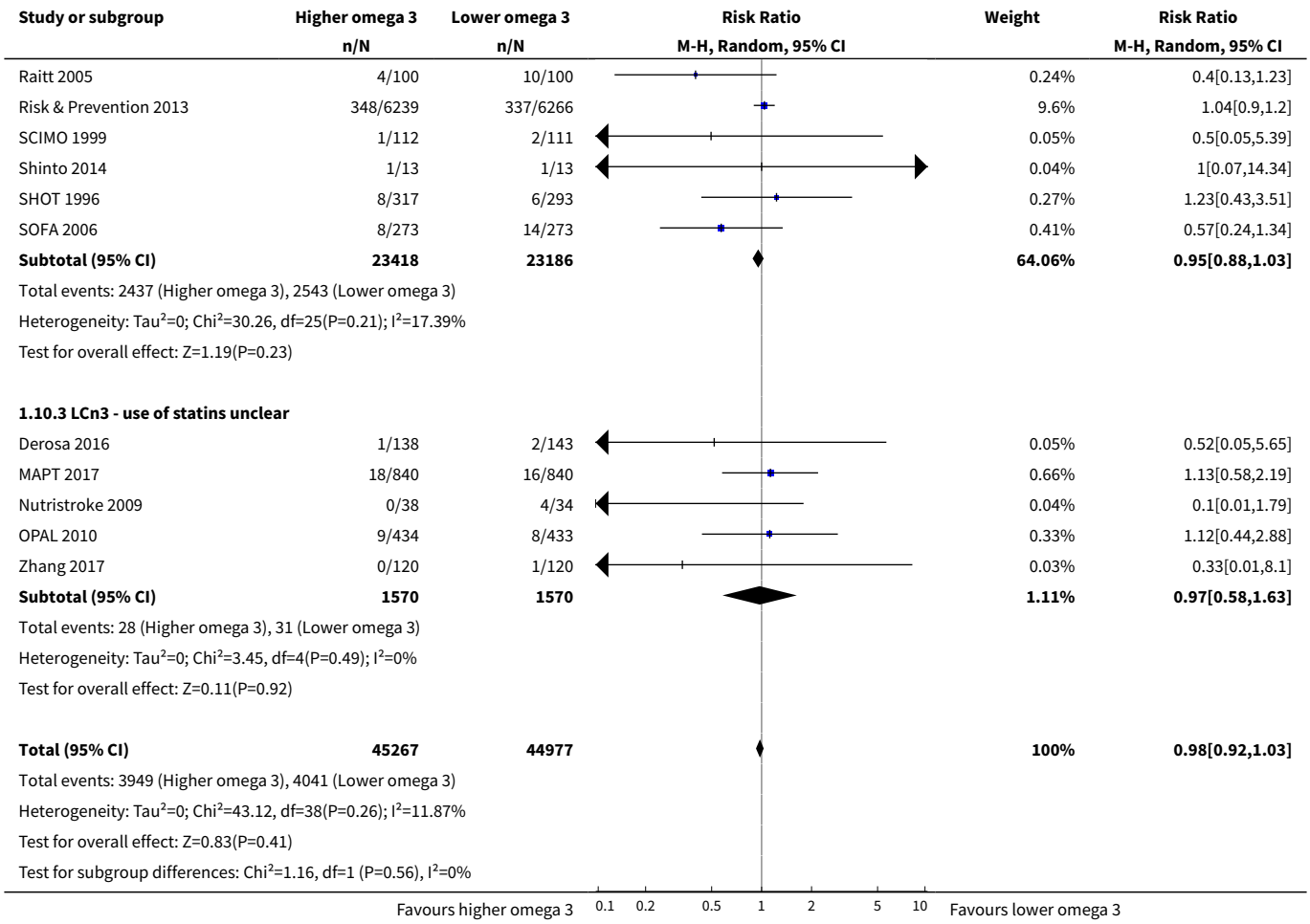
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=1.11(P=0.27)					
Total (95% CI)	**46479**	**46174**		**100%**	**0.98[0.93,1.03]**
Total events: 4040 (Higher omega 3), 4132 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=43.01, df=38(P=0.27); I^2=11.64%					
Test for overall effect: Z=0.85(P=0.39)					
Test for subgroup differences: Chi^2=1.03, df=1 (P=0.31), I^2=2.54%					



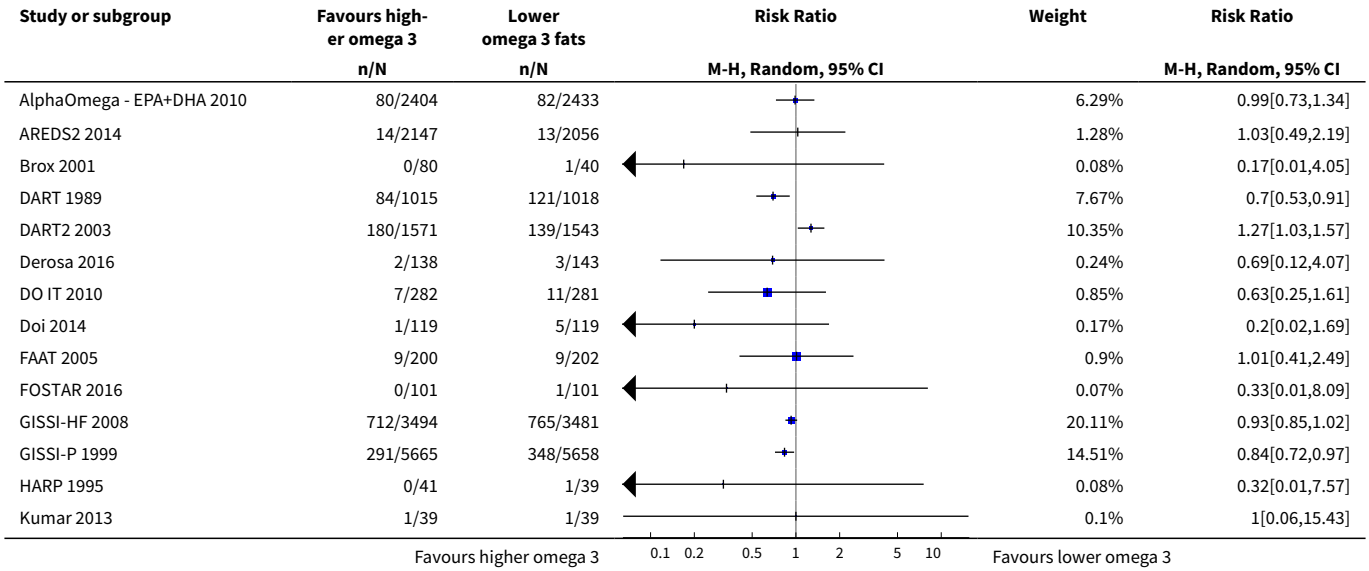
Analysis 1.10. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 10 All-cause mortality - LCn3 - subgroup by statin use.

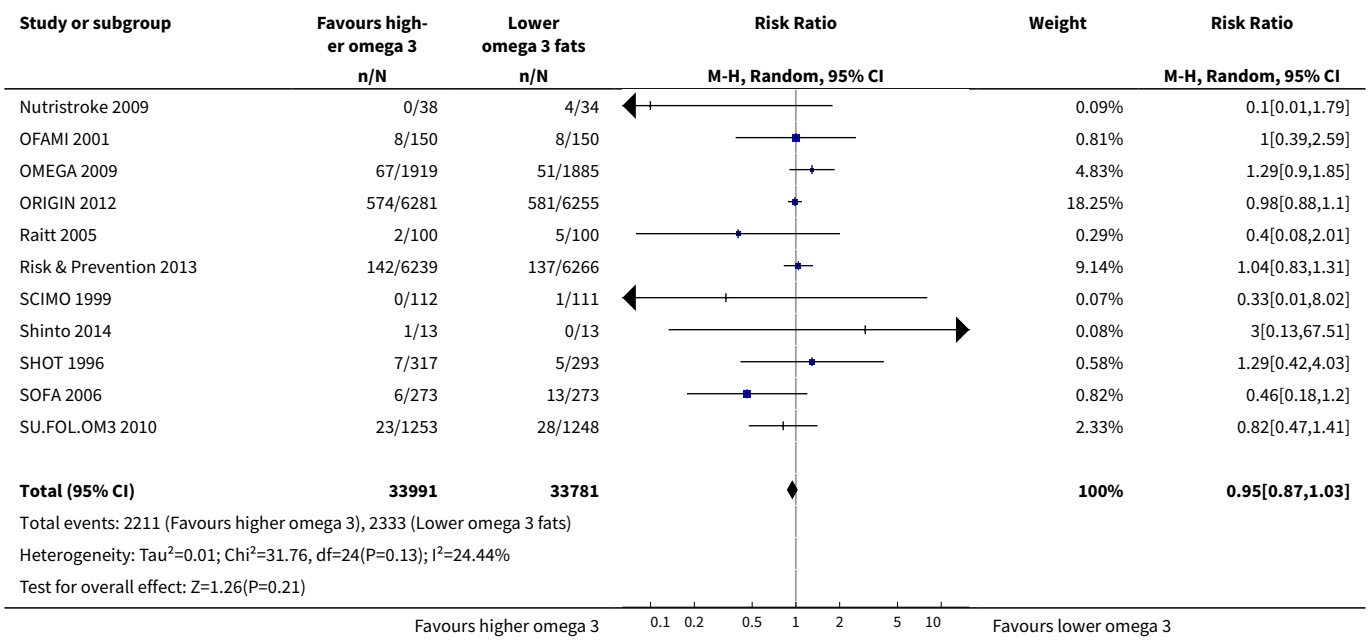
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.10.1 LCn3 - ≥50% of control group on statins					
AlphaOmega - EPA+DHA 2010	95/1192	93/1236		3.52%	1.06[0.8,1.39]
Doi 2014	2/119	9/119		0.13%	0.22[0.05,1.01]
JELIS 2007	286/9326	265/9319		8.08%	1.08[0.91,1.27]
Kumar 2013	1/39	1/39		0.04%	1[0.06,15.43]
NAT2 2013	3/150	6/150		0.16%	0.5[0.13,1.96]
OMEGA 2009	88/1919	70/1885		2.87%	1.23[0.91,1.68]
ORIGIN 2012	951/6281	964/6225		17.8%	0.98[0.9,1.06]
SU.FOL.OM3 2010	58/1253	59/1248		2.22%	0.98[0.69,1.39]
Subtotal (95% CI)	**20279**	**20221**		**34.83%**	**1.02[0.93,1.11]**
Total events: 1484 (Higher omega 3), 1467 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=7.85, df=7(P=0.35); I^2=10.86%					
Test for overall effect: Z=0.38(P=0.7)					
1.10.2 LCn3 - < 50% of control group on statins					
ADCS 2010	11/238	4/164		0.23%	1.89[0.61,5.85]
AFFORD 2013	0/153	1/163		0.03%	0.35[0.01,8.65]
AREDS2 2014	200/2147	168/2056		6.2%	1.14[0.94,1.39]
Bates 1989	1/155	0/157		0.03%	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		4.13%	0.72[0.56,0.92]
DART2 2003	283/1571	242/1543		8.69%	1.15[0.98,1.34]
DIPP 2015	2/104	3/101		0.1%	0.65[0.11,3.79]
DISAF 2003	6/201	8/206		0.28%	0.77[0.27,2.18]
DO IT 2010	14/282	24/281		0.72%	0.58[0.31,1.1]
EPIC-1 2008	1/183	0/180		0.03%	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		0.51%	1.09[0.51,2.34]
FORWARD 2013	4/289	5/297		0.18%	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		19.15%	0.94[0.87,1.01]
GISSI-P 1999	472/5666	545/5658		12.57%	0.86[0.77,0.97]
HARP 1995	0/41	1/39		0.03%	0.32[0.01,7.57]
OFAMI 2001	11/150	11/150		0.46%	1[0.45,2.24]





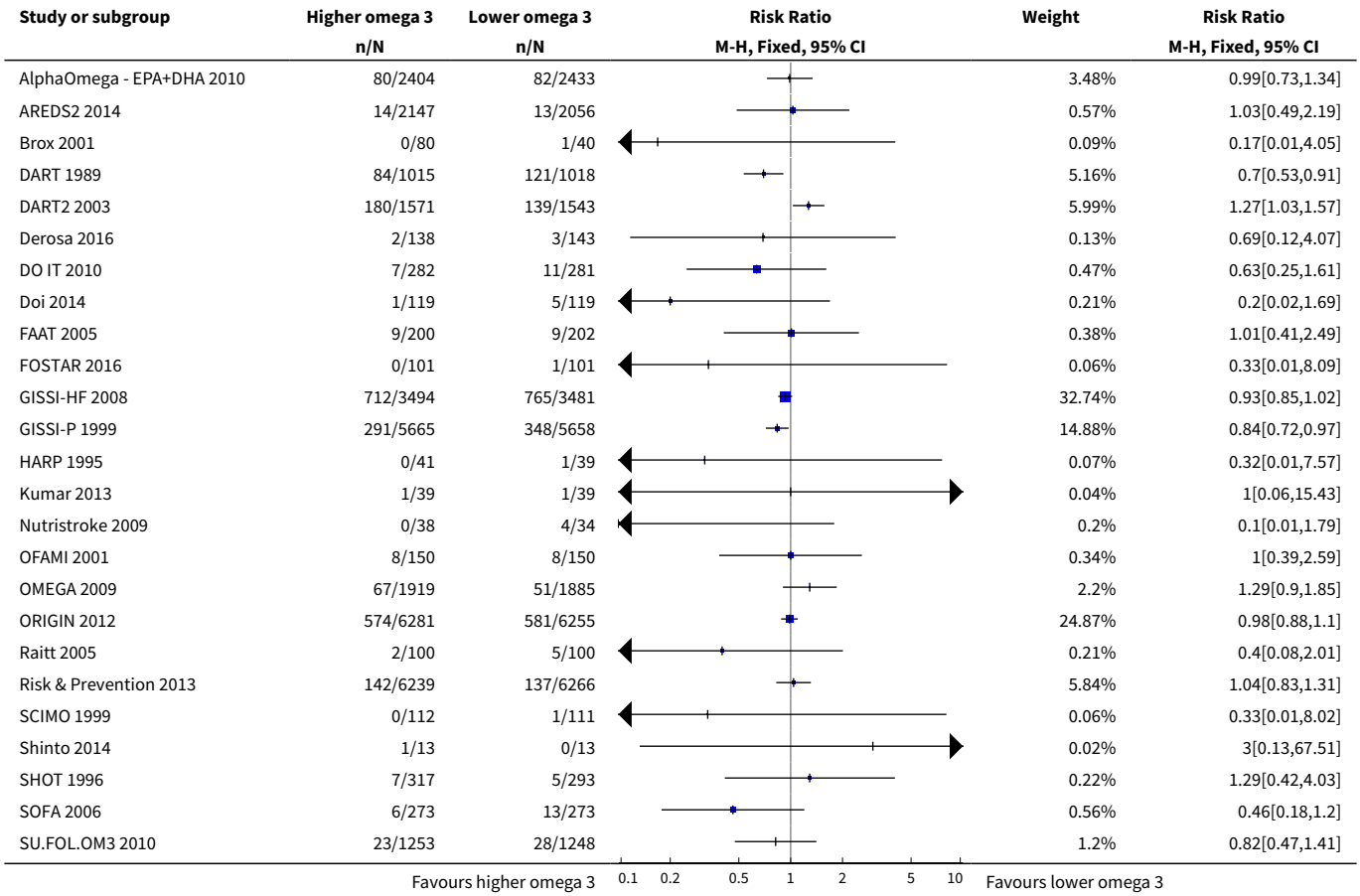
Analysis 1.11. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 11 Cardiovascular mortality (overall) - LCn3.





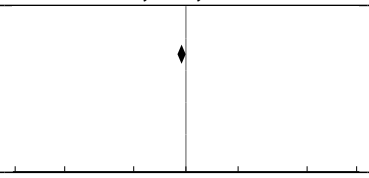
Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 fats n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Nutristroke 2009	0/38	4/34		0.09%	0.1[0.01,1.79]
OFAMI 2001	8/150	8/150		0.81%	1[0.39,2.59]
OMEGA 2009	67/1919	51/1885		4.83%	1.29[0.9,1.85]
ORIGIN 2012	574/6281	581/6255		18.25%	0.98[0.88,1.1]
Raitt 2005	2/100	5/100		0.29%	0.4[0.08,2.01]
Risk & Prevention 2013	142/6239	137/6266		9.14%	1.04[0.83,1.31]
SCIMO 1999	0/112	1/111		0.07%	0.33[0.01,8.02]
Shinto 2014	1/13	0/13		0.08%	3[0.13,67.51]
SHOT 1996	7/317	5/293		0.58%	1.29[0.42,4.03]
SOFA 2006	6/273	13/273		0.82%	0.46[0.18,1.2]
SU.FOL.OM3 2010	23/1253	28/1248		2.33%	0.82[0.47,1.41]
Total (95% CI)	**33991**	**33781**		**100%**	**0.95[0.87,1.03]**
Total events: 2211 (Favours higher omega 3), 2333 (Lower omega 3 fats)					
Heterogeneity: Tau²=0.01; Chi²=31.76, df=24(P=0.13); I²=24.44%					
Test for overall effect: Z=1.26(P=0.21)					

Analysis 1.12. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 12 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		3.48%	0.99[0.73,1.34]
AREDS2 2014	14/2147	13/2056		0.57%	1.03[0.49,2.19]
Brox 2001	0/80	1/40		0.09%	0.17[0.01,4.05]
DART 1989	84/1015	121/1018		5.16%	0.7[0.53,0.91]
DART2 2003	180/1571	139/1543		5.99%	1.27[1.03,1.57]
Derosa 2016	2/138	3/143		0.13%	0.69[0.12,4.07]
DO IT 2010	7/282	11/281		0.47%	0.63[0.25,1.61]
Doi 2014	1/119	5/119		0.21%	0.2[0.02,1.69]
FAAT 2005	9/200	9/202		0.38%	1.01[0.41,2.49]
FOSTAR 2016	0/101	1/101		0.06%	0.33[0.01,8.09]
GISSI-HF 2008	712/3494	765/3481		32.74%	0.93[0.85,1.02]
GISSI-P 1999	291/5665	348/5658		14.88%	0.84[0.72,0.97]
HARP 1995	0/41	1/39		0.07%	0.32[0.01,7.57]
Kumar 2013	1/39	1/39		0.04%	1[0.06,15.43]
Nutristroke 2009	0/38	4/34		0.2%	0.1[0.01,1.79]
OFAMI 2001	8/150	8/150		0.34%	1[0.39,2.59]
OMEGA 2009	67/1919	51/1885		2.2%	1.29[0.9,1.85]
ORIGIN 2012	574/6281	581/6255		24.87%	0.98[0.88,1.1]
Raitt 2005	2/100	5/100		0.21%	0.4[0.08,2.01]
Risk & Prevention 2013	142/6239	137/6266		5.84%	1.04[0.83,1.31]
SCIMO 1999	0/112	1/111		0.06%	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		0.22%	1.29[0.42,4.03]
SOFA 2006	6/273	13/273		0.56%	0.46[0.18,1.2]
SU.FOL.OM3 2010	23/1253	28/1248		1.2%	0.82[0.47,1.41]

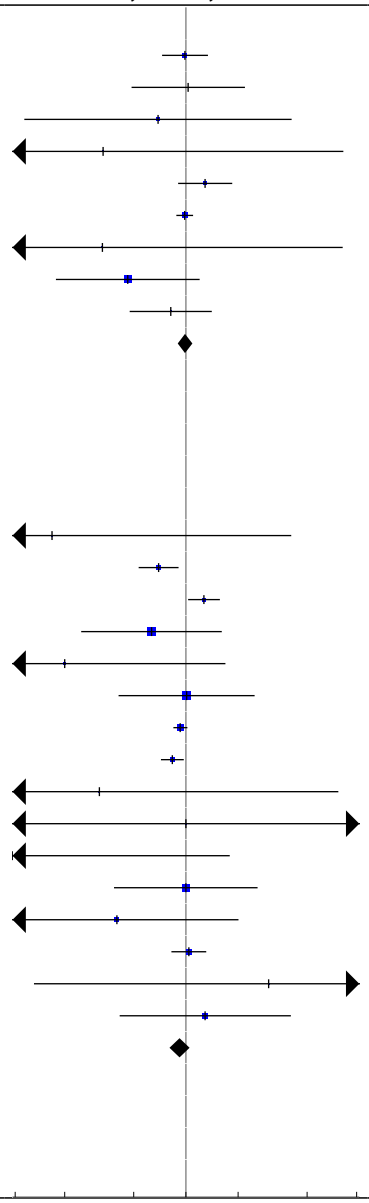
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)	**33991**	**33781**		**100%**	**0.94[0.89,1]**
Total events: 2211 (Higher omega 3), 2333 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=31.76, df=24(P=0.13); I^2=24.44%					
Test for overall effect: Z=2.07(P=0.04)					



Favours higher omega 3 — Favours lower omega 3

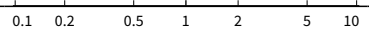
Analysis 1.13. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 13 CVD mortality - LCn3 - SA by summary risk of bias.

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
1.13.1 Low risk of bias					
AlphaOmega - EPA+DHA 2010	80/2404	82/2433		6.29%	0.99[0.73,1.34]
AREDS2 2014	14/2147	13/2056		1.28%	1.03[0.49,2.19]
Derosa 2016	2/138	3/143		0.24%	0.69[0.12,4.07]
FOSTAR 2016	0/101	1/101		0.07%	0.33[0.01,8.09]
OMEGA 2009	67/1919	51/1885		4.83%	1.29[0.9,1.85]
ORIGIN 2012	574/6281	581/6255		18.25%	0.98[0.88,1.1]
SCIMO 1999	0/112	1/111		0.07%	0.33[0.01,8.02]
SOFA 2006	6/273	13/273		0.82%	0.46[0.18,1.2]
SU.FOL.OM3 2010	23/1253	28/1248		2.33%	0.82[0.47,1.41]
Subtotal (95% CI)	**14628**	**14505**		**34.19%**	**0.99[0.9,1.09]**
Total events: 766 (Higher omega 3), 773 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=6.11, df=8(P=0.63); I^2=0%					
Test for overall effect: Z=0.25(P=0.81)					
1.13.2 Moderate/high risk of bias					
Brox 2001	0/80	1/40		0.08%	0.17[0.01,4.05]
DART 1989	84/1015	121/1018		7.67%	0.7[0.53,0.91]
DART2 2003	180/1571	139/1543		10.35%	1.27[1.03,1.57]
DO IT 2010	7/282	11/281		0.85%	0.63[0.25,1.61]
Doi 2014	1/119	5/119		0.17%	0.2[0.02,1.69]
FAAT 2005	9/200	9/202		0.9%	1.01[0.41,2.49]
GISSI-HF 2008	712/3494	765/3481		20.11%	0.93[0.85,1.02]
GISSI-P 1999	291/5665	348/5658		14.51%	0.84[0.72,0.97]
HARP 1995	0/41	1/39		0.08%	0.32[0.01,7.57]
Kumar 2013	1/39	1/39		0.1%	1[0.06,15.43]
Nutristroke 2009	0/38	4/34		0.09%	0.1[0.01,1.79]
OFAMI 2001	8/150	8/150		0.81%	1[0.39,2.59]
Raitt 2005	2/100	5/100		0.29%	0.4[0.08,2.01]
Risk & Prevention 2013	142/6239	137/6266		9.14%	1.04[0.83,1.31]
Shinto 2014	1/13	0/13		0.08%	3[0.13,67.51]
SHOT 1996	7/317	5/293		0.58%	1.29[0.42,4.03]
Subtotal (95% CI)	**19363**	**19276**		**65.81%**	**0.92[0.8,1.05]**
Total events: 1445 (Higher omega 3), 1560 (Lower omega 3)					
Heterogeneity: Tau^2=0.02; Chi^2=24.46, df=15(P=0.06); I^2=38.67%					
Test for overall effect: Z=1.23(P=0.22)					



Favours higher omega 3 — Favours lower omega 3

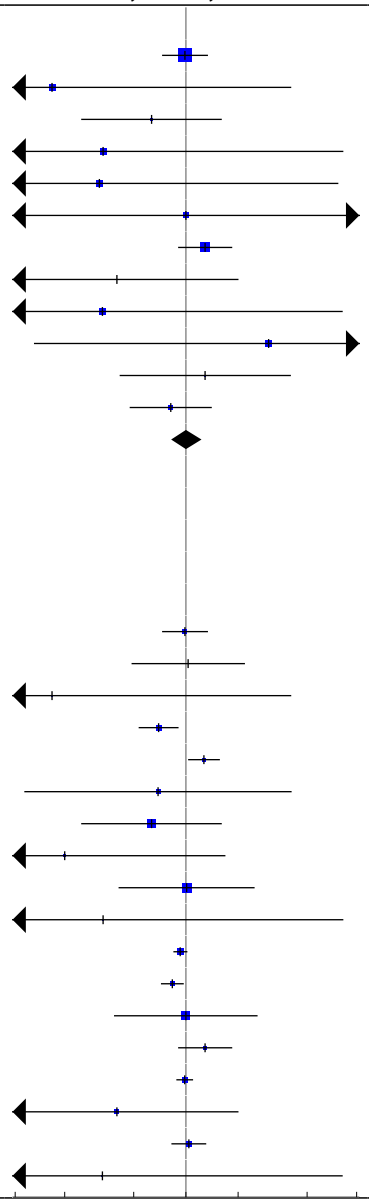
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total (95% CI)	**33991**	**33781**		**100%**	**0.95[0.87,1.03]**
Total events: 2211 (Higher omega 3), 2333 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=31.76, df=24(P=0.13); I^2=24.44%					
Test for overall effect: Z=1.26(P=0.21)					
Test for subgroup differences: Chi^2=0.73, df=1 (P=0.39), I^2=0%					



Favours higher omega 3 — Favours lower omega 3

Analysis 1.14. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 14 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
1.14.1 SA - low risk of compliance bias					
AlphaOmega - EPA+DHA 2010	80/2404	82/2433		43.67%	0.99[0.73,1.34]
Brox 2001	0/80	1/40		0.4%	0.17[0.01,4.05]
DO IT 2010	7/282	11/281		4.6%	0.63[0.25,1.61]
FOSTAR 2016	0/101	1/101		0.39%	0.33[0.01,8.09]
HARP 1995	0/41	1/39		0.4%	0.32[0.01,7.57]
Kumar 2013	1/39	1/39		0.53%	1[0.06,15.43]
OMEGA 2009	67/1919	51/1885		31.13%	1.29[0.9,1.85]
Raitt 2005	2/100	5/100		1.53%	0.4[0.08,2.01]
SCIMO 1999	0/112	1/111		0.39%	0.33[0.01,8.02]
Shinto 2014	1/13	0/13		0.41%	3[0.13,67.51]
SHOT 1996	7/317	5/293		3.1%	1.29[0.42,4.03]
SU.FOL.OM3 2010	23/1253	28/1248		13.43%	0.82[0.47,1.41]
Subtotal (95% CI)	**6661**	**6583**		**100%**	**1[0.82,1.23]**
Total events: 188 (Higher omega 3), 187 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=7.92, df=11(P=0.72); I^2=0%					
Test for overall effect: Z=0.04(P=0.97)					
1.14.2 SA - 100+ randomised					
AlphaOmega - EPA+DHA 2010	80/2404	82/2433		6.45%	0.99[0.73,1.34]
AREDS2 2014	14/2147	13/2056		1.34%	1.03[0.49,2.19]
Brox 2001	0/80	1/40		0.08%	0.17[0.01,4.05]
DART 1989	84/1015	121/1018		7.82%	0.7[0.53,0.91]
DART2 2003	180/1571	139/1543		10.47%	1.27[1.03,1.57]
Derosa 2016	2/138	3/143		0.25%	0.69[0.12,4.07]
DO IT 2010	7/282	11/281		0.89%	0.63[0.25,1.61]
Doi 2014	1/119	5/119		0.18%	0.2[0.02,1.69]
FAAT 2005	9/200	9/202		0.94%	1.01[0.41,2.49]
FOSTAR 2016	0/101	1/101		0.08%	0.33[0.01,8.09]
GISSI-HF 2008	712/3494	765/3481		19.69%	0.93[0.85,1.02]
GISSI-P 1999	291/5665	348/5658		14.47%	0.84[0.72,0.97]
OFAMI 2001	8/150	8/150		0.85%	1[0.39,2.59]
OMEGA 2009	67/1919	51/1885		4.97%	1.29[0.9,1.85]
ORIGIN 2012	574/6281	581/6255		17.98%	0.98[0.88,1.1]
Raitt 2005	2/100	5/100		0.3%	0.4[0.08,2.01]
Risk & Prevention 2013	142/6239	137/6266		9.28%	1.04[0.83,1.31]
SCIMO 1999	0/112	1/111		0.08%	0.33[0.01,8.02]



Favours higher omega 3 — Favours lower omega 3

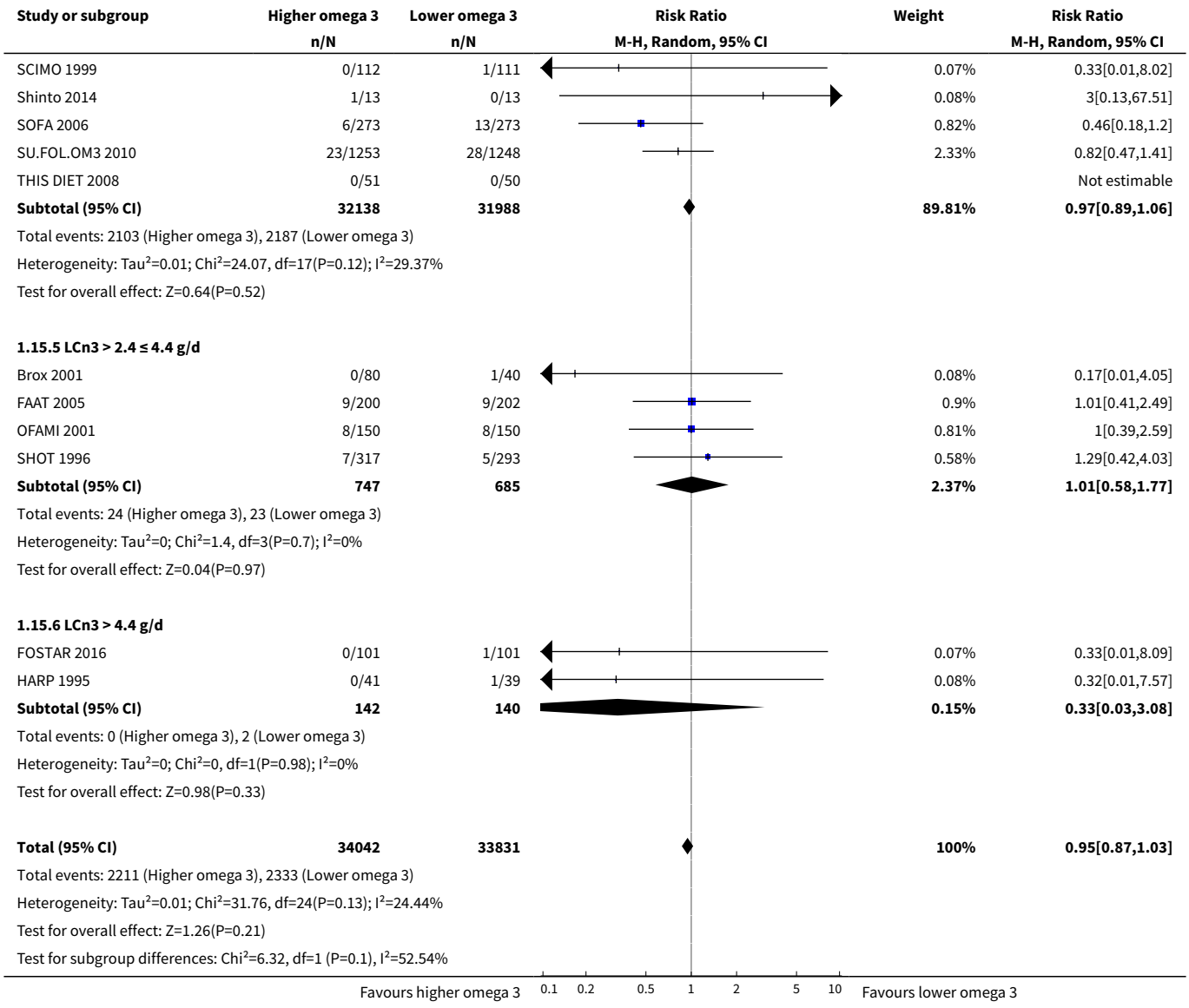
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
SHOT 1996	7/317	5/293		0.6%	1.29[0.42,4.03]
SOFA 2006	6/273	13/273		0.85%	0.46[0.18,1.2]
SU.FOL.OM3 2010	23/1253	28/1248		2.42%	0.82[0.47,1.41]
Subtotal (95% CI)	**33860**	**33656**		**100%**	**0.95[0.87,1.04]**
Total events: 2209 (Higher omega 3), 2327 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=28.44, df=20(P=0.1); I^2=29.68%					
Test for overall effect: Z=1.19(P=0.23)					
Test for subgroup differences: Chi^2=0.27, df=1 (P=0.6), I^2=0%					

Favours higher omega 3 — 0.1 0.2 0.5 1 2 5 10 — Favours lower omega 3

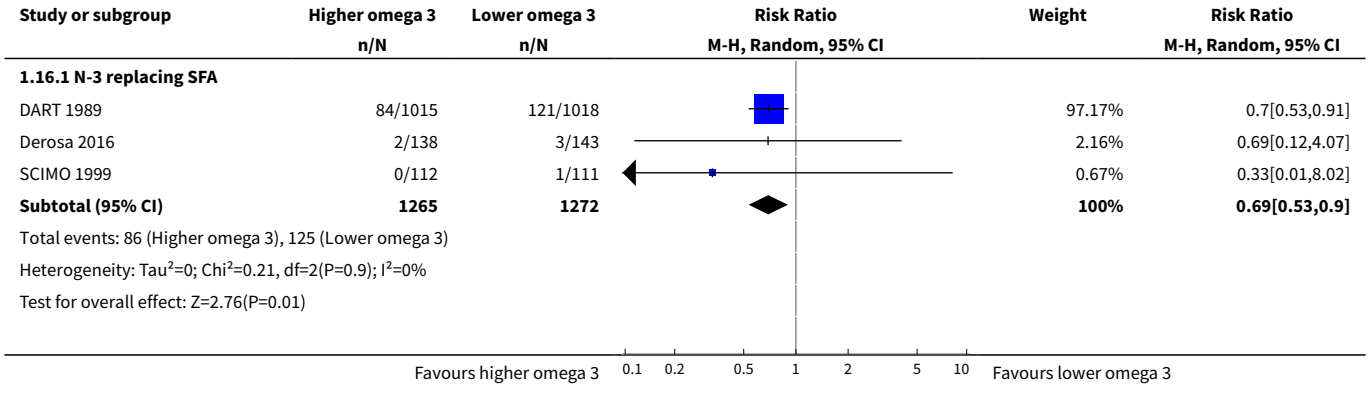
Analysis 1.15. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 15 CVD mortality - LCn3 - subgroup by dose.

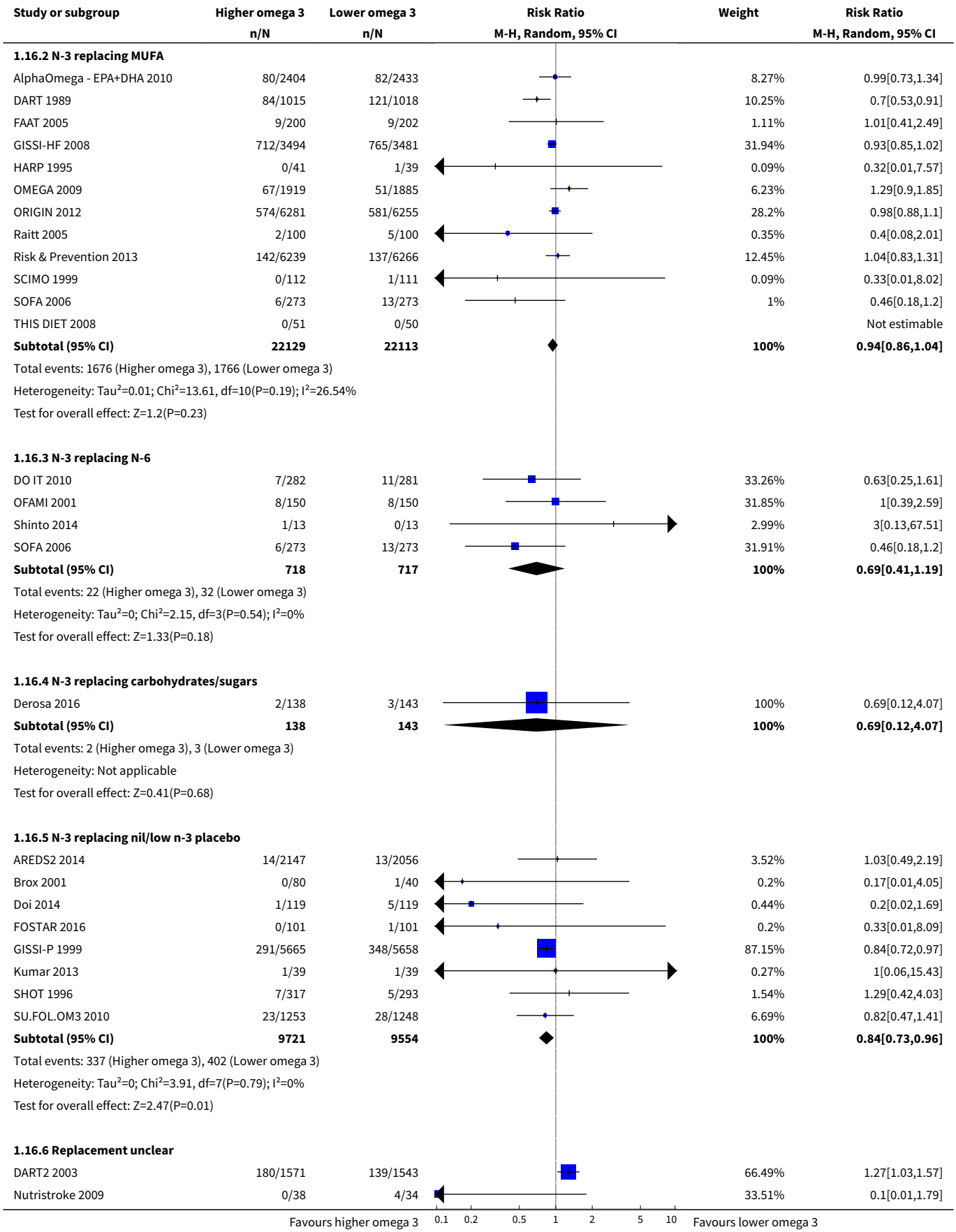
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.15.1 LCn3 ≤ 150 mg/d					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 3), 0 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.15.2 LCn3 > 150 ≤ 250 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					
1.15.3 LCn3 > 250 ≤ 400 mg/d					
DART 1989	84/1015	121/1018		7.67%	0.7[0.53,0.91]
Subtotal (95% CI)	**1015**	**1018**		**7.67%**	**0.7[0.53,0.91]**
Total events: 84 (Higher omega 3), 121 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.68(P=0.01)					
1.15.4 LCn3 > 400 ≤ 2400 mg/d					
AlphaOmega - EPA+DHA 2010	80/2404	82/2433		6.29%	0.99[0.73,1.34]
AREDS2 2014	14/2147	13/2056		1.28%	1.03[0.49,2.19]
DART2 2003	180/1571	139/1543		10.35%	1.27[1.03,1.57]
Derosa 2016	2/138	3/143		0.24%	0.69[0.12,4.07]
DO IT 2010	7/282	11/281		0.85%	0.63[0.25,1.61]
Doi 2014	1/119	5/119		0.17%	0.2[0.02,1.69]
GISSI-HF 2008	712/3494	765/3481		20.11%	0.93[0.85,1.02]
GISSI-P 1999	291/5665	348/5658		14.51%	0.84[0.72,0.97]
Kumar 2013	1/39	1/39		0.1%	1[0.06,15.43]
Nutristroke 2009	0/38	4/34		0.09%	0.1[0.01,1.79]
OMEGA 2009	67/1919	51/1885		4.83%	1.29[0.9,1.85]
ORIGIN 2012	574/6281	581/6255		18.25%	0.98[0.88,1.1]
Raitt 2005	2/100	5/100		0.29%	0.4[0.08,2.01]
Risk & Prevention 2013	142/6239	137/6266		9.14%	1.04[0.83,1.31]

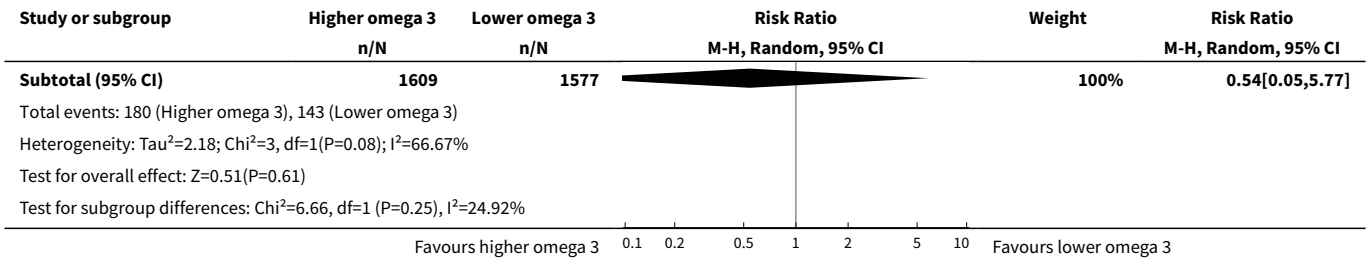
Favours higher omega 3 — 0.1 0.2 0.5 1 2 5 10 — Favours lower omega 3



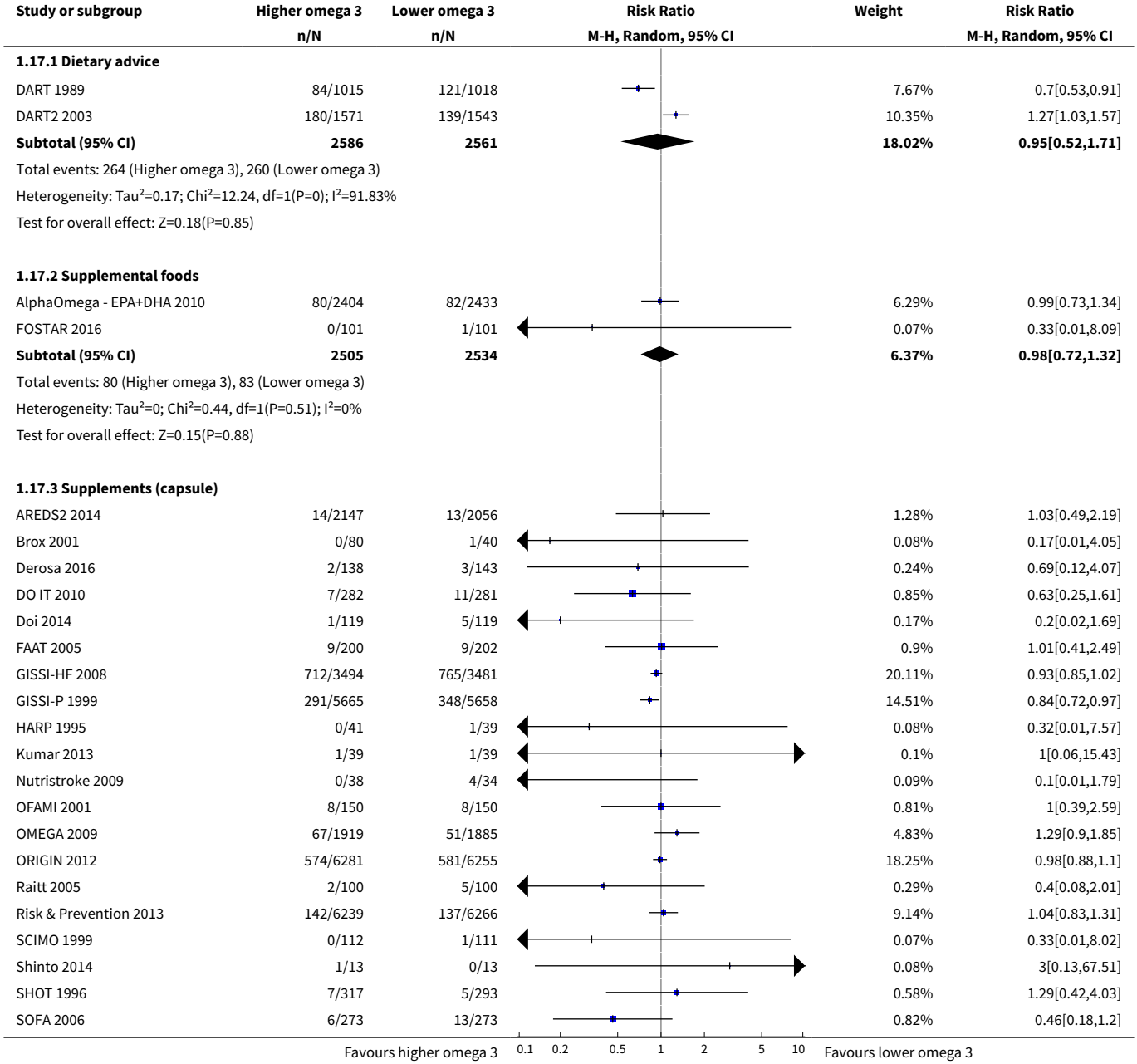
Analysis 1.16. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 16 CVD mortality - LCn3 - subgroup by replacement.



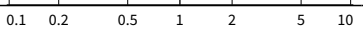




Analysis 1.17. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 17 CVD mortality - LCn3 - subgroup by intervention type.



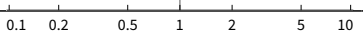
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
SU.FOL.OM3 2010	23/1253	28/1248		2.33%	0.82[0.47,1.41]
Subtotal (95% CI)	**28900**	**28686**		**75.61%**	**0.94[0.88,0.99]**
Total events: 1867 (Higher omega 3), 1990 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=18.36, df=20(P=0.56); I²=0%					
Test for overall effect: Z=2.18(P=0.03)					
1.17.4 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)	**33991**	**33781**		**100%**	**0.95[0.87,1.03]**
Total events: 2211 (Higher omega 3), 2333 (Lower omega 3)					
Heterogeneity: Tau²=0.01; Chi²=31.76, df=24(P=0.13); I²=24.44%					
Test for overall effect: Z=1.26(P=0.21)					
Test for subgroup differences: Chi²=0.08, df=1 (P=0.96), I²=0%					



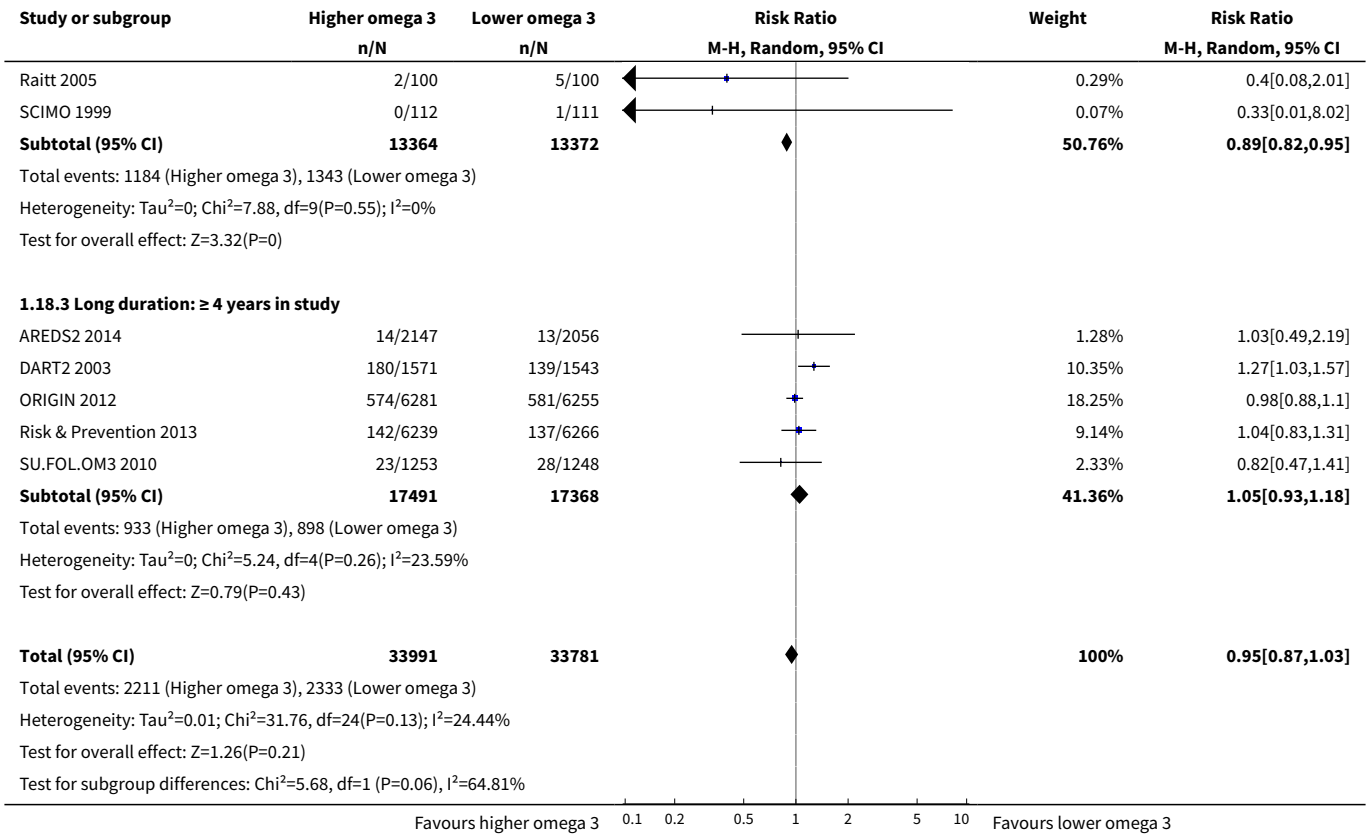
Favours higher omega 3 — Favours lower omega 3

Analysis 1.18. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 18 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
1.18.1 Medium duration 1 to < 2 years in study					
Brox 2001	0/80	1/40		0.08%	0.17[0.01,4.05]
Derosa 2016	2/138	3/143		0.24%	0.69[0.12,4.07]
Doi 2014	1/119	5/119		0.17%	0.2[0.02,1.69]
FAAT 2005	9/200	9/202		0.9%	1.01[0.41,2.49]
Kumar 2013	1/39	1/39		0.1%	1[0.06,15.43]
Nutristroke 2009	0/38	4/34		0.09%	0.1[0.01,1.79]
OMEGA 2009	67/1919	51/1885		4.83%	1.29[0.9,1.85]
Shinto 2014	1/13	0/13		0.08%	3[0.13,67.51]
SHOT 1996	7/317	5/293		0.58%	1.29[0.42,4.03]
SOFA 2006	6/273	13/273		0.82%	0.46[0.18,1.2]
Subtotal (95% CI)	**3136**	**3041**		**7.88%**	**0.88[0.57,1.36]**
Total events: 94 (Higher omega 3), 92 (Lower omega 3)					
Heterogeneity: Tau²=0.09; Chi²=11.17, df=9(P=0.26); I²=19.45%					
Test for overall effect: Z=0.57(P=0.57)					
1.18.2 Medium-long duration: 2 to < 4 years in study					
AlphaOmega - EPA+DHA 2010	80/2404	82/2433		6.29%	0.99[0.73,1.34]
DART 1989	84/1015	121/1018		7.67%	0.7[0.53,0.91]
DO IT 2010	7/282	11/281		0.85%	0.63[0.25,1.61]
FOSTAR 2016	0/101	1/101		0.07%	0.33[0.01,8.09]
GISSI-HF 2008	712/3494	765/3481		20.11%	0.93[0.85,1.02]
GISSI-P 1999	291/5665	348/5658		14.51%	0.84[0.72,0.97]
HARP 1995	0/41	1/39		0.08%	0.32[0.01,7.57]
OFAMI 2001	8/150	8/150		0.81%	1[0.39,2.59]

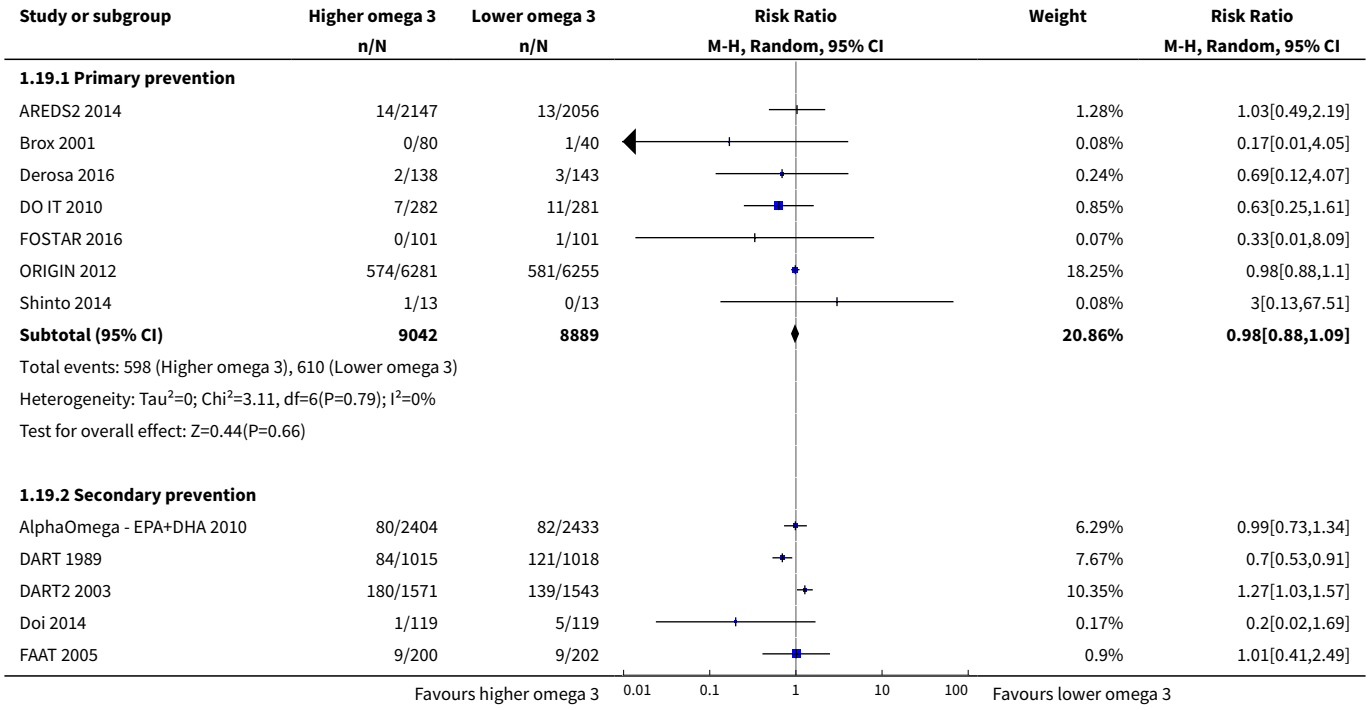


Favours higher omega 3 — Favours lower omega 3

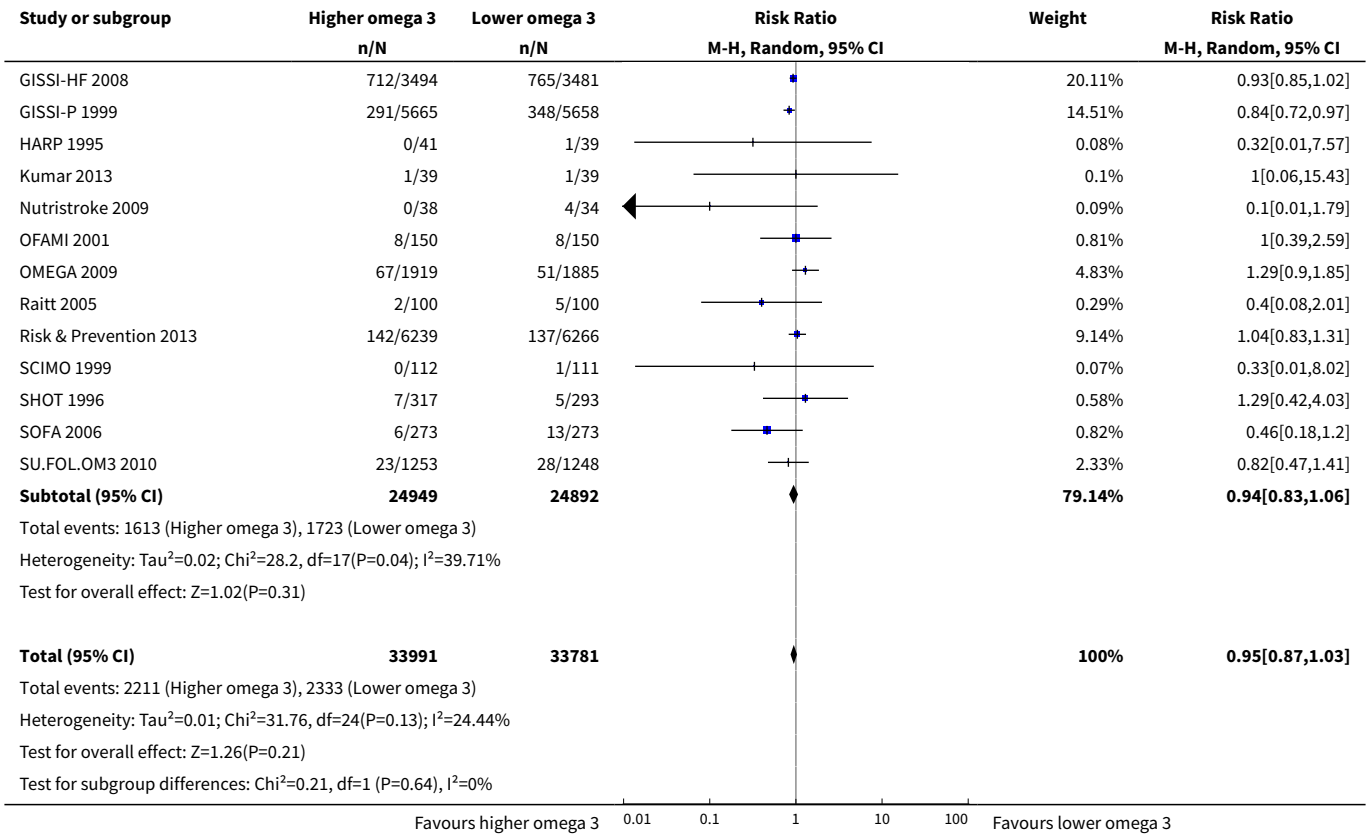


Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Raitt 2005	2/100	5/100		0.29%	0.4[0.08,2.01]
SCIMO 1999	0/112	1/111		0.07%	0.33[0.01,8.02]
Subtotal (95% CI)	**13364**	**13372**		**50.76%**	**0.89[0.82,0.95]**
Total events: 1184 (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)					
1.18.3 Long duration: ≥ 4 years in study					
AREDS2 2014	14/2147	13/2056		1.28%	1.03[0.49,2.19]
DART2 2003	180/1571	139/1543		10.35%	1.27[1.03,1.57]
ORIGIN 2012	574/6281	581/6255		18.25%	0.98[0.88,1.1]
Risk & Prevention 2013	142/6239	137/6266		9.14%	1.04[0.83,1.31]
SU.FOL.OM3 2010	23/1253	28/1248		2.33%	0.82[0.47,1.41]
Subtotal (95% CI)	**17491**	**17368**		**41.36%**	**1.05[0.93,1.18]**
Total events: 933 (Higher omega 3), 898 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=5.24, df=4(P=0.26); I²=23.59%					
Test for overall effect: Z=0.79(P=0.43)					
Total (95% CI)	**33991**	**33781**		**100%**	**0.95[0.87,1.03]**
Total events: 2211 (Higher omega 3), 2333 (Lower omega 3)					
Heterogeneity: Tau²=0.01; Chi²=31.76, df=24(P=0.13); I²=24.44%					
Test for overall effect: Z=1.26(P=0.21)					
Test for subgroup differences: Chi²=5.68, df=1 (P=0.06), I²=64.81%					

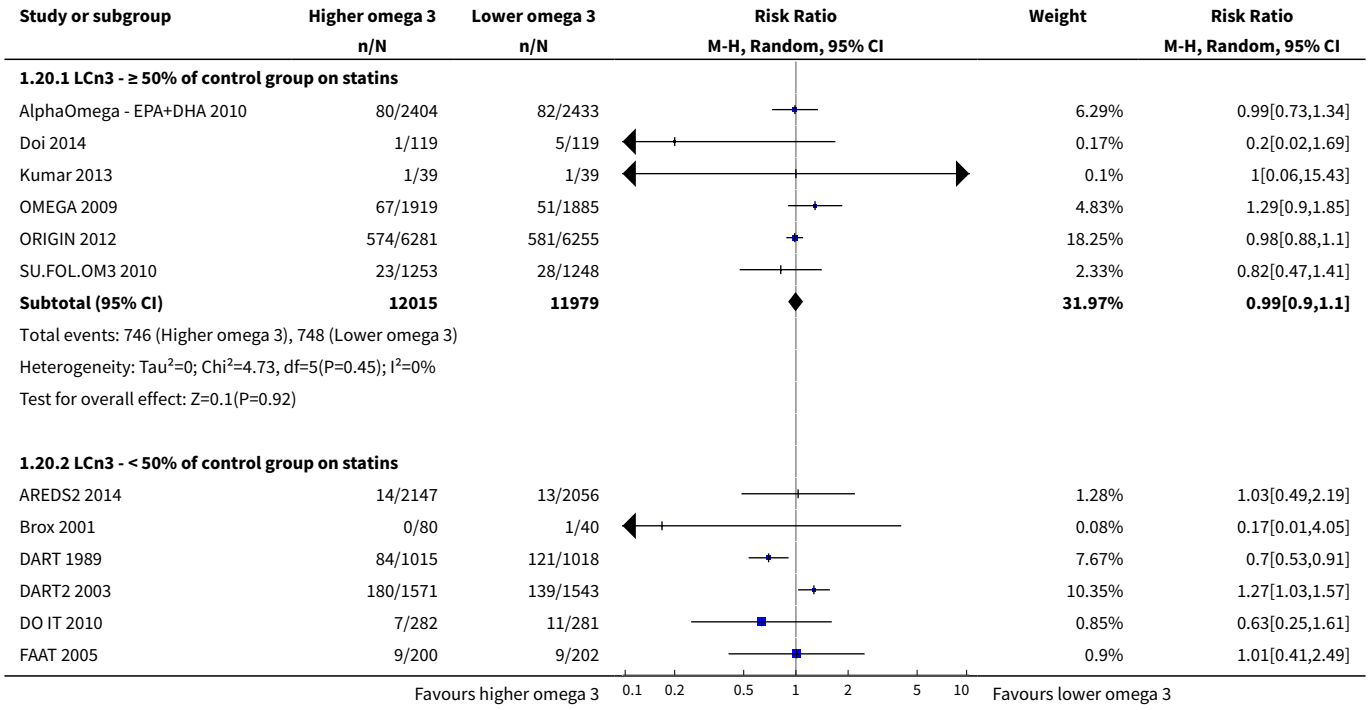
Analysis 1.19. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 19 CVD mortality - LCn3 - subgroup by primary or secondary prevention.

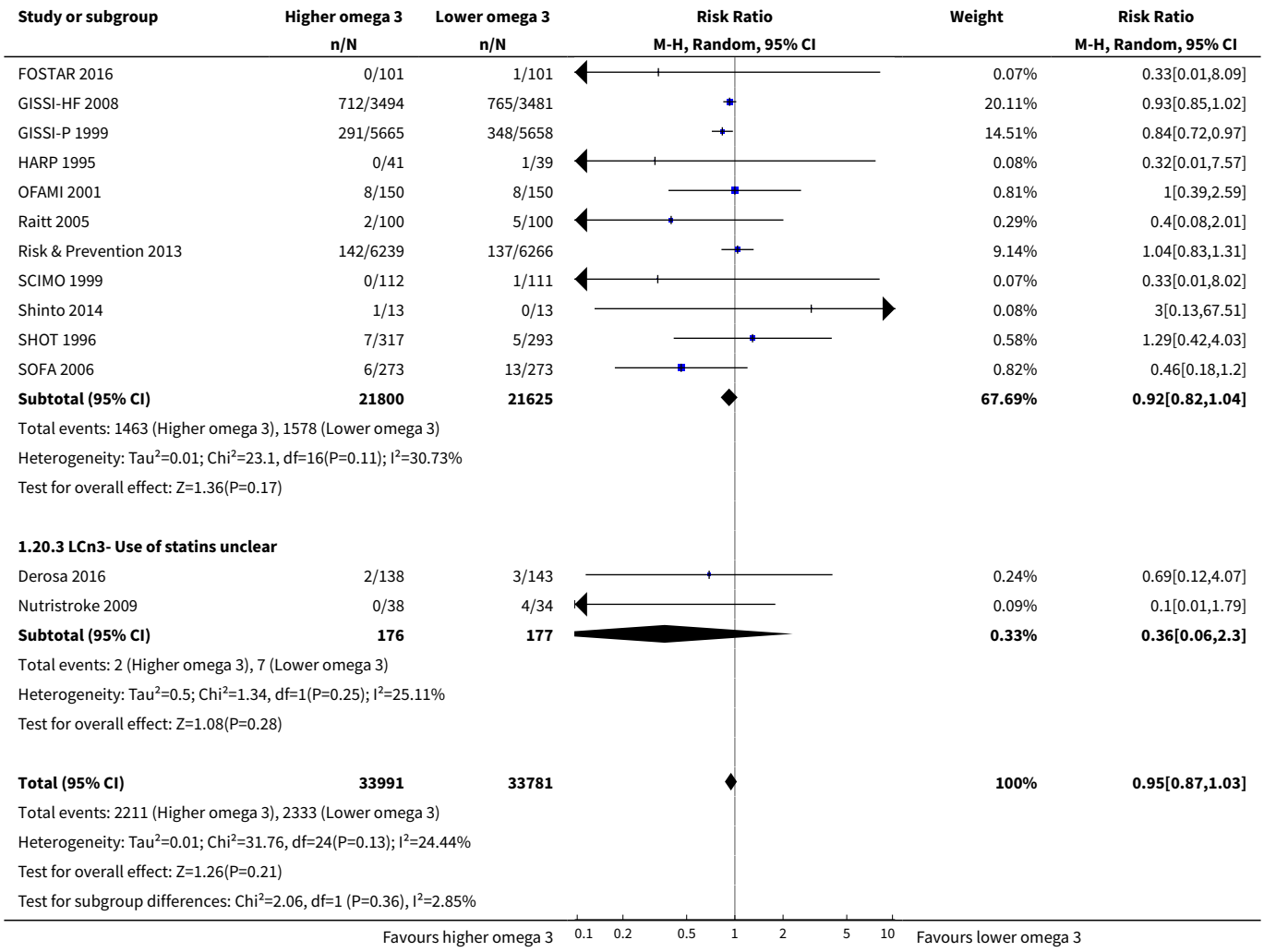


Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.19.1 Primary prevention					
AREDS2 2014	14/2147	13/2056		1.28%	1.03[0.49,2.19]
Brox 2001	0/80	1/40		0.08%	0.17[0.01,4.05]
Derosa 2016	2/138	3/143		0.24%	0.69[0.12,4.07]
DO IT 2010	7/282	11/281		0.85%	0.63[0.25,1.61]
FOSTAR 2016	0/101	1/101		0.07%	0.33[0.01,8.09]
ORIGIN 2012	574/6281	581/6255		18.25%	0.98[0.88,1.1]
Shinto 2014	1/13	0/13		0.08%	3[0.13,67.51]
Subtotal (95% CI)	**9042**	**8889**		**20.86%**	**0.98[0.88,1.09]**
Total events: 598 (Higher omega 3), 610 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=3.11, df=6(P=0.79); I²=0%					
Test for overall effect: Z=0.44(P=0.66)					
1.19.2 Secondary prevention					
AlphaOmega - EPA+DHA 2010	80/2404	82/2433		6.29%	0.99[0.73,1.34]
DART 1989	84/1015	121/1018		7.67%	0.7[0.53,0.91]
DART2 2003	180/1571	139/1543		10.35%	1.27[1.03,1.57]
Doi 2014	1/119	5/119		0.17%	0.2[0.02,1.69]
FAAT 2005	9/200	9/202		0.9%	1.01[0.41,2.49]

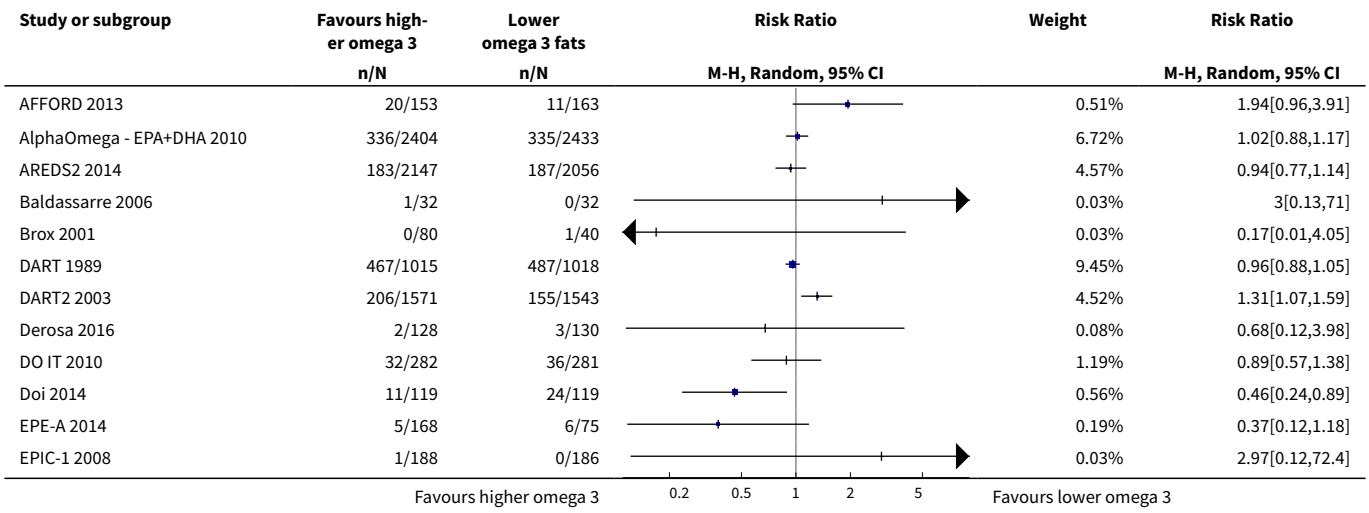


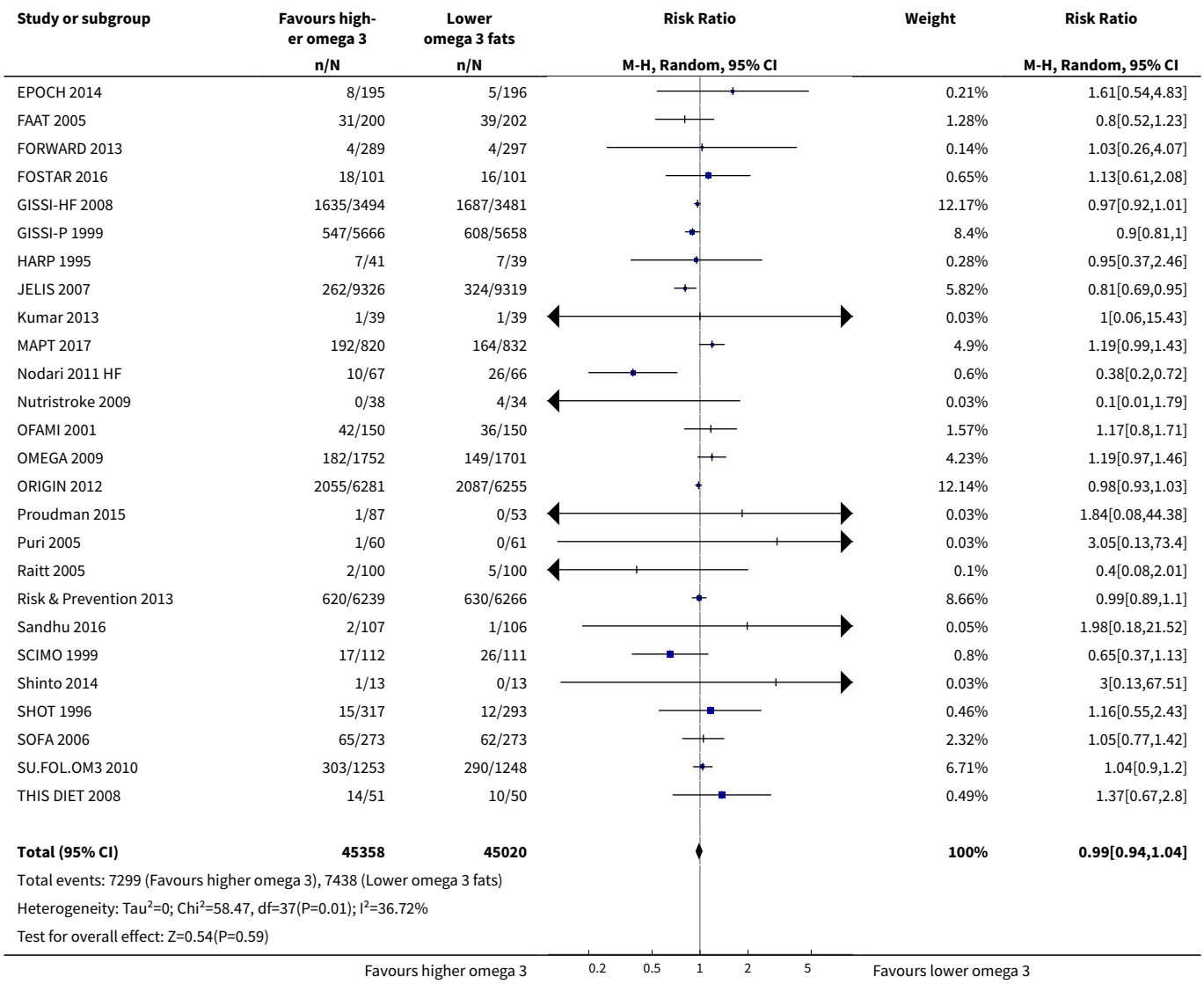
Analysis 1.20. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 20 CVD mortality - LCn3 - subgroup by statin uses.





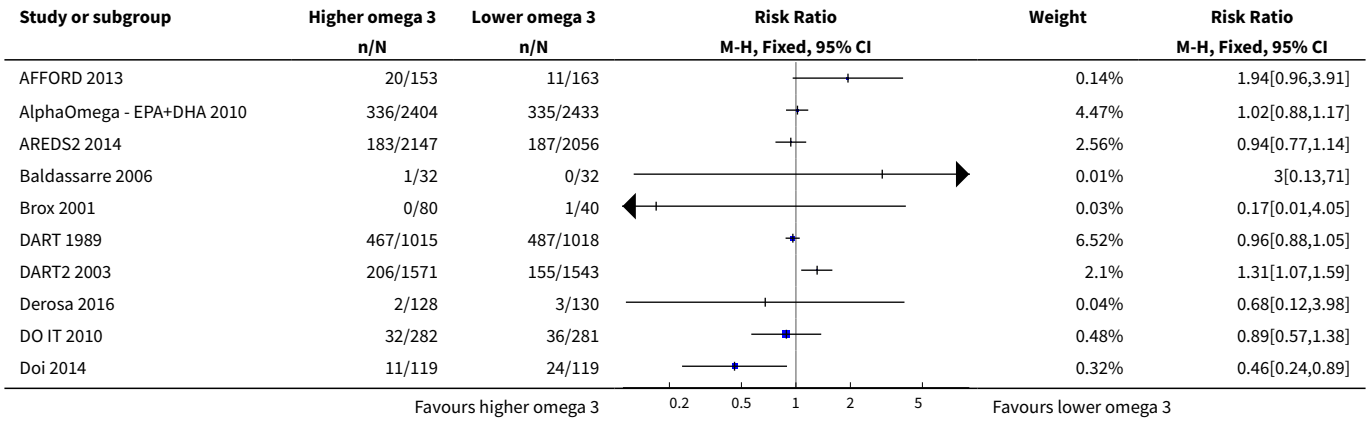
Analysis 1.21. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 21 Cardiovascular events (overall) - LCn3.





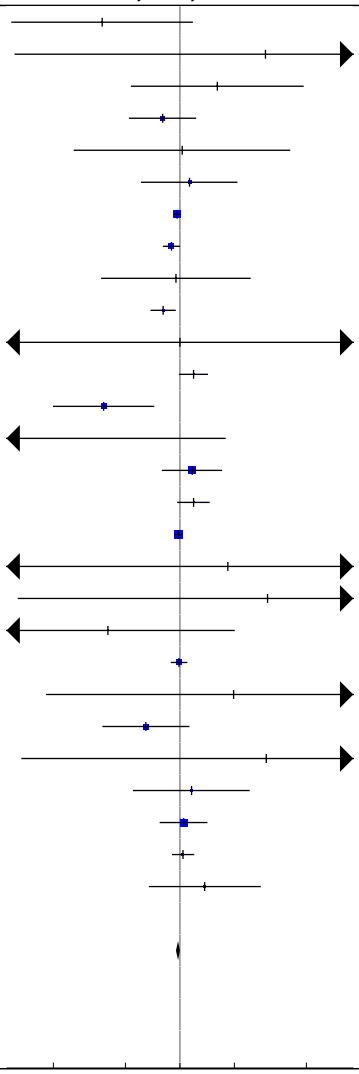
Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 fats n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
EPOCH 2014	8/195	5/196		0.21%	1.61[0.54,4.83]
FAAT 2005	31/200	39/202		1.28%	0.8[0.52,1.23]
FORWARD 2013	4/289	4/297		0.14%	1.03[0.26,4.07]
FOSTAR 2016	18/101	16/101		0.65%	1.13[0.61,2.08]
GISSI-HF 2008	1635/3494	1687/3481		12.17%	0.97[0.92,1.01]
GISSI-P 1999	547/5666	608/5658		8.4%	0.9[0.81,1]
HARP 1995	7/41	7/39		0.28%	0.95[0.37,2.46]
JELIS 2007	262/9326	324/9319		5.82%	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		4.9%	1.19[0.99,1.43]
Nodari 2011 HF	10/67	26/66		0.6%	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		1.57%	1.17[0.8,1.71]
OMEGA 2009	182/1752	149/1701		4.23%	1.19[0.97,1.46]
ORIGIN 2012	2055/6281	2087/6255		12.14%	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]
Risk & Prevention 2013	620/6239	630/6266		8.66%	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		0.8%	0.65[0.37,1.13]
Shinto 2014	1/13	0/13		0.03%	3[0.13,67.51]
SHOT 1996	15/317	12/293		0.46%	1.16[0.55,2.43]
SOFA 2006	65/273	62/273		2.32%	1.05[0.77,1.42]
SU.FOL.OM3 2010	303/1253	290/1248		6.71%	1.04[0.9,1.2]
THIS DIET 2008	14/51	10/50		0.49%	1.37[0.67,2.8]
Total (95% CI)	**45358**	**45020**		**100%**	**0.99[0.94,1.04]**
Total events: 7299 (Favours higher omega 3), 7438 (Lower omega 3 fats)					
Heterogeneity: Tau²=0; Chi²=58.47, df=37(P=0.01); I²=36.72%					
Test for overall effect: Z=0.54(P=0.59)					

Analysis 1.22. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 22 CVD events - LCn3 - SA fixed-effect.



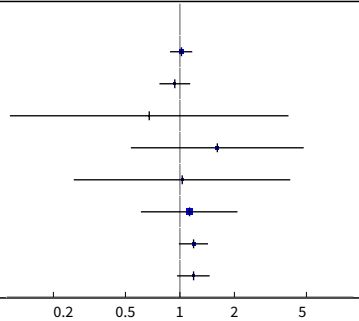
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
AFFORD 2013	20/153	11/163		0.14%	1.94[0.96,3.91]
AlphaOmega - EPA+DHA 2010	336/2404	335/2433		4.47%	1.02[0.88,1.17]
AREDS2 2014	183/2147	187/2056		2.56%	0.94[0.77,1.14]
Baldassarre 2006	1/32	0/32		0.01%	3[0.13,71]
Brox 2001	0/80	1/40		0.03%	0.17[0.01,4.05]
DART 1989	467/1015	487/1018		6.52%	0.96[0.88,1.05]
DART2 2003	206/1571	155/1543		2.1%	1.31[1.07,1.59]
Derosa 2016	2/128	3/130		0.04%	0.68[0.12,3.98]
DO IT 2010	32/282	36/281		0.48%	0.89[0.57,1.38]
Doi 2014	11/119	24/119		0.32%	0.46[0.24,0.89]

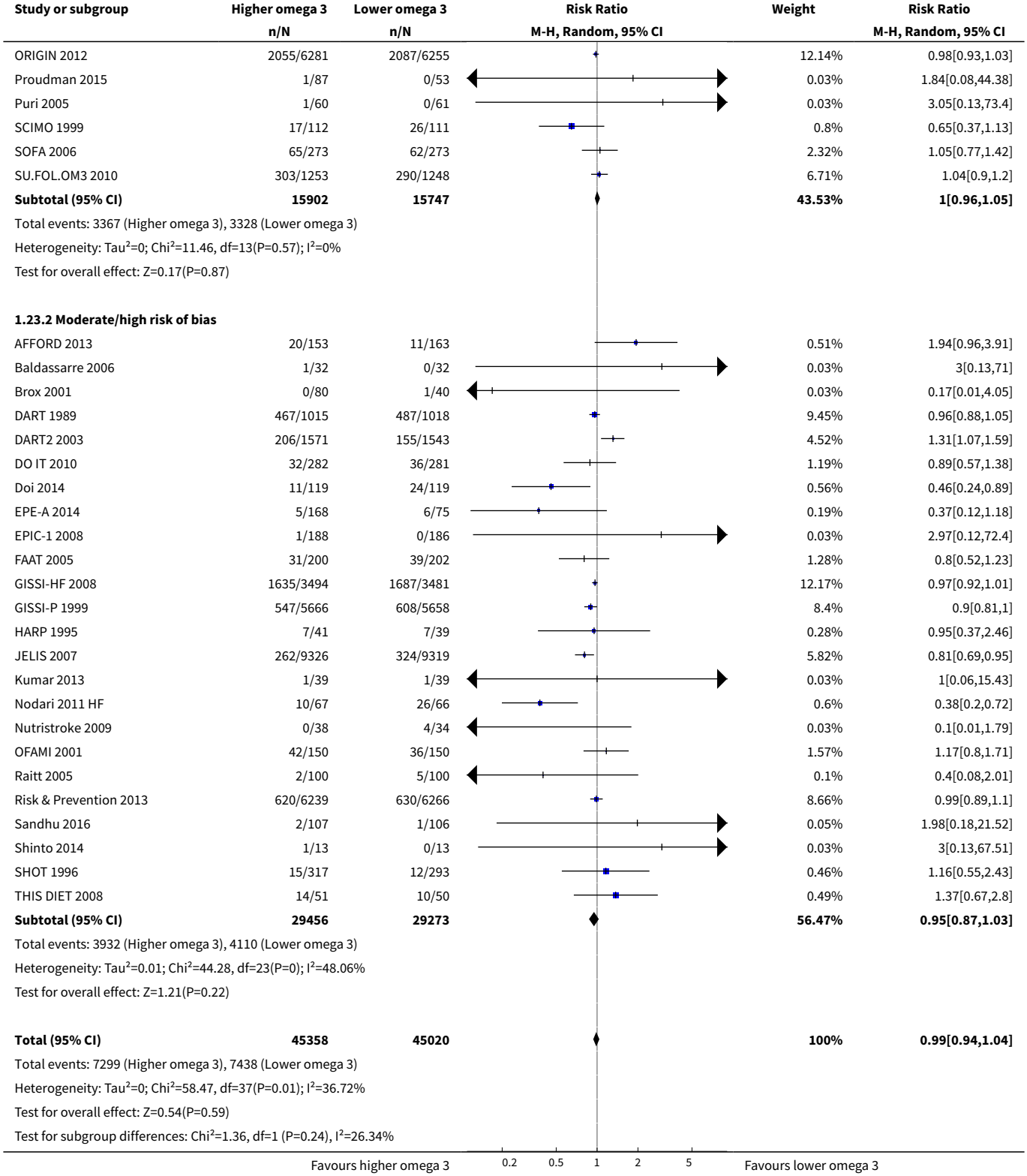
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
EPE-A 2014	5/168	6/75		0.11%	0.37[0.12,1.18]
EPIC-1 2008	1/188	0/186		0.01%	2.97[0.12,72.4]
EPOCH 2014	8/195	5/196		0.07%	1.61[0.54,4.83]
FAAT 2005	31/200	39/202		0.52%	0.8[0.52,1.23]
FORWARD 2013	4/289	4/297		0.05%	1.03[0.26,4.07]
FOSTAR 2016	18/101	16/101		0.21%	1.13[0.61,2.08]
GISSI-HF 2008	1635/3494	1687/3481		22.67%	0.97[0.92,1.01]
GISSI-P 1999	547/5666	608/5658		8.16%	0.9[0.81,1]
HARP 1995	7/41	7/39		0.1%	0.95[0.37,2.46]
JELIS 2007	262/9326	324/9319		4.35%	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		2.18%	1.19[0.99,1.43]
Nodari 2011 HF	10/67	26/66		0.35%	0.38[0.2,0.72]
Nutristroke 2009	0/38	4/34		0.06%	0.1[0.01,1.79]
OFAMI 2001	42/150	36/150		0.48%	1.17[0.8,1.71]
OMEGA 2009	182/1752	149/1701		2.03%	1.19[0.97,1.46]
ORIGIN 2012	2055/6281	2087/6255		28.05%	0.98[0.93,1.03]
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		0.07%	0.4[0.08,2.01]
Risk & Prevention 2013	620/6239	630/6266		8.43%	0.99[0.89,1.1]
Sandhu 2016	2/107	1/106		0.01%	1.98[0.18,21.52]
SCIMO 1999	17/112	26/111		0.35%	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		0.17%	1.16[0.55,2.43]
SOFA 2006	65/273	62/273		0.83%	1.05[0.77,1.42]
SU.FOL.OM3 2010	303/1253	290/1248		3.9%	1.04[0.9,1.2]
THIS DIET 2008	14/51	10/50		0.14%	1.37[0.67,2.8]
Total (95% CI)	**45358**	**45020**		**100%**	**0.98[0.95,1]**
Total events: 7299 (Higher omega 3), 7438 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=58.47, df=37(P=0.01); I^2=36.72%					
Test for overall effect: Z=1.63(P=0.1)					



Analysis 1.23. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 23 CVD events - LCn3 - SA by summary risk of bias.

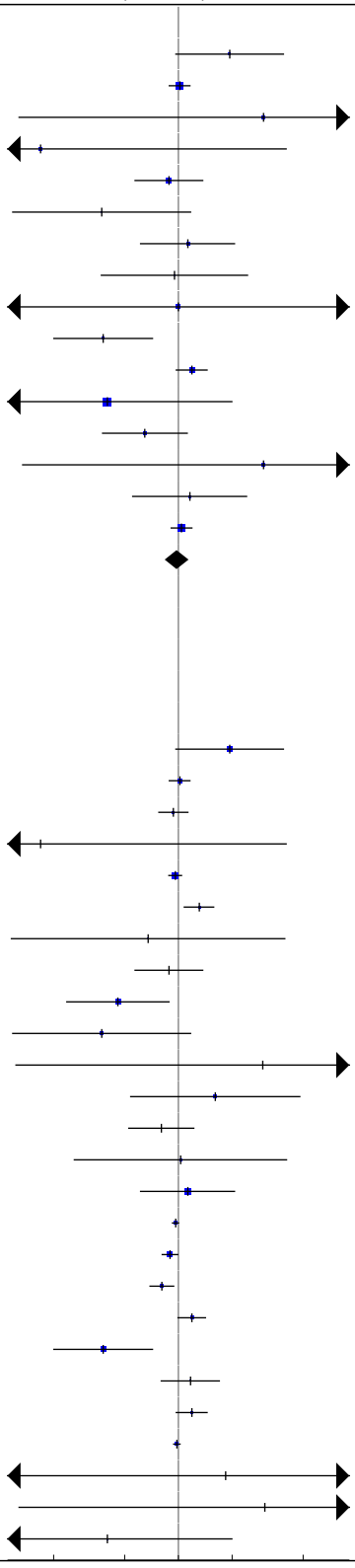
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.23.1 Low risk of bias					
AlphaOmega - EPA+DHA 2010	336/2404	335/2433		6.72%	1.02[0.88,1.17]
AREDS2 2014	183/2147	187/2056		4.57%	0.94[0.77,1.14]
Derosa 2016	2/128	3/130		0.08%	0.68[0.12,3.98]
EPOCH 2014	8/195	5/196		0.21%	1.61[0.54,4.83]
FORWARD 2013	4/289	4/297		0.14%	1.03[0.26,4.07]
FOSTAR 2016	18/101	16/101		0.65%	1.13[0.61,2.08]
MAPT 2017	192/820	164/832		4.9%	1.19[0.99,1.43]
OMEGA 2009	182/1752	149/1701		4.23%	1.19[0.97,1.46]



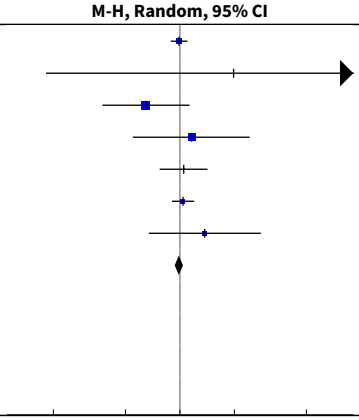


Analysis 1.24. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 24 CVD events - LCn3 - SA by compliance and study size.

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
1.24.1 SA - low risk of compliance bias					
AFFORD 2013	20/153	11/163		4.03%	1.94[0.96,3.91]
AlphaOmega - EPA+DHA 2010	336/2404	335/2433		22.19%	1.02[0.88,1.17]
Baldassarre 2006	1/32	0/32		0.23%	3[0.13,71]
Brox 2001	0/80	1/40		0.23%	0.17[0.01,4.05]
DO IT 2010	32/282	36/281		8.18%	0.89[0.57,1.38]
EPE-A 2014	5/168	6/75		1.64%	0.37[0.12,1.18]
FOSTAR 2016	18/101	16/101		5.03%	1.13[0.61,2.08]
HARP 1995	7/41	7/39		2.35%	0.95[0.37,2.46]
Kumar 2013	1/39	1/39		0.31%	1[0.06,15.43]
Nodari 2011 HF	10/67	26/66		4.64%	0.38[0.2,0.72]
OMEGA 2009	182/1752	149/1701		18.24%	1.19[0.97,1.46]
Raitt 2005	2/100	5/100		0.86%	0.4[0.08,2.01]
SCIMO 1999	17/112	26/111		5.97%	0.65[0.37,1.13]
Shinto 2014	1/13	0/13		0.24%	3[0.13,67.51]
SHOT 1996	15/317	12/293		3.66%	1.16[0.55,2.43]
SU.FOL.OM3 2010	303/1253	290/1248		22.18%	1.04[0.9,1.2]
Subtotal (95% CI)	**6914**	**6735**		**100%**	**0.98[0.84,1.14]**
Total events: 950 (Higher omega 3), 921 (Lower omega 3)					
Heterogeneity: Tau^2=0.02; Chi^2=23.95, df=15(P=0.07); I^2=37.37%					
Test for overall effect: Z=0.31(P=0.76)					
1.24.2 SA - 100+ randomised					
AFFORD 2013	20/153	11/163		0.53%	1.94[0.96,3.91]
AlphaOmega - EPA+DHA 2010	336/2404	335/2433		6.78%	1.02[0.88,1.17]
AREDS2 2014	183/2147	187/2056		4.66%	0.94[0.77,1.14]
Brox 2001	0/80	1/40		0.03%	0.17[0.01,4.05]
DART 1989	467/1015	487/1018		9.39%	0.96[0.88,1.05]
DART2 2003	206/1571	155/1543		4.61%	1.31[1.07,1.59]
Derosa 2016	2/128	3/130		0.09%	0.68[0.12,3.98]
DO IT 2010	32/282	36/281		1.24%	0.89[0.57,1.38]
Doi 2014	11/119	24/119		0.58%	0.46[0.24,0.89]
EPE-A 2014	5/168	6/75		0.2%	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		0.22%	1.61[0.54,4.83]
FAAT 2005	31/200	39/202		1.33%	0.8[0.52,1.23]
FORWARD 2013	4/289	4/297		0.14%	1.03[0.26,4.07]
FOSTAR 2016	18/101	16/101		0.68%	1.13[0.61,2.08]
GISSI-HF 2008	1635/3494	1687/3481		11.92%	0.97[0.92,1.01]
GISSI-P 1999	547/5666	608/5658		8.4%	0.9[0.81,1]
JELIS 2007	262/9326	324/9319		5.9%	0.81[0.69,0.95]
MAPT 2017	192/820	164/832		4.98%	1.19[0.99,1.43]
Nodari 2011 HF	10/67	26/66		0.62%	0.38[0.2,0.72]
OFAMI 2001	42/150	36/150		1.62%	1.17[0.8,1.71]
OMEGA 2009	182/1752	149/1701		4.32%	1.19[0.97,1.46]
ORIGIN 2012	2055/6281	2087/6255		11.89%	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]

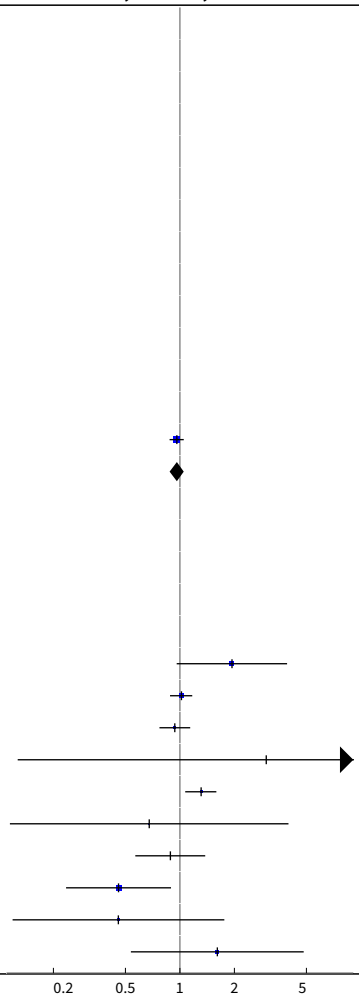


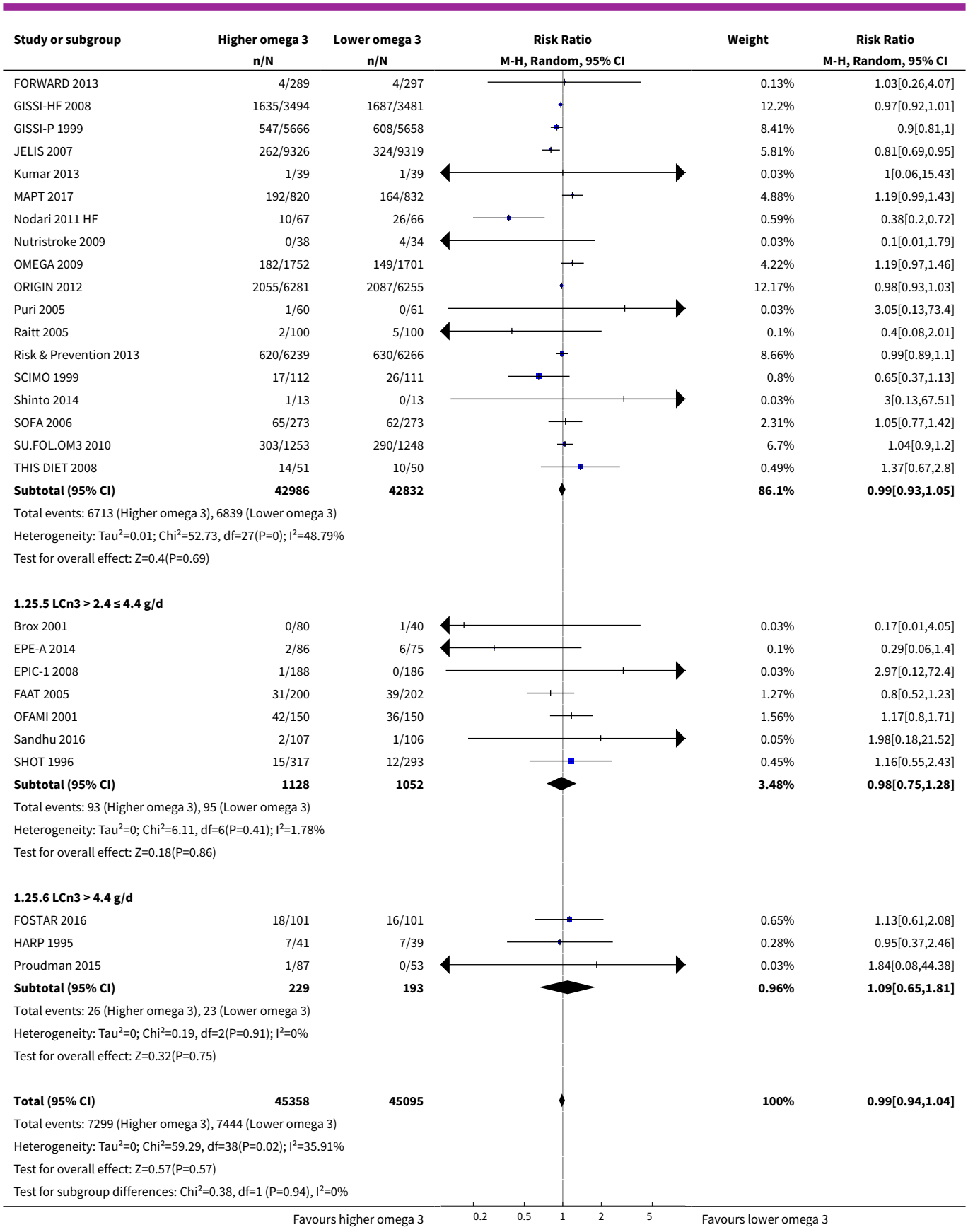
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Risk & Prevention 2013	620/6239	630/6266		8.64%	0.99[0.89,1.1]
Sandhu 2016	2/107	1/106		0.05%	1.98[0.18,21.52]
SCIMO 1999	17/112	26/111		0.84%	0.65[0.37,1.13]
SHOT 1996	15/317	12/293		0.48%	1.16[0.55,2.43]
SOFA 2006	65/273	62/273		2.4%	1.05[0.77,1.42]
SU.FOL.OM3 2010	303/1253	290/1248		6.77%	1.04[0.9,1.2]
THIS DIET 2008	14/51	10/50		0.52%	1.37[0.67,2.8]
Subtotal (95% CI)	**45195**	**44863**		**100%**	**0.99[0.94,1.04]**
Total events: 7289 (Higher omega 3), 7426 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=55.08, df=32(P=0.01); I^2=41.91%					
Test for overall effect: Z=0.52(P=0.6)					
Test for subgroup differences: Chi^2=0.02, df=1 (P=0.9), I^2=0%					



Analysis 1.25. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 25 CVD events - LCn3 - subgroup by dose.

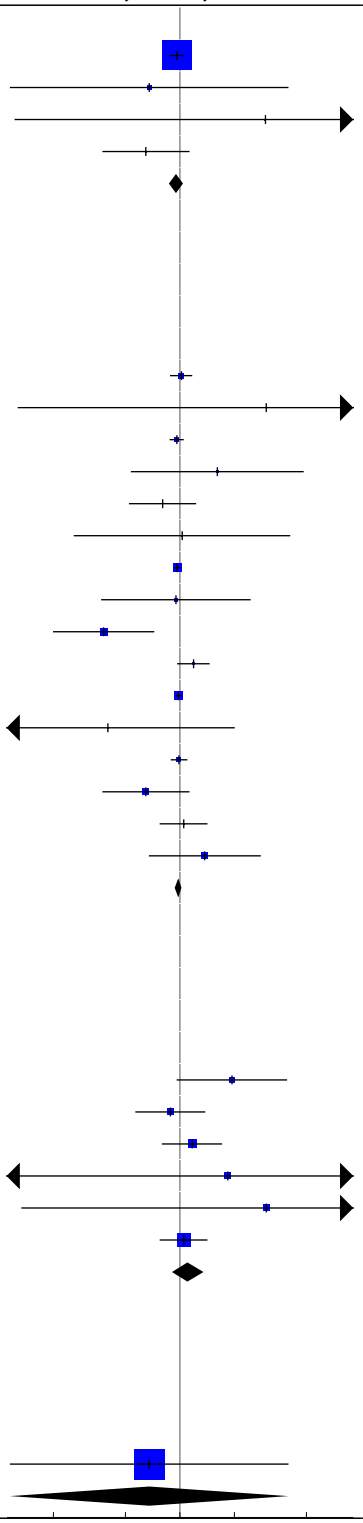
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.25.1 LCn3 ≤ 150 mg/d					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 3), 0 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.25.2 LCn3 > 150 ≤ 250 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					
1.25.3 LCn3 > 250 ≤ 400 mg/d					
DART 1989	467/1015	487/1018		9.46%	0.96[0.88,1.05]
Subtotal (95% CI)	**1015**	**1018**		**9.46%**	**0.96[0.88,1.05]**
Total events: 467 (Higher omega 3), 487 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.83(P=0.41)					
1.25.4 LCn3 > 400 ≤ 2400 mg/d					
AFFORD 2013	20/153	11/163		0.51%	1.94[0.96,3.91]
AlphaOmega - EPA+DHA 2010	336/2404	335/2433		6.71%	1.02[0.88,1.17]
AREDS2 2014	183/2147	187/2056		4.56%	0.94[0.77,1.14]
Baldassarre 2006	1/32	0/32		0.03%	3[0.13,71]
DART2 2003	206/1571	155/1543		4.51%	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		1.18%	0.89[0.57,1.38]
Doi 2014	11/119	24/119		0.56%	0.46[0.24,0.89]
EPE-A 2014	3/82	6/75		0.14%	0.46[0.12,1.76]
EPOCH 2014	8/195	5/196		0.21%	1.61[0.54,4.83]

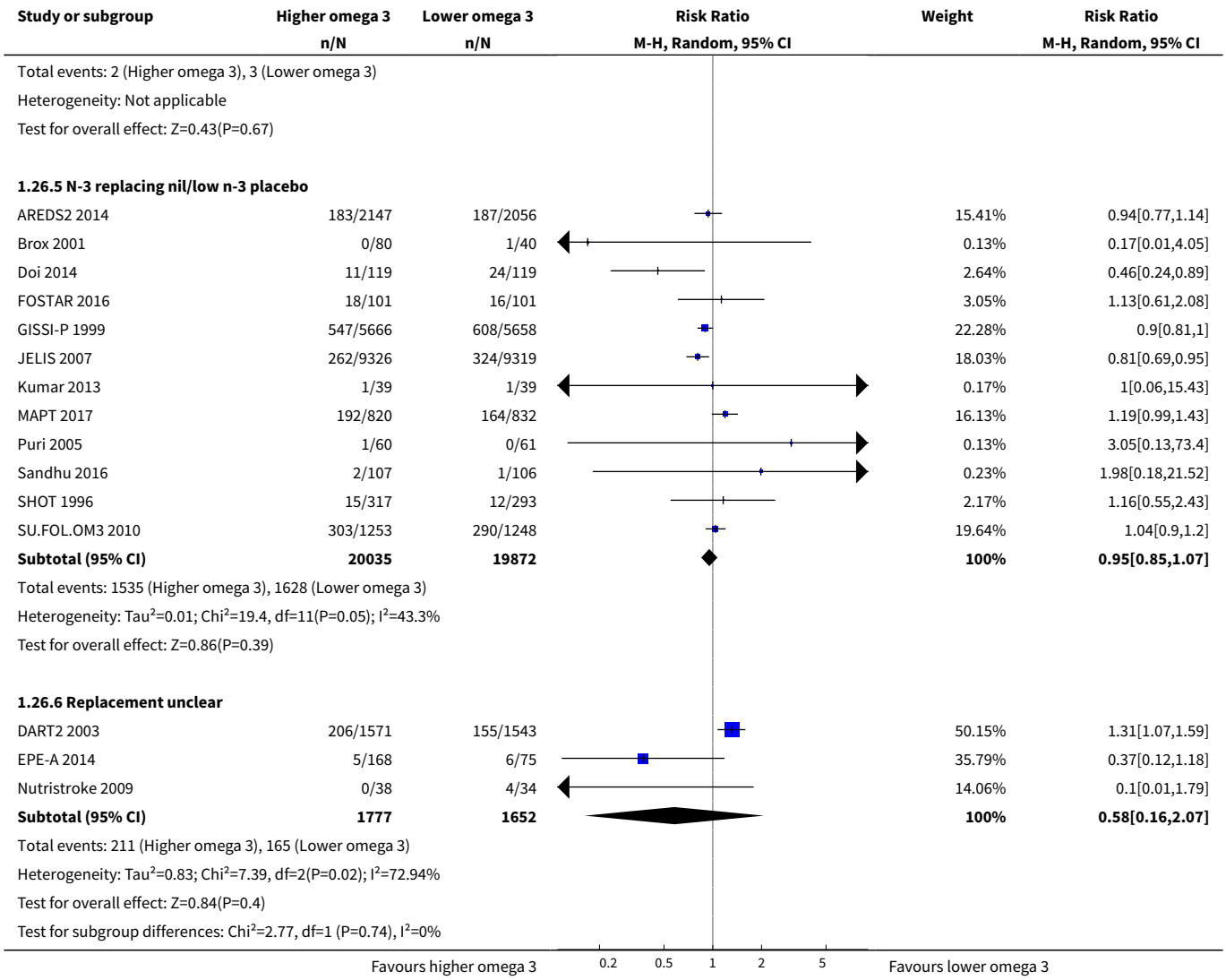




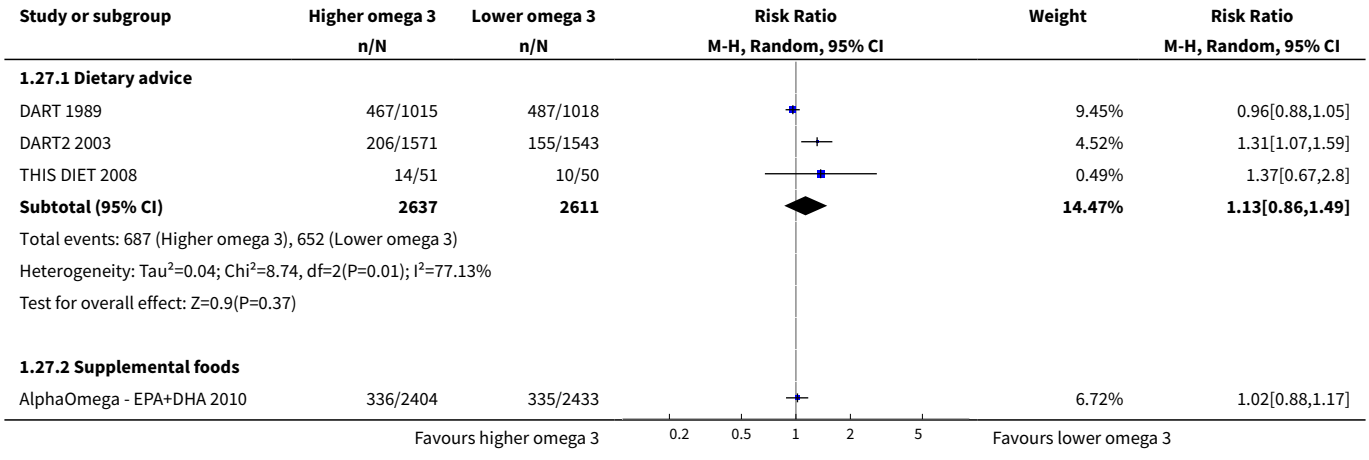
Analysis 1.26. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 26 CVD events - LCn3 - subgroup by replacement.

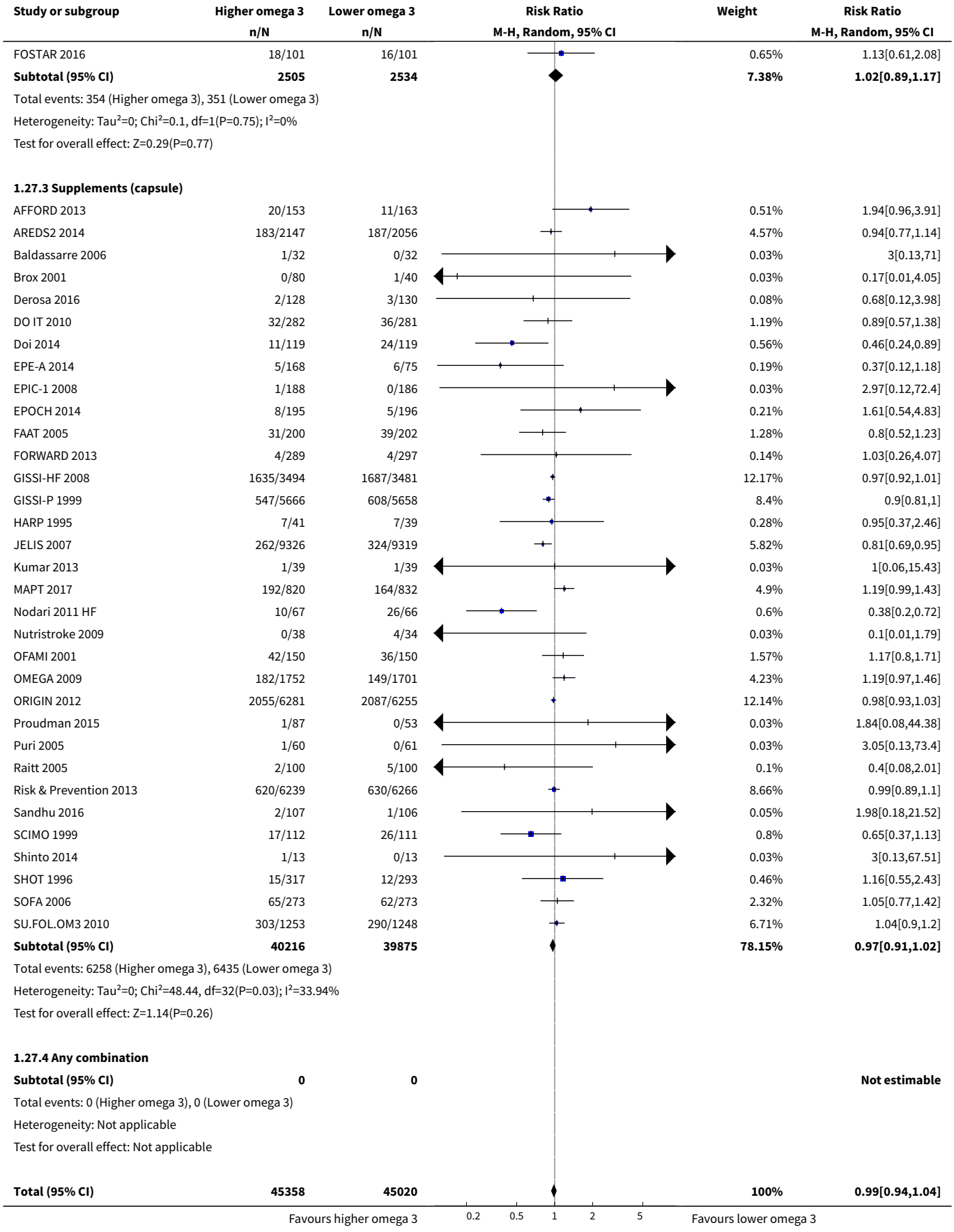
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.26.1 N-3 replacing SFA					
DART 1989	467/1015	487/1018		96.93%	0.96[0.88,1.05]
Derosa 2016	2/128	3/130		0.26%	0.68[0.12,3.98]
EPIC-1 2008	1/188	0/186		0.08%	2.97[0.12,72.4]
SCIMO 1999	17/112	26/111		2.72%	0.65[0.37,1.13]
Subtotal (95% CI)	**1443**	**1445**		**100%**	**0.95[0.87,1.04]**
Total events: 487 (Higher omega 3), 516 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=2.55, df=3(P=0.47); I^2=0%					
Test for overall effect: Z=1.07(P=0.28)					
1.26.2 N-3 replacing MUFA					
AlphaOmega - EPA+DHA 2010	336/2404	335/2433		8.12%	1.02[0.88,1.17]
Baldassarre 2006	1/32	0/32		0.02%	3[0.13,71]
DART 1989	467/1015	487/1018		14.92%	0.96[0.88,1.05]
EPOCH 2014	8/195	5/196		0.16%	1.61[0.54,4.83]
FAAT 2005	31/200	39/202		1.05%	0.8[0.52,1.23]
FORWARD 2013	4/289	4/297		0.1%	1.03[0.26,4.07]
GISSI-HF 2008	1635/3494	1687/3481		27.61%	0.97[0.92,1.01]
HARP 1995	7/41	7/39		0.22%	0.95[0.37,2.46]
Nodari 2011 HF	10/67	26/66		0.47%	0.38[0.2,0.72]
OMEGA 2009	182/1752	149/1701		4.22%	1.19[0.97,1.46]
ORIGIN 2012	2055/6281	2087/6255		27.38%	0.98[0.93,1.03]
Raitt 2005	2/100	5/100		0.08%	0.4[0.08,2.01]
Risk & Prevention 2013	620/6239	630/6266		12.56%	0.99[0.89,1.1]
SCIMO 1999	17/112	26/111		0.64%	0.65[0.37,1.13]
SOFA 2006	65/273	62/273		2.04%	1.05[0.77,1.42]
THIS DIET 2008	14/51	10/50		0.39%	1.37[0.67,2.8]
Subtotal (95% CI)	**22545**	**22520**		**100%**	**0.98[0.94,1.02]**
Total events: 5454 (Higher omega 3), 5559 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=18.85, df=15(P=0.22); I^2=20.44%					
Test for overall effect: Z=0.93(P=0.35)					
1.26.3 N-3 replacing n-6					
AFFORD 2013	20/153	11/163		8.18%	1.94[0.96,3.91]
DO IT 2010	32/282	36/281		20.21%	0.89[0.57,1.38]
OFAMI 2001	42/150	36/150		27.43%	1.17[0.8,1.71]
Proudman 2015	1/87	0/53		0.4%	1.84[0.08,44.38]
Shinto 2014	1/13	0/13		0.42%	3[0.13,67.51]
SOFA 2006	65/273	62/273		43.37%	1.05[0.77,1.42]
Subtotal (95% CI)	**958**	**933**		**100%**	**1.1[0.9,1.35]**
Total events: 161 (Higher omega 3), 145 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=4.09, df=5(P=0.54); I^2=0%					
Test for overall effect: Z=0.97(P=0.33)					
1.26.4 N-3 replacing carbohydrates/sugars					
Derosa 2016	2/128	3/130		100%	0.68[0.12,3.98]
Subtotal (95% CI)	**128**	**130**		**100%**	**0.68[0.12,3.98]**





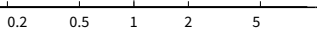
Analysis 1.27. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 27 CVD events - LCn3 - subgroup by intervention type.





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
FOSTAR 2016	18/101	16/101		0.65%	1.13[0.61,2.08]
Subtotal (95% CI)	**2505**	**2534**		**7.38%**	**1.02[0.89,1.17]**
Total events: 354 (Higher omega 3), 351 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=0.1, df=1(P=0.75); I²=0%					
Test for overall effect: Z=0.29(P=0.77)					
1.27.3 Supplements (capsule)					
AFFORD 2013	20/153	11/163		0.51%	1.94[0.96,3.91]
AREDS2 2014	183/2147	187/2056		4.57%	0.94[0.77,1.14]
Baldassarre 2006	1/32	0/32		0.03%	3[0.13,71]
Brox 2001	0/80	1/40		0.03%	0.17[0.01,4.05]
Derosa 2016	2/128	3/130		0.08%	0.68[0.12,3.98]
DO IT 2010	32/282	36/281		1.19%	0.89[0.57,1.38]
Doi 2014	11/119	24/119		0.56%	0.46[0.24,0.89]
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		1.28%	0.8[0.52,1.23]
FORWARD 2013	4/289	4/297		0.14%	1.03[0.26,4.07]
GISSI-HF 2008	1635/3494	1687/3481		12.17%	0.97[0.92,1.01]
GISSI-P 1999	547/5666	608/5658		8.4%	0.9[0.81,1]
HARP 1995	7/41	7/39		0.28%	0.95[0.37,2.46]
JELIS 2007	262/9326	324/9319		5.82%	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		4.9%	1.19[0.99,1.43]
Nodari 2011 HF	10/67	26/66		0.6%	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		1.57%	1.17[0.8,1.71]
OMEGA 2009	182/1752	149/1701		4.23%	1.19[0.97,1.46]
ORIGIN 2012	2055/6281	2087/6255		12.14%	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]
Risk & Prevention 2013	620/6239	630/6266		8.66%	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		0.8%	0.65[0.37,1.13]
Shinto 2014	1/13	0/13		0.03%	3[0.13,67.51]
SHOT 1996	15/317	12/293		0.46%	1.16[0.55,2.43]
SOFA 2006	65/273	62/273		2.32%	1.05[0.77,1.42]
SU.FOL.OM3 2010	303/1253	290/1248		6.71%	1.04[0.9,1.2]
Subtotal (95% CI)	**40216**	**39875**		**78.15%**	**0.97[0.91,1.02]**
Total events: 6258 (Higher omega 3), 6435 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=48.44, df=32(P=0.03); I²=33.94%					
Test for overall effect: Z=1.14(P=0.26)					
1.27.4 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)	**45358**	**45020**		**100%**	**0.99[0.94,1.04]**

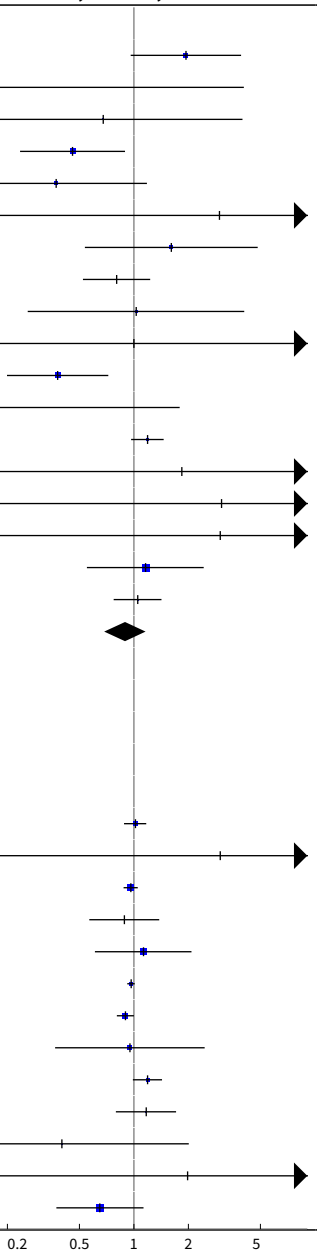
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 7299 (Higher omega 3), 7438 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=58.47, df=37(P=0.01); I²=36.72%					
Test for overall effect: Z=0.54(P=0.59)					
Test for subgroup differences: Chi²=1.61, df=1 (P=0.45), I²=0%					



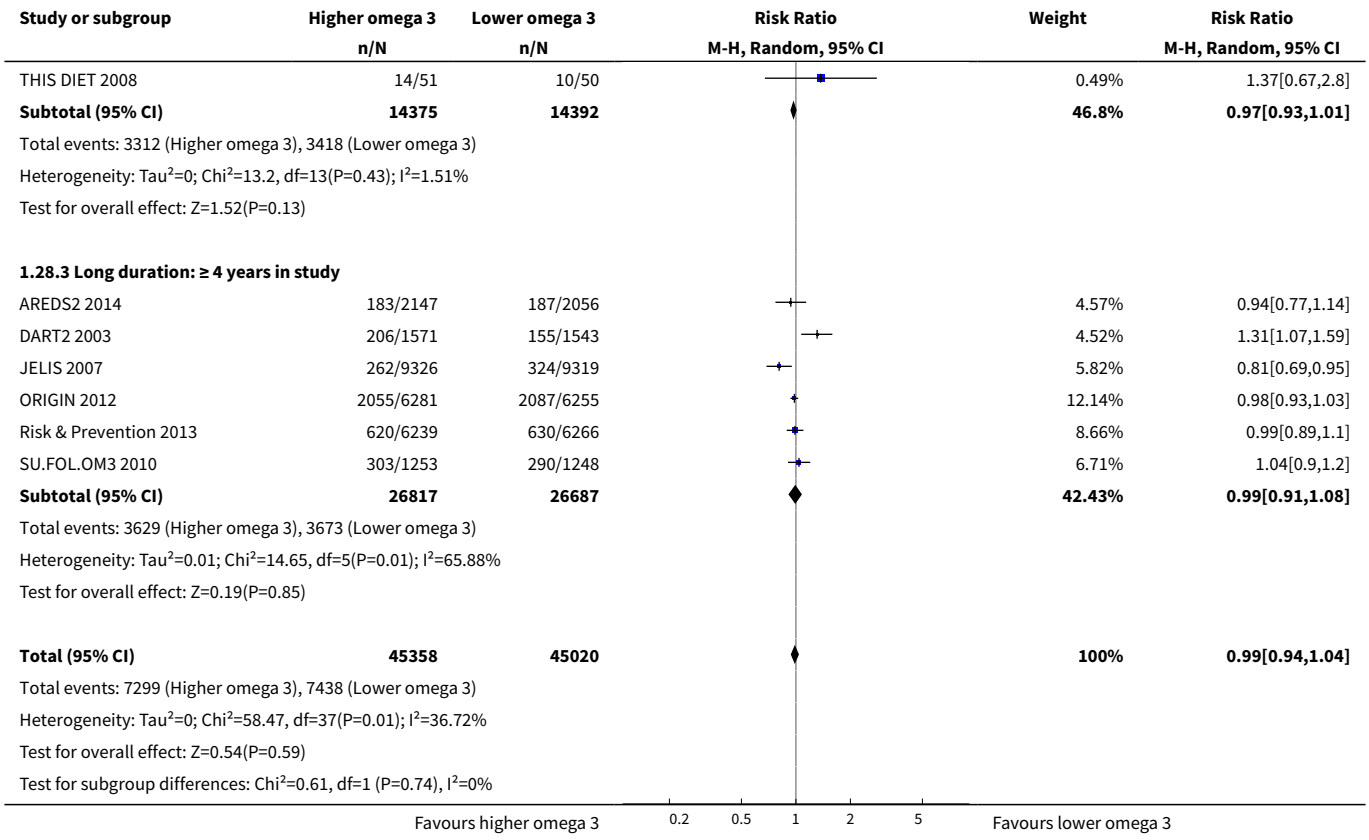
Favours higher omega 3 — Favours lower omega 3

Analysis 1.28. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 28 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
1.28.1 Medium duration 1 to < 2 years in study					
AFFORD 2013	20/153	11/163		0.51%	1.94[0.96,3.91]
Brox 2001	0/80	1/40		0.03%	0.17[0.01,4.05]
Derosa 2016	2/128	3/130		0.08%	0.68[0.12,3.98]
Doi 2014	11/119	24/119		0.56%	0.46[0.24,0.89]
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		1.28%	0.8[0.52,1.23]
FORWARD 2013	4/289	4/297		0.14%	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		0.6%	0.38[0.2,0.72]
Nutristroke 2009	0/38	4/34		0.03%	0.1[0.01,1.79]
OMEGA 2009	182/1752	149/1701		4.23%	1.19[0.97,1.46]
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]
Shinto 2014	1/13	0/13		0.03%	3[0.13,67.51]
SHOT 1996	15/317	12/293		0.46%	1.16[0.55,2.43]
SOFA 2006	65/273	62/273		2.32%	1.05[0.77,1.42]
Subtotal (95% CI)	**4166**	**3941**		**10.77%**	**0.89[0.68,1.16]**
Total events: 358 (Higher omega 3), 347 (Lower omega 3)					
Heterogeneity: Tau²=0.09; Chi²=30.14, df=17(P=0.03); I²=43.6%					
Test for overall effect: Z=0.84(P=0.4)					
1.28.2 Medium-long duration: 2 to < 4 years in study					
AlphaOmega - EPA+DHA 2010	336/2404	335/2433		6.72%	1.02[0.88,1.17]
Baldassarre 2006	1/32	0/32		0.03%	3[0.13,71]
DART 1989	467/1015	487/1018		9.45%	0.96[0.88,1.05]
DO IT 2010	32/282	36/281		1.19%	0.89[0.57,1.38]
FOSTAR 2016	18/101	16/101		0.65%	1.13[0.61,2.08]
GISSI-HF 2008	1635/3494	1687/3481		12.17%	0.97[0.92,1.01]
GISSI-P 1999	547/5666	608/5658		8.4%	0.9[0.81,1]
HARP 1995	7/41	7/39		0.28%	0.95[0.37,2.46]
MAPT 2017	192/820	164/832		4.9%	1.19[0.99,1.43]
OFAMI 2001	42/150	36/150		1.57%	1.17[0.8,1.71]
Raitt 2005	2/100	5/100		0.1%	0.4[0.08,2.01]
Sandhu 2016	2/107	1/106		0.05%	1.98[0.18,21.52]
SCIMO 1999	17/112	26/111		0.8%	0.65[0.37,1.13]

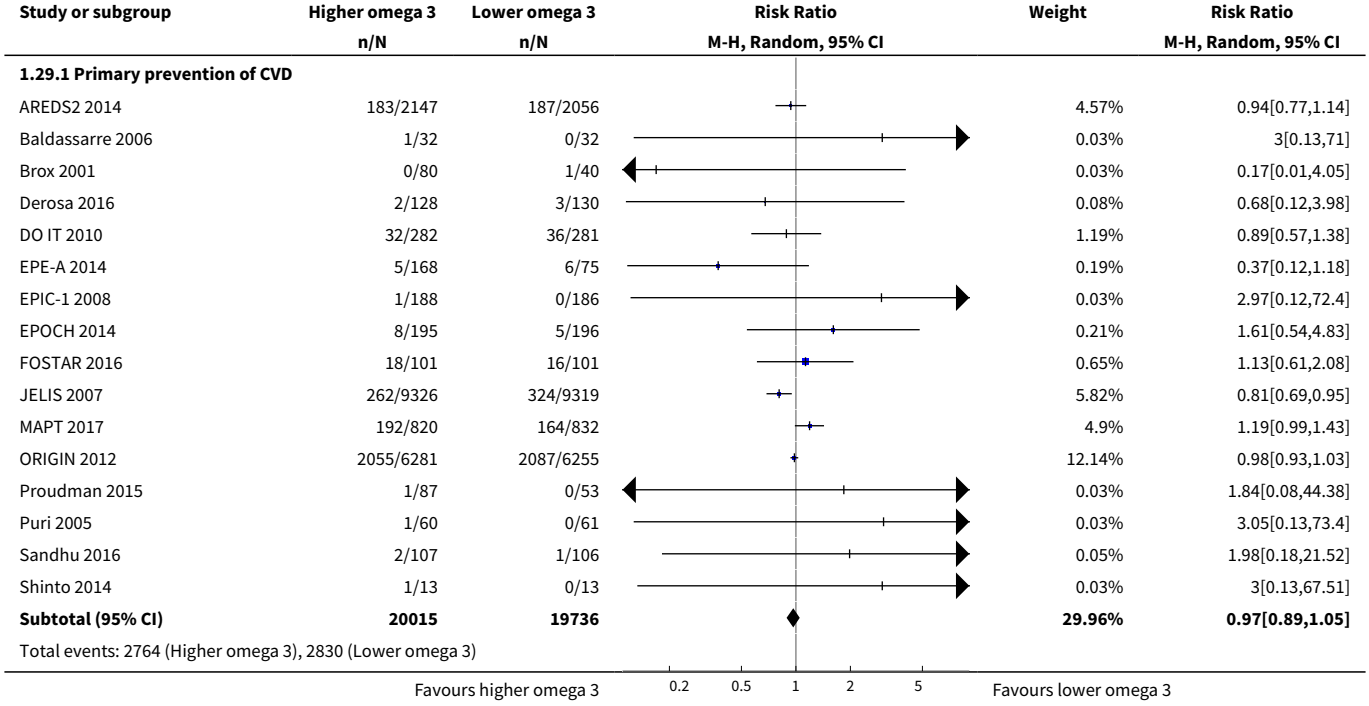


Favours higher omega 3 — Favours lower omega 3



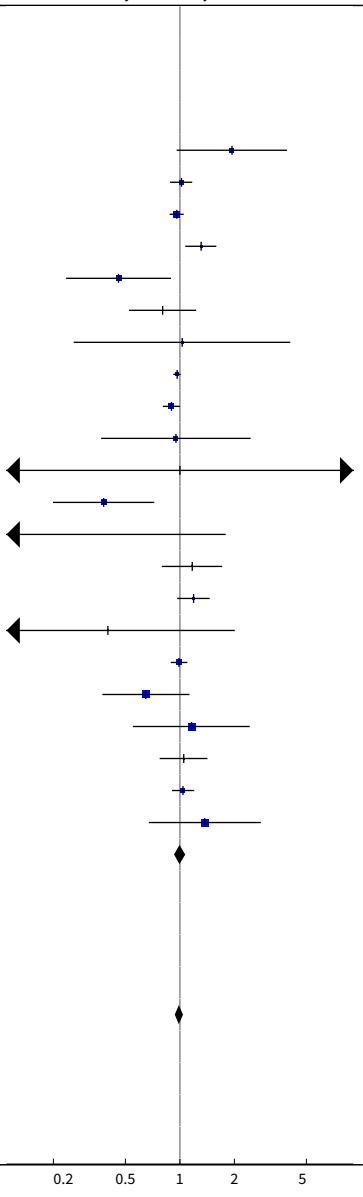
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
THIS DIET 2008	14/51	10/50		0.49%	1.37[0.67,2.8]
Subtotal (95% CI)	**14375**	**14392**		**46.8%**	**0.97[0.93,1.01]**
Total events: 3312 (Higher omega 3), 3418 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=13.2, df=13(P=0.43); I²=1.51%					
Test for overall effect: Z=1.52(P=0.13)					
1.28.3 Long duration: ≥ 4 years in study					
AREDS2 2014	183/2147	187/2056		4.57%	0.94[0.77,1.14]
DART2 2003	206/1571	155/1543		4.52%	1.31[1.07,1.59]
JELIS 2007	262/9326	324/9319		5.82%	0.81[0.69,0.95]
ORIGIN 2012	2055/6281	2087/6255		12.14%	0.98[0.93,1.03]
Risk & Prevention 2013	620/6239	630/6266		8.66%	0.99[0.89,1.1]
SU.FOL.OM3 2010	303/1253	290/1248		6.71%	1.04[0.9,1.2]
Subtotal (95% CI)	**26817**	**26687**		**42.43%**	**0.99[0.91,1.08]**
Total events: 3629 (Higher omega 3), 3673 (Lower omega 3)					
Heterogeneity: Tau²=0.01; Chi²=14.65, df=5(P=0.01); I²=65.88%					
Test for overall effect: Z=0.19(P=0.85)					
Total (95% CI)	**45358**	**45020**		**100%**	**0.99[0.94,1.04]**
Total events: 7299 (Higher omega 3), 7438 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=58.47, df=37(P=0.01); I²=36.72%					
Test for overall effect: Z=0.54(P=0.59)					
Test for subgroup differences: Chi²=0.61, df=1 (P=0.74), I²=0%					

Analysis 1.29. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 29 CVD events - LCn3 - subgroup by primary or secondary prevention.



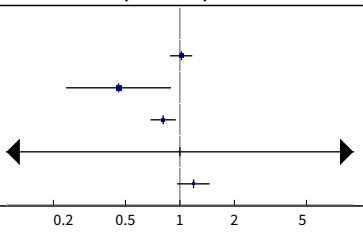
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.29.1 Primary prevention of CVD					
AREDS2 2014	183/2147	187/2056		4.57%	0.94[0.77,1.14]
Baldassarre 2006	1/32	0/32		0.03%	3[0.13,71]
Brox 2001	0/80	1/40		0.03%	0.17[0.01,4.05]
Derosa 2016	2/128	3/130		0.08%	0.68[0.12,3.98]
DO IT 2010	32/282	36/281		1.19%	0.89[0.57,1.38]
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]
FOSTAR 2016	18/101	16/101		0.65%	1.13[0.61,2.08]
JELIS 2007	262/9326	324/9319		5.82%	0.81[0.69,0.95]
MAPT 2017	192/820	164/832		4.9%	1.19[0.99,1.43]
ORIGIN 2012	2055/6281	2087/6255		12.14%	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]
Sandhu 2016	2/107	1/106		0.05%	1.98[0.18,21.52]
Shinto 2014	1/13	0/13		0.03%	3[0.13,67.51]
Subtotal (95% CI)	**20015**	**19736**		**29.96%**	**0.97[0.89,1.05]**
Total events: 2764 (Higher omega 3), 2830 (Lower omega 3)					

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; Chi²=17.54, df=15(P=0.29); I²=14.48%					
Test for overall effect: Z=0.76(P=0.45)					
1.29.2 Secondary prevention					
AFFORD 2013	20/153	11/163		0.51%	1.94[0.96,3.91]
AlphaOmega - EPA+DHA 2010	336/2404	335/2433		6.72%	1.02[0.88,1.17]
DART 1989	467/1015	487/1018		9.45%	0.96[0.88,1.05]
DART2 2003	206/1571	155/1543		4.52%	1.31[1.07,1.59]
Doi 2014	11/119	24/119		0.56%	0.46[0.24,0.89]
FAAT 2005	31/200	39/202		1.28%	0.8[0.52,1.23]
FORWARD 2013	4/289	4/297		0.14%	1.03[0.26,4.07]
GISSI-HF 2008	1635/3494	1687/3481		12.17%	0.97[0.92,1.01]
GISSI-P 1999	547/5666	608/5658		8.4%	0.9[0.81,1]
HARP 1995	7/41	7/39		0.28%	0.95[0.37,2.46]
Kumar 2013	1/39	1/39		0.03%	1[0.06,15.43]
Nodari 2011 HF	10/67	26/66		0.6%	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		1.57%	1.17[0.8,1.71]
OMEGA 2009	182/1752	149/1701		4.23%	1.19[0.97,1.46]
Raitt 2005	2/100	5/100		0.1%	0.4[0.08,2.01]
Risk & Prevention 2013	620/6239	630/6266		8.66%	0.99[0.89,1.1]
SCIMO 1999	17/112	26/111		0.8%	0.65[0.37,1.13]
SHOT 1996	15/317	12/293		0.46%	1.16[0.55,2.43]
SOFA 2006	65/273	62/273		2.32%	1.05[0.77,1.42]
SU.FOL.OM3 2010	303/1253	290/1248		6.71%	1.04[0.9,1.2]
THIS DIET 2008	14/51	10/50		0.49%	1.37[0.67,2.8]
Subtotal (95% CI)	**25343**	**25284**		**70.04%**	**1[0.93,1.07]**
Total events: 4535 (Higher omega 3), 4608 (Lower omega 3)					
Heterogeneity: Tau²=0.01; Chi²=40.98, df=21(P=0.01); I²=48.75%					
Test for overall effect: Z=0.14(P=0.89)					
Total (95% CI)	**45358**	**45020**		**100%**	**0.99[0.94,1.04]**
Total events: 7299 (Higher omega 3), 7438 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=58.47, df=37(P=0.01); I²=36.72%					
Test for overall effect: Z=0.54(P=0.59)					
Test for subgroup differences: Chi²=0.25, df=1 (P=0.61), I²=0%					

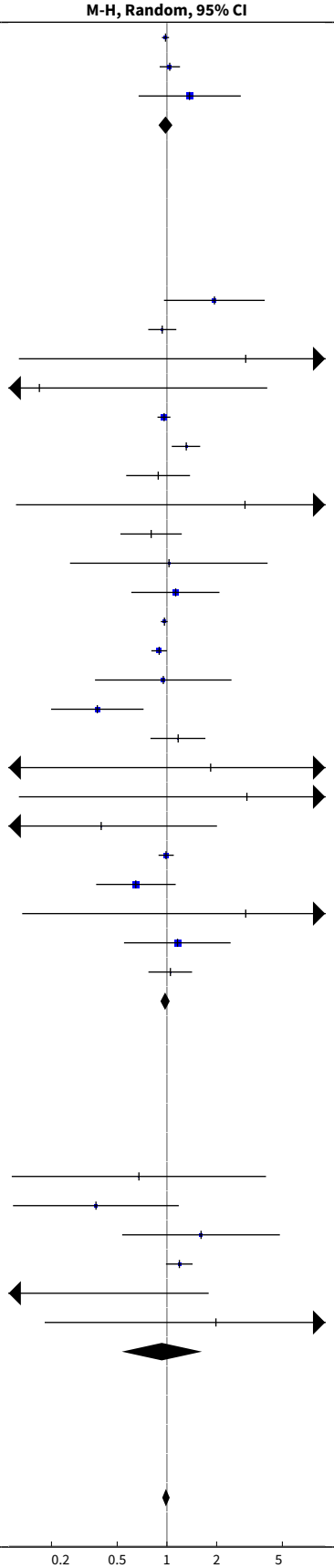


Analysis 1.30. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 30 CVD events - LCn3 - subgroup by statin use.

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
1.30.1 LCn3 - ≥ 50% of control group on statins					
AlphaOmega - EPA+DHA 2010	336/2404	335/2433		6.72%	1.02[0.88,1.17]
Doi 2014	11/119	24/119		0.56%	0.46[0.24,0.89]
JELIS 2007	262/9326	324/9319		5.82%	0.81[0.69,0.95]
Kumar 2013	1/39	1/39		0.03%	1[0.06,15.43]
OMEGA 2009	182/1752	149/1701		4.23%	1.19[0.97,1.46]



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
ORIGIN 2012	2055/6281	2087/6255		12.14%	0.98[0.93,1.03]
SU.FOL.OM3 2010	303/1253	290/1248		6.71%	1.04[0.9,1.2]
THIS DIET 2008	14/51	10/50		0.49%	1.37[0.67,2.8]
Subtotal (95% CI)	**21225**	**21164**		**36.71%**	**0.98[0.89,1.08]**
Total events: 3164 (Higher omega 3), 3220 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=15.66, df=7(P=0.03); I^2=55.29%					
Test for overall effect: Z=0.38(P=0.7)					
1.30.2 LCn3 - < 50% of control group on statins					
AFFORD 2013	20/153	11/163		0.51%	1.94[0.96,3.91]
AREDS2 2014	183/2147	187/2056		4.57%	0.94[0.77,1.14]
Baldassarre 2006	1/32	0/32		0.03%	3[0.13,71]
Brox 2001	0/80	1/40		0.03%	0.17[0.01,4.05]
DART 1989	467/1015	487/1018		9.45%	0.96[0.88,1.05]
DART2 2003	206/1571	155/1543		4.52%	1.31[1.07,1.59]
DO IT 2010	32/282	36/281		1.19%	0.89[0.57,1.38]
EPIC-1 2008	1/188	0/186		0.03%	2.97[0.12,72.4]
FAAT 2005	31/200	39/202		1.28%	0.8[0.52,1.23]
FORWARD 2013	4/289	4/297		0.14%	1.03[0.26,4.07]
FOSTAR 2016	18/101	16/101		0.65%	1.13[0.61,2.08]
GISSI-HF 2008	1635/3494	1687/3481		12.17%	0.97[0.92,1.01]
GISSI-P 1999	547/5666	608/5658		8.4%	0.9[0.81,1]
HARP 1995	7/41	7/39		0.28%	0.95[0.37,2.46]
Nodari 2011 HF	10/67	26/66		0.6%	0.38[0.2,0.72]
OFAMI 2001	42/150	36/150		1.57%	1.17[0.8,1.71]
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]
Risk & Prevention 2013	620/6239	630/6266		8.66%	0.99[0.89,1.1]
SCIMO 1999	17/112	26/111		0.8%	0.65[0.37,1.13]
Shinto 2014	1/13	0/13		0.03%	3[0.13,67.51]
SHOT 1996	15/317	12/293		0.46%	1.16[0.55,2.43]
SOFA 2006	65/273	62/273		2.32%	1.05[0.77,1.42]
Subtotal (95% CI)	**22677**	**22483**		**57.83%**	**0.98[0.91,1.04]**
Total events: 3926 (Higher omega 3), 4035 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=31.84, df=23(P=0.1); I^2=27.77%					
Test for overall effect: Z=0.77(P=0.44)					
1.30.3 LCn3 - use of statins unclear					
Derosa 2016	2/128	3/130		0.08%	0.68[0.12,3.98]
EPE-A 2014	5/168	6/75		0.19%	0.37[0.12,1.18]
EPOCH 2014	8/195	5/196		0.21%	1.61[0.54,4.83]
MAPT 2017	192/820	164/832		4.9%	1.19[0.99,1.43]
Nutristroke 2009	0/38	4/34		0.03%	0.1[0.01,1.79]
Sandhu 2016	2/107	1/106		0.05%	1.98[0.18,21.52]
Subtotal (95% CI)	**1456**	**1373**		**5.46%**	**0.93[0.53,1.63]**
Total events: 209 (Higher omega 3), 183 (Lower omega 3)					
Heterogeneity: Tau^2=0.15; Chi^2=7.48, df=5(P=0.19); I^2=33.15%					
Test for overall effect: Z=0.25(P=0.8)					
Total (95% CI)	**45358**	**45020**		**100%**	**0.99[0.94,1.04]**
Total events: 7299 (Higher omega 3), 7438 (Lower omega 3)					



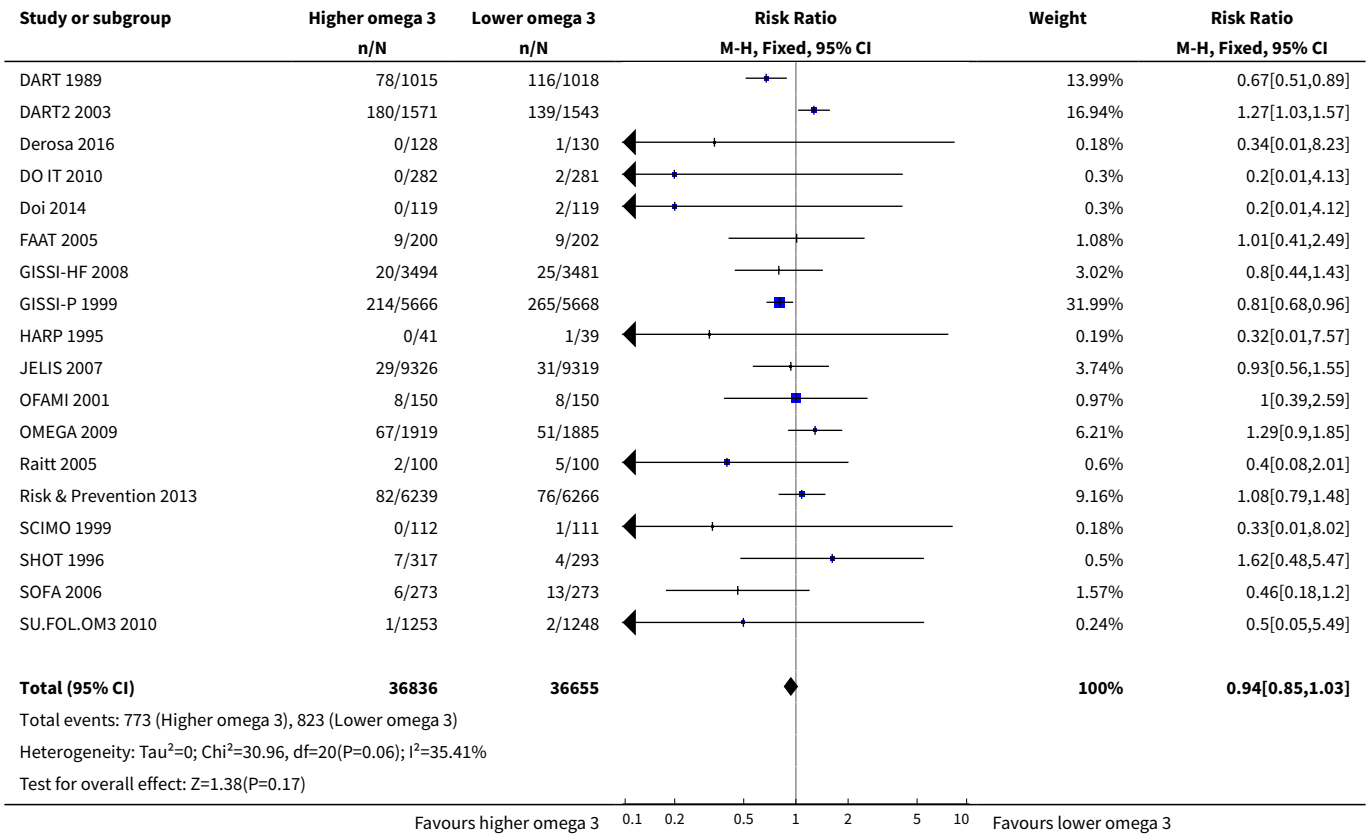
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0; Chi²=58.47, df=37(P=0.01); I²=36.72%					
Test for overall effect: Z=0.54(P=0.59)					
Test for subgroup differences: Chi²=0.04, df=1 (P=0.98), I²=0%					

Analysis 1.31. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 31 Coronary heart disease mortality (overall) - LCn3.

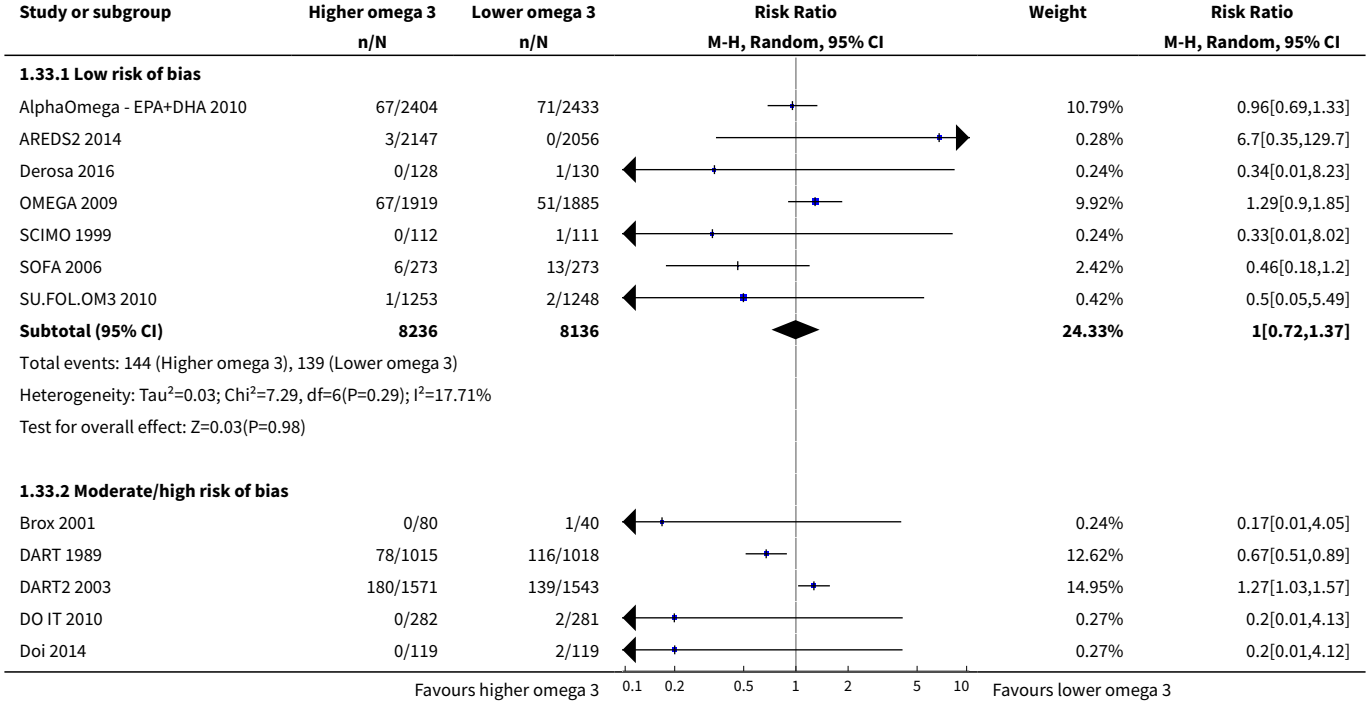
Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 fats n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
AlphaOmega - EPA+DHA 2010	67/2404	71/2433		10.79%	0.96[0.69,1.33]
AREDS2 2014	3/2147	0/2056		0.28%	6.7[0.35,129.7]
Brox 2001	0/80	1/40		0.24%	0.17[0.01,4.05]
DART 1989	78/1015	116/1018		12.62%	0.67[0.51,0.89]
DART2 2003	180/1571	139/1543		14.95%	1.27[1.03,1.57]
Derosa 2016	0/128	1/130		0.24%	0.34[0.01,8.23]
DO IT 2010	0/282	2/281		0.27%	0.2[0.01,4.13]
Doi 2014	0/119	2/119		0.27%	0.2[0.01,4.12]
FAAT 2005	9/200	9/202		2.66%	1.01[0.41,2.49]
GISSI-HF 2008	20/3494	25/3481		5.35%	0.8[0.44,1.43]
GISSI-P 1999	214/5666	265/5668		16.2%	0.81[0.68,0.96]
HARP 1995	0/41	1/39		0.25%	0.32[0.01,7.57]
JELIS 2007	29/9326	31/9319		6.59%	0.93[0.56,1.55]
OFAMI 2001	8/150	8/150		2.42%	1[0.39,2.59]
OMEGA 2009	67/1919	51/1885		9.92%	1.29[0.9,1.85]
Raitt 2005	2/100	5/100		0.91%	0.4[0.08,2.01]
Risk & Prevention 2013	82/6239	76/6266		11.39%	1.08[0.79,1.48]
SCIMO 1999	0/112	1/111		0.24%	0.33[0.01,8.02]
SHOT 1996	7/317	4/293		1.55%	1.62[0.48,5.47]
SOFA 2006	6/273	13/273		2.42%	0.46[0.18,1.2]
SU.FOL.OM3 2010	1/1253	2/1248		0.42%	0.5[0.05,5.49]
Total (95% CI)	**36836**	**36655**		**100%**	**0.93[0.79,1.09]**
Total events: 773 (Favours higher omega 3), 823 (Lower omega 3 fats)					
Heterogeneity: Tau²=0.03; Chi²=30.96, df=20(P=0.06); I²=35.41%					
Test for overall effect: Z=0.91(P=0.36)					

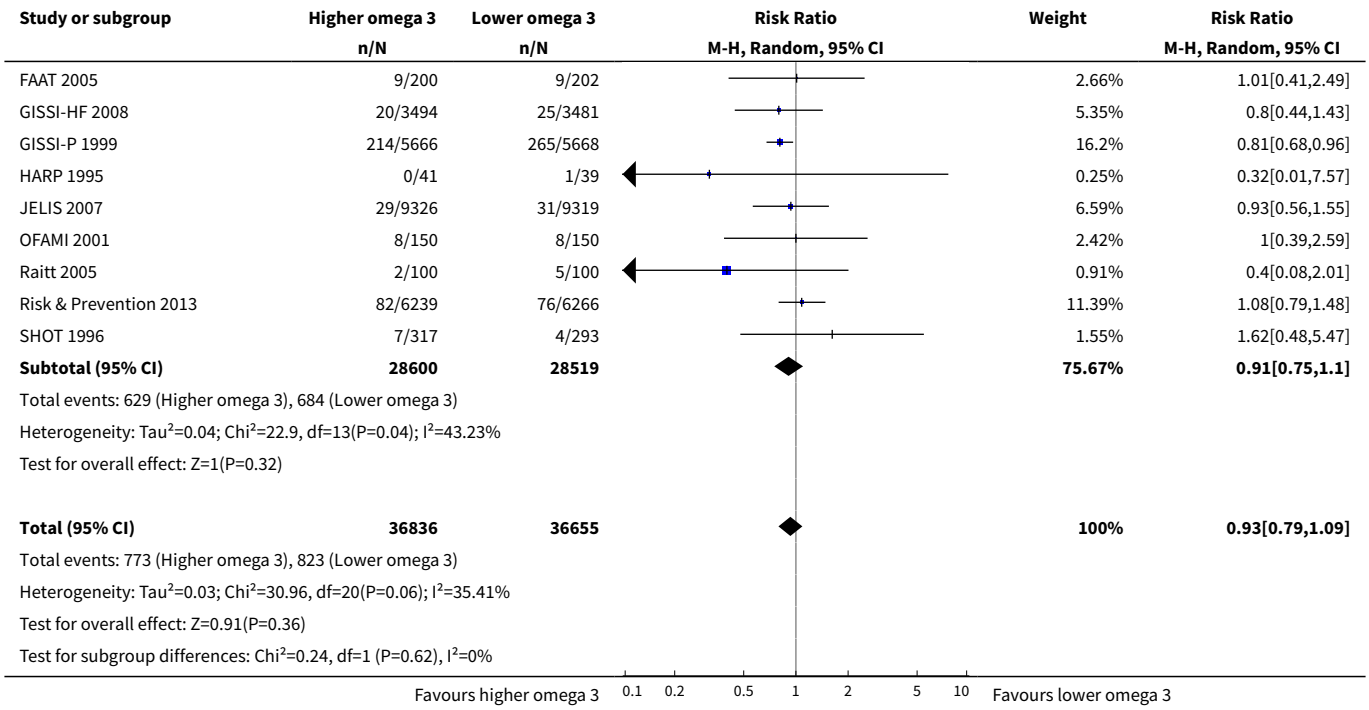
Analysis 1.32. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 32 CHD mortality - LCn3 - SA fixed-effect.

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	67/2404	71/2433		8.52%	0.96[0.69,1.33]
AREDS2 2014	3/2147	0/2056		0.06%	6.7[0.35,129.7]
Brox 2001	0/80	1/40		0.24%	0.17[0.01,4.05]



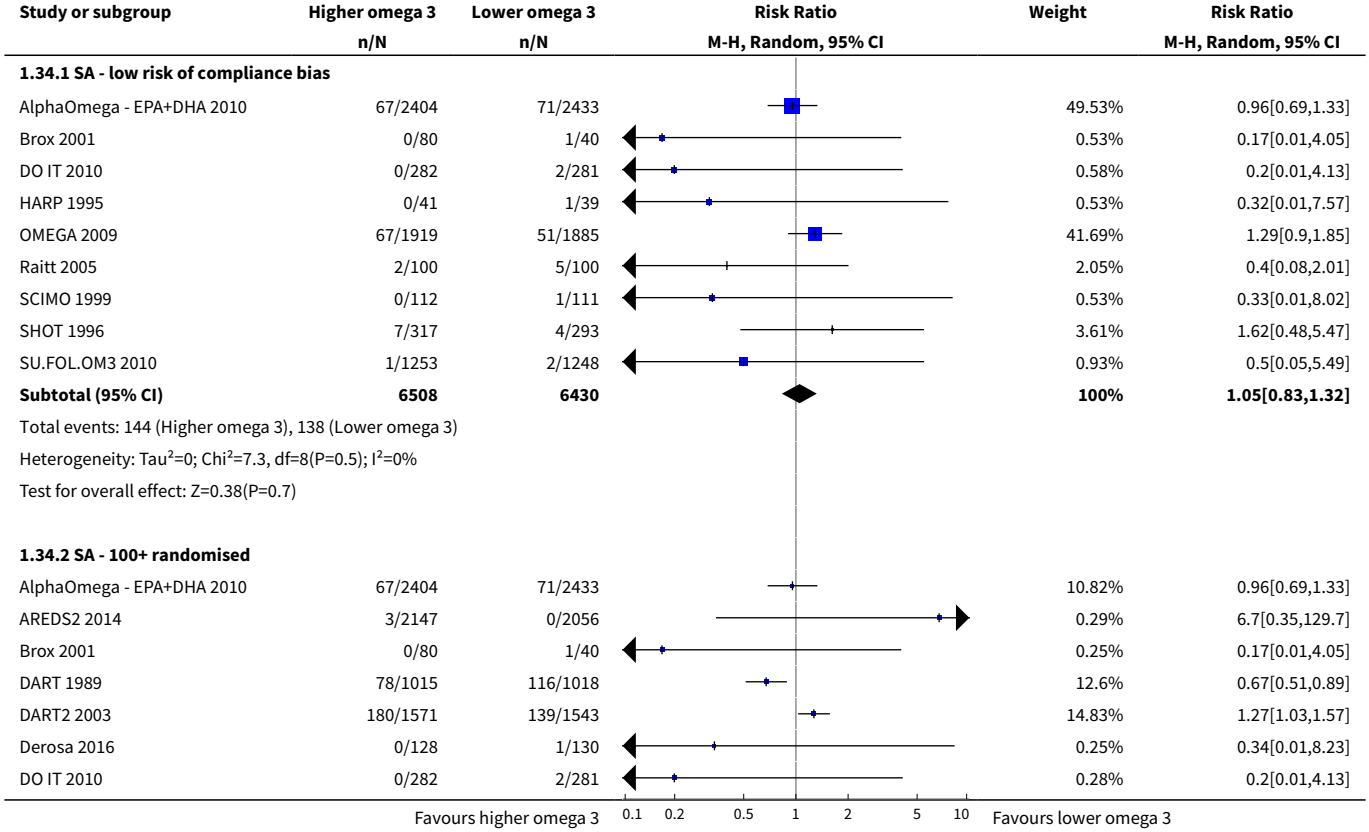
Analysis 1.33. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 33 CHD mortality - LCn3 - SA by summary risk of bias.





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
FAAT 2005	9/200	9/202		2.66%	1.01[0.41,2.49]
GISSI-HF 2008	20/3494	25/3481		5.35%	0.8[0.44,1.43]
GISSI-P 1999	214/5666	265/5668		16.2%	0.81[0.68,0.96]
HARP 1995	0/41	1/39		0.25%	0.32[0.01,7.57]
JELIS 2007	29/9326	31/9319		6.59%	0.93[0.56,1.55]
OFAMI 2001	8/150	8/150		2.42%	1[0.39,2.59]
Raitt 2005	2/100	5/100		0.91%	0.4[0.08,2.01]
Risk & Prevention 2013	82/6239	76/6266		11.39%	1.08[0.79,1.48]
SHOT 1996	7/317	4/293		1.55%	1.62[0.48,5.47]
Subtotal (95% CI)	**28600**	**28519**		**75.67%**	**0.91[0.75,1.1]**
Total events: 629 (Higher omega 3), 684 (Lower omega 3)					
Heterogeneity: Tau^2=0.04; Chi^2=22.9, df=13(P=0.04); I^2=43.23%					
Test for overall effect: Z=1(P=0.32)					
Total (95% CI)	**36836**	**36655**		**100%**	**0.93[0.79,1.09]**
Total events: 773 (Higher omega 3), 823 (Lower omega 3)					
Heterogeneity: Tau^2=0.03; Chi^2=30.96, df=20(P=0.06); I^2=35.41%					
Test for overall effect: Z=0.91(P=0.36)					
Test for subgroup differences: Chi^2=0.24, df=1 (P=0.62), I^2=0%					

Analysis 1.34. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 34 CHD mortality - LCn3 - SA by compliance and study size.

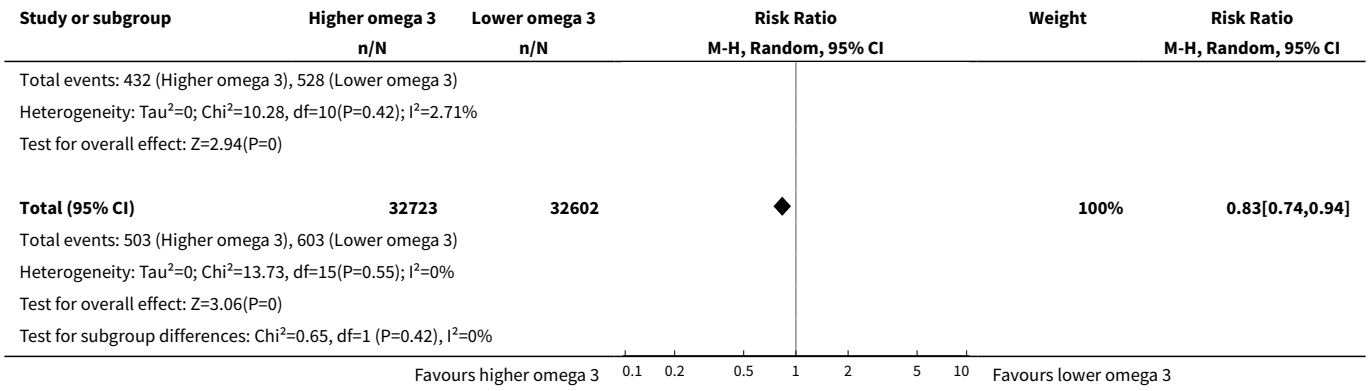


Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.34.1 SA - low risk of compliance bias					
AlphaOmega - EPA+DHA 2010	67/2404	71/2433		49.53%	0.96[0.69,1.33]
Brox 2001	0/80	1/40		0.53%	0.17[0.01,4.05]
DO IT 2010	0/282	2/281		0.58%	0.2[0.01,4.13]
HARP 1995	0/41	1/39		0.53%	0.32[0.01,7.57]
OMEGA 2009	67/1919	51/1885		41.69%	1.29[0.9,1.85]
Raitt 2005	2/100	5/100		2.05%	0.4[0.08,2.01]
SCIMO 1999	0/112	1/111		0.53%	0.33[0.01,8.02]
SHOT 1996	7/317	4/293		3.61%	1.62[0.48,5.47]
SU.FOL.OM3 2010	1/1253	2/1248		0.93%	0.5[0.05,5.49]
Subtotal (95% CI)	**6508**	**6430**		**100%**	**1.05[0.83,1.32]**
Total events: 144 (Higher omega 3), 138 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=7.3, df=8(P=0.5); I^2=0%					
Test for overall effect: Z=0.38(P=0.7)					
1.34.2 SA - 100+ randomised					
AlphaOmega - EPA+DHA 2010	67/2404	71/2433		10.82%	0.96[0.69,1.33]
AREDS2 2014	3/2147	0/2056		0.29%	6.7[0.35,129.7]
Brox 2001	0/80	1/40		0.25%	0.17[0.01,4.05]
DART 1989	78/1015	116/1018		12.6%	0.67[0.51,0.89]
DART2 2003	180/1571	139/1543		14.83%	1.27[1.03,1.57]
Derosa 2016	0/128	1/130		0.25%	0.34[0.01,8.23]
DO IT 2010	0/282	2/281		0.28%	0.2[0.01,4.13]

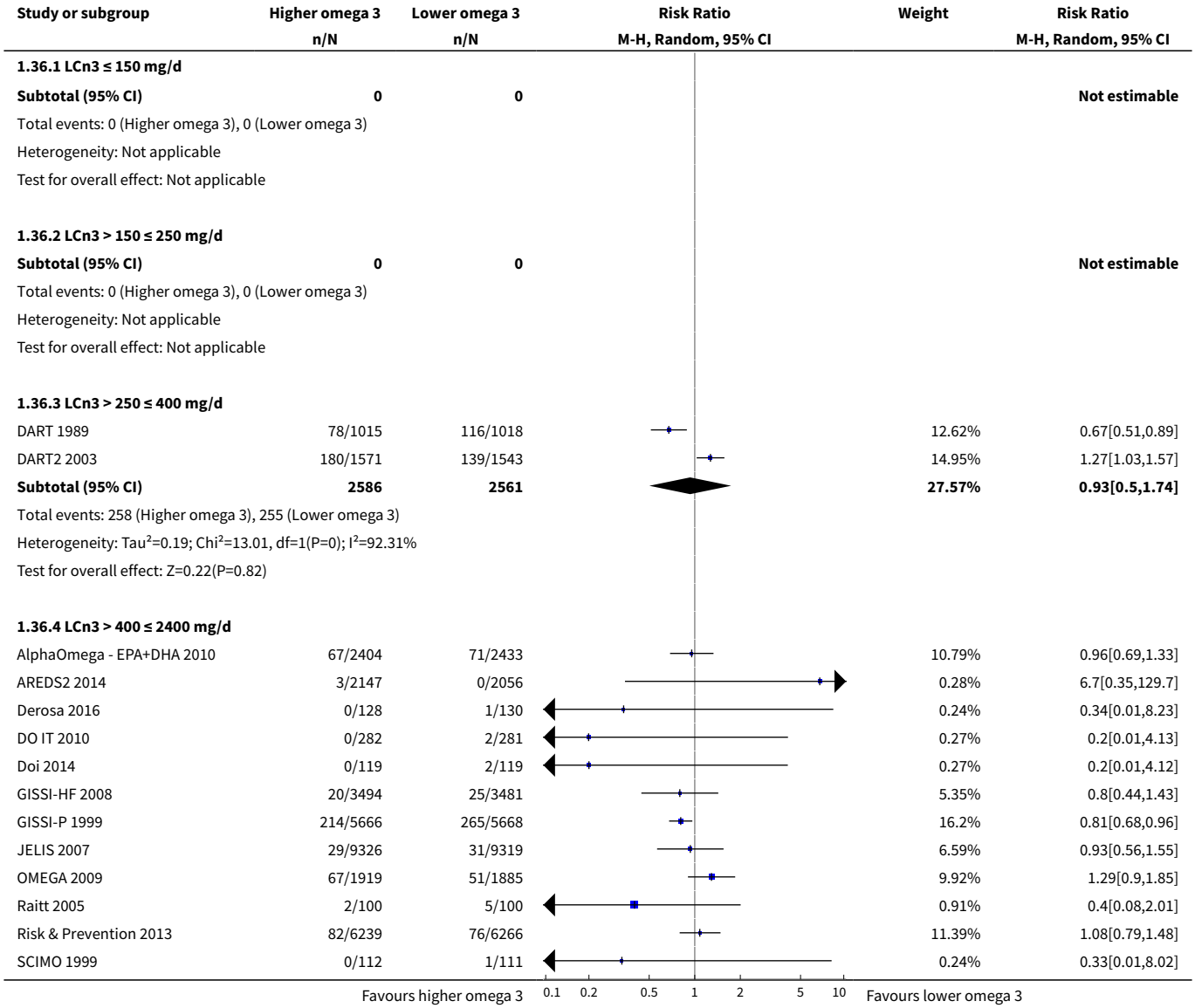
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Doi 2014	0/119	2/119		0.28%	0.2[0.01,4.12]
FAAT 2005	9/200	9/202		2.72%	1.01[0.41,2.49]
GISSI-HF 2008	20/3494	25/3481		5.44%	0.8[0.44,1.43]
GISSI-P 1999	214/5666	265/5668		16.03%	0.81[0.68,0.96]
JELIS 2007	29/9326	31/9319		6.68%	0.93[0.56,1.55]
OFAMI 2001	8/150	8/150		2.48%	1[0.39,2.59]
OMEGA 2009	67/1919	51/1885		9.97%	1.29[0.9,1.85]
Raitt 2005	2/100	5/100		0.94%	0.4[0.08,2.01]
Risk & Prevention 2013	82/6239	76/6266		11.4%	1.08[0.79,1.48]
SCIMO 1999	0/112	1/111		0.25%	0.33[0.01,8.02]
SHOT 1996	7/317	4/293		1.59%	1.62[0.48,5.47]
SOFA 2006	6/273	13/273		2.48%	0.46[0.18,1.2]
SU.FOL.OM3 2010	1/1253	2/1248		0.44%	0.5[0.05,5.49]
Subtotal (95% CI)	**36795**	**36616**		**100%**	**0.93[0.79,1.09]**
Total events: 773 (Higher omega 3), 822 (Lower omega 3)					
Heterogeneity: Tau^2=0.03; Chi^2=30.51, df=19(P=0.05); I^2=37.73%					
Test for overall effect: Z=0.88(P=0.38)					
Test for subgroup differences: Chi^2=0.66, df=1 (P=0.42), I^2=0%					

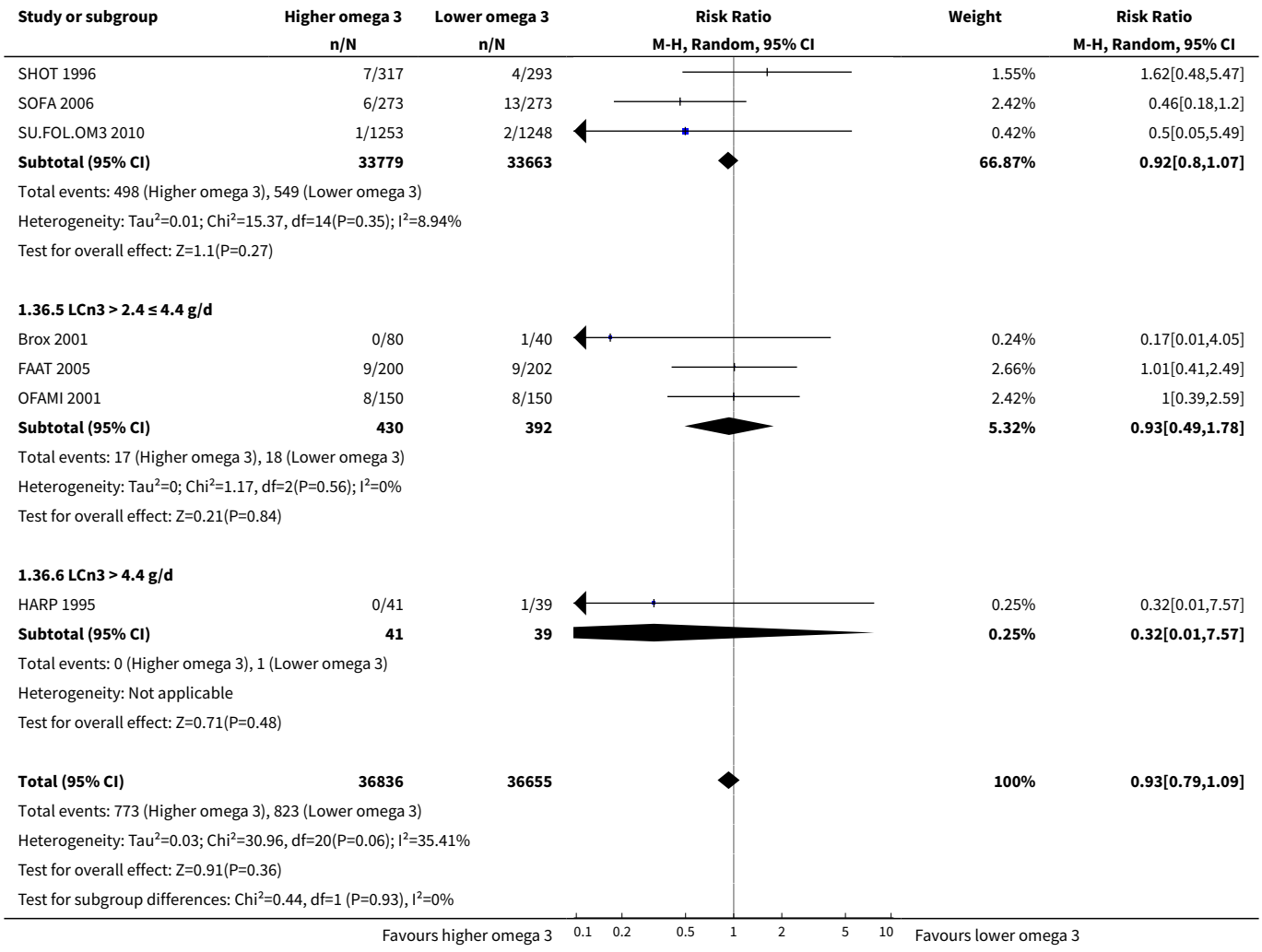
Analysis 1.35. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 35 CHD mortality - LCn3 - SA omitting cardiac death.

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
1.35.1 Low risk of bias					
AlphaOmega - EPA+DHA 2010	67/2404	71/2433		12.49%	0.96[0.69,1.33]
AREDS2 2014	3/2147	0/2056		0.15%	6.7[0.35,129.7]
Derosa 2016	0/128	1/130		0.13%	0.34[0.01,8.23]
SCIMO 1999	0/112	1/111		0.13%	0.33[0.01,8.02]
SU.FOL.OM3 2010	1/1253	2/1248		0.23%	0.5[0.05,5.49]
Subtotal (95% CI)	**6044**	**5978**		**13.15%**	**0.95[0.69,1.3]**
Total events: 71 (Higher omega 3), 75 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=2.78, df=4(P=0.6); I^2=0%					
Test for overall effect: Z=0.34(P=0.73)					
1.35.2 Moderate/high risk of bias					
Brox 2001	0/80	1/40		0.13%	0.17[0.01,4.05]
DART 1989	78/1015	116/1018		18.08%	0.67[0.51,0.89]
DO IT 2010	0/282	2/281		0.15%	0.2[0.01,4.13]
Doi 2014	0/119	2/119		0.15%	0.2[0.01,4.12]
GISSI-HF 2008	20/3494	25/3481		3.94%	0.8[0.44,1.43]
GISSI-P 1999	214/5666	265/5668		43.49%	0.81[0.68,0.96]
HARP 1995	0/41	1/39		0.13%	0.32[0.01,7.57]
JELIS 2007	29/9326	31/9319		5.29%	0.93[0.56,1.55]
Raitt 2005	2/100	5/100		0.52%	0.4[0.08,2.01]
Risk & Prevention 2013	82/6239	76/6266		14.06%	1.08[0.79,1.48]
SHOT 1996	7/317	4/293		0.91%	1.62[0.48,5.47]
Subtotal (95% CI)	**26679**	**26624**		**86.85%**	**0.82[0.72,0.94]**

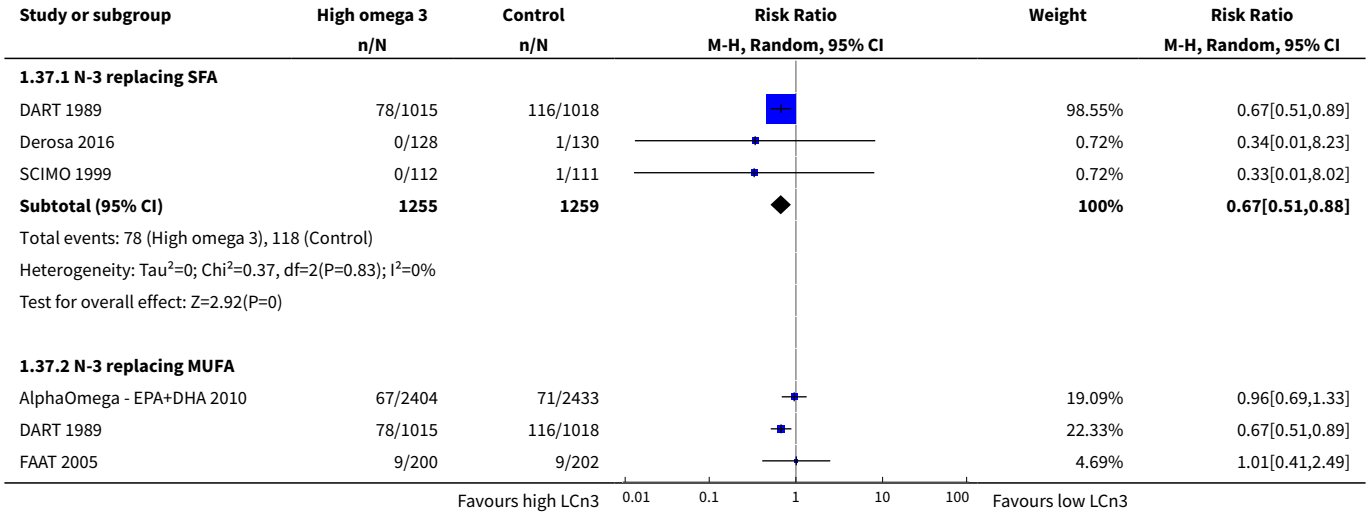


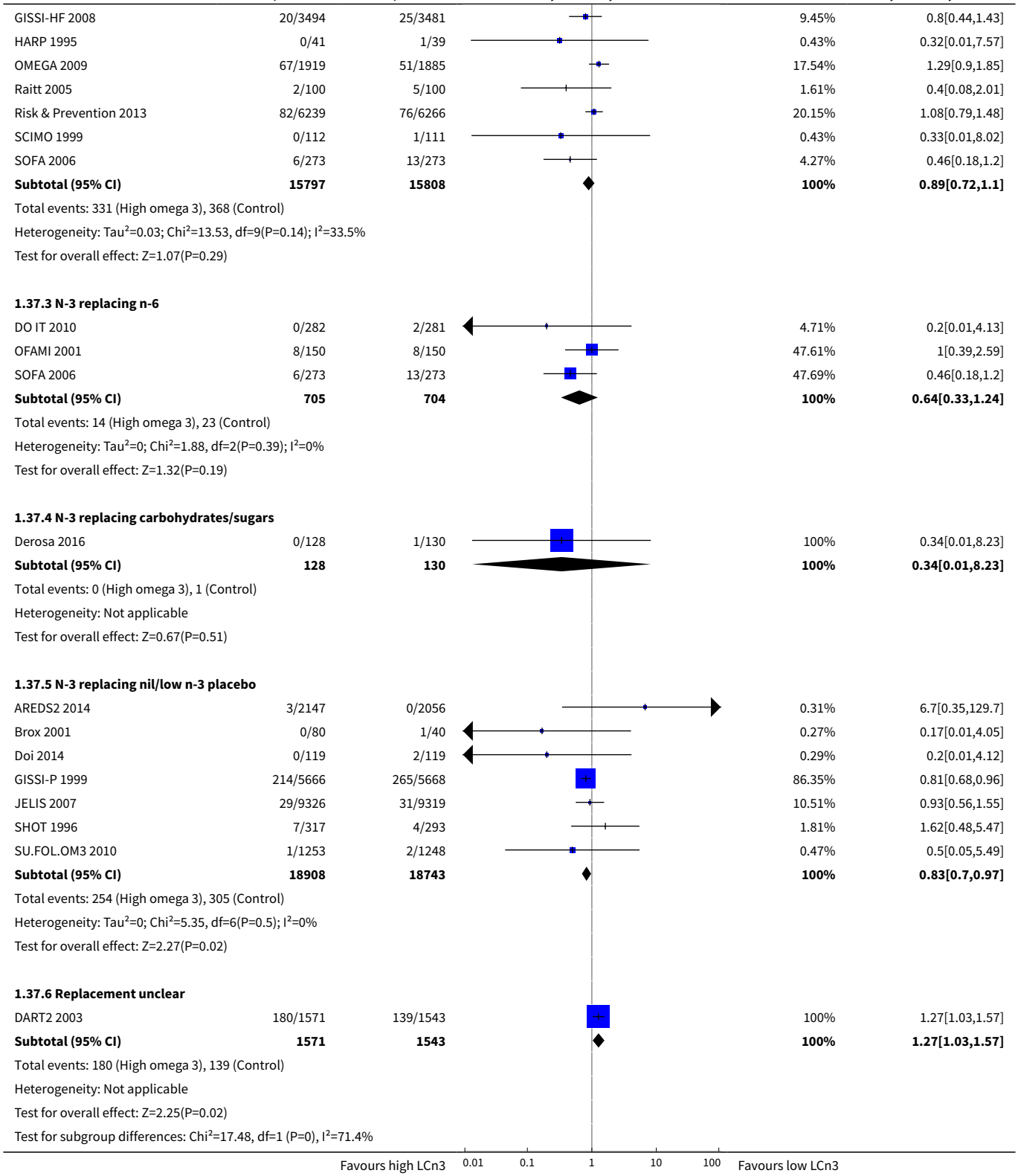
Analysis 1.36. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 36 CHD mortality - LCn3 - subgroup by dose.





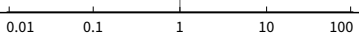
Analysis 1.37. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 37 CHD mortality - LCn3 - subgroup by replacement.





Analysis 1.38. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 38 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
1.38.1 Dietary advice					
DART 1989	78/1015	116/1018		12.62%	0.67[0.51,0.89]
DART2 2003	180/1571	139/1543		14.95%	1.27[1.03,1.57]
Subtotal (95% CI)	**2586**	**2561**		**27.57%**	**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)					
1.38.2 Supplemental foods					
AlphaOmega - EPA+DHA 2010	67/2404	71/2433		10.79%	0.96[0.69,1.33]
Subtotal (95% CI)	**2404**	**2433**		**10.79%**	**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)					
1.38.3 Supplements (capsule)					
AREDS2 2014	3/2147	0/2056		0.28%	6.7[0.35,129.7]
Brox 2001	0/80	1/40		0.24%	0.17[0.01,4.05]
Derosa 2016	0/128	1/130		0.24%	0.34[0.01,8.23]
DO IT 2010	0/282	2/281		0.27%	0.2[0.01,4.13]
Doi 2014	0/119	2/119		0.27%	0.2[0.01,4.12]
FAAT 2005	9/200	9/202		2.66%	1.01[0.41,2.49]
GISSI-HF 2008	20/3494	25/3481		5.35%	0.8[0.44,1.43]
GISSI-P 1999	214/5666	265/5668		16.2%	0.81[0.68,0.96]
HARP 1995	0/41	1/39		0.25%	0.32[0.01,7.57]
JELIS 2007	29/9326	31/9319		6.59%	0.93[0.56,1.55]
OFAMI 2001	8/150	8/150		2.42%	1[0.39,2.59]
OMEGA 2009	67/1919	51/1885		9.92%	1.29[0.9,1.85]
Raitt 2005	2/100	5/100		0.91%	0.4[0.08,2.01]
Risk & Prevention 2013	82/6239	76/6266		11.39%	1.08[0.79,1.48]
SCIMO 1999	0/112	1/111		0.24%	0.33[0.01,8.02]
SHOT 1996	7/317	4/293		1.55%	1.62[0.48,5.47]
SOFA 2006	6/273	13/273		2.42%	0.46[0.18,1.2]
SU.FOL.OM3 2010	1/1253	2/1248		0.42%	0.5[0.05,5.49]
Subtotal (95% CI)	**31846**	**31661**		**61.64%**	**0.9[0.79,1.02]**
Total events: 448 (High omega 3), 497 (Control)					
Heterogeneity: Tau^2=0; Chi^2=16.86, df=17(P=0.46); I^2=0%					
Test for overall effect: Z=1.64(P=0.1)					
1.38.4 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)	**36836**	**36655**		**100%**	**0.93[0.79,1.09]**
Total events: 773 (High omega 3), 823 (Control)					
Heterogeneity: Tau^2=0.03; Chi^2=30.96, df=20(P=0.06); I^2=35.41%					
Test for overall effect: Z=0.91(P=0.36)					



Favours high ALA Favours low ALA

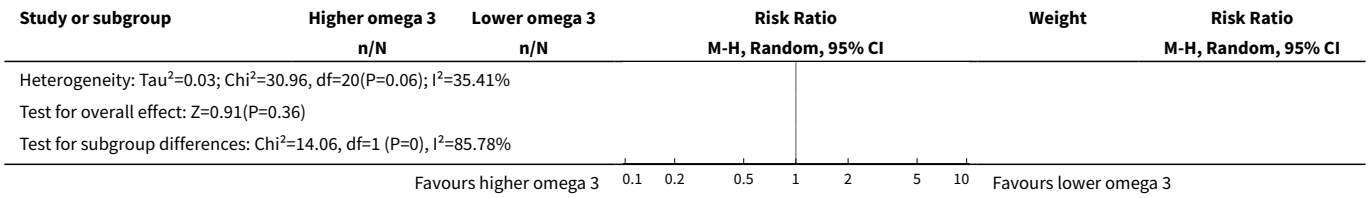
Study or subgroup	High omega 3 n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for subgroup differences: Chi²=0.12, df=1 (P=0.94), I²=0%					

Favours high ALA 0.01 0.1 1 10 100 Favours low ALA

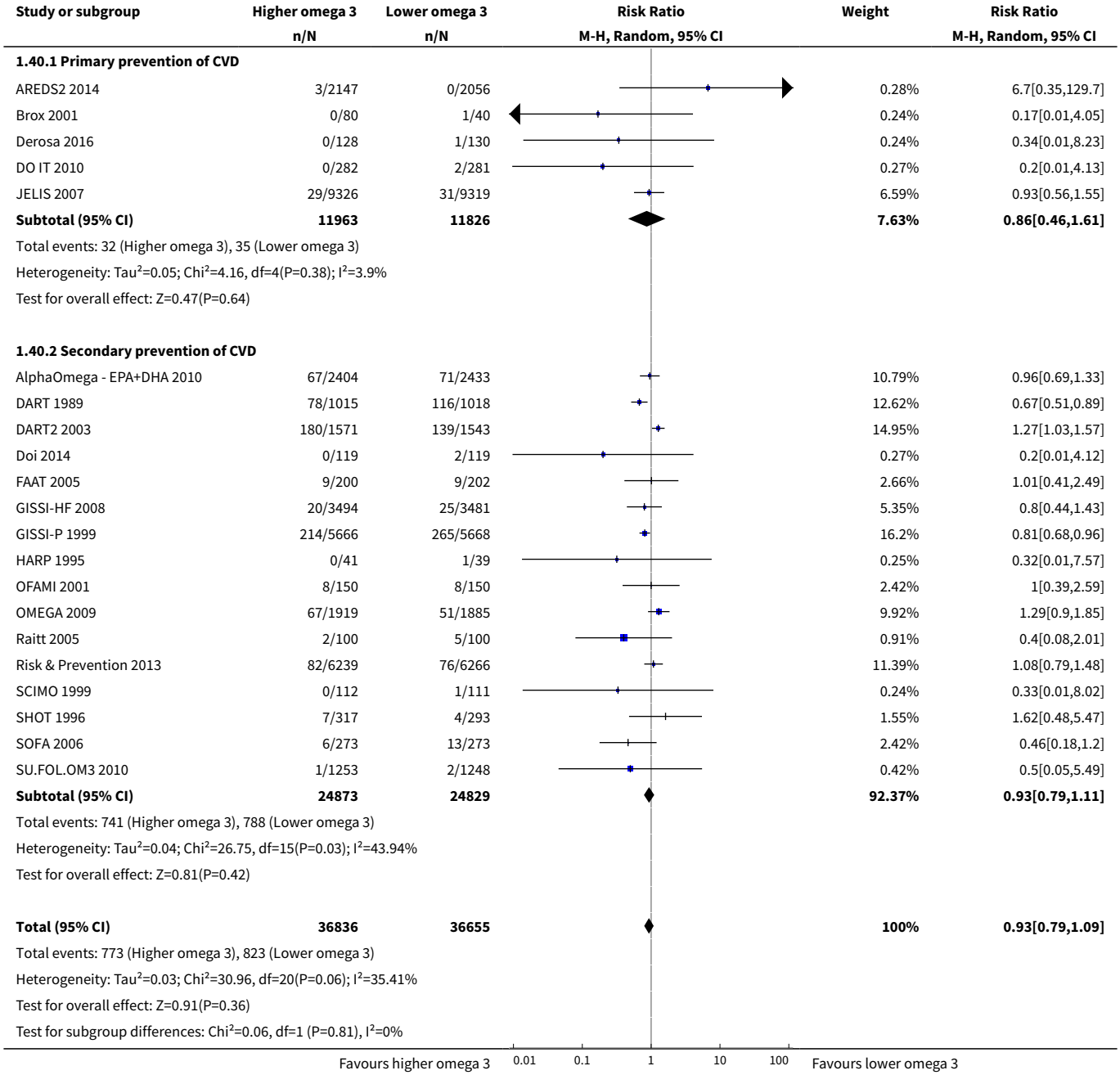
Analysis 1.39. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 39 CHD mortality - LCn3 - subgroup by duration.

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
1.39.1 Medium duration 1 to < 2 years in study					
Brox 2001	0/80	1/40		0.24%	0.17[0.01,4.05]
Derosa 2016	0/128	1/130		0.24%	0.34[0.01,8.23]
Doi 2014	0/119	2/119		0.27%	0.2[0.01,4.12]
FAAT 2005	9/200	9/202		2.66%	1.01[0.41,2.49]
OMEGA 2009	67/1919	51/1885		9.92%	1.29[0.9,1.85]
SHOT 1996	7/317	4/293		1.55%	1.62[0.48,5.47]
SOFA 2006	6/273	13/273		2.42%	0.46[0.18,1.2]
Subtotal (95% CI)	**3036**	**2942**		**17.31%**	**0.96[0.62,1.5]**
Total events: 89 (Higher omega 3), 81 (Lower omega 3)					
Heterogeneity: Tau²=0.07; Chi²=7.47, df=6(P=0.28); I²=19.71%					
Test for overall effect: Z=0.16(P=0.87)					
1.39.2 Medium-long duration: 2 to < 4 years in study					
AlphaOmega - EPA+DHA 2010	67/2404	71/2433		10.79%	0.96[0.69,1.33]
DART 1989	78/1015	116/1018		12.62%	0.67[0.51,0.89]
DO IT 2010	0/282	2/281		0.27%	0.2[0.01,4.13]
GISSI-HF 2008	20/3494	25/3481		5.35%	0.8[0.44,1.43]
GISSI-P 1999	214/5666	265/5668		16.2%	0.81[0.68,0.96]
HARP 1995	0/41	1/39		0.25%	0.32[0.01,7.57]
OFAMI 2001	8/150	8/150		2.42%	1[0.39,2.59]
Raitt 2005	2/100	5/100		0.91%	0.4[0.08,2.01]
SCIMO 1999	0/112	1/111		0.24%	0.33[0.01,8.02]
Subtotal (95% CI)	**13264**	**13281**		**49.05%**	**0.79[0.69,0.9]**
Total events: 389 (Higher omega 3), 494 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=4.94, df=8(P=0.76); I²=0%					
Test for overall effect: Z=3.55(P=0)					
1.39.3 Long duration: ≥ 4 years in study					
AREDS2 2014	3/2147	0/2056		0.28%	6.7[0.35,129.7]
DART2 2003	180/1571	139/1543		14.95%	1.27[1.03,1.57]
JELIS 2007	29/9326	31/9319		6.59%	0.93[0.56,1.55]
Risk & Prevention 2013	82/6239	76/6266		11.39%	1.08[0.79,1.48]
SU.FOL.OM3 2010	1/1253	2/1248		0.42%	0.5[0.05,5.49]
Subtotal (95% CI)	**20536**	**20432**		**33.64%**	**1.18[1,1.39]**
Total events: 295 (Higher omega 3), 248 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=3.41, df=4(P=0.49); I²=0%					
Test for overall effect: Z=1.97(P=0.05)					
Total (95% CI)	**36836**	**36655**		**100%**	**0.93[0.79,1.09]**
Total events: 773 (Higher omega 3), 823 (Lower omega 3)					

Favours higher omega 3 0.1 0.2 0.5 1 2 5 10 Favours lower omega 3

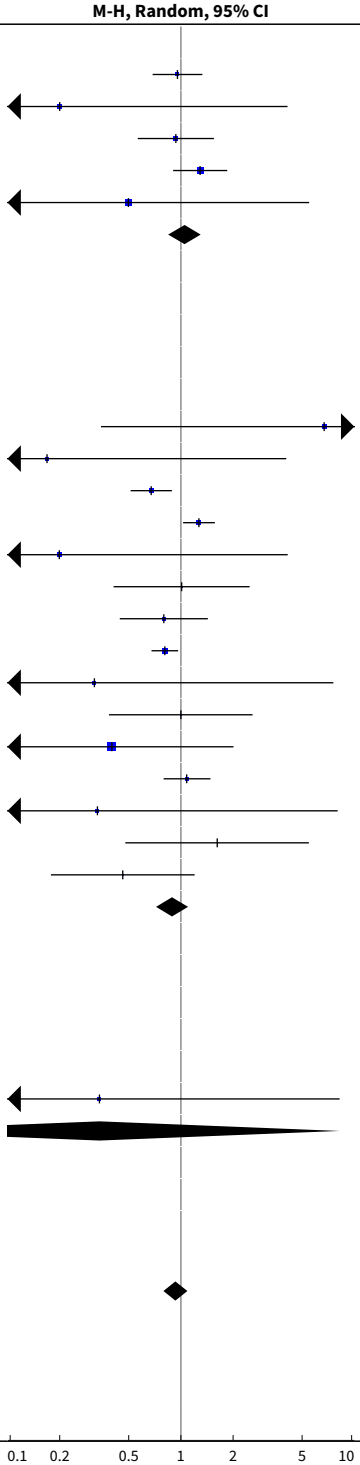


Analysis 1.40. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 40 CHD mortality - LCn3 - subgroup by primary or secondary prevention.



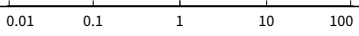
Analysis 1.41. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 41 CHD mortality - LCn3 - subgroup by statin use.

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
1.41.1 LCn3 - ≥ 50% of control group on statins					
AlphaOmega - EPA+DHA 2010	67/2404	71/2433		10.79%	0.96[0.69,1.33]
Doi 2014	0/119	2/119		0.27%	0.2[0.01,4.12]
JELIS 2007	29/9326	31/9319		6.59%	0.93[0.56,1.55]
OMEGA 2009	67/1919	51/1885		9.92%	1.29[0.9,1.85]
SU.FOL.OM3 2010	1/1253	2/1248		0.42%	0.5[0.05,5.49]
Subtotal (95% CI)	**15021**	**15004**		**28%**	**1.05[0.84,1.3]**
Total events: 164 (Higher omega 3), 157 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=3.32, df=4(P=0.51); I^2=0%					
Test for overall effect: Z=0.42(P=0.67)					
1.41.2 LCn3 - < 50% of control group on statins					
AREDS2 2014	3/2147	0/2056		0.28%	6.7[0.35,129.7]
Brox 2001	0/80	1/40		0.24%	0.17[0.01,4.05]
DART 1989	78/1015	116/1018		12.62%	0.67[0.51,0.89]
DART2 2003	180/1571	139/1543		14.95%	1.27[1.03,1.57]
DO IT 2010	0/282	2/281		0.27%	0.2[0.01,4.13]
FAAT 2005	9/200	9/202		2.66%	1.01[0.41,2.49]
GISSI-HF 2008	20/3494	25/3481		5.35%	0.8[0.44,1.43]
GISSI-P 1999	214/5666	265/5668		16.2%	0.81[0.68,0.96]
HARP 1995	0/41	1/39		0.25%	0.32[0.01,7.57]
OFAMI 2001	8/150	8/150		2.42%	1[0.39,2.59]
Raitt 2005	2/100	5/100		0.91%	0.4[0.08,2.01]
Risk & Prevention 2013	82/6239	76/6266		11.39%	1.08[0.79,1.48]
SCIMO 1999	0/112	1/111		0.24%	0.33[0.01,8.02]
SHOT 1996	7/317	4/293		1.55%	1.62[0.48,5.47]
SOFA 2006	6/273	13/273		2.42%	0.46[0.18,1.2]
Subtotal (95% CI)	**21687**	**21521**		**71.76%**	**0.89[0.72,1.1]**
Total events: 609 (Higher omega 3), 665 (Lower omega 3)					
Heterogeneity: Tau^2=0.05; Chi^2=26.04, df=14(P=0.03); I^2=46.24%					
Test for overall effect: Z=1.11(P=0.27)					
1.41.3 LCn3 - use of statins unclear					
Derosa 2016	0/128	1/130		0.24%	0.34[0.01,8.23]
Subtotal (95% CI)	**128**	**130**		**0.24%**	**0.34[0.01,8.23]**
Total events: 0 (Higher omega 3), 1 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.67(P=0.51)					
Total (95% CI)	**36836**	**36655**		**100%**	**0.93[0.79,1.09]**
Total events: 773 (Higher omega 3), 823 (Lower omega 3)					
Heterogeneity: Tau^2=0.03; Chi^2=30.96, df=20(P=0.06); I^2=35.41%					
Test for overall effect: Z=0.91(P=0.36)					
Test for subgroup differences: Chi^2=1.57, df=1 (P=0.46), I^2=0%					



Analysis 1.42. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 42 CHD mortality - 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
1.42.1 Previous CAD					
AlphaOmega - EPA+DHA 2010	67/2404	71/2433		10.82%	0.96[0.69,1.33]
DART 1989	78/1015	116/1018		12.65%	0.67[0.51,0.89]
DART2 2003	180/1571	139/1543		14.98%	1.27[1.03,1.57]
Doi 2014	0/119	0/119			Not estimable
GISSI-P 1999	214/5666	265/5668		16.24%	0.81[0.68,0.96]
HARP 1995	0/41	1/39		0.25%	0.32[0.01,7.57]
OFAMI 2001	8/150	8/150		2.43%	1[0.39,2.59]
OMEGA 2009	67/1919	51/1885		9.95%	1.29[0.9,1.85]
SCIMO 1999	0/112	1/111		0.24%	0.33[0.01,8.02]
SHOT 1996	7/317	4/293		1.56%	1.62[0.48,5.47]
SU.FOL.OM3 2010	1/1253	2/1248		0.43%	0.5[0.05,5.49]
Subtotal (95% CI)	**14567**	**14507**		**69.55%**	**0.96[0.77,1.2]**
Total events: 622 (High omega 3), 658 (Control)					
Heterogeneity: Tau^2=0.05; Chi^2=21.39, df=9(P=0.01); I^2=57.93%					
Test for overall effect: Z=0.36(P=0.72)					
1.42.2 No previous CAD					
AREDS2 2014	3/2147	0/2056		0.28%	6.7[0.35,129.7]
Brox 2001	0/80	1/40		0.24%	0.17[0.01,4.05]
Derosa 2016	0/128	1/130		0.24%	0.34[0.01,8.23]
DO IT 2010	0/282	2/281		0.27%	0.2[0.01,4.13]
FAAT 2005	9/200	9/202		2.67%	1.01[0.41,2.49]
GISSI-HF 2008	20/3494	25/3481		5.37%	0.8[0.44,1.43]
JELIS 2007	29/9326	31/9319		6.61%	0.93[0.56,1.55]
Raitt 2005	2/100	5/100		0.92%	0.4[0.08,2.01]
Risk & Prevention 2013	82/6239	76/6266		11.42%	1.08[0.79,1.48]
SOFA 2006	6/273	13/273		2.43%	0.46[0.18,1.2]
Subtotal (95% CI)	**22269**	**22148**		**30.45%**	**0.93[0.74,1.16]**
Total events: 151 (High omega 3), 163 (Control)					
Heterogeneity: Tau^2=0; Chi^2=8.55, df=9(P=0.48); I^2=0%					
Test for overall effect: Z=0.66(P=0.51)					
Total (95% CI)	**36836**	**36655**		**100%**	**0.93[0.8,1.09]**
Total events: 773 (High omega 3), 821 (Control)					
Heterogeneity: Tau^2=0.03; Chi^2=29.96, df=19(P=0.05); I^2=36.58%					
Test for overall effect: Z=0.86(P=0.39)					
Test for subgroup differences: Chi^2=0.05, df=1 (P=0.82), I^2=0%					



Favours high LCn3 — Favours low LCn3

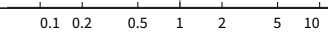
Analysis 1.43. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 43 Coronary heart disease events (overall) - LCn3.

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
AlphaOmega - EPA+DHA 2010	122/2404	132/2433		4.11%	0.94[0.74,1.19]

Favours higher omega 3 — Favours lower omega 3

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
AREDS2 2014	28/2147	30/2056		0.9%	0.89[0.54,1.49]
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	337/1015	366/1018		16.46%	0.92[0.82,1.04]
Derosa 2016	0/128	4/130		0.03%	0.11[0.01,2.07]
DO IT 2010	11/282	9/281		0.32%	1.22[0.51,2.89]
Doi 2014	1/119	0/119		0.02%	3[0.12,72.91]
EPE-A 2014	2/168	1/75		0.04%	0.89[0.08,9.7]
EPOCH 2014	1/195	0/196		0.02%	3.02[0.12,73.57]
FORWARD 2013	1/289	1/297		0.03%	1.03[0.06,16.35]
FOSTAR 2016	10/101	10/101		0.34%	1[0.44,2.3]
GISSI-HF 2008	107/3494	129/3481		3.72%	0.83[0.64,1.06]
GISSI-P 1999	424/5666	485/5658		15.11%	0.87[0.77,0.99]
HARP 1995	7/41	7/39		0.26%	0.95[0.37,2.46]
JELIS 2007	262/9326	324/9319		9.19%	0.81[0.69,0.95]
Nye 1990	5/36	11/37		0.26%	0.47[0.18,1.21]
OFAMI 2001	42/150	36/150		1.61%	1.17[0.8,1.71]
OMEGA 2009	547/1919	568/1885		24.22%	0.95[0.86,1.04]
ORIGIN 2012	344/6281	316/6255		10.68%	1.08[0.93,1.26]
Proudman 2015	1/87	0/53		0.02%	1.84[0.08,44.38]
Raitt 2005	1/100	3/100		0.05%	0.33[0.04,3.15]
Risk & Prevention 2013	310/6239	324/6266		10.25%	0.96[0.83,1.12]
SCIMO 1999	1/112	4/111		0.05%	0.25[0.03,2.18]
SHOT 1996	7/317	12/293		0.28%	0.54[0.22,1.35]
SOFA 2006	1/273	3/273		0.05%	0.33[0.03,3.18]
SU.FOL.OM3 2010	51/1253	53/1248		1.67%	0.96[0.66,1.4]
THIS DIET 2008	10/51	6/50		0.27%	1.63[0.64,4.16]
Total (95% CI)	**42305**	**41996**		**100%**	**0.93[0.88,0.97]**

Total events: 2634 (Favours higher omega 3), 2835 (Lower omega 3 fats)
Heterogeneity: Tau^2=0; Chi^2=23.63, df=27(P=0.65); I^2=0%
Test for overall effect: Z=3.02(P=0)

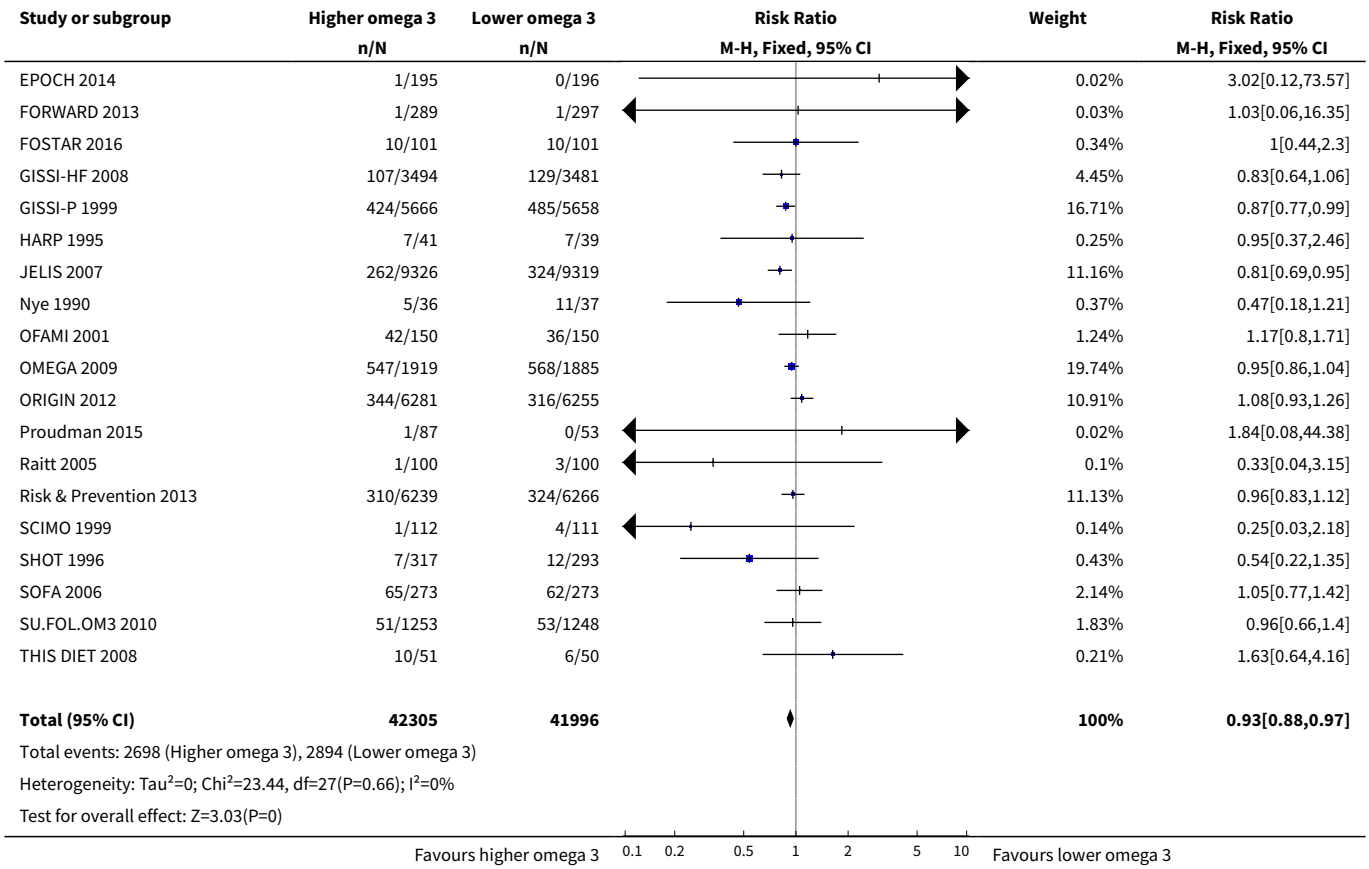


Favours higher omega 3 — Favours lower omega 3

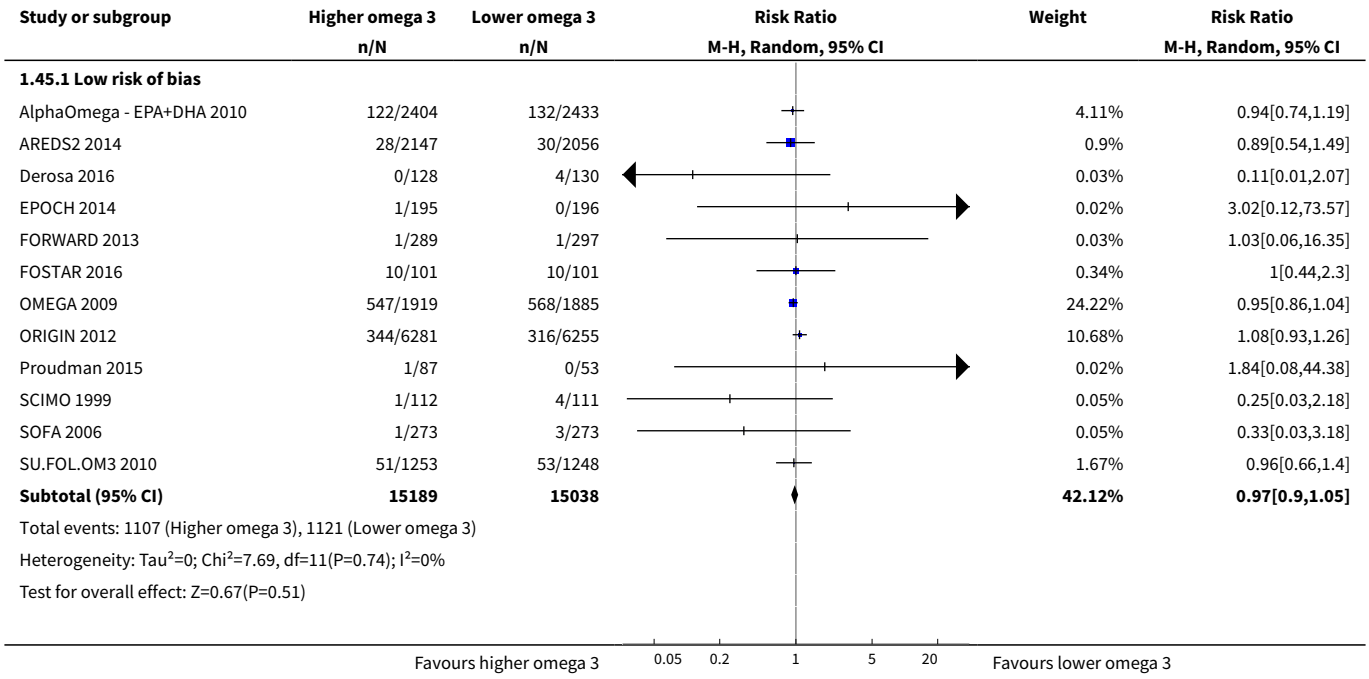
Analysis 1.44. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 44 CHD events - LCn3 - SA fixed-effect.

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	122/2404	132/2433		4.52%	0.94[0.74,1.19]
AREDS2 2014	28/2147	30/2056		1.06%	0.89[0.54,1.49]
Baldassarre 2006	1/32	0/32		0.02%	3[0.13,71]
Brox 2001	0/80	1/40		0.07%	0.17[0.01,4.05]
DART 1989	337/1015	366/1018		12.59%	0.92[0.82,1.04]
Derosa 2016	0/128	4/130		0.15%	0.11[0.01,2.07]
DO IT 2010	11/282	9/281		0.31%	1.22[0.51,2.89]
Doi 2014	1/119	0/119		0.02%	3[0.12,72.91]
EPE-A 2014	2/168	1/75		0.05%	0.89[0.08,9.7]

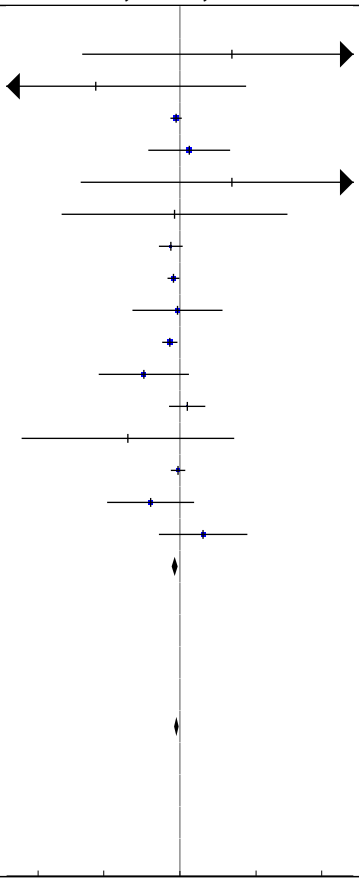
Favours higher omega 3 — Favours lower omega 3



Analysis 1.45. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 45 CHD events - LCn3 - SA by summary risk of bias.

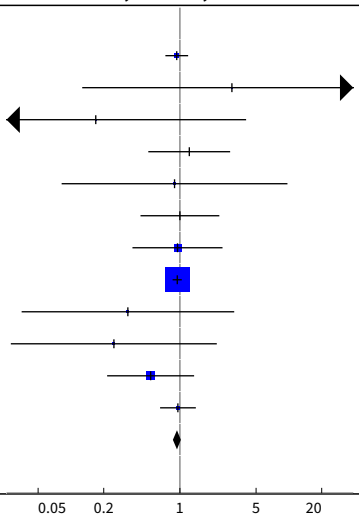


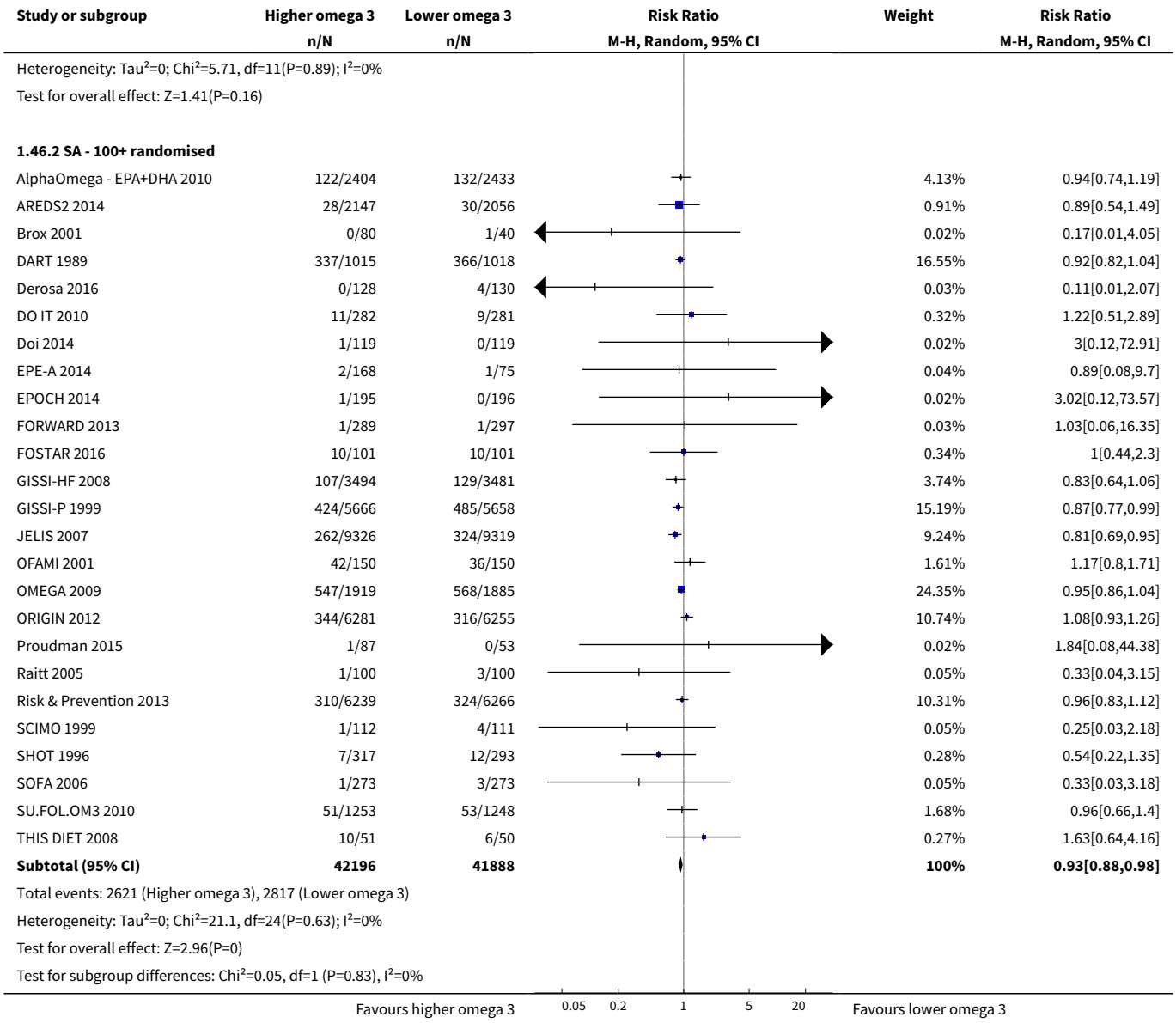
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.45.2 Moderate/high risk of bias					
Baldassarre 2006	1/32	0/32		0.02%	3[0.13,71]
Brox 2001	0/80	1/40		0.02%	0.17[0.01,4.05]
DART 1989	337/1015	366/1018		16.46%	0.92[0.82,1.04]
DO IT 2010	11/282	9/281		0.32%	1.22[0.51,2.89]
Doi 2014	1/119	0/119		0.02%	3[0.12,72.91]
EPE-A 2014	2/168	1/75		0.04%	0.89[0.08,9.7]
GISSI-HF 2008	107/3494	129/3481		3.72%	0.83[0.64,1.06]
GISSI-P 1999	424/5666	485/5658		15.11%	0.87[0.77,0.99]
HARP 1995	7/41	7/39		0.26%	0.95[0.37,2.46]
JELIS 2007	262/9326	324/9319		9.19%	0.81[0.69,0.95]
Nye 1990	5/36	11/37		0.26%	0.47[0.18,1.21]
OFAMI 2001	42/150	36/150		1.61%	1.17[0.8,1.71]
Raitt 2005	1/100	3/100		0.05%	0.33[0.04,3.15]
Risk & Prevention 2013	310/6239	324/6266		10.25%	0.96[0.83,1.12]
SHOT 1996	7/317	12/293		0.28%	0.54[0.22,1.35]
THIS DIET 2008	10/51	6/50		0.27%	1.63[0.64,4.16]
Subtotal (95% CI)	**27116**	**26958**		**57.88%**	**0.89[0.84,0.95]**
Total events: 1527 (Higher omega 3), 1714 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=13.04, df=15(P=0.6); I^2=0%					
Test for overall effect: Z=3.41(P=0)					
Total (95% CI)	**42305**	**41996**		**100%**	**0.93[0.88,0.97]**
Total events: 2634 (Higher omega 3), 2835 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=23.63, df=27(P=0.65); I^2=0%					
Test for overall effect: Z=3.02(P=0)					
Test for subgroup differences: Chi^2=2.91, df=1 (P=0.09), I^2=65.62%					



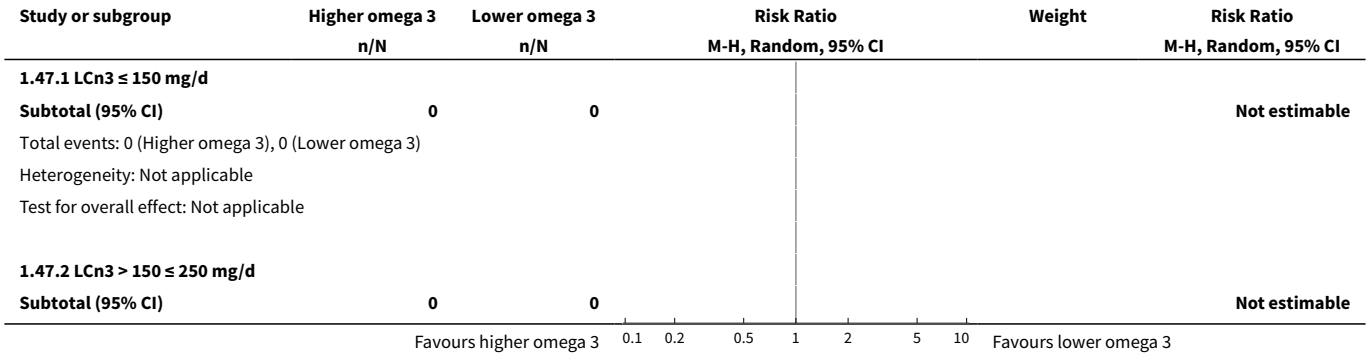
Analysis 1.46. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 46 CHD events - LCn3 - SA by compliance and study size.

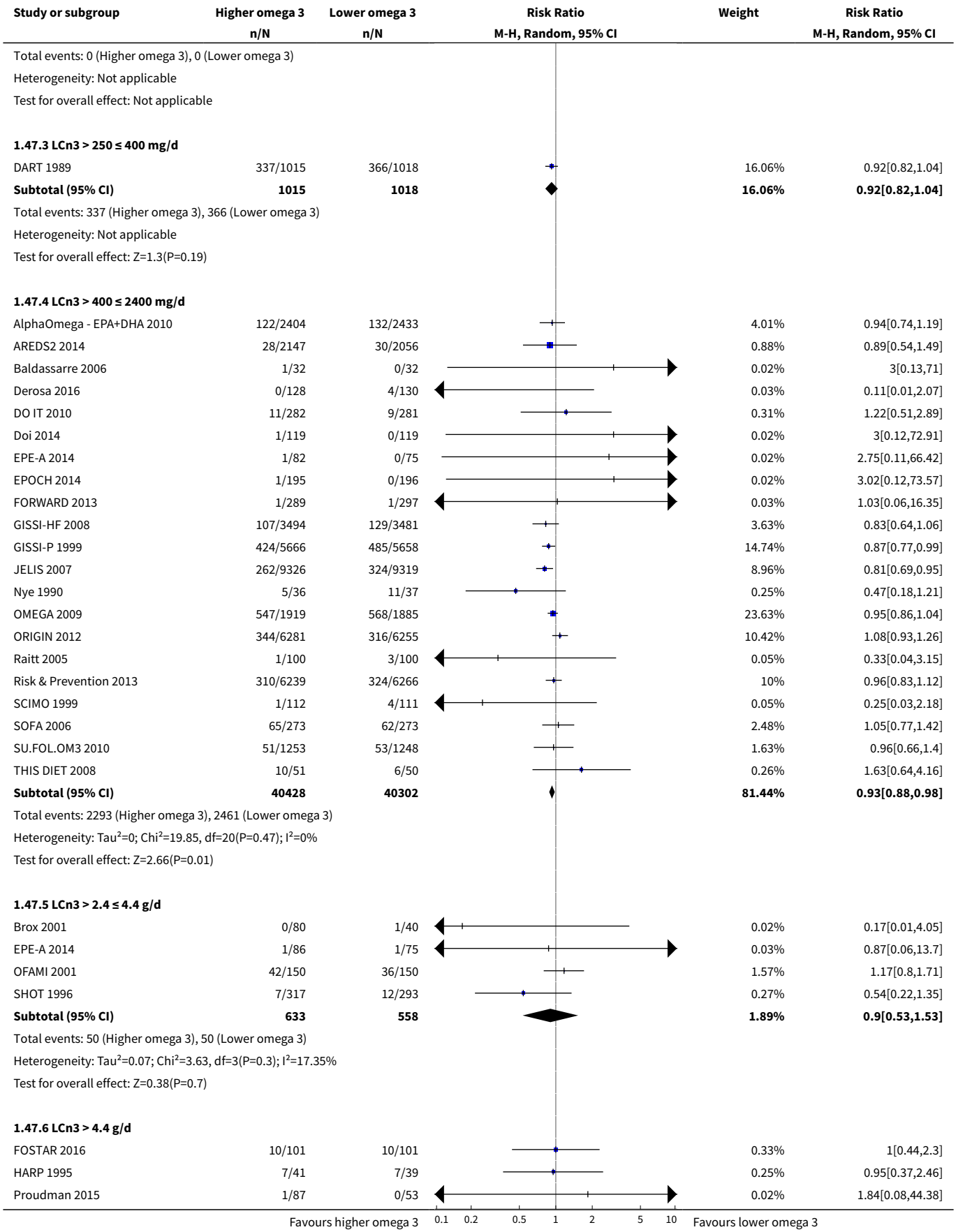
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.46.1 SA - low risk of compliance bias					
AlphaOmega - EPA+DHA 2010	122/2404	132/2433		13.1%	0.94[0.74,1.19]
Baldassarre 2006	1/32	0/32		0.08%	3[0.13,71]
Brox 2001	0/80	1/40		0.07%	0.17[0.01,4.05]
DO IT 2010	11/282	9/281		1%	1.22[0.51,2.89]
EPE-A 2014	2/168	1/75		0.13%	0.89[0.08,9.7]
FOSTAR 2016	10/101	10/101		1.09%	1[0.44,2.3]
HARP 1995	7/41	7/39		0.83%	0.95[0.37,2.46]
OMEGA 2009	547/1919	568/1885		77.18%	0.95[0.86,1.04]
Raitt 2005	1/100	3/100		0.15%	0.33[0.04,3.15]
SCIMO 1999	1/112	4/111		0.16%	0.25[0.03,2.18]
SHOT 1996	7/317	12/293		0.89%	0.54[0.22,1.35]
SU.FOL.OM3 2010	51/1253	53/1248		5.31%	0.96[0.66,1.4]
Subtotal (95% CI)	**6809**	**6638**		**100%**	**0.94[0.86,1.02]**
Total events: 760 (Higher omega 3), 800 (Lower omega 3)					



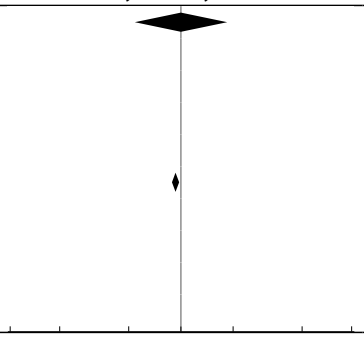


Analysis 1.47. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 47 CHD events - LCn3 - subgroup by dose.





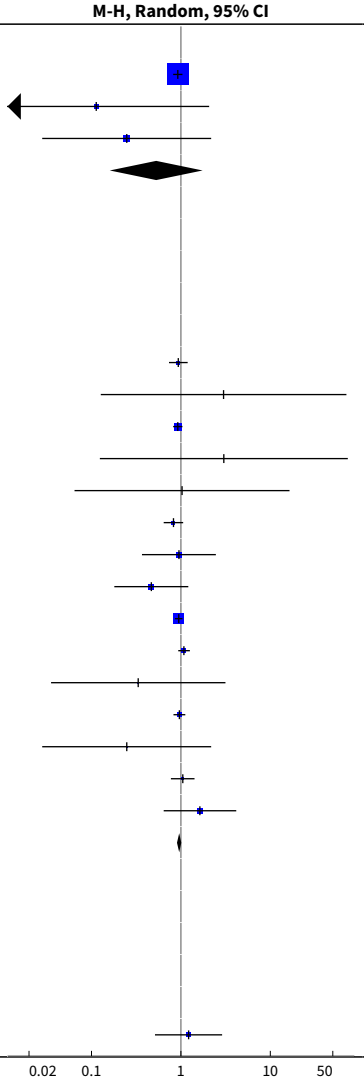
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Subtotal (95% CI)	**229**	**193**		**0.61%**	**1[0.54,1.85]**
Total events: 18 (Higher omega 3), 17 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.15, df=2(P=0.93); I^2=0%					
Test for overall effect: Z=0.01(P=1)					
Total (95% CI)	**42305**	**42071**		**100%**	**0.93[0.89,0.98]**
Total events: 2698 (Higher omega 3), 2894 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=23.88, df=28(P=0.69); I^2=0%					
Test for overall effect: Z=2.91(P=0)					
Test for subgroup differences: Chi^2=0.08, df=1 (P=0.99), I^2=0%					



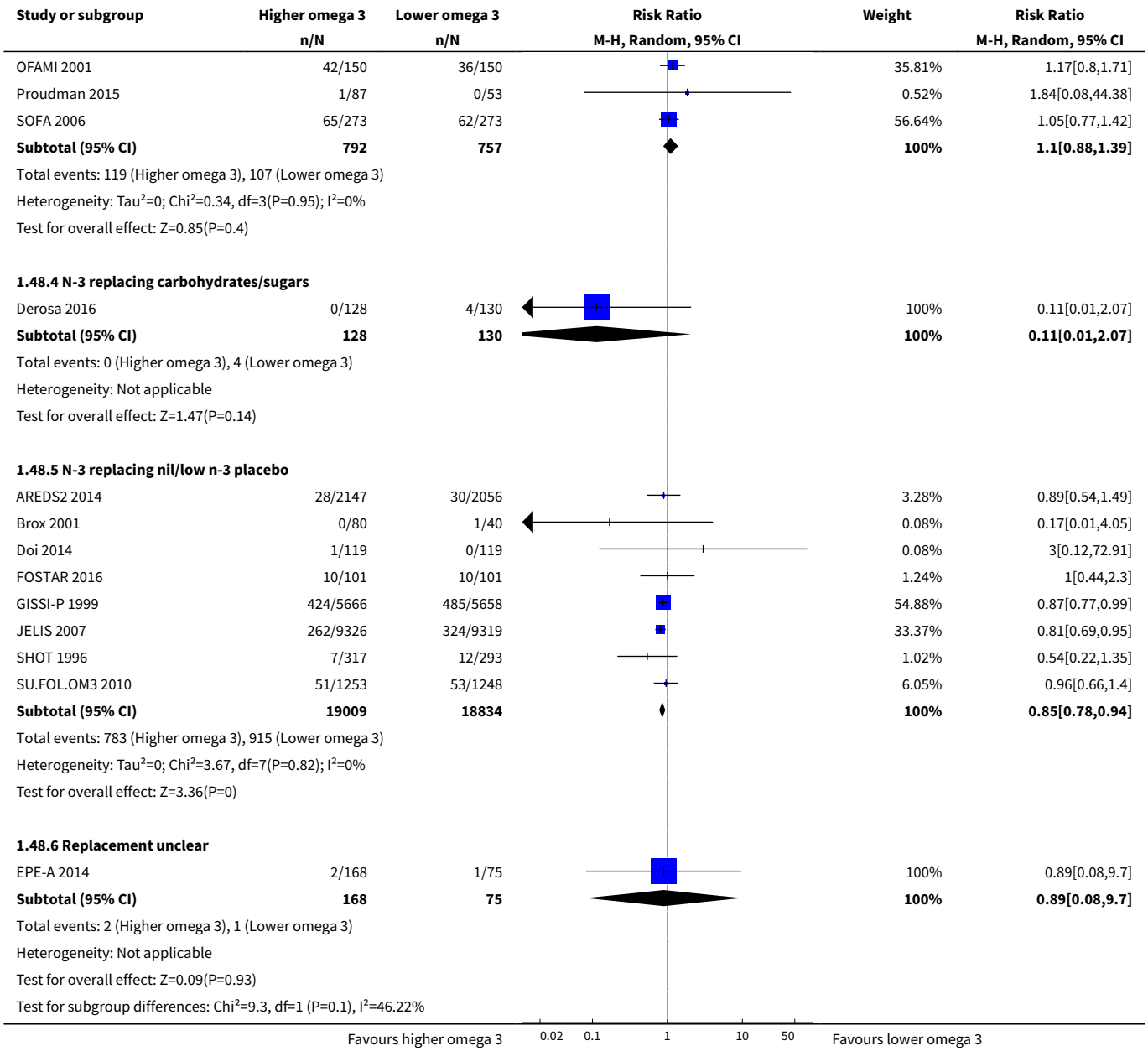
Favours higher omega 3 — Favours lower omega 3

Analysis 1.48. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 48 CHD events - LCn3 - subgroup by replacement.

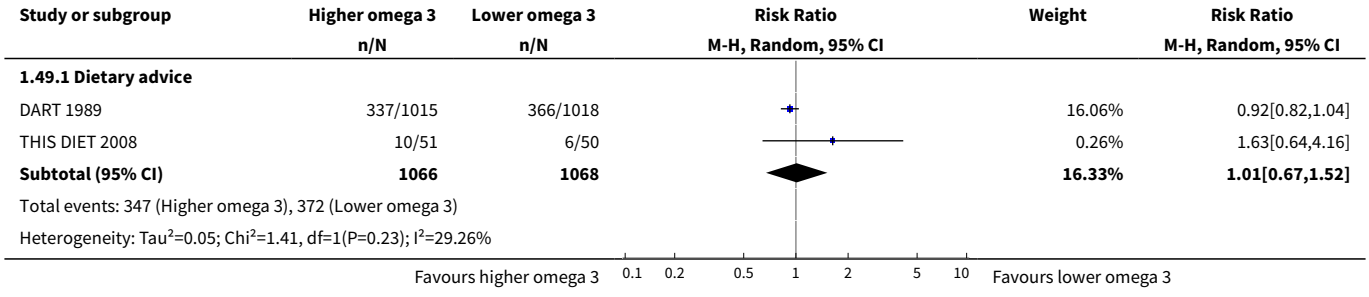
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.48.1 N-3 replacing SFA					
DART 1989	337/1015	366/1018		65.71%	0.92[0.82,1.04]
Derosa 2016	0/128	4/130		13.49%	0.11[0.01,2.07]
SCIMO 1999	1/112	4/111		20.8%	0.25[0.03,2.18]
Subtotal (95% CI)	**1255**	**1259**		**100%**	**0.53[0.16,1.75]**
Total events: 338 (Higher omega 3), 374 (Lower omega 3)					
Heterogeneity: Tau^2=0.57; Chi^2=3.43, df=2(P=0.18); I^2=41.61%					
Test for overall effect: Z=1.04(P=0.3)					
1.48.2 N-3 replacing MUFA					
AlphaOmega - EPA+DHA 2010	122/2404	132/2433		5.64%	0.94[0.74,1.19]
Baldassarre 2006	1/32	0/32		0.03%	3[0.13,71]
DART 1989	337/1015	366/1018		22.57%	0.92[0.82,1.04]
EPOCH 2014	1/195	0/196		0.03%	3.02[0.12,73.57]
FORWARD 2013	1/289	1/297		0.04%	1.03[0.06,16.35]
GISSI-HF 2008	107/3494	129/3481		5.1%	0.83[0.64,1.06]
HARP 1995	7/41	7/39		0.36%	0.95[0.37,2.46]
Nye 1990	5/36	11/37		0.36%	0.47[0.18,1.21]
OMEGA 2009	547/1919	568/1885		33.2%	0.95[0.86,1.04]
ORIGIN 2012	344/6281	316/6255		14.64%	1.08[0.93,1.26]
Raitt 2005	1/100	3/100		0.06%	0.33[0.04,3.15]
Risk & Prevention 2013	310/6239	324/6266		14.06%	0.96[0.83,1.12]
SCIMO 1999	1/112	4/111		0.07%	0.25[0.03,2.18]
SOFA 2006	65/273	62/273		3.48%	1.05[0.77,1.42]
THIS DIET 2008	10/51	6/50		0.37%	1.63[0.64,4.16]
Subtotal (95% CI)	**22481**	**22473**		**100%**	**0.96[0.9,1.01]**
Total events: 1859 (Higher omega 3), 1929 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=11.56, df=14(P=0.64); I^2=0%					
Test for overall effect: Z=1.52(P=0.13)					
1.48.3 N-3 replacing n-6					
DO IT 2010	11/282	9/281		7.03%	1.22[0.51,2.89]

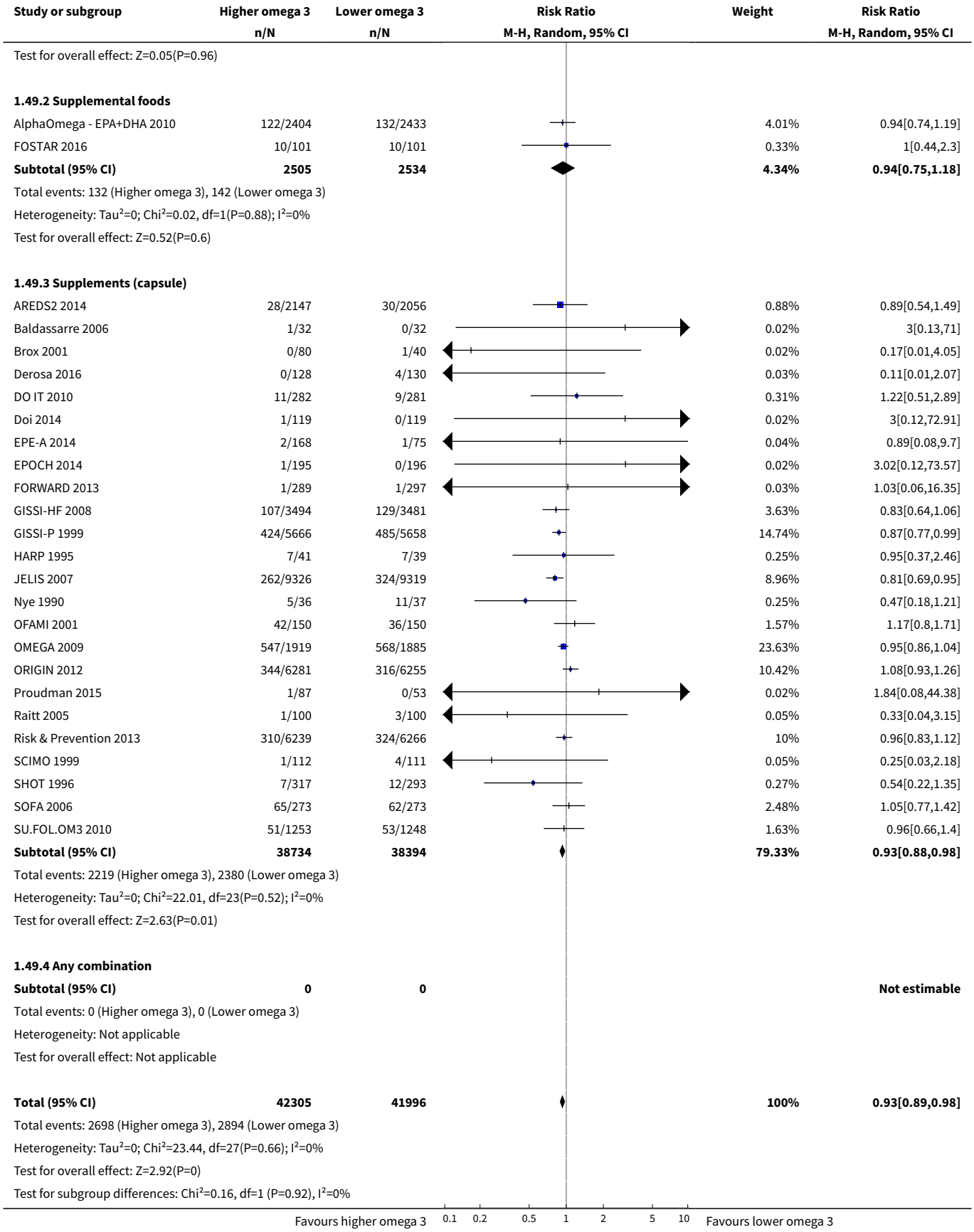


Favours higher omega 3 — Favours lower omega 3



Analysis 1.49. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 49 CHD events - LCn3 - subgroup by intervention type.

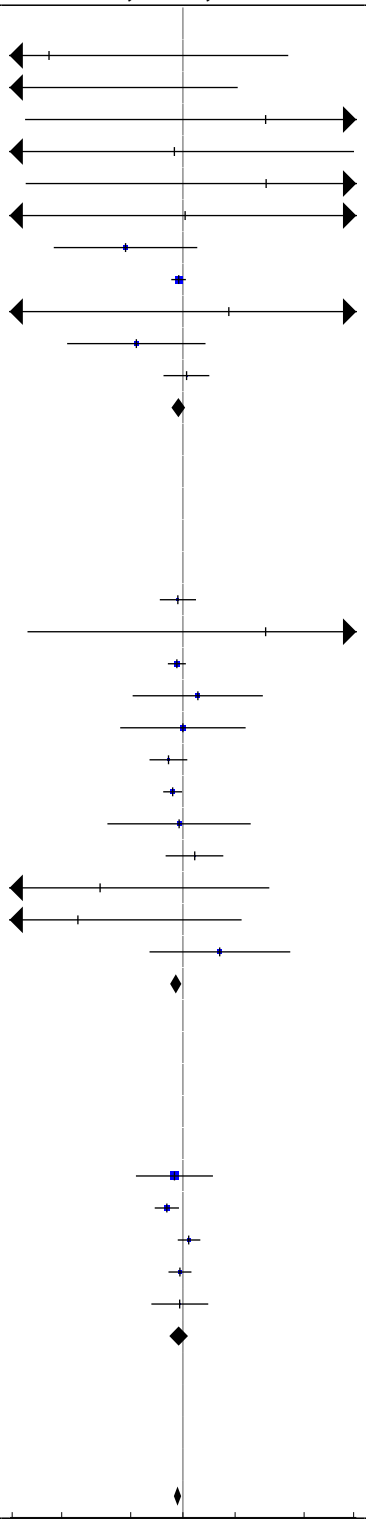




Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=0.05(P=0.96)					
1.49.2 Supplemental foods					
AlphaOmega - EPA+DHA 2010	122/2404	132/2433		4.01%	0.94[0.74,1.19]
FOSTAR 2016	10/101	10/101		0.33%	1[0.44,2.3]
Subtotal (95% CI)	**2505**	**2534**		**4.34%**	**0.94[0.75,1.18]**
Total events: 132 (Higher omega 3), 142 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.88); I^2=0%					
Test for overall effect: Z=0.52(P=0.6)					
1.49.3 Supplements (capsule)					
AREDS2 2014	28/2147	30/2056		0.88%	0.89[0.54,1.49]
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	0/128	4/130		0.03%	0.11[0.01,2.07]
DO IT 2010	11/282	9/281		0.31%	1.22[0.51,2.89]
Doi 2014	1/119	0/119		0.02%	3[0.12,72.91]
EPE-A 2014	2/168	1/75		0.04%	0.89[0.08,9.7]
EPOCH 2014	1/195	0/196		0.02%	3.02[0.12,73.57]
FORWARD 2013	1/289	1/297		0.03%	1.03[0.06,16.35]
GISSI-HF 2008	107/3494	129/3481		3.63%	0.83[0.64,1.06]
GISSI-P 1999	424/5666	485/5658		14.74%	0.87[0.77,0.99]
HARP 1995	7/41	7/39		0.25%	0.95[0.37,2.46]
JELIS 2007	262/9326	324/9319		8.96%	0.81[0.69,0.95]
Nye 1990	5/36	11/37		0.25%	0.47[0.18,1.21]
OFAMI 2001	42/150	36/150		1.57%	1.17[0.8,1.71]
OMEGA 2009	547/1919	568/1885		23.63%	0.95[0.86,1.04]
ORIGIN 2012	344/6281	316/6255		10.42%	1.08[0.93,1.26]
Proudman 2015	1/87	0/53		0.02%	1.84[0.08,44.38]
Raitt 2005	1/100	3/100		0.05%	0.33[0.04,3.15]
Risk & Prevention 2013	310/6239	324/6266		10%	0.96[0.83,1.12]
SCIMO 1999	1/112	4/111		0.05%	0.25[0.03,2.18]
SHOT 1996	7/317	12/293		0.27%	0.54[0.22,1.35]
SOFA 2006	65/273	62/273		2.48%	1.05[0.77,1.42]
SU.FOL.OM3 2010	51/1253	53/1248		1.63%	0.96[0.66,1.4]
Subtotal (95% CI)	**38734**	**38394**		**79.33%**	**0.93[0.88,0.98]**
Total events: 2219 (Higher omega 3), 2380 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=22.01, df=23(P=0.52); I^2=0%					
Test for overall effect: Z=2.63(P=0.01)					
1.49.4 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)	**42305**	**41996**		**100%**	**0.93[0.89,0.98]**
Total events: 2698 (Higher omega 3), 2894 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=23.44, df=27(P=0.66); I^2=0%					
Test for overall effect: Z=2.92(P=0)					
Test for subgroup differences: Chi^2=0.16, df=1 (P=0.92), I^2=0%					

Analysis 1.50. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 50 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
1.50.1 Medium duration 1 to < 2 years in study					
Brox 2001	0/80	1/40		0.02%	0.17[0.01,4.05]
Derosa 2016	0/128	4/130		0.03%	0.11[0.01,2.07]
Doi 2014	1/119	0/119		0.02%	3[0.12,72.91]
EPE-A 2014	2/168	1/75		0.04%	0.89[0.08,9.7]
EPOCH 2014	1/195	0/196		0.02%	3.02[0.12,73.57]
FORWARD 2013	1/289	1/297		0.03%	1.03[0.06,16.35]
Nye 1990	5/36	11/37		0.25%	0.47[0.18,1.21]
OMEGA 2009	547/1919	568/1885		23.63%	0.95[0.86,1.04]
Proudman 2015	1/87	0/53		0.02%	1.84[0.08,44.38]
SHOT 1996	7/317	12/293		0.27%	0.54[0.22,1.35]
SOFA 2006	65/273	62/273		2.48%	1.05[0.77,1.42]
Subtotal (95% CI)	**3611**	**3398**		**26.82%**	**0.94[0.86,1.03]**
Total events: 630 (Higher omega 3), 660 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=8.36, df=10(P=0.59); I^2=0%					
Test for overall effect: Z=1.26(P=0.21)					
1.50.2 Medium-long duration: 2 to < 4 years in study					
AlphaOmega - EPA+DHA 2010	122/2404	132/2433		4.01%	0.94[0.74,1.19]
Baldassarre 2006	1/32	0/32		0.02%	3[0.13,71]
DART 1989	337/1015	366/1018		16.06%	0.92[0.82,1.04]
DO IT 2010	11/282	9/281		0.31%	1.22[0.51,2.89]
FOSTAR 2016	10/101	10/101		0.33%	1[0.44,2.3]
GISSI-HF 2008	107/3494	129/3481		3.63%	0.83[0.64,1.06]
GISSI-P 1999	424/5666	485/5658		14.74%	0.87[0.77,0.99]
HARP 1995	7/41	7/39		0.25%	0.95[0.37,2.46]
OFAMI 2001	42/150	36/150		1.57%	1.17[0.8,1.71]
Raitt 2005	1/100	3/100		0.05%	0.33[0.04,3.15]
SCIMO 1999	1/112	4/111		0.05%	0.25[0.03,2.18]
THIS DIET 2008	10/51	6/50		0.26%	1.63[0.64,4.16]
Subtotal (95% CI)	**13448**	**13454**		**41.28%**	**0.91[0.84,0.98]**
Total events: 1073 (Higher omega 3), 1187 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=7.42, df=11(P=0.76); I^2=0%					
Test for overall effect: Z=2.49(P=0.01)					
1.50.3 Long duration: ≥ 4 years in study					
AREDS2 2014	28/2147	30/2056		0.88%	0.89[0.54,1.49]
JELIS 2007	262/9326	324/9319		8.96%	0.81[0.69,0.95]
ORIGIN 2012	344/6281	316/6255		10.42%	1.08[0.93,1.26]
Risk & Prevention 2013	310/6239	324/6266		10%	0.96[0.83,1.12]
SU.FOL.OM3 2010	51/1253	53/1248		1.63%	0.96[0.66,1.4]
Subtotal (95% CI)	**25246**	**25144**		**31.89%**	**0.95[0.83,1.07]**
Total events: 995 (Higher omega 3), 1047 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=7.03, df=4(P=0.13); I^2=43.08%					
Test for overall effect: Z=0.88(P=0.38)					
Total (95% CI)	**42305**	**41996**		**100%**	**0.93[0.89,0.98]**

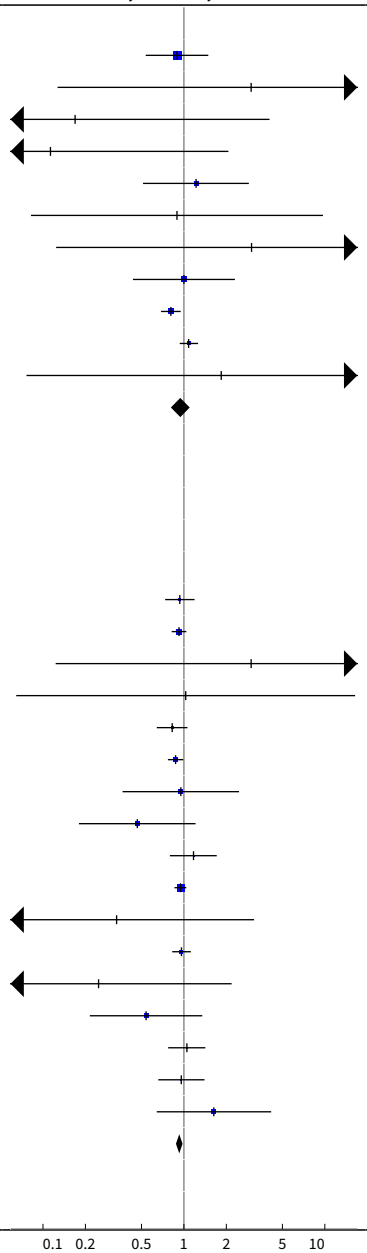


Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 2698 (Higher omega 3), 2894 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=23.44, df=27(P=0.66); I²=0%					
Test for overall effect: Z=2.92(P=0)					
Test for subgroup differences: Chi²=0.46, df=1 (P=0.79), I²=0%					

Favours higher omega 3 — Favours lower omega 3

Analysis 1.51. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 51 CHD 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
1.51.1 Primary prevention of CVD					
AREDS2 2014	28/2147	30/2056		0.88%	0.89[0.54,1.49]
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	0/128	4/130		0.03%	0.11[0.01,2.07]
DO IT 2010	11/282	9/281		0.31%	1.22[0.51,2.89]
EPE-A 2014	2/168	1/75		0.04%	0.89[0.08,9.7]
EPOCH 2014	1/195	0/196		0.02%	3.02[0.12,73.57]
FOSTAR 2016	10/101	10/101		0.33%	1[0.44,2.3]
JELIS 2007	262/9326	324/9319		8.96%	0.81[0.69,0.95]
ORIGIN 2012	344/6281	316/6255		10.42%	1.08[0.93,1.26]
Proudman 2015	1/87	0/53		0.02%	1.84[0.08,44.38]
Subtotal (95% CI)	**18827**	**18538**		**21.06%**	**0.94[0.81,1.1]**
Total events: 660 (Higher omega 3), 695 (Lower omega 3)					
Heterogeneity: Tau²=0.01; Chi²=11.71, df=10(P=0.31); I²=14.59%					
Test for overall effect: Z=0.75(P=0.45)					
1.51.2 Secondary prevention of CVD					
AlphaOmega - EPA+DHA 2010	122/2404	132/2433		4.01%	0.94[0.74,1.19]
DART 1989	337/1015	366/1018		16.06%	0.92[0.82,1.04]
Doi 2014	1/119	0/119		0.02%	3[0.12,72.91]
FORWARD 2013	1/289	1/297		0.03%	1.03[0.06,16.35]
GISSI-HF 2008	107/3494	129/3481		3.63%	0.83[0.64,1.06]
GISSI-P 1999	424/5666	485/5658		14.74%	0.87[0.77,0.99]
HARP 1995	7/41	7/39		0.25%	0.95[0.37,2.46]
Nye 1990	5/36	11/37		0.25%	0.47[0.18,1.21]
OFAMI 2001	42/150	36/150		1.57%	1.17[0.8,1.71]
OMEGA 2009	547/1919	568/1885		23.63%	0.95[0.86,1.04]
Raitt 2005	1/100	3/100		0.05%	0.33[0.04,3.15]
Risk & Prevention 2013	310/6239	324/6266		10%	0.96[0.83,1.12]
SCIMO 1999	1/112	4/111		0.05%	0.25[0.03,2.18]
SHOT 1996	7/317	12/293		0.27%	0.54[0.22,1.35]
SOFA 2006	65/273	62/273		2.48%	1.05[0.77,1.42]
SU.FOL.OM3 2010	51/1253	53/1248		1.63%	0.96[0.66,1.4]
THIS DIET 2008	10/51	6/50		0.26%	1.63[0.64,4.16]
Subtotal (95% CI)	**23478**	**23458**		**78.94%**	**0.93[0.88,0.98]**
Total events: 2038 (Higher omega 3), 2199 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=11.61, df=16(P=0.77); I²=0%					



Favours higher omega 3 — Favours lower omega 3

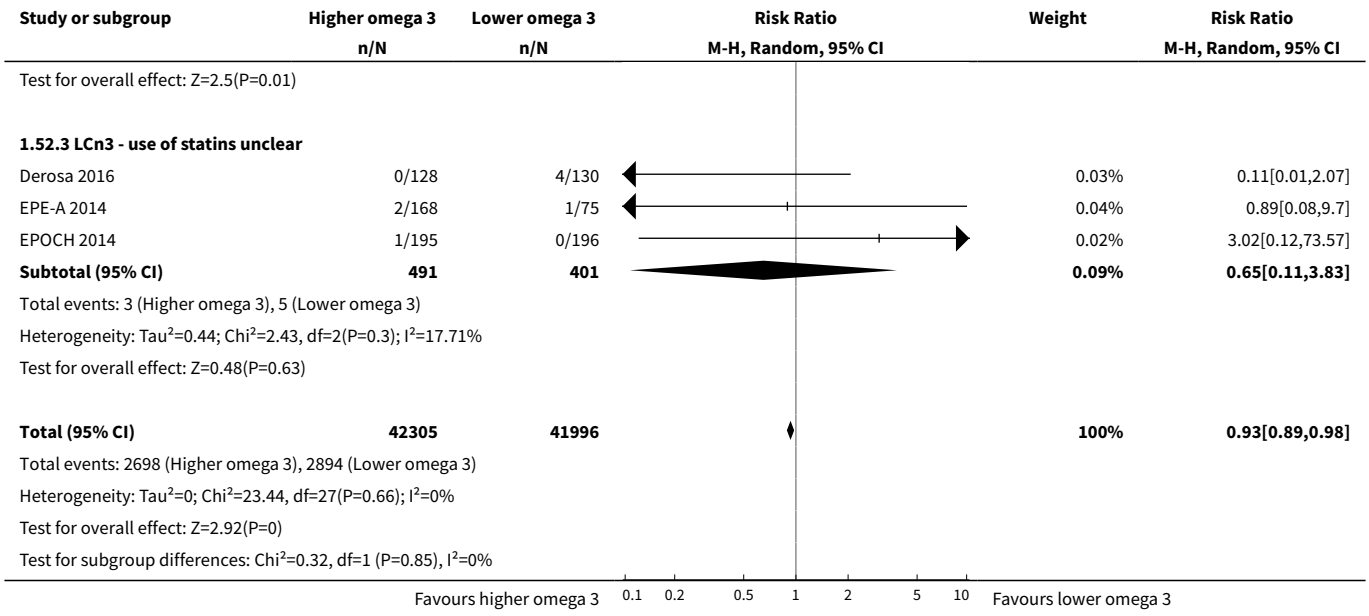
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=2.76(P=0.01)					
Total (95% CI)	**42305**	**41996**		**100%**	**0.93[0.89,0.98]**
Total events: 2698 (Higher omega 3), 2894 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=23.44, df=27(P=0.66); I^2=0%					
Test for overall effect: Z=2.92(P=0)					
Test for subgroup differences: Chi^2=0.04, df=1 (P=0.84), I^2=0%					

Favours higher omega 3 — 0.1 0.2 0.5 1 2 5 10 — Favours lower omega 3

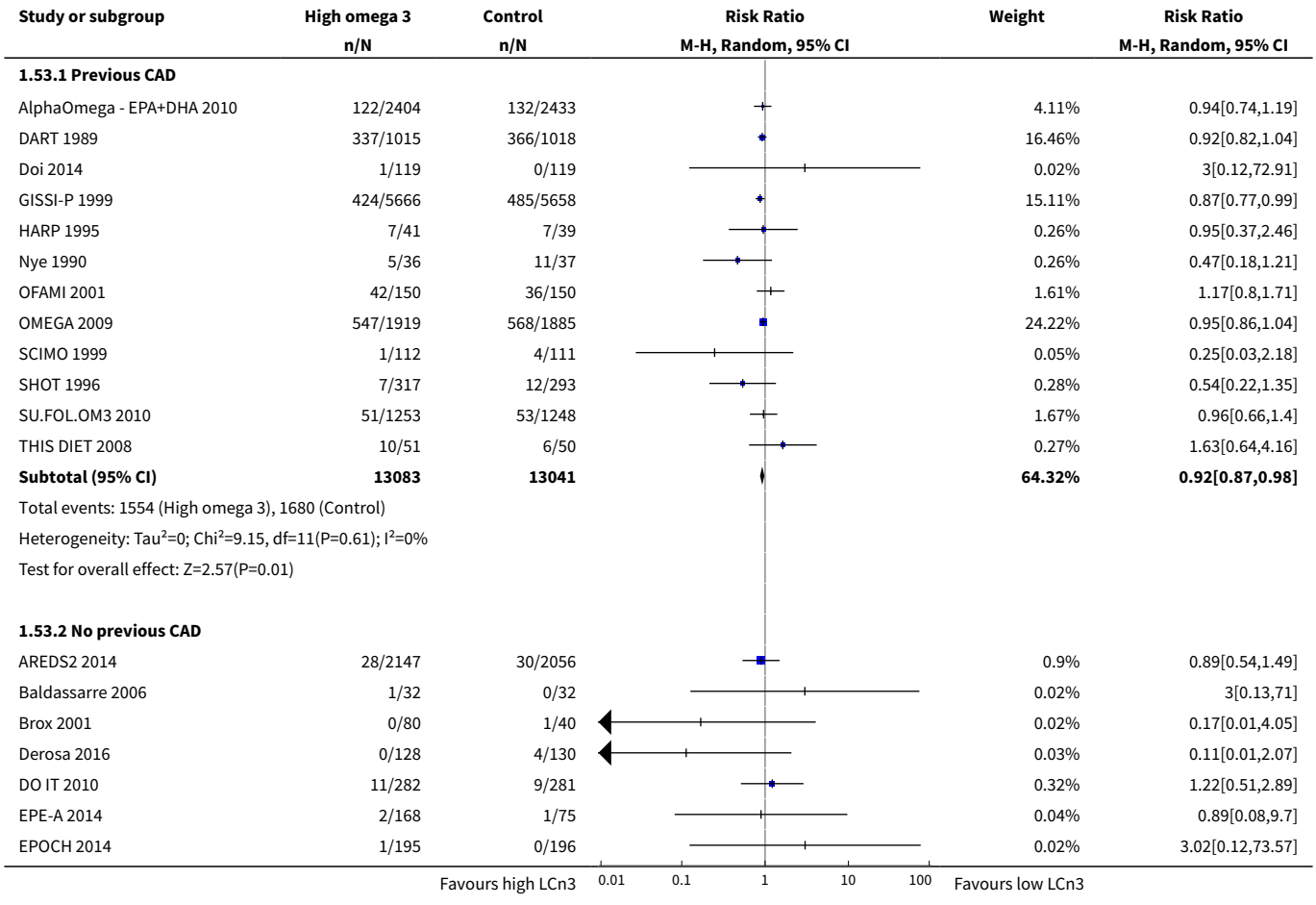
Analysis 1.52. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 52 CHD events - LCn3 - subgroup by statin use.

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
1.52.1 LCn3 - ≥ 50% of control group on statins					
AlphaOmega - EPA+DHA 2010	122/2404	132/2433		4.01%	0.94[0.74,1.19]
Doi 2014	1/119	0/119		0.02%	3[0.12,72.91]
JELIS 2007	262/9326	324/9319		8.96%	0.81[0.69,0.95]
Nye 1990	5/36	11/37		0.25%	0.47[0.18,1.21]
OMEGA 2009	547/1919	568/1885		23.63%	0.95[0.86,1.04]
ORIGIN 2012	344/6281	316/6255		10.42%	1.08[0.93,1.26]
SU.FOL.OM3 2010	51/1253	53/1248		1.63%	0.96[0.66,1.4]
THIS DIET 2008	10/51	6/50		0.26%	1.63[0.64,4.16]
Subtotal (95% CI)	**21389**	**21346**		**49.19%**	**0.94[0.85,1.05]**
Total events: 1342 (Higher omega 3), 1410 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=10.88, df=7(P=0.14); I^2=35.68%					
Test for overall effect: Z=1.08(P=0.28)					
1.52.2 LCn3 - < 50% of control group on statins					
AREDS2 2014	28/2147	30/2056		0.88%	0.89[0.54,1.49]
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	337/1015	366/1018		16.06%	0.92[0.82,1.04]
DO IT 2010	11/282	9/281		0.31%	1.22[0.51,2.89]
FORWARD 2013	1/289	1/297		0.03%	1.03[0.06,16.35]
FOSTAR 2016	10/101	10/101		0.33%	1[0.44,2.3]
GISSI-HF 2008	107/3494	129/3481		3.63%	0.83[0.64,1.06]
GISSI-P 1999	424/5666	485/5658		14.74%	0.87[0.77,0.99]
HARP 1995	7/41	7/39		0.25%	0.95[0.37,2.46]
OFAMI 2001	42/150	36/150		1.57%	1.17[0.8,1.71]
Proudman 2015	1/87	0/53		0.02%	1.84[0.08,44.38]
Raitt 2005	1/100	3/100		0.05%	0.33[0.04,3.15]
Risk & Prevention 2013	310/6239	324/6266		10%	0.96[0.83,1.12]
SCIMO 1999	1/112	4/111		0.05%	0.25[0.03,2.18]
SHOT 1996	7/317	12/293		0.27%	0.54[0.22,1.35]
SOFA 2006	65/273	62/273		2.48%	1.05[0.77,1.42]
Subtotal (95% CI)	**20425**	**20249**		**50.72%**	**0.92[0.86,0.98]**
Total events: 1353 (Higher omega 3), 1479 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=9.65, df=16(P=0.88); I^2=0%					

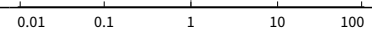
Favours higher omega 3 — 0.1 0.2 0.5 1 2 5 10 — Favours lower omega 3



Analysis 1.53. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 53 CHD events - LCn3 subgroup by CAD history.



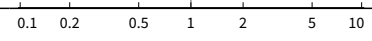
Study or subgroup	High omega 3 n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
FORWARD 2013	1/289	1/297		0.03%	1.03[0.06,16.35]
FOSTAR 2016	10/101	10/101		0.34%	1[0.44,2.3]
GISSI-HF 2008	107/3494	129/3481		3.72%	0.83[0.64,1.06]
JELIS 2007	262/9326	324/9319		9.19%	0.81[0.69,0.95]
ORIGIN 2012	344/6281	316/6255		10.68%	1.08[0.93,1.26]
Proudman 2015	1/87	0/53		0.02%	1.84[0.08,44.38]
Raitt 2005	1/100	3/100		0.05%	0.33[0.04,3.15]
Risk & Prevention 2013	310/6239	324/6266		10.25%	0.96[0.83,1.12]
SOFA 2006	1/273	3/273		0.05%	0.33[0.03,3.18]
Subtotal (95% CI)	**29222**	**28955**		**35.68%**	**0.94[0.86,1.01]**
Total events: 1080 (High omega 3), 1155 (Control)					
Heterogeneity: Tau^2=0; Chi^2=14.43, df=15(P=0.49); I^2=0%					
Test for overall effect: Z=1.62(P=0.11)					
Total (95% CI)	**42305**	**41996**		**100%**	**0.93[0.88,0.97]**
Total events: 2634 (High omega 3), 2835 (Control)					
Heterogeneity: Tau^2=0; Chi^2=23.63, df=27(P=0.65); I^2=0%					
Test for overall effect: Z=3.02(P=0)					
Test for subgroup differences: Chi^2=0.06, df=1 (P=0.81), I^2=0%					



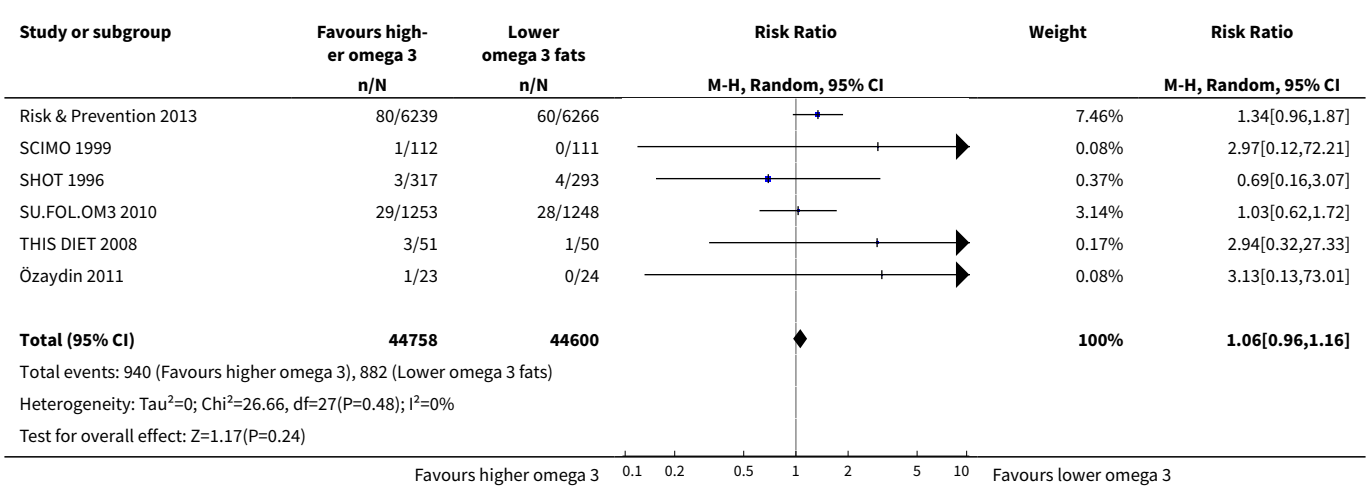
Favours high LCn3 — Favours low LCn3

Analysis 1.54. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 54 Stroke (overall) - LCn3.

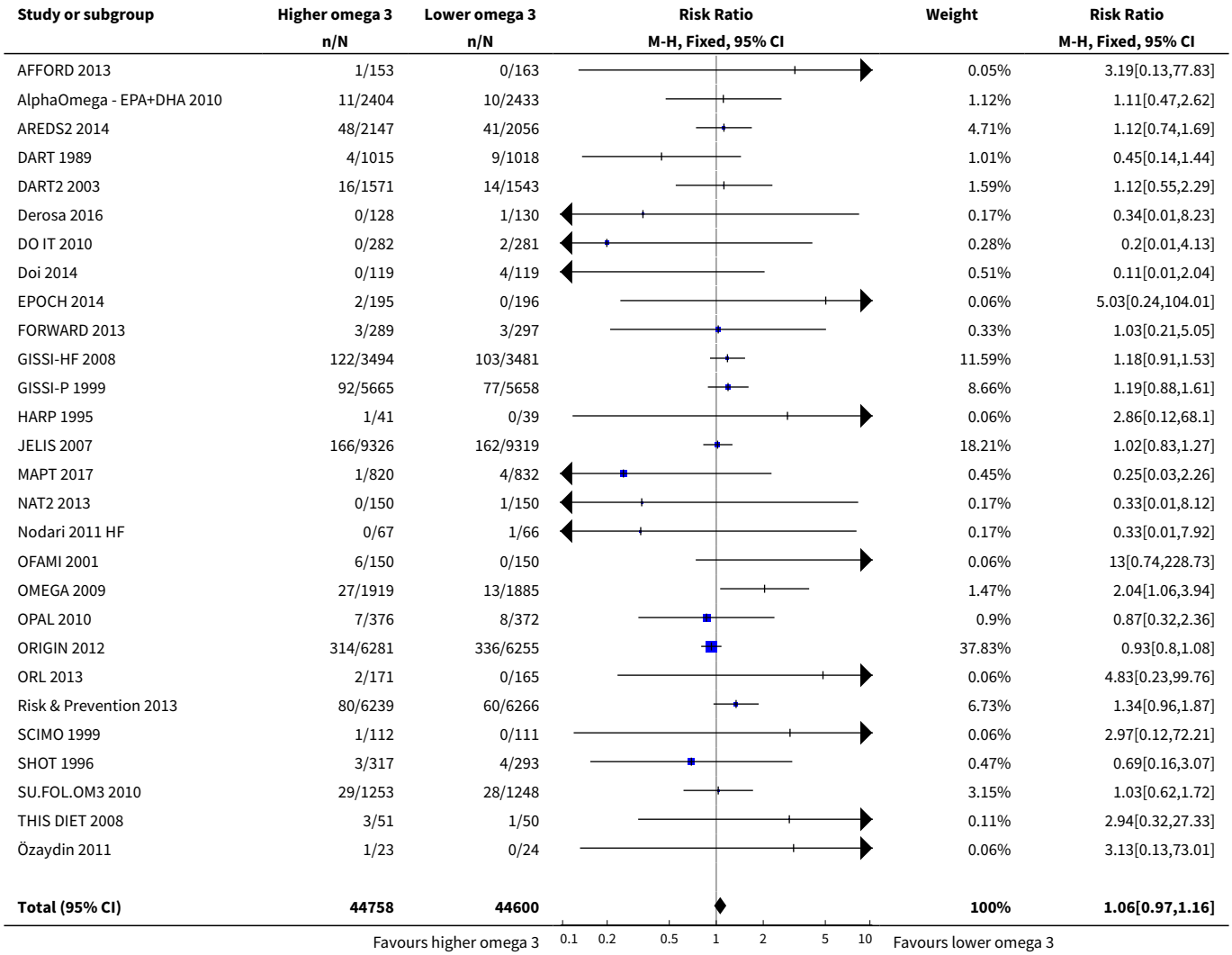
Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 fats n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
AFFORD 2013	1/153	0/163		0.08%	3.19[0.13,77.83]
AlphaOmega - EPA+DHA 2010	11/2404	10/2433		1.13%	1.11[0.47,2.62]
AREDS2 2014	48/2147	41/2056		4.86%	1.12[0.74,1.69]
DART 1989	4/1015	9/1018		0.6%	0.45[0.14,1.44]
DART2 2003	16/1571	14/1543		1.62%	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		0.1%	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		0.33%	1.03[0.21,5.05]
GISSI-HF 2008	122/3494	103/3481		12.42%	1.18[0.91,1.53]
GISSI-P 1999	92/5665	77/5658		9.16%	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		17.96%	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		1.91%	2.04[1.06,3.94]
OPAL 2010	7/376	8/372		0.82%	0.87[0.32,2.36]
ORIGIN 2012	314/6281	336/6255		36.84%	0.93[0.8,1.08]
ORL 2013	2/171	0/165		0.09%	4.83[0.23,99.76]



Favours higher omega 3 — Favours lower omega 3



Analysis 1.55. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 55 Stroke - 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
Total events: 940 (Higher omega 3), 882 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=26.66, df=27(P=0.48); I²=0%					
Test for overall effect: Z=1.27(P=0.2)					

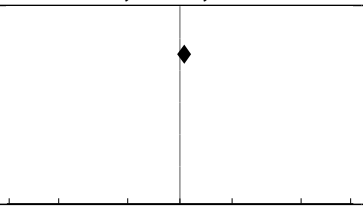
Favours higher omega 3 — 0.1 0.2 0.5 1 2 5 10 — Favours lower omega 3

Analysis 1.56. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 56 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
1.56.1 Low risk of bias					
AlphaOmega - EPA+DHA 2010	11/2404	10/2433		1.13%	1.11[0.47,2.62]
AREDS2 2014	48/2147	41/2056		4.86%	1.12[0.74,1.69]
Derosa 2016	0/128	1/130		0.08%	0.34[0.01,8.23]
EPOCH 2014	2/195	0/196		0.09%	5.03[0.24,104.01]
FORWARD 2013	3/289	3/297		0.33%	1.03[0.21,5.05]
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]
OMEGA 2009	27/1919	13/1885		1.91%	2.04[1.06,3.94]
OPAL 2010	7/376	8/372		0.82%	0.87[0.32,2.36]
ORIGIN 2012	314/6281	336/6255		36.84%	0.93[0.8,1.08]
SCIMO 1999	1/112	0/111		0.08%	2.97[0.12,72.21]
SU.FOL.OM3 2010	29/1253	28/1248		3.14%	1.03[0.62,1.72]
Subtotal (95% CI)	**16074**	**15965**		**49.53%**	**0.98[0.86,1.12]**
Total events: 443 (Higher omega 3), 445 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=9.72, df=11(P=0.56); I²=0%					
Test for overall effect: Z=0.25(P=0.81)					
1.56.2 Moderate/high risk of bias					
AFFORD 2013	1/153	0/163		0.08%	3.19[0.13,77.83]
DART 1989	4/1015	9/1018		0.6%	0.45[0.14,1.44]
DART2 2003	16/1571	14/1543		1.62%	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		0.1%	0.11[0.01,2.04]
GISSI-HF 2008	122/3494	103/3481		12.42%	1.18[0.91,1.53]
GISSI-P 1999	92/5665	77/5658		9.16%	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		17.96%	1.02[0.83,1.27]
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]
ORL 2013	2/171	0/165		0.09%	4.83[0.23,99.76]
Risk & Prevention 2013	80/6239	60/6266		7.46%	1.34[0.96,1.87]
SHOT 1996	3/317	4/293		0.37%	0.69[0.16,3.07]
THIS DIET 2008	3/51	1/50		0.17%	2.94[0.32,27.33]
Özaydin 2011	1/23	0/24		0.08%	3.13[0.13,73.01]
Subtotal (95% CI)	**28684**	**28635**		**50.47%**	**1.13[1,1.29]**
Total events: 497 (Higher omega 3), 437 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=14.66, df=15(P=0.48); I²=0%					
Test for overall effect: Z=1.9(P=0.06)					

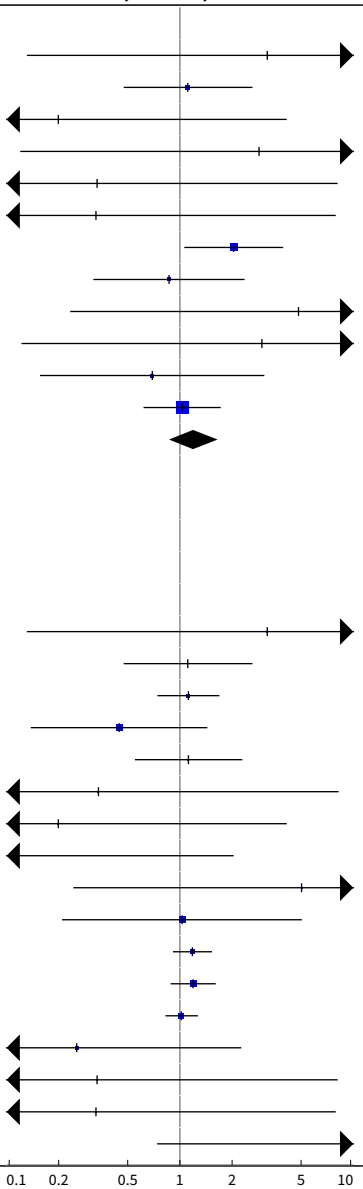
Favours higher omega 3 — 0.1 0.2 0.5 1 2 5 10 — Favours lower omega 3

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)	**44758**	**44600**		**100%**	**1.06[0.96,1.16]**
Total events: 940 (Higher omega 3), 882 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=26.66, df=27(P=0.48); I²=0%					
Test for overall effect: Z=1.17(P=0.24)					
Test for subgroup differences: Chi²=2.28, df=1 (P=0.13), I²=56.09%					

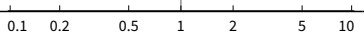


Analysis 1.57. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 57 Stroke - LCn3 - SA by compliance and study size.

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
1.57.1 SA - low risk of compliance bias					
AFFORD 2013	1/153	0/163		1.02%	3.19[0.13,77.83]
AlphaOmega - EPA+DHA 2010	11/2404	10/2433		14.23%	1.11[0.47,2.62]
DO IT 2010	0/282	2/281		1.13%	0.2[0.01,4.13]
HARP 1995	1/41	0/39		1.03%	2.86[0.12,68.1]
NAT2 2013	0/150	1/150		1.02%	0.33[0.01,8.12]
Nodari 2011 HF	0/67	1/66		1.03%	0.33[0.01,7.92]
OMEGA 2009	27/1919	13/1885		23.96%	2.04[1.06,3.94]
OPAL 2010	7/376	8/372		10.3%	0.87[0.32,2.36]
ORL 2013	2/171	0/165		1.13%	4.83[0.23,99.76]
SCIMO 1999	1/112	0/111		1.02%	2.97[0.12,72.21]
SHOT 1996	3/317	4/293		4.69%	0.69[0.16,3.07]
SU.FOL.OM3 2010	29/1253	28/1248		39.43%	1.03[0.62,1.72]
Subtotal (95% CI)	**7245**	**7206**		**100%**	**1.19[0.86,1.65]**
Total events: 82 (Higher omega 3), 67 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=8.16, df=11(P=0.7); I²=0%					
Test for overall effect: Z=1.08(P=0.28)					
1.57.2 SA - 100+ randomised					
AFFORD 2013	1/153	0/163		0.1%	3.19[0.13,77.83]
AlphaOmega - EPA+DHA 2010	11/2404	10/2433		1.34%	1.11[0.47,2.62]
AREDS2 2014	48/2147	41/2056		5.53%	1.12[0.74,1.69]
DART 1989	4/1015	9/1018		0.71%	0.45[0.14,1.44]
DART2 2003	16/1571	14/1543		1.91%	1.12[0.55,2.29]
Derosa 2016	0/128	1/130		0.1%	0.34[0.01,8.23]
DO IT 2010	0/282	2/281		0.11%	0.2[0.01,4.13]
Doi 2014	0/119	4/119		0.12%	0.11[0.01,2.04]
EPOCH 2014	2/195	0/196		0.11%	5.03[0.24,104.01]
FORWARD 2013	3/289	3/297		0.39%	1.03[0.21,5.05]
GISSI-HF 2008	122/3494	103/3481		13.15%	1.18[0.91,1.53]
GISSI-P 1999	92/5665	77/5658		10%	1.19[0.88,1.61]
JELIS 2007	166/9326	162/9319		18.1%	1.02[0.83,1.27]
MAPT 2017	1/820	4/832		0.21%	0.25[0.03,2.26]
NAT2 2013	0/150	1/150		0.1%	0.33[0.01,8.12]
Nodari 2011 HF	0/67	1/66		0.1%	0.33[0.01,7.92]
OFAMI 2001	6/150	0/150		0.12%	13[0.74,228.73]

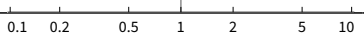


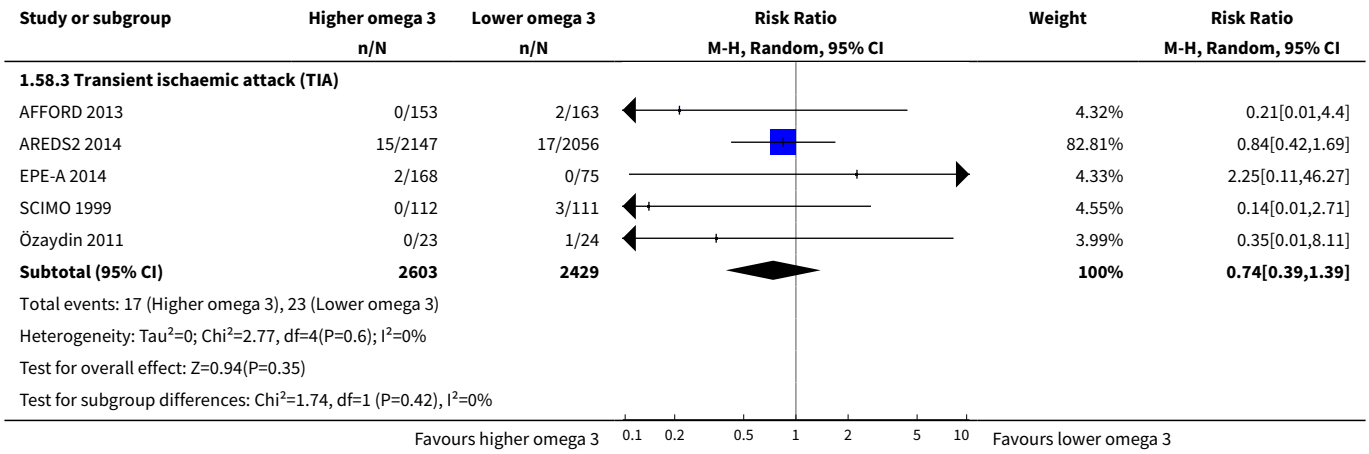
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
OMEGA 2009	27/1919	13/1885		2.23%	2.04[1.06,3.94]
OPAL 2010	7/376	8/372		0.97%	0.87[0.32,2.36]
ORIGIN 2012	314/6281	336/6255		31.86%	0.93[0.8,1.08]
ORL 2013	2/171	0/165		0.11%	4.83[0.23,99.76]
Risk & Prevention 2013	80/6239	60/6266		8.28%	1.34[0.96,1.87]
SCIMO 1999	1/112	0/111		0.1%	2.97[0.12,72.21]
SHOT 1996	3/317	4/293		0.44%	0.69[0.16,3.07]
SU.FOL.OM3 2010	29/1253	28/1248		3.63%	1.03[0.62,1.72]
THIS DIET 2008	3/51	1/50		0.2%	2.94[0.32,27.33]
Subtotal (95% CI)	**44694**	**44537**		**100%**	**1.07[0.97,1.18]**
Total events: 938 (Higher omega 3), 882 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=25.83, df=25(P=0.42); I²=3.2%					
Test for overall effect: Z=1.26(P=0.21)					
Test for subgroup differences: Chi²=0.43, df=1 (P=0.51), I²=0%					



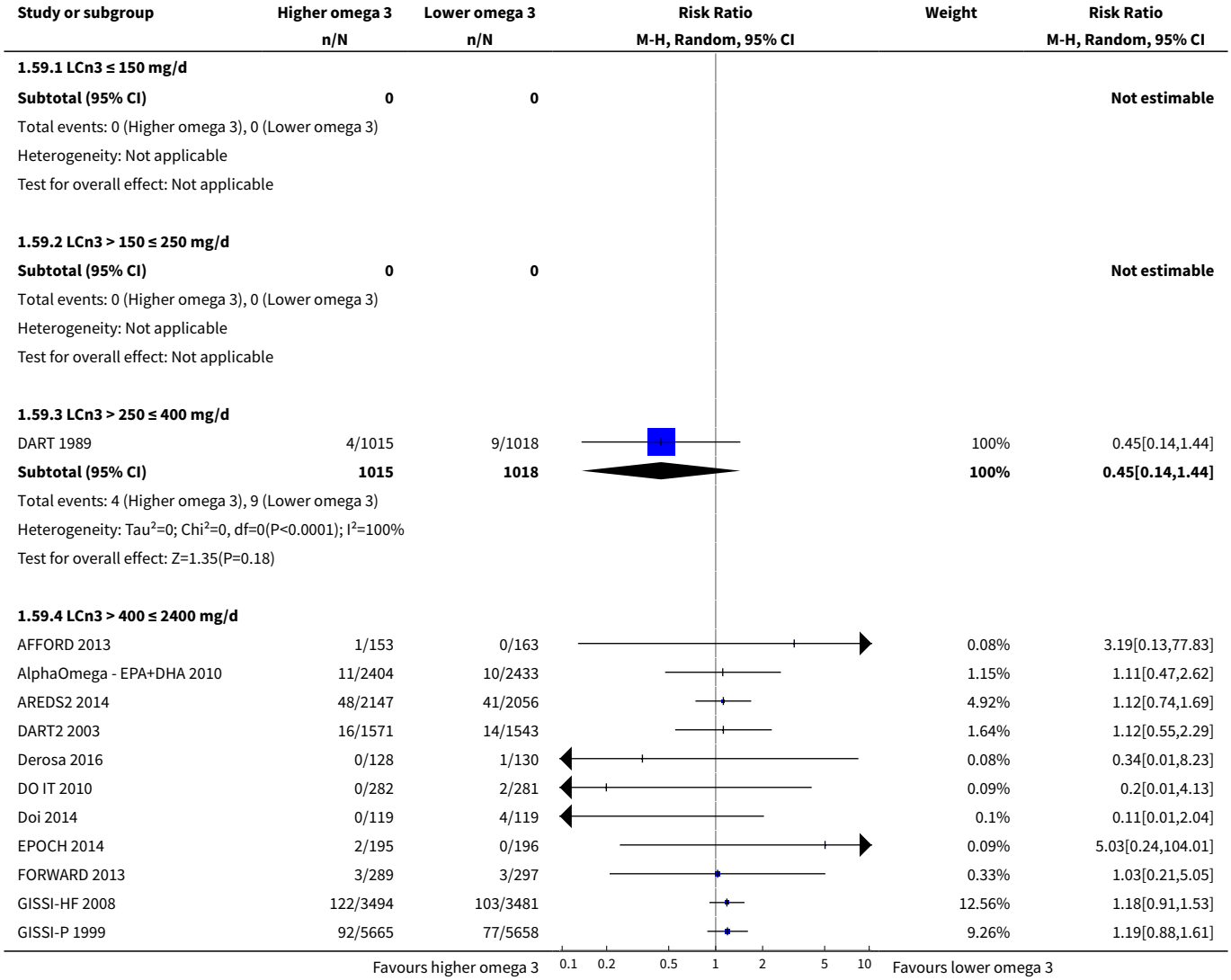
Analysis 1.58. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 58 Stroke - LCn3 - subgroup by stroke type.

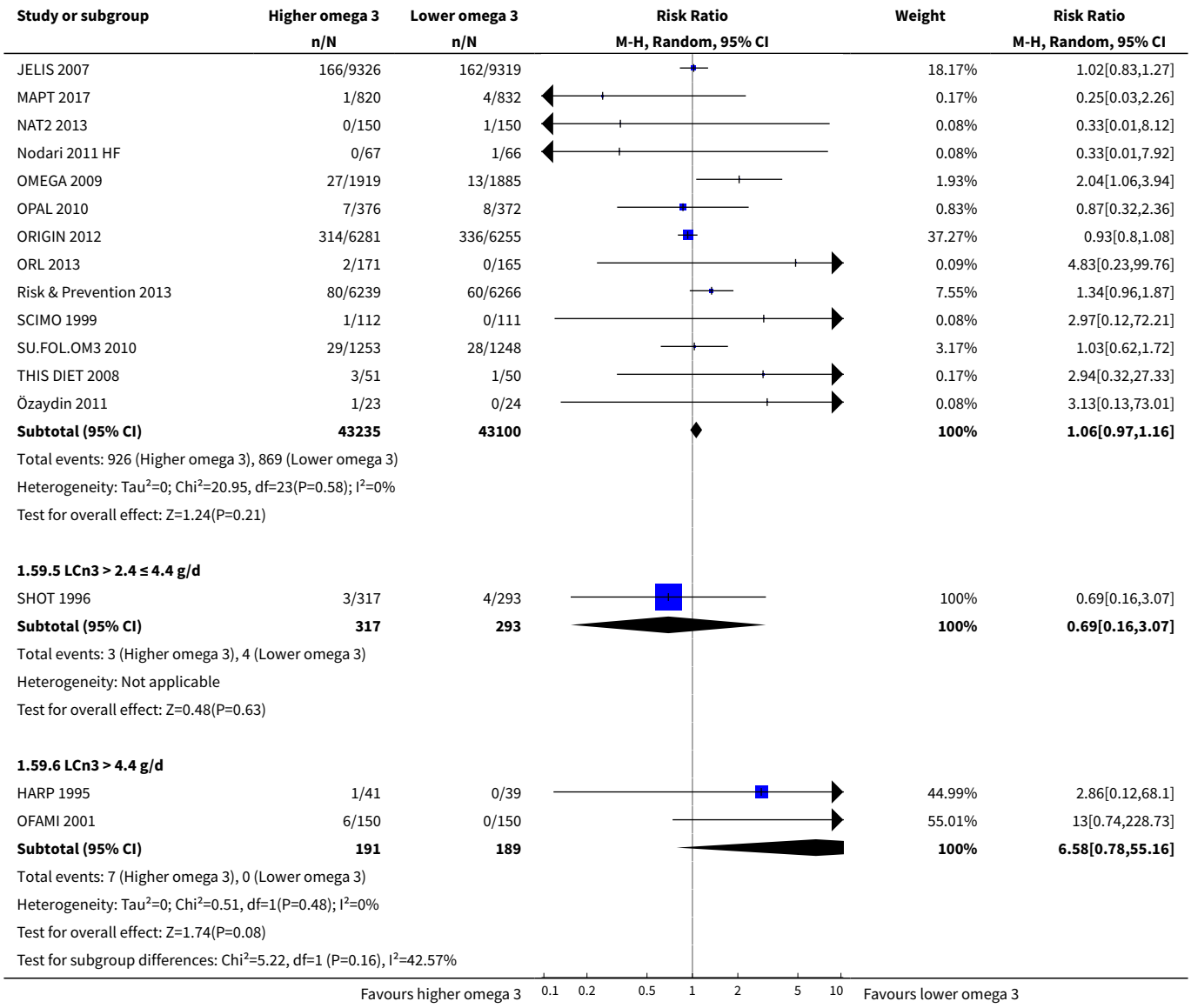
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.58.1 Ischaemic stroke - LCn3					
AREDS2 2014	40/2147	31/2056		15.54%	1.24[0.78,1.97]
DART 1989	2/1015	6/1018		1.55%	0.33[0.07,1.65]
GISSI-HF 2008	97/3494	79/3481		31.22%	1.22[0.91,1.64]
JELIS 2007	115/9326	123/9319		37.7%	0.93[0.73,1.2]
OFAMI 2001	6/150	0/150		0.49%	13[0.74,228.73]
ORL 2013	1/171	0/165		0.39%	2.9[0.12,70.57]
SU.FOL.OM3 2010	29/1253	26/1248		12.71%	1.11[0.66,1.88]
Özaydin 2011	1/23	0/24		0.4%	3.13[0.13,73.01]
Subtotal (95% CI)	**17579**	**17461**		**100%**	**1.09[0.89,1.33]**
Total events: 291 (Higher omega 3), 265 (Lower omega 3)					
Heterogeneity: Tau²=0.01; Chi²=8.07, df=7(P=0.33); I²=13.25%					
Test for overall effect: Z=0.86(P=0.39)					
1.58.2 Haemorrhagic stroke - LCn3					
AREDS2 2014	3/2147	1/2056		2.34%	2.87[0.3,27.6]
DART 1989	2/1015	3/1018		3.75%	0.67[0.11,3.99]
GISSI-HF 2008	13/3494	10/3481		17.68%	1.3[0.57,2.95]
JELIS 2007	49/9326	39/9319		68.04%	1.26[0.83,1.91]
MAPT 2017	1/820	2/832		2.08%	0.51[0.05,5.58]
NAT2 2013	0/150	1/150		1.18%	0.33[0.01,8.12]
ORL 2013	1/171	0/165		1.17%	2.9[0.12,70.57]
SU.FOL.OM3 2010	2/1253	3/1248		3.75%	0.66[0.11,3.97]
Subtotal (95% CI)	**18376**	**18269**		**100%**	**1.2[0.85,1.69]**
Total events: 71 (Higher omega 3), 59 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=2.89, df=7(P=0.9); I²=0%					
Test for overall effect: Z=1.02(P=0.31)					



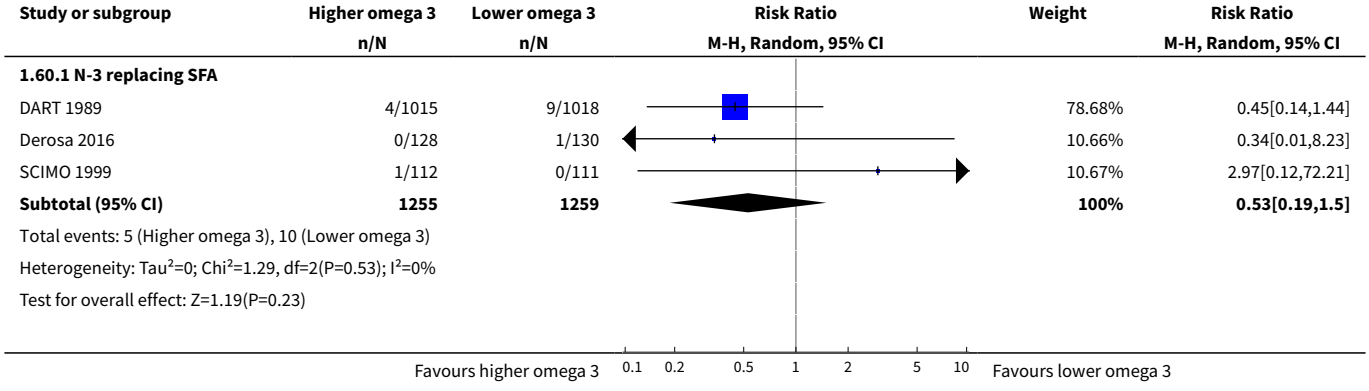


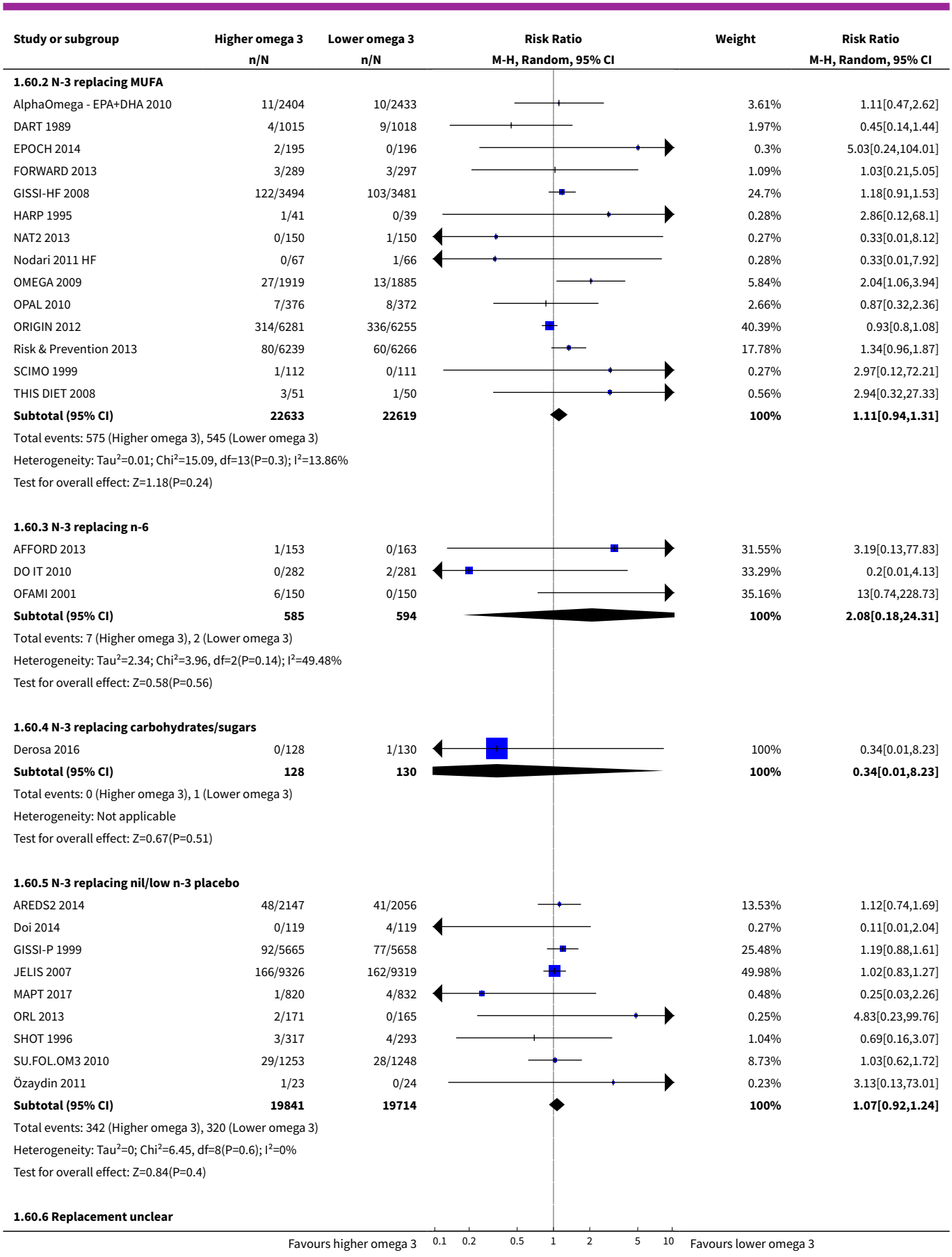
Analysis 1.59. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 59 Stroke - LCn3 - subgroup by dose.

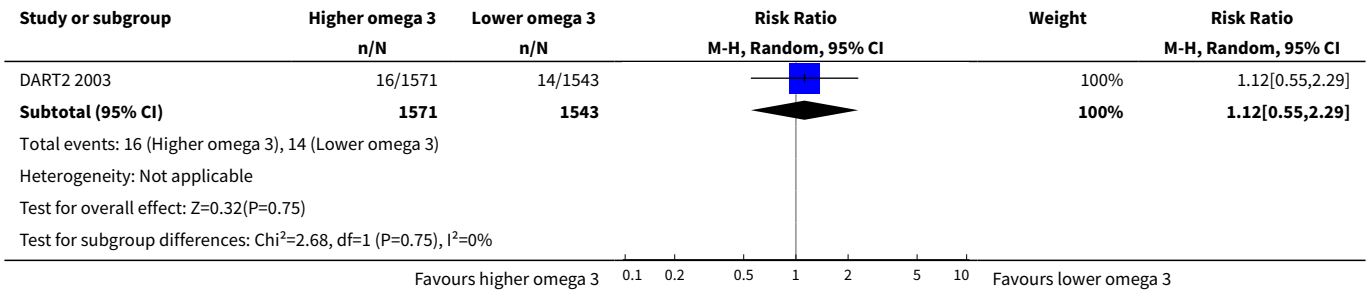




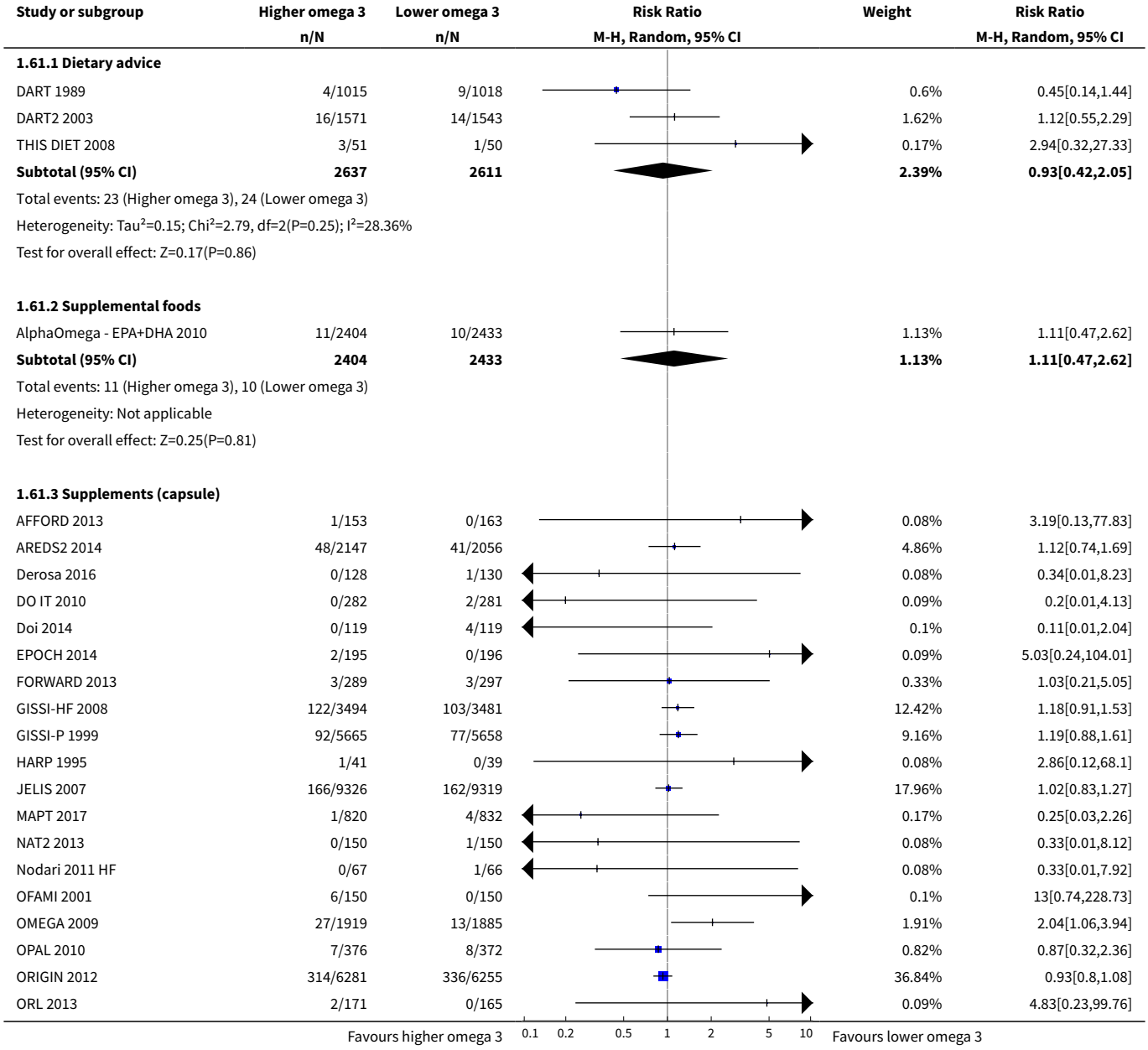
Analysis 1.60. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 60 Stroke - LCn3 - subgroup by replacement.







Analysis 1.61. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 61 Stroke - LCn3 - subgroup by intervention type.



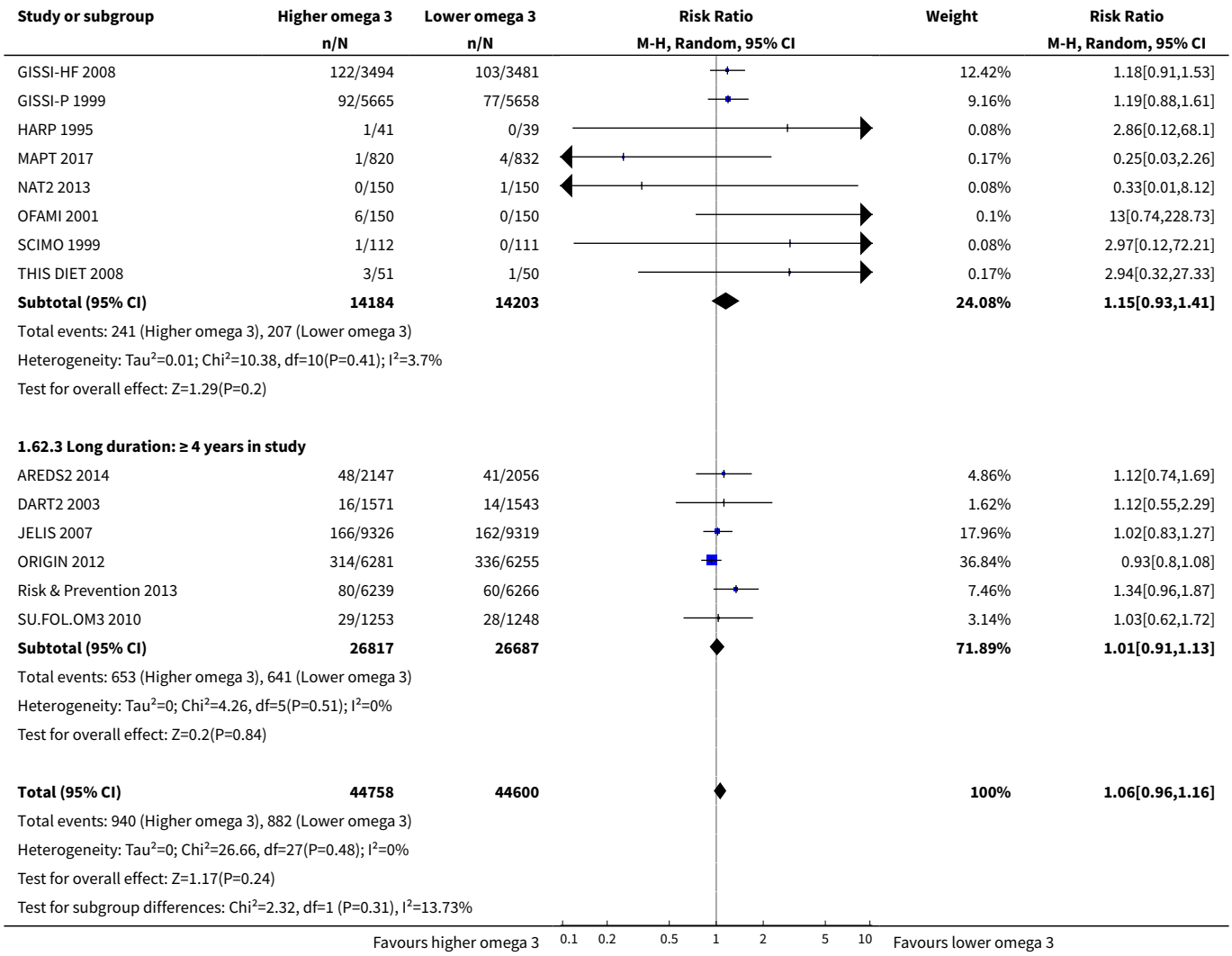
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Risk & Prevention 2013	80/6239	60/6266		7.46%	1.34[0.96,1.87]
SCIMO 1999	1/112	0/111		0.08%	2.97[0.12,72.21]
SHOT 1996	3/317	4/293		0.37%	0.69[0.16,3.07]
SU.FOL.OM3 2010	29/1253	28/1248		3.14%	1.03[0.62,1.72]
Özaydin 2011	1/23	0/24		0.08%	3.13[0.13,73.01]
Subtotal (95% CI)	**39717**	**39556**		**96.48%**	**1.07[0.97,1.18]**
Total events: 906 (Higher omega 3), 848 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=23.74, df=23(P=0.42); I²=3.11%					
Test for overall effect: Z=1.32(P=0.19)					
1.61.4 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)	**44758**	**44600**		**100%**	**1.06[0.96,1.16]**
Total events: 940 (Higher omega 3), 882 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=26.66, df=27(P=0.48); I²=0%					
Test for overall effect: Z=1.17(P=0.24)					
Test for subgroup differences: Chi²=0.12, df=1 (P=0.94), I²=0%					

Favours higher omega 3 — 0.1 0.2 0.5 1 2 5 10 — Favours lower omega 3

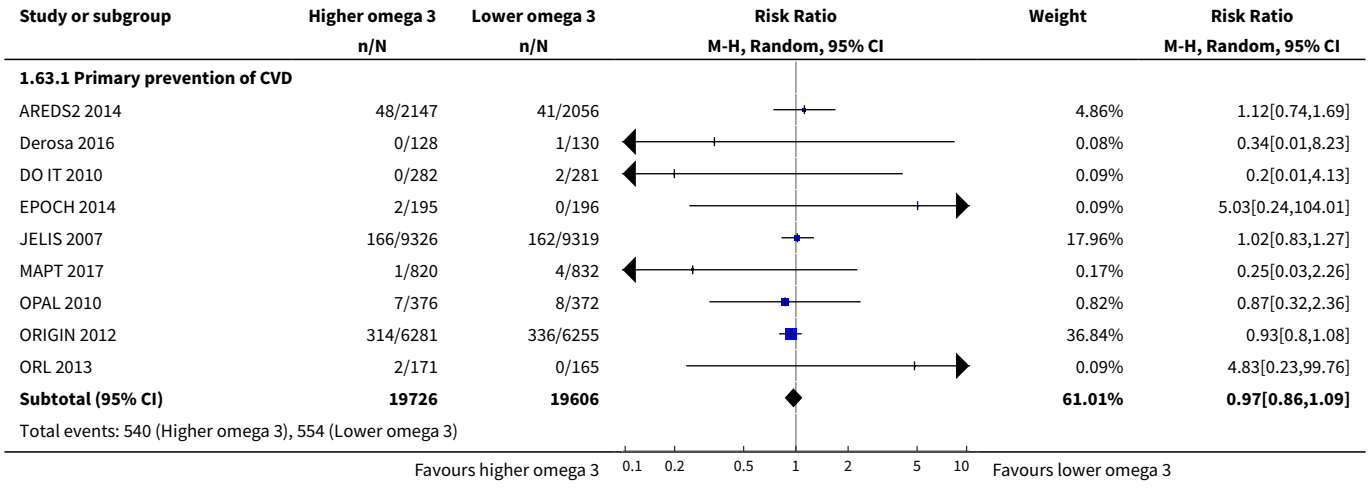
Analysis 1.62. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 62 Stroke - LCn3 - subgroup by duration.

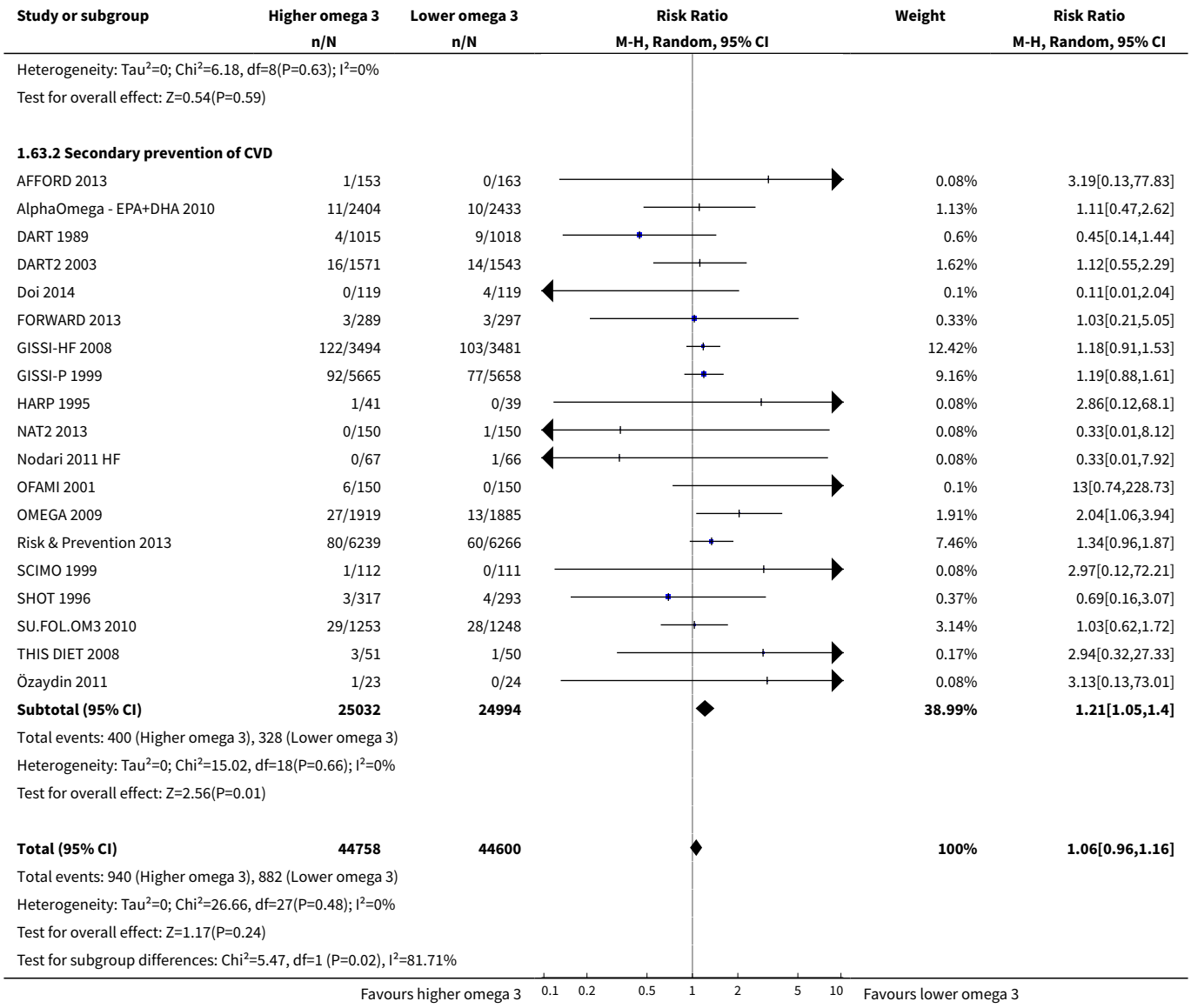
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.62.1 Medium duration 1 to < 2 years in study					
AFFORD 2013	1/153	0/163		0.08%	3.19[0.13,77.83]
Derosa 2016	0/128	1/130		0.08%	0.34[0.01,8.23]
Doi 2014	0/119	4/119		0.1%	0.11[0.01,2.04]
EPOCH 2014	2/195	0/196		0.09%	5.03[0.24,104.01]
FORWARD 2013	3/289	3/297		0.33%	1.03[0.21,5.05]
Nodari 2011 HF	0/67	1/66		0.08%	0.33[0.01,7.92]
OMEGA 2009	27/1919	13/1885		1.91%	2.04[1.06,3.94]
OPAL 2010	7/376	8/372		0.82%	0.87[0.32,2.36]
ORL 2013	2/171	0/165		0.09%	4.83[0.23,99.76]
SHOT 1996	3/317	4/293		0.37%	0.69[0.16,3.07]
Özaydin 2011	1/23	0/24		0.08%	3.13[0.13,73.01]
Subtotal (95% CI)	**3757**	**3710**		**4.03%**	**1.35[0.86,2.12]**
Total events: 46 (Higher omega 3), 34 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=9.43, df=10(P=0.49); I²=0%					
Test for overall effect: Z=1.28(P=0.2)					
1.62.2 Medium-long duration: 2 to < 4 years in study					
AlphaOmega - EPA+DHA 2010	11/2404	10/2433		1.13%	1.11[0.47,2.62]
DART 1989	4/1015	9/1018		0.6%	0.45[0.14,1.44]
DO IT 2010	0/282	2/281		0.09%	0.2[0.01,4.13]

Favours higher omega 3 — 0.1 0.2 0.5 1 2 5 10 — Favours lower omega 3



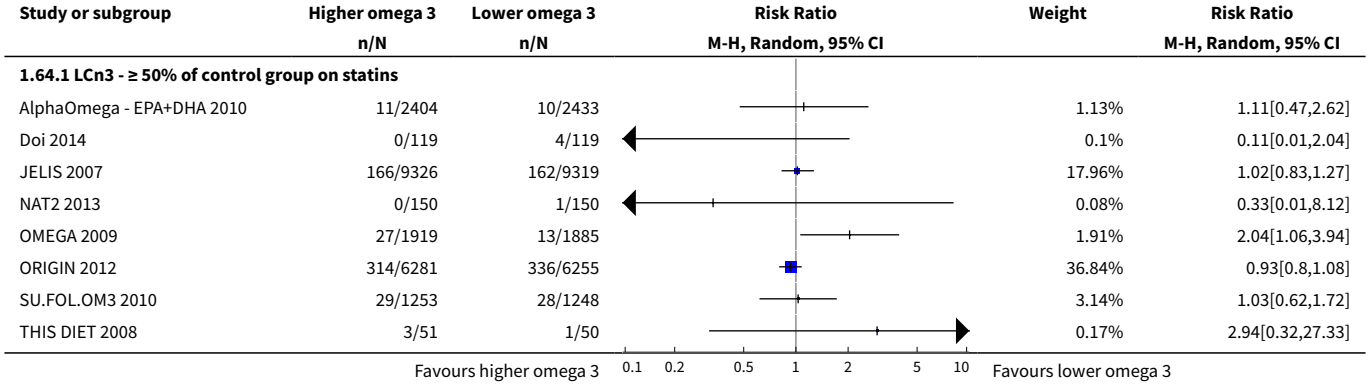
Analysis 1.63. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 63 Stroke - LCn3 - subgroup by primary or secondary prevention.



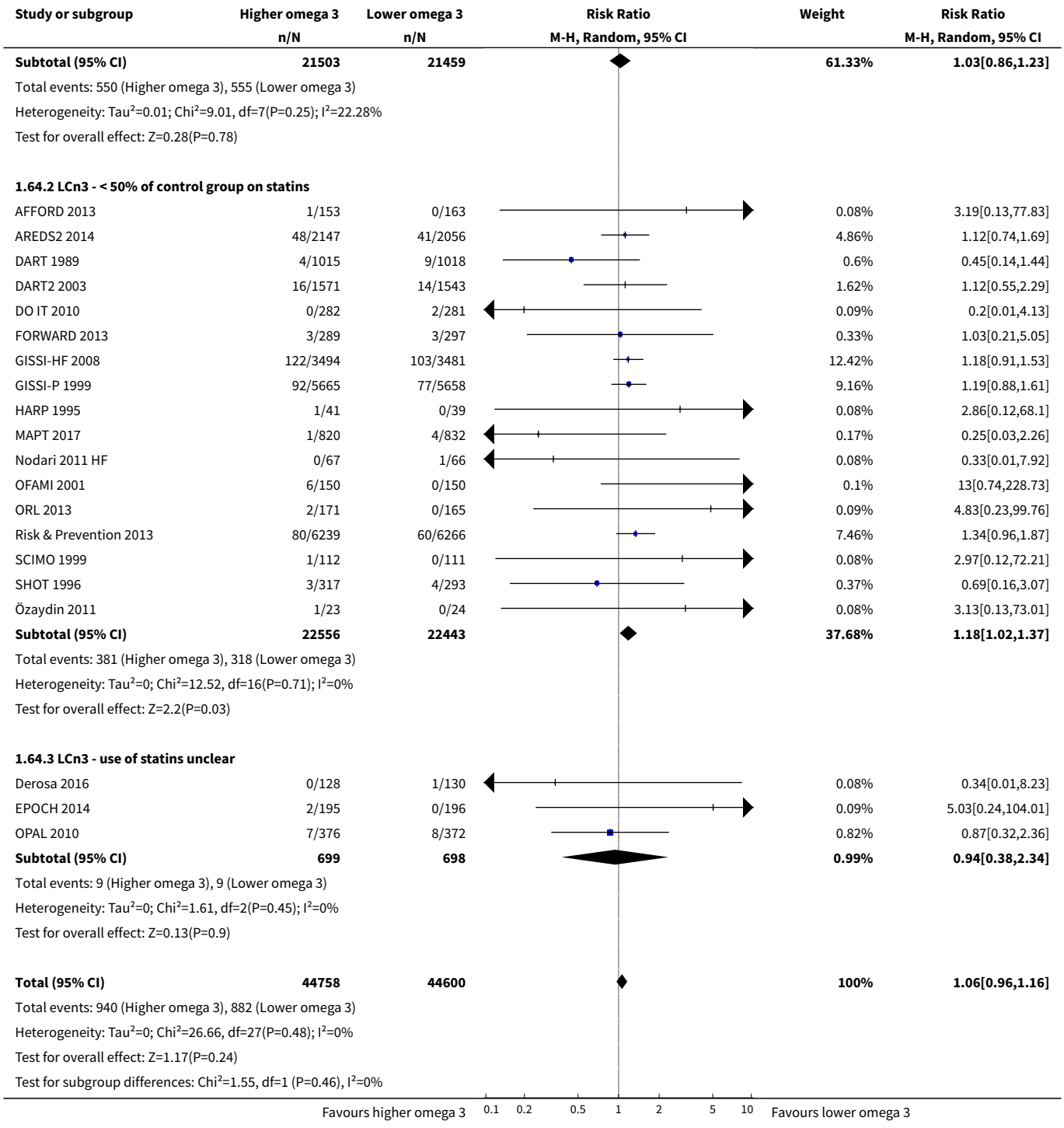


Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0; Chi²=6.18, df=8(P=0.63); I²=0%					
Test for overall effect: Z=0.54(P=0.59)					
1.63.2 Secondary prevention of CVD					
AFFORD 2013	1/153	0/163		0.08%	3.19[0.13,77.83]
AlphaOmega - EPA+DHA 2010	11/2404	10/2433		1.13%	1.11[0.47,2.62]
DART 1989	4/1015	9/1018		0.6%	0.45[0.14,1.44]
DART2 2003	16/1571	14/1543		1.62%	1.12[0.55,2.29]
Doi 2014	0/119	4/119		0.1%	0.11[0.01,2.04]
FORWARD 2013	3/289	3/297		0.33%	1.03[0.21,5.05]
GISSI-HF 2008	122/3494	103/3481		12.42%	1.18[0.91,1.53]
GISSI-P 1999	92/5665	77/5658		9.16%	1.19[0.88,1.61]
HARP 1995	1/41	0/39		0.08%	2.86[0.12,68.1]
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		1.91%	2.04[1.06,3.94]
Risk & Prevention 2013	80/6239	60/6266		7.46%	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		0.37%	0.69[0.16,3.07]
SU.FOL.OM3 2010	29/1253	28/1248		3.14%	1.03[0.62,1.72]
THIS DIET 2008	3/51	1/50		0.17%	2.94[0.32,27.33]
Özaydin 2011	1/23	0/24		0.08%	3.13[0.13,73.01]
Subtotal (95% CI)	**25032**	**24994**		**38.99%**	**1.21[1.05,1.4]**
Total events: 400 (Higher omega 3), 328 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=15.02, df=18(P=0.66); I²=0%					
Test for overall effect: Z=2.56(P=0.01)					
Total (95% CI)	**44758**	**44600**		**100%**	**1.06[0.96,1.16]**
Total events: 940 (Higher omega 3), 882 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=26.66, df=27(P=0.48); I²=0%					
Test for overall effect: Z=1.17(P=0.24)					
Test for subgroup differences: Chi²=5.47, df=1 (P=0.02), I²=81.71%					

Analysis 1.64. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 64 Stroke - 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
1.64.1 LCn3 - ≥ 50% of control group on statins					
AlphaOmega - EPA+DHA 2010	11/2404	10/2433		1.13%	1.11[0.47,2.62]
Doi 2014	0/119	4/119		0.1%	0.11[0.01,2.04]
JELIS 2007	166/9326	162/9319		17.96%	1.02[0.83,1.27]
NAT2 2013	0/150	1/150		0.08%	0.33[0.01,8.12]
OMEGA 2009	27/1919	13/1885		1.91%	2.04[1.06,3.94]
ORIGIN 2012	314/6281	336/6255		36.84%	0.93[0.8,1.08]
SU.FOL.OM3 2010	29/1253	28/1248		3.14%	1.03[0.62,1.72]
THIS DIET 2008	3/51	1/50		0.17%	2.94[0.32,27.33]



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
Subtotal (95% CI)	**21503**	**21459**		**61.33%**	**1.03[0.86,1.23]**
Total events: 550 (Higher omega 3), 555 (Lower omega 3)					
Heterogeneity: Tau²=0.01; Chi²=9.01, df=7(P=0.25); I²=22.28%					
Test for overall effect: Z=0.28(P=0.78)					
1.64.2 LCn3 - < 50% of control group on statins					
AFFORD 2013	1/153	0/163		0.08%	3.19[0.13,77.83]
AREDS2 2014	48/2147	41/2056		4.86%	1.12[0.74,1.69]
DART 1989	4/1015	9/1018		0.6%	0.45[0.14,1.44]
DART2 2003	16/1571	14/1543		1.62%	1.12[0.55,2.29]
DO IT 2010	0/282	2/281		0.09%	0.2[0.01,4.13]
FORWARD 2013	3/289	3/297		0.33%	1.03[0.21,5.05]
GISSI-HF 2008	122/3494	103/3481		12.42%	1.18[0.91,1.53]
GISSI-P 1999	92/5665	77/5658		9.16%	1.19[0.88,1.61]
HARP 1995	1/41	0/39		0.08%	2.86[0.12,68.1]
MAPT 2017	1/820	4/832		0.17%	0.25[0.03,2.26]
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]
ORL 2013	2/171	0/165		0.09%	4.83[0.23,99.76]
Risk & Prevention 2013	80/6239	60/6266		7.46%	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		0.37%	0.69[0.16,3.07]
Özaydin 2011	1/23	0/24		0.08%	3.13[0.13,73.01]
Subtotal (95% CI)	**22556**	**22443**		**37.68%**	**1.18[1.02,1.37]**
Total events: 381 (Higher omega 3), 318 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=12.52, df=16(P=0.71); I²=0%					
Test for overall effect: Z=2.2(P=0.03)					
1.64.3 LCn3 - use of statins unclear					
Derosa 2016	0/128	1/130		0.08%	0.34[0.01,8.23]
EPOCH 2014	2/195	0/196		0.09%	5.03[0.24,104.01]
OPAL 2010	7/376	8/372		0.82%	0.87[0.32,2.36]
Subtotal (95% CI)	**699**	**698**		**0.99%**	**0.94[0.38,2.34]**
Total events: 9 (Higher omega 3), 9 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=1.61, df=2(P=0.45); I²=0%					
Test for overall effect: Z=0.13(P=0.9)					
Total (95% CI)	**44758**	**44600**		**100%**	**1.06[0.96,1.16]**
Total events: 940 (Higher omega 3), 882 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=26.66, df=27(P=0.48); I²=0%					
Test for overall effect: Z=1.17(P=0.24)					
Test for subgroup differences: Chi²=1.55, df=1 (P=0.46), I²=0%					

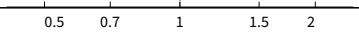
Analysis 1.65. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 65 Arrythmia (overall) - LCn3.

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		7.52%	1.01[0.86,1.2]
AlphaOmega - EPA+DHA 2010	67/2404	74/2433		3.81%	0.92[0.66,1.27]
Derosa 2016	1/128	3/130		0.12%	0.34[0.04,3.21]
DISAF 2003	154/201	157/206		9.41%	1.01[0.9,1.12]
EPIC-1 2008	1/188	0/186		0.06%	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		6.91%	0.89[0.74,1.07]
FAAT 2005	60/200	79/202		4.76%	0.77[0.58,1.01]
FORWARD 2013	68/289	56/297		3.99%	1.25[0.91,1.71]
FOSTAR 2016	4/101	4/101		0.32%	1[0.26,3.89]
GISSI-HF 2008	76/278	98/284		5.25%	0.79[0.62,1.02]
GISSI-HF 2008	444/2921	408/2914		8.89%	1.09[0.96,1.23]
GISSI-P 1999	40/2836	46/2828		2.63%	0.87[0.57,1.32]
Kumar 2012	61/91	78/87		7.71%	0.75[0.64,0.88]
Nodari 2011 AF	37/100	56/99		4.09%	0.65[0.48,0.89]
Nodari 2011 HF	1/67	4/66		0.13%	0.25[0.03,2.15]
OFAMI 2001	8/150	15/150		0.82%	0.53[0.23,1.22]
OMEGA 2009	99/1919	84/1885		4.54%	1.16[0.87,1.54]
ORIGIN 2012	288/6281	259/6255		7.6%	1.11[0.94,1.3]
ORL 2013	0/171	1/165		0.06%	0.32[0.01,7.84]
Proudman 2015	1/87	0/53		0.06%	1.84[0.08,44.38]
Raitt 2005	65/100	59/100		6.05%	1.1[0.89,1.37]
Risk & Prevention 2013	113/6239	92/6266		4.75%	1.23[0.94,1.62]
Sianni 2013	147/268	29/60		4.55%	1.13[0.85,1.51]
SOFA 2006	36/273	34/273		2.47%	1.06[0.68,1.64]
SU.FOL.OM3 2010	33/1253	32/1248		2.13%	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		1.04%	1.04[0.51,2.16]
Total (95% CI)	**27021**	**26775**		**100%**	**0.97[0.9,1.05]**

Total events: 1956 (Favours higher omega 3), 1832 (Lower omega 3)

Heterogeneity: Tau^2=0.01; Chi^2=47.34, df=27(P=0.01); I^2=42.97%

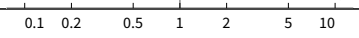
Test for overall effect: Z=0.83(P=0.41)



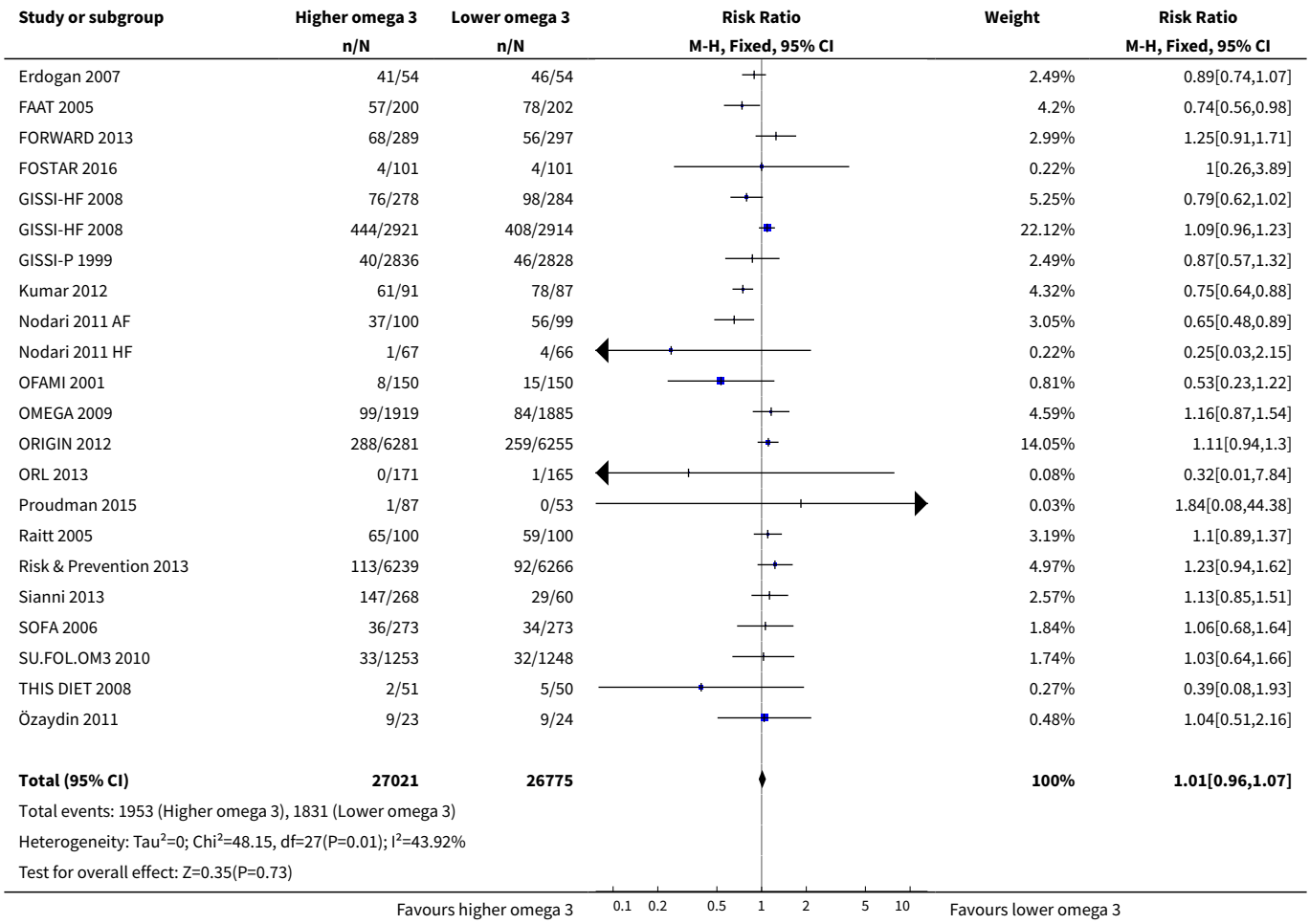
Favours higher omega 3 — Favours lower omega 3

Analysis 1.66. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 66 Arrhythmia- 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
AFFORD 2013	98/153	103/163		5.4%	1.01[0.86,1.2]
AlphaOmega - EPA+DHA 2010	67/2404	74/2433		3.98%	0.92[0.66,1.27]
Derosa 2016	1/128	3/130		0.16%	0.34[0.04,3.21]
DISAF 2003	154/201	157/206		8.4%	1.01[0.9,1.12]
EPIC-1 2008	1/188	0/186		0.03%	2.97[0.12,72.4]
EPOCH 2014	2/195	1/196		0.05%	2.01[0.18,21.99]

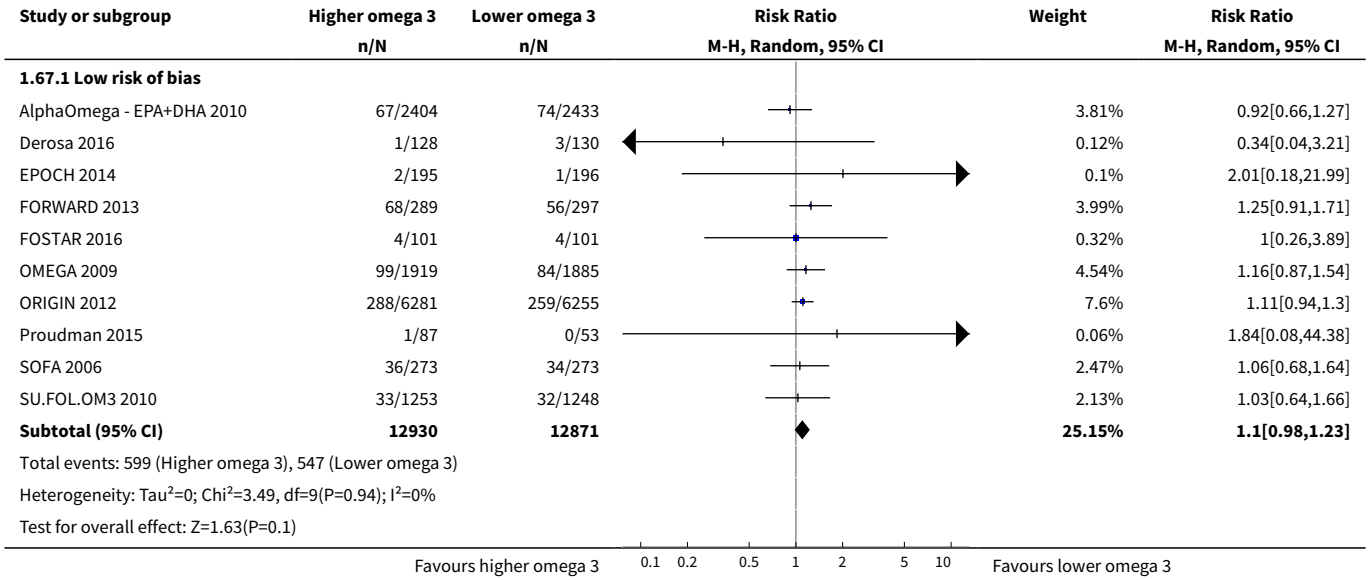


Favours higher omega 3 — Favours lower omega 3

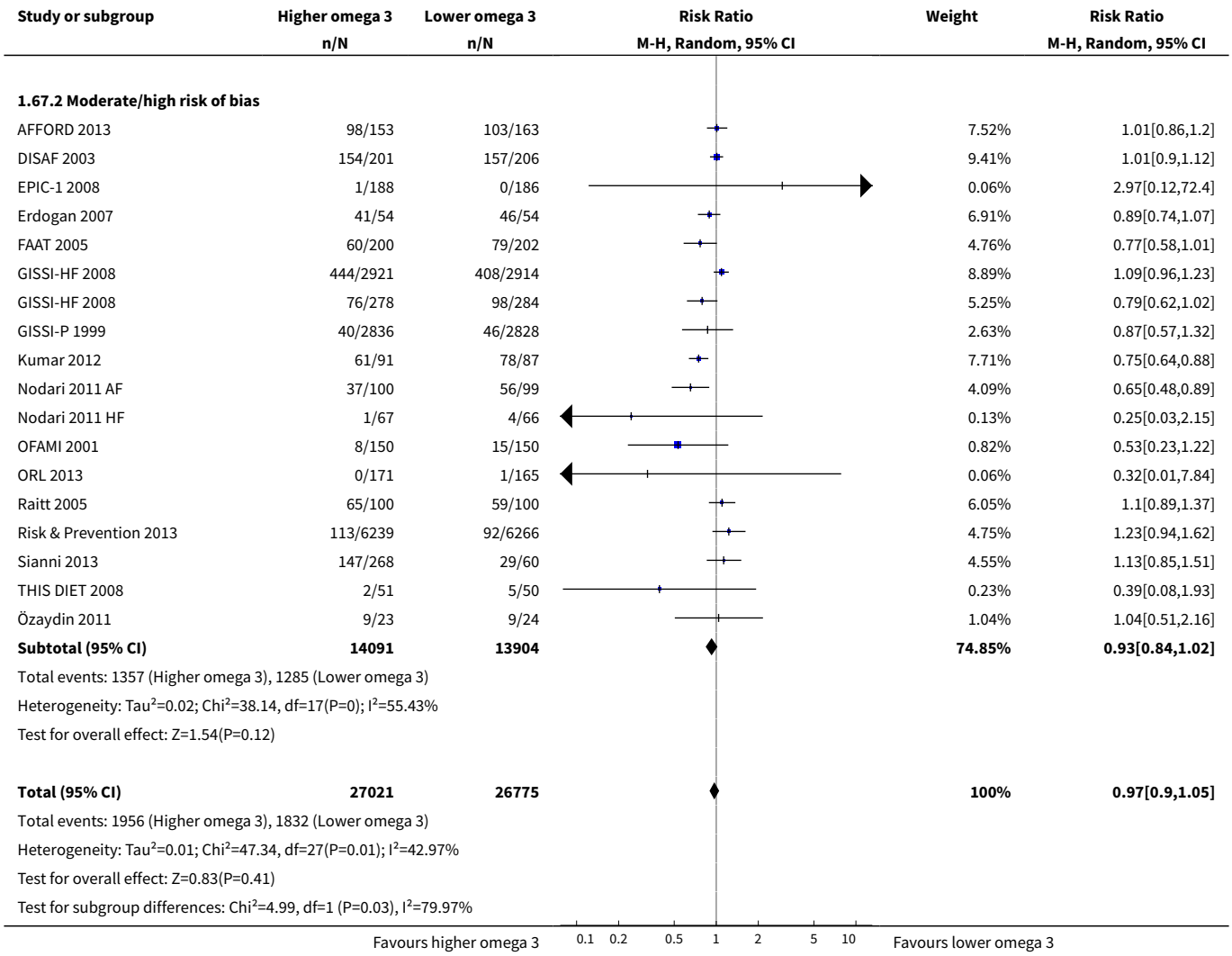


Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Erdogan 2007	41/54	46/54		2.49%	0.89[0.74,1.07]
FAAT 2005	57/200	78/202		4.2%	0.74[0.56,0.98]
FORWARD 2013	68/289	56/297		2.99%	1.25[0.91,1.71]
FOSTAR 2016	4/101	4/101		0.22%	1[0.26,3.89]
GISSI-HF 2008	76/278	98/284		5.25%	0.79[0.62,1.02]
GISSI-HF 2008	444/2921	408/2914		22.12%	1.09[0.96,1.23]
GISSI-P 1999	40/2836	46/2828		2.49%	0.87[0.57,1.32]
Kumar 2012	61/91	78/87		4.32%	0.75[0.64,0.88]
Nodari 2011 AF	37/100	56/99		3.05%	0.65[0.48,0.89]
Nodari 2011 HF	1/67	4/66		0.22%	0.25[0.03,2.15]
OFAMI 2001	8/150	15/150		0.81%	0.53[0.23,1.22]
OMEGA 2009	99/1919	84/1885		4.59%	1.16[0.87,1.54]
ORIGIN 2012	288/6281	259/6255		14.05%	1.11[0.94,1.3]
ORL 2013	0/171	1/165		0.08%	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		3.19%	1.1[0.89,1.37]
Risk & Prevention 2013	113/6239	92/6266		4.97%	1.23[0.94,1.62]
Sianni 2013	147/268	29/60		2.57%	1.13[0.85,1.51]
SOFA 2006	36/273	34/273		1.84%	1.06[0.68,1.64]
SU.FOL.OM3 2010	33/1253	32/1248		1.74%	1.03[0.64,1.66]
THIS DIET 2008	2/51	5/50		0.27%	0.39[0.08,1.93]
Özaydin 2011	9/23	9/24		0.48%	1.04[0.51,2.16]
Total (95% CI)	**27021**	**26775**		**100%**	**1.01[0.96,1.07]**
Total events: 1953 (Higher omega 3), 1831 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=48.15, df=27(P=0.01); I^2=43.92%					
Test for overall effect: Z=0.35(P=0.73)					

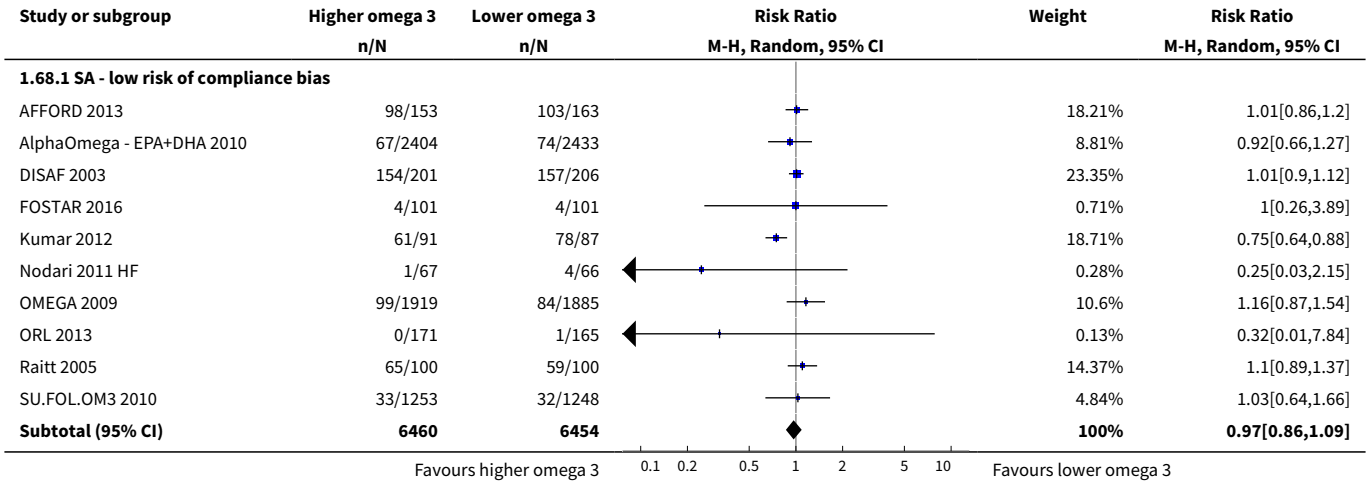
Analysis 1.67. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 67 Arrhythmia- LCn3 - SA by summary risk of bias.

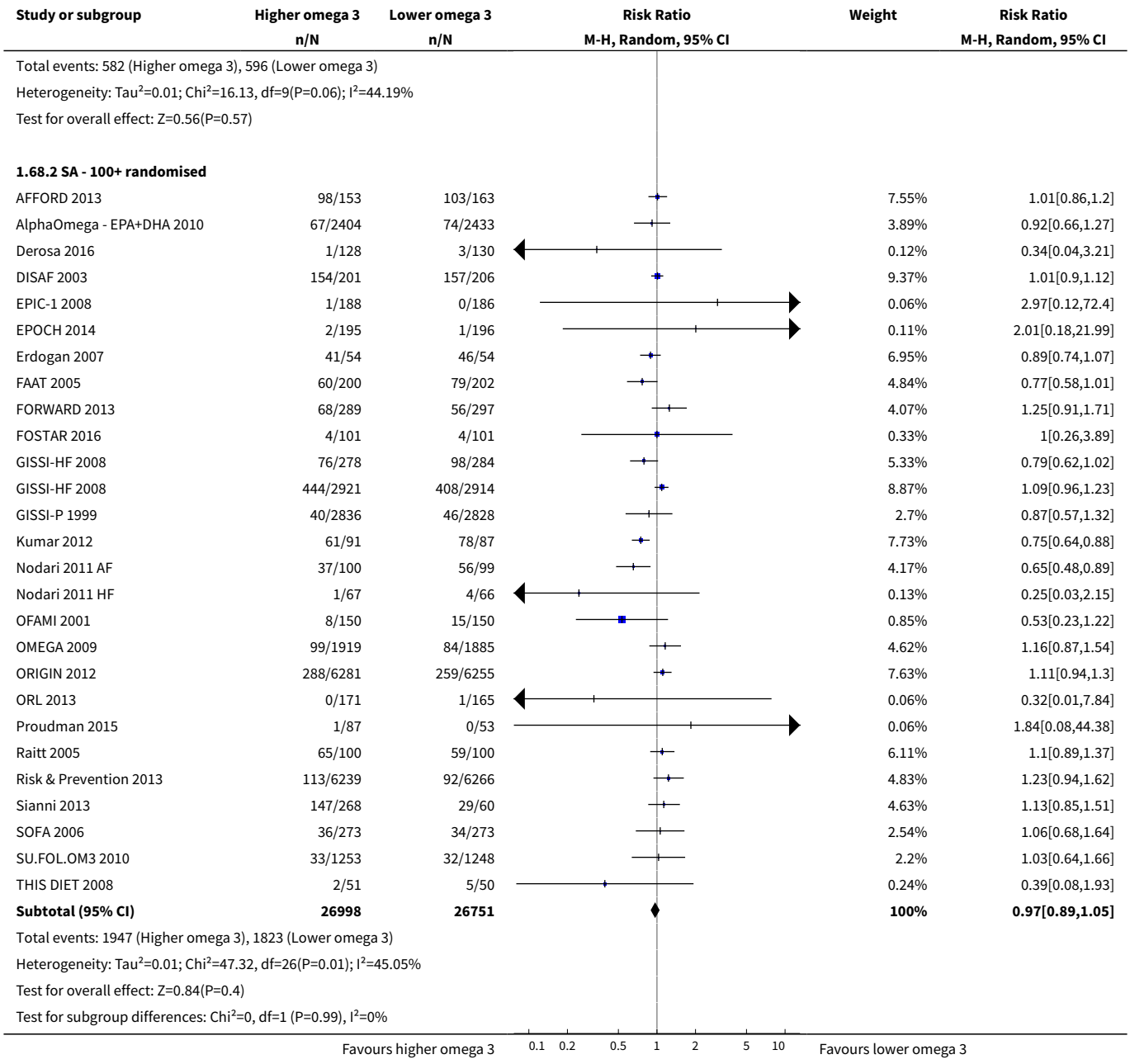


Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.67.1 Low risk of bias					
AlphaOmega - EPA+DHA 2010	67/2404	74/2433		3.81%	0.92[0.66,1.27]
Derosa 2016	1/128	3/130		0.12%	0.34[0.04,3.21]
EPOCH 2014	2/195	1/196		0.1%	2.01[0.18,21.99]
FORWARD 2013	68/289	56/297		3.99%	1.25[0.91,1.71]
FOSTAR 2016	4/101	4/101		0.32%	1[0.26,3.89]
OMEGA 2009	99/1919	84/1885		4.54%	1.16[0.87,1.54]
ORIGIN 2012	288/6281	259/6255		7.6%	1.11[0.94,1.3]
Proudman 2015	1/87	0/53		0.06%	1.84[0.08,44.38]
SOFA 2006	36/273	34/273		2.47%	1.06[0.68,1.64]
SU.FOL.OM3 2010	33/1253	32/1248		2.13%	1.03[0.64,1.66]
Subtotal (95% CI)	**12930**	**12871**		**25.15%**	**1.1[0.98,1.23]**
Total events: 599 (Higher omega 3), 547 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=3.49, df=9(P=0.94); I^2=0%					
Test for overall effect: Z=1.63(P=0.1)					

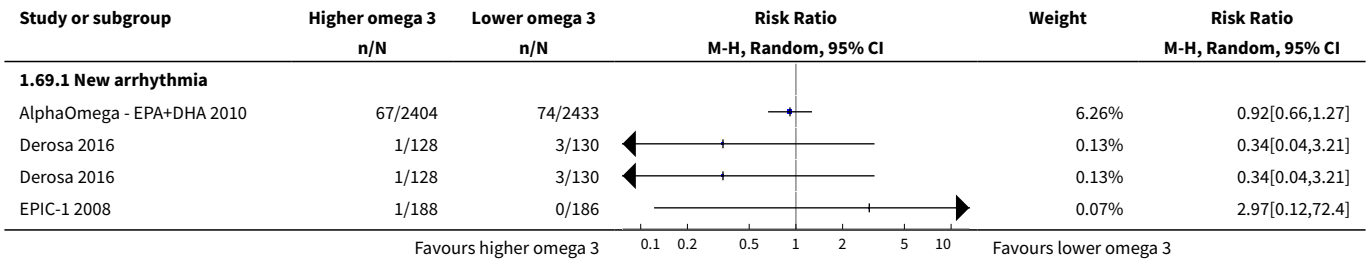


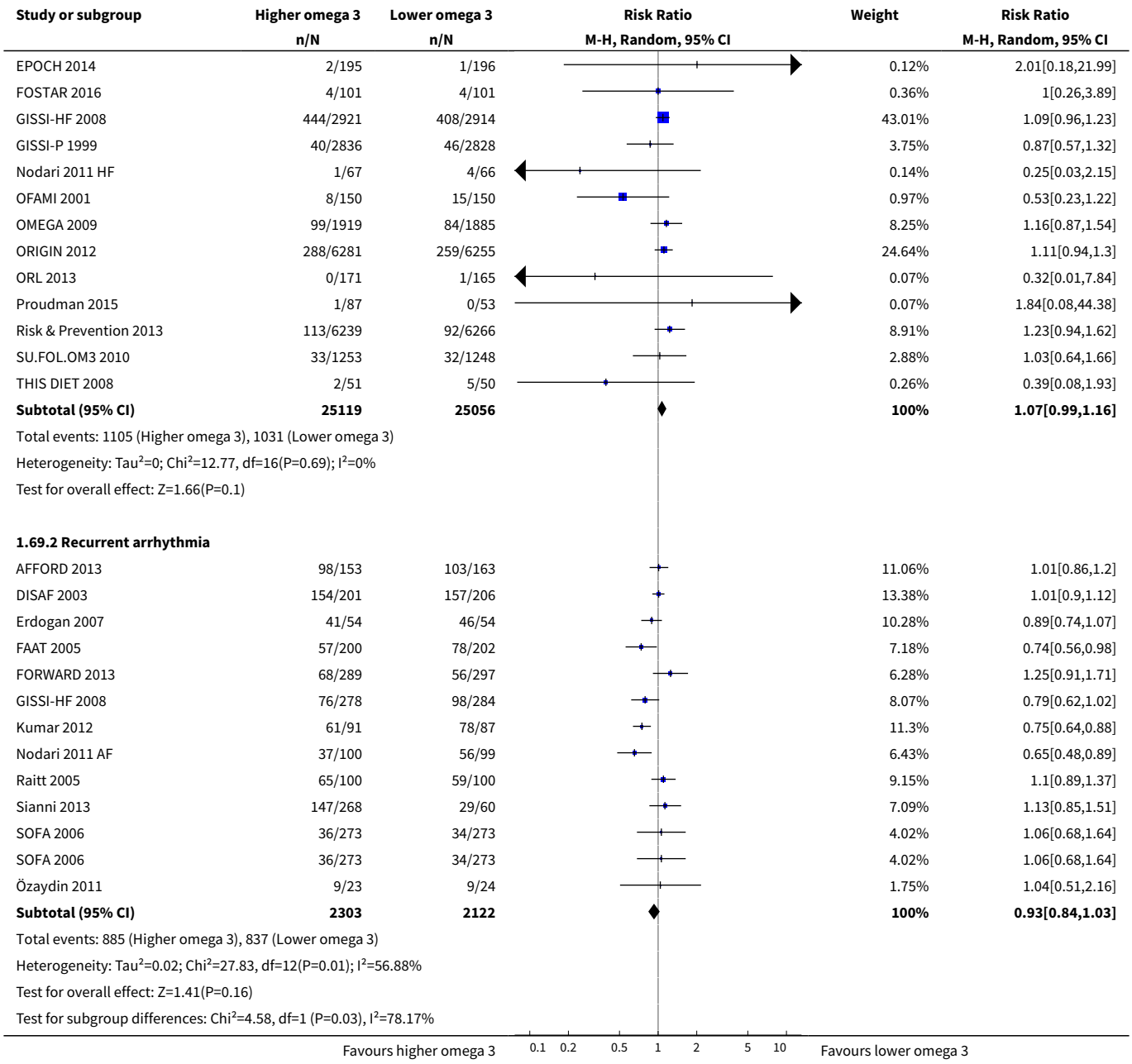
Analysis 1.68. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 68 Arrhythmia- LCn3 - SA by compliance and study size.





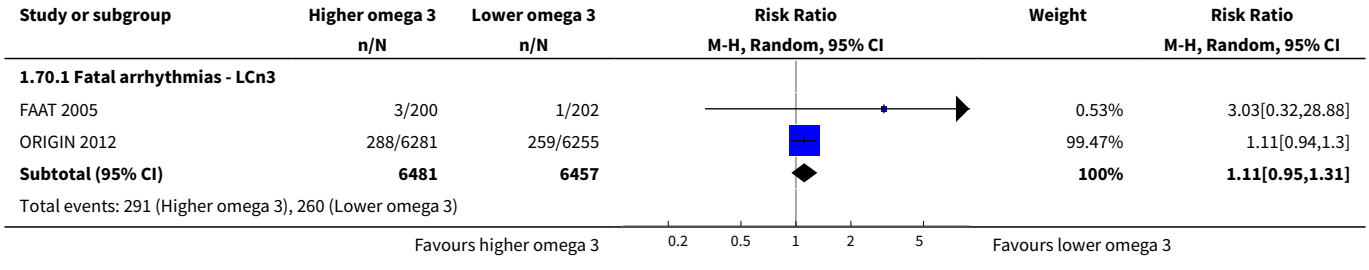
Analysis 1.69. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 69 Arrhythmia - LCn3 - subgroup by new or recurrent.



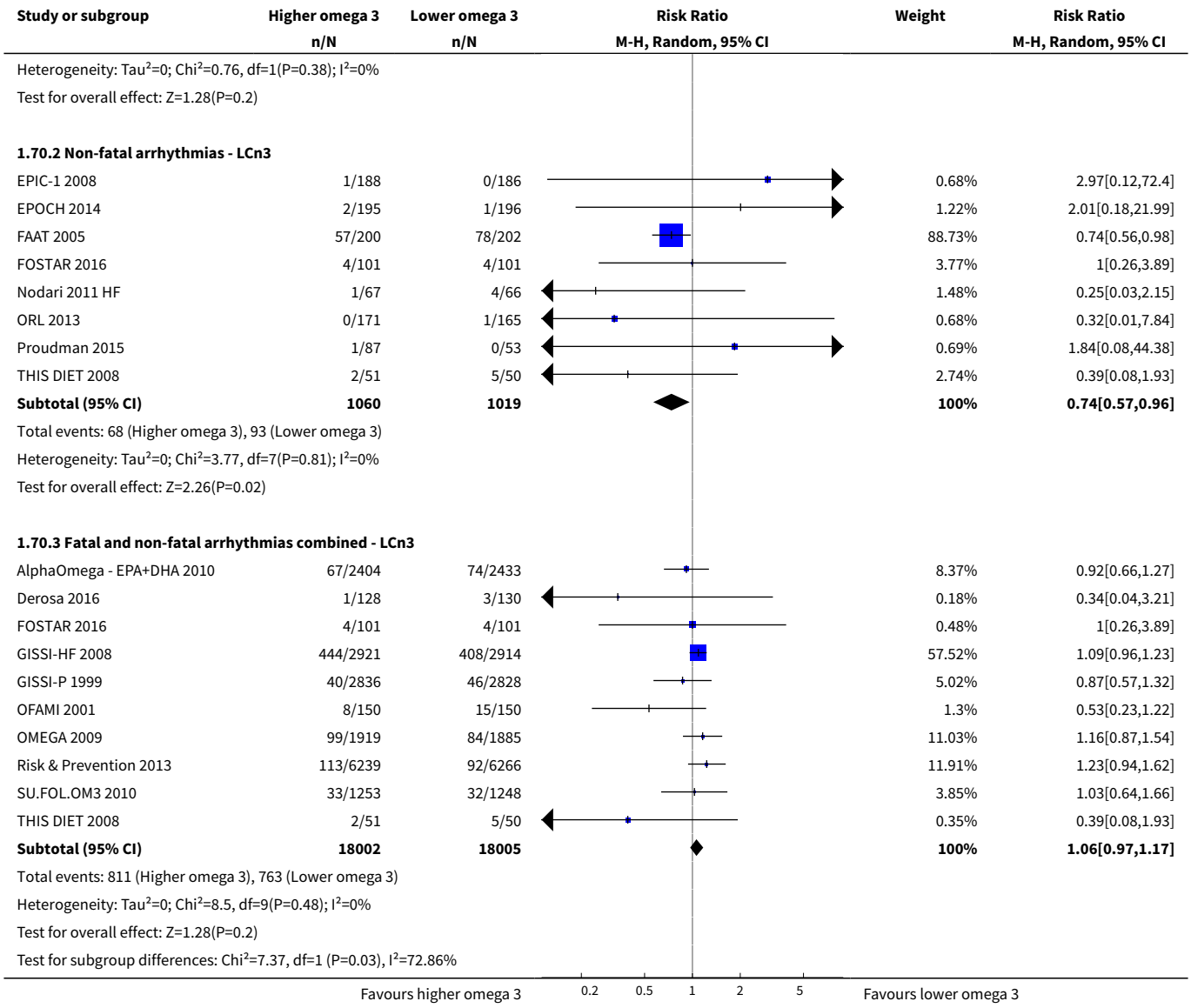


Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
EPOCH 2014	2/195	1/196		0.12%	2.01[0.18,21.99]
FOSTAR 2016	4/101	4/101		0.36%	1[0.26,3.89]
GISSI-HF 2008	444/2921	408/2914		43.01%	1.09[0.96,1.23]
GISSI-P 1999	40/2836	46/2828		3.75%	0.87[0.57,1.32]
Nodari 2011 HF	1/67	4/66		0.14%	0.25[0.03,2.15]
OFAMI 2001	8/150	15/150		0.97%	0.53[0.23,1.22]
OMEGA 2009	99/1919	84/1885		8.25%	1.16[0.87,1.54]
ORIGIN 2012	288/6281	259/6255		24.64%	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		0.07%	1.84[0.08,44.38]
Risk & Prevention 2013	113/6239	92/6266		8.91%	1.23[0.94,1.62]
SU.FOL.OM3 2010	33/1253	32/1248		2.88%	1.03[0.64,1.66]
THIS DIET 2008	2/51	5/50		0.26%	0.39[0.08,1.93]
Subtotal (95% CI)	**25119**	**25056**		**100%**	**1.07[0.99,1.16]**
Total events: 1105 (Higher omega 3), 1031 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=12.77, df=16(P=0.69); I^2=0%					
Test for overall effect: Z=1.66(P=0.1)					
1.69.2 Recurrent arrhythmia					
AFFORD 2013	98/153	103/163		11.06%	1.01[0.86,1.2]
DISAF 2003	154/201	157/206		13.38%	1.01[0.9,1.12]
Erdogan 2007	41/54	46/54		10.28%	0.89[0.74,1.07]
FAAT 2005	57/200	78/202		7.18%	0.74[0.56,0.98]
FORWARD 2013	68/289	56/297		6.28%	1.25[0.91,1.71]
GISSI-HF 2008	76/278	98/284		8.07%	0.79[0.62,1.02]
Kumar 2012	61/91	78/87		11.3%	0.75[0.64,0.88]
Nodari 2011 AF	37/100	56/99		6.43%	0.65[0.48,0.89]
Raitt 2005	65/100	59/100		9.15%	1.1[0.89,1.37]
Sianni 2013	147/268	29/60		7.09%	1.13[0.85,1.51]
SOFA 2006	36/273	34/273		4.02%	1.06[0.68,1.64]
SOFA 2006	36/273	34/273		4.02%	1.06[0.68,1.64]
Özaydin 2011	9/23	9/24		1.75%	1.04[0.51,2.16]
Subtotal (95% CI)	**2303**	**2122**		**100%**	**0.93[0.84,1.03]**
Total events: 885 (Higher omega 3), 837 (Lower omega 3)					
Heterogeneity: Tau^2=0.02; Chi^2=27.83, df=12(P=0.01); I^2=56.88%					
Test for overall effect: Z=1.41(P=0.16)					
Test for subgroup differences: Chi^2=4.58, df=1 (P=0.03), I^2=78.17%					

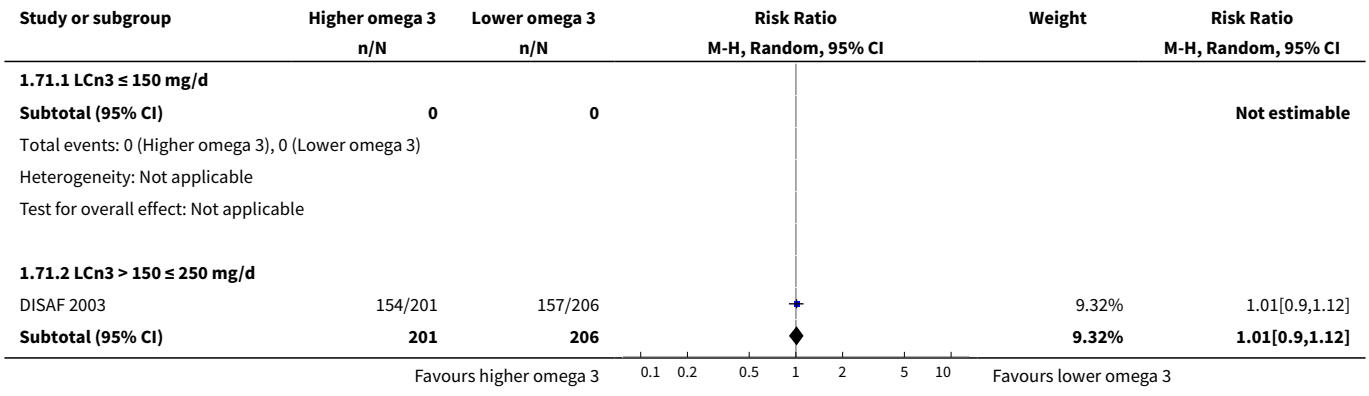
Analysis 1.70. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 70 Arrhythmia - LCn3 - subgroup by fatality.

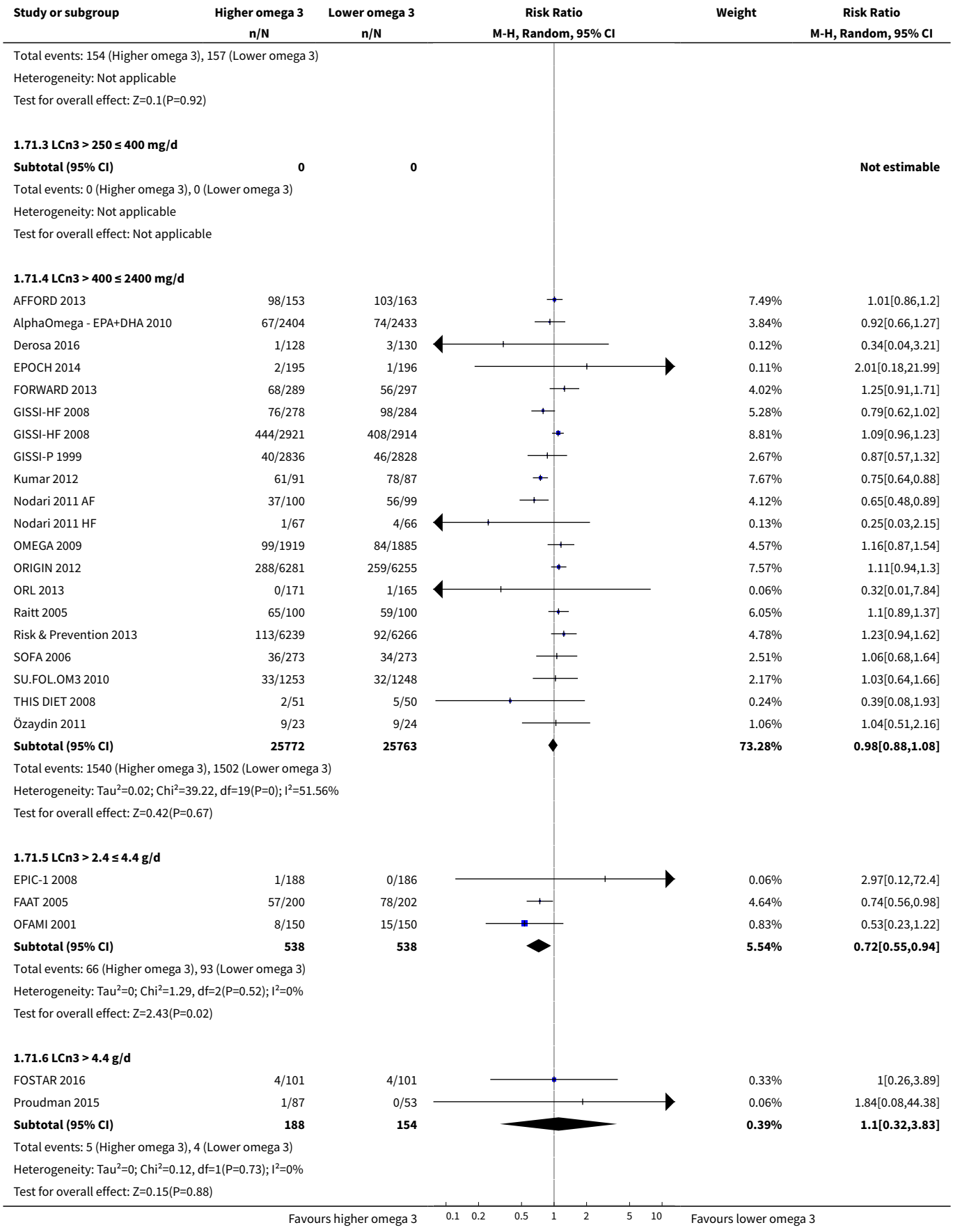


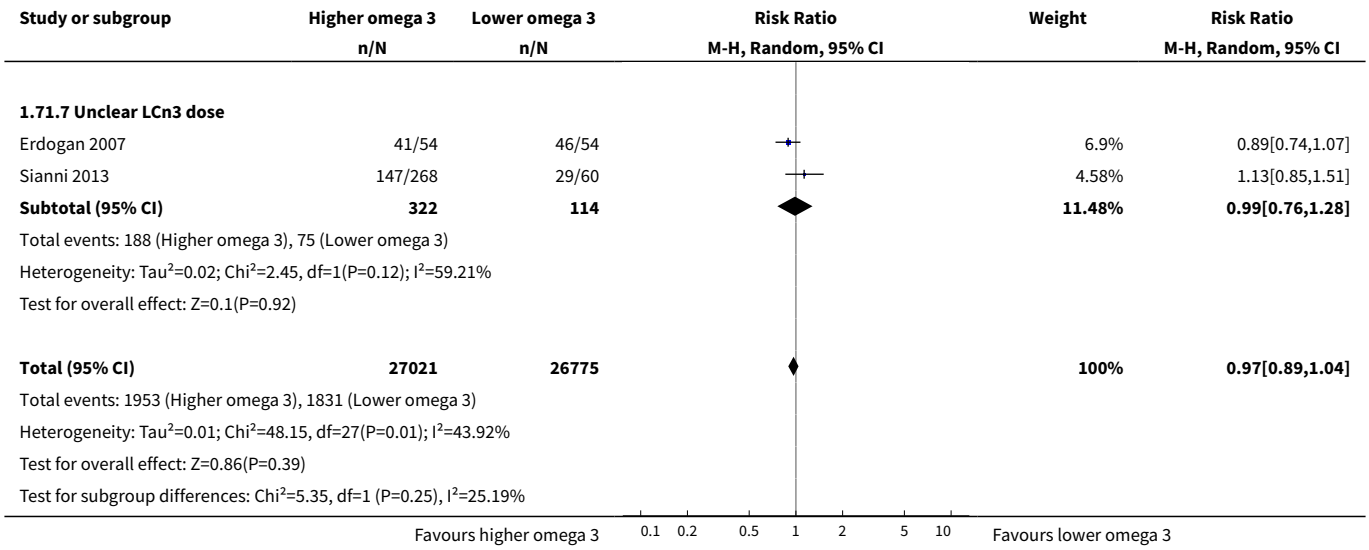
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.70.1 Fatal arrhythmias - LCn3					
FAAT 2005	3/200	1/202		0.53%	3.03[0.32,28.88]
ORIGIN 2012	288/6281	259/6255		99.47%	1.11[0.94,1.3]
Subtotal (95% CI)	**6481**	**6457**		**100%**	**1.11[0.95,1.31]**
Total events: 291 (Higher omega 3), 260 (Lower omega 3)					



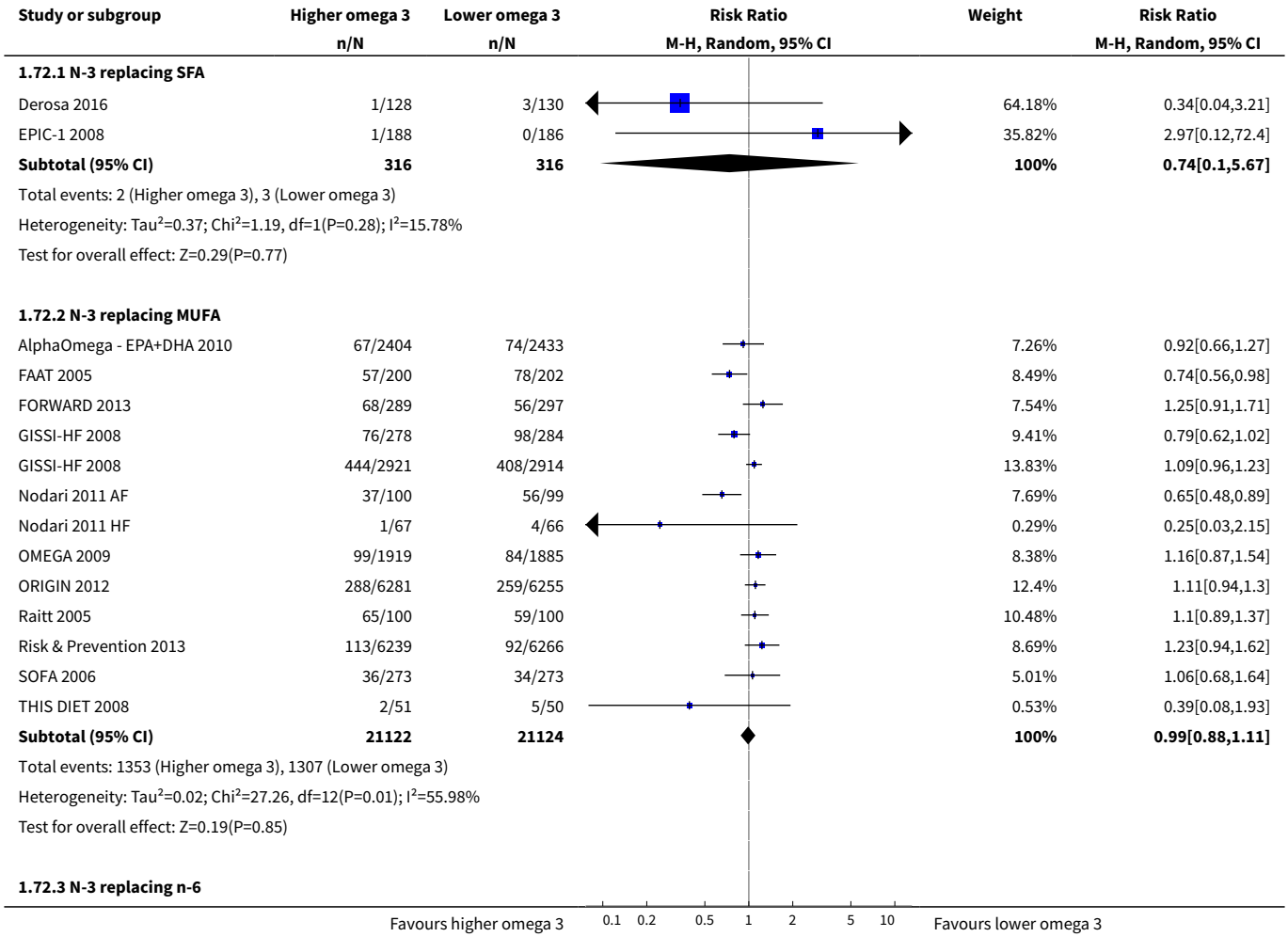
Analysis 1.71. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 71 Arrhythmia - LCn3 - subgroup by dose.

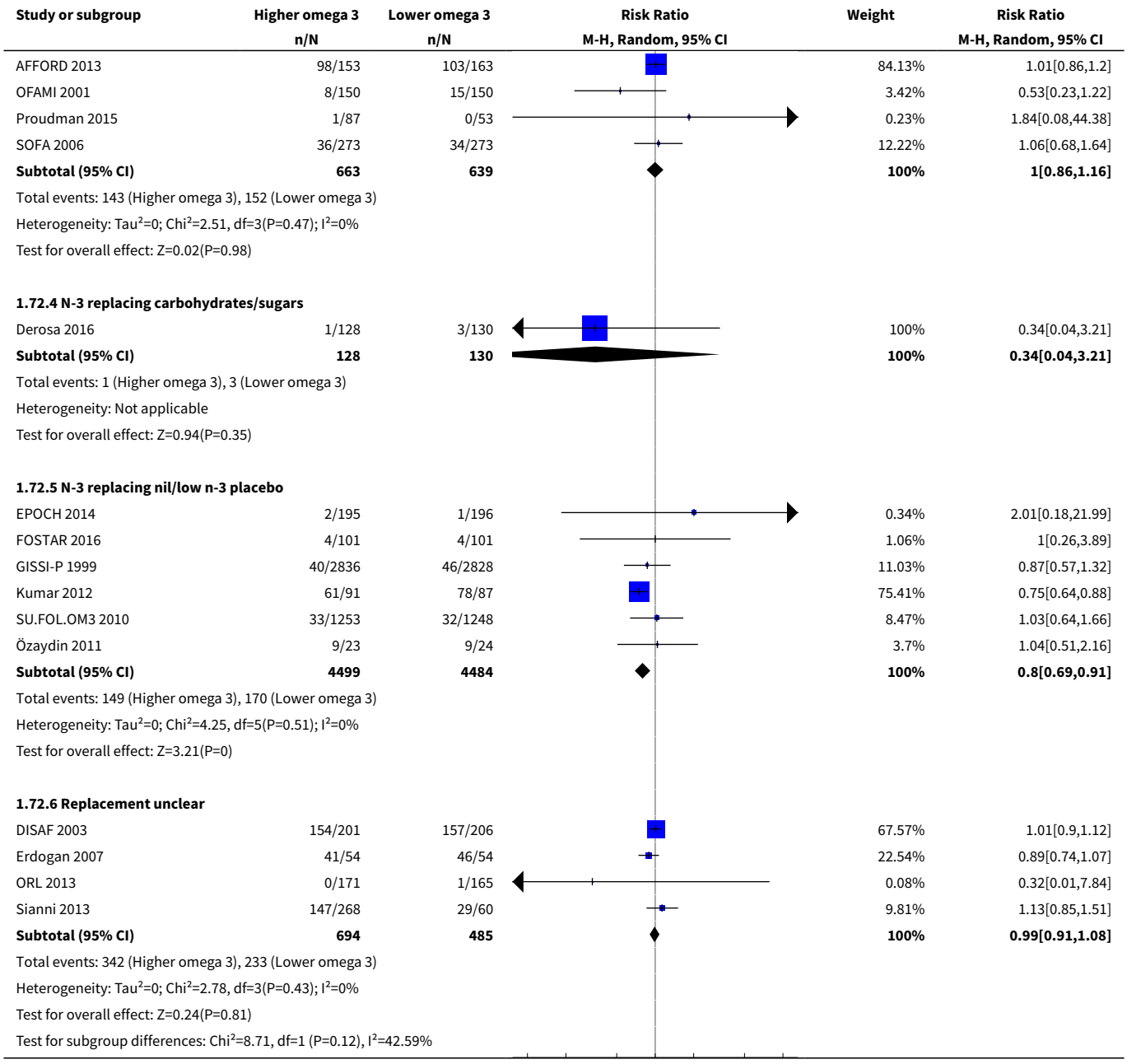






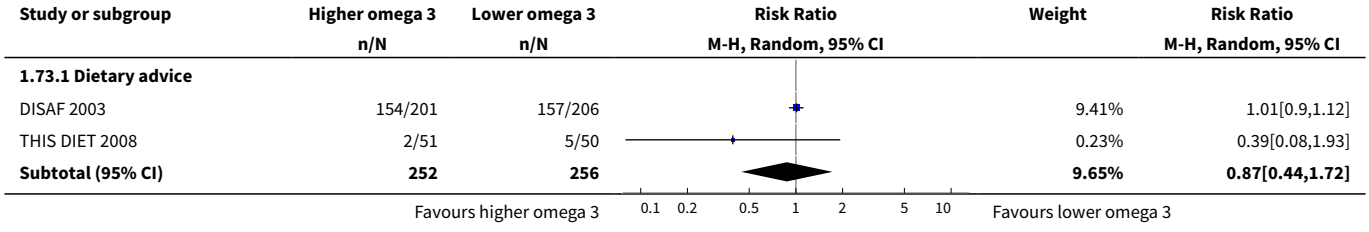
Analysis 1.72. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 72 Arrhythmia - LCn3 - subgroup by replacement.



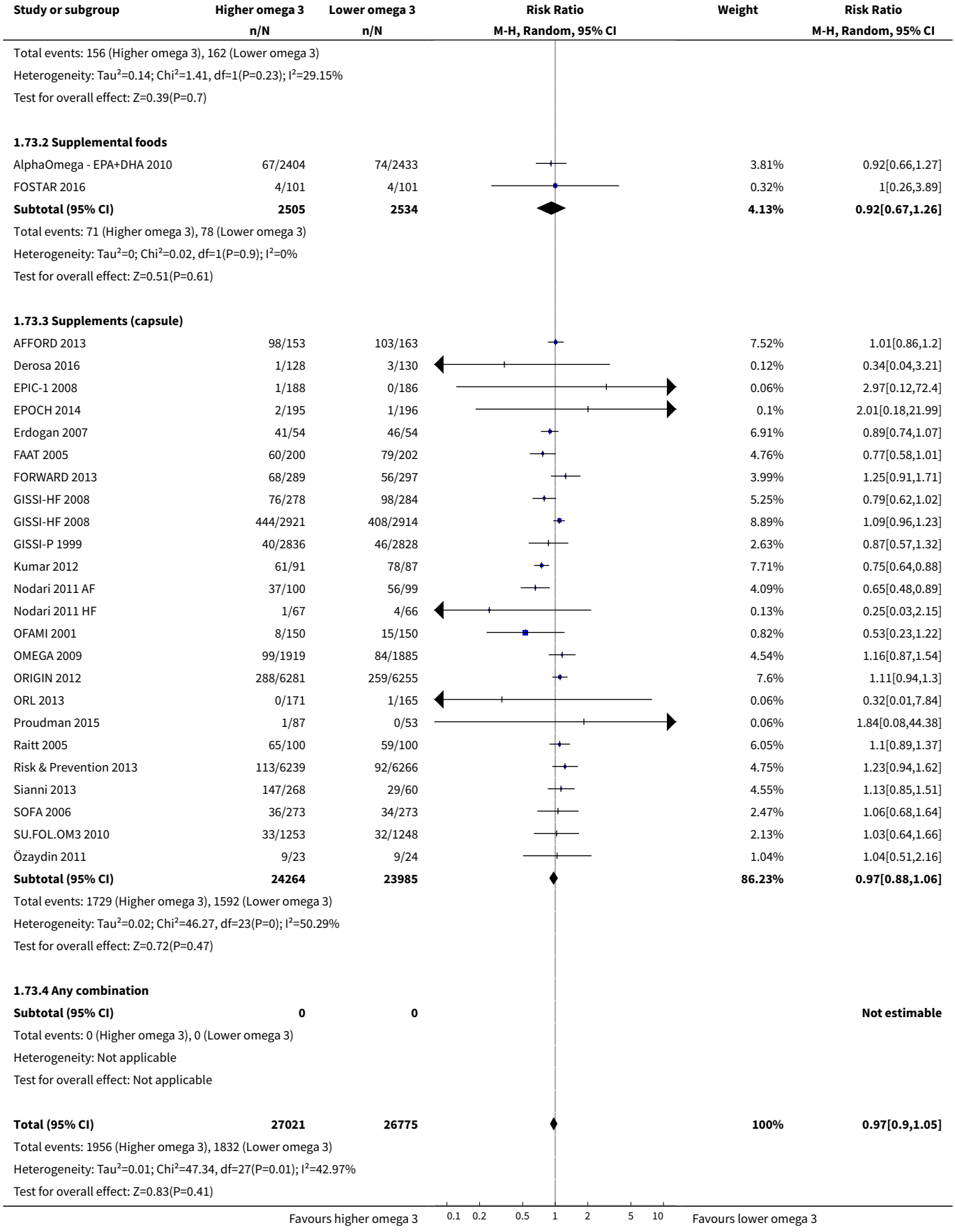


Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
AFFORD 2013	98/153	103/163		84.13%	1.01[0.86,1.2]
OFAMI 2001	8/150	15/150		3.42%	0.53[0.23,1.22]
Proudman 2015	1/87	0/53		0.23%	1.84[0.08,44.38]
SOFA 2006	36/273	34/273		12.22%	1.06[0.68,1.64]
Subtotal (95% CI)	**663**	**639**		**100%**	**1[0.86,1.16]**
Total events: 143 (Higher omega 3), 152 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=2.51, df=3(P=0.47); I²=0%					
Test for overall effect: Z=0.02(P=0.98)					
1.72.4 N-3 replacing carbohydrates/sugars					
Derosa 2016	1/128	3/130		100%	0.34[0.04,3.21]
Subtotal (95% CI)	**128**	**130**		**100%**	**0.34[0.04,3.21]**
Total events: 1 (Higher omega 3), 3 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.94(P=0.35)					
1.72.5 N-3 replacing nil/low n-3 placebo					
EPOCH 2014	2/195	1/196		0.34%	2.01[0.18,21.99]
FOSTAR 2016	4/101	4/101		1.06%	1[0.26,3.89]
GISSI-P 1999	40/2836	46/2828		11.03%	0.87[0.57,1.32]
Kumar 2012	61/91	78/87		75.41%	0.75[0.64,0.88]
SU.FOL.OM3 2010	33/1253	32/1248		8.47%	1.03[0.64,1.66]
Özaydin 2011	9/23	9/24		3.7%	1.04[0.51,2.16]
Subtotal (95% CI)	**4499**	**4484**		**100%**	**0.8[0.69,0.91]**
Total events: 149 (Higher omega 3), 170 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=4.25, df=5(P=0.51); I²=0%					
Test for overall effect: Z=3.21(P=0)					
1.72.6 Replacement unclear					
DISAF 2003	154/201	157/206		67.57%	1.01[0.9,1.12]
Erdogan 2007	41/54	46/54		22.54%	0.89[0.74,1.07]
ORL 2013	0/171	1/165		0.08%	0.32[0.01,7.84]
Sianni 2013	147/268	29/60		9.81%	1.13[0.85,1.51]
Subtotal (95% CI)	**694**	**485**		**100%**	**0.99[0.91,1.08]**
Total events: 342 (Higher omega 3), 233 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=2.78, df=3(P=0.43); I²=0%					
Test for overall effect: Z=0.24(P=0.81)					
Test for subgroup differences: Chi²=8.71, df=1 (P=0.12), I²=42.59%					

Analysis 1.73. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 73 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
1.73.1 Dietary advice					
DISAF 2003	154/201	157/206		9.41%	1.01[0.9,1.12]
THIS DIET 2008	2/51	5/50		0.23%	0.39[0.08,1.93]
Subtotal (95% CI)	**252**	**256**		**9.65%**	**0.87[0.44,1.72]**



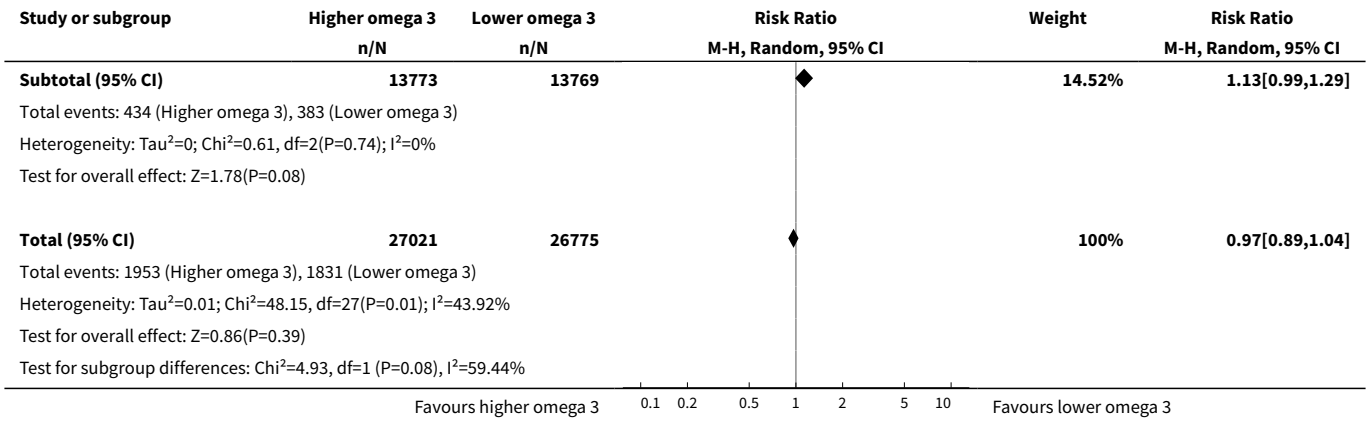
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for subgroup differences: Chi²=0.16, df=1 (P=0.92), I²=0%					

Favours higher omega 3 — 0.1 0.2 0.5 1 2 5 10 — Favours lower omega 3

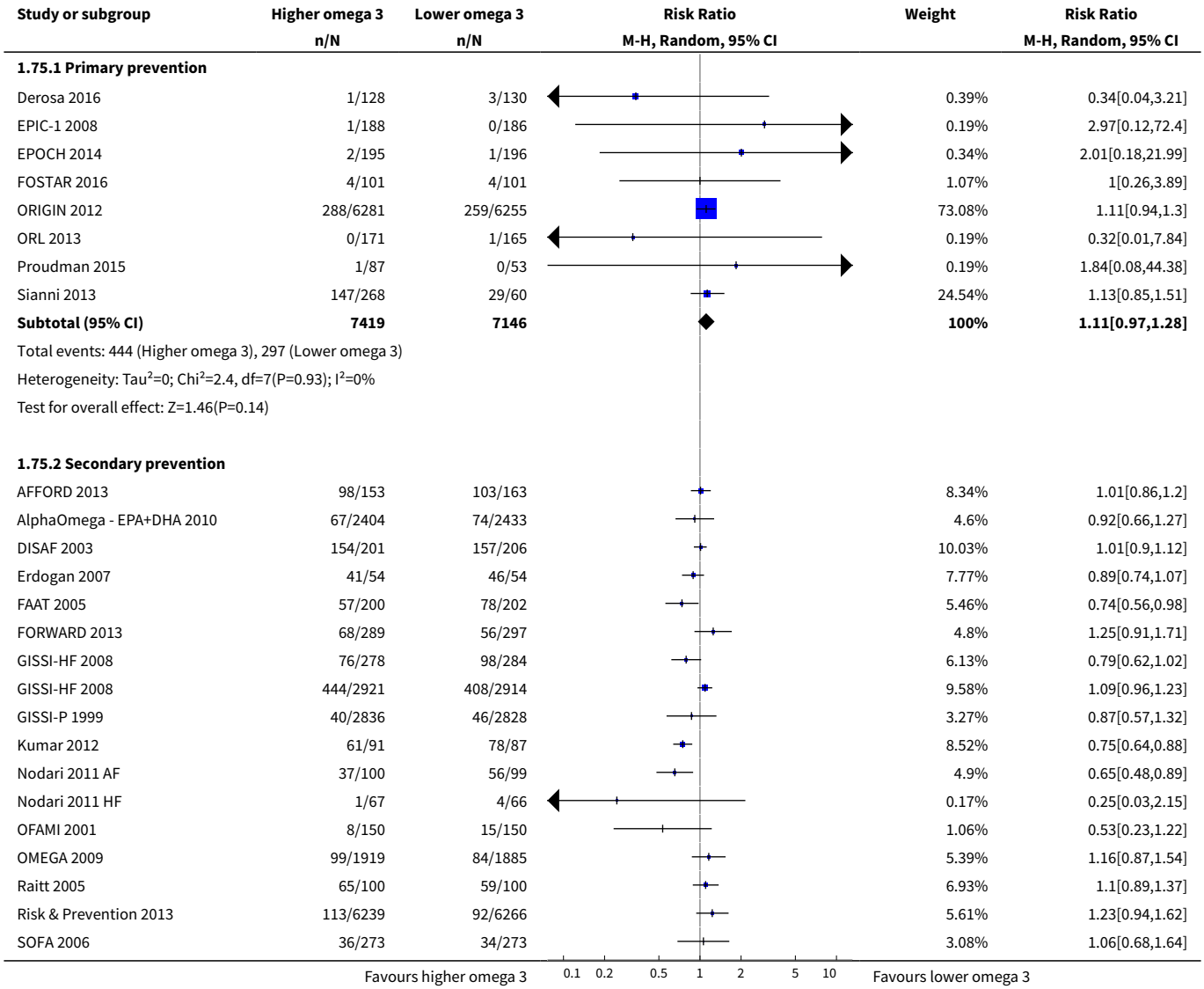
Analysis 1.74. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 74 Arrhythmia - LCn3 - subgroup by duration.

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
1.74.1 Medium duration 1 to < 2 years in study					
AFFORD 2013	98/153	103/163		7.49%	1.01[0.86,1.2]
Derosa 2016	1/128	3/130		0.12%	0.34[0.04,3.21]
DISAF 2003	154/201	157/206		9.32%	1.01[0.9,1.12]
EPIC-1 2008	1/188	0/186		0.06%	2.97[0.12,72.4]
EPOCH 2014	2/195	1/196		0.11%	2.01[0.18,21.99]
Erdogan 2007	41/54	46/54		6.9%	0.89[0.74,1.07]
FAAT 2005	57/200	78/202		4.64%	0.74[0.56,0.98]
FORWARD 2013	68/289	56/297		4.02%	1.25[0.91,1.71]
Kumar 2012	61/91	78/87		7.67%	0.75[0.64,0.88]
Nodari 2011 AF	37/100	56/99		4.12%	0.65[0.48,0.89]
Nodari 2011 HF	1/67	4/66		0.13%	0.25[0.03,2.15]
OMEGA 2009	99/1919	84/1885		4.57%	1.16[0.87,1.54]
ORL 2013	0/171	1/165		0.06%	0.32[0.01,7.84]
Proudman 2015	1/87	0/53		0.06%	1.84[0.08,44.38]
Sianni 2013	147/268	29/60		4.58%	1.13[0.85,1.51]
SOFA 2006	36/273	34/273		2.51%	1.06[0.68,1.64]
Özaydin 2011	9/23	9/24		1.06%	1.04[0.51,2.16]
Subtotal (95% CI)	**4407**	**4146**		**57.42%**	**0.93[0.84,1.04]**
Total events: 813 (Higher omega 3), 739 (Lower omega 3)					
Heterogeneity: Tau²=0.02; Chi²=30.04, df=16(P=0.02); I²=46.73%					
Test for overall effect: Z=1.21(P=0.23)					
1.74.2 Medium-long duration: 2 to < 4 years in study					
AlphaOmega - EPA+DHA 2010	67/2404	74/2433		3.84%	0.92[0.66,1.27]
FOSTAR 2016	4/101	4/101		0.33%	1[0.26,3.89]
GISSI-HF 2008	76/278	98/284		5.28%	0.79[0.62,1.02]
GISSI-HF 2008	444/2921	408/2914		8.81%	1.09[0.96,1.23]
GISSI-P 1999	40/2836	46/2828		2.67%	0.87[0.57,1.32]
OFAMI 2001	8/150	15/150		0.83%	0.53[0.23,1.22]
Raitt 2005	65/100	59/100		6.05%	1.1[0.89,1.37]
THIS DIET 2008	2/51	5/50		0.24%	0.39[0.08,1.93]
Subtotal (95% CI)	**8841**	**8860**		**28.06%**	**0.96[0.84,1.1]**
Total events: 706 (Higher omega 3), 709 (Lower omega 3)					
Heterogeneity: Tau²=0.01; Chi²=10.05, df=7(P=0.19); I²=30.38%					
Test for overall effect: Z=0.58(P=0.56)					
1.74.3 Long duration: ≥ 4 years in study					
ORIGIN 2012	288/6281	259/6255		7.57%	1.11[0.94,1.3]
Risk & Prevention 2013	113/6239	92/6266		4.78%	1.23[0.94,1.62]
SU.FOL.OM3 2010	33/1253	32/1248		2.17%	1.03[0.64,1.66]

Favours higher omega 3 — 0.1 0.2 0.5 1 2 5 10 — Favours lower omega 3



Analysis 1.75. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 75 Arrhythmia - LCn3 - subgroup by primary or secondary prevention3.



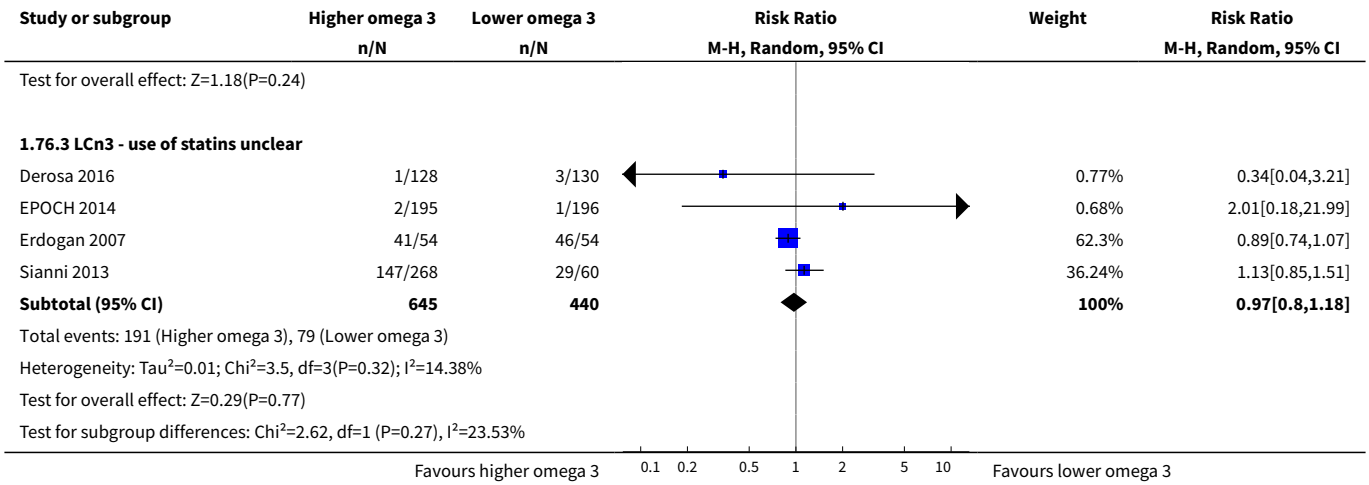
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
SU.FOL.OM3 2010	33/1253	32/1248		2.68%	1.03[0.64,1.66]
THIS DIET 2008	2/51	5/50		0.31%	0.39[0.08,1.93]
Özaydin 2011	9/23	9/24		1.35%	1.04[0.51,2.16]
Subtotal (95% CI)	**19602**	**19629**		**100%**	**0.95[0.86,1.03]**
Total events: 1509 (Higher omega 3), 1534 (Lower omega 3)					
Heterogeneity: Tau^2=0.02; Chi^2=41.83, df=19(P=0); I^2=54.57%					
Test for overall effect: Z=1.24(P=0.22)					
Test for subgroup differences: Chi^2=3.61, df=1 (P=0.06), I^2=72.27%					

Favours higher omega 3 — 0.1 0.2 0.5 1 2 5 10 — Favours lower omega 3

Analysis 1.76. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 76 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
1.76.1 LCn3 - ≥ 50% of control group on statins					
AlphaOmega - EPA+DHA 2010	67/2404	74/2433		14.8%	0.92[0.66,1.27]
OMEGA 2009	99/1919	84/1885		19.5%	1.16[0.87,1.54]
ORIGIN 2012	288/6281	259/6255		58.26%	1.11[0.94,1.3]
SU.FOL.OM3 2010	33/1253	32/1248		6.82%	1.03[0.64,1.66]
THIS DIET 2008	2/51	5/50		0.62%	0.39[0.08,1.93]
Subtotal (95% CI)	**11908**	**11871**		**100%**	**1.07[0.95,1.22]**
Total events: 489 (Higher omega 3), 454 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=2.89, df=4(P=0.58); I^2=0%					
Test for overall effect: Z=1.11(P=0.27)					
1.76.2 LCn3 - < 50% of control group on statins					
AFFORD 2013	98/153	103/163		10.31%	1.01[0.86,1.2]
DISAF 2003	154/201	157/206		12.22%	1.01[0.9,1.12]
EPIC-1 2008	1/188	0/186		0.1%	2.97[0.12,72.4]
FAAT 2005	57/200	78/202		6.92%	0.74[0.56,0.98]
FORWARD 2013	68/289	56/297		6.11%	1.25[0.91,1.71]
FOSTAR 2016	4/101	4/101		0.56%	1[0.26,3.89]
GISSI-HF 2008	444/2921	408/2914		11.71%	1.09[0.96,1.23]
GISSI-HF 2008	76/278	98/284		7.73%	0.79[0.62,1.02]
GISSI-P 1999	40/2836	46/2828		4.22%	0.87[0.57,1.32]
Kumar 2012	61/91	78/87		10.51%	0.75[0.64,0.88]
Nodari 2011 AF	37/100	56/99		6.24%	0.65[0.48,0.89]
Nodari 2011 HF	1/67	4/66		0.22%	0.25[0.03,2.15]
OFAMI 2001	8/150	15/150		1.4%	0.53[0.23,1.22]
ORL 2013	0/171	1/165		0.1%	0.32[0.01,7.84]
Proudman 2015	1/87	0/53		0.1%	1.84[0.08,44.38]
Raitt 2005	65/100	59/100		8.67%	1.1[0.89,1.37]
Risk & Prevention 2013	113/6239	92/6266		7.1%	1.23[0.94,1.62]
SOFA 2006	36/273	34/273		3.99%	1.06[0.68,1.64]
Özaydin 2011	9/23	9/24		1.77%	1.04[0.51,2.16]
Subtotal (95% CI)	**14468**	**14464**		**100%**	**0.94[0.85,1.04]**
Total events: 1273 (Higher omega 3), 1298 (Lower omega 3)					
Heterogeneity: Tau^2=0.02; Chi^2=38.89, df=18(P=0); I^2=53.72%					

Favours higher omega 3 — 0.1 0.2 0.5 1 2 5 10 — Favours lower omega 3



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	23	72159	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.88, 1.03]
3 Total MI - sensitivity analysis (SA) by summary risk of bias	23	72159	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.88, 1.03]
3.1 Low summary risk of bias	11	30025	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.92, 1.15]
3.2 Moderate to high risk of bias	12	42134	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.79, 0.99]
4 Total MI - LCn3 - SA by compliance and study size	23		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 SA - low risk of compliance bias	10	13002	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.79, 1.13]
4.2 SA - 100+ randomised	21	72015	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.88, 1.03]
5 Total MI - LCn3 - subgroup by fatality	23		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Fatal MI	15	60471	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.53, 1.10]
5.2 Non-fatal MI	21	70407	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.87, 1.06]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
6 Sudden cardiac death (overall) - LCn3	14	65004	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.80, 1.18]
7 Angina - LCn3	11	39907	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.91, 1.06]
8 Heart failure - LCn3	15	49644	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.85, 1.03]
8.1 Low summary risk of bias	6	24176	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.89, 1.06]
8.2 Moderate to high risk of bias	9	25468	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.57, 1.08]
9 Revascularisation - LCn3	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 CABG - LCn3	5	1535	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.15, 2.14]
9.2 Angioplasty - LCn3	4	3195	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.74, 1.24]
9.3 Any revascularisation - LCn3	12	66095	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.94, 1.03]
10 Peripheral arterial disease - LCn3	6	49035	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.74, 1.18]
11 PAD - LCn3 - SA by summary risk of bias	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Low summary risk of bias	2	12738	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.75, 1.62]
11.2 Moderate to high summary risk of bias	4	36297	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.64, 1.14]
12 PAD - LCn3 - SA compliance and study size	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 SA compliance	1	202	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.06, 15.77]
12.2 SA study size 100+	6	49035	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.74, 1.18]
13 Acute coronary syndrome - LCn3	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 LCn3	2	2703	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.71, 2.00]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14 Body weight, kg - LCn3	12	15812	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.84, 0.82]
15 Weight, kg - LCn3 - SA by summary risk of bias	12	15812	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.84, 0.82]
15.1 Low risk of bias	7	15458	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.91, 0.90]
15.2 Moderate/high risk of bias	5	354	Mean Difference (IV, Random, 95% CI)	-0.28 [-3.12, 2.55]
16 Weight, kg - LCn3 - SA by compliance and study size	10		Mean Difference (IV, Random, 95% CI)	Subtotals only
16.1 SA - low risk of compliance bias	7	828	Mean Difference (IV, Random, 95% CI)	0.58 [-0.52, 1.69]
16.2 SA - 100+ randomised	7	15545	Mean Difference (IV, Random, 95% CI)	0.07 [-0.84, 0.97]
17 Weight, kg - LCn3 - subgroup by dose	12		Mean Difference (IV, Random, 95% CI)	Subtotals only
17.1 LCn3 ≤ 150 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
17.2 LCn3 > 150 ≤ 250 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
17.3 LCn3 > 250 ≤ 400 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
17.4 LCn3 > 400 ≤ 2400 mg/d	8	15420	Mean Difference (IV, Random, 95% CI)	-0.29 [-1.16, 0.58]
17.5 LCn3 > 2.4 ≤ 4.4 g/d	3	241	Mean Difference (IV, Random, 95% CI)	0.07 [-6.38, 6.51]
17.6 LCn3 > 4.4 g/d	2	261	Mean Difference (IV, Random, 95% CI)	1.51 [0.28, 2.75]
18 Weight, kg - LCn3 - subgroup by replacement	12		Mean Difference (IV, Random, 95% CI)	Subtotals only
18.1 N-3 replacing SFA	2	433	Mean Difference (IV, Random, 95% CI)	-2.51 [-4.30, -0.72]
18.2 N-3 replacing MUFA	7	15088	Mean Difference (IV, Random, 95% CI)	0.23 [-0.28, 0.75]
18.3 N-3 replacing n-6	1	41	Mean Difference (IV, Random, 95% CI)	-1.3 [-3.83, 1.23]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
18.4 N-3 replacing carbs/sugars	1	258	Mean Difference (IV, Random, 95% CI)	-2.70 [-4.75, -0.65]
18.5 N-3 replacing nil/low n-3 placebo	1	202	Mean Difference (IV, Random, 95% CI)	1.5 [0.25, 2.75]
18.6 Replacement unclear	2	223	Mean Difference (IV, Random, 95% CI)	0.60 [-4.93, 6.13]
19 Weight, kg - LCn3 - subgroup by intervention type	12	15812	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.84, 0.82]
19.1 Dietary advice	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
19.2 Supplemental foods	1	202	Mean Difference (IV, Random, 95% CI)	1.5 [0.25, 2.75]
19.3 Supplement (capsule)	9	15538	Mean Difference (IV, Random, 95% CI)	-0.23 [-1.08, 0.63]
19.4 Any combination	2	72	Mean Difference (IV, Random, 95% CI)	-0.43 [-6.47, 5.61]
20 Weight, kg - LCn3 - subgroup by duration	12		Mean Difference (IV, Random, 95% CI)	Subtotals only
20.1 Medium duration 1 to < 2 years in study	8	840	Mean Difference (IV, Random, 95% CI)	-0.54 [-2.21, 1.12]
20.2 Medium-long duration: 2 to < 4 years in study	3	436	Mean Difference (IV, Random, 95% CI)	0.67 [-1.58, 2.91]
20.3 Long duration ≥ 4 years in study	1	14536	Mean Difference (IV, Random, 95% CI)	0.10 [-0.48, 0.68]
21 Weight, kg - LCn3 - subgroup by primary or secondary prevention	12		Mean Difference (IV, Random, 95% CI)	Subtotals only
21.1 Primary CVD prevention	10	15578	Mean Difference (IV, Random, 95% CI)	0.05 [-0.83, 0.92]
21.2 Secondary CVD prevention	2	234	Mean Difference (IV, Random, 95% CI)	-1.13 [-4.43, 2.16]
22 Weight, kg - LCn3 - subgroup by statin use	12		Mean Difference (IV, Random, 95% CI)	Subtotals only
22.1 LCn3 - ≥ 50% of control group on statins	2	14631	Mean Difference (IV, Random, 95% CI)	0.64 [-1.88, 3.17]
22.2 LCn3 - < 50% of control group on statins	5	614	Mean Difference (IV, Random, 95% CI)	0.47 [-0.66, 1.60]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
22.3 LCn3 - use of statins unclear	5	567	Mean Difference (IV, Random, 95% CI)	-1.51 [-3.30, 0.27]
23 Body mass index, kg/m^2 - LCn3	14	15234	Mean Difference (IV, Random, 95% CI)	0.04 [-0.16, 0.24]
24 BMI, kg/m^2- LCn3 - SA by summary risk of bias	14	15234	Mean Difference (IV, Random, 95% CI)	0.04 [-0.16, 0.24]
24.1 Low risk of bias	5	14190	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.36, 0.33]
24.2 Moderate/high risk of bias	9	1044	Mean Difference (IV, Random, 95% CI)	0.04 [-0.13, 0.20]
25 BMI, kg/m^2- LCn3 - SA by compliance and study size	10		Mean Difference (IV, Random, 95% CI)	Subtotals only
25.1 SA - low risk of compliance bias	5	1848	Mean Difference (IV, Random, 95% CI)	0.09 [-0.21, 0.38]
25.2 SA - 100+ randomised	9	14982	Mean Difference (IV, Random, 95% CI)	0.01 [-0.12, 0.14]
26 BMI, kg/m^2 - LCn3 - subgroup by dose	14		Mean Difference (IV, Random, 95% CI)	Subtotals only
26.1 LCn3 > 150 ≤ 250 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
26.2 LCn3 ≤ 150 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
26.3 LCn3 > 250 ≤ 400 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
26.4 LCn3 > 400 ≤ 2400 mg/d	11	14789	Mean Difference (IV, Random, 95% CI)	0.01 [-0.11, 0.13]
26.5 LCn3 > 2.4 ≤ 4.4 g/d	3	445	Mean Difference (IV, Random, 95% CI)	1.42 [-0.51, 3.35]
26.6 LCn3 > 4.4 g/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
27 BMI, kg/m^2 - LCn3 - subgroup by replace-ment	14		Mean Difference (IV, Random, 95% CI)	Subtotals only
27.1 N-3 replacing SFA	1	258	Mean Difference (IV, Random, 95% CI)	-0.60 [-1.14, -0.06]
27.2 N-3 replacing MUFA	7	14180	Mean Difference (IV, Random, 95% CI)	0.08 [-0.12, 0.28]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
27.3 N-3 replacing n-6	3	513	Mean Difference (IV, Random, 95% CI)	0.18 [-0.46, 0.81]
27.4 N-3 replacing carbs/sugars	1	258	Mean Difference (IV, Random, 95% CI)	-0.60 [-1.14, -0.06]
27.5 N-3 replacing nil/low n-3 placebo	1	60	Mean Difference (IV, Random, 95% CI)	1.0 [-1.18, 3.18]
27.6 Replacement unclear	2	223	Mean Difference (IV, Random, 95% CI)	0.58 [-1.17, 2.33]
28 BMI, kg/m² - LCn3 - subgroup by intervention type	14	15234	Mean Difference (IV, Random, 95% CI)	0.04 [-0.16, 0.24]
28.1 Dietary advice	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
28.2 Supplemental foods	1	1260	Mean Difference (IV, Random, 95% CI)	0.1 [-0.10, 0.30]
28.3 Supplement (capsule)	12	13929	Mean Difference (IV, Random, 95% CI)	0.01 [-0.25, 0.27]
28.4 Any combination	1	45	Mean Difference (IV, Random, 95% CI)	1.60 [-0.43, 3.63]
29 BMI, kg/m² - LCn3 - subgroup by duration	14		Mean Difference (IV, Random, 95% CI)	Subtotals only
29.1 Medium duration 1 to < 2 years in study	9	906	Mean Difference (IV, Random, 95% CI)	0.24 [-0.40, 0.88]
29.2 Medium-long duration: 2 to < 4 years in study	4	1792	Mean Difference (IV, Random, 95% CI)	0.12 [-0.07, 0.31]
29.3 Long duration ≥ 4 years in study	1	12536	Mean Difference (IV, Random, 95% CI)	0.0 [-0.20, 0.20]
30 BMI, kg/m² - LCn3 - subgroup by primary or secondary prevention	14		Mean Difference (IV, Random, 95% CI)	Subtotals only
30.1 Primary CVD prevention	11	13610	Mean Difference (IV, Random, 95% CI)	0.15 [-0.36, 0.66]
30.2 Secondary CVD prevention	3	1624	Mean Difference (IV, Random, 95% CI)	0.05 [-0.08, 0.18]
31 BMI, kg/m² - LCn3 - subgroup by statin use	14		Mean Difference (IV, Random, 95% CI)	Subtotals only
31.1 LCn3 - ≥ 50% of control group on statins	3	13891	Mean Difference (IV, Random, 95% CI)	0.13 [-0.22, 0.48]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
31.2 LCn3 - < 50% of control group on statins	4	665	Mean Difference (IV, Random, 95% CI)	0.02 [-0.15, 0.19]
31.3 LCn3 - use of statins unclear	7	678	Mean Difference (IV, Random, 95% CI)	0.06 [-0.86, 0.97]
32 Other measures of adiposity - LCn3	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
32.1 Percentage body fat	2	127	Mean Difference (IV, Random, 95% CI)	0.85 [-6.87, 8.57]
32.2 Percentage visceral fat	1	95	Mean Difference (IV, Random, 95% CI)	-1.80 [-15.03, 11.43]
32.3 Waist circumference, cm	3	676	Mean Difference (IV, Random, 95% CI)	0.66 [-0.09, 1.42]
32.4 Waist-hip ratio	1	100	Mean Difference (IV, Random, 95% CI)	0.0 [-0.01, 0.01]
32.5 Abdominal circumference, cm	1	256	Mean Difference (IV, Random, 95% CI)	-0.70 [-8.78, 7.38]
32.6 Hip circumference, cm	1	258	Mean Difference (IV, Random, 95% CI)	-2.40 [-9.80, 5.00]
33 Total cholesterol, serum, mmoL/L - LCn3	28	37281	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.05, 0.04]
34 TC, mmoL/L - LCn3 - SA by summary risk of bias	28	37281	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.05, 0.03]
34.1 Low risk of bias	9	14930	Mean Difference (IV, Random, 95% CI)	0.01 [-0.05, 0.06]
34.2 Moderate/high risk of bias	19	22351	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.09, 0.03]
35 TC, mmoL/L - LCn3 - SA by compliance and study size	20		Mean Difference (IV, Random, 95% CI)	Subtotals only
35.1 SA - low risk of compliance bias	14	3341	Mean Difference (IV, Random, 95% CI)	0.02 [-0.05, 0.09]
35.2 SA - 100+ randomised	15	36622	Mean Difference (IV, Random, 95% CI)	0.00 [-0.05, 0.06]
36 TC, mmoL/L - LCn3 - subgroup by dose	28		Mean Difference (IV, Random, 95% CI)	Subtotals only
36.1 LCn3 ≤ 150 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
36.2 LCn3 > 150 ≤ 250 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
36.3 LCn3 > 250 ≤ 400 mg/d	1	1715	Mean Difference (IV, Random, 95% CI)	0.10 [-0.01, 0.21]
36.4 LCn3 > 400 ≤ 2400 mg/d	18	34262	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.06, 0.00]
36.5 LCn3 > 2.4 ≤ 4.4 g/d	7	1216	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.28, -0.01]
36.6 LCn3 > 4.4 g/d	2	88	Mean Difference (IV, Random, 95% CI)	0.08 [-0.28, 0.45]
37 TC, mmoL/L - LCn3 - subgroup by replacement	28		Mean Difference (IV, Random, 95% CI)	Subtotals only
37.1 N-3 replacing SFA	3	2148	Mean Difference (IV, Random, 95% CI)	0.10 [-0.01, 0.20]
37.2 N-3 replacing MUFA	15	16504	Mean Difference (IV, Random, 95% CI)	0.01 [-0.04, 0.06]
37.3 N-3 replacing n-6	5	895	Mean Difference (IV, Random, 95% CI)	0.02 [-0.22, 0.26]
37.4 N-3 replacing carbs/sugars	1	258	Mean Difference (IV, Random, 95% CI)	-0.20 [-1.03, 0.63]
37.5 N-3 replacing nil/low n-3 placebo	5	19431	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.07, -0.03]
37.6 Replacement unclear	2	193	Mean Difference (IV, Random, 95% CI)	-0.15 [-0.47, 0.17]
38 TC, mmoL/L - LCn3 - subgroup by intervention type	28		Mean Difference (IV, Random, 95% CI)	Subtotals only
38.1 Dietary advice	1	1715	Mean Difference (IV, Random, 95% CI)	0.10 [-0.01, 0.21]
38.2 Supplemental foods	1	1210	Mean Difference (IV, Random, 95% CI)	0.02 [-0.09, 0.13]
38.3 Supplement (capsule)	24	34145	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.07, -0.03]
38.4 Any combination	2	211	Mean Difference (IV, Random, 95% CI)	0.13 [-0.10, 0.37]
39 TC, mmoL/L - LCn3 - subgroup by duration	28		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
39.1 Medium duration 1 to < 2 years in study	15	1661	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.16, 0.04]
39.2 Medium-long duration: 2 to < 4 years in study	10	4231	Mean Difference (IV, Random, 95% CI)	0.02 [-0.05, 0.10]
39.3 Long duration ≥ 4 years in study	3	31389	Mean Difference (IV, Random, 95% CI)	0.00 [-0.09, 0.09]
40 TC, mmoL/L - LCn3 - subgroup by primary or secondary prevention	28		Mean Difference (IV, Random, 95% CI)	Subtotals only
40.1 Primary prevention	17	32796	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.07, -0.02]
40.2 Secondary prevention	11	4485	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.09, 0.08]
41 TC, mmoL/L - LCn3 - subgroup by statin use	28		Mean Difference (IV, Random, 95% CI)	Subtotals only
41.1 LCn3 - ≥ 50% of control group on statins	6	32823	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.07, -0.02]
41.2 LCn3 - < 50% of control group on statins	15	3871	Mean Difference (IV, Random, 95% CI)	0.01 [-0.08, 0.10]
41.3 LCn3 - use of statins unclear	7	587	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.27, 0.22]
42 Triglycerides, fasting, serum, mmoL/L - LCn3	25	35579	Mean Difference (IV, Random, 95% CI)	-0.24 [-0.31, -0.16]
43 TG, fasting, mmoL/L - LCn3 - SA by summary risk of bias	25	35579	Mean Difference (IV, Random, 95% CI)	-0.23 [-0.30, -0.16]
43.1 Low risk of bias	8	14654	Mean Difference (IV, Random, 95% CI)	-0.17 [-0.25, -0.09]
43.2 Moderate/high risk of bias	17	20925	Mean Difference (IV, Random, 95% CI)	-0.25 [-0.35, -0.15]
44 TG, fasting, mmoL/L - LCn3 - SA by compliance and study size	19		Mean Difference (IV, Random, 95% CI)	Subtotals only
44.1 SA - low risk of compliance bias	12	3306	Mean Difference (IV, Random, 95% CI)	-0.26 [-0.36, -0.16]
44.2 SA - 100+ randomised	18	35197	Mean Difference (IV, Random, 95% CI)	-0.24 [-0.32, -0.16]
45 TG, fasting, mmoL/L - LCn3 - subgroup by dose	25		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
45.1 LCn3 ≤ 150 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
45.2 LCn3 > 150 ≤ 250 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
45.3 LCn3 > 250 ≤ 400 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
45.4 LCn3 > 400 ≤ 2400 mg/d	18	34388	Mean Difference (IV, Random, 95% CI)	-0.18 [-0.25, -0.11]
45.5 LCn3 > 2.4 ≤ 4.4 g/d	5	1107	Mean Difference (IV, Random, 95% CI)	-0.36 [-0.53, -0.20]
45.6 LCn3 > 4.4 g/d	2	84	Mean Difference (IV, Random, 95% CI)	-0.41 [-0.68, -0.14]
46 TG, fasting, mmoL/L - LCn3 - subgroup by replacement	25		Mean Difference (IV, Random, 95% CI)	Subtotals only
46.1 N-3 replacing SFA	2	429	Mean Difference (IV, Random, 95% CI)	-0.27 [-0.59, 0.04]
46.2 N-3 replacing MUFA	13	14634	Mean Difference (IV, Random, 95% CI)	-0.18 [-0.25, -0.10]
46.3 N-3 replacing n-6	5	876	Mean Difference (IV, Random, 95% CI)	-0.27 [-0.45, -0.08]
46.4 N-3 replacing carbs/sugars	1	258	Mean Difference (IV, Random, 95% CI)	-0.5 [-1.49, 0.49]
46.5 N-3 replacing nil/low n-3 placebo	4	19357	Mean Difference (IV, Random, 95% CI)	-0.18 [-0.51, 0.14]
46.6 Replacement unclear	2	454	Mean Difference (IV, Random, 95% CI)	-0.38 [-0.57, -0.19]
47 TG, fasting, mmoL/L - LCn3 - subgroup by intervention type	25		Mean Difference (IV, Random, 95% CI)	Subtotals only
47.1 Dietary advice	1	71	Mean Difference (IV, Random, 95% CI)	0.02 [-0.36, 0.40]
47.2 Supplemental foods	1	1210	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.15, 0.09]
47.3 Supplement (capsule)	22	34137	Mean Difference (IV, Random, 95% CI)	-0.19 [-0.38, -0.00]
47.4 Any combination	1	161	Mean Difference (IV, Random, 95% CI)	0.01 [-0.28, 0.30]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
48 TG, fasting, mmoL/L - LCn3 - subgroup by duration	25		Mean Difference (IV, Random, 95% CI)	Subtotals only
48.1 Medium duration 1 to < 2 years in study	13	1880	Mean Difference (IV, Random, 95% CI)	-0.27 [-0.36, -0.19]
48.2 Medium-long duration: 2 to < 4 years in study	9	2310	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.31, -0.02]
48.3 Long duration ≥ 4 years in study	3	31389	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.32, -0.07]
49 TG, fasting, mmoL/L - LCn3 - subgroup by primary or secondary prevention	25		Mean Difference (IV, Random, 95% CI)	Subtotals only
49.1 Primary prevention	17	33114	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.26, -0.14]
49.2 Secondary prevention	8	2465	Mean Difference (IV, Random, 95% CI)	-0.27 [-0.44, -0.10]
50 TG, fasting, mmoL/L - LCn3 - subgroup by statin use	25		Mean Difference (IV, Random, 95% CI)	Subtotals only
50.1 LCn3 - ≥ 50% of control group on statins	5	32557	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.21, -0.01]
50.2 LCn3 - < 50% of control group on statins	14	2414	Mean Difference (IV, Random, 95% CI)	-0.27 [-0.36, -0.18]
50.3 LCn3 - use of statins unclear	6	608	Mean Difference (IV, Random, 95% CI)	-0.23 [-0.38, -0.08]
51 High-density lipoprotein, serum, mmoL/L - LCn3	27	37237	Mean Difference (IV, Random, 95% CI)	0.02 [0.00, 0.04]
52 HDL, mmoL/L - LCn3 - SA by summary risk of bias	27	37237	Mean Difference (IV, Random, 95% CI)	0.03 [0.01, 0.05]
52.1 Low risk of bias	8	14892	Mean Difference (IV, Random, 95% CI)	0.03 [-0.01, 0.07]
52.2 Moderate/high risk of bias	19	22345	Mean Difference (IV, Random, 95% CI)	0.03 [0.00, 0.06]
53 HDL, mmoL/L - LCn3 - SA by compliance and study size	20		Mean Difference (IV, Random, 95% CI)	Subtotals only
53.1 SA - low risk of compliance bias	13	3202	Mean Difference (IV, Random, 95% CI)	0.05 [0.01, 0.10]
53.2 SA - 100+ randomised	15	36573	Mean Difference (IV, Random, 95% CI)	0.03 [0.00, 0.05]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
54 HDL, mmoL/L - LCn3 - subgroup by dose	27		Mean Difference (IV, Random, 95% CI)	Subtotals only
54.1 LCn3 ≤ 150 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
54.2 LCn3 > 150 ≤ 250 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
54.3 LCn3 > 250 ≤ 400 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
54.4 LCn3 > 400 ≤ 2400 mg/d	19	35972	Mean Difference (IV, Random, 95% CI)	0.02 [-0.00, 0.04]
54.5 LCn3 > 2.4 ≤ 4.4 g/d	7	1206	Mean Difference (IV, Random, 95% CI)	0.06 [0.00, 0.12]
54.6 LCn3 > 4.4 g/d	1	59	Mean Difference (IV, Random, 95% CI)	0.0 [-0.16, 0.16]
55 HDL, mmoL/L - LCn3 - subgroup by replacement	27		Mean Difference (IV, Random, 95% CI)	Subtotals only
55.1 N-3 replacing SFA	3	2143	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.10, 0.07]
55.2 N-3 replacing MUFA	15	16505	Mean Difference (IV, Random, 95% CI)	0.02 [-0.01, 0.06]
55.3 N-3 replacing n-6	4	850	Mean Difference (IV, Random, 95% CI)	0.04 [-0.01, 0.09]
55.4 N-3 replacing carbs/sugars	1	258	Mean Difference (IV, Random, 95% CI)	0.10 [-0.17, 0.37]
55.5 N-3 replacing nil/low n-3 placebo	5	19431	Mean Difference (IV, Random, 95% CI)	0.04 [-0.03, 0.11]
55.6 Replacement unclear	2	193	Mean Difference (IV, Random, 95% CI)	0.05 [-0.10, 0.20]
56 HDL, mmoL/L - LCn3 - subgroup by intervention type	27		Mean Difference (IV, Random, 95% CI)	Subtotals only
56.1 Dietary advice	2	1785	Mean Difference (IV, Random, 95% CI)	0.01 [-0.02, 0.04]
56.2 Supplemental foods	1	1210	Mean Difference (IV, Random, 95% CI)	0.03 [0.00, 0.06]
56.3 Supplement (capsule)	21	34008	Mean Difference (IV, Random, 95% CI)	0.03 [0.00, 0.06]

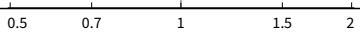
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
56.4 Any combination	3	234	Mean Difference (IV, Random, 95% CI)	0.10 [-0.10, 0.31]
57 HDL, mmoL/L - LCn3 - subgroup by duration	27		Mean Difference (IV, Random, 95% CI)	Subtotals only
57.1 Medium duration 1 to < 2 years in study	13	1562	Mean Difference (IV, Random, 95% CI)	0.08 [0.01, 0.14]
57.2 Medium-long duration: 2 to < 4 years in study	11	4286	Mean Difference (IV, Random, 95% CI)	0.02 [-0.01, 0.04]
57.3 Long duration ≥ 4 years in study	3	31389	Mean Difference (IV, Random, 95% CI)	0.00 [-0.01, 0.01]
58 HDL, mmoL/L - LCn3 - subgroup by primary or secondary prevention	26		Mean Difference (IV, Random, 95% CI)	Subtotals only
58.1 Primary prevention	17	32856	Mean Difference (IV, Random, 95% CI)	0.03 [-0.00, 0.05]
58.2 Secondary prevention	9	4307	Mean Difference (IV, Random, 95% CI)	0.03 [-0.01, 0.07]
59 HDL, mmoL/L - LCn3 - subgroup by statin use	27		Mean Difference (IV, Random, 95% CI)	Subtotals only
59.1 LCn3 - ≥ 50% of control group on statins	7	32894	Mean Difference (IV, Random, 95% CI)	0.01 [-0.01, 0.03]
59.2 LCn3 - < 50% of control group on statins	13	3690	Mean Difference (IV, Random, 95% CI)	0.04 [-0.00, 0.08]
59.3 LCn3 - use of statins unclear	7	653	Mean Difference (IV, Random, 95% CI)	0.07 [-0.07, 0.21]
60 Low-density lipoprotein, serum, mmoL/L - LCn3	23	35035	Mean Difference (IV, Random, 95% CI)	0.01 [-0.01, 0.03]
61 LDL, mmoL/L - LCn3 - SA by summary risk of bias	23	35035	Mean Difference (IV, Random, 95% CI)	0.01 [-0.01, 0.03]
61.1 Low risk of bias	9	14840	Mean Difference (IV, Random, 95% CI)	0.02 [-0.03, 0.07]
61.2 Moderate/high risk of bias	14	20195	Mean Difference (IV, Random, 95% CI)	0.00 [-0.02, 0.03]
62 LDL, mmoL/L - LCn3 - SA by compliance and study size	17	37718	Mean Difference (IV, Random, 95% CI)	0.02 [-0.01, 0.05]
62.1 SA - low risk of compliance bias	13	3165	Mean Difference (IV, Random, 95% CI)	0.05 [-0.02, 0.11]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
62.2 SA - 100+ randomised	14	34553	Mean Difference (IV, Random, 95% CI)	0.01 [-0.02, 0.04]
63 LDL, mmoL/L - LCn3 - subgroup by dose	23		Mean Difference (IV, Random, 95% CI)	Subtotals only
63.1 LCn3 ≤ 150 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
63.2 LCn3 > 150 ≤ 250 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
63.3 LCn3 > 250 ≤ 400 mg/d	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
63.4 LCn3 > 400 ≤ 2400 mg/d	16	34054	Mean Difference (IV, Random, 95% CI)	0.01 [-0.01, 0.02]
63.5 LCn3 > 2.4 ≤ 4.4 g/d	5	893	Mean Difference (IV, Random, 95% CI)	0.01 [-0.14, 0.15]
63.6 LCn3 > 4.4 g/d	2	88	Mean Difference (IV, Random, 95% CI)	0.22 [-0.09, 0.54]
64 LDL, mmoL/L - LCn3 - subgroup by replacement	23		Mean Difference (IV, Random, 95% CI)	Subtotals only
64.1 N-3 replacing SFA	2	429	Mean Difference (IV, Random, 95% CI)	0.17 [-0.14, 0.47]
64.2 N-3 replacing MUFA	14	14710	Mean Difference (IV, Random, 95% CI)	0.01 [-0.03, 0.05]
64.3 N-3 replacing n-6	2	242	Mean Difference (IV, Random, 95% CI)	0.14 [-0.26, 0.55]
64.4 N-3 replacing carbs/sugars	1	258	Mean Difference (IV, Random, 95% CI)	0.20 [-0.51, 0.91]
64.5 N-3 replacing nil/low n-3 placebo	3	19297	Mean Difference (IV, Random, 95% CI)	0.00 [-0.02, 0.02]
64.6 Replacement unclear	3	528	Mean Difference (IV, Random, 95% CI)	0.10 [-0.03, 0.23]
65 LDL, mmoL/L - LCn3 - subgroup by intervention type	23		Mean Difference (IV, Random, 95% CI)	Subtotals only
65.1 Dietary advice	1	71	Mean Difference (IV, Random, 95% CI)	0.08 [-0.22, 0.38]
65.2 Supplemental foods	1	1124	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.10, 0.06]

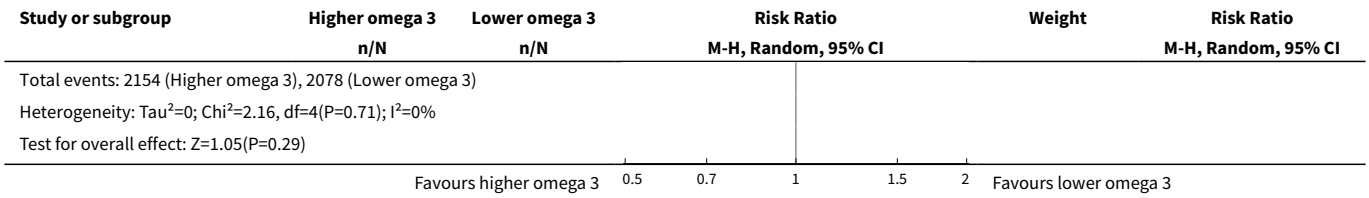
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
65.3 Supplement (capsule)	19	33768	Mean Difference (IV, Random, 95% CI)	0.01 [-0.01, 0.03]
65.4 Any combination	2	72	Mean Difference (IV, Random, 95% CI)	0.08 [-0.44, 0.61]
66 LDL, mmoL/L - LCn3 - subgroup by duration	23		Mean Difference (IV, Random, 95% CI)	Subtotals only
66.1 Medium duration 1 to < 2 years in study	14	1862	Mean Difference (IV, Random, 95% CI)	0.06 [-0.03, 0.14]
66.2 Medium-long duration: 2 to < 4 years in study	6	1784	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.08, 0.06]
66.3 Long duration ≥ 4 years in study	3	31389	Mean Difference (IV, Random, 95% CI)	0.03 [-0.04, 0.10]
67 LDL, mmoL/L - LCn3 - subgroup by primary or secondary prevention	23		Mean Difference (IV, Random, 95% CI)	Subtotals only
67.1 Primary prevention	16	32717	Mean Difference (IV, Random, 95% CI)	0.01 [-0.01, 0.03]
67.2 Secondary prevention	7	2318	Mean Difference (IV, Random, 95% CI)	0.01 [-0.05, 0.08]
68 LDL, mmoL/L - LCn3 - subgroup by statin use	23		Mean Difference (IV, Random, 95% CI)	Subtotals only
68.1 LCn3 - ≥ 50% of control group on statins	7	32808	Mean Difference (IV, Random, 95% CI)	0.00 [-0.02, 0.02]
68.2 LCn3 - < 50% of control group on statins	9	1564	Mean Difference (IV, Random, 95% CI)	0.12 [0.03, 0.21]
68.3 LCn3 - use of statins unclear	7	663	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.17, 0.14]

Analysis 2.1. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 1 MACCEs - LCn3.

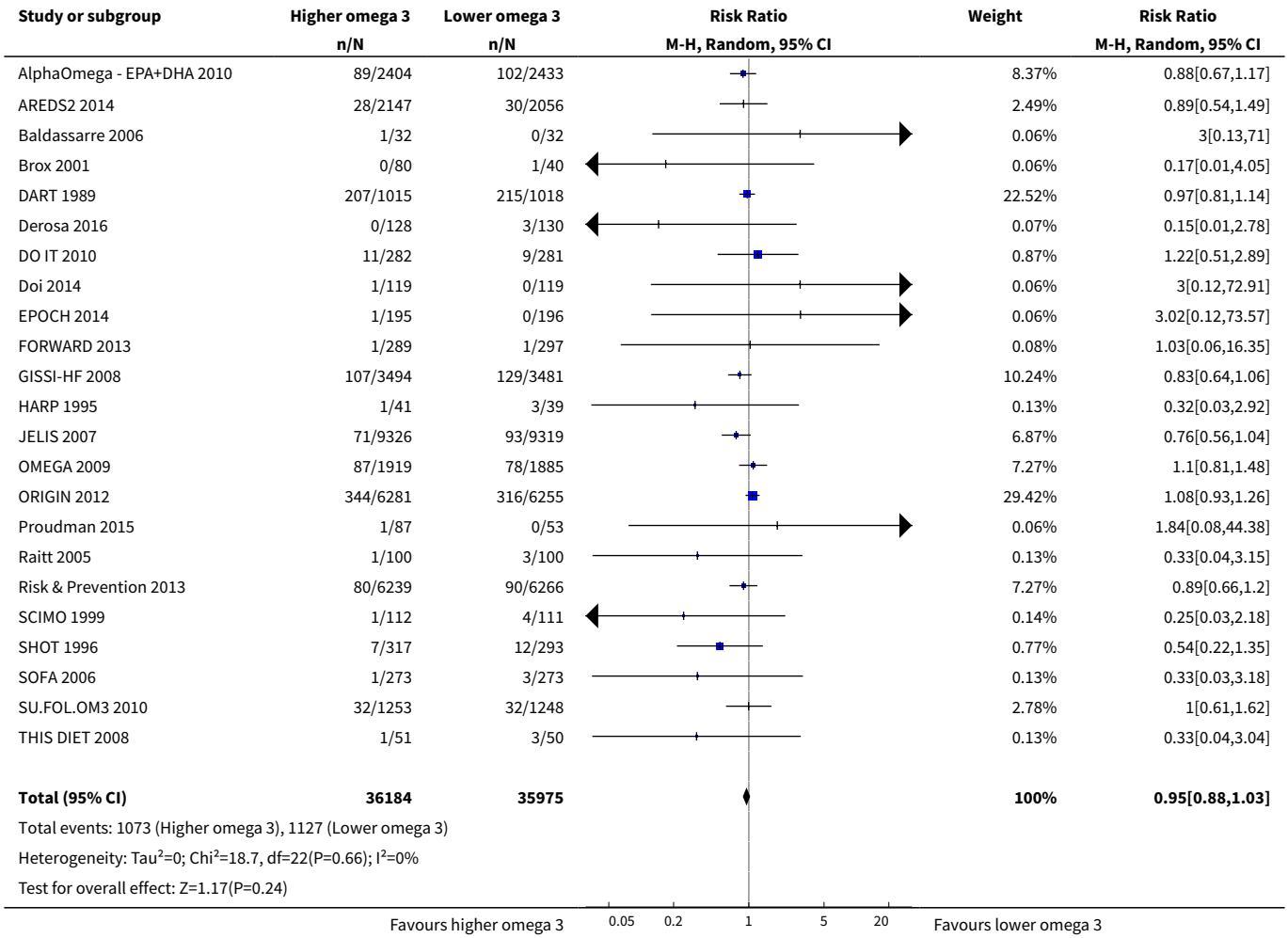
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
AREDS2 2014	116/2147	113/2056		4.76%	0.98[0.76,1.26]
DART 1989	338/1015	332/1018		19.65%	1.02[0.9,1.16]
OMEGA 2009	182/1752	149/1701		7.12%	1.19[0.97,1.46]
ORIGIN 2012	1034/6281	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]**



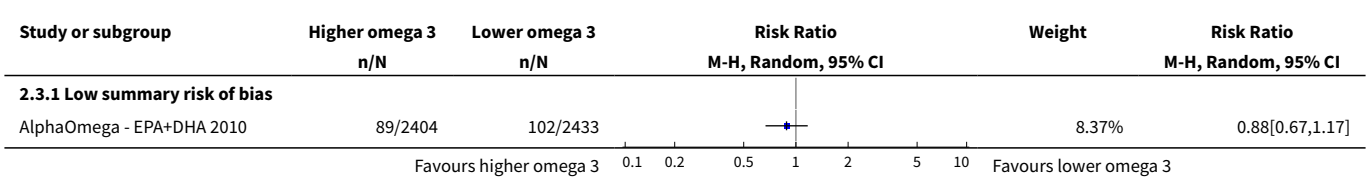
Favours higher omega 3 — Favours lower omega 3

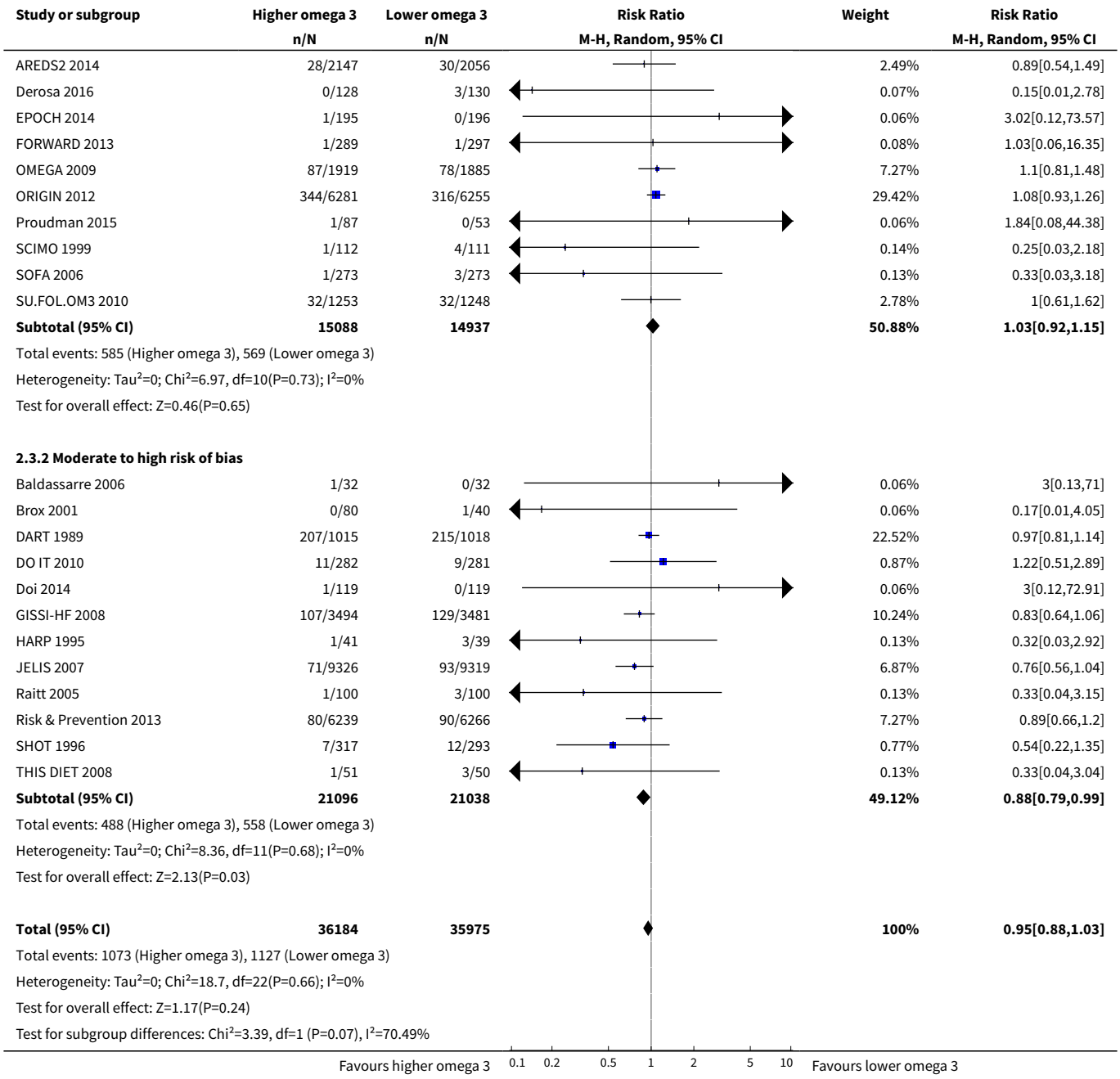


Analysis 2.2. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 2 Myocardial infarction (overall) - LCn3.

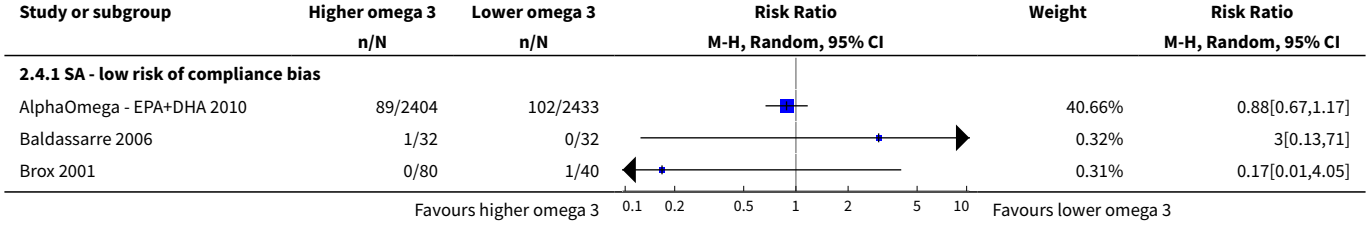


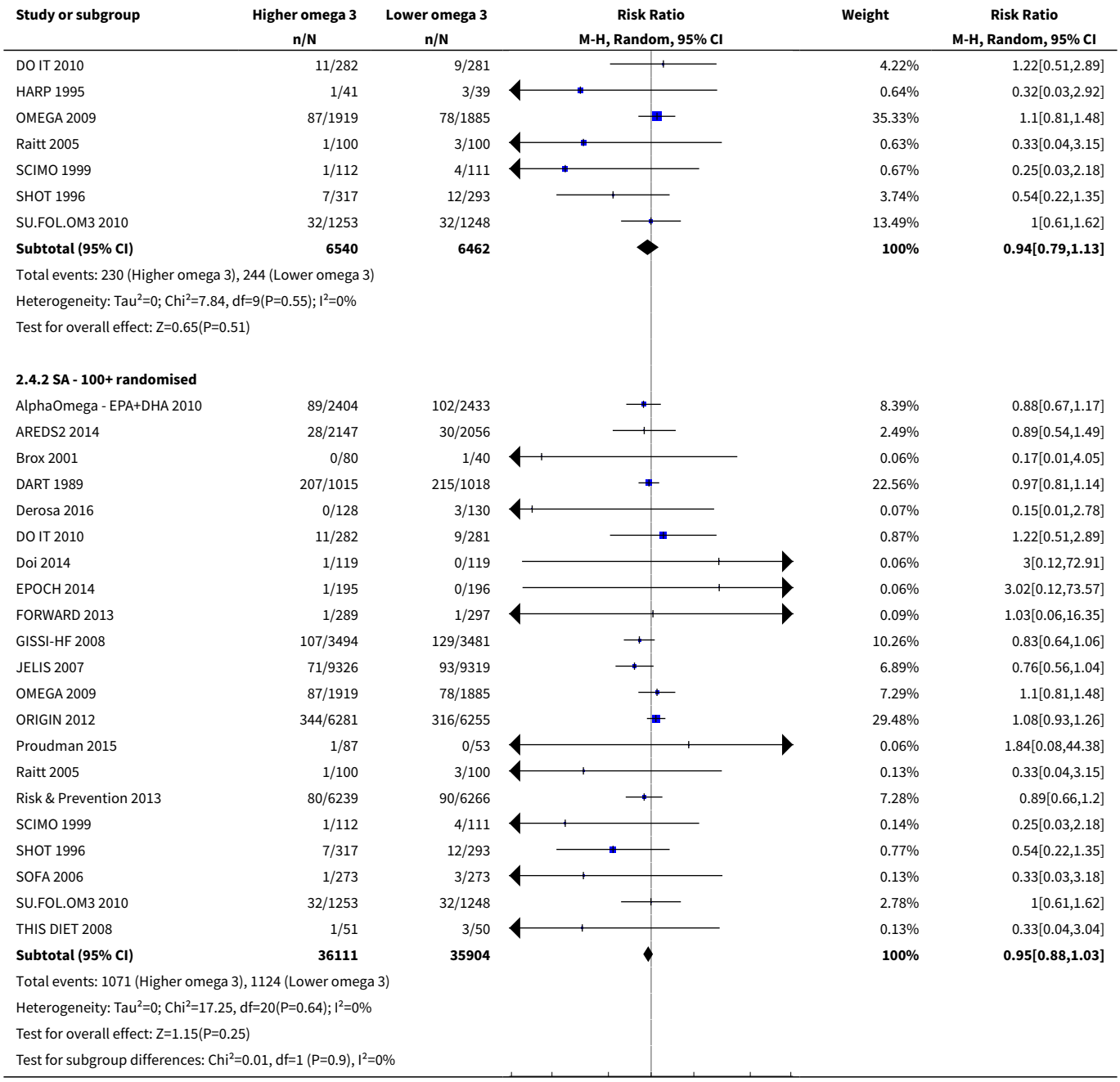
Analysis 2.3. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 3 Total MI - sensitivity analysis (SA) by summary risk of bias.





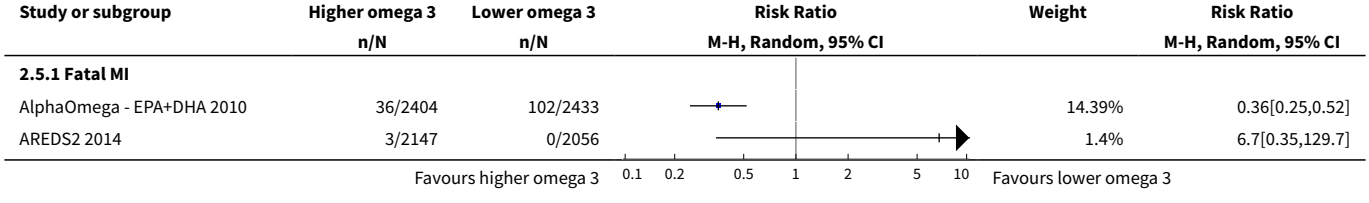
Analysis 2.4. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 4 Total MI - LCn3 - SA by compliance and study size.



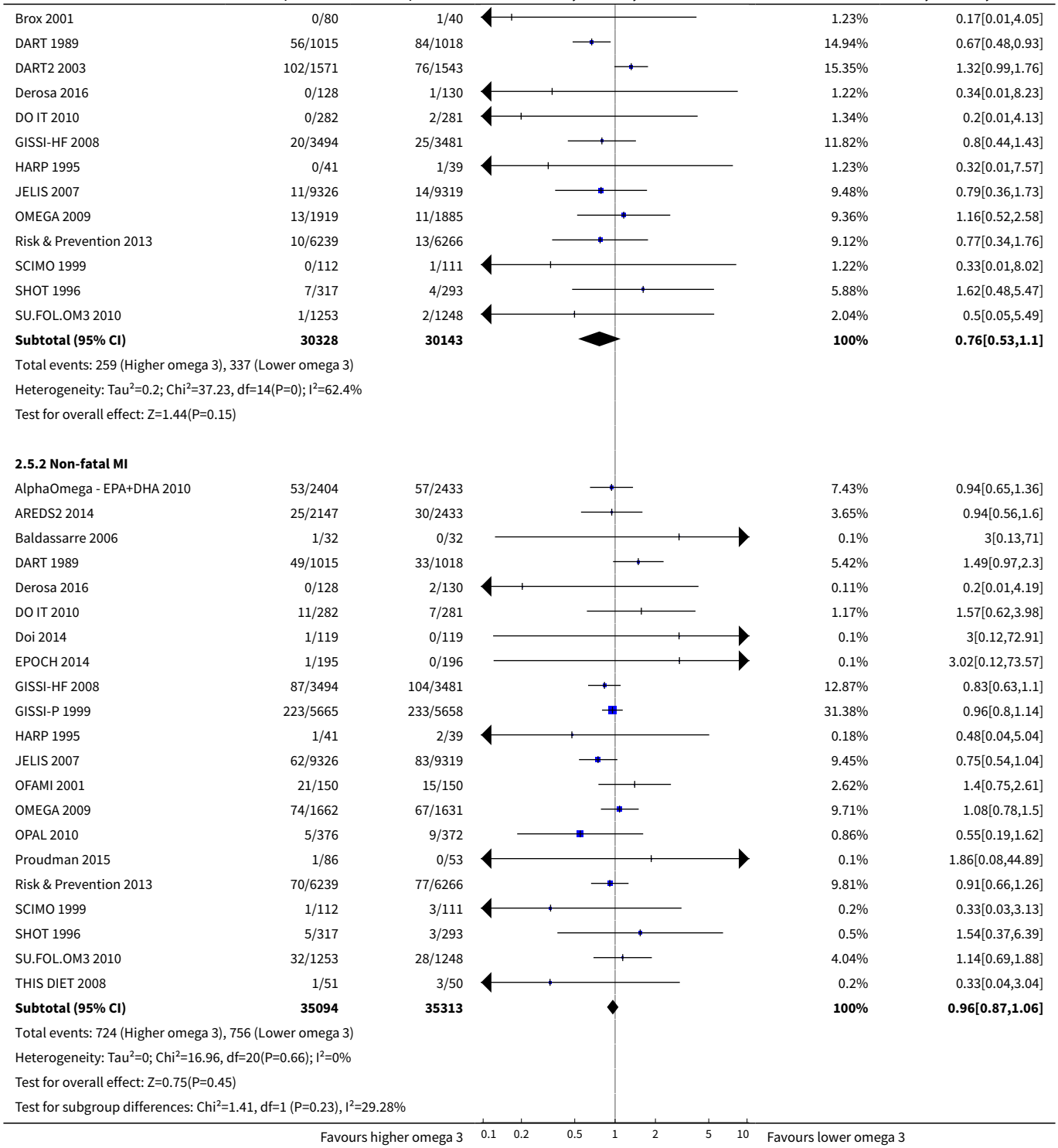


Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
DO IT 2010	11/282	9/281		4.22%	1.22[0.51,2.89]
HARP 1995	1/41	3/39		0.64%	0.32[0.03,2.92]
OMEGA 2009	87/1919	78/1885		35.33%	1.1[0.81,1.48]
Raitt 2005	1/100	3/100		0.63%	0.33[0.04,3.15]
SCIMO 1999	1/112	4/111		0.67%	0.25[0.03,2.18]
SHOT 1996	7/317	12/293		3.74%	0.54[0.22,1.35]
SU.FOL.OM3 2010	32/1253	32/1248		13.49%	1[0.61,1.62]
Subtotal (95% CI)	**6540**	**6462**		**100%**	**0.94[0.79,1.13]**
Total events: 230 (Higher omega 3), 244 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=7.84, df=9(P=0.55); I²=0%					
Test for overall effect: Z=0.65(P=0.51)					
2.4.2 SA - 100+ randomised					
AlphaOmega - EPA+DHA 2010	89/2404	102/2433		8.39%	0.88[0.67,1.17]
AREDS2 2014	28/2147	30/2056		2.49%	0.89[0.54,1.49]
Brox 2001	0/80	1/40		0.06%	0.17[0.01,4.05]
DART 1989	207/1015	215/1018		22.56%	0.97[0.81,1.14]
Derosa 2016	0/128	3/130		0.07%	0.15[0.01,2.78]
DO IT 2010	11/282	9/281		0.87%	1.22[0.51,2.89]
Doi 2014	1/119	0/119		0.06%	3[0.12,72.91]
EPOCH 2014	1/195	0/196		0.06%	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		10.26%	0.83[0.64,1.06]
JELIS 2007	71/9326	93/9319		6.89%	0.76[0.56,1.04]
OMEGA 2009	87/1919	78/1885		7.29%	1.1[0.81,1.48]
ORIGIN 2012	344/6281	316/6255		29.48%	1.08[0.93,1.26]
Proudman 2015	1/87	0/53		0.06%	1.84[0.08,44.38]
Raitt 2005	1/100	3/100		0.13%	0.33[0.04,3.15]
Risk & Prevention 2013	80/6239	90/6266		7.28%	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		0.77%	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		2.78%	1[0.61,1.62]
THIS DIET 2008	1/51	3/50		0.13%	0.33[0.04,3.04]
Subtotal (95% CI)	**36111**	**35904**		**100%**	**0.95[0.88,1.03]**
Total events: 1071 (Higher omega 3), 1124 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=17.25, df=20(P=0.64); I²=0%					
Test for overall effect: Z=1.15(P=0.25)					
Test for subgroup differences: Chi²=0.01, df=1 (P=0.9), I²=0%					

Analysis 2.5. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 5 Total MI - LCn3 - subgroup by fatality.

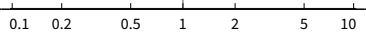


Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 Fatal MI					
AlphaOmega - EPA+DHA 2010	36/2404	102/2433		14.39%	0.36[0.25,0.52]
AREDS2 2014	3/2147	0/2056		1.4%	6.7[0.35,129.7]



Analysis 2.6. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 6 Sudden cardiac death (overall) - LCn3.

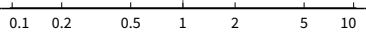
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
AREDS2 2014	7/2147	9/2056		3.39%	0.74[0.28,2]
Brox 2001	0/80	0/40			Not estimable
DART2 2003	73/1571	47/1543		14.55%	1.53[1.06,2.19]
DO IT 2010	3/282	5/281		1.73%	0.6[0.14,2.48]
Doi 2014	0/119	2/119		0.4%	0.2[0.01,4.12]
FOSTAR 2016	0/101	1/101		0.36%	0.33[0.01,8.09]
GISSI-HF 2008	307/3494	325/3481		25.08%	0.94[0.81,1.09]
GISSI-P 1999	122/5666	164/5658		20.69%	0.74[0.59,0.94]
JELIS 2007	18/9326	17/9319		6.58%	1.06[0.55,2.05]
OMEGA 2009	28/1919	29/1885		9.49%	0.95[0.57,1.59]
Raitt 2005	2/100	0/100		0.4%	5[0.24,102.85]
Risk & Prevention 2013	49/6239	40/6266		12.42%	1.23[0.81,1.87]
SHOT 1996	7/317	4/293		2.31%	1.62[0.48,5.47]
SU.FOL.OM3 2010	4/1253	11/1248		2.6%	0.36[0.12,1.13]
Total (95% CI)	**32614**	**32390**		**100%**	**0.97[0.8,1.18]**
Total events: 620 (Higher omega 3), 654 (Lower omega 3)					
Heterogeneity: Tau^2=0.03; Chi^2=19.29, df=12(P=0.08); I^2=37.79%					
Test for overall effect: Z=0.29(P=0.77)					



Favours higher omega 3 — Favours lower omega 3

Analysis 2.7. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 7 Angina - LCn3.

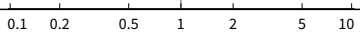
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
AREDS2 2014	26/2147	25/2056		1.93%	1[0.58,1.72]
EPE-A 2014	2/168	1/75		0.1%	0.89[0.08,9.7]
FAAT 2005	0/200	4/202		0.07%	0.11[0.01,2.07]
GISSI-P 1999	254/2836	249/2828		20.67%	1.02[0.86,1.2]
Nye 1990	5/36	11/37		0.63%	0.47[0.18,1.21]
OMEGA 2009	21/1661	25/1651		1.73%	0.83[0.47,1.49]
ORIGIN 2012	724/6281	725/6255		61.36%	0.99[0.9,1.1]
Raitt 2005	10/100	7/100		0.67%	1.43[0.57,3.6]
Risk & Prevention 2013	143/6239	148/6266		11.16%	0.97[0.77,1.22]
SCIMO 1999	9/112	11/111		0.81%	0.81[0.35,1.88]
SOFA 2006	10/273	12/273		0.85%	0.83[0.37,1.9]
Total (95% CI)	**20053**	**19854**		**100%**	**0.99[0.91,1.06]**
Total events: 1204 (Higher omega 3), 1218 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=6, df=10(P=0.82); I^2=0%					
Test for overall effect: Z=0.35(P=0.72)					



Favours higher omega 3 — Favours lower omega 3

Analysis 2.8. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 8 Heart failure - LCn3.

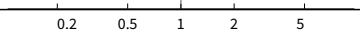
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.8.1 Low summary risk of bias					
AREDS2 2014	55/2147	49/2056		5.8%	1.07[0.73,1.57]
FORWARD 2013	5/289	6/297		0.71%	0.86[0.26,2.78]
OMEGA 2009	467/1919	492/1885		24.45%	0.93[0.84,1.04]
ORIGIN 2012	331/6281	320/6255		19.53%	1.03[0.89,1.2]
SOFA 2006	22/273	19/273		2.67%	1.16[0.64,2.09]
SU.FOL.OM3 2010	21/1253	22/1248		2.65%	0.95[0.53,1.72]
Subtotal (95% CI)	**12162**	**12014**		**55.8%**	**0.97[0.89,1.06]**
Total events: 901 (Higher omega 3), 908 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=1.81, df=5(P=0.87); I^2=0%					
Test for overall effect: Z=0.63(P=0.53)					
2.8.2 Moderate to high risk of bias					
DART 1989	5/1015	4/1018		0.58%	1.25[0.34,4.66]
DART2 2003	1/1571	2/1543		0.17%	0.49[0.04,5.41]
FAAT 2005	6/200	8/202		0.91%	0.76[0.27,2.14]
GISSI-HF 2008	978/3494	995/3481		28.96%	0.98[0.91,1.06]
HARP 1995	0/41	1/39		0.1%	0.32[0.01,7.57]
Nodari 2011 HF	4/67	20/66		0.94%	0.2[0.07,0.55]
Raitt 2005	14/100	12/100		1.84%	1.17[0.57,2.4]
Risk & Prevention 2013	96/6239	142/6266		10.6%	0.68[0.53,0.88]
Shinto 2014	1/13	0/13		0.1%	3[0.13,67.51]
Subtotal (95% CI)	**12740**	**12728**		**44.2%**	**0.78[0.57,1.08]**
Total events: 1105 (Higher omega 3), 1184 (Lower omega 3)					
Heterogeneity: Tau^2=0.07; Chi^2=18.5, df=8(P=0.02); I^2=56.75%					
Test for overall effect: Z=1.51(P=0.13)					
Total (95% CI)	**24902**	**24742**		**100%**	**0.93[0.85,1.03]**
Total events: 2006 (Higher omega 3), 2092 (Lower omega 3)					
Heterogeneity: Tau^2=0.01; Chi^2=20.4, df=14(P=0.12); I^2=31.36%					
Test for overall effect: Z=1.32(P=0.19)					
Test for subgroup differences: Chi^2=1.68, df=1 (P=0.19), I^2=40.52%					



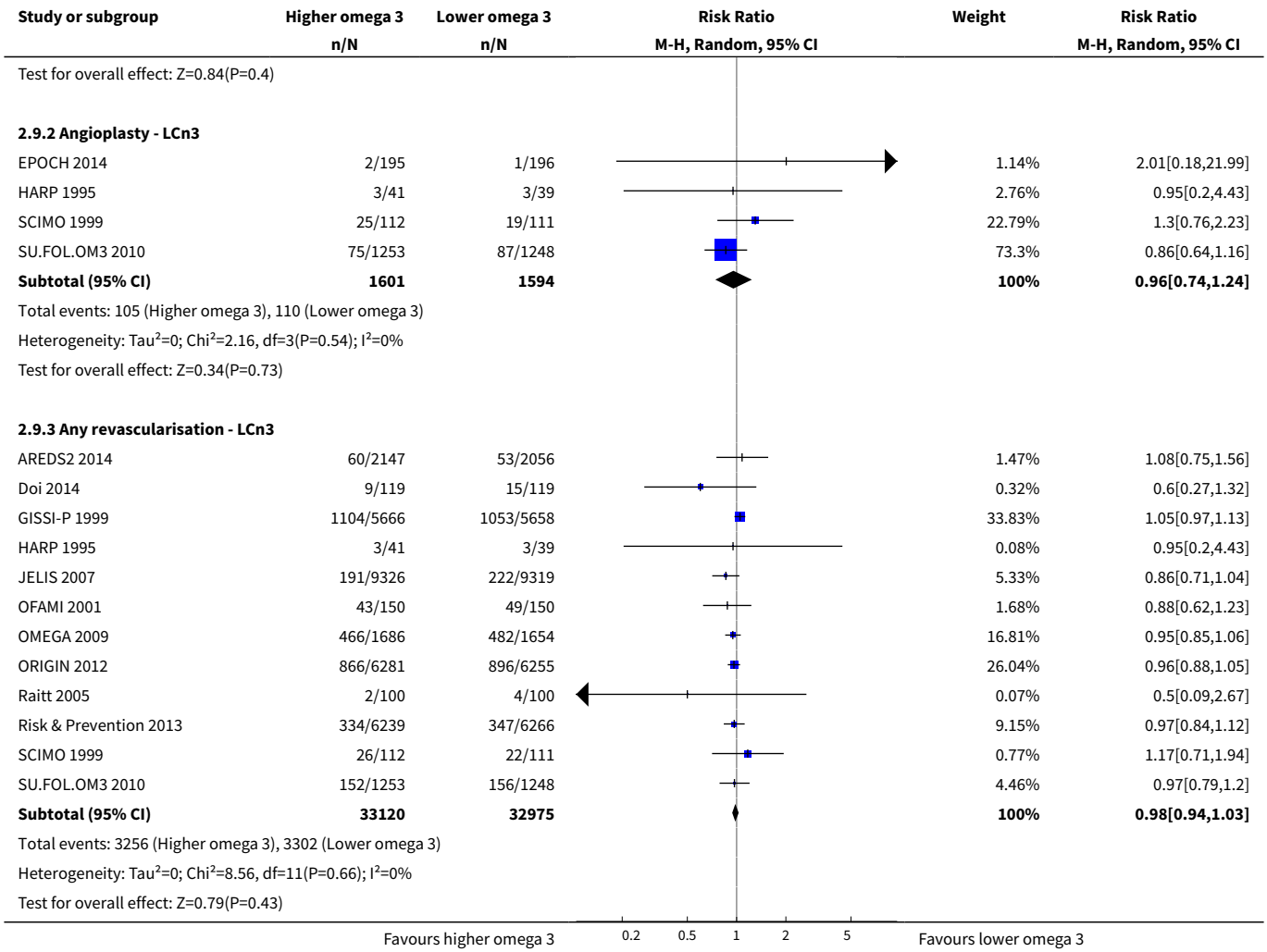
Favours higher omega 3 — Favours lower omega 3

Analysis 2.9. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 9 Revascularisation - LCn3.

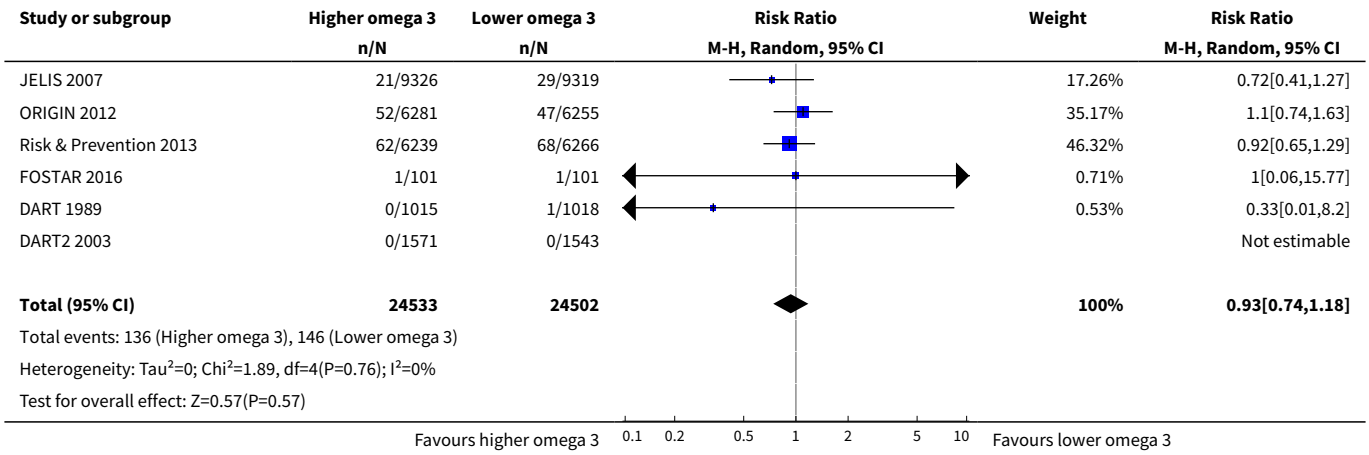
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.9.1 CABG - LCn3					
Doi 2014	1/119	1/119		23.4%	1[0.06,15.8]
EPOCH 2014	0/195	1/196		17.47%	0.34[0.01,8.17]
Nye 1990	1/36	1/37		23.86%	1.03[0.07,15.82]
SCIMO 1999	1/112	3/111		35.28%	0.33[0.03,3.13]
SHOT 1996	0/317	0/293			Not estimable
Subtotal (95% CI)	**779**	**756**		**100%**	**0.56[0.15,2.14]**
Total events: 3 (Higher omega 3), 6 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.67, df=3(P=0.88); I^2=0%					



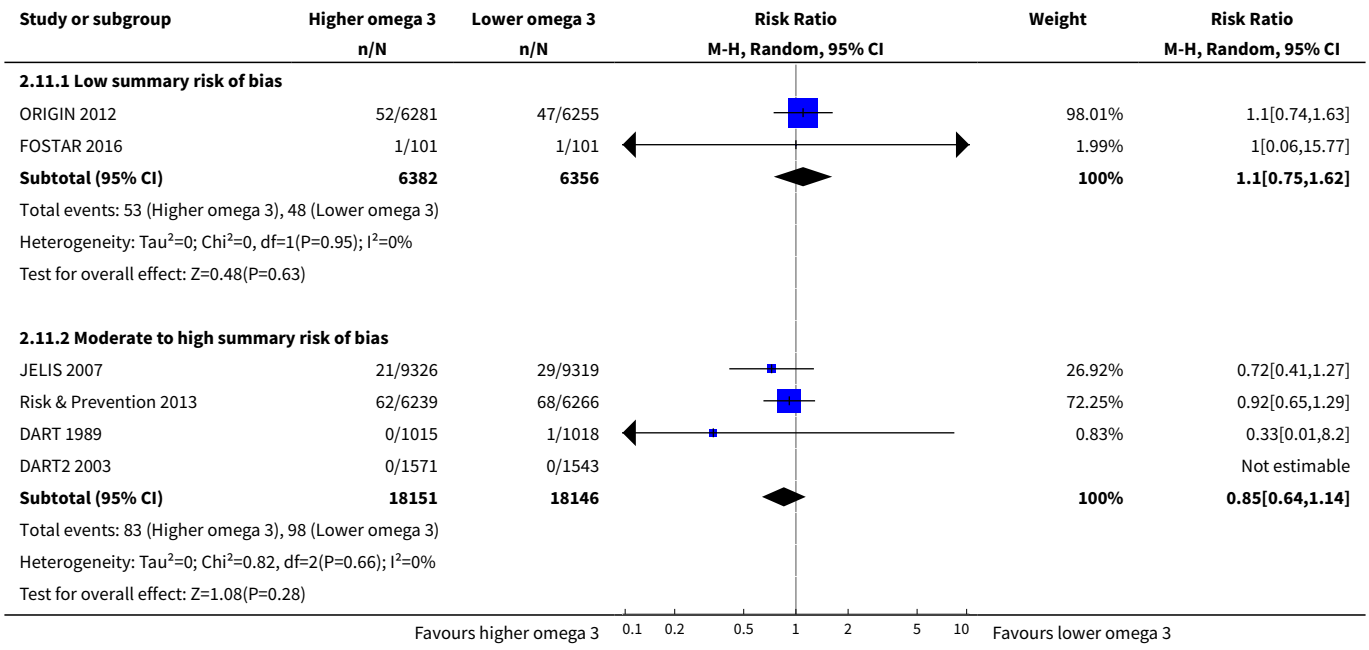
Favours higher omega 3 — Favours lower omega 3



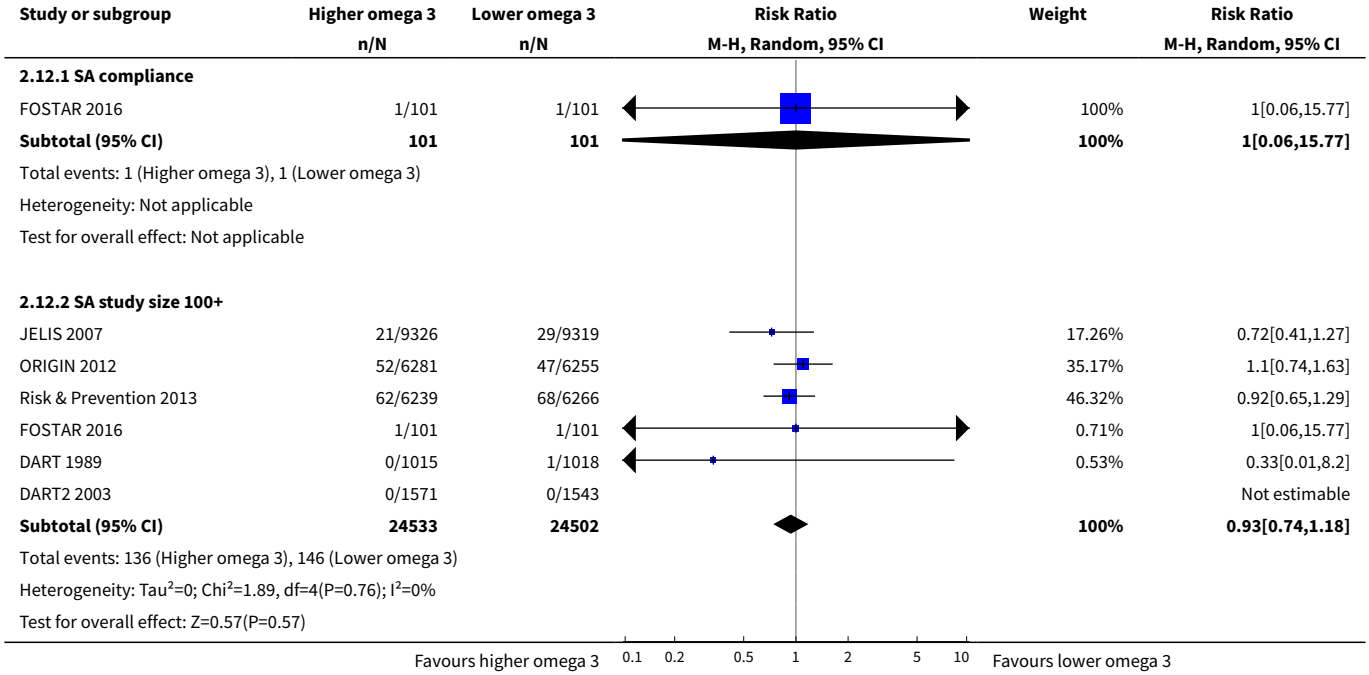
Analysis 2.10. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 10 Peripheral arterial disease - LCn3.



Analysis 2.11. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 11 PAD - LCn3 - SA by summary risk of bias.

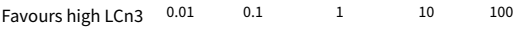


Analysis 2.12. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 12 PAD - LCn3 - SA compliance and study size.



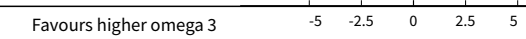
Analysis 2.13. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 13 Acute coronary syndrome - LCn3.

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
2.13.1 LCn3					
FOSTAR 2016	10/101	10/101		38.97%	1[0.44,2.3]
SU.FOL.OM3 2010	20/1253	15/1248		61.03%	1.33[0.68,2.58]
Subtotal (95% CI)	**1354**	**1349**		**100%**	**1.19[0.71,2]**
Total events: 30 (Higher omega 3), 25 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.27, df=1(P=0.6); I^2=0%					
Test for overall effect: Z=0.65(P=0.51)					



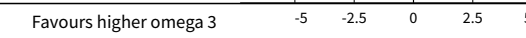
Analysis 2.14. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 14 Body weight, kg - LCn3.

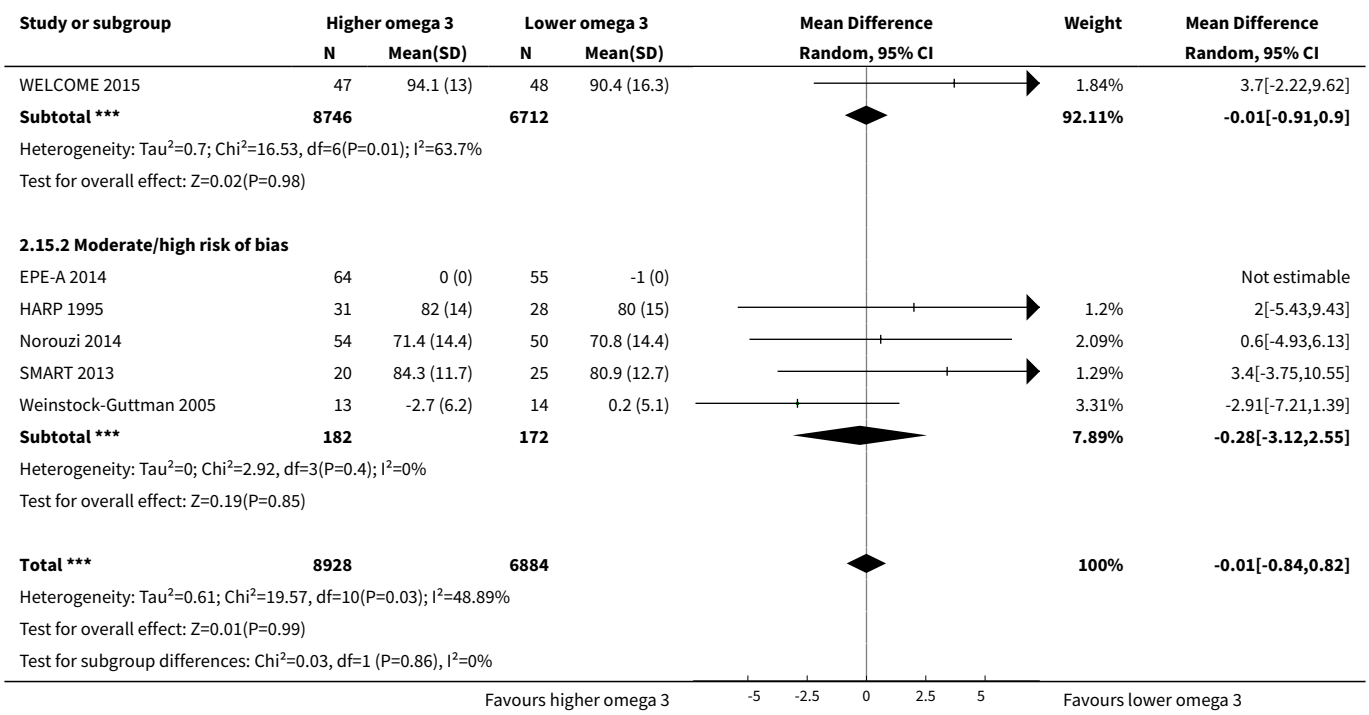
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Caldwell 2011	20	-1.5 (4.5)	21	-0.2 (3.7)		7.89%	-1.3[-3.83,1.23]
Derosa 2016	128	78.7 (7.9)	130	81.4 (8.9)		10.51%	-2.7[-4.75,-0.65]
EPE-A 2014	64	0 (0)	55	-1 (0)			Not estimable
FOSTAR 2016	101	1.8 (5)	101	0.3 (4)		17.6%	1.5[0.25,2.75]
HARP 1995	31	82 (14)	28	80 (15)		1.2%	2[-5.43,9.43]
MARINA 2011	80	0.2 (1.8)	71	-0.3 (2.5)		24.22%	0.5[-0.21,1.21]
Norouzi 2014	54	71.4 (14.4)	50	70.8 (14.4)		2.09%	0.6[-4.93,6.13]
ORIGIN 2012	8281	83.9 (17.8)	6255	83.8 (17.6)		25.7%	0.1[-0.48,0.68]
SCIMO 1999	89	79.1 (12.5)	86	81 (12.3)		4.35%	-1.9[-5.57,1.77]
SMART 2013	20	84.3 (11.7)	25	80.9 (12.7)		1.29%	3.4[-3.75,10.55]
Weinstock-Guttman 2005	13	-2.7 (6.2)	14	0.2 (5.1)		3.31%	-2.91[-7.21,1.39]
WELCOME 2015	47	94.1 (13)	48	90.4 (16.3)		1.84%	3.7[-2.22,9.62]
Total ***	**8928**		**6884**			**100%**	**-0.01[-0.84,0.82]**
Heterogeneity: Tau^2=0.61; Chi^2=19.57, df=10(P=0.03); I^2=48.89%							
Test for overall effect: Z=0.01(P=0.99)							



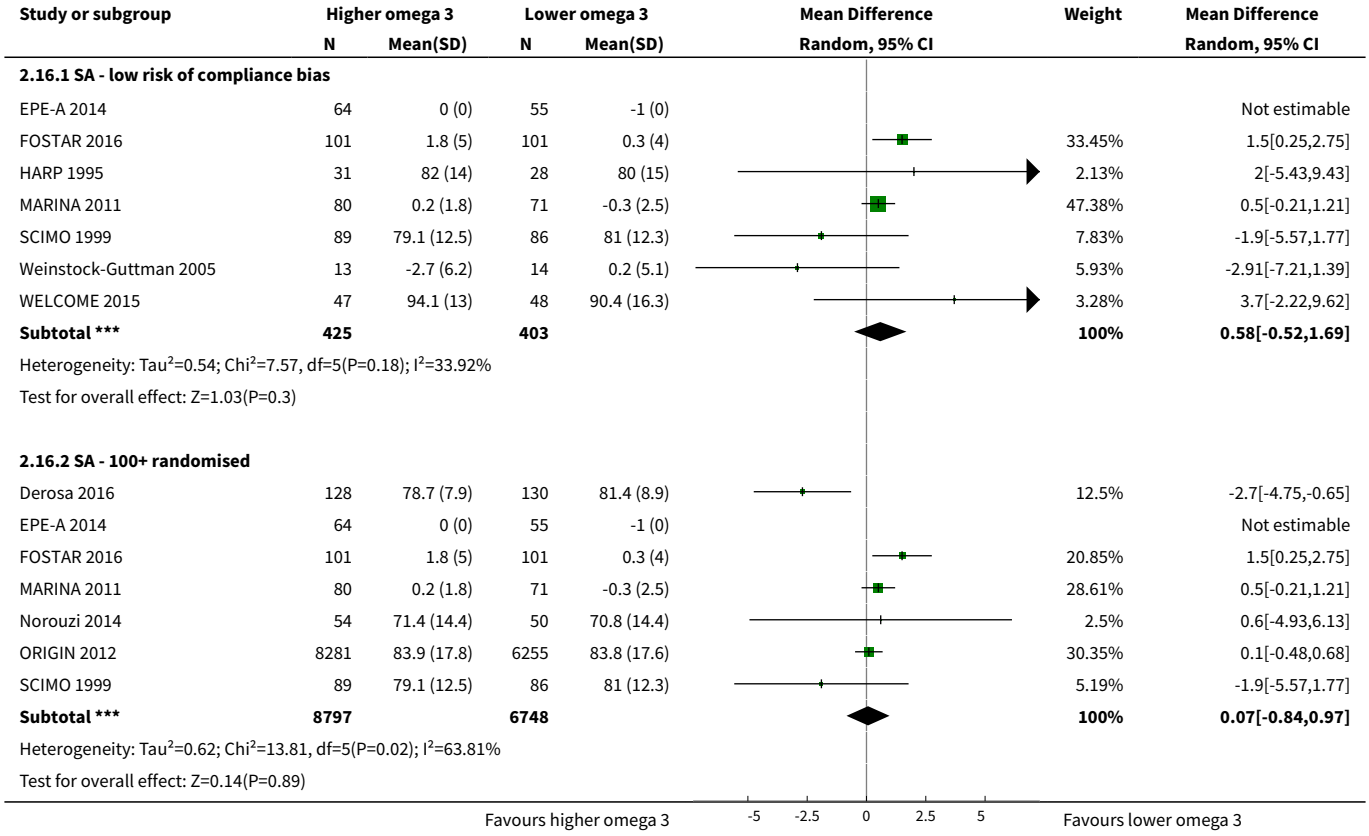
Analysis 2.15. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 15 Weight, kg - LCn3 - SA by summary risk of bias.

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
2.15.1 Low risk of bias							
Caldwell 2011	20	-1.5 (4.5)	21	-0.2 (3.7)		7.89%	-1.3[-3.83,1.23]
Derosa 2016	128	78.7 (7.9)	130	81.4 (8.9)		10.51%	-2.7[-4.75,-0.65]
FOSTAR 2016	101	1.8 (5)	101	0.3 (4)		17.6%	1.5[0.25,2.75]
MARINA 2011	80	0.2 (1.8)	71	-0.3 (2.5)		24.22%	0.5[-0.21,1.21]
ORIGIN 2012	8281	83.9 (17.8)	6255	83.8 (17.6)		25.7%	0.1[-0.48,0.68]
SCIMO 1999	89	79.1 (12.5)	86	81 (12.3)		4.35%	-1.9[-5.57,1.77]





Analysis 2.16. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 16 Weight, kg - 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
Test for subgroup differences: Chi²=0.5, df=1 (P=0.48), I²=0%							

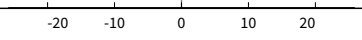
Favours higher omega 3 -5 -2.5 0 2.5 5 Favours lower omega 3

Analysis 2.17. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 17 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
2.17.1 LCn3 ≤ 150 mg/d							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.17.2 LCn3 > 150 ≤ 250 mg/d							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.17.3 LCn3 > 250 ≤ 400 mg/d							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.17.4 LCn3 > 400 ≤ 2400 mg/d							
Caldwell 2011	20	-1.5 (4.5)	21	-0.2 (3.7)		9.27%	-1.3[-3.83,1.23]
Derosa 2016	128	78.7 (7.9)	130	81.4 (8.9)		12.65%	-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)		33.38%	0.5[-0.21,1.21]
Norouzi 2014	54	71.4 (14.4)	50	70.8 (14.4)		2.33%	0.6[-4.93,6.13]
ORIGIN 2012	8281	83.9 (17.8)	6255	83.8 (17.6)		35.99%	0.1[-0.48,0.68]
SCIMO 1999	89	79.1 (12.5)	86	81 (12.3)		4.95%	-1.9[-5.57,1.77]
SMART 2013	20	84.3 (11.7)	25	80.9 (12.7)		1.43%	3.4[-3.75,10.55]
Subtotal ***	**8727**		**6693**			**100%**	**-0.29[-1.16,0.58]**
Heterogeneity: Tau²=0.46; Chi²=11.52, df=6(P=0.07); I²=47.92%							
Test for overall effect: Z=0.65(P=0.51)							
2.17.5 LCn3 > 2.4 ≤ 4.4 g/d							
EPE-A 2014	64	0 (0)	55	-1 (0)			Not estimable
Weinstock-Guttman 2005	13	-2.7 (6.2)	14	0.2 (5.1)		54.95%	-2.91[-7.21,1.39]
WELCOME 2015	47	94.1 (13)	48	90.4 (16.3)		45.05%	3.7[-2.22,9.62]
Subtotal ***	**124**		**117**			**100%**	**0.07[-6.38,6.51]**
Heterogeneity: Tau²=14.88; Chi²=3.13, df=1(P=0.08); I²=68.09%							
Test for overall effect: Z=0.02(P=0.98)							
2.17.6 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: Tau²=0; Chi²=0.02, df=1(P=0.9); I²=0%							

Favours higher omega 3 -20 -10 0 10 20 Favours lower omega 3

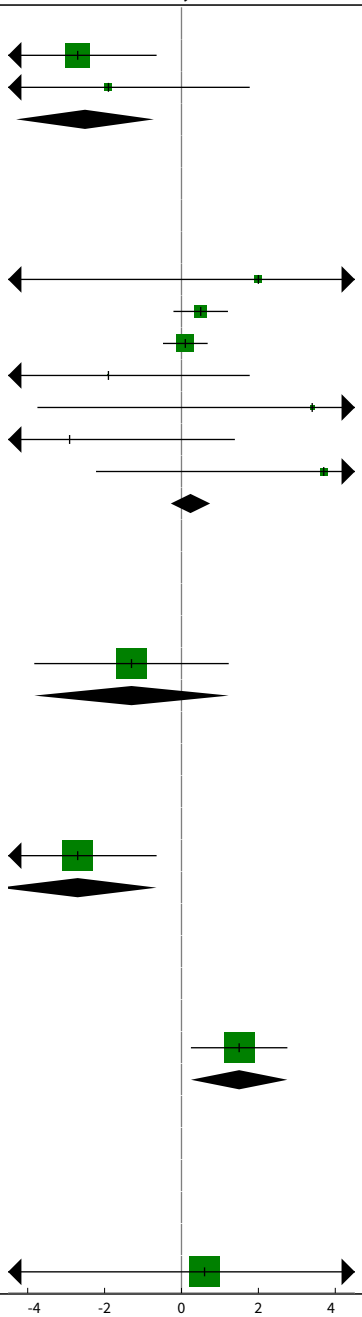
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for overall effect: Z=2.4(P=0.02)							
Test for subgroup differences: Chi²=5.48, df=1 (P=0.06), I²=63.49%							



Favours higher omega 3 — Favours lower omega 3

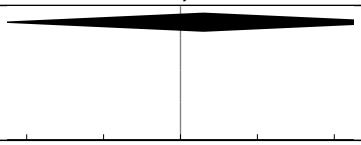
Analysis 2.18. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 18 Weight, kg - LCn3 - subgroup by replacement.

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
2.18.1 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: Tau²=0; Chi²=0.14, df=1(P=0.71); I²=0%							
Test for overall effect: Z=2.74(P=0.01)							
2.18.2 N-3 replacing MUFA							
HARP 1995	31	82 (14)	28	80 (15)		0.47%	2[-5.43,9.43]
MARINA 2011	80	0.2 (1.8)	71	-0.3 (2.5)		40.53%	0.5[-0.21,1.21]
ORIGIN 2012	8281	83.9 (17.8)	6255	83.8 (17.6)		54.42%	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)		1.4%	-2.91[-7.21,1.39]
WELCOME 2015	47	94.1 (13)	48	90.4 (16.3)		0.74%	3.7[-2.22,9.62]
Subtotal ***	**8561**		**6527**			**100%**	**0.23[-0.28,0.75]**
Heterogeneity: Tau²=0.04; Chi²=6.38, df=6(P=0.38); I²=6.01%							
Test for overall effect: Z=0.9(P=0.37)							
2.18.3 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)							
2.18.4 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)							
2.18.5 N-3 replacing nil/low n-3 placebo							
FOSTAR 2016	101	1.8 (5)	101	0.3 (4)		100%	1.5[0.25,2.75]
Subtotal ***	**101**		**101**			**100%**	**1.5[0.25,2.75]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.34(P=0.02)							
2.18.6 Replacement unclear							
EPE-A 2014	64	0 (0)	55	-1 (0)			Not estimable
Norouzi 2014	54	71.4 (14.4)	50	70.8 (14.4)		100%	0.6[-4.93,6.13]



Favours higher omega 3 — Favours lower omega 3

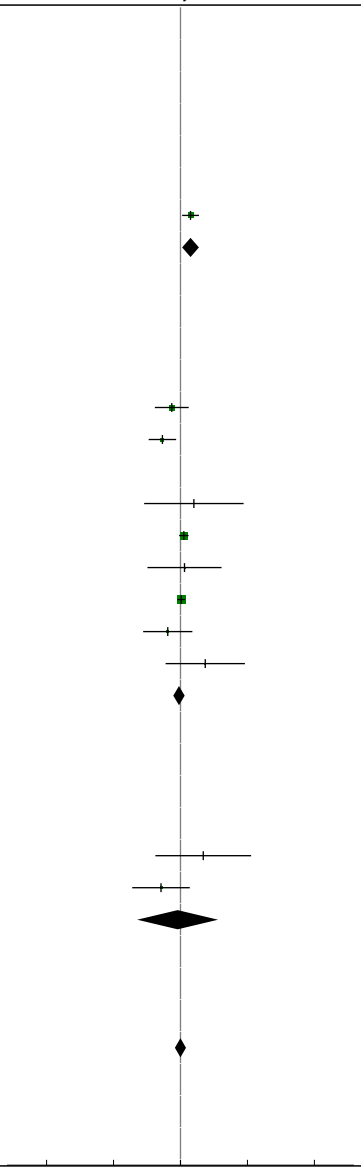
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Subtotal ***	**118**		**105**			**100%**	**0.6[-4.93,6.13]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.21(P=0.83)							
Test for subgroup differences: Chi²=21.5, df=1 (P=0), I²=76.74%							



Favours higher omega 3 — Favours lower omega 3

Analysis 2.19. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 19 Weight, kg - LCn3 - subgroup by intervention type.

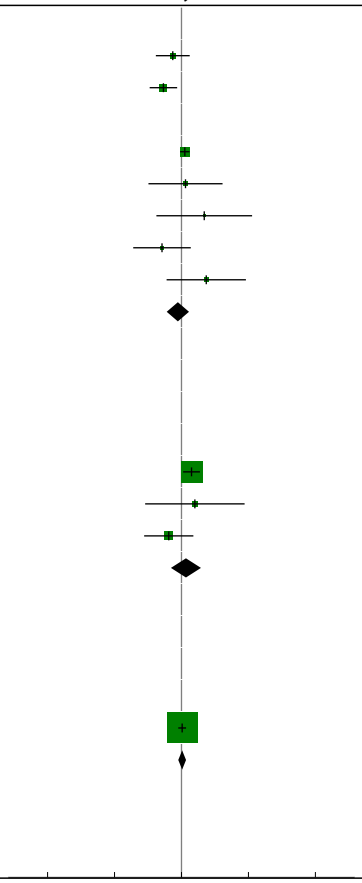
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.19.1 Dietary advice							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.19.2 Supplemental foods							
FOSTAR 2016	101	1.8 (5)	101	0.3 (4)		17.6%	1.5[0.25,2.75]
Subtotal ***	**101**		**101**			**17.6%**	**1.5[0.25,2.75]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.34(P=0.02)							
2.19.3 Supplement (capsule)							
Caldwell 2011	20	-1.5 (4.5)	21	-0.2 (3.7)		7.89%	-1.3[-3.83,1.23]
Derosa 2016	128	78.7 (7.9)	130	81.4 (8.9)		10.51%	-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)		1.2%	2[-5.43,9.43]
MARINA 2011	80	0.2 (1.8)	71	-0.3 (2.5)		24.22%	0.5[-0.21,1.21]
Norouzi 2014	54	71.4 (14.4)	50	70.8 (14.4)		2.09%	0.6[-4.93,6.13]
ORIGIN 2012	8281	83.9 (17.8)	6255	83.8 (17.6)		25.7%	0.1[-0.48,0.68]
SCIMO 1999	89	79.1 (12.5)	86	81 (12.3)		4.35%	-1.9[-5.57,1.77]
WELCOME 2015	47	94.1 (13)	48	90.4 (16.3)		1.84%	3.7[-2.22,9.62]
Subtotal ***	**8794**		**6744**			**77.8%**	**-0.23[-1.08,0.63]**
Heterogeneity: Tau²=0.44; Chi²=12.39, df=7(P=0.09); I²=43.48%							
Test for overall effect: Z=0.52(P=0.6)							
2.19.4 Any combination							
SMART 2013	20	84.3 (11.7)	25	80.9 (12.7)		1.29%	3.4[-3.75,10.55]
Weinstock-Guttman 2005	13	-2.7 (6.2)	14	0.2 (5.1)		3.31%	-2.91[-7.21,1.39]
Subtotal ***	**33**		**39**			**4.6%**	**-0.43[-6.47,5.61]**
Heterogeneity: Tau²=10.86; Chi²=2.2, df=1(P=0.14); I²=54.53%							
Test for overall effect: Z=0.14(P=0.89)							
Total ***	**8928**		**6884**			**100%**	**-0.01[-0.84,0.82]**
Heterogeneity: Tau²=0.61; Chi²=19.57, df=10(P=0.03); I²=48.89%							
Test for overall effect: Z=0.01(P=0.99)							
Test for subgroup differences: Chi²=5.04, df=1 (P=0.08), I²=60.3%							



Favours higher omega 3 — Favours lower omega 3

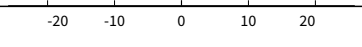
Analysis 2.20. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 20 Weight, kg - LCn3 - subgroup by duration.

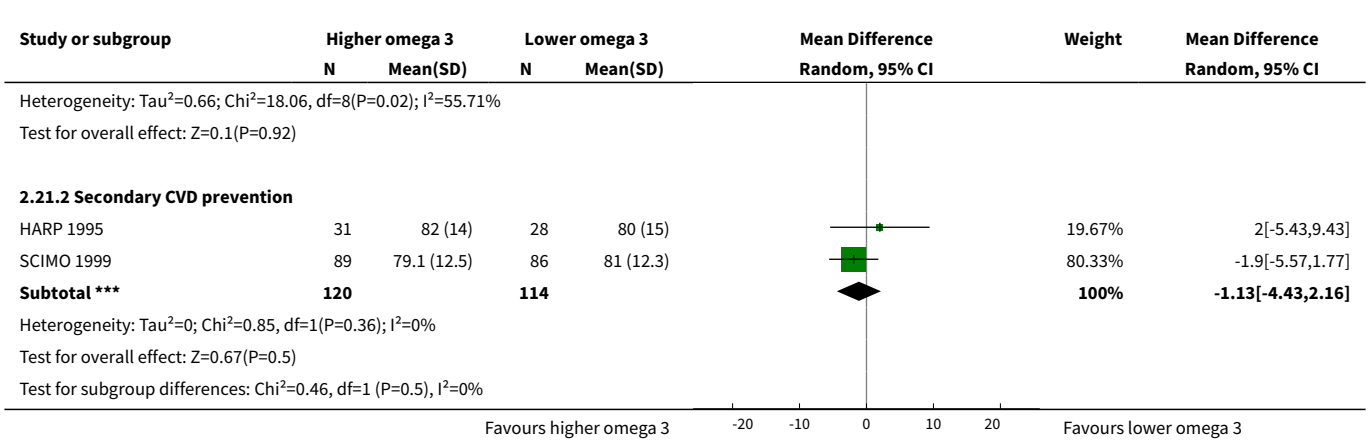
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.20.1 Medium duration 1 to < 2 years in study							
Caldwell 2011	20	-1.5 (4.5)	21	-0.2 (3.7)		18.68%	-1.3[-3.83,1.23]
Derosa 2016	128	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: Tau^2=2.2; Chi^2=13.7, df=6(P=0.03); I^2=56.19%							
Test for overall effect: Z=0.64(P=0.52)							
2.20.2 Medium-long duration: 2 to < 4 years in study							
FOSTAR 2016	101	1.8 (5)	101	0.3 (4)		66.05%	1.5[0.25,2.75]
HARP 1995	31	82 (14)	28	80 (15)		8.22%	2[-5.43,9.43]
SCIMO 1999	89	79.1 (12.5)	86	81 (12.3)		25.74%	-1.9[-5.57,1.77]
Subtotal ***	**221**		**215**			**100%**	**0.67[-1.58,2.91]**
Heterogeneity: Tau^2=1.57; Chi^2=3, df=2(P=0.22); I^2=33.23%							
Test for overall effect: Z=0.58(P=0.56)							
2.20.3 Long duration ≥ 4 years in study							
ORIGIN 2012	8281	83.9 (17.8)	6255	83.8 (17.6)		100%	0.1[-0.48,0.68]
Subtotal ***	**8281**		**6255**			**100%**	**0.1[-0.48,0.68]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.34(P=0.74)							
Test for subgroup differences: Chi^2=0.8, df=1 (P=0.67), I^2=0%							



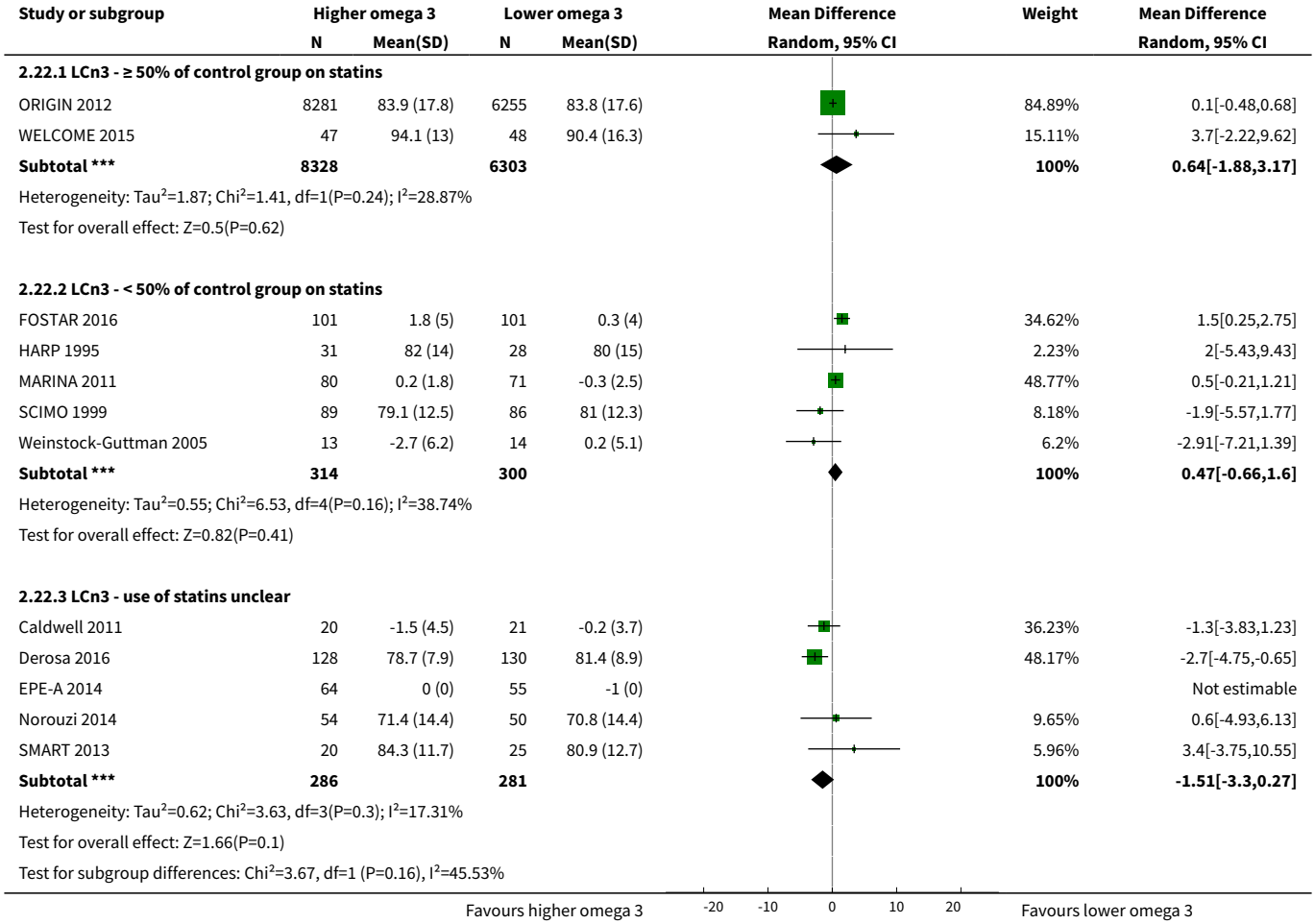
Analysis 2.21. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 21 Weight, kg - LCn3 - subgroup by primary or secondary prevention.

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
2.21.1 Primary CVD prevention							
Caldwell 2011	20	-1.5 (4.5)	21	-0.2 (3.7)		8.6%	-1.3[-3.83,1.23]
Derosa 2016	128	78.7 (7.9)	130	81.4 (8.9)		11.37%	-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)		18.67%	1.5[0.25,2.75]
MARINA 2011	80	0.2 (1.8)	71	-0.3 (2.5)		25.24%	0.5[-0.21,1.21]
Norouzi 2014	54	71.4 (14.4)	50	70.8 (14.4)		2.32%	0.6[-4.93,6.13]
ORIGIN 2012	8281	83.9 (17.8)	6255	83.8 (17.6)		26.68%	0.1[-0.48,0.68]
SMART 2013	20	84.3 (11.7)	25	80.9 (12.7)		1.43%	3.4[-3.75,10.55]
Weinstock-Guttman 2005	13	-2.7 (6.2)	14	0.2 (5.1)		3.66%	-2.91[-7.21,1.39]
WELCOME 2015	47	94.1 (13)	48	90.4 (16.3)		2.04%	3.7[-2.22,9.62]
Subtotal ***	**8808**		**6770**			**100%**	**0.05[-0.83,0.92]**



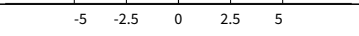


Analysis 2.22. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 22 Weight, kg - LCn3 - subgroup by statin use.



Analysis 2.23. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 23 Body mass index, kg/m² - LCn3.

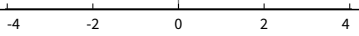
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
AlphaOmega - EPA+DHA 2010	630	0 (1.8)	630	-0.1 (1.8)		25.26%	0.1[-0.1,0.3]
Caldwell 2011	20	-0.5 (4.5)	21	-0.2 (3.7)		0.6%	-0.3[-2.83,2.23]
Derosa 2016	128	28.6 (2.1)	130	29.2 (2.3)		9.65%	-0.6[-1.14,-0.06]
DO IT 2010	124	26.8 (3.5)	117	27 (3.9)		3.92%	-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)		0.8%	1[-1.18,3.18]
Nodari 2011 HF	67	26 (0.4)	66	26 (0.6)		26.9%	0[-0.17,0.17]
Norouzi 2014	54	24.8 (4.9)	50	24.2 (4.2)		1.22%	0.58[-1.17,2.33]
OFAMI 2001	115	26.6 (3.9)	116	26 (3.2)		4.04%	0.6[-0.32,1.52]
ORIGIN 2012	6281	30.3 (5.6)	6255	30.3 (5.6)		25.44%	0[-0.2,0.2]
SMART 2013	20	29.8 (3.5)	25	28.2 (3.4)		0.92%	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)		1.05%	2.6[0.71,4.49]
Total ***	**7636**		**7598**			**100%**	**0.04[-0.16,0.24]**
Heterogeneity: Tau²=0.03; Chi²=18.44, df=11(P=0.07); I²=40.34%							
Test for overall effect: Z=0.41(P=0.68)							



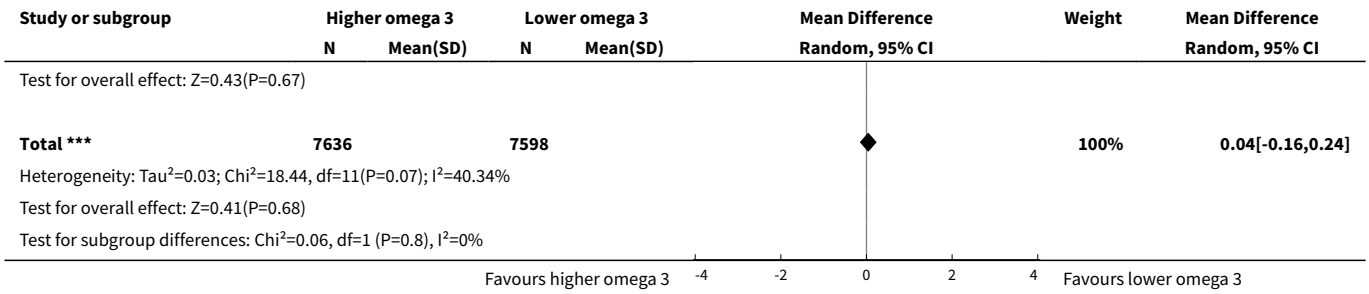
Favours higher omega 3 — Favours lower omega 3

Analysis 2.24. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 24 BMI, kg/m²- LCn3 - SA by summary risk of bias.

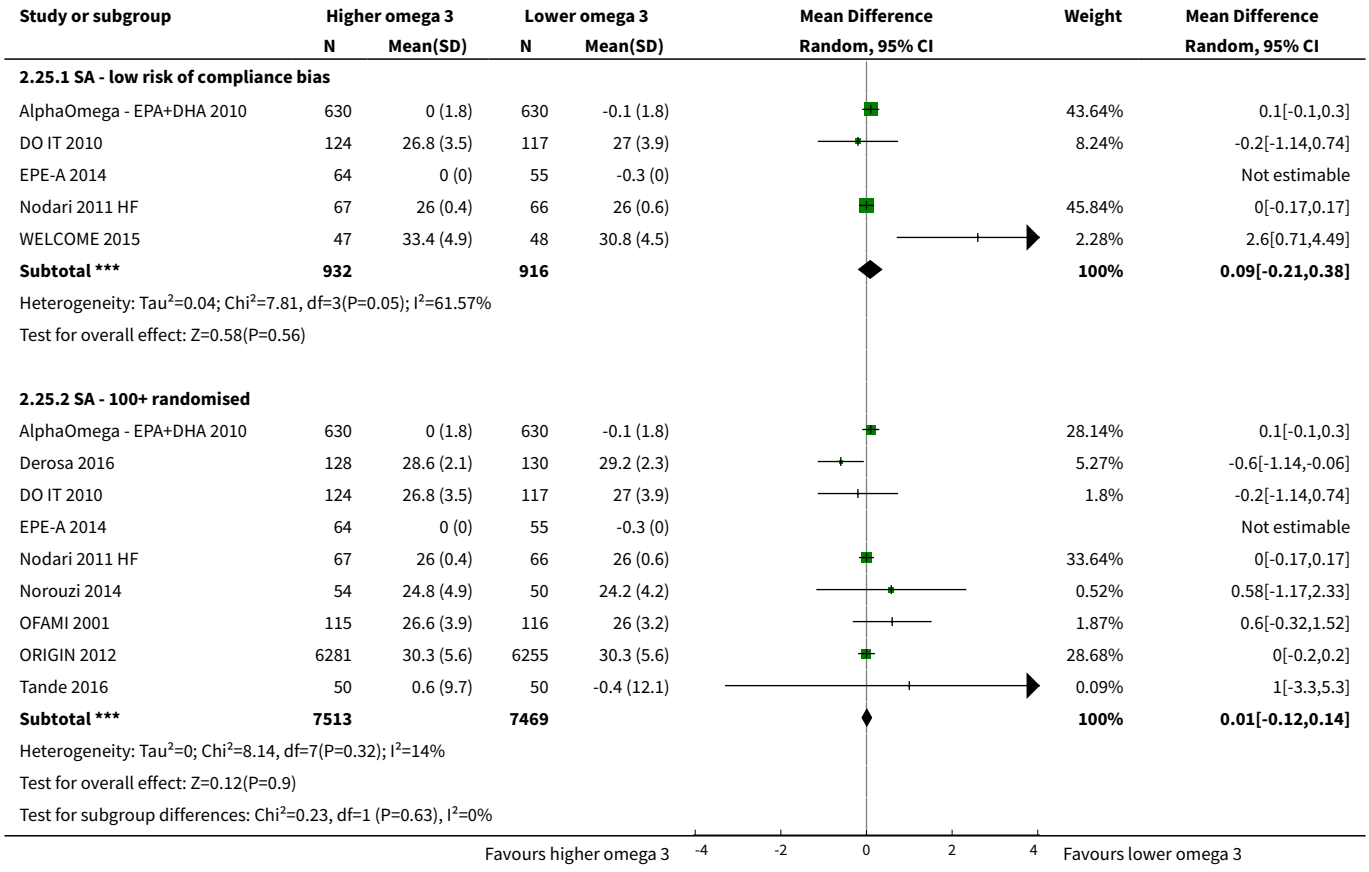
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.24.1 Low risk of bias							
AlphaOmega - EPA+DHA 2010	630	0 (1.8)	630	-0.1 (1.8)		25.26%	0.1[-0.1,0.3]
Caldwell 2011	20	-0.5 (4.5)	21	-0.2 (3.7)		0.6%	-0.3[-2.83,2.23]
Derosa 2016	128	28.6 (2.1)	130	29.2 (2.3)		9.65%	-0.6[-1.14,-0.06]
ORIGIN 2012	6281	30.3 (5.6)	6255	30.3 (5.6)		25.44%	0[-0.2,0.2]
WELCOME 2015	47	33.4 (4.9)	48	30.8 (4.5)		1.05%	2.6[0.71,4.49]
Subtotal ***	**7106**		**7084**			**61.99%**	**-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)							
2.24.2 Moderate/high risk of bias							
DO IT 2010	124	26.8 (3.5)	117	27 (3.9)		3.92%	-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)		0.8%	1[-1.18,3.18]
Nodari 2011 HF	67	26 (0.4)	66	26 (0.6)		26.9%	0[-0.17,0.17]
Norouzi 2014	54	24.8 (4.9)	50	24.2 (4.2)		1.22%	0.58[-1.17,2.33]
OFAMI 2001	115	26.6 (3.9)	116	26 (3.2)		4.04%	0.6[-0.32,1.52]
SMART 2013	20	29.8 (3.5)	25	28.2 (3.4)		0.92%	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]
Subtotal ***	**530**		**514**			**38.01%**	**0.04[-0.13,0.2]**
Heterogeneity: Tau²=0; Chi²=5.44, df=6(P=0.49); I²=0%							



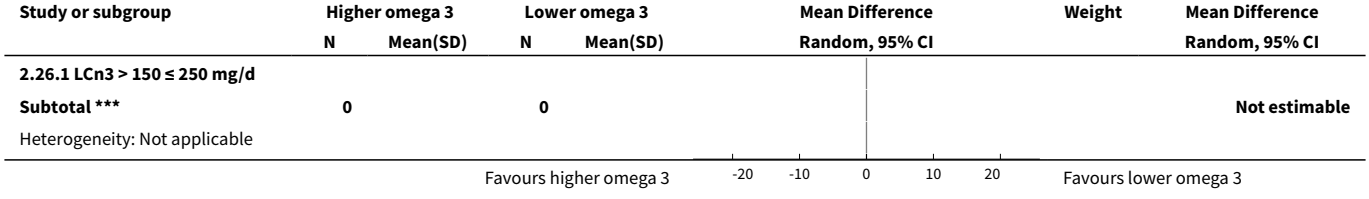
Favours higher omega 3 — Favours lower omega 3



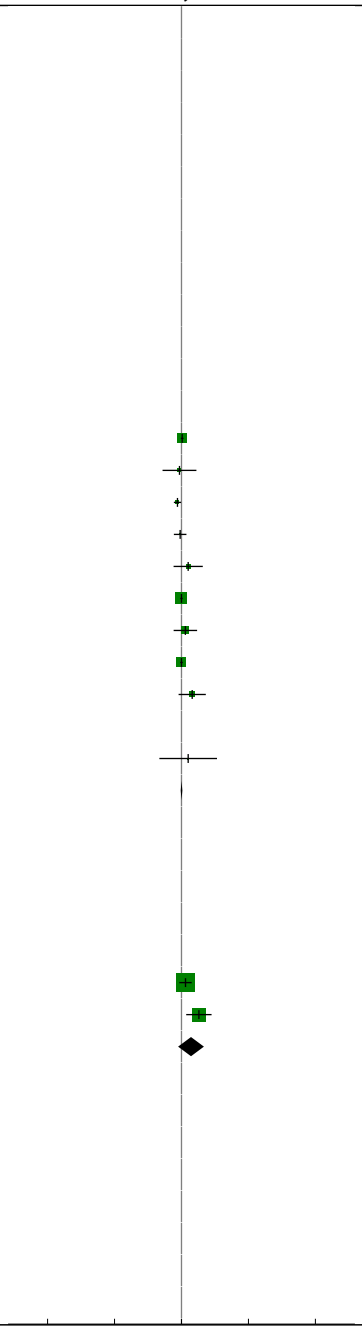
Analysis 2.25. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 25 BMI, kg/m²- LCn3 - SA by compliance and study size.



Analysis 2.26. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 26 BMI, kg/m² - LCn3 - subgroup by dose.

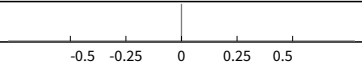


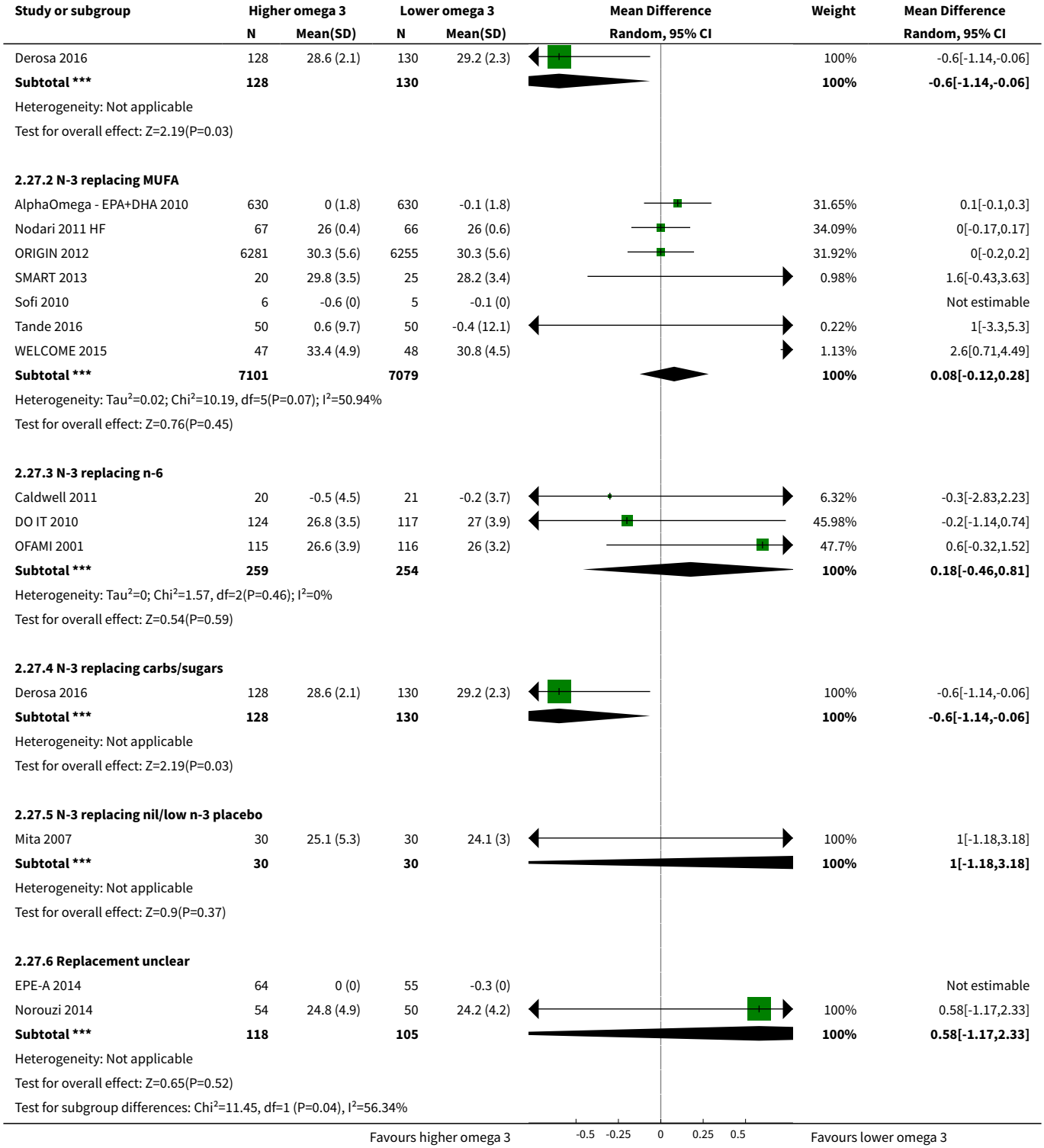
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for overall effect: Not applicable							
2.26.2 LCn3 ≤ 150 mg/d							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.26.3 LCn3 > 250 ≤ 400 mg/d							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.26.4 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: Tau^2=0; Chi^2=9.77, df=9(P=0.37); I^2=7.85%							
Test for overall effect: Z=0.12(P=0.9)							
2.26.5 LCn3 > 2.4 ≤ 4.4 g/d							
EPE-A 2014	64	0 (0)	55	-0.3 (0)			Not estimable
OFAMI 2001	115	26.6 (3.9)	116	26 (3.2)		58.9%	0.6[-0.32,1.52]
WELCOME 2015	47	33.4 (4.9)	48	30.8 (4.5)		41.1%	2.6[0.71,4.49]
Subtotal ***	**226**		**219**			**100%**	**1.42[-0.51,3.35]**
Heterogeneity: Tau^2=1.42; Chi^2=3.47, df=1(P=0.06); I^2=71.17%							
Test for overall effect: Z=1.45(P=0.15)							
2.26.6 LCn3 > 4.4 g/d							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Chi^2=2.06, df=1 (P=0.15), I^2=51.41%							



Analysis 2.27. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 27 BMI, kg/m² - LCn3 - subgroup by replacement.

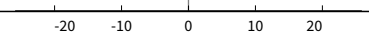
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.27.1 N-3 replacing SFA							





Analysis 2.28. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 28 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
2.28.1 Dietary advice							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.28.2 Supplemental foods							
AlphaOmega - EPA+DHA 2010	630	0 (1.8)	630	-0.1 (1.8)		25.26%	0.1[-0.1,0.3]
Subtotal ***	**630**		**630**			**25.26%**	**0.1[-0.1,0.3]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.99(P=0.32)							
2.28.3 Supplement (capsule)							
Caldwell 2011	20	-0.5 (4.5)	21	-0.2 (3.7)		0.6%	-0.3[-2.83,2.23]
Derosa 2016	128	28.6 (2.1)	130	29.2 (2.3)		9.65%	-0.6[-1.14,-0.06]
DO IT 2010	124	26.8 (3.5)	117	27 (3.9)		3.92%	-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)		0.8%	1[-1.18,3.18]
Nodari 2011 HF	67	26 (0.4)	66	26 (0.6)		26.9%	0[-0.17,0.17]
Norouzi 2014	54	24.8 (4.9)	50	24.2 (4.2)		1.22%	0.58[-1.17,2.33]
OFAMI 2001	115	26.6 (3.9)	116	26 (3.2)		4.04%	0.6[-0.32,1.52]
ORIGIN 2012	6281	30.3 (5.6)	6255	30.3 (5.6)		25.44%	0[-0.2,0.2]
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)		1.05%	2.6[0.71,4.49]
Subtotal ***	**6986**		**6943**			**73.82%**	**0.01[-0.25,0.27]**
Heterogeneity: Tau²=0.04; Chi²=15.32, df=9(P=0.08); I²=41.27%							
Test for overall effect: Z=0.08(P=0.94)							
2.28.4 Any combination							
SMART 2013	20	29.8 (3.5)	25	28.2 (3.4)		0.92%	1.6[-0.43,3.63]
Subtotal ***	**20**		**25**			**0.92%**	**1.6[-0.43,3.63]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.54(P=0.12)							
Total ***	**7636**		**7598**			**100%**	**0.04[-0.16,0.24]**
Heterogeneity: Tau²=0.03; Chi²=18.44, df=11(P=0.07); I²=40.34%							
Test for overall effect: Z=0.41(P=0.68)							
Test for subgroup differences: Chi²=2.47, df=1 (P=0.29), I²=19.04%							



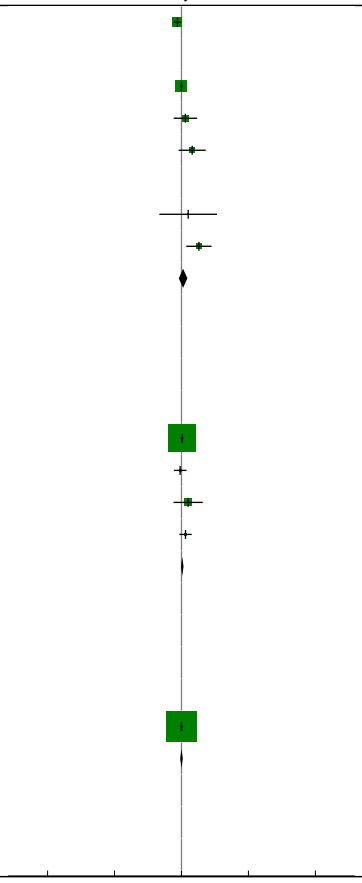
Favours higher omega 3 — Favours lower omega 3

Analysis 2.29. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 29 BMI, kg/m² - 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
2.29.1 Medium duration 1 to < 2 years in study							
Caldwell 2011	20	-0.5 (4.5)	21	-0.2 (3.7)		5.5%	-0.3[-2.83,2.23]

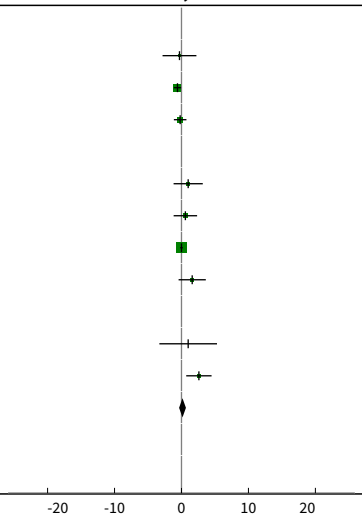
Favours higher omega 3 — Favours lower omega 3

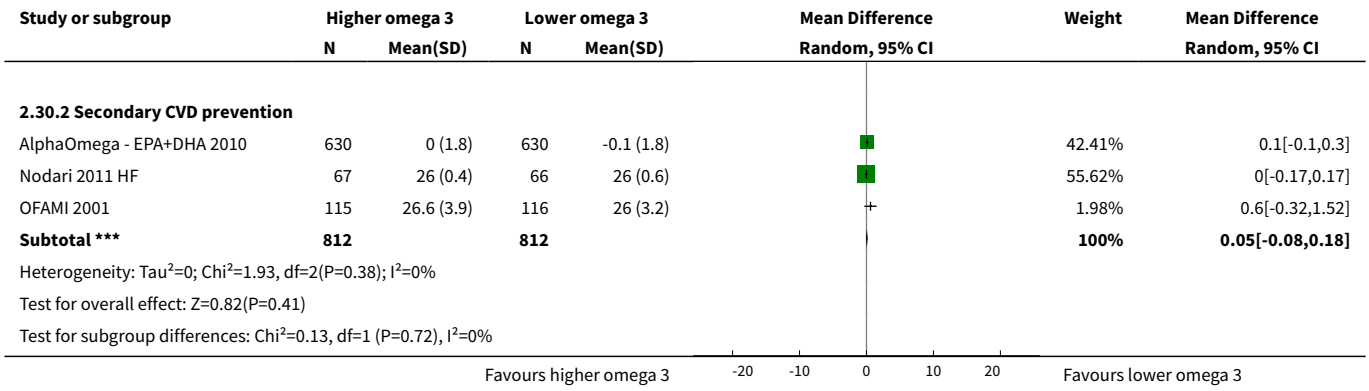
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Derosa 2016	128	28.6 (2.1)	130	29.2 (2.3)		29.57%	-0.6[-1.14,-0.06]
EPE-A 2014	64	0 (0)	55	-0.3 (0)			Not estimable
Nodari 2011 HF	67	26 (0.4)	66	26 (0.6)		36.29%	0[-0.17,0.17]
Norouzi 2014	54	24.8 (4.9)	50	24.2 (4.2)		9.87%	0.58[-1.17,2.33]
SMART 2013	20	29.8 (3.5)	25	28.2 (3.4)		7.88%	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)		2.1%	1[-3.3,5.3]
WELCOME 2015	47	33.4 (4.9)	48	30.8 (4.5)		8.79%	2.6[0.71,4.49]
Subtotal ***	**456**		**450**			**100%**	**0.24[-0.4,0.88]**
Heterogeneity: Tau^2=0.29; Chi^2=15.04, df=6(P=0.02); I^2=60.11%							
Test for overall effect: Z=0.73(P=0.47)							
2.29.2 Medium-long duration: 2 to < 4 years in study							
AlphaOmega - EPA+DHA 2010	630	0 (1.8)	630	-0.1 (1.8)		90.92%	0.1[-0.1,0.3]
DO IT 2010	124	26.8 (3.5)	117	27 (3.9)		4.09%	-0.2[-1.14,0.74]
Mita 2007	30	25.1 (5.3)	30	24.1 (3)		0.76%	1[-1.18,3.18]
OFAMI 2001	115	26.6 (3.9)	116	26 (3.2)		4.24%	0.6[-0.32,1.52]
Subtotal ***	**899**		**893**			**100%**	**0.12[-0.07,0.31]**
Heterogeneity: Tau^2=0; Chi^2=2.16, df=3(P=0.54); I^2=0%							
Test for overall effect: Z=1.2(P=0.23)							
2.29.3 Long duration ≥ 4 years in study							
ORIGIN 2012	6281	30.3 (5.6)	6255	30.3 (5.6)		100%	0[-0.2,0.2]
Subtotal ***	**6281**		**6255**			**100%**	**0[-0.2,0.2]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Chi^2=0.98, df=1 (P=0.61), I^2=0%							



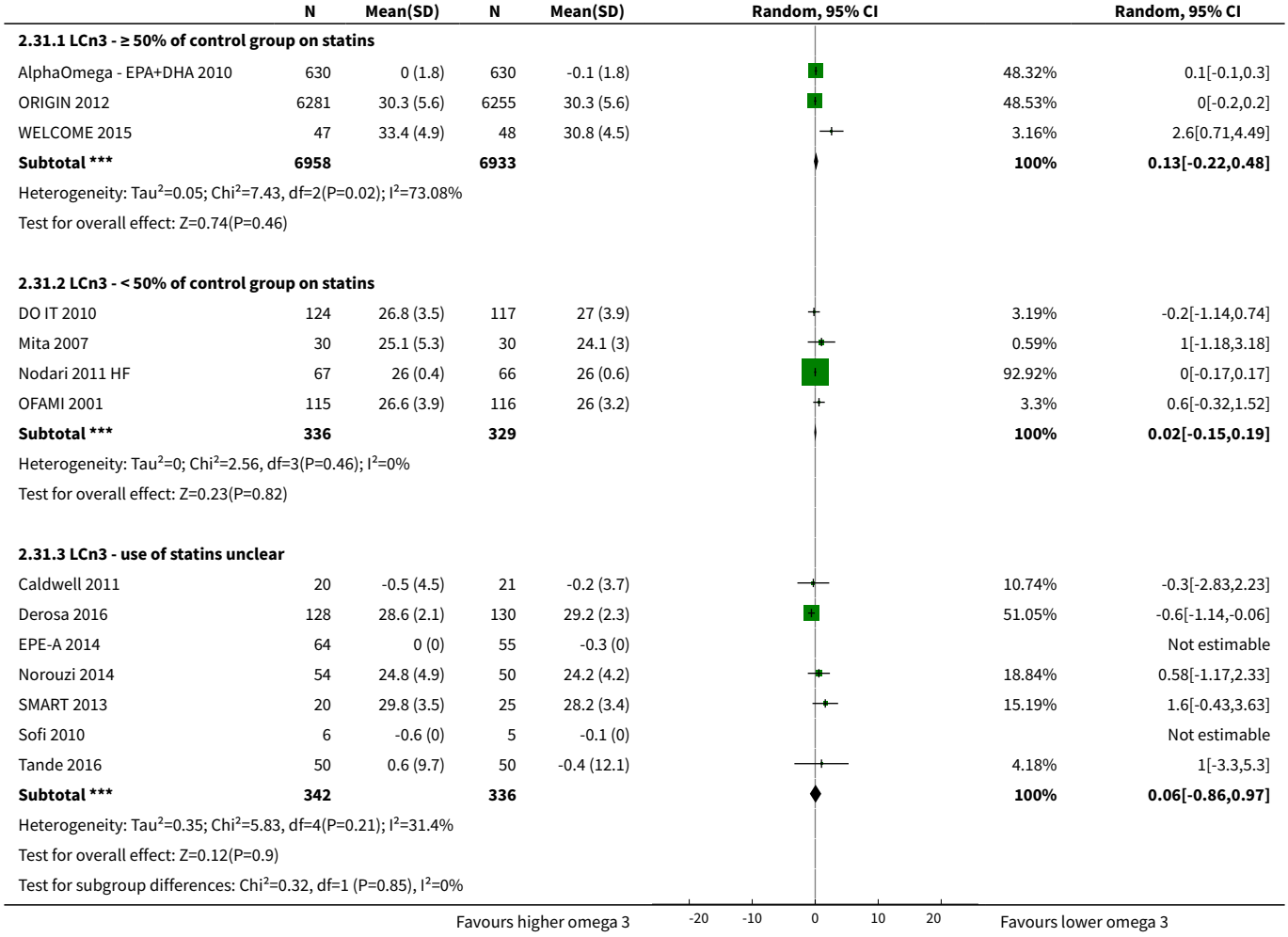
Analysis 2.30. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 30 BMI, kg/m² - LCn3 - subgroup by primary or secondary prevention.

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
2.30.1 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)							

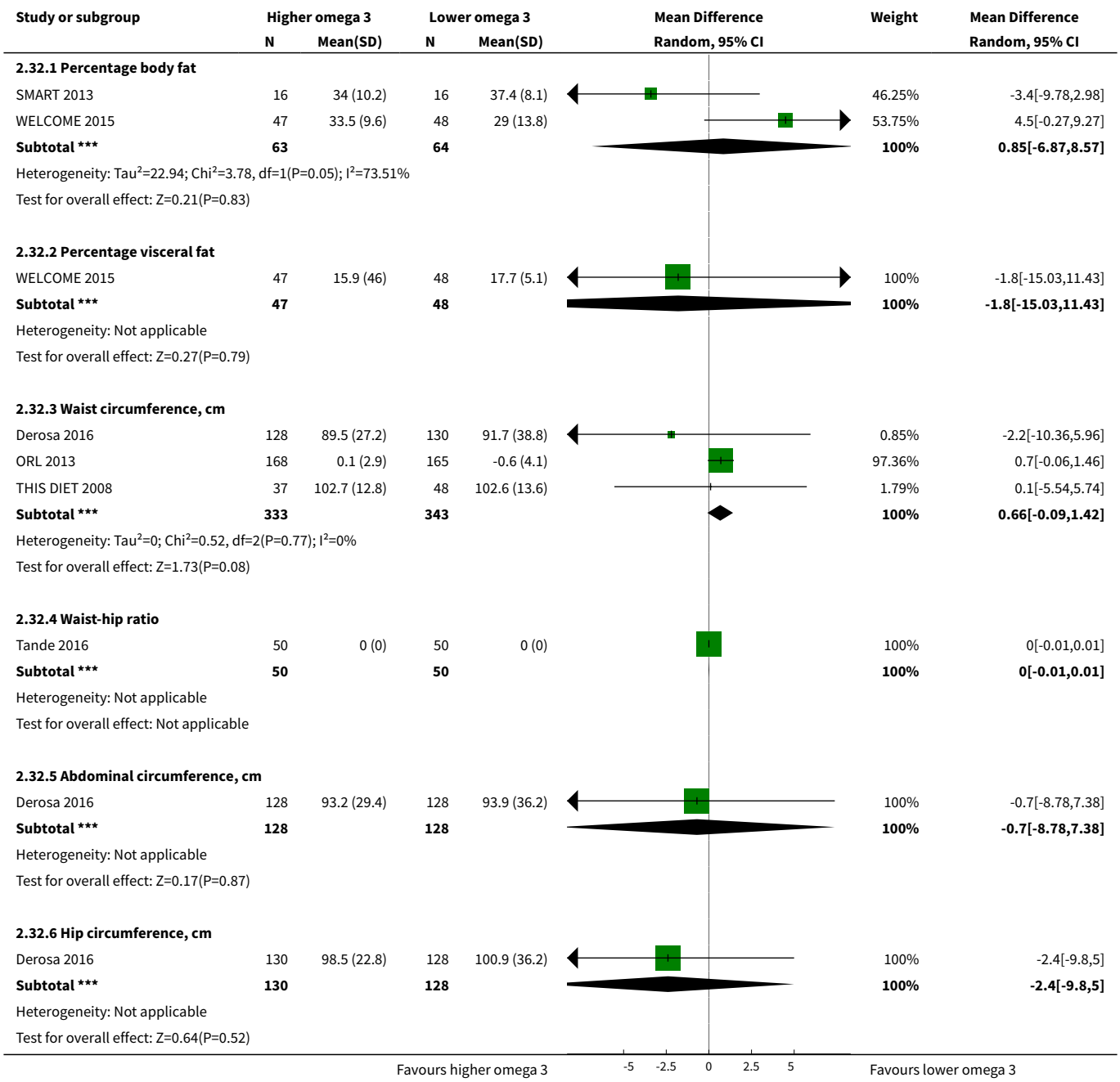




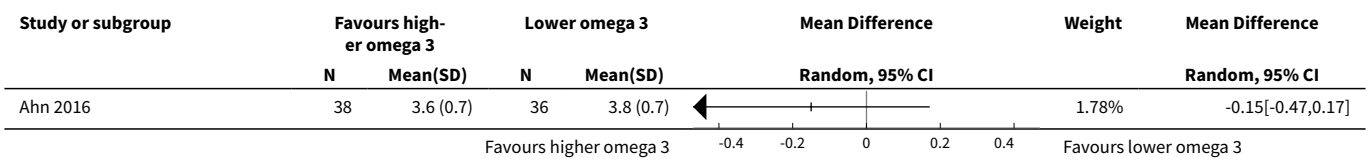
Analysis 2.31. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 31 BMI, kg/m² - LCn3 - subgroup by statin use.

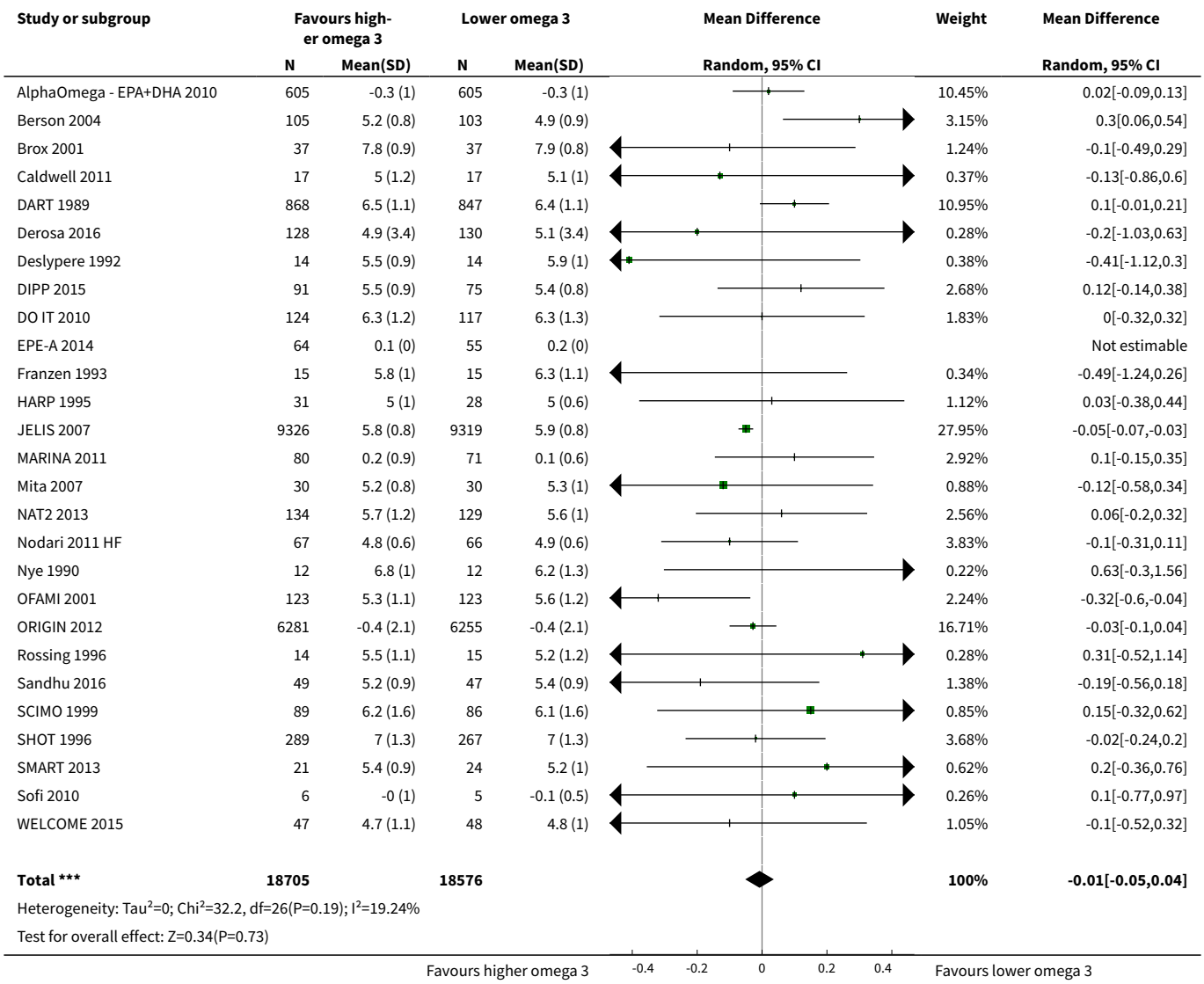


Analysis 2.32. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 32 Other measures of adiposity - LCn3.

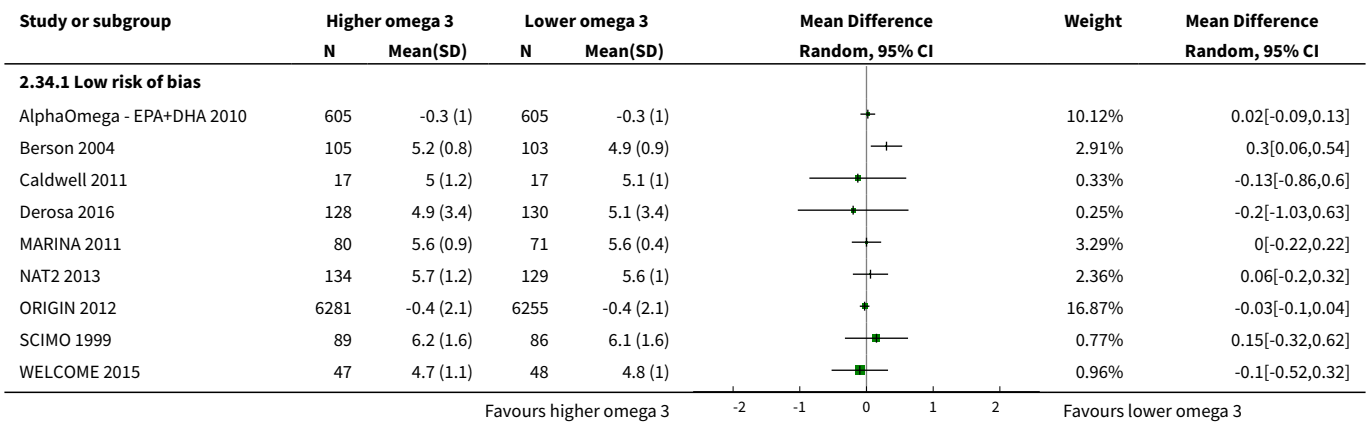


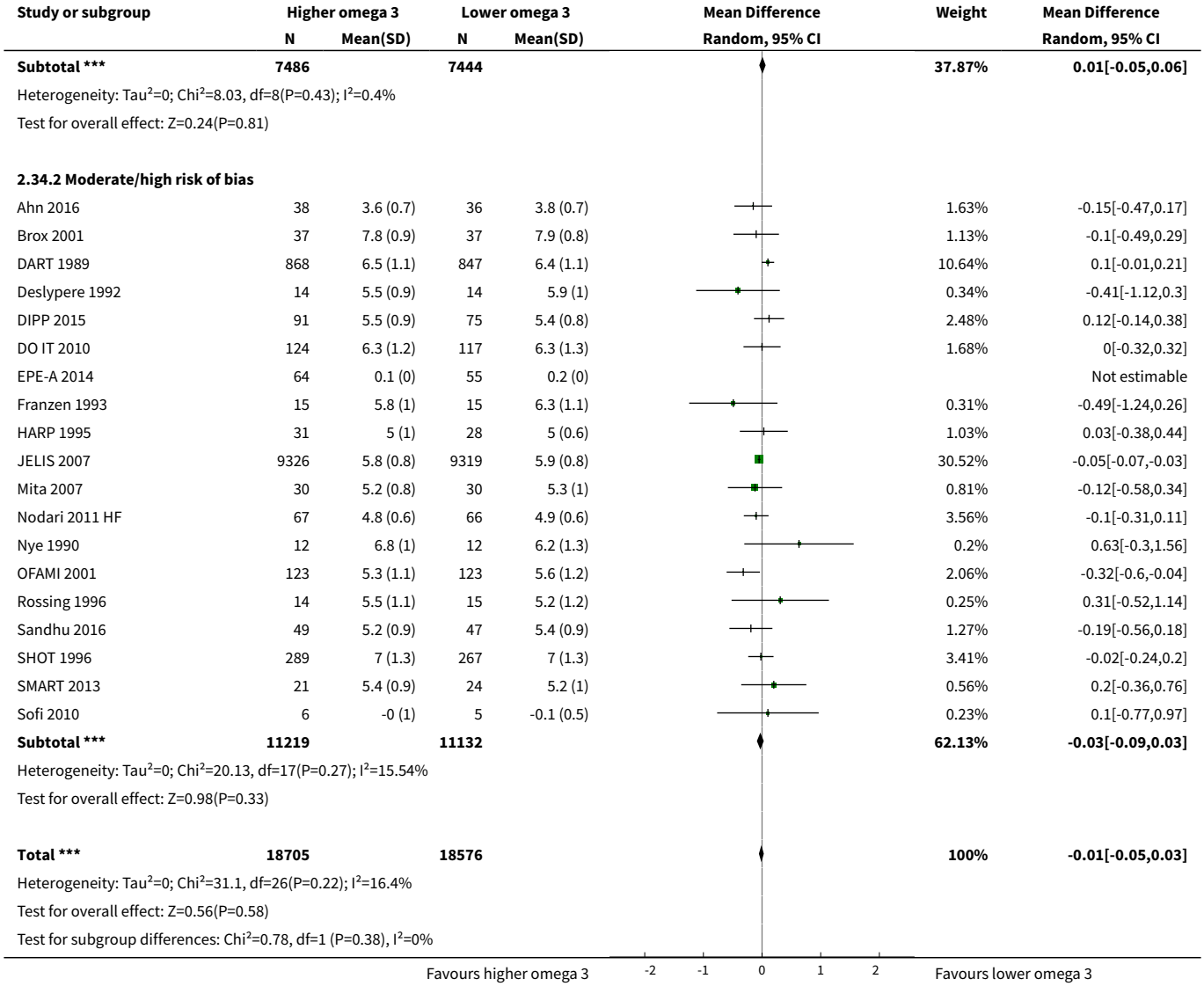
Analysis 2.33. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 33 Total cholesterol, serum, mmoL/L - LCn3.



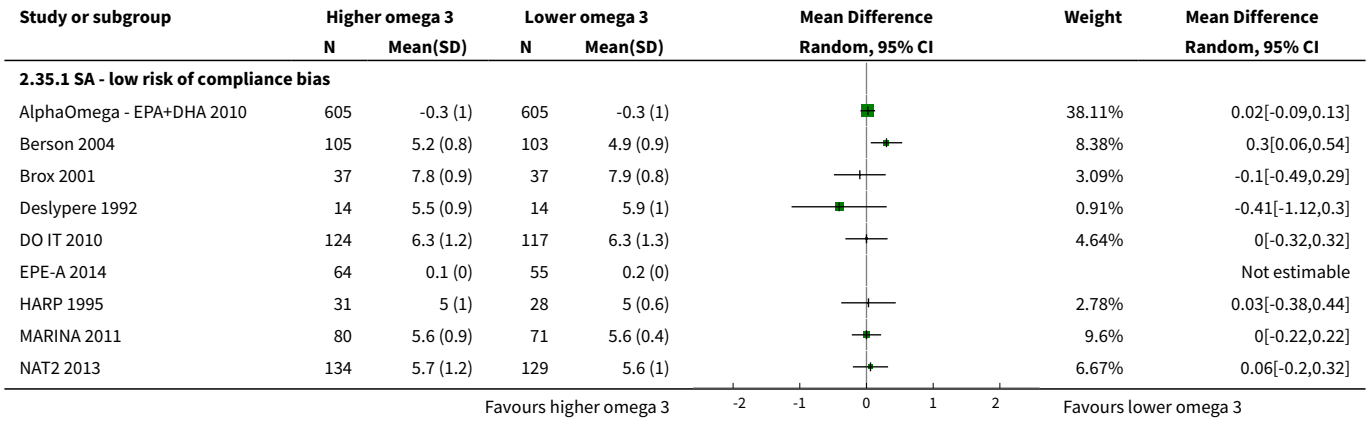


Analysis 2.34. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 34 TC, mmoL/L - LCn3 - SA by summary risk of bias.

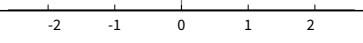




Analysis 2.35. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 35 TC, mmoL/L - LCn3 - SA by compliance and study size.

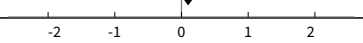


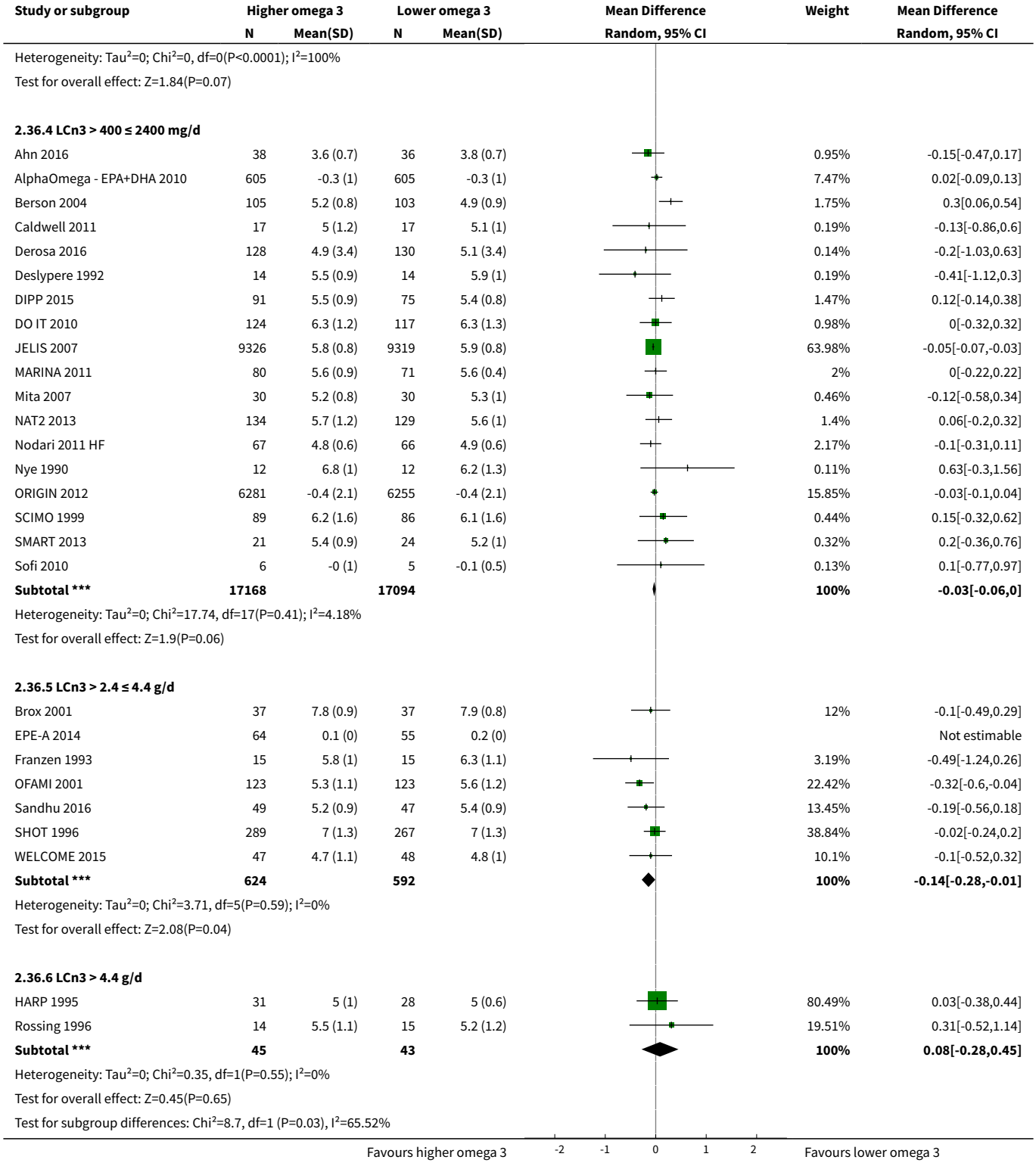
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Nodari 2011 HF	67	4.8 (0.6)	66	4.9 (0.6)		10.47%	-0.1[-0.31,0.11]
Rossing 1996	14	5.5 (1.1)	15	5.2 (1.2)		0.67%	0.31[-0.52,1.14]
SCIMO 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)							
2.35.2 SA - 100+ randomised							
AlphaOmega - EPA+DHA 2010	605	-0.3 (1)	605	-0.3 (1)		12.2%	0.02[-0.09,0.13]
Berson 2004	105	5.2 (0.8)	103	4.9 (0.9)		4.38%	0.3[0.06,0.54]
DART 1989	868	6.5 (1.1)	847	6.4 (1.1)		12.65%	0.1[-0.01,0.21]
Derosa 2016	128	4.9 (3.4)	130	5.1 (3.4)		0.42%	-0.2[-1.03,0.63]
DIPP 2015	91	5.5 (0.9)	75	5.4 (0.8)		3.78%	0.12[-0.14,0.38]
DO IT 2010	124	6.3 (1.2)	117	6.3 (1.3)		2.64%	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)		23.54%	-0.05[-0.07,-0.03]
MARINA 2011	80	5.6 (0.9)	71	5.6 (0.4)		4.89%	0[-0.22,0.22]
NAT2 2013	134	5.7 (1.2)	129	5.6 (1)		3.62%	0.06[-0.2,0.32]
Nodari 2011 HF	67	4.8 (0.6)	66	4.9 (0.6)		5.24%	-0.1[-0.31,0.11]
OFAMI 2001	123	5.3 (1.1)	123	5.6 (1.2)		3.19%	-0.32[-0.6,-0.04]
ORIGIN 2012	6281	-0.4 (2.1)	6255	-0.4 (2.1)		17.15%	-0.03[-0.1,0.04]
SCIMO 1999	89	6.2 (1.6)	86	6.1 (1.6)		1.25%	0.15[-0.32,0.62]
SHOT 1996	289	7 (1.3)	267	7 (1.3)		5.05%	-0.02[-0.24,0.2]
Subtotal ***	**18374**		**18248**			**100%**	**0[-0.05,0.06]**
Heterogeneity: Tau²=0; Chi²=23.61, df=13(P=0.03); I²=44.94%							
Test for overall effect: Z=0.11(P=0.92)							
Test for subgroup differences: Chi²=0.16, df=1 (P=0.69), I²=0%							



Analysis 2.36. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 36 TC, mmoL/L - LCn3 - subgroup by dose.

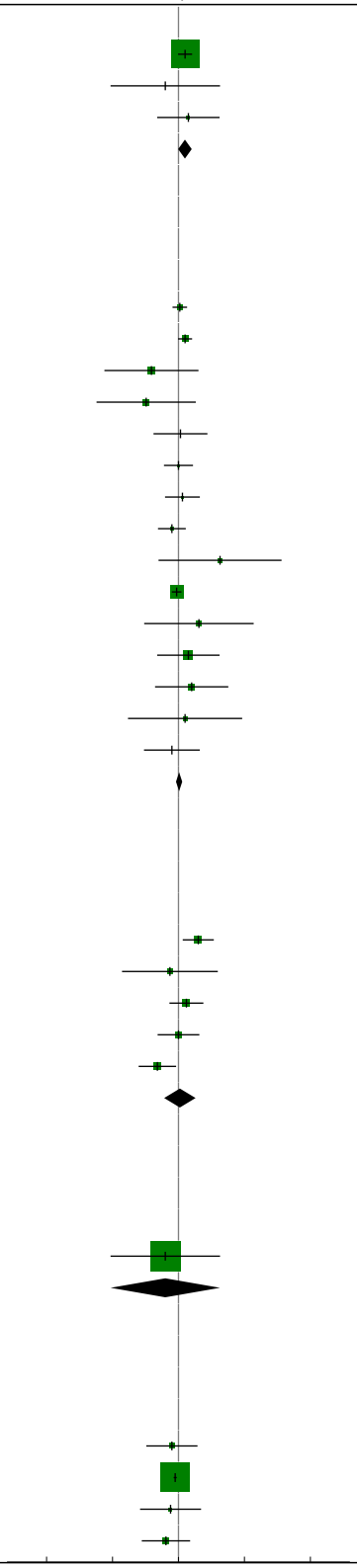
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.36.1 LCn3 ≤ 150 mg/d							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.36.2 LCn3 > 150 ≤ 250 mg/d							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.36.3 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]**



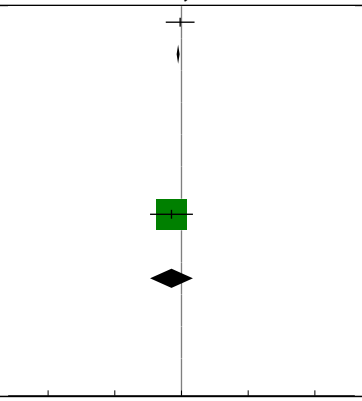


Analysis 2.37. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 37 TC, mmoL/L - LCn3 - subgroup by replacement.

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
2.37.1 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: Tau²=0; Chi²=0.54, df=2(P=0.76); I²=0%							
Test for overall effect: Z=1.86(P=0.06)							
2.37.2 N-3 replacing MUFA							
AlphaOmega - EPA+DHA 2010	605	-0.3 (1)	605	-0.3 (1)		18.35%	0.02[-0.09,0.13]
DART 1989	868	6.5 (1.1)	847	6.4 (1.1)		19.73%	0.1[-0.01,0.21]
Deslypere 1992	14	5.5 (0.9)	14	5.9 (1)		0.44%	-0.41[-1.12,0.3]
Franzen 1993	15	5.8 (1)	15	6.3 (1.1)		0.4%	-0.49[-1.24,0.26]
HARP 1995	31	5 (1)	28	5 (0.6)		1.34%	0.03[-0.38,0.44]
MARINA 2011	80	5.6 (0.9)	71	5.6 (0.4)		4.62%	0[-0.22,0.22]
NAT2 2013	134	5.7 (1.2)	129	5.6 (1)		3.21%	0.06[-0.2,0.32]
Nodari 2011 HF	67	4.8 (0.6)	66	4.9 (0.6)		5.04%	-0.1[-0.31,0.11]
Nye 1990	12	6.8 (1)	12	6.2 (1.3)		0.26%	0.63[-0.3,1.56]
ORIGIN 2012	6281	-0.4 (2.1)	6255	-0.4 (2.1)		43.02%	-0.03[-0.1,0.04]
Rossing 1996	14	5.5 (1.1)	15	5.2 (1.2)		0.32%	0.31[-0.52,1.14]
SCIMO 1999	89	6.2 (1.6)	86	6.1 (1.6)		1%	0.15[-0.32,0.62]
SMART 2013	21	5.4 (0.9)	24	5.2 (1)		0.73%	0.2[-0.36,0.76]
Sofi 2010	6	-0 (1)	5	-0.1 (0.5)		0.3%	0.1[-0.77,0.97]
WELCOME 2015	47	4.7 (1.1)	48	4.8 (1)		1.25%	-0.1[-0.52,0.32]
Subtotal ***	**8284**		**8220**			**100%**	**0.01[-0.04,0.06]**
Heterogeneity: Tau²=0; Chi²=11.36, df=14(P=0.66); I²=0%							
Test for overall effect: Z=0.4(P=0.69)							
2.37.3 N-3 replacing n-6							
Berson 2004	105	5.2 (0.8)	103	4.9 (0.9)		24.89%	0.3[0.06,0.54]
Caldwell 2011	17	5 (1.2)	17	5.1 (1)		8.11%	-0.13[-0.86,0.6]
DIPP 2015	91	5.5 (0.9)	75	5.4 (0.8)		23.77%	0.12[-0.14,0.38]
DO IT 2010	124	6.3 (1.2)	117	6.3 (1.3)		20.81%	0[-0.32,0.32]
OFAMI 2001	123	5.3 (1.1)	123	5.6 (1.2)		22.42%	-0.32[-0.6,-0.04]
Subtotal ***	**460**		**435**			**100%**	**0.02[-0.22,0.26]**
Heterogeneity: Tau²=0.04; Chi²=11.47, df=4(P=0.02); I²=65.12%							
Test for overall effect: Z=0.17(P=0.86)							
2.37.4 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: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=0.47(P=0.64)							
2.37.5 N-3 replacing nil/low n-3 placebo							
Brox 2001	37	7.8 (0.9)	37	7.9 (0.8)		0.33%	-0.1[-0.49,0.29]
JELIS 2007	9326	5.8 (0.8)	9319	5.9 (0.8)		97.97%	-0.05[-0.07,-0.03]
Mita 2007	30	5.2 (0.8)	30	5.3 (1)		0.24%	-0.12[-0.58,0.34]
Sandhu 2016	49	5.2 (0.9)	47	5.4 (0.9)		0.38%	-0.19[-0.56,0.18]



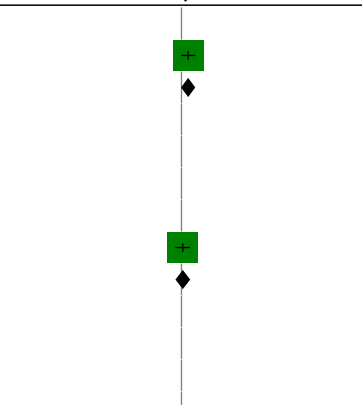
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
SHOT 1996	289	7 (1.3)	267	7 (1.3)		1.08%	-0.02[-0.24,0.2]
Subtotal ***	**9731**		**9700**			**100%**	**-0.05[-0.07,-0.03]**
Heterogeneity: Tau^2=0; Chi^2=0.78, df=4(P=0.94); I^2=0%							
Test for overall effect: Z=4.41(P<0.0001)							
2.37.6 Replacement unclear							
Ahn 2016	38	3.6 (0.7)	36	3.8 (0.7)		100%	-0.15[-0.47,0.17]
EPE-A 2014	64	0.1 (0)	55	0.2 (0)			Not estimable
Subtotal ***	**102**		**91**			**100%**	**-0.15[-0.47,0.17]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.91(P=0.36)							
Test for subgroup differences: Chi^2=12.47, df=1 (P=0.03), I^2=59.89%							



Favours higher omega 3 — Favours lower omega 3

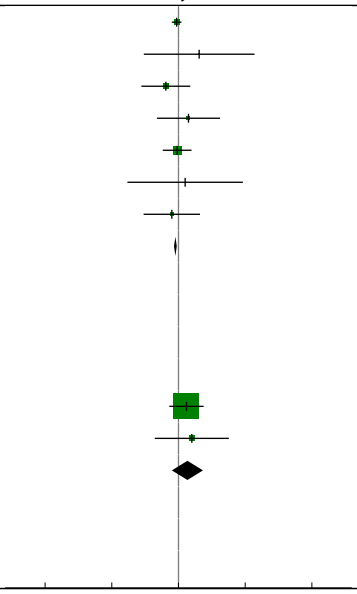
Analysis 2.38. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 38 TC, mmoL/L - LCn3 - subgroup by intervention type.

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
2.38.1 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: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=1.84(P=0.07)							
2.38.2 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)							
2.38.3 Supplement (capsule)							
Ahn 2016	38	3.6 (0.7)	36	3.8 (0.7)		0.42%	-0.15[-0.47,0.17]
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)		0.09%	-0.41[-1.12,0.3]
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
Franzen 1993	15	5.8 (1)	15	6.3 (1.1)		0.08%	-0.49[-1.24,0.26]
HARP 1995	31	5 (1)	28	5 (0.6)		0.26%	0.03[-0.38,0.44]
JELIS 2007	9326	5.8 (0.8)	9319	5.9 (0.8)		84.11%	-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]
NAT2 2013	134	5.7 (1.2)	129	5.6 (1)		0.62%	0.06[-0.2,0.32]
Nodari 2011 HF	67	4.8 (0.6)	66	4.9 (0.6)		0.97%	-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)		0.54%	-0.32[-0.6,-0.04]



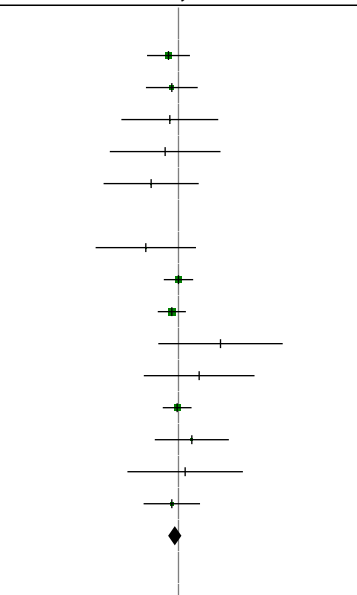
Favours higher omega 3 — Favours lower omega 3

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
ORIGIN 2012	6281	-0.4 (2.1)	6255	-0.4 (2.1)		8.32%	-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]
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)		0.93%	-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)		0.24%	-0.1[-0.52,0.32]
Subtotal * **	**17120**		**17025**			**100%**	**-0.05[-0.07,-0.03]**
Heterogeneity: Tau²=0; Chi²=20.78, df=22(P=0.53); I²=0%							
Test for overall effect: Z=4.39(P<0.0001)							
2.38.4 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)							
Test for subgroup differences: Chi²=10.26, df=1 (P=0.02), I²=70.75%							

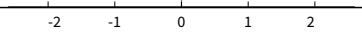


Analysis 2.39. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 39 TC, mmoL/L - LCn3 - subgroup by duration.

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
2.39.1 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)							
2.39.2 Medium-long duration: 2 to < 4 years in study							
AlphaOmega - EPA+DHA 2010	605	-0.3 (1)	605	-0.3 (1)		30.06%	0.02[-0.09,0.13]
DART 1989	868	6.5 (1.1)	847	6.4 (1.1)		31.53%	0.1[-0.01,0.21]
DIPP 2015	91	5.5 (0.9)	75	5.4 (0.8)		7.62%	0.12[-0.14,0.38]



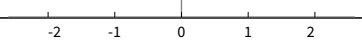
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
DO IT 2010	124	6.3 (1.2)	117	6.3 (1.3)		5.18%	0[-0.32,0.32]
HARP 1995	31	5 (1)	28	5 (0.6)		3.18%	0.03[-0.38,0.44]
Mita 2007	30	5.2 (0.8)	30	5.3 (1)		2.5%	-0.12[-0.58,0.34]
NAT2 2013	134	5.7 (1.2)	129	5.6 (1)		7.26%	0.06[-0.2,0.32]
OFAMI 2001	123	5.3 (1.1)	123	5.6 (1.2)		6.35%	-0.32[-0.6,-0.04]
Sandhu 2016	49	5.2 (0.9)	47	5.4 (0.9)		3.92%	-0.19[-0.56,0.18]
SCIMO 1999	89	6.2 (1.6)	86	6.1 (1.6)		2.39%	0.15[-0.32,0.62]
Subtotal ***	**2144**		**2087**			**100%**	**0.02[-0.05,0.1]**
Heterogeneity: Tau²=0; Chi²=10.11, df=9(P=0.34); I²=11.01%							
Test for overall effect: Z=0.66(P=0.51)							
2.39.3 Long duration ≥ 4 years in study							
Berson 2004	105	5.2 (0.8)	103	4.9 (0.9)		12.04%	0.3[0.06,0.54]
JELIS 2007	9326	5.8 (0.8)	9319	5.9 (0.8)		49.08%	-0.05[-0.07,-0.03]
ORIGIN 2012	6281	-0.4 (2.1)	6255	-0.4 (2.1)		38.88%	-0.03[-0.1,0.04]
Subtotal ***	**15712**		**15677**			**100%**	**0[-0.09,0.09]**
Heterogeneity: Tau²=0; Chi²=8.64, df=2(P=0.01); I²=76.85%							
Test for overall effect: Z=0.01(P=0.99)							
Test for subgroup differences: Chi²=1.62, df=1 (P=0.45), I²=0%							



Favours higher omega 3 — Favours lower omega 3

Analysis 2.40. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 40 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
2.40.1 Primary prevention							
Berson 2004	105	5.2 (0.8)	103	4.9 (0.9)		0.81%	0.3[0.06,0.54]
Brox 2001	37	7.8 (0.9)	37	7.9 (0.8)		0.3%	-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)		0.09%	-0.41[-1.12,0.3]
DIPP 2015	91	5.5 (0.9)	75	5.4 (0.8)		0.68%	0.12[-0.14,0.38]
DO IT 2010	124	6.3 (1.2)	117	6.3 (1.3)		0.45%	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)		86.95%	-0.05[-0.07,-0.03]
MARINA 2011	80	5.6 (0.9)	71	5.6 (0.4)		0.92%	0[-0.22,0.22]
Mita 2007	30	5.2 (0.8)	30	5.3 (1)		0.21%	-0.12[-0.58,0.34]
ORIGIN 2012	6281	-0.4 (2.1)	6255	-0.4 (2.1)		8.6%	-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)		0.33%	-0.19[-0.56,0.18]
SMART 2013	21	5.4 (0.9)	24	5.2 (1)		0.15%	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)		0.25%	-0.1[-0.52,0.32]
Subtotal ***	**16434**		**16362**			**100%**	**-0.04[-0.07,-0.02]**
Heterogeneity: Tau²=0; Chi²=14.05, df=15(P=0.52); I²=0%							
Test for overall effect: Z=4.09(P<0.0001)							
2.40.2 Secondary prevention							



Favours higher omega 3 — Favours lower omega 3

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
Ahn 2016	38	3.6 (0.7)	36	3.8 (0.7)		5.94%	-0.15[-0.47,0.17]
AlphaOmega - EPA+DHA 2010	605	-0.3 (1)	605	-0.3 (1)		23.21%	0.02[-0.09,0.13]
DART 1989	868	6.5 (1.1)	847	6.4 (1.1)		23.87%	0.1[-0.01,0.21]
Franzen 1993	15	5.8 (1)	15	6.3 (1.1)		1.24%	-0.49[-1.24,0.26]
HARP 1995	31	5 (1)	28	5 (0.6)		3.91%	0.03[-0.38,0.44]
NAT2 2013	134	5.7 (1.2)	129	5.6 (1)		8.19%	0.06[-0.2,0.32]
Nodari 2011 HF	67	4.8 (0.6)	66	4.9 (0.6)		11.45%	-0.1[-0.31,0.11]
Nye 1990	12	6.8 (1)	12	6.2 (1.3)		0.82%	0.63[-0.3,1.56]
OFAMI 2001	123	5.3 (1.1)	123	5.6 (1.2)		7.29%	-0.32[-0.6,-0.04]
SCIMO 1999	89	6.2 (1.6)	86	6.1 (1.6)		2.99%	0.15[-0.32,0.62]
SHOT 1996	289	7 (1.3)	267	7 (1.3)		11.08%	-0.02[-0.24,0.2]
Subtotal * **	**2271**		**2214**			**100%**	**-0.01[-0.09,0.08]**
Heterogeneity: Tau^2=0; Chi^2=13.89, df=10(P=0.18); I^2=28.03%							
Test for overall effect: Z=0.18(P=0.86)							
Test for subgroup differences: Chi^2=0.66, df=1 (P=0.42), I^2=0%							

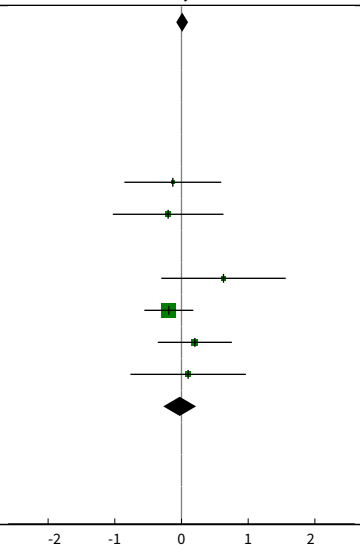
Favours higher omega 3 -2 -1 0 1 2 Favours lower omega 3

Analysis 2.41. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 41 TC, mmoL/L - LCn3 - subgroup by 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
2.41.1 LCn3 - ≥ 50% of control group on statins							
Ahn 2016	38	3.6 (0.7)	36	3.8 (0.7)		0.43%	-0.15[-0.47,0.17]
AlphaOmega - EPA+DHA 2010	605	-0.3 (1)	605	-0.3 (1)		3.65%	0.02[-0.09,0.13]
JELIS 2007	9326	5.8 (0.8)	9319	5.9 (0.8)		86.48%	-0.05[-0.07,-0.03]
NAT2 2013	134	5.7 (1.2)	129	5.6 (1)		0.64%	0.06[-0.2,0.32]
ORIGIN 2012	6281	-0.4 (2.1)	6255	-0.4 (2.1)		8.55%	-0.03[-0.1,0.04]
WELCOME 2015	47	4.7 (1.1)	48	4.8 (1)		0.25%	-0.1[-0.52,0.32]
Subtotal * **	**16431**		**16392**			**100%**	**-0.05[-0.07,-0.02]**
Heterogeneity: Tau^2=0; Chi^2=2.81, df=5(P=0.73); I^2=0%							
Test for overall effect: Z=4.22(P<0.0001)							
2.41.2 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]

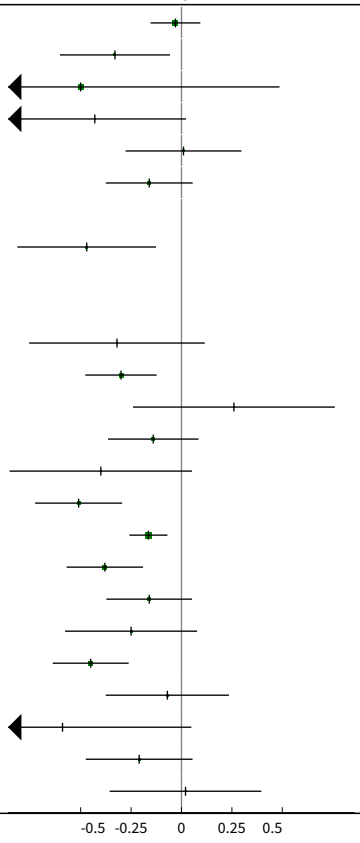
Favours higher omega 3 -2 -1 0 1 2 Favours lower omega 3

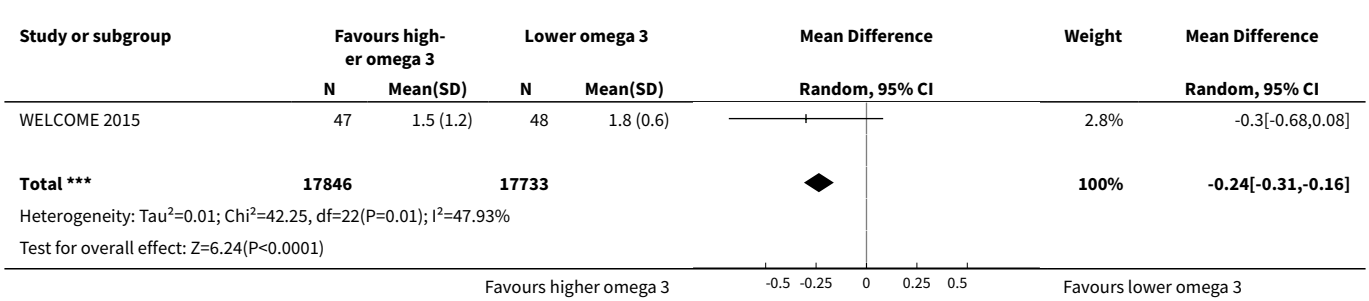
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Subtotal ***	**1977**		**1894**			**100%**	**0.01[-0.08,0.1]**
Heterogeneity: Tau²=0.01; Chi²=19.6, df=14(P=0.14); I²=28.57%							
Test for overall effect: Z=0.22(P=0.82)							
2.41.3 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]
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=1.44, df=1 (P=0.49), I²=0%							



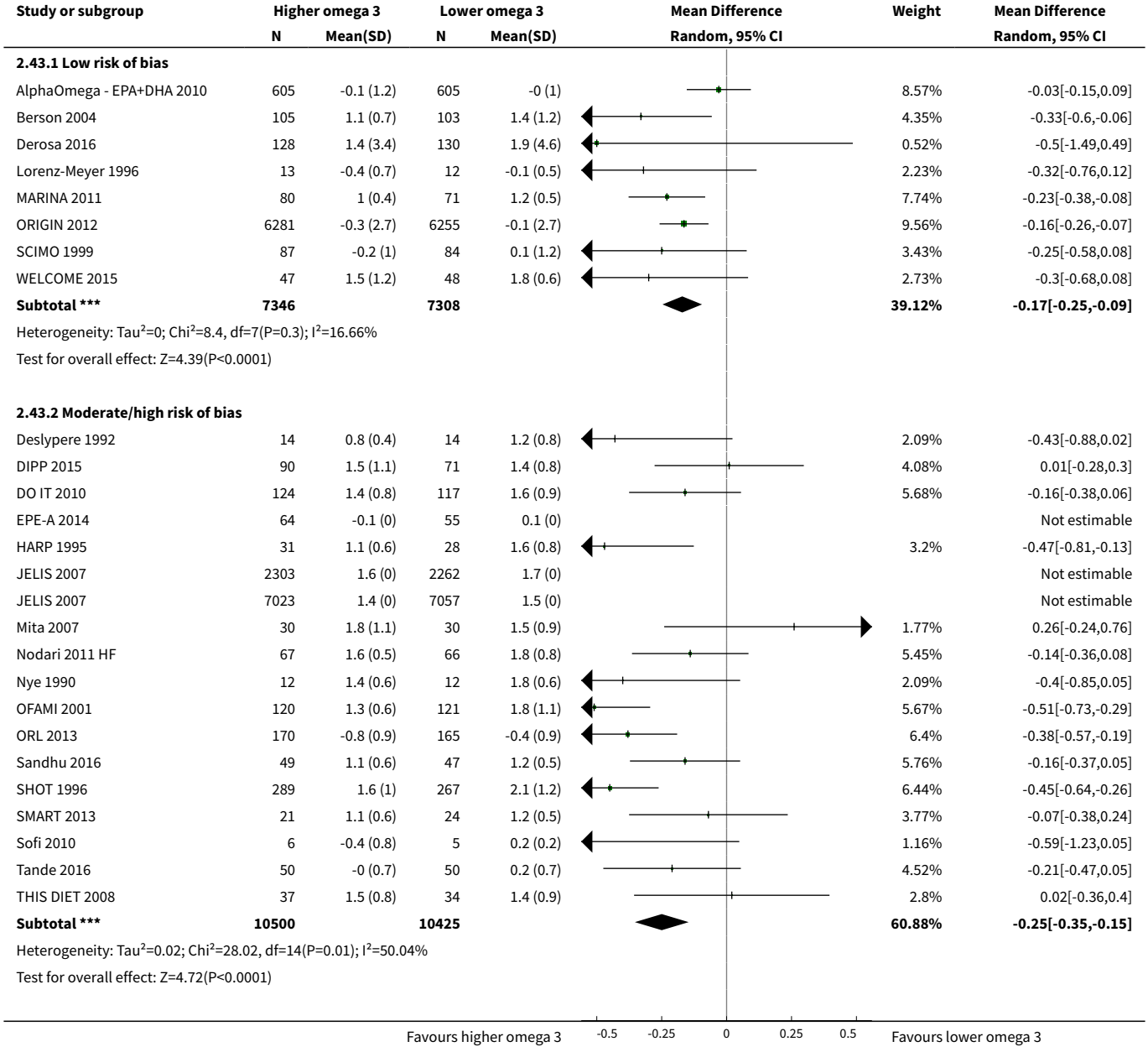
Analysis 2.42. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 42 Triglycerides, fasting, serum, mmoL/L - LCn3.

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]
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)		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]
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]

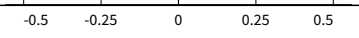




Analysis 2.43. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 43 TG, fasting, mmoL/L - LCn3 - SA by summary risk of bias.



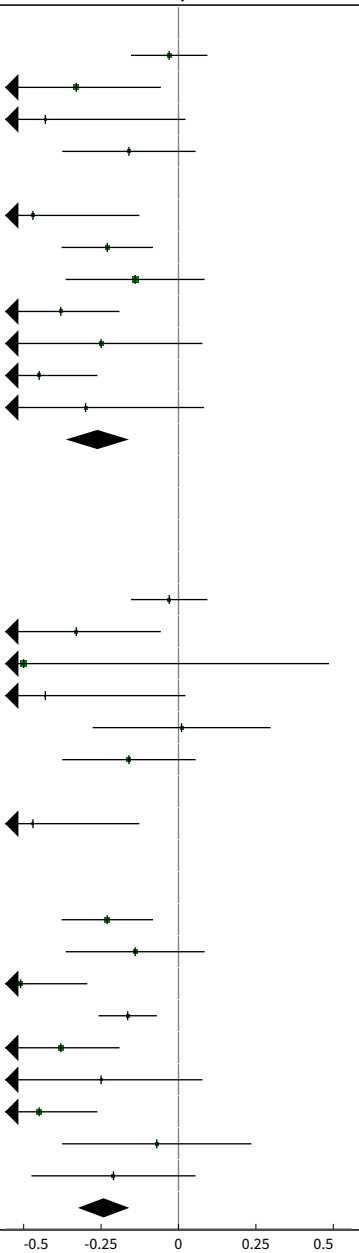
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Total ***	**17846**		**17733**			**100%**	**-0.23[-0.3,-0.16]**
Heterogeneity: Tau²=0.01; Chi²=41.33, df=22(P=0.01); I²=46.77%							
Test for overall effect: Z=6.25(P<0.0001)							
Test for subgroup differences: Chi²=1.45, df=1 (P=0.23), I²=31.05%							



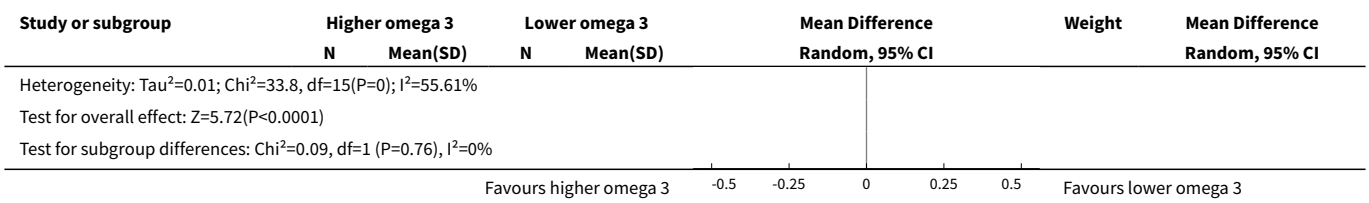
Favours higher omega 3 — Favours lower omega 3

Analysis 2.44. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 44 TG, fasting, mmoL/L - LCn3 - SA by compliance and study size.

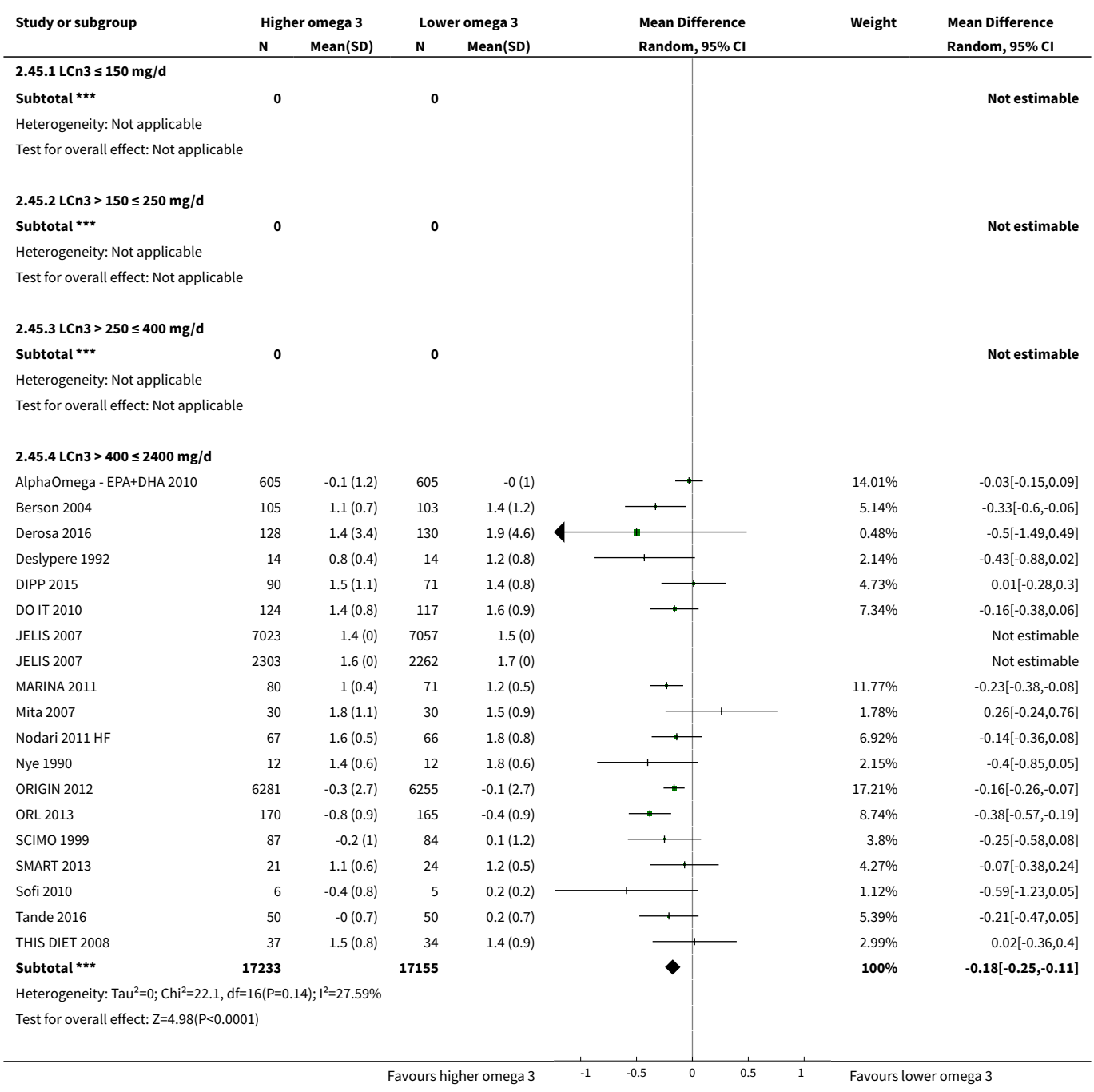
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.44.1 SA - low risk of compliance bias							
AlphaOmega - EPA+DHA 2010	605	-0.1 (1.2)	605	-0 (1)		14.6%	-0.03[-0.15,0.09]
Berson 2004	105	1.1 (0.7)	103	1.4 (1.2)		7.97%	-0.33[-0.6,-0.06]
Deslypere 1992	14	0.8 (0.4)	14	1.2 (0.8)		3.98%	-0.43[-0.88,0.02]
DO IT 2010	124	1.4 (0.8)	117	1.6 (0.9)		10.15%	-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)		5.97%	-0.47[-0.81,-0.13]
MARINA 2011	80	1 (0.4)	71	1.2 (0.5)		13.37%	-0.23[-0.38,-0.08]
Nodari 2011 HF	67	1.6 (0.5)	66	1.8 (0.8)		9.78%	-0.14[-0.36,0.08]
ORL 2013	170	-0.8 (0.9)	165	-0.4 (0.9)		11.31%	-0.38[-0.57,-0.19]
SCIMO 1999	87	-0.2 (1)	84	0.1 (1.2)		6.37%	-0.25[-0.58,0.08]
SHOT 1996	289	1.6 (1)	267	2.1 (1.2)		11.37%	-0.45[-0.64,-0.26]
WELCOME 2015	47	1.5 (1.2)	48	1.8 (0.6)		5.13%	-0.3[-0.68,0.08]
Subtotal ***	**1683**		**1623**			**100%**	**-0.26[-0.36,-0.16]**
Heterogeneity: Tau²=0.01; Chi²=22.03, df=10(P=0.01); I²=54.6%							
Test for overall effect: Z=5.04(P<0.0001)							
2.44.2 SA - 100+ randomised							
AlphaOmega - EPA+DHA 2010	605	-0.1 (1.2)	605	-0 (1)		10.25%	-0.03[-0.15,0.09]
Berson 2004	105	1.1 (0.7)	103	1.4 (1.2)		5.44%	-0.33[-0.6,-0.06]
Derosa 2016	128	1.4 (3.4)	130	1.9 (4.6)		0.67%	-0.5[-1.49,0.49]
Deslypere 1992	14	0.8 (0.4)	14	1.2 (0.8)		2.68%	-0.43[-0.88,0.02]
DIPP 2015	90	1.5 (1.1)	71	1.4 (0.8)		5.12%	0.01[-0.28,0.3]
DO IT 2010	124	1.4 (0.8)	117	1.6 (0.9)		7%	-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)		4.05%	-0.47[-0.81,-0.13]
JELIS 2007	2303	1.6 (0)	2262	1.7 (0)			Not estimable
JELIS 2007	7023	1.4 (0)	7057	1.5 (0)			Not estimable
MARINA 2011	80	1 (0.4)	71	1.2 (0.5)		9.34%	-0.23[-0.38,-0.08]
Nodari 2011 HF	67	1.6 (0.5)	66	1.8 (0.8)		6.73%	-0.14[-0.36,0.08]
OFAMI 2001	120	1.3 (0.6)	121	1.8 (1.1)		6.99%	-0.51[-0.73,-0.29]
ORIGIN 2012	6281	-0.3 (2.7)	6255	-0.1 (2.7)		11.33%	-0.16[-0.26,-0.07]
ORL 2013	170	-0.8 (0.9)	165	-0.4 (0.9)		7.83%	-0.38[-0.57,-0.19]
SCIMO 1999	87	-0.2 (1)	84	0.1 (1.2)		4.32%	-0.25[-0.58,0.08]
SHOT 1996	289	1.6 (1)	267	2.1 (1.2)		7.88%	-0.45[-0.64,-0.26]
SMART 2013	21	1.1 (0.6)	24	1.2 (0.5)		4.74%	-0.07[-0.38,0.24]
Tande 2016	50	-0 (0.7)	50	0.2 (0.7)		5.64%	-0.21[-0.47,0.05]
Subtotal ***	**17652**		**17545**			**100%**	**-0.24[-0.32,-0.16]**

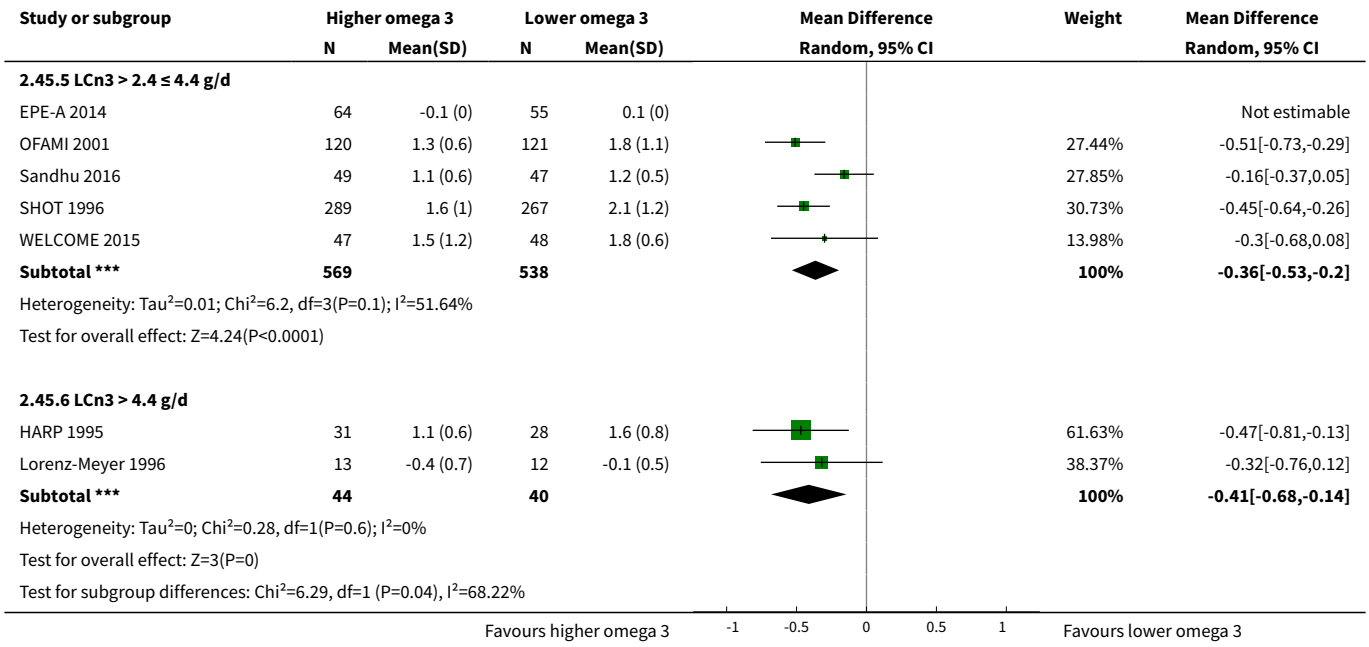


Favours higher omega 3 — Favours lower omega 3

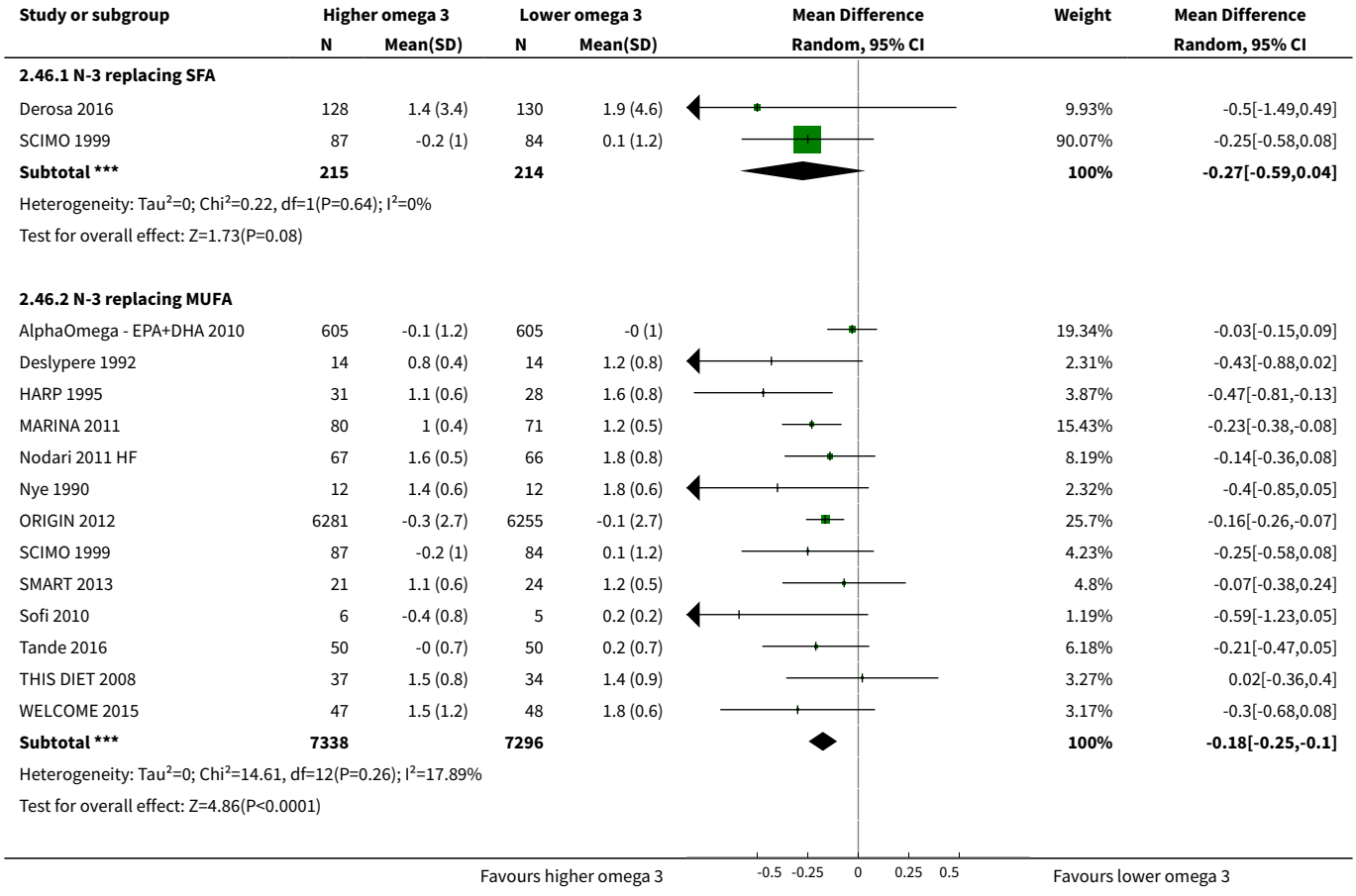


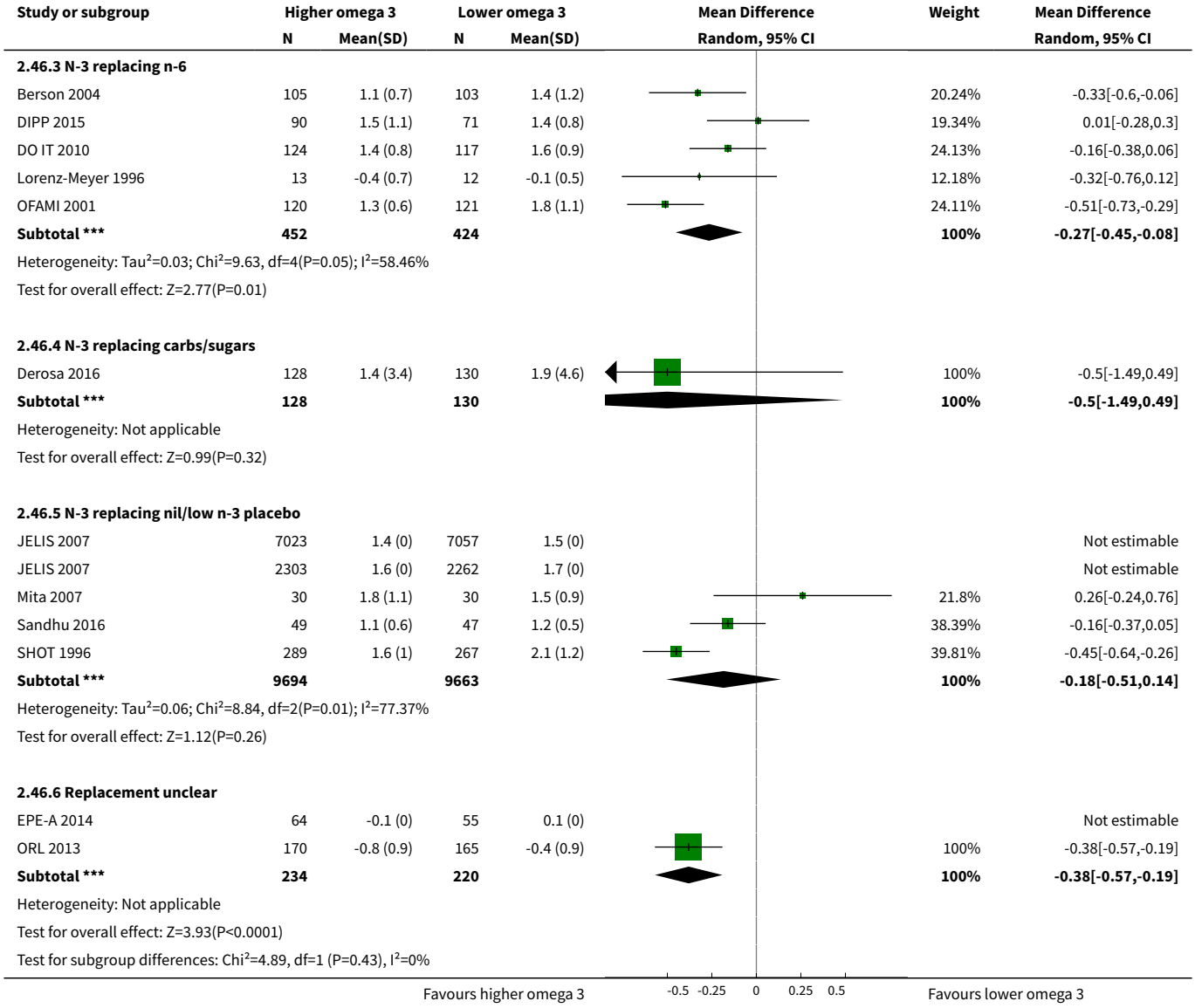
Analysis 2.45. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 45 TG, fasting, mmoL/L - LCn3 - subgroup by dose.



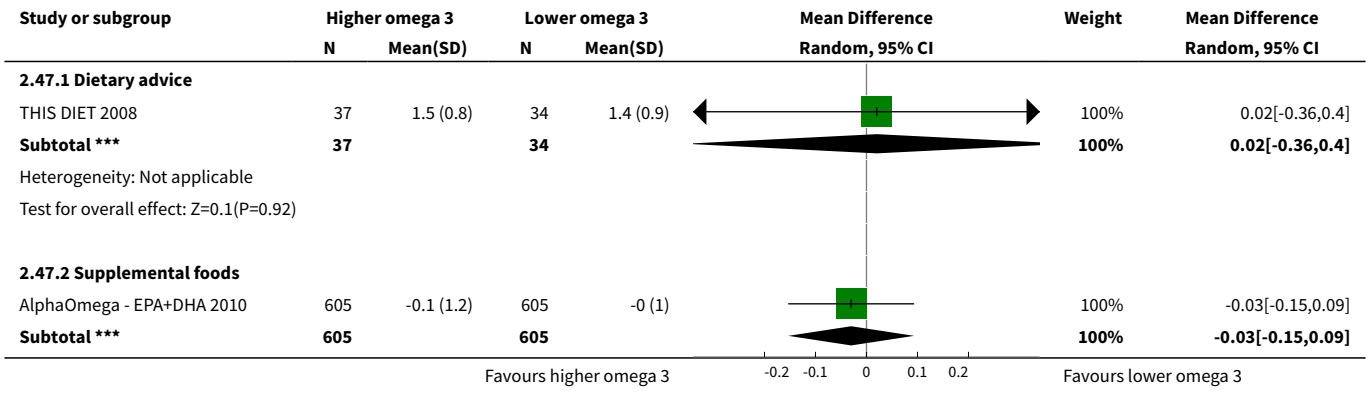


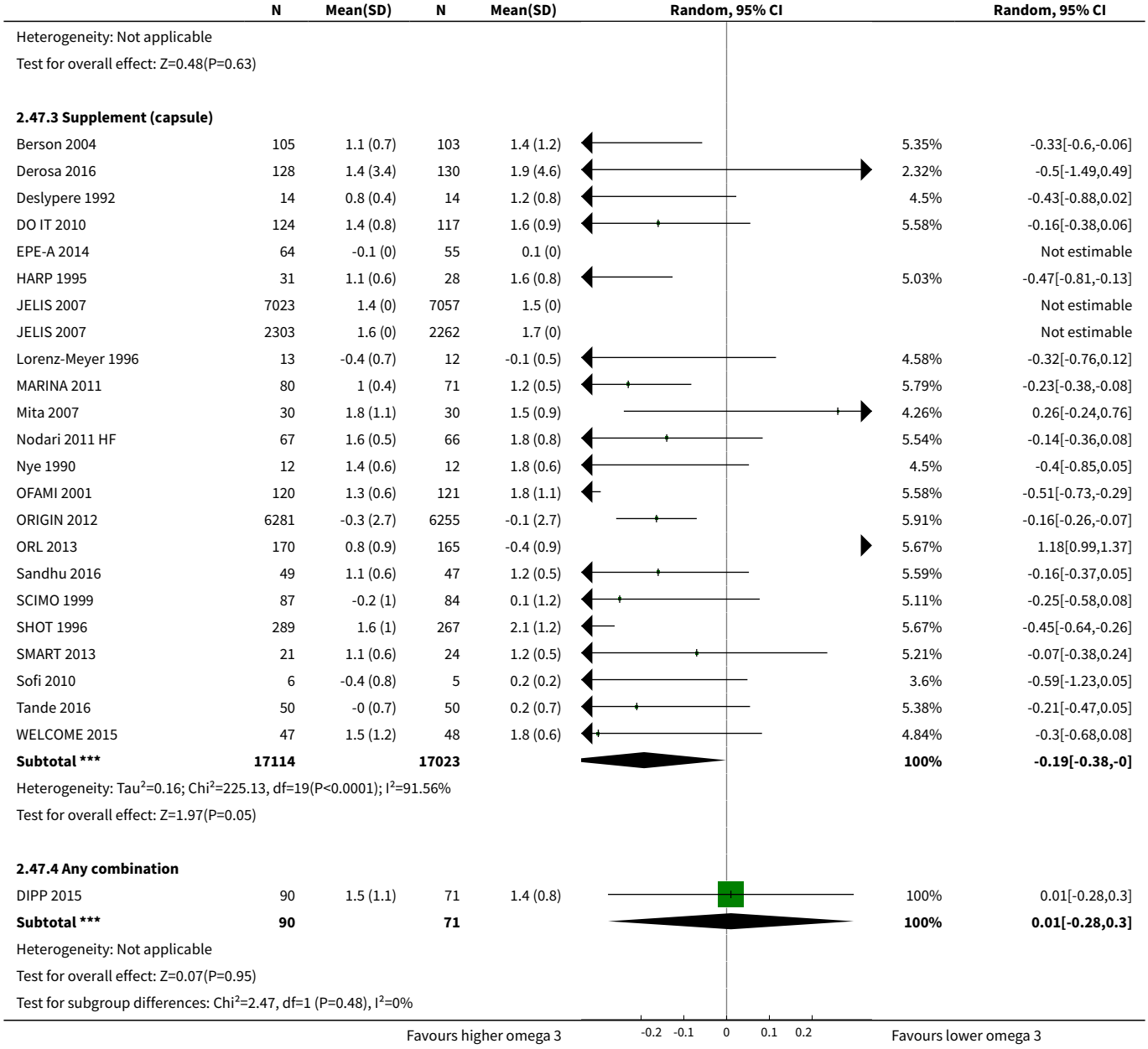
Analysis 2.46. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 46 TG, fasting, mmoL/L - LCn3 - subgroup by replacement.



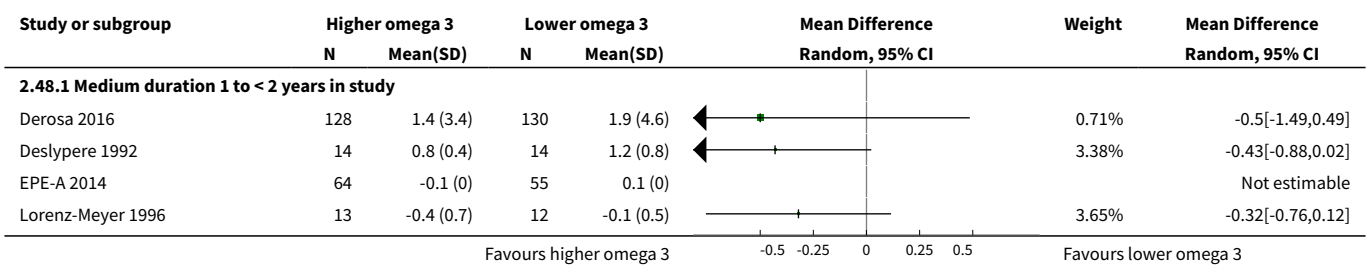


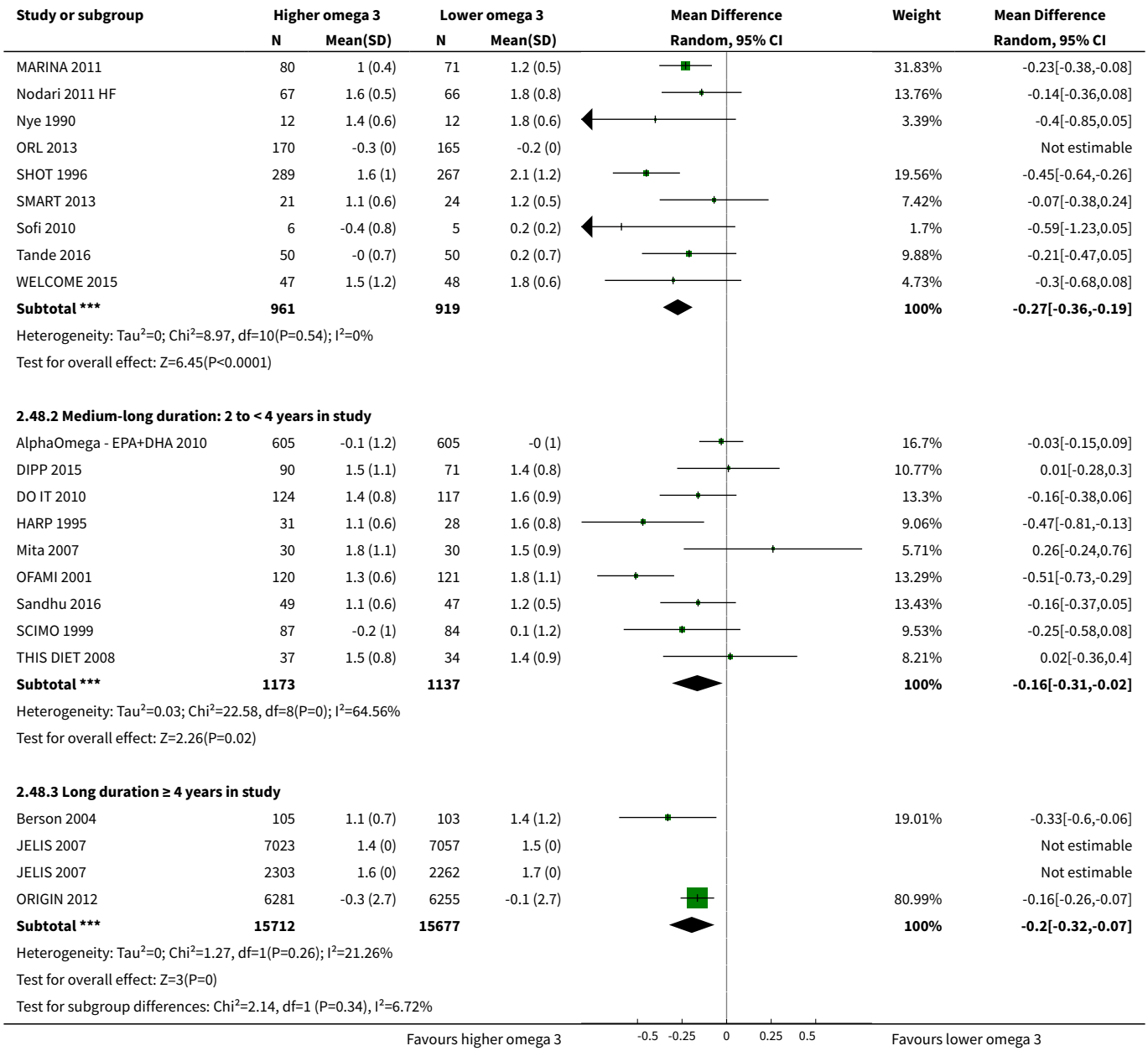
Analysis 2.47. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 47 TG, fasting, mmoL/L - LCn3 - subgroup by intervention type.



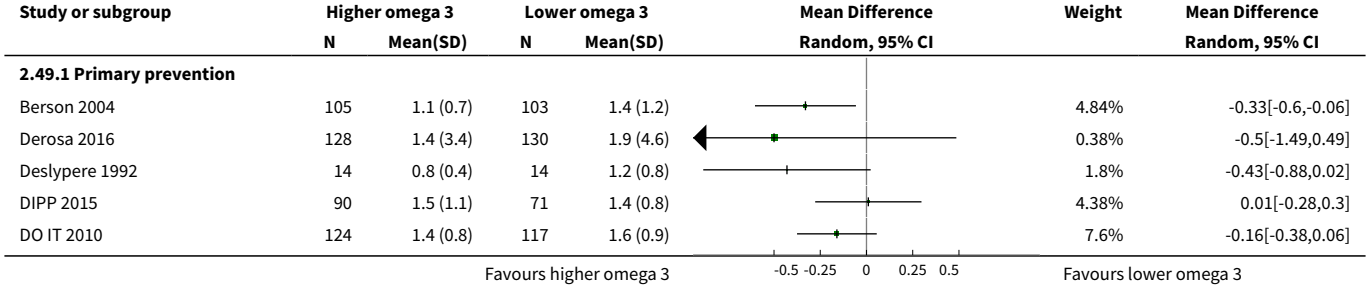


Analysis 2.48. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 48 TG, fasting, mmoL/L - LCn3 - subgroup by duration.

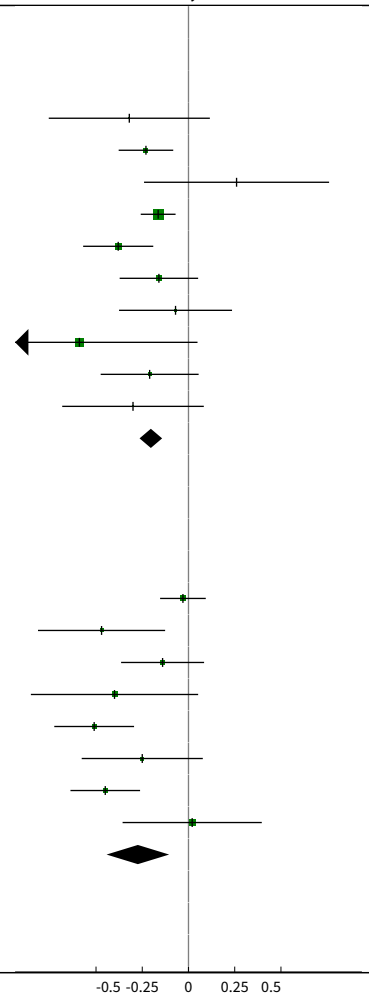




Analysis 2.49. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 49 TG, fasting, mmoL/L - LCn3 - subgroup by primary or secondary prevention.

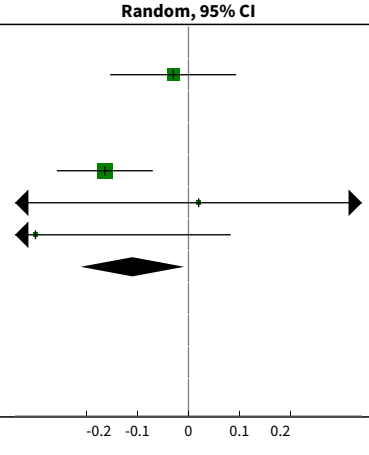


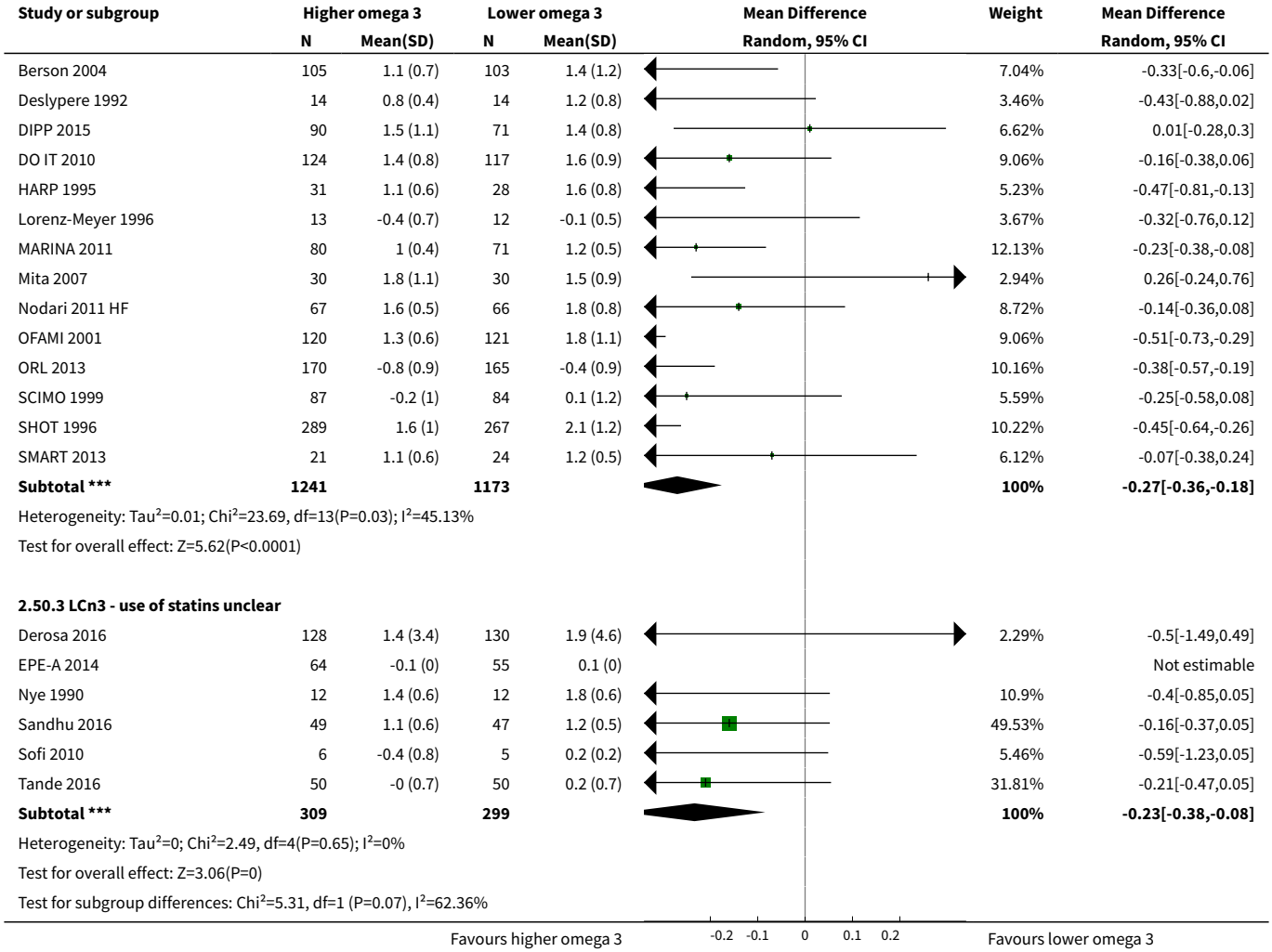
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
EPE-A 2014	64	-0.1 (0)	55	0.1 (0)			Not estimable
JELIS 2007	7023	1.4 (0)	7057	1.5 (0)			Not estimable
JELIS 2007	2303	1.6 (0)	2262	1.7 (0)			Not estimable
Lorenz-Meyer 1996	13	-0.4 (0.7)	12	-0.1 (0.5)		1.94%	-0.32[-0.76,0.12]
MARINA 2011	80	1 (0.4)	71	1.2 (0.5)		15.28%	-0.23[-0.38,-0.08]
Mita 2007	30	1.8 (1.1)	30	1.5 (0.9)		1.47%	0.26[-0.24,0.76]
ORIGIN 2012	6281	-0.3 (2.7)	6255	-0.1 (2.7)		32.39%	-0.16[-0.26,-0.07]
ORL 2013	170	-0.8 (0.9)	165	-0.4 (0.9)		9.67%	-0.38[-0.57,-0.19]
Sandhu 2016	49	1.1 (0.6)	47	1.2 (0.5)		7.83%	-0.16[-0.37,0.05]
SMART 2013	21	1.1 (0.6)	24	1.2 (0.5)		3.89%	-0.07[-0.38,0.24]
Sofi 2010	6	-0.4 (0.8)	5	0.2 (0.2)		0.91%	-0.59[-1.23,0.05]
Tande 2016	50	-0 (0.7)	50	0.2 (0.7)		5.13%	-0.21[-0.47,0.05]
WELCOME 2015	47	1.5 (1.2)	48	1.8 (0.6)		2.5%	-0.3[-0.68,0.08]
Subtotal ***	**16598**		**16516**			**100%**	**-0.2[-0.26,-0.14]**
Heterogeneity: Tau²=0; Chi²=14.66, df=14(P=0.4); I²=4.48%							
Test for overall effect: Z=6.53(P<0.0001)							
2.49.2 Secondary prevention							
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]
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 ***	**1248**		**1217**			**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)							
Test for subgroup differences: Chi²=0.58, df=1 (P=0.44), I²=0%							



Analysis 2.50. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 50 TG, fasting, mmoL/L - LCn3 - subgroup by statin use.

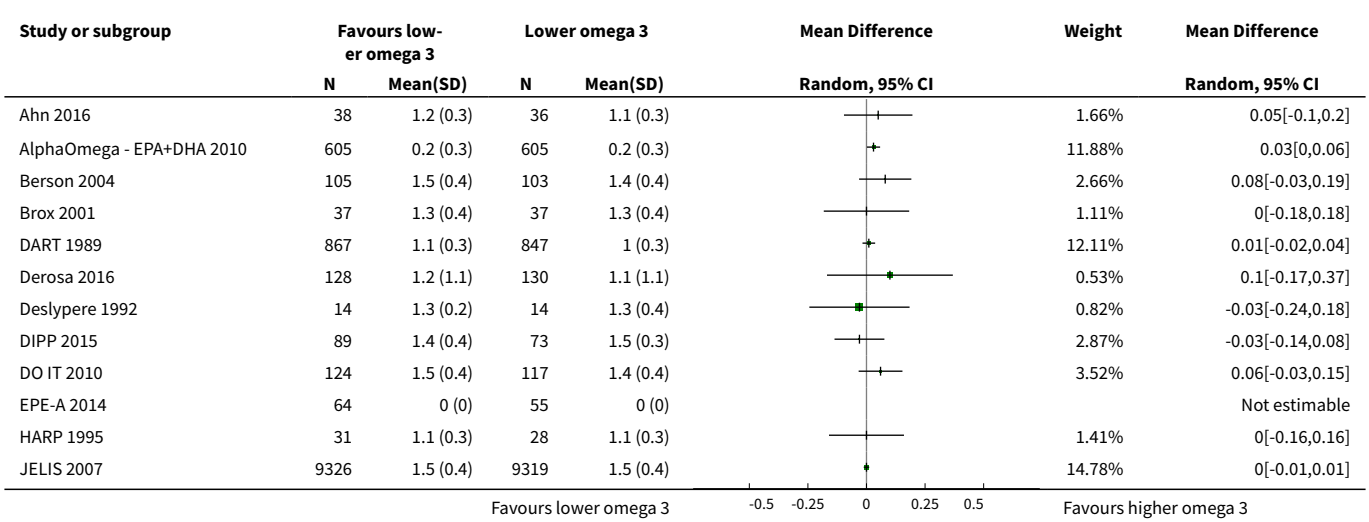
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.50.1 LCn3 - ≥ 50% of control group on statins							
AlphaOmega - EPA+DHA 2010	605	-0.1 (1.2)	605	-0 (1)		37.68%	-0.03[-0.15,0.09]
JELIS 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]
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 ***	**16296**		**16261**			**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)							
2.50.2 LCn3 - < 50% of control group on statins							





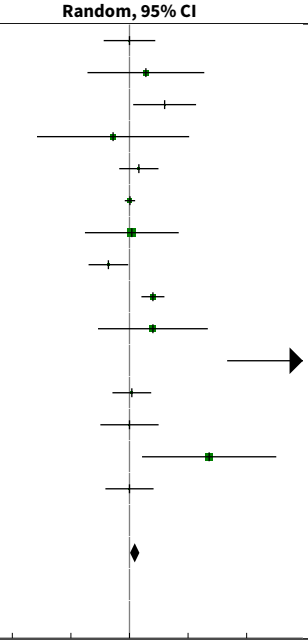
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Berson 2004	105	1.1 (0.7)	103	1.4 (1.2)		7.04%	-0.33[-0.6,-0.06]
Deslypere 1992	14	0.8 (0.4)	14	1.2 (0.8)		3.46%	-0.43[-0.88,0.02]
DIPP 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]
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)							
2.50.3 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 2.51. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 51 High-density lipoprotein, serum, mmoL/L - LCn3.



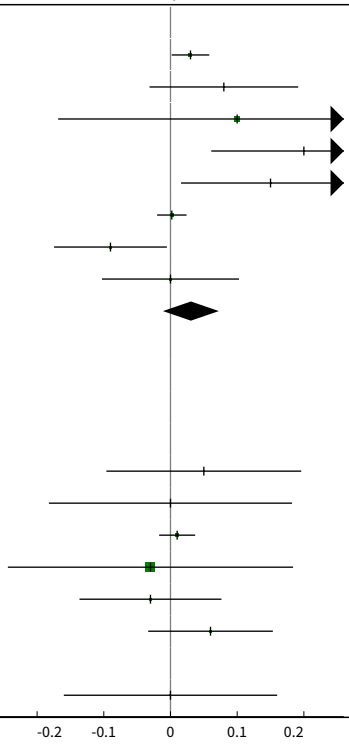
Study or subgroup	Favours lower omega 3 N	Favours lower omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Ahn 2016	38	1.2 (0.3)	36	1.1 (0.3)		1.66%	0.05[-0.1,0.2]
AlphaOmega - EPA+DHA 2010	605	0.2 (0.3)	605	0.2 (0.3)		11.88%	0.03[0,0.06]
Berson 2004	105	1.5 (0.4)	103	1.4 (0.4)		2.66%	0.08[-0.03,0.19]
Brox 2001	37	1.3 (0.4)	37	1.3 (0.4)		1.11%	0[-0.18,0.18]
DART 1989	867	1.1 (0.3)	847	1 (0.3)		12.11%	0.01[-0.02,0.04]
Derosa 2016	128	1.2 (1.1)	130	1.1 (1.1)		0.53%	0.1[-0.17,0.37]
Deslypere 1992	14	1.3 (0.2)	14	1.3 (0.4)		0.82%	-0.03[-0.24,0.18]
DIPP 2015	89	1.4 (0.4)	73	1.5 (0.3)		2.87%	-0.03[-0.14,0.08]
DO IT 2010	124	1.5 (0.4)	117	1.4 (0.4)		3.52%	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)		1.41%	0[-0.16,0.16]
JELIS 2007	9326	1.5 (0.4)	9319	1.5 (0.4)		14.78%	0[-0.01,0.01]

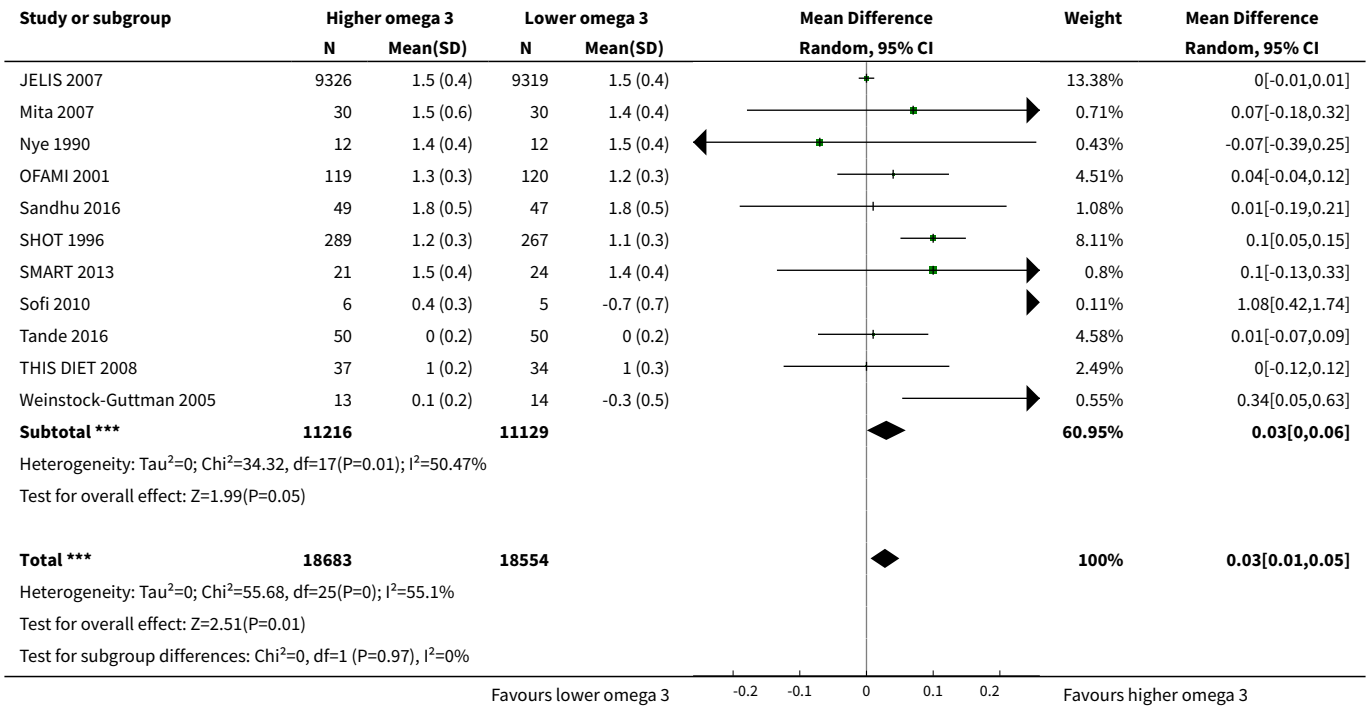
Study or subgroup	Favours lower omega 3 N	Mean(SD)	Lower omega 3 N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
MARINA 2011	80	0 (0.5)	71	0 (0.2)		2.71%	0[-0.11,0.11]
Mita 2007	30	1.5 (0.6)	30	1.4 (0.4)		0.61%	0.07[-0.18,0.32]
NAT2 2013	134	2 (0.6)	129	1.8 (0.5)		1.93%	0.15[0.02,0.28]
Nye 1990	12	1.4 (0.4)	12	1.5 (0.4)		0.37%	-0.07[-0.39,0.25]
OFAMI 2001	119	1.3 (0.3)	120	1.2 (0.3)		4.16%	0.04[-0.04,0.12]
ORIGIN 2012	6281	-0 (0.6)	6255	-0 (0.6)		13.08%	0[-0.02,0.02]
Sandhu 2016	49	1.8 (0.5)	47	1.8 (0.5)		0.93%	0.01[-0.19,0.21]
SCIMO 1999	87	0 (0.3)	84	0.1 (0.3)		4.1%	-0.09[-0.17,-0.01]
SHOT 1996	289	1.2 (0.3)	267	1.1 (0.3)		8.02%	0.1[0.05,0.15]
SMART 2013	21	1.5 (0.4)	24	1.4 (0.4)		0.69%	0.1[-0.13,0.33]
Sofi 2010	6	0.4 (0.3)	5	-0.7 (0.7)		0.09%	1.08[0.42,1.74]
Tande 2016	50	0 (0.2)	50	0 (0.2)		4.23%	0.01[-0.07,0.09]
THIS DIET 2008	37	1 (0.2)	34	1 (0.3)		2.21%	0[-0.12,0.12]
Weinstock-Guttman 2005	13	0.1 (0.2)	14	-0.3 (0.5)		0.47%	0.34[0.05,0.63]
WELCOME 2015	47	1.1 (0.3)	48	1.1 (0.2)		3.03%	0[-0.1,0.1]
Total * **	**18683**		**18554**			**100%**	**0.02[0,0.04]**
Heterogeneity: Tau^2=0; Chi^2=48.46, df=25(P=0); I^2=48.41%							
Test for overall effect: Z=2.2(P=0.03)							



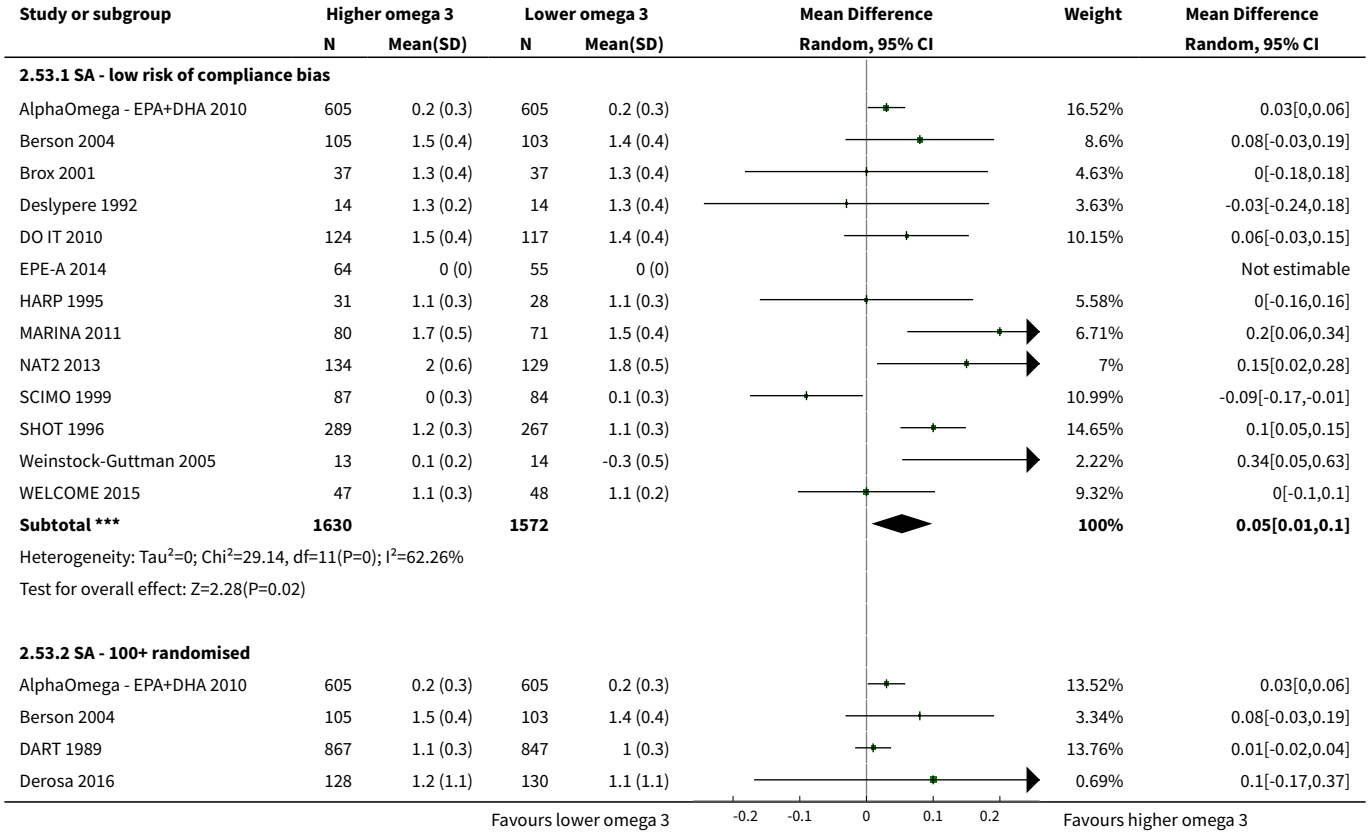
Analysis 2.52. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 52 HDL, mmoL/L - LCn3 - SA by summary risk of bias.

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
2.52.1 Low risk of bias							
AlphaOmega - EPA+DHA 2010	605	0.2 (0.3)	605	0.2 (0.3)		11.26%	0.03[0,0.06]
Berson 2004	105	1.5 (0.4)	103	1.4 (0.4)		2.96%	0.08[-0.03,0.19]
Derosa 2016	128	1.2 (1.1)	130	1.1 (1.1)		0.62%	0.1[-0.17,0.37]
MARINA 2011	80	1.7 (0.5)	71	1.5 (0.4)		2.06%	0.2[0.06,0.34]
NAT2 2013	134	2 (0.6)	129	1.8 (0.5)		2.19%	0.15[0.02,0.28]
ORIGIN 2012	6281	-0 (0.6)	6255	-0 (0.6)		12.16%	0[-0.02,0.02]
SCIMO 1999	87	0 (0.3)	84	0.1 (0.3)		4.44%	-0.09[-0.17,-0.01]
WELCOME 2015	47	1.1 (0.3)	48	1.1 (0.2)		3.36%	0[-0.1,0.1]
Subtotal * **	**7467**		**7425**			**39.05%**	**0.03[-0.01,0.07]**
Heterogeneity: Tau^2=0; Chi^2=20.83, df=7(P=0); I^2=66.4%							
Test for overall effect: Z=1.43(P=0.15)							
2.52.2 Moderate/high risk of bias							
Ahn 2016	38	1.2 (0.3)	36	1.1 (0.3)		1.89%	0.05[-0.1,0.2]
Brox 2001	37	1.3 (0.4)	37	1.3 (0.4)		1.28%	0[-0.18,0.18]
DART 1989	867	1.1 (0.3)	847	1 (0.3)		11.44%	0.01[-0.02,0.04]
Deslypere 1992	14	1.3 (0.2)	14	1.3 (0.4)		0.95%	-0.03[-0.24,0.18]
DIPP 2015	89	1.4 (0.4)	73	1.5 (0.3)		3.18%	-0.03[-0.14,0.08]
DO IT 2010	124	1.5 (0.4)	117	1.4 (0.4)		3.86%	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)		1.61%	0[-0.16,0.16]

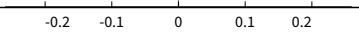




Analysis 2.53. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 53 HDL, mmoL/L - LCn3 - SA by compliance and study size.



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
DIPP 2015	89	1.4 (0.4)	73	1.5 (0.3)		3.59%	-0.03[-0.14,0.08]
DO IT 2010	124	1.5 (0.4)	117	1.4 (0.4)		4.38%	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)		16.34%	0[-0.01,0.01]
MARINA 2011	80	1.7 (0.5)	71	1.5 (0.4)		2.31%	0.2[0.06,0.34]
NAT2 2013	134	2 (0.6)	129	1.8 (0.5)		2.45%	0.15[0.02,0.28]
OFAMI 2001	119	1.3 (0.3)	120	1.2 (0.3)		5.14%	0.04[-0.04,0.12]
ORIGIN 2012	6281	-0 (0.6)	6255	-0 (0.6)		14.71%	0[-0.02,0.02]
SCIMO 1999	87	0 (0.3)	84	0.1 (0.3)		5.06%	-0.09[-0.17,-0.01]
SHOT 1996	289	1.2 (0.3)	267	1.1 (0.3)		9.5%	0.1[0.05,0.15]
Tande 2016	50	0 (0.2)	50	0 (0.2)		5.22%	0.01[-0.07,0.09]
Subtotal * **	**18348**		**18225**			**100%**	**0.03[0,0.05]**
Heterogeneity: Tau^2=0; Chi^2=39.02, df=13(P=0); I^2=66.68%							
Test for overall effect: Z=2.28(P=0.02)							
Test for subgroup differences: Chi^2=1.05, df=1 (P=0.31), I^2=4.46%							

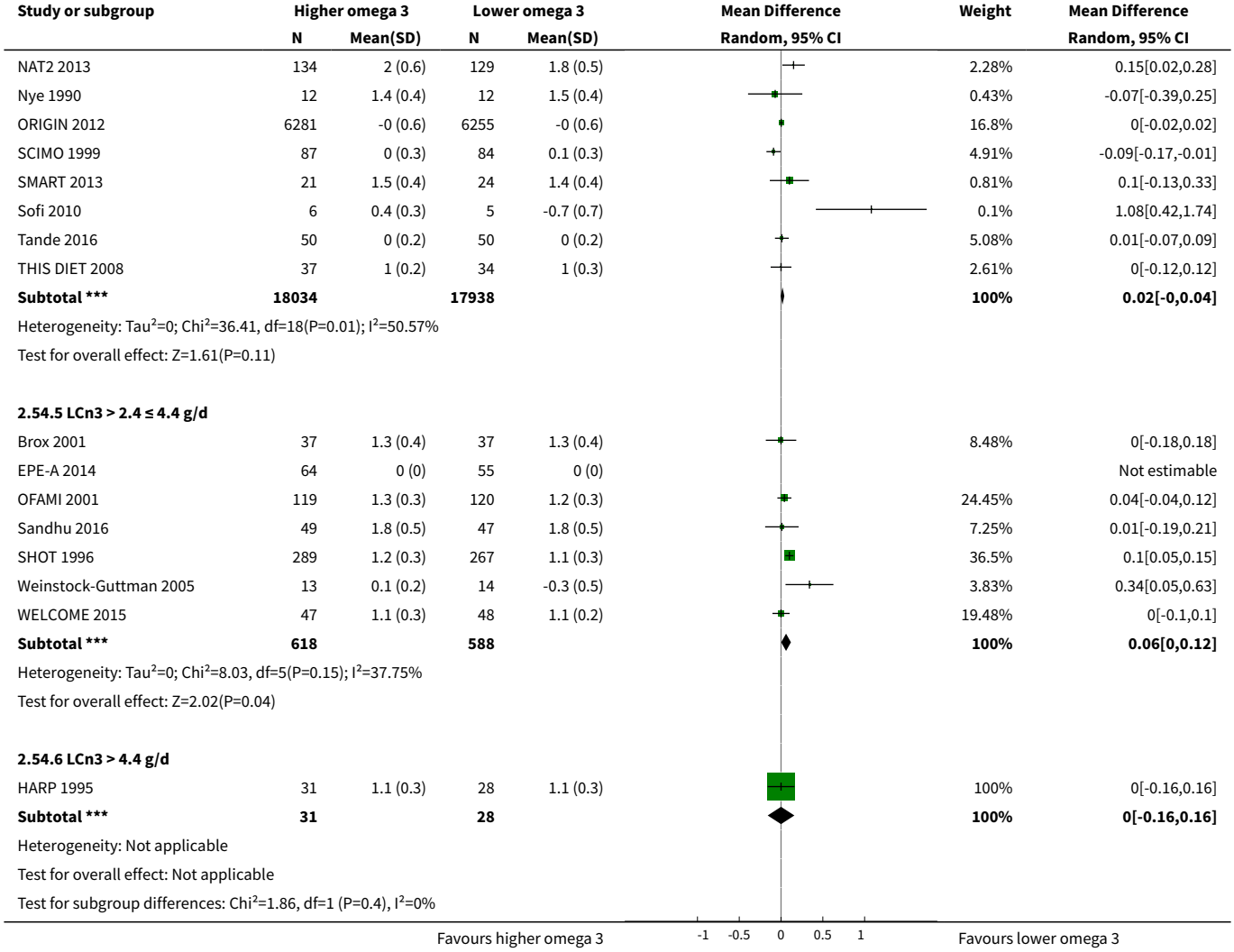


Favours lower omega 3 — Favours higher omega 3

Analysis 2.54. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 54 HDL, mmoL/L - LCn3 - subgroup by dose.

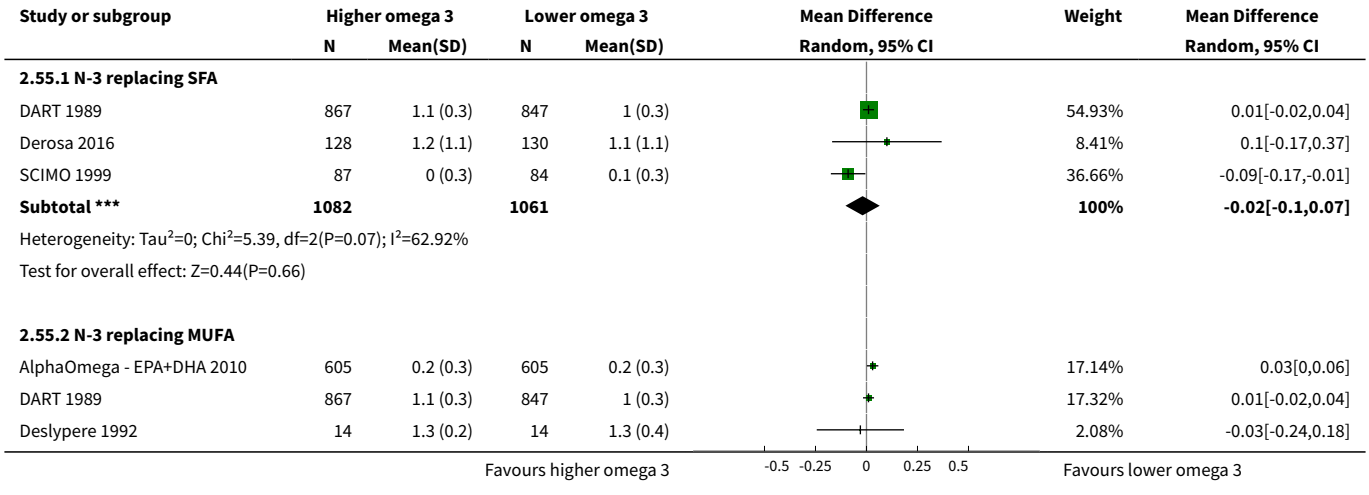
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.54.1 LCn3 ≤ 150 mg/d							
Subtotal * **	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.54.2 LCn3 > 150 ≤ 250 mg/d							
Subtotal * **	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.54.3 LCn3 > 250 ≤ 400 mg/d							
Subtotal * **	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.54.4 LCn3 > 400 ≤ 2400 mg/d							
Ahn 2016	38	1.2 (0.3)	36	1.1 (0.3)		1.96%	0.05[-0.1,0.2]
AlphaOmega - EPA+DHA 2010	605	0.2 (0.3)	605	0.2 (0.3)		15.11%	0.03[0,0.06]
Berson 2004	105	1.5 (0.4)	103	1.4 (0.4)		3.15%	0.08[-0.03,0.19]
DART 1989	867	1.1 (0.3)	847	1 (0.3)		15.44%	0.01[-0.02,0.04]
Derosa 2016	128	1.2 (1.1)	130	1.1 (1.1)		0.62%	0.1[-0.17,0.37]
Deslypere 1992	14	1.3 (0.2)	14	1.3 (0.4)		0.96%	-0.03[-0.24,0.18]
DIPP 2015	89	1.4 (0.4)	73	1.5 (0.3)		3.4%	-0.03[-0.14,0.08]
DO IT 2010	124	1.5 (0.4)	117	1.4 (0.4)		4.2%	0.06[-0.03,0.15]
JELIS 2007	9326	1.5 (0.4)	9319	1.5 (0.4)		19.26%	0[-0.01,0.01]
MARINA 2011	80	1.7 (0.5)	71	1.5 (0.4)		2.15%	0.2[0.06,0.34]
Mita 2007	30	1.5 (0.6)	30	1.4 (0.4)		0.72%	0.07[-0.18,0.32]

Favours higher omega 3 — Favours lower omega 3



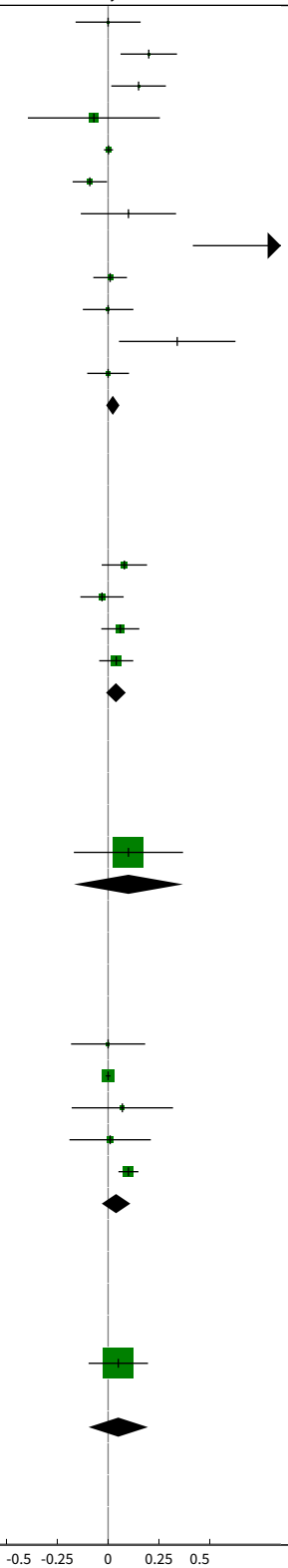
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
NAT2 2013	134	2 (0.6)	129	1.8 (0.5)		2.28%	0.15[0.02,0.28]
Nye 1990	12	1.4 (0.4)	12	1.5 (0.4)		0.43%	-0.07[-0.39,0.25]
ORIGIN 2012	6281	-0 (0.6)	6255	-0 (0.6)		16.8%	0[-0.02,0.02]
SCIMO 1999	87	0 (0.3)	84	0.1 (0.3)		4.91%	-0.09[-0.17,-0.01]
SMART 2013	21	1.5 (0.4)	24	1.4 (0.4)		0.81%	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)		5.08%	0.01[-0.07,0.09]
THIS DIET 2008	37	1 (0.2)	34	1 (0.3)		2.61%	0[-0.12,0.12]
Subtotal ***	**18034**		**17938**			**100%**	**0.02[-0,0.04]**
Heterogeneity: Tau^2=0; Chi^2=36.41, df=18(P=0.01); I^2=50.57%							
Test for overall effect: Z=1.61(P=0.11)							
2.54.5 LCn3 > 2.4 ≤ 4.4 g/d							
Brox 2001	37	1.3 (0.4)	37	1.3 (0.4)		8.48%	0[-0.18,0.18]
EPE-A 2014	64	0 (0)	55	0 (0)			Not estimable
OFAMI 2001	119	1.3 (0.3)	120	1.2 (0.3)		24.45%	0.04[-0.04,0.12]
Sandhu 2016	49	1.8 (0.5)	47	1.8 (0.5)		7.25%	0.01[-0.19,0.21]
SHOT 1996	289	1.2 (0.3)	267	1.1 (0.3)		36.5%	0.1[0.05,0.15]
Weinstock-Guttman 2005	13	0.1 (0.2)	14	-0.3 (0.5)		3.83%	0.34[0.05,0.63]
WELCOME 2015	47	1.1 (0.3)	48	1.1 (0.2)		19.48%	0[-0.1,0.1]
Subtotal ***	**618**		**588**			**100%**	**0.06[0,0.12]**
Heterogeneity: Tau^2=0; Chi^2=8.03, df=5(P=0.15); I^2=37.75%							
Test for overall effect: Z=2.02(P=0.04)							
2.54.6 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: Chi^2=1.86, df=1 (P=0.4), I^2=0%							

Analysis 2.55. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 55 HDL, mmoL/L - LCn3 - subgroup by replacement.



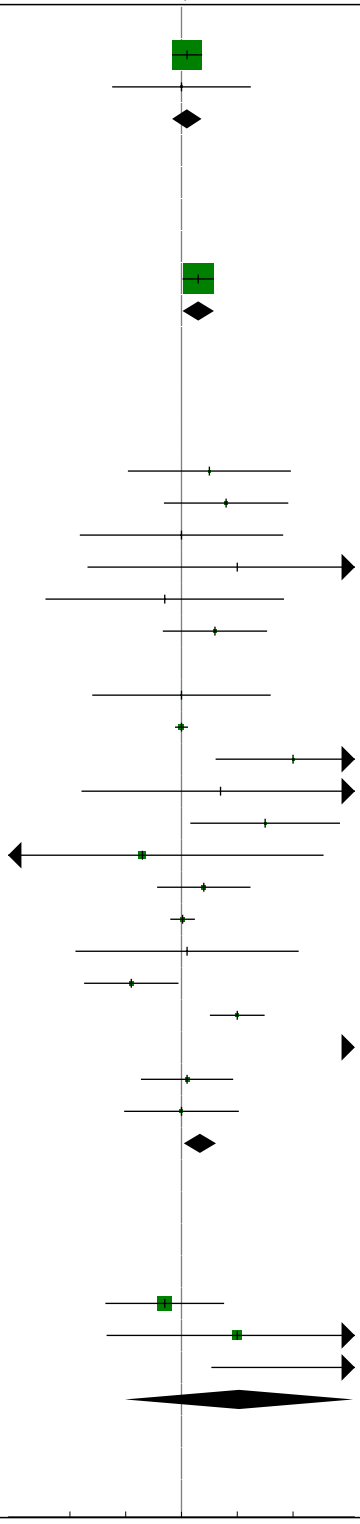
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.55.1 N-3 replacing SFA							
DART 1989	867	1.1 (0.3)	847	1 (0.3)		54.93%	0.01[-0.02,0.04]
Derosa 2016	128	1.2 (1.1)	130	1.1 (1.1)		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: Tau^2=0; Chi^2=5.39, df=2(P=0.07); I^2=62.92%							
Test for overall effect: Z=0.44(P=0.66)							
2.55.2 N-3 replacing MUFA							
AlphaOmega - EPA+DHA 2010	605	0.2 (0.3)	605	0.2 (0.3)		17.14%	0.03[0,0.06]
DART 1989	867	1.1 (0.3)	847	1 (0.3)		17.32%	0.01[-0.02,0.04]
Deslypere 1992	14	1.3 (0.2)	14	1.3 (0.4)		2.08%	-0.03[-0.24,0.18]

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
HARP 1995	31	1.1 (0.3)	28	1.1 (0.3)		3.44%	0[-0.16,0.16]
MARINA 2011	80	1.7 (0.5)	71	1.5 (0.4)		4.31%	0.2[0.06,0.34]
NAT2 2013	134	2 (0.6)	129	1.8 (0.5)		4.55%	0.15[0.02,0.28]
Nye 1990	12	1.4 (0.4)	12	1.5 (0.4)		0.96%	-0.07[-0.39,0.25]
ORIGIN 2012	6281	-0 (0.6)	6255	-0 (0.6)		18.03%	0[-0.02,0.02]
SCIMO 1999	87	0 (0.3)	84	0.1 (0.3)		8.47%	-0.09[-0.17,-0.01]
SMART 2013	21	1.5 (0.4)	24	1.4 (0.4)		1.77%	0.1[-0.13,0.33]
Sofi 2010	6	0.4 (0.3)	5	-0.7 (0.7)		0.24%	1.08[0.42,1.74]
Tande 2016	50	0 (0.2)	50	0 (0.2)		8.69%	0.01[-0.07,0.09]
THIS DIET 2008	37	1 (0.2)	34	1 (0.3)		5.11%	0[-0.12,0.12]
Weinstock-Guttman 2005	13	0.1 (0.2)	14	-0.3 (0.5)		1.22%	0.34[0.05,0.63]
WELCOME 2015	47	1.1 (0.3)	48	1.1 (0.2)		6.67%	0[-0.1,0.1]
Subtotal ***	**8285**		**8220**			**100%**	**0.02[-0.01,0.06]**
Heterogeneity: Tau^2=0; Chi^2=35.1, df=14(P=0); I^2=60.11%							
Test for overall effect: Z=1.39(P=0.16)							
2.55.3 N-3 replacing n-6							
Berson 2004	105	1.5 (0.4)	103	1.4 (0.4)		18.89%	0.08[-0.03,0.19]
DIPP 2015	89	1.4 (0.4)	73	1.5 (0.3)		20.72%	-0.03[-0.14,0.08]
DO IT 2010	124	1.5 (0.4)	117	1.4 (0.4)		26.87%	0.06[-0.03,0.15]
OFAMI 2001	119	1.3 (0.3)	120	1.2 (0.3)		33.52%	0.04[-0.04,0.12]
Subtotal ***	**437**		**413**			**100%**	**0.04[-0.01,0.09]**
Heterogeneity: Tau^2=0; Chi^2=2.33, df=3(P=0.51); I^2=0%							
Test for overall effect: Z=1.55(P=0.12)							
2.55.4 N-3 replacing carbs/sugars							
Derosa 2016	128	1.2 (1.1)	130	1.1 (1.1)		100%	0.1[-0.17,0.37]
Subtotal ***	**128**		**130**			**100%**	**0.1[-0.17,0.37]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.73(P=0.47)							
2.55.5 N-3 replacing nil/low n-3 placebo							
Brox 2001	37	1.3 (0.4)	37	1.3 (0.4)		10.85%	0[-0.18,0.18]
JELIS 2007	9326	1.5 (0.4)	9319	1.5 (0.4)		39.58%	0[-0.01,0.01]
Mita 2007	30	1.5 (0.6)	30	1.4 (0.4)		6.64%	0.07[-0.18,0.32]
Sandhu 2016	49	1.8 (0.5)	47	1.8 (0.5)		9.44%	0.01[-0.19,0.21]
SHOT 1996	289	1.2 (0.3)	267	1.1 (0.3)		33.5%	0.1[0.05,0.15]
Subtotal ***	**9731**		**9700**			**100%**	**0.04[-0.03,0.11]**
Heterogeneity: Tau^2=0; Chi^2=15.38, df=4(P=0); I^2=74%							
Test for overall effect: Z=1.09(P=0.28)							
2.55.6 Replacement unclear							
Ahn 2016	38	1.2 (0.3)	36	1.1 (0.3)		100%	0.05[-0.1,0.2]
EPE-A 2014	64	0 (0)	55	0 (0)			Not estimable
Subtotal ***	**102**		**91**			**100%**	**0.05[-0.1,0.2]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.67(P=0.5)							
Test for subgroup differences: Chi^2=1.91, df=1 (P=0.86), I^2=0%							



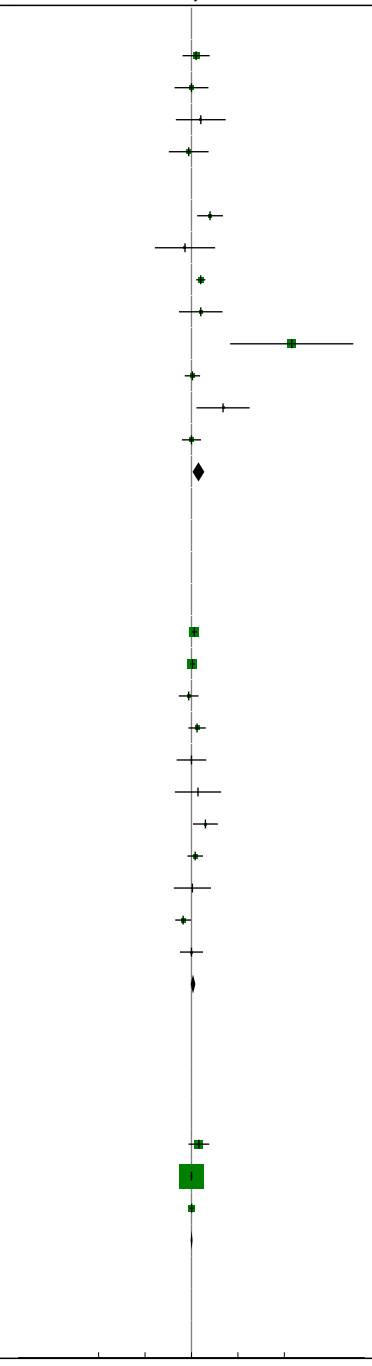
Analysis 2.56. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 56 HDL, mmoL/L - LCn3 - subgroup by intervention type.

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
2.56.1 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: Tau^2=0; Chi^2=0.02, df=1(P=0.88); I^2=0%							
Test for overall effect: Z=0.71(P=0.48)							
2.56.2 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)							
2.56.3 Supplement (capsule)							
Ahn 2016	38	1.2 (0.3)	36	1.1 (0.3)		3.15%	0.05[-0.1,0.2]
Berson 2004	105	1.5 (0.4)	103	1.4 (0.4)		4.75%	0.08[-0.03,0.19]
Brox 2001	37	1.3 (0.4)	37	1.3 (0.4)		2.17%	0[-0.18,0.18]
Derosa 2016	128	1.2 (1.1)	130	1.1 (1.1)		1.08%	0.1[-0.17,0.37]
Deslypere 1992	14	1.3 (0.2)	14	1.3 (0.4)		1.64%	-0.03[-0.24,0.18]
DO IT 2010	124	1.5 (0.4)	117	1.4 (0.4)		6%	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)		2.71%	0[-0.16,0.16]
JELIS 2007	9326	1.5 (0.4)	9319	1.5 (0.4)		15.76%	0[-0.01,0.01]
MARINA 2011	80	1.7 (0.5)	71	1.5 (0.4)		3.41%	0.2[0.06,0.34]
Mita 2007	30	1.5 (0.6)	30	1.4 (0.4)		1.24%	0.07[-0.18,0.32]
NAT2 2013	134	2 (0.6)	129	1.8 (0.5)		3.6%	0.15[0.02,0.28]
Nye 1990	12	1.4 (0.4)	12	1.5 (0.4)		0.75%	-0.07[-0.39,0.25]
OFAMI 2001	119	1.3 (0.3)	120	1.2 (0.3)		6.86%	0.04[-0.04,0.12]
ORIGIN 2012	6281	-0 (0.6)	6255	-0 (0.6)		14.78%	0[-0.02,0.02]
Sandhu 2016	49	1.8 (0.5)	47	1.8 (0.5)		1.85%	0.01[-0.19,0.21]
SCIMO 1999	87	0 (0.3)	84	0.1 (0.3)		6.77%	-0.09[-0.17,-0.01]
SHOT 1996	289	1.2 (0.3)	267	1.1 (0.3)		11.03%	0.1[0.05,0.15]
Sofi 2010	6	0.4 (0.3)	5	-0.7 (0.7)		0.19%	1.08[0.42,1.74]
Tande 2016	50	0 (0.2)	50	0 (0.2)		6.95%	0.01[-0.07,0.09]
WELCOME 2015	47	1.1 (0.3)	48	1.1 (0.2)		5.31%	0[-0.1,0.1]
Subtotal ***	**17051**		**16957**			**100%**	**0.03[0,0.06]**
Heterogeneity: Tau^2=0; Chi^2=47.19, df=19(P=0); I^2=59.73%							
Test for overall effect: Z=2.24(P=0.03)							
2.56.4 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: Tau^2=0.02; Chi^2=6.06, df=2(P=0.05); I^2=67.01%							
Test for overall effect: Z=0.99(P=0.32)							
Test for subgroup differences: Chi^2=2.28, df=1 (P=0.52), I^2=0%							



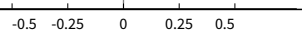
Analysis 2.57. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 57 HDL, mmoL/L - LCn3 - subgroup by duration.

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
2.57.1 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: Tau^2=0.01; Chi^2=23.18, df=11(P=0.02); I^2=52.54%							
Test for overall effect: Z=2.3(P=0.02)							
2.57.2 Medium-long duration: 2 to < 4 years in study							
AlphaOmega - EPA+DHA 2010	605	0.2 (0.3)	605	0.2 (0.3)		29.88%	0.03[0,0.06]
DART 1989	867	1.1 (0.3)	847	1 (0.3)		30.8%	0.01[-0.02,0.04]
DIPP 2015	89	1.4 (0.4)	73	1.5 (0.3)		5.14%	-0.03[-0.14,0.08]
DO IT 2010	124	1.5 (0.4)	117	1.4 (0.4)		6.46%	0.06[-0.03,0.15]
HARP 1995	31	1.1 (0.3)	28	1.1 (0.3)		2.42%	0[-0.16,0.16]
Mita 2007	30	1.5 (0.6)	30	1.4 (0.4)		1.03%	0.07[-0.18,0.32]
NAT2 2013	134	2 (0.6)	129	1.8 (0.5)		3.37%	0.15[0.02,0.28]
OFAMI 2001	119	1.3 (0.3)	120	1.2 (0.3)		7.79%	0.04[-0.04,0.12]
Sandhu 2016	49	1.8 (0.5)	47	1.8 (0.5)		1.58%	0.01[-0.19,0.21]
SCIMO 1999	87	0 (0.3)	84	0.1 (0.3)		7.65%	-0.09[-0.17,-0.01]
THIS DIET 2008	37	1 (0.2)	34	1 (0.3)		3.89%	0[-0.12,0.12]
Subtotal ***	**2172**		**2114**			**100%**	**0.02[-0.01,0.04]**
Heterogeneity: Tau^2=0; Chi^2=13.14, df=10(P=0.22); I^2=23.9%							
Test for overall effect: Z=1.27(P=0.2)							
2.57.3 Long duration ≥ 4 years in study							
Berson 2004	105	1.5 (0.4)	103	1.4 (0.4)		0.85%	0.08[-0.03,0.19]
JELIS 2007	9326	1.5 (0.4)	9319	1.5 (0.4)		77.57%	0[-0.01,0.01]
ORIGIN 2012	6281	-0 (0.6)	6255	-0 (0.6)		21.58%	0[-0.02,0.02]
Subtotal ***	**15712**		**15677**			**100%**	**0[-0.01,0.01]**
Heterogeneity: Tau^2=0; Chi^2=1.97, df=2(P=0.37); I^2=0%							
Test for overall effect: Z=0.21(P=0.83)							
Test for subgroup differences: Chi^2=5.95, df=1 (P=0.05), I^2=66.4%							



Analysis 2.58. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 58 HDL, mmoL/L - LCn3 - subgroup by primary or secondary prevention.

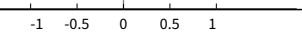
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.58.1 Primary prevention							
Berson 2004	105	1.5 (0.4)	103	1.4 (0.4)		5.59%	0.08[-0.03,0.19]
Brox 2001	37	1.3 (0.4)	37	1.3 (0.4)		2.39%	0[-0.18,0.18]
Derosa 2016	128	1.2 (1.1)	130	1.1 (1.1)		1.16%	0.1[-0.17,0.37]
Deslypere 1992	14	1.3 (0.2)	14	1.3 (0.4)		1.78%	-0.03[-0.24,0.18]
DIPP 2015	89	1.4 (0.4)	73	1.5 (0.3)		6.01%	-0.03[-0.14,0.08]
DO IT 2010	124	1.5 (0.4)	117	1.4 (0.4)		7.33%	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)		26.66%	0[-0.01,0.01]
MARINA 2011	80	1.7 (0.5)	71	1.5 (0.4)		3.88%	0.2[0.06,0.34]
Mita 2007	30	1.5 (0.6)	30	1.4 (0.4)		1.33%	0.07[-0.18,0.32]
ORIGIN 2012	6281	-0 (0.6)	6255	-0 (0.6)		24.07%	0[-0.02,0.02]
Sandhu 2016	49	1.8 (0.5)	47	1.8 (0.5)		2.01%	0.01[-0.19,0.21]
SMART 2013	21	1.5 (0.4)	24	1.4 (0.4)		1.5%	0.1[-0.13,0.33]
Sofi 2010	6	0.4 (0.3)	5	-0.7 (0.7)		0.2%	1.08[0.42,1.74]
Tande 2016	50	0 (0.2)	50	0 (0.2)		8.72%	0.01[-0.07,0.09]
Weinstock-Guttman 2005	13	0.1 (0.2)	14	-0.3 (0.5)		1.02%	0.34[0.05,0.63]
WELCOME 2015	47	1.1 (0.3)	48	1.1 (0.2)		6.35%	0[-0.1,0.1]
Subtotal ***	**16464**		**16392**			**100%**	**0.03[-0,0.05]**
Heterogeneity: Tau^2=0; Chi^2=28.63, df=15(P=0.02); I^2=47.61%							
Test for overall effect: Z=1.66(P=0.1)							
2.58.2 Secondary prevention							
AlphaOmega - EPA+DHA 2010	605	0.2 (0.3)	605	0.2 (0.3)		21.6%	0.03[0,0.06]
DART 1989	867	1.1 (0.3)	847	1 (0.3)		21.83%	0.01[-0.02,0.04]
HARP 1995	31	1.1 (0.3)	28	1.1 (0.3)		4.36%	0[-0.16,0.16]
NAT2 2013	134	2 (0.6)	129	1.8 (0.5)		5.77%	0.15[0.02,0.28]
Nye 1990	12	1.4 (0.4)	12	1.5 (0.4)		1.22%	-0.07[-0.39,0.25]
OFAMI 2001	119	1.3 (0.3)	120	1.2 (0.3)		10.85%	0.04[-0.04,0.12]
SCIMO 1999	87	0 (0.3)	84	0.1 (0.3)		10.72%	-0.09[-0.17,-0.01]
SHOT 1996	289	1.2 (0.3)	267	1.1 (0.3)		17.18%	0.1[0.05,0.15]
THIS DIET 2008	37	1 (0.2)	34	1 (0.3)		6.47%	0[-0.12,0.12]
Subtotal ***	**2181**		**2126**			**100%**	**0.03[-0.01,0.07]**
Heterogeneity: Tau^2=0; Chi^2=21.38, df=8(P=0.01); I^2=62.59%							
Test for overall effect: Z=1.51(P=0.13)							
Test for subgroup differences: Chi^2=0.02, df=1 (P=0.89), I^2=0%							



Favours higher omega 3 — Favours lower omega 3

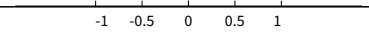
Analysis 2.59. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 59 HDL, mmoL/L - LCn3 - subgroup by statin use.

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
2.59.1 LCn3 - ≥ 50% of control group on statins							
Ahn 2016	38	1.2 (0.3)	36	1.1 (0.3)		1.25%	0.05[-0.1,0.2]
AlphaOmega - EPA+DHA 2010	605	0.2 (0.3)	605	0.2 (0.3)		21.31%	0.03[0,0.06]
JELIS 2007	9326	1.5 (0.4)	9319	1.5 (0.4)		43.75%	0[-0.01,0.01]



Favours higher omega 3 — Favours lower omega 3

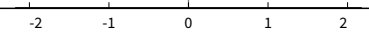
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
NAT2 2013	134	2 (0.6)	129	1.8 (0.5)		1.48%	0.15[0.02,0.28]
ORIGIN 2012	6281	-0 (0.6)	6255	-0 (0.6)		28.01%	0[-0.02,0.02]
THIS DIET 2008	37	1 (0.2)	34	1 (0.3)		1.72%	0[-0.12,0.12]
WELCOME 2015	47	1.1 (0.3)	48	1.1 (0.2)		2.48%	0[-0.1,0.1]
Subtotal ***	**16468**		**16426**			**100%**	**0.01[-0.01,0.03]**
Heterogeneity: Tau^2=0; Chi^2=8.67, df=6(P=0.19); I^2=30.81%							
Test for overall effect: Z=1.16(P=0.25)							
2.59.2 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)							
2.59.3 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
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: Tau^2=0.01; Chi^2=10.86, df=5(P=0.05); I^2=53.96%							
Test for overall effect: Z=1.01(P=0.31)							
Test for subgroup differences: Chi^2=2.28, df=1 (P=0.32), I^2=12.34%							



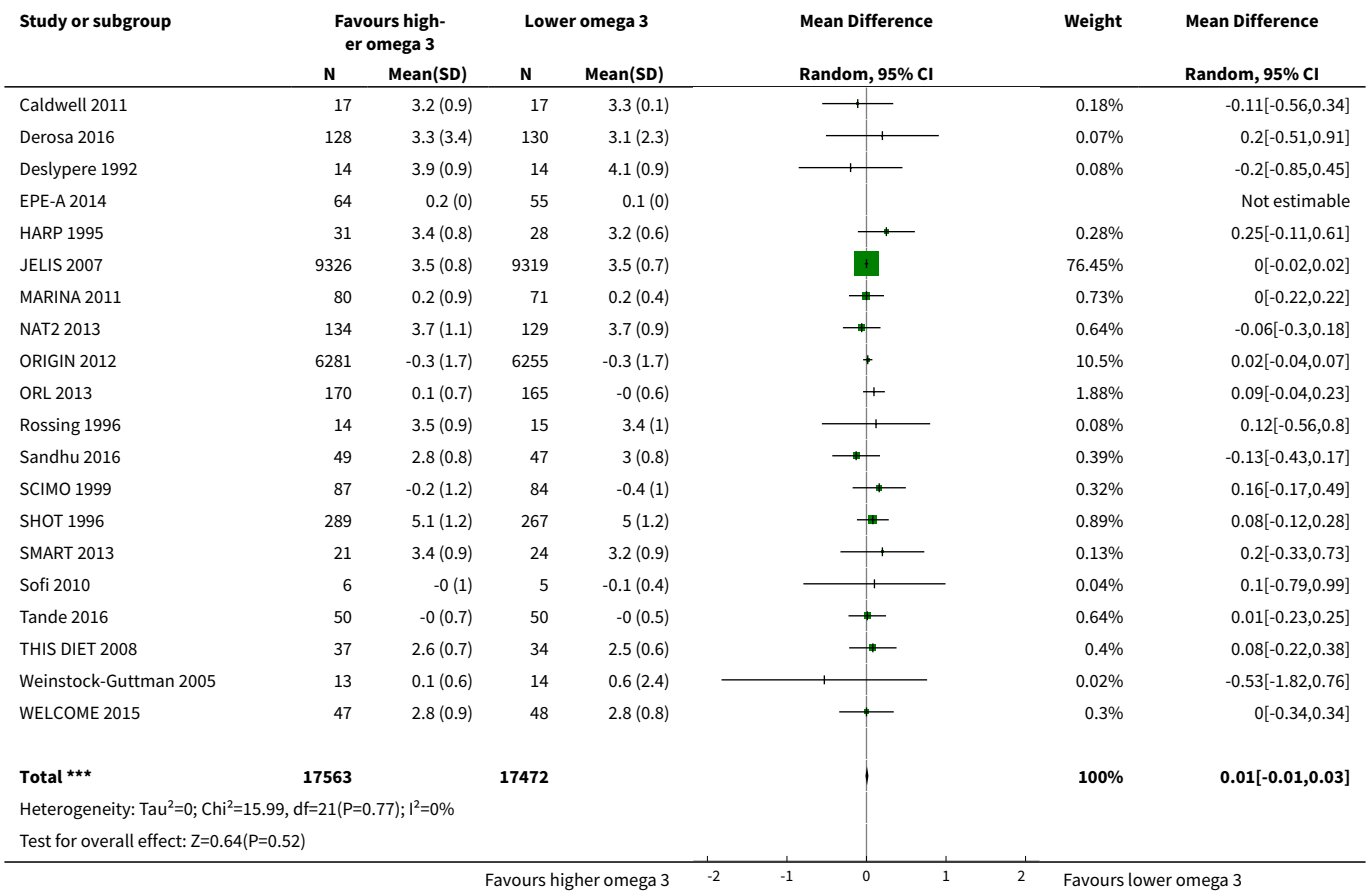
Favours higher omega 3 — Favours lower omega 3

Analysis 2.60. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 60 Low-density lipoprotein, serum, mmoL/L - LCn3.

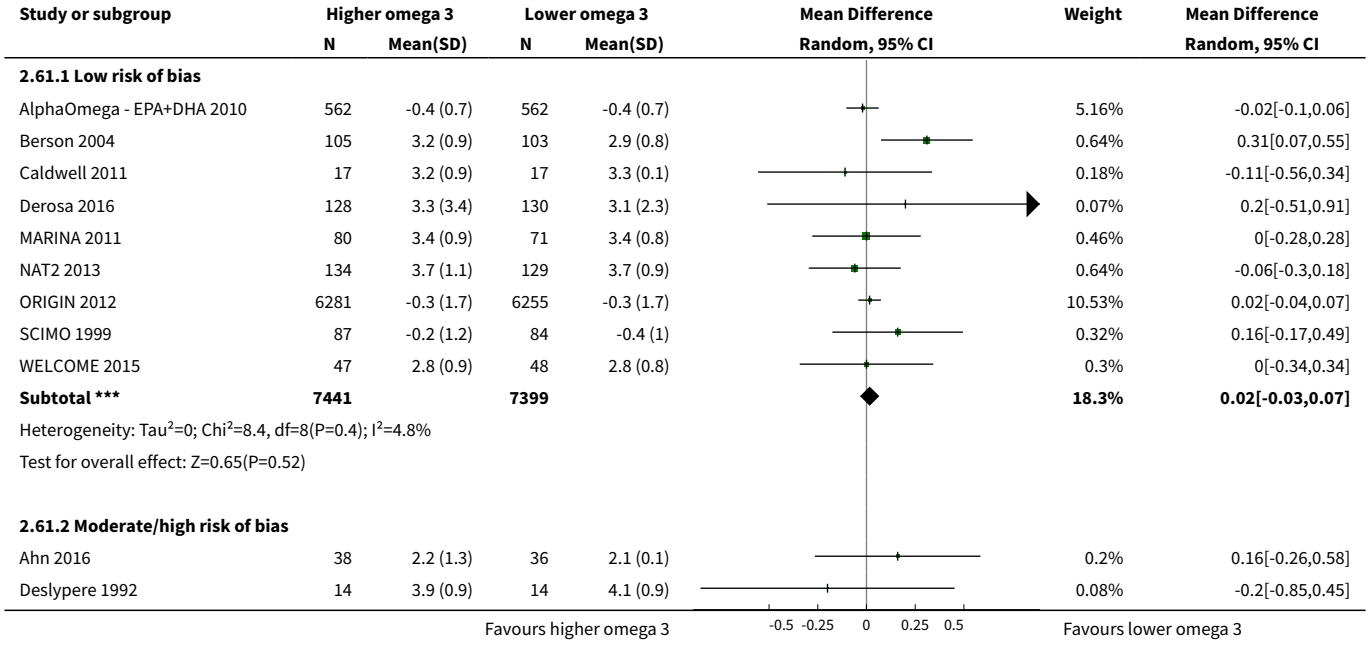
Study or subgroup	Favours higher omega 3 N	Favours higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Ahn 2016	38	2.2 (1.3)	36	2.1 (0.1)		0.2%	0.16[-0.26,0.58]
AlphaOmega - EPA+DHA 2010	562	-0.4 (0.7)	562	-0.4 (0.7)		5.15%	-0.02[-0.1,0.06]
Berson 2004	105	3.2 (0.9)	103	2.9 (0.8)		0.64%	0.31[0.07,0.55]

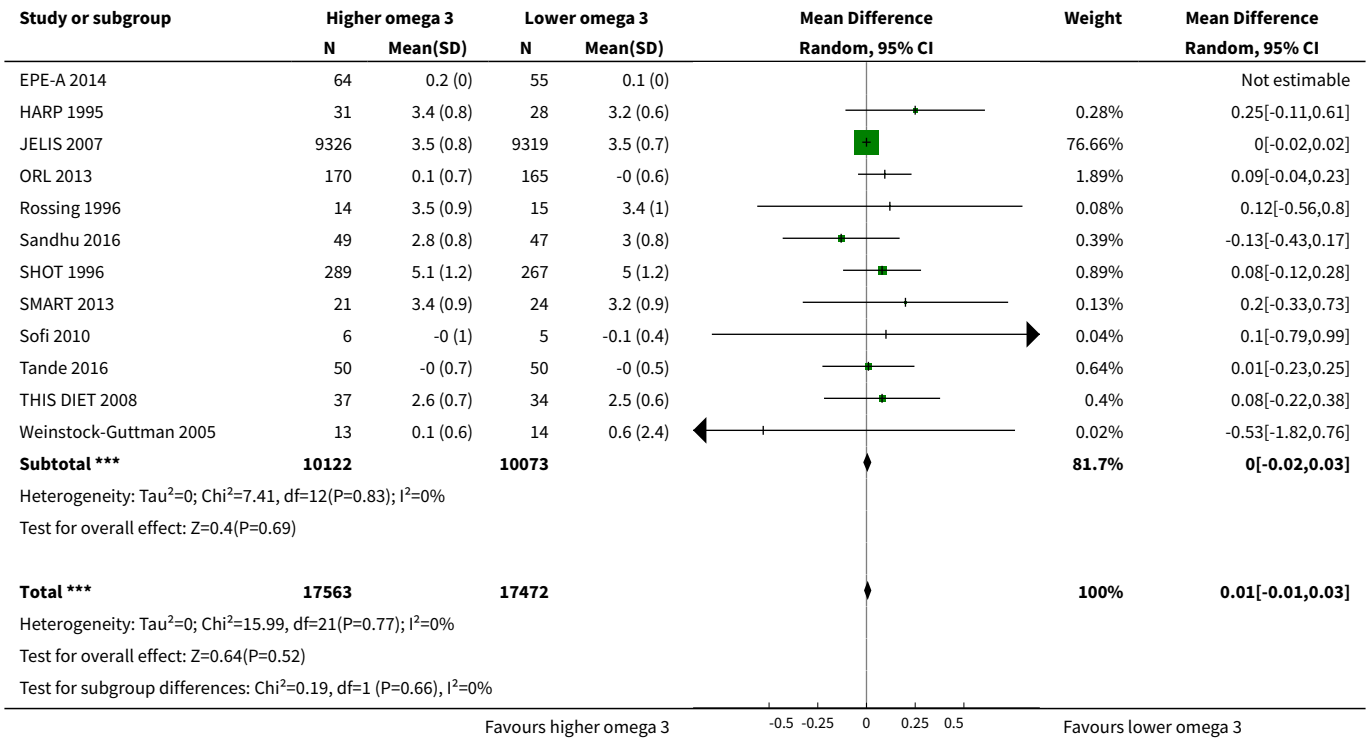


Favours higher omega 3 — Favours lower omega 3

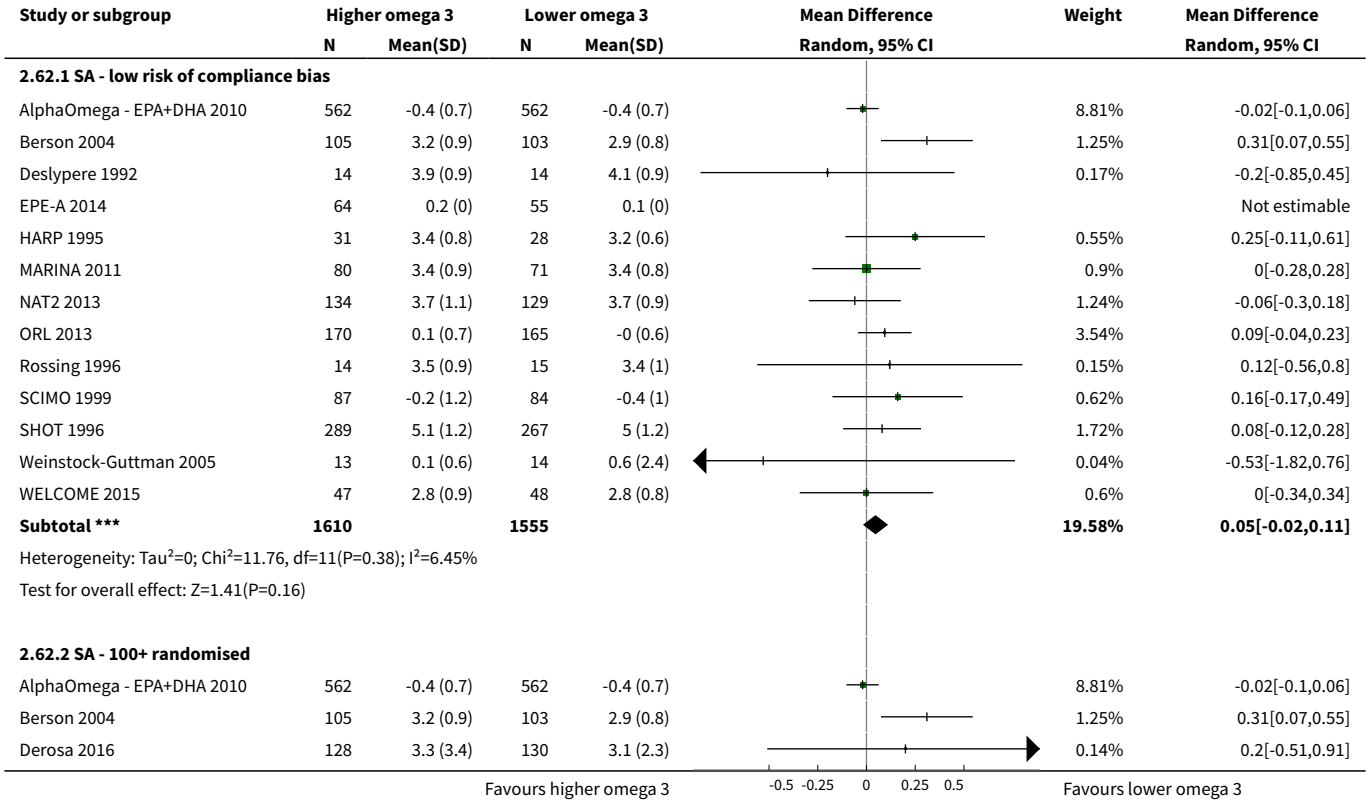


Analysis 2.61. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 61 LDL, mmoL/L - LCn3 - SA by summary risk of bias.

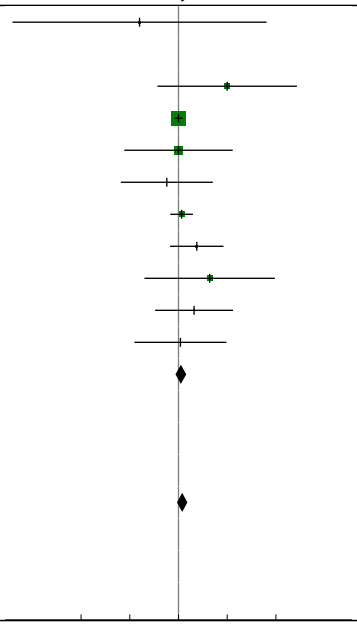




Analysis 2.62. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 62 LDL, mmoL/L - LCn3 - SA by compliance and study size.

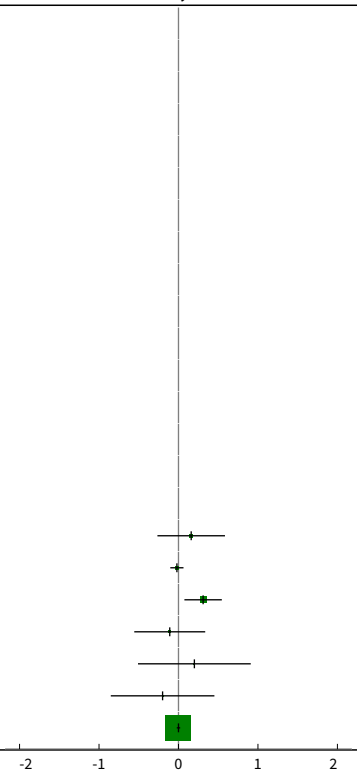


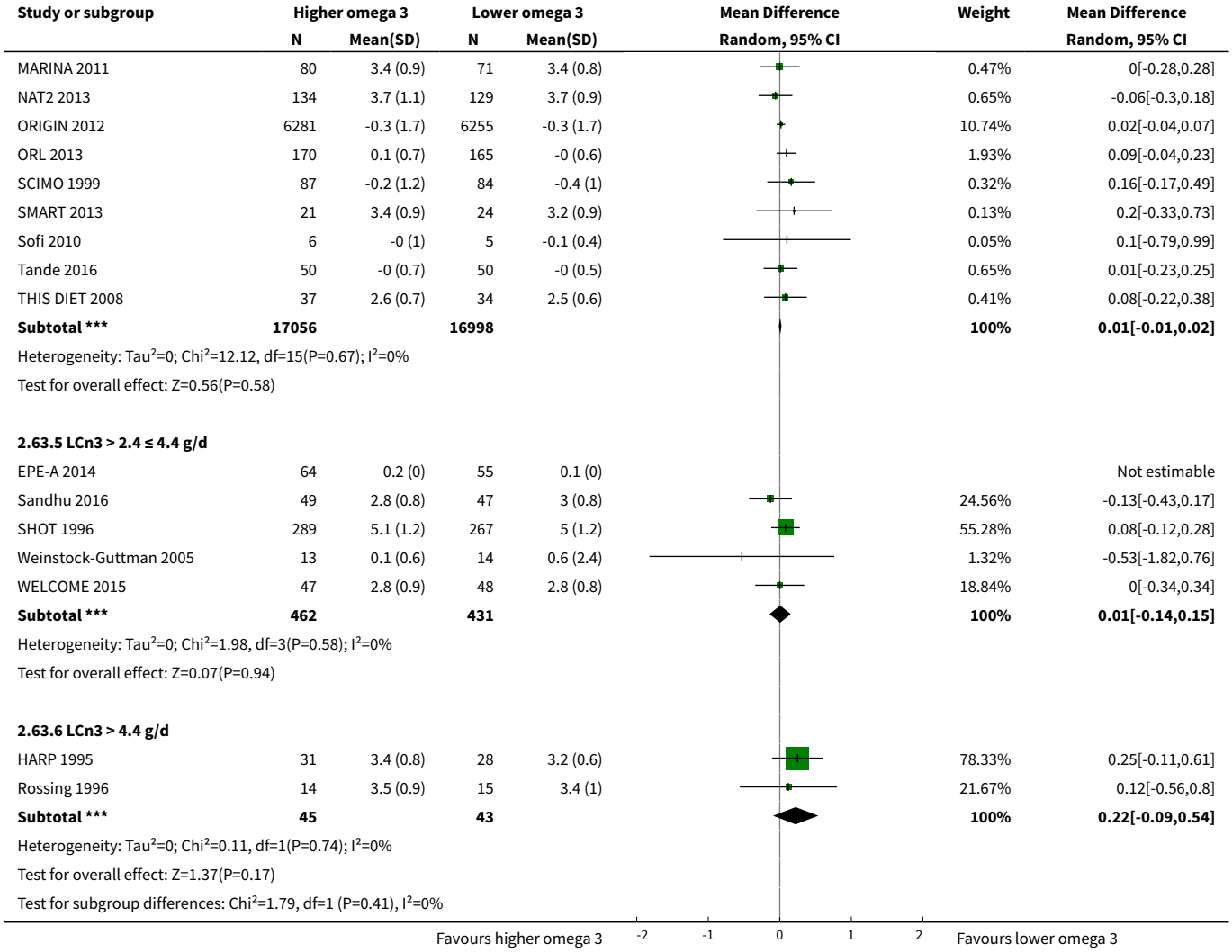
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Deslypere 1992	14	3.9 (0.9)	14	4.1 (0.9)		0.17%	-0.2[-0.85,0.45]
EPE-A 2014	64	0.2 (0)	55	0.1 (0)			Not estimable
HARP 1995	31	3.4 (0.8)	28	3.2 (0.6)		0.55%	0.25[-0.11,0.61]
JELIS 2007	9326	3.5 (0.8)	9319	3.5 (0.7)		44.55%	0[-0.02,0.02]
MARINA 2011	80	3.4 (0.9)	71	3.4 (0.8)		0.9%	0[-0.28,0.28]
NAT2 2013	134	3.7 (1.1)	129	3.7 (0.9)		1.24%	-0.06[-0.3,0.18]
ORIGIN 2012	6281	-0.3 (1.7)	6255	-0.3 (1.7)		15.7%	0.02[-0.04,0.07]
ORL 2013	170	0.1 (0.7)	165	-0 (0.6)		3.54%	0.09[-0.04,0.23]
SCIMO 1999	87	-0.2 (1.2)	84	-0.4 (1)		0.62%	0.16[-0.17,0.49]
SHOT 1996	289	5.1 (1.2)	267	5 (1.2)		1.72%	0.08[-0.12,0.28]
Tande 2016	50	-0 (0.7)	50	-0 (0.5)		1.24%	0.01[-0.23,0.25]
Subtotal * **	**17321**		**17232**			**80.42%**	**0.01[-0.02,0.04]**
Heterogeneity: Tau^2=0; Chi^2=12.87, df=12(P=0.38); I^2=6.76%							
Test for overall effect: Z=0.86(P=0.39)							
Total * **	**18931**		**18787**			**100%**	**0.02[-0.01,0.05]**
Heterogeneity: Tau^2=0; Chi^2=25.69, df=24(P=0.37); I^2=6.56%							
Test for overall effect: Z=1.41(P=0.16)							
Test for subgroup differences: Chi^2=0.91, df=1 (P=0.34), I^2=0%							



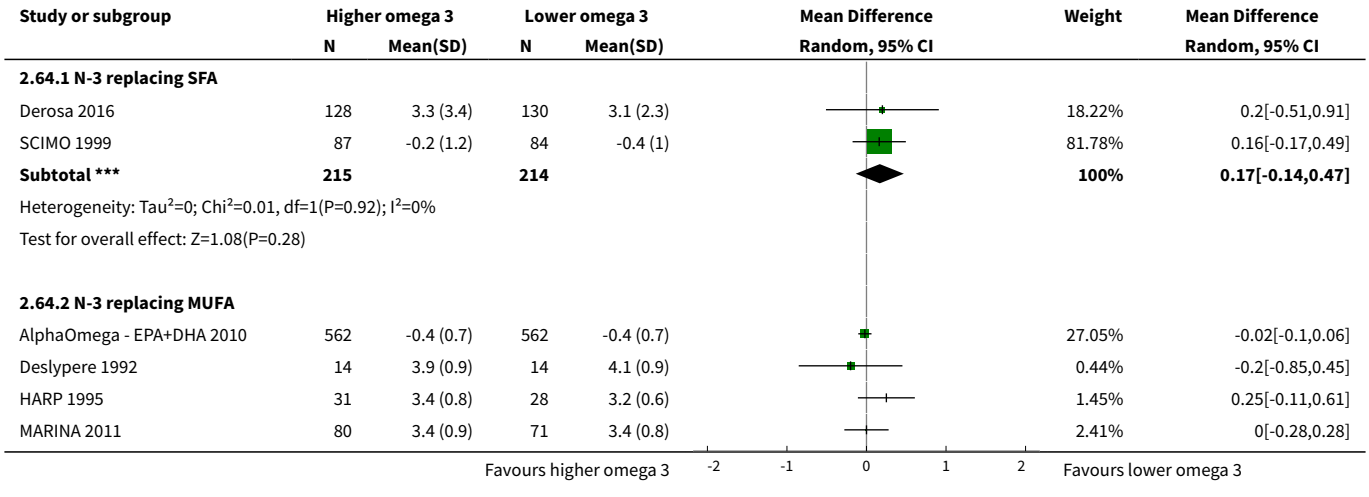
Analysis 2.63. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 63 LDL, mmoL/L - LCn3 - subgroup by dose.

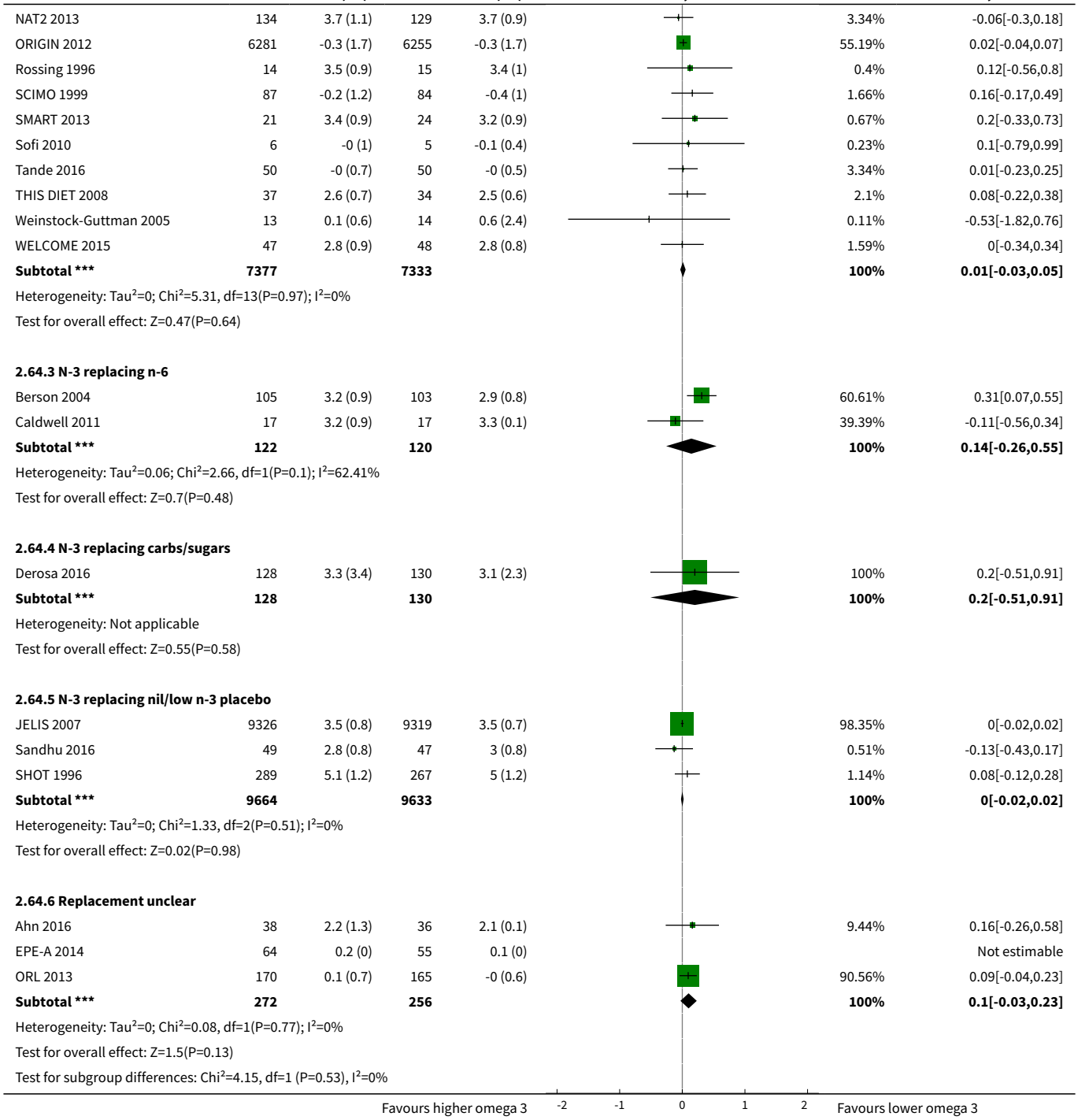
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.63.1 LCn3 ≤ 150 mg/d							
Subtotal * **	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.63.2 LCn3 > 150 ≤ 250 mg/d							
Subtotal * **	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.63.3 LCn3 > 250 ≤ 400 mg/d							
Subtotal * **	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.63.4 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]
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]





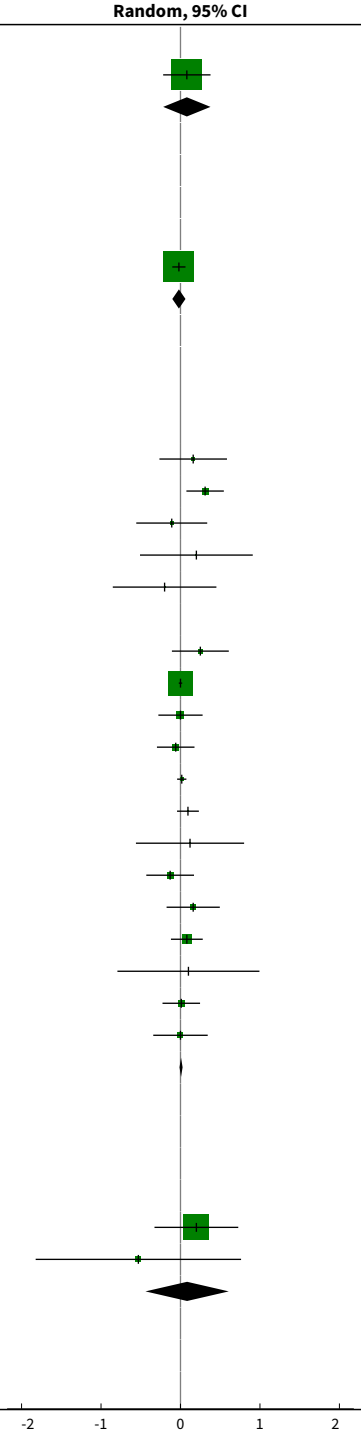
Analysis 2.64. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 64 LDL, mmoL/L - LCn3 - subgroup by replacement.





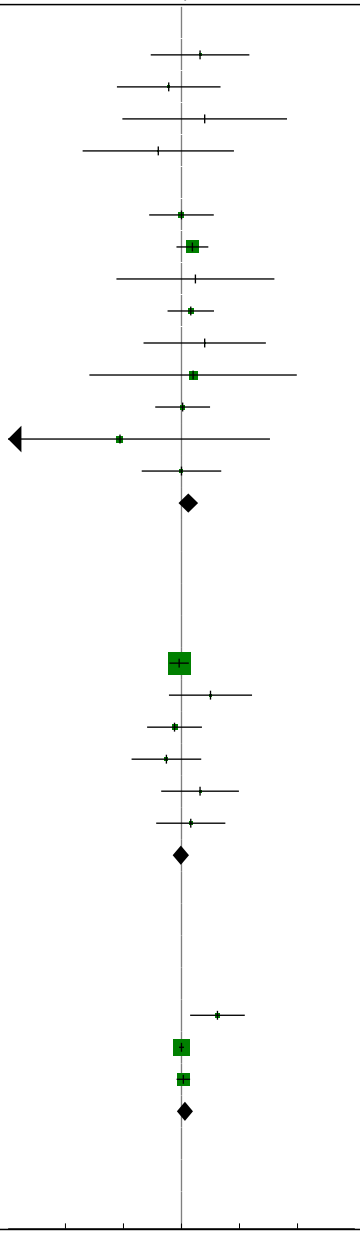
Analysis 2.65. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 65 LDL, mmoL/L - LCn3 - subgroup by intervention type.

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
2.65.1 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)							
2.65.2 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)							
2.65.3 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)		0.68%	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]
JELIS 2007	9326	3.5 (0.8)	9319	3.5 (0.7)		81.31%	0[-0.02,0.02]
MARINA 2011	80	3.4 (0.9)	71	3.4 (0.8)		0.49%	0[-0.28,0.28]
NAT2 2013	134	3.7 (1.1)	129	3.7 (0.9)		0.68%	-0.06[-0.3,0.18]
ORIGIN 2012	6281	-0.3 (1.7)	6255	-0.3 (1.7)		11.17%	0.02[-0.04,0.07]
ORL 2013	170	0.1 (0.7)	165	-0 (0.6)		2%	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)		0.42%	-0.13[-0.43,0.17]
SCIMO 1999	87	-0.2 (1.2)	84	-0.4 (1)		0.34%	0.16[-0.17,0.49]
SHOT 1996	289	5.1 (1.2)	267	5 (1.2)		0.94%	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)		0.68%	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 ***	**16930**		**16838**			**100%**	**0.01[-0.01,0.03]**
Heterogeneity: Tau^2=0; Chi^2=14.18, df=17(P=0.65); I^2=0%							
Test for overall effect: Z=0.72(P=0.47)							
2.65.4 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=0.71, df=1 (P=0.87), I^2=0%							



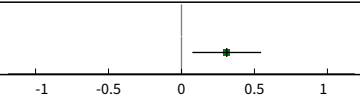
Analysis 2.66. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 66 LDL, mmoL/L - LCn3 - subgroup by duration.

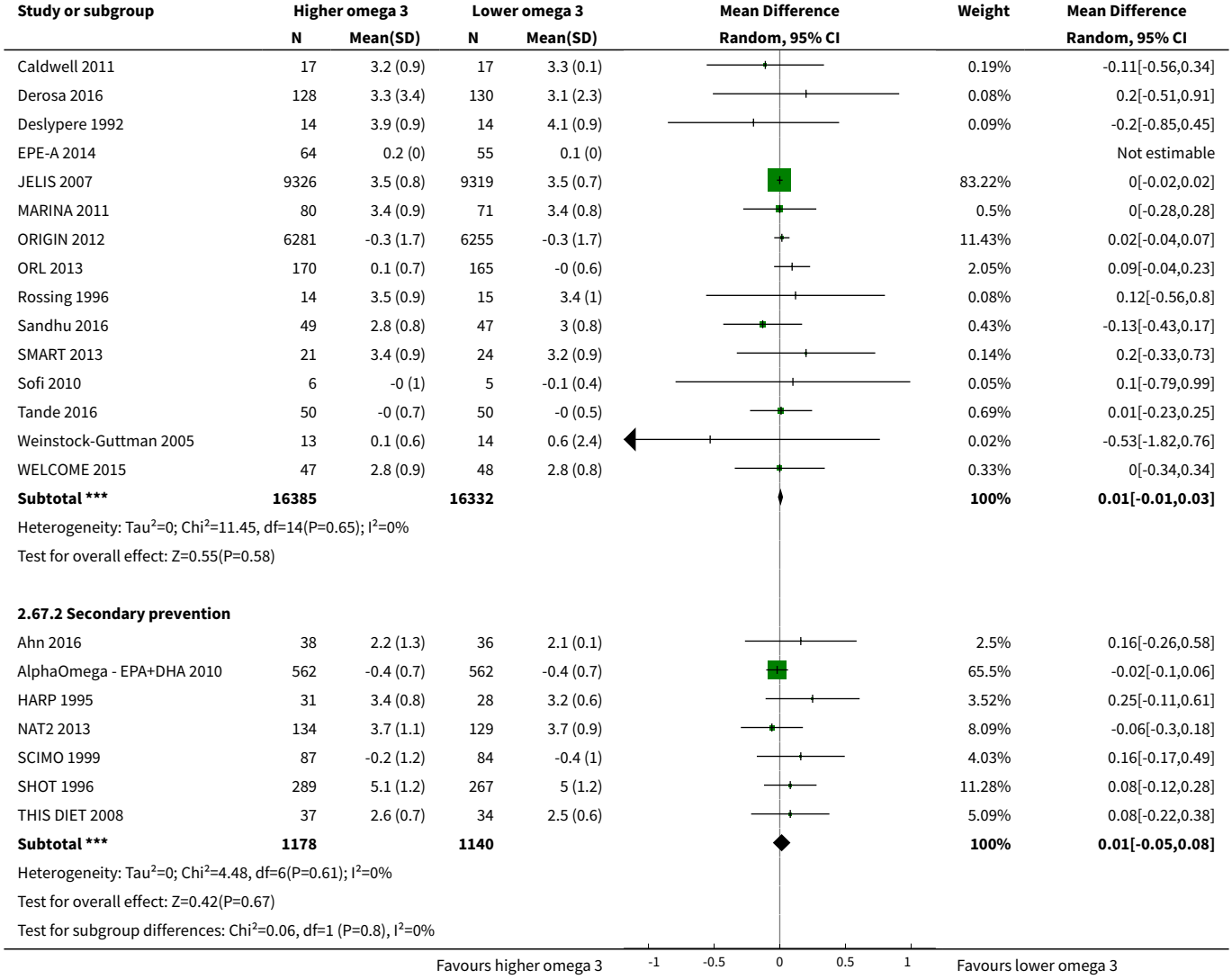
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.66.1 Medium duration 1 to < 2 years in study							
Ahn 2016	38	2.2 (1.3)	36	2.1 (0.1)		3.96%	0.16[-0.26,0.58]
Caldwell 2011	17	3.2 (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)							
2.66.2 Medium-long duration: 2 to < 4 years in study							
AlphaOmega - EPA+DHA 2010	562	-0.4 (0.7)	562	-0.4 (0.7)		71.79%	-0.02[-0.1,0.06]
HARP 1995	31	3.4 (0.8)	28	3.2 (0.6)		3.86%	0.25[-0.11,0.61]
NAT2 2013	134	3.7 (1.1)	129	3.7 (0.9)		8.87%	-0.06[-0.3,0.18]
Sandhu 2016	49	2.8 (0.8)	47	3 (0.8)		5.49%	-0.13[-0.43,0.17]
SCIMO 1999	87	-0.2 (1.2)	84	-0.4 (1)		4.41%	0.16[-0.17,0.49]
THIS DIET 2008	37	2.6 (0.7)	34	2.5 (0.6)		5.57%	0.08[-0.22,0.38]
Subtotal ***	**900**		**884**			**100%**	**-0.01[-0.08,0.06]**
Heterogeneity: Tau^2=0; Chi^2=4.19, df=5(P=0.52); I^2=0%							
Test for overall effect: Z=0.16(P=0.88)							
2.66.3 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]
Subtotal ***	**15712**		**15677**			**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=1.36, df=1 (P=0.51), I^2=0%							



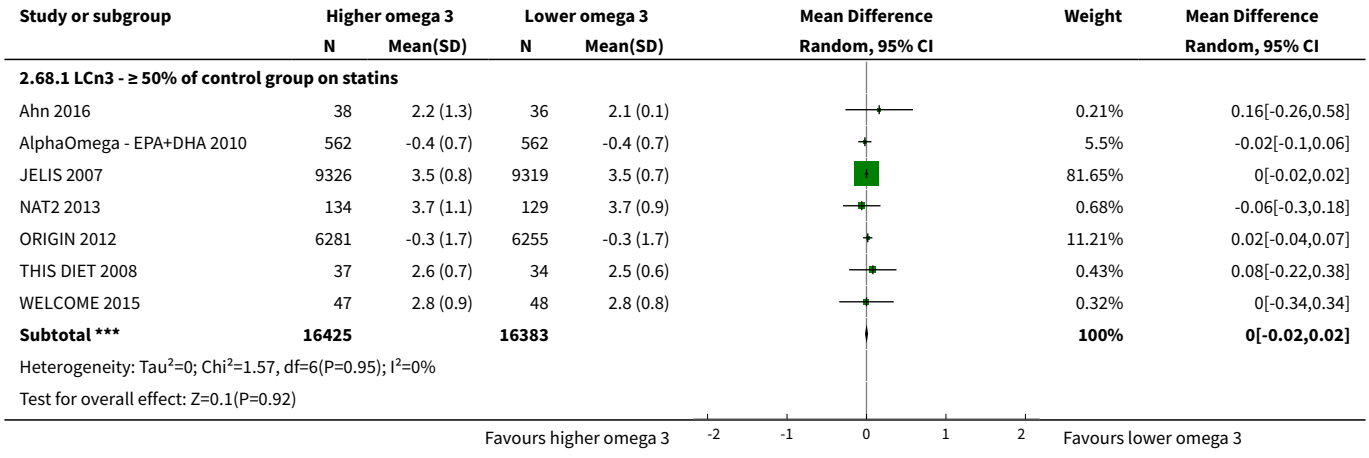
Analysis 2.67. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 67 LDL, mmoL/L - LCn3 - subgroup by primary or secondary prevention.

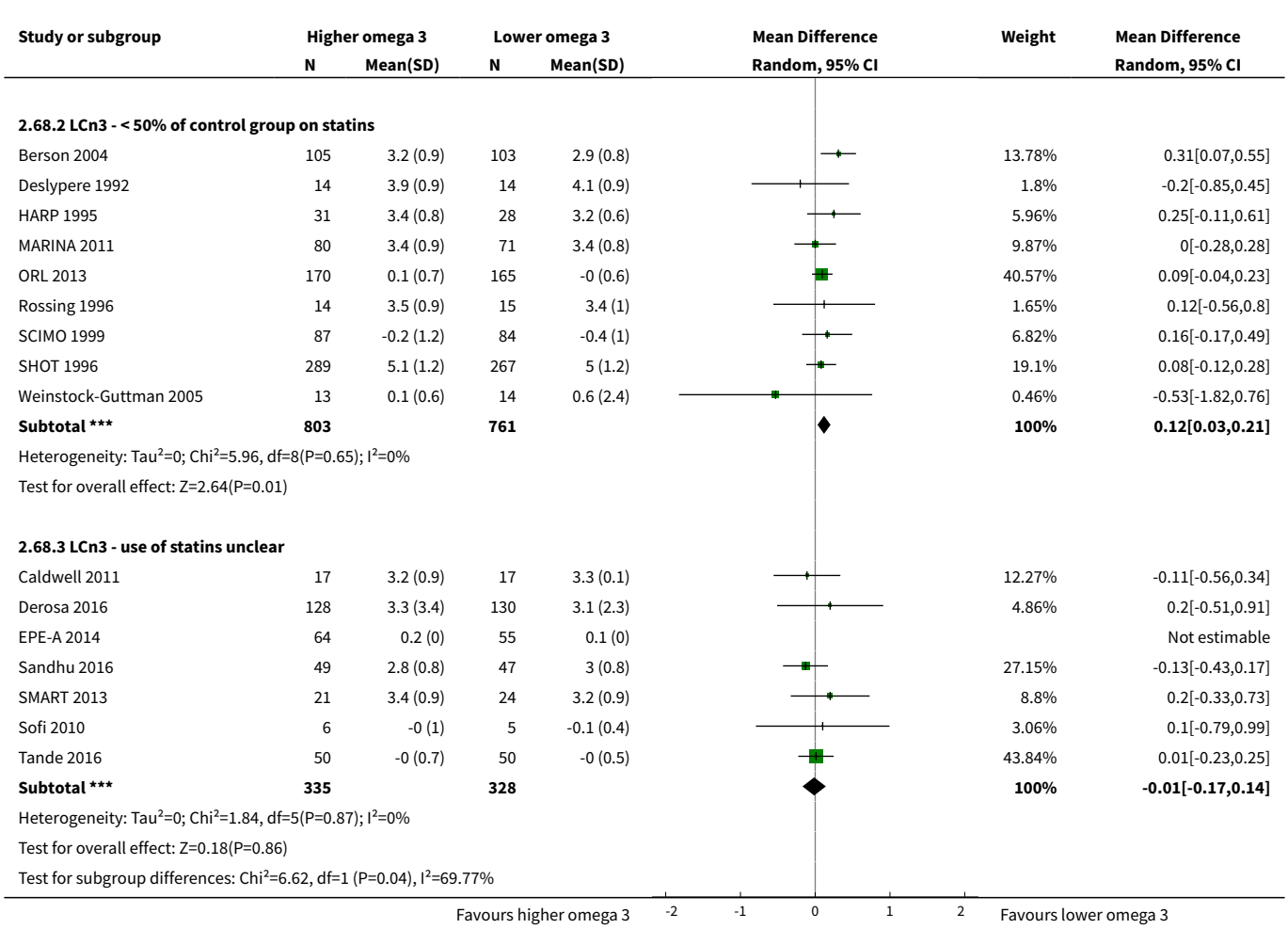
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.67.1 Primary prevention							
Berson 2004	105	3.2 (0.9)	103	2.9 (0.8)		0.7%	0.31[0.07,0.55]





Analysis 2.68. Comparison 2 High vs low LCn3 omega-3 fats (secondary outcomes), Outcome 68 LDL, mmoL/L - LCn3 - subgroup by statin use.





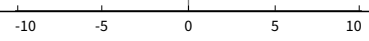
Comparison 3. High vs low LCn3 omega-3 fats (tertiary outcomes)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Blood pressure, mmHg - LCn3	15		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Systolic BP - LCn3	15	34413	Mean Difference (IV, Random, 95% CI)	0.02 [-0.32, 0.35]
1.2 Diastolic BP - LCn3	14	35386	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.22, 0.17]
2 Serious adverse events - LCn3	14		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Any serious adverse events	1	402	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.78, 1.41]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.2 Bleeding	8	45562	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.73, 1.52]
2.3 GI hospitalisation	1	200	Risk Ratio (M-H, Random, 95% CI)	1.75 [0.53, 5.79]
2.4 Pulmonary embolus or DVT - LCn3	4	3011	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.41, 3.78]
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	33		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	7	14650	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.84, 1.45]
3.3 Diarrhoea	10	2428	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.92, 1.43]
3.4 Nausea	5	1234	Risk Ratio (M-H, Random, 95% CI)	1.73 [1.23, 2.44]
3.5 Any gastrointestinal side effect - LCn3 fats	29	65185	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.94, 1.34]
3.6 Skin problems (itching, rashes)	8	36186	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.47, 2.30]
3.7 Headache or worsening migraine	3	991	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.48, 1.35]
3.8 Reflux	1	202	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.71, 2.81]
3.9 Pain (joint, lumbar, muscle pain)	1	18645	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.64, 0.99]
3.10 All side effects combined	13	38904	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.95, 1.08]
4 Dropouts - LCn3	30	31321	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.95, 1.09]

Analysis 3.1. Comparison 3 High vs low LCn3 omega-3 fats (tertiary outcomes), Outcome 1 Blood pressure, mmHg - LCn3.

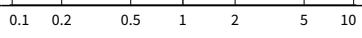
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.1.1 Systolic BP - LCn3							
AlphaOmega - EPA+DHA 2010	632	-0.6 (20)	632	-2.3 (21.3)		2.15%	1.65[-0.63,3.93]
DART 1989	871	138.1 (21.9)	852	137.7 (21.2)		2.7%	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)		0.47%	0[-4.88,4.88]
HARP 1995	31	129 (16)	28	137 (29)		0.08%	-8[-20.13,4.13]
JELIS 2007	9326	133.3 (14)	9319	133.3 (13)		74.25%	0[-0.39,0.39]
MARINA 2011	80	118.3 (12.1)	71	122.1 (12.7)		0.71%	-3.8[-7.77,0.17]
OFAMI 2001	127	132.2 (24.4)	130	136 (19.3)		0.38%	-3.8[-9.19,1.59]
ORIGIN 2012	6281	-4.4 (22.5)	5255	-4.5 (22.5)		16.43%	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)		0.26%	0[-6.55,6.55]
SMART 2013	20	120 (13)	23	128 (17)		0.14%	-8[-16.98,0.98]
Tande 2016	50	2.7 (6.3)	50	2 (7.1)		1.61%	0.73[-1.9,3.36]
THIS DIET 2008	37	123 (16)	34	123 (12)		0.26%	0[-6.55,6.55]
WELCOME 2015	47	133.3 (13.7)	48	133.9 (11.3)		0.44%	-0.6[-5.66,4.46]
Subtotal ***	**17741**		**16672**			**100%**	**0.02[-0.32,0.35]**
Heterogeneity: Tau^2=0; Chi^2=12.83, df=14(P=0.54); I^2=0%							
Test for overall effect: Z=0.09(P=0.93)							
3.1.2 Diastolic BP - LCn3							
AlphaOmega - EPA+DHA 2010	632	-3.2 (10.5)	632	-2.7 (10.3)		2.89%	-0.42[-1.57,0.73]
DART 1989	870	81.4 (12.5)	852	81.6 (11.9)		2.87%	-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)		0.45%	0[-2.91,2.91]
HARP 1995	31	77 (7)	28	77 (7)		0.3%	0[-3.58,3.58]
JELIS 2007	9326	78 (8)	9319	78 (8)		71.94%	0[-0.23,0.23]
MARINA 2011	80	71.2 (6.2)	71	72.9 (6.3)		0.95%	-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)		18.45%	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)		0.56%	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)		0.43%	-1.2[-4.18,1.78]
Subtotal ***	**17726**		**17660**			**100%**	**-0.02[-0.22,0.17]**
Heterogeneity: Tau^2=0; Chi^2=7.93, df=13(P=0.85); I^2=0%							
Test for overall effect: Z=0.24(P=0.81)							



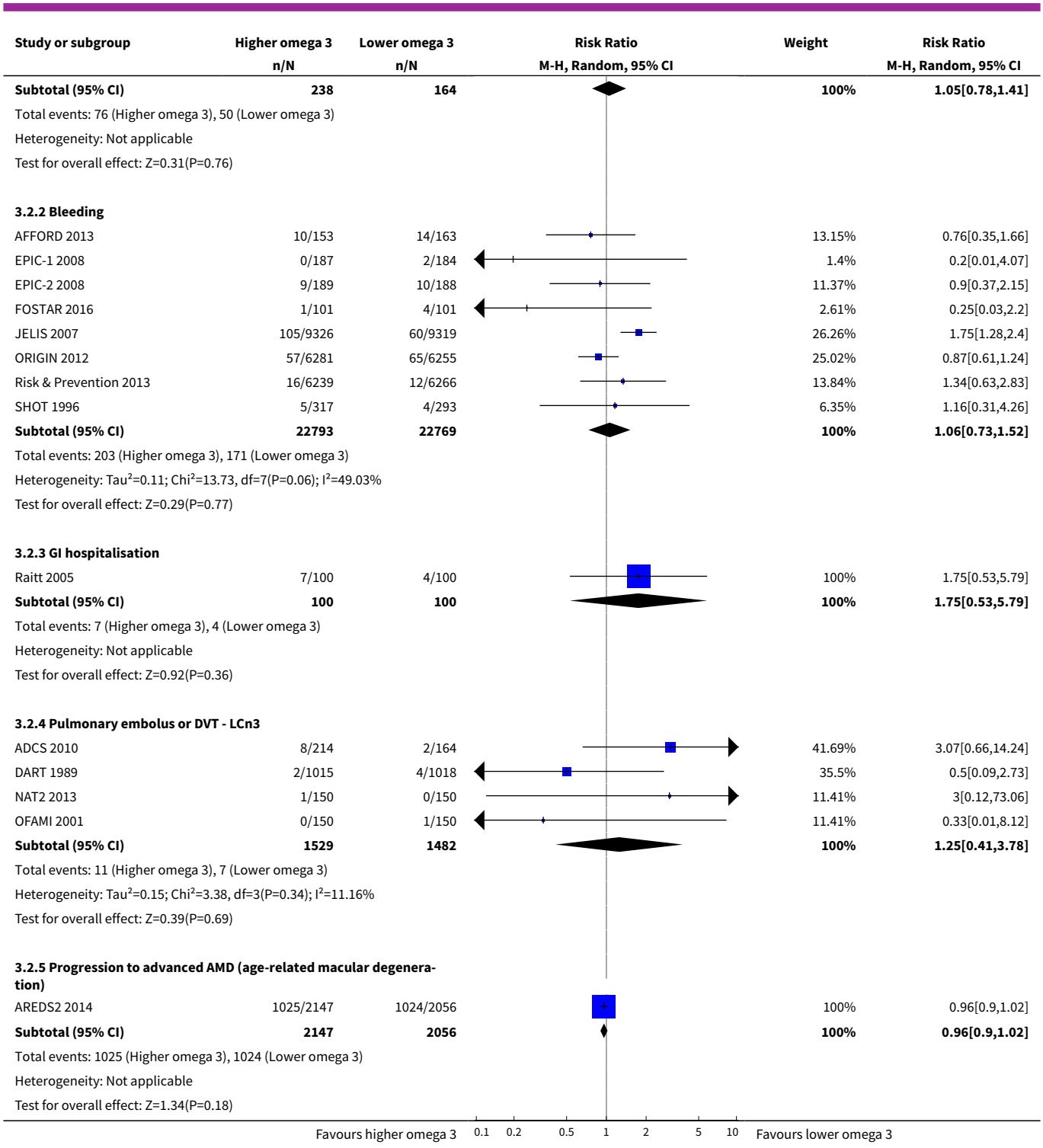
Favours higher omega 3 — Favours lower omega 3

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		100%	1.05[0.78,1.41]

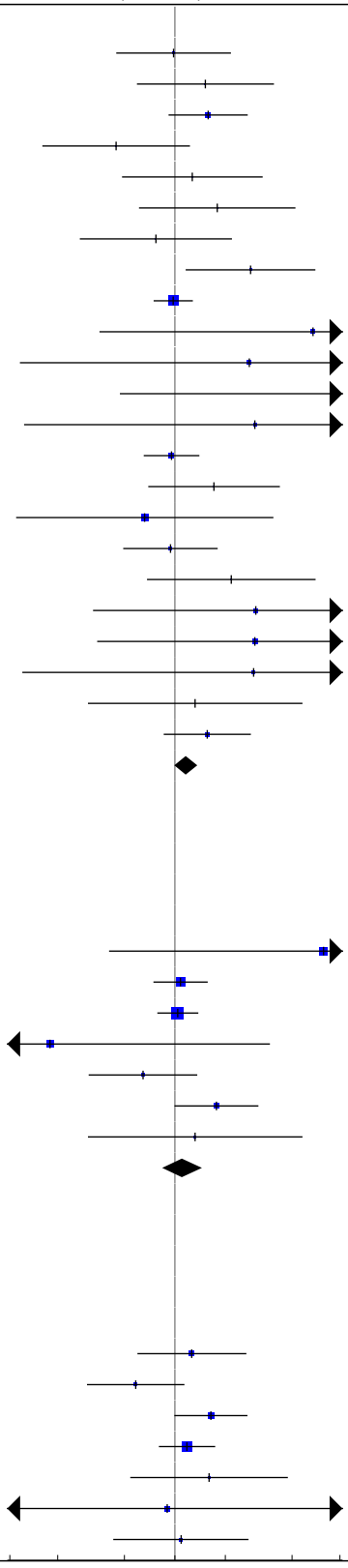


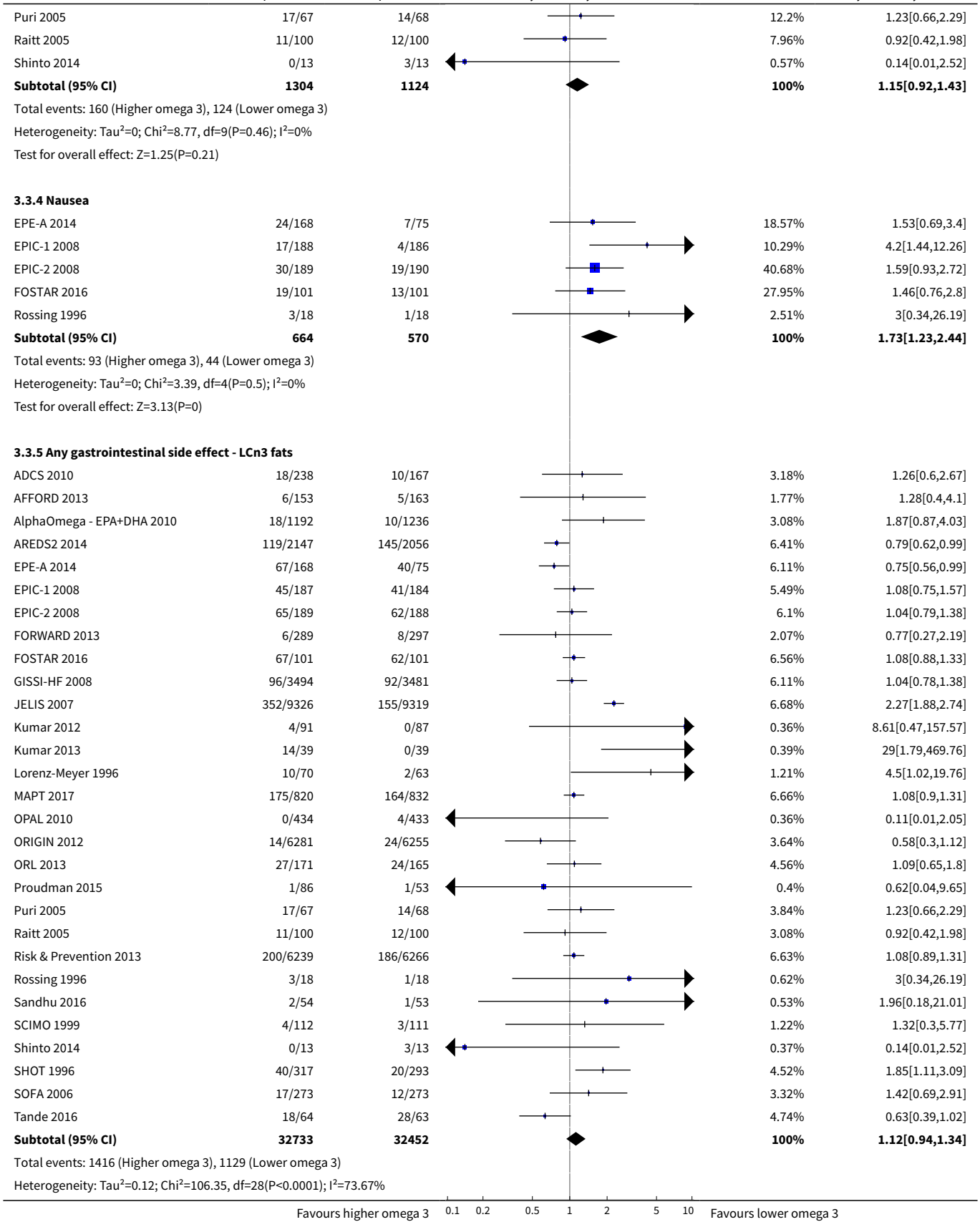
Favours higher omega 3 — Favours lower omega 3



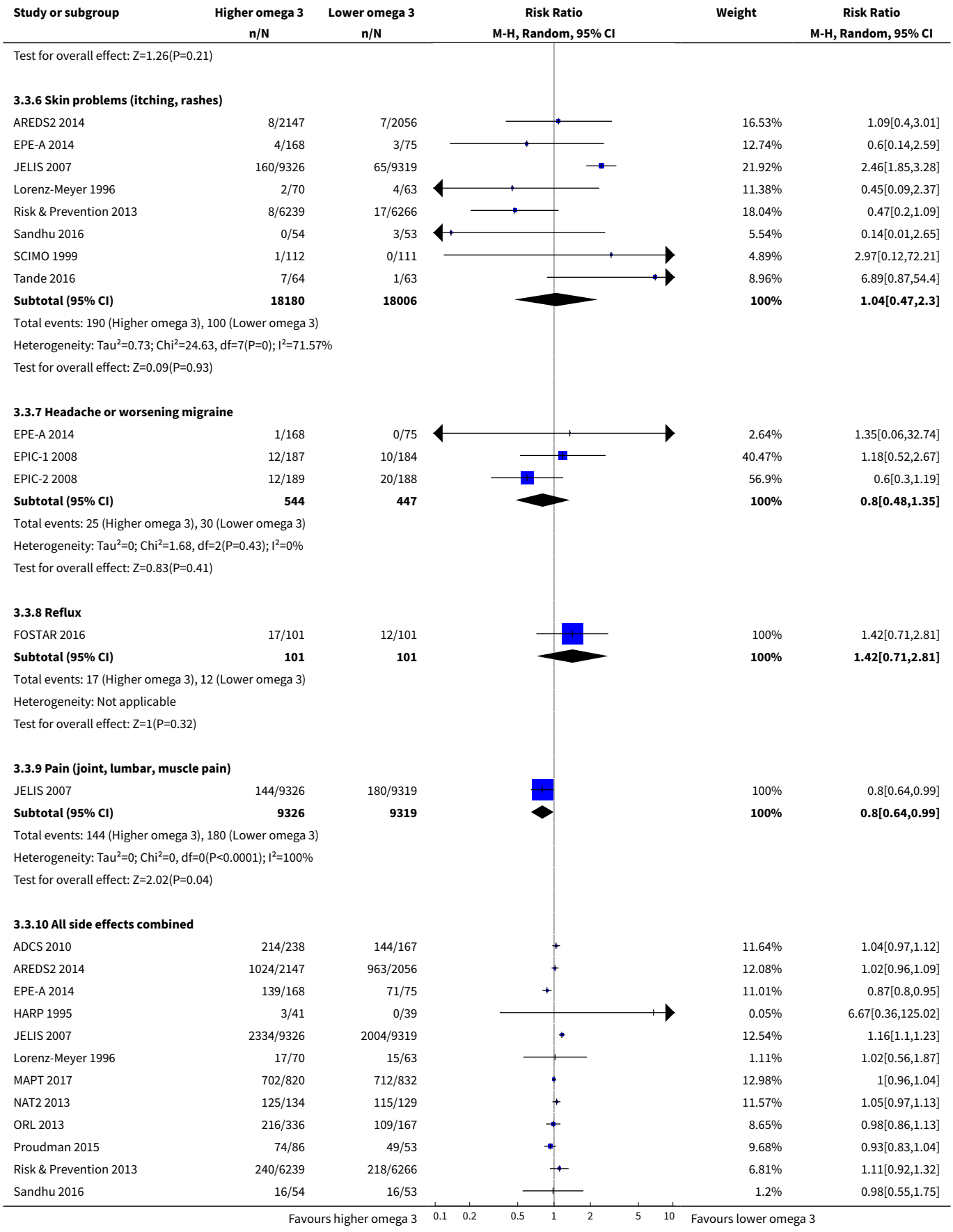
Analysis 3.3. Comparison 3 High vs low LCn3 omega-3 fats (tertiary outcomes), Outcome 3 Side effects - LCn3.

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: Tau^2=0; Chi^2=22.11, df=22(P=0.45); I^2=0.51%					
Test for overall effect: Z=1.86(P=0.06)					
3.3.2 Abdominal pain or discomfort					
EPE-A 2014	3/68	0/75		0.84%	7.71[0.41,146.61]
EPIC-1 2008	45/187	41/184		29.42%	1.08[0.75,1.57]
EPIC-2 2008	65/189	62/188		38.15%	1.04[0.79,1.38]
Lorenz-Meyer 1996	0/70	2/63		0.8%	0.18[0.01,3.69]
OPAL 2010	11/434	17/433		11%	0.65[0.31,1.36]
ORIGIN 2012	32/6281	18/6255		16.56%	1.77[0.99,3.15]
SCIMO 1999	4/112	3/111		3.23%	1.32[0.3,5.77]
Subtotal (95% CI)	**7341**	**7309**		**100%**	**1.1[0.84,1.45]**
Total events: 160 (Higher omega 3), 143 (Lower omega 3)					
Heterogeneity: Tau^2=0.03; Chi^2=7.86, df=6(P=0.25); I^2=23.68%					
Test for overall effect: Z=0.7(P=0.48)					
3.3.3 Diarrhoea					
ADCS 2010	18/238	10/167		8.45%	1.26[0.6,2.67]
EPE-A 2014	17/168	13/75		10.54%	0.58[0.3,1.14]
EPIC-1 2008	35/187	21/184		18.77%	1.64[0.99,2.71]
EPIC-2 2008	44/189	37/188		31.37%	1.18[0.8,1.74]
FOSTAR 2016	8/101	5/101		4.02%	1.6[0.54,4.72]
Lorenz-Meyer 1996	1/70	1/63		0.62%	0.9[0.06,14.09]
ORL 2013	9/171	8/165		5.48%	1.09[0.43,2.75]

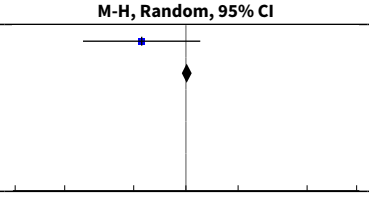




Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Puri 2005	17/67	14/68		12.2%	1.23[0.66,2.29]
Raitt 2005	11/100	12/100		7.96%	0.92[0.42,1.98]
Shinto 2014	0/13	3/13		0.57%	0.14[0.01,2.52]
Subtotal (95% CI)	**1304**	**1124**		**100%**	**1.15[0.92,1.43]**
Total events: 160 (Higher omega 3), 124 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=8.77, df=9(P=0.46); I²=0%					
Test for overall effect: Z=1.25(P=0.21)					
3.3.4 Nausea					
EPE-A 2014	24/168	7/75		18.57%	1.53[0.69,3.4]
EPIC-1 2008	17/188	4/186		10.29%	4.2[1.44,12.26]
EPIC-2 2008	30/189	19/190		40.68%	1.59[0.93,2.72]
FOSTAR 2016	19/101	13/101		27.95%	1.46[0.76,2.8]
Rossing 1996	3/18	1/18		2.51%	3[0.34,26.19]
Subtotal (95% CI)	**664**	**570**		**100%**	**1.73[1.23,2.44]**
Total events: 93 (Higher omega 3), 44 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=3.39, df=4(P=0.5); I²=0%					
Test for overall effect: Z=3.13(P=0)					
3.3.5 Any gastrointestinal side effect - LCn3 fats					
ADCS 2010	18/238	10/167		3.18%	1.26[0.6,2.67]
AFFORD 2013	6/153	5/163		1.77%	1.28[0.4,4.1]
AlphaOmega - EPA+DHA 2010	18/1192	10/1236		3.08%	1.87[0.87,4.03]
AREDS2 2014	119/2147	145/2056		6.41%	0.79[0.62,0.99]
EPE-A 2014	67/168	40/75		6.11%	0.75[0.56,0.99]
EPIC-1 2008	45/187	41/184		5.49%	1.08[0.75,1.57]
EPIC-2 2008	65/189	62/188		6.1%	1.04[0.79,1.38]
FORWARD 2013	6/289	8/297		2.07%	0.77[0.27,2.19]
FOSTAR 2016	67/101	62/101		6.56%	1.08[0.88,1.33]
GISSI-HF 2008	96/3494	92/3481		6.11%	1.04[0.78,1.38]
JELIS 2007	352/9326	155/9319		6.68%	2.27[1.88,2.74]
Kumar 2012	4/91	0/87		0.36%	8.61[0.47,157.57]
Kumar 2013	14/39	0/39		0.39%	29[1.79,469.76]
Lorenz-Meyer 1996	10/70	2/63		1.21%	4.5[1.02,19.76]
MAPT 2017	175/820	164/832		6.66%	1.08[0.9,1.31]
OPAL 2010	0/434	4/433		0.36%	0.11[0.01,2.05]
ORIGIN 2012	14/6281	24/6255		3.64%	0.58[0.3,1.12]
ORL 2013	27/171	24/165		4.56%	1.09[0.65,1.8]
Proudman 2015	1/86	1/53		0.4%	0.62[0.04,9.65]
Puri 2005	17/67	14/68		3.84%	1.23[0.66,2.29]
Raitt 2005	11/100	12/100		3.08%	0.92[0.42,1.98]
Risk & Prevention 2013	200/6239	186/6266		6.63%	1.08[0.89,1.31]
Rossing 1996	3/18	1/18		0.62%	3[0.34,26.19]
Sandhu 2016	2/54	1/53		0.53%	1.96[0.18,21.01]
SCIMO 1999	4/112	3/111		1.22%	1.32[0.3,5.77]
Shinto 2014	0/13	3/13		0.37%	0.14[0.01,2.52]
SHOT 1996	40/317	20/293		4.52%	1.85[1.11,3.09]
SOFA 2006	17/273	12/273		3.32%	1.42[0.69,2.91]
Tande 2016	18/64	28/63		4.74%	0.63[0.39,1.02]
Subtotal (95% CI)	**32733**	**32452**		**100%**	**1.12[0.94,1.34]**
Total events: 1416 (Higher omega 3), 1129 (Lower omega 3)					
Heterogeneity: Tau²=0.12; Chi²=106.35, df=28(P<0.0001); I²=73.67%					

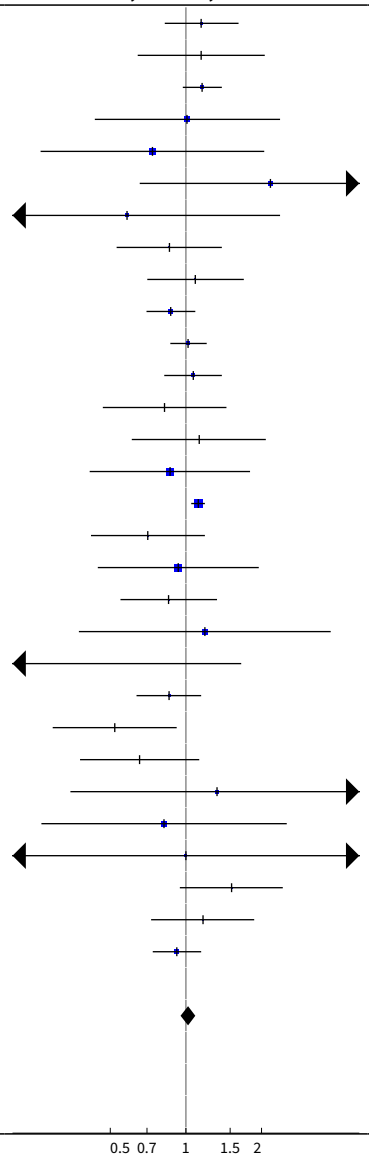


Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Shinto 2014	5/13	9/13		0.69%	0.56[0.26,1.21]
Subtotal (95% CI)	**19672**	**19232**		**100%**	**1.01[0.95,1.08]**
Total events: 5109 (Higher omega 3), 4425 (Lower omega 3)					
Heterogeneity: Tau²=0.01; Chi²=62.03, df=12(P<0.0001); I²=80.65%					
Test for overall effect: Z=0.36(P=0.72)					



Analysis 3.4. Comparison 3 High vs low LCn3 omega-3 fats (tertiary outcomes), Outcome 4 Dropouts - 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
ADCS 2010	67/238	40/164		3.57%	1.15[0.82,1.62]
AFFORD 2013	21/165	19/172		1.28%	1.15[0.64,2.06]
AlphaOmega - EPA+DHA 2010	214/1192	191/1236		10.2%	1.16[0.97,1.39]
Bates 1989	10/155	10/157		0.62%	1.01[0.43,2.37]
Berson 2004	6/105	8/103		0.43%	0.74[0.26,2.05]
Brox 2001	13/80	3/40		0.31%	2.17[0.65,7.17]
DIPP 2015	3/104	5/101		0.23%	0.58[0.14,2.37]
DISAF 2003	26/201	31/206		1.83%	0.86[0.53,1.39]
EPE-A 2014	49/168	20/75		2.16%	1.09[0.7,1.7]
EPIC-1 2008	80/188	91/186		7.32%	0.87[0.7,1.09]
EPIC-2 2008	114/189	112/190		11.3%	1.02[0.87,1.21]
FAAT 2005	73/200	69/202		5.46%	1.07[0.82,1.39]
FORWARD 2013	20/289	25/297		1.36%	0.82[0.47,1.45]
FOSTAR 2016	18/101	16/101		1.16%	1.13[0.61,2.08]
HARP 1995	10/41	11/39		0.81%	0.86[0.41,1.8]
JELIS 2007	1766/9326	1582/9319		27.76%	1.12[1.05,1.19]
MARINA 2011	38/279	17/88		1.6%	0.71[0.42,1.19]
Mita 2007	10/40	11/41		0.81%	0.93[0.45,1.95]
NAT2 2013	29/150	34/150		2.18%	0.85[0.55,1.33]
Nodari 2011 AF	6/100	5/99		0.34%	1.19[0.37,3.77]
Norouzi 2014	1/55	5/55		0.1%	0.2[0.02,1.66]
OPAL 2010	67/434	78/433		4.45%	0.86[0.64,1.15]
ORL 2013	22/336	21/167		1.34%	0.52[0.29,0.92]
Raitt 2005	17/100	26/100		1.46%	0.65[0.38,1.13]
Rossing 1996	4/18	3/18		0.25%	1.33[0.35,5.13]
Sandhu 2016	5/54	6/53		0.35%	0.82[0.27,2.52]
Shinto 2014	2/13	2/13		0.14%	1[0.16,6.07]
SHOT 1996	41/317	25/293		1.92%	1.52[0.95,2.43]
SMART 2013	20/41	18/43		1.92%	1.17[0.73,1.87]
SU.FOL.OM3 2010	134/1253	145/1248		7.34%	0.92[0.74,1.15]
Total (95% CI)	**15932**	**15389**		**100%**	**1.02[0.95,1.09]**
Total events: 2886 (Higher omega 3), 2629 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=32.74, df=29(P=0.29); I²=11.41%					
Test for overall effect: Z=0.51(P=0.61)					



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	16923	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.84, 1.34]
3 All-cause mortality - ALA - SA by summary risk of bias	5	19327	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.84, 1.20]
3.1 Low risk of bias	3	5213	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.72, 1.45]
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]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.3 Supplements (capsule)	1	13406	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.70, 1.64]
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	16923	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.84, 1.33]
10.1 ALA - ≥ 50% of control group on statins	2	2543	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.77, 1.34]
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	18619	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.74, 1.25]
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	23722	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.78, 1.16]
14.1 SA - low risk of compliance bias	2	5103	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.70, 1.27]
14.2 SA - 100+ randomised	4	18619	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.74, 1.25]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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]
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]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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	19327	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.83, 1.07]
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]
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]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
27 CVD events - ALA - subgroup by intervention type	6	19526	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	5	6120	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]
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	18353	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.72, 1.26]
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]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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]
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]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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]
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	19061	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.82, 1.22]
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]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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
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]
51 CHD events - ALA - subgroup by statin use	4	19061	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.82, 1.22]

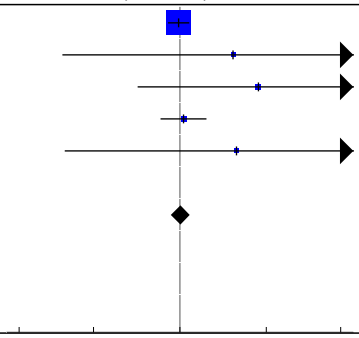
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
51.1 ALA - ≥ 50% of control group on statins	2	4947	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.71, 1.15]
51.2 ALA - < 50% of control group on statins	2	14114	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.86, 1.67]
52 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	19327	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.66, 2.01]
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	25138	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.66, 1.64]
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]
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]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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]
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	1	4837	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.57, 1.10]
64.1 ALA - new arrhythmias	1	4837	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.57, 1.10]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
64.2 ALA - recurrent arrhythmias	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
65 Arrhythmia - ALA - SA by summary risk of bias	1	4837	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.57, 1.10]
65.1 Low risk of bias	1	4837	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.57, 1.10]
65.2 Moderate/high risk of bias	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

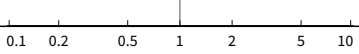
Analysis 4.1. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 1 All-cause mortality (overall) - ALA.

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)					



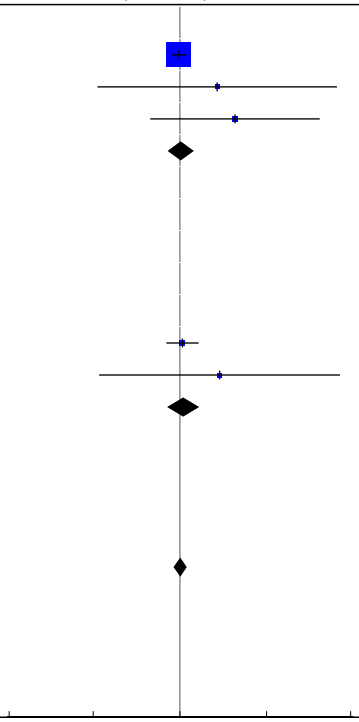
Analysis 4.2. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 2 All-cause mortality - ALA - sensitivity analysis (SA) fixed-effect.

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	91/1197	93/1236		68.57%	1.01[0.77,1.33]
FLAX-PAD 2013	1/58	0/52		0.39%	2.69[0.11,64.74]
MARGARIN 2002	3/109	1/157		0.61%	4.32[0.46,41]
Norwegian 1968	43/6716	40/6690		30.03%	1.07[0.7,1.64]
WAHA 2016	1/362	0/346		0.38%	2.87[0.12,70.16]
Total (95% CI)	**8442**	**8481**		**100%**	**1.06[0.84,1.34]**
Total events: 139 (Higher omega 3), 134 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=2.32, df=4(P=0.68); I^2=0%					
Test for overall effect: Z=0.52(P=0.6)					



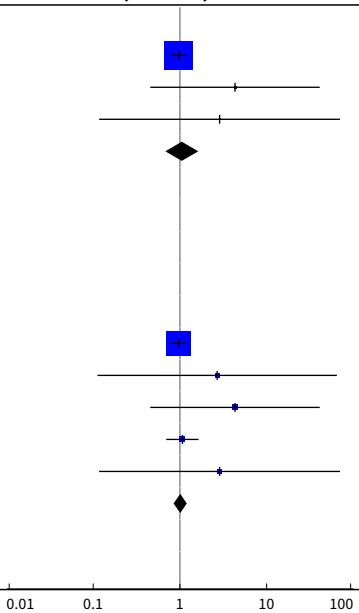
Analysis 4.3. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 3 All-cause mortality - ALA - SA by summary risk of bias.

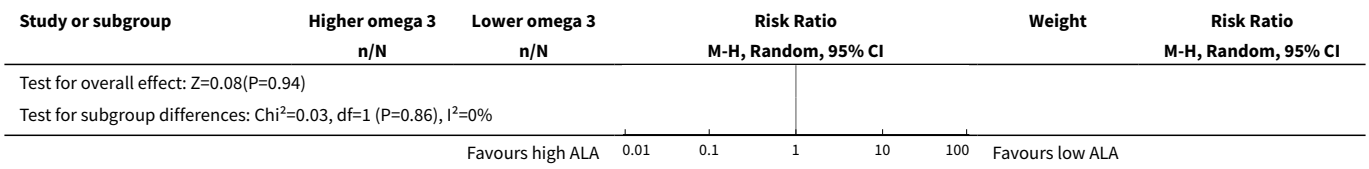
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.3.1 Low risk of bias					
AlphaOmega - ALA 2010	182/2409	188/2428		81.74%	0.98[0.8,1.19]
FLAX-PAD 2013	1/58	0/52		0.31%	2.69[0.11,64.74]
MARGARIN 2002	3/109	1/157		0.62%	4.32[0.46,41]
Subtotal (95% CI)	**2576**	**2637**		**82.67%**	**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)					
4.3.2 Moderate/high risk of bias					
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]
Subtotal (95% CI)	**7078**	**7036**		**17.33%**	**1.09[0.71,1.67]**
Total events: 44 (Higher omega 3), 40 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.36, df=1(P=0.55); I^2=0%					
Test for overall effect: Z=0.4(P=0.69)					
Total (95% CI)	**9654**	**9673**		**100%**	**1.01[0.84,1.2]**
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=0.08(P=0.94)					
Test for subgroup differences: Chi^2=0.05, df=1 (P=0.82), I^2=0%					



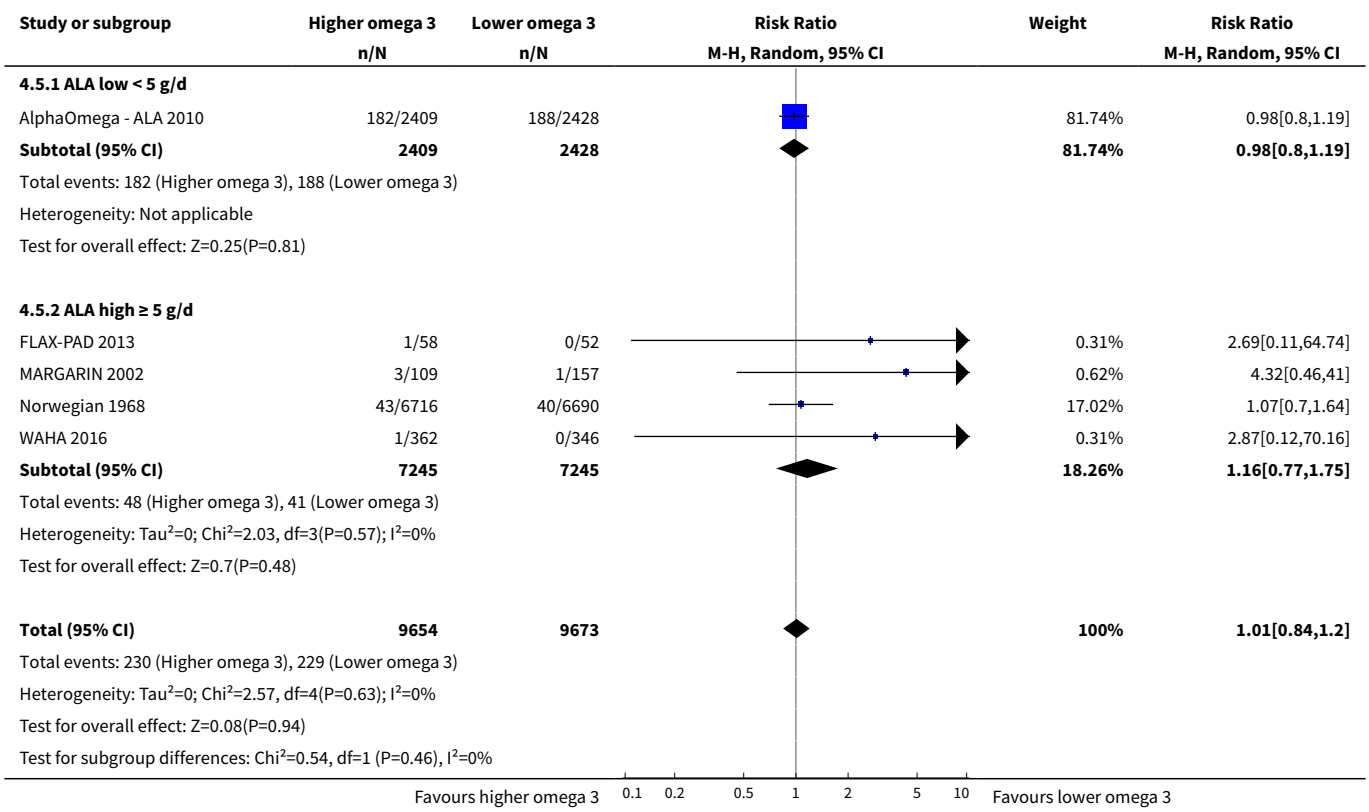
Analysis 4.4. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 4 All-cause mortality - ALA - SA by compliance and study size.

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
4.4.1 SA - low risk of compliance bias					
AlphaOmega - ALA 2010	182/2409	188/2428		94.49%	0.98[0.8,1.19]
MARGARIN 2002	3/109	1/157		3.67%	4.32[0.46,41]
WAHA 2016	1/362	0/346		1.84%	2.87[0.12,70.16]
Subtotal (95% CI)	**2880**	**2931**		**100%**	**1.05[0.68,1.63]**
Total events: 186 (Higher omega 3), 189 (Lower omega 3)					
Heterogeneity: Tau^2=0.04; Chi^2=2.1, df=2(P=0.35); I^2=4.59%					
Test for overall effect: Z=0.22(P=0.82)					
4.4.2 SA - 100+ randomised					
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]
Subtotal (95% CI)	**9654**	**9673**		**100%**	**1.01[0.84,1.2]**
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%					

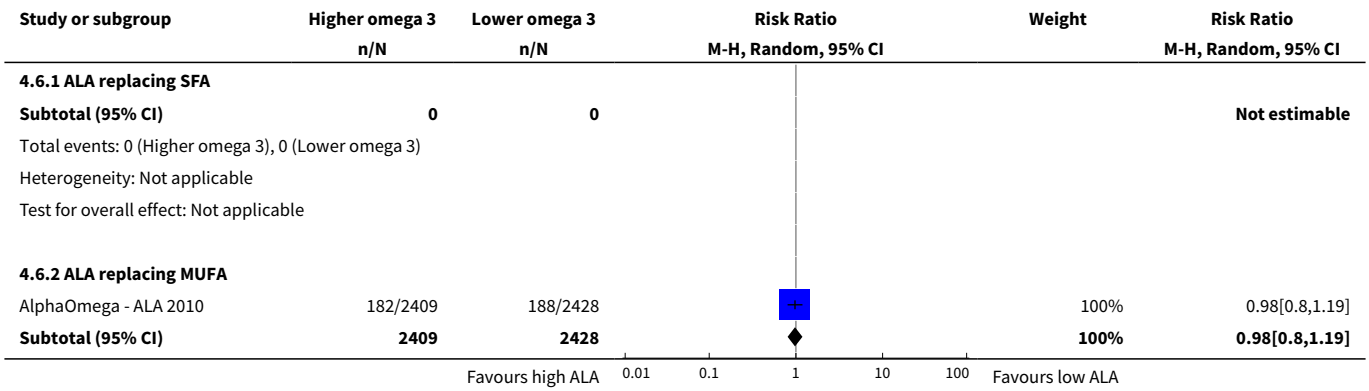


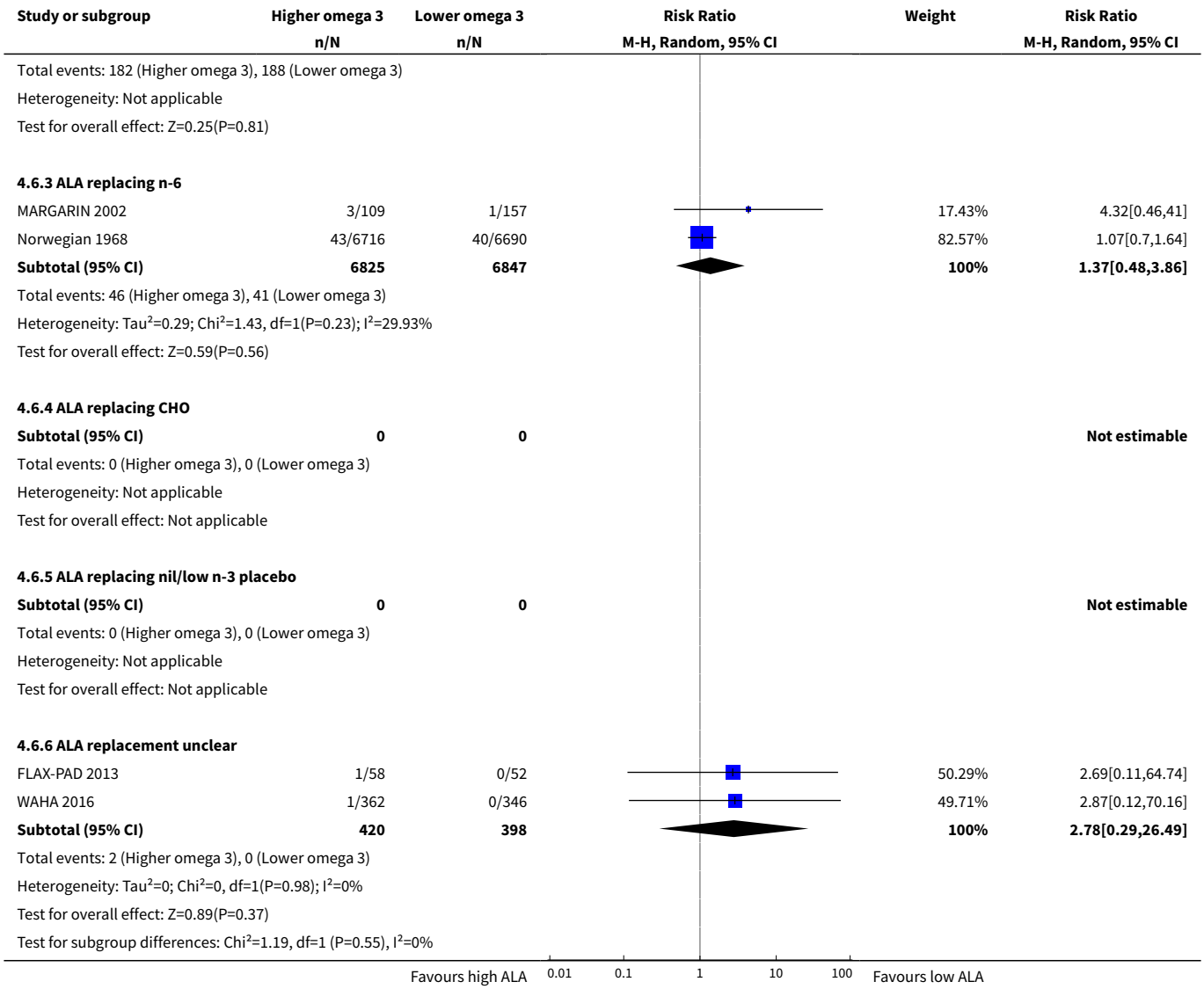


Analysis 4.5. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 5 All-cause mortality - ALA - subgroup by dose.

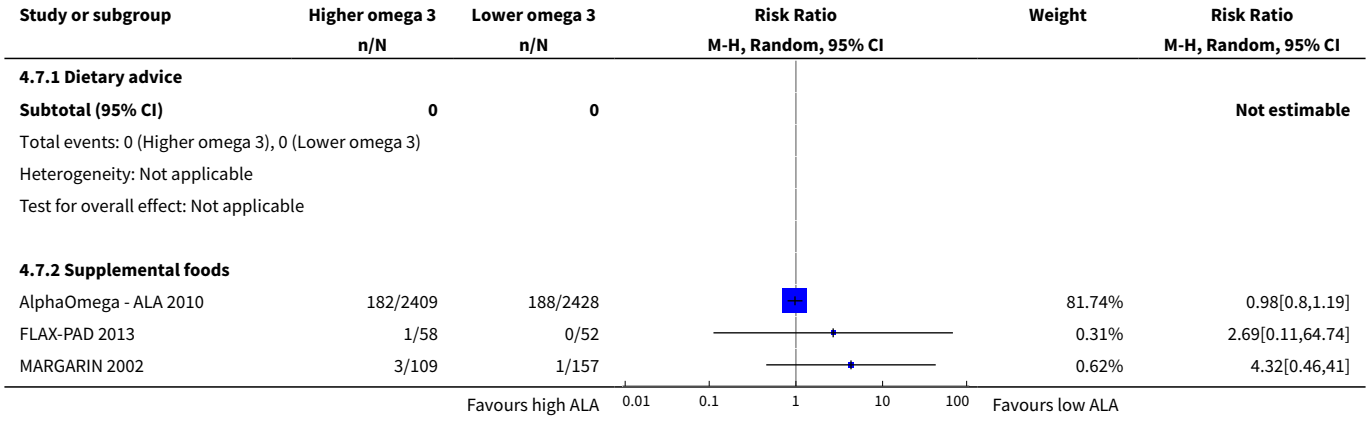


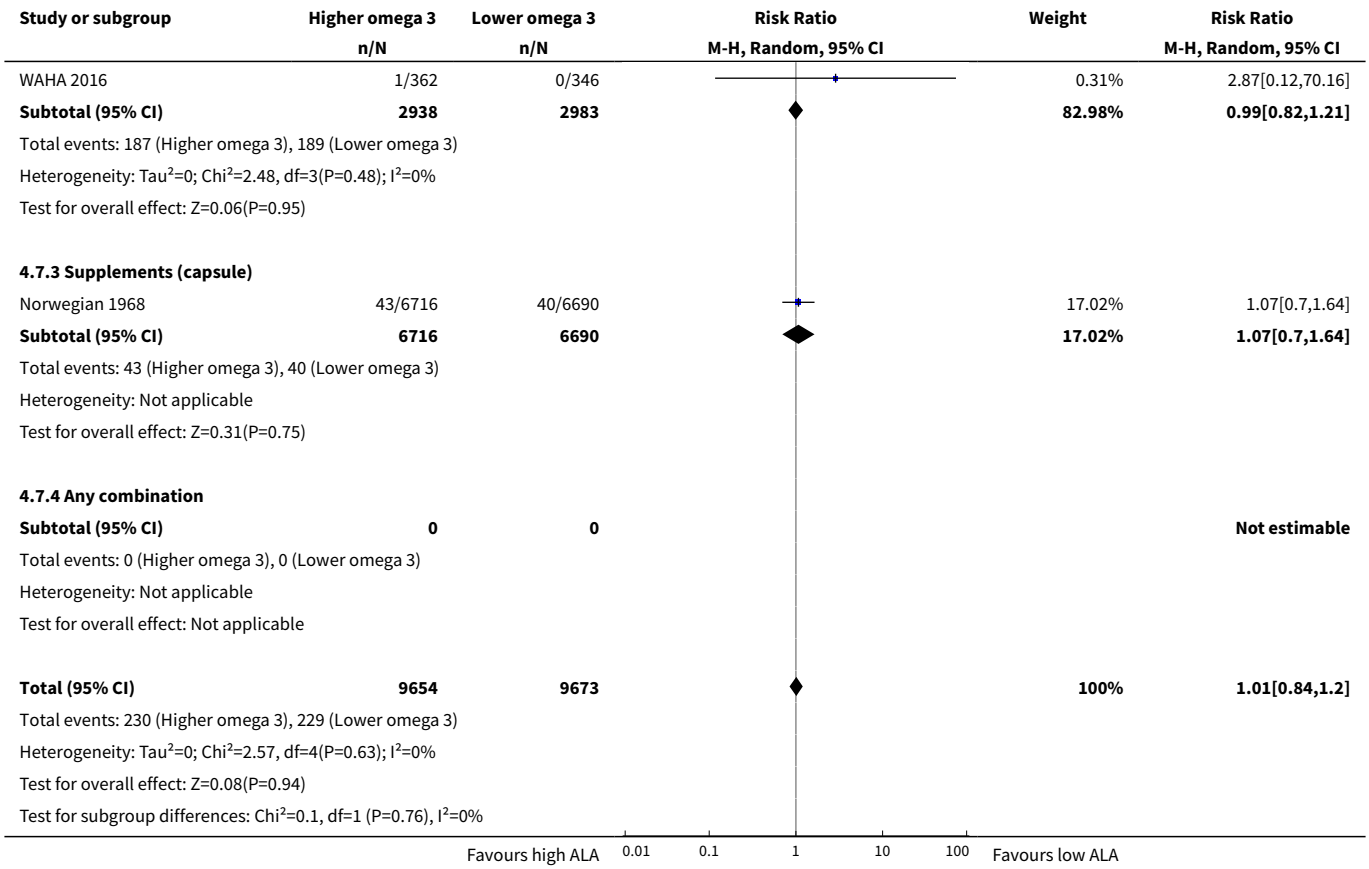
Analysis 4.6. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 6 All-cause mortality - ALA - subgroup by replacement.



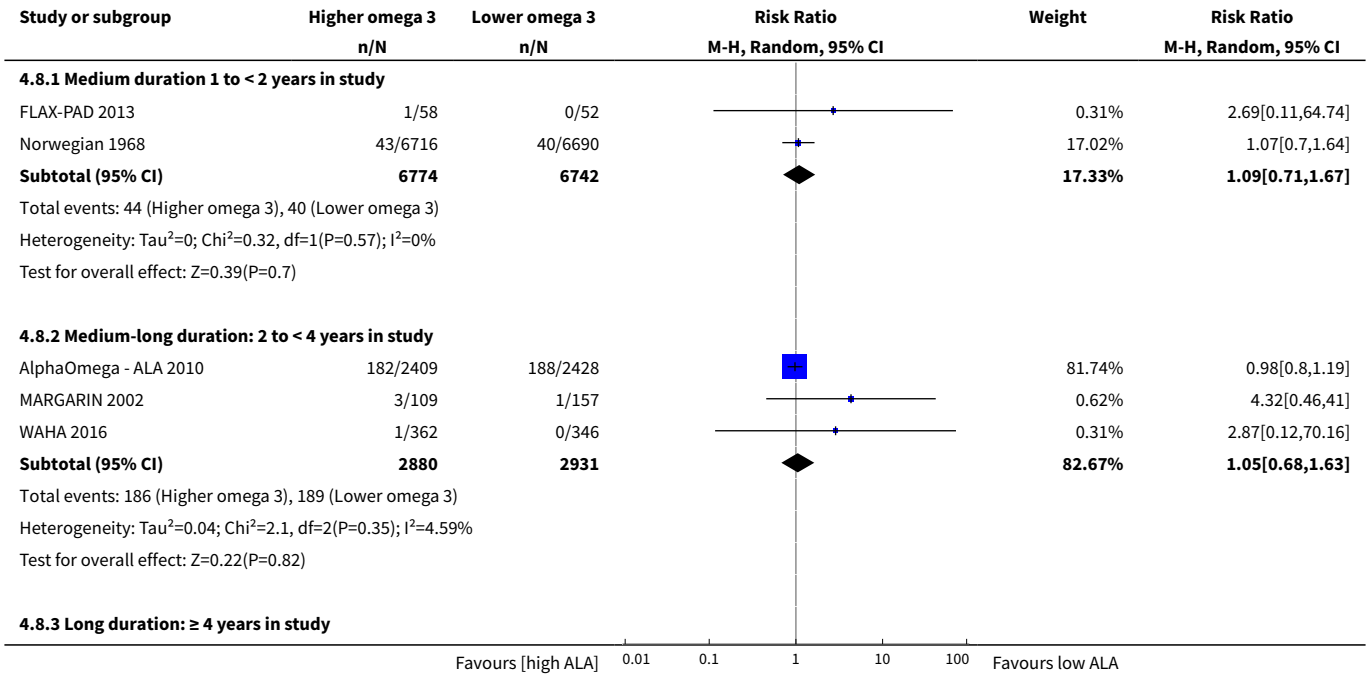


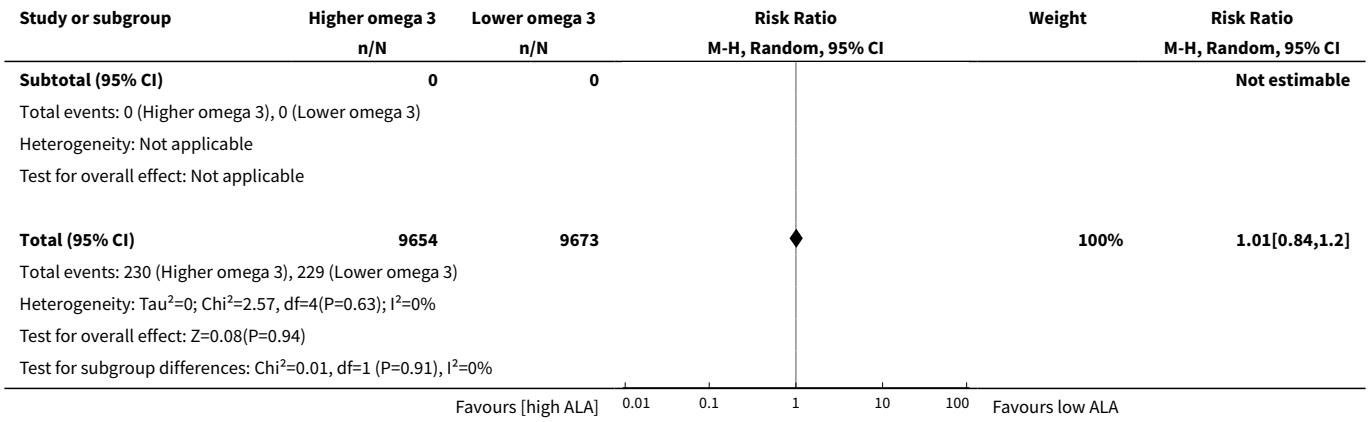
Analysis 4.7. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 7 All cause mortality - ALA - subgroup by intervention type.



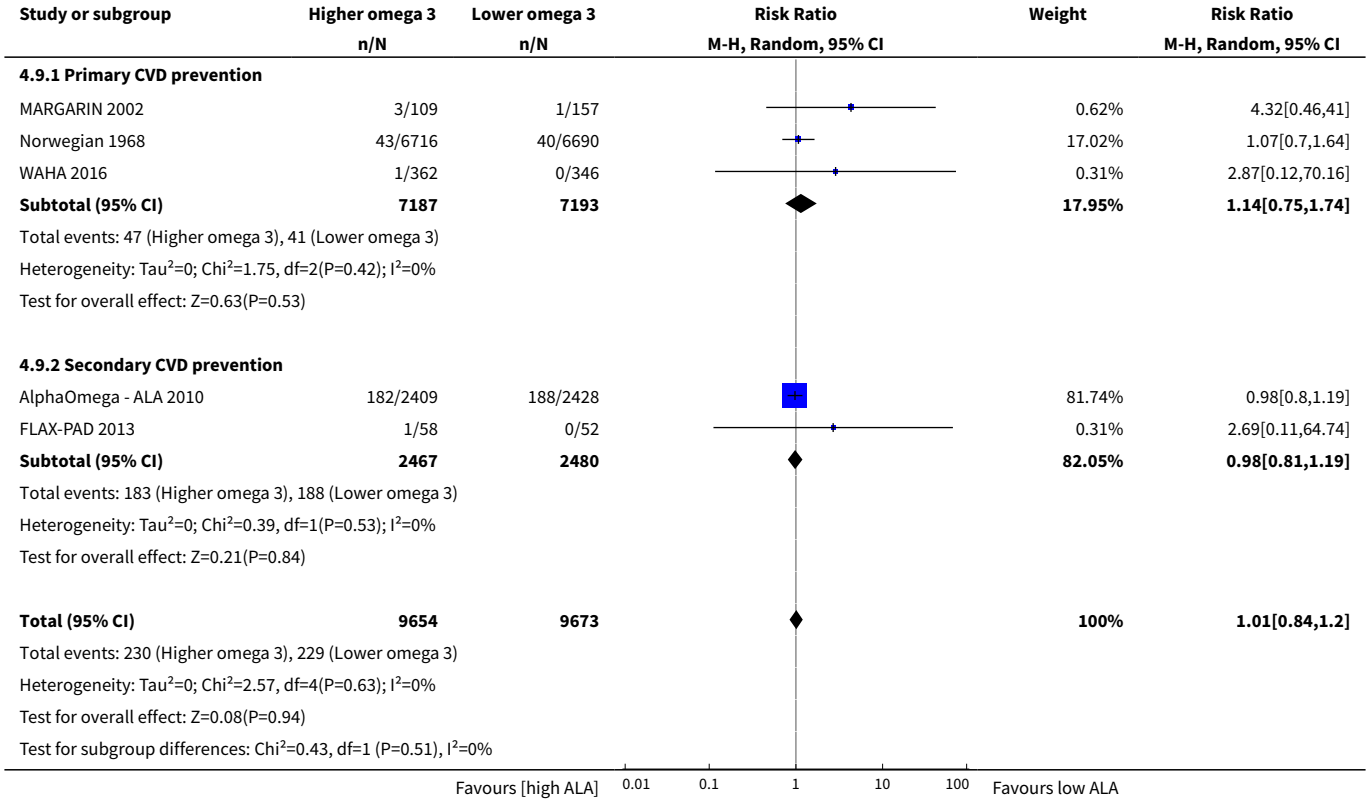


Analysis 4.8. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 8 All-cause mortality - ALA - subgroup by duration.

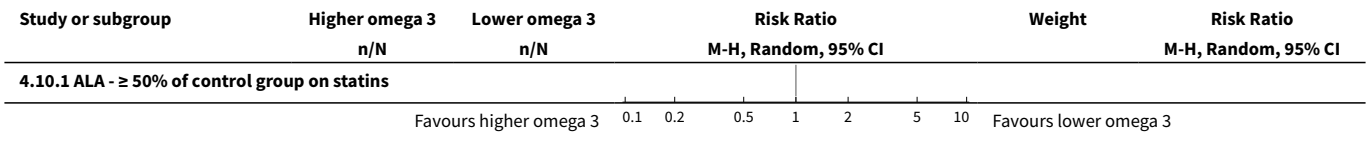


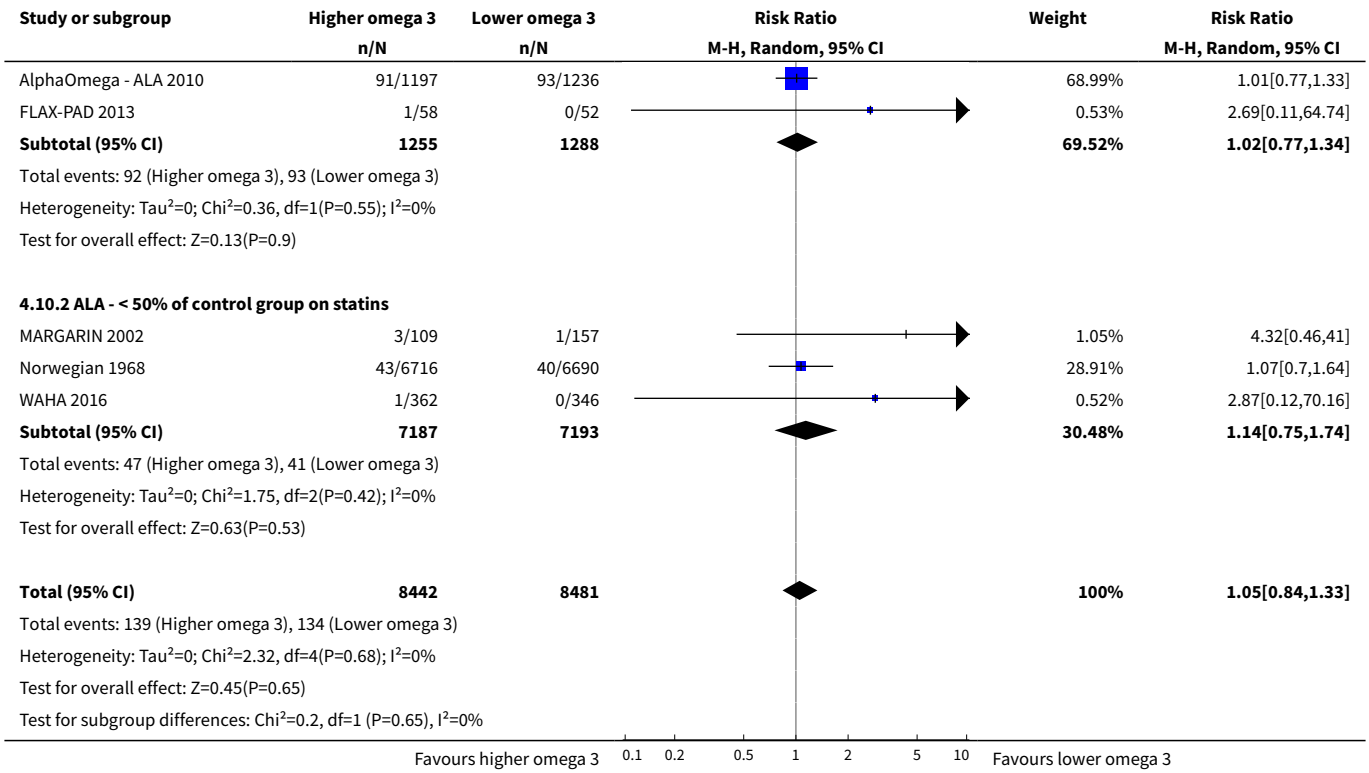


Analysis 4.9. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 9 All-cause mortality - ALA - subgroup by primary or secondary prevention.

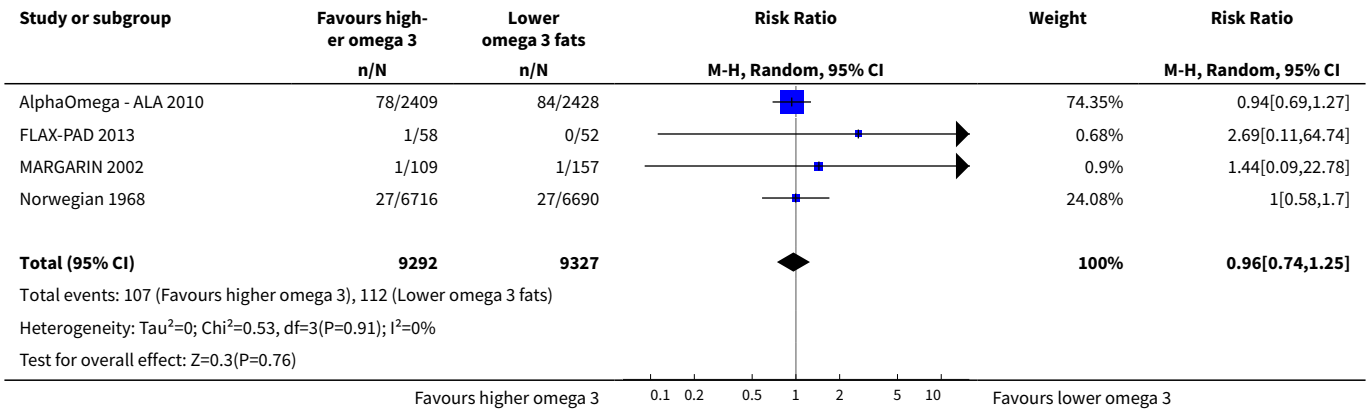


Analysis 4.10. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 10 All-cause mortality - ALA - subgroup by statin use.

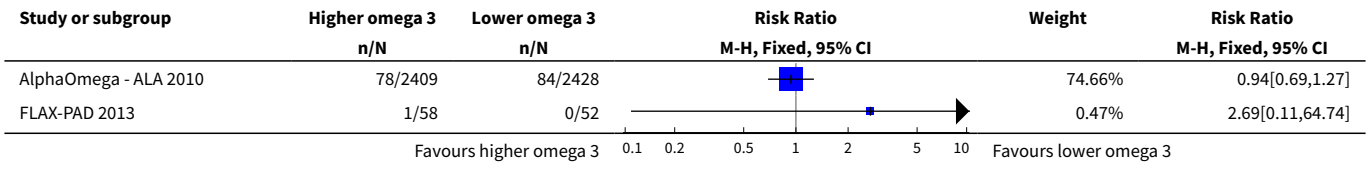


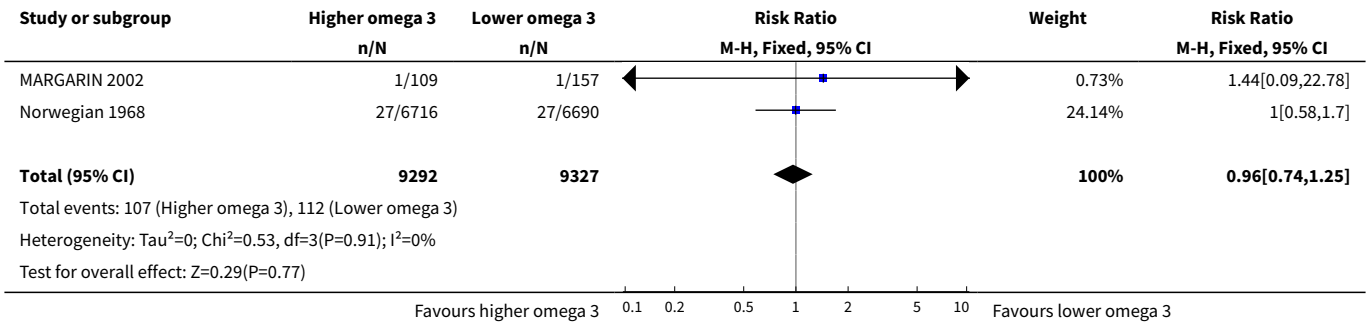


Analysis 4.11. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 11 Cardiovascular mortality (overall) - ALA.

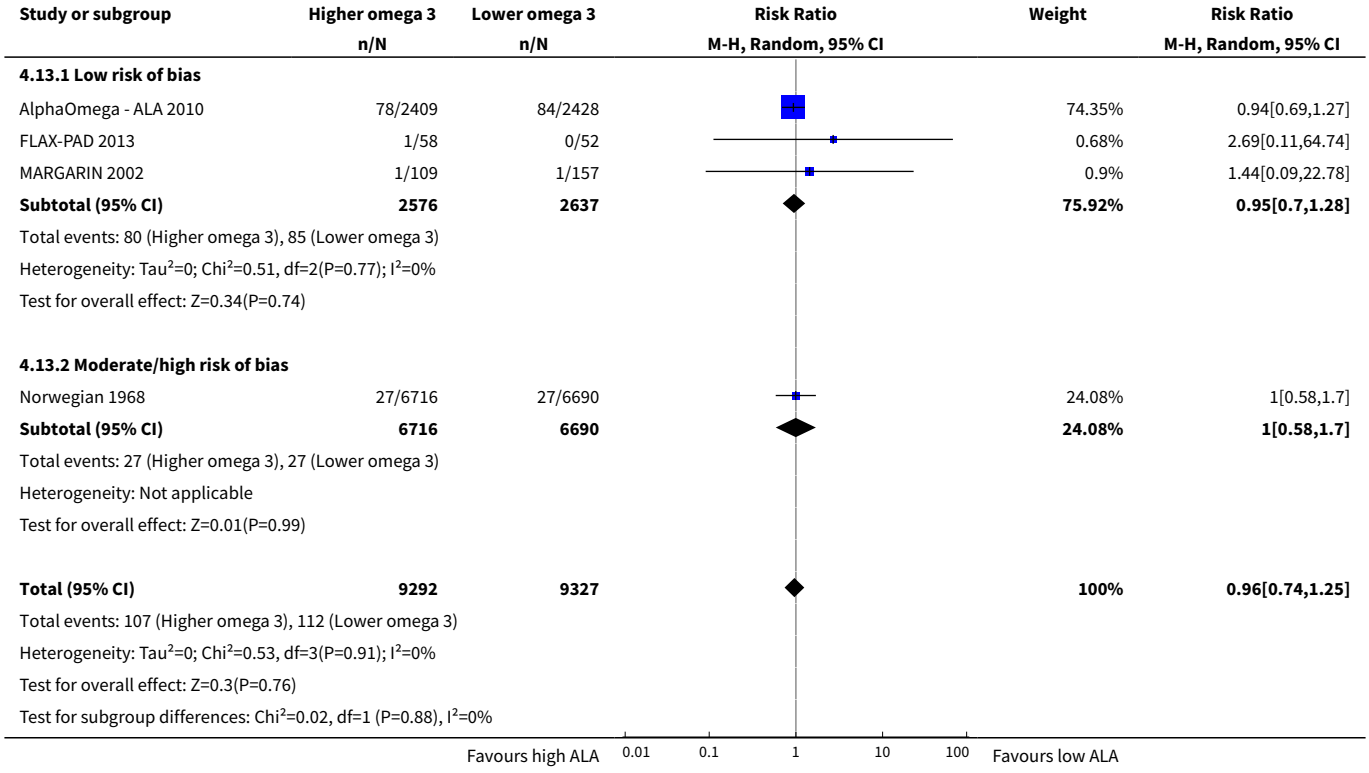


Analysis 4.12. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 12 CVD mortality - ALA - SA fixed-effect.

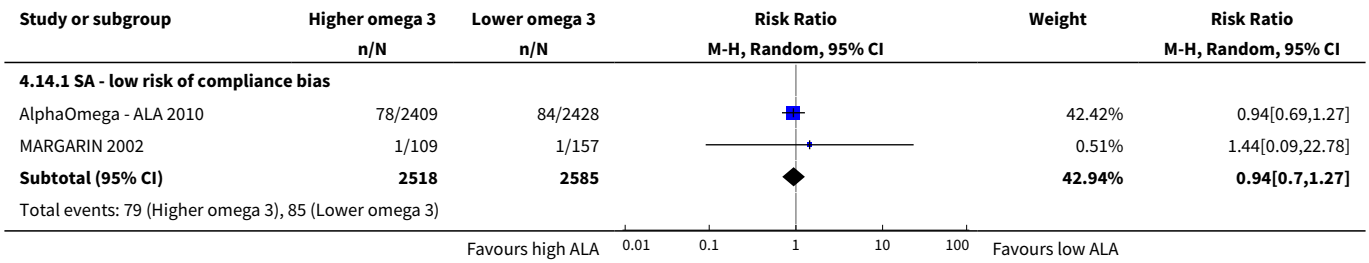


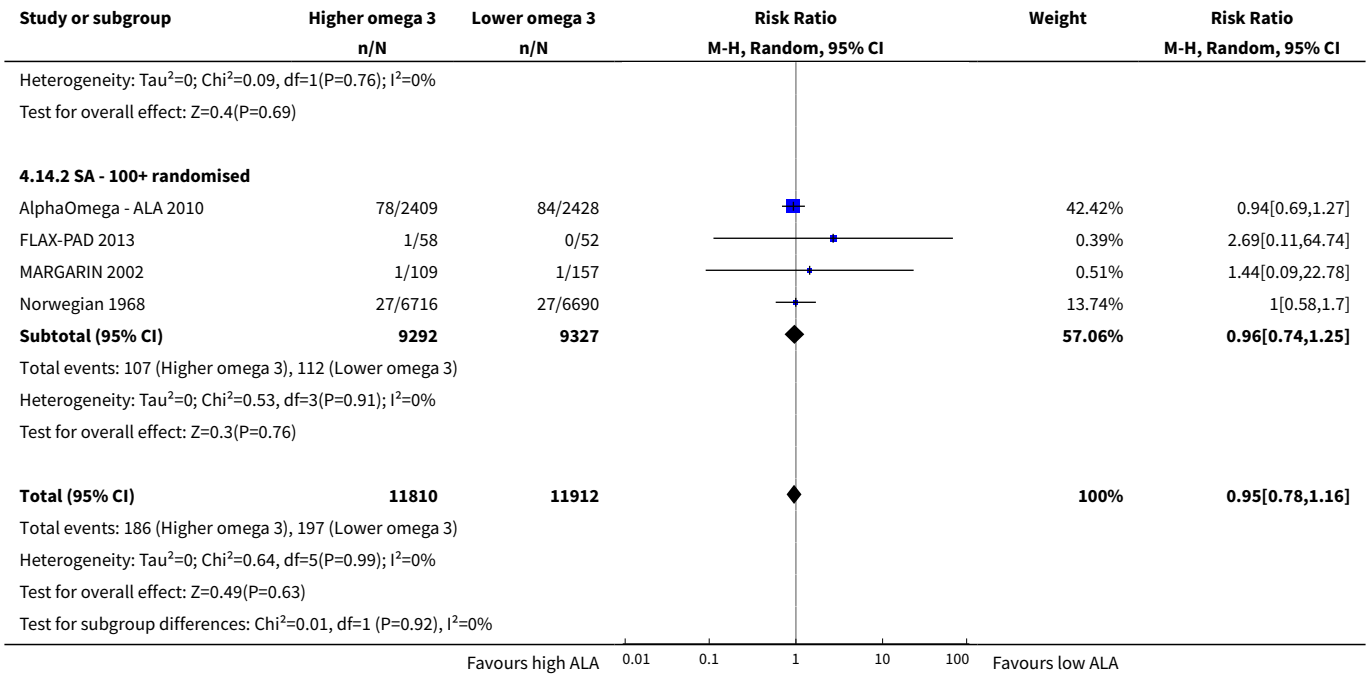


Analysis 4.13. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 13 CVD mortality - ALA - SA by summary risk of bias.

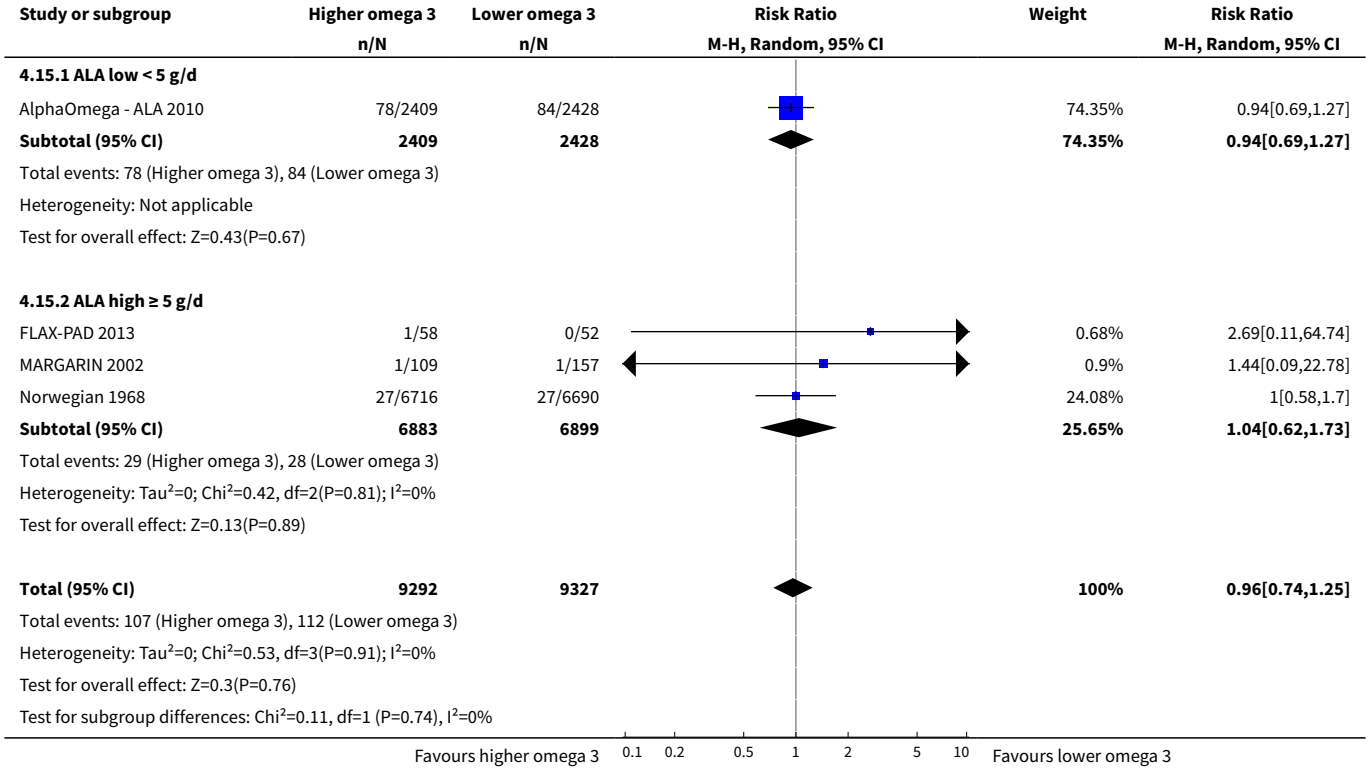


Analysis 4.14. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 14 CVD mortality - ALA - SA by compliance and study size.

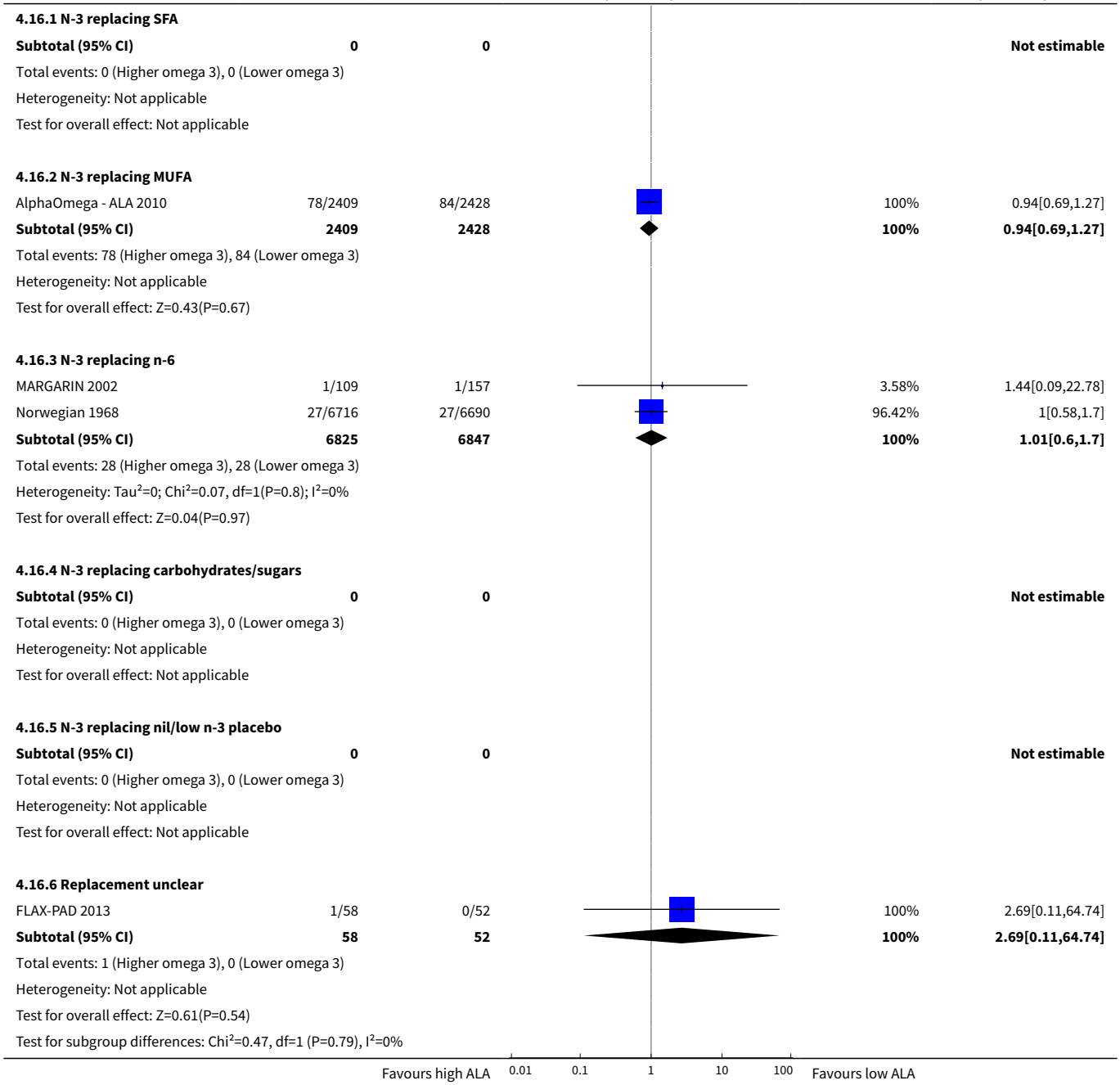




Analysis 4.15. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 15 CVD mortality - ALA - subgroup by dose.



Analysis 4.16. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 16 CVD mortality - ALA - subgroup by replacement.

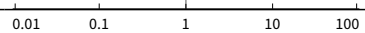


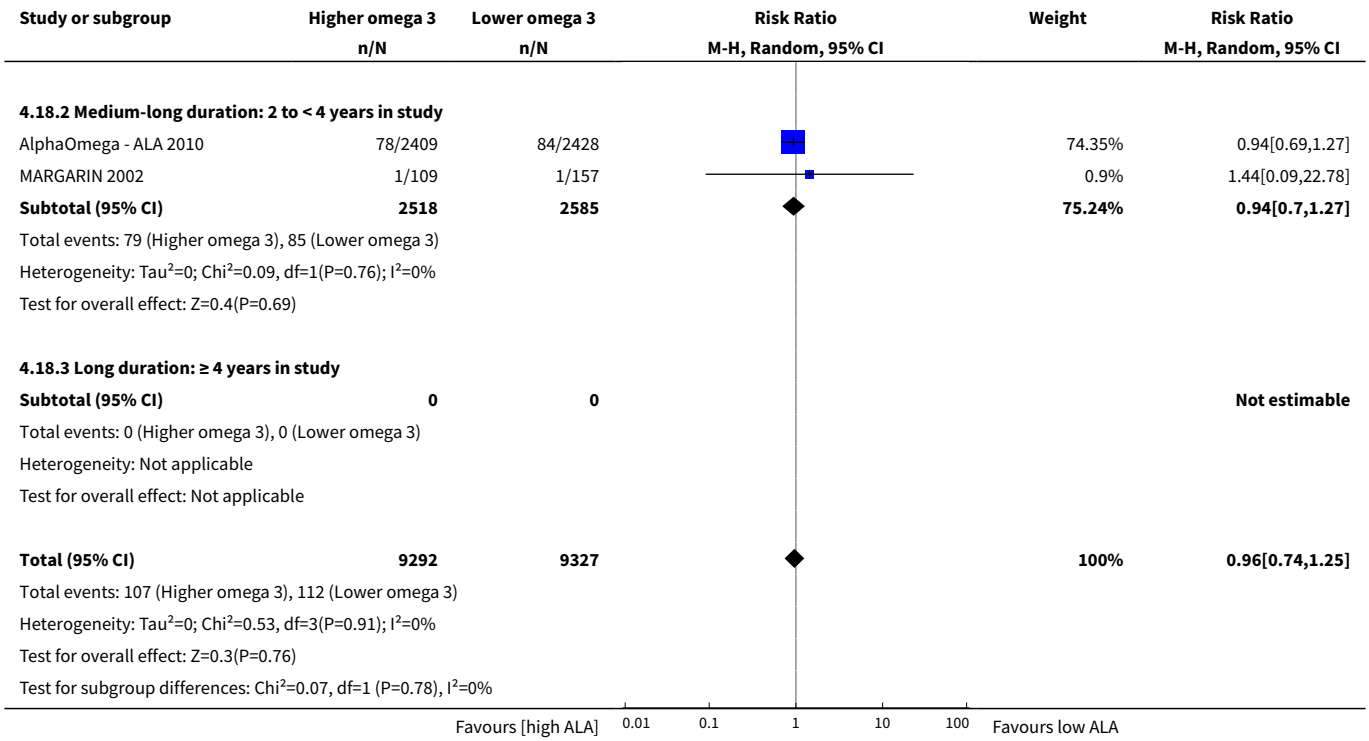
Analysis 4.17. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 17 CVD mortality - ALA - subgroup by intervention type.

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
4.17.1 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					
4.17.2 Supplemental foods					
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)					
4.17.3 Supplements (capsule)					
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)					
4.17.4 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)	**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%					

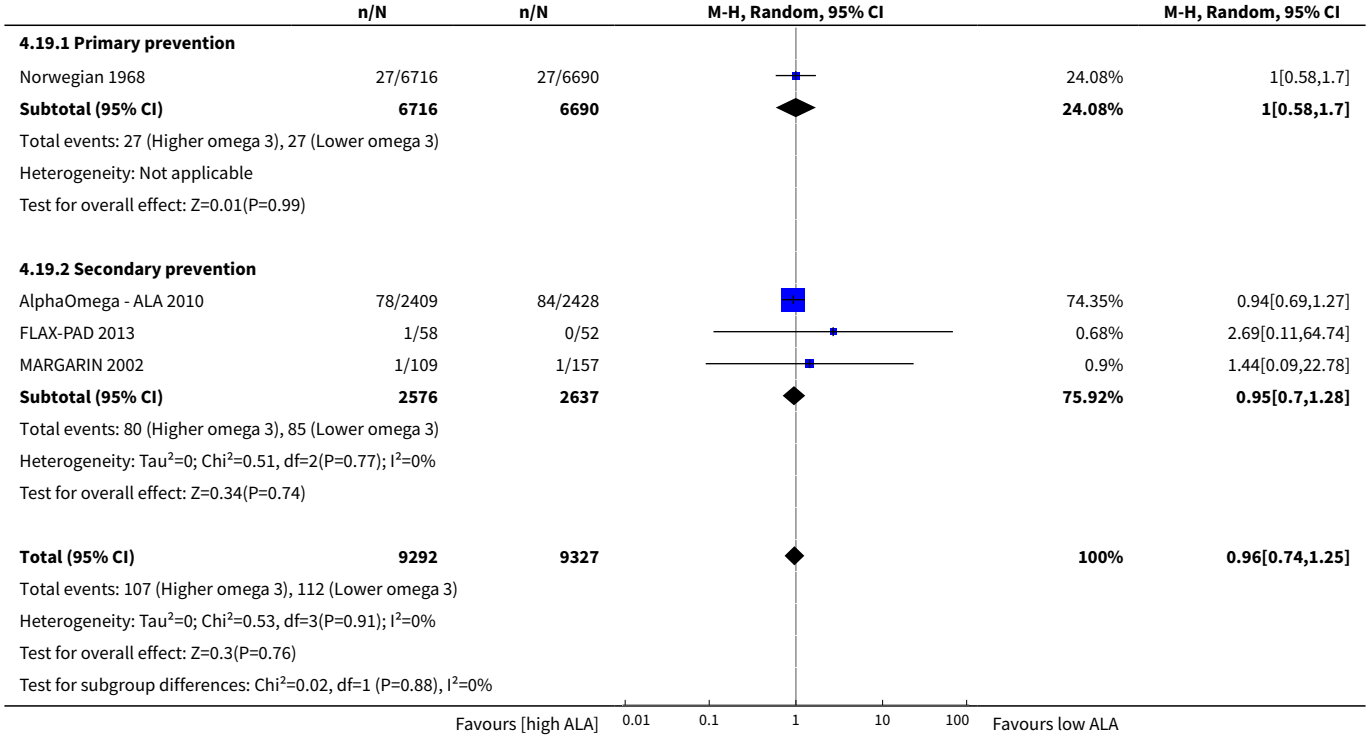
Analysis 4.18. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 18 CVD mortality - ALA - subgroup by duration.

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
4.18.1 Medium duration 1 to < 2 years in study					
FLAX-PAD 2013	1/58	0/52		0.68%	2.69[0.11,64.74]
Norwegian 1968	27/6716	27/6690		24.08%	1[0.58,1.7]
Subtotal (95% CI)	**6774**	**6742**		**24.76%**	**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)					



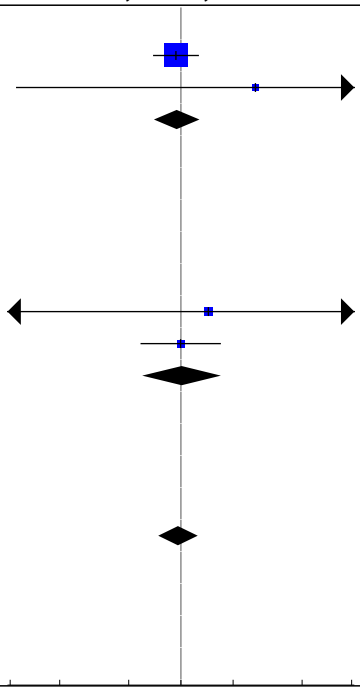


Analysis 4.19. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 19 CVD mortality - ALA - subgroup by primary or secondary prevention.



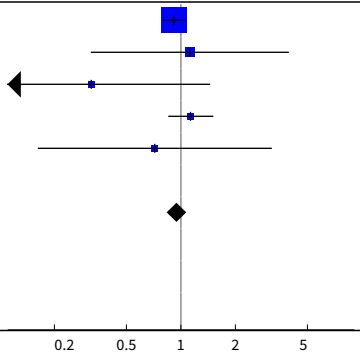
Analysis 4.20. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 20 CVD mortality - ALA - subgroup by statin uses.

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%					
Test for overall effect: Z=0.3(P=0.76)					
Test for subgroup differences: Chi^2=0.05, df=1 (P=0.83), I^2=0%					



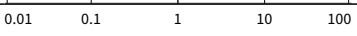
Analysis 4.21. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 21 Cardiovascular events (overall) - ALA.

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: 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)					



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)					



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		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]
Subtotal (95% CI)	**2576**	**2637**		**80.29%**	**0.91[0.79,1.04]**
Total events: 326 (Higher omega 3), 365 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=1.94, df=2(P=0.38); I²=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		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)	**7078**	**7036**		**19.71%**	**1.12[0.84,1.48]**
Total events: 102 (Higher omega 3), 91 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=0.35, df=1(P=0.55); I²=0%					
Test for overall effect: Z=0.76(P=0.45)					
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=1.66, df=1 (P=0.2), I²=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%					

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%					

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=0.89(P=0.38)					
Test for subgroup differences: Chi²=1.06, df=1 (P=0.3), I²=6.05%					

Favours higher omega 3 — 0.2 — 0.5 — 1 — 2 — 5 — Favours lower omega 3

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)					
Heterogeneity: Tau²=0.49; Chi²=2.6, df=1(P=0.11); I²=61.56%					
Test for overall effect: Z=0.47(P=0.64)					
4.26.4 N-3 replacing carbohydrates/sugars					
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					
4.26.5 N-3 replacing nil/low n-3 placebo					
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					
4.26.6 Replacement unclear					
FLAX-PAD 2013	5/58	4/52		58.28%	1.12[0.32,3.95]
WAHA 2016	3/362	4/346		41.72%	0.72[0.16,3.18]
Subtotal (95% CI)	**420**	**398**		**100%**	**0.93[0.36,2.43]**
Total events: 8 (Higher omega 3), 8 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=0.2, df=1(P=0.65); I²=0%					
Test for overall effect: Z=0.15(P=0.88)					

Favours high ALA — 0.01 — 0.1 — 1 — 10 — 100 — Favours low 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
Test for subgroup differences: Chi²=0.1, df=1 (P=0.95), I²=0%					

Favours high ALA 0.01 0.1 1 10 100 Favours low ALA

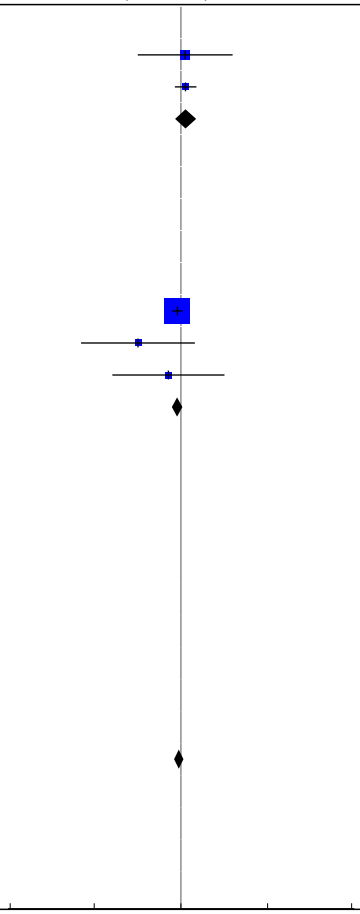
Analysis 4.27. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 27 CVD events - ALA - subgroup by intervention type.

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
4.27.1 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					
4.27.2 Supplemental foods					
AlphaOmega - ALA 2010	319/2409	352/2428		78.63%	0.91[0.79,1.05]
Dodin 2005	0/101	0/98			Not estimable
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]
WAHA 2016	3/362	4/346		0.7%	0.72[0.16,3.18]
Subtotal (95% CI)	**3039**	**3081**		**80.99%**	**0.91[0.79,1.04]**
Total events: 329 (Higher omega 3), 369 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=2.04, df=3(P=0.56); I²=0%					
Test for overall effect: Z=1.4(P=0.16)					
4.27.3 Supplements (capsule)					
Norwegian 1968	99/6716	87/6690		19.01%	1.13[0.85,1.51]
Subtotal (95% CI)	**6716**	**6690**		**19.01%**	**1.13[0.85,1.51]**
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)	**9755**	**9771**		**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=1.91, df=1 (P=0.17), I²=47.75%					

Favours high ALA 0.01 0.1 1 10 100 Favours low ALA

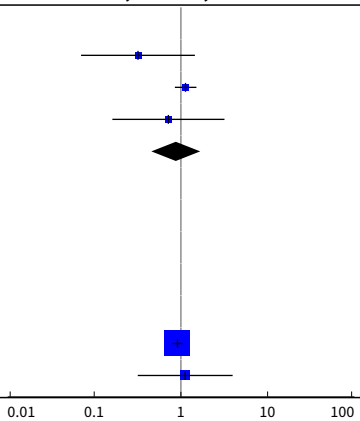
Analysis 4.28. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 28 CVD events - ALA - subgroup by duration.

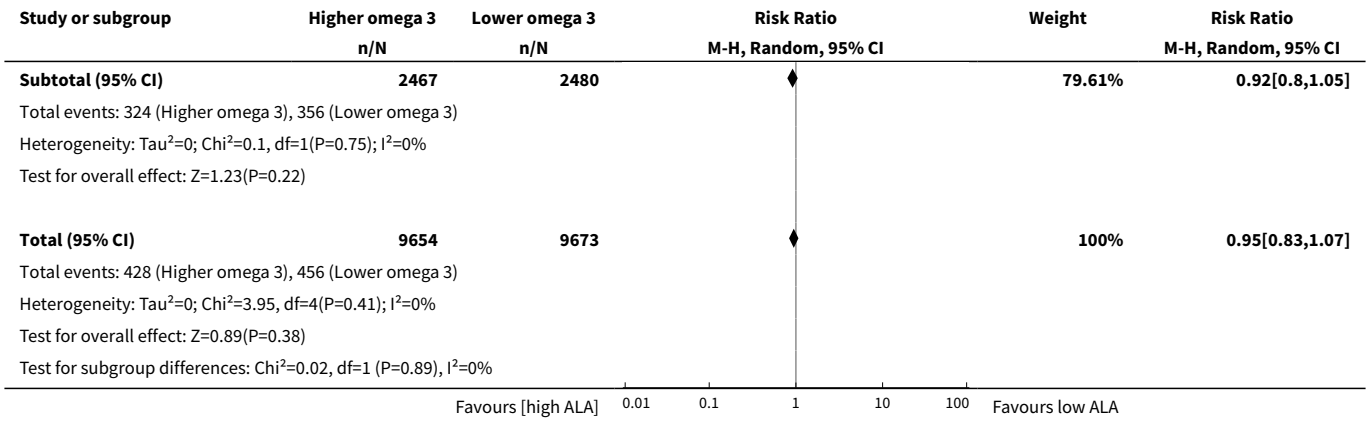
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.28.1 Medium duration 1 to < 2 years in study					
FLAX-PAD 2013	5/58	4/52		0.98%	1.12[0.32,3.95]
Norwegian 1968	99/6716	87/6690		19.01%	1.13[0.85,1.51]
Subtotal (95% CI)	**6774**	**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)					
Test for subgroup differences: Chi^2=2.02, df=1 (P=0.15), I^2=50.61%					



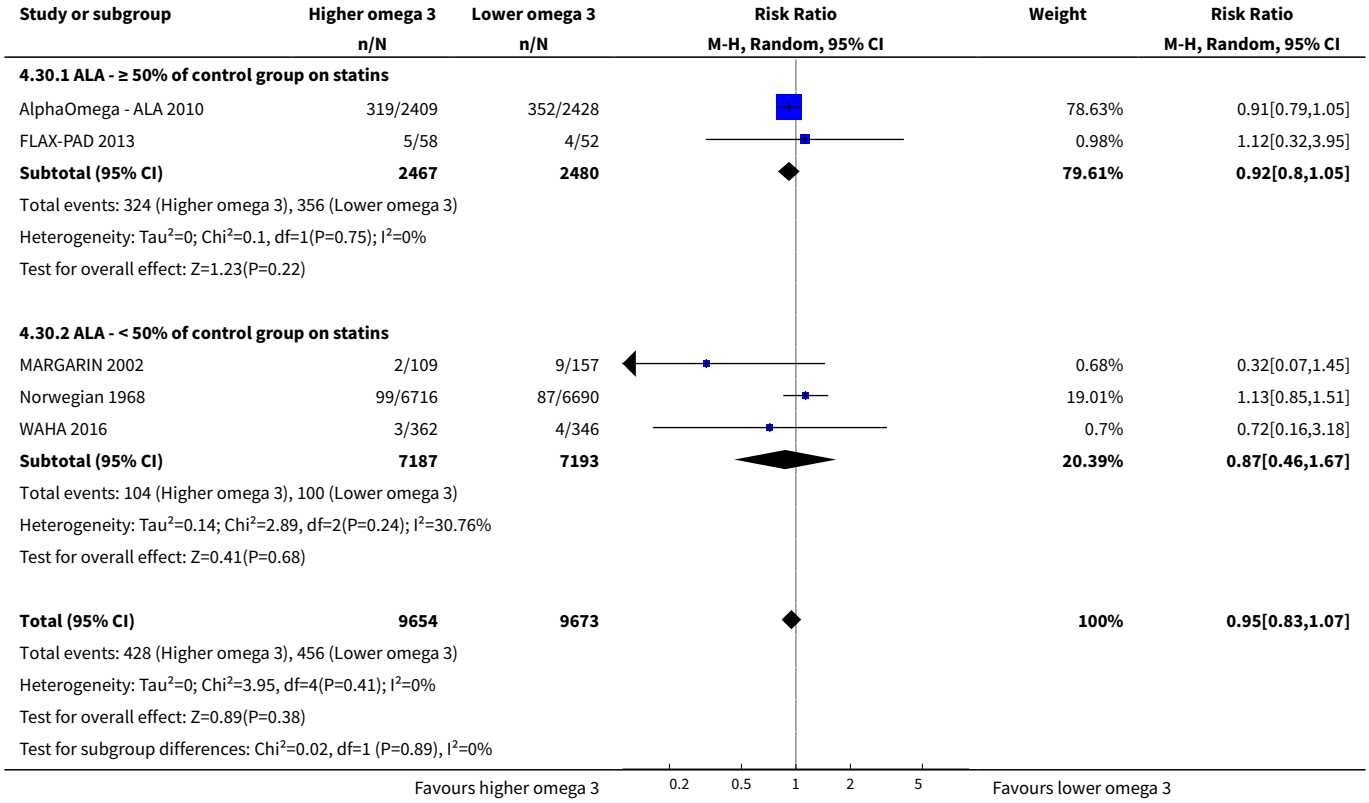
Analysis 4.29. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 29 CVD events - ALA - subgroup by primary or secondary prevention.

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: Tau^2=0.14; Chi^2=2.89, df=2(P=0.24); I^2=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]

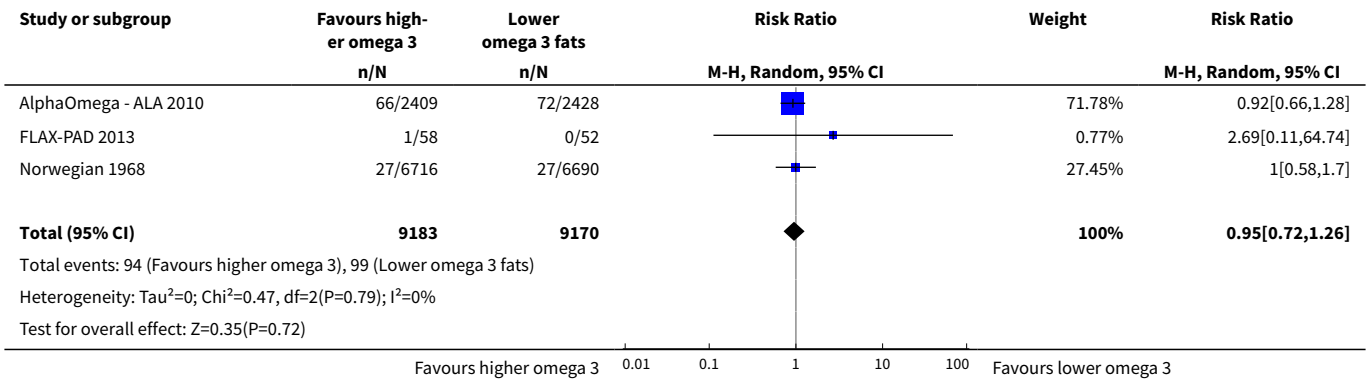




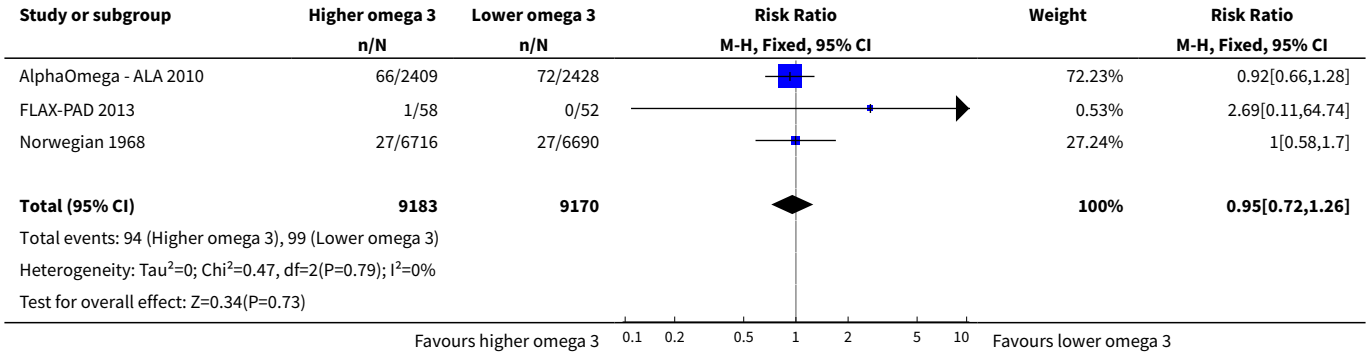
Analysis 4.30. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 30 CVD events - ALA - subgroup by statin use.



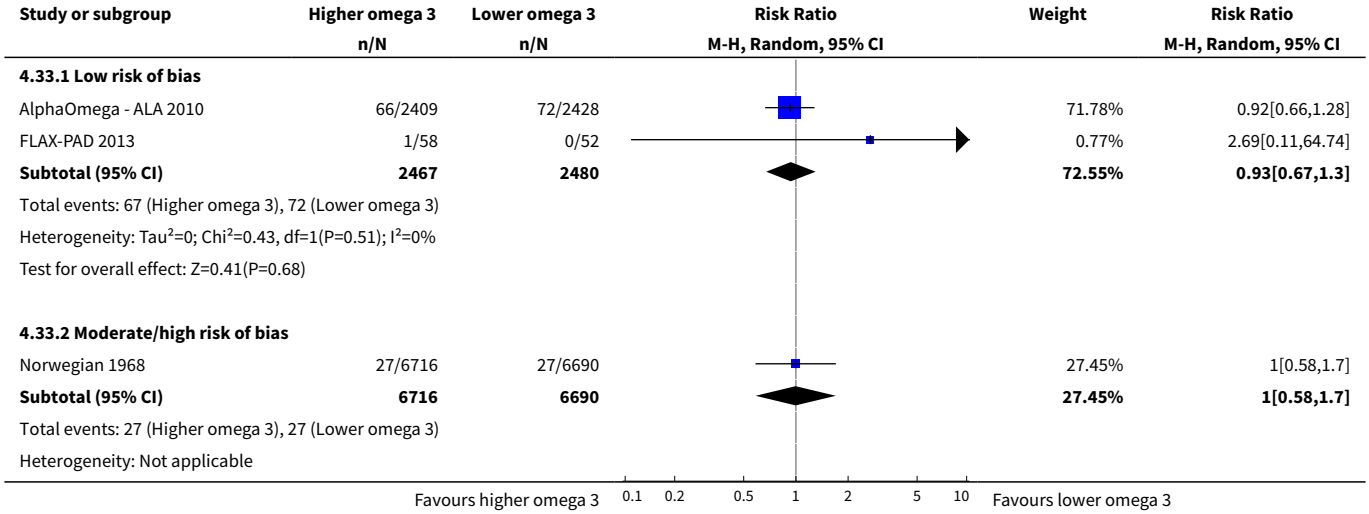
Analysis 4.31. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 31 Coronary heart disease mortality (overall) - ALA.

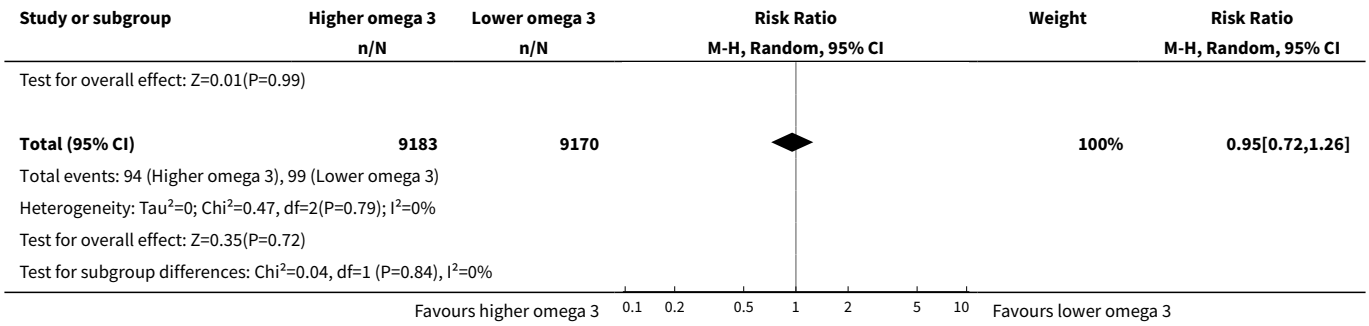


Analysis 4.32. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 32 CHD mortality - ALA - SA fixed-effect.

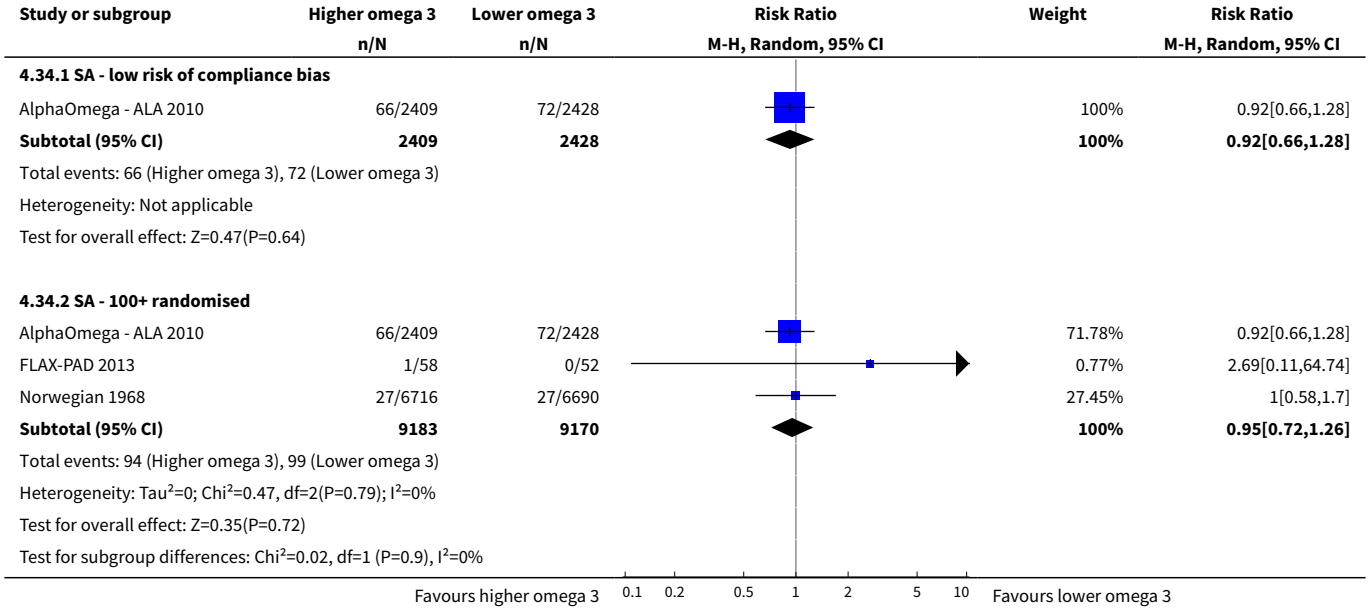


Analysis 4.33. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 33 CHD mortality - ALA - SA by summary risk of bias.

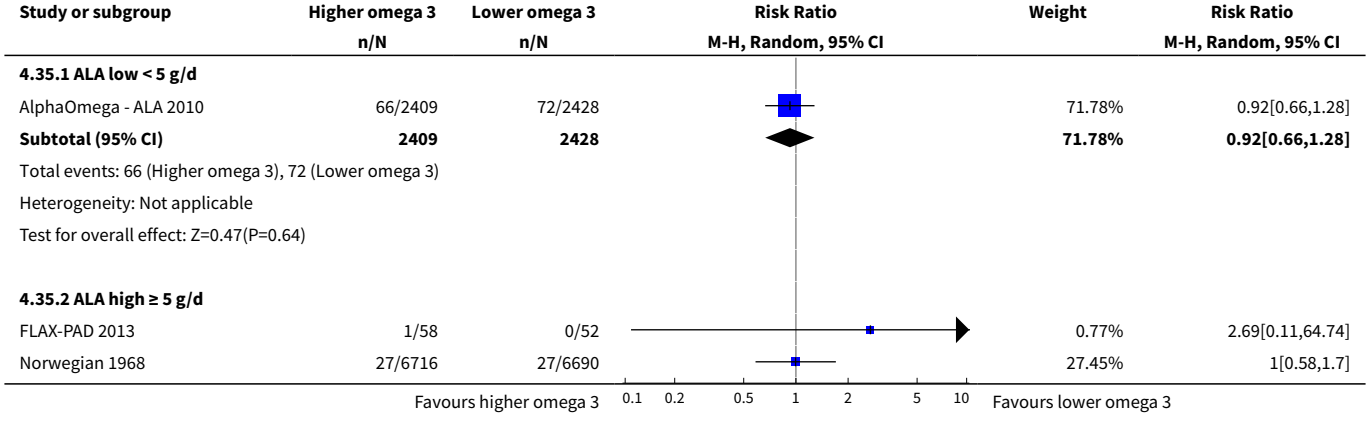




Analysis 4.34. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 34 CHD mortality - ALA - SA by compliance and study size.



Analysis 4.35. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 35 CHD mortality - ALA - subgroup by dose.



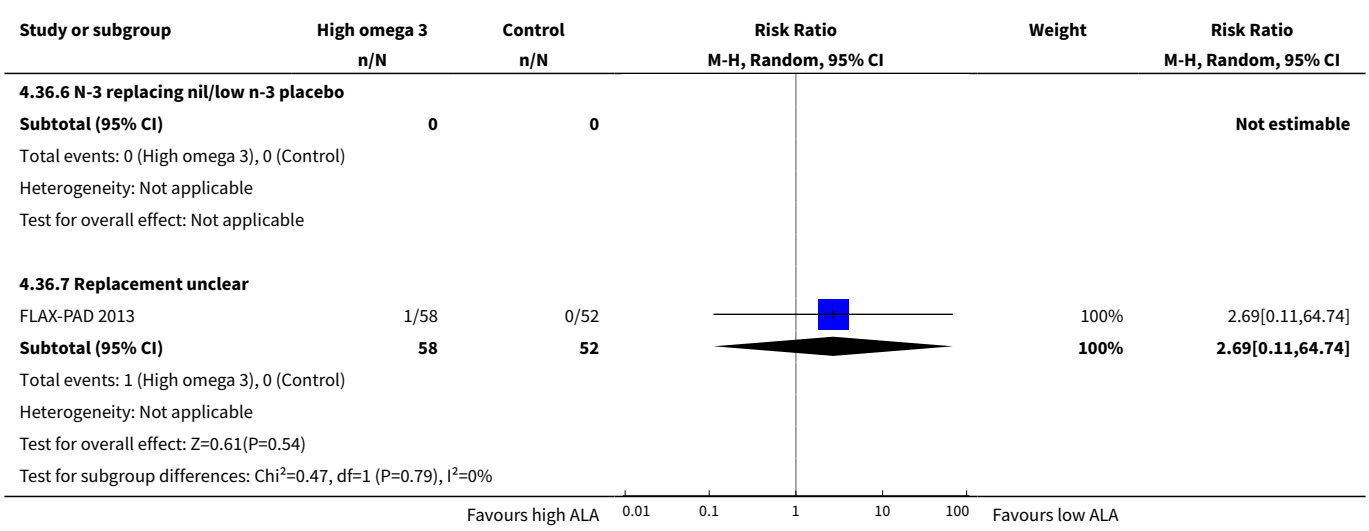
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Subtotal (95% CI)	**6774**	**6742**		**28.22%**	**1.02[0.61,1.73]**
Total events: 28 (Higher omega 3), 27 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.37, df=1(P=0.54); I^2=0%					
Test for overall effect: Z=0.09(P=0.93)					
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%					

Favours higher omega 3 — 0.1 0.2 0.5 1 2 5 10 — Favours lower omega 3

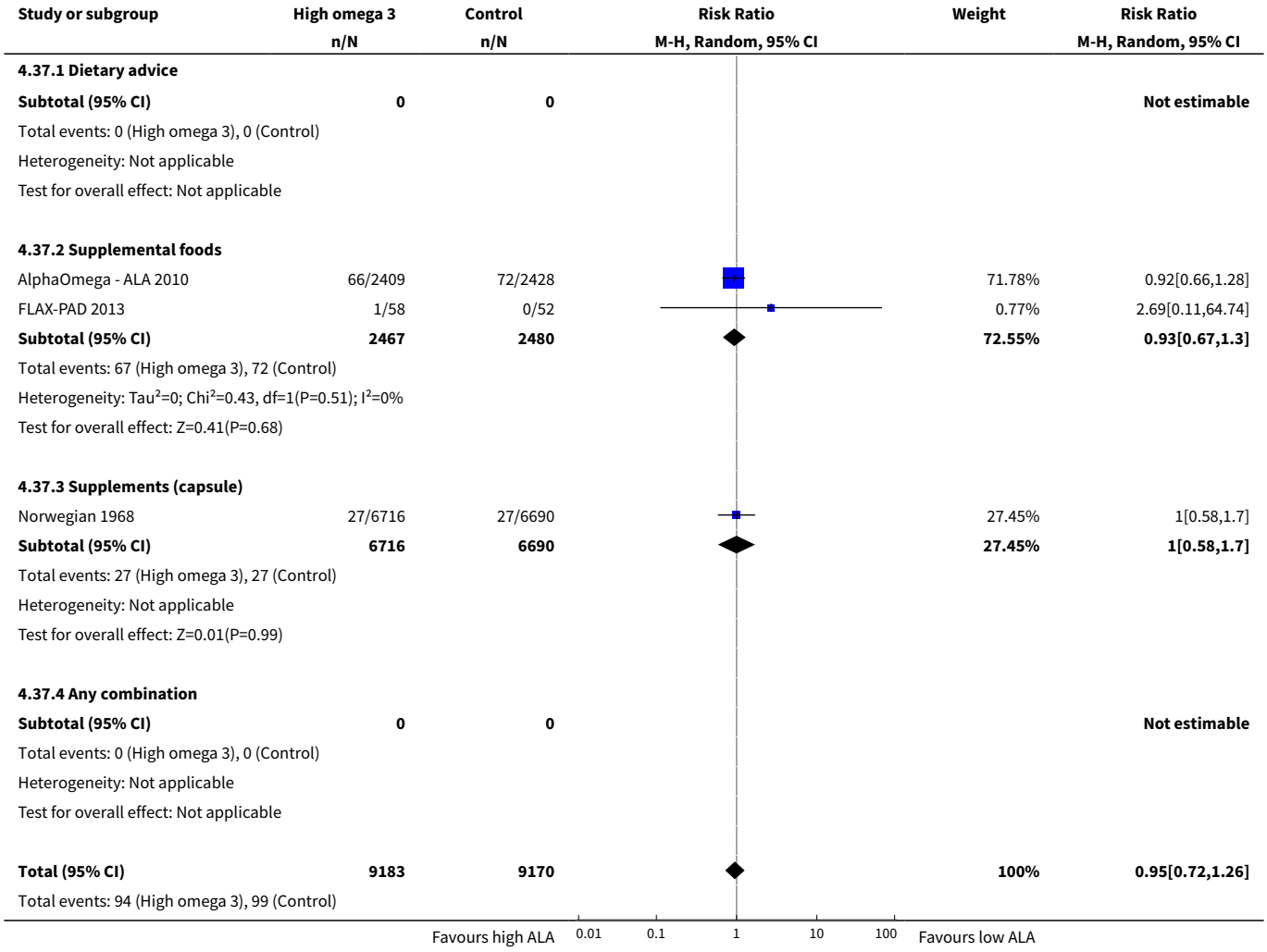
Analysis 4.36. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 36 CHD mortality - ALA - subgroup by replacement.

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
4.36.1 N-3 replacing SFA					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (High omega 3), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
4.36.2 Coronary heart mortality- ALA					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (High omega 3), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
4.36.3 N-3 replacing MUFA					
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 (High omega 3), 72 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.47(P=0.64)					
4.36.4 N-3 replacing n-6					
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 (High omega 3), 27 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.01(P=0.99)					
4.36.5 N-3 replacing carbohydrates/sugars					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (High omega 3), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Favours high ALA — 0.01 0.1 1 10 100 — Favours low ALA



Analysis 4.37. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 37 CHD mortality - ALA - 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
Heterogeneity: Tau²=0; Chi²=0.47, df=2(P=0.79); I²=0%					
Test for overall effect: Z=0.35(P=0.72)					
Test for subgroup differences: Chi²=0.04, df=1 (P=0.84), I²=0%					

Favours high ALA 0.01 0.1 1 10 100 Favours low ALA

Analysis 4.38. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 38 CHD mortality - ALA - subgroup by duration.

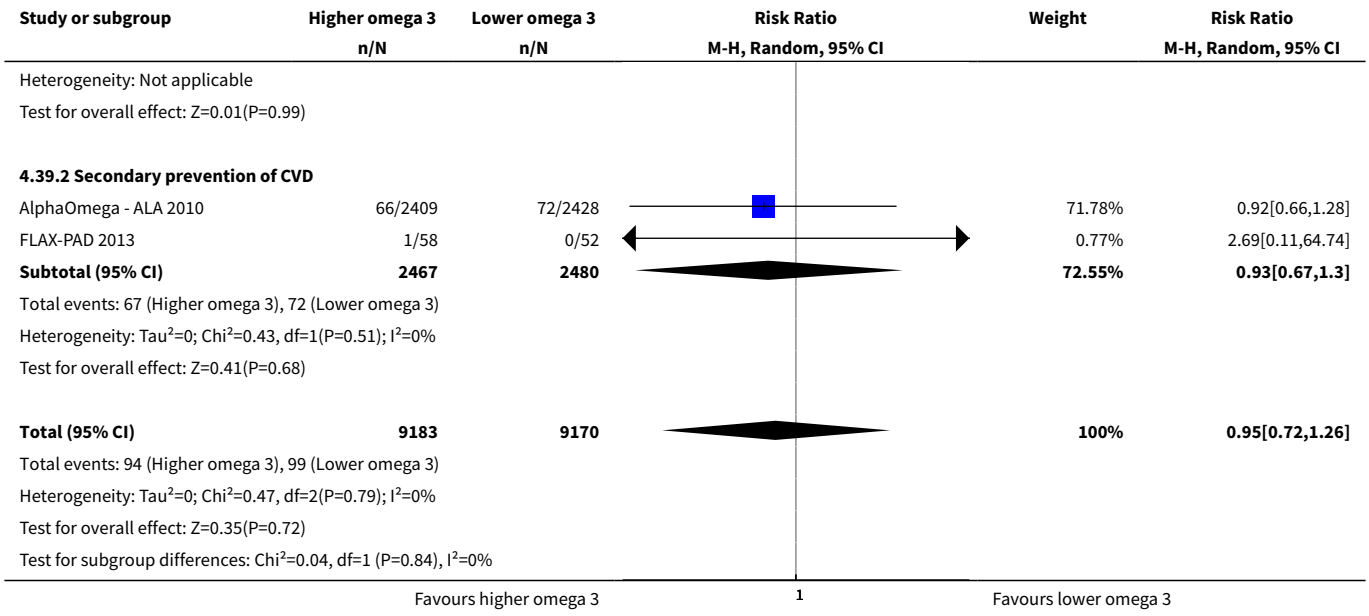
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.38.1 Medium duration 1 to < 2 years in study					
FLAX-PAD 2013	1/58	0/52		0.77%	2.69[0.11,64.74]
Norwegian 1968	27/6716	27/6690		27.45%	1[0.58,1.7]
Subtotal (95% CI)	**6774**	**6742**		**28.22%**	**1.02[0.61,1.73]**
Total events: 28 (Higher omega 3), 27 (Lower omega 3)					
Heterogeneity: Tau²=0; Chi²=0.37, df=1(P=0.54); I²=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: Tau²=0; Chi²=0.47, df=2(P=0.79); I²=0%					
Test for overall effect: Z=0.35(P=0.72)					
Test for subgroup differences: Chi²=0.1, df=1 (P=0.75), I²=0%					

Favours higher omega 3 0.1 0.2 0.5 1 2 5 10 Favours lower omega 3

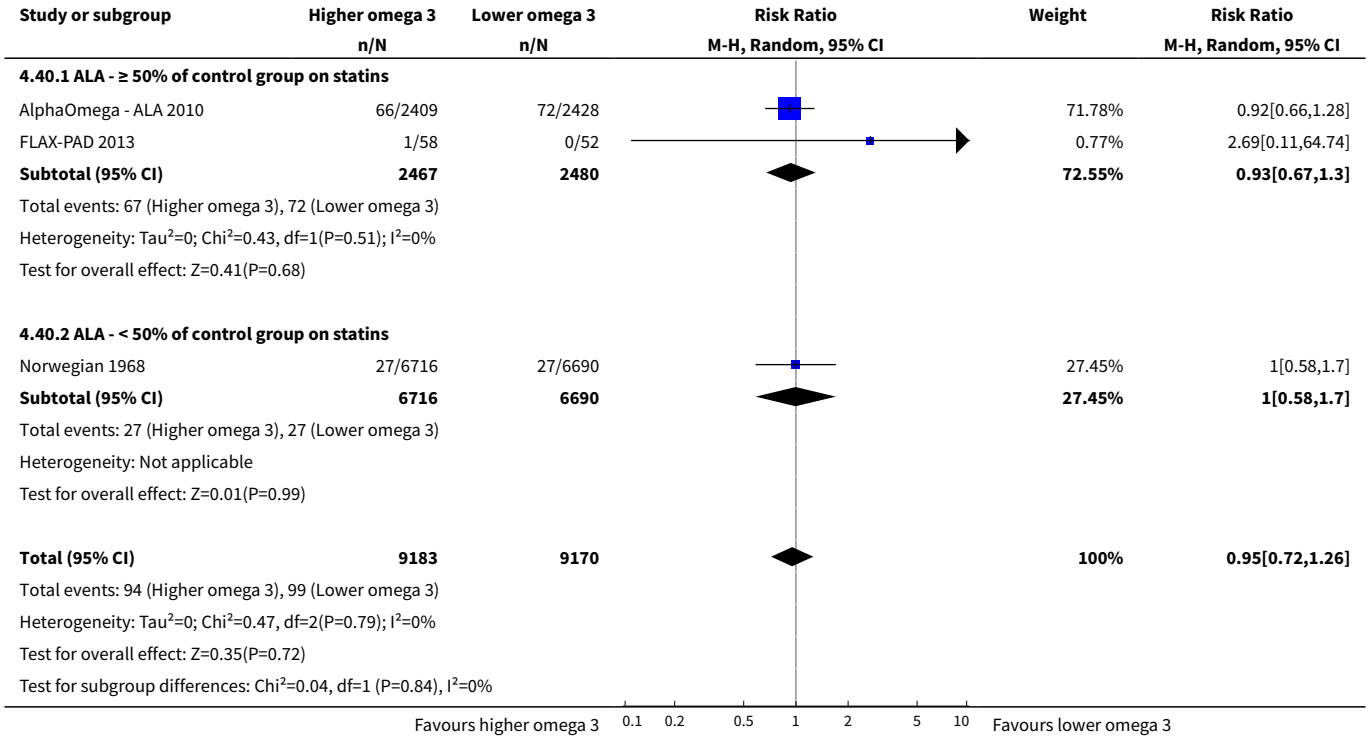
Analysis 4.39. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 39 CHD mortality - ALA - subgroup by primary or secondary prevention.

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)					

Favours higher omega 3 1 Favours lower omega 3

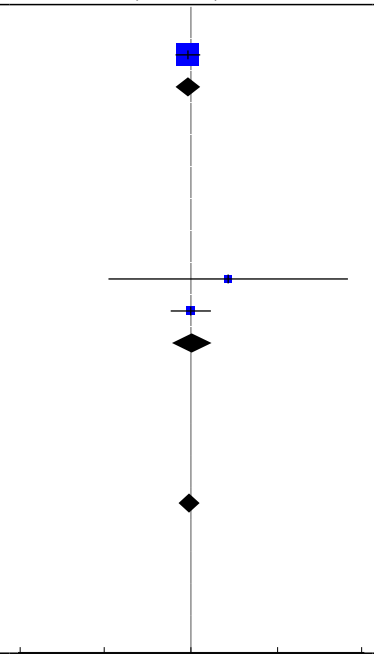


Analysis 4.40. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 40 CHD mortality - ALA - subgroup by statin use.



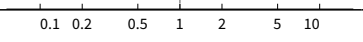
Analysis 4.41. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 41 CHD mortality - ALA - subgroup by CAD history.

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
4.41.1 Previous CAD					
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 (High omega 3), 72 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.47(P=0.64)					
4.41.2 No previous CAD					
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 (High omega 3), 27 (Control)					
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)					
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=0.1, df=1 (P=0.75), I^2=0%					



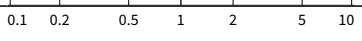
Analysis 4.42. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 42 Coronary heart disease events (overall) - ALA.

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	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]
Norwegian 1968	75/6716	63/6690		34.39%	1.19[0.85,1.65]
WAHA 2016	1/362	0/346		0.39%	2.87[0.12,70.16]
Total (95% CI)	**9545**	**9516**		**100%**	**1[0.82,1.22]**
Total events: 198 (Favours higher omega 3), 199 (Lower omega 3 fats)					
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)					



Analysis 4.43. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 43 CHD events - ALA - SA fixed-effect.

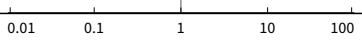
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
AlphaOmega - ALA 2010	121/2409	133/2428		66.48%	0.92[0.72,1.17]
FLAX-PAD 2013	1/58	3/52		1.59%	0.3[0.03,2.78]
Norwegian 1968	75/6716	63/6690		31.68%	1.19[0.85,1.65]
WAHA 2016	1/362	0/346		0.26%	2.87[0.12,70.16]
Total (95% CI)	**9545**	**9516**		**100%**	**1[0.82,1.21]**
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)					



Favours higher omega 3 — Favours lower omega 3

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.

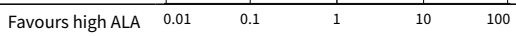
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.44.1 Low risk of bias					
AlphaOmega - ALA 2010	121/2409	133/2428		64.43%	0.92[0.72,1.17]
FLAX-PAD 2013	1/58	3/52		0.79%	0.3[0.03,2.78]
Subtotal (95% CI)	**2467**	**2480**		**65.22%**	**0.91[0.71,1.15]**
Total events: 122 (Higher omega 3), 136 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.96, df=1(P=0.33); I^2=0%					
Test for overall effect: Z=0.82(P=0.41)					
4.44.2 Moderate/high risk of bias					
Norwegian 1968	75/6716	63/6690		34.39%	1.19[0.85,1.65]
WAHA 2016	1/362	0/346		0.39%	2.87[0.12,70.16]
Subtotal (95% CI)	**7078**	**7036**		**34.78%**	**1.2[0.86,1.67]**
Total events: 76 (Higher omega 3), 63 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.29, df=1(P=0.59); I^2=0%					
Test for overall effect: Z=1.06(P=0.29)					
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=1.8, df=1 (P=0.18), I^2=44.45%					



Favours high ALA — Favours low ALA

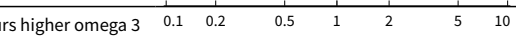
Analysis 4.45. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 45 CHD events - ALA - SA by compliance and study size.

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
4.45.1 SA - low risk of compliance bias					
AlphaOmega - ALA 2010	121/2409	133/2428		99.44%	0.92[0.72,1.17]
WAHA 2016	1/362	0/346		0.56%	2.87[0.12,70.16]
Subtotal (95% CI)	**2771**	**2774**		**100%**	**0.92[0.73,1.17]**
Total events: 122 (Higher omega 3), 133 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.49, df=1(P=0.49); I^2=0%					
Test for overall effect: Z=0.66(P=0.51)					
4.45.2 SA - 100+ randomised					
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]
Norwegian 1968	75/6716	63/6690		34.39%	1.19[0.85,1.65]
WAHA 2016	1/362	0/346		0.39%	2.87[0.12,70.16]
Subtotal (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=0.24, df=1 (P=0.62), I^2=0%					

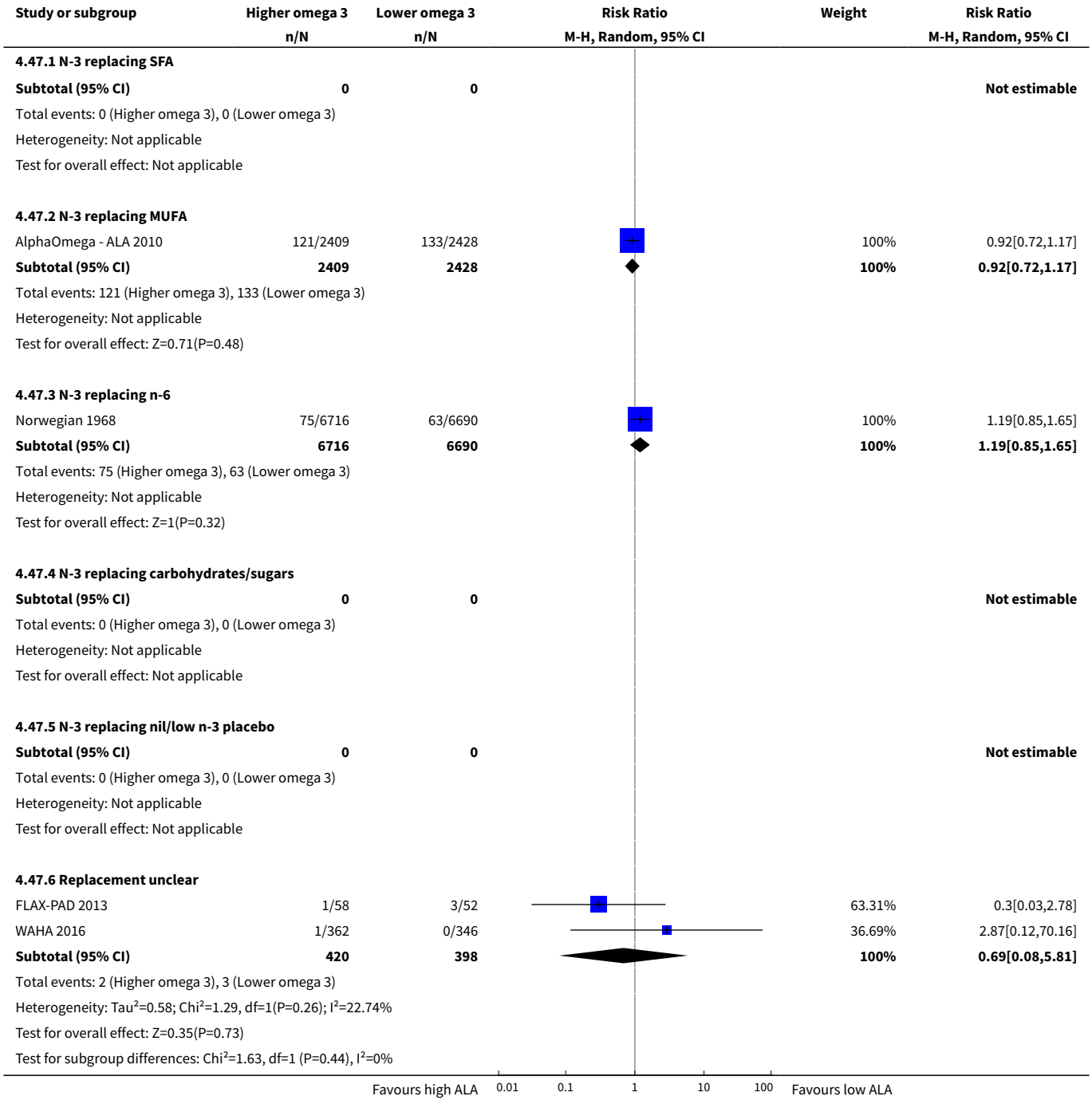


Analysis 4.46. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 46 CHD events - ALA - subgroup by dose.

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
4.46.1 ALA low < 5 g/d					
AlphaOmega - ALA 2010	121/2409	133/2428		64.43%	0.92[0.72,1.17]
Subtotal (95% CI)	**2409**	**2428**		**64.43%**	**0.92[0.72,1.17]**
Total events: 121 (Higher omega 3), 133 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.71(P=0.48)					
4.46.2 ALA high ≥ 5 g/d					
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]
WAHA 2016	1/362	0/346		0.39%	2.87[0.12,70.16]
Subtotal (95% CI)	**7136**	**7088**		**35.57%**	**1.16[0.84,1.61]**
Total events: 77 (Higher omega 3), 66 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=1.74, df=2(P=0.42); I^2=0%					
Test for overall effect: Z=0.9(P=0.37)					
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=1.31, df=1 (P=0.25), I^2=23.38%					



Analysis 4.47. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 47 CHD events - ALA - subgroup by replacement.

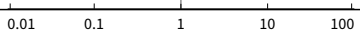


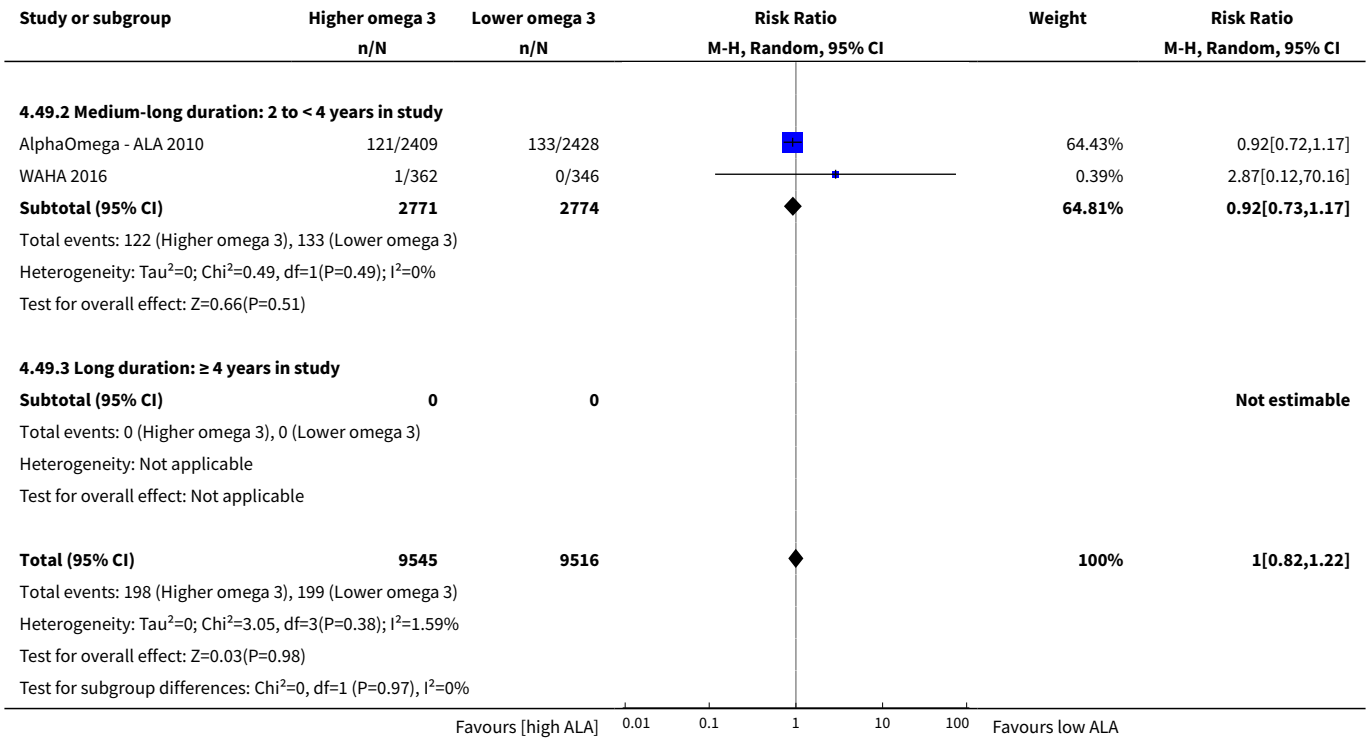
Analysis 4.48. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 48 CHD events - ALA - subgroup by intervention type.

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%					

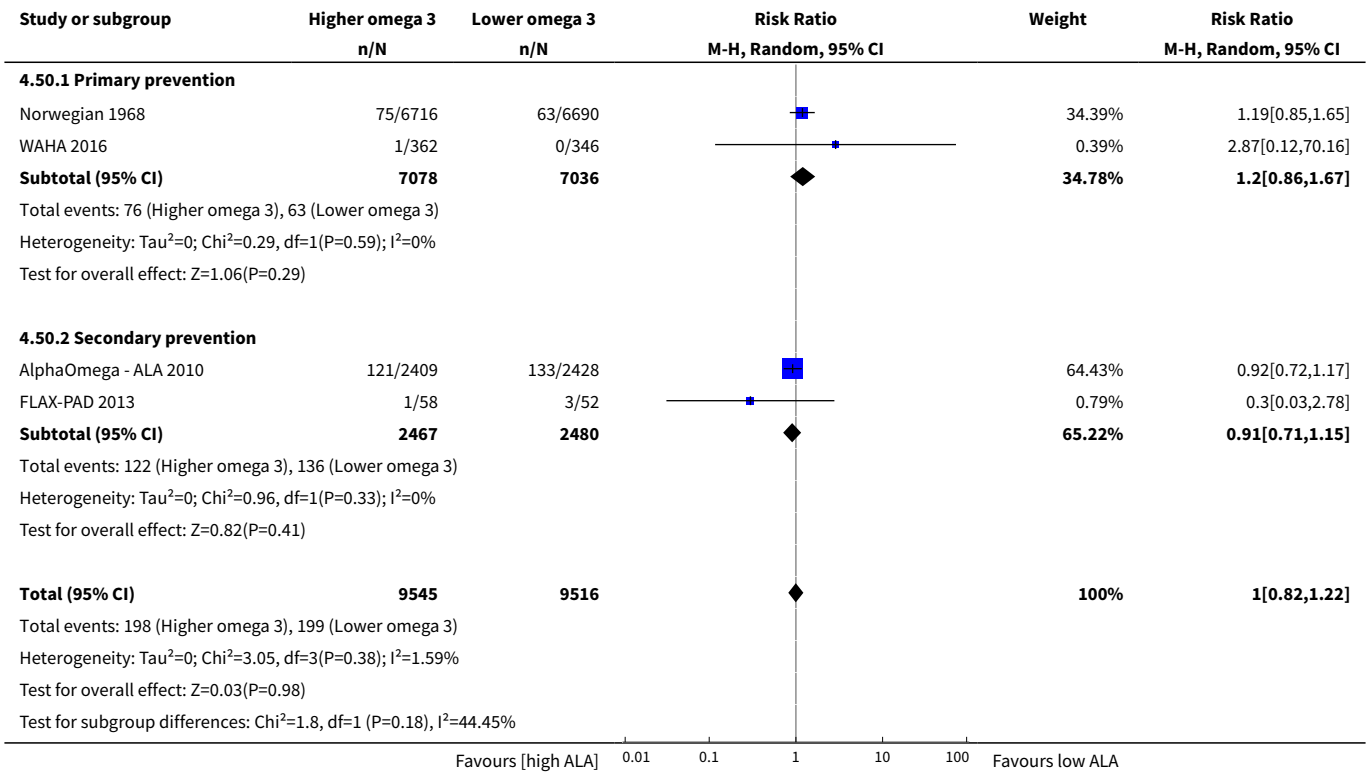
Analysis 4.49. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 49 CHD events - ALA - subgroup by duration.

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)					



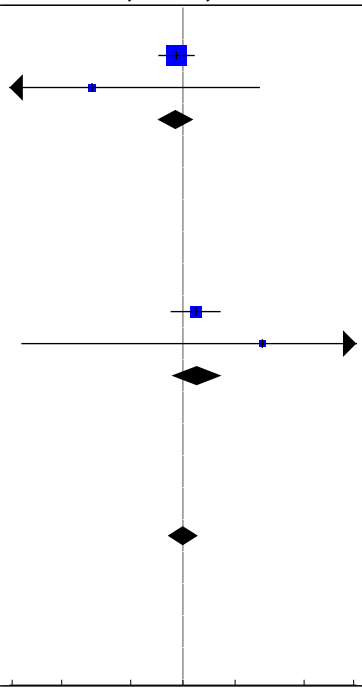


Analysis 4.50. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 50 CHD events - ALA - subgroup by primary or secondary prevention.



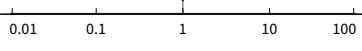
Analysis 4.51. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 51 CHD events - ALA - subgroup by statin use.

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
4.51.1 ALA - ≥ 50% of control group on statins					
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]
Subtotal (95% CI)	**2467**	**2480**		**65.22%**	**0.91[0.71,1.15]**
Total events: 122 (Higher omega 3), 136 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.96, df=1(P=0.33); I^2=0%					
Test for overall effect: Z=0.82(P=0.41)					
4.51.2 ALA - < 50% of control group on statins					
Norwegian 1968	75/6716	63/6690		34.39%	1.19[0.85,1.65]
WAHA 2016	1/362	0/346		0.39%	2.87[0.12,70.16]
Subtotal (95% CI)	**7078**	**7036**		**34.78%**	**1.2[0.86,1.67]**
Total events: 76 (Higher omega 3), 63 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=0.29, df=1(P=0.59); I^2=0%					
Test for overall effect: Z=1.06(P=0.29)					
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=1.8, df=1 (P=0.18), I^2=44.45%					

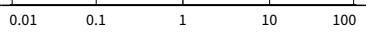


Analysis 4.52. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 52 CHD events - ALA - subgroup by CAD history.

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
4.52.1 Previous CAD					
AlphaOmega - ALA 2010	121/2409	133/2428		64.43%	0.92[0.72,1.17]
Subtotal (95% CI)	**2409**	**2428**		**64.43%**	**0.92[0.72,1.17]**
Total events: 121 (High omega 3), 133 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.71(P=0.48)					
4.52.2 No previous CAD					
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]
WAHA 2016	1/362	0/346		0.39%	2.87[0.12,70.16]
Subtotal (95% CI)	**7136**	**7088**		**35.57%**	**1.16[0.84,1.61]**
Total events: 77 (High omega 3), 66 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.74, df=2(P=0.42); I^2=0%					
Test for overall effect: Z=0.9(P=0.37)					
Total (95% CI)	**9545**	**9516**		**100%**	**1[0.82,1.22]**

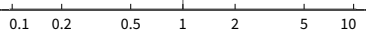


Study or subgroup	High omega 3 n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 198 (High omega 3), 199 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.05, df=3(P=0.38); I^2=1.59%					
Test for overall effect: Z=0.03(P=0.98)					
Test for subgroup differences: Chi^2=1.31, df=1 (P=0.25), I^2=23.38%					



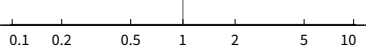
Analysis 4.53. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 53 Stroke (overall) - ALA.

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	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]
Total (95% CI)	**9654**	**9673**		**100%**	**1.15[0.66,2.01]**
Total events: 27 (Favours higher omega 3), 24 (Lower omega 3 fats)					
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)					



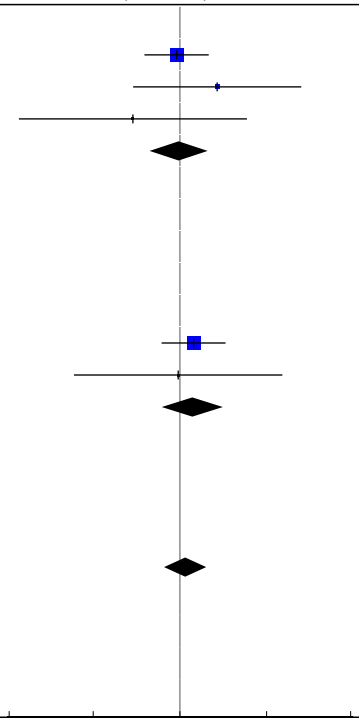
Analysis 4.54. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 54 Stroke - ALA - SA fixed-effect.

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 - EPA+DHA 2010	11/2404	10/2433		43.05%	1.11[0.47,2.62]
FLAX-PAD 2013	3/58	1/52		4.57%	2.69[0.29,25.06]
MARGARIN 2002	0/109	2/157		8.89%	0.29[0.01,5.93]
Norwegian 1968	13/6716	9/6690		39.06%	1.44[0.62,3.36]
WAHA 2016	1/362	1/346		4.43%	0.96[0.06,15.22]
Total (95% CI)	**9649**	**9678**		**100%**	**1.23[0.71,2.13]**
Total events: 28 (Higher omega 3), 23 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=1.57, df=4(P=0.81); I^2=0%					
Test for overall effect: Z=0.74(P=0.46)					



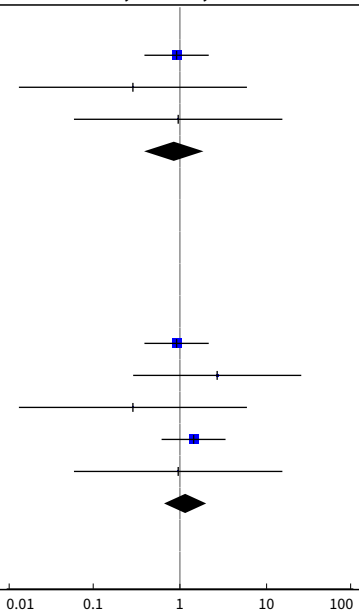
Analysis 4.55. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 55 Stroke - ALA - SA by summary risk of bias.

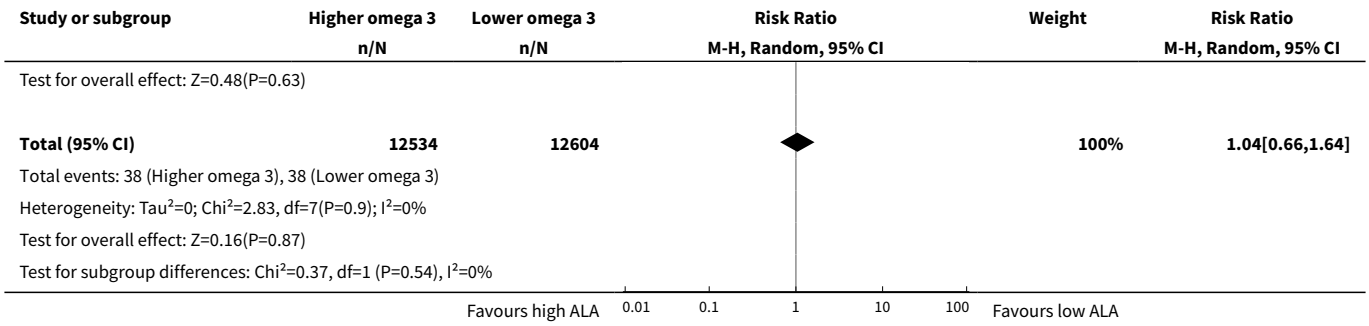
Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.55.1 Low risk of bias					
AlphaOmega - ALA 2010	10/2409	11/2428		42.84%	0.92[0.39,2.15]
FLAX-PAD 2013	3/58	1/52		6.28%	2.69[0.29,25.06]
MARGARIN 2002	0/109	2/157		3.42%	0.29[0.01,5.93]
Subtotal (95% CI)	**2576**	**2637**		**52.54%**	**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		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)	**7078**	**7036**		**47.46%**	**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)					
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=0.4, df=1 (P=0.53), I^2=0%					



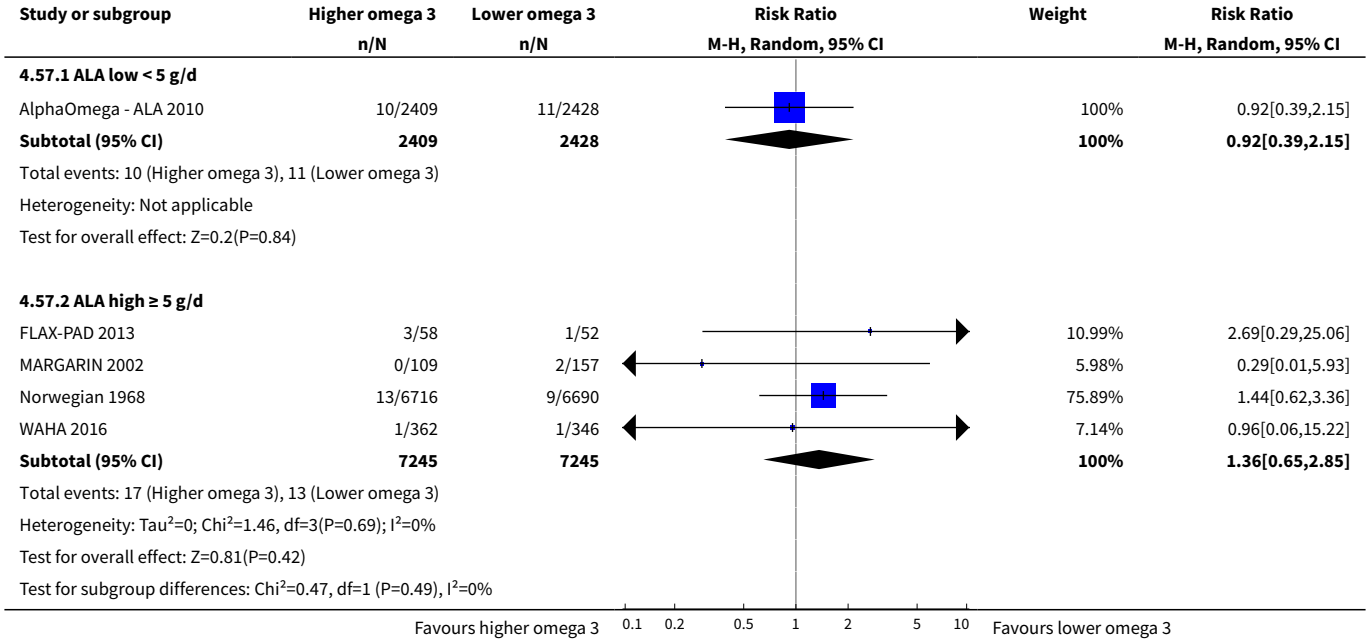
Analysis 4.56. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 56 Stroke - ALA - SA by compliance and study size.

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		28.5%	0.92[0.39,2.15]
MARGARIN 2002	0/109	2/157		2.27%	0.29[0.01,5.93]
WAHA 2016	1/362	1/346		2.72%	0.96[0.06,15.22]
Subtotal (95% CI)	**2880**	**2931**		**33.48%**	**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		28.5%	0.92[0.39,2.15]
FLAX-PAD 2013	3/58	1/52		4.18%	2.69[0.29,25.06]
MARGARIN 2002	0/109	2/157		2.27%	0.29[0.01,5.93]
Norwegian 1968	13/6716	9/6690		28.85%	1.44[0.62,3.36]
WAHA 2016	1/362	1/346		2.72%	0.96[0.06,15.22]
Subtotal (95% CI)	**9654**	**9673**		**66.52%**	**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%					

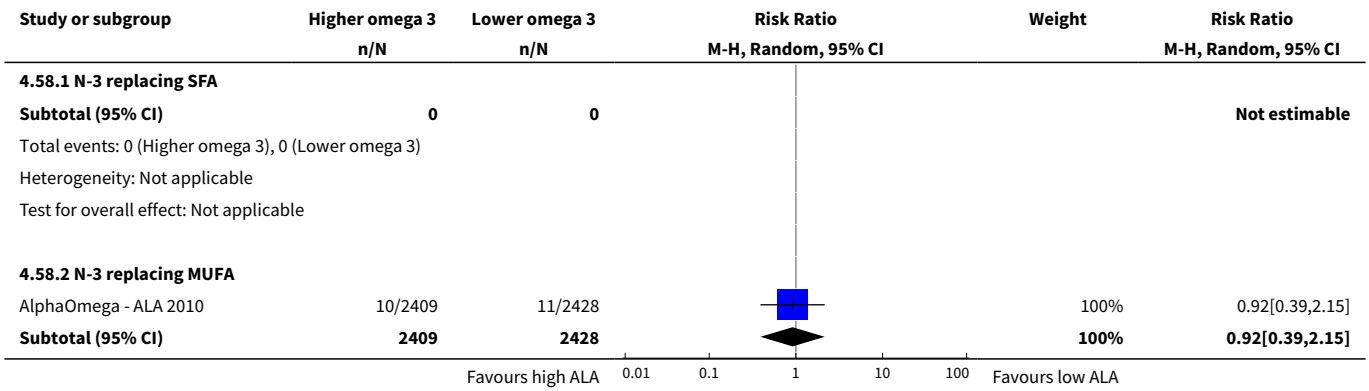


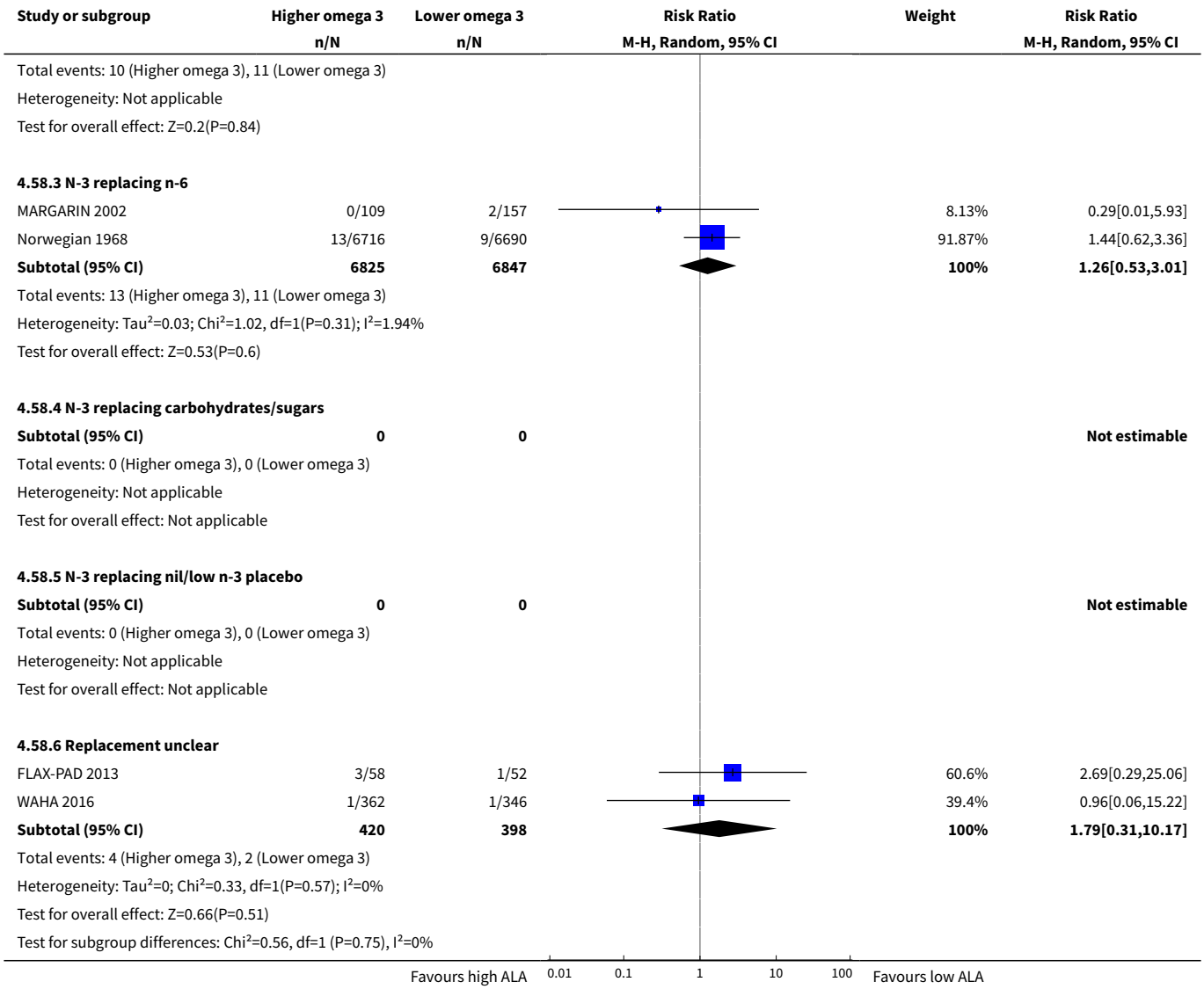


Analysis 4.57. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 57 Stroke - ALA - subgroup by dose.

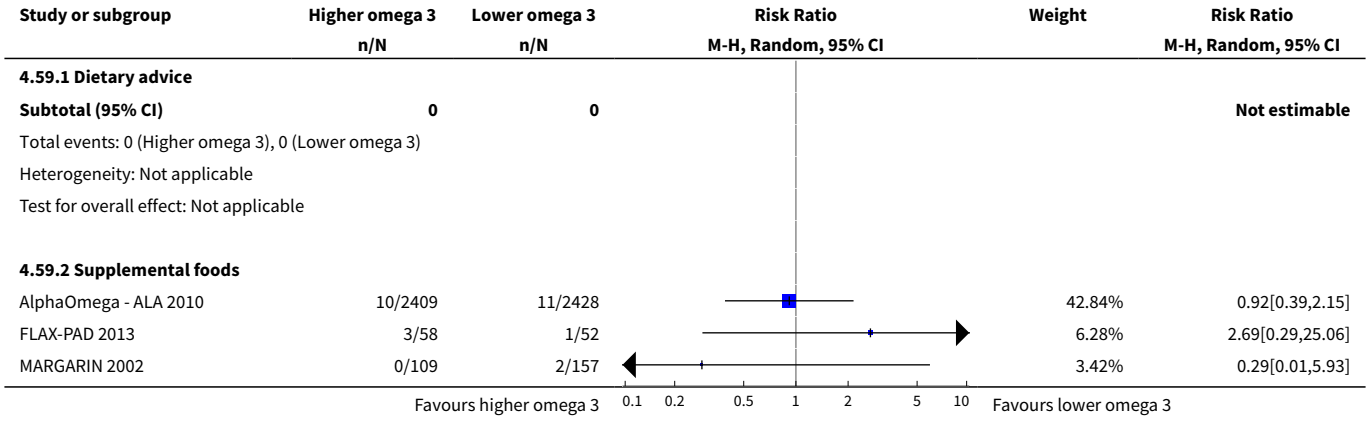


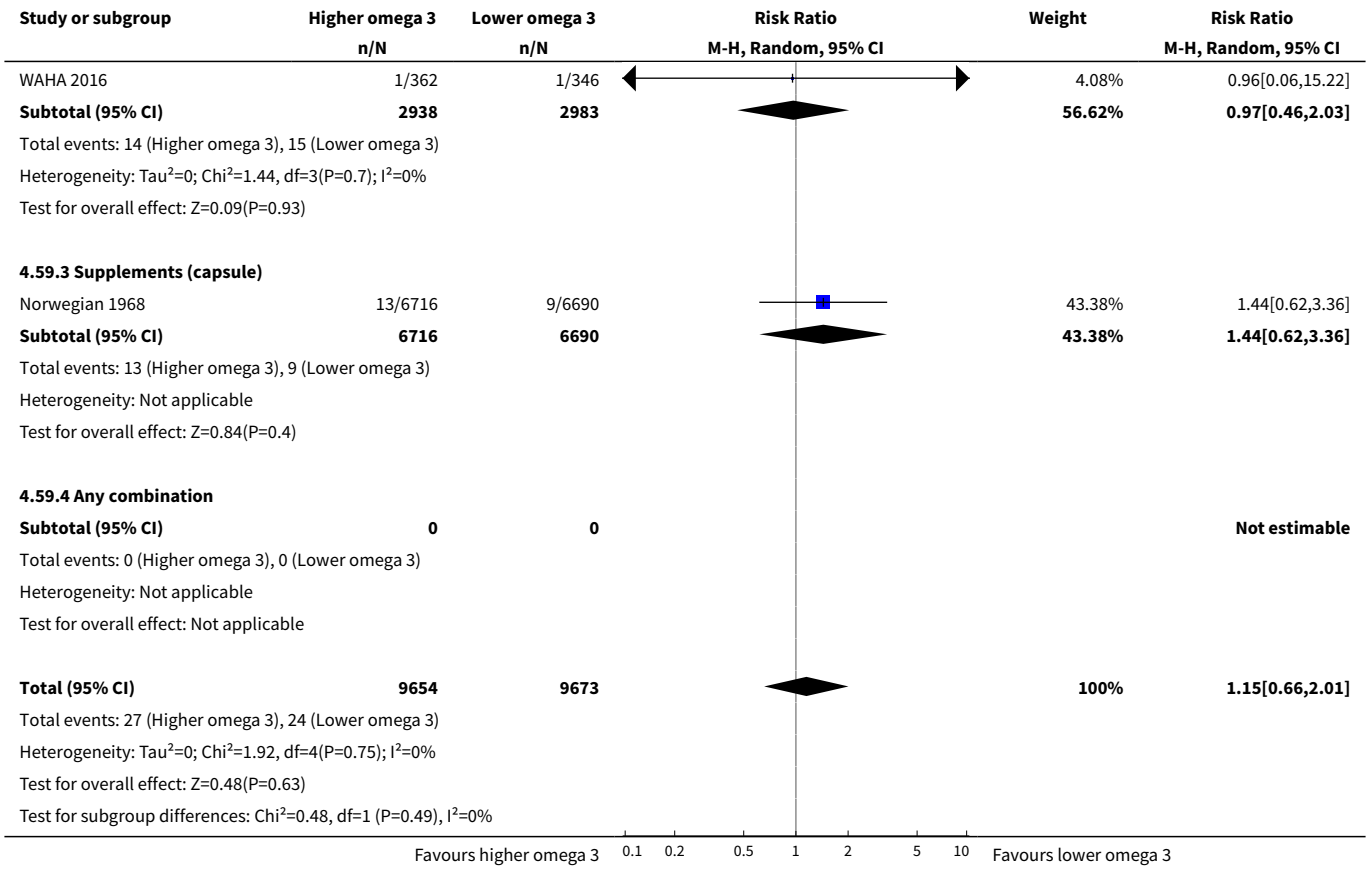
Analysis 4.58. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 58 Stroke - ALA - subgroup by replacement.



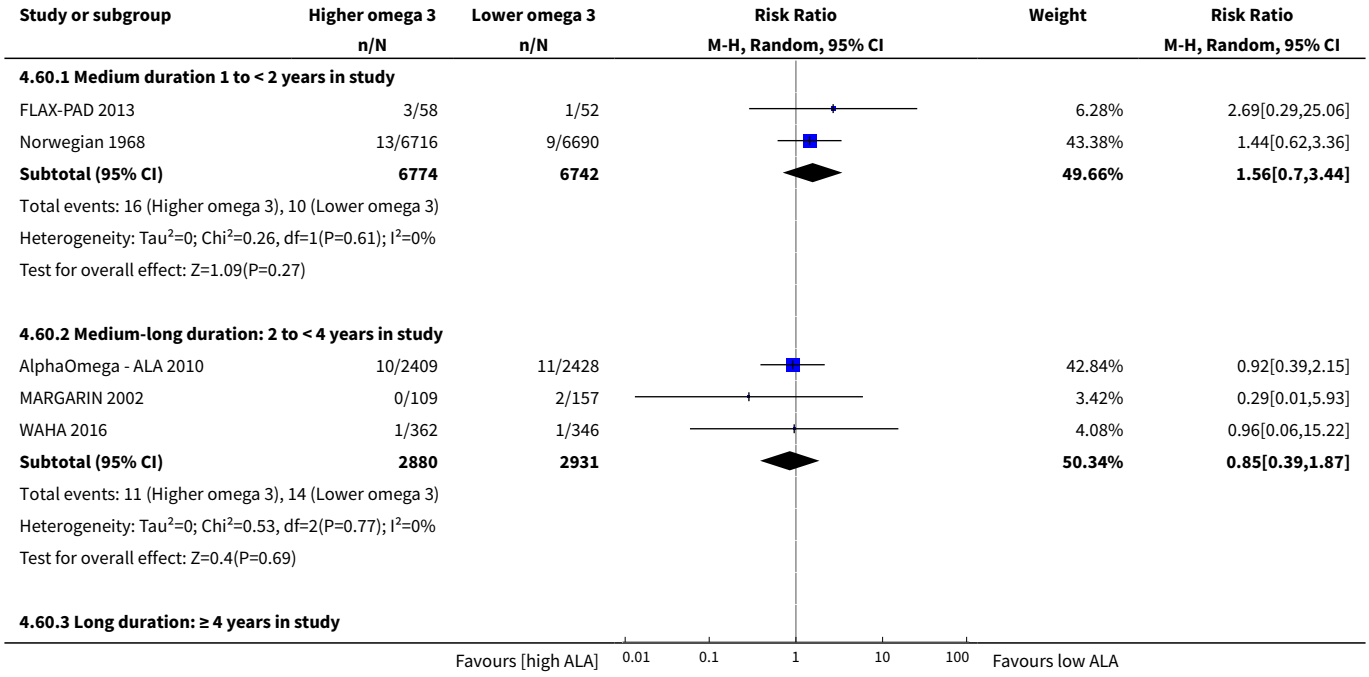


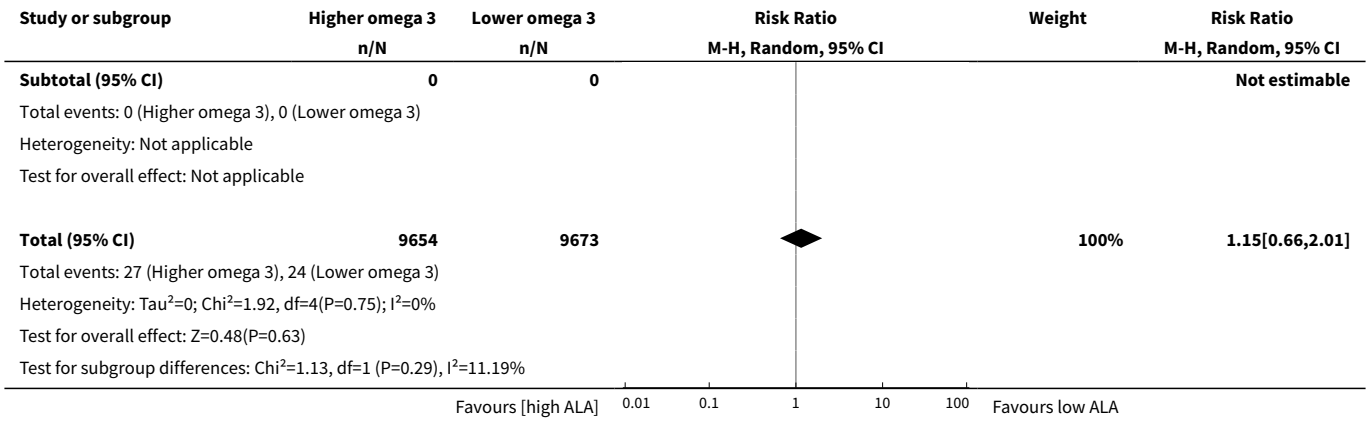
Analysis 4.59. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 59 Stroke - ALA - subgroup by intervention type.



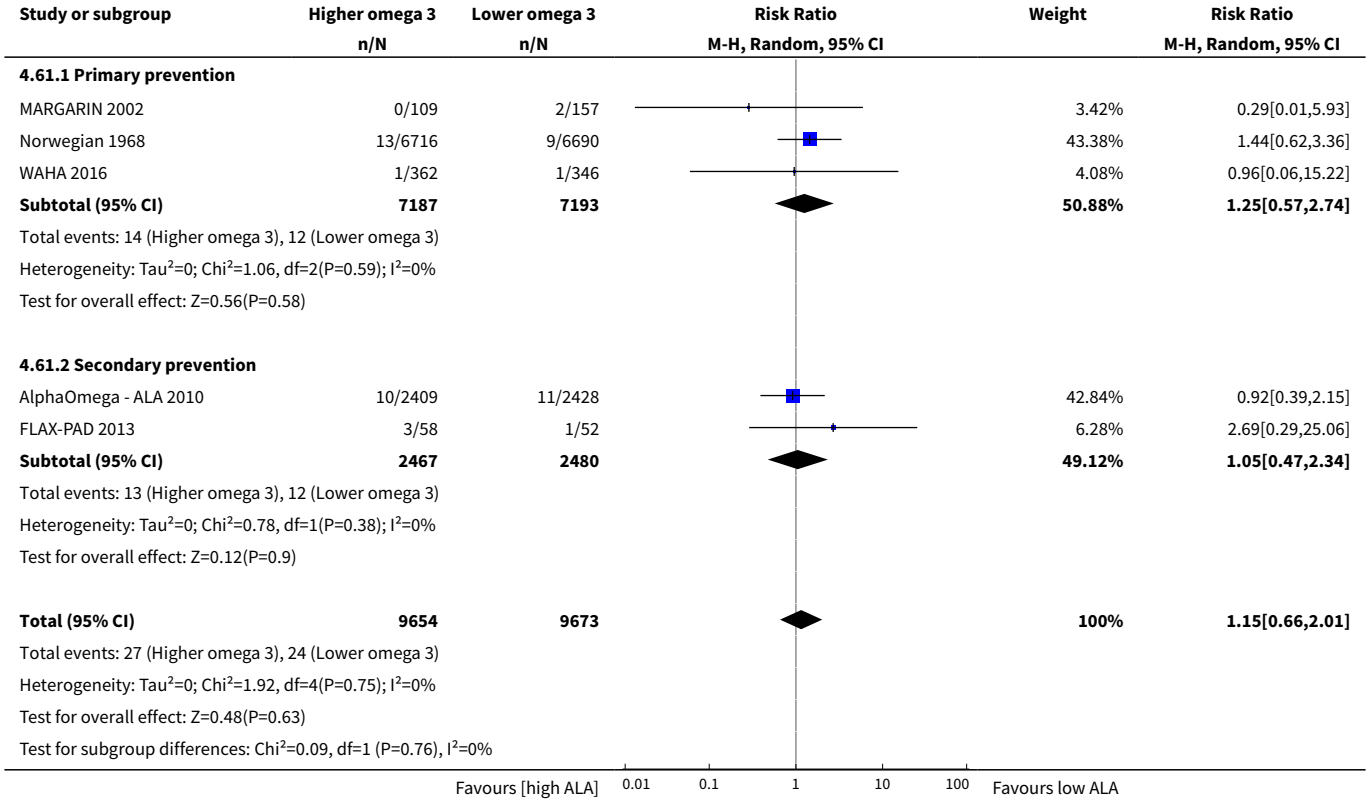


Analysis 4.60. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 60 Stroke - ALA - subgroup by duration.

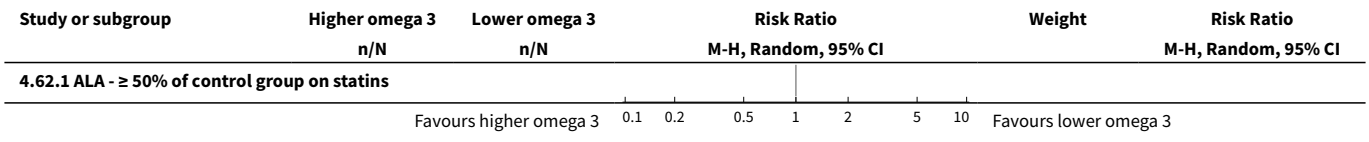


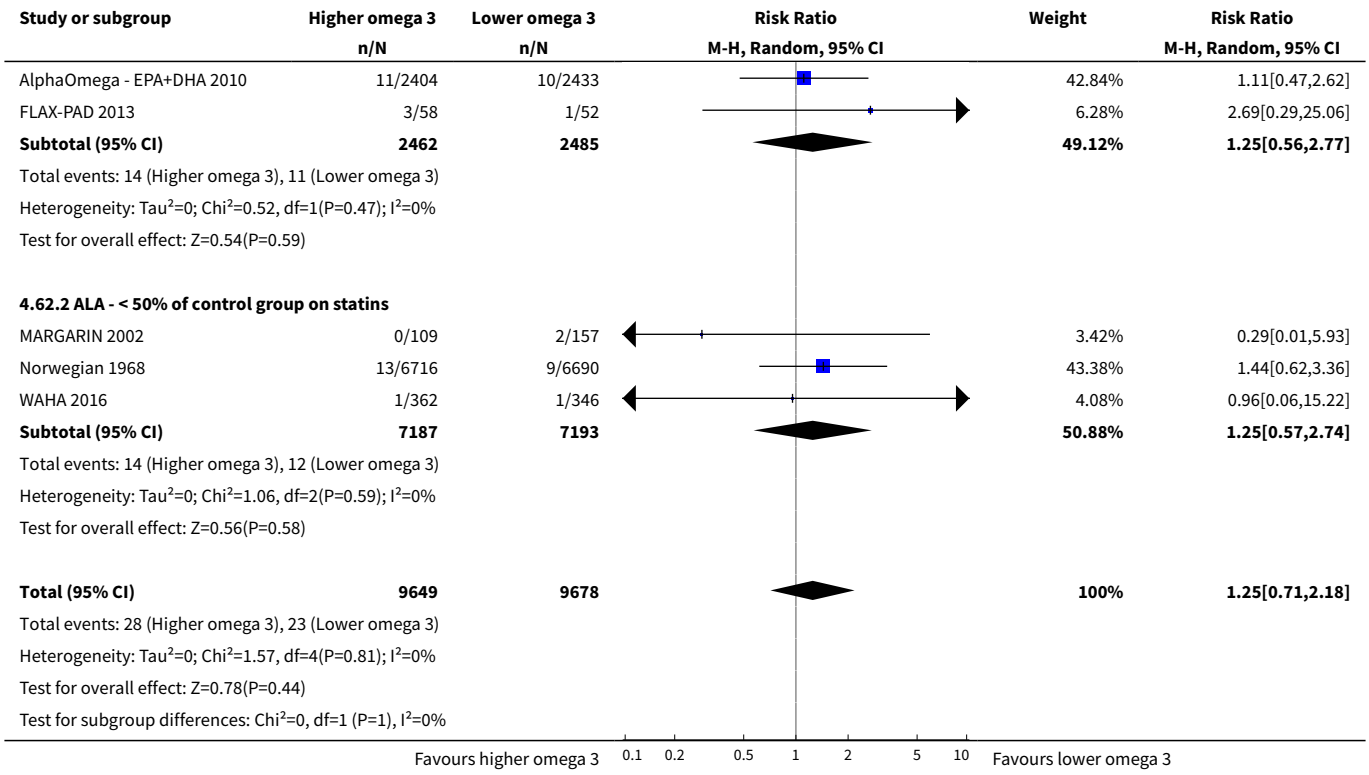


Analysis 4.61. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 61 Stroke - ALA - subgroup by primary or secondary prevention.

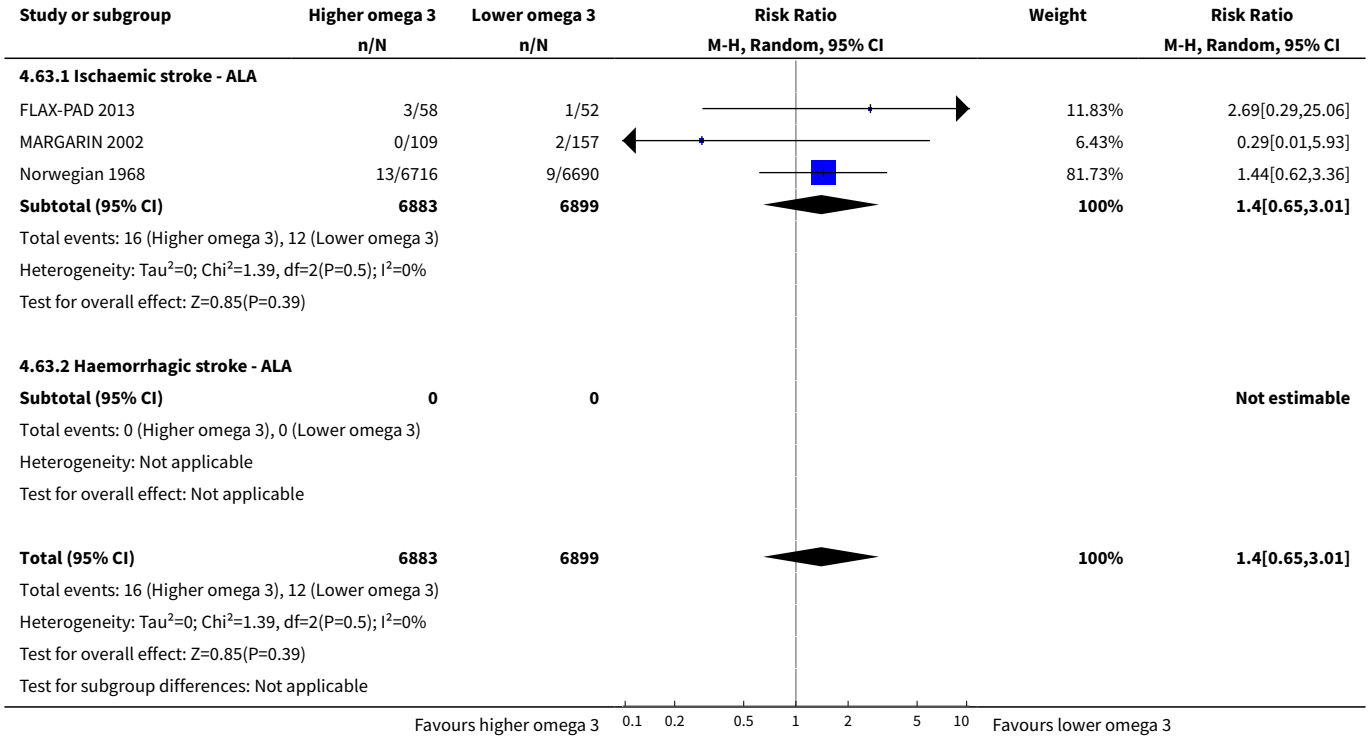


Analysis 4.62. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 62 Stroke - ALA - subgroup by statin use.

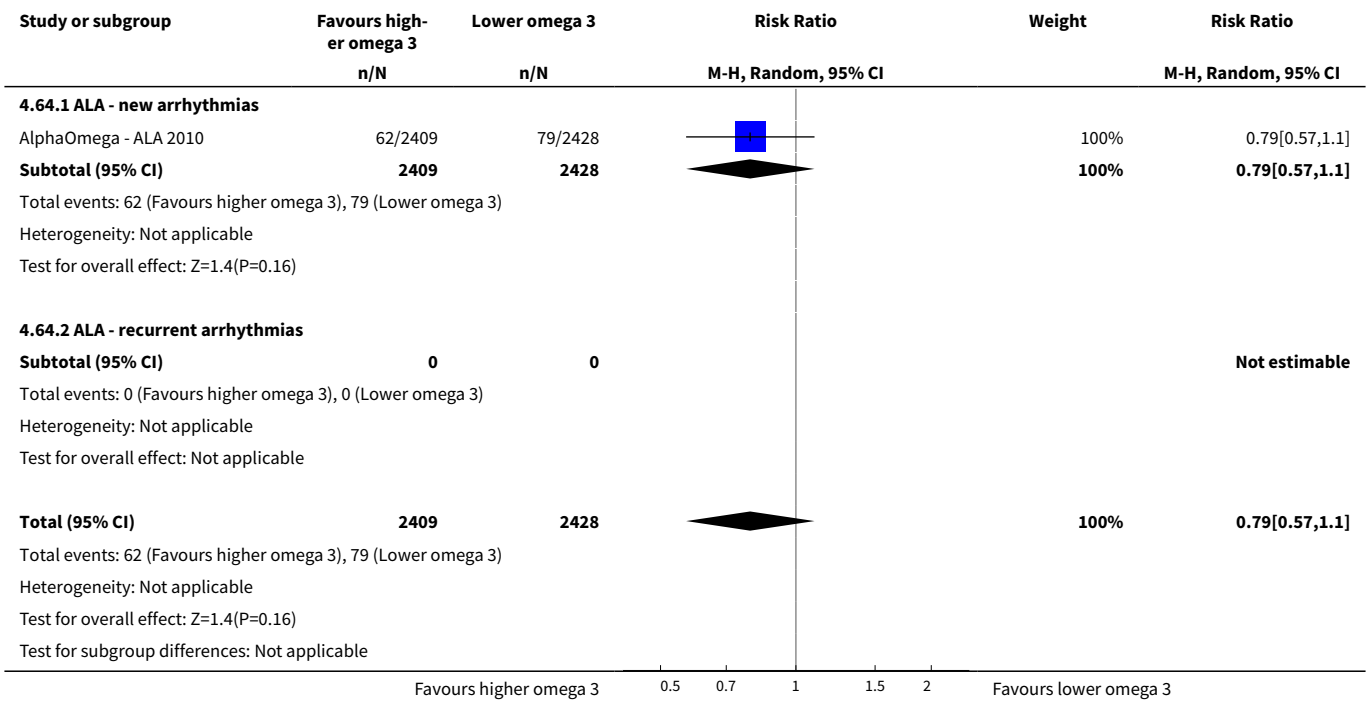




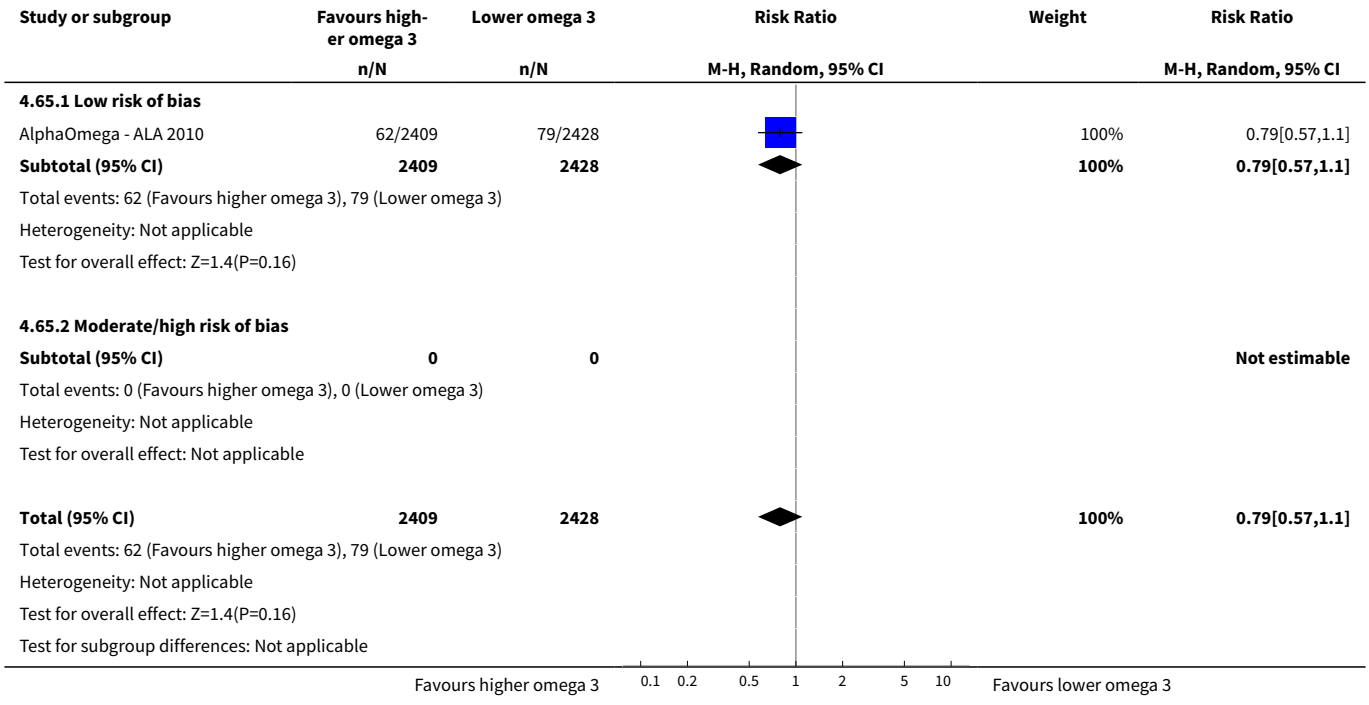
Analysis 4.63. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 63 Stroke - ALA - subgroup by stroke type.



Analysis 4.64. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 64 Arrythmia (overall) - ALA.



Analysis 4.65. Comparison 4 High vs low ALA omega-3 fat (primary outcomes), Outcome 65 Arrhythmia - ALA - SA by summary risk of bias.



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]
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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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]
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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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
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/m^2 - ALA	3	1581	Mean Difference (IV, Random, 95% CI)	-0.42 [-1.53, 0.69]
18 BMI, kg/m^2 - ALA - SA fixed-effect	3	1581	Mean Difference (IV, Fixed, 95% CI)	0.12 [-0.06, 0.30]
19 BMI, kg/m^2 - 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/m^2 - 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]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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]
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	1581	Mean Difference (IV, Random, 95% CI)	-0.42 [-1.53, 0.69]
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]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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/m^2 - 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/m^2 - 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]
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]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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]
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]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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]
37 TC, mmoL/L - ALA - subgroup by primary or secondary preventionA	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]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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]
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 replacementA	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]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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]
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

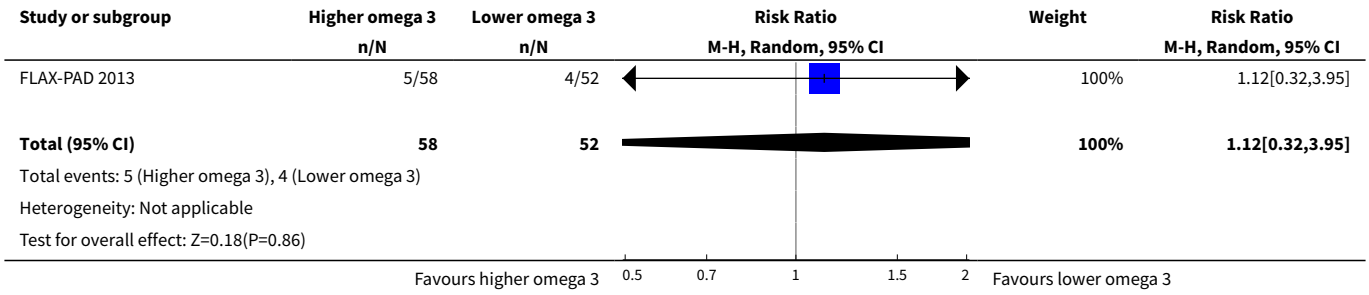
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
52.1 ALA low < 5 g/d	3	1371	Mean Difference (IV, Random, 95% CI)	0.06 [-0.08, 0.19]
52.2 ALA high > 5 g/d	3	405	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.12, -0.01]
53 HDL, mmoL/L - ALA - subgroup by intervention 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
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]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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	7		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	3	1368	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.08, 0.03]
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]

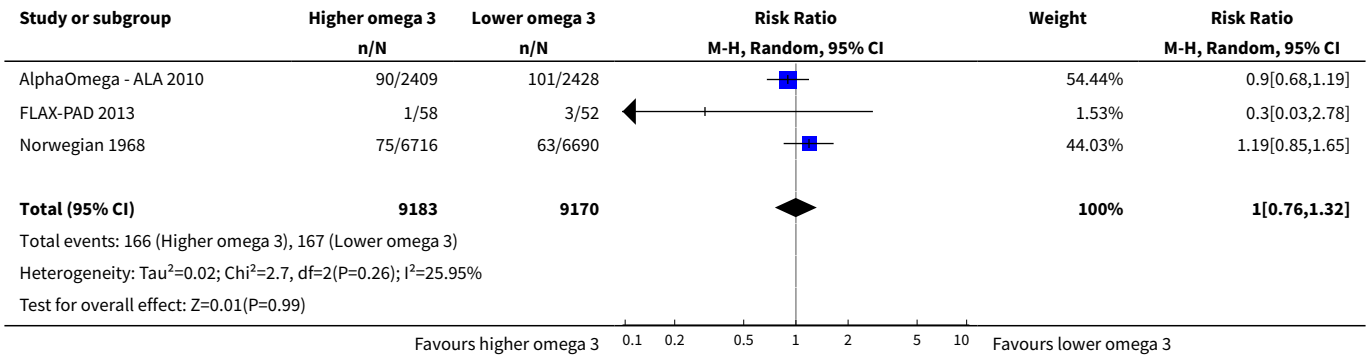
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
62.2 ALA high > 5 g/d	3	405	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.28, 0.19]
63 LDL, mmoL/L - ALA - subgroup by intervention type	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
63.1 Dietary advice	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	7		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]
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]
64.6 Replacement unclear	3	777	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.24, -0.07]
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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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]

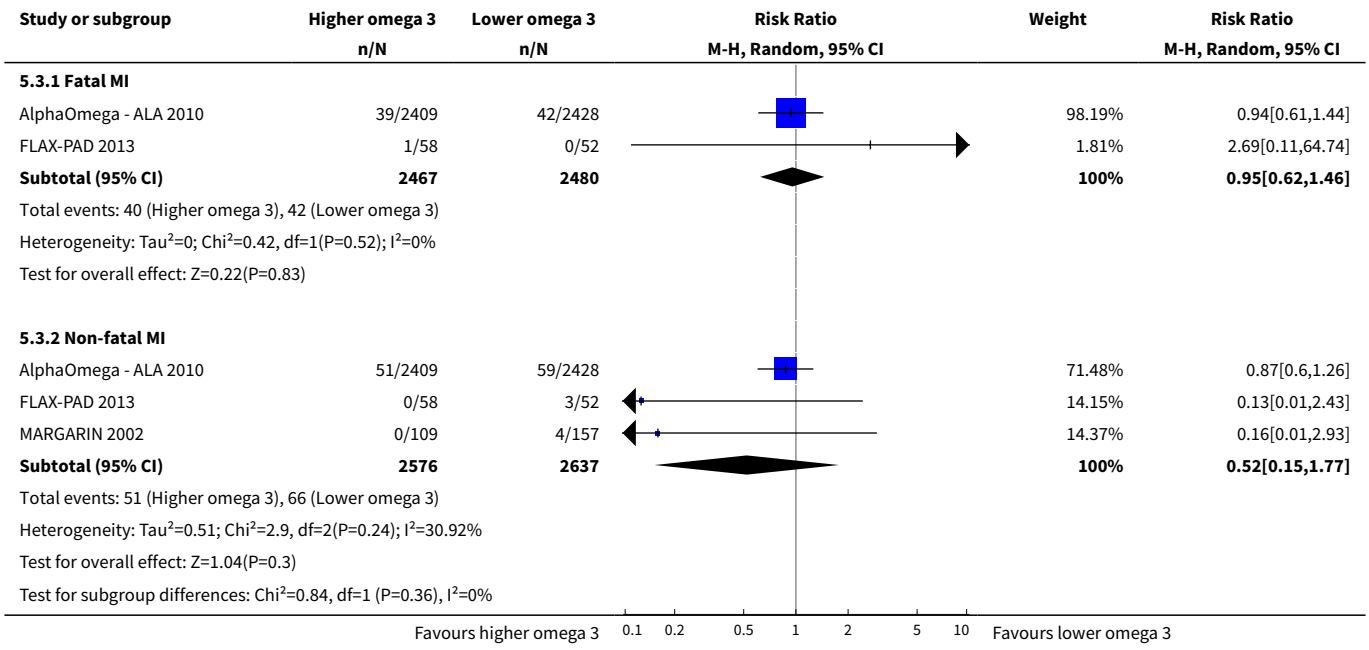
Analysis 5.1. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 1 MACCEs - ALA.



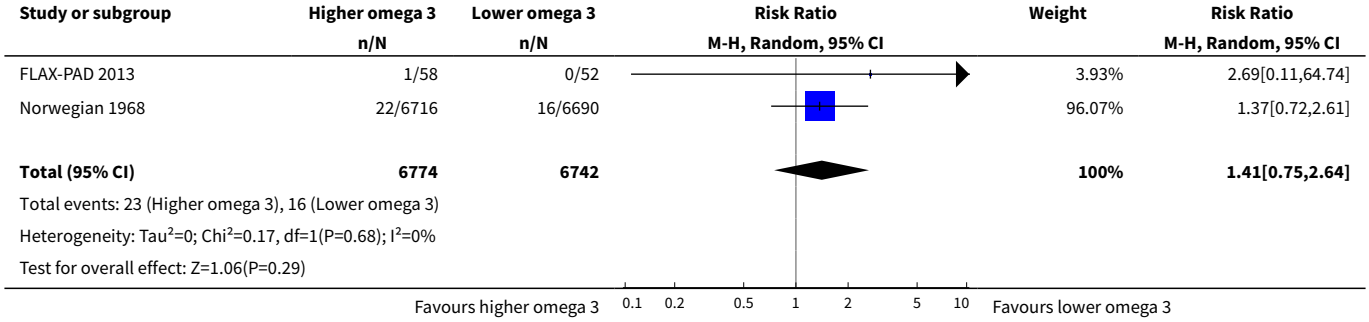
Analysis 5.2. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 2 Myocardial infarction (overall) - ALA.



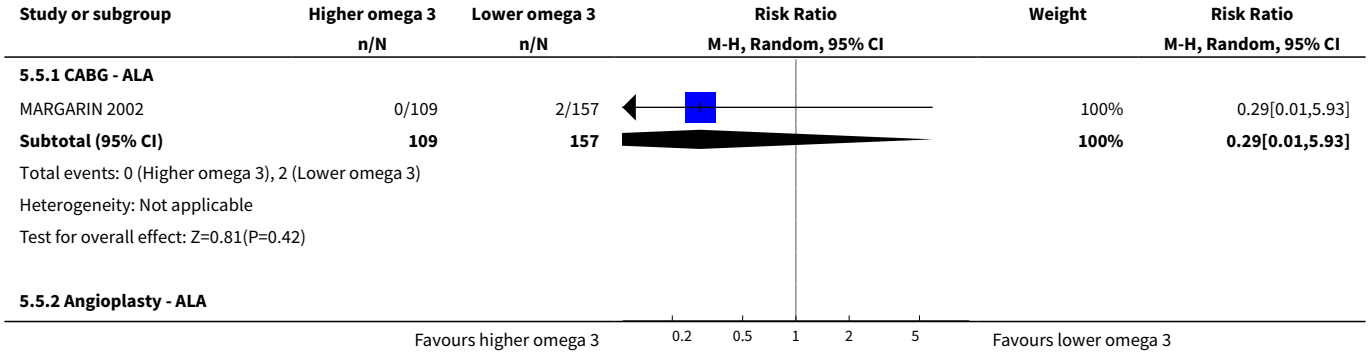
Analysis 5.3. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 3 Total MI - ALA - subgroup by fatality.

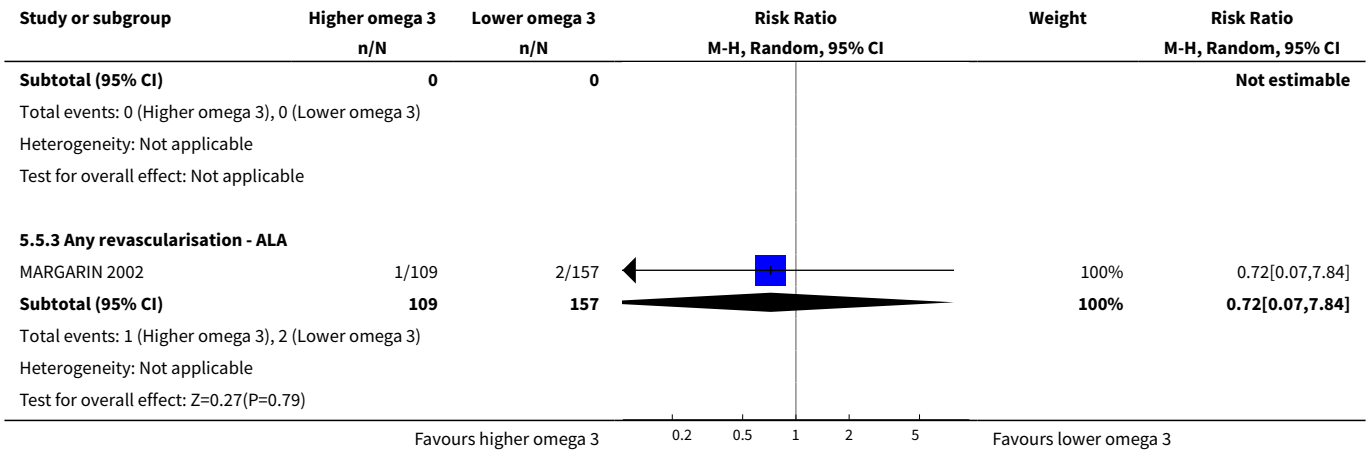


Analysis 5.4. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 4 Angina - ALA.

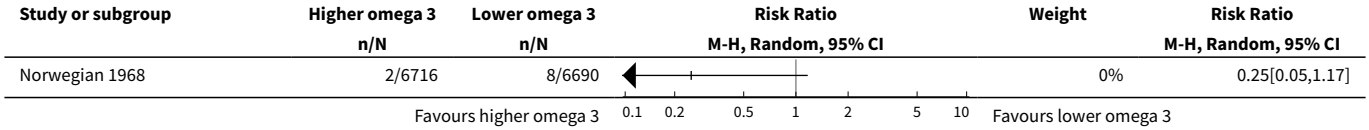


Analysis 5.5. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 5 Revascularisation - ALA.

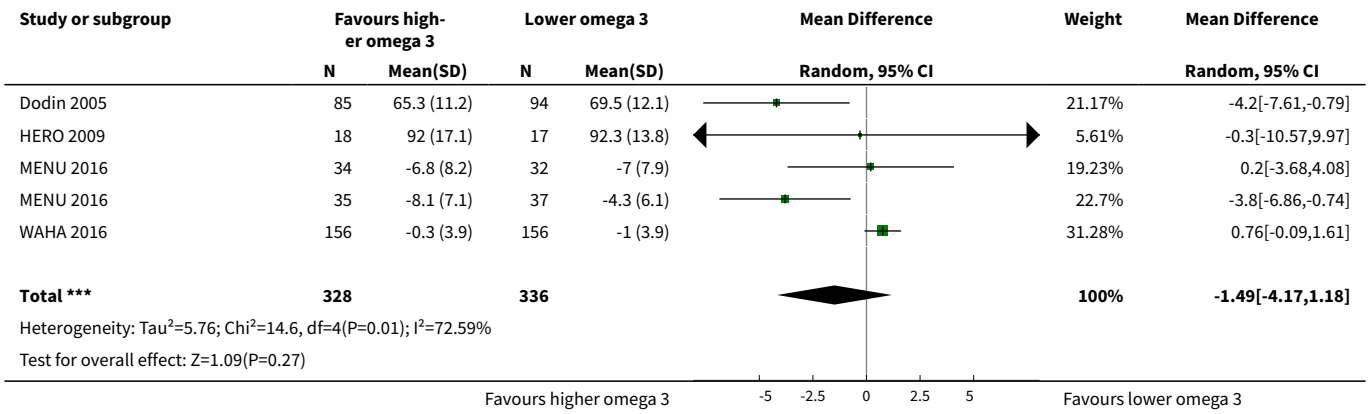




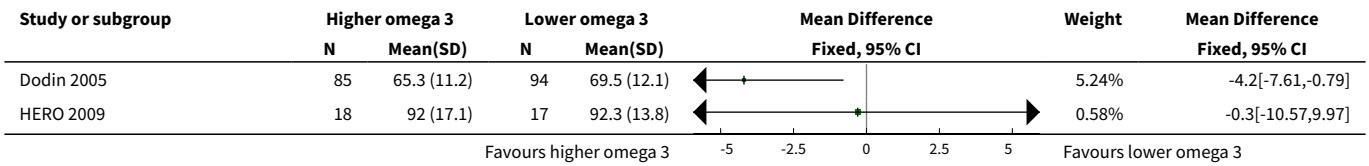
Analysis 5.6. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 6 Peripheral arterial disease - ALA.

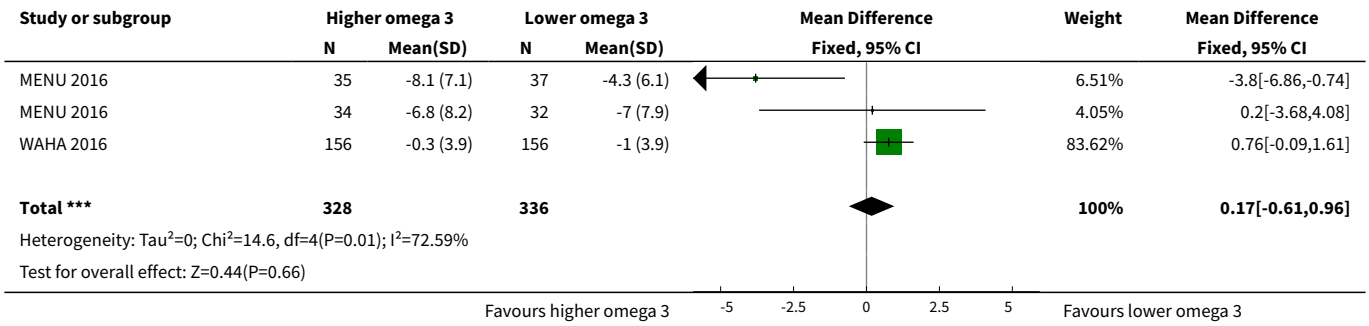


Analysis 5.7. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 7 Body weight, kg - ALA.

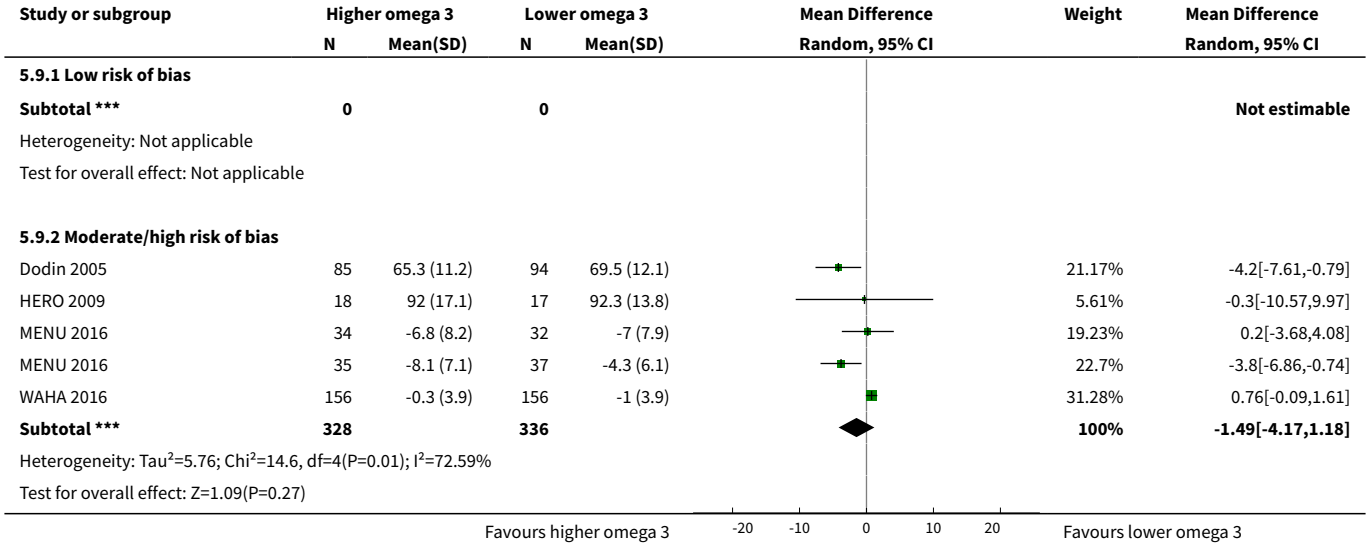


Analysis 5.8. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 8 Weight, kg - ALA - sensitivity analysis (SA) fixed-effect.

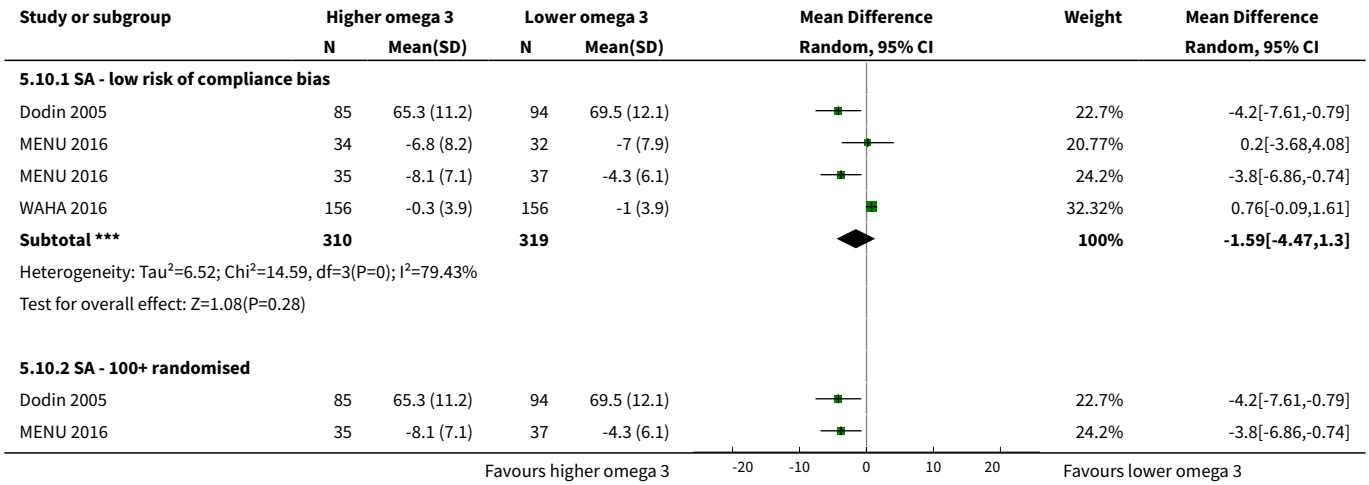


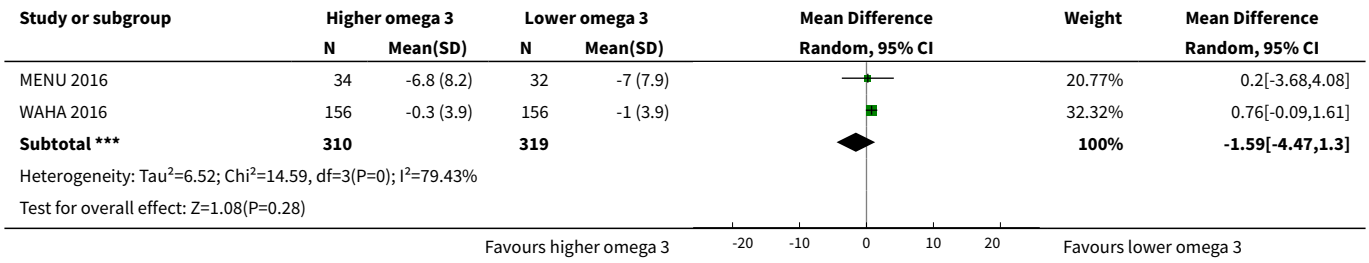


Analysis 5.9. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 9 Weight, kg - ALA - SA by summary risk of bias.

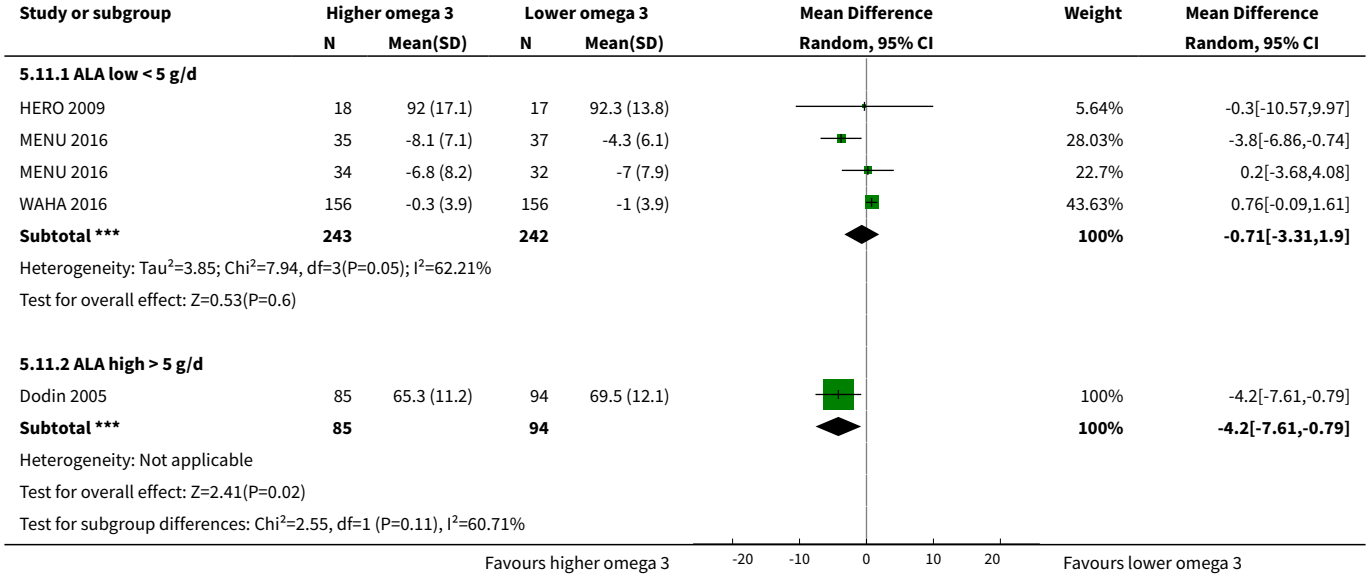


Analysis 5.10. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 10 Weight, kg - ALA - SA by compliance and study size.

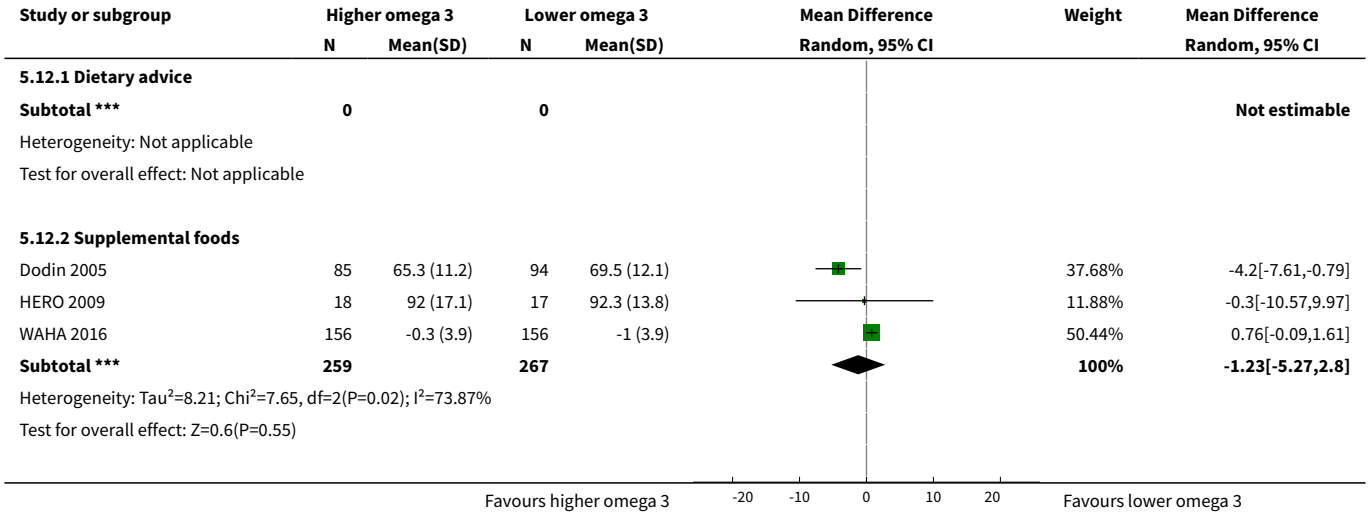


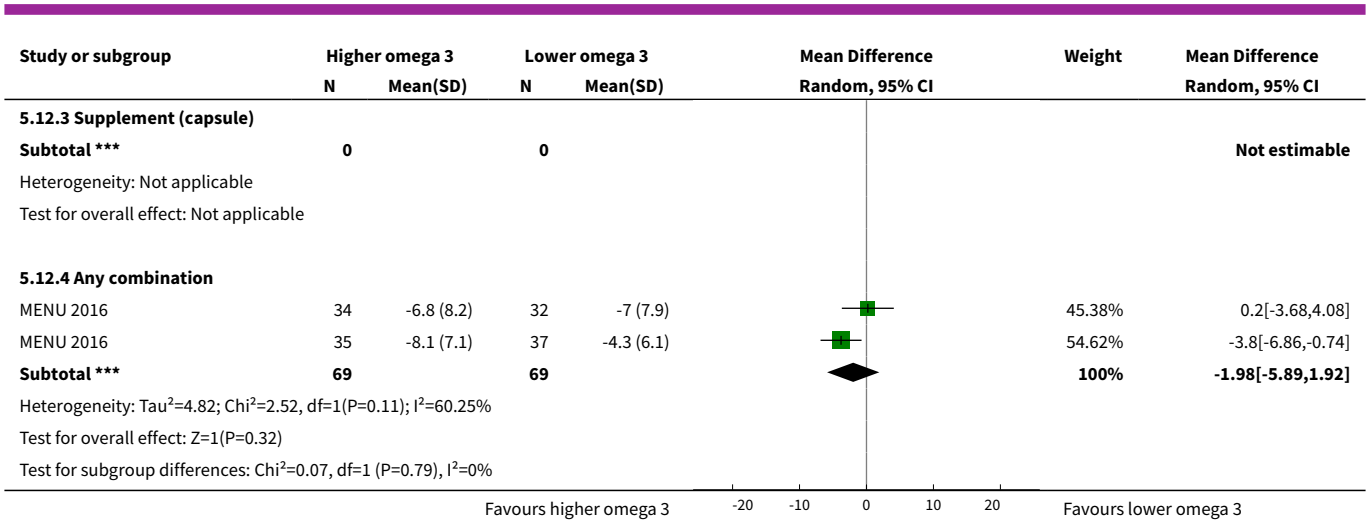


Analysis 5.11. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 11 Weight, kg - ALA - subgroup by dose.

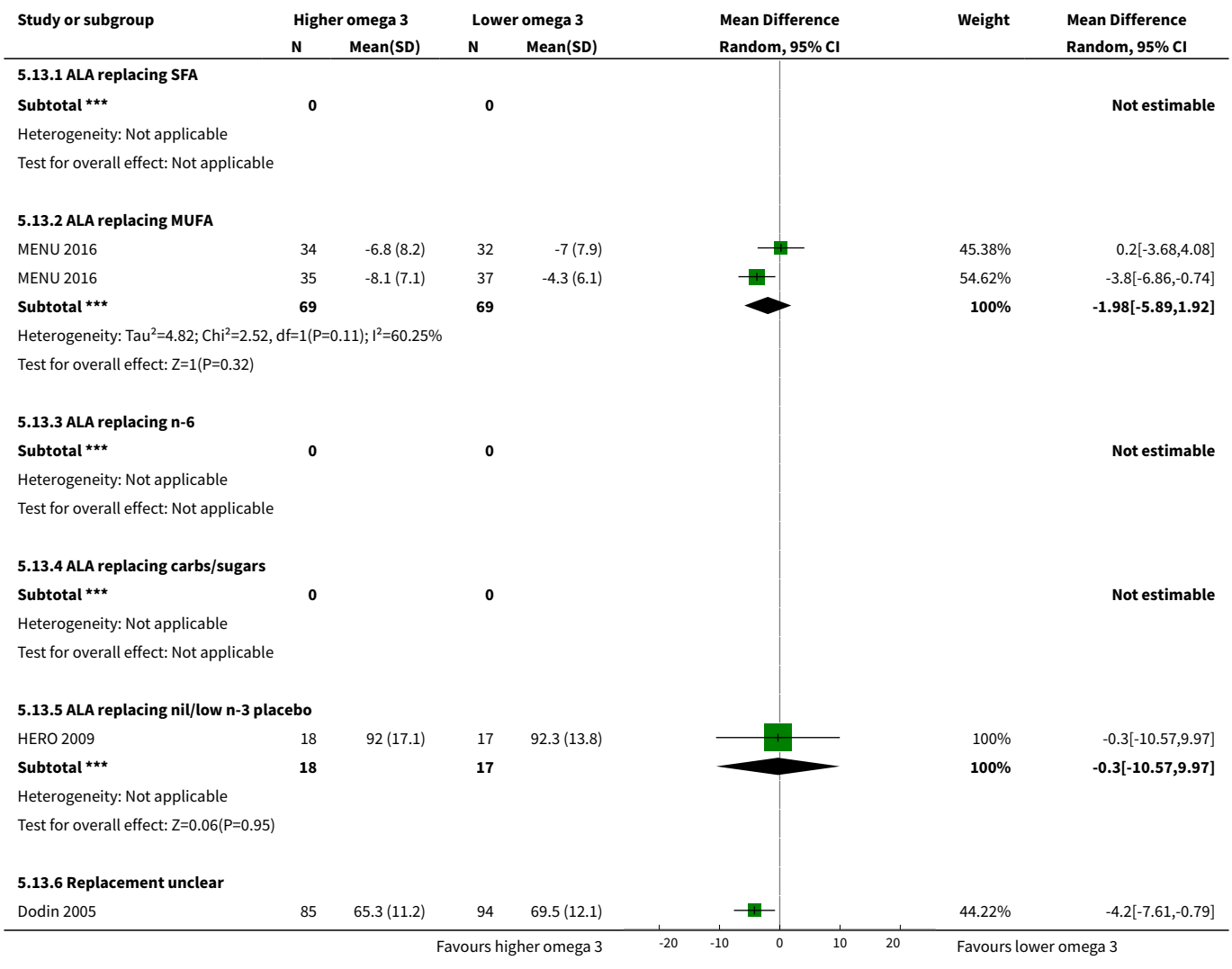


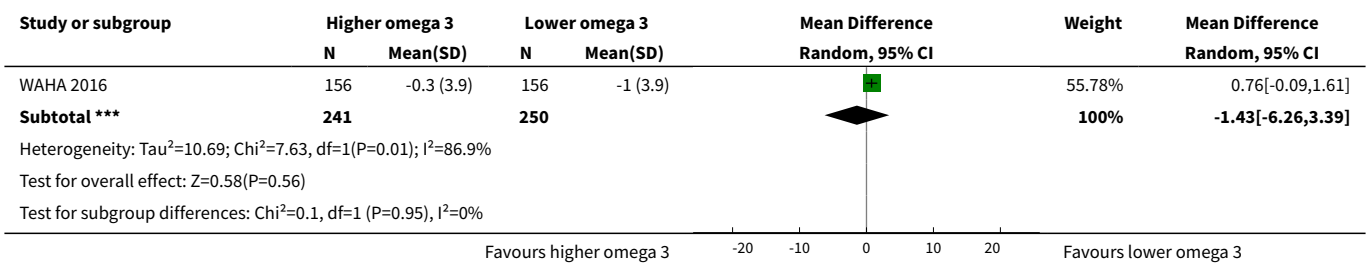
Analysis 5.12. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 12 Weight, kg - ALA - subgroup by intervention type.



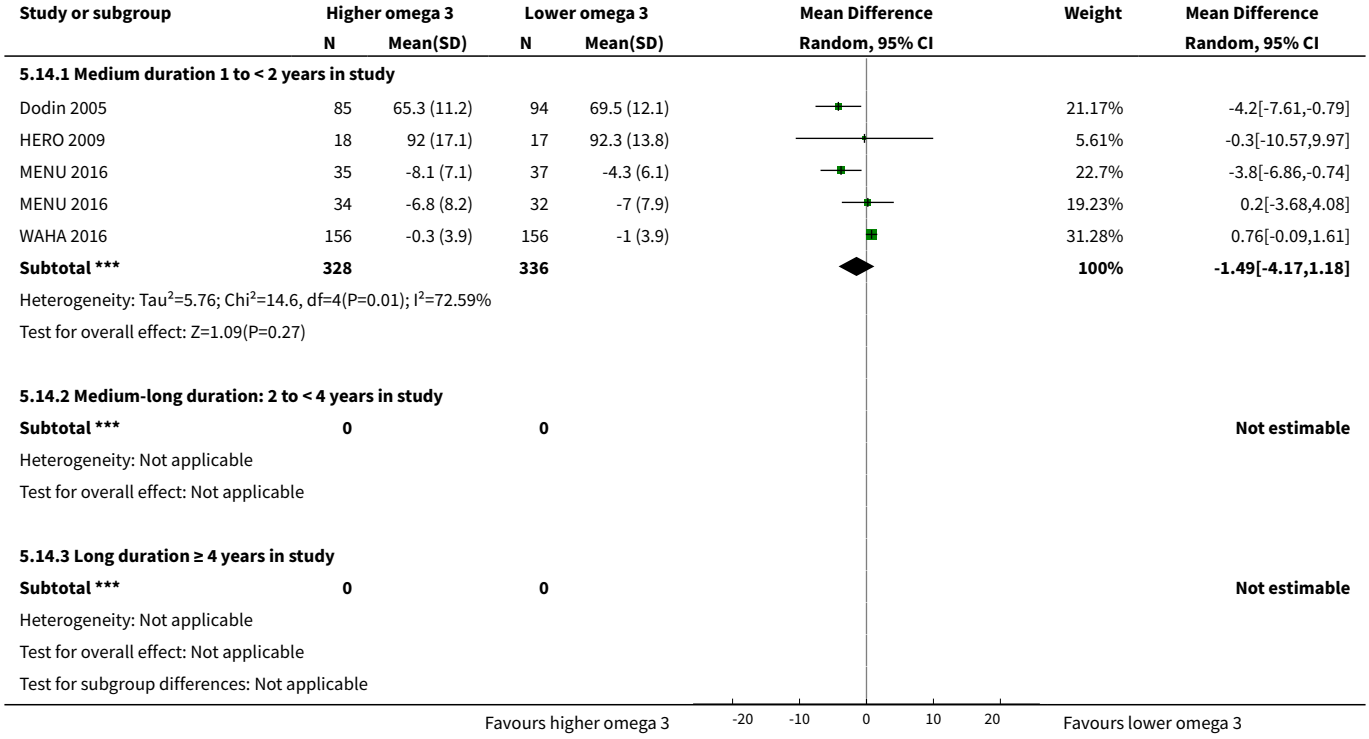


Analysis 5.13. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 13 Weight, kg - ALA - subgroup by replacement.

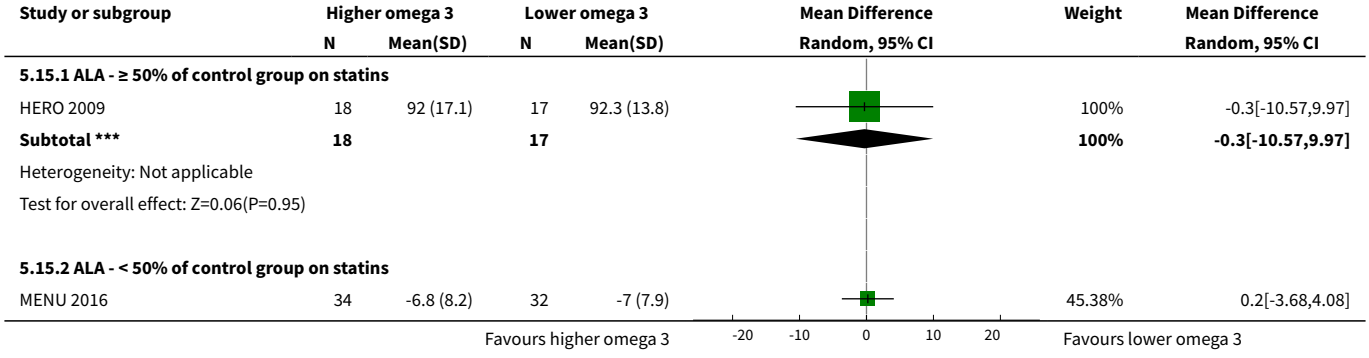


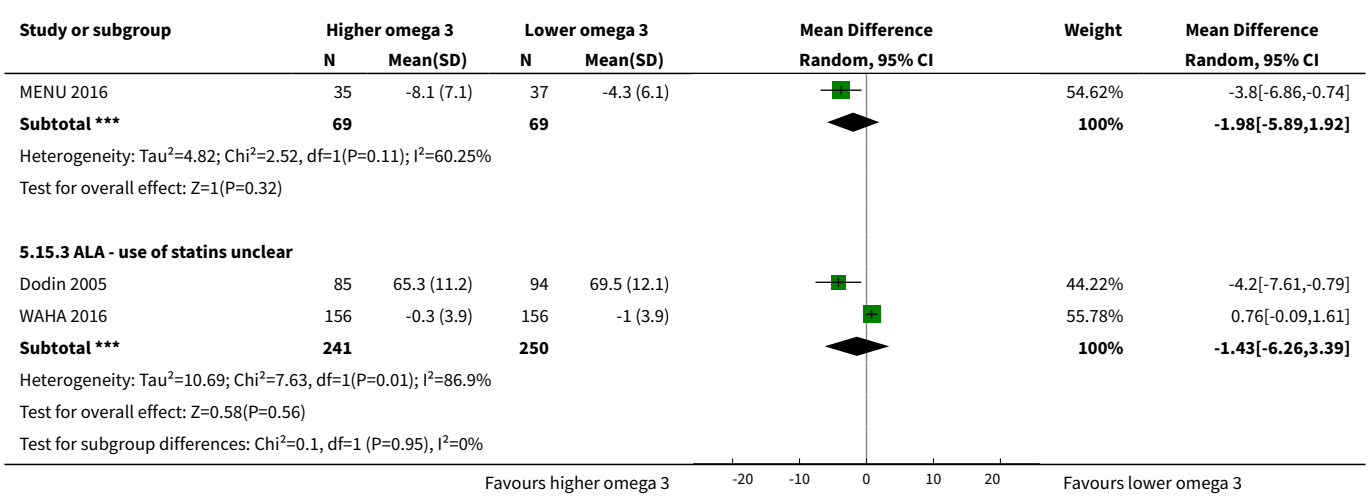


Analysis 5.14. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 14 Weight, kg - ALA - subgroup by duration.

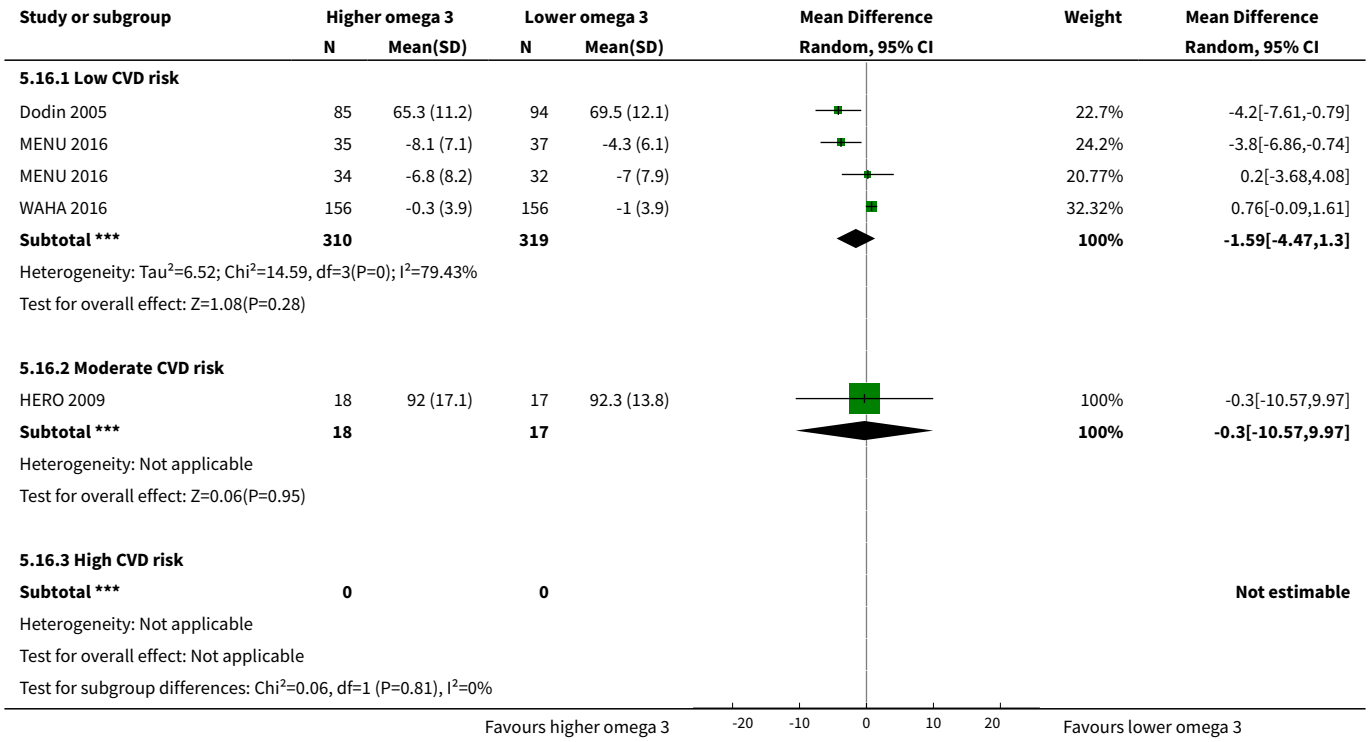


Analysis 5.15. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 15 Weight, kg - ALA - subgroup by statin use.



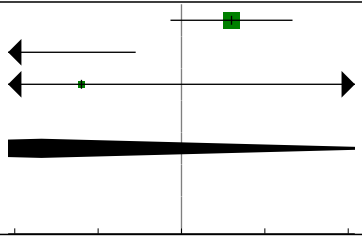


Analysis 5.16. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 16 Weight, kg - ALA - subgroup by primary or secondary prevention.



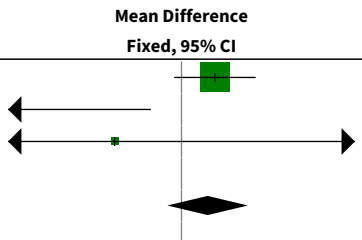
Analysis 5.17. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 17 Body mass index, kg/m² - ALA.

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
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]
Total ***	**764**		**817**			**100%**	**-0.42[-1.53,0.69]**
Heterogeneity: Tau²=0.62; Chi²=5.7, df=2(P=0.06); I²=64.93%							
Test for overall effect: Z=0.74(P=0.46)							



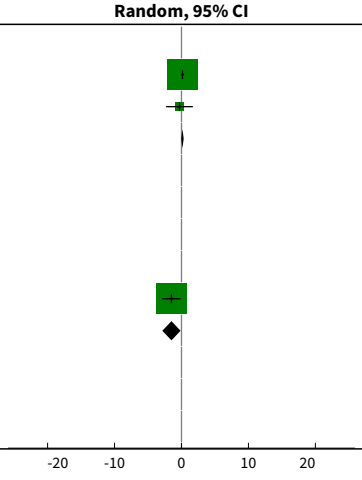
Analysis 5.18. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 18 BMI, kg/m² - ALA - SA fixed-effect.

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
AlphaOmega - ALA 2010	630	0.1 (1.5)	630	-0.1 (1.8)		97.42%	0.15[-0.03,0.33]
Dodin 2005	85	25.9 (4.5)	94	27.4 (4.8)		1.76%	-1.5[-2.86,-0.14]
MARGARIN 2002	49	0.2 (1.4)	93	0.5 (9.6)		0.82%	-0.3[-2.29,1.69]
Total ***	**764**		**817**			**100%**	**0.12[-0.06,0.3]**
Heterogeneity: Tau²=0; Chi²=5.7, df=2(P=0.06); I²=64.93%							
Test for overall effect: Z=1.27(P=0.2)							



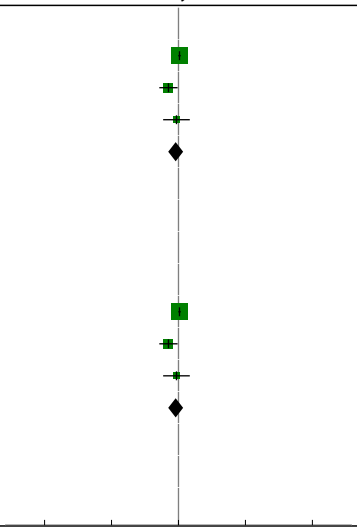
Analysis 5.19. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 19 BMI, kg/m² - ALA - SA by summary risk of bias.

Study or subgroup	Higher omega 3 N	Mean(SD)	Lower omega 3 N	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: Tau²=0; Chi²=0.19, df=1(P=0.66); I²=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: Chi²=5.51, df=1 (P=0.02), I²=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: Tau²=0.62; Chi²=5.7, df=2(P=0.06); I²=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: Tau²=0.62; Chi²=5.7, df=2(P=0.06); I²=64.93%							
Test for overall effect: Z=0.74(P=0.46)							
Test for subgroup differences: Not applicable							



Favours higher omega 3 — Favours lower omega 3

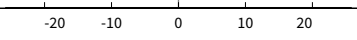
Analysis 5.21. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 21 BMI, kg/m² - ALA - subgroup by dose.

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							
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)							
5.21.2 ALA high > 5 g/d							
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]**
Heterogeneity: Tau²=0; Chi²=0.95, df=1(P=0.33); I²=0%							
Test for overall effect: Z=1.95(P=0.05)							
Test for subgroup differences: Chi²=4.75, df=1 (P=0.03), I²=78.96%							

Favours higher omega 3 — Favours lower omega 3

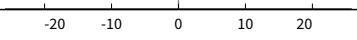
Analysis 5.22. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 22 BMI, kg/m² - ALA - subgroup by intervention type.

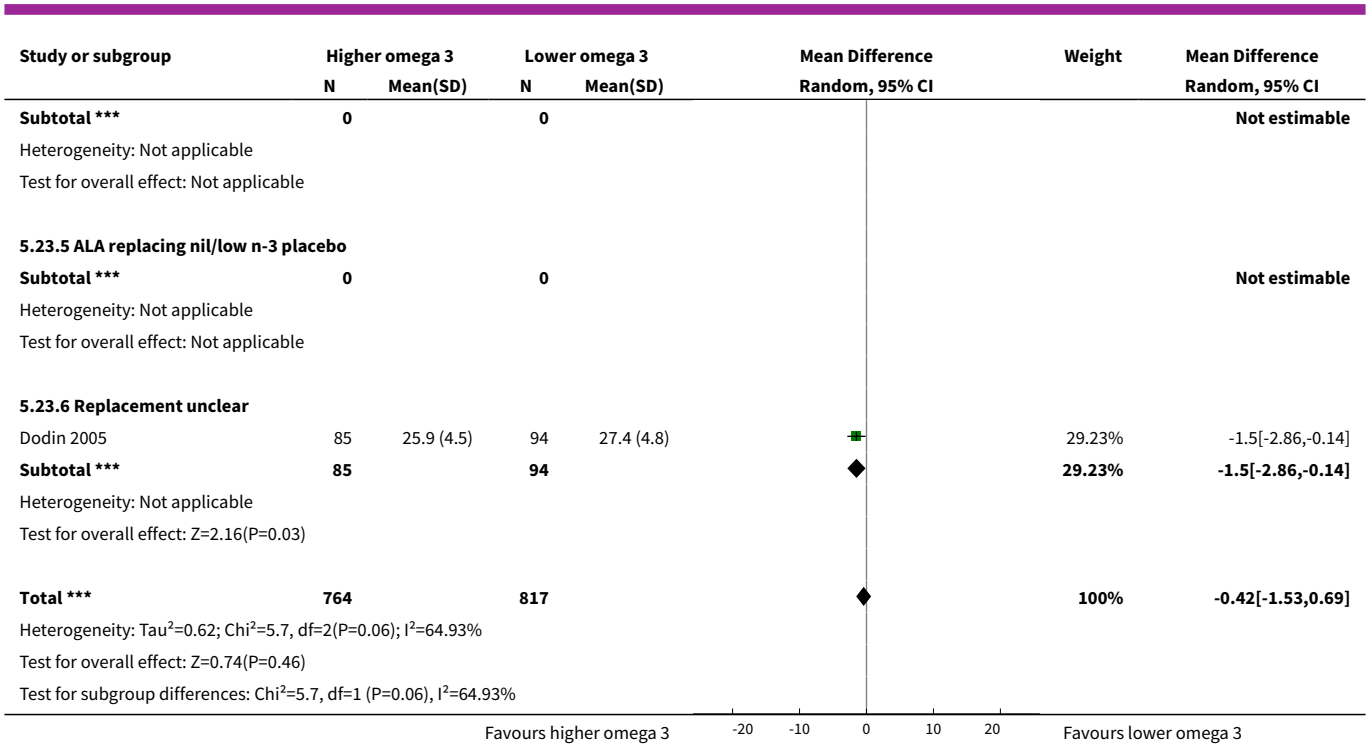
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.22.1 Dietary advice							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.22.2 Supplemental foods							
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)							
5.22.3 Supplement (capsule)							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.22.4 Any combination							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



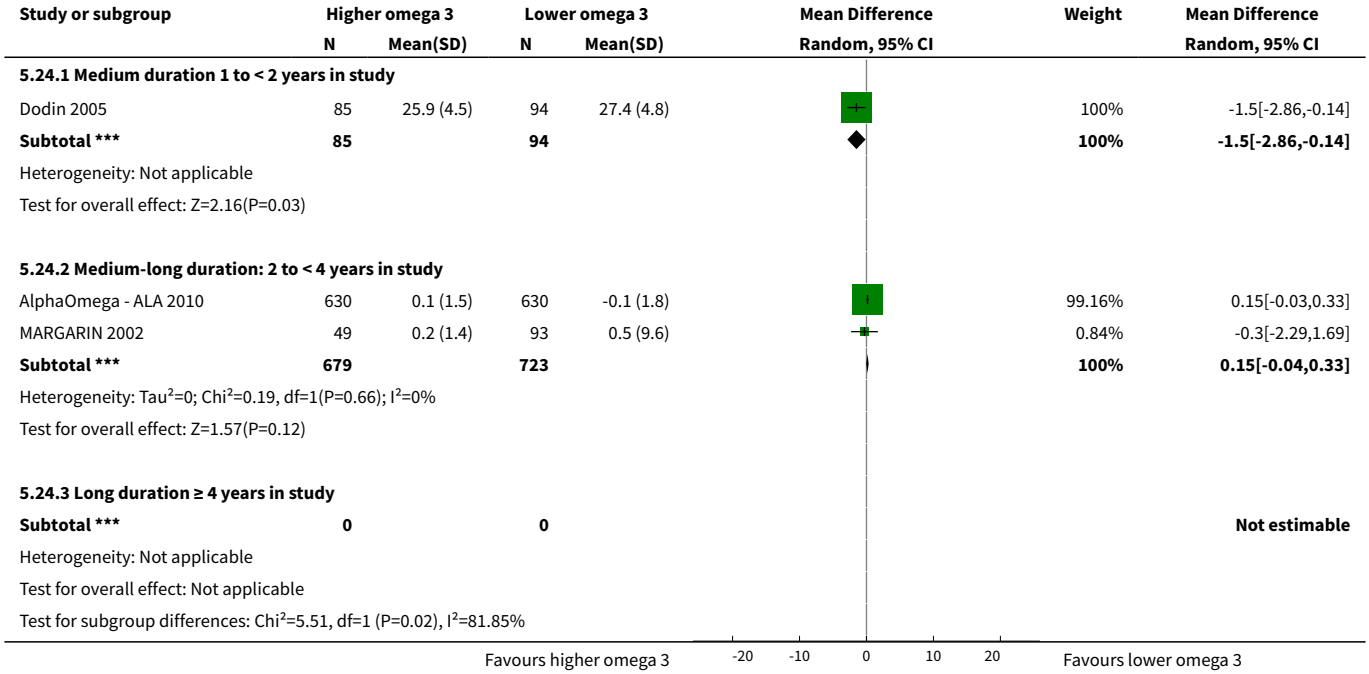
Analysis 5.23. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 23 BMI, kg/m² - ALA - subgroup by replacement.

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)		51.23%	0.15[-0.03,0.33]
Subtotal ***	**630**		**630**			**51.23%**	**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)		19.54%	-0.3[-2.29,1.69]
Subtotal ***	**49**		**93**			**19.54%**	**-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							



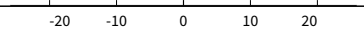


Analysis 5.24. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 24 BMI, kg/m² - ALA - subgroup by duration.



Analysis 5.25. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 25 BMI, kg/m² - ALA - subgroup by statin use.

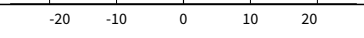
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.25.1 ALA - ≥ 50% of control group on statins							
AlphaOmega - ALA 2010	630	0.1 (1.5)	630	-0.1 (1.8)		100%	0.15[-0.03,0.33]
Subtotal ***	**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.

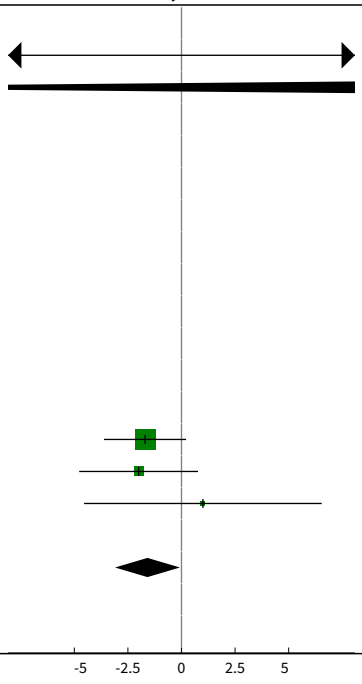
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.26.1 Primary prevention of CVD							
Dodin 2005	85	25.9 (4.5)	94	27.4 (4.8)		68.08%	-1.5[-2.86,-0.14]
MARGARIN 2002	49	0.2 (1.4)	93	0.5 (9.6)		31.92%	-0.3[-2.29,1.69]
Subtotal ***	**134**		**187**			**100%**	**-1.12[-2.24,0.01]**
Heterogeneity: Tau²=0; Chi²=0.95, df=1(P=0.33); I²=0%							
Test for overall effect: Z=1.95(P=0.05)							
5.26.2 Secondary prevention of CVD							
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)							
Test for subgroup differences: Chi²=4.75, df=1 (P=0.03), I²=78.96%							



Favours higher omega 3 — Favours lower omega 3

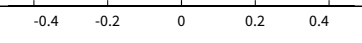
Analysis 5.27. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 27 Other measures of adiposity - ALA.

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 Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
5.27.1 Visceral adipose tissue, cm²							
HERO 2009	18	194.6 (73.5)	17	167.6 (72.2)		100%	27[-21.28,75.28]
Subtotal ***	**18**		**17**			**100%**	**27[-21.28,75.28]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.1(P=0.27)							
5.27.2 Subcutaneous adipose tissue, cm²							
HERO 2009	18	7.5 (0)	17	-28.1 (0)			Not estimable
Subtotal ***	**18**		**17**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.27.3 Waist circumference, cm							
Dodin 2005	85	1.7 (6.8)	94	3.4 (6.2)		62.67%	-1.7[-3.61,0.21]
MENU 2016	35	-6 (5.9)	37	-4 (6.1)		29.86%	-2[-4.77,0.77]
MENU 2016	34	-7 (11.7)	32	-8 (11.3)		7.47%	1[-4.54,6.54]
WAHA 2016	156	2.3 (0)	156	1.9 (0)			Not estimable
Subtotal ***	**310**		**319**			**100%**	**-1.59[-3.1,-0.07]**
Heterogeneity: Tau^2=0; Chi^2=0.94, df=2(P=0.63); I^2=0%							
Test for overall effect: Z=2.05(P=0.04)							



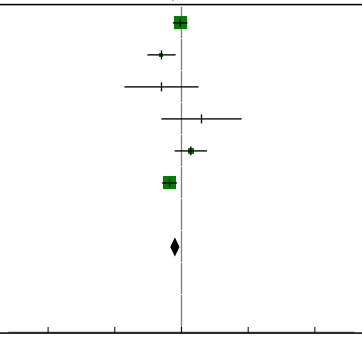
Analysis 5.28. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 28 Total cholesterol, serum, mmoL/L - ALA.

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	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]
Total ***	**1060**		**1104**			**100%**	**-0.09[-0.23,0.05]**
Heterogeneity: Tau^2=0.02; Chi^2=13.4, df=5(P=0.02); I^2=62.69%							
Test for overall effect: Z=1.25(P=0.21)							



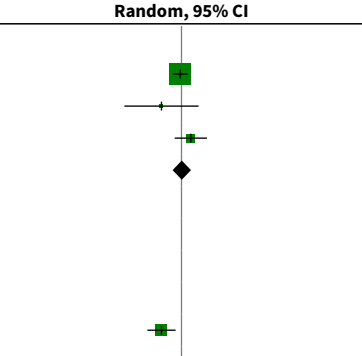
Analysis 5.29. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 29 TC, mmoL/L - ALA - SA fixed-effect.

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	-0.3 (1)	605	-0.3 (1)		39.45%	-0.02[-0.13,0.09]
Dodin 2005	85	5.7 (0.7)	94	6 (0.7)		10.78%	-0.3[-0.51,-0.09]
FLAX-PAD 2013	43	4.2 (1.3)	41	4.5 (1.3)		1.56%	-0.3[-0.86,0.26]
HERO 2009	18	4.9 (0.8)	17	4.6 (1)		1.33%	0.3[-0.3,0.9]
MARGARIN 2002	49	-0.2 (0.7)	93	-0.4 (0.7)		8.2%	0.14[-0.1,0.38]
WAHA 2016	260	-0.2 (0.7)	254	-0 (0.6)		38.68%	-0.18[-0.29,-0.07]
Total * **	**1060**		**1104**			**100%**	**-0.1[-0.17,-0.03]**
Heterogeneity: Tau^2=0; Chi^2=13.4, df=5(P=0.02); I^2=62.69%							
Test for overall effect: Z=2.8(P=0.01)							



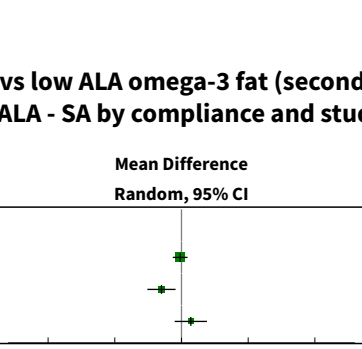
Analysis 5.30. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 30 TC, mmoL/L - ALA - SA by summary risk of bias.

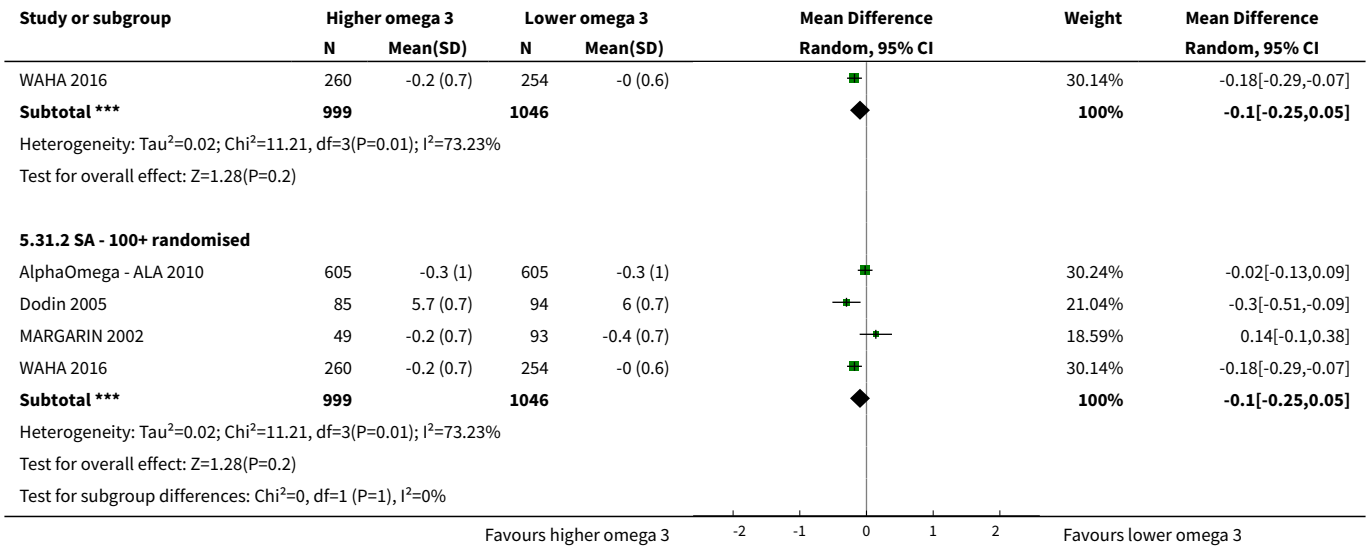
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.30.1 Low risk of bias							
AlphaOmega - ALA 2010	605	-0.3 (1)	605	-0.3 (1)		68.48%	-0.02[-0.13,0.09]
FLAX-PAD 2013	43	4.2 (1.3)	41	4.5 (1.3)		5.87%	-0.3[-0.86,0.26]
MARGARIN 2002	49	-0.2 (0.7)	93	-0.4 (0.7)		25.66%	0.14[-0.1,0.38]
Subtotal * **	**697**		**739**			**100%**	**0[-0.13,0.14]**
Heterogeneity: Tau^2=0; Chi^2=2.53, df=2(P=0.28); I^2=20.81%							
Test for overall effect: Z=0.07(P=0.95)							
5.30.2 Moderate/high risk of bias							
Dodin 2005	85	5.7 (0.7)	94	6 (0.7)		35.51%	-0.3[-0.51,-0.09]
HERO 2009	18	4.9 (0.8)	17	4.6 (1)		7.52%	0.3[-0.3,0.9]
WAHA 2016	260	-0.2 (0.7)	254	-0 (0.6)		56.97%	-0.18[-0.29,-0.07]
Subtotal * **	**363**		**365**			**100%**	**-0.19[-0.36,-0.01]**
Heterogeneity: Tau^2=0.01; Chi^2=3.61, df=2(P=0.16); I^2=44.65%							
Test for overall effect: Z=2.1(P=0.04)							
Test for subgroup differences: Chi^2=2.84, df=1 (P=0.09), I^2=64.8%							



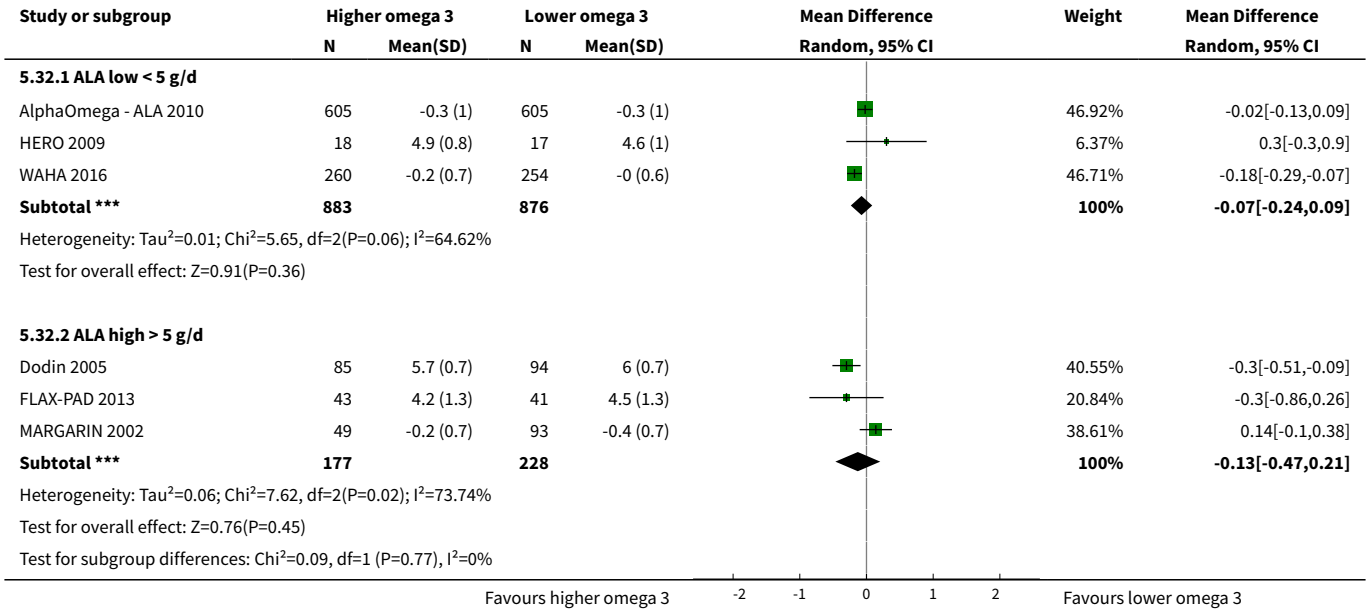
Analysis 5.31. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 31 TC, mmoL/L - ALA - SA by compliance and study size.

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]

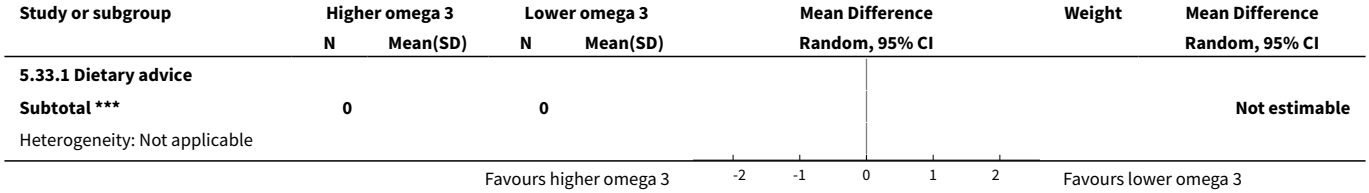


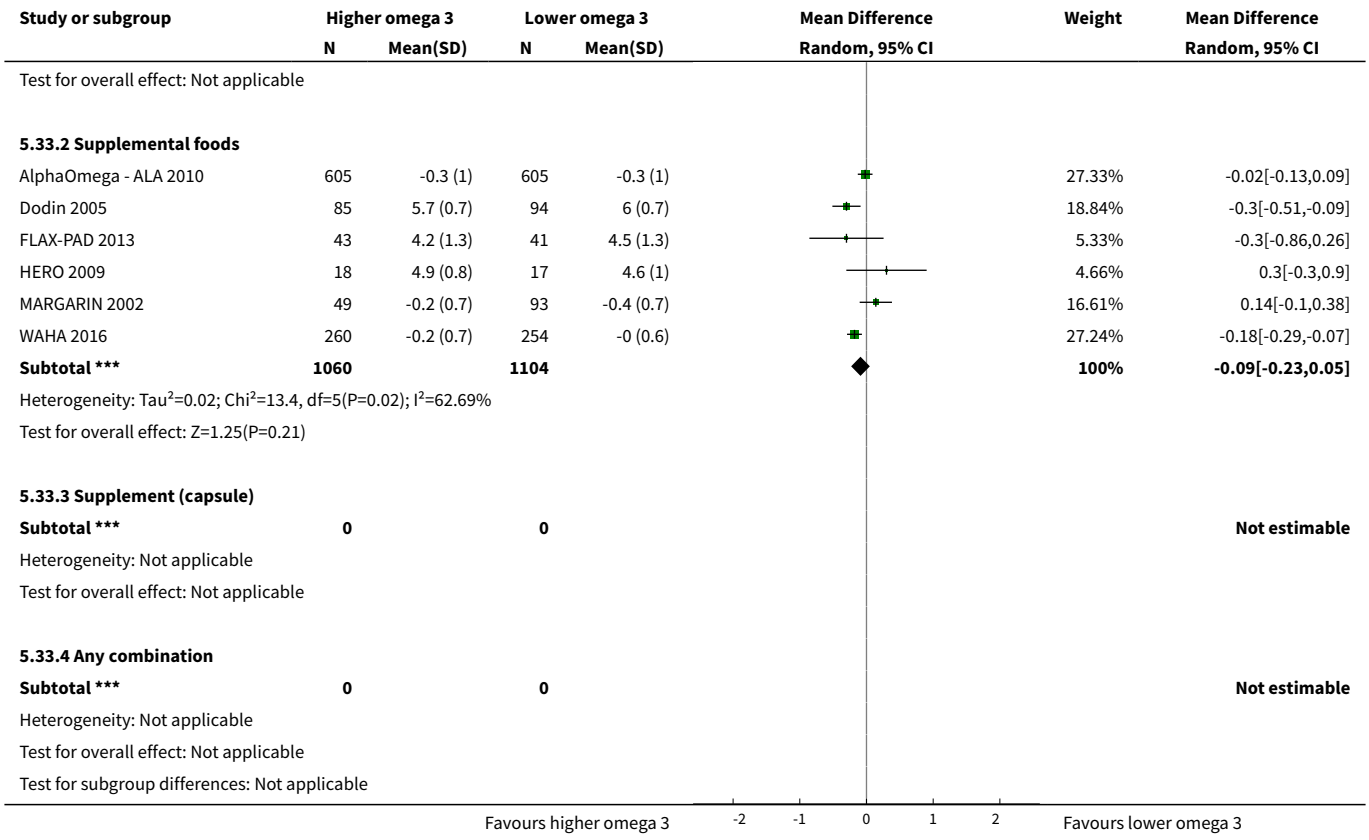


Analysis 5.32. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 32 TC, mmoL/L - ALA - subgroup by dose.

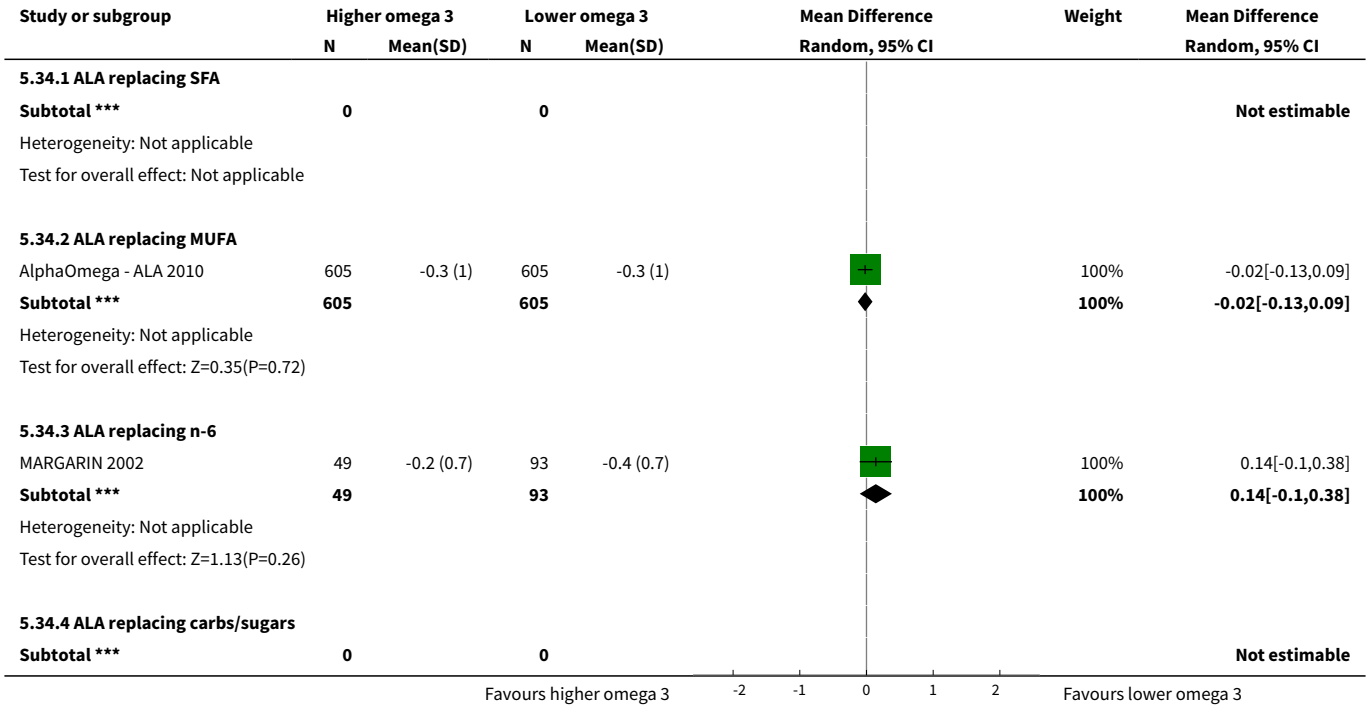


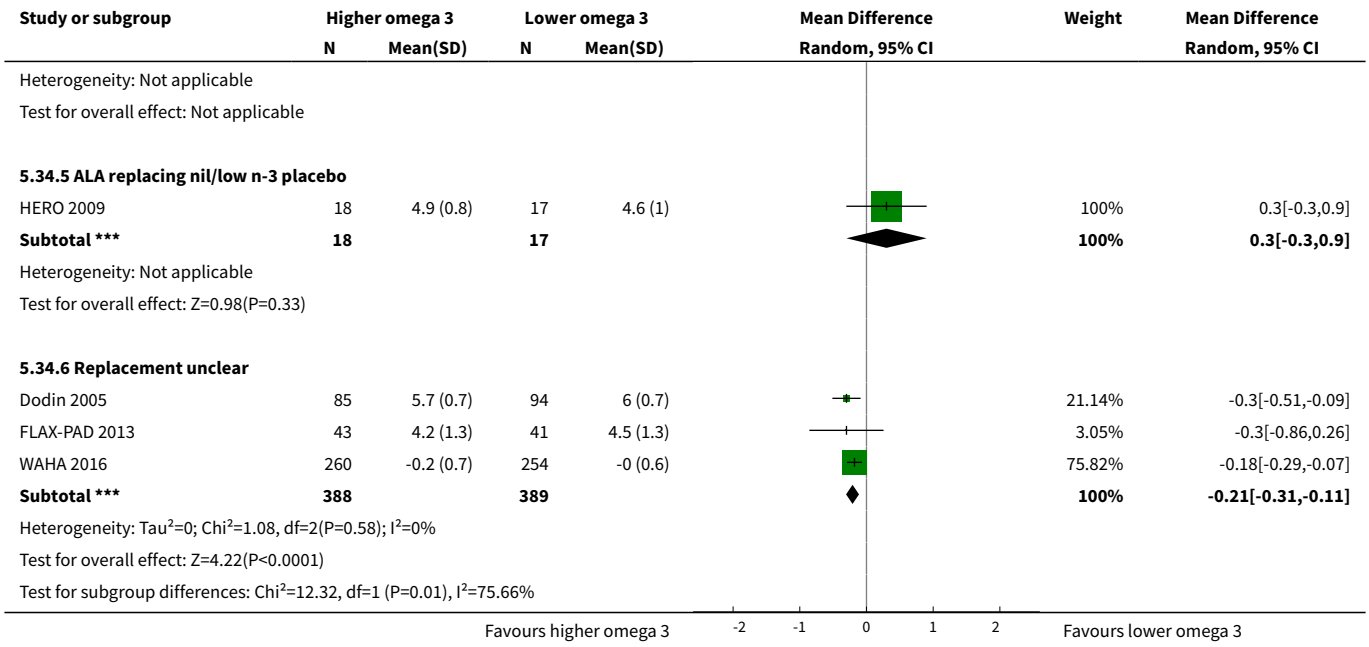
Analysis 5.33. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 33 TC, mmoL/L - ALA - subgroup by intervention type.





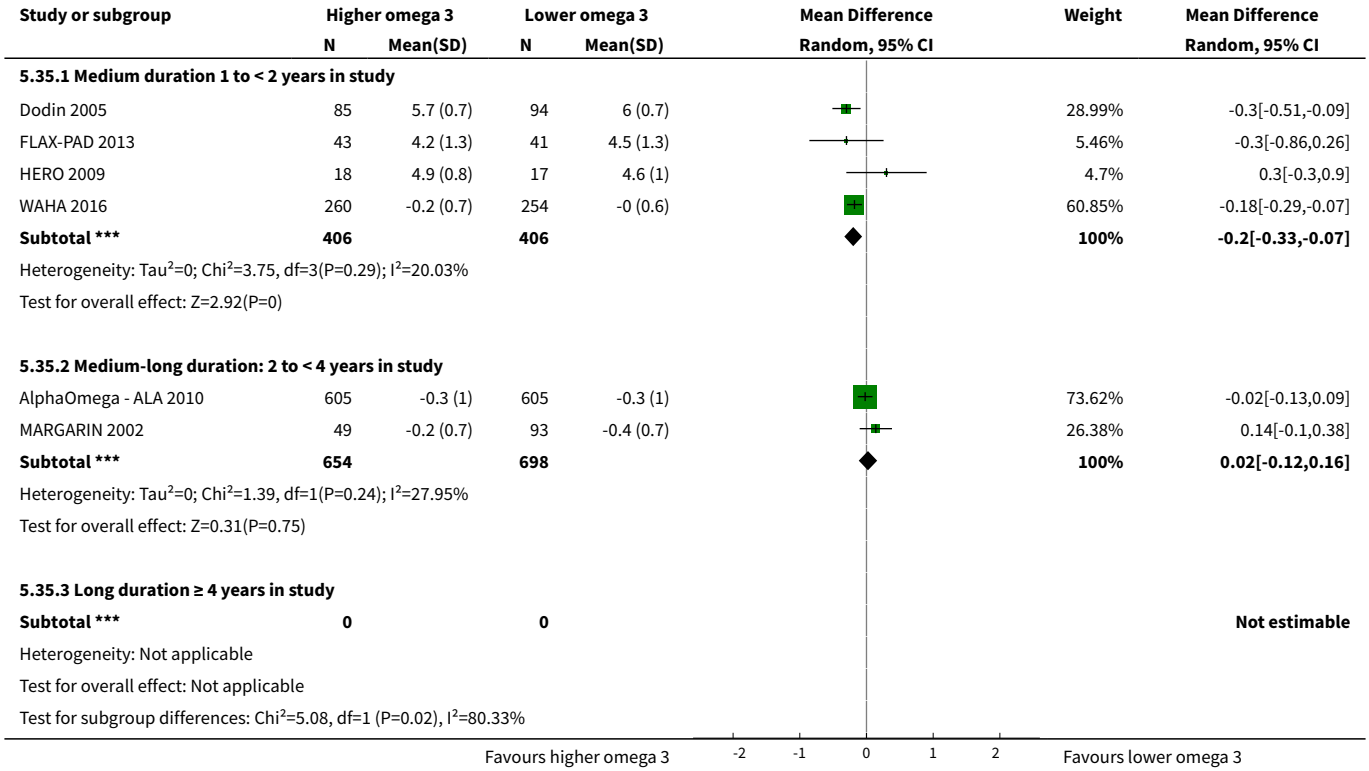
Analysis 5.34. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 34 TC, mmoL/L - ALA - subgroup by replacement.





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
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: Tau²=0; Chi²=1.08, df=2(P=0.58); I²=0%							
Test for overall effect: Z=4.22(P<0.0001)							
Test for subgroup differences: Chi²=12.32, df=1 (P=0.01), I²=75.66%							

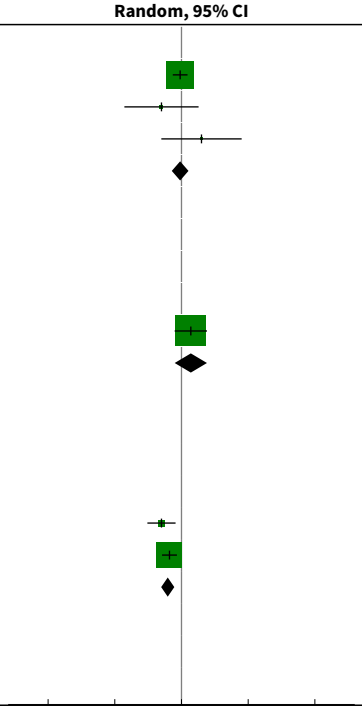
Analysis 5.35. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 35 TC, mmoL/L - ALA - subgroup by duration.



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: Tau²=0; Chi²=3.75, df=3(P=0.29); I²=20.03%							
Test for overall effect: Z=2.92(P=0)							
5.35.2 Medium-long duration: 2 to < 4 years in study							
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%							

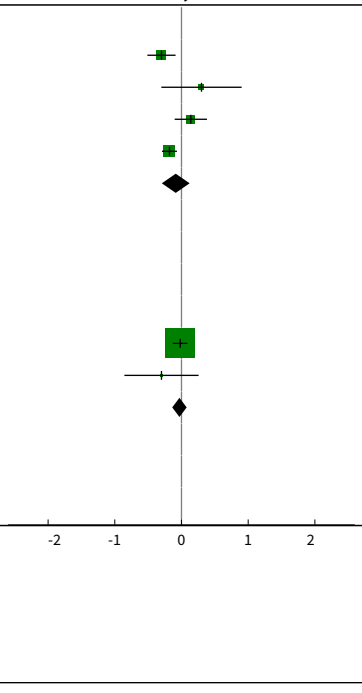
Analysis 5.36. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 36 TC, mmoL/L - ALA - subgroup by statin use.

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%							



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 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
5.37.1 Primary prevention of CVD							
Dodin 2005	85	5.7 (0.7)	94	6 (0.7)		28.51%	-0.3[-0.51,-0.09]
HERO 2009	18	4.9 (0.8)	17	4.6 (1)		9.26%	0.3[-0.3,0.9]
MARGARIN 2002	49	-0.2 (0.7)	93	-0.4 (0.7)		26.12%	0.14[-0.1,0.38]
WAHA 2016	260	-0.2 (0.7)	254	-0 (0.6)		36.11%	-0.18[-0.29,-0.07]
Subtotal ***	**412**		**458**			**100%**	**-0.09[-0.3,0.12]**
Heterogeneity: Tau²=0.03; Chi²=9.86, df=3(P=0.02); I²=69.59%							
Test for overall effect: Z=0.81(P=0.42)							
5.37.2 Secondary prevention of CVD							
AlphaOmega - ALA 2010	605	-0.3 (1)	605	-0.3 (1)		96.21%	-0.02[-0.13,0.09]
FLAX-PAD 2013	43	4.2 (1.3)	41	4.5 (1.3)		3.79%	-0.3[-0.86,0.26]
Subtotal ***	**648**		**646**			**100%**	**-0.03[-0.14,0.08]**
Heterogeneity: Tau²=0; Chi²=0.94, df=1(P=0.33); I²=0%							
Test for overall effect: Z=0.55(P=0.58)							
Test for subgroup differences: Chi²=0.21, df=1 (P=0.64), I²=0%							

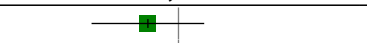


Analysis 5.38. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 38 Triglycerides, fasting, serum, mmoL/L - ALA.

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
AlphaOmega - ALA 2010	605	-0.1 (1)	605	-0 (1)		52.2%	-0.06[-0.17,0.05]
Dodin 2005	85	1.2 (0.5)	94	1.2 (0.7)		18.79%	-0.02[-0.2,0.16]
FLAX-PAD 2013	43	1.9 (0.9)	41	1.7 (0.7)		5.38%	0.2[-0.14,0.54]
HERO 2009	18	2.1 (1.3)	17	1.8 (0.7)		1.35%	0.3[-0.39,0.99]
MARGARIN 2002	49	0.2 (0.8)	93	0.1 (0.9)		7.61%	0.13[-0.16,0.42]
MENU 2016	65	1.1 (0.6)	61	1.3 (0.6)		14.67%	-0.12[-0.33,0.09]
Total ***	**865**		**911**			**100%**	**-0.03[-0.11,0.05]**
Heterogeneity: Tau^2=0; Chi^2=4.79, df=5(P=0.44); I^2=0%							
Test for overall effect: Z=0.69(P=0.49)							

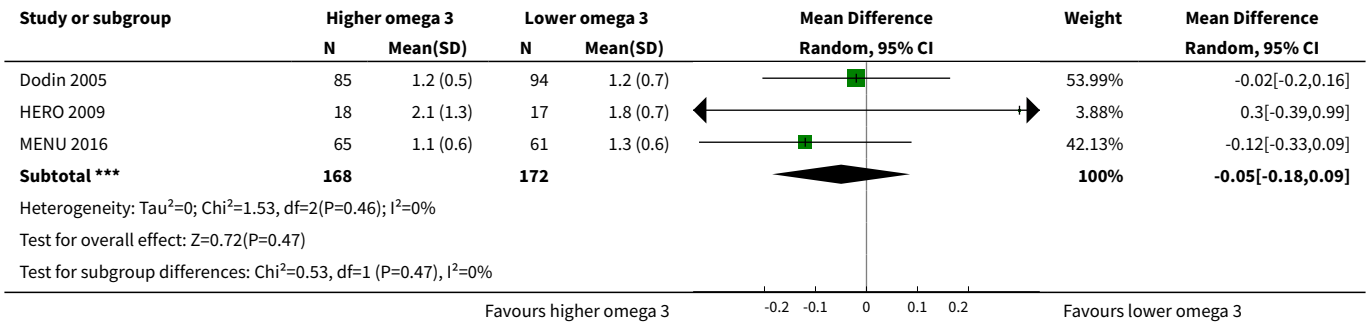
Analysis 5.39. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 39 TG, fasting, mmoL/L - ALA - SA fixed-effect.

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
AlphaOmega - ALA 2010	605	-0.1 (1)	605	-0 (1)		52.2%	-0.06[-0.17,0.05]
Dodin 2005	85	1.2 (0.5)	94	1.2 (0.7)		18.79%	-0.02[-0.2,0.16]
FLAX-PAD 2013	43	1.9 (0.9)	41	1.7 (0.7)		5.38%	0.2[-0.14,0.54]
HERO 2009	18	2.1 (1.3)	17	1.8 (0.7)		1.35%	0.3[-0.39,0.99]
MARGARIN 2002	49	0.2 (0.8)	93	0.1 (0.9)		7.61%	0.13[-0.16,0.42]
MENU 2016	65	1.1 (0.6)	61	1.3 (0.6)		14.67%	-0.12[-0.33,0.09]
Total ***	**865**		**911**			**100%**	**-0.03[-0.11,0.05]**
Heterogeneity: Tau^2=0; Chi^2=4.79, df=5(P=0.44); I^2=0%							
Test for overall effect: Z=0.69(P=0.49)							

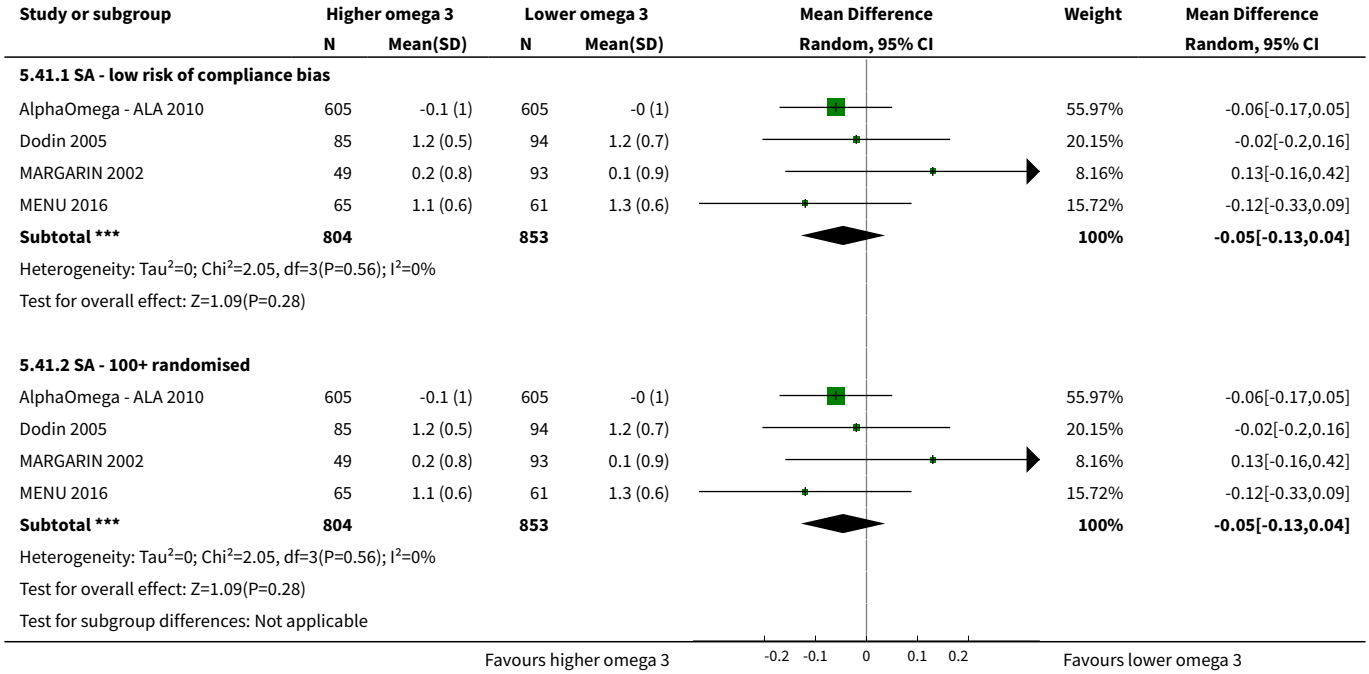


Analysis 5.40. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 40 TG, fasting, mmoL/L- ALA - SA by summary risk of bias.

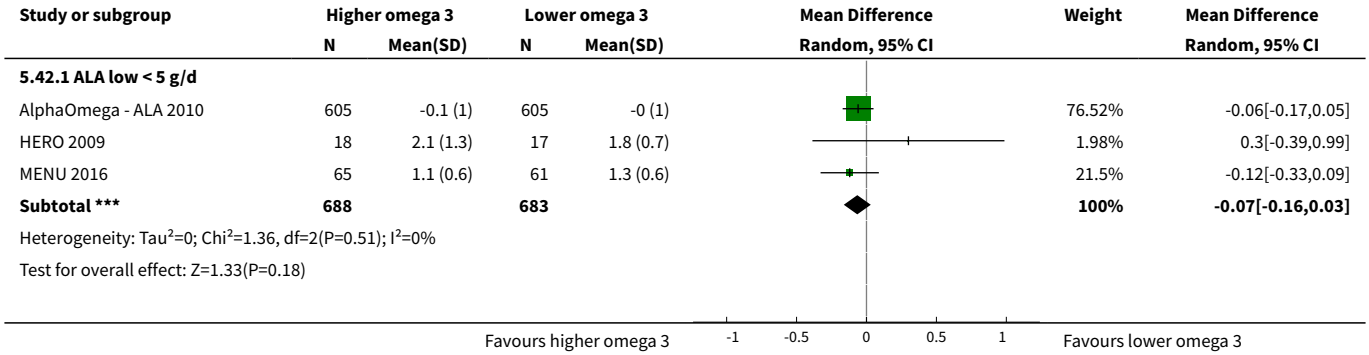
Study or subgroup	Higher omega 3 N	Mean(SD)	Lower omega 3 N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.40.1 Low risk of bias							
AlphaOmega - ALA 2010	605	-0.1 (1)	605	-0 (1)		59.71%	-0.06[-0.17,0.05]
FLAX-PAD 2013	43	1.9 (0.9)	41	1.7 (0.7)		17.52%	0.2[-0.14,0.54]
MARGARIN 2002	49	0.2 (0.8)	93	0.1 (0.9)		22.77%	0.13[-0.16,0.42]
Subtotal ***	**697**		**739**			**100%**	**0.03[-0.13,0.19]**
Heterogeneity: Tau^2=0.01; Chi^2=3.1, df=2(P=0.21); I^2=35.57%							
Test for overall effect: Z=0.35(P=0.73)							
5.40.2 Moderate/high risk of bias							

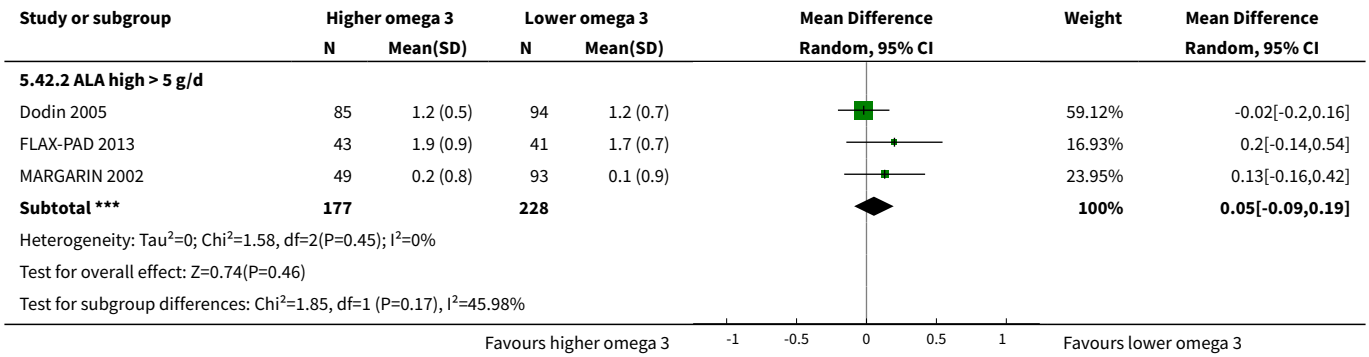


Analysis 5.41. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 41 TG, fasting, mmoL/L- ALA - SA by compliance and study size.

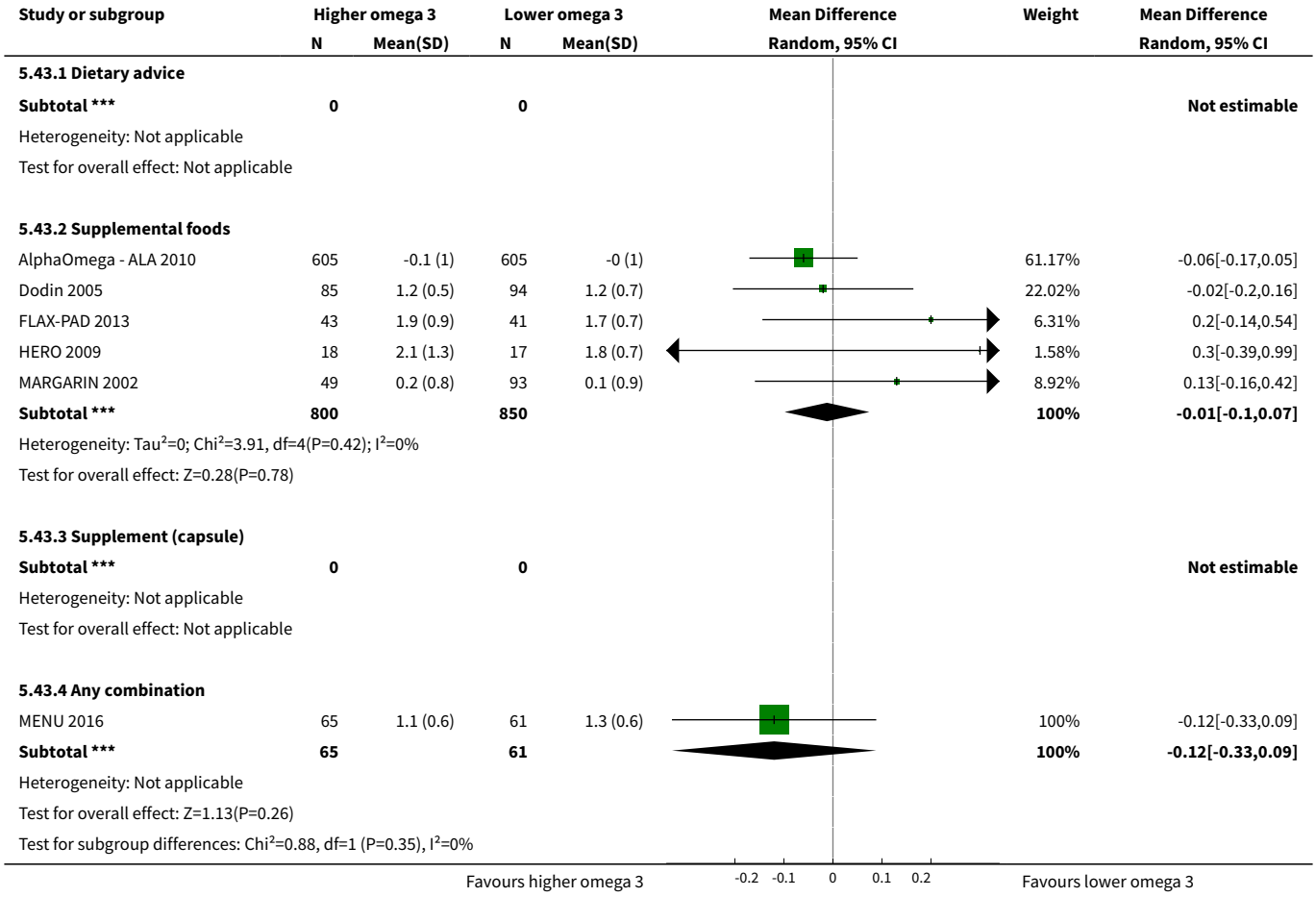


Analysis 5.42. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 42 TG, fasting, mmoL/L - ALA - subgroup by dose.





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.



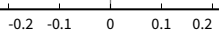
Analysis 5.44. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 44 TG, fasting, mmoL/L-AL - subgroup by replacementA.

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
5.44.1 ALA replacing SFA							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.44.2 ALA replacing MUFA							
AlphaOmega - ALA 2010	605	-0.1 (1)	605	-0 (1)		78.07%	-0.06[-0.17,0.05]
MENU 2016	65	1.1 (0.6)	61	1.3 (0.6)		21.93%	-0.12[-0.33,0.09]
Subtotal ***	**670**		**666**			**100%**	**-0.07[-0.17,0.02]**
Heterogeneity: Tau²=0; Chi²=0.25, df=1(P=0.62); I²=0%							
Test for overall effect: Z=1.47(P=0.14)							
5.44.3 ALA replacing n-6							
MARGARIN 2002	49	0.2 (0.8)	93	0.1 (0.9)		100%	0.13[-0.16,0.42]
Subtotal ***	**49**		**93**			**100%**	**0.13[-0.16,0.42]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.88(P=0.38)							
5.44.4 ALA replacing carbs/sugars							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.44.5 ALA replacing nil/low n-3 placebo							
HERO 2009	18	2.1 (1.3)	17	1.8 (0.7)		100%	0.3[-0.39,0.99]
Subtotal ***	**18**		**17**			**100%**	**0.3[-0.39,0.99]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.86(P=0.39)							
5.44.6 Replacement unclear							
Dodin 2005	85	1.2 (0.5)	94	1.2 (0.7)		72.7%	-0.02[-0.2,0.16]
FLAX-PAD 2013	43	1.9 (0.9)	41	1.7 (0.7)		27.3%	0.2[-0.14,0.54]
Subtotal ***	**128**		**135**			**100%**	**0.04[-0.15,0.23]**
Heterogeneity: Tau²=0; Chi²=1.22, df=1(P=0.27); I²=18.17%							
Test for overall effect: Z=0.41(P=0.68)							
Test for subgroup differences: Chi²=3.33, df=1 (P=0.34), I²=9.8%							

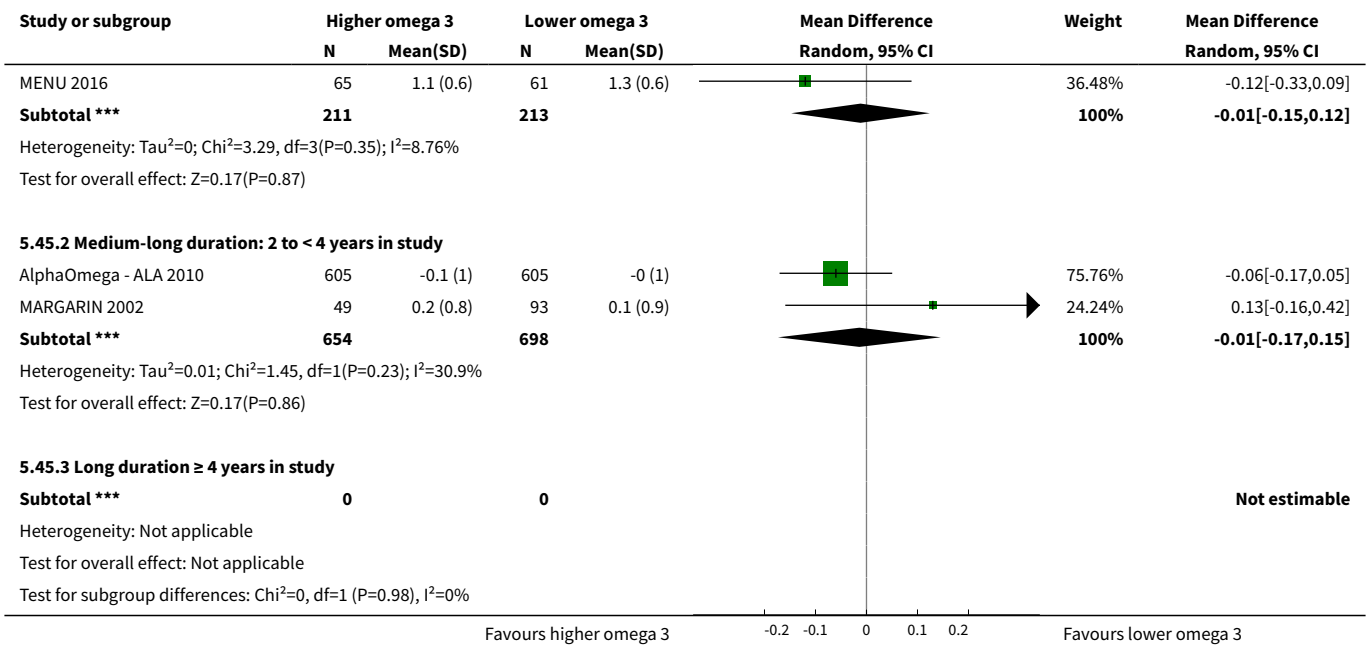
Favours higher omega 3 — Favours lower omega 3

Analysis 5.45. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 45 TG, fasting, mmoL/L- ALA - subgroup by duration.

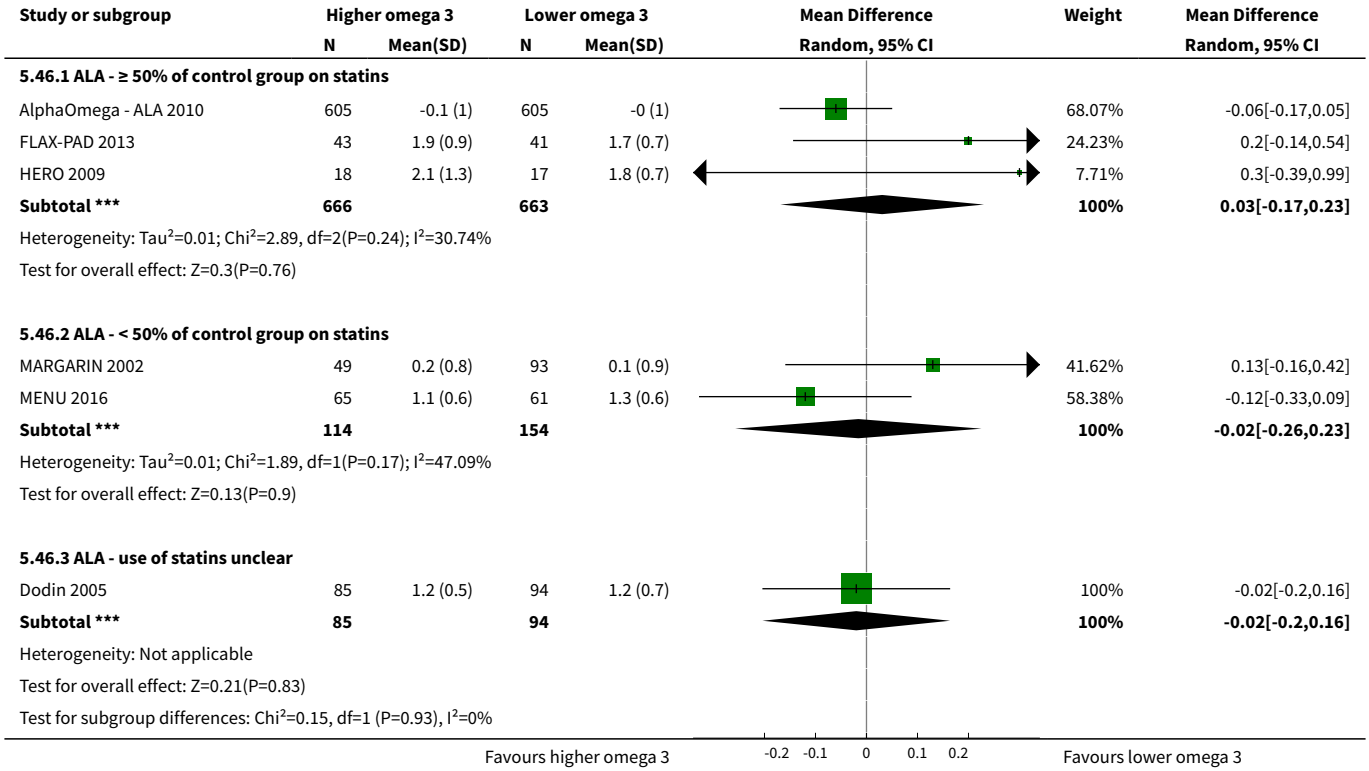
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.45.1 Medium duration 1 to < 2 years in study							
Dodin 2005	85	1.2 (0.5)	94	1.2 (0.7)		44.93%	-0.02[-0.2,0.16]
FLAX-PAD 2013	43	1.9 (0.9)	41	1.7 (0.7)		14.72%	0.2[-0.14,0.54]
HERO 2009	18	2.1 (1.3)	17	1.8 (0.7)		3.86%	0.3[-0.39,0.99]



Favours higher omega 3 — Favours lower omega 3

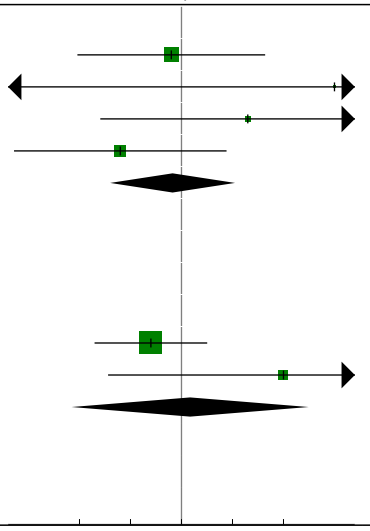


Analysis 5.46. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 46 TG, fasting, mmoL/L - ALA - subgroup by statin use.



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.

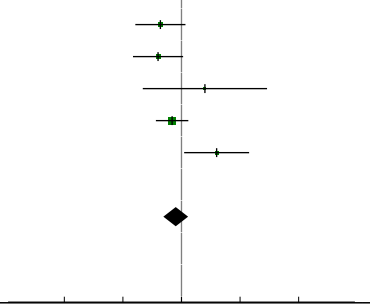
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.47.1 Primary prevention							
Dodin 2005	85	1.2 (0.5)	94	1.2 (0.7)		44.3%	-0.02[-0.2,0.16]
HERO 2009	18	2.1 (1.3)	17	1.8 (0.7)		3.18%	0.3[-0.39,0.99]
MARGARIN 2002	49	0.2 (0.8)	93	0.1 (0.9)		17.95%	0.13[-0.16,0.42]
MENU 2016	65	1.1 (0.6)	61	1.3 (0.6)		34.57%	-0.12[-0.33,0.09]
Subtotal ***	**217**		**265**			**100%**	**-0.02[-0.14,0.11]**
Heterogeneity: Tau^2=0; Chi^2=2.75, df=3(P=0.43); I^2=0%							
Test for overall effect: Z=0.28(P=0.78)							
5.47.2 Secondary prevention							
AlphaOmega - ALA 2010	605	-0.1 (1)	605	-0 (1)		70.42%	-0.06[-0.17,0.05]
FLAX-PAD 2013	43	1.9 (0.9)	41	1.7 (0.7)		29.58%	0.2[-0.14,0.54]
Subtotal ***	**648**		**646**			**100%**	**0.02[-0.22,0.25]**
Heterogeneity: Tau^2=0.02; Chi^2=1.99, df=1(P=0.16); I^2=49.76%							
Test for overall effect: Z=0.14(P=0.89)							
Test for subgroup differences: Chi^2=0.07, df=1 (P=0.8), I^2=0%							



Favours higher omega 3 — Favours lower omega 3

Analysis 5.48. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 48 High-density lipoprotein, serum, mmoL/L - ALA.

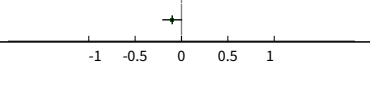
Study or subgroup	Favours lower omega 3 N	Favours lower omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
AlphaOmega - ALA 2010	605	0.1 (0.3)	605	0.2 (0.3)		33.71%	-0.02[-0.05,0.01]
Dodin 2005	85	1.7 (0.4)	94	1.8 (0.4)		14.75%	-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]



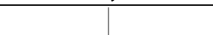
Favours higher omega 3 — Favours lower omega 3

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
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							
Dodin 2005	85	1.7 (0.4)	94	1.8 (0.4)		40.29%	-0.09[-0.2,0.02]
HERO 2009	18	1.5 (0.4)	17	1.4 (0.4)		23.05%	0.1[-0.17,0.37]
MENU 2016	65	1.7 (0.4)	61	1.6 (0.4)		36.67%	0.15[0.01,0.29]
Subtotal ***	**168**		**172**			**100%**	**0.04[-0.14,0.22]**
Heterogeneity: Tau^2=0.02; Chi^2=7.72, df=2(P=0.02); I^2=74.1%							
Test for overall effect: Z=0.46(P=0.65)							
Test for subgroup differences: Chi^2=0.59, df=1 (P=0.44), I^2=0%							

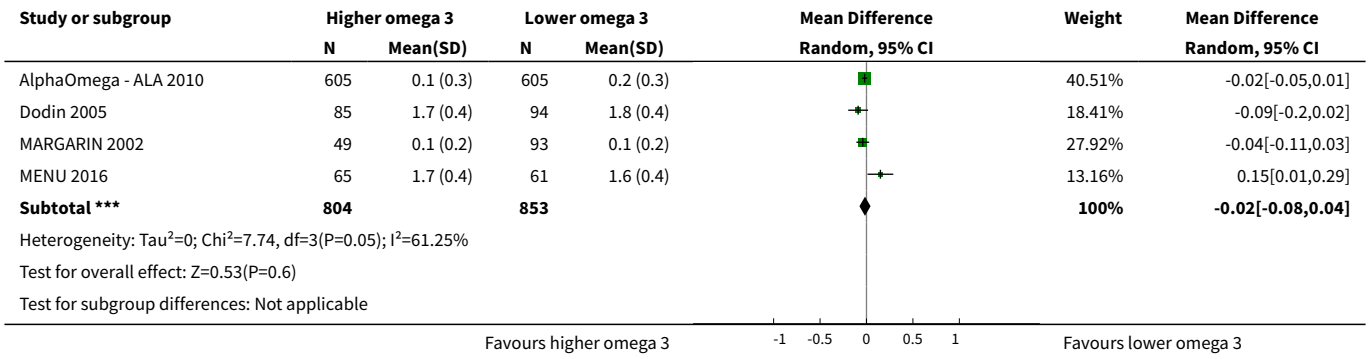


Favours higher omega 3 — Favours lower omega 3

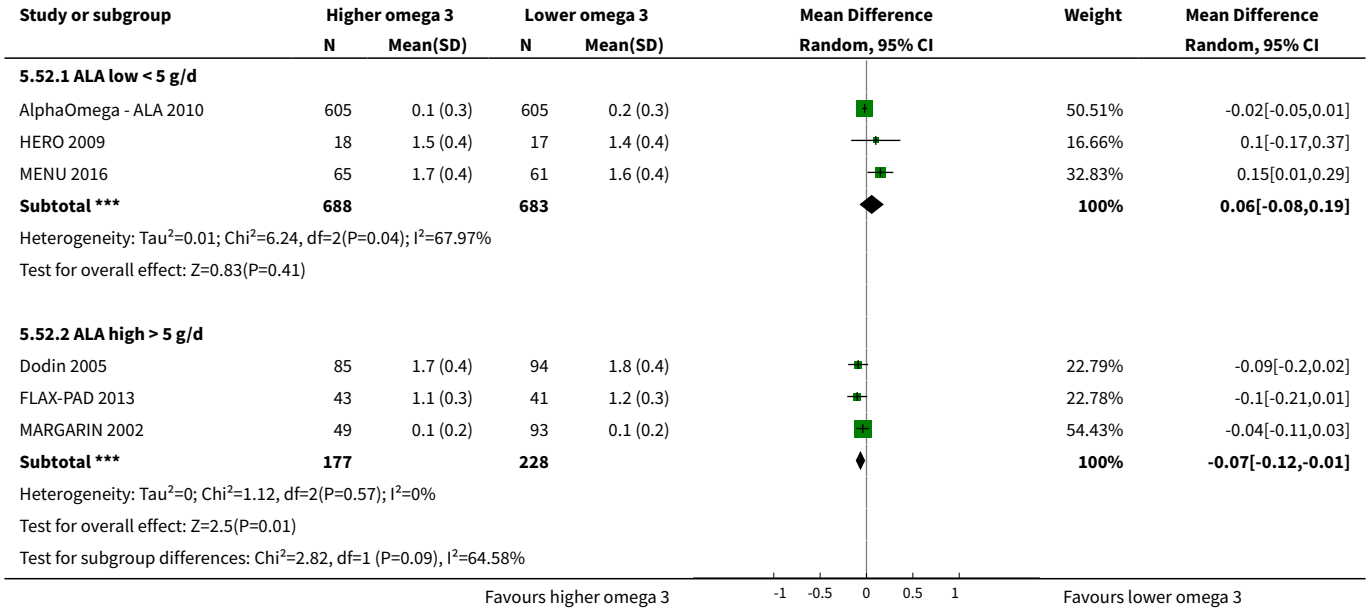
Analysis 5.51. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 51 HDL, mmoL/L - ALA - SA by compliance and study size.

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
5.51.1 SA - low risk of compliance bias							
AlphaOmega - ALA 2010	605	0.1 (0.3)	605	0.2 (0.3)		40.51%	-0.02[-0.05,0.01]
Dodin 2005	85	1.7 (0.4)	94	1.8 (0.4)		18.41%	-0.09[-0.2,0.02]
MARGARIN 2002	49	0.1 (0.2)	93	0.1 (0.2)		27.92%	-0.04[-0.11,0.03]
MENU 2016	65	1.7 (0.4)	61	1.6 (0.4)		13.16%	0.15[0.01,0.29]
Subtotal ***	**804**		**853**			**100%**	**-0.02[-0.08,0.04]**
Heterogeneity: Tau^2=0; Chi^2=7.74, df=3(P=0.05); I^2=61.25%							
Test for overall effect: Z=0.53(P=0.6)							
5.51.2 SA - 100+ randomised							

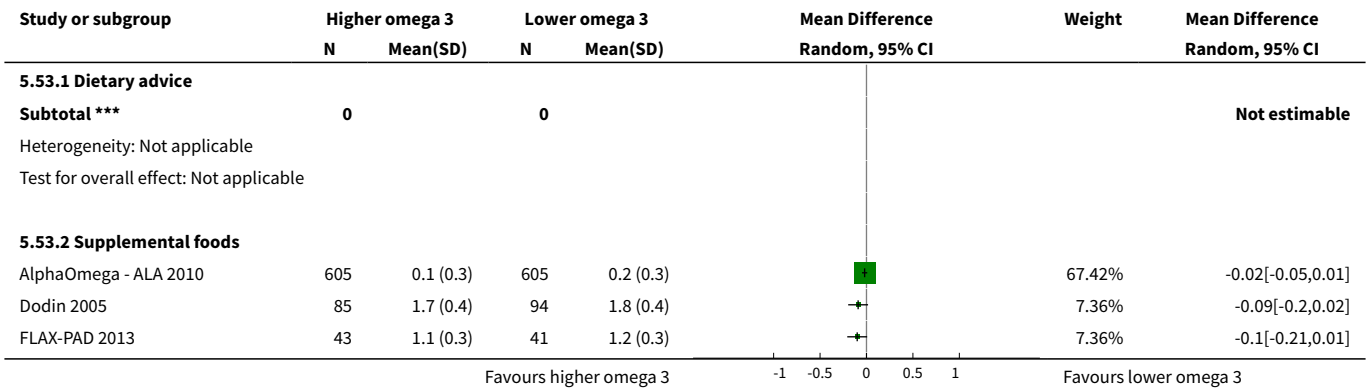
Favours higher omega 3 — Favours lower omega 3

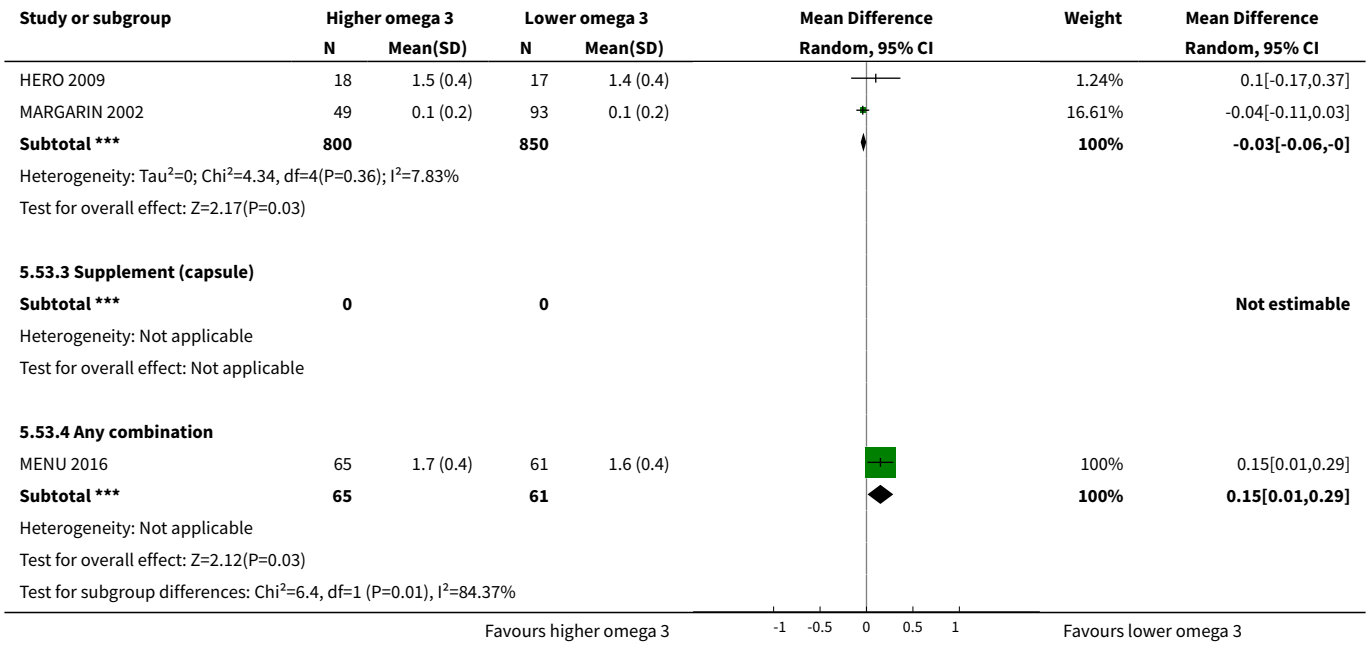


Analysis 5.52. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 52 HDL, mmoL/L - ALA - subgroup by dose.

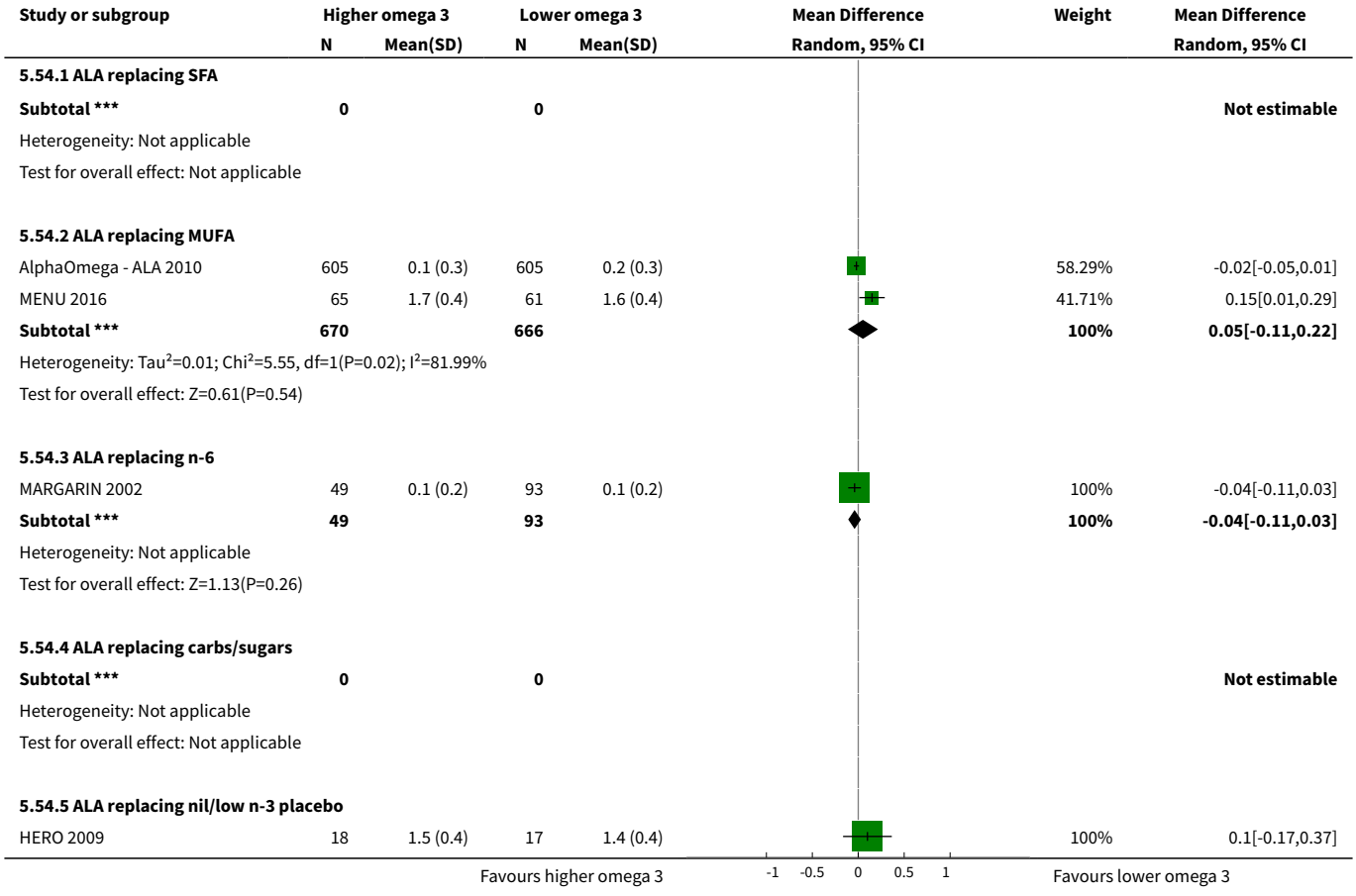


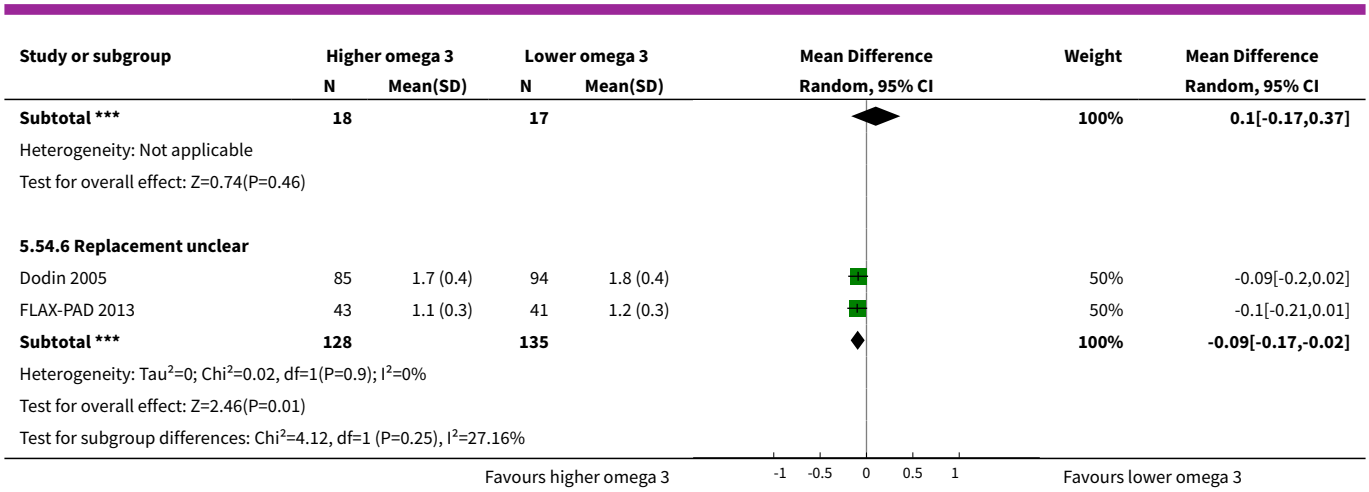
Analysis 5.53. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 53 HDL, mmoL/L - ALA - subgroup by intervention type.



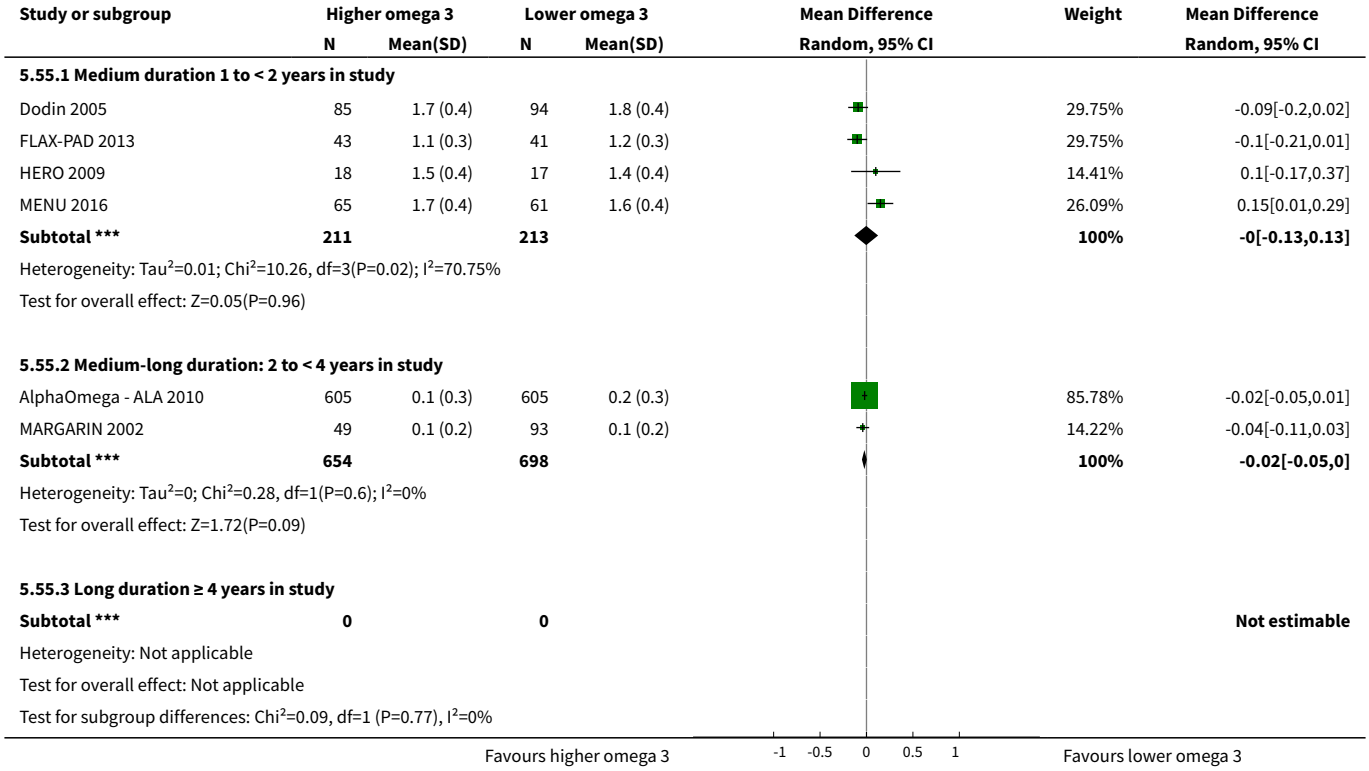


Analysis 5.54. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 54 HDL, mmoL/L - ALA - subgroup by replacement.

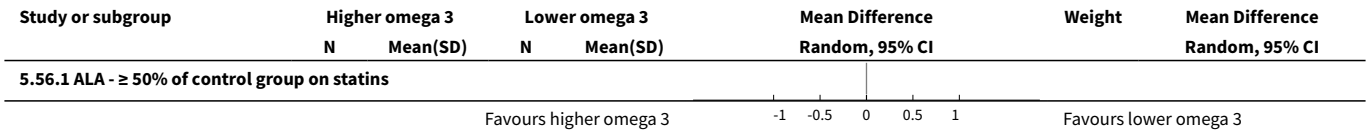




Analysis 5.55. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 55 HDL, mmoL/L - ALA - subgroup by duration.



Analysis 5.56. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 56 HDL, 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
AlphaOmega - ALA 2010	605	0.1 (0.3)	605	0.2 (0.3)		71.25%	-0.02[-0.05,0.01]
FLAX-PAD 2013	43	1.1 (0.3)	41	1.2 (0.3)		23.7%	-0.1[-0.21,0.01]
HERO 2009	18	1.5 (0.4)	17	1.4 (0.4)		5.05%	0.1[-0.17,0.37]
Subtotal ***	**666**		**663**			**100%**	**-0.03[-0.09,0.03]**
Heterogeneity: Tau²=0; Chi²=2.86, df=2(P=0.24); I²=30%							
Test for overall effect: Z=1.05(P=0.29)							
5.56.2 ALA - < 50% of control group on statins							
MARGARIN 2002	49	0.1 (0.2)	93	0.1 (0.2)		55.2%	-0.04[-0.11,0.03]
MENU 2016	65	1.7 (0.4)	61	1.6 (0.4)		44.8%	0.15[0.01,0.29]
Subtotal ***	**114**		**154**			**100%**	**0.05[-0.14,0.23]**
Heterogeneity: Tau²=0.01; Chi²=5.78, df=1(P=0.02); I²=82.7%							
Test for overall effect: Z=0.48(P=0.63)							
5.56.3 ALA - use of statins unclear							
Dodin 2005	85	1.7 (0.4)	94	1.8 (0.4)		100%	-0.09[-0.2,0.02]
Subtotal ***	**85**		**94**			**100%**	**-0.09[-0.2,0.02]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.65(P=0.1)							
Test for subgroup differences: Chi²=1.7, df=1 (P=0.43), I²=0%							

Favours higher omega 3 -1 -0.5 0 0.5 1 Favours lower omega 3

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: Tau²=0.02; Chi²=7.22, df=1(P=0.01); I²=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: Tau²=0; Chi²=1, df=1(P=0.32); I²=0.27%							
Test for overall effect: Z=0.9(P=0.37)							
5.57.3 High CVD risk							
Ahn 2016	38	1.2 (0.3)	36	1.1 (0.3)		12.61%	0.05[-0.1,0.2]
AlphaOmega - ALA 2010	605	0.1 (0.3)	605	0.2 (0.3)		66.69%	-0.02[-0.05,0.01]
FLAX-PAD 2013	43	1.1 (0.3)	41	1.2 (0.3)		20.7%	-0.1[-0.21,0.01]
Subtotal ***	**686**		**682**			**100%**	**-0.03[-0.08,0.03]**
Heterogeneity: Tau²=0; Chi²=2.99, df=2(P=0.22); I²=33.19%							
Test for overall effect: Z=0.96(P=0.34)							
Test for subgroup differences: Chi²=0.21, df=1 (P=0.9), I²=0%							

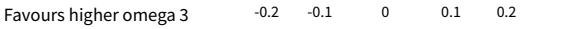
Favours higher omega 3 -1 -0.5 0 0.5 1 Favours lower omega 3

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)

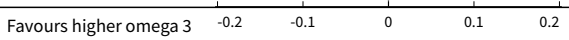


Analysis 5.59. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 59 LDL, mmoL/L - ALA - SA fixed-effect.

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%

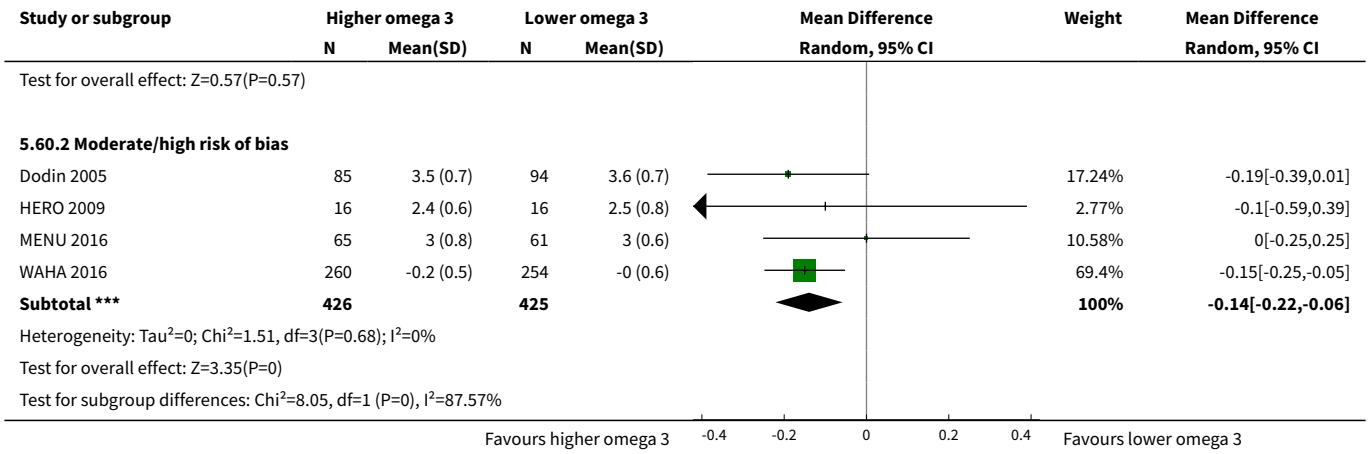
Test for overall effect: Z=1.88(P=0.06)



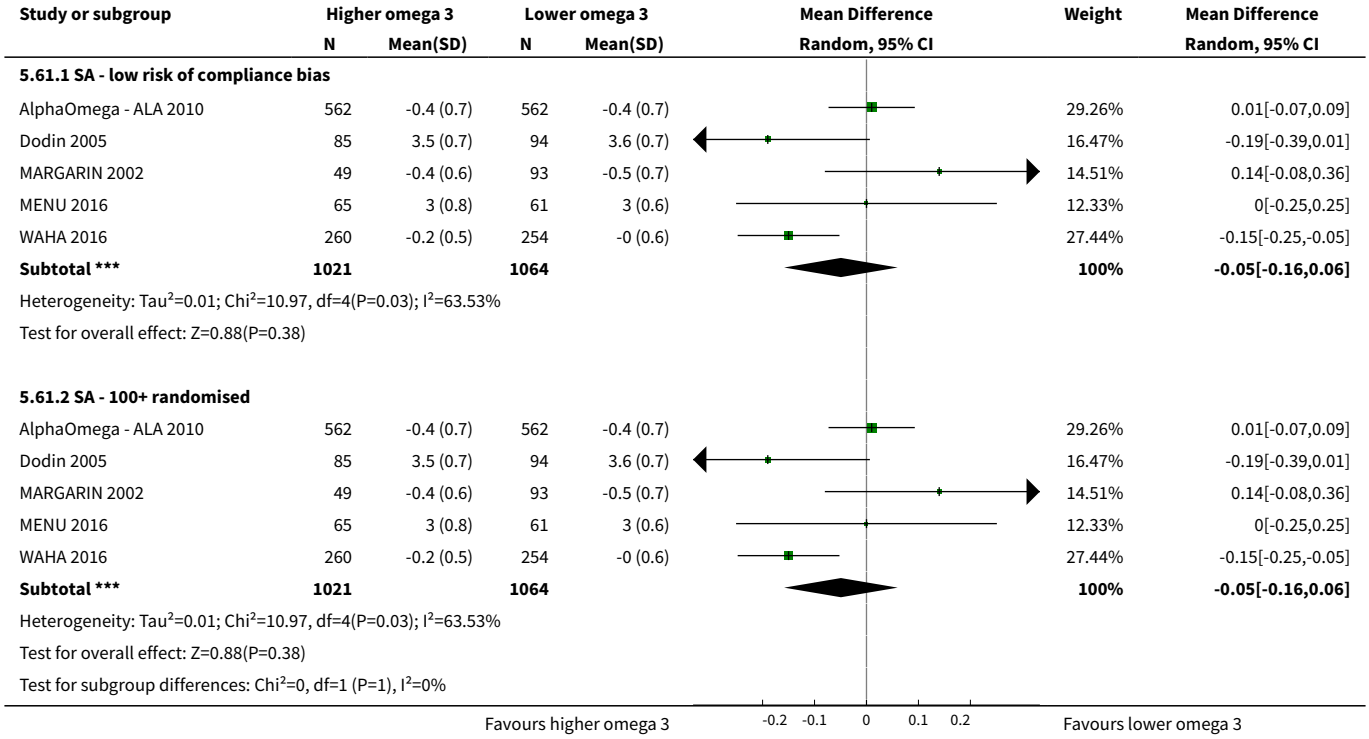
Analysis 5.60. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 60 LDL, mmoL/L - ALA - SA by summary risk of bias.

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]**

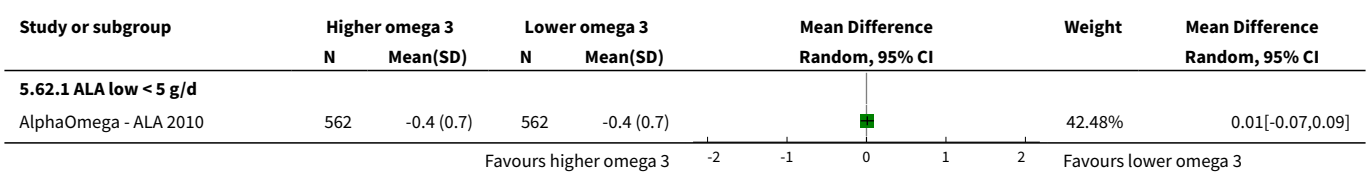
Heterogeneity: Tau^2=0; Chi^2=1.49, df=2(P=0.47); I^2=0%



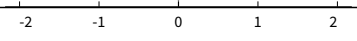
Analysis 5.61. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 61 LDL, mmoL/L - ALA - SA by compliance and study size.



Analysis 5.62. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 62 LDL, mmoL/L - ALA - subgroup by dose.



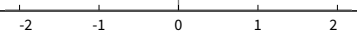
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
HERO 2009	16	2.4 (0.6)	16	2.5 (0.8)		4.57%	-0.1[-0.59,0.39]
MENU 2016	65	3 (0.8)	61	3 (0.6)		14.19%	0[-0.25,0.25]
WAHA 2016	260	-0.2 (0.5)	254	-0 (0.6)		38.75%	-0.15[-0.25,-0.05]
Subtotal ***	**903**		**893**			**100%**	**-0.06[-0.17,0.05]**
Heterogeneity: Tau^2=0.01; Chi^2=6.18, df=3(P=0.1); I^2=51.48%							
Test for overall effect: Z=1.05(P=0.29)							
5.62.2 ALA high > 5 g/d							
Dodin 2005	85	3.5 (0.7)	94	3.6 (0.7)		41.51%	-0.19[-0.39,0.01]
FLAX-PAD 2013	43	2.3 (1.1)	41	2.4 (0.9)		19.84%	-0.1[-0.53,0.33]
MARGARIN 2002	49	-0.4 (0.6)	93	-0.5 (0.7)		38.65%	0.14[-0.08,0.36]
Subtotal ***	**177**		**228**			**100%**	**-0.04[-0.28,0.19]**
Heterogeneity: Tau^2=0.02; Chi^2=4.86, df=2(P=0.09); I^2=58.87%							
Test for overall effect: Z=0.37(P=0.71)							
Test for subgroup differences: Chi^2=0.01, df=1 (P=0.92), I^2=0%							



Favours higher omega 3 — Favours lower omega 3

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%							



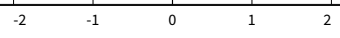
Favours higher omega 3 — Favours lower omega 3

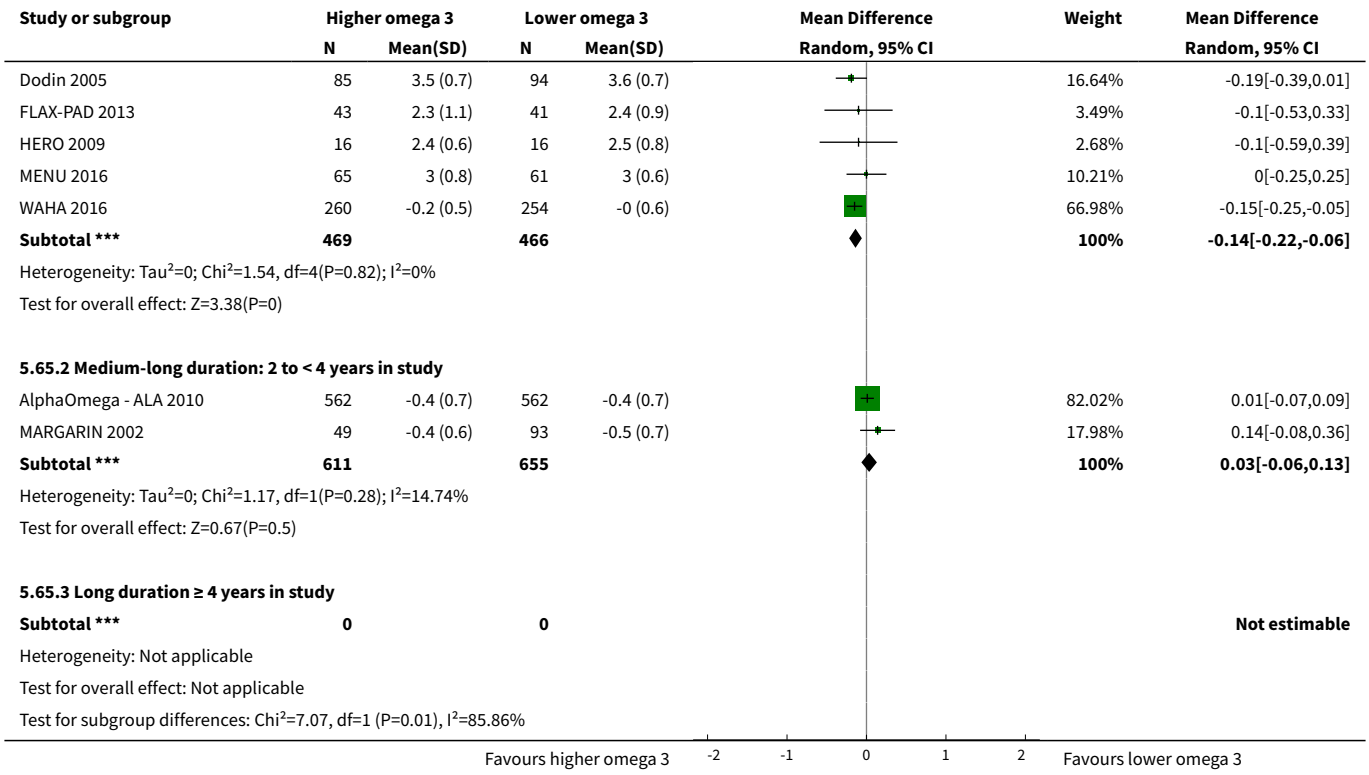
Analysis 5.64. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 64 LDL, mmoL/L - ALA - subgroup by replacement.

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							
MARGARIN 2002	49	-0.4 (0.6)	93	-0.5 (0.7)		100%	0.14[-0.08,0.36]
Subtotal * **	**49**		**93**			**100%**	**0.14[-0.08,0.36]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.25(P=0.21)							
5.64.4 ALA replacing carbs/sugars							
Subtotal * **	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.64.5 ALA replacing nil/low n-3 placebo							
HERO 2009	16	2.4 (0.6)	16	2.5 (0.8)		100%	-0.1[-0.59,0.39]
Subtotal * **	**16**		**16**			**100%**	**-0.1[-0.59,0.39]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.4(P=0.69)							
5.64.6 Replacement unclear							
Dodin 2005	85	3.5 (0.7)	94	3.6 (0.7)		19.1%	-0.19[-0.39,0.01]
FLAX-PAD 2013	43	2.3 (1.1)	41	2.4 (0.9)		4.01%	-0.1[-0.53,0.33]
WAHA 2016	260	-0.2 (0.5)	254	-0 (0.6)		76.89%	-0.15[-0.25,-0.05]
Subtotal * **	**388**		**389**			**100%**	**-0.16[-0.24,-0.07]**
Heterogeneity: Tau^2=0; Chi^2=0.19, df=2(P=0.91); I^2=0%							
Test for overall effect: Z=3.55(P=0)							
Test for subgroup differences: Chi^2=10.85, df=1 (P=0.01), I^2=72.35%							

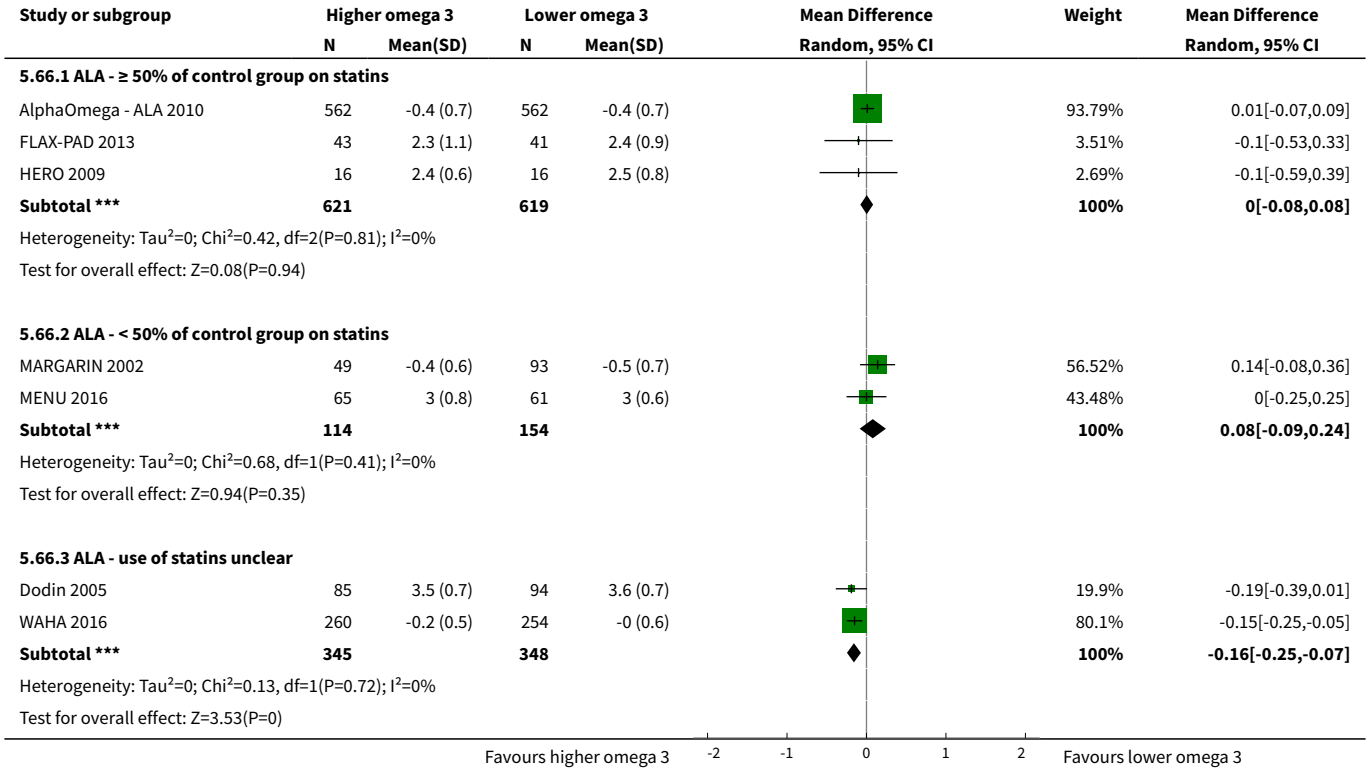
Analysis 5.65. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 65 LDL, mmoL/L - ALA - subgroup by duration.

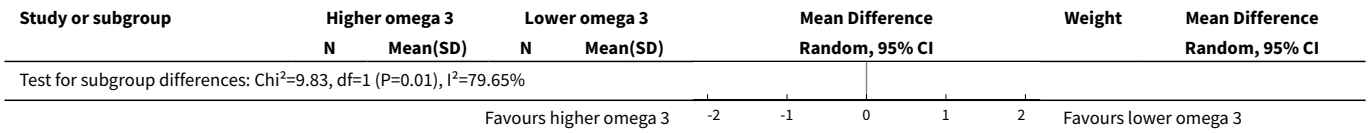
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.65.1 Medium duration 1 to < 2 years in study							



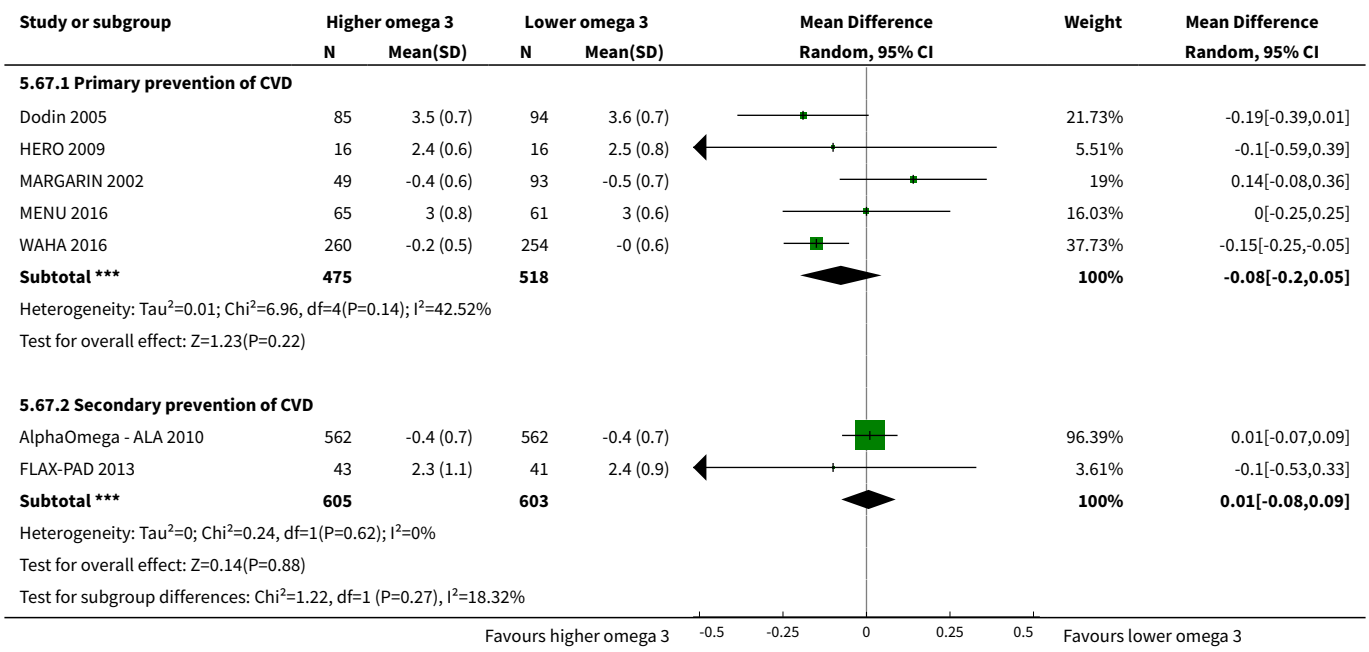


Analysis 5.66. Comparison 5 High vs low ALA omega-3 fat (secondary outcomes), Outcome 66 LDL, mmoL/L - ALA - subgroup by statin use.





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.



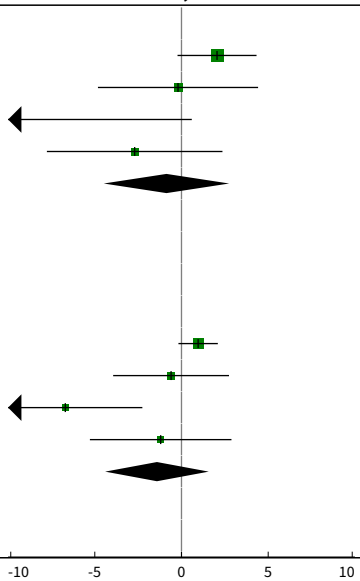
Comparison 6. High vs low ALA omega-3 fats (tertiary outcomes)

Outcome or subgroup title	No. of studies	No. of partici-pants	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 GI hospitalisation	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

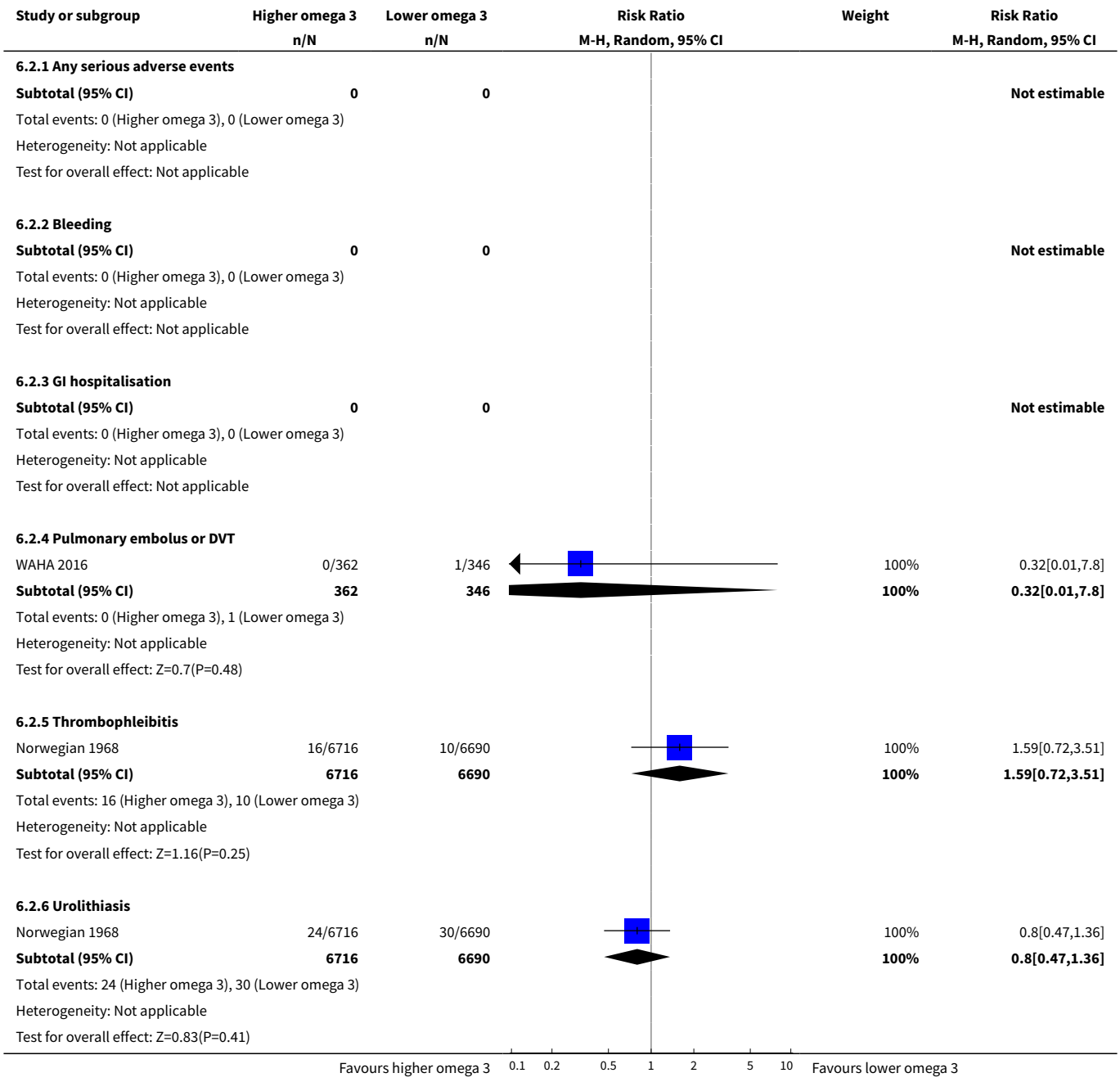
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.4 Pulmonary embolus or DVT	1	708	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.80]
2.5 Thrombophleibitis	1	13406	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.72, 3.51]
2.6 Urolithiasis	1	13406	Risk Ratio (M-H, 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]

Analysis 6.1. Comparison 6 High vs low ALA omega-3 fats (tertiary outcomes), Outcome 1 Blood pressure, mmHg - ALA.

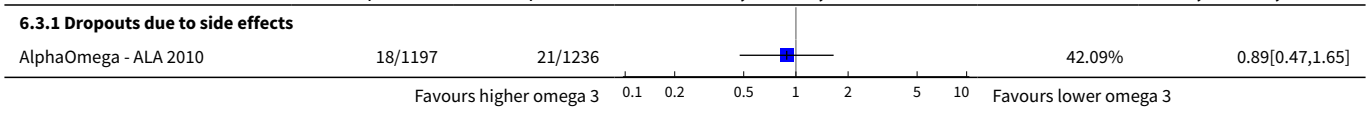
Study or subgroup	Higher omega 3 N	Higher omega 3 Mean(SD)	Lower omega 3 N	Lower omega 3 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
6.1.1 Systolic BP - ALA							
AlphaOmega - ALA 2010	632	-0.2 (20)	632	-2.3 (21.3)		39.11%	2.05[-0.23,4.33]
Dodin 2005	85	120.6 (14.4)	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)							

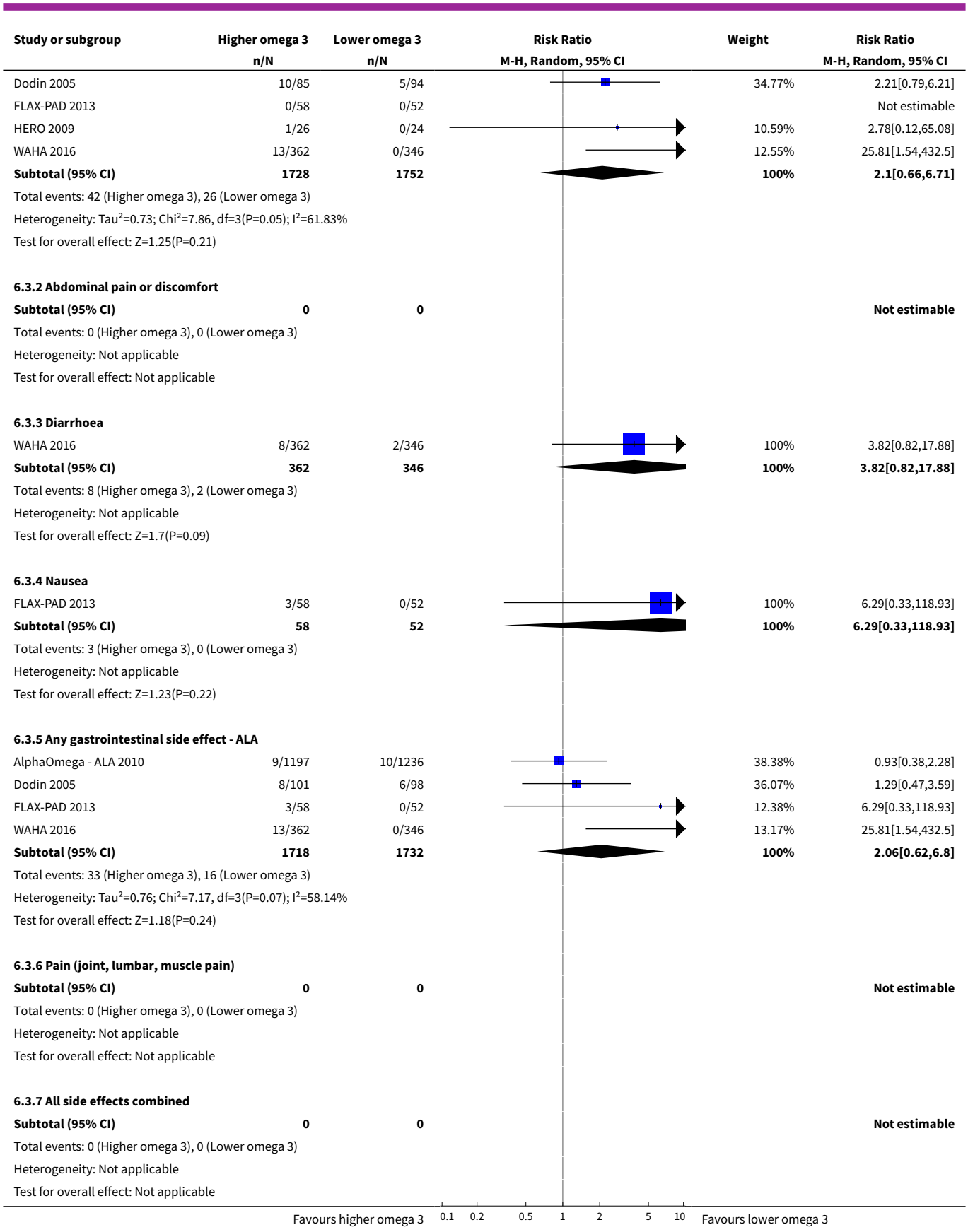


Analysis 6.2. Comparison 6 High vs low ALA omega-3 fats (tertiary outcomes), Outcome 2 Serious adverse events - ALA.



Analysis 6.3. Comparison 6 High vs low ALA omega-3 fats (tertiary outcomes), Outcome 3 Side effects - ALA.

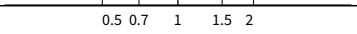




Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Dodin 2005	10/85	5/94		34.77%	2.21[0.79,6.21]
FLAX-PAD 2013	0/58	0/52			Not estimable
HERO 2009	1/26	0/24		10.59%	2.78[0.12,65.08]
WAHA 2016	13/362	0/346		12.55%	25.81[1.54,432.5]
Subtotal (95% CI)	**1728**	**1752**		**100%**	**2.1[0.66,6.71]**
Total events: 42 (Higher omega 3), 26 (Lower omega 3)					
Heterogeneity: Tau²=0.73; Chi²=7.86, df=3(P=0.05); I²=61.83%					
Test for overall effect: Z=1.25(P=0.21)					
6.3.2 Abdominal pain or discomfort					
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					
6.3.3 Diarrhoea					
WAHA 2016	8/362	2/346		100%	3.82[0.82,17.88]
Subtotal (95% CI)	**362**	**346**		**100%**	**3.82[0.82,17.88]**
Total events: 8 (Higher omega 3), 2 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.7(P=0.09)					
6.3.4 Nausea					
FLAX-PAD 2013	3/58	0/52		100%	6.29[0.33,118.93]
Subtotal (95% CI)	**58**	**52**		**100%**	**6.29[0.33,118.93]**
Total events: 3 (Higher omega 3), 0 (Lower omega 3)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.23(P=0.22)					
6.3.5 Any gastrointestinal side effect - ALA					
AlphaOmega - ALA 2010	9/1197	10/1236		38.38%	0.93[0.38,2.28]
Dodin 2005	8/101	6/98		36.07%	1.29[0.47,3.59]
FLAX-PAD 2013	3/58	0/52		12.38%	6.29[0.33,118.93]
WAHA 2016	13/362	0/346		13.17%	25.81[1.54,432.5]
Subtotal (95% CI)	**1718**	**1732**		**100%**	**2.06[0.62,6.8]**
Total events: 33 (Higher omega 3), 16 (Lower omega 3)					
Heterogeneity: Tau²=0.76; Chi²=7.17, df=3(P=0.07); I²=58.14%					
Test for overall effect: Z=1.18(P=0.24)					
6.3.6 Pain (joint, lumbar, muscle pain)					
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					
6.3.7 All side effects combined					
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					

Analysis 6.4. Comparison 6 High vs low ALA omega-3 fats (tertiary outcomes), Outcome 4 Dropouts - 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
AlphaOmega - ALA 2010	189/1197	191/1236		68.26%	1.02[0.85,1.23]
Dodin 2005	26/101	17/98		7.86%	1.48[0.86,2.56]
FLAX-PAD 2013	15/58	11/52		5.01%	1.22[0.62,2.42]
HERO 2009	7/26	5/24		2.31%	1.29[0.47,3.53]
MENU 2016	13/82	12/81		4.47%	1.07[0.52,2.2]
WAHA 2016	38/362	34/346		12.11%	1.07[0.69,1.66]
Total (95% CI)	**1826**	**1837**		**100%**	**1.08[0.92,1.25]**
Total events: 288 (Higher omega 3), 270 (Lower omega 3)					
Heterogeneity: Tau^2=0; Chi^2=1.9, df=5(P=0.86); I^2=0%					
Test for overall effect: Z=0.93(P=0.35)					



ADDITIONAL TABLES

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 study authors needed to have described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. For example "the 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 study authors have not described their method in sufficient detail for the assessment of whether it would produce comparable groups. For example, the authors state "the trial was randomised" and provide no further information.	The randomisation method was assessed as not truly random, and may not produce comparable groups.
Selection bias: allocation concealment	The study 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	The authors gave insufficient detail as to method.	The allocation was known in advance of participants consenting to take part in the study.

Table 1. Risk of bias assessment methods in greater detail *(Continued)*

	random number that links to a specific set of capsules prepared and distributed centrally or by an arms-length pharmacist.		
Performance bias: blinding of participants and personnel	The study authors needed to have described all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Ideally, they should also have provided information relating to whether the intended blinding was effective. For example, the authors could say "both the intervention and placebo capsules looked and tasted the same." However, if the study authors did not provide information on whether the blinding was effective, but sufficient detail was given on a good method of blinding, then it was assumed that the blinding was effective and the risk of bias was low.	Insufficient methodological details were provided e.g. "the study was blinded."	The study was unblinded or where blinding was broken, e.g. "the capsules were visually identical but the participants reported a strong fishy flavour in the intervention group only."
Detection bias: blinding of outcome assessment	Study 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 study authors did not provide information on whether the blinding was effective, but sufficient detail was given on a good method of blinding of the assessors, then it was assumed that the blinding was effective and the risk of bias is low. All biochemical assessment (lipids, glucose, CRP, insulin, PSA, etc.) were considered at low risk of detection bias if outcome assessor blinding or double blinding was stated.	Insufficient methodological details were provided e.g. "the study was blinded."	The study 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 higher risk of bias but noted that that risk of bias was lower for other outcomes.
Attrition bias: incomplete outcome data	The study authors needed to describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. They needed to report the number of 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 study 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 study arm.	The authors demonstrated a substantial difference in the rates of attrition/exclusions between the study arms and/or > 20% of the baseline sample was lost over a year (> 10% over 6 months).
Reporting bias: selective outcome reporting	The study authors needed to have published their trial protocol or trials registry entry before the end of the study's recruitment period i.e. prospectively. They needed to have reported on all of the primary and secondary outcomes listed in the protocol/registry entry. Reporting additional secondary outcomes in the results paper(s), although not ideal, was deemed 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 recruit-	The study 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.

Table 1. Risk of bias assessment methods in greater detail *(Continued)*

		ment were unclear.	
Other sources of bias: attention bias	The study authors needed to have reported that participants in all study 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 study only differed by the content of the capsules, and the assessment schedule was not stated to differ between the two arms, it was assumed 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 study authors needed to have reported on the level of compliance in all arms in sufficient detail to determine whether the study 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 text 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 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 study 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	0.61
ALA dose	0.91
Omega-6 dose	0.81
Total PUFA dose	0.82
Duration, months	0.68

Table 2. Meta-regression results for cardiovascular mortality[a] *(Continued)*

Primary or secondary CVD prevention	0.88
Food or capsule	0.54
Risk of bias	0.94
Food or capsule	0.70
+ LCn3 dose	0.96
+ duration	0.69

ALA: alpha-linolenic acid; **CVD**: cardiovascular disease; **LCn3**: long-chain omega-3 fatty acids; **PUFA**: poly-unsaturated fatty acids.
[a]Random-effects meta-regression exploring effects of LCn3 dose, ALA dose, omega-6 dose, total PUFA dose, study 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 (update of Hooper 2018, and Abdelhamid 2018). 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
LCn3 dose	0.91
ALA dose	0.70
omega-6 dose	0.34
Total PUFA dose	0.34
Duration, months	0.62
Primary or secondary CVD prevention	0.78
Food or capsule	0.83
Risk of bias	0.24
Risk of bias	0.25
+ PUFA dose	0.87
+ Omega-6 dose	0.83

ALA: alpha-linolenic acid; **CVD**: cardiovascular disease; **LCn3**: long-chain omega-3 fatty acids; **PUFA**: poly-unsaturated fatty acids.
[a]Random-effects meta-regression exploring effects of LCn3 dose, ALA dose, omega-6 dose, total PUFA dose, study 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 (update of Hooper 2018, and Abdelhamid 2018). 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 CHD deaths[a]

Variable assessed	P value
LCn3 dose	0.94
ALA dose	0.93
Omega-6 dose	0.66
Total PUFA dose	0.64
Duration, months	0.41
Primary or secondary CVD prevention	0.63
Food or capsule	0.78
Risk of bias	0.89
Duration	0.73
+ Primary or secondary prevention	0.90
+ PUFA dose	0.76

ALA: alpha-linolenic acid; **CVD**: cardiovascular disease; **LCn3**: long-chain omega-3 fatty acids; **PUFA**: poly-unsaturated fatty acids.
[a]Random-effects meta-regression exploring effects of LCn3 dose, ALA dose, omega-6 dose, total PUFA dose, study duration, primary or secondary prevention, food or capsule intervention, and summary risk of bias (low or moderate to high) on CHD mortality. We ran the meta-regression using all included trials that reported this outcome in this review, and its sister reviews (update of Hooper 2018, and Abdelhamid 2018). 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 CHD events[a]

Variable assessed	P value
LCn3 dose	0.68
ALA dose	0.23
Omega-6 dose	0.84
Total PUFA dose	0.79
Duration, months	0.87
Primary or secondary CVD prevention	0.42
Food or capsule	0.91
Risk of bias	0.98
ALA dose	0.32
+ Prim or sec prev	0.46

Table 5. Metaregression results for CHD events[a] *(Continued)*

+ LCn3 dose	0.86

ALA: alpha-linolenic acid; **CVD**: cardiovascular disease; **LCn3**: long-chain omega-3 fatty acids; **PUFA**: poly-unsaturated fatty acids.
[a]Random-effects meta-regression exploring effects of LCn3 dose, ALA dose, omega-6 dose, total PUFA dose, study 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 (update of Hooper 2018, and Abdelhamid 2018). 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
LCn3 dose	0.42	—
ALA dose	0.81	—
Omega-6 dose	0.19	—
Total PUFA dose	0.21	—
Duration, months	0.012	Negative (greater effect with shorter duration)
Primary or secondary CVD prevention	0.04	Positive (greater effect with secondary prevention)
Food or capsule	0.21	—
Risk of bias	0.25	—
Duration	0.21	—
+ primary or secondary prevention	0.67	
+ omega-6	0.38	

ALA: alpha-linolenic acid; **CVD**: cardiovascular disease; **LCn3**: long-chain omega-3 fatty acids; **PUFA**: poly-unsaturated fatty acids.
[a]Random-effects meta-regression exploring effects of LCn3 dose, ALA dose, omega-6 dose, total PUFA dose, study 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 (update of Hooper 2018, and Abdelhamid 2018). 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 arrhythmias[a]

Variable assessed	P value	Coefficient sign where P < 0.10
LCn3 dose	0.06	Negative (greater effect at lower dose)
ALA dose	0.67	—
Omega-6 dose	0.59	—

Table 7. Meta-regression results for arrhythmias[a] *(Continued)*

Total PUFA dose	0.54	—
Duration, months	0.16	—
Primary or secondary CVD prevention	0.07	Negative (greater effect with primary prevention)
Food or capsule	0.82	—
Risk of bias	0.51	—
LCn3 dose	0.09	—
+ Primary secondary prevention	0.12	
+ duration	0.46	

ALA: alpha-linolenic acid; **CVD**: cardiovascular disease; **LCn3**: long-chain omega-3 fatty acids; **PUFA**: poly-unsaturated fatty acids.
[a]Random-effects meta-regression exploring effects of LCn3 dose, ALA dose, omega-6 dose, total PUFA dose, study 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 (update of Hooper 2018, and Abdelhamid 2018). 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 8. Comparison of the results of LCn3 interventions in this review with Balk 2016 and Aung 2018[a] *(Continued)*

	Balk 2016		Aung 2018		**This review**	
	No. of people experiencing events	**RR (95% CI)**	**No, of people experiencing events**	**RR (95% CI)**	**No. of people experiencing events**	**RR (95% CI)**
All-cause mortality	8480	0.97 (0.92 to 1.03)	—	Not assessed	8647	0.98 (0.93 to 1.03)
Cardiovascular deaths	3799	0.92 (0.82 to 1.02)	—	Not assessed	4763	0.95 (0.87 to 1.03)
CVD events (MACCEs in Balk 2016)	8085	0.96 (0.91 to 1.02)	12001	0.97 (0.93 to 1.01)	15614	0.99 (0.94 to 1.04)
CHD deaths	—	Not pooled	2695	0.93, (0.83 to 1.03)	1791	0.93 (0.79 to 1.09)
CHD events	—	Not assessed	6273	0.96, (0.90 to 1.01)	5865	0.93 (0.88 to 0.97)
Stroke	1467	0.98 (0.88 to 1.09)	1713	1.03 (0.93 to 1.13)	1871	1.06 (0.96, 1.16)
Arrhythmia	—	Not pooled	—	Not assessed	3788	0.97 (0.90 to 1.05)

CHD: coronary heart disease; **CI**: confidence interval; **CVD**: cardiovascular disease; **MACCE**: major adverse cerebrovascular or cardiovascular event; **RR**: risk ratio.
[a]Meta-analysis of effects of LCn3 in Balk 2016 and Aung 2018 systematic reviews, comparing their findings with our findings for our primary outcomes.

APPENDICES

Appendix 1. Medline (Ovid) search strategy run in 2002 for the previous version of this review.

1 exp Fish Oils/
2 exp Linseed Oil/
3 linolenic acids/ or exp alpha-linolenic acid/
4 exp Fatty Acids, Omega-3/
5 (fish adj5 (diet$ or nutrit$ or oil$ or supplement$)).tw.
6 (oil$ adj3 (cod$ or marin$ or rapeseed$ or canola$)).tw.
7 (omega-3 or omega3).tw.
8 (eicosapentaen$ or icosapentaen$).tw.
9 docosahexaen$.tw.
10 (Linolen$ or alpha-linolen$ or alphalinolen$).tw.
11 (maxepa$ or omacor$).tw.
12 (trout or kipper$ or salmon or mackerel$ or tuna or tunafish or sardine$ or pilchard$ or herring$).tw.
13 flax$.tw.
14 rapeseed$.tw.
15 canola$.tw.
16 alphalinolen$.tw.
17 perilla$.tw.
18 linolen$.tw.
19 linseed$.tw.
20 maxepa$.tw.
21 (oil$ adj3 colza).tw.
22 (marin$ adj3 (lipid$ or oil$)).tw.
23 naudicelle$.tw.
24 sild.tw.
25 (clupe$ adj3 hareng$).tw.
26 whitebait$.tw.
27 sprat$.tw.
28 brisling$.tw.
29 (salmo adj3 trut$).tw.
30 bloater.tw.
31 scomb$.tw.
32 conger$.tw.
33 tunny.tw.
34 tuna-fish.tw.
35 thunnus$.tw.
36 swordfish$.tw.
37 xiphias$.tw.
38 dogfish.tw.
39 scyliorhinus$.tw.
40 (crab or crabs).tw.
41 (cancer adj3 pagurus).tw.
42 (laks or lax).tw.
43 exp Flax/
44 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
45 randomized controlled trial.pt.
46 controlled clinical trial.pt.
47 randomized.ab.
48 placebo.ab.
49 clinical trials as topic.sh.
50 randomly.ab.
51 trial.ti.
52 50 or 47 or 51 or 46 or 45 or 48 or 49
53 (animals not (human and animals)).sh.
54 52 not 53

55 44 and 54
56 (20$ not (2000$ or 2001$)).ed.
57 55 and 56

Appendix 2. Searches run in July 2016 to update the omega-3 review

CENTRAL

#1 MeSH descriptor: [Fish Oils] explode all trees

#2 MeSH descriptor: [Linseed Oil] this term only

#3 MeSH descriptor: [Linolenic Acids] this term only

#4 MeSH descriptor: [Fatty Acids, Omega-3] explode all trees

#5 (fish near/3 oil*)

#6 (oil* near/3 (cod* or marin*))

#7 (omega-3 or omega3 or (omega* near/5 fat*))

#8 eicosapentaen*

#9 docosahexaen*

#10 (oil* near/3 (flax* or rapeseed* or canola*))

#11 (Linolen* or alpha-linolen* or alphalinolen*)

#12 (perilla* or linseed* or maxepa*)

#13 (oil* near/3 (rape or colza))

#14 (marin* near/3 lipid*)

#15 (naudicelle* or herring* or sild)

#16 (clupe* near/3 hareng*)

#17 (whitebait or sardine* or sardina* or pilchard* or sprat* or brisling*)

#18 (salmo* near/3 trut*)

#19 (trout or bloater or kipper* or salmon or mackerel* or scomb* or conger* or tuna or tunny or tunafish or tuna-fish)

#20 (thunnus* or swordfish* or xiphias* or dogfish or scyliorrhinus*)

#21 (crab or crabs or (cancer pagarus))

#22 (DHA or EPA)

#23 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 Publication Year from 2002 to 2016

#24 MeSH descriptor: [Salmoniformes] explode all trees

#25 MeSH descriptor: [Tuna] this term only

#26 MeSH descriptor: [alpha-Linolenic Acid] this term only

#27 MeSH descriptor: [Flax] this term only

#28 (fish near/3 (diet* or capsul* or nutrit* or supplement*))

#29 (icosapentaen* or docosapentaen*)

#30 (oil* near/3 (purslane or mustard* or candlenut* or stillingia or walnut*))

#31 (laks or lax)

#32 (ALA or DPA)

#33 (algal near oil*)

#34 #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33

#35 #23 or #34

MEDLINE Ovid

1. exp Fish Oils/

2. Linseed Oil/

3. linolenic acids/ or alpha-linolenic acid/

4. Flax/

5. exp Fatty Acids, Omega-3/

6. (fish adj3 (diet* or nutrit* or oil* or supplement*)).ti,ab.

7. (oil* adj3 (cod* or marin*)).ti,ab.

8. (omega-3 or omega3 or (omega* adj5 fat*)).ti,ab.

9. eicosapentaen*.ti,ab.

10. docosahexaen*.ti,ab.

11. (oil* adj3 (flax* or rapeseed* or canola*)).ti,ab.

12. (Linolen* or alpha-linolen* or alphalinolen*).ti,ab.

13. (perilla* or linseed* or maxepa*).ti,ab.

14. (oil* adj3 (rape or colza)).ti,ab.

15. (marin* adj3 lipid*).ti,ab.

16. (naudicelle* or herring* or sild).ti,ab.

17. (clupe* adj3 hareng*).ti,ab.

18. (whitebait or sardine* or sardina* or pilchard* or sprat* or brisling*).ti,ab.

19. (salmo* adj3 trut*).ti,ab.

20. (trout or bloater or kipper* or salmon or mackerel* or scomb* or conger* or tuna or tunny or tunafish or tuna-fish).ti,ab.

21. (thunnus* or swordfish* or xiphias* or dogfish or scyliorrhinus* or laks or lax).ti,ab.

22. (crab or crabs or cancer pagarus).ti,ab.

23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22

24. randomized controlled trial.pt.

25. controlled clinical trial.pt.

26. randomized.ab.

27. placebo.ab.

28. clinical trials as topic.sh.

29. randomly.ab.

30. trial.ti.

31. 24 or 25 or 26 or 27 or 28 or 29 or 30

32. exp animals/ not humans.sh.

33. 31 not 32

34. 23 and 33

35. limit 34 to ed=20020201-20160721

36. exp salmoniformes/ or tuna/

37. (fish adj3 capsul*).ti,ab.

38. icosapentaen*.ti,ab.

39. docosapentaen*.ti,ab.

40. (oil* adj3 (purslane or mustard* or candlenut* or stillingia or walnut*)).ti,ab.

41. 36 or 37 or 38 or 39 or 40

42. 33 and 41

43. 35 or 42

Embase Ovid

1. exp salmoniformes/ or tuna/

2. fish oil/

3. linseed oil/

4. linolenic acid/

5. Flax/

6. omega 3 fatty acid/

7. (fish adj3 (diet* or nutrit* or oil* or supplement*)).ti,ab.

8. (oil* adj3 (cod* or marin*)).ti,ab.

9. (omega-3 or omega3 or (omega* adj5 fat*)).ti,ab.

10. (eicosapentaen* or icosapentaen*).ti,ab.

11. docosahexaen*.ti,ab.

12. (oil* adj3 (flax* or rapeseed* or canola*)).ti,ab.

13. (Linolen* or alpha-linolen* or alphalinolen*).ti,ab.

14. (perilla* or linseed* or maxepa*).ti,ab.

15. (marin* adj3 lipid*).ti,ab.

16. (naudicelle* or herring* or sild).ti,ab.

17. (clupe* adj3 hareng*).ti,ab.

18. (whitebait or sardine* or sardina* or pilchard* or sprat* or brisling*).ti,ab.

19. (salmo* adj3 trut*).ti,ab.

20. (trout or bloater or kipper* or salmon or mackerel* or scomb* or conger* or tuna or tunny or tunafish or tuna-fish).ti,ab.

21. (thunnus* or swordfish* or xiphias* or dogfish or scyliorrhinus* or laks or lax).ti,ab.

22. (crab or crabs or (cancer adj3 pagarus)).ti,ab.

23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22

24. random$.tw.

25. placebo$.tw.

26. (doubl$ adj blind$).tw.

27. (singl$ adj blind$).tw.

28. double blind procedure/

29. randomized controlled trial/

30. single blind procedure/

31. 24 or 25 or 26 or 27 or 28 or 29 or 30

32. (animal/ or nonhuman/) not human/

33. 31 not 32

34. 23 and 33

35. (2002* or 2003* or 2004* or 2005* or 2006* or 2007* or 2008* or 2009* or 2010* or 2011* or 2012* or 2013* or 2014* or 2015* or 2016*).dd,em.

36. 34 and 35

37. exp salmonine/

38. (fish adj3 capsul*).ti,ab.

39. docosapentaen*.ti,ab.

40. (ALA or DHA or DPA or EPA).ti,ab.

41. (algal adj oil*).ti,ab.

42. 37 or 38 or 39 or 40 or 41

43. 33 and 42

44. 36 or 43

Appendix 3. Searches run in April 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 PUFA fats (Abdelhamid 2018) 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, terms as recommended in the Cochrane Handbook have been applied (Lefebvre 2011).

CENTRAL

#1 MeSH descriptor: [Fatty Acids, Essential] explode all trees

#2 MeSH descriptor: [Fatty Acids, Unsaturated] this term only

#3 ((polyunsaturat* or poly-unsaturat*) near/3 fat*)

#4 (poly* adj4 unsat* near/4 fatty acid*)

#5 PUFA

#6 MeSH descriptor: [Fatty Acids, Omega-6] explode all trees

#7 omega-6

#8 (n-6 near/4 acid*) or ("n 6" near/4 acid*)

#9 linoleic acid*

#10 MeSH descriptor: [Corn Oil] this term only

#11 MeSH descriptor: [Cottonseed Oil] this term only

#12 MeSH descriptor: [Olive Oil] this term only

#13 MeSH descriptor: [Safflower Oil] this term only

#14 MeSH descriptor: [Sesame Oil] this term only

#15 MeSH descriptor: [Soybean Oil] this term only

#16 ((corn or maize or mazola) near/4 oil*)

#17 (cottonseed* or (cotton next seed*))

#18 (olive near/4 oil*)

#19 (safflower near/4 oil*)

#20 (sesame near/4 oil*)

#21 ((soy bean or soybean) near/4 (oil* or fat*))

#22 (so?a near/4 oil*)

#23 so?aoil*

#24 (soy near/4 oil*)

#25 (sunflower near/4 oil*)

#26 helianth*

#27 (grapeseed near/4 oil*)

#28 (canola near/4 oil*)

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

MEDLINE Ovid

1. exp fatty acids, essential/

2. fatty acids, unsaturated/

3. ((polyunsaturat* or poly-unsaturat*) adj3 fat*).ti,ab.

4. (poly* adj4 unsat* adj4 fatty acid*).ti,ab.

5. PUFA.ti,ab.

6. exp fatty acids, omega-6/

7. omega-6.ti,ab.

8. (n-6 adj4 acid*).ti,ab.

9. linoleic acid*.ti,ab.

10. corn oil/ or cottonseed oil/ or olive oil/ or safflower oil/ or sesame oil/ or soybean oil/

11. ((corn or maize or mazola) adj4 oil*).ti,ab.

12. (cottonseed* or (cotton adj seed*)).ti,ab.

13. (olive adj4 oil*).ti,ab.

14. (safflower adj4 oil*).ti,ab.

15. (sesame adj4 oil*).ti,ab.

16. ((soy bean or soybean) adj4 (oil* or fat*)).ti,ab.

17. (so?a adj4 oil*).ti,ab.

18. so?aoil*.ti,ab.

19. (soy adj4 oil*).ti,ab.

20. (sunflower adj4 oil*).ti,ab.

21. helianth*.ti,ab.

22. (grapeseed adj4 oil*).ti,ab.

23. (canola adj4 oil*).ti,ab.

24. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23

25. randomized controlled trial.pt.

26. controlled clinical trial.pt.

27. randomized.ab.

28. placebo.ab.

29. clinical trials as topic.sh.

30. randomly.ab.

31. trial.ti.

32. 25 or 26 or 27 or 28 or 29 or 30 or 31

33. exp animals/ not humans.sh.

34. 32 not 33

35. 24 and 34

Embase Ovid

1. exp essential fatty acid/

2. unsaturated fatty acid/ or docosapentaenoic acid/ or omega 6 fatty acid/ or polyunsaturated fatty acid/

3. ((polyunsaturat* or poly-unsaturat*) adj3 fat*).ti,ab.

4. (poly* adj4 unsat* adj4 fatty acid*).ti,ab.

5. PUFA.ti,ab.

6. omega-6.ti,ab.

7. (n-6 adj4 acid*).ti,ab.

8. linoleic acid*.ti,ab.

9. edible oil/ or canola oil/ or corn oil/ or cotton seed oil/ or olive oil/ or safflower oil/ or safflower oil plus soybean oil/ or sesame seed oil/ or soybean oil/ or sunflower oil/

10. ((corn or maize or mazola) adj4 oil*).ti,ab.

11. (cottonseed* or (cotton adj seed*)).ti,ab.

12. (olive adj4 oil*).ti,ab.

13. (safflower adj4 oil*).ti,ab.

14. (sesame adj4 oil*).ti,ab.

15. ((soy bean or soybean) adj4 (oil* or fat*)).ti,ab.

16. (so?a adj4 oil*).ti,ab.

17. so?aoil*.ti,ab.

18. (soy adj4 oil*).ti,ab.

19. (sunflower adj4 oil*).ti,ab.

20. helianth*.ti,ab.

21. (grapeseed adj4 oil*).ti,ab.

22. (canola adj4 oil*).ti,ab.

23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22

24. double blind procedure/

25. single blind procedure/

26. randomized controlled trial/

27. ((double* or single*) adj blind*).ti,ab.

28. (random* or placebo*).ti,ab.

29. 24 or 25 or 26 or 27 or 28

30. (animal/ or nonhuman/) not human/

31. 29 not 30

32. 23 and 31

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 quality 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,
- 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 NNT 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 quality 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

WHAT'S NEW

Date	Event	Description
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%.

Date	Event	Description
		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.
28 November 2018	New citation required but conclusions have not changed	The amendments did not change our conclusions.

HISTORY

Protocol first published: Issue 2, 1999
Review first published: Issue 4, 2004

Date	Event	Description
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) Nutrition 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.

Date	Event	Description
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 study 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 RevMan 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.
CDS: none known.
HVW: none known.
FS: none known.
LH: none known.

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- University of East Anglia, UK.
- Cochrane Heart Group, UK.

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External sources

- World Health Organization nutrition guidance expert advisory group (NUGAG), Not specified.

WHO NUGAG Subgroup on Diet and Health requested and funded the update and extension of this review.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Differences between the previous version of this review (2004) and this update (2018):

- **Authors** altered. The Acknowledgments recognise authors of the previous version who chose not to participate in this update.
- **Background** updated.
- **Objectives: primary objective** altered from 'Do dietary or supplemental omega-3 fatty acids alter total mortality, cardiovascular events, cancers or other adverse events?' to 'Do long-chain omega-3 (LCn3, fish-based omega-3 fats) or ALA (plant-based omega-3 fats) fats alter risk of all-cause mortality, cardiovascular deaths, cardiovascular events, coronary heart disease deaths, coronary heart disease events, stroke, arrhythmia, adiposity and lipids?' This change in emphasis, which we anticipated in the original review, focuses on long-chain omega-3 fats (EPA, DHA, DPA) and ALA separately. We discuss changes in outcomes assessed below.

- **Secondary questions**: we added assessment of effects of omega-3 fats (including both LCn3 and ALA) as a secondary question.
- **Types of studies included**: included RCTs had to be at least one year in duration in the update (the limit was six months in the original review). We excluded cohort studies from the update.
- T**ypes of outcomes: primary outcomes** assessed were updated, removing cancers and adverse events as primary outcomes and adding cardiovascular deaths, coronary heart disease deaths and events, stroke and arrhythmia (atrial fibrillation) as primary outcomes. Adiposity and lipids were added as key secondary outcomes. Cancer outcomes and other non-cardiovascular outcomes, including diabetes, were assessed in separate reviews (Abdelhamid 2018; Abdelhamid 2017; Brown 2017; Hanson 2017a; Hanson 2017b; Jimoh 2017; Thorpe 2017).
- **Secondary outcomes**: we added new secondary outcomes (major adverse cardiac or cerebrovascular events (MACCEs), myocardial infarction, sudden cardiac death, angina, heart failure, peripheral arterial disease, re-vascularisation and acute coronary syndrome). Blood pressure (a secondary outcome in the original review) became a tertiary outcome in the update. We dropped urinary thromboxane and participant fatty acid data as secondary outcomes but collected fatty acid data to help assess compliance.
- **Risk of bias**: we updated this review to incorporate the Cochrane 'Risk of bias' tool (for all included studies). We slightly updated our assessment of summary risk of bias from low summary risk when "allocation concealment was adequate, and participant, provider and outcome assessor blinding were all coded 'yes'" to low summary risk for a supplement or capsule type trial where "we judged randomisation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessors to be adequate" and for a dietary advice or all-food provided type trial where "we judged randomisation, allocation concealment, and blinding of outcome assessors to be adequate".
- **Subgroup analyses**: in the update we carried out separate subgroup analyses for LCn3 and ALA studies. Subgrouping in the update was as in the original review (by dose, dietary or supplemental source and trial duration), with the addition of some new subgroups. We added new subgroup analyses at the request of the WHO NUGAG Subgroup on Diet and Health.
  * Replacement of SFA, MUFA, omega-6 fats, fat mixture, carbohydrates or sugars, non-fat or no placebo (or unclear) by LCn3 or ALA.
  * Primary prevention versus secondary prevention of CVD.
  * Statin use (< 50% of control group on statins, ≥ 50% of control group on statins, use of statins unclear).
  * Baseline LCn3 or ALA intake.
- **Sensitivity analyses**: updated for this review. Limiting analyses to studies at low summary risk of bias was continued in the update from the original review, and we added sensitivity analyses by study size (retaining only trials that randomised at least 100 participants across all study arms), fixed-effect meta-analysis and compliance (retaining only studies at low risk of compliance bias, this latter at the request of WHO NUGAG Subgroup on Diet and Health).
- **Heterogeneity**: the original review used Cochran's test while the update used I^2. This reflects current best methodology.

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; 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]; Primary Prevention; Randomized Controlled Trials as Topic; Secondary Prevention; Stroke [epidemiology]; Treatment Outcome; alpha-Linolenic Acid [therapeutic use]

MeSH check words

Adult; Humans