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Omega-6 fats for the primary and secondary prevention of cardiovascular disease (Review)

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[Intervention Review]

Omega-6 fats for the primary and secondary prevention of cardiovascular disease

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A B S T R A C T

Background

Omega-6 fats are polyunsaturated fats vital for many physiological functions, but their effect on cardiovascular disease (CVD) risk is debated.

Objectives

To assess effects of increasing omega-6 fats (linoleic acid (LA), gamma-linolenic acid (GLA), dihomo-gamma-linolenic acid (DGLA) and arachidonic acid (AA)) on CVD and all-cause mortality.

Search methods

We searched CENTRAL, MEDLINE and Embase to May 2017 and clinicaltrials.gov and the World Health Organization International Clinical Trials Registry Platform to September 2016, without language restrictions. We checked trials included in relevant systematic reviews.

Selection criteria

We included randomised controlled trials (RCTs) comparing higher versus lower omega-6 fat intake in adults with or without CVD, assessing effects over at least 12 months. We included full texts, abstracts, trials registry entries and unpublished studies. Outcomes were all-cause mortality, CVD mortality, CVD events, risk factors (blood lipids, adiposity, blood pressure), and potential adverse events. We excluded trials where we could not separate omega-6 fat effects from those of other dietary, lifestyle or medication interventions.

Data collection and analysis

Two authors independently screened titles/abstracts, assessed trials for inclusion, extracted data, and assessed risk of bias of included trials. We wrote to authors of included studies. Meta-analyses used random-effects analysis, while sensitivity analyses used fixed-effects and limited analyses to trials at low summary risk of bias. We assessed GRADE quality of evidence for 'Summary of findings' tables.

Main results

We included 19 RCTs in 6461 participants who were followed for one to eight years. Seven trials assessed the effects of supplemental GLA and 12 of LA; none DGLA or AA; the omega-6 fats usually displaced dietary saturated or monounsaturated fats. We assessed three RCTs as being at low summary risk of bias.

Primary outcomes: we found low-quality evidence that increased intake of omega-6 fats may make **little or no difference to all-cause mortality** (risk ratio (RR) 1.00, 95% confidence interval (CI) 0.88 to 1.12, 740 deaths, 4506 randomised, 10 trials) or **CVD events** (RR 0.97, 95% CI 0.81 to 1.15, 1404 people experienced events of 4962 randomised, 7 trials). We are **uncertain whether increasing omega-6 fats affects CVD mortality** (RR 1.09, 95% CI 0.76 to 1.55, 472 deaths, 4019 randomised, 7 trials), **coronary heart disease events** (RR 0.88, 95% CI 0.66 to 1.17, 1059 people with events of 3997 randomised, 7 trials), **major adverse cardiac and cerebrovascular events** (RR 0.84, 95% CI 0.59 to 1.20, 817 events, 2879 participants, 2 trials) or **stroke** (RR 1.36, 95% CI 0.45 to 4.11, 54 events, 3730 participants, 4 trials), as we assessed the evidence as being of very low quality. We 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.

Additional key outcomes: we found increased intake of omega-6 fats **may reduce myocardial infarction** (MI) risk (RR 0.88, 95% CI 0.76 to 1.02, 609 events, 4606 participants, 7 trials, low-quality evidence). High-quality evidence suggests increasing omega-6 fats **reduces total serum cholesterol** a little in the long term (mean difference (MD) −0.33 mmol/L, 95% CI −0.50 to −0.16, I^2 = 81%; heterogeneity partially explained by dose, 4280 participants, 10 trials). Increasing omega-6 fats **probably has little or no effect on adiposity** (body mass index (BMI) MD −0.20 kg/m^2, 95% CI −0.56 to 0.16, 371 participants, 1 trial, moderate-quality evidence). It may make **little or no difference to serum triglycerides** (MD −0.01 mmol/L, 95% CI −0.23 to 0.21, 834 participants, 5 trials), **HDL** (MD −0.01 mmol/L, 95% CI −0.03 to 0.02, 1995 participants, 4 trials) or **low-density lipoprotein** (MD −0.04 mmol/L, 95% CI −0.21 to 0.14, 244 participants, 2 trials, low-quality evidence).

Authors' conclusions

This is the most extensive systematic assessment of effects of omega-6 fats on cardiovascular health, mortality, lipids and adiposity to date, using previously unpublished data. We found no evidence that increasing omega-6 fats reduces cardiovascular outcomes other than MI, where 53 people may need to increase omega-6 fat intake to prevent 1 person from experiencing MI. Although benefits of omega-6 fats remain to be proven, increasing omega-6 fats may be of benefit in people at high risk of MI. Increased omega-6 fats reduce serum total cholesterol but not other blood fat fractions or adiposity.

P L A I N   L A N G U A G E   S U M M A R Y

Omega-6 fats to prevent and treat heart and circulatory diseases

Review question

We reviewed randomised trials (participants had an equal chance to be assigned to either treatment) examining effects of higher omega-6 fats compared to lower omega-6 fats on deaths and heart and circulatory diseases (cardiovascular diseases (CVD), which include heart attacks and strokes).

Background

Omega-6 fats are essential, we must obtain some from food. They are important for regulating energy production (part of metabolism), bone, skin and hair health. Many foods contain omega-6 fats, particularly vegetable oils and nuts. Omega-6 fats include linoleic acid (LA), gamma-linolenic acid (GLA), dihomo-gamma-linolenic acid (DGLA) and arachidonic acid (AA).

Some evidence suggests that a higher intake of omega-6 fats, along with a lower intake of saturated fat (from animal sources such as meat and cheese) can reduce coronary heart disease. In contrast, there is concern that high levels of omega-6 fats may worsen cardiovascular risk by increasing inflammation. Overall, there is no conclusive evidence on the benefits or harms of omega-6 fat intake on heart and circulatory diseases or on other health outcomes.

Study characteristics

Evidence in this review is current to May 2017. We found 19 studies recruiting 6461 adults. These studies assessed the effects of higher compared to lower omega-6 fat intake on heart and circulatory diseases as well as deaths. We found that three trials were highly trustworthy (with good designs that produce reliable evidence). Studies took place in North America, Asia, Europe and Australia, and eight were funded only by national or charitable agencies. Participants increased their omega-6 fats or maintained their usual fats for at least one year and up to eight years.

Key results

We found that increasing omega-6 fats may make little or no difference to deaths or cardiovascular events but may reduce risk of heart attacks (low-quality evidence). Evidence was weakened by study design problems, small numbers of events, low numbers of participants from developing countries, and few women.

Evidence suggests that increasing omega-6 fats reduces blood cholesterol (high-quality evidence), probably has little or no effect on body weight adjusted for height (all moderate-quality evidence), and may make little or no difference to triglycerides, high-density lipoprotein (HDL, the 'good' cholesterol) or low-density lipoprotein (LDL, the 'bad' cholesterol, low-quality evidence).

SUMMARY OF FINDINGS

Summary of findings for the main comparison.   Higher versus lower omega-6: primary outcomes

Higher versus lower omega-6 for adults with or without CVD

Patient or population: adults with or without existing CVD
Setting: includes free-living participants and those living in institutions. Includes participants from North America, Australia, Asia and Europe but most events occurred in studies carried out in Europe or North America
Intervention: higher omega-6
Comparison: lower omega-6

Eligible trials compared higher with lower omega-6 fat (including LA, GLA, DGLA, AA, or any combination) intakes. The intervention had to be dietary supplementation, or a provided diet, or advice on diet

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with lower omega-6	Risk with higher omega-6				
All-cause mortality Study duration range 12-96 months Omega-6 dose range 1.5%-24.5% E	Study population		RR 1.00 (0.88 to 1.12)	4506 (10 RCTs)	⊕⊕⊝⊝ Low[a]	Increasing omega-6 fats may make little or no difference to risk of all-cause mortality. Downgraded once each for risk of bias and imprecision. As there was no suggestion of benefit or harm the number needed to treat (NNTB) was infinite (NNTB ∞, 95% CI NNTH 50 to NNTB 50)
	167 per 1000	167 per 1000 (147 to 187)				
Cardiovascular mortality Study duration range 24-96 months Omega-6 dose range 2.8%-24.5% E	Study population		RR 1.09 (0.76 to 1.55)	4019 (7 RCTs)	⊕⊝⊝⊝ Very low[b]	We are uncertain whether increasing omega-6 fats affects CVD mortality risk. Downgraded for risk of bias, imprecision and inconsistency
	114 per 1000	125 per 1000 (87 to 177)				
Cardiovascular events: any Study duration range 12-96 months Omega-6 dose range 2.8%-24.5% E	Study population		RR 0.97 (0.81 to 1.15)	4962 (7 RCTs)	⊕⊕⊝⊝ Low[c]	Increasing omega-6 fats may make little or no difference to risk of cardiovascular events. Downgraded once each for risk of bias and imprecision. 100 people would need to increase the amount of omega-6 fat in their diet to prevent 1 person having a CVD event (NNTB 100, 95% CI −21 to 17)
	311 per 1000	301 per 1000 (252 to 357)				

Outcome	Study population		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
CHD events: myocardial infarction (fatal or non-fatal) or angina Study duration range 12-96 months Omega-6 dose range 2.8%-24.5% E	Study population		RR 0.88 (0.66 to 1.17)	3997 (7 RCTs)	⊕⊝⊝⊝ Very low[d]	We are uncertain whether increasing omega-6 fats affects CHD risk. Downgraded for risk of bias, imprecision and inconsistency
	277 per 1,000	244 per 1000 (183 to 324)				
MACCEs Study duration range 24-96 months Omega-6 dose range 2.8%-12.0% E	Study population		RR 0.84 (0.59 to 1.20)	2879 (2 RCTs)	⊕⊝⊝⊝ Very low[e]	We are uncertain whether increasing omega-6 affects MACCE risk. Downgraded for risk of bias, inconsistency and imprecision
	295 per 1000	248 per 1000 (174 to 354)				
Stroke: fatal or non-fatal Study duration range 24-96 months Omega-6 dose range 2.8%-21.9% E	Study population		RR 1.36 (0.45 to 4.11)	3730 (4 RCTs)	⊕⊝⊝⊝ Very low[f]	We are uncertain whether increasing omega-6 fats affects stroke risk. Downgraded once for risk of bias, twice for imprecision
	14 per 1000	20 per 1000 (7 to 59)				

*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).

AA: arachidonic acid; CI: confidence interval; CHD: coronary heart disease; CVD: cardiovascular disease; DGLA: dihomo-gamma-linolenic acid; GLA: gamma-linolenic acid; LA: linoleic acid; MACCE: major adverse cardiovascular or cerebrovascular event; NNTB: number needed to treat for an additional beneficial outcome; NNTH: number needed to treat for an additional harmful outcome; RCT: randomised controlled trial; RR: risk ratio; % E: percentage of energy intake from this nutrient.

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

- **Risk of bias**: two included trials were at low summary risk of bias, including 682 participants reporting 69 deaths. Limiting analyses to these trials suggested that increasing omega-6 fats may increase mortality risk, as did limiting to studies with no commercial funding. Other sensitivity analyses suggested little or no effect. It was further noted by the WHO NUGAG Subgroup on Diet and Health that most studies did not report on allocation concealment or otherwise had unclear risk of bias for allocation concealment. Although low risk of bias in other elements of bias assessment (e.g. randomisation, blinding of outcome assessment) might suggest that the trials were well-conducted and thus allocation concealment may have been maintained, many of the trials are older and detailed information on the conduct of the trials can be scarce. Therefore, a conservative approach was taken. Downgraded once.

- **Inconsistency**: there was little or no indication of heterogeneity between trials ($I^2 < 30\%$). Not downgraded.
- **Indirectness**: Most data related to high-income countries, and trials of men, but included people with and without CVD at baseline. Not downgraded.
- **Imprecision**: the 95% CI crossed the null and did not exclude important benefits or harms. Downgraded once.
- **Publication bias**: no suggestion of publication or small study bias in the funnel plot. Not downgraded.

[b]**Cardiovascular mortality**

- **Risk of bias**: one included study with 458 participants, 62 of whom died of CVD, was at low summary risk of bias. Limiting analyses to this trial suggested that increasing omega-6 fats may increase risk of CVD death, as did limiting to studies without commercial funding, while trials at low risk of attention bias suggested benefit from increasing omega-6 fats. WHO NUGAG Subgroup on Diet and Health notes: "Most studies did not report on allocation concealment or otherwise had unclear risk of bias for allocation concealment. Although low risk of bias in other elements of bias assessment (e.g. randomisation, blinding of outcome assessment) might suggest that the trials were well-conducted and thus allocation concealment may have been maintained, many of the trials are older, and detailed information on the conduct of the trials can be scarce. Therefore, a conservative approach was taken. Downgraded once.
- **Inconsistency**: $I^2 > 60\%$. Downgraded for inconsistency.
- **Indirectness**: Most data related to high-income countries, and trials of men, but included people with and without CVD at baseline. Not downgraded.
- **Imprecision**: the 95% CI crossed the null and did not exclude important benefits or harms. Downgraded once.
- **Publication bias**: fewer than 10 included studies so no funnel plot run. Not downgraded.

[c]**Cardiovascular events**

- **Risk of bias**: two included trials in 1525 participants, 68 of whom experienced at least 1 CVD event, were at low summary risk of bias. This sensitivity analysis, limiting to trials of low summary risk of bias, suggested that increasing omega-6 fats increased risk of experiencing CVD events, as did limiting to studies with no commercial funding, while limiting to studies at low risk of bias from attention differences suggested benefit from increasing omega-6 fats. It was further noted by the WHO NUGAG Subgroup on Diet and Health that most studies did not report on allocation concealment or otherwise had unclear risk of bias for allocation concealment. Although low risk of bias in other elements of bias assessment (e.g. randomisation, blinding of outcome assessment) might suggest that the trials were well-conducted and thus allocation concealment may have been maintained, many of the trials are older and detailed information on the conduct of the trials can be scarce. Therefore, a conservative approach was taken. Downgraded once.
- **Inconsistency**: I^2 was between 30 and 60%. Not downgraded.
- **Indirectness**: Most data related to high-income countries, and trials of men, but included people with and without CVD at baseline. Not downgraded.
- **Imprecision**: the 95% CI crossed the null and did not exclude important benefits or harms. Downgraded once.
- **Publication bias**: fewer than 10 included studies so no funnel plot run. Not downgraded.

[d]**Coronary heart disease events**

- **Risk of bias**: one included study in 458 participants, 58 of whom experienced at least 1 CHD event, was at low summary risk of bias. This study suggested an increased risk with higher omega-6 intake (RR 1.63, 95% CI 1.00 to 2.67), though this was not mirrored in any other sensitivity analysis. Limiting to pre-2010 or trials registry registered trials, those with no commercial funding, those at low risk of attention bias and those that randomised at least 100 participants all suggested some benefit of increasing omega-6 fats. It was further noted by the WHO NUGAG Subgroup on Diet and Health that most studies did not report on allocation concealment or otherwise had unclear risk of bias for allocation concealment. Although low risk of bias in other elements of bias assessment (e.g. randomisation, blinding of outcome assessment) might suggest that the trials were well-conducted and thus allocation concealment may have been maintained, many of the trials are older and detailed information on the conduct of the trials can be scarce. Therefore, a conservative approach was taken. Downgraded once.
- **Inconsistency**: $I^2 > 60\%$. Downgraded once.
- **Indirectness**: Most data related to high-income countries, and trials of men, but included people with and without CVD at baseline. Not downgraded.
- **Imprecision**: the 95% CI crossed the null and did not exclude important benefits or harms. Downgraded once.
- **Publication bias**: fewer than 10 included studies so no funnel plot run. Not downgraded.

[e] **Major adverse cardiac and cerebrovascular events**

- **Risk of bias**: no included studies were at low summary risk of bias or were without commercial funding. All other sensitivity analyses suggested benefits from increasing omega-6 fats. Downgraded once.
- **Inconsistency**: $I^2 > 60\%$. Downgraded once.

- **Indirectness**: Most data related to high-income countries, and trials of men, but included people with and without CVD at baseline. Not downgraded.
- **Imprecision**: the 95% CI crossed the null and did not exclude important benefits or harms. Downgraded once.
- **Publication bias**: fewer than 10 included studies so no funnel plot run. Not downgraded.

[f] **Stroke**
- **Risk of bias**: one included study with 458 participants, 4 of whom experienced a stroke, was at low summary risk of bias. Sensitivity analyses including pre-2010 or trials registry registered trials, only trials without commercial funding and larger trials all suggested that increasing omega-6 fats increased stroke risk, while the single study at low risk of attention bias suggested reduced stroke risk, and fixed-effect analysis suggested little or no effect of increasing omega-6 fats. It was further noted by the WHO NUGAG Subgroup on Diet and Health that most studies did not report on allocation concealment or otherwise had unclear risk of bias for allocation concealment. Although low risk of bias in other elements of bias assessment (e.g. randomisation, blinding of outcome assessment) might suggest that the trials were well-conducted and thus allocation concealment may have been maintained, many of the trials are older and detailed information on the conduct of the trials can be scarce. Therefore, a conservative approach was taken. Downgraded once.
- **Inconsistency**: I^2 was between 30 and 60%. Not downgraded.
- **Indirectness**: Most data related to high-income countries, and trials of men, but included people with and without CVD at baseline. Not downgraded.
- **Imprecision**: the 95% CI crossed the null and included large benefits (RR < 0.5) and large harms (RR > 2.0) from omega-6 fats. Downgraded twice.
- **Publication bias**: fewer than 10 included studies so no funnel plot run. Not downgraded.

Summary of findings 2. Higher versus lower omega-6: additional key outcomes

Higher versus lower omega-6 for adults with or without CVD

Patient or population: adults with or without existing CVD
Setting: includes free-living participants and those living in institutions. Includes participants from North America, Australia, Asia and Europe, but most events occurred in studies carried out in Europe or North America
Intervention: higher omega-6
Comparison: lower omega-6

Eligible trials compared higher with lower omega-6 fat (including LA, GLA, DGLA, AA, or any combination) intakes. The intervention had to be dietary supplementation, or a provided diet, or advice on diet.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with lower omega-6	Risk with higher omega-6				
MI Study duration range 12-96 months Omega-6 dose range 2.8%-24.5% E	Study population		RR 0.88 (0.76 to 1.02)	4606 (7 RCTs)	⊕⊕⊝⊝ Low[a]	Increasing omega-6 fats may reduce risk of myocardial infarction. Downgraded once each for risk of bias and imprecision. 53 people would need to increase the amount of omega-6 fat in their diet to prevent one person having a myocardial infarction (NNTB 53, 95% CI −334 to 28).
	154 per 1000	135 per 1000 (117 to 157)				

Outcome	Illustrative comparative risks	Effect		No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Serum TC Study duration range 12-96 months Omega-6 dose range 2.0%-24.5% E	The mean serum total cholesterol was 5.88 mmol/L	MD 0.33 mmol/L lower (0.5 lower to 0.16 lower)	—	4280 (10 RCTs)	⊕⊕⊕⊕ High[b]	Increasing omega-6 fats reduces serum total cholesterol over at least 1 year; not downgraded
Serum TG Study duration range 12-72 months Omega-6 dose range 2.0%-15.0% E	The mean serum triglycerides was 1.45 mmol/L	MD 0.01 mmol/L lower (0.23 lower to 0.21 higher)	—	834 (5 RCTs)	⊕⊕⊝⊝ Low[c]	Increasing omega-6 fats may make little or no difference to serum triglycerides over at least one year. Downgraded once for imprecision, and once for inconsistency and risk of bias combined
LDL Study duration range 12-24 months Omega-6 dose range 2.0%-15.0% E	The mean low density lipoprotein was 2.35 mmol/L	MD 0.04 mmol/L lower (0.21 lower to 0.14 higher)	—	244 (2 RCTs)	⊕⊕⊝⊝ Low[d]	Increasing omega-6 fats may make little or no difference to LDL over at least one year. Downgraded for risk of bias and imprecision
HDL Study duration range 12-24 months Omega-6 dose range 2.0%-15.0% E	The mean high density lipoprotein was 1.15 mmol/L	MD 0.01 mmol/L lower (0.03 lower to 0.02 higher)	—	1995 (4 RCTs)	⊕⊕⊝⊝ Low[e]	Increasing omega-6 fats may have little or no effect on HDL over at least one year. Downgraded once each for risk of bias and imprecision
Body weight (kg) Study duration range 12-48 months Omega-6 dose range 0.8%-2.8% E	The mean body weight was 77.9 kg	MD 3.12 kg lower (12.6 lower to 6.36 higher)	—	358 (4 RCTs)	⊕⊝⊝⊝ Very low[f]	We are uncertain whether increasing omega-6 fats alters body weight as the evidence is of very low quality. Downgraded for risk of bias, imprecision and publication bias
BMI Study duration 51 months Omega-6 dose 6.6% E	The mean body mass index was 24.5 kg/m²	MD 0.2 kg/m² lower (0.56 lower to 0.16 higher)	—	371 (1 RCT)	⊕⊕⊕⊝ Moderate[g]	Increasing omega-6 fats probably has little or no effect on body mass index over at least one year. Downgraded for imprecision

***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).

AA: arachidonic acid; **BMI**: body mass index; **CI**: confidence interval; **DGLA**: dihomo-gamma-linolenic acid; **GLA**: gamma-linolenic acid; **HDL**: high-density lipoprotein; **LA**: linoleic acid; **LDL**: low-density lipoprotein; **MD**: mean difference; **MI**: myocardial infarction; **NNTB**: number needed to treat for an additional beneficial outcome; **RCT**: randomised controlled trial; **RR**: risk ratio; **TC**: total cholesterol; **TG**: triglycerides; **% E**: percentage of energy intake from this nutrient.

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

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[a]**Myocardial infarction**
- **Risk of bias**: only one trial with fewer than 10 participants experiencing events was at low summary risk of bias. All other sensitivity analyses suggested that increasing omega-6 fats reduced risk of MI. It was further noted by the WHO NUGAG Subgroup on Diet and Health that most studies did not report on allocation concealment or otherwise had unclear risk of bias for allocation concealment. Although low risk of bias in other elements of bias assessment (e.g. randomisation, blinding of outcome assessment) might suggest that the trials were well-conducted and thus allocation concealment may have been maintained, many of the trials are older and detailed information on the conduct of the trials can be scarce. Therefore, a conservative approach was taken. Downgraded once.
- **Inconsisency**: $I^2 = 0\%$, not downgraded.
- **Indirectness**: Most events occurred in men living in high-income countries, but included people with and without CVD at baseline. Not downgraded.
- **Imprecision**: the 95% CI crossed the null. Downgraded once.
- **Publication bias**: fewer than 10 trials were included so funnel plot not useful. Not downgraded.

[b]**Serum total cholesterol**
- **Risk of bias**: reductions in total serum cholesterol were greater in studies with low summary risk of bias, and all sensitivity analyses suggested that increasing omega-6 fats reduced serum total cholesterol. Not downgraded.
- **Inconsistency**: $I^2 > 60\%$ but partly explained by dose effects in subgrouping. There was a suggestion of greater reductions in TC with greater increases in omega-6 fats in subgrouping. Not downgraded.
- **Indirectness**: data came from men and women with and without baseline CVD, and from low- to middle income and high-income countries. Not downgraded.
- **Imprecision**: 95% CI did not cross the null and included only benefits (reductions in total serum cholesterol with increased omega-6 fats). Not downgraded.
- **Publication bias**: the funnel plot did not suggest small study bias. Not downgraded.

[c] **Serum triglycerides**
- **Risk of bias**: the one study at low summary risk of bias included 458 participants and found that omega-6 fats caused a small reduction in TG (MD −0.10mmol/L, 95% CI −0.26 to 0.06), but single study. Sensitivity analyses not conducted. Downgraded once (in combination with inconsistency).
- **Inconsistency**: $I^2 > 60\%$. Downgraded once (in combination with risk of bias).
- **Indirectness**: data came from men and women with and without baseline CVD, and from low- to middle income and high-income countries. Not downgraded.
- **Imprecision**: the 95% CI included small benefits and harms of omega-6. Downgraded once.
- **Publication bias**: fewer than 10 trials were included so funnel plot not useful. Not downgraded.

[d] **Low-density lipoprotein**
- **Risk of bias**: no included studies were at low summary risk of bias. Sensitivity analyses not conducted. Downgraded once.
- **Inconsistency**: $I^2 = 0\%$, not downgraded.

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- **Indirectness**: only trials of men and women living in developing countries were included. Not downgraded.
- **Imprecision**: the 95% CI crossed the null and included small benefits and harms of omega-6. Downgraded once.
- **Publication bias**: fewer than 10 trials were included so funnel plot not useful. Not downgraded.

[e] **High-density lipoprotein**
- **Risk of bias**: No included studies were at low summary risk of bias. Sensitivity analyses not conducted. Downgraded once.
- **Inconsistency**: $I^2 = 0\%$, not downgraded.
- **Indirectness**: data came from men and women with and without baseline CVD, and from low- to middle income and high-income countries. Not downgraded.
- **Imprecision**: the 95% CI crossed the null and included small benefits and harms of omega-6. Downgraded once.
- **Publication bias**: fewer than 10 trials were included so funnel plot not useful. Not downgraded.

[f] **Body weight**
- **Risk of bias**: no included studies were at low summary risk of bias. Sensitivity analyses not conducted. It was further noted by the WHO NUGAG Subgroup on Diet and Health that most studies did not report on allocation concealment or otherwise had unclear risk of bias for allocation concealment. Although low risk of bias in other elements of bias assessment (e.g. randomisation, blinding of outcome assessment) might suggest that the trials were well-conducted and thus allocation concealment may have been maintained, many of the trials are older and detailed information on the conduct of the trials can be scarce. Therefore, a conservative approach was taken. Downgraded once.
- **Inconsistency**: $I^2 = 30$ to 60%. Not downgraded.
- **Indirectness**: Most data related to men and women without existing CVD living in high-income countries. Not downgraded.
- **Imprecision**: 95% CI crossed the null and included important harms and benefits of omega-6. Downgraded once.
- **Publication bias**: fewer than 10 trials so funnel plot not attempted. However we are aware of at least 2 studies with data that could not be added to the meta-analysis. Downgraded once.

[g] **Body mass index**
- **Risk of bias**: the single included trial was at low summary risk of bias. Sensitivity analyses not conducted. Not downgraded.
- **Inconsistency**: only one trial included. Not downgraded.
- **Indirectness**: only one trial included, of men with previous MI and in a developed country. Not downgraded.
- **Imprecision**: the 95% CI crossed the null and included small benefits and harms of omega-6. Downgraded once.
- **Publication bias**: fewer than 10 trials were included so funnel plot not useful. Not downgraded.

Trusted evidence.
Informed decisions.
Better health.

BACKGROUND

Description of the condition

Cardiovascular diseases (CVDs) are a group of conditions that affect the heart and blood vessels (WHO 2017), and they include cerebrovascular disease, coronary heart disease (CHD), and peripheral arterial disease (PAD). One mechanism thought to cause CVD is atherosclerosis, which is when a person's arteries become narrowed by plaques or atheroma (NHS 2016). This narrowing can lead to angina. Atherosclerosis can cause myocardial infarction (MI) or stroke when part of the plaque breaks off and blocks a smaller vessel, or when a blood clot is formed on the rough plaque surface, blocking the vessel. A narrowed or blocked artery restricts blood flow limiting the amount of blood and oxygen reaching organs or tissue (BHF 2017). Arteries may narrow and become less elastic with age, and the atherosclerotic process may accelerate under conditions including smoking, high cholesterol, hypertension, obesity, sedentary lifestyle, and specific ethnicity (NHS 2016). Rupture of unstable plaques may also cause CVD by activating an inflammatory response. This causes the atherosclerotic plaque structure to weaken and rupture further, leading to superimposed thrombosis (blood clots, Spagnoli 2007).

CVDs are the leading causes of death worldwide (WHO 2017). In 2015 an estimated 31% of all global deaths were due to CVD (WHO 2017). The burden of CVD also varies substantially between regions (Müller-Nordhorn 2008), with low- and middle-income countries (LMICs) disproportionally affected (WHO 2017). In 2001, three-quarters of global deaths from CHD took place in LMICs (Gaziano 2010), and in 2015 37% of premature deaths (deaths before 70 years of age) in LMICs were from CVD (WHO 2017). Gaziano 2010 suggested that this rapid increase in CHD burden is attributable to increased lifespan, socioeconomic changes and acquisition of behavioural risk factors.

Targeting modifiable risk factors, including dietary factors, for CVD prevention is a key public health priority. Studies have found a number of diet and dietary factors to be associated with CVD risk, including low consumption of potassium, fruit and vegetables (Aburto 2013b; AIHW 2016), as well as high intake of salt and saturated fat (Aburto 2013a; Hooper 2015). Such risk factors are extremely important since their modification has the potential to lower CVD risk, making them a main target for CVD primary prevention.

Description of the intervention

Polyunsaturated fatty acids (PUFAs) are characterised by the presence of at least two carbon-carbon double bonds. Omega-6 (n-6) and omega-3 (n-3) fats are both PUFAs. The distinction between omega-6 and omega-3 fats is based on the position and distance of this double bond from the methyl group end of the fatty acid molecule (Calder 2013; Hall 2009). For omega-6 fats, the double bond pair is sixth from the methyl terminus while for omega-3 fats, it is third (Calder 2013; Harris 2009). Linoleic acid (LA) (18:2n6), one of the omega-6 fats, is an essential fatty acid because the human body is unable to synthesise it, so people must obtain it through diet (Groff 1995). Gamma-linolenic acid (GLA, 18:3n6), another omega-6 fat, may become conditionally essential in the event of reduced activity of delta-6-desaturase (the enzyme that converts LA into GLA, Rincón-Cervera 2009).

Other members of the omega-6 fats group include dihomo-gamma-linolenic acid (DGLA) (20:3n6) and arachidonic acid (AA) (20:4n6), which can be derived from LA and synthesised in the healthy human body (though synthesis is minimal, Hussein 2005). LA is widely available in the diet from a variety of sources, such as vegetable oils, nut oils, nuts, poultry, meat, egg, milk, margarines and spreads (Russo 2009), while DGLA is not found in the diet.

Omega-6 fats play a vital role in many physiological functions, stimulating skin and hair growth, regulating metabolism and maintaining bone health (Baylink 1993). However, evidence on the effect of omega-6 fats on CVD risk remains controversial.

How the intervention might work

Dietary fat modification may improve CVD risk and risk factors. Mensink 2003 searched for trials between 1979 to 1999 examining effects of individual fatty acids on blood lipids. They included 60 trials randomising 1672 participants and suggested a beneficial effect of PUFAs (including omega-6 fats) on blood lipids (Mensink 2003). Other studies suggest that a proportionally higher intake of omega-6 fats along with a low intake of saturated fat is associated with significant reductions in CHD (Katan 2009).

A meta-analysis of observational studies aimed to evaluate studies assessing the relationship between blood/tissue omega-6 fat content and CHD events and was based on 25 case-control studies with 1998 cases and 6913 controls. Harris 2007 found that LA content of blood and tissues was inversely associated with CHD risk, while AA was not related to CHD risk. A more recent meta-analysis included only prospective cohort studies that provided multivariate-adjusted risk estimates for dietary LA consumption on CHD endpoints (Farvid 2014). The search identified 13 cohort studies that included 310,602 individuals and 12,479 CHD events, including 5882 CHD deaths. Farvid 2014 reported an inverse relationship between LA intake and CHD events and deaths. They estimated that replacing 5% of energy (5% E) from saturated fat intake with LA would be associated with 9% lower risk of CHD events and a 13% lower risk of CHD deaths (Farvid 2014).

These observational data are supported by a meta-analysis of eight RCTs including 13,614 participants, which found that replacing saturated fatty acids by increasing PUFA consumption, including omega-6 fats, reduced the occurrence of CHD events (Mozaffarian 2010). A Cochrane Review of RCTs investigated the effect of reducing or modifying dietary fats on total CVD mortality and morbidity over at least six months. The findings suggest that modifying dietary fat by replacing saturated fats with monounsaturated fatty acids or PUFAs reduces CVD risk (Hooper 2011). The American Heart Association recommends replacing saturated and trans fats with monounsaturated or polyunsaturated fats, stating that "consumption of at least 5% to 10% of energy from omega-6 PUFAs reduces the risk of CHD relative to lower intakes" (Eckel 2014; Harris 2009).

However, there is concern that consuming a relatively high proportion of dietary omega-6 fats compared with omega-3 fats increases production of 2-series prostaglandins and 4-series leukotrienes to the detriment of 3-series prostaglandins and 5-series leukotrienes. As the 2-series prostaglandins and 4-series leukotrienes exert a more potent pro-inflammatory effect, and inflammation leads to increased blood clotting, omega-6 fats may theoretically worsen cardiovascular risk (Russo 2009; Siriwardhana

2012; Tortosa-Caparós 2017). This relationship is disputed, but it has led to the concept that the ratio between omega-6 and omega-3 fats, rather than absolute intakes, may be crucial (Bibus 2015). Increasing omega-3 fat intake may have different effects than reducing omega-6 fat intakes, even though their effect on the ratio may be identical (Bibus 2015). There is also concern that highly unsaturated fatty acids such as AA may increase the susceptibility of lipoproteins such as low- and very low-density lipoproteins to oxidation, making them more atherogenic (Russo 2009).

Some studies have found no association between omega-6 fat intake and risk of CVD. Earlier prospective cohort studies found no association between dietary intakes of omega-6 fats and stroke (He 2003), CHD (McGee 1984; Pietinen 1997), and CHD mortality (Esrey 1996). Chowdhury 2014 conducted a systematic review of prospective, observational studies and RCTs, reporting non-significant associations between omega-6 fat supplementation and coronary disease or outcomes.

Why it is important to do this review

Omega-6 fats are essential fatty acids that play a vital role in many physiological functions, and everyone consumes some. There is controversy concerning the effect of increasing the amount people eat on cardiovascular risk. Although data tend to support a protective role for omega-6 fats in CVD, results from clinical trials and observational studies are inconsistent. There is a need to review the current evidence from randomised controlled trials (RCTs). An up-to-date systematic review is required to clarify the association between CVD risk and omega-6 fat intake. This can underpin guidance for national and international agencies, practitioners, and members of the public.

The World Health Organization (WHO) is currently updating its guidance on polyunsaturated fatty acid intake in adults and children. The update and extension of scope 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. This review updates Al-Khudairy 2015 and forms a set with Abdelhamid 2018a (assessing effects of omega-3 fats), Abdelhamid 2018b (which overviews health effects of increasing polyunsaturated fats generally), reviews of diabetes and glucose tolerance (Brown 2017), inflammatory bowel disease (IBD) (Thorpe 2017), cognition (Jimoh 2017), depression (Hanson 2017a), bone and muscle health (Abdelhamid 2017), and cancers (Hanson 2017b). This review systematically assessed effects of omega-6 fats on cardiovascular outcomes, mortality, lipids and body fatness.

We undertook this Cochrane Review to assess the current evidence. The review extends Al-Khudairy 2015 in that it includes studies on participants with or without CVD at baseline and slightly extends the outcomes of interest. We included RCTs that stated an intention to increase omega-6 fats by following dietary advice, omega-6 fat supplementation, or a provided diet, compared to usual diets or diets providing fewer omega-6 fats. We examined effects over longer time periods (at least 12 months) as these are most relevant for public health interventions and assessing effects on CVD events, deaths and adiposity.

OBJECTIVES

To assess the effects of increasing omega-6 fats (linoleic acid (LA), gamma-linolenic acid (GLA), dihomo-gamma-linolenic acid (DGLA) and arachidonic acid (AA)) for CVD and all-cause mortality.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) that compared higher versus lower omega-6 fat intake and assessed effects over at least 12 months of continuous involvement. We included studies reported as full texts, those published as abstracts only, as trials registry entries and/or unpublished data. We did not include cross-over studies (unless we could use data from the first part of the cross-over only), as this design is inappropriate for outcomes such as CVD events or mortality, but we did include cluster-randomised studies, as long as there were at least six clusters (to facilitate appropriate statistical testing, MRC 2002).

Types of participants

We included studies in adults (18 years of age and above) regardless of whether they were healthy, at increased risk of cancer, undergoing – or had undergone – coronary artery bypass grafting or angioplasty, or if they had current or previous CVD, diabetes mellitus, rheumatoid arthritis, depression, cognitive impairment or multiple sclerosis. We were interested in both primary and secondary prevention, so we included people with or without a history of CVD.

We excluded participants who were pregnant or acutely ill, defining acute illness as having a current diagnosis of cancer, HIV or AIDS; undergoing heart or renal transplantation; on haemodialysis; with immunoglobulin A (IgA) glomerulonephritis; or having any other renal problem except diabetic nephropathy. Our reasoning was to exclude people with conditions that may affect the relationship between polyunsaturated fats and CVD events.

Where trials included some adults and some people under 18 years of age, we included the study if at least 90% of the participants were aged 18 years or over at baseline, or where outcomes for adults could be separated from those for younger people.

Types of interventions

Eligible trials compared higher versus lower omega-6 fat (including LA, GLA, DGLA, AA, or any combination) intakes. The intervention had to be dietary supplementation, a provided diet, or advice on diet. The advice, foodstuffs or supplements had to aim to increase or decrease intake of omega-6 fats, or a dietary component high in omega-6 fats such as sunflower oil, or, if no clear aim was stated (but implied, such as aiming to provide a 'heart health' or 'Mediterranean' diet) then the intervention had to achieve an increase or decrease of at least 10% of the baseline omega-6 fat level. Energy replacement for changes in omega-6 fat intake could be by carbohydrates, saturated fats, protein, alcohol, or monounsaturated fats.

Supplementation had to be in oil or capsule form, or as foodstuffs provided to be consumed by mouth (we excluded enteral and parenteral feeds and enemas).

We excluded studies that included multiple risk factor intervention on lifestyle factors such as weight reduction, smoking or physical activity, 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 this intervention versus usual diet, no advice, no supplementation or placebo (as appropriate) with a lower omega-6 fat intake. We excluded studies that aimed to increase both omega-6 and omega-3 fats (these were included in Abdelhamid 2018a).

Types of outcome measures

We included studies where data on any primary or secondary outcome had been collected by the investigators.

Where it was clear that no participants experienced a particular primary or secondary outcome (and data were not available on other primary or secondary outcomes), we included the trial or study arm in the review for comprehensiveness, but these did not contribute data.

Primary outcomes

1. All-cause mortality
2. CVD mortality
3. CVD events (all available data on fatal and non-fatal myocardial infarction, angina and/or stroke)
4. Coronary heart disease events: myocardial infarction (fatal or non-fatal) or angina
5. Major adverse cardiac and cerebrovascular events (MACCEs), used where we could assess the numbers of participants experiencing fatal and non-fatal myocardial infarction, unstable angina and stroke
6. Stroke (total, fatal and non-fatal, ischaemic and haemorrhagic)

We assessed dichotomous outcomes at the latest point of available follow-up within the RCT and continuous outcomes at the latest point available in the trial (and after at least 12 months).

Secondary outcomes

1. Myocardial infarction (MI, total, fatal and non-fatal)
2. Angina
3. Sudden cardiac death
4. Atrial fibrillation (AF) (new or recurrent, ventricular tachycardia and/or ventricular fibrillation)
5. Heart failure
6. Revascularisation (angioplasty or coronary artery bypass grafting)
7. Peripheral arterial disease (PAD)
8. Serum lipids (including total cholesterol, fasting triglycerides, high- (HDL) and low-density lipoprotein (LDL) cholesterol)
9. Body mass index (BMI), body weight and other measures of adiposity

Tertiary outcomes

1. Blood pressure (systolic and diastolic)
2. Quality of life measures (such as self-reported health and time off work)

3. Economic costs
4. Serious adverse events (including breast cancer, all cancers, inflammatory bowel disease, diabetes, depression, and neurocognitive outcomes such as dementia)

We collated data on tertiary outcomes where they were present in included trials (so we did not truly systematically review them in this paper). Data on cancers (Hanson 2017b), inflammatory bowel disease (Thorpe 2017), neurocognitive outcomes including dementia (Jimoh 2017), diabetes (Brown 2017), bone and functional outcomes (Abdelhamid 2017), and depression (Hanson 2017a) are reported fully and systematically in associated reviews within this series.

Key outcomes

When the World Health Organization (WHO) Nutrition Guidance Expert Advisory Group (NUGAG) requested this review update they named the following as key outcomes to inform their planned dietary guidance:

1. All-cause mortality
2. CVD mortality
3. CVD events
4. CHD events
5. Stroke
6. Myocardial infarction
7. Serum lipids including total cholesterol, fasting triglycerides, HDL and LDL
8. Measures of adiposity (body weight and BMI)

We were not able make all of these key 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. We explained this change to our methods in Differences between protocol and review.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases on 2 May 2017 to identify reports of relevant randomised clinical trials.

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2017 Issue 4) in the Cochrane Library.
2. Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE Ovid (1946 to 2 May 2017).
3. Embase Classic and Embase Ovid (1947 to 1 May 2017).

We adapted the search strategy for MEDLINE (Ovid) from the search strategy in Al-Khudairy 2015 (Appendix 1), and we used the single search strategy to locate trials for this review and for Abdelhamid 2018b. We adapted this complex strategy for use in the other databases (Appendix 2). We applied the Cochrane sensitivity and precision-maximising RCT filter to MEDLINE (Ovid) and Embase, applying terms recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011).

As we were also running searches in April 2017 for a concurrent Cochrane Review of the effects of omega-3 fats on health outcomes

(Abdelhamid 2018a), and there was a great deal of overlap between the searches, the results of these searches were de-duplicated with the results from the searches for this review and all the titles and abstracts assessed as a single set. We created a dataset of RCTs that compared higher versus lower omega-6 fats, omega-3 fats or total PUFA in adults with a duration of at least six months. We used this dataset as the wider study pool from which to select studies for all reviews (Abdelhamid 2018a; Abdelhamid 2018b; Abdelhamid 2017; Al-Khudairy 2015; Brown 2017; Hanson 2017a; Hanson 2017b; Jimoh 2017; Thorpe 2017).

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

Searching other resources

We checked included trials of relevant systematic reviews and wrote to authors of included studies for additional studies and trial data (including unpublished outcome data).

We attempted to obtain full-text translations and/or evaluations of all relevant non-English articles. Where these were not available we translated papers ourselves using our existing language skills and language translation software.

Data collection and analysis

Selection of studies

All authors carried out screening, with each record being independently screened by two review authors. We initially screened titles and abstracts of all the potential studies identified as a result of the searches and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved the full text of all records that either reviewer had coded for retrieval. Two review authors (LH and one other reviewer) independently screened the full texts, assessed studies for inclusion, and identified and recorded reasons for exclusion of ineligible studies. We resolved any disagreement through discussion or consulted a third reviewer (AA). Where a study fit all our inclusion criteria except the reporting of any relevant outcomes, we wrote to the study author to ask whether they had measured but not reported any outcomes relevant to our review. Where we learnt that no primary or secondary outcome events had occurred (for example no deaths or CVD events occurred and no continuous outcomes measured), we included the study, but it did not contribute data to the meta-analyses.

We identified and excluded duplicates and collated multiple reports of the same study (as each study – rather than each report – was the unit of interest in the review). We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and Characteristics of excluded studies table.

Data extraction and management

We developed a draft data collection form for collating study characteristics and outcome data, then all reviewers piloted the form on a single included study to standardise data extraction and improve the data extraction form. All authors took part in data extraction. Two review authors each extracted the following study characteristics from included studies, independently and in duplicate.

1. Bibliographic details.
2. Trial registration database and number.
3. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals and date of study.
4. Participants: number randomised in each arm, number analysed in each arm, mean age, age range, sex, health status, baseline CVD risk and a brief description of participants. We categorised baseline CVD risk as low (no specific CVD risk factors in the inclusion criteria), moderate (people recruited on the basis of hyperlipidaemia, diabetes, metabolic syndrome, familial risk, high blood pressure, obesity or a high CVD risk score) or high (those with existing CVD such as angina or a previous stroke or myocardial infarction).
5. Interventions: intervention (including composition and dose of omega-6 intake advised or supplement used), comparison, concomitant medications and excluded medications.
6. Outcomes: primary and secondary outcomes specified in trial registry, data on outcomes reported in publications and by contact with authors, time points reported.
7. Process data: mean and standard deviation (SD) of total PUFA, omega-3 fat, omega-6 fat, total fat, saturated fat (SFA), monounsaturated fat (MUFA) and trans fat intake plus erythrocyte, serum or adipose tissue fatty acid status data in intervention and control groups at latest point available during RCT.
8. Trial funding and notable conflicts of interest of trial authors.

We resolved disagreements between data extractions by consensus and/or by involving a third reviewer (LH or AA). One review author (AA or LH) transferred data into the Review Manager 5 file (RevMan 2014). We double-checked that data were entered correctly from the agreed data extraction by comparing the data presented in the systematic review with data extraction (AA, JB, TB or LH).

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study, alongside data extraction, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011, all review authors carried out data extraction and assessment of risk of bias). We resolved disagreements by discussion or by involving another author (LH or AA). We assessed the risk of bias according to the following domains.

1. Random sequence generation (selection bias).
2. Allocation concealment (selection bias).
3. Blinding of participants and personnel (performance bias).
4. Blinding of outcome assessment (detection bias).
5. Incomplete outcome data (attrition bias).
6. Selective outcome reporting (reporting bias).
7. Attention bias (another aspect of performance bias, where the intervention or control groups receive more time and/or attention from study or health personnel during the trial).
8. Compliance bias (we considered studies to be at low risk of compliance bias when they assessed and clearly reported compliance for both intervention and control arms, and where most participants appeared to have taken at least 64% of the intended PUFA dose).
9. Other risk of bias.

These are the domains of the Cochrane Risk of Bias tool, with the exceptions of attention and compliance bias, which were specific to our review. We followed recommendations in Higgins 2011, recording funding data in the Characteristics of included studies but not using them as a separate issue for assessing risk of bias.

We graded each potential source of bias as conferring high, low or unclear risk of bias and provided details from the study and/or a quotation from the study report together with a justification for our judgment in the 'Risk of bias' tables. We summarised the risk of bias judgements across different studies for each of the domains listed. Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' tables. Table 1 presents further details of how we interpreted the risk of bias elements across studies.

Summary risk of bias

Schultz 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). Most of our outcomes were objectively measured. Although we originally planned to assess summary risk of bias for all included trials in the same way across this review (Al-Khudairy 2015), the omega-3 review (Abdelhamid 2018a), and the total PUFA review (Abdelhamid 2018b), we adopted a different approach after discussing the different nature of supplement trials compared to dietary advice or food provision trials with the NUGAG Subgroup on Diet and Health. Discussion centred on blinding for supplement-type trials and on compliance for dietary advice type trials.

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 (selection, performance and detection bias) to be adequate. All other trials were considered 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 (selection and detection bias) to be adequate. We considered all other trials to be at moderate or high risk of bias (a single category).

Assessment of bias in conducting the systematic review

We conducted this Cochrane Review according to the methods used in Al-Khudairy 2015 and reported deviations from it in the Differences between protocol and review section.

Measures of treatment effect

We analysed dichotomous data as risk ratios (RRs) with 95% confidence intervals (CIs) and continuous data as mean difference (MD) with 95% CIs. We presented continuous data with a consistent direction of effect (as a smaller reading is generally beneficial), with the exception of HDL cholesterol, where an increase was beneficial.

We used change data (change from baseline to latest point in study in each arm) for continuous data where available with appropriate variance data. When change data were not available and baseline data were comparable between arms, we used absolute data from the latest point in each study arm. We considered absolute data too different to use when the change in both arms (from baseline to end data) was smaller than the baseline difference between arms. Where continuous data were too different to use, we noted this in the 'Outcomes' section of Characteristics of included studies but did not add data to meta-analyses.

We intended a narrative description of skewed data reported as medians and interquartile ranges or as medians without variance data. We added these data to forest plots to enable visual comparison of findings (though we did not include these data in meta-analysis). We intended to use standardised mean differences (SMD) to combine data where trials used different scales to measure the same variable (such as quality of life). We found no such data so did not use SMDs.

Unit of analysis issues

Studies with multiple intervention groups

Within this review, most included studies with more than two intervention arms also had separate control arms relevant to each of the intervention arms, so we used the relevant control arm for each of the intervention arms. We never had to use the same control group twice. For the exceptions (NDHS Faribault 1968; NDHS Open 1st 1968), we combined the intervention arms and compared them with the single control arm. This meant there were no problems with study participants appearing more than once in any forest plot.

Cluster-RCTs

For cluster-randomised trials, we planned to account for unit of analysis issues by extracting a direct estimate of the required effect measure (for example, a risk ratio with its confidence interval) from an analysis that accounted for the cluster design properly (for example, an analysis based on a 'multilevel model', a 'variance components analysis' or that used 'generalised estimating equations (GEEs)'). Where these data were available, we would have used them in meta-analysis using the generic inverse-variance method (Higgins 2011). Where no such correct analysis of the cluster-randomised data were available, we planned to use approximate analyses using intracluster correlation coefficient (ICC) analysis as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011, section 16.3.4). We identified no such cluster randomised trials, so did not need this methodology.

Dealing with missing data

We contacted (or attempted to contact) the authors of all potentially included, included and ongoing RCTs to request available data on all of the study outcomes relevant to our set of reviews and key information on risk of bias. We sent an email and a posted letter to the corresponding author at the latest address we were able to obtain (tracking latest publications in MEDLINE). Where data on at least one review outcome were available, we included the RCT and asked the authors to provide any additional data about study methodology or risk of bias.

Where papers reported continuous results as change from baseline, we used these data, otherwise we used data at the latest point available. We did not impute change data.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. Where we identified substantial heterogeneity (assumed when I^2 was greater than 60%, as 30% to 60% represents moderate heterogeneity and we were allowing for the varied dietary interventions included as well as potential dose-response effects) we reported it and explored possible causes by prespecified subgroup analysis.

Assessment of reporting biases

We assessed reporting biases using a funnel plot where we were able to pool at least 10 trials. We ran a funnel plot for all-cause mortality and serum total cholesterol because these analyses included 10 trials. We did not create funnel plots for other outcomes, as fewer than 10 trials were available for meta-analyses. We noted where we were aware of missing data. This occurred where trialists noted measuring but not reporting an outcome (or not reporting it by study arm), where continuous data were unbalanced at baseline, or where trialists presented data as medians or as means but without variance information.

Data synthesis

We undertook meta-analyses only where we considered this meaningful, i.e. where the treatments, participants and the underlying clinical question were similar enough for pooling to make sense. We carried out statistical analysis using RevMan 2014. We used a random-effects model, as dietary interventions are complex and somewhat heterogeneous by nature (more so than most medical treatments), but we compared the results of random-effects and fixed-effect meta-analyses in sensitivity analyses. As the random-effects model assigns more weight to smaller studies, it is more conservative and may lead to imprecise estimates of effect. We also carried out sensitivity analyses to assess the effects of methodological rigour, removing studies at moderate to high summary risk of bias (for other sensitivity analyses see below).

When we judged evidence from dichotomous outcomes to be low, moderate or high GRADE quality, we calculated the number needed to treat for an additional beneficial outcome (NNTB) and its 95% confidence interval using standard equations (Evidence Based Medicine Toolkit 2008).

Subgroup analysis and investigation of heterogeneity

We explored the effects of omega-6 fat intake on all primary review outcomes and also key review outcomes where these were secondary outcomes in our review and included at least six studies by subgroup. The planned subgroup analyses were by:

1. omega-6 fat type (primarily LA vs GLA);
2. intervention type (dietary advice, supplements (capsules), supplemental foods or all foods provided);
3. replacement of SFA, MUFA, carbohydrate, protein or alcohol with omega-6 fat;
4. baseline risk of CVD (low or moderate risk, equivalent to primary prevention, or secondary prevention);
5. omega-6 fat dose (and dose-response, < 4% E from omega-6 fats, 4% to 12% E from omega-6 fats and > 12% E from omega-6 fats in the intervention compared with control). We added the > 12% E subgroup post hoc to provide some separation between studies with a wide range of higher doses. The original 4% E cut-

off was suggested when the PICO question for the review was set out as part of a 2016 WHO NUGAG Subgroup on Diet and Health meeting;

6. trial duration: studies with medium follow-up (12 to 23 months), medium to long follow-up (24 to 47 months), and long follow-up (48 months or more). There was some discussion within WHO NUGAG Subgroup on Diet and Health about whether to limit trials to those of at least two years' duration, but as some proposed omega-6 fat mechanisms may affect cardiovascular health more quickly (anti-thrombotic and anti-inflammatory mechanisms for example), we agreed to include trials of at least 12 months, subgrouping to assess for duration effects;
7. statin use (at least 50% of control group on statins versus fewer than 50% on statins);
8. baseline omega-6 fat intake (we used omega-6 fat intake where available, but otherwise used baseline PUFA intake, usually mostly LA, where this was available): < 5% E from omega-6 fats, 5% to < 8% E from omega-6 fats, ≥ 8% E from omega-6 fats, with cut-offs based on recommendations that populations should consume 5% to 8% of dietary energy from omega-6 fats (WHO 2003); and
9. participants' sex.

We also planned to subgroup by change in the omega-3/omega-6 fat ratio (assessing whether the intervention primarily increased omega-3 fats (putting up the ratio) or omega-6 fats (lowering the ratio)). However, we rarely had enough information to calculate this ratio so did not carry out the subgroup analysis.

WHO NUGAG Subgroup on Diet and Health requested these analyses to better help them understand the data. The danger of having so many subgroup analyses is over-interpretation, increasing the risk of a type 1 error. We used the formal test for subgroup interactions in RevMan 2014 to minimise this risk.

Meta-regression

We used meta-regression to further explore effects of omega-6 fat dose (looking for evidence of dose response), baseline omega-6 fat dose and duration on primary outcomes. We used the dataset of all included trials (of at least 12 months' duration) that reported each outcome from this review and its sister reviews (omega-6 fat trials from this review, omega-3 fat trials from Abdelhamid 2018a, and total PUFA trials from Abdelhamid 2018b) to assess effects of omega-6 fat dose. We also used the set of trials within this review alone to assess relationships between omega-6 fat dose, baseline omega-6 dose and duration with each of the dichotomous primary outcomes with at least seven included trials.

We carried out random-effects meta-regression, as described in Berkley 1995, using the STATA command metareg (Sharp 1998): log(e) relative risk vs (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 we would have entered a trial with 10 people experiencing stroke in one arm but none in the other arm as 10.1 and 0.1).

Sensitivity analysis

We carried out the following sensitivity analyses on all primary outcomes (regardless of the number of included trials) as well as on

secondary outcomes that were key outcomes and where at least six trials provided data. These were our main sensitivity analyses.

1. Using fixed-effect meta-analysis.
2. Limiting analyses to studies at low summary risk of bias.

These were additional sensitivity analyses.

1. Only including all studies up to 2010, plus studies post-2010 that were registered on a trials register (Roberts 2015).
2. Only including studies with no industry funding (where funding was stated, but did not include any commercial funds or gifts).
3. Only including studies with less than 10% difference in intake of trans fats between study arms during the intervention (trans fats are formed when solidifying polyunsaturated oils so may have been given at increased doses in early diets high in omega-6 fats where those fats were solidified to use in margarines and baking – however, we now know that they are likely to increase our risk of CVD so may confound any beneficial effects of increasing omega-6 fats).
4. Only including studies with a low risk of attention bias.
5. Only including studies that randomised at least 250 participants, or at least 100 participants.

Unfortunately almost no data on trans fats were available, so we did not perform sensitivity analyses around this variable.

'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 PUFA 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 for key outcomes. We used the five GRADE considerations (study limitations, 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 created a 'Summary of findings' table for the primary outcomes.

1. All-cause mortality
2. CVD mortality
3. CVD events
4. Coronary heart disease events
5. Major adverse cardiac and cerebrovascular events
6. Stroke

To enable readers to easily access data on the key outcomes that were secondary outcomes in this review, and which were also formally systematically reviewed, we created a second 'Summary of findings' table for key secondary outcomes.

1. Myocardial infarction
2. Total serum cholesterol
3. Serum triglycerides
4. Low-density lipoprotein
5. High-density lipoprotein
6. Body weight
7. Body mass index

R E S U L T S

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 fats, omega-3 fats or PUFA over at least six months) generated 37,810 titles and abstracts, or 19,772 unique records after de-duplication. We assessed these along with 53 previously included studies (from Al-Khudairy 2015 and Abdelhamid 2018a, to reassess for inclusion), 986 potentially relevant trials registry entries and 35 new references gained from other systematic review reference lists, so that we assessed a total of 20,846 titles and abstracts in duplicate to decide on potential inclusion. We retrieved 2155 full texts, including 226 systematic reviews and 1929 papers whose full text we assessed in duplicate for inclusion and to group into studies. Of these, we included 364 RCTs of omega-3 fats, omega-6 fats or total PUFA interventions with a duration of at least 24 weeks, regardless of what outcomes were reported in our wider study pool. This was the database of trials we used for the full set of reviews. Of this dataset, 28 studies assessed the effects of omega-6 fats, and of these, 19 were of at least 12 months' duration, had collected relevant outcome data and are included in this review.

We identified a single ongoing trial, which we describe in Characteristics of ongoing studies. Figure 1 presents details of the flow of studies.

Figure 1. Study flow diagram.


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┌─────────────────────┐   ┌─────────────────────┐
│ 19772 records       │   │ 1074 additional     │
│ identified through  │   │ records identified  │
│ database            │   │ through other       │
│ searching:          │   │ sources:            │
│                     │   │                     │
│ Joint searches for  │   │ Trials register     │
│ omega-3,            │   │ searches: 986       │
│ omega-6 and         │   │                     │
│ PUFA trials         │   │ ClinicalTrials.gov: │
│                     │   │ 519                 │
│ *CENTRAL:           │   │                     │
│ 13,073              │   │ WHO ICTRP: 467      │
│                     │   │                     │
│ *MEDLINE: 10,948    │   │ Checks of existing  │
│                     │   │ systematic          │
│ *Embase: 13,789     │   │ reviews: 88         │
│                     │   │                     │
│ Total: 37,810;      │   │ Total: 1074         │
│ de-duplicated:      │   │                     │
│ 19,772              │   │                     │
└─────────────────────┘   └─────────────────────┘
```

20,846 records after duplicates removed

20,846 records screened → 18,691 records excluded

2155 full-text articles, conference abstracts and trials registry entries assessed for eligibility → 1216 full-text articles, abstracts and trials registry entries excluded, with reasons

Included records grouped into 364 RCTs, further 81 RCT publications, abstracts or registry entries searched out (part of identified RCTs)

Figure 1.   (Continued)

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                    ┌─────────────┐
                    │             │
                    └──────┬──────┘
                           │
                           ▼
        ┌──────────────────────┐
        │ 364 RCTs             │        ┌────────────────────────────┐
        │ included in the      │        │ 96 RCTs included in dataset,│
        │ dataset for the full │        │ but without health outcomes │
        │ set of reviews       │        │ for current reviews (including│
        │ (RCTs of             │        │ 147 papers and abstracts, 8 │
        │ omega-3,             │───────▶│ trial registrations and 25 sets│
        │ omega-6 or total     │        │ of author correspondence).  │
        │ PUFA, duration       │        │                            │
        │ ≥ 6 months,          │        │ 57 Ongoing RCTs, no results │
        │ reported in 1020     │        │ found to date (including 31 │
        │ papers, abstracts    │        │ papers, 60 trial registrations, 5│
        │ and trials registry  │        │ sets of author             │
        │ entries, plus        │        │ correspondence).           │
        │ additional data      │        └────────────────────────────┘
        │ from 121 authors).   │
        └──────────┬───────────┘
                   │
                   ▼
        ┌──────────────────────┐        ┌────────────────────────────┐
        │ 211 RCTs included in at│      │ 192 trials excluded as:     │
        │ least one systematic  │       │                            │
        │ review of health      │       │ ● duration was < 52 weeks,  │
        │ outcomes (including   │──────▶ │ ● intervention was not      │
        │ 683 papers and abstracts, 91│  │   omega-6 or              │
        │ trial registrations, 91 sets│  │ ● did not collect data on at│
        │ of author correspondence).│    │   least one key review     │
        └──────────┬───────────┘        │   outcome.                 │
                   │                    └────────────────────────────┘
                   ▼
        ┌──────────────────────┐
        │ 19 RCTs included (55 papers│
        │ and abstracts): 17 were│
        │ included in quantitative│
        │ synthesis (meta-analysis), 2│
        │ were included narratively only.│
        │                       │
        │ All 19 included RCTs altered│
        │ omega-6 fats with duration ≥│
        │ 12 months and measured│
        │ review primary and/or │
        │ secondary outcomes    │
        └──────────────────────┘
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Included studies

Details of methods, participants, intervention, comparison, and outcome measures for each included trial are shown in Characteristics of included studies. We found that 19 trials including 6461 randomised participants met the inclusion criteria. Trial duration varied from one year (our minimum for inclusion) up to eight years (Veterans Admin 1969), with a median of 24 months and mean duration of over 31 months (for the 17 trials that provided data for the review). However, the mean duration of participants experiencing the intervention was slightly shorter (as participants dropped out over time).

Participants in 17 of the 19 included trials had experienced at least one outcome event or had a relevant continuous outcome measured. We included two other trials in the review as we are fairly certain that no deaths or CVD events occurred in participants, and none of our continuous outcomes were assessed (Belch 1988; Mansel 1990). One trial provided data on two useful comparisons (Bates 1977); however, although mortality appears to have occurred in several arms, the numbers of deaths are no longer available to the authors (for this reason we included both arms but they constitute missing data that could not be used in the all-cause mortality meta-analysis). Another trial ran two comparisons (Bates

1978), but no deaths or other events occurred in one comparison (so the relevant intervention and control arms are included but not represented in the analyses); only the other comparison is included in meta-analyses. The 2 × 2 × 2 factorial trial only provided one comparison relevant to this review (DART 1989), and we combined several smaller arms into a single comparison for NDHS Faribault 1968 and NDHS Open 1st 1968. All in all, we included 19 trials, 17 of which contributed data to 18 comparisons. No cluster-RCTs met the inclusion criteria.

Ten trials recruited both men and women, but DART 1989, MRC 1968, NDHS Faribault 1968, NDHS Open 1st 1968, Sydney Diet-Heart 1978 and Veterans Admin 1969 recruited only men, one trial recruited 94% women (Belch 1988), and one trial only women (Mansel 1990). One trial did not specify the sex of its participants (Rose 1965). Participants were generally of early to late middle age, but some studies included a few older adults (aged 65 years or more). Mean age of study participants ranged from 33 years in Bates 1978 to 65 years in Veterans Admin 1969, with a median mean age of 50 years in the 13 trials that reported mean age (estimated as 50 years in NDHS Faribault 1968 and NDHS Open 1st 1968, which included participants aged 45 to 54 years). Bates 1977 and Houtsmuller 1979 did not report age details, while Mendis 2001 recruited participants aged 22 to 55 years; Mansel 1990, women aged 36 to 60 years; and MRC 1968, participants aged less than 60 years.

The trials varied in the types of participants recruited and their level of CVD risk. Participants in 10 trials were at low risk of CVD. Bates 1977 and Bates 1978 recruited people with multiple sclerosis; NDHS Faribault 1968, men living in mental hospitals; Veterans Admin 1969, men living in a Veterans Administration Centre; Schirmer 2007, healthy adults following weight loss; Mendis 2001, healthy adults; McIllmurray 1987, people following treatment for colorectal cancer; Black 1994, people with non-melanoma skin cancer; Mansel 1990, women with breast cysts; Belch 1988, people with rheumatoid arthritis; and NDHS Open 1st 1968, free-living men without particular CVD risk or other disease. Three trials included people at moderate CVD risk (GLAMT 1993 recruited people with mild diabetic neuropathy; Dullart 1992, people with diabetes; and Houtsmuller 1979, people with newly diagnosed diabetes), while five trials included those with existing CVD (DART 1989, MRC 1968 and Sydney Diet-Heart 1978 recruited men following myocardial infarction; Vijayakumar 2014, people with stable coronary artery disease; and Rose 1965, people with ischaemic heart disease).

Five trials took place in North America (Black 1994; NDHS Faribault 1968; NDHS Open 1st 1968; Schirmer 2007; Veterans Admin 1969), 1 in Australia (Sydney Diet-Heart 1978), 2 in Asia (Mendis 2001; Vijayakumar 2014), and 11 in Europe (Bates 1977; Bates 1978; Belch 1988, DART 1989; Dullart 1992; GLAMT 1993; Houtsmuller 1979; Mansel 1990; McIllmurray 1987; MRC 1968; Rose 1965).

The interventions and controls varied. Seven trials assessed effects of GLA: providing supplementary capsules, of GLA plus LA vs oleic acid (both comparisons of Bates 1977 and the single included comparison of Bates 1978), GLA versus monounsaturated fats (Schirmer 2007), GLA capsules versus paraffin (Belch 1988; GLAMT 1993; Mansel 1990), or GLA versus an 'inert placebo' that was not described further (McIllmurray 1987). Twelve trials altered LA intake, most increasing LA in the intervention arm, but Black 1994 aimed to reduce total fat intake in the intervention arm, reducing LA intake in the process (this trial was entered in meta-analysis

with the control arm as the higher omega-6 fat arm). In some trials the LA mainly replaced a single dietary component, but in others LA replaced several components (the description below is not additive). No studies assessed effects of DGLA or AA. The omega-6 fat dose delivered was the difference between omega-6 fats in the intervention and the control. Doses ranged from 0.8% of energy intake (% E) from omega-6 fats in Schirmer 2007 to 20.6% E in Rose 1965. Eight trials provided a dose of less than 4% E from omega-6 fats (Bates 1977; Bates 1978; Belch 1988; Black 1994; DART 1989; McIllmurray 1987; Mendis 2001; Schirmer 2007); six trials, 4% to 12% E (Dullart 1992; GLAMT 1993; Houtsmuller 1979; NDHS Open 1st 1968; Sydney Diet-Heart 1978; Veterans Admin 1969); and four trials, a dose of over 12% E omega-6 fats (MRC 1968; NDHS Faribault 1968; Rose 1965; Vijayakumar 2014). Baseline omega-6 fat intake was less than 5% E in three trials (NDHS Faribault 1968; NDHS Open 1st 1968; Veterans Admin 1969), 5% to < 8% E in three trials (DART 1989; Dullart 1992; Sydney Diet-Heart 1978), and at least 8% E in one trial (Black 1994). The remaining 12 trials did not report baseline intake.

As the omega-6 fat LA rose, saturated fat intake fell in nine trials (DART 1989; Dullart 1992; Houtsmuller 1979; MRC 1968; NDHS Faribault 1968; NDHS Open 1st 1968; Sydney Diet-Heart 1978; Veterans Admin 1969; Vijayakumar 2014), MUFA fell in five (NDHS Faribault 1968; NDHS Open 1st 1968; Rose 1965; Sydney Diet-Heart 1978; Veterans Admin 1969), both carbohydrates and protein intake fell in one (Black 1994), and carbohydrates fell in one other (Houtsmuller 1979). For Mansel 1990, Mendis 2001 and Belch 1988 the replacement for omega-6 LA was unclear, and in MRC 1968, while LA partially replaced SFA the remainder of the replacement was unclear. Readers should keep in mind that we have assessed these effects from either the trial's intentions or reported intakes in both arms, but papers frequently omit the mention of important dietary components; replacement can be considered our best understanding, but it is not definitive.

Included trials were published over 50 years between 1965 and 2014, with five published during the 1960s, four during the 1970s, three during the 1980s, four during the 1990s, two during the 2000s and one in 2014.

Mansel 1990 and Rose 1965 did not report funding sources. Funding appeared to be purely from national or charitable agencies in eight trials (Black 1994; Dullart 1992; Houtsmuller 1979; Mendis 2001; MRC 1968; NDHS Faribault 1968; NDHS Open 1st 1968; Sydney Diet-Heart 1978). A further six trials had funding from mixed national or charitable sources, with some products or funding appearing to come from commercial sources (Bates 1977; Bates 1978; Belch 1988; DART 1989; Veterans Admin 1969; Vijayakumar 2014). Three trials acknowledged only commercial funding sources or sources of intervention products (GLAMT 1993; McIllmurray 1987; Schirmer 2007).

The single ongoing trial we identified was in people with pre-diabetes, comparing a low fat diet with raised PUFA to SFA ratio versus a control diet over three years (Chandrakala 2010). The authors have presented this study in several conference abstracts, without usable outcome data. They confirmed that it is not yet fully published and declined to provide further information (Characteristics of ongoing studies).

Excluded studies

We have presented details and reasons for exclusion of the studies that most closely missed the inclusion criteria in the Characteristics of excluded studies table. Appendix 3 lists studies of less than 12 months' duration (as there were so many). Other than short duration, the most common reasons for exclusion of studies were a non-RCT design or an inappropriate intervention or comparison.

Risk of bias in included studies

We have provided details regarding the risk of bias judgements for the included trials in the 'Risk of bias' tables in Characteristics of included studies, with details of how we made specific judgements in Table 1. We have presented a 'Risk of bias' summary in Figure 2.

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

We judged three studies to be at low summary risk of bias (NDHS Faribault 1968; NDHS Open 1st 1968; Sydney Diet-Heart 1978). All three were dietary advice trials, so they were at low risk of bias from random sequence generation, allocation concealment and blinding of outcome assessors. We considered the remaining 16 trials to be at moderate to high risk of bias.

Allocation

We judged 10 of the 19 studies to be at low risk of bias for random sequence generation, while the remainder were at unclear risk (often simply described as "randomised" in the Methodology sections). We considered only four trials to be at low risk of bias for allocation concealment (Dullart 1992; NDHS Faribault 1968; NDHS Open 1st 1968; Sydney Diet-Heart 1978), with the rest providing too few details of the randomisation process to make a judgement. This was despite trying to elicit information on the process of randomisation from authors. When asking open questions about the randomisation process, many authors quoted or referred to their published papers or stated that they did not remember. We did not push further with these questions, as asking closed questions was likely to elicit inappropriate answers.

Blinding

Blinding of participants and personnel is often very difficult in dietary trials, but we considered 9 of the 19 studies to be at low risk of performance bias. This included five capsule-supplemented trials (Bates 1977; Bates 1978; Belch 1988; GLAMT 1993; Schirmer 2007), three institutional or shop-based studies where participants received all or most food (NDHS Faribault 1968; NDHS Open 1st 1968; Veterans Admin 1969), and one study providing oils to both intervention and control groups (Rose 1965). Lack of blinding of participants and/or personnel put six trials at high risk of bias (Black 1994; DART 1989; Dullart 1992; Mendis 2001; MRC 1968; Sydney Diet-Heart 1978), while the remaining studies were at unclear risk. We considered nine studies to be at low risk of detection bias for blinding of outcome assessors (Black 1994; DART 1989; MRC 1968; NDHS Faribault 1968; NDHS Open 1st 1968; Rose 1965; Schirmer 2007; Sydney Diet-Heart 1978; Veterans Admin 1969), while this domain was unclear in the remainder.

Incomplete outcome data

We judged 11 trials to be at low risk of attrition bias (Bates 1978; Black 1994; Belch 1988; DART 1989; Mansel 1990; NDHS Faribault 1968; NDHS Open 1st 1968; Rose 1965; Sydney Diet-Heart 1978; Veterans Admin 1969; Vijayakumar 2014), 4 at high risk (GLAMT 1993; Mendis 2001; MRC 1968; Schirmer 2007), and the remainder at unclear risk.

Selective reporting

We did not find a pre-published trials registry entry or protocol for any of the included studies (most were published many years before trials registries became available), so we found all to be at unclear risk of reporting bias.

Other potential sources of bias

We assessed risk of bias from differences in trialists' attention or time between arms (attention bias) and compliance problems, as well as noting any other sources of bias.

We noted high risk of attention bias for five dietary advice trials where the control participants were told to consume their normal diets (Black 1994; DART 1989; Dullart 1992; MRC 1968; Sydney Diet-Heart 1978). The remaining 14 trials were judged at low risk of attention bias.

We judged compliance adequate (at low risk of causing bias) for seven trials (Black 1994; DART 1989; Houtsmuller 1979; NDHS Faribault 1968; NDHS Open 1st 1968; Schirmer 2007; Sydney Diet-Heart 1978), poor in six where biomarkers suggested that dietary goals had not altered omega-6 fats appreciably (Bates 1978; Dullart 1992; Mendis 2001; Rose 1965; Veterans Admin 1969; Vijayakumar 2014), and unclear in the remaining six.

We did not note sources of other bias in 16 trials (resulting in low risk of other bias), but McIllmurray 1987 did not specify the composition of their placebo capsules, and Mendis 2001 did not state the form or composition of the intervention or control fats, resulting in unclear risk of other bias. We found Houtsmuller 1979 to be at high risk of other bias as concerns about fraud of the first author were raised around his later research (on cancer diets), and numbers of events were unclear by arm and had to be assessed across several unclear publications. Additionally, this study was extremely vague across all publications about its methods.

Effects of interventions

See: **Summary of findings for the main comparison** Higher versus lower omega-6: primary outcomes; **Summary of findings 2** Higher versus lower omega-6: additional key outcomes

Primary outcomes

See Summary of findings for the main comparison.

All-cause mortality

Increasing omega-6 fats may make little or no difference to the risk of all-cause mortality (low-quality evidence, downgraded for risk of bias and imprecision, Summary of findings for the main comparison). This section reports the data and gives the reasoning for this assessment.

Ten trials contributed data to assess effects of increasing omega-6 fats on all-cause mortality, with 740 deaths in 4506 participants (Figure 3; Analysis 1.1). We found little or no effect of increasing omega-6 fats on mortality (RR 1.00, 95% CI 0.88 to 1.12) and this lack of effect was consistent across trials (I^2 = 0%). The funnel plot for all-cause mortality did not suggest serious small study bias (not shown), but we are aware of some missing data on all-cause mortality. Some deaths occurred in Bates 1977, but the trialists no longer have access to this information (7 of 76 randomised participants died or withdrew in the two intervention arms and 11 of 76 in the two control arms). There were also deaths in Houtsmuller 1979, but we know only numbers of CHD deaths. We were unable to establish contact with authors of two trials (that randomised 111 participants between them), which appeared eligible for inclusion but where no deaths or other relevant outcomes were reported, so these may include some further missing data (Harbige 2007; Millar 1973).

Figure 3. Forest plot of comparison: 1 Primary outcomes - higher omega-6 vs lower omega-6, outcome: 1.1 All-cause mortality (overall).
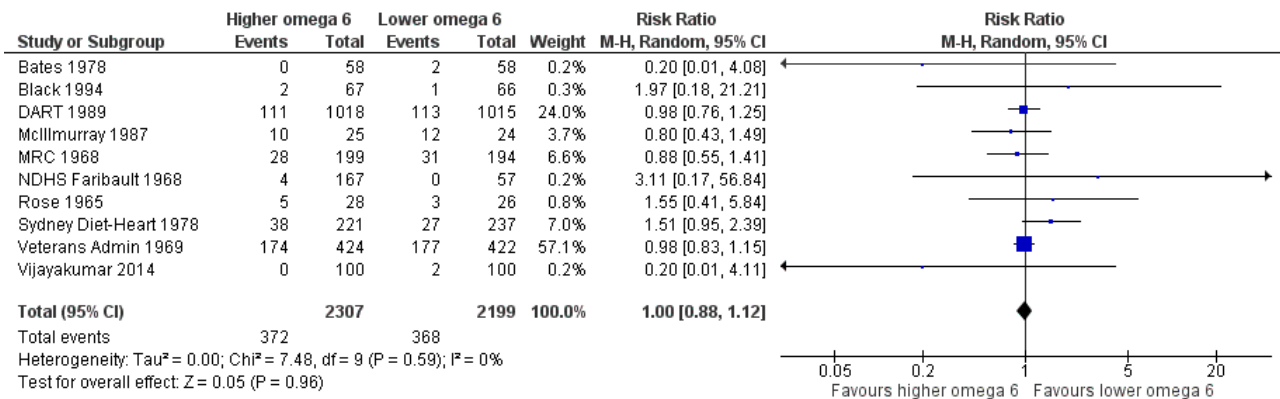
Sensitivity analyses limited to studies at low risk of summary bias (RR 1.54, 95% CI 0.98 to 2.41, 69 deaths in two trials; Analysis 1.3) or using fixed-effect meta-analysis did not alter this lack of effect (RR 1.00, 95% CI 0.89 to 1.13; Analysis 1.2). Other sensitivity analyses, limited to studies: up to 2010, plus studies post-2010 that were registered on a trials register (Roberts 2015); with no industry funding; with a low risk of attention bias; randomising at least 250 participants, or at least 100 participants; all concurred in suggesting little or no effect of omega-6 fats on all-cause mortality (Analysis 1.3). We intended another sensitivity analysis with studies reporting less than 10% difference in intake of trans fats between study arms during the intervention, but as information on trans fats was almost completely lacking we did not attempt it.

None of the subgroup analyses, by omega-6 fat type (Analysis 1.4), intervention type (Analysis 1.5), energy replacement (Analysis 1.6), primary or secondary prevention of CVD (Analysis 1.7), omega-6 fat dose (Analysis 1.8), trial duration (Analysis 1.9), statin use (Analysis 1.10), baseline omega-6 fat intake (Analysis 1.11) or participant sex (Analysis 1.12) suggested important differences between subgroups or any effect of omega-6 fats on all-cause mortality. Trials often failed to report baseline omega-6 fat intake, and where feasible we estimated this from omega-6 fat or PUFA goals or dietary intake data. Replacement data were also unclear, but we considered dietary factors that reduced as omega-6 fat intake went up (or vice versa) to be replacements, and we assessed them separately from other dietary changes aimed at or assessed. The extent in the change in omega-3/omega-6 fat ratio was generally unclear, so we did not use this subgrouping.

There was no suggestion of any effect of omega-6 fats on all-cause mortality or heterogeneity among studies (RR 1.0 and I^2 = 0%), and meta-regression did not suggest any relationships between risk of all-cause mortality and omega-6 fat dose in trials across the omega-6, omega-3 and total PUFA reviews, or from this review alone (P = 0.82); baseline omega-6 intake (P = 0.68); or trial duration (P = 0.87).

More than half of the weight of the meta-analysis came from one study, Veterans Admin 1969, with a further 24% from DART 1989. Veterans Admin 1969 and DART 1989 both included a substantial number of person-years (Veterans Admin 1969 included 846 men for an average of 4 years, or 3384 person-years, while DART 1989 included 2033 men for an average of 1.79 years, or 3639 person-

years). Veterans Admin 1969 had longer follow-up, allowing more time for effects of the intervention to be expressed. The death rate in Veterans Admin 1969 was 10% per year while in DART 1989 it was 6% per year, perhaps reflecting socioeconomic and age differences. Veterans Admin 1969 participants were older, so more likely to die, with a mean age of 65 (up to 88 years) compared to DART 1989 with a mean age of 56 (all aged < 70 years).

In GRADE assessment, we downgraded the data for risk of bias (there was a suggestion that increasing omega-6 fats increased risk of death in the two trials at low summary risk of bias) and imprecision (the 95% CI crossed the null). Increasing omega-6 fats may make little or no difference to risk of all-cause mortality (low-quality evidence, Summary of findings for the main comparison). As there is no suggestion of protection or harm the number needed to treat for an additional beneficial outcome (NNTB) is infinitely large – an infinite number of people would need to increase the amount of omega-6 fat in their diet to prevent one person dying of any cause (NNTB ∞, 95% CI NNTH (number needed to treat for an additional harmful outcome) 50 to NNTB 50).

Cardiovascular mortality (CVD mortality)

We are uncertain whether increasing omega-6 fats alters risk of CVD mortality, as the quality of evidence was very low (downgraded for risk of bias, imprecision and inconsistency, Summary of findings for the main comparison).

There was important heterogeneity between trials increasing omega-6 fats when assessing effects on CVD mortality (RR 1.09, 95% CI 0.76 to 1.55, I^2 = 61%, 472 CVD deaths in 4019 participants randomised into 7 trials, Analysis 1.13). Effects in included trials varied from statistically significantly protective (Veterans Admin 1969, 138 CVD deaths, taking 26% of the weight of the meta-analysis) to almost statistically significantly harmful (Sydney Diet-Heart 1978, 62 CVD deaths and DART 1989 with 205 CVD deaths, taking 20% and 28% of the weight in the meta-analysis, respectively). This variation in effects in different trials results in a high level of heterogeneity (I^2 = 61%). Effects in sensitivity (Analysis 1.14; Analysis 1.15) and subgroup analyses appear to depend on which of these trials we included in each analysis or subgroup. This heterogeneity led to downgrading for inconsistency in GRADE assessment. As there were only seven trials we did not create a funnel plot.

One included trial was at low summary risk of bias (RR 1.59, 95% CI 0.99 to 2.55, 62 people died of CVD). Because this trial suggested that increasing omega-6 intake may increase risk of CVD deaths, we downgraded for risk of bias in GRADE, Analysis 1.15). No included trials had published protocols or trials register entries, but all were published before 2010. Almost all CVD deaths occurred in men and in high-income countries.

All included trials increased LA, and all were in low statin use trials. Subgrouping by baseline omega-6 fat intake reduced heterogeneity and suggested significant differences between subgroups (Analysis 1.21), though there were few trials in each subgroup. The data suggested that in populations with low omega-6 fat intake (< 5% E) additional omega-6 fats may be beneficial, but as baseline omega-6 fat intake increases there is suggestion that adding more leads to harm. Subgroup analysis by intervention type suggested a significant difference between subgroups, with harmful effects of omega-6 fat suggested in four dietary advice trials (RR 1.33, 95% CI 0.86 to 2.05, I^2 = 38%), and beneficial effects in the single trial where all foods were provided (RR 0.70, 95% CI 0.51 to 0.96), with a statistically significant difference between subgroups (P = 0.04, Analysis 1.16). Subgrouping by primary or secondary prevention of CVD did not suggest important differences between subgroups but did reduce heterogeneity and suggested harmful effects of omega-6 fat in secondary prevention trials (Analysis 1.18). None of the other subgroup analyses, by energy replacement (Analysis 1.17) or participant sex (Analysis 1.22) suggested significant differences between subgroups.

We did not note dose-response or duration effects; higher omega-6 fat dose and longer duration appeared to cause smaller effects of omega-6 fats on CVD mortality (Analysis 1.19; Analysis 1.20), which is counterintuitive. Meta-regression did not suggest any relationships between risk of CVD mortality and: omega-6 fat dose in the wider set of trials (P = 0.81), omega-6 fat dose in trials of this review alone (P = 0.64), baseline omega-6 intake (P = 0.29) or trial duration (P = 0.13). However, as there were only seven included trials in this review we had very little power to see any potential relationships, and this lack of power was exacerbated with regard to omega-6 baseline intake, as several studies did not report this measure.

We found that effects of omega-6 fats on CVD deaths were unclear, as results were imprecise, inconsistent and at risk of bias, so we assessed evidence as being of very low quality (Summary of findings for the main comparison).

Cardiovascular events (CVD events)

Increasing omega-6 fats may make little or no difference to risk of CVD events (low-quality evidence, downgraded for risk of bias and imprecision, Summary of findings for the main comparison).

There was little or no effect of increasing omega-6 fats on CVD events in seven trials including 4962 participants, 1404 of whom experienced a CVD event (RR 0.97, 95% CI 0.81 to 1.15, I^2 = 45%, Figure 4; Analysis 1.23). This lack of effect was not altered in any sensitivity analyses apart from the one for risk of bias (Analysis 1.24; Analysis 1.25). Meta-analysis of the two studies at low summary risk of bias suggested harm from increased omega-6 (RR 1.62, 95% CI 1.02 to 2.57, 68 people experienced at least one CVD event). As this effect was distinct from the lack of effect seen overall we downgraded for risk of bias in GRADE assessment. Almost all CVD events occurred in men and in high-income countries.

Figure 4.   Forest plot of comparison: 1 Primary outcomes - higher omega-6 vs lower omega-6, outcome: 1.23 Any cardiovascular event (overall).
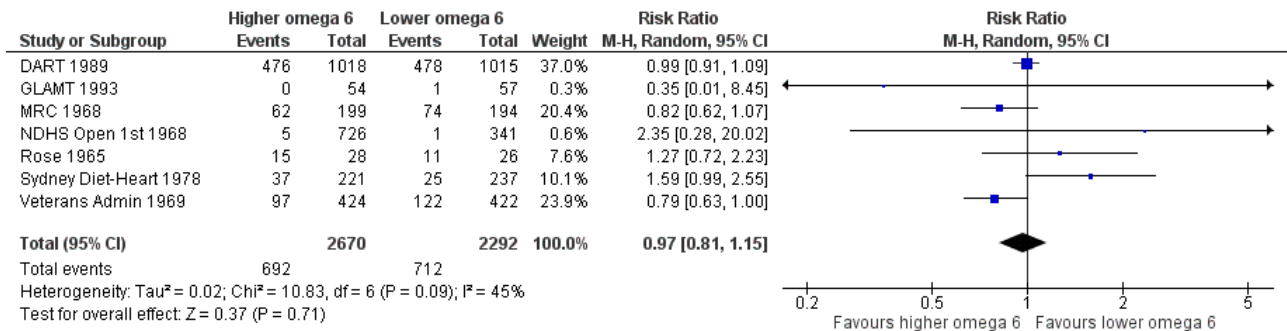
There were no statistically significant differences for any subgroup (Analysis 1.26; Analysis 1.27; Analysis 1.28; Analysis 1.29; Analysis 1.30; Analysis 1.31; Analysis 1.32; Analysis 1.33; Analysis 1.34). All trials used low levels only of statins. There was no suggestion of greater effect with higher omega-6 fat dose or longer study duration. Meta-regression within the wider set of trials did not suggest any effect of omega-6 fat dose on CVD events (P = 0.34), or omega-6 fat dose in trials of this review alone (P = 0.55), baseline omega-6 intake (P = 0.63) or trial duration (P = 0.37). As there were only seven included trials in this review, we had very little power to see any potential relationships, and this lack of power was exacerbated with regard to omega-6 baseline intake, as several studies did not report this measure.

We found that increasing omega-6 fats may make little or no difference to risk of CVD events (low-quality evidence, downgraded due to risk of bias and imprecision, Summary of findings for the main comparison). One hundred people would need to increase the amount of omega-6 fat in their diet to prevent one person having a CVD event (the NNTB is 100, 95% CI −21 to 17, or from treating 21 people to cause one additional person to experience a cardiovascular event to treating 17 people to prevent one person having a CVD event).

Coronary heart disease events (CHD events, including MI or angina)

We are uncertain whether increasing omega-6 fats alters the risk of CHD events, as the quality of evidence was very low (downgraded for risk of bias, imprecision and inconsistency, Summary of findings for the main comparison).

Seven trials in 3997 participants, 1059 of whom experienced coronary heart disease events, assessed whether increasing omega-6 fats alters the risk of CHD events. The meta-analysis was highly heterogeneous (RR 0.88, 95% CI 0.66 to 1.17, I^2 = 71%, Analysis 1.35, GRADE downgraded for inconsistency). Heterogeneity only fell below I^2 = 50% in one sensitivity analysis, limited to studies at low risk of attention bias (RR 0.83, 95% CI 0.62 to 1.09, I^2 = 0%, 160 of 1011 participants experienced a CHD event in 3 trials, Analysis 1.37). One study was at low summary risk of bias (RR 1.63, 95% CI 1.00 to 2.67, 58 people experienced CHD events, P = 0.05), and the suggested increase in CHD event risk with increased omega-6 fats led to us downgrade the quality of evidence for risk of bias in GRADE assessment. CHD events almost all occurred in men and in high-income countries. Fixed-effect analysis suggested similar effect size to random-effects analysis (Analysis 1.36).

Subgrouping did not explain the high levels of heterogeneity (Analysis 1.38; Analysis 1.39; Analysis 1.41; Analysis 1.42; Analysis 1.43; Analysis 1.44; Analysis 1.45), but there were significant differences in subgroup analyses by CVD risk at baseline, sex and replacement. Where omega-6 fat replaced MUFA, there was an increased risk of CHD events, while omega-6 fat replacing carbohydrates appeared to reduce CHD event risk (Analysis 1.40). Illogically there were effects in subgroups of men and women, but not of men or women alone (Analysis 1.45), and effects in people with moderate CVD risk but not high or low baseline CVD risk (Analysis 1.41). All trials used low levels only of statins. However there were only one to three trials in each relevant subgroup, so caution is warranted when drawing conclusions.

There were no statistically significant differences between subgroups for dose (Analysis 1.42) or duration (Analysis 1.43). As meta-regression did not suggest any effect of omega-6 fat dose on coronary heart disease events in the wider set of trials (P = 0.76) or only in trials in this review (P = 0.79), we assumed these effects were likely to be spurious. Meta-regression did not suggest any relationships between baseline omega-6 intake (P = 0.66) or trial duration (P = 0.39) and risk of CHD events, but as there were only seven included trials in this review we had little power to see potential relationships.

We found that effects of omega-6 fats on coronary heart disease events were unclear, as evidence was very low quality (downgraded for risk of bias, imprecision and inconsistency, Summary of findings for the main comparison).

Major adverse cardiac and cerebrovascular events (MACCEs)

We are uncertain whether increasing omega-6 fats alters risk of MACCEs, as the quality of evidence was very low (downgraded for risk of bias, imprecision and inconsistency, Summary of findings for the main comparison).

Only two trials in 2879 participants, 817 of whom experienced a MACCE, provided data on this outcome (RR 0.84, 95% CI 0.59 to 1.20, I^2 = 79%, Analysis 1.46; wide confidence intervals did not exclude important benefits or harms, so we downgraded for imprecision). The two trials provided highly heterogeneous results (so were downgraded for inconsistency). There was a suggestion of reduced risk of MACCEs in the single trial at low risk of attention bias, but no trials were at low summary risk of bias (downgraded for risk of bias) and no other sensitivity analyses suggested important effects of omega-6 fats on MACCEs (Analysis 1.48; Analysis 1.47). Both included studies were in men only, studied increased LA, and had low levels of statin use. There were only two included trials, but these were very different, so that there were significant differences in subgroup analyses with more than one subgroup (Analysis 1.49; Analysis 1.50; Analysis 1.51; Analysis 1.52; Analysis 1.53; Analysis 1.54), and there were insufficient data to carry out meta-regression. Both included trials were in men living in developed countries.

We are uncertain whether increasing omega-6 fats affects risk of MACCEs, as the quality of evidence has been assessed as very low (downgraded for risk of bias, imprecision and inconsistency, Summary of findings for the main comparison).

Stroke (fatal or non-fatal)

We are uncertain whether increasing omega-6 fats alters risk of stroke, as the quality of evidence was very low (downgraded for once for risk of bias, twice for imprecision, Summary of findings for the main comparison).

Only four trials provided stroke data, and only 54 of 3730 included participants experienced a stroke (Analysis 1.55). These studies suggested that omega-6 fats increase stroke risk (RR 1.36, 95% CI 0.45 to 4.11, I^2 = 56%), but studies were heterogeneous and confidence intervals very wide (as important benefits and harms were not excluded, we downgraded for imprecision). One study with only four people experiencing a stroke was at low summary risk of bias (RR 1.07, 95% CI 0.15 to 7.55; we downgraded for risk of bias as there were almost no data from studies at low summary risk of bias). The single study at low risk of attention bias suggested a reduction in stroke risk with increased omega-6 fats (Analysis 1.57). Fixed-effect analysis suggested little or no effect of omega-6 fats (RR 1.0, 95% CI 0.59 to 1.68, Analysis 1.56), while other sensitivity analyses suggested increased risk of stroke with increased omega-6 fat (Analysis 1.57).

All included studies were of LA rather than GLA, in men only, and none were in populations using statins. None were from low- and middle-income countries. Subgrouping by intervention type (Analysis 1.58: dietary advice was harmful, and providing all foods had a protective effect), baseline CVD risk (Analysis 1.60: increasing omega-6 fat was protective in primary prevention and harmful in people with existing CVD), omega-6 fat dose (Analysis 1.61: a low omega-6 fat dose was harmful and a higher dose protective), duration (Analysis 1.62: in trials under four years duration omega-6 fats were harmful and in longer trials protective) and baseline omega-6 dose (Analysis 1.63: omega-6 fat supplementation is useful when baseline dose is low) appeared to reduce heterogeneity, but with only four trials contributing, this appeared to relate to whether DART 1989 and Veterans Admin 1969 were in the same or different subgroups. Other analyses were not informative (Analysis 1.60; Analysis 1.63; Analysis 1.64; Analysis 1.65).

Effects of dose and duration were counter-intuitive (as above) and meta-regression did not suggest any effect of omega-6 fat dose on

stroke (P = 0.19) in the wider set of trials. There were insufficient trials to carry out meta-regression on data from trials within this review only.

We are uncertain whether increasing omega-6 fats affects stroke risk, as the quality of evidence was very low (GRADE assessment was downgraded once for risk of bias and twice for imprecision, Summary of findings for the main comparison).

Secondary outcomes

We formally systematically reviewed secondary outcomes, including all relevant studies that assessed any of these outcomes in the review, so results below are systematic review results for effects of omega-6 fats on these outcomes over at least one year duration. Summary of findings 2 presents results for key outcomes.

We carried out sensitivity and subgroup analyses for key outcomes that were secondary outcomes in this review when the main forest plot included at least six trials contributing data to the analysis. These outcomes were myocardial infarction, lipids and adiposity, but only myocardial infarction and total cholesterol included enough studies for us to run sensitivity analyses and subgroups.

Other CVD events

Myocardial infarction (MI)

Increasing omega-6 fats may reduce risk of myocardial infarction. Seven included studies reported on risk of a new or recurrent MI, and meta-analysis suggested a 12% reduction in risk of MI with increased omega-6 fat from 15.4% to 13.5% (RR 0.88, 95% CI 0.76 to 1.02, 609 events, I² = 0%, Figure 5; Analysis 2.1). Few reported MIs (only 49) were fatal, and the effect on non-fatal MIs appeared protective (RR 0.76, 95% CI 0.58 to 1.01, 189 people experiencing non-fatal MI, data not shown). Sensitivity analyses included one trial (with 5 participants having an MI) at low summary risk of bias (downgraded for risk of bias as most event data were from trials at moderate to high summary risk of bias). All the other sensitivity analyses suggested reduction in MI risk with increasing omega-6 fats (Analysis 2.3; Analysis 2.2).

Figure 5. Forest plot of comparison: 2 Secondary outcomes - higher omega-6 vs lower omega-6, outcome: 2.1 Myocardial infarction (MI), overall.

Study or Subgroup	Higher omega 6 Events	Total	Lower omega 6 Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	197	1018	225	1015	71.1%	0.87 [0.74, 1.04]
GLAMT 1993	0	54	1	57	0.2%	0.35 [0.01, 8.45]
Houtsmuller 1979	0	51	6	51	0.3%	0.08 [0.00, 1.33]
MRC 1968	39	199	40	194	13.3%	0.95 [0.64, 1.41]
NDHS Open 1st 1968	4	726	1	341	0.4%	1.88 [0.21, 16.75]
Rose 1965	9	28	7	26	3.0%	1.19 [0.52, 2.74]
Veterans Admin 1969	36	424	44	422	11.7%	0.81 [0.54, 1.24]
Total (95% CI)		**2500**		**2106**	**100.0%**	**0.88 [0.76, 1.02]**
Total events	285		324			

Heterogeneity: Tau² = 0.00; Chi² = 4.43, df = 6 (P = 0.62); I² = 0%
Test for overall effect: Z = 1.75 (P = 0.08)

Favours higher omega 6   Favours lower omega 6

There were no statistically significant differences between subgroups for intervention type (Analysis 2.4), replacement (Analysis 2.5), CVD risk (Analysis 2.6), omega-6 dose (Analysis 2.7), duration (Analysis 2.8), statin use (Analysis 2.9), baseline omega-6 intake (Analysis 2.10) or sex (Analysis 2.11). Almost all MIs in included trials occurred in men living in high-income countries.

We found that increasing omega-6 fats may reduce risk of myocardial infarction (low-quality evidence, GRADE downgraded for risk of bias and imprecision, Summary of findings 2). Fifty-three people would need to increase the amount of omega-6 fat in their diet to prevent one person having a myocardial infarction (the NNTB is 53, 95% CI −334 to 28, or from 334 people increasing their omega-6 fats to cause one additional person to have an MI to 28 people increasing their omega-6 fats to prevent one person experiencing an MI).

Angina

Trials reported few cases of new or worsening angina, but there was a suggestion of protection against angina with omega-6 fats (RR 0.61, 95% CI 0.27 to 1.40, 63 events in 4 trials, I² = 51%, Analysis 2.12). We are uncertain whether increasing omega-6 fats affects risk of angina as the quality of evidence was very low.

Sudden cardiac death

Three trials reported sudden cardiac death, including 65 sudden cardiac deaths. Meta-analysis suggested reduced risk of sudden cardiac death with omega-6 fats (RR 0.79, 95% CI 0.49 to 1.29, I² = 0%, Analysis 2.13). We are uncertain whether omega-6 fats alter the risk of sudden cardiac death as the evidence is of very low quality.

New or recurrent arrhythmia, including atrial fibrillation (AF), ventricular tachycardia (VT) and ventricular fibrillation (VF)

No included trials reported any of these events.

Heart failure

With only 10 heart failure diagnoses (in two trials) the effect of omega-6 fats on heart failure was unclear (RR 0.66, 95% CI 0.19 to 2.35, I² = 0%, Analysis 2.14). We are uncertain whether omega-6 fats alter the risk of heart failure, as the evidence is of very low quality.

Revascularisation

Only four participants in a single trial reported on revascularisation (RR 1.00, 95% CI 0.14 to 6.96, Analysis 2.15). We are uncertain whether omega-6 fats alter the risk of revascularisation as the evidence is of very low quality.

Peripheral arterial disease (PAD) events

Three studies reported 53 PAD events, with no suggestion of any effect of omega-6 fats (RR 1.01, 95% CI 0.60 to 1.70, I² = 0%, Analysis 2.16) .We are uncertain whether omega-6 fats alter the risk of PAD, as the evidence is of very low quality.

Risk factors

Serum lipids

Increasing omega-6 fats reduces serum total cholesterol (high-quality evidence, not downgraded), and may make little or no difference to serum triglycerides (TG), LDL or HDL (low-quality evidence, TG downgraded once for imprecision and once for inconsistency and risk of bias (combined), LDL and HDL both downgraded for risk of bias and imprecision, Summary of findings 2).

There was a 6% reduction in total serum cholesterol in participants who increased omega-6 fats compared to control (MD −0.33 mmol/L, 95% CI −0.50 to −0.16, I² = 81%, including data from 4280 participants in 10 trials, Figure 6; Analysis 2.17). As serum total cholesterol was a key outcome, we ran sensitivity and subgroup analyses. All sensitivity analyses showed reduced total serum cholesterol with increased omega-6 fats, including the trials at low summary risk of bias (MD −0.53 mmol/L, 95% CI −0.82 to −0.26, 1179 participants, Analysis 2.19; Analysis 2.18).

Figure 6. Forest plot of comparison: 2 Secondary outcomes - higher omega-6 vs lower omega-6, outcome: 2.17 Serum total cholesterol (TC), mmol/L.

Study or Subgroup	Higher omega 6 Mean	SD	Total	Lower omega 6 Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
DART 1989	6.29	1.13	855	6.55	1.1	860	15.4%	-0.26 [-0.37, -0.15]
Houtsmuller 1979	6.43	0.65	48	6.9	0.81	48	11.0%	-0.47 [-0.76, -0.18]
Mendis 2001 (1)	-0.42	0.5447	26	-0.58	0.7221	28	9.9%	0.16 [-0.18, 0.50]
MRC 1968 (2)	-1.11	0	88	-0.47	0	89		Not estimable
NDHS Faribault 1968 (3)	-1.09	0.73	50	-0.18	0.59	51	11.9%	-0.91 [-1.17, -0.65]
NDHS Open 1st 1968 (4)	-0.7	0.69	311	-0.25	0.6	309	15.4%	-0.45 [-0.55, -0.35]
Rose 1965 (5)	-0.51	1.25	13	-0.02	0.94	13	3.2%	-0.49 [-1.34, 0.36]
Sydney Diet-Heart 1978	6.5	1.2	221	6.8	1.1	237	13.1%	-0.30 [-0.51, -0.09]
Veterans Admin 1969	4.93	3.72	423	5.3	1.87	420	8.7%	-0.37 [-0.77, 0.03]
Vijayakumar 2014	3.92	1.15	94	3.86	0.74	96	11.4%	0.06 [-0.22, 0.34]
Total (95% CI)			**2129**			**2151**	**100.0%**	**-0.33 [-0.50, -0.16]**

Heterogeneity: Tau² = 0.05; Chi² = 42.56, df = 8 (P < 0.00001); I² = 81%
Test for overall effect: Z = 3.84 (P = 0.0001)

Footnotes
(1) change data
(2) change data, no measure of variance provided
(3) change data
(4) change data
(5) change data

All included studies increased LA, rather than GLA. There were statistically significant differences between subgroups by intervention type, replacement and statin use. Subgroup analyses by intervention type suggested reduced serum total cholesterol with dietary advice and interventions providing all food, but not with supplementary foods or advice plus supplementary foods (Analysis 2.20). There was reduced total cholesterol when omega-6 fat replaced saturated fat, monounsaturated fat and carbohydrate, but not in the subgroup analysis where the replacement was unclear (Analysis 2.21). Subgroup analyses by statin use suggested greater reductions in TC in people not taking statins (only one trial included most people on statins, Analysis 2.25). There were no statistically significant differences between subgroups by baseline omega-6 fat intake (Analysis 2.26), sex (Analysis 2.27), baseline CVD risk (Analysis 2.22), duration (Analysis 2.24) or omega-6 fat dose (Analysis 2.23).

The funnel plot did not suggest any publication or small study bias (not shown). We are aware of missing data on total cholesterol in MRC 1968, as the provided data lacked any information on variance, but data clearly corroborated the greater reductions in total cholesterol in the higher omega-6 fat arm in meta-analysis (data shown in Analysis 2.17). Total cholesterol data in Dullart 1992 were too different between study arms at baseline to include in analysis.

We found that increasing omega-6 fats reduces serum total cholesterol over at least one year (high-quality evidence, inconsistency partially explained by dose effects, Summary of findings 2).

Data on serum triglycerides (MD −0.01 mmol/L, 95% CI −0.23 to 0.21, I² = 72%, 834 participants in 5 trials, Analysis 2.28), HDL (MD −0.01 mmol/L, 95% CI −0.03 to 0.02, I² = 0%, 1995 participants in 4 trials, Analysis 2.30), and LDL cholesterol (MD −0.04 mmol/L, 95% CI −0.21 to 0.14, I² = 0%, 244 participants in 2 trials, Analysis 2.29) were much more limited, without any clear suggestion of alteration with increased omega-6 fats. Due to the limited numbers of trials for these outcomes, we did not run sensitivity or subgroup analyses. We are aware of missing data on TGs from NDHS Faribault 1968 and NDHS Open 1st 1968, and missing data on LDL in Dullart 1992. In NDHS Faribault 1968 the percentage change for TG from baseline to 44 week was −6.4% in the control group and −12.7% in intervention group B, −7.1% in C, −16.9% in E, but data were less clear for NDHS Open 1st 1968. LDL data in Dullart 1992 were too different between study arms at baseline to include in analysis.

We found that increasing omega-6 fat may have little or no effect on serum HDL or LDL (both low-quality evidence, downgraded for risk of bias and imprecision), or triglycerides (low-quality evidence, downgraded once for imprecision and once for inconsistency and risk of bias combined, Summary of findings 2).

Adiposity

Only two small trials in 66 participants fully reported on body weight (MD −3.12 kg, 95% CI −12.6 to 6.36, I^2 = 58%, Analysis 2.31), and one trial in 371 participants on body mass index (MD −0.20 kg/m^2, 95% CI −0.56 to 0.16, Analysis 2.32; this study was at low summary risk of bias). Both outcomes suggested slightly lower adiposity associated with higher omega-6 fat intake (though body weight was higher in the omega-6 fat arms of the two trials that could not be included in body weight assessment due to lack of variance information, suggesting possible publication bias, Analysis 2.31). One small trial (30 participants) suggested that omega-6 fats resulted in lower fat weight (MD −7.7 kg, 95% CI −14.6 to −0.8, Analysis 2.33) – a surprisingly large suggested effect. Weight data were measured but not included in analyses for Black 1994 and MRC 1968 (shown in Analysis 2.31 but not included in meta-analysis because variance data were missing), as well as NDHS Faribault 1968 and NDHS Open 1st 1968, so publication bias may be an issue for this outcome.

Overall, we found that increasing omega-6 fats probably has little or no effect on adiposity, measured using body mass index, over at least one year (moderate-quality evidence, downgraded for imprecision, evidence for body weight and fat weight were of very low quality, Summary of findings 2).

Tertiary outcomes

We did not formally systematically review these outcomes, but where included studies reported them, we collated and analysed them.

Blood pressure

We found limited information on blood pressure, and there were no important effects of omega-6 fats on either systolic or diastolic blood pressure. One trial fully reported systolic and diastolic blood pressure (sBP MD −1.10 mmHg, 95% CI −4.05 to 1.85, 458 participants, dBP MD −0.30 mmHg, 95% CI −2.04 to 1.44, 458 participants), and another partially reported it (Analysis 3.1). Lack of data on this commonly collected outcome may suggest publication bias.

Quality of life, economic costs, dropouts

No included trials assessed effects of increased omega-6 fats on quality of life or economic costs. The effect of the intervention on dropouts was heterogeneous, suggesting that increasing omega-6 fats was fairly acceptable in some trials, but not in others. The pooled risk ratio suggested greater risk of dropping out in the higher omega-6 fat arms (RR 1.49, 95% CI 1.18 to 1.89, 242 events in 8 trials, I^2 = 61%, Analysis 3.2, with almost 60% of the weight from one trial that had many more dropouts in the higher omega-6 arm (Veterans Admin 1969)).

Adverse and other potential health effects

Effects of omega-6 fats on dementia and neurocognitive outcomes (Jimoh 2017), type 2 diabetes and measures of glucose metabolism (Brown 2017), inflammatory bowel disease and inflammatory markers (Thorpe 2017), cancers (Hanson 2017b), depression and anxiety (Hanson 2017a), and functional outcomes (Abdelhamid 2017) are systematically reviewed elsewhere, so we do not report the results of effects seen in studies included in this review (as they are potentially misleading). The systematic reviews on these health outcomes are not yet published, so references are provided to the protocols so the systematic reviews can be located.

We found limited data on multiple sclerosis progress and pulmonary embolism. Two trials reported only seven cases of pulmonary embolism, so that effects of omega-6 fats were unclear (RR 2.15, 95% CI 0.48 to 9.57, I^2 = 0%, Analysis 3.3). Two trials reported risk of worsening multiple sclerosis or an acute attack, with a suggestion of increased risk of worsening MS with GLA supplementation (RR 1.11, 95% CI 0.95 to 1.30, 142 events in 2 trials, I^2 = 0%, Analysis 3.3), although the confidence intervals were very wide.

DISCUSSION

Summary of main results

We included 19 RCTs in 6461 randomised participants followed up for one to eight years in this Cochrane Review. We identified one ongoing trial. Seven trials assessed effects of small quantities of GLA as supplements, while 12 assessed effects of larger versus smaller quantities of dietary LA, usually displacing SFA or MUFA in the diet. We judged three studies to be at low summary risk of bias. We found that increasing omega-6 fats may make little or no difference to all-cause mortality or CVD events, but evidence for both outcomes was of low quality. We are uncertain whether increasing omega-6 fats affects risk of CVD mortality, CHD events, MACCEs or stroke, as evidence for all of these outcomes was of very low quality.

For secondary outcomes we found that increasing omega-6 fats may reduce risk of myocardial infarction, but we are uncertain whether increasing omega-6 fat affects risk of angina, sudden cardiac death, heart failure, revascularisation or PAD (all very low-quality evidence). We found no data on arrhythmia.

High-quality evidence suggests that increasing omega-6 fats reduces total serum cholesterol by 6% over at least one year, and this effect was consistent in sensitivity analysis including only trials at low summary risk of bias. Increasing omega-6 fats probably has little or no effect on body mass index (moderate-quality evidence), and may make little or no difference to triglycerides, HDL or LDL cholesterol (low-quality evidence).

We found limited information on blood pressure, quality of life, economic outcomes and adverse health effects. Effects of omega-6 fats on serious adverse health effects (cancers, inflammatory bowel disease, depression or anxiety, neurocognitive outcomes, functional outcomes and diabetes) are reported elsewhere.

Overall completeness and applicability of evidence

Included trials randomised 6461 participants for at least a year. Participants were men and women aged from their 20s into their 80s, but the median mean age was 50 years old. While we included 6 trials in men, 10 in both men and women, and 2 in mostly women (1 trial did not report participant gender), most deaths (703/740) and CVD events (1377/1404) occurred in the trials of men, so it is not clear whether any effects also apply to women. Similarly, while younger adults are included, most events occurred in older adults, which partly explains the lack of appearance of some studies of younger adults in many of the analyses on health events. We included these trials because they reported data on lipids and/or adiposity and sometimes one or two health events.

Two included trials were from lower middle-income countries (Mendis 2001 from Sri Lanka and Vijayakumar 2014 from India), but while both provided data on lipids, the only events were two deaths in Vijayakumar 2014. This means that the bulk of the information in this review is from high-income countries, and much of it from trials carried out 30 to 50 years ago.

Participants were at low CVD risk in 11 trials (they were recruited for living in mental hospital or veterans accomodation, having multiple sclerosis, rheumatoid arthritis or breast cysts, having had cancer or lost weight or simply being healthy), had diabetes in three trials (moderate CVD risk) or had existing CVD in five trials, so results relate to both primary and secondary prevention of CVD. However, most events occurred in those with existing CVD.

We are aware of a missing study – we were unable to access data for Chandrakala 2010, which is completed but unpublished (see Characteristics of ongoing studies). We are also aware of some missing data within included studies – for example there were deaths in Bates 1977, but they were reported combined with dropouts, and the author no longer has the data. Houtsmuller 1979 reported CHD events and mortality, but not all-cause deaths or CVD events. Black 1994, MRC 1968, NDHS Faribault 1968, NDHS Open 1st 1968 and Schirmer 2007 each reported at least one continuous outcome without variance data (so we missed at least one set of data on total cholesterol, two sets on blood pressure and triglycerides, four sets on weight), and Dullart 1992 provided total cholesterol and LDL data that were too different between study arms at baseline to use (with no change data). On the other hand, we were provided the full dataset on events for DART 1989, so we were able to include data for almost all of our outcomes. Data for Sydney Diet-Heart 1978 were also well reported in recent re-analyses, and the authors kindly augmented these data, and outcome data in Veterans Admin 1969 were very well reported, so data are probably almost complete for these trials.

We have included trials of LA and GLA, but other omega-6 fats such as DGLA or AA do not appear to have been tested in RCTs lasting at least one year. We have gathered some information on effects of LA on mortality, CVD events, lipids and adiposity, but we have limited data on both LA and GLA for dichotomous outcomes such as all-cause mortality. Data on effects of GLA on CVD mortality, CVD events, and CHD events are almost entirely absent. DGLA and AA can be synthesised from LA, although conversion may be minimal. DGLA is not part of the diet (it is present only following metabolism), but AA is a dietary component. Trials of increasing LA will presumably also increase availability of DGLA and AA, even if only a small amount, so trials of DGLA and AA may be unnecessary.

In this review, we aimed to assess effects of omega-6 fats on CVD outcomes. Because omega-6 fats are an essential nutrient for humans (we all eat it already), it would be useful to understand whether increasing omega-6 fats in people who eat very little has the same effect as increasing omega-6 fats in people already consuming large amounts. Unfortunately, only 7 of the 17 included trials reported baseline omega-6 or PUFA intake, so our understanding of this aspect is limited. That said, across outcomes there is a suggestion of benefit from increasing omega-6 fats where baseline omega-6 fat intake is below 5% E, and this effect is lost where omega-6 fat intake is at least 5% E (seen in subgroup analyses for baseline omega-6 fat intake for all primary outcomes, including all-cause mortality, CVD mortality , CVD events, CHD events, MACCEs and stroke). We also subgrouped

by baseline omega-6 intake for serum total cholesterol, finding greater cholesterol reductions where baseline omega-6 fats were below 5% E but also seeing reductions, though smaller ones, in populations with higher omega-6 fats at baseline. We carried out meta-regression to assess effects of omega-6 fat intake at baseline on primary outcomes with at least seven included trials. We did not see any suggested effects for all-cause mortality, CVD mortality, CVD events or CHD events (other outcomes included too few trials), but as there were only seven trials in most of these data sets, and some included trials didn't provide omega-6 fat intake at baseline, our power to see any effects was extremely low. Future trials should evaluate this relationship.

Another key question relates to trans fat intake. It is possible that in trying to increase omega-6 fat intake, some trials may have increased intake of hydrogenated vegetable oils high in trans fats. Trans fats are associated with increased risk of CVD (De Souza 2015), so that we may see increases in CVD due to increased trans fat intake, balanced against any underlying benefits of omega-6 fats. Unfortunately, none of the included trials provided data on trans fats. Some trials clearly did not increase trans fats in the higher omega-6 fat arms, as they specifically provided liquid oils (e.g. MRC 1968; Rose 1965), but these were unpalatable to participants, and later trials altered their interventions to provide other products or advice to increase omega-6 fat intake. These studies provide little detail on types of fats taken by participants advised to increase their omega-6 fat intake – in at least some of these, trans fats may have been substantially increased in higher omega-6 fat arms, which may confound our understanding of the effects of increasing omega-6 fats.

Overall, included data are highly applicable but not entirely complete. At present the dataset of RCTs appears to be underpowered for truly understanding the health effects of omega-6 fats. We suggest that further large, long duration, high-quality trials of LA are needed, particularly in women and in countries across income brackets to help clarify the health effects of omega-6 fats. These trials should include participants with low omega-6 intake at baseline, as well as those with higher intake. Dietary advice needs to ensure that trans fat intake is kept low as omega-6 fats increase, and omega-6 fat adherence and trans fat intakes should be checked using biomarkers.

Quality of the evidence

GRADE assessment includes consideration of risk of bias, inconsistency, indirectness, publication bias and imprecision (Summary of findings for the main comparison; Summary of findings 2).

We assessed risk of bias by assessing whether effect sizes altered in sensitivity analyses when limited to studies at low summary risk of bias, those with trials registry entries, those without commercial funding, with low risk from attention bias and larger trials. We defined supplement studies as being at low summary risk of bias where we considered randomisation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessors to be adequate. We defined dietary advice and diet provision trials as being at low summary risk of bias where we considered randomisation, allocation concealment and blinding of outcome assessors to be adequate.

We assessed only 3 of 19 included trials as being at low summary risk of bias (NDHS Faribault 1968; NDHS Open 1st 1968; Sydney Diet-Heart 1978). These were all dietary advice trials, and we judged randomisation, allocation concealment and compliance to be adequate. As poorly concealed allocation has been associated with a 40% greater effect size (Schultz 1995), this is particularly important for assessing risk of bias. Four included trials were at low risk of bias from allocation concealment (Dullart 1992; NDHS Faribault 1968; NDHS Open 1st 1968; Sydney Diet-Heart 1978), but most were at unclear risk despite our enquiring about the method of randomisation in some detail of all authors we were able to contact. We downgraded all dichotomous primary and secondary outcomes for risk of bias, as sensitivity analyses limited to these trials tended to suggest that increasing omega-6 fats increased the risk of mortality and CVD events, unlike the main analyses, or there were very few if any events in trials at low summary risk of bias.

We judged imprecision by whether the 95% CI in the main analysis crossed the null, randomised at least 4000 participants (as suggested by Schünemann 2013), and whether the 95% CI included important benefits and harms. Where the 95% CI crossed the null we downgraded. Despite there being large numbers of participants randomised in primary outcomes, confidence intervals were often wide, suggesting that included studies may still be underpowered to determine effectiveness on these outcomes. Further studies of effects of omega-6 fats on mortality and CVD outcomes are needed.

We assessed inconsistency using I^2 for each primary and secondary outcome. We considered I^2 values of more than 60% to be a problem and downgraded for inconsistency unless we found an element that explained that inconsistency (through subgroup analysis or meta-regression). We downgraded the primary outcomes of CVD mortality, CHD events and MACCEs, along with the secondary outcomes of angina and serum triglycerides, for this reason.

We assessed indirectness according to whether data on an outcome related to women and men, those with and without CVD at baseline, and whether low-, middle- and high-income countries were represented. While indirectness is important, we suspect that the mechanisms of action of omega-6 fats are similar in men and women, and those with and without CVD at baseline, and in different countries Information on indirectness is reported in the summary of findings tables, but we did not downgrade for this factor.

We judged publication bias according to whether there was any suggestion of publication or small study bias in the funnel plot, or where we knew that data were missing that differed from the summary assessment (where we included fewer than 10 trials). We downgraded evidence for body weight alone for publication bias.

Study funding can be an important indicator of study bias, but we did not include it in the 'Risk of bias' assessment. Funding appeared to be from only national or charitable agencies in eight trials, and from mixed charitable or national sources with some commercial products or funds provided in a further five trials. Three trials reported only commercial sources: GLAMT 1993, which reported only one MI, one CHD event and one CVD event; McIllmurray 1987, with 22 deaths and with no data on CVD events; and Schirmer 2007, which provided data on adiposity only. As data from these studies were very limited, they were unlikely to have biased results greatly,

though omission of data from other outcomes could have. Rose 1965 did not mention funding.

Trial pre-registration or early publication of a study protocol is helpful in understanding potential biases in data presentation (including outcome selection bias). We ran sensitivity analyses assessing whether trials that were pre-registered or had a published protocol suggested different effects than trials without such documentation. Unfortunately, we did not find a trials registry entry or pre-published protocol for any of our included trials (most were published before the availability of trials registers). Pre-registration would be helpful for future trials, helping ensure that important outcomes are published regardless of direction of effect or statistical significance. Making datasets of all outcomes available via trials registers would also help systematic reviewers to gather all appropriate data, minimising publication bias.

A particular issue for dietary trials (the LA trials in this review) is adherence. Where we see little effect on key outcomes, all-cause mortality and CVD events, we need to consider whether this is due to omega-6 fats not having any effect on these outcomes, or to participants not actually increasing their omega-6 fat intake substantially following dietary advice. Dietary trials often assess adherence by asking participants what they are eating, but this may be subject to participant exaggeration or wanting to believe that they are indeed following advice provided. Objective biomarkers such as serum total cholesterol or fatty acid tissue markers are more conclusive (Sacks 2017). We assessed adherence in included trials and found that five trials showed statistically significant reductions in serum total cholesterol in the higher omega-6 fat arm compared to the lower omega-6 fat arm (DART 1989; Houtsmuller 1979; NDHS Faribault 1968; NDHS Open 1st 1968; Sydney Diet-Heart 1978). Four studies did not show a statistically significant effect on total cholesterol (Mendis 2001; Rose 1965; Veterans Admin 1969; Vijayakumar 2014) and one did not provide any variance data (so statistical significance was not clear; MRC 1968, Analysis 2.17). Other trials assessed change in tissue fatty acids, finding significant changes in higher omega-6 arms compared to the lower omega-6 fat arms (Black 1994; Schirmer 2007), or lack of any statistically significant difference in these markers (Bates 1978; Dullart 1992), while others provided no biomarker data for compliance (Bates 1977; GLAMT 1993; McIllmurray 1987). Although biomarkers are not perfect markers of compliance (the degree of total cholesterol change will depend on whether omega-6 fats are replacing saturated or monounsaturated fats, or other dietary components, for example) the lack of change in biomarkers in some studies highlights the difficulty of interpreting this limited dataset and the possibility that we are not seeing health effects because omega-6 fats did not alter much in some studies.

Applying the GRADE criteria suggests that we have high-quality evidence on effects of omega-6 fats on serum total cholesterol (not downgraded), moderate-quality evidence on BMI (downgraded once), and low-quality evidence for all-cause mortality and CVD events, myocardial infarction, TG, HDL and and LDL (each downgraded for risk of bias and imprecision). All other evidence was of very low quality. We present justifications for grading and statements of findings based on these levels in Summary of findings for the main comparison and Summary of findings 2.

Potential biases in the review process

We performed a comprehensive search across major databases for interventions involving increased omega-6 fat intake for this review update. In addition, we checked reference lists of all primary studies and relevant systematic and non-systematic reviews for additional references. While we may have missed trials, we believe that we have included most of the larger studies, including some we missed in the original version of this review (Al-Khudairy 2015).

Two review authors independently performed all screening, inclusion and exclusion determination, data extraction and assessment of risk of bias. We contacted authors of all included studies to ask for information on all relevant outcomes and methodology related to risk of bias. We conducted sensitivity analyses to check whether the outcomes were stable to a range of quality assessments.

We conducted a large number of sensitivity and subgroup analyses for each primary outcome, as well as some secondary outcomes. The danger in these is that statistical significance may be spurious in subgroups, but rather than be informed by effects in small subgroups we assessed whether there were statistically significant differences between subgroups. We also looked for dose-response and duration effects using meta-regression. We have tried not to over-interpret these analyses.

We only considered trials with interventions or follow-up periods of 12 months or more, which makes the studies relevant for public health interventions. We considered including shorter studies, but we were concerned that if we found little or no effect then this might be due to including studies too short to reflect any effects of the omega-6 fat intervention. The decision on duration depends on the assumed mechanism of action of omega-6 fats. If we assume a cholesterol-led atherosclerotic mechanism, then we could justify deciding to include only studies of at least two years (as in Hooper 2015; Sacks 2017). However, another mechanism discussed for omega-3 and omega-6 fats is inflammation – likely to work more quickly than atherosclerosis, so allowing six months for equilibration of body tissues with the new dietary intake, and a further six months to allow for reflection of this new status in health outcomes, appears appropriate to us. We hope this compromise is a reasonable balance between excluding useful studies and including unhelpful ones. We ran subgroup analyses to assess whether study duration made an important difference to our primary outcomes. We did not find any suggestion of greater effects in longer trials (those of at least 4 years) compared to shorter trials (1 to < 2 years, or 2 to < 4 years) for all-cause mortality or CVD mortality. There may arguably be slightly greater protective effects in longer trials for CVD events, CHD events, MACCEs and stroke, but meta-regression did not confirm this. Trials of 1 to < 2 years contributed few or no data to primary outcomes so would be unlikely to dilute any effects in longer trials. There were only important differences between duration subgroups for MACCEs and stroke. This suggests we need more longer trials and that carrying out more short trials, or adding trials of less than one year duration to this review, would be unhelpful.

Within the review we have combined data on GLA and LA (apart from in subgroup analyses), which may be inappropriate. LA is an essential fat available from a variety of dietary fats and oils (Sacks 2017), while GLA has to be provided by supplemental capsules in trials, so their effects could be distinct. However, data on GLA are very limited, so they probably neither substantially add to nor detract from the LA data.

Agreements and disagreements with other studies or reviews

This update has built on the findings of the previous version of this review (Al-Khudairy 2015), which included five comparisons randomising 660 participants each for 24 weeks. This version included no studies reporting CVD outcomes, and effects of omega-6 fats on lipids, blood pressure, diabetes or adverse events were unclear. This update excluded all of these trials (as they were all of less than one year duration) and included 17 more, many of which did assess mortality and/or CVD events. This updated review includes a much greater volume of data (more studies, more participants, longer term and larger studies), though there are still limited numbers of studies and of our primary outcome events.

A review of highly controlled (metabolic-type) trials found that replacement of saturated fats with cis-PUFAs (which the authors considered equivalent to omega-6 fats) significantly reduced total cholesterol levels (estimated regression coefficient for mean change, −0.066 mmol/L per 1% E replaced, 95% CI −0.073 to −0.060, Mensink 2016). Replacing carbohydrates and monounsaturated fats also resulted in reductions in total cholesterol, but smaller reductions (−0.019 mmol/L per 1% E from carbohydrates replaced, 95% CI −0.025 to −0.013, and −0.016 mmol/L per 1% E MUFA replaced, 95% CI −0.022 to −0.011). This careful analysis confirmed earlier findings using the same methodology (Mensink 2003). This analysis of highly controlled trials also found that replacing SFA, MUFA and carbohydrates with cis-omega-6 fats reduced LDL cholesterol (−0.058 mmol/L per 1% E from SFA replaced, 95% CI −0.064 to −0.052 with smaller effects when MUFA and carbohydrates are replaced), HDL cholesterol (−0.005 mmol/L per 1% E from SFA replaced, 95% CI −0.007 to −0.004 with smaller effects when MUFA are replaced, and opposite effects when carbohydrates are replaced) and triglycerides (−0.010 mmol/L per 1% E from SFA replaced, 95% CI −0.014 to −0.006 with smaller effects when MUFA are replaced, and larger effects when carbohydrates are replaced). This confirms our findings of reduced serum total cholesterol with increased omega-6 fats and suggests that we were underpowered to see effects on other lipids (in our less highly controlled trial environments over much longer durations we didn't see changes in TG, LDL or HDL). Effects clearly depend on which dietary elements omega-6 fats are replacing in the diet, and this is probably responsible for some of the heterogeneity between studies assessing effects on triglycerides and lack of effect on LDL.

A meta-analysis of cohort studies that examined associations between LA intake and CHD outcomes (myocardial infarction, ischaemic heart disease, coronary artery bypass graft, sudden cardiac arrest, acute coronary syndrome, and CHD deaths) found an inverse dose-response association between dietary LA intake and CHD risk (Farvid 2014). Observational studies are at greater risk of confounding from a variety of lifestyle factors, though they are often larger and of longer duration than trials. The Farvid 2014 analysis agreed with this reviews' suggested reduction in risk of myocardial infarction with increased omega-6 fats, but we did not see any effect of omega-6 fat intake on CHD or CVD events. A recent meta-analysis of 20 cohort studies has suggested that higher LA in body tissues was associated with reduced diabetes risk (Wu 2017), but we did not assess diabetes risk in this review (as Brown 2017 assesses it in part of this review series).

A systematic review of RCTs increasing omega-6 fats, Ramsden 2010, found no significant effects on all-cause mortality (RR 1.16, 95%CI 0.95 to 1.42), non-fatal MI (RR 1.03, 95% CI 0.62 to 1.73), CHD death (RR 1.17, 95% CI 0.82 to 1.68) or CVD events RR 1.13, 95% CI 0.84 to 1.53), and these results have not altered substantially in their most recent update of the review (Ramsden 2016). A recent review of systematic reviews and presidential advisory from the American Heart Association found that increasing LA to replace saturated fats in the diet significantly reduced CVD outcomes (Sacks 2017). Sacks 2017 combined data from four key trials (MRC 1968; Veterans Admin 1969; Finnish Mental Hosp 1972; Oslo Diet Heart 1966) comparing high PUFA diets with high saturated fat diets, controlled diets over at least two years, proved adherence using biomarkers such as tissue lipids or serum cholesterol, collected and validated CVD outcomes of some type, and limited trans fat differences between arms. We included only two of their four key trials (MRC 1968; Veterans Admin 1969), excluding Oslo Diet Heart 1966 as it increased both omega-3 and omega-6 fats and included a multivitamin in the intervention group (so was multifactorial), and Finnish Mental Hosp 1972 as it was a cluster-randomised trial, with only two clusters (and used a cross-over approach inappropriate for outcomes that develop over time such as CVD). Both trials we excluded reported statistically significant reductions in their primary outcomes. Sacks 2017 took the unusual step of meta-analysing only the primary outcome of each trial (using a different outcome for each trial). They state that this reduces outcome selection bias as they used pre-specified primary outcomes, but as none of these trials pre-published protocols, their published composite primary outcomes may have already experienced outcome selection bias (Chan 2004a; Chan 2004b). Our review avoided selection bias by assessing effects over a wide selection of prespecified outcomes. Combining these diverse outcomes for these four trials, Sacks 2017 found that CVD events were reduced by 29% (RR 0.71, 95% CI 0.62 to 0.81, I² = 20%, with 60% of the weight of the analysis coming from the two studies we excluded). This Cochrane Review concurs with Sacks 2017 in seeing reductions in serum total cholesterol where omega-6 fats replace saturated fats. We did not subgroup by replacement for secondary outcomes like myocardial infarction. We found little or no effect of increasing omega-6 fats at the expense of saturated fats (when subgrouping for replacement) for all-cause mortality or CVD mortality. We did see the suggestion of protection against CVD events, CHD events and MACCEs when assessing effects of omega-6 fats replacing saturated fats. However, all of these analyses would be downgraded for risk of bias and imprecision (as a minimum), so evidence would be of low quality at best.

We recently published a Cochrane Review of long-term RCTs that assessed effects of reducing saturated fats, replacing them with a variety of other energy sources (Hooper 2015). This review found little or no effect of reducing saturated fats on all-cause mortality or CVD mortality, but the evidence suggested that reducing saturated fats reduced the risk of CVD events (RR 0.83, 95% CI 0.72 to 0.96, I² = 65%, including 4377 events in over 53,000 randomised participants). Subgroup analyses assessing whether the saturated fats were being replaced by PUFA, MUFA, carbohydrates and/or protein found that only where PUFA was replacing SFA did this protection occur (RR 0.73, 95% CI 0.58 to 0.92, I² = 69%, 884 events in over 3000 participants). The trials included in the saturated fat review and this one are distinct due to rather different inclusion criteria (for example, the saturated fat review only included trials of at least two years' duration and included trials with

dietary interventions of increased saturated fat plus other dietary variables). The implications of the reviews are different, but related: Hooper 2015 and Sacks 2017 suggest that reducing saturated fat and replacement by polyunsaturated fats reduces the risk of CVD events, while the present review suggests that increasing omega-6 fats may reduce the risk of myocardial infarction, but we did not find evidence of an effect on CVD events.

AUTHORS' CONCLUSIONS

Implications for practice

We found that increasing omega-6 fats may reduce risk of myocardial infarction (low-quality evidence), but 53 people would need to increase the amount of omega-6 fat in their diet to prevent one person having a myocardial infarction (NNTB 53, 95% CI −334 to 28). Increasing omega-6 fats may make little or no difference to all-cause mortality or CVD events (low-quality evidence), and we are uncertain of effects on CVD mortality, coronary heart disease, MACCEs and stroke (very low-quality evidence). Overall the evidence is limited by low numbers of events (data are imprecise), and risk of bias of included studies. Increasing omega-6 fats does reduce serum total cholesterol in the long term, so increasing omega-6 fats at the expense of saturated or monounsaturated fats will support lower serum cholesterol (high-quality evidence).

In spite of its limitations, the weak evidence we collected in this review appears to suggest that omega-6 fats are not harmful. There is no evidence for increasing omega-6 fats to reduce cardiovascular outcomes other than myocardial infarction. Although the potential benefit of omega-6 fats in reducing myocardial infarction remains to be proven, increasing omega-6 fats may be of benefit in patients with high risk of MI.

Implications for research

While we have included 19 trials in 6461 participants, there is a need for further large trials of LA of at least five years' duration that are well randomised, with good allocation concealment, well masked with pre-published trials registry entries. These large trials should assess baseline omega-6 fat intake and include participants with low omega-6 intakes at baseline, as well as those with higher intakes. Trials are needed particularly in women and in low- and middle-income countries as well as in high-income countries. Dietary advice needs to ensure that trans fat intake is kept low as omega-6 fats increase, and omega-6 fat compliance and trans fat status should be checked using biomarkers. These trials need to assess effects of increasing dietary omega-6 fats (not supplements) in place of saturated or monounsaturated fats and report important adverse outcomes such as mortality and CVD events (including coronary heart disease and stroke), plus potential harms such as cancers, inflammatory bowel disease (IBD), diabetes, functional outcomes, depression and dementia.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Bates 1977

Methods	RCT, parallel, 4 arms (n-6 GLA + LA vs MUFA using either margarines or supplements), 2 years
	Summary risk of bias: moderate to high
Participants	People with chronic progressive multiple sclerosis
	CVD risk: low
	Intervention A, C: 38 per arm
	Control B, D: 38 per arm
	Mean years in trial: 2
	% male: unclear (quote: "no statistically significant difference between groups")
	Age: unclear (quote: "no statistically significant difference between groups")
	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: UK

Bates 1977 *(Continued)*

	Ethnicity: not reported
Interventions	Type: supplement
	Comparison: GLA + linoleic (n-6) vs oleic (MUFA)
	Intervention aims A: increase polyunsaturated fats with addition of 8 × 0.6 mL/d of evening primrose oil (Naudicelle) in capsules (360 mg/d GLA plus 3.42 g/d linoleic acid plus < 1% ALA)
	Control aims B: increase monounsaturated fats with addition of 8 × 0.6mL/d of oleic acid in capsules (4.8 g oleic acid/d)
	A vs B dose aim: increase 0.34 g/d GLA, 3.78 g/d or 34 kcal or **1.7% E n-6**
	Intervention aims C: increase linoleic acid with addition of 11.5 g/d in a spread
	Control aims D: increase oleic acid with addition of 4 g/d in a spread
	C vs D dose aim: increase 11.5 g/d or 104 kcal or **5% E n-6**
	Baseline n-6: unclear
	Compliance by biomarkers: unclear, no serum total cholesterol reported, no tissue fatty acids reported
	Compliance by dietary intake assessment: unclear, not reported
	• Energy intake: not reported • Total fat intake: not reported • Saturated fat intake: not reported • PUFA intake: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • Trans fat intake: not reported • MUFA intake: not reported • CHO intake: not reported • Sugars intake: not reported • Protein intake: not reported • Alcohol intake: not reported
	Duration of intervention: 2 years
Outcomes	Main study outcome: progression or regression of multiple sclerosis (MS)
	Dropouts: A, 4; B, 7; C, 3; D, 4. (reported as died/withdrawn and not separated)
	Available outcomes: MS progression (deaths clearly occurred, but reported with dropouts (not separated) and the author did not have access to the data any longer)
Notes	Study funding: Multiple Sclerosis Society, Van den Berghs provided intervention and control spreads free.
	Response to contact: yes, Prof Bates states that data on mortality are no longer available. Similar reply from Prof Robert Dworkin (who used Professor Bates' data later for a joint publication)

Risk of bias

Bias	Authors' judgement	Support for judgement

Bates 1977 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Paper states "double blind", capsules of "identical appearance" and "similar spread"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Paper states "double blind" with no further details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Deaths and dropouts combined; no reasons for dropping out provided
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry located
Attention Bias	Low risk	Capsules and spreads provided to all participants; no suggestion of attention bias
Compliance	Unclear risk	Not reported
Other bias	Low risk	None found

Bates 1978

Methods	RCT, parallel, 4 arms (n-6 GLA + LA vs MUFA and n-6 LA vs MUFA), 2 years Summary risk of bias: moderate to high
Participants	People with acute remitting multiple sclerosis CVD risk: low Intervention A, C: 29 per arm Control B, D: 29 per arm Mean years in trial: 2 % male: intervention A 34.48%; intervention C 17.24%; control B 34.48%; control D 37.93% Mean age (SD) in years: intervention A 35 (9); intervention C 34 (8); control B 32 (7); control D 33 (5) 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

Bates 1978 *(Continued)*

Medications taken by some, but less than 20% of the control group: not reported

Location: UK

Ethnicity: not reported

Interventions	Type: Supplement
	Comparison: GLA and linoleic (n-6) vs oleic (MUFA)
	Intervention aims A: 8 × evening primrose oil capsules (Naudicelle)/d, 2.92 g/d LA plus 0.34 g/d GLA
	Control aims B: 8 × capsules/d (4 g/d oleic acid), 4 g/d MUFA
	A vs B dose aim: increase 0.34 g/d GLA, 3.26 g/d or 29 kcal or **1.5% E n-6**
	Intervention aims C: linoleic acid spread (23 g/d linoleic acid)
	Control aims D: oleic acid spread (16 g/d oleic acid)
	C vs D dose aim: increase 23 g/d LA or 207 kcal or **10.4% E n-6**
	Baseline n-6: unclear
	Compliance by biomarkers: good for C vs D, poor for A vs B, no serum total cholesterol reported, "estimations of total fatty acids in patients before and after 12-24 months' treatment showed that the percentage of linoleic and arachidonic acids increased significantly only in those patients taking the linoleic acid spread (group C)".
	Compliance by dietary intake: unclear, not reported
	- Energy intake: not reported - Total fat intake: not reported - Saturated fat intake: not reported - PUFA intake: not reported - PUFA n-3 intake: not reported - PUFA n-6 intake: not reported - Trans fat intake: not reported - MUFA intake: not reported - CHO intake: not reported - Sugars intake: not reported - Protein intake: not reported - Alcohol intake: not reported
	Duration of intervention: 2 years
Outcomes	Main study outcome: progression or regression of multiple sclerosis
	Dropouts: A 0, B 1, C 3, D 6
	Available outcomes: MS progression, deaths (no deaths in arms A, C and D, so only A vs B has usable outcome data)
Notes	Study funding: Multiple Sclerosis Society, Van den Berghs provided intervention and control spreads free
	Response to contact: yes, Prof Bates stated that the data are no longer available. Similar reply from Prof Robert Dworkin (who used Professor Bates' data later for a joint publication).

Risk of bias

Bates 1978 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Quote: "randomly allocated"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Paper states "double blind", capsules of "identical appearance" and "similar spread"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Paper states "double blind" with no further details
Incomplete outcome data (attrition bias) All outcomes	Low risk	Fairly well described, from 0 to 6 dropouts per arm over 2 years (each 29 randomised)
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry located
Attention Bias	Low risk	Capsules and spreads provided to all participants, no suggestion of attention bias
Compliance	High risk	A vs B compliance poor by biomarkers
Other bias	Low risk	None found

Belch 1988

Methods	RCT, parallel, 2 arms (n-6 evening primrose oil vs non-fat paraffin), 12 months
	Summary risk of bias: moderate to high
Participants	People with rheumatoid arthritis (RA)
	CVD risk: low
	Intervention 16 randomised, 16 analysed
	Control 18 randomised, 18 analysed
	Mean years in trial: 1
	% male: intervention 6%; control 6%
	Age, years: intervention median 46 years, control 48 years
	Age range: intervention 35-68 years, control 30-74 years
	Smokers: unclear
	Hypertension: unclear
	Medications taken by at least 50% of those in the control group: NSAIDs

Belch 1988 *(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: UK
	Ethnicity: not reported
Interventions	Type: supplement
	Comparison: GLA (n-6) vs non-fat
	Intervention aims: 12 capsules of evening primrose oil (Efamol), including 540 mg of gamma linolenic acid (GLA) per day
	Control aims B: 12 capsules of liquid paraffin per day
	Dose aim: increase 0.54 g/d GLA, 5 kcal or **0.25% E GLA**, assume 70% LA*, 4.2 g/d or 37.8 kcal/d or **1.9% E LA**, **2.2% E n-6**
	Baseline n-6: unclear
	Compliance by biomarkers: no serum total cholesterol or blood markers reported
	Compliance by dietary intake: unclear, not reported
	• Energy intake: not reported • Total fat intake: not reported • Saturated fat intake: not reported • PUFA intake: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • Trans fat intake: not reported • MUFA intake: not reported • CHO intake: not reported • Sugars intake: not reported • Protein intake: not reported • Alcohol intake: not reported
	Duration of intervention: 1 year
Outcomes	Main study outcome: RA activity and NSAID dose
	Dropouts: intervention 0, control 0
	Available outcomes: ESR, CRP, functional status, RA status, NSAID use (authors stated that no deaths or CVD events occurred during the trial)
Notes	Study funding: Action Research for the Crippled Child, and Efamol Ltd provided the supplements
	Response to contact: Dr Belch contacted and provided some additional information, stating that no deaths or CVD events occurred

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized double blind fashion", no detail provided

Belch 1988 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	As above, randomisation method not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All three types of capsules were supplied by Efamol Ltd and were visually identical. The capsules were issued to the patients in a randomized double blind fashion". Participants and personnel were probably blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Table 2 shows the number of patients withdrawn from the study by 12 months. One patient in the EPO group and two in the EPO/fish oil group were withdrawn owing to increasing symptoms of RA, compared with 10/18 of the placebo patients (both P < 0.001, Mann-Whitney). The results from all patients who were withdrawn were analyzed throughout the study on an intention to treat basis".
Selective reporting (reporting bias)	Unclear risk	No trial protocol or trials registry entry located
Attention Bias	Low risk	Appeared appropriate. Quote: "All participants in all groups needed to attend the clinic at monthly intervals for the first six months and thereafter at 3 monthly intervals."
Compliance	Unclear risk	No serum lipid, serum fatty acid or dietary intake data provided
Other bias	Low risk	None noted

Black 1994

Methods	RCT, parallel, (low fat diet vs usual diet), 24 months
	Summary risk of bias: moderate or high
Participants	People with non-melanoma skin cancer
	N: 66 intervention, 67 control (analysed, 57 intervention, 58 control)
	Level of risk for CVD: low
	Male: 54% intervention, 67% control
	Mean age in years (SD): 50.6 (9.7) intervention, 52.3 (13.2) 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

Black 1994 *(Continued)*

Ethenicity: white 100% (excluded from study if of Asian, Black, Hispanic or American Indian ancestry)

Interventions	Type: dietary advice
	Comparison: reduced fat (lower omega-6 + total PUFA) vs usual diet (CHO + protein)
	Intervention: aims total fat 20% E, protein 15% E, CHO 65% E; methods 8 × weekly classes plus monthly follow up sessions, with behavioural techniques being taught following individual approach (not clear if in a group or individual). At 4-month intervals, clinic examination by dermatologist. Intervention delivered face-to-face by a dietitian
	Control: aims usual diet; methods no dietary change, clinic examination by dermatologist at 4-month intervals
	Dose aim: reduce total fat to 20% E, including omega-6 and total PUFA (no aim provided)
	Baseline n-6: unclear, but baseline PUFA 8% E
	Compliance by biomarkers: unclear, no serum total cholesterol reported, no tissue fatty acids
	Compliance by dietary intake: all assessed "during study", months 4-24, using 7-day food records verified by a dietitian
	• Energy intake: control 2196 kcal/d (SD 615), intervention 1995 kcal/d (SD 564)
	• Total fat intake: control 37.8% E (SD 4.1), intervention 20.7% E (SD 5.5) (MD −17.10%, 95% CI −18.88 to −15.32) significant reduction
	• Saturated fat intake: control 12.8% E (SD 2.0), intervention 6.6% E (SD 1.8), (MD −6.20%, 95% CI −6.90 to −5.50) significant reduction
	• PUFA intake: control 7.8% E (SD 1.4), intervention 4.5% E (SD 1.3), (MD −3.30%, 95% CI −3.79 to −2.81) significant reduction
	• PUFA n-3 intake: not reported
	• PUFA n-6 intake: LA, control 16.9 g (SD 5.6), intervention 8.5 (SD 3.3)
	• Trans fat intake: not reported
	• MUFA intake: control 14.4% E (SD 1.7), intervention 7.6% E (SD 2.2), (MD −6.80%, 95% CI −7.52 to −6.08) significant reduction
	• CHO intake: control 44.6% E (SD 6.9), intervention 60.3% E (SD 6.3), (MD 15.70%, 95% CI 13.29 to 18.11) significant increase
	• Sugars intake: not reported
	• Protein intake: control 15.7% E (SD 2.4), intervention 17.7% E (SD 2.2), (MD 2.00%, 95% CI 1.16 to 2.84) significant increase
	• Alcohol intake: control 3.2% E (SD 3.9), intervention 3.2% E (SD 3.4)
	Duration of intervention: 24 months (mean 1.9 years in trial)
Outcomes	Main study outcome: incidence of actinic keratosis and non-melanoma skin cancer
	Dropouts: unclear intervention, unclear control
	Available outcomes: deaths, CVD deaths, cancer deaths (none), (weight data provided but without variance)
Notes	Study funding: National Cancer Institute
	Response to contact: Prof Black provided data on mortality
	NOTE: for this trial the higher PUFA arm is the control, and lower PUFA arm is the intervention

Risk of bias

Bias	Authors' judgement	Support for judgement

Black 1994 *(Continued)*

Random sequence genera-tion (selection bias)	Low risk	Quote: "list of randomly generated numbers"
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Dietary advice provided, so participants not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "examined …. by dermatologists unaware of their treatment assignments". Deaths (all-cause and CVD) not considered relevant to the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	For mortality. Unclear for other outcomes
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry found
Attention Bias	High risk	Weekly classes and monthly follow-up in intervention group, 4-monthly check-ups only in control
Compliance	Low risk	Dietary intake data suggest omega-6 and total PUFA were significantly reduced in the intervention arm
Other bias	Low risk	None noted

DART 1989

Methods	Diet And Reinfarction Trial (DART)
	RCT, 2 × 2 × 2 factorial (n-6 LA vs SFA), also increased fish and increased fibre arms, 2 years
	Summary risk of bias: moderate to high
Participants	Men recovering from an MI
	CVD risk: high
	Control: randomised 1015, analysed unclear
	Intervention: randomised 1018, analysed unclear
	Mean years in trial: control 1.9, intervention 1.9
	% male: 100%
	Mean age in years: control 56.8, intervention 56.4
	Age range: all < 70 years
	Smokers: control 62.7%, intervention 61.2%
	Hypertension: control 23.3%, intervention 24%
	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: beta-blockers, other anti-hypertensive drugs, anti-anginals

Medications taken by some, but less than 20% of the control group: anti-coagulant, aspirin, other anti-platelets, digoxin, other cardiac drugs

Location: UK

Ethnicity: not reported

Interventions	Type: dietary advice
	Comparison: increased polyunsaturated oil and margarines (n-6) vs usual dietary fats (SFA)
	Intervention aims: reduce fat intake to 30% E, increase polyunsaturated: saturated fatty acid ratio to 1.0 (using polyunsaturated oils and margarines), weight reducing advice if BMI > 30 kg/m^2 (dietitians provided the participants and their wives with initial individual advice and a diet information sheet; participants were revisited for further advice, recipes, encouragement at 1, 3, 6, 9, 12, 15, 18 and 21 months)
	Control aims: no dietary advice on fat, weight reducing advice if BMI > 30 kg/m^2 (dietitians provided 'sensible eating' advice without specific information on fats)
	Dose aim: unclear
	Baseline n-6: unclear, but control PUFA intake 6.6% E
	Compliance by biomarkers: good, serum total cholesterol significantly reduced in intervention compared to control (−0.26 mmol/L, 95% CI −0.37 to −0.15).
	Compliance by dietary intake: assessed using a 7 day weighted food diary, of a 25% random sub-sample
	- Energy intake: intervention 7.3 MJ/d (SD 1.8), control 7.7 MJ/d(SD 1.9) - Total fat intake: intervention 31% E (SD 7), control 35% E (SD 6) - Saturated fat intake: intervention 11% E (SD 3), control 15% E (SD 3), dose −4% E - PUFA intake: intervention 9.4% E, control 6.6% E, dose +2.8% E (most of which omega-6) - PUFA n-3 intake: not reported - PUFA n-6 intake: not reported - Trans fat intake: not reported - MUFA intake: not reported - CHO intake: intervention 46% E (SD 7), control 44% E (SD 6) - Sugars intake: not reported - Protein intake: intervention 18 % E (SD 4), control 17 % E (SD 4) - Alcohol intake: intervention 5% E (SD 6), control 4% E (SD 6)
	Duration of intervention: 2 years
Outcomes	Main study outcomes: mortality, reinfarction
	Dropouts: all followed for events regardless of compliance (ITT)
	Available outcomes: CVD events (CVD deaths plus non-fatal MI), cancer deaths, total MI, non-fatal MI, total and HDL cholesterol. Data set used to examine causes of death during trial, these data added.
Notes	Note: this was a 2 × 2 × 2 factorial trial, and so some in each group were randomised to increased fatty fish and/or increased cereal fibre
	Study funding: Welsh Scheme for Development of Health and Social Research, Welsh Heart Research Foundation, Flora Project (commercial), Health Promotion Research Trust

DART 1989 *(Continued)*

Response to contact: yes, ProfBurr provided extensive additional data and information on methodology

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using sealed envelopes. The random sequence was generated by the trials unit and sequentially numbered (personal communication with Prof Burr).
Allocation concealment (selection bias)	Unclear risk	Unclear if envelopes were opaque (Professor Burr, personal communication, stated that he did not know)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Very difficult to blind trials where participants need to make their own dietary changes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "outcome assessors were not aware of study allocation" (Prof Burr, personal communication). Method of blinding not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	GPs contacted for information on mortality and morbidity when patients did not attend
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry located
Attention Bias	High risk	Almost all participants received dietary advice – some on 3 diets, some 2, some 1 and some none. All those receiving dietary fat advice will have received dietary advice, while 25% of those in the control received no dietary advice, dietetic time or attention.
Compliance	Low risk	Compliance good as assessed by biomarkers
Other bias	Low risk	None found

Dullart 1992

Methods	RCT, parallel, 2 arms (n-6 LA vs SFA), 2 years
	Summary risk of bias: moderate to high
Participants	Type I diabetics with elevated urinary albumin
	CVD risk: moderate
	Control: randomised 20, analysed 20
	Intervention: randomised 18, analysed 16
	% male: 81% intervention, 75% control
	Mean (SD) age in years: control 41 (14), intervention 44 (12)
	Age range: unclear (21-65 inclusion)

Dullart 1992 *(Continued)*

Smokers: control 55%, intervention 50%

Hypertension: control 10%, intervention 6%

Medications taken by at least 50% of those in the control group: insulin

Medications taken by 20%-49% of those in the control group: not reported

Medications taken by some, but less than 20% of the control group: anti-hypertensive drugs

Location: Netherlands

Ethnicty: not reported

Interventions	Type: dietary advice
	Comparison: LA (n-6) vs usual diet
	Intervention: diet advice given at every visit throughout the 2-year period to increase linoleic acid achieving a polyunsaturated: saturated fatty acid ratio close to 1.0. Advice to replace butter or saturated margarines by polyunsaturated margarines and to restrict the intake of saturated fat from meat and milk products
	Control: to continue their usual diet. All participants were urged not to alter total fat and protein content.
	Dose: (intake data) intervention group 13% E SFA, P/S 0.985, PUFA 9.4% E. Control group 15% E SFA, P/S 0.45, PUFA 6.6% E (CHO and protein were consistent between groups across the trial). **Increase 2.8% E PUFA, most of which n-6**
	Baseline n-6: unclear, 6.6% E PUFA, most of which was n-6
	Compliance: poor, no significant difference between plasma cholesteryl ester LA in intervention and control at 2 years
	Plasma cholesteryl esters at 2 years
	• LA mol %: intervention 62.2% (SD 4.2), control 57.4% (SD 4.9) • Oleic acid mol %: intervention 13.7% (SD 1.8), control 16.5% (SD 1.4)
	Dietary assessment using 1 week dietary recall, reported at 2 years
	• Energy intake: intervention 7.42 MJ/d (SD 2.02), control 8.48 MJ/d (SD 2.48) • Total fat intake: intervention 37% E (SD 4), control 40% E (SD 7) • Saturated fat intake: intervention 13% E (SD 2), control 16% E (SD 3) • PUFA intake: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • n-6 LA: intervention 11% E (SD 2), control 7% E (SD 3) • PUFA/SFA ratio: intervention 0.96% E (SD 0.16), control 0.56% E (SD 0.25) • MUFA intake: not reported • CHO intake: intervention 43% E (SD 4), control 41% E (SD 7) • Protein intake: intervention 18% E (SD 4), control 17% E (SD 3) • Trans fat intake: not reported • Cholesterol intake, mg/d: intervention 174 (SD 49), control 245 (SD 120)
	Duration of intervention: 2 years
Outcomes	Main study outcomes: albuminurea and lipids
	Dropouts: intervention 2 of 20, control 4 of 20

Dullart 1992 *(Continued)*

Available outcomes: weight, HDL cholesterol, TGs, HbA1c (total cholesterol, LDL, glucose, insulin reported but too different at baseline to use, renal outcomes such as GFR, albuminurea, mean arterial pressure not used)

Notes	Most outcomes are estimated from figures
	Study funding: Dutch Diabetes Research Fund
	Response to contact: yes, Prof Dullart confirmed that no CVD events or deaths occurred

Risk of bias

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

GLAMT 1993

Methods	Gamma linolenic acid multicentre trial (GLAMT)
	RCT, 2-arm, parallel (n-6 GLA vs non-fat), 1 year
	Summary risk of bias: moderate to high
Participants	People with mild diabetic neuropathy
	CVD risk: moderate
	Control: randomised 57, analysed 48 (with at least one evaluation)

GLAMT 1993 *(Continued)*

Intervention: randomised 54, analysed 52

Mean years in trial: control 1.0, randomised 1.0

% male: control 79%, intervention 67%

Mean age (SD) in years: control 52.9 (11.4), intervention 53.3 (11.1)

Age range: unclear

Smokers: unclear

Hypertension: unclear

Medications taken by at least 50% of those in the control group: insulin

Medications taken by 20%-49% of those in the control group: not reported

Medications taken by some, but less than 20% of the control group: not reported

Location: UK and Finland

Ethnicity: not reported

Interventions	Type: supplement
	Comparison: GLA (n-6) vs placebo (paraffin)
	Control aims: 12 capsules/d paraffin Intervention aims: 12 capsules/d evening primrose oil (EP4, equivalent to Epogam): 0.48 g/d GLA plus LA (stated as the major constituent, dose not given, if assume 0.7 g/capsule then 8.4 g/d*)
	Dose aim: increase 0.48 g/d GLA or 4 kcal or **0.2% E GLA,** increase ˜8.4 g/d LA or 76 kcal or **3.8% E LA, total 4% E n-6**
	Baseline n-6: unclear
	Compliance by biomarkers: unclear, no serum total cholesterol or tissue fatty acid levels reported
	Compliance by dietary intake: unclear
	• Energy intake: not reported • Total fat intake: not reported • Saturated fat intake: not reported • PUFA intake: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • Trans fat intake: not reported • MUFA intake: not reported • CHO intake: not reported • Sugars intake: not reported • Protein intake: not reported • Alcohol intake: not reported
	Duration of intervention: 1 year
Outcomes	Main study outcome: measures of diabetic neuropathy Dropouts: control 17, intervention 10 Available outcomes: MI, cancer (no deaths)
Notes	Study funding: Scotia Pharmaceuticals

GLAMT 1993 *(Continued)*

*EPO described as being ~70% LA in some publications, this and a 1-g capsule size have been assumed where no other details are provided

Response to contact: no response to our attempted contact

Risk of bias

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

Houtsmuller 1979

Methods	RCT, parallel, (increase LA vs usual diet), 72 months maximum
	Summary risk of bias: moderate or high
Participants	Adults with newly diagnosed diabetes
	N: 51 intervention, 51 control (analysed unclear intervention, unclear control)
	Level of risk for CVD: moderate
	Male: 56% overall (not stated by intervention arm)
	Mean age (SD): not reported
	Age range: not reported
	Smokers: not reported
	Hypertension: not reported

Houtsmuller 1979 *(Continued)*

Medications taken by at least 50% of those in the control group: not reported

Medications taken by 20%-49% of those in the control group: not reported

Medications taken by some, but less than 20% of the control group: statins (probably)

Location: Netherlands

Ethenicity: not reported

Interventions	Type: dietary advice
	Comparison: omega-6 vs SFA and CHO
	Intervention: aims total fat 40% E, 1/3 linoleic acid, CHO 45% E, protein 15% E; methods unclear, surveyed by dietitian. Intervention appears to be delivered by dietitian but no clear details on format or frequency
	Control: aims SFA 35% E, CHO 50% E, protein 15% E; methods unclear, surveyed by dietitian
	Dose aims: increase ˜9% E LA (aims imply no LA in control, but paper states LA was 4 × higher in intervention than control, est 3% E control, 12% E intervention, so increase of ˜9% E)
	Baseline n-6: unclear
	Compliance by biomarkers: good, serum total cholesterol significantly reduced in intervention compared to control (−0.47mmol/L, 95% CI −0.76 to −0.18), no significant differences in men, but significant improvements in women from 3 years
	Compliance by dietary intake: unclear (not reported)
	• Energy intake: not reported
	• Total fat intake: not reported
	• Saturated fat intake: not reported
	• PUFA intake: not reported
	• PUFA n-3 intake: not reported
	• PUFA n-6 intake: not reported
	• Trans fat intake: not reported
	• MUFA intake: not reported
	• CHO intake: not reported
	• Sugars intake: not reported
	• Protein intake: not reported
	• Alcohol intake: not reported
	Duration of intervention: 72 months
Outcomes	Main study outcome: progression of diabetic retinopathy
	Dropouts: unclear
	Available outcomes: CHD events (total MI and angina), total cholesterol, TGs (data read off graph), CHD mortality (fatal MI), progression of retinopathy, GTT and insulin (measured but results are reported in figures for a subgroup)
Notes	Study funding: Dutch Heart Foundation
	Response to contact: attempted but no contact established

Risk of bias

Bias	Authors' judgement	Support for judgement

Houtsmuller 1979 *(Continued)*

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

Mansel 1990

Methods	RCT, 2 arm, parallel (n-6 GLA vs non-fat), 1 year
	Summary risk of bias: moderate to high
Participants	Women with macroscopic breast cysts
	CVD risk: low
	Intervention: 100
	Control: 100
	Mean years in trial: 1
	% male: 0
	Age: unclear (no statistically significant difference between groups)
	Age range: 35 to 60 years
	Smokers: unclear
	Hypertension: unclear
	Medications taken by at least 50% of those in the control group: not reported

Mansel 1990 *(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: UK
	Ethnicity: not reported
Interventions	Type: supplement
	Comparison: GLA (n-6) vs placebo (paraffin)
	Intervention aims: 6 capsules/d EPO (Efamol) containing ≥ 9% GLA (total volume unclear)
	Control aims: 6 capsules/d paraffin (total volume unclear)
	Dose: (assuming each capsule is 1 g) increase **0.54 g/d GLA**, increase 6 g/d or 54 kcal or **2.7% E n-6**
	Baseline n-6: unclear
	Compliance: unclear
	Duration of intervention: 1 year
Outcomes	Main study outcome: unclear, recurrent cysts?
	Dropouts: intervention 7, control 8
	Available outcomes: breast cancer (no deaths or CVD events appear to have occurred)
	Response to contact: no response to attempted contact
Notes	Study funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised"
Allocation concealment (selection bias)	Unclear risk	Randomisation process not discussed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo controlled but similarity of placebo unclear; paper suggests that participants and physicians were blinded to allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "examined by a clinician who was blind to the treatment allocated" but method of this blinding unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition below 20% and well documented
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry found
Attention Bias	Low risk	All seen 2-monthly, all took capsules, clinicians blind to treatment allocation

Mansel 1990 *(Continued)*

Compliance	Unclear risk	Not reported
Other bias	Low risk	None noted

McIllmurray 1987

Methods	RCT, parallel, 2 arms (GLA vs "inert placebo"), 40 months
	Summary risk of bias: moderate to high
Participants	People within one month following operation to remove Dukes's C colorectal cancer
	N: intervention 25 (plus some dropouts), control: 24 (plus some dropouts (analysed intervention 25, control 24). 5 dropped out, but arms unclear
	Level of risk for CVD: low
	Male: not reported
	Mean age (SD) in years: intervention 62.1 (not reported), control 64.8 (not reported)
	Age range: intervention 48-81, control 45-77
	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: UK
	Ethnicity: not reported
Interventions	Type: supplement (EPO)
	Comparison: GLA vs "inert placebo" (unclear what)
	Intervention: 6 capsules/d containing 500 mg GLA plus 10 mg natural vitamin E (Efamol). GLA 0.5 g/d, 60 mg/d vitamin E plus vitamin supplements including vitamin C, zinc sulphate and pyridoxine.
	Control: 6 capsules/d containing an inert placebo, identical in appearance (not specified what). Plus vitamin supplements including vitamin C, zinc sulphate and pyridoxine
	Dose aim: (assuming placebo contains no PUFA) increase **0.5 g/d GLA**, 5 kcal or **0.2% E GLA**, assume 70% LA*, 4.2 g/d or 37.8 kcal/d or **1.9% E LA**, **2.1% E n-6**
	Baseline n-6: unclear
	Compliance by biomarkers: unclear, no serum total cholesterol or tissue fatty acid levels reported
	Compliance by dietary intake: unclear, states that one participant stopped taking the supplements at 12 months
	- Energy intake: not reported - Total fat intake: not reported - Saturated fat intake: not reported - PUFA intake: not reported

McIllmurray 1987 *(Continued)*

- PUFA n-3 intake: not reported
- PUFA n-6 intake: not reported
- Trans fat intake: not reported
- MUFA intake: not reported
- CHO intake: not reported
- Sugars intake: not reported
- Protein intake: not reported
- Alcohol intake: not reported

Duration of intervention: 40 months

Outcomes	Main study outcome: unclear, "survival", probably mortality
	Dropouts: 5 (unclear from which groups)
	Available outcomes: mortality, cancer mortality (face flushing reported as a side effect, but no numbers provided and assumed due to concomitant pyridoxine)
Notes	Study funding: not stated, Efamol Ltd provided the EPO capsules and inert capsules.
	*EPO described as being ~70% LA in some publications, this and a 1 g capsule size have been assumed where no other details are provided
	Response to contact: Prof McIllmurray replied "I don't have the records ... so I have nothing more than what appears in the publication. I do not recall there being any cardiovascular events."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "assigned at random"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details apart from the placebo was identical in appearance to the EPO capsules
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5 dropouts, unclear from which arms
Selective reporting (reporting bias)	Unclear risk	No protocol or trials register entry found
Attention Bias	Low risk	Probably as intervention was capsules in both groups
Compliance	Unclear risk	Not stated
Other bias	Unclear risk	None noted, but contents of placebo capsules unclear

Mendis 2001 *(Continued)*

Methods	RCT, 2 arm, parallel (n-6 LA vs non-fat), 1 year
	Summary risk of bias: moderate to high
Participants	Healthy volunteers responding to survey. Some had hyperlipidaemia.
	CVD risk: low
	N: 30 intervention, 30 control (analysed 26 intervention, 28 control)
	% male: 78% (total)
	Mean age: not reported
	Age range: 20-65 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
	*Lipid lowering medications as well as many others were not allowed.
	Location: Sri Lanka
	Ethnicity: 100% Sri Lanakan
Interventions	Type: diet advice plus test fat supplement
	Comparison: n-6 vs non-fat (unclear if CHO, protein or both)
	Intervention: group B received a diet containing 20% E as fat (4.7% coconut fat) plus 7.5 g/day test fat containing soybean fat-sesame fat (3:1, v/v containing PUFA:MUFA ratio 2). Fat intake in group B was, therefore, 24% E (test fat provided additional 5 g/d PUFA mainly LA)
	Control: group A received a diet containing 20% E as fat (4.7% E coconut fat)
	Dose aim: increase 5 g/d PUFA or 45 kcal or **2.2% E PUFA,** assume˜**2% E LA**
	Baseline n-6: unclear
	Compliance by biomarkers: poor, serum total cholesterol was not significantly reduced in intervention compared to control (0.16 mmol/L, 95% CI −0.18 to 0.50). The intervention group were stated as having higher dietary PUFA:SFA ratio than controls, but no blood levels of FAs were reported.
	Compliance by dietary intake: unclear, measured by field workers' visits and using food diaries
	• Energy intake: intervention 7962 kJ/d (SD 1568), control 8030 kJ/d (SD 1465)
	• Total fat intake: intervention 24% E (SD not reported), control 20% E (SD not reported)
	• Saturated fat intake: intervention 11.4% E (SD not reported), control 11.8% E (SD not reported)
	• PUFA intake: not reported (unsaturated fat intake intervention 12.6% E, control 8.2% E, test fat reported as mainly LA)
	• PUFA n-3 intake: not reported
	• PUFA n-6 intake: (unsaturated fat intake intervention 12.6% E, control 8.2% E, test fat reported as mainly LA)
	• Trans fat intake: not reported

Mendis 2001 *(Continued)*

- MUFA intake: not reported
- CHO intake, % E: intervention 64 (SD not reported), control 67 (SD not reported)
- Sugars intake: not reported
- Protein intake: intervention 12.2% E (SD not reported), control 12.1% E (SD not reported)
- Alcohol intake: not reported

Duration of intervention: 1 year

Outcomes	Main study outcome: serum lipids
	Dropouts: intervention 4, control 2
	Available outcomes: lipids
Notes	Study funding: National Science Foundation of Sri Lanka
	Response to contact: no response to attempted contact

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomised to 2 groups (groups A and B). This was done in such a way that the 38 hyperlipidaemic subjects were equally divided between the 2 groups
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	The groups had different diets with test fat added to intervention group
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	High risk	6 participants dropped out at 6 months but their data is not included in the analysis at all
Selective reporting (reporting bias)	Unclear risk	No protocol or trial register entry found
Attention Bias	Low risk	Both groups had twice weekly visits by field workers
Compliance	High risk	Compliance poor when assessed by biomarkers
Other bias	Unclear risk	No details provided on the form or method of supply of diet or test fat

MRC 1968

Methods	Medical Research Council (MRC)
	RCT, 2 arm, parallel (n-6 LA vs mixed fats), 4 years

	Summary risk of bias: moderate to high
Participants	Free-living men who have survived a first MI (UK) CVD risk: high Control: randomised 194, analysed 181 at 2 years Intervention: randomised 199, analysed 172 at 2 years Mean years in trial: control 3.7, intervention 3.8 % male: 100 Age: unclear Age range: all < 60 years Smokers: control 84%, intervention 81% Hypertension: control 12%, intervention 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: not reported Medications taken by some, but less than 20% of the control group: not reported Location: UK Ethnicty: not reported
Interventions	Type: diet advice plus supplement Comparison: increased soya oil (n-6) vs usual diet (some SFA replacement, otherwise unclear) Control aims: usual diet Intervention aims: reduce dietary fat to 35 g/d fat, add 84 g/d soya oil **Dose aim**: increase 84 g/d soya oil or 756 kcal or **37.8% E soya** (assume 50% LA, so **18.9% E LA**, assume 58% PUFA so **21.9% E PUFA)** Baseline n-6: unclear **Compliance by biomarkers**: unclear, serum total cholesterol reported but without any variance info. Report stated that "tissue fat of the men on the soya-bean oil diet was less saturated than that of the controls" and that further information would be published elsewhere. No statistical significance or variance data mentioned **Compliance by dietary intake**: unclear • Energy intake: intervention 2380 kcal/d (SD not reported), control 2274 kcal/d (SD not reported) • Total fat intake: not reported • Saturated fat intake: not reported • PUFA intake: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • Trans fat intake: not reported • MUFA intake: not reported • CHO intake: intervention 243 g/d (SD not reported), control 228 g/d (SD not reported) • Sugars intake: intervention 66 g/d (SD not reported), control 60 g/d (SD not reported) • Protein intake: intervention 80 g/d (SD not reported), control 88 g/d (SD not reported) • Alcohol intake: not reported

MRC 1968 *(Continued)*

	Duration of intervention: 4 years
Outcomes	Main study outcomes: MI or sudden death
	Dropouts: intervention 199 randomised, 181 at 2 years, 91 at 4 years. Control: 194 randomised, 172 at 2 years, 85 at 4 years
	Available outcomes: mortality, CVD mortality (CVD deaths plus non-fatal MI), total MI, non-fatal MI (data for weight, total cholesterol and BP, but no variance info)
Notes	Study funding: Medical Research Council
	Response to contact: reply from retired trial statistician, JA Heady, in 1999

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "using random numbers, by blocks within hospitals"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Big changes to fat intake in intervention group while control group ate their usual diet
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "[s]uspected relapses were assessed at regular intervals by a review committee unaware of the patients diet group"
Incomplete outcome data (attrition bias) All outcomes	High risk	Data collection was thorough, but some participants dropped out and contact was lost
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry located
Attention Bias	High risk	Likely that intervention group received more time, training and encouragement (as dietary intervention, and control ate usual diet)
Compliance	Unclear risk	Not reported
Other bias	Low risk	None noted

NDHS Faribault 1968

Methods	National Diet-Heart Study (NDHS) – Faribault site
	RCT, several arms, parallel (n-6 LA vs SFA + MUFA), 1 year
	Summary risk of bias: low
Participants	Men living in a mental health institute
	CVD risk: low

NDHS Faribault 1968 *(Continued)*

	Control: randomised 57, analysed 52
	Interventions B, C, E combined: randomised 167, analysed 143
	Mean years in trial: control 1.0, Interventions 0.9
	% male: 100
	Age: unclear
	Age range: all 45-54 years
	Smokers: 55% to 59% current smokers in each arm
	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: USA
	Ethnicty: not reported
Interventions	Type: diet provided (residential institution)
	Comparison: increased PUFA (n-6) vs usual institutional diet (SFA + MUFA)
	Control aims: total fat 40% E, SFA 16-18% E, dietary cholesterol 650-750 mg/d, P/S 0.4 (so PUFA 6.8% E) (whole diet provided)
	Intervention aims: B (C, E) total fat 30% E (40% E, 40% E), SFA < 9% E (< 9% E, not stated), dietary cholesterol 350-450 mg/d (350-450 mg/d, not stated), PUFA 15% E (18-20% E, not stated), P/S 1.5 (2.0, 4.4) (equivalent to Minnesota Coronary Study diet) (whole diet provided)
	Dose aim: increase **B 8.2% E, C 12.2% E, E unclear** n-6
	Baseline n-6 (table IX2): 4.4% E LA, 4.8% E PUFA
	Compliance by biomarkers: good, serum total cholesterol significantly reduced in intervention compared to control (−0.91 mmol/L, 95% CI −1.17 to −0.65). Data on fatty acid composition of red blood cells provided in chapter 10 (table X6: LA rose by 4 in control, by 5 to 7 in other arms, at the expense of MUFA which rose by 1 in control, fell by 4 or 5 in other arms. Palmitic acid fell by 5 in control, and fell by 4 in intervention arms, stearic did not alter in control, rose by 1 or 2 in intervention arms – no statistical significance or variance info provided, units unclear, probably % of LA + oleic + palmitic + stearic)
	Compliance by dietary intake: good. Assessed from 7-day food records after 28 and 44 weeks combined (tables IX8 and 9)
	• Energy intake: intervention B 2549 kcal/d, intervention C 2599 kcal/d, intervention E 2560 kcal/d, control D 2593 kcal/d
	• Total fat intake: intervention B 29.0% E, intervention C 38.5% E, intervention E 37.1% E, control 39.5% E (decrease **B 10.5% E, C 1.0% E, E 2.4 total fat**)
	• Saturated fat intake: intervention B 6.1% E, intervention C 7.0% E, intervention E 4.6% E, control D 15.6% E (decrease **B 9.5% E, C 8.6% E, E 11.0% E SFA**)
	• PUFA intake: intervention B 12.1% E, intervention C 17.8% E, intervention E 22.3% E, control D 4.6% E (increase **B 7.5% E, C 13.2% E, E 17.7% E PUFA**)
	• PUFA n-3 intake: not reported
	• PUFA n-6 intake, % E LA: intervention B 11.6% E, intervention C 16.9% E, intervention E 21.9% E, control D 4.3% E (increase **B 7.3% E, C 12.6% E, E 17.6% E LA**)
	• Trans fat intake: not reported

NDHS Faribault 1968 *(Continued)*

- MUFA intake: intervention B 10.8% E, intervention C 13.7% E, intervention E 10.2% E, control D 19.3% E (decrease **B 8.5% E, C 5.6% E, E 9.1% E MUFA**)
- CHO intake: intervention B 55.3% E, intervention C 45.8% E, intervention E 48.6% E, control D 45.1% E (increase **B 10.1% E, C 0.7% E, E 3.5% E CHO**)
- Sugars intake: not reported
- Protein intake: intervention B 17.0% E, intervention C 16.7% E, intervention E 15.7% E, control D 16.4% E (increase **B 0.6% E, C 0.3% E, E −0.7% E protein**)
- Alcohol intake: not reported

Duration of intervention: 1 year

Outcomes	Main study outcomes: lipid levels and dietary assessment
	Dropouts: B 7, C 10, E 7, D (control) 5
	Available outcomes: mortality, total cholesterol (weight and TG data available but without SDs)
Notes	Data entered as all interventions combined (B + C + E) vs control (D)
	Study funding: National Heart Institute
	Response to contact: not attempted as study completed in 1967

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified randomisation by the statistical centre
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Institution so all participants and study staff blinded to allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were reported as blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Institution so able to follow up all participants through study
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry found
Attention Bias	Low risk	Interventions and follow ups delivered in an equivalent way across arms
Compliance	Low risk	Good compliance by biomarkers
Other bias	Low risk	None found

NDHS Open 1st 1968

Methods	National Diet-Heart Study (NDHS) – Open First phase
	RCT, several arms, parallel (n-6 LA vs SFA + MUFA), 1 year
	Summary risk of bias: low
Participants	Free-living men aged 45-54 years
	CVD risk: low
	Control: randomised 382, analysed 341
	Interventions B, C, X combined: randomised 829, analysed 726
	Mean years in trial: control 0.95, intervention 0.93
	% male: 100 Age: unclear
	Age range: all 45-54 years
	Smokers: 39% to 40% current smokers in each arm
	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: USA
	Ethnicty: white 98.2%, non-white 1.8% (not reported by intervention arm)
Interventions	Type: diet provided (bought from a trial shop)
	Comparison: increased PUFA (n-6) vs usual diet (replacement of SFA + MUFA)
	Control aims: total fat 40% E, dietary cholesterol 650-750 mg/d, P/S 0.4 (assume PUFA 6.8% E as at Faribault) (foods bought from a trial shop – normal foods)
	Intervention aims: B (C, X) total fat 30% E (40% E, 30% E), SFA < 9% E (< 9% E, < 9% E), dietary cholesterol 350-450 mg/d (350-450 mg/d, 350-450 mg/d), PUFA 15% E (18-20% E, 15% E), P/S 1.5 (2.0, 1.5) (foods bought from a trial shop – saturated fats removed and replaced by polyunsaturated oils and fats)
	Dose aim:**increase B 8.2% E, C 12.2% E, X 8.2% E n-6**
	Baseline n-6 (tables IX 1 and 3): 3.7% LA, 3.9% PUFA
	Compliance by biomarkers: good, serum total cholesterol significantly reduced in intervention compared to control (−0.45 mmol/L, 95% CI −0.55 to −0.35). Data on fatty acid composition of red blood cells provided in chapter 10 (table X6: LA rose by 1 in control, by 2 to 3 in other arms, at the expense of MUFA which did not alter in control, fell by 2 or 3 in other arms. Palmitic acid remained constant in control and remained constant or fell by 1 in intervention arms, stearic did not alter in control and remained constant or rose by 1 in intervention arms – no statistical significance or variance info provided, units unclear, probably % of LA + oleic + palmitic+stearic)
	Compliance by dietary intake: good. Nutritionists subjective adherence ratings of excellent or good (as compared to fair or poor) intervention B 58%, intervention C 60%, control D 55%. Dietary intake computed from 7-day food records at 28 weeks (table IX3, no later data found):
	• Energy intake: intervention B 2154 kcal/d (SD 432), intervention C 2262 kcal/d (SD 435), intervention X 2117 kcal/d (SD 447), control D 2228 kcal/d (SD 456)

- Total fat intake: intervention B 29.7% E, intervention C 34.4% E, intervention X 31.7% E, control D 34.9% E (decrease **B 5.2% E, C 0.5% E, X 3.2 total fat**)
- Saturated fat intake: intervention B 7.1% E, intervention C 7.4% E, intervention X 8.9% E, control D 11.6% E (decrease **B 4.5% E, C 4.2% E, X 2.7% E SFA**)
- PUFA intake: intervention B 9.9% E, intervention C 13.2% E, intervention X 6.5% E, control D 4.9% E (increase **B 5.0% E, C 8.3% E, X 1.6 PUFA**)
- PUFA n-3 intake: not reported
- PUFA n-6 intake: not reported, probably similar to PUFA
- Trans fat intake: not reported
- MUFA intake (by subtraction of SFA and PUFA from total fat): intervention B 12.7% E, intervention C 13.8% E, intervention X 16.3% E, control D 18.4% E (decrease **B 5.7% E, C 4.6% E, X 2.1% E MUFA**)
- CHO intake: intervention B 48.7% E, intervention C 45.3% E, intervention X 49.5% E, control D 44.7% E (increase **B 4.0% E, C 0.6% E, X 4.8% E CHO**)
- Sugars intake: not reported
- Protein intake: intervention B 18.6% E, intervention C 17.6% E, intervention X 17.1% E, control D 17.4% E (increase **B 1.2% E, C 0.2% E, X −0.3% E protein, little change**)
- Alcohol intake: intervention B 2.1% E, intervention C 2.1% E, intervention X 1.7% E, control D 2.2% E (minimal change)

Duration of intervention: 1 year

Outcomes	Main study outcomes: lipid levels and dietary assessment
	Dropouts: intervention B 42, C 34, X 5, control D 36
	Available outcomes: CVD events (MI and PAD events), cancer diagnoses, total cholesterol (weight, diastolic BP and TG data available but without SDs)
Notes	Study funding: National Heart Institute
	Response to contact: not attempted as study completed in 1967

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified randomisation by the statistical centre
Allocation concealment (selection bias)	Low risk	Stratified randomisation by the statistical centre
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and study personnel (aside from the store manager) were blinded to allocation. Blinding of participants was checked using a questionnaire which found no difference between intervention and control participants in guesses at dietary composition.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were reported as blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	12% dropouts, well described
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registry entry found

NDHS Open 1st 1968 *(Continued)*

Attention Bias	Low risk	Interventions and follow-ups delivered in an equivalent way across arms
Compliance	Low risk	Good compliance by biomarkers
Other bias	Low risk	None noted

Rose 1965

Methods	RCT, 2-arm, parallel (n-6 LA vs MUFA), 24 months
	Summary risk of bias: moderate to high
Participants	Patients with ischaemic heart disease (IHD)
	CVD risk: high
	N: 28 intervention, 26 control (analysed 15 intervention, 12 control)
	% male: not reported
	Mean age in years: 52.6 intervention, 55 control (no SDs)
	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: UK
	Ethnicty: not reported
Interventions	Type: dietary advice + test oil provided
	Comparison: n-6 vs MUFA
	Intervention: 80 g/d corn oil to be taken in 3 equal doses at meal-times plus patients were instructed to avoid fried foods, fatty meat, sausages, pastry, ice-cream, cheese, cakes, milk, eggs, butter were restricted: assuming 80% LA in corn oil, 64 g/d LA or 576 kcal/d or 28.8% E from LA
	Control: 80 g/day olive oil plus patients were instructed to avoid fried foods, fatty meat, sausages, pastry, ice-cream, cheese, cakes, milk, eggs, butter were restricted. assuming 12% LA and 69% MUFA in olive oil, 9.6 g/d LA or 4.3% E LA and 55.2 g/d MUFA or 24.8% E
	Dose aim: +24.5% E from LA, −24.8% E MUFA
	Baseline n-6: unclear
	Compliance using biomarkers: poor, serum total cholesterol not significantly reduced in intervention compared to control (−0.49 mmol/L, 95% CI −1.34 to 0.36)
	Compliance using dietary assessment: poor. Measured using questionnaire
	Mean intake of oil in intervention was 595 kcal/d or 476 kcal/d LA or 23.8% E, in control 540 kcal/d or 3.2% E LA and 18.6% E MUFA

Rose 1965 *(Continued)*

Dose achieved: +20.6% E from LA, −18.6% E MUFA within the oils, unclear how diet altered

- Energy intake: intervention 2070 kcal/d control 2045 kcal/d
- Total fat intake: intervention 50 g/d + 595 kcal from oil or 1045 kcal/d or 52% E, control 45 g/d + 540 kcal from oil or 945 kcal/d or 47.3% E
- Saturated fat intake: not reported
- PUFA intake: not reported
- PUFA n-3 intake: not reported
- PUFA n-6 intake: +20.6% E (higher in intervention than control)
- Trans fat intake: not reported (oils provided so not likely to be a problem)
- MUFA intake: −18.6% E (lower in intervention than control)
- CHO intake: intervention 189 g/d or 756 kcal/d or 37.8% E, control 216 g/d or 864 kcal/d or 43.2% E
- Sugars intake: not reported
- Protein intake: intervention 57 g/d or 228 kcal/d or 11.4% E, control 49 g/d or 196 kcal/d or 9.8% E
- Alcohol intake: not reported

Duration of intervention: 2 years

Outcomes	Main study outcome: occurrence of infarction Dropouts: 6 intervention, 11? control, details provided in table but unclear how many dropped out Available outcomes: major CVD events, MI (fatal and non-fatal), sudden death, serum cholesterol
Notes	Study funding: no details The study had a third control arm (no intervention) which has not been used here. Response to contact: contact attempted but not achieved

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	When a new patient was accepted for the trial a sealed envelope was opened containing the allocation instructions. In the case of patients allocated to an oil group the instructions referred only to a code number.
Allocation concealment (selection bias)	Unclear risk	As above, opacity of envelope unclear
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Physicians in charge knew which patients were receiving oil, but they did not know until the end of the trial the kind of oil that they were receiving.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The electrocardiograms were assessed without the knowledge of the patients treatment group
Incomplete outcome data (attrition bias) All outcomes	Low risk	52% intervention, and 57% control remained in the trial after 24 months. However, the list of reasons and complications is provided.
Selective reporting (reporting bias)	Unclear risk	No trial registry record or protocol found
Attention Bias	Low risk	Both groups appear to have the same treatment

Rose 1965 *(Continued)*

Compliance	High risk	Compliance poor; assessed by biomarkers
Other bias	Low risk	None noted

Schirmer 2007

Methods	RCT, 2 arm, parallel (n-6 GLA vs MUFA), 1 year
	Summary risk of bias: moderate to high
Participants	Formerly obese adults with a recent minimum weight loss of 12 kg, a current BMI of < 34 kg/m^2, otherwise healthy
	CVD risk: low
	N: 23 intervention, 22 control (analysed only completers 13 intervention, 17 control)
	% male: 8% intervention, 6% control
	Mean age (SD) in years: 44.2 (10.1) intervention, 52.6 (8.1) control
	Age range: not reported
	Smokers: not reported
	Hypertension: 0%
	Medications taken by at least 50% of those in the control group: anorexigenic agent
	Medications taken by 20%-49% of those in the control group: not reported
	Medications taken by some, but less than 20% of the control group: not reported
	Location: USA
	Ethnicty: not reported
Interventions	Type: supplement (capsule)
	Comparison: n-6 (GLA) vs MUFA
	Intervention: 5 g/d of 500 mg borage oil capsules providing 0.89 g/d GLA
	Control: 5 g/d of identical 500 mg olive oil capsules
	Subjects in both groups were required to take a balanced multivitamin-mineral supplement daily, which included 80 mg of d-alpha-tocopherol
	Dose aim: increase 0.89 g/d GLA or 8 kcal or **0.4% E GLA,** plus approx 0.9 g/d LA or **0.4% E LA, 0.8% E n-6**
	Baseline n-6: unclear
	Compliance by biomarkers: good. Measurement of adipose GLA showed increased GLA in intervention (2.16 µmol/g of adipose TG at baseline to 5.39 µmol/g at 1 year) but not in control (2.51 µmol/g of adipose TG at baseline to 2.87 µmol/g at 1 year, statistically significant difference suggested). DGLA increased in intervention group, but fell in control
	Compliance by dietary intake: unclear, participants maintained daily food intake and exercise records
	• Energy intake: not reported
	• Total fat intake: not reported

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Schirmer 2007 *(Continued)*

- Saturated fat intake: not reported
- PUFA intake: not reported
- PUFA n-3 intake: not reported
- PUFA n-6 intake: not reported
- Trans fat intake: not reported
- MUFA intake: not reported
- CHO intake: not reported
- Sugars intake: not reported
- Protein intake: not reported
- Alcohol intake: not reported

Duration of intervention: 1 year (results reported only for participants completing a minimum of 50 weeks)

Outcomes	Main study outcome: measures of adiposity
	Dropouts: unclear, only one withdrew after randomisation but trial was terminated and only reported on 30/45 completers
	Available outcomes: weight, fat weight (fasting blood glucose and blood pressure measured but not reported)
Notes	Study funding: supported in part by a gift from Shaklee Technica
	Response to contact: Prof Phinney replied "I am sorry to inform you that I cannot provide meaningful feedback within the parameters of your survey"

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	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both oil supplements were administered in a double-blind protocol as identical 500 mg capsules"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The initial study was terminated, and all remaining subjects were assessed over a 6-wk period. Unblinding revealed" …"the monitoring of their weights (simple ANOVA of group means while investigators and subjects remained unaware of treatment)"
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "At the termination of the randomized placebo-controlled trial, 45 subjects remained in the study". Mentions one dropped out between randomisation and treatment commencement but no details/explanation of remaining dropouts/non-completers
Selective reporting (reporting bias)	Unclear risk	No protocol or trial register entry
Attention Bias	Low risk	Both groups appear to have the same care

Compliance	Low risk	Adipose GLA was significantly higher in intervention group compared to control (P < 0.0001)
Other bias	Low risk	None noted

Sydney Diet-Heart 1978

Methods	Sydney Diet-Heart Study
	RCT, 2 arm, parallel (n-6 LA vs SFA + MUFA), 4.3 years
	Summary risk of bias: low
Participants	Men with previous MI
	CVD risk: high
	Control: randomised 237, analysed 221 at 2 years
	Intervention: randomised 221, analysed 205 at 2 years
	Mean years in trial: control 4.3, intervention 4.3
	% male: 100
	Mean age (SD) in years: control 49.1 (6.5), intervention 48.7 (6.8)
	Age range: 30-59 years
	Smokers: control 68.8%, intervention 71.5%
	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: Australia
	Ethnicity: not reported
Interventions	Type: diet advice
	Comparison: increased safflower oil and safflower oil based margarine (n-6) vs usual diet (reduced SFA and MUFA)
	Control aims: reduction in energy if overweight, no other specific dietary advice, allowed to use PUFA margarine instead of butter (no specific dietary instruction, except re weight)
	Intervention aims: SFA 10% E, PUFA 15% E, reduction in energy if overweight, dietary cholesterol < 300 mg/d through provision of safflower oil and safflower margarine (advised and tutored individually, diet assessed 3 times in first year, twice annually thereafter)
	Dose aim: **increase 6.6% E PUFA, most of which n-6**
	Baseline n-6: unclear, 6.1% E PUFA, mostly n-6
	Compliance by biomarkers: good, serum total cholesterol significantly reduced in intervention compared to control (−0.30 mmol/L, 95% CI −0.51 to −0.09)

Compliance by dietary intake: good. From diet records, medians provided.

- Energy intake: intervention 2256 kcal/d, control 2194 kcal/d
- Total fat intake: intervention −1.9% E, control −1.1% E (reduction of **0.8% E total fat**)
- Saturated fat intake: intervention −6.9% E, control −2.1% E (reduction of **4.8% E SFA**)
- PUFA intake: intervention +9.3% E, control +2.2% E (increase of **7.1% E PUFA**)
- PUFA n-3 intake: not reported
- PUFA n-6 intake: not reported
- Trans fat intake: not reported
- MUFA intake: intervention −3.4% E, control −0.7% E (reduction of **2.7% E MUFA**)
- CHO intake: intervention +1.4% E, control +0.1% E (increase of **1.3% E CHO**)
- Sugars intake: not reported
- Protein intake: intervention +0.4% E, control +1.2% E (decrease of **0.8% E protein**)
- Alcohol intake: intervention +0.7% E, control +1.7% E (decrease of **1.0% E alcohol**)

Duration of intervention: 2-7 years

Outcomes	Main study outcomes: CVD mortality and morbidity
	Dropouts: unclear, probably 16 dropouts in each arm, but participants were included from 2 to 7 years
	Available outcomes: mortality, total cholesterol, TG. Additional data provided or checked on all-cause mortality, CHD events, stroke and CVD mortality
Notes	Study funding: Life Insurance Medical Research Fund of Australia and New Zealand
	Response to contact: Dr Leelarthepin and Dr Zamora both provided additional data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "table of random numbers … generated by a research assistant and was concealed until after medical evaluations and testing at baseline were completed"
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias) All outcomes	High risk	Very difficult to blind trials where participants need to make their own dietary changes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Initially masked to group assignment (though success of blinding not checked)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Survival analysis used
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry located
Attention Bias	High risk	Different levels of dietary support (non-dietary aspects were equivalent)
Compliance	Low risk	Compliance good assessed by biomarkers

Other bias	Low risk	None noted

Veterans Admin 1969

Methods	Veterans Administration Study
	RCT, 2 arms, parallel (n-6 LA vs SFA + MUFA), up to 8 years
	Summary risk of bias: moderate to high
Participants	Men living at the Veterans Administration Centre
	CVD risk: low
	Control: randomised 422, analysed 422
	Intervention: randomised 424, analysed 424
	Mean years in trial: control 3.7, intervention 3.7
	% male: 100
	Mean age in years: control 65.6, intervention 65.4
	Age range: all 54 to 88 years
	Smokers: intervention 283, control 279 (unknown intervention 41, control 58)
	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: digitalis, diuretics, estrogens, corticoids, androgens, coumarins, nicotinic acid
	Location: USA
	Ethnicity: white 90%, black 7%, Asian 1%, Mexican 1%, other 1%
Interventions	Type: diet provided (residential institution)
	Comparison: increased corn, soybean, safflower and cottonseed oils (n-6) vs usual institutional diet
	Control aims: provided, total fat 40% E (whole diet provided)
	Intervention aims: total fat 40% E, 2/3 of SFA replaced by unsaturated fats (from corn, soybean, safflower and cottonseed oils), dietary cholesterol reduced (whole diet provided)
	Dose aim: 2/3 of baseline SFA is increase of ˜**12% E PUFA**
	Baseline n-6: 4% E LA
	Compliance by biomarkers: poor, serum total cholesterol not significantly reduced in intervention compared to control (−0.37 mmol/L, 95% CI −0.77 to 0.03)
	Compliance by dietary intake: unclear, checked using coloured tickets to assess dining room attendance – described as 49% in intervention and 56% in controls. Laboratory analysis of the mean of over 400 weekly collections of diet provided:
	• Energy intake: intervention 2496 kcal/d, control 2496 kcal/d

Veterans Admin 1969 *(Continued)*

- Total fat intake: intervention 38.9% E (SD 1.9), control 40.1% E (SD 2.2)
- Saturated fat intake: intervention 8.3% E, control 18.5% E (decrease **10.2% E SFA**)
- PUFA intake: not reported but shown in graph as stearate being almost half in intervention compared to control, and palmate similar
- PUFA n-3 intake: intervention 16.1% E (SD not reported), control 4.4% E (SD not reported) (increase of **11.8% E PUFA**)
- PUFA n-6 intake: intervention 16.1% E, control 4.4% E (increase **11.7% E LA**)
- Trans fat intake: not reported
- MUFA intake: intervention 14.6% E, control 17.1% E (decrease **2.5% E MUFA**s)
- CHO intake: not reported
- Sugars intake: not reported
- Protein intake: intervention 15.6% E (SD not reported), control 15.4% E (SD not reported)
- Alcohol intake: not reported

Duration of intervention: up to 8-9 years

Outcomes	Main study outcomes: mortality, heart disease
	Dropouts: intervention 117, control 58 withdrawals over whole study, a few participants were involved for up to 8-9 years
	Available outcomes: mortality, CVD mortality (sudden death, definite MI, definite stroke, angina, peripheral vascular events), cancer deaths, cancer diagnoses, stroke, non-fatal MI, total MI, CHD deaths (fatal MI and sudden death due to CHD), CHD events (any MI or sudden death due to CHD), total cholesterol
Notes	Trial dates: recruitment 1959 to 1967
	Study funding: mainly US Public Health Service, Los Angeles County Heart Assoc, Arthur Dodd Fuller Assoc, but Corn Products Co (provided Corn oil and margarine), National Soybean Processors Assoc (provided soybean oil), Pitman-Moore Co (provided margarine), Frozen Desserts Co (imitation ice cream). All authors worked for academic or health institutions
	Response to contact: not contacted as the study started in 1959.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "table of random numbers used"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Institution provided diet in a masked fashion
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Physician knowledge of allocation was assessed and found not much better than random
Incomplete outcome data (attrition bias) All outcomes	Low risk	All followed up via Veterans Admin system

Veterans Admin 1969 *(Continued)*

Selective reporting (re-porting bias)	Unclear risk	No protocol or trials registry entry located
Attention Bias	Low risk	Both groups appear to have been treated very similarly
Compliance	High risk	Compliance poor assessed by biomarkers
Other bias	Low risk	None found

Vijayakumar 2014

Methods	RCT, 2 arms, parallel (n-6 LA vs SFA), 2 years
	Summary risk of bias: moderate to high
Participants	People with stable coronary artery disease
	CVD risk: high
	Intervention (sunflower oil): 100 randomised, analysed at 2 years 94
	Control (coconut oil): 100 randomised, analysed at 2 years 96
	Mean years in trial: 2
	% male: intervention 92.9%, control 93.9%
	Mean age (SD) in years: intervention 59.0 (8.9), control 59.0 (8.4)
	Age range: unclear
	Smokers, ex: intervention 57.1%, control 54.1%
	Hypertension: intervention 55.1%, 58.2%
	Medications taken by at least 50% of those in the control group: statins
	Medications taken by 20%-49% of those in the control group: not reported
	Medications taken by some, but less than 20% of the control group: fibrates, nicotinic acid
	Location: India
	Ethnicity: not reported
Interventions	Type: food (cooking oil) provided
	Comparison: sunflower oil (n-6) vs coconut oil (SFA)
	Intervention aims: whole family to use branded sunflower oil for cooking (15% E provided in form of sunflower oil)
	Control aims: whole family to use branded coconut oil for cooking (15% E provided in form of coconut oil)
	Dose aim: increase **15% E n-6**
	Baseline n-6: unclear
	Compliance by biomarkers:poor, serum total cholesterol not significantly reduced in intervention compared to control (0.06 mmol/L, 95% CI −0.22 to 0.34)

Vijayakumar 2014 *(Continued)*

Compliance by dietary intake:unclear. Reports that 7-day recall and diet diaries were used to monitor intake, but results not provided

- Energy intake: not reported
- Total fat intake: not reported
- Saturated fat intake: not reported
- PUFA intake: not reported
- PUFA n-3 intake: not reported
- PUFA n-6 intake: not reported
- Trans fat intake: not reported
- MUFA intake: not reported
- CHO intake: not reported
- Sugars intake: not reported
- Protein intake: not reported
- Alcohol intake: not reported

Duration of intervention: 2 years

Outcomes	Main study outcome: CVD risk factors
	Dropouts: intervention 6 lost, control 4 lost
	Available outcomes: lipids, death, re-vascularisation (glycaemic control, weight, BMI available but unbalanced at baseline). Author confirmed no CVD events or deaths, no atrial fibrillation. Provided data on HbA1c and CRP
Notes	Study funding: Coconut development board, Amrita Institute of Medical Science and Research. Sponsors had no role in study design or analysis.
	Response to contact: Dr Vijayakumar replied with information on outcomes and methodology

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation with 5 blocks of 40
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open label. Participants and their families used branded oils, which were not identical in taste and other properties. Author states that only the dietitian was aware of the oil allocation.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear, as above. Author suggests that outcomes assessors were blinded but does not provide a method for this.
Incomplete outcome data (attrition bias) All outcomes	Low risk	5% withdrawals. Clear, with reasons
Selective reporting (reporting bias)	Unclear risk	Unclear, no protocol or trials register entry found

Vijayakumar 2014 *(Continued)*

Attention Bias	Low risk	Unlikely as cooking oil was the intervention, and assessments appeared similarly timed
Compliance	High risk	Compliance poor assessed by biomarkers
Other bias	Low risk	None noted

ALA: alpha linolenic acid (n-3 18:3); **BP**: blood pressure; **CHD**: coronary heart disease; **CHO**: carbohydrate; **CRP**: C-reactive protein; **CVD**: cardiovascular disease; **DHA**: docosahexaenoic acid (n-3 22:6); **DPA**: docosapentaenoic acid (n-3 22:5); **EPA**: eicosapentaenoic acid (n-3 20:5); **EPO**: evening primrose oil; **ESR**: erythrocyte sedimentation rate; **GFR**: glomerular filtration rate; **GLA**: gamma linolenic acid (n-6 18:3); **GP**: general practitioner; **GTT**: glucose tolerance test; **HbA1c**: glycated haemoglobin (a measure of glucose metabolism); **HDL**: high-density lipoprotein, a lipid (fat) fraction measured in human blood. HDL is thought to be protective; **IHD**: ischaemic heart disease; intervention: intervention arm; **ITT**: intention-to-treat; **LA**: linoleic acid (n-6 18:2); **LDL**: low-density lipoprotein, a lipid (fat) fraction measured in human blood. LDL is thought to contribute to atherosclerosis; **MI**: myocardial infarction; **MS**: multiple sclerosis; **MUFA**: monounsaturated fatty acid; **NSAID**: non-steroidal anti-inflammatory drug; **PAD**: peripheral arterial disease; **P/S**: polyunsaturated: saturated fatty acid ratio; **PUFA**: polyunsaturated fatty acid; **RA**: rheumatoid arthritis; **RCT**: randomised controlled trial; **SD**: standard deviation; **SE**: standard error; **SFA**: saturated fatty acid; **TC**: total cholesterol (combined lipid or fat, measured in human blood, includes TG, HDL and LDL); **TG**: triglyceride (a type of lipid or fat, measured in human blood); **% E**: percentage of energy intake from this nutrient.

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

Study	Reason for exclusion
Bierenbaum 1963	Duration only 50 weeks
Bramkamp 1974	Not an RCT
Dembinska-Kiec 2010	Not an RCT
Dembinska-Kiec 2011	Not an RCT
Elisha 2011	Not an RCT
Finnegan 2003a	Irrelevant outcomes and control not minimal
Finnegan 2003b	Irrelevant intervention
Finnish Mental Hosp 1972	Not randomised (cluster-randomised, but < 6 clusters)
Gaullier 2004	Irrelevant intervention
Gaullier 2005	Not an RCT and control irrelevant
Gaullier 2007	Irrelevant intervention
Ghafoorunissa 1995	Control not minimal and short term trial (8 weeks)
Ghafoorunissa 2002	Not an RCT
Harbige 2007	No relevant outcomes reported and no author contact established
Harris 2009	Not an RCT
Heine 1989	Irrelevant participants

Study	Reason for exclusion
Hui 1989	Intervention in rats
Jamal 1990	First author of this publication Goran Jamal, was reprimanded by the General Medical Council in 2003 after being found guilty of research fraud in a drug trial involving EPO, the topic of this paper. The professional conduct committee of the GMC found Dr Jamal guilty of serious professional mis-conduct for falsifying his results in a multicentre trial of the drug Tarabetic, also known as Efamol, a constituent of evening primrose oil, intended for the treatment of diabetic peripheral neuropathy. We believe that this throws doubt on Dr Jamal's work on Efamol, including this trial
Khan 2003	Duration was 8 months only
Kruger 1998	GLA + EPA vs olive oil
Lands 1992	Not an RCT
Larsen 2006	Irrelevant intervention (CLA)
Leng 1998	GLA + EPA vs sunflower oil (so n-6 + n-3 vs n-6), no assessment of n-6
Ley 2004	No aim to increase omega-6 or PUFA, PUFA increased by over 10% but no information provided on omega-6 fats
MARGARIN 2002	Irrelevant intervention, ALA vs LA
Michalsen 2006	Multifactorial (assessment of stress reduction and activity as well as diet)
Middleton 2002	EPA + DHA + GLA vs LA, unclear which arm was higher in PUFA
Millar 1973	No relevant outcomes reported and no reply from trialists
Minnesota Coronary 1989	While participants were involved in this study for over 1 year on average they could move in and out of the institution in which the study took place, and therefore in and out of the study over the duration of the trial. Most participants were not involved in the study continuously for at least one year.
Moy 2001	Aim was to reduce dietary fat (total and saturated fat reductions appear to have been achieved) but effects on PUFAs unclear (total, omega-6 and omega-3 intakes not reported)
Oslo Diet Heart 1966	Intervention group received dietary advice for a diet rich in vegetable oils and low in animal fats, and also received a multivitamin. Multifactorial. Recommended that whale meat be substituted for land animal meats
Oxford Retinopathy 1978	Advice in intervention was to alter fats and also to raise carbohydrates while limiting simple sugars, multifactorial
Reed 2014	GLA plus omega-3 vs sunflower oil plus omega-3 – both arms high in n-6
Roche 2009	Intervention and control irrelevant
Simon 1997	No intention stated to alter omega-6 or PUFA fats, and omega-6 intake not reported
Sluijs 2010	Trial of CLA, not relevant
STARS 1992	Intervention encouraged to increase plant-derived soluble fibre as well as alter dietary fats, multi-factorial

Study	Reason for exclusion
Van der Merwe 1990	Intervention <1 year
Vergroesen 1980	Not an RCT
WHI 2006	Dietary intervention was of dietary fat and also fruit and vegetables, multifactorial
WINS 2006	Aim was to reduce total fat, no aim for omega-6 fats and omega-6 intakes not reported
Ziboh 2004	GLA vs LA, not relevant intervention and control

ALA: alpha linolenic acid (n-3 18:3); **CLA**: conjugated linoleic acid (a family of isomers of linoleic acid, some of which are trans fats); **DHA**: docosahexaenoic acid (n-3 22:6); **EPA**: eicosapentaenoic acid (n-3 20:5); **EPO**: evening primrose oil; **GLA**: gamma linolenic acid (n-6 18:3); **LA**: linoleic acid (n-6 18:2); **PUFA**: polyunsaturated fatty acid; **RCT**: randomised controlled trial.

Characteristics of ongoing studies [ordered by study ID]

Chandrakala 2010

Trial name or title	Long-term effects of a reduced fat diet intervention in pre-diabetes
Methods	RCT
Participants	Participants with pre-diabetes (IFG/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 reported Estimated study completion date: not reported
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

BMI: body mass index; **HbA1c**: glycated haemoglobin (a measure of glucose metabolism); **IFG**: impaired fasting glucose, another name for IGT; **IGT**: impaired glucose tolerance (a pre-diabetic state); **PUFA**: polyunsaturated fatty acid; **RCT**: randomised controlled trial; **SFA**: saturated fatty acid

DATA AND ANALYSES

Comparison 1.   Primary outcomes - higher omega-6 vs lower omega-6

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality (overall)	10	4506	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.88, 1.12]
2 All-cause mortality - sensitivity analysis by fixed-effect analysis	10	4506	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.89, 1.13]
3 All-cause mortality - sensitivity analyses	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Studies at low risk of bias	2	682	Risk Ratio (M-H, Random, 95% CI)	1.54 [0.98, 2.41]
3.2 Pre-2010 or prospective trials registry entry	9	4306	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.89, 1.13]
3.3 No commercial funding	4	1208	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.84, 1.69]
3.4 Low risk of attention bias	6	1489	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.83, 1.13]
3.5 Randomised 250+ participants	4	3730	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.87, 1.17]
3.6 Randomised 100+ participants	8	4403	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.88, 1.13]
4 All-cause mortality - subgroup by LA or GLA	10	4506	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.88, 1.12]
4.1 Mainly LA	8	4341	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.89, 1.14]
4.2 GLA supplements	2	165	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.41, 1.39]
5 All-cause mortality - subgroup by intervention type	10	4506	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.88, 1.12]
5.1 Dietary advice	3	2624	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.82, 1.61]
5.2 Supplements (capsules)	2	165	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.41, 1.39]
5.3 Supplemental foods	1	200	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.11]
5.4 Dietary advice plus supplement	2	447	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.60, 1.46]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.5 Diet (all foods) provided	2	1070	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.84, 1.15]
6 All-cause mortality - subgroup by replacement	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 N-6 replacing SFA	6	4154	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.88, 1.15]
6.2 N-6 replacing MUFA	5	1698	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.83, 1.53]
6.3 N-6 replacing nil, low n-6	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.4 N-6 replacement unclear	2	442	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.58, 1.24]
6.5 N-6 replacing CHO	1	133	Risk Ratio (M-H, Random, 95% CI)	1.97 [0.18, 21.21]
6.6 N-6 replacing protein	1	133	Risk Ratio (M-H, Random, 95% CI)	1.97 [0.18, 21.21]
7 All-cause mortality - subgroup by baseline CVD risk	10	4506	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.88, 1.12]
7.1 Primary prevention - low CVD risk	5	1368	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.83, 1.13]
7.2 Primary prevention - moderate CVD risk	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.3 Secondary prevention - existing CVD	5	3138	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.83, 1.35]
8 All-cause mortality - subgroup by omega-6 dose	10	4506	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.88, 1.12]
8.1 N-6 < 4% E	4	2331	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.76, 1.19]
8.2 N-6 4% to 12% E	2	1304	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.76, 1.74]
8.3 N-6 > 12% E	4	871	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.60, 1.44]
9 All-cause mortality - subgroup by duration	10	4506	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.88, 1.12]
9.1 Medium duration 1 to < 2 years in study	1	224	Risk Ratio (M-H, Random, 95% CI)	3.11 [0.17, 56.84]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.2 Medium-long duration 2 to < 4 years	6	2585	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.76, 1.20]
9.3 Long duration 4+ years in study	3	1697	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.81, 1.36]
10 All-cause mortality - subgroup by statin use	10	4506	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.88, 1.12]
10.1 ≥ 50% of control group on statins	1	200	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.11]
10.2 < 50% of control group on statins	9	4306	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.89, 1.13]
10.3 Statin use unclear	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11 All-cause mortality - subgroup by baseline omega-6	10	4506	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.88, 1.12]
11.1 ≥ 8% E from n-6	1	133	Risk Ratio (M-H, Random, 95% CI)	1.97 [0.18, 21.21]
11.2 5% to < 8% E from n-6	2	2491	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.77, 1.76]
11.3 < 5% E from n-6	2	1070	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.84, 1.15]
11.4 baseline n-6 not reported	5	812	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.60, 1.22]
12 All-cause mortality - subgroup by sex	10	4506	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.88, 1.12]
12.1 Men only	5	3954	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.89, 1.14]
12.2 Women only	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12.3 Men and women	4	498	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.43, 1.36]
12.4 Sex not reported	1	54	Risk Ratio (M-H, Random, 95% CI)	1.55 [0.41, 5.84]
13 Cardiovascular mortality (overall)	7	4019	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.76, 1.55]
14 CVD mortality - sensitivity analysis by fixed-effect analysis	7	4019	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.89, 1.25]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15 CVD mortality - sensitivity analyses	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
15.1 Studies at low risk of bias	1	458	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.99, 2.55]
15.2 Pre-2010 or prospective trials registry entry	7	4019	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.76, 1.55]
15.3 No commercial funding	4	1086	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.67, 2.23]
15.4 Low risk of attention bias	2	900	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.45, 1.39]
15.5 Randomised 250+ participants	4	3730	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.76, 1.54]
15.6 Randomised 100+ participants	6	3965	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.73, 1.55]
16 CVD mortality - subgroup by intervention type	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
16.1 Dietary advice	4	2726	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.86, 2.05]
16.2 Supplements (capsules)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.3 Supplemental foods	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.4 Dietary advice plus supplement	2	447	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.69, 1.78]
16.5 Diet (all foods) provided	1	846	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.51, 0.96]
17 CVD mortality - subgroup by replacement	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
17.1 N-6 replacing SFA	5	3832	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.71, 1.52]
17.2 N-6 replacing MUFA	3	1358	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.56, 2.16]
17.3 N-6 replacing nil, low n-6	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.4 N-6 replacement unclear	1	393	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.63, 1.75]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.5 N-6 replacing CHO	2	235	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.01, 33.17]
17.6 N-6 replacing protein	1	133	Risk Ratio (M-H, Random, 95% CI)	4.93 [0.24, 100.70]
18 CVD mortality - subgroup by baseline CVD risk	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
18.1 Primary prevention - low CVD risk	2	979	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.22, 4.66]
18.2 Primary prevention - moderate CVD risk	1	102	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.01, 1.60]
18.3 Secondary prevention - existing CVD	4	2938	Risk Ratio (M-H, Random, 95% CI)	1.28 [1.04, 1.57]
19 CVD mortality - subgroup by omega-6 dose	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
19.1 N-6 < 4% E	2	2166	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.97, 1.64]
19.2 N-6 4% to 12% E	3	1406	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.38, 1.99]
19.3 N-6 > 12% E	2	447	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.69, 1.78]
20 CVD mortality - subgroup by duration	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
20.1 Medium duration 1 to < 2 years in study	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
20.2 Medium-long duration 2 to < 4 years	3	2220	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.98, 1.64]
20.3 Long duration 4+ years in study	4	1799	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.56, 1.63]
21 CVD mortality - subgroup by baseline omega-6	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
21.1 ≥ 8% E from n-6	1	133	Risk Ratio (M-H, Random, 95% CI)	4.93 [0.24, 100.70]
21.2 5% to < 8% E from n-6	2	2491	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.05, 1.66]
21.3 < 5% E from n-6	1	846	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.51, 0.96]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21.4 Baseline n-6 not reported	3	549	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.38, 2.34]
22 CVD mortality - subgroup by sex	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
22.1 Men only	4	3730	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.76, 1.54]
22.2 Women only	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
22.3 Men and women	2	235	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.01, 33.17]
22.4 Sex not reported	1	54	Risk Ratio (M-H, Random, 95% CI)	1.55 [0.41, 5.84]
23 Any cardiovascular event (overall)	7	4962	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.81, 1.15]
24 CVD events - sensitivity analysis by fixed-effect analysis	7	4962	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.89, 1.05]
25 CVD events - sensitivity analyses	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
25.1 Studies at low risk of bias	2	1525	Risk Ratio (M-H, Random, 95% CI)	1.62 [1.02, 2.57]
25.2 Pre-2010 or prospective trials registry entry	7	4962	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.81, 1.15]
25.3 No commercial funding	3	1918	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.64, 2.12]
25.4 Low risk of attention bias	4	2078	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.66, 1.22]
25.5 Randomised 250+ participants	5	4797	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.78, 1.16]
25.6 Randomised 100+ participants	6	4908	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.79, 1.14]
26 CVD events - subgroup by LA or GLA	7	4962	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.81, 1.15]
26.1 Mainly LA	6	4851	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.81, 1.17]
26.2 GLA supplements	1	111	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.01, 8.45]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
27 CVD events - subgroup by intervention type	7	4962	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.81, 1.15]
27.1 Dietary advice	2	2491	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.76, 1.85]
27.2 Supplements (capsules)	1	111	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.01, 8.45]
27.3 Supplemental foods	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
27.4 Dietary advice plus supplement	2	447	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.63, 1.42]
27.5 Diet (all foods) provided	2	1913	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.64, 1.01]
28 CVD events - subgroup by replacement	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
28.1 N-6 replacing SFA	5	4797	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.78, 1.16]
28.2 N-6 replacing MUFA	4	2425	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.73, 1.81]
28.3 N-6 replacing nil, low n-6	1	111	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.01, 8.45]
28.4 N-6 replacement unclear	1	393	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.62, 1.07]
28.5 N-6 replacing CHO	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
28.6 N-6 replacing protein	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
29 CVD events - subgroup by baseline CVD risk	7	4962	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.81, 1.15]
29.1 Primary prevention - low CVD risk	2	1913	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.64, 1.01]
29.2 Primary prevention - moderate CVD risk	1	111	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.01, 8.45]
29.3 Secondary prevention - existing CVD	4	2938	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.83, 1.29]
30 CVD events - subgroup by primary vs secondary prevention	7	4962	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.81, 1.15]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
30.1 Primary prevention - low or mod CVD risk	3	2024	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.64, 1.00]
30.2 Secondary prevention - existing CVD	4	2938	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.83, 1.29]
31 CVD events - subgroup by omega-6 dose	7	4962	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.81, 1.15]
31.1 N-6 < 4% E	2	2144	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.90, 1.09]
31.2 N-6 4% to 12% E	3	2371	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.61, 2.16]
31.3 N-6 > 12% E	2	447	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.63, 1.42]
32 CVD events - subgroup by duration	7	4962	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.81, 1.15]
32.1 Medium duration 1 to < 2 years in study	2	1178	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.22, 7.67]
32.2 Medium-long duration 2 to < 4 years	2	2087	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.91, 1.09]
32.3 Long duration 4+ years in study	3	1697	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.68, 1.33]
33 CVD events - subgroup by baseline omega-6	7	4962	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.81, 1.15]
33.1 ≥ 8% E from n-6	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
33.2 5% to < 8% E from n-6	2	2491	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.76, 1.85]
33.3 < 5% E from n-6	2	1913	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.64, 1.01]
33.4 baseline n-6 not reported	3	558	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.67, 1.21]
34 CVD events - subgroup by sex	7	4962	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.81, 1.15]
34.1 Men only	5	4797	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.78, 1.16]
34.2 Men and women	1	111	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.01, 8.45]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
34.3 Sex not reported	1	54	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.72, 2.23]
35 Coronary heart disease events (overall): myocardial infarction (fatal or non-fatal) or angina	7	3997	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.66, 1.17]
36 CHD events - sensitivity analysis by fixed-effect analysis	7	3997	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.82, 1.00]
37 CHD events - sensitivity analyses	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
37.1 Studies at low risk of bias	1	458	Risk Ratio (M-H, Random, 95% CI)	1.63 [1.00, 2.67]
37.2 Pre-2010 or prospective trials registry entry	7	3997	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.66, 1.17]
37.3 No commercial funding	3	953	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.33, 1.82]
37.4 Low risk of attention bias	3	1011	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.62, 1.09]
37.5 Randomised 250+ participants	4	3730	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.78, 1.19]
37.6 Randomised 100+ participants	6	3943	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.61, 1.15]
38 CHD events - subgroup by LA or GLA	7	3997	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.66, 1.17]
38.1 Mainly LA	6	3886	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.66, 1.19]
38.2 GLA supplements	1	111	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.01, 8.45]
39 CHD events - subgroup by intervention type	7	3997	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.66, 1.17]
39.1 Dietary advice	3	2593	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.38, 1.61]
39.2 Dietary advice plus supplement	2	447	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.76, 1.38]
39.3 Supplemental foods	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
39.4 Supplements (capsules)	1	111	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.01, 8.45]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
39.5 Diet (all foods) provided	1	846	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.56, 1.04]
40 CHD events - subgroup by replacement	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
40.1 N-6 replacing SFA	5	3832	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.61, 1.17]
40.2 N-6 replacing MUFA	3	1358	Risk Ratio (M-H, Random, 95% CI)	1.38 [1.07, 1.77]
40.3 N-6 replacing nil, low n-6	1	111	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.01, 8.45]
40.4 N-6 replacement unclear	1	393	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.69, 1.37]
40.5 N-6 replacing CHO	1	102	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.14, 0.52]
40.6 N-6 replacing protein	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
41 CHD events - subgroup by baseline CVD risk	7	3997	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.66, 1.17]
41.1 Primary prevention - low CVD risk	1	846	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.56, 1.04]
41.2 Primary prevention - moderate CVD risk	2	213	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.14, 0.52]
41.3 Secondary prevention - existing CVD	4	2938	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.84, 1.32]
42 CHD events - subgroup by omega-6 dose	7	3997	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.66, 1.17]
42.1 N-6 < 4% E	2	2144	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.82, 1.05]
42.2 N-6 4% to 12% E	3	1406	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.31, 1.64]
42.3 N-6 > 12% E	2	447	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.76, 1.38]
43 CHD events - subgroup by duration	7	3997	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.66, 1.17]
43.1 Medium duration 1 to < 2 years in study	1	111	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.01, 8.45]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
43.2 Medium-long duration 2 to < 4 years	2	2087	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.83, 1.05]
43.3 Long duration 4+ years in study	4	1799	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.46, 1.35]
44 CHD events - subgroup by baseline omega-6	7	3997	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.66, 1.17]
44.1 ≥ 8% E from n-6	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
44.2 5% to < 8% E from n-6	2	2491	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.68, 2.01]
44.3 < 5% E from n-6	1	846	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.56, 1.04]
44.4 Baseline omega 6 not reported	4	660	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.31, 1.47]
45 CHD events - subgroup by sex	7	3997	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.66, 1.17]
45.1 Men only	4	3730	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.78, 1.19]
45.2 Women only	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
45.3 Men and women	2	213	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.14, 0.52]
45.4 Sex not reported	1	54	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.63, 2.44]
46 Major adverse cardiac and cerebrovascular events (MACCEs), overall	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
47 MACCEs - sensitivity analysis by fixed-effect analysis	2	2879	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.82, 1.04]
48 MACCEs - sensitivity analyses	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
48.1 Low risk of bias	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
48.2 Pre-2010 or prospective trials registry entry	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
48.3 No commercial funding	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
48.4 Low risk of attention bias	1	846	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.93]
48.5 Randomised 250+ partici-pants	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
48.6 Randomised 100+ partici-pants	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
49 MACCEs - subgroup by inter-vention type	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
49.1 Dietary advice	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.87, 1.12]
49.2 Supplements (capsules)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
49.3 Supplemental foods	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
49.4 Dietary advice plus supple-ment	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
49.5 Diet (all foods) provided	1	846	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.93]
50 MACCEs - subgroup by re-placement	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
50.1 N-6 replacing SFA	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
50.2 N-6 replacing MUFA	1	846	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.93]
50.3 N-6 replacing nil, low n-6	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
50.4 N-6 replacement unclear	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
50.5 N-6 replacing CHO	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
50.6 N-6 replacing protein	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
51 MACCEs - subgroup by base-line CVD risk	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
51.1 Primary prevention - low CVD risk	1	846	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.93]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
51.2 Primary prevention - moderate CVD risk	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
51.3 Secondary prevention - existing CVD	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.87, 1.12]
52 MACCEs - subgroup by omega-6 dose	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
52.1 N-6 < 4% E	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.87, 1.12]
52.2 N-6 4% to 12% E	1	846	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.93]
52.3 N-6 > 12% E	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
53 MACCEs - subgroup by duration	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
53.1 Medium duration 1 to < 2 years in study	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
53.2 Medium-long duration 2 to < 4 years	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.87, 1.12]
53.3 Long duration 4+ years in study	1	846	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.93]
54 MACCEs - subgroup by baseline omega-6	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
54.1 ≥ 8% E from n-6	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
54.2 5% to < 8% E from n-6	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.87, 1.12]
54.3 < 5% E from n-6	1	846	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.93]
54.4 Baseline n-6 not reported	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
55 Stroke: fatal or non-fatal (overall)	4	3730	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.45, 4.11]
56 Stroke - sensitivity analysis by fixed-effect analysis	4	3730	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.59, 1.68]
57 Stroke - sensitivity analyses	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
57.1 Low risk of bias	1	458	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.15, 7.55]
57.2 Pre-2010 or prospective trials registry entry	4	3730	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.45, 4.11]
57.3 No commercial funding	2	851	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.32, 8.62]
57.4 Low risk of attention bias	1	846	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.30, 1.15]
57.5 Randomised 250+ participants	4	3730	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.45, 4.11]
57.6 Randomised 100+ participants	4	3730	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.45, 4.11]
58 Stroke - subgroup by intervention type	4	3730	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.45, 4.11]
58.1 Dietary advice	2	2491	Risk Ratio (M-H, Random, 95% CI)	2.36 [0.81, 6.91]
58.2 Supplements (capsules)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
58.3 Supplemental foods	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
58.4 Dietary advice plus supplement	1	393	Risk Ratio (M-H, Random, 95% CI)	4.88 [0.24, 100.89]
58.5 Diet (all foods) provided	1	846	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.30, 1.15]
59 Stroke - subgroup by replacement	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
59.1 N-6 replacing SFA	4	3730	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.45, 4.11]
59.2 N-6 replacing MUFA	2	1304	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.33, 1.18]
59.3 N-6 replacing nil, low n-6	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
59.4 N-6 replacement unclear	1	393	Risk Ratio (M-H, Random, 95% CI)	4.88 [0.24, 100.89]
59.5 N-6 replacing CHO	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
59.6 N-6 replacing protein	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
60 Stroke - subgroup by baseline CVD risk	4	3730	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.45, 4.11]
60.1 Primary prevention - low CVD risk	1	846	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.30, 1.15]
60.2 Primary prevention - moderate CVD risk	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
60.3 Secondary prevention - existing CVD	3	2884	Risk Ratio (M-H, Random, 95% CI)	2.56 [0.93, 7.04]
61 Stroke - subgroup by omega-6 dose	4	3730	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.45, 4.11]
61.1 N-6 < 4% E	1	2033	Risk Ratio (M-H, Random, 95% CI)	3.32 [0.92, 12.04]
61.2 N-6 ≥ 4% to < 12% E	2	1304	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.33, 1.18]
61.3 N-6 ≥ 12% E	1	393	Risk Ratio (M-H, Random, 95% CI)	4.88 [0.24, 100.89]
62 Stroke - subgroup by duration	4	3730	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.45, 4.11]
62.1 Medium duration 1 to < 2 years in study	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
62.2 Medium-long duration 2 to < 4 years	1	2033	Risk Ratio (M-H, Random, 95% CI)	3.32 [0.92, 12.04]
62.3 Long duration 4+ years in study	3	1697	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.36, 1.33]
63 Stroke - subgroup by baseline omega-6	4	3730	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.45, 4.11]
63.1 ≥ 8% E from n-6	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
63.2 5% to < 8% E from n-6	2	2491	Risk Ratio (M-H, Random, 95% CI)	2.36 [0.81, 6.91]
63.3 < 5% E from n-6	1	846	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.30, 1.15]
63.4 Baseline n-6 not reported	1	393	Risk Ratio (M-H, Random, 95% CI)	4.88 [0.24, 100.89]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
64 Stroke - subgroup by stroke type	1	4066	Risk Ratio (M-H, Random, 95% CI)	2.93 [0.64, 13.49]
64.1 Ischaemic stroke	1	2033	Risk Ratio (M-H, Random, 95% CI)	6.98 [0.86, 56.62]
64.2 Haemorrhagic stroke	1	2033	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.25, 8.93]
65 Stroke - subgroup by fatality	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
65.1 Fatal stroke	2	1304	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.16, 1.40]
65.2 Non-fatal stroke	1	846	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.34, 1.73]

Analysis 1.1. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 1 All-cause mortality (overall).

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bates 1978	0/58	2/58		0.16%	0.2[0.01,4.08]
Black 1994	2/67	1/66		0.26%	1.97[0.18,21.21]
DART 1989	111/1018	113/1015		23.97%	0.98[0.76,1.25]
McIllmurray 1987	10/25	12/24		3.75%	0.8[0.43,1.49]
MRC 1968	28/199	31/194		6.59%	0.88[0.55,1.41]
NDHS Faribault 1968	4/167	0/57		0.17%	3.11[0.17,56.84]
Rose 1965	5/28	3/26		0.83%	1.55[0.41,5.84]
Sydney Diet-Heart 1978	38/221	27/237		6.98%	1.51[0.95,2.39]
Veterans Admin 1969	174/424	177/422		57.13%	0.98[0.83,1.15]
Vijayakumar 2014	0/100	2/100		0.16%	0.2[0.01,4.11]
Total (95% CI)	**2307**	**2199**		**100%**	**1[0.88,1.12]**

Total events: 372 (Higher omega 6), 368 (Lower omega 6)

Heterogeneity: Tau^2=0; Chi^2=7.48, df=9(P=0.59); I^2=0%

Test for overall effect: Z=0.05(P=0.96)

Favours higher omega 6   0.05   0.2   1   5   20   Favours lower omega 6

Analysis 1.2. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 2 All-cause mortality - sensitivity analysis by fixed-effect analysis.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bates 1978	0/58	2/58		0.68%	0.2[0.01,4.08]
Black 1994	2/67	1/66		0.27%	1.97[0.18,21.21]

Favours higher omega 6   0.05   0.2   1   5   20   Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
DART 1989	111/1018	113/1015		30.57%	0.98[0.76,1.25]
McIllmurray 1987	10/25	12/24		3.31%	0.8[0.43,1.49]
MRC 1968	28/199	31/194		8.48%	0.88[0.55,1.41]
NDHS Faribault 1968	4/167	0/57		0.2%	3.11[0.17,56.84]
Rose 1965	5/28	3/26		0.84%	1.55[0.41,5.84]
Sydney Diet-Heart 1978	38/221	27/237		7.04%	1.51[0.95,2.39]
Veterans Admin 1969	174/424	177/422		47.93%	0.98[0.83,1.15]
Vijayakumar 2014	0/100	2/100		0.68%	0.2[0.01,4.11]
Total (95% CI)	**2307**	**2199**		**100%**	**1[0.89,1.13]**
Total events: 372 (Higher omega 6), 368 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=7.48, df=9(P=0.59); I²=0%					
Test for overall effect: Z=0.05(P=0.96)					

Favours higher omega 6   0.05   0.2   1   5   20   Favours lower omega 6

Analysis 1.3.   Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 3 All-cause mortality - sensitivity analyses.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Studies at low risk of bias					
NDHS Faribault 1968	4/167	0/57		2.42%	3.11[0.17,56.84]
Sydney Diet-Heart 1978	38/221	27/237		97.58%	1.51[0.95,2.39]
Subtotal (95% CI)	**388**	**294**		**100%**	**1.54[0.98,2.41]**
Total events: 42 (Higher omega 6), 27 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.23, df=1(P=0.63); I²=0%					
Test for overall effect: Z=1.86(P=0.06)					
1.3.2 Pre-2010 or prospective trials registry entry					
Bates 1978	0/58	2/58		0.16%	0.2[0.01,4.08]
Black 1994	2/67	1/66		0.26%	1.97[0.18,21.21]
DART 1989	111/1018	113/1015		24.01%	0.98[0.76,1.25]
McIllmurray 1987	10/25	12/24		3.75%	0.8[0.43,1.49]
MRC 1968	28/199	31/194		6.6%	0.88[0.55,1.41]
NDHS Faribault 1968	4/167	0/57		0.17%	3.11[0.17,56.84]
Rose 1965	5/28	3/26		0.83%	1.55[0.41,5.84]
Sydney Diet-Heart 1978	38/221	27/237		6.99%	1.51[0.95,2.39]
Veterans Admin 1969	174/424	177/422		57.22%	0.98[0.83,1.15]
Subtotal (95% CI)	**2207**	**2099**		**100%**	**1[0.89,1.13]**
Total events: 372 (Higher omega 6), 366 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=6.4, df=8(P=0.6); I²=0%					
Test for overall effect: Z=0.01(P=0.99)					
1.3.3 No commercial funding					
Black 1994	2/67	1/66		2.17%	1.97[0.18,21.21]
MRC 1968	28/199	31/194		47.04%	0.88[0.55,1.41]
NDHS Faribault 1968	4/167	0/57		1.45%	3.11[0.17,56.84]
Sydney Diet-Heart 1978	38/221	27/237		49.34%	1.51[0.95,2.39]
Subtotal (95% CI)	**654**	**554**		**100%**	**1.19[0.84,1.69]**

Favours higher omega 6   0.5   0.7   1   1.5   2   Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 72 (Higher omega 6), 59 (Lower omega 6)					
Heterogeneity: Tau²=0.01; Chi²=3.2, df=3(P=0.36); I²=6.33%					
Test for overall effect: Z=0.97(P=0.33)					
1.3.4 Low risk of attention bias					
Bates 1978	0/58	2/58		0.26%	0.2[0.01,4.08]
McIlllmurray 1987	10/25	12/24		6.02%	0.8[0.43,1.49]
NDHS Faribault 1968	4/167	0/57		0.28%	3.11[0.17,56.84]
Rose 1965	5/28	3/26		1.33%	1.55[0.41,5.84]
Veterans Admin 1969	174/424	177/422		91.85%	0.98[0.83,1.15]
Vijayakumar 2014	0/100	2/100		0.26%	0.2[0.01,4.11]
Subtotal (95% CI)	**802**	**687**		**100%**	**0.97[0.83,1.13]**
Total events: 193 (Higher omega 6), 196 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=3.57, df=5(P=0.61); I²=0%					
Test for overall effect: Z=0.42(P=0.68)					
1.3.5 Randomised 250+ participants					
DART 1989	111/1018	113/1015		28.12%	0.98[0.76,1.25]
MRC 1968	28/199	31/194		8.9%	0.88[0.55,1.41]
Sydney Diet-Heart 1978	38/221	27/237		9.39%	1.51[0.95,2.39]
Veterans Admin 1969	174/424	177/422		53.59%	0.98[0.83,1.15]
Subtotal (95% CI)	**1862**	**1868**		**100%**	**1.01[0.87,1.17]**
Total events: 351 (Higher omega 6), 348 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=3.49, df=3(P=0.32); I²=14.05%					
Test for overall effect: Z=0.13(P=0.89)					
1.3.6 Randomised 100+ participants					
Bates 1978	0/58	2/58		0.17%	0.2[0.01,4.08]
Black 1994	2/67	1/66		0.27%	1.97[0.18,21.21]
DART 1989	111/1018	113/1015		25.12%	0.98[0.76,1.25]
MRC 1968	28/199	31/194		6.91%	0.88[0.55,1.41]
NDHS Faribault 1968	4/167	0/57		0.18%	3.11[0.17,56.84]
Sydney Diet-Heart 1978	38/221	27/237		7.31%	1.51[0.95,2.39]
Veterans Admin 1969	174/424	177/422		59.87%	0.98[0.83,1.15]
Vijayakumar 2014	0/100	2/100		0.17%	0.2[0.01,4.11]
Subtotal (95% CI)	**2254**	**2149**		**100%**	**1[0.88,1.13]**
Total events: 357 (Higher omega 6), 353 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=6.57, df=7(P=0.48); I²=0%					
Test for overall effect: Z=0.02(P=0.98)					

Favours higher omega 6 0.5 0.7 1 1.5 2 Favours lower omega 6

Analysis 1.4. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 4 All-cause mortality - subgroup by LA or GLA.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Mainly LA					
Black 1994	2/67	1/66		0.26%	1.97[0.18,21.21]
DART 1989	111/1018	113/1015		23.97%	0.98[0.76,1.25]

Favours higher omega 6 0.05 0.2 1 5 20 Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
MRC 1968	28/199	31/194		6.59%	0.88[0.55,1.41]
NDHS Faribault 1968	4/167	0/57		0.17%	3.11[0.17,56.84]
Rose 1965	5/28	3/26		0.83%	1.55[0.41,5.84]
Sydney Diet-Heart 1978	38/221	27/237		6.98%	1.51[0.95,2.39]
Veterans Admin 1969	174/424	177/422		57.13%	0.98[0.83,1.15]
Vijayakumar 2014	0/100	2/100		0.16%	0.2[0.01,4.11]
Subtotal (95% CI)	**2224**	**2117**		**96.09%**	**1.01[0.89,1.14]**

Total events: 362 (Higher omega 6), 354 (Lower omega 6)

Heterogeneity: Tau²=0; Chi²=5.88, df=7(P=0.55); I²=0%

Test for overall effect: Z=0.13(P=0.9)

1.4.2 GLA supplements					
Bates 1978	0/58	2/58		0.16%	0.2[0.01,4.08]
McIllmurray 1987	10/25	12/24		3.75%	0.8[0.43,1.49]
Subtotal (95% CI)	**83**	**82**		**3.91%**	**0.76[0.41,1.39]**

Total events: 10 (Higher omega 6), 14 (Lower omega 6)

Heterogeneity: Tau²=0; Chi²=0.84, df=1(P=0.36); I²=0%

Test for overall effect: Z=0.9(P=0.37)

Total (95% CI)	**2307**	**2199**		**100%**	**1[0.88,1.12]**

Total events: 372 (Higher omega 6), 368 (Lower omega 6)

Heterogeneity: Tau²=0; Chi²=7.48, df=9(P=0.59); I²=0%

Test for overall effect: Z=0.05(P=0.96)

Test for subgroup differences: Chi²=0.82, df=1 (P=0.37), I²=0%

Favours higher omega 6   0.05   0.2   1   5   20   Favours lower omega 6

Analysis 1.5.   Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 5 All-cause mortality - subgroup by intervention type.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Dietary advice					
Black 1994	2/67	1/66		0.26%	1.97[0.18,21.21]
DART 1989	111/1018	113/1015		23.97%	0.98[0.76,1.25]
Sydney Diet-Heart 1978	38/221	27/237		6.98%	1.51[0.95,2.39]
Subtotal (95% CI)	**1306**	**1318**		**31.21%**	**1.15[0.82,1.61]**

Total events: 151 (Higher omega 6), 141 (Lower omega 6)

Heterogeneity: Tau²=0.03; Chi²=2.9, df=2(P=0.23); I²=30.96%

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

1.5.2 Supplements (capsules)					
Bates 1978	0/58	2/58		0.16%	0.2[0.01,4.08]
McIllmurray 1987	10/25	12/24		3.75%	0.8[0.43,1.49]
Subtotal (95% CI)	**83**	**82**		**3.91%**	**0.76[0.41,1.39]**

Total events: 10 (Higher omega 6), 14 (Lower omega 6)

Heterogeneity: Tau²=0; Chi²=0.84, df=1(P=0.36); I²=0%

Test for overall effect: Z=0.9(P=0.37)

1.5.3 Supplemental foods					

Favours higher omega 6   0.05   0.2   1   5   20   Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Vijayakumar 2014	0/100	2/100		0.16%	0.2[0.01,4.11]
Subtotal (95% CI)	**100**	**100**		**0.16%**	**0.2[0.01,4.11]**

Total events: 0 (Higher omega 6), 2 (Lower omega 6)

Heterogeneity: Not applicable

Test for overall effect: Z=1.04(P=0.3)

1.5.4 Dietary advice plus supplement

MRC 1968	28/199	31/194		6.59%	0.88[0.55,1.41]
Rose 1965	5/28	3/26		0.83%	1.55[0.41,5.84]
Subtotal (95% CI)	**227**	**220**		**7.42%**	**0.94[0.6,1.46]**

Total events: 33 (Higher omega 6), 34 (Lower omega 6)

Heterogeneity: Tau²=0; Chi²=0.62, df=1(P=0.43); I²=0%

Test for overall effect: Z=0.28(P=0.78)

1.5.5 Diet (all foods) provided

NDHS Faribault 1968	4/167	0/57		0.17%	3.11[0.17,56.84]
Veterans Admin 1969	174/424	177/422		57.13%	0.98[0.83,1.15]
Subtotal (95% CI)	**591**	**479**		**57.3%**	**0.98[0.84,1.15]**

Total events: 178 (Higher omega 6), 177 (Lower omega 6)

Heterogeneity: Tau²=0; Chi²=0.61, df=1(P=0.43); I²=0%

Test for overall effect: Z=0.22(P=0.82)

Total (95% CI)	**2307**	**2199**		**100%**	**1[0.88,1.12]**

Total events: 372 (Higher omega 6), 368 (Lower omega 6)

Heterogeneity: Tau²=0; Chi²=7.48, df=9(P=0.59); I²=0%

Test for overall effect: Z=0.05(P=0.96)

Test for subgroup differences: Chi²=2.68, df=1 (P=0.61), I²=0%

Favours higher omega 6   0.05   0.2   1   5   20   Favours lower omega 6

Analysis 1.6. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 6 All-cause mortality - subgroup by replacement.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 N-6 replacing SFA					
DART 1989	111/1018	113/1015		26.39%	0.98[0.76,1.25]
MRC 1968	28/199	31/194		7.63%	0.88[0.55,1.41]
NDHS Faribault 1968	4/167	0/57		0.2%	3.11[0.17,56.84]
Sydney Diet-Heart 1978	38/221	27/237		8.07%	1.51[0.95,2.39]
Veterans Admin 1969	174/424	177/422		57.52%	0.98[0.83,1.15]
Vijayakumar 2014	0/100	2/100		0.19%	0.2[0.01,4.11]
Subtotal (95% CI)	**2129**	**2025**		**100%**	**1[0.88,1.15]**

Total events: 355 (Higher omega 6), 350 (Lower omega 6)

Heterogeneity: Tau²=0; Chi²=5.16, df=5(P=0.4); I²=3.14%

Test for overall effect: Z=0.07(P=0.94)

1.6.2 N-6 replacing MUFA

Bates 1978	0/58	2/58		1.02%	0.2[0.01,4.08]
NDHS Faribault 1968	4/167	0/57		1.1%	3.11[0.17,56.84]

Favours higher omega 6   0.05   0.2   1   5   20   Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Rose 1965	5/28	3/26		4.98%	1.55[0.41,5.84]
Sydney Diet-Heart 1978	38/221	27/237		28.46%	1.51[0.95,2.39]
Veterans Admin 1969	174/424	177/422		64.44%	0.98[0.83,1.15]
Subtotal (95% CI)	**898**	**800**		**100%**	**1.13[0.83,1.53]**

Total events: 221 (Higher omega 6), 209 (Lower omega 6)

Heterogeneity: Tau²=0.03; Chi²=5.19, df=4(P=0.27); I²=22.94%

Test for overall effect: Z=0.77(P=0.44)

1.6.3 N-6 replacing nil, low n-6

Subtotal (95% CI)	**0**	**0**			**Not estimable**

Total events: 0 (Higher omega 6), 0 (Lower omega 6)

Heterogeneity: Not applicable

Test for overall effect: Not applicable

1.6.4 N-6 replacement unclear

McIllmurray 1987	10/25	12/24		36.24%	0.8[0.43,1.49]
MRC 1968	28/199	31/194		63.76%	0.88[0.55,1.41]
Subtotal (95% CI)	**224**	**218**		**100%**	**0.85[0.58,1.24]**

Total events: 38 (Higher omega 6), 43 (Lower omega 6)

Heterogeneity: Tau²=0; Chi²=0.06, df=1(P=0.81); I²=0%

Test for overall effect: Z=0.84(P=0.4)

1.6.5 N-6 replacing CHO

Black 1994	2/67	1/66		100%	1.97[0.18,21.21]
Subtotal (95% CI)	**67**	**66**		**100%**	**1.97[0.18,21.21]**

Total events: 2 (Higher omega 6), 1 (Lower omega 6)

Heterogeneity: Not applicable

Test for overall effect: Z=0.56(P=0.58)

1.6.6 N-6 replacing protein

Black 1994	2/67	1/66		100%	1.97[0.18,21.21]
Subtotal (95% CI)	**67**	**66**		**100%**	**1.97[0.18,21.21]**

Total events: 2 (Higher omega 6), 1 (Lower omega 6)

Heterogeneity: Not applicable

Test for overall effect: Z=0.56(P=0.58)

Test for subgroup differences: Chi²=1.92, df=1 (P=0.75), I²=0%

Favours higher omega 6   0.05   0.2   1   5   20   Favours lower omega 6

Analysis 1.7. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 7 All-cause mortality - subgroup by baseline CVD risk.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 Primary prevention - low CVD risk					
Bates 1978	0/58	2/58		0.16%	0.2[0.01,4.08]
Black 1994	2/67	1/66		0.26%	1.97[0.18,21.21]
McIllmurray 1987	10/25	12/24		3.75%	0.8[0.43,1.49]
NDHS Faribault 1968	4/167	0/57		0.17%	3.11[0.17,56.84]
Veterans Admin 1969	174/424	177/422		57.13%	0.98[0.83,1.15]

Favours higher omega 6   0.1   0.2   0.5   1   2   5   10   Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Subtotal (95% CI)	741	627		61.47%	0.97[0.83,1.13]
Total events: 190 (Higher omega 6), 192 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=2.39, df=4(P=0.66); I²=0%					
Test for overall effect: Z=0.41(P=0.68)					
1.7.2 Primary prevention - moderate CVD risk					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.7.3 Secondary prevention - existing CVD					
DART 1989	111/1018	113/1015		23.97%	0.98[0.76,1.25]
MRC 1968	28/199	31/194		6.59%	0.88[0.55,1.41]
Rose 1965	5/28	3/26		0.83%	1.55[0.41,5.84]
Sydney Diet-Heart 1978	38/221	27/237		6.98%	1.51[0.95,2.39]
Vijayakumar 2014	0/100	2/100		0.16%	0.2[0.01,4.11]
Subtotal (95% CI)	1566	1572		38.53%	1.06[0.83,1.35]
Total events: 182 (Higher omega 6), 176 (Lower omega 6)					
Heterogeneity: Tau²=0.01; Chi²=4.73, df=4(P=0.32); I²=15.48%					
Test for overall effect: Z=0.47(P=0.64)					
Total (95% CI)	2307	2199		100%	1[0.88,1.12]
Total events: 372 (Higher omega 6), 368 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=7.48, df=9(P=0.59); I²=0%					
Test for overall effect: Z=0.05(P=0.96)					
Test for subgroup differences: Chi²=0.38, df=1 (P=0.54), I²=0%					

Favours higher omega 6   0.1 0.2   0.5   1   2   5   10   Favours lower omega 6

Analysis 1.8.   Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 8 All-cause mortality - subgroup by omega-6 dose.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 N-6 < 4% E					
Bates 1978	0/58	2/58		0.16%	0.2[0.01,4.08]
Black 1994	2/67	1/66		0.26%	1.97[0.18,21.21]
DART 1989	111/1018	113/1015		23.97%	0.98[0.76,1.25]
McIllmurray 1987	10/25	12/24		3.75%	0.8[0.43,1.49]
Subtotal (95% CI)	1168	1163		28.14%	0.95[0.76,1.19]
Total events: 123 (Higher omega 6), 128 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=1.74, df=3(P=0.63); I²=0%					
Test for overall effect: Z=0.43(P=0.66)					
1.8.2 N-6 4% to 12% E					
Sydney Diet-Heart 1978	38/221	27/237		6.98%	1.51[0.95,2.39]
Veterans Admin 1969	174/424	177/422		57.13%	0.98[0.83,1.15]
Subtotal (95% CI)	645	659		64.1%	1.15[0.76,1.74]
Total events: 212 (Higher omega 6), 204 (Lower omega 6)					

Favours higher omega 6   0.1 0.2   0.5   1   2   5   10   Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI

Heterogeneity: Tau²=0.07; Chi²=3.13, df=1(P=0.08); I²=68.09%

Test for overall effect: Z=0.66(P=0.51)

1.8.3 N-6 > 12% E

MRC 1968	28/199	31/194		6.59%	0.88[0.55,1.41]
NDHS Faribault 1968	4/167	0/57		0.17%	3.11[0.17,56.84]
Rose 1965	5/28	3/26		0.83%	1.55[0.41,5.84]
Vijayakumar 2014	0/100	2/100		0.16%	0.2[0.01,4.11]
Subtotal (95% CI)	**494**	**377**		**7.75%**	**0.93[0.6,1.44]**

Total events: 37 (Higher omega 6), 36 (Lower omega 6)

Heterogeneity: Tau²=0; Chi²=2.27, df=3(P=0.52); I²=0%

Test for overall effect: Z=0.31(P=0.75)

| **Total (95% CI)** | **2307** | **2199** | | **100%** | **1[0.88,1.12]** |

Total events: 372 (Higher omega 6), 368 (Lower omega 6)

Heterogeneity: Tau²=0; Chi²=7.48, df=9(P=0.59); I²=0%

Test for overall effect: Z=0.05(P=0.96)

Test for subgroup differences: Chi²=0.69, df=1 (P=0.71), I²=0%

Favours higher omega 6   0.1   0.2   0.5   1   2   5   10   Favours lower omega 6

Analysis 1.9. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 9 All-cause mortality - subgroup by duration.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI

1.9.1 Medium duration 1 to < 2 years in study

| NDHS Faribault 1968 | 4/167 | 0/57 | | 0.17% | 3.11[0.17,56.84] |
| **Subtotal (95% CI)** | **167** | **57** | | **0.17%** | **3.11[0.17,56.84]** |

Total events: 4 (Higher omega 6), 0 (Lower omega 6)

Heterogeneity: Not applicable

Test for overall effect: Z=0.76(P=0.44)

1.9.2 Medium-long duration 2 to < 4 years

Bates 1978	0/58	2/58		0.16%	0.2[0.01,4.08]
Black 1994	2/67	1/66		0.26%	1.97[0.18,21.21]
DART 1989	111/1018	113/1015		23.97%	0.98[0.76,1.25]
McIllmurray 1987	10/25	12/24		3.75%	0.8[0.43,1.49]
Rose 1965	5/28	3/26		0.83%	1.55[0.41,5.84]
Vijayakumar 2014	0/100	2/100		0.16%	0.2[0.01,4.11]
Subtotal (95% CI)	**1296**	**1289**		**29.13%**	**0.96[0.76,1.2]**

Total events: 128 (Higher omega 6), 133 (Lower omega 6)

Heterogeneity: Tau²=0; Chi²=3.27, df=5(P=0.66); I²=0%

Test for overall effect: Z=0.39(P=0.69)

1.9.3 Long duration 4+ years in study

MRC 1968	28/199	31/194		6.59%	0.88[0.55,1.41]
Sydney Diet-Heart 1978	38/221	27/237		6.98%	1.51[0.95,2.39]
Veterans Admin 1969	174/424	177/422		57.13%	0.98[0.83,1.15]
Subtotal (95% CI)	**844**	**853**		**70.7%**	**1.05[0.81,1.36]**

Favours higher omega 6   0.1   0.2   0.5   1   2   5   10   Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 240 (Higher omega 6), 235 (Lower omega 6)					
Heterogeneity: Tau²=0.02; Chi²=3.46, df=2(P=0.18); I²=42.23%					
Test for overall effect: Z=0.39(P=0.7)					
Total (95% CI)	**2307**	**2199**		**100%**	**1[0.88,1.12]**
Total events: 372 (Higher omega 6), 368 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=7.48, df=9(P=0.59); I²=0%					
Test for overall effect: Z=0.05(P=0.96)					
Test for subgroup differences: Chi²=0.89, df=1 (P=0.64), I²=0%					

Favours higher omega 6   0.1   0.2   0.5   1   2   5   10   Favours lower omega 6

Analysis 1.10. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 10 All-cause mortality - subgroup by statin use.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.10.1 ≥ 50% of control group on statins					
Vijayakumar 2014	0/100	2/100		0.16%	0.2[0.01,4.11]
Subtotal (95% CI)	**100**	**100**		**0.16%**	**0.2[0.01,4.11]**
Total events: 0 (Higher omega 6), 2 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.04(P=0.3)					
1.10.2 < 50% of control group on statins					
Bates 1978	0/58	2/58		0.16%	0.2[0.01,4.08]
Black 1994	2/67	1/66		0.26%	1.97[0.18,21.21]
DART 1989	111/1018	113/1015		23.97%	0.98[0.76,1.25]
McIllmurray 1987	10/25	12/24		3.75%	0.8[0.43,1.49]
MRC 1968	28/199	31/194		6.59%	0.88[0.55,1.41]
NDHS Faribault 1968	4/167	0/57		0.17%	3.11[0.17,56.84]
Rose 1965	5/28	3/26		0.83%	1.55[0.41,5.84]
Sydney Diet-Heart 1978	38/221	27/237		6.98%	1.51[0.95,2.39]
Veterans Admin 1969	174/424	177/422		57.13%	0.98[0.83,1.15]
Subtotal (95% CI)	**2207**	**2099**		**99.84%**	**1[0.89,1.13]**
Total events: 372 (Higher omega 6), 366 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=6.4, df=8(P=0.6); I²=0%					
Test for overall effect: Z=0.01(P=0.99)					
1.10.3 Statin use unclear					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**2307**	**2199**		**100%**	**1[0.88,1.12]**
Total events: 372 (Higher omega 6), 368 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=7.48, df=9(P=0.59); I²=0%					
Test for overall effect: Z=0.05(P=0.96)					
Test for subgroup differences: Chi²=1.09, df=1 (P=0.3), I²=7.88%					

Favours higher omega 6   0.1   0.2   0.5   1   2   5   10   Favours lower omega 6

Analysis 1.11. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 11 All-cause mortality - subgroup by baseline omega-6.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.11.1 ≥ 8% E from n-6					
Black 1994	2/67	1/66		0.26%	1.97[0.18,21.21]
Subtotal (95% CI)	**67**	**66**		**0.26%**	**1.97[0.18,21.21]**
Total events: 2 (Higher omega 6), 1 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.56(P=0.58)					
1.11.2 5% to < 8% E from n-6					
DART 1989	111/1018	113/1015		23.97%	0.98[0.76,1.25]
Sydney Diet-Heart 1978	38/221	27/237		6.98%	1.51[0.95,2.39]
Subtotal (95% CI)	**1239**	**1252**		**30.95%**	**1.16[0.77,1.76]**
Total events: 149 (Higher omega 6), 140 (Lower omega 6)					
Heterogeneity: Tau²=0.06; Chi²=2.65, df=1(P=0.1); I²=62.3%					
Test for overall effect: Z=0.71(P=0.48)					
1.11.3 < 5% E from n-6					
NDHS Faribault 1968	4/167	0/57		0.17%	3.11[0.17,56.84]
Veterans Admin 1969	174/424	177/422		57.13%	0.98[0.83,1.15]
Subtotal (95% CI)	**591**	**479**		**57.3%**	**0.98[0.84,1.15]**
Total events: 178 (Higher omega 6), 177 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.61, df=1(P=0.43); I²=0%					
Test for overall effect: Z=0.22(P=0.82)					
1.11.4 baseline n-6 not reported					
Bates 1978	0/58	2/58		0.16%	0.2[0.01,4.08]
McIllmurray 1987	10/25	12/24		3.75%	0.8[0.43,1.49]
MRC 1968	28/199	31/194		6.59%	0.88[0.55,1.41]
Rose 1965	5/28	3/26		0.83%	1.55[0.41,5.84]
Vijayakumar 2014	0/100	2/100		0.16%	0.2[0.01,4.11]
Subtotal (95% CI)	**410**	**402**		**11.49%**	**0.85[0.6,1.22]**
Total events: 43 (Higher omega 6), 50 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=2.62, df=4(P=0.62); I²=0%					
Test for overall effect: Z=0.87(P=0.38)					
Total (95% CI)	**2307**	**2199**		**100%**	**1[0.88,1.12]**
Total events: 372 (Higher omega 6), 368 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=7.48, df=9(P=0.59); I²=0%					
Test for overall effect: Z=0.05(P=0.96)					
Test for subgroup differences: Chi²=1.57, df=1 (P=0.67), I²=0%					

Favours higher omega 6   0.1 0.2   0.5   1   2   5   10   Favours lower omega 6

Analysis 1.12. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 12 All-cause mortality - subgroup by sex.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 Men only					
DART 1989	111/1018	113/1015		23.97%	0.98[0.76,1.25]
MRC 1968	28/199	31/194		6.59%	0.88[0.55,1.41]
NDHS Faribault 1968	4/167	0/57		0.17%	3.11[0.17,56.84]
Sydney Diet-Heart 1978	38/221	27/237		6.98%	1.51[0.95,2.39]
Veterans Admin 1969	174/424	177/422		57.13%	0.98[0.83,1.15]
Subtotal (95% CI)	**2029**	**1925**		**94.84%**	**1.01[0.89,1.14]**
Total events: 355 (Higher omega 6), 348 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=4.08, df=4(P=0.4); I²=1.95%					
Test for overall effect: Z=0.1(P=0.92)					
1.12.2 Women only					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.12.3 Men and women					
Bates 1978	0/58	2/58		0.16%	0.2[0.01,4.08]
Black 1994	2/67	1/66		0.26%	1.97[0.18,21.21]
McIllmurray 1987	10/25	12/24		3.75%	0.8[0.43,1.49]
Vijayakumar 2014	0/100	2/100		0.16%	0.2[0.01,4.11]
Subtotal (95% CI)	**250**	**248**		**4.33%**	**0.76[0.43,1.36]**
Total events: 12 (Higher omega 6), 17 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=2.23, df=3(P=0.53); I²=0%					
Test for overall effect: Z=0.92(P=0.36)					
1.12.4 Sex not reported					
Rose 1965	5/28	3/26		0.83%	1.55[0.41,5.84]
Subtotal (95% CI)	**28**	**26**		**0.83%**	**1.55[0.41,5.84]**
Total events: 5 (Higher omega 6), 3 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.64(P=0.52)					
Total (95% CI)	**2307**	**2199**		**100%**	**1[0.88,1.12]**
Total events: 372 (Higher omega 6), 368 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=7.48, df=9(P=0.59); I²=0%					
Test for overall effect: Z=0.05(P=0.96)					
Test for subgroup differences: Chi²=1.26, df=1 (P=0.53), I²=0%					

Favours higher omega 6   0.1 0.2   0.5   1   2   5   10   Favours lower omega 6

Analysis 1.13. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 13 Cardiovascular mortality (overall).

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Black 1994	2/67	0/66		1.3%	4.93[0.24,100.7]

Favours higher omega 6   0.5   0.7   1   1.5   2   Favours lower omega 6

Study or subgroup	Higher omega 6	Lower omega 6	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
DART 1989	114/1018	91/1015		26.93%	1.25[0.96,1.62]
Houtsmuller 1979	0/51	5/51		1.43%	0.09[0.01,1.6]
MRC 1968	27/199	25/194		19.1%	1.05[0.63,1.75]
Rose 1965	5/28	3/26		5.74%	1.55[0.41,5.84]
Sydney Diet-Heart 1978	37/221	25/237		20.12%	1.59[0.99,2.55]
Veterans Admin 1969	57/424	81/422		25.37%	0.7[0.51,0.96]
Total (95% CI)	**2008**	**2011**		**100%**	**1.09[0.76,1.55]**
Total events: 242 (Higher omega 6), 230 (Lower omega 6)					
Heterogeneity: Tau²=0.1; Chi²=15.26, df=6(P=0.02); I²=60.68%					
Test for overall effect: Z=0.47(P=0.64)					

Favours higher omega 6   0.5 0.7 1 1.5 2   Favours lower omega 6

Analysis 1.14. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 14 CVD mortality - sensitivity analysis by fixed-effect analysis.

Study or subgroup	Higher omega 6	Lower omega 6	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Black 1994	2/67	0/66		0.22%	4.93[0.24,100.7]
DART 1989	114/1018	91/1015		39.47%	1.25[0.96,1.62]
Houtsmuller 1979	0/51	5/51		2.38%	0.09[0.01,1.6]
MRC 1968	27/199	25/194		10.97%	1.05[0.63,1.75]
Rose 1965	5/28	3/26		1.35%	1.55[0.41,5.84]
Sydney Diet-Heart 1978	37/221	25/237		10.45%	1.59[0.99,2.55]
Veterans Admin 1969	57/424	81/422		35.17%	0.7[0.51,0.96]
Total (95% CI)	**2008**	**2011**		**100%**	**1.05[0.89,1.25]**
Total events: 242 (Higher omega 6), 230 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=15.26, df=6(P=0.02); I²=60.68%					
Test for overall effect: Z=0.62(P=0.54)					

Favours higher omega 6   0.5 0.7 1 1.5 2   Favours lower omega 6

Analysis 1.15. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 15 CVD mortality - sensitivity analyses.

Study or subgroup	Higher omega 6	Lower omega 6	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
1.15.1 Studies at low risk of bias					
Sydney Diet-Heart 1978	37/221	25/237		100%	1.59[0.99,2.55]
Subtotal (95% CI)	**221**	**237**		**100%**	**1.59[0.99,2.55]**
Total events: 37 (Higher omega 6), 25 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.91(P=0.06)					
1.15.2 Pre-2010 or prospective trials registry entry					
Black 1994	2/67	0/66		1.3%	4.93[0.24,100.7]
DART 1989	114/1018	91/1015		26.93%	1.25[0.96,1.62]

Favours higher omega 6   0.5 0.7 1 1.5 2   Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Houtsmuller 1979	0/51	5/51		1.43%	0.09[0.01,1.6]
MRC 1968	27/199	25/194		19.1%	1.05[0.63,1.75]
Rose 1965	5/28	3/26		5.74%	1.55[0.41,5.84]
Sydney Diet-Heart 1978	37/221	25/237		20.12%	1.59[0.99,2.55]
Veterans Admin 1969	57/424	81/422		25.37%	0.7[0.51,0.96]
Subtotal (95% CI)	**2008**	**2011**		**100%**	**1.09[0.76,1.55]**

Total events: 242 (Higher omega 6), 230 (Lower omega 6)

Heterogeneity: Tau²=0.1; Chi²=15.26, df=6(P=0.02); I²=60.68%

Test for overall effect: Z=0.47(P=0.64)

1.15.3 No commercial funding

Black 1994	2/67	0/66		3.76%	4.93[0.24,100.7]
Houtsmuller 1979	0/51	5/51		4.13%	0.09[0.01,1.6]
MRC 1968	27/199	25/194		45.09%	1.05[0.63,1.75]
Sydney Diet-Heart 1978	37/221	25/237		47.02%	1.59[0.99,2.55]
Subtotal (95% CI)	**538**	**548**		**100%**	**1.22[0.67,2.23]**

Total events: 66 (Higher omega 6), 55 (Lower omega 6)

Heterogeneity: Tau²=0.14; Chi²=5.47, df=3(P=0.14); I²=45.12%

Test for overall effect: Z=0.65(P=0.51)

1.15.4 Low risk of attention bias

Rose 1965	5/28	3/26		15.49%	1.55[0.41,5.84]
Veterans Admin 1969	57/424	81/422		84.51%	0.7[0.51,0.96]
Subtotal (95% CI)	**452**	**448**		**100%**	**0.79[0.45,1.39]**

Total events: 62 (Higher omega 6), 84 (Lower omega 6)

Heterogeneity: Tau²=0.07; Chi²=1.3, df=1(P=0.25); I²=22.97%

Test for overall effect: Z=0.81(P=0.42)

1.15.5 Randomised 250+ participants

DART 1989	114/1018	91/1015		29.72%	1.25[0.96,1.62]
MRC 1968	27/199	25/194		20.62%	1.05[0.63,1.75]
Sydney Diet-Heart 1978	37/221	25/237		21.79%	1.59[0.99,2.55]
Veterans Admin 1969	57/424	81/422		27.87%	0.7[0.51,0.96]
Subtotal (95% CI)	**1862**	**1868**		**100%**	**1.08[0.76,1.54]**

Total events: 235 (Higher omega 6), 222 (Lower omega 6)

Heterogeneity: Tau²=0.09; Chi²=11.14, df=3(P=0.01); I²=73.07%

Test for overall effect: Z=0.43(P=0.67)

1.15.6 Randomised 100+ participants

Black 1994	2/67	0/66		1.48%	4.93[0.24,100.7]
DART 1989	114/1018	91/1015		28.19%	1.25[0.96,1.62]
Houtsmuller 1979	0/51	5/51		1.63%	0.09[0.01,1.6]
MRC 1968	27/199	25/194		20.49%	1.05[0.63,1.75]
Sydney Diet-Heart 1978	37/221	25/237		21.52%	1.59[0.99,2.55]
Veterans Admin 1969	57/424	81/422		26.69%	0.7[0.51,0.96]
Subtotal (95% CI)	**1980**	**1985**		**100%**	**1.06[0.73,1.55]**

Total events: 237 (Higher omega 6), 227 (Lower omega 6)

Heterogeneity: Tau²=0.11; Chi²=14.94, df=5(P=0.01); I²=66.54%

Test for overall effect: Z=0.32(P=0.75)

Favours higher omega 6   0.5 0.7 1 1.5 2   Favours lower omega 6

Analysis 1.16. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 16 CVD mortality - subgroup by intervention type.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.16.1 Dietary advice					
Black 1994	2/67	0/66		1.99%	4.93[0.24,100.7]
DART 1989	114/1018	91/1015		57.14%	1.25[0.96,1.62]
Houtsmuller 1979	0/51	5/51		2.19%	0.09[0.01,1.6]
Sydney Diet-Heart 1978	37/221	25/237		38.68%	1.59[0.99,2.55]
Subtotal (95% CI)	**1357**	**1369**		**100%**	**1.33[0.86,2.05]**
Total events: 153 (Higher omega 6), 121 (Lower omega 6)					
Heterogeneity: Tau²=0.07; Chi²=4.86, df=3(P=0.18); I²=38.27%					
Test for overall effect: Z=1.29(P=0.2)					
1.16.2 Supplements (capsules)					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.16.3 Supplemental foods					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.16.4 Dietary advice plus supplement					
MRC 1968	27/199	25/194		87.29%	1.05[0.63,1.75]
Rose 1965	5/28	3/26		12.71%	1.55[0.41,5.84]
Subtotal (95% CI)	**227**	**220**		**100%**	**1.11[0.69,1.78]**
Total events: 32 (Higher omega 6), 28 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.28, df=1(P=0.6); I²=0%					
Test for overall effect: Z=0.42(P=0.68)					
1.16.5 Diet (all foods) provided					
Veterans Admin 1969	57/424	81/422		100%	0.7[0.51,0.96]
Subtotal (95% CI)	**424**	**422**		**100%**	**0.7[0.51,0.96]**
Total events: 57 (Higher omega 6), 81 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.25(P=0.02)					
Test for subgroup differences: Chi²=6.33, df=1 (P=0.04), I²=68.42%					

Favours higher omega 6   0.5 0.7 1 1.5 2   Favours lower omega 6

Analysis 1.17. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 17 CVD mortality - subgroup by replacement.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.17.1 N-6 replacing SFA					
DART 1989	114/1018	91/1015		28.6%	1.25[0.96,1.62]
Houtsmuller 1979	0/51	5/51		1.66%	0.09[0.01,1.6]

Favours higher omega 6   0.5 0.7 1 1.5 2   Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
MRC 1968	27/199	25/194		20.81%	1.05[0.63,1.75]
Sydney Diet-Heart 1978	37/221	25/237		21.85%	1.59[0.99,2.55]
Veterans Admin 1969	57/424	81/422		27.08%	0.7[0.51,0.96]
Subtotal (95% CI)	**1913**	**1919**		**100%**	**1.04[0.71,1.52]**

Total events: 235 (Higher omega 6), 227 (Lower omega 6)

Heterogeneity: Tau^2=0.11; Chi^2=13.94, df=4(P=0.01); I^2=71.3%

Test for overall effect: Z=0.2(P=0.84)

1.17.2 N-6 replacing MUFA

Rose 1965	5/28	3/26		16.83%	1.55[0.41,5.84]
Sydney Diet-Heart 1978	37/221	25/237		39.17%	1.59[0.99,2.55]
Veterans Admin 1969	57/424	81/422		44%	0.7[0.51,0.96]
Subtotal (95% CI)	**673**	**685**		**100%**	**1.1[0.56,2.16]**

Total events: 99 (Higher omega 6), 109 (Lower omega 6)

Heterogeneity: Tau^2=0.24; Chi^2=8.65, df=2(P=0.01); I^2=76.88%

Test for overall effect: Z=0.28(P=0.78)

1.17.3 N-6 replacing nil, low n-6

Subtotal (95% CI)	**0**	**0**			**Not estimable**

Total events: 0 (Higher omega 6), 0 (Lower omega 6)

Heterogeneity: Not applicable

Test for overall effect: Not applicable

1.17.4 N-6 replacement unclear

MRC 1968	27/199	25/194		100%	1.05[0.63,1.75]
Subtotal (95% CI)	**199**	**194**		**100%**	**1.05[0.63,1.75]**

Total events: 27 (Higher omega 6), 25 (Lower omega 6)

Heterogeneity: Not applicable

Test for overall effect: Z=0.2(P=0.84)

1.17.5 N-6 replacing CHO

Black 1994	2/67	0/66		49.29%	4.93[0.24,100.7]
Houtsmuller 1979	0/51	5/51		50.71%	0.09[0.01,1.6]
Subtotal (95% CI)	**118**	**117**		**100%**	**0.65[0.01,33.17]**

Total events: 2 (Higher omega 6), 5 (Lower omega 6)

Heterogeneity: Tau^2=5.79; Chi^2=3.57, df=1(P=0.06); I^2=71.96%

Test for overall effect: Z=0.21(P=0.83)

1.17.6 N-6 replacing protein

Black 1994	2/67	0/66		100%	4.93[0.24,100.7]
Subtotal (95% CI)	**67**	**66**		**100%**	**4.93[0.24,100.7]**

Total events: 2 (Higher omega 6), 0 (Lower omega 6)

Heterogeneity: Not applicable

Test for overall effect: Z=1.04(P=0.3)

Test for subgroup differences: Chi^2=1.08, df=1 (P=0.9), I^2=0%

Favours higher omega 6   0.5 0.7 1 1.5 2   Favours lower omega 6

Analysis 1.18. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 18 CVD mortality - subgroup by baseline CVD risk.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.18.1 Primary prevention - low CVD risk					
Black 1994	2/67	0/66		19.39%	4.93[0.24,100.7]
Veterans Admin 1969	57/424	81/422		80.61%	0.7[0.51,0.96]
Subtotal (95% CI)	**491**	**488**		**100%**	**1.02[0.22,4.66]**
Total events: 59 (Higher omega 6), 81 (Lower omega 6)					
Heterogeneity: Tau²=0.72; Chi²=1.6, df=1(P=0.21); I²=37.46%					
Test for overall effect: Z=0.03(P=0.98)					
1.18.2 Primary prevention - moderate CVD risk					
Houtsmuller 1979	0/51	5/51		100%	0.09[0.01,1.6]
Subtotal (95% CI)	**51**	**51**		**100%**	**0.09[0.01,1.6]**
Total events: 0 (Higher omega 6), 5 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.64(P=0.1)					
1.18.3 Secondary prevention - existing CVD					
DART 1989	114/1018	91/1015		62.1%	1.25[0.96,1.62]
MRC 1968	27/199	25/194		16.53%	1.05[0.63,1.75]
Rose 1965	5/28	3/26		2.41%	1.55[0.41,5.84]
Sydney Diet-Heart 1978	37/221	25/237		18.96%	1.59[0.99,2.55]
Subtotal (95% CI)	**1466**	**1472**		**100%**	**1.28[1.04,1.57]**
Total events: 183 (Higher omega 6), 144 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=1.48, df=3(P=0.69); I²=0%					
Test for overall effect: Z=2.33(P=0.02)					
Test for subgroup differences: Chi²=3.31, df=1 (P=0.19), I²=39.64%					

Favours higher omega 6   0.5 0.7 1 1.5 2   Favours lower omega 6

Analysis 1.19. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 19 CVD mortality - subgroup by omega-6 dose.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.19.1 N-6 < 4% E					
Black 1994	2/67	0/66		0.75%	4.93[0.24,100.7]
DART 1989	114/1018	91/1015		99.25%	1.25[0.96,1.62]
Subtotal (95% CI)	**1085**	**1081**		**100%**	**1.26[0.97,1.64]**
Total events: 116 (Higher omega 6), 91 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.79, df=1(P=0.37); I²=0%					
Test for overall effect: Z=1.75(P=0.08)					
1.19.2 N-6 4% to 12% E					
Houtsmuller 1979	0/51	5/51		7.16%	0.09[0.01,1.6]
Sydney Diet-Heart 1978	37/221	25/237		44.42%	1.59[0.99,2.55]
Veterans Admin 1969	57/424	81/422		48.42%	0.7[0.51,0.96]
Subtotal (95% CI)	**696**	**710**		**100%**	**0.87[0.38,1.99]**
Total events: 94 (Higher omega 6), 111 (Lower omega 6)					
Heterogeneity: Tau²=0.34; Chi²=10.46, df=2(P=0.01); I²=80.89%					

Favours higher omega 6   0.5 0.7 1 1.5 2   Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=0.33(P=0.74)					
1.19.3 N-6 > 12% E					
MRC 1968	27/199	25/194		87.29%	1.05[0.63,1.75]
Rose 1965	5/28	3/26		12.71%	1.55[0.41,5.84]
Subtotal (95% CI)	**227**	**220**		**100%**	**1.11[0.69,1.78]**
Total events: 32 (Higher omega 6), 28 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.28, df=1(P=0.6); I²=0%					
Test for overall effect: Z=0.42(P=0.68)					
Test for subgroup differences: Chi²=0.84, df=1 (P=0.66), I²=0%					

Favours higher omega 6   0.5   0.7   1   1.5   2   Favours lower omega 6

Analysis 1.20. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 20 CVD mortality - subgroup by duration.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.20.1 Medium duration 1 to < 2 years in study					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.20.2 Medium-long duration 2 to < 4 years					
Black 1994	2/67	0/66		0.72%	4.93[0.24,100.7]
DART 1989	114/1018	91/1015		95.58%	1.25[0.96,1.62]
Rose 1965	5/28	3/26		3.7%	1.55[0.41,5.84]
Subtotal (95% CI)	**1113**	**1107**		**100%**	**1.27[0.98,1.64]**
Total events: 121 (Higher omega 6), 94 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.88, df=2(P=0.64); I²=0%					
Test for overall effect: Z=1.84(P=0.07)					
1.20.3 Long duration 4+ years in study					
Houtsmuller 1979	0/51	5/51		3.19%	0.09[0.01,1.6]
MRC 1968	27/199	25/194		29.9%	1.05[0.63,1.75]
Sydney Diet-Heart 1978	37/221	25/237		30.97%	1.59[0.99,2.55]
Veterans Admin 1969	57/424	81/422		35.94%	0.7[0.51,0.96]
Subtotal (95% CI)	**895**	**904**		**100%**	**0.96[0.56,1.63]**
Total events: 121 (Higher omega 6), 136 (Lower omega 6)					
Heterogeneity: Tau²=0.18; Chi²=10.85, df=3(P=0.01); I²=72.34%					
Test for overall effect: Z=0.17(P=0.87)					
Test for subgroup differences: Chi²=0.9, df=1 (P=0.34), I²=0%					

Favours higher omega 6   0.5   0.7   1   1.5   2   Favours lower omega 6

Analysis 1.21. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 21 CVD mortality - subgroup by baseline omega-6.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.21.1 ≥ 8% E from n-6					
Black 1994	2/67	0/66		100%	4.93[0.24,100.7]
Subtotal (95% CI)	**67**	**66**		**100%**	**4.93[0.24,100.7]**
Total events: 2 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.04(P=0.3)					
1.21.2 5% to < 8% E from n-6					
DART 1989	114/1018	91/1015		76.61%	1.25[0.96,1.62]
Sydney Diet-Heart 1978	37/221	25/237		23.39%	1.59[0.99,2.55]
Subtotal (95% CI)	**1239**	**1252**		**100%**	**1.32[1.05,1.66]**
Total events: 151 (Higher omega 6), 116 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.75, df=1(P=0.39); I²=0%					
Test for overall effect: Z=2.38(P=0.02)					
1.21.3 < 5% E from n-6					
Veterans Admin 1969	57/424	81/422		100%	0.7[0.51,0.96]
Subtotal (95% CI)	**424**	**422**		**100%**	**0.7[0.51,0.96]**
Total events: 57 (Higher omega 6), 81 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.25(P=0.02)					
1.21.4 Baseline n-6 not reported					
Houtsmuller 1979	0/51	5/51		8.81%	0.09[0.01,1.6]
MRC 1968	27/199	25/194		62.19%	1.05[0.63,1.75]
Rose 1965	5/28	3/26		29%	1.55[0.41,5.84]
Subtotal (95% CI)	**278**	**271**		**100%**	**0.95[0.38,2.34]**
Total events: 32 (Higher omega 6), 33 (Lower omega 6)					
Heterogeneity: Tau²=0.28; Chi²=3.27, df=2(P=0.19); I²=38.87%					
Test for overall effect: Z=0.11(P=0.91)					
Test for subgroup differences: Chi²=11.43, df=1 (P=0.01), I²=73.76%					

Favours higher omega 6   0.5 0.7 1 1.5 2   Favours lower omega 6

Analysis 1.22. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 22 CVD mortality - subgroup by sex.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.22.1 Men only					
DART 1989	114/1018	91/1015		29.72%	1.25[0.96,1.62]
MRC 1968	27/199	25/194		20.62%	1.05[0.63,1.75]
Sydney Diet-Heart 1978	37/221	25/237		21.79%	1.59[0.99,2.55]
Veterans Admin 1969	57/424	81/422		27.87%	0.7[0.51,0.96]
Subtotal (95% CI)	**1862**	**1868**		**100%**	**1.08[0.76,1.54]**
Total events: 235 (Higher omega 6), 222 (Lower omega 6)					
Heterogeneity: Tau²=0.09; Chi²=11.14, df=3(P=0.01); I²=73.07%					
Test for overall effect: Z=0.43(P=0.67)					

Favours higher omega 6   0.5 0.7 1 1.5 2   Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.22.2 Women only					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.22.3 Men and women					
Black 1994	2/67	0/66		49.29%	4.93[0.24,100.7]
Houtsmuller 1979	0/51	5/51		50.71%	0.09[0.01,1.6]
Subtotal (95% CI)	118	117		100%	0.65[0.01,33.17]
Total events: 2 (Higher omega 6), 5 (Lower omega 6)					
Heterogeneity: Tau²=5.79; Chi²=3.57, df=1(P=0.06); I²=71.96%					
Test for overall effect: Z=0.21(P=0.83)					
1.22.4 Sex not reported					
Rose 1965	5/28	3/26		100%	1.55[0.41,5.84]
Subtotal (95% CI)	28	26		100%	1.55[0.41,5.84]
Total events: 5 (Higher omega 6), 3 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.64(P=0.52)					
Test for subgroup differences: Chi²=0.33, df=1 (P=0.85), I²=0%					

Favours higher omega 6   0.5   0.7   1   1.5   2   Favours lower omega 6

Analysis 1.23. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 23 Any cardiovascular event (overall).

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	476/1018	478/1015		36.99%	0.99[0.91,1.09]
GLAMT 1993	0/54	1/57		0.3%	0.35[0.01,8.45]
MRC 1968	62/199	74/194		20.38%	0.82[0.62,1.07]
NDHS Open 1st 1968	5/726	1/341		0.64%	2.35[0.28,20.02]
Rose 1965	15/28	11/26		7.64%	1.27[0.72,2.23]
Sydney Diet-Heart 1978	37/221	25/237		10.13%	1.59[0.99,2.55]
Veterans Admin 1969	97/424	122/422		23.92%	0.79[0.63,1]
Total (95% CI)	2670	2292		100%	0.97[0.81,1.15]
Total events: 692 (Higher omega 6), 712 (Lower omega 6)					
Heterogeneity: Tau²=0.02; Chi²=10.83, df=6(P=0.09); I²=44.6%					
Test for overall effect: Z=0.37(P=0.71)					

Favours higher omega 6   0.2   0.5   1   2   5   Favours lower omega 6

Analysis 1.24. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 24 CVD events - sensitivity analysis by fixed-effect analysis.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
DART 1989	476/1018	478/1015		67.02%	0.99[0.91,1.09]
GLAMT 1993	0/54	1/57		0.2%	0.35[0.01,8.45]
MRC 1968	62/199	74/194		10.49%	0.82[0.62,1.07]
NDHS Open 1st 1968	5/726	1/341		0.19%	2.35[0.28,20.02]
Rose 1965	15/28	11/26		1.6%	1.27[0.72,2.23]
Sydney Diet-Heart 1978	37/221	25/237		3.38%	1.59[0.99,2.55]
Veterans Admin 1969	97/424	122/422		17.12%	0.79[0.63,1]
Total (95% CI)	**2670**	**2292**		**100%**	**0.97[0.89,1.05]**
Total events: 692 (Higher omega 6), 712 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=10.83, df=6(P=0.09); I²=44.6%					
Test for overall effect: Z=0.85(P=0.39)					

Favours higher omega 6 0.2 0.5 1 2 5 Favours lower omega 6

Analysis 1.25. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 25 CVD events - sensitivity analyses.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.25.1 Studies at low risk of bias					
NDHS Open 1st 1968	5/726	1/341		4.65%	2.35[0.28,20.02]
Sydney Diet-Heart 1978	37/221	25/237		95.35%	1.59[0.99,2.55]
Subtotal (95% CI)	**947**	**578**		**100%**	**1.62[1.02,2.57]**
Total events: 42 (Higher omega 6), 26 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.12, df=1(P=0.73); I²=0%					
Test for overall effect: Z=2.04(P=0.04)					
1.25.2 Pre-2010 or prospective trials registry entry					
DART 1989	476/1018	478/1015		36.99%	0.99[0.91,1.09]
GLAMT 1993	0/54	1/57		0.3%	0.35[0.01,8.45]
MRC 1968	62/199	74/194		20.38%	0.82[0.62,1.07]
NDHS Open 1st 1968	5/726	1/341		0.64%	2.35[0.28,20.02]
Rose 1965	15/28	11/26		7.64%	1.27[0.72,2.23]
Sydney Diet-Heart 1978	37/221	25/237		10.13%	1.59[0.99,2.55]
Veterans Admin 1969	97/424	122/422		23.92%	0.79[0.63,1]
Subtotal (95% CI)	**2670**	**2292**		**100%**	**0.97[0.81,1.15]**
Total events: 692 (Higher omega 6), 712 (Lower omega 6)					
Heterogeneity: Tau²=0.02; Chi²=10.83, df=6(P=0.09); I²=44.6%					
Test for overall effect: Z=0.37(P=0.71)					
1.25.3 No commercial funding					
MRC 1968	62/199	74/194		50.95%	0.82[0.62,1.07]
NDHS Open 1st 1968	5/726	1/341		6.93%	2.35[0.28,20.02]
Sydney Diet-Heart 1978	37/221	25/237		42.12%	1.59[0.99,2.55]
Subtotal (95% CI)	**1146**	**772**		**100%**	**1.16[0.64,2.12]**
Total events: 104 (Higher omega 6), 100 (Lower omega 6)					
Heterogeneity: Tau²=0.17; Chi²=6.49, df=2(P=0.04); I²=69.18%					

Favours higher omega 6 0.2 0.5 1 2 5 Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=0.49(P=0.62)					
1.25.4 Low risk of attention bias					
GLAMT 1993	0/54	1/57		0.92%	0.35[0.01,8.45]
NDHS Open 1st 1968	5/726	1/341		2.02%	2.35[0.28,20.02]
Rose 1965	15/28	11/26		23.78%	1.27[0.72,2.23]
Veterans Admin 1969	97/424	122/422		73.28%	0.79[0.63,1]
Subtotal (95% CI)	**1232**	**846**		**100%**	**0.9[0.66,1.22]**
Total events: 117 (Higher omega 6), 135 (Lower omega 6)					
Heterogeneity: Tau²=0.02; Chi²=3.45, df=3(P=0.33); I²=12.94%					
Test for overall effect: Z=0.69(P=0.49)					
1.25.5 Randomised 250+ participants					
DART 1989	476/1018	478/1015		38.08%	0.99[0.91,1.09]
MRC 1968	62/199	74/194		22.82%	0.82[0.62,1.07]
NDHS Open 1st 1968	5/726	1/341		0.81%	2.35[0.28,20.02]
Sydney Diet-Heart 1978	37/221	25/237		12%	1.59[0.99,2.55]
Veterans Admin 1969	97/424	122/422		26.3%	0.79[0.63,1]
Subtotal (95% CI)	**2588**	**2209**		**100%**	**0.95[0.78,1.16]**
Total events: 677 (Higher omega 6), 700 (Lower omega 6)					
Heterogeneity: Tau²=0.02; Chi²=9.56, df=4(P=0.05); I²=58.16%					
Test for overall effect: Z=0.49(P=0.63)					
1.25.6 Randomised 100+ participants					
DART 1989	476/1018	478/1015		39.06%	0.99[0.91,1.09]
GLAMT 1993	0/54	1/57		0.34%	0.35[0.01,8.45]
MRC 1968	62/199	74/194		22.39%	0.82[0.62,1.07]
NDHS Open 1st 1968	5/726	1/341		0.74%	2.35[0.28,20.02]
Sydney Diet-Heart 1978	37/221	25/237		11.41%	1.59[0.99,2.55]
Veterans Admin 1969	97/424	122/422		26.05%	0.79[0.63,1]
Subtotal (95% CI)	**2642**	**2266**		**100%**	**0.95[0.79,1.14]**
Total events: 677 (Higher omega 6), 701 (Lower omega 6)					
Heterogeneity: Tau²=0.02; Chi²=9.95, df=5(P=0.08); I²=49.74%					
Test for overall effect: Z=0.56(P=0.57)					

Favours higher omega 6　0.2　0.5　1　2　5　Favours lower omega 6

Analysis 1.26.   Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 26 CVD events - subgroup by LA or GLA.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.26.1 Mainly LA					
DART 1989	476/1018	478/1015		36.99%	0.99[0.91,1.09]
MRC 1968	62/199	74/194		20.38%	0.82[0.62,1.07]
NDHS Open 1st 1968	5/726	1/341		0.64%	2.35[0.28,20.02]
Rose 1965	15/28	11/26		7.64%	1.27[0.72,2.23]
Sydney Diet-Heart 1978	37/221	25/237		10.13%	1.59[0.99,2.55]
Veterans Admin 1969	97/424	122/422		23.92%	0.79[0.63,1]
Subtotal (95% CI)	**2616**	**2235**		**99.7%**	**0.97[0.81,1.17]**

Favours higher omega 6　0.2　0.5　1　2　5　Favours lower omega 6

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Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 692 (Higher omega 6), 711 (Lower omega 6)					
Heterogeneity: Tau²=0.02; Chi²=10.44, df=5(P=0.06); I²=52.1%					
Test for overall effect: Z=0.29(P=0.77)					
1.26.2 GLA supplements					
GLAMT 1993	0/54	1/57		0.3%	0.35[0.01,8.45]
Subtotal (95% CI)	**54**	**57**		**0.3%**	**0.35[0.01,8.45]**
Total events: 0 (Higher omega 6), 1 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.64(P=0.52)					
Total (95% CI)	**2670**	**2292**		**100%**	**0.97[0.81,1.15]**
Total events: 692 (Higher omega 6), 712 (Lower omega 6)					
Heterogeneity: Tau²=0.02; Chi²=10.83, df=6(P=0.09); I²=44.6%					
Test for overall effect: Z=0.37(P=0.71)					
Test for subgroup differences: Chi²=0.39, df=1 (P=0.53), I²=0%					

Favours higher omega 6 0.2 0.5 1 2 5 Favours lower omega 6

Analysis 1.27.   Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 27 CVD events - subgroup by intervention type.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.27.1 Dietary advice					
DART 1989	476/1018	478/1015		36.99%	0.99[0.91,1.09]
Sydney Diet-Heart 1978	37/221	25/237		10.13%	1.59[0.99,2.55]
Subtotal (95% CI)	**1239**	**1252**		**47.12%**	**1.18[0.76,1.85]**
Total events: 513 (Higher omega 6), 503 (Lower omega 6)					
Heterogeneity: Tau²=0.08; Chi²=3.69, df=1(P=0.05); I²=72.93%					
Test for overall effect: Z=0.74(P=0.46)					
1.27.2 Supplements (capsules)					
GLAMT 1993	0/54	1/57		0.3%	0.35[0.01,8.45]
Subtotal (95% CI)	**54**	**57**		**0.3%**	**0.35[0.01,8.45]**
Total events: 0 (Higher omega 6), 1 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.64(P=0.52)					
1.27.3 Supplemental foods					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.27.4 Dietary advice plus supplement					
MRC 1968	62/199	74/194		20.38%	0.82[0.62,1.07]
Rose 1965	15/28	11/26		7.64%	1.27[0.72,2.23]
Subtotal (95% CI)	**227**	**220**		**28.02%**	**0.95[0.63,1.42]**
Total events: 77 (Higher omega 6), 85 (Lower omega 6)					

Favours higher omega 6 0.2 0.5 1 2 5 Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0.05; Chi²=1.88, df=1(P=0.17); I²=46.78%					
Test for overall effect: Z=0.27(P=0.79)					
1.27.5 Diet (all foods) provided					
NDHS Open 1st 1968	5/726	1/341		0.64%	2.35[0.28,20.02]
Veterans Admin 1969	97/424	122/422		23.92%	0.79[0.63,1]
Subtotal (95% CI)	**1150**	**763**		**24.56%**	**0.8[0.64,1.01]**
Total events: 102 (Higher omega 6), 123 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.98, df=1(P=0.32); I²=0%					
Test for overall effect: Z=1.9(P=0.06)					
Total (95% CI)	**2670**	**2292**		**100%**	**0.97[0.81,1.15]**
Total events: 692 (Higher omega 6), 712 (Lower omega 6)					
Heterogeneity: Tau²=0.02; Chi²=10.83, df=6(P=0.09); I²=44.6%					
Test for overall effect: Z=0.37(P=0.71)					
Test for subgroup differences: Chi²=2.77, df=1 (P=0.43), I²=0%					

Favours higher omega 6   0.2 0.5 1 2 5   Favours lower omega 6

Analysis 1.28. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 28 CVD events - subgroup by replacement.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.28.1 N-6 replacing SFA					
DART 1989	476/1018	478/1015		38.08%	0.99[0.91,1.09]
MRC 1968	62/199	74/194		22.82%	0.82[0.62,1.07]
NDHS Open 1st 1968	5/726	1/341		0.81%	2.35[0.28,20.02]
Sydney Diet-Heart 1978	37/221	25/237		12%	1.59[0.99,2.55]
Veterans Admin 1969	97/424	122/422		26.3%	0.79[0.63,1]
Subtotal (95% CI)	**2588**	**2209**		**100%**	**0.95[0.78,1.16]**
Total events: 677 (Higher omega 6), 700 (Lower omega 6)					
Heterogeneity: Tau²=0.02; Chi²=9.56, df=4(P=0.05); I²=58.16%					
Test for overall effect: Z=0.49(P=0.63)					
1.28.2 N-6 replacing MUFA					
NDHS Open 1st 1968	5/726	1/341		4.05%	2.35[0.28,20.02]
Rose 1965	15/28	11/26		26.21%	1.27[0.72,2.23]
Sydney Diet-Heart 1978	37/221	25/237		29.9%	1.59[0.99,2.55]
Veterans Admin 1969	97/424	122/422		39.84%	0.79[0.63,1]
Subtotal (95% CI)	**1399**	**1026**		**100%**	**1.15[0.73,1.81]**
Total events: 154 (Higher omega 6), 159 (Lower omega 6)					
Heterogeneity: Tau²=0.12; Chi²=8.63, df=3(P=0.03); I²=65.25%					
Test for overall effect: Z=0.61(P=0.54)					
1.28.3 N-6 replacing nil, low n-6					
GLAMT 1993	0/54	1/57		100%	0.35[0.01,8.45]
Subtotal (95% CI)	**54**	**57**		**100%**	**0.35[0.01,8.45]**
Total events: 0 (Higher omega 6), 1 (Lower omega 6)					
Heterogeneity: Not applicable					

Favours higher omega 6   0.2 0.5 1 2 5   Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=0.64(P=0.52)					
1.28.4 N-6 replacement unclear					
MRC 1968	62/199	74/194		100%	0.82[0.62,1.07]
Subtotal (95% CI)	199	194		100%	**0.82[0.62,1.07]**
Total events: 62 (Higher omega 6), 74 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.45(P=0.15)					
1.28.5 N-6 replacing CHO					
Subtotal (95% CI)	0	0			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.28.6 N-6 replacing protein					
Subtotal (95% CI)	0	0			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Chi²=2.14, df=1 (P=0.54), I²=0%					

Favours higher omega 6   0.2   0.5   1   2   5   Favours lower omega 6

Analysis 1.29.   Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 29 CVD events - subgroup by baseline CVD risk.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.29.1 Primary prevention - low CVD risk					
NDHS Open 1st 1968	5/726	1/341		0.64%	2.35[0.28,20.02]
Veterans Admin 1969	97/424	122/422		23.92%	0.79[0.63,1]
Subtotal (95% CI)	1150	763		24.56%	**0.8[0.64,1.01]**
Total events: 102 (Higher omega 6), 123 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.98, df=1(P=0.32); I²=0%					
Test for overall effect: Z=1.9(P=0.06)					
1.29.2 Primary prevention - moderate CVD risk					
GLAMT 1993	0/54	1/57		0.3%	0.35[0.01,8.45]
Subtotal (95% CI)	54	57		0.3%	**0.35[0.01,8.45]**
Total events: 0 (Higher omega 6), 1 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.64(P=0.52)					
1.29.3 Secondary prevention - existing CVD					
DART 1989	476/1018	478/1015		36.99%	0.99[0.91,1.09]
MRC 1968	62/199	74/194		20.38%	0.82[0.62,1.07]
Rose 1965	15/28	11/26		7.64%	1.27[0.72,2.23]
Sydney Diet-Heart 1978	37/221	25/237		10.13%	1.59[0.99,2.55]
Subtotal (95% CI)	1466	1472		75.14%	**1.04[0.83,1.29]**

Favours higher omega 6   0.2   0.5   1   2   5   Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 590 (Higher omega 6), 588 (Lower omega 6)					
Heterogeneity: Tau²=0.02; Chi²=6.46, df=3(P=0.09); I²=53.54%					
Test for overall effect: Z=0.32(P=0.75)					
Total (95% CI)	**2670**	**2292**		**100%**	**0.97[0.81,1.15]**
Total events: 692 (Higher omega 6), 712 (Lower omega 6)					
Heterogeneity: Tau²=0.02; Chi²=10.83, df=6(P=0.09); I²=44.6%					
Test for overall effect: Z=0.37(P=0.71)					
Test for subgroup differences: Chi²=2.91, df=1 (P=0.23), I²=31.18%					

Favours higher omega 6   0.2   0.5   1   2   5   Favours lower omega 6

Analysis 1.30. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 30 CVD events - subgroup by primary vs secondary prevention.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.30.1 Primary prevention - low or mod CVD risk					
GLAMT 1993	0/54	1/57		0.3%	0.35[0.01,8.45]
NDHS Open 1st 1968	5/726	1/341		0.64%	2.35[0.28,20.02]
Veterans Admin 1969	97/424	122/422		23.92%	0.79[0.63,1]
Subtotal (95% CI)	**1204**	**820**		**24.86%**	**0.8[0.64,1]**
Total events: 102 (Higher omega 6), 124 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=1.24, df=2(P=0.54); I²=0%					
Test for overall effect: Z=1.94(P=0.05)					
1.30.2 Secondary prevention - existing CVD					
DART 1989	476/1018	478/1015		36.99%	0.99[0.91,1.09]
MRC 1968	62/199	74/194		20.38%	0.82[0.62,1.07]
Rose 1965	15/28	11/26		7.64%	1.27[0.72,2.23]
Sydney Diet-Heart 1978	37/221	25/237		10.13%	1.59[0.99,2.55]
Subtotal (95% CI)	**1466**	**1472**		**75.14%**	**1.04[0.83,1.29]**
Total events: 590 (Higher omega 6), 588 (Lower omega 6)					
Heterogeneity: Tau²=0.02; Chi²=6.46, df=3(P=0.09); I²=53.54%					
Test for overall effect: Z=0.32(P=0.75)					
Total (95% CI)	**2670**	**2292**		**100%**	**0.97[0.81,1.15]**
Total events: 692 (Higher omega 6), 712 (Lower omega 6)					
Heterogeneity: Tau²=0.02; Chi²=10.83, df=6(P=0.09); I²=44.6%					
Test for overall effect: Z=0.37(P=0.71)					
Test for subgroup differences: Chi²=2.65, df=1 (P=0.1), I²=62.26%					

Favours higher omega 6   0.2   0.5   1   2   5   Favours lower omega 6

Analysis 1.31. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 31 CVD events - subgroup by omega-6 dose.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.31.1 N-6 < 4% E					
DART 1989	476/1018	478/1015		36.99%	0.99[0.91,1.09]
GLAMT 1993	0/54	1/57		0.3%	0.35[0.01,8.45]
Subtotal (95% CI)	**1072**	**1072**		**37.29%**	**0.99[0.9,1.09]**
Total events: 476 (Higher omega 6), 479 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.41, df=1(P=0.52); I²=0%					
Test for overall effect: Z=0.17(P=0.86)					
1.31.2 N-6 4% to 12% E					
NDHS Open 1st 1968	5/726	1/341		0.64%	2.35[0.28,20.02]
Sydney Diet-Heart 1978	37/221	25/237		10.13%	1.59[0.99,2.55]
Veterans Admin 1969	97/424	122/422		23.92%	0.79[0.63,1]
Subtotal (95% CI)	**1371**	**1000**		**34.69%**	**1.15[0.61,2.16]**
Total events: 139 (Higher omega 6), 148 (Lower omega 6)					
Heterogeneity: Tau²=0.19; Chi²=7.54, df=2(P=0.02); I²=73.46%					
Test for overall effect: Z=0.43(P=0.67)					
1.31.3 N-6 > 12% E					
MRC 1968	62/199	74/194		20.38%	0.82[0.62,1.07]
Rose 1965	15/28	11/26		7.64%	1.27[0.72,2.23]
Subtotal (95% CI)	**227**	**220**		**28.02%**	**0.95[0.63,1.42]**
Total events: 77 (Higher omega 6), 85 (Lower omega 6)					
Heterogeneity: Tau²=0.05; Chi²=1.88, df=1(P=0.17); I²=46.78%					
Test for overall effect: Z=0.27(P=0.79)					
Total (95% CI)	**2670**	**2292**		**100%**	**0.97[0.81,1.15]**
Total events: 692 (Higher omega 6), 712 (Lower omega 6)					
Heterogeneity: Tau²=0.02; Chi²=10.83, df=6(P=0.09); I²=44.6%					
Test for overall effect: Z=0.37(P=0.71)					
Test for subgroup differences: Chi²=0.26, df=1 (P=0.88), I²=0%					

Favours higher omega 6   0.2   0.5   1   2   5   Favours lower omega 6

Analysis 1.32. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 32 CVD events - subgroup by duration.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.32.1 Medium duration 1 to < 2 years in study					
GLAMT 1993	0/54	1/57		0.3%	0.35[0.01,8.45]
NDHS Open 1st 1968	5/726	1/341		0.64%	2.35[0.28,20.02]
Subtotal (95% CI)	**780**	**398**		**0.94%**	**1.3[0.22,7.67]**
Total events: 5 (Higher omega 6), 2 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.94, df=1(P=0.33); I²=0%					
Test for overall effect: Z=0.29(P=0.77)					
1.32.2 Medium-long duration 2 to < 4 years					
DART 1989	476/1018	478/1015		36.99%	0.99[0.91,1.09]

Favours higher omega 6   0.2   0.5   1   2   5   Favours lower omega 6

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Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Rose 1965	15/28	11/26		7.64%	1.27[0.72,2.23]
Subtotal (95% CI)	**1046**	**1041**		**44.63%**	**1[0.91,1.09]**
Total events: 491 (Higher omega 6), 489 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.69, df=1(P=0.41); I²=0%					
Test for overall effect: Z=0.02(P=0.99)					
1.32.3 Long duration 4+ years in study					
MRC 1968	62/199	74/194		20.38%	0.82[0.62,1.07]
Sydney Diet-Heart 1978	37/221	25/237		10.13%	1.59[0.99,2.55]
Veterans Admin 1969	97/424	122/422		23.92%	0.79[0.63,1]
Subtotal (95% CI)	**844**	**853**		**54.43%**	**0.95[0.68,1.33]**
Total events: 196 (Higher omega 6), 221 (Lower omega 6)					
Heterogeneity: Tau²=0.06; Chi²=7.1, df=2(P=0.03); I²=71.84%					
Test for overall effect: Z=0.3(P=0.76)					
Total (95% CI)	**2670**	**2292**		**100%**	**0.97[0.81,1.15]**
Total events: 692 (Higher omega 6), 712 (Lower omega 6)					
Heterogeneity: Tau²=0.02; Chi²=10.83, df=6(P=0.09); I²=44.6%					
Test for overall effect: Z=0.37(P=0.71)					
Test for subgroup differences: Chi²=0.17, df=1 (P=0.92), I²=0%					

Favours higher omega 6   0.2   0.5   1   2   5   Favours lower omega 6

Analysis 1.33.   Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 33 CVD events - subgroup by baseline omega-6.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.33.1 ≥ 8% E from n-6					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.33.2 5% to < 8% E from n-6					
DART 1989	476/1018	478/1015		36.99%	0.99[0.91,1.09]
Sydney Diet-Heart 1978	37/221	25/237		10.13%	1.59[0.99,2.55]
Subtotal (95% CI)	**1239**	**1252**		**47.12%**	**1.18[0.76,1.85]**
Total events: 513 (Higher omega 6), 503 (Lower omega 6)					
Heterogeneity: Tau²=0.08; Chi²=3.69, df=1(P=0.05); I²=72.93%					
Test for overall effect: Z=0.74(P=0.46)					
1.33.3 < 5% E from n-6					
NDHS Open 1st 1968	5/726	1/341		0.64%	2.35[0.28,20.02]
Veterans Admin 1969	97/424	122/422		23.92%	0.79[0.63,1]
Subtotal (95% CI)	**1150**	**763**		**24.56%**	**0.8[0.64,1.01]**
Total events: 102 (Higher omega 6), 123 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.98, df=1(P=0.32); I²=0%					
Test for overall effect: Z=1.9(P=0.06)					

Favours higher omega 6   0.2   0.5   1   2   5   Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.33.4 baseline n-6 not reported					
GLAMT 1993	0/54	1/57		0.3%	0.35[0.01,8.45]
MRC 1968	62/199	74/194		20.38%	0.82[0.62,1.07]
Rose 1965	15/28	11/26		7.64%	1.27[0.72,2.23]
Subtotal (95% CI)	**281**	**277**		**28.31%**	**0.9[0.67,1.21]**
Total events: 77 (Higher omega 6), 86 (Lower omega 6)					
Heterogeneity: Tau²=0.01; Chi²=2.21, df=2(P=0.33); I²=9.57%					
Test for overall effect: Z=0.69(P=0.49)					
Total (95% CI)	**2670**	**2292**		**100%**	**0.97[0.81,1.15]**
Total events: 692 (Higher omega 6), 712 (Lower omega 6)					
Heterogeneity: Tau²=0.02; Chi²=10.83, df=6(P=0.09); I²=44.6%					
Test for overall effect: Z=0.37(P=0.71)					
Test for subgroup differences: Chi²=2.35, df=1 (P=0.31), I²=14.83%					

Favours higher omega 6   0.2   0.5   1   2   5   Favours lower omega 6

Analysis 1.34. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 34 CVD events - subgroup by sex.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.34.1 Men only					
DART 1989	476/1018	478/1015		36.99%	0.99[0.91,1.09]
MRC 1968	62/199	74/194		20.38%	0.82[0.62,1.07]
NDHS Open 1st 1968	5/726	1/341		0.64%	2.35[0.28,20.02]
Sydney Diet-Heart 1978	37/221	25/237		10.13%	1.59[0.99,2.55]
Veterans Admin 1969	97/424	122/422		23.92%	0.79[0.63,1]
Subtotal (95% CI)	**2588**	**2209**		**92.06%**	**0.95[0.78,1.16]**
Total events: 677 (Higher omega 6), 700 (Lower omega 6)					
Heterogeneity: Tau²=0.02; Chi²=9.56, df=4(P=0.05); I²=58.16%					
Test for overall effect: Z=0.49(P=0.63)					
1.34.2 Men and women					
GLAMT 1993	0/54	1/57		0.3%	0.35[0.01,8.45]
Subtotal (95% CI)	**54**	**57**		**0.3%**	**0.35[0.01,8.45]**
Total events: 0 (Higher omega 6), 1 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.64(P=0.52)					
1.34.3 Sex not reported					
Rose 1965	15/28	11/26		7.64%	1.27[0.72,2.23]
Subtotal (95% CI)	**28**	**26**		**7.64%**	**1.27[0.72,2.23]**
Total events: 15 (Higher omega 6), 11 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.82(P=0.41)					
Total (95% CI)	**2670**	**2292**		**100%**	**0.97[0.81,1.15]**
Total events: 692 (Higher omega 6), 712 (Lower omega 6)					
Heterogeneity: Tau²=0.02; Chi²=10.83, df=6(P=0.09); I²=44.6%					

Favours higher omega 6   0.2   0.5   1   2   5   Favours lower omega 6

Study or subgroup	Higher omega 6	Lower omega 6	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Test for overall effect: Z=0.37(P=0.71)					
Test for subgroup differences: Chi²=1.27, df=1 (P=0.53), I²=0%					

Favours higher omega 6   0.2   0.5   1   2   5   Favours lower omega 6

Analysis 1.35. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 35 Coronary heart disease events (overall): myocardial infarction (fatal or non-fatal) or angina.

Study or subgroup	Higher omega 6	Lower omega 6	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
DART 1989	339/1018	364/1015		24.6%	0.93[0.82,1.05]
GLAMT 1993	0/54	1/57		0.79%	0.35[0.01,8.45]
Houtsmuller 1979	8/51	30/51		10.62%	0.27[0.14,0.52]
MRC 1968	50/199	50/194		18.95%	0.97[0.69,1.37]
Rose 1965	12/28	9/26		10.56%	1.24[0.63,2.44]
Sydney Diet-Heart 1978	35/221	23/237		14.64%	1.63[1,2.67]
Veterans Admin 1969	60/424	78/422		19.84%	0.77[0.56,1.04]
Total (95% CI)	**1995**	**2002**		**100%**	**0.88[0.66,1.17]**
Total events: 504 (Higher omega 6), 555 (Lower omega 6)					
Heterogeneity: Tau²=0.08; Chi²=20.67, df=6(P=0); I²=70.97%					
Test for overall effect: Z=0.89(P=0.37)					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Analysis 1.36. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 36 CHD events - sensitivity analysis by fixed-effect analysis.

Study or subgroup	Higher omega 6	Lower omega 6	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
DART 1989	339/1018	364/1015		65.52%	0.93[0.82,1.05]
GLAMT 1993	0/54	1/57		0.26%	0.35[0.01,8.45]
Houtsmuller 1979	8/51	30/51		5.39%	0.27[0.14,0.52]
MRC 1968	50/199	50/194		9.1%	0.97[0.69,1.37]
Rose 1965	12/28	9/26		1.68%	1.24[0.63,2.44]
Sydney Diet-Heart 1978	35/221	23/237		3.99%	1.63[1,2.67]
Veterans Admin 1969	60/424	78/422		14.05%	0.77[0.56,1.04]
Total (95% CI)	**1995**	**2002**		**100%**	**0.91[0.82,1]**
Total events: 504 (Higher omega 6), 555 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=20.67, df=6(P=0); I²=70.97%					
Test for overall effect: Z=1.92(P=0.06)					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Analysis 1.37. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 37 CHD events - sensitivity analyses.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.37.1 Studies at low risk of bias					
Sydney Diet-Heart 1978	35/221	23/237		100%	1.63[1,2.67]
Subtotal (95% CI)	**221**	**237**		**100%**	**1.63[1,2.67]**
Total events: 35 (Higher omega 6), 23 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%					
Test for overall effect: Z=1.95(P=0.05)					
1.37.2 Pre-2010 or prospective trials registry entry					
DART 1989	339/1018	364/1015		24.6%	0.93[0.82,1.05]
GLAMT 1993	0/54	1/57		0.79%	0.35[0.01,8.45]
Houtsmuller 1979	8/51	30/51		10.62%	0.27[0.14,0.52]
MRC 1968	50/199	50/194		18.95%	0.97[0.69,1.37]
Rose 1965	12/28	9/26		10.56%	1.24[0.63,2.44]
Sydney Diet-Heart 1978	35/221	23/237		14.64%	1.63[1,2.67]
Veterans Admin 1969	60/424	78/422		19.84%	0.77[0.56,1.04]
Subtotal (95% CI)	**1995**	**2002**		**100%**	**0.88[0.66,1.17]**
Total events: 504 (Higher omega 6), 555 (Lower omega 6)					
Heterogeneity: Tau²=0.08; Chi²=20.67, df=6(P=0); I²=70.97%					
Test for overall effect: Z=0.89(P=0.37)					
1.37.3 No commercial funding					
Houtsmuller 1979	8/51	30/51		30.58%	0.27[0.14,0.52]
MRC 1968	50/199	50/194		35.78%	0.97[0.69,1.37]
Sydney Diet-Heart 1978	35/221	23/237		33.64%	1.63[1,2.67]
Subtotal (95% CI)	**471**	**482**		**100%**	**0.78[0.33,1.82]**
Total events: 93 (Higher omega 6), 103 (Lower omega 6)					
Heterogeneity: Tau²=0.5; Chi²=18.2, df=2(P=0); I²=89.01%					
Test for overall effect: Z=0.57(P=0.57)					
1.37.4 Low risk of attention bias					
GLAMT 1993	0/54	1/57		0.77%	0.35[0.01,8.45]
Rose 1965	12/28	9/26		16.94%	1.24[0.63,2.44]
Veterans Admin 1969	60/424	78/422		82.29%	0.77[0.56,1.04]
Subtotal (95% CI)	**506**	**505**		**100%**	**0.83[0.62,1.09]**
Total events: 72 (Higher omega 6), 88 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=1.89, df=2(P=0.39); I²=0%					
Test for overall effect: Z=1.34(P=0.18)					
1.37.5 Randomised 250+ participants					
DART 1989	339/1018	364/1015		41.57%	0.93[0.82,1.05]
MRC 1968	50/199	50/194		21.48%	0.97[0.69,1.37]
Sydney Diet-Heart 1978	35/221	23/237		13.25%	1.63[1,2.67]
Veterans Admin 1969	60/424	78/422		23.7%	0.77[0.56,1.04]
Subtotal (95% CI)	**1862**	**1868**		**100%**	**0.97[0.78,1.19]**
Total events: 484 (Higher omega 6), 515 (Lower omega 6)					
Heterogeneity: Tau²=0.02; Chi²=6.59, df=3(P=0.09); I²=54.47%					
Test for overall effect: Z=0.32(P=0.75)					
1.37.6 Randomised 100+ participants					

Favours higher omega 6 0.01 0.1 1 10 100 Favours lower omega 6

Study or subgroup	Higher omega 6	Lower omega 6	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
DART 1989	339/1018	364/1015		26.96%	0.93[0.82,1.05]
GLAMT 1993	0/54	1/57		0.95%	0.35[0.01,8.45]
Houtsmuller 1979	8/51	30/51		12.21%	0.27[0.14,0.52]
MRC 1968	50/199	50/194		21.18%	0.97[0.69,1.37]
Sydney Diet-Heart 1978	35/221	23/237		16.61%	1.63[1,2.67]
Veterans Admin 1969	60/424	78/422		22.1%	0.77[0.56,1.04]
Subtotal (95% CI)	**1967**	**1976**		**100%**	**0.84[0.61,1.15]**
Total events: 492 (Higher omega 6), 546 (Lower omega 6)					
Heterogeneity: Tau²=0.09; Chi²=19.88, df=5(P=0); I²=74.85%					
Test for overall effect: Z=1.09(P=0.28)					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Analysis 1.38. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 38 CHD events - subgroup by LA or GLA.

Study or subgroup	Higher omega 6	Lower omega 6	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
1.38.1 Mainly LA					
DART 1989	339/1018	364/1015		24.6%	0.93[0.82,1.05]
Houtsmuller 1979	8/51	30/51		10.62%	0.27[0.14,0.52]
MRC 1968	50/199	50/194		18.95%	0.97[0.69,1.37]
Rose 1965	12/28	9/26		10.56%	1.24[0.63,2.44]
Sydney Diet-Heart 1978	35/221	23/237		14.64%	1.63[1,2.67]
Veterans Admin 1969	60/424	78/422		19.84%	0.77[0.56,1.04]
Subtotal (95% CI)	**1941**	**1945**		**99.21%**	**0.88[0.66,1.19]**
Total events: 504 (Higher omega 6), 554 (Lower omega 6)					
Heterogeneity: Tau²=0.09; Chi²=20.32, df=5(P=0); I²=75.39%					
Test for overall effect: Z=0.83(P=0.41)					
1.38.2 GLA supplements					
GLAMT 1993	0/54	1/57		0.79%	0.35[0.01,8.45]
Subtotal (95% CI)	**54**	**57**		**0.79%**	**0.35[0.01,8.45]**
Total events: 0 (Higher omega 6), 1 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.64(P=0.52)					
Total (95% CI)	**1995**	**2002**		**100%**	**0.88[0.66,1.17]**
Total events: 504 (Higher omega 6), 555 (Lower omega 6)					
Heterogeneity: Tau²=0.08; Chi²=20.67, df=6(P=0); I²=70.97%					
Test for overall effect: Z=0.89(P=0.37)					
Test for subgroup differences: Chi²=0.32, df=1 (P=0.57), I²=0%					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Analysis 1.39.   Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 39 CHD events - subgroup by intervention type.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.39.1 Dietary advice					
DART 1989	339/1018	364/1015		24.6%	0.93[0.82,1.05]
Houtsmuller 1979	8/51	30/51		10.62%	0.27[0.14,0.52]
Sydney Diet-Heart 1978	35/221	23/237		14.64%	1.63[1,2.67]
Subtotal (95% CI)	**1290**	**1303**		**49.86%**	**0.78[0.38,1.61]**
Total events: 382 (Higher omega 6), 417 (Lower omega 6)					
Heterogeneity: Tau²=0.36; Chi²=18.09, df=2(P=0); I²=88.94%					
Test for overall effect: Z=0.68(P=0.5)					
1.39.2 Dietary advice plus supplement					
MRC 1968	50/199	50/194		18.95%	0.97[0.69,1.37]
Rose 1965	12/28	9/26		10.56%	1.24[0.63,2.44]
Subtotal (95% CI)	**227**	**220**		**29.51%**	**1.02[0.76,1.38]**
Total events: 62 (Higher omega 6), 59 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.38, df=1(P=0.54); I²=0%					
Test for overall effect: Z=0.14(P=0.89)					
1.39.3 Supplemental foods					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.39.4 Supplements (capsules)					
GLAMT 1993	0/54	1/57		0.79%	0.35[0.01,8.45]
Subtotal (95% CI)	**54**	**57**		**0.79%**	**0.35[0.01,8.45]**
Total events: 0 (Higher omega 6), 1 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.64(P=0.52)					
1.39.5 Diet (all foods) provided					
Veterans Admin 1969	60/424	78/422		19.84%	0.77[0.56,1.04]
Subtotal (95% CI)	**424**	**422**		**19.84%**	**0.77[0.56,1.04]**
Total events: 60 (Higher omega 6), 78 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.7(P=0.09)					
Total (95% CI)	**1995**	**2002**		**100%**	**0.88[0.66,1.17]**
Total events: 504 (Higher omega 6), 555 (Lower omega 6)					
Heterogeneity: Tau²=0.08; Chi²=20.67, df=6(P=0); I²=70.97%					
Test for overall effect: Z=0.89(P=0.37)					
Test for subgroup differences: Chi²=2.15, df=1 (P=0.54), I²=0%					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Analysis 1.40. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 40 CHD events - subgroup by replacement.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.40.1 N-6 replacing SFA					
DART 1989	339/1018	364/1015		26.96%	0.93[0.82,1.05]
Houtsmuller 1979	8/51	30/51		12.51%	0.27[0.14,0.52]
MRC 1968	50/199	50/194		21.38%	0.97[0.69,1.37]
Sydney Diet-Heart 1978	35/221	23/237		16.89%	1.63[1,2.67]
Veterans Admin 1969	60/424	78/422		22.27%	0.77[0.56,1.04]
Subtotal (95% CI)	**1913**	**1919**		**100%**	**0.85[0.61,1.17]**
Total events: 492 (Higher omega 6), 545 (Lower omega 6)					
Heterogeneity: Tau²=0.1; Chi²=19.54, df=4(P=0); I²=79.52%					
Test for overall effect: Z=1.02(P=0.31)					
1.40.2 N-6 replacing MUFA					
Rose 1965	12/28	9/26		13.86%	1.24[0.63,2.44]
Sydney Diet-Heart 1978	35/221	23/237		26.33%	1.63[1,2.67]
Veterans Admin 1969	71/424	54/422		59.81%	1.31[0.94,1.82]
Subtotal (95% CI)	**673**	**685**		**100%**	**1.38[1.07,1.77]**
Total events: 118 (Higher omega 6), 86 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.64, df=2(P=0.72); I²=0%					
Test for overall effect: Z=2.47(P=0.01)					
1.40.3 N-6 replacing nil, low n-6					
GLAMT 1993	0/54	1/57		100%	0.35[0.01,8.45]
Subtotal (95% CI)	**54**	**57**		**100%**	**0.35[0.01,8.45]**
Total events: 0 (Higher omega 6), 1 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.64(P=0.52)					
1.40.4 N-6 replacement unclear					
MRC 1968	50/199	50/194		100%	0.97[0.69,1.37]
Subtotal (95% CI)	**199**	**194**		**100%**	**0.97[0.69,1.37]**
Total events: 50 (Higher omega 6), 50 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.15(P=0.88)					
1.40.5 N-6 replacing CHO					
Houtsmuller 1979	8/51	30/51		100%	0.27[0.14,0.52]
Subtotal (95% CI)	**51**	**51**		**100%**	**0.27[0.14,0.52]**
Total events: 8 (Higher omega 6), 30 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.83(P=0)					
1.40.6 N-6 replacing protein					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Chi²=22.26, df=1 (P=0), I²=82.03%					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

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Analysis 1.41.   Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 41 CHD events - subgroup by baseline CVD risk.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.41.1 Primary prevention - low CVD risk					
Veterans Admin 1969	60/424	78/422		19.84%	0.77[0.56,1.04]
Subtotal (95% CI)	**424**	**422**		**19.84%**	**0.77[0.56,1.04]**
Total events: 60 (Higher omega 6), 78 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.7(P=0.09)					
1.41.2 Primary prevention - moderate CVD risk					
GLAMT 1993	0/54	1/57		0.79%	0.35[0.01,8.45]
Houtsmuller 1979	8/51	30/51		10.62%	0.27[0.14,0.52]
Subtotal (95% CI)	**105**	**108**		**11.41%**	**0.27[0.14,0.52]**
Total events: 8 (Higher omega 6), 31 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.03, df=1(P=0.87); I²=0%					
Test for overall effect: Z=3.88(P=0)					
1.41.3 Secondary prevention - existing CVD					
DART 1989	339/1018	364/1015		24.6%	0.93[0.82,1.05]
MRC 1968	50/199	50/194		18.95%	0.97[0.69,1.37]
Rose 1965	12/28	9/26		10.56%	1.24[0.63,2.44]
Sydney Diet-Heart 1978	35/221	23/237		14.64%	1.63[1,2.67]
Subtotal (95% CI)	**1466**	**1472**		**68.75%**	**1.05[0.84,1.32]**
Total events: 436 (Higher omega 6), 446 (Lower omega 6)					
Heterogeneity: Tau²=0.02; Chi²=5.3, df=3(P=0.15); I²=43.45%					
Test for overall effect: Z=0.45(P=0.65)					
Total (95% CI)	**1995**	**2002**		**100%**	**0.88[0.66,1.17]**
Total events: 504 (Higher omega 6), 555 (Lower omega 6)					
Heterogeneity: Tau²=0.08; Chi²=20.67, df=6(P=0); I²=70.97%					
Test for overall effect: Z=0.89(P=0.37)					
Test for subgroup differences: Chi²=15.42, df=1 (P=0), I²=87.03%					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Analysis 1.42.   Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 42 CHD events - subgroup by omega-6 dose.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.42.1 N-6 < 4% E					
DART 1989	339/1018	364/1015		24.6%	0.93[0.82,1.05]
GLAMT 1993	0/54	1/57		0.79%	0.35[0.01,8.45]
Subtotal (95% CI)	**1072**	**1072**		**25.39%**	**0.93[0.82,1.05]**
Total events: 339 (Higher omega 6), 365 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.36, df=1(P=0.55); I²=0%					
Test for overall effect: Z=1.24(P=0.22)					
1.42.2 N-6 4% to 12% E					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Houtsmuller 1979	8/51	30/51		10.62%	0.27[0.14,0.52]
Sydney Diet-Heart 1978	35/221	23/237		14.64%	1.63[1,2.67]
Veterans Admin 1969	60/424	78/422		19.84%	0.77[0.56,1.04]
Subtotal (95% CI)	**696**	**710**		**45.1%**	**0.72[0.31,1.64]**
Total events: 103 (Higher omega 6), 131 (Lower omega 6)					
Heterogeneity: Tau²=0.47; Chi²=18.24, df=2(P=0); I²=89.04%					
Test for overall effect: Z=0.79(P=0.43)					
1.42.3 N-6 > 12% E					
MRC 1968	50/199	50/194		18.95%	0.97[0.69,1.37]
Rose 1965	12/28	9/26		10.56%	1.24[0.63,2.44]
Subtotal (95% CI)	**227**	**220**		**29.51%**	**1.02[0.76,1.38]**
Total events: 62 (Higher omega 6), 59 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.38, df=1(P=0.54); I²=0%					
Test for overall effect: Z=0.14(P=0.89)					
Total (95% CI)	**1995**	**2002**		**100%**	**0.88[0.66,1.17]**
Total events: 504 (Higher omega 6), 555 (Lower omega 6)					
Heterogeneity: Tau²=0.08; Chi²=20.67, df=6(P=0); I²=70.97%					
Test for overall effect: Z=0.89(P=0.37)					
Test for subgroup differences: Chi²=0.75, df=1 (P=0.69), I²=0%					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Analysis 1.43. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 43 CHD events - subgroup by duration.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.43.1 Medium duration 1 to < 2 years in study					
GLAMT 1993	0/54	1/57		0.79%	0.35[0.01,8.45]
Subtotal (95% CI)	**54**	**57**		**0.79%**	**0.35[0.01,8.45]**
Total events: 0 (Higher omega 6), 1 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.64(P=0.52)					
1.43.2 Medium-long duration 2 to < 4 years					
DART 1989	339/1018	364/1015		24.6%	0.93[0.82,1.05]
Rose 1965	12/28	9/26		10.56%	1.24[0.63,2.44]
Subtotal (95% CI)	**1046**	**1041**		**35.15%**	**0.94[0.83,1.05]**
Total events: 351 (Higher omega 6), 373 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.67, df=1(P=0.41); I²=0%					
Test for overall effect: Z=1.09(P=0.28)					
1.43.3 Long duration 4+ years in study					
Houtsmuller 1979	8/51	30/51		10.62%	0.27[0.14,0.52]
MRC 1968	50/199	50/194		18.95%	0.97[0.69,1.37]
Sydney Diet-Heart 1978	35/221	23/237		14.64%	1.63[1,2.67]
Veterans Admin 1969	60/424	78/422		19.84%	0.77[0.56,1.04]
Subtotal (95% CI)	**895**	**904**		**64.05%**	**0.79[0.46,1.35]**

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 153 (Higher omega 6), 181 (Lower omega 6)					
Heterogeneity: Tau²=0.24; Chi²=19.08, df=3(P=0); I²=84.28%					
Test for overall effect: Z=0.86(P=0.39)					
Total (95% CI)	**1995**	**2002**		**100%**	**0.88[0.66,1.17]**
Total events: 504 (Higher omega 6), 555 (Lower omega 6)					
Heterogeneity: Tau²=0.08; Chi²=20.67, df=6(P=0); I²=70.97%					
Test for overall effect: Z=0.89(P=0.37)					
Test for subgroup differences: Chi²=0.72, df=1 (P=0.7), I²=0%					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Analysis 1.44.   Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 44 CHD events - subgroup by baseline omega-6.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.44.1 ≥ 8% E from n-6					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.44.2 5% to < 8% E from n-6					
DART 1989	339/1018	364/1015		24.6%	0.93[0.82,1.05]
Sydney Diet-Heart 1978	35/221	23/237		14.64%	1.63[1,2.67]
Subtotal (95% CI)	**1239**	**1252**		**39.24%**	**1.17[0.68,2.01]**
Total events: 374 (Higher omega 6), 387 (Lower omega 6)					
Heterogeneity: Tau²=0.13; Chi²=4.78, df=1(P=0.03); I²=79.07%					
Test for overall effect: Z=0.56(P=0.58)					
1.44.3 < 5% E from n-6					
Veterans Admin 1969	60/424	78/422		19.84%	0.77[0.56,1.04]
Subtotal (95% CI)	**424**	**422**		**19.84%**	**0.77[0.56,1.04]**
Total events: 60 (Higher omega 6), 78 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.7(P=0.09)					
1.44.4 Baseline omega 6 not reported					
GLAMT 1993	0/54	1/57		0.79%	0.35[0.01,8.45]
Houtsmuller 1979	8/51	30/51		10.62%	0.27[0.14,0.52]
MRC 1968	50/199	50/194		18.95%	0.97[0.69,1.37]
Rose 1965	12/28	9/26		10.56%	1.24[0.63,2.44]
Subtotal (95% CI)	**332**	**328**		**40.92%**	**0.68[0.31,1.47]**
Total events: 70 (Higher omega 6), 90 (Lower omega 6)					
Heterogeneity: Tau²=0.41; Chi²=13.5, df=3(P=0); I²=77.78%					
Test for overall effect: Z=0.99(P=0.32)					
Total (95% CI)	**1995**	**2002**		**100%**	**0.88[0.66,1.17]**
Total events: 504 (Higher omega 6), 555 (Lower omega 6)					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI

Heterogeneity: Tau²=0.08; Chi²=20.67, df=6(P=0); I²=70.97%

Test for overall effect: Z=0.89(P=0.37)

Test for subgroup differences: Chi²=2.04, df=1 (P=0.36), I²=2.06%

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Analysis 1.45.   Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 45 CHD events - subgroup by sex.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.45.1 Men only					
DART 1989	339/1018	364/1015		24.6%	0.93[0.82,1.05]
MRC 1968	50/199	50/194		18.95%	0.97[0.69,1.37]
Sydney Diet-Heart 1978	35/221	23/237		14.64%	1.63[1,2.67]
Veterans Admin 1969	60/424	78/422		19.84%	0.77[0.56,1.04]
Subtotal (95% CI)	**1862**	**1868**		**78.03%**	**0.97[0.78,1.19]**

Total events: 484 (Higher omega 6), 515 (Lower omega 6)

Heterogeneity: Tau²=0.02; Chi²=6.59, df=3(P=0.09); I²=54.47%

Test for overall effect: Z=0.32(P=0.75)

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.45.2 Women only					
Subtotal (95% CI)	**0**	**0**			**Not estimable**

Total events: 0 (Higher omega 6), 0 (Lower omega 6)

Heterogeneity: Not applicable

Test for overall effect: Not applicable

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.45.3 Men and women					
GLAMT 1993	0/54	1/57		0.79%	0.35[0.01,8.45]
Houtsmuller 1979	8/51	30/51		10.62%	0.27[0.14,0.52]
Subtotal (95% CI)	**105**	**108**		**11.41%**	**0.27[0.14,0.52]**

Total events: 8 (Higher omega 6), 31 (Lower omega 6)

Heterogeneity: Tau²=0; Chi²=0.03, df=1(P=0.87); I²=0%

Test for overall effect: Z=3.88(P=0)

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.45.4 Sex not reported					
Rose 1965	12/28	9/26		10.56%	1.24[0.63,2.44]
Subtotal (95% CI)	**28**	**26**		**10.56%**	**1.24[0.63,2.44]**

Total events: 12 (Higher omega 6), 9 (Lower omega 6)

Heterogeneity: Not applicable

Test for overall effect: Z=0.62(P=0.54)

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total (95% CI)	**1995**	**2002**		**100%**	**0.88[0.66,1.17]**

Total events: 504 (Higher omega 6), 555 (Lower omega 6)

Heterogeneity: Tau²=0.08; Chi²=20.67, df=6(P=0); I²=70.97%

Test for overall effect: Z=0.89(P=0.37)

Test for subgroup differences: Chi²=13.97, df=1 (P=0), I²=85.69%

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Analysis 1.46. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 46 Major adverse cardiac and cerebrovascular events (MACCEs), overall.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	333/1018	337/1015		57.38%	0.99[0.87,1.12]
Veterans Admin 1969	60/424	87/422		42.62%	0.69[0.51,0.93]
Total (95% CI)	**1442**	**1437**		**100%**	**0.84[0.59,1.2]**

Total events: 393 (Higher omega 6), 424 (Lower omega 6)

Heterogeneity: Tau²=0.05; Chi²=4.8, df=1(P=0.03); I²=79.17%

Test for overall effect: Z=0.94(P=0.35)

Favours higher omega 6   0.5 0.7 1 1.5 2   Favours lower omega 6

Analysis 1.47. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 47 MACCEs - sensitivity analysis by fixed-effect analysis.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
DART 1989	333/1018	337/1015		79.47%	0.99[0.87,1.12]
Veterans Admin 1969	60/424	87/422		20.53%	0.69[0.51,0.93]
Total (95% CI)	**1442**	**1437**		**100%**	**0.92[0.82,1.04]**

Total events: 393 (Higher omega 6), 424 (Lower omega 6)

Heterogeneity: Tau²=0; Chi²=4.8, df=1(P=0.03); I²=79.17%

Test for overall effect: Z=1.35(P=0.18)

Favours higher omega 6   0.5 0.7 1 1.5 2   Favours lower omega 6

Analysis 1.48. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 48 MACCEs - sensitivity analyses.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.48.1 Low risk of bias					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.48.2 Pre-2010 or prospective trials registry entry					
DART 1989	333/1018	337/1015		57.38%	0.99[0.87,1.12]
Veterans Admin 1969	60/424	87/422		42.62%	0.69[0.51,0.93]
Subtotal (95% CI)	**1442**	**1437**		**100%**	**0.84[0.59,1.2]**
Total events: 393 (Higher omega 6), 424 (Lower omega 6)					
Heterogeneity: Tau²=0.05; Chi²=4.8, df=1(P=0.03); I²=79.17%					
Test for overall effect: Z=0.94(P=0.35)					
1.48.3 No commercial funding					
Subtotal (95% CI)	**0**	**0**			**Not estimable**

Favours higher omega 6   0.01 0.1 1 10 100   Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.48.4 Low risk of attention bias					
Veterans Admin 1969	60/424	87/422		100%	0.69[0.51,0.93]
Subtotal (95% CI)	**424**	**422**		**100%**	**0.69[0.51,0.93]**
Total events: 60 (Higher omega 6), 87 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.46(P=0.01)					
1.48.5 Randomised 250+ participants					
DART 1989	333/1018	337/1015		57.38%	0.99[0.87,1.12]
Veterans Admin 1969	60/424	87/422		42.62%	0.69[0.51,0.93]
Subtotal (95% CI)	**1442**	**1437**		**100%**	**0.84[0.59,1.2]**
Total events: 393 (Higher omega 6), 424 (Lower omega 6)					
Heterogeneity: Tau²=0.05; Chi²=4.8, df=1(P=0.03); I²=79.17%					
Test for overall effect: Z=0.94(P=0.35)					
1.48.6 Randomised 100+ participants					
DART 1989	333/1018	337/1015		57.38%	0.99[0.87,1.12]
Veterans Admin 1969	60/424	87/422		42.62%	0.69[0.51,0.93]
Subtotal (95% CI)	**1442**	**1437**		**100%**	**0.84[0.59,1.2]**
Total events: 393 (Higher omega 6), 424 (Lower omega 6)					
Heterogeneity: Tau²=0.05; Chi²=4.8, df=1(P=0.03); I²=79.17%					
Test for overall effect: Z=0.94(P=0.35)					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Analysis 1.49.   Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 49 MACCEs - subgroup by intervention type.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.49.1 Dietary advice					
DART 1989	333/1018	337/1015		57.38%	0.99[0.87,1.12]
Subtotal (95% CI)	**1018**	**1015**		**57.38%**	**0.99[0.87,1.12]**
Total events: 333 (Higher omega 6), 337 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.24(P=0.81)					
1.49.2 Supplements (capsules)					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.49.3 Supplemental foods					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.49.4 Dietary advice plus supplement					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.49.5 Diet (all foods) provided					
Veterans Admin 1969	60/424	87/422		42.62%	0.69[0.51,0.93]
Subtotal (95% CI)	**424**	**422**		42.62%	**0.69[0.51,0.93]**
Total events: 60 (Higher omega 6), 87 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.46(P=0.01)					
Total (95% CI)	**1442**	**1437**		**100%**	**0.84[0.59,1.2]**
Total events: 393 (Higher omega 6), 424 (Lower omega 6)					
Heterogeneity: Tau²=0.05; Chi²=4.8, df=1(P=0.03); I²=79.17%					
Test for overall effect: Z=0.94(P=0.35)					
Test for subgroup differences: Chi²=4.76, df=1 (P=0.03), I²=78.99%					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Analysis 1.50.   Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 50 MACCEs - subgroup by replacement.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.50.1 N-6 replacing SFA					
DART 1989	333/1018	337/1015		57.38%	0.99[0.87,1.12]
Veterans Admin 1969	60/424	87/422		42.62%	0.69[0.51,0.93]
Subtotal (95% CI)	**1442**	**1437**		**100%**	**0.84[0.59,1.2]**
Total events: 393 (Higher omega 6), 424 (Lower omega 6)					
Heterogeneity: Tau²=0.05; Chi²=4.8, df=1(P=0.03); I²=79.17%					
Test for overall effect: Z=0.94(P=0.35)					
1.50.2 N-6 replacing MUFA					
Veterans Admin 1969	60/424	87/422		100%	0.69[0.51,0.93]
Subtotal (95% CI)	**424**	**422**		**100%**	**0.69[0.51,0.93]**
Total events: 60 (Higher omega 6), 87 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.46(P=0.01)					
1.50.3 N-6 replacing nil, low n-6					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.50.4 N-6 replacement unclear					
Subtotal (95% CI)	0	0			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.50.5 N-6 replacing CHO					
Subtotal (95% CI)	0	0			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.50.6 N-6 replacing protein					
Subtotal (95% CI)	0	0			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Chi²=0.77, df=1 (P=0.38), I²=0%					

Favours higher omega 6 0.01 0.1 1 10 100 Favours lower omega 6

Analysis 1.51. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 51 MACCEs - subgroup by baseline CVD risk.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.51.1 Primary prevention - low CVD risk					
Veterans Admin 1969	60/424	87/422		42.62%	0.69[0.51,0.93]
Subtotal (95% CI)	424	422		42.62%	**0.69[0.51,0.93]**
Total events: 60 (Higher omega 6), 87 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.46(P=0.01)					
1.51.2 Primary prevention - moderate CVD risk					
Subtotal (95% CI)	0	0			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.51.3 Secondary prevention - existing CVD					
DART 1989	333/1018	337/1015		57.38%	0.99[0.87,1.12]
Subtotal (95% CI)	1018	1015		57.38%	**0.99[0.87,1.12]**
Total events: 333 (Higher omega 6), 337 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.24(P=0.81)					
Total (95% CI)	1442	1437		100%	**0.84[0.59,1.2]**
Total events: 393 (Higher omega 6), 424 (Lower omega 6)					
Heterogeneity: Tau²=0.05; Chi²=4.8, df=1(P=0.03); I²=79.17%					
Test for overall effect: Z=0.94(P=0.35)					

Favours higher omega 6 0.01 0.1 1 10 100 Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for subgroup differences: Chi²=4.76, df=1 (P=0.03), I²=78.99%					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Analysis 1.52. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 52 MACCEs - subgroup by omega-6 dose.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.52.1 N-6 < 4% E					
DART 1989	333/1018	337/1015		57.38%	0.99[0.87,1.12]
Subtotal (95% CI)	**1018**	**1015**		**57.38%**	**0.99[0.87,1.12]**
Total events: 333 (Higher omega 6), 337 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.24(P=0.81)					
1.52.2 N-6 4% to 12% E					
Veterans Admin 1969	60/424	87/422		42.62%	0.69[0.51,0.93]
Subtotal (95% CI)	**424**	**422**		**42.62%**	**0.69[0.51,0.93]**
Total events: 60 (Higher omega 6), 87 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.46(P=0.01)					
1.52.3 N-6 > 12% E					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**1442**	**1437**		**100%**	**0.84[0.59,1.2]**
Total events: 393 (Higher omega 6), 424 (Lower omega 6)					
Heterogeneity: Tau²=0.05; Chi²=4.8, df=1(P=0.03); I²=79.17%					
Test for overall effect: Z=0.94(P=0.35)					
Test for subgroup differences: Chi²=4.76, df=1 (P=0.03), I²=78.99%					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Analysis 1.53. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 53 MACCEs - subgroup by duration.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.53.1 Medium duration 1 to < 2 years in study					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.53.2 Medium-long duration 2 to < 4 years					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	333/1018	337/1015		57.38%	0.99[0.87,1.12]
Subtotal (95% CI)	**1018**	**1015**		**57.38%**	**0.99[0.87,1.12]**
Total events: 333 (Higher omega 6), 337 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.24(P=0.81)					
1.53.3 Long duration 4+ years in study					
Veterans Admin 1969	60/424	87/422		42.62%	0.69[0.51,0.93]
Subtotal (95% CI)	**424**	**422**		**42.62%**	**0.69[0.51,0.93]**
Total events: 60 (Higher omega 6), 87 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.46(P=0.01)					
Total (95% CI)	**1442**	**1437**		**100%**	**0.84[0.59,1.2]**
Total events: 393 (Higher omega 6), 424 (Lower omega 6)					
Heterogeneity: Tau²=0.05; Chi²=4.8, df=1(P=0.03); I²=79.17%					
Test for overall effect: Z=0.94(P=0.35)					
Test for subgroup differences: Chi²=4.76, df=1 (P=0.03), I²=78.99%					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Analysis 1.54. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 54 MACCEs - subgroup by baseline omega-6.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.54.1 ≥ 8% E from n-6					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.54.2 5% to < 8% E from n-6					
DART 1989	333/1018	337/1015		57.38%	0.99[0.87,1.12]
Subtotal (95% CI)	**1018**	**1015**		**57.38%**	**0.99[0.87,1.12]**
Total events: 333 (Higher omega 6), 337 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.24(P=0.81)					
1.54.3 < 5% E from n-6					
Veterans Admin 1969	60/424	87/422		42.62%	0.69[0.51,0.93]
Subtotal (95% CI)	**424**	**422**		**42.62%**	**0.69[0.51,0.93]**
Total events: 60 (Higher omega 6), 87 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.46(P=0.01)					
1.54.4 Baseline n-6 not reported					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Not applicable					
Total (95% CI)	**1442**	**1437**	◆	**100%**	**0.84[0.59,1.2]**
Total events: 393 (Higher omega 6), 424 (Lower omega 6)					
Heterogeneity: Tau²=0.05; Chi²=4.8, df=1(P=0.03); I²=79.17%					
Test for overall effect: Z=0.94(P=0.35)					
Test for subgroup differences: Chi²=4.76, df=1 (P=0.03), I²=78.99%					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Analysis 1.55.   Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 55 Stroke: fatal or non-fatal (overall).

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	10/1018	3/1015	■	29.21%	3.32[0.92,12.04]
MRC 1968	2/199	0/194	►	10.41%	4.88[0.24,100.89]
Sydney Diet-Heart 1978	2/221	2/237	■	19.27%	1.07[0.15,7.55]
Veterans Admin 1969	13/424	22/422	■	41.11%	0.59[0.3,1.15]
Total (95% CI)	**1862**	**1868**	◆	**100%**	**1.36[0.45,4.11]**
Total events: 27 (Higher omega 6), 27 (Lower omega 6)					
Heterogeneity: Tau²=0.65; Chi²=6.79, df=3(P=0.08); I²=55.84%					
Test for overall effect: Z=0.55(P=0.58)					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Analysis 1.56.   Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 56 Stroke - sensitivity analysis by fixed-effect analysis.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
DART 1989	10/1018	3/1015	■	10.93%	3.32[0.92,12.04]
MRC 1968	2/199	0/194	►	1.84%	4.88[0.24,100.89]
Sydney Diet-Heart 1978	2/221	2/237	■	7.02%	1.07[0.15,7.55]
Veterans Admin 1969	13/424	22/422	■	80.21%	0.59[0.3,1.15]
Total (95% CI)	**1862**	**1868**	◆	**100%**	**1[0.59,1.68]**
Total events: 27 (Higher omega 6), 27 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=6.79, df=3(P=0.08); I²=55.84%					
Test for overall effect: Z=0(P=1)					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Analysis 1.57. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 57 Stroke - sensitivity analyses.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.57.1 Low risk of bias					
Sydney Diet-Heart 1978	2/221	2/237		100%	1.07[0.15,7.55]
Subtotal (95% CI)	**221**	**237**		**100%**	**1.07[0.15,7.55]**
Total events: 2 (Higher omega 6), 2 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.07(P=0.94)					
1.57.2 Pre-2010 or prospective trials registry entry					
DART 1989	10/1018	3/1015		29.21%	3.32[0.92,12.04]
MRC 1968	2/199	0/194		10.41%	4.88[0.24,100.89]
Sydney Diet-Heart 1978	2/221	2/237		19.27%	1.07[0.15,7.55]
Veterans Admin 1969	13/424	22/422		41.11%	0.59[0.3,1.15]
Subtotal (95% CI)	**1862**	**1868**		**100%**	**1.36[0.45,4.11]**
Total events: 27 (Higher omega 6), 27 (Lower omega 6)					
Heterogeneity: Tau²=0.65; Chi²=6.79, df=3(P=0.08); I²=55.84%					
Test for overall effect: Z=0.55(P=0.58)					
1.57.3 No commercial funding					
MRC 1968	2/199	0/194		29.32%	4.88[0.24,100.89]
Sydney Diet-Heart 1978	2/221	2/237		70.68%	1.07[0.15,7.55]
Subtotal (95% CI)	**420**	**431**		**100%**	**1.67[0.32,8.62]**
Total events: 4 (Higher omega 6), 2 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.69, df=1(P=0.4); I²=0%					
Test for overall effect: Z=0.61(P=0.54)					
1.57.4 Low risk of attention bias					
Veterans Admin 1969	13/424	22/422		100%	0.59[0.3,1.15]
Subtotal (95% CI)	**424**	**422**		**100%**	**0.59[0.3,1.15]**
Total events: 13 (Higher omega 6), 22 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.55(P=0.12)					
1.57.5 Randomised 250+ participants					
DART 1989	10/1018	3/1015		29.21%	3.32[0.92,12.04]
MRC 1968	2/199	0/194		10.41%	4.88[0.24,100.89]
Sydney Diet-Heart 1978	2/221	2/237		19.27%	1.07[0.15,7.55]
Veterans Admin 1969	13/424	22/422		41.11%	0.59[0.3,1.15]
Subtotal (95% CI)	**1862**	**1868**		**100%**	**1.36[0.45,4.11]**
Total events: 27 (Higher omega 6), 27 (Lower omega 6)					
Heterogeneity: Tau²=0.65; Chi²=6.79, df=3(P=0.08); I²=55.84%					
Test for overall effect: Z=0.55(P=0.58)					
1.57.6 Randomised 100+ participants					
DART 1989	10/1018	3/1015		29.21%	3.32[0.92,12.04]
MRC 1968	2/199	0/194		10.41%	4.88[0.24,100.89]
Sydney Diet-Heart 1978	2/221	2/237		19.27%	1.07[0.15,7.55]
Veterans Admin 1969	13/424	22/422		41.11%	0.59[0.3,1.15]
Subtotal (95% CI)	**1862**	**1868**		**100%**	**1.36[0.45,4.11]**
Total events: 27 (Higher omega 6), 27 (Lower omega 6)					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0.65; Chi²=6.79, df=3(P=0.08); I²=55.84%					
Test for overall effect: Z=0.55(P=0.58)					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

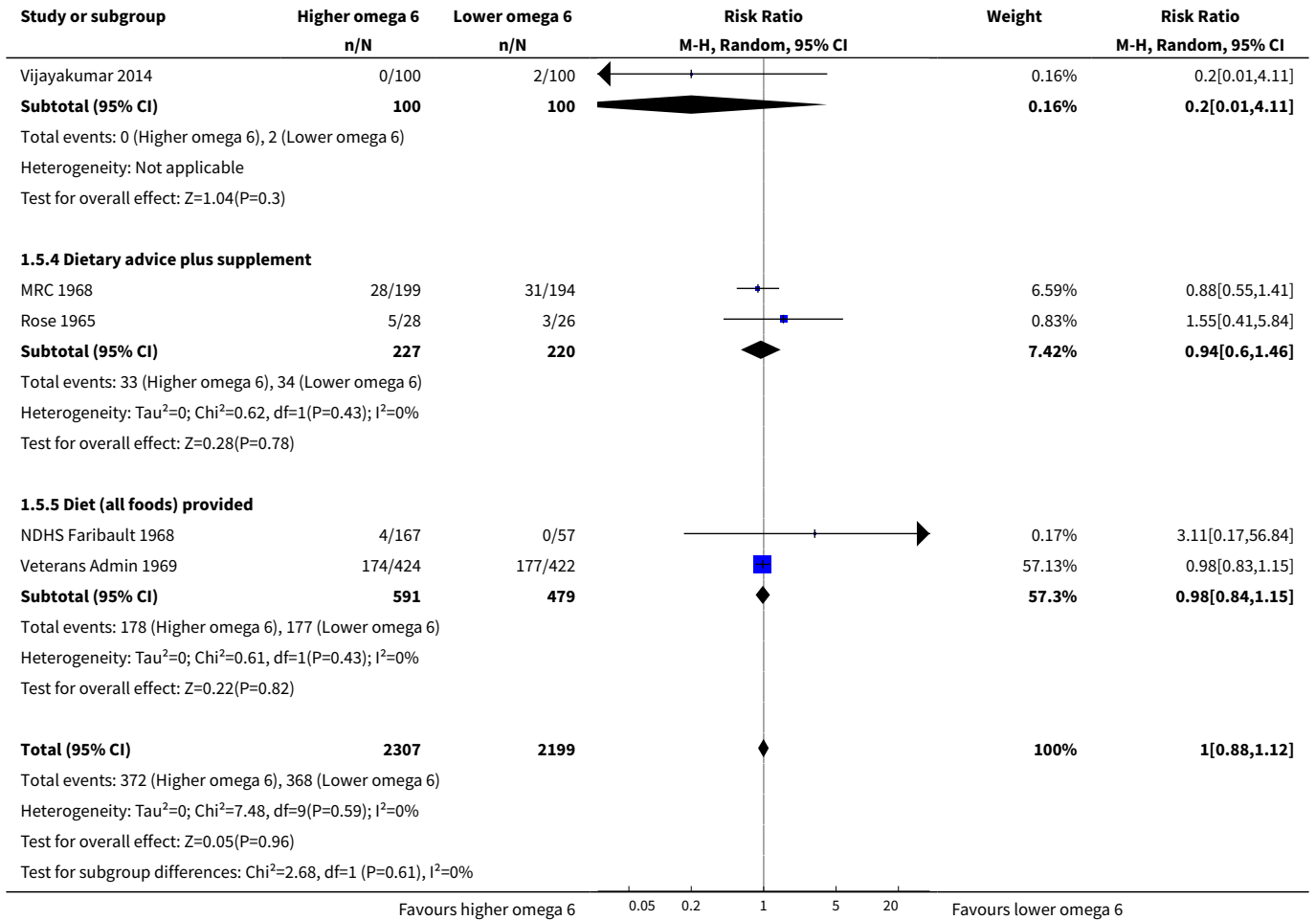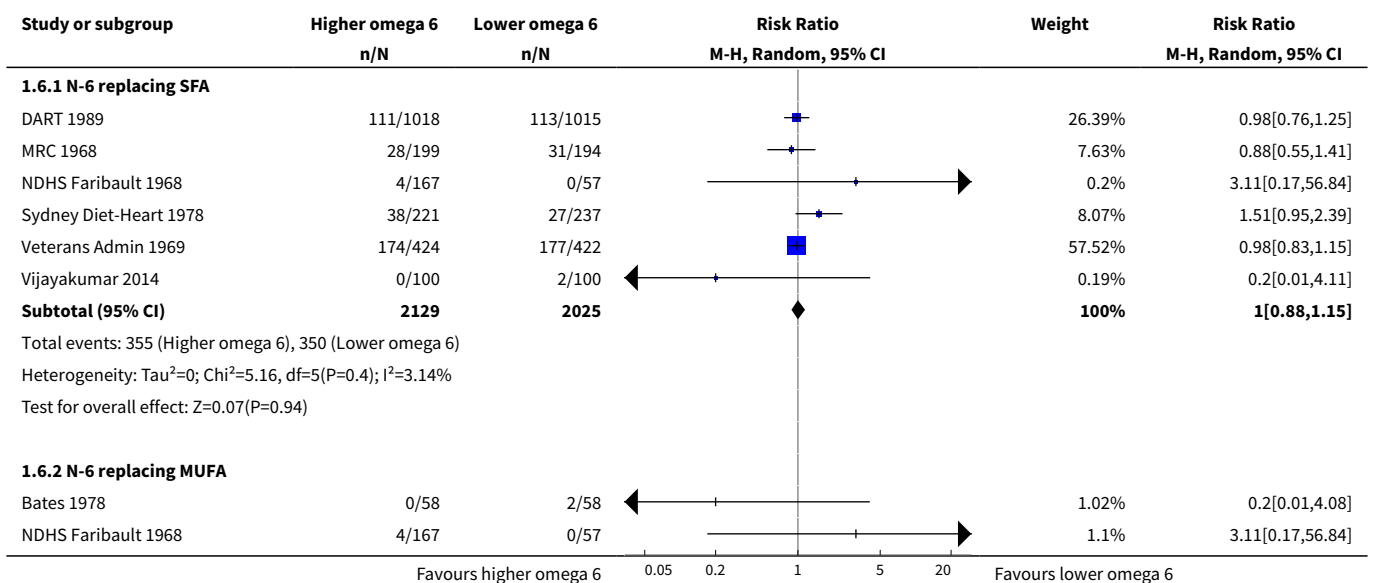## Analysis 1.58.   Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 58 Stroke - subgroup by intervention type.

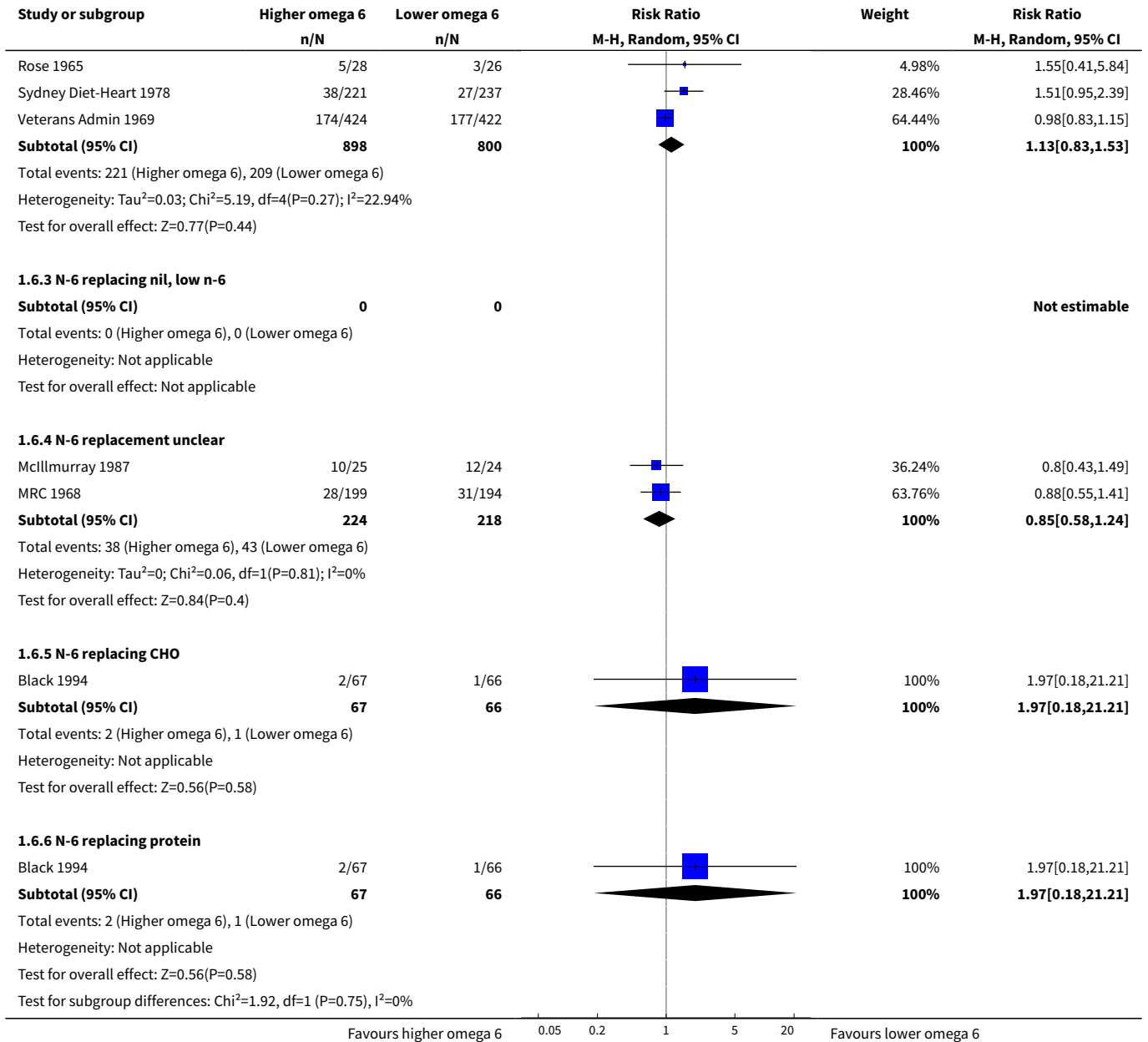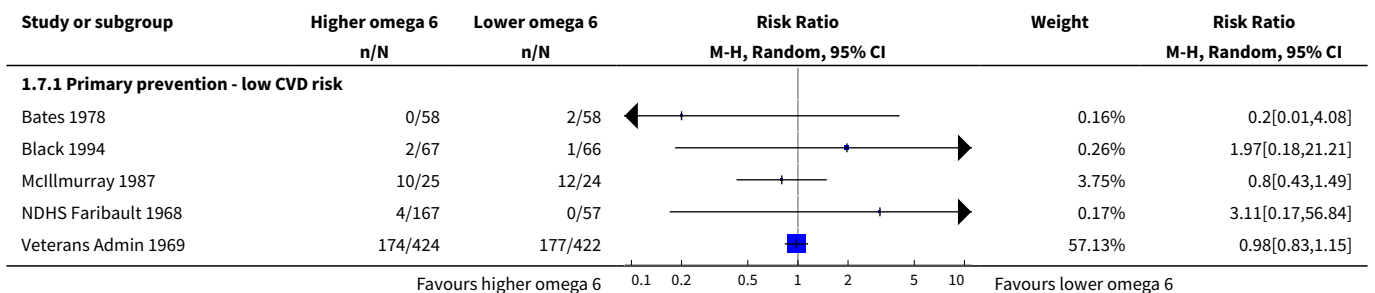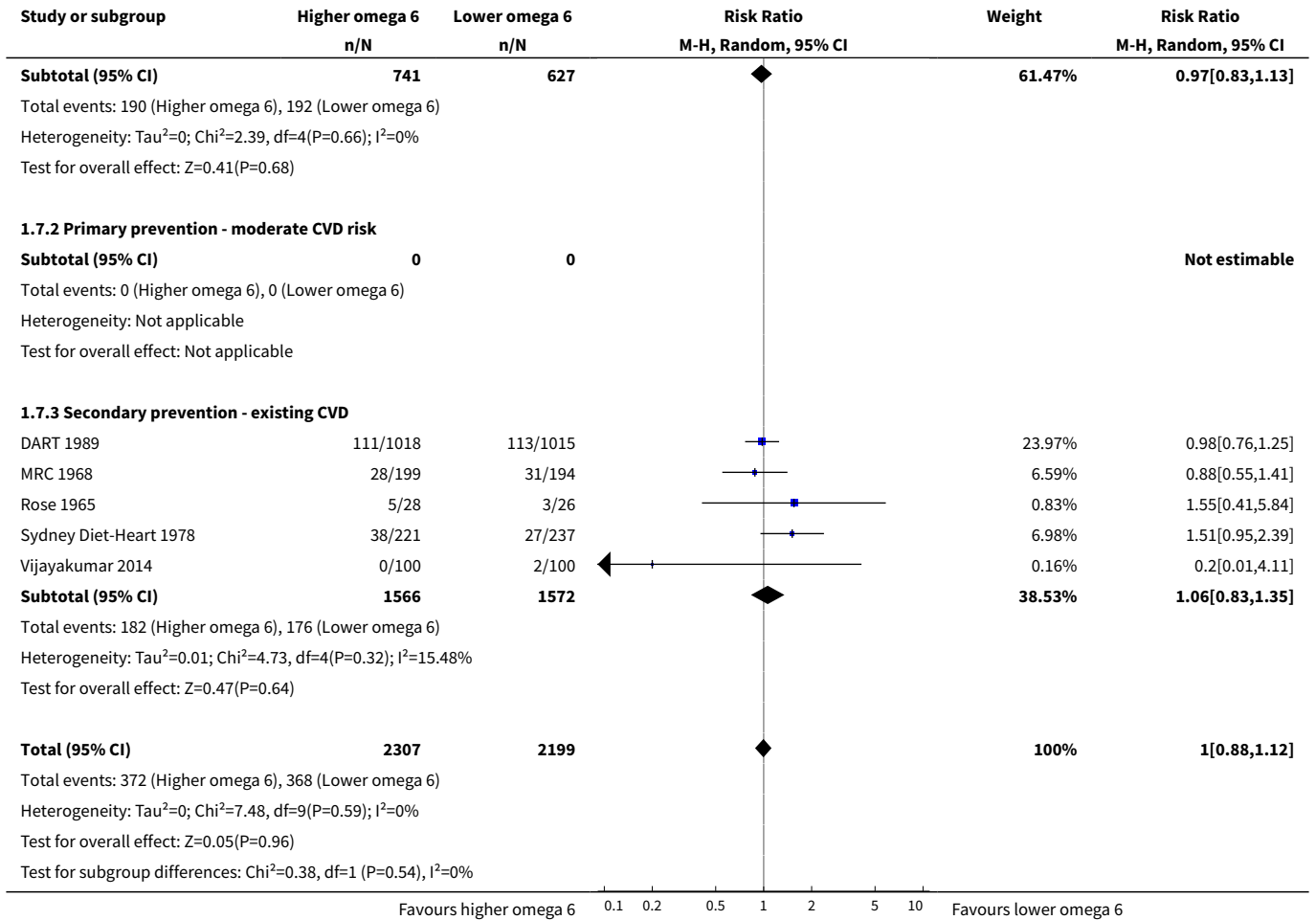| Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.58.1 Dietary advice					
DART 1989	10/1018	3/1015		29.21%	3.32[0.92,12.04]
Sydney Diet-Heart 1978	2/221	2/237		19.27%	1.07[0.15,7.55]
Subtotal (95% CI)	**1239**	**1252**		**48.48%**	**2.36[0.81,6.91]**
Total events: 12 (Higher omega 6), 5 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.9, df=1(P=0.34); I²=0%					
Test for overall effect: Z=1.57(P=0.12)					
1.58.2 Supplements (capsules)					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.58.3 Supplemental foods					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.58.4 Dietary advice plus supplement					
MRC 1968	2/199	0/194		10.41%	4.88[0.24,100.89]
Subtotal (95% CI)	**199**	**194**		**10.41%**	**4.88[0.24,100.89]**
Total events: 2 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.02(P=0.31)					
1.58.5 Diet (all foods) provided					
Veterans Admin 1969	13/424	22/422		41.11%	0.59[0.3,1.15]
Subtotal (95% CI)	**424**	**422**		**41.11%**	**0.59[0.3,1.15]**
Total events: 13 (Higher omega 6), 22 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.55(P=0.12)					
Total (95% CI)	**1862**	**1868**		**100%**	**1.36[0.45,4.11]**
Total events: 27 (Higher omega 6), 27 (Lower omega 6)					
Heterogeneity: Tau²=0.65; Chi²=6.79, df=3(P=0.08); I²=55.84%					
Test for overall effect: Z=0.55(P=0.58)					
Test for subgroup differences: Chi²=5.81, df=1 (P=0.05), I²=65.6%					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Analysis 1.59. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 59 Stroke - subgroup by replacement.
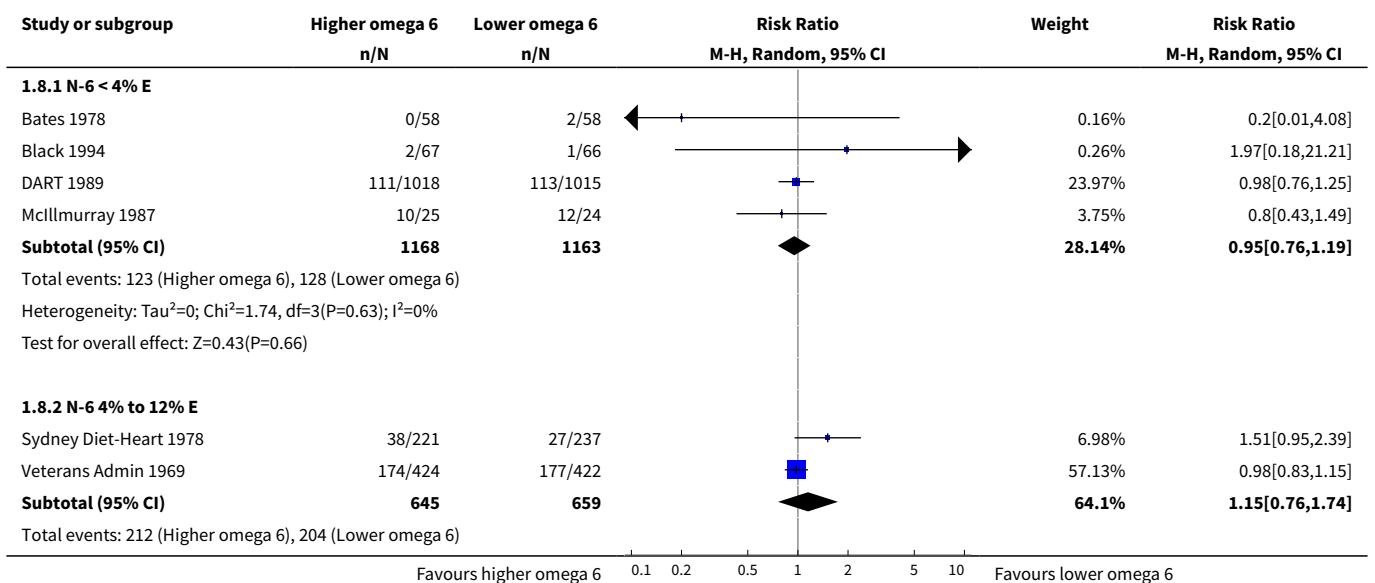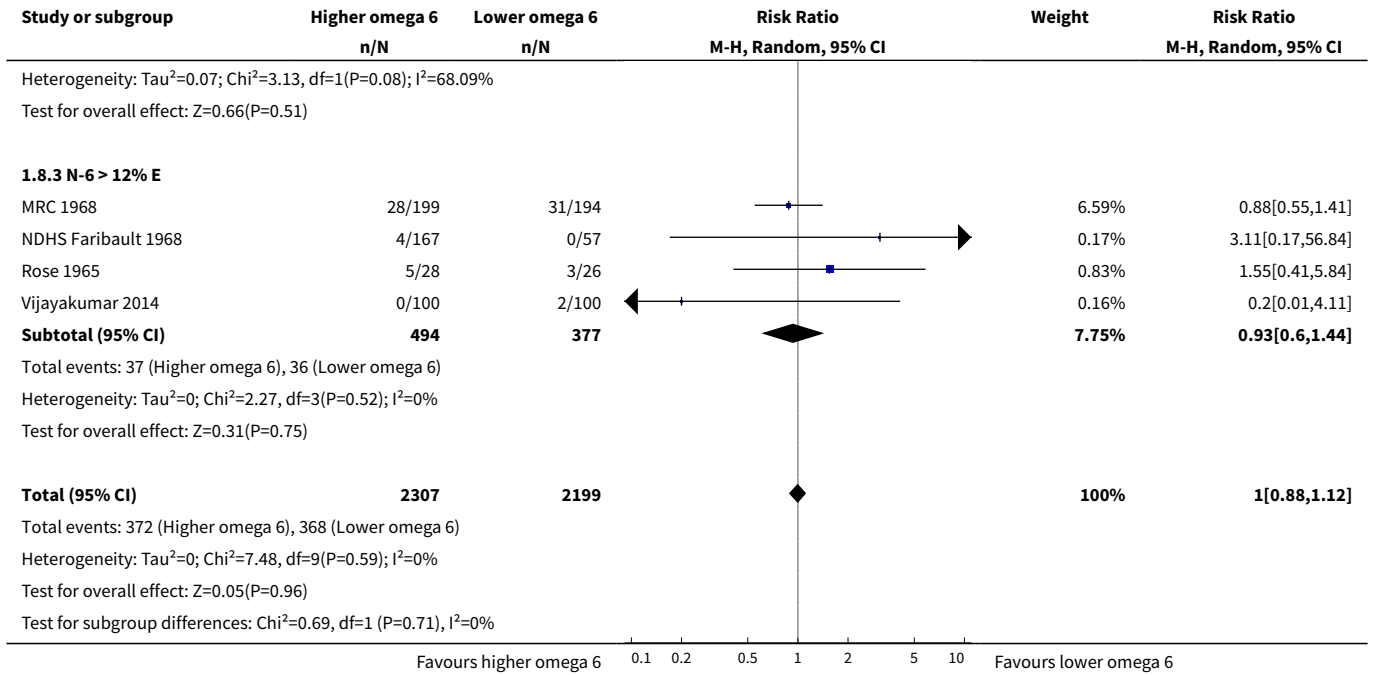
Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.59.1 N-6 replacing SFA					
DART 1989	10/1018	3/1015		29.21%	3.32[0.92,12.04]
MRC 1968	2/199	0/194		10.41%	4.88[0.24,100.89]
Sydney Diet-Heart 1978	2/221	2/237		19.27%	1.07[0.15,7.55]
Veterans Admin 1969	13/424	22/422		41.11%	0.59[0.3,1.15]
Subtotal (95% CI)	**1862**	**1868**		**100%**	**1.36[0.45,4.11]**
Total events: 27 (Higher omega 6), 27 (Lower omega 6)					
Heterogeneity: Tau²=0.65; Chi²=6.79, df=3(P=0.08); I²=55.84%					
Test for overall effect: Z=0.55(P=0.58)					
1.59.2 N-6 replacing MUFA					
Sydney Diet-Heart 1978	2/221	2/237		10.61%	1.07[0.15,7.55]
Veterans Admin 1969	13/424	22/422		89.39%	0.59[0.3,1.15]
Subtotal (95% CI)	**645**	**659**		**100%**	**0.63[0.33,1.18]**
Total events: 15 (Higher omega 6), 24 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.33, df=1(P=0.57); I²=0%					
Test for overall effect: Z=1.44(P=0.15)					
1.59.3 N-6 replacing nil, low n-6					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.59.4 N-6 replacement unclear					
MRC 1968	2/199	0/194		100%	4.88[0.24,100.89]
Subtotal (95% CI)	**199**	**194**		**100%**	**4.88[0.24,100.89]**
Total events: 2 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.02(P=0.31)					
1.59.5 N-6 replacing CHO					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.59.6 N-6 replacing protein					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Chi²=2.83, df=1 (P=0.24), I²=29.38%					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Analysis 1.60. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 60 Stroke - subgroup by baseline CVD risk.

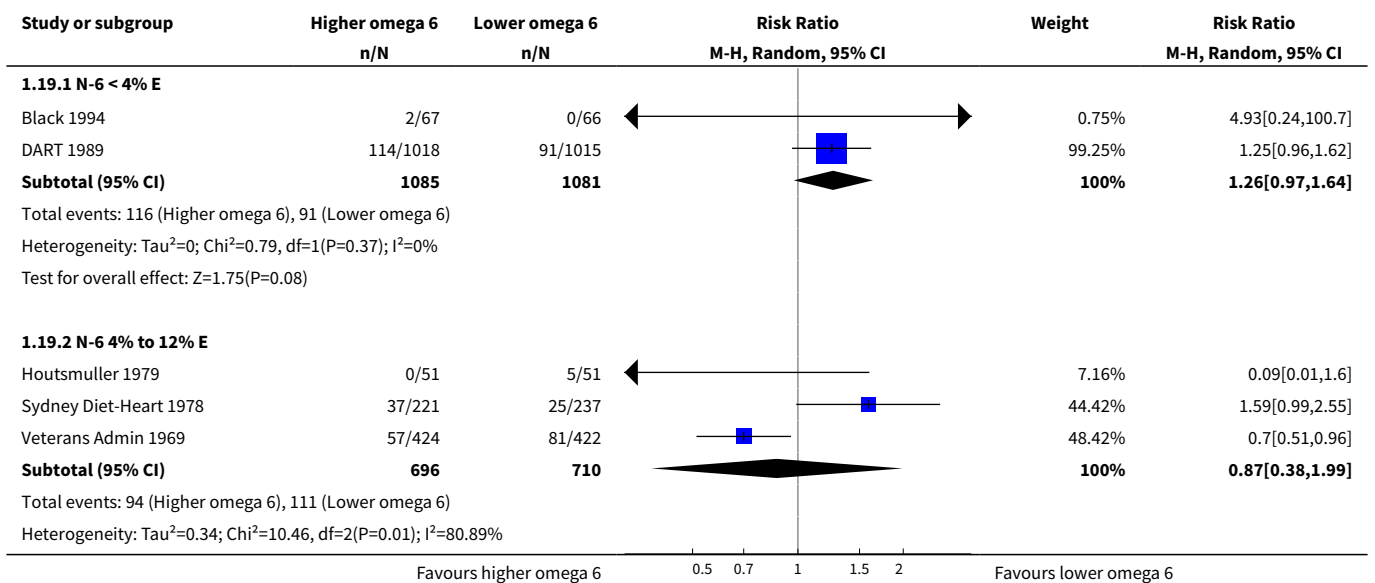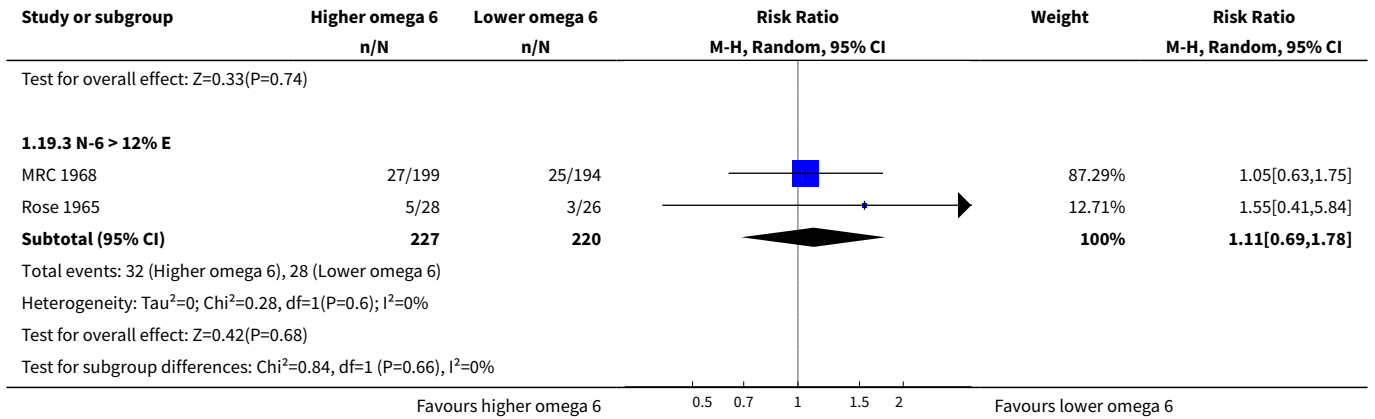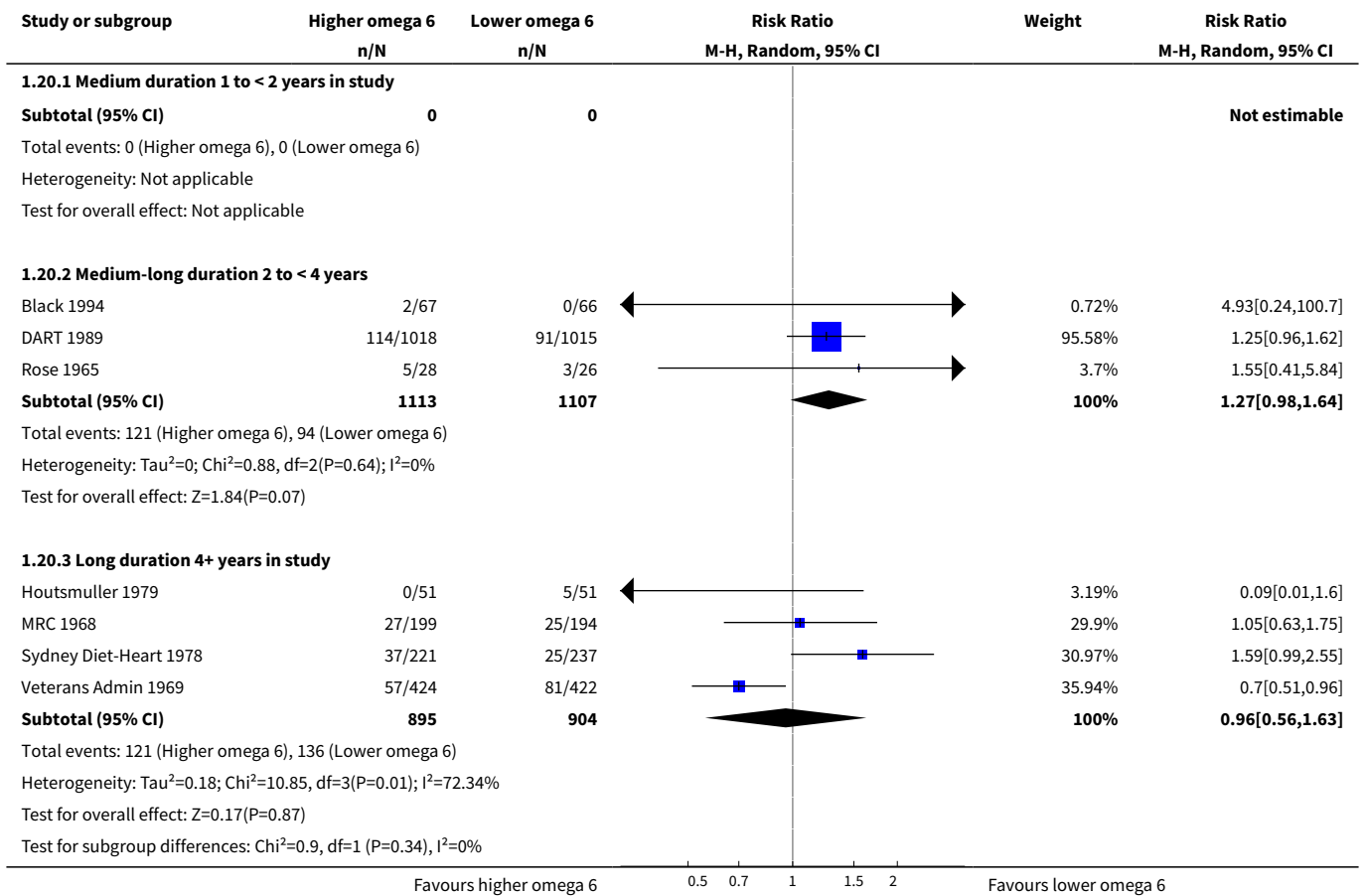| Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.60.1 Primary prevention - low CVD risk					
Veterans Admin 1969	13/424	22/422		41.11%	0.59[0.3,1.15]
Subtotal (95% CI)	**424**	**422**		**41.11%**	**0.59[0.3,1.15]**
Total events: 13 (Higher omega 6), 22 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.55(P=0.12)					
1.60.2 Primary prevention - moderate CVD risk					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.60.3 Secondary prevention - existing CVD					
DART 1989	10/1018	3/1015		29.21%	3.32[0.92,12.04]
MRC 1968	2/199	0/194		10.41%	4.88[0.24,100.89]
Sydney Diet-Heart 1978	2/221	2/237		19.27%	1.07[0.15,7.55]
Subtotal (95% CI)	**1438**	**1446**		**58.89%**	**2.56[0.93,7.04]**
Total events: 14 (Higher omega 6), 5 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=1.1, df=2(P=0.58); I²=0%					
Test for overall effect: Z=1.82(P=0.07)					
Total (95% CI)	**1862**	**1868**		**100%**	**1.36[0.45,4.11]**
Total events: 27 (Higher omega 6), 27 (Lower omega 6)					
Heterogeneity: Tau²=0.65; Chi²=6.79, df=3(P=0.08); I²=55.84%					
Test for overall effect: Z=0.55(P=0.58)					
Test for subgroup differences: Chi²=5.62, df=1 (P=0.02), I²=82.2%					

Favours higher omega 6 0.01 0.1 1 10 100 Favours lower omega 6

Analysis 1.61. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 61 Stroke - subgroup by omega-6 dose.

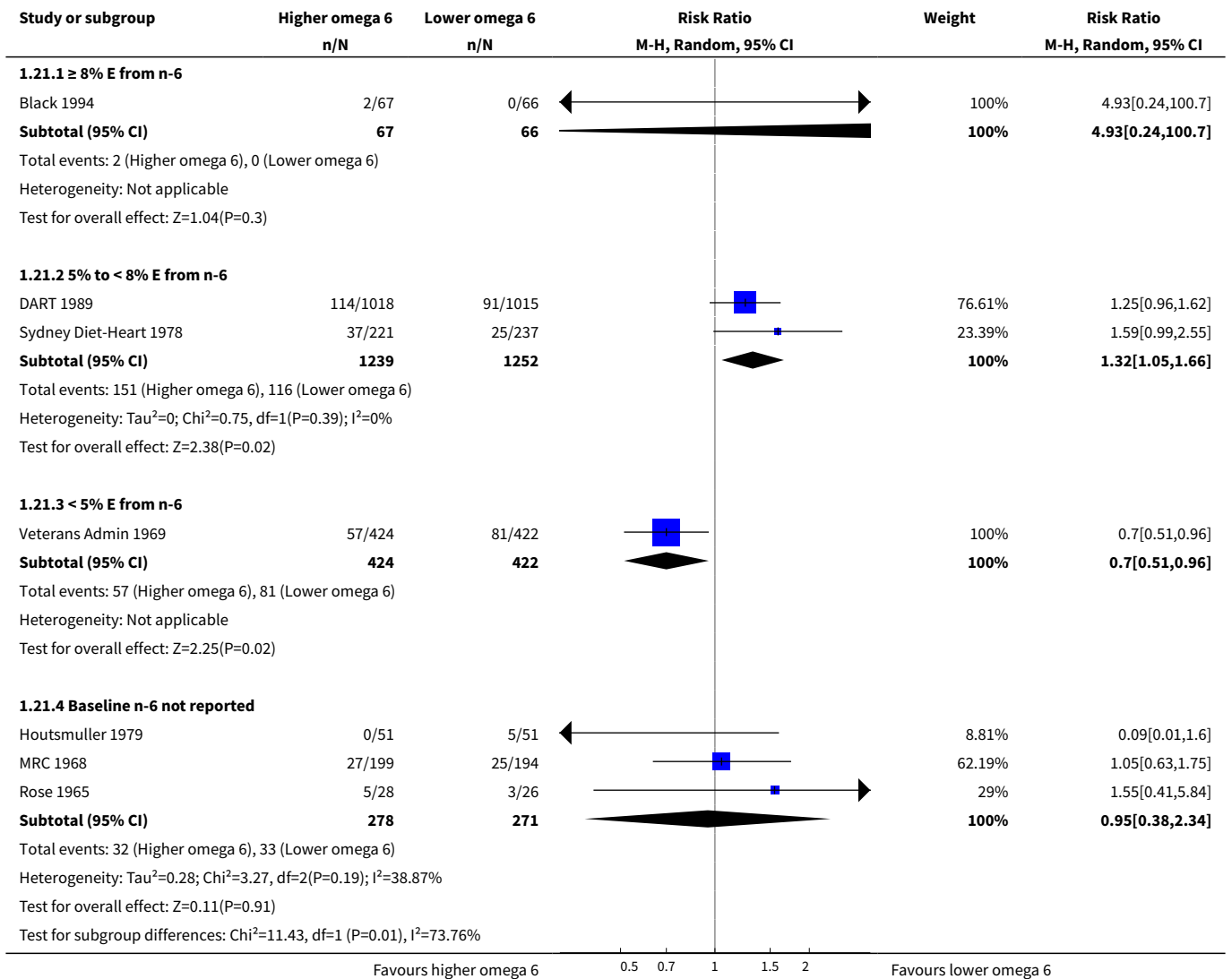| Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.61.1 N-6 < 4% E					
DART 1989	10/1018	3/1015		29.21%	3.32[0.92,12.04]
Subtotal (95% CI)	**1018**	**1015**		**29.21%**	**3.32[0.92,12.04]**
Total events: 10 (Higher omega 6), 3 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.83(P=0.07)					
1.61.2 N-6 ≥ 4% to < 12% E					
Sydney Diet-Heart 1978	2/221	2/237		19.27%	1.07[0.15,7.55]
Veterans Admin 1969	13/424	22/422		41.11%	0.59[0.3,1.15]
Subtotal (95% CI)	**645**	**659**		**60.37%**	**0.63[0.33,1.18]**
Total events: 15 (Higher omega 6), 24 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.33, df=1(P=0.57); I²=0%					

Favours higher omega 6 0.01 0.1 1 10 100 Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=1.44(P=0.15)					
1.61.3 N-6 ≥ 12% E					
MRC 1968	2/199	0/194		10.41%	4.88[0.24,100.89]
Subtotal (95% CI)	**199**	**194**		**10.41%**	**4.88[0.24,100.89]**
Total events: 2 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.02(P=0.31)					
Total (95% CI)	**1862**	**1868**		**100%**	**1.36[0.45,4.11]**
Total events: 27 (Higher omega 6), 27 (Lower omega 6)					
Heterogeneity: Tau²=0.65; Chi²=6.79, df=3(P=0.08); I²=55.84%					
Test for overall effect: Z=0.55(P=0.58)					
Test for subgroup differences: Chi²=6.39, df=1 (P=0.04), I²=68.69%					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Analysis 1.62. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 62 Stroke - subgroup by duration.
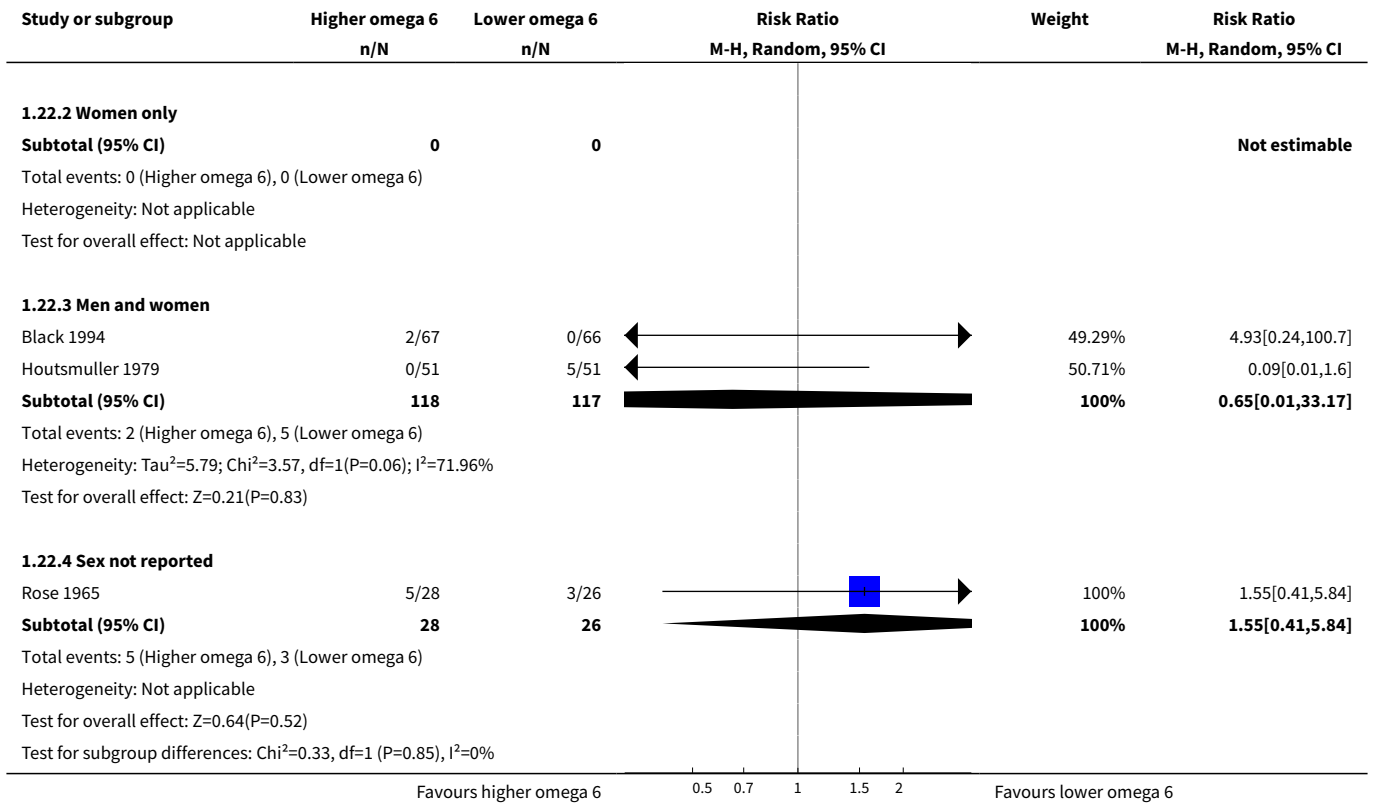
Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.62.1 Medium duration 1 to < 2 years in study					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.62.2 Medium-long duration 2 to < 4 years					
DART 1989	10/1018	3/1015		29.21%	3.32[0.92,12.04]
Subtotal (95% CI)	**1018**	**1015**		**29.21%**	**3.32[0.92,12.04]**
Total events: 10 (Higher omega 6), 3 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.83(P=0.07)					
1.62.3 Long duration 4+ years in study					
MRC 1968	2/199	0/194		10.41%	4.88[0.24,100.89]
Sydney Diet-Heart 1978	2/221	2/237		19.27%	1.07[0.15,7.55]
Veterans Admin 1969	13/424	22/422		41.11%	0.59[0.3,1.15]
Subtotal (95% CI)	**844**	**853**		**70.79%**	**0.69[0.36,1.33]**
Total events: 17 (Higher omega 6), 24 (Lower omega 6)					
Heterogeneity: Tau²=0.01; Chi²=2.03, df=2(P=0.36); I²=1.57%					
Test for overall effect: Z=1.11(P=0.27)					
Total (95% CI)	**1862**	**1868**		**100%**	**1.36[0.45,4.11]**
Total events: 27 (Higher omega 6), 27 (Lower omega 6)					
Heterogeneity: Tau²=0.65; Chi²=6.79, df=3(P=0.08); I²=55.84%					
Test for overall effect: Z=0.55(P=0.58)					
Test for subgroup differences: Chi²=4.55, df=1 (P=0.03), I²=78.01%					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Analysis 1.63.   Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 63 Stroke - subgroup by baseline omega-6.

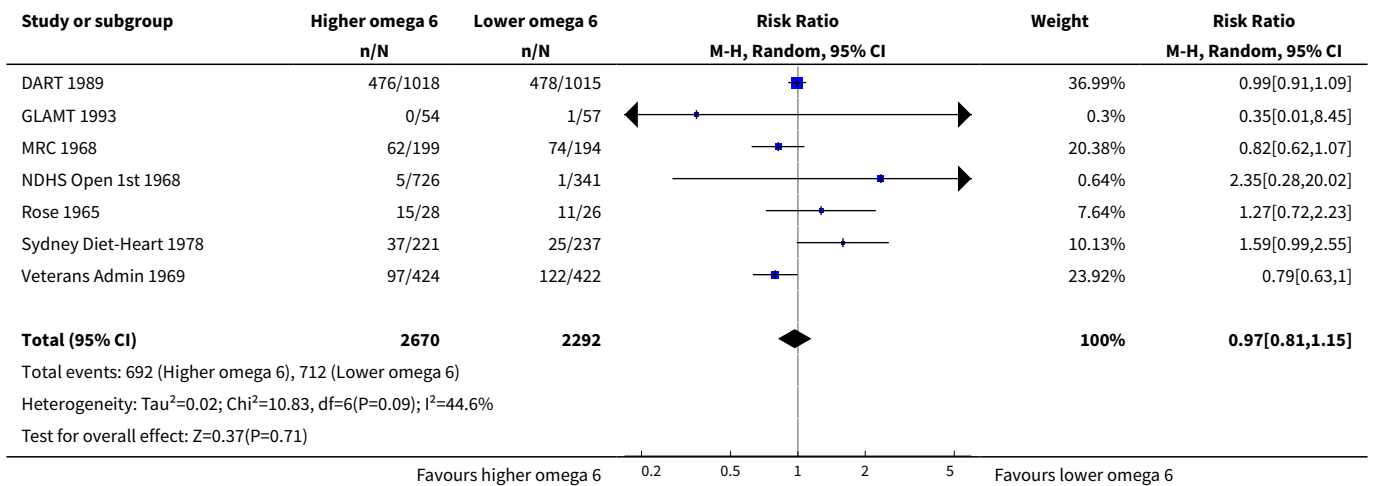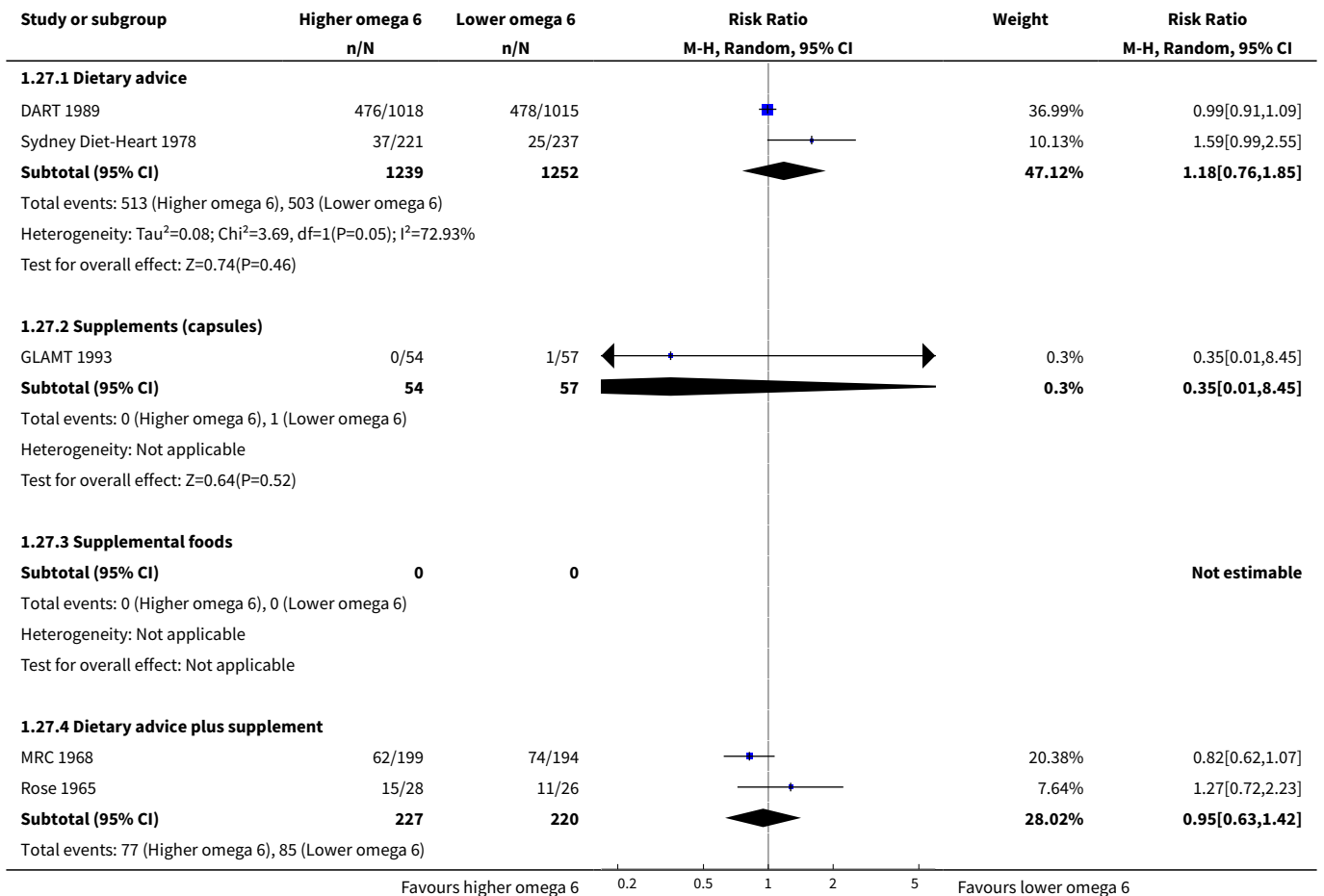| Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.63.1 ≥ 8% E from n-6					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.63.2 5% to < 8% E from n-6					
DART 1989	10/1018	3/1015		29.21%	3.32[0.92,12.04]
Sydney Diet-Heart 1978	2/221	2/237		19.27%	1.07[0.15,7.55]
Subtotal (95% CI)	**1239**	**1252**		**48.48%**	**2.36[0.81,6.91]**
Total events: 12 (Higher omega 6), 5 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.9, df=1(P=0.34); I²=0%					
Test for overall effect: Z=1.57(P=0.12)					
1.63.3 < 5% E from n-6					
Veterans Admin 1969	13/424	22/422		41.11%	0.59[0.3,1.15]
Subtotal (95% CI)	**424**	**422**		**41.11%**	**0.59[0.3,1.15]**
Total events: 13 (Higher omega 6), 22 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.55(P=0.12)					
1.63.4 Baseline n-6 not reported					
MRC 1968	2/199	0/194		10.41%	4.88[0.24,100.89]
Subtotal (95% CI)	**199**	**194**		**10.41%**	**4.88[0.24,100.89]**
Total events: 2 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.02(P=0.31)					
Total (95% CI)	**1862**	**1868**		**100%**	**1.36[0.45,4.11]**
Total events: 27 (Higher omega 6), 27 (Lower omega 6)					
Heterogeneity: Tau²=0.65; Chi²=6.79, df=3(P=0.08); I²=55.84%					
Test for overall effect: Z=0.55(P=0.58)					
Test for subgroup differences: Chi²=5.81, df=1 (P=0.05), I²=65.6%					

Favours higher omega 6 0.01 0.1 1 10 100 Favours lower omega 6

Analysis 1.64.   Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 64 Stroke - subgroup by stroke type.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.64.1 Ischaemic stroke					
DART 1989	7/1018	1/1015		43.72%	6.98[0.86,56.62]
Subtotal (95% CI)	**1018**	**1015**		**43.72%**	**6.98[0.86,56.62]**
Total events: 7 (Higher omega 6), 1 (Lower omega 6)					
Heterogeneity: Not applicable					

Favours higher omega 6 0.01 0.1 1 10 100 Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=1.82(P=0.07)					
1.64.2 Haemorrhagic stroke					
DART 1989	3/1018	2/1015		56.28%	1.5[0.25,8.93]
Subtotal (95% CI)	**1018**	**1015**		**56.28%**	**1.5[0.25,8.93]**
Total events: 3 (Higher omega 6), 2 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.44(P=0.66)					
Total (95% CI)	**2036**	**2030**		**100%**	**2.93[0.64,13.49]**
Total events: 10 (Higher omega 6), 3 (Lower omega 6)					
Heterogeneity: Tau²=0.25; Chi²=1.25, df=1(P=0.26); I²=19.96%					
Test for overall effect: Z=1.38(P=0.17)					
Test for subgroup differences: Chi²=1.2, df=1 (P=0.27), I²=16.89%					

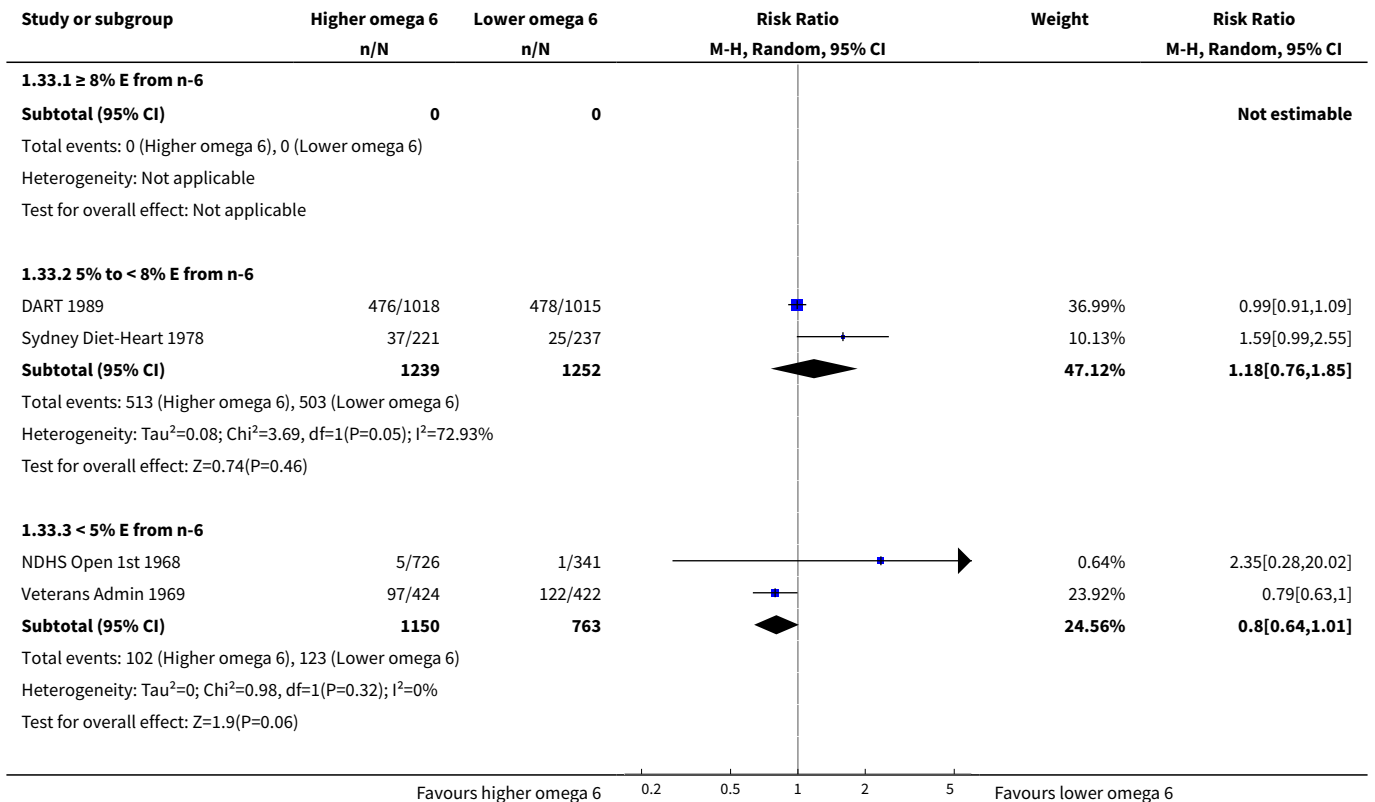Favours higher omega 6 0.01 0.1 1 10 100 Favours lower omega 6

Analysis 1.65. Comparison 1 Primary outcomes - higher omega-6 vs lower omega-6, Outcome 65 Stroke - subgroup by fatality.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.65.1 Fatal stroke					
Sydney Diet-Heart 1978	2/221	2/237		30.73%	1.07[0.15,7.55]
Veterans Admin 1969	3/424	9/422		69.27%	0.33[0.09,1.22]
Subtotal (95% CI)	**645**	**659**		**100%**	**0.48[0.16,1.4]**
Total events: 5 (Higher omega 6), 11 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.96, df=1(P=0.33); I²=0%					
Test for overall effect: Z=1.35(P=0.18)					
1.65.2 Non-fatal stroke					
Veterans Admin 1969	10/424	13/422		100%	0.77[0.34,1.73]
Subtotal (95% CI)	**424**	**422**		**100%**	**0.77[0.34,1.73]**
Total events: 10 (Higher omega 6), 13 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.64(P=0.52)					
Test for subgroup differences: Chi²=0.47, df=1 (P=0.49), I²=0%					

Favours higher omega 6 0.01 0.1 1 10 100 Favours lower omega 6

Comparison 2. Secondary outcomes - higher omega-6 vs lower omega-6

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Myocardial infarction (MI), overall	7	4606	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.76, 1.02]
2 MI - sensitivity analysis by fixed-effect analysis	7	4606	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.75, 1.00]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3 MI - sensitivity analyses	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Low summary risk of bias	1	1067	Risk Ratio (M-H, Random, 95% CI)	1.88 [0.21, 16.75]
3.2 Pre-2010 or prospective trials registry entry	7	4606	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.76, 1.02]
3.3 No commercial funding	3	1562	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.22, 2.65]
3.4 Low risk of attention bias	4	2078	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.62, 1.28]
3.5 Randomised 250+ partici-pants	4	4339	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.76, 1.02]
3.6 Randomised 100+ partici-pants	6	4552	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.75, 1.01]
4 MI - subgroup by interven-tion type	7	4606	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.76, 1.02]
4.1 Dietary advice	2	2135	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.04, 3.75]
4.2 Supplements (capsules)	1	111	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.01, 8.45]
4.3 Supplemental foods	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.4 Dietary advice plus sup-plement	2	447	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.69, 1.42]
4.5 Diet (all foods) provided	2	1913	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.56, 1.27]
5 MI - subgroup by replace-ment	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 N-6 replacing SFA	5	4441	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.75, 1.01]
5.2 N-6 replacing MUFA	3	1967	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.62, 1.30]
5.3 N-6 replacing nil, low n-6	1	111	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.01, 8.45]
5.4 N-6 replacement unclear	1	393	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.64, 1.41]
5.5 N-6 replacing CHO	1	102	Risk Ratio (M-H, Random, 95% CI)	0.08 [0.00, 1.33]
5.6 N-6 replacing protein	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 MI - subgroup by baseline CVD risk	7	4606	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.76, 1.02]
6.1 Primary prevention - low CVD risk	2	1913	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.56, 1.27]
6.2 Primary prevention - moderate CVD risk	2	213	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.02, 1.26]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.3 Secondary prevention - existing CVD	3	2480	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.77, 1.04]
7 MI - subgroup by omega-6 dose	7	4606	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.76, 1.02]
7.1 N-6 < 4% E	2	2144	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.73, 1.03]
7.2 N-6 4% to 12% E	3	2015	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.21, 2.29]
7.3 N-6 > 12% E	2	447	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.69, 1.42]
8 MI - subgroup by duration	7	4606	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.76, 1.02]
8.1 Medium duration 1 to < 2 years in study	2	1178	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.18, 6.65]
8.2 Medium-long duration 2 to < 4 years in study	2	2087	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.75, 1.04]
8.3 Long duration 4+ years in study	3	1341	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.55, 1.27]
9 MI - subgroup by statin use	7	4606	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.76, 1.02]
9.1 ≥ 50% of control group on statins	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.2 < 50% of control group on statins	6	4495	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.76, 1.02]
9.3 Statin use unclear	1	111	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.01, 8.45]
10 MI - subgroup by baseline omega-6	7	4606	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.76, 1.02]
10.1 ≥ 8% E from n-6	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10.2 5% to < 8% E from n-6	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.74, 1.04]
10.3 < 5% E from omega 6	2	1913	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.56, 1.27]
10.4 Baseline n-6 not reported	4	660	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.52, 1.57]
11 MI - subgroup by sex	7	4606	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.76, 1.02]
11.1 Men and women	2	213	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.02, 1.26]
11.2 Sex not reported	1	54	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.52, 2.74]
11.3 Men only	4	4339	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.76, 1.02]
12 Angina	4	1395	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.27, 1.40]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13 Sudden cardiac death	3	1293	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.49, 1.29]
14 Heart failure	2	2426	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.19, 2.35]
15 Revascularisation - angioplasty or coronary artery bypass grafting	1	200	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.14, 6.96]
16 Peripheral arterial disease events	3	3946	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.60, 1.70]
17 Serum total cholesterol (TC), mmol/L	10	4280	Mean Difference (IV, Random, 95% CI)	-0.33 [-0.50, -0.16]
18 TC, mmol/L - sensitivity analysis by fixed-effect analysis	10	4280	Mean Difference (IV, Fixed, 95% CI)	-0.35 [-0.41, -0.29]
19 TC, mmol/L - sensitivity analyses	10		Mean Difference (IV, Random, 95% CI)	Subtotals only
19.1 Studies at low risk of bias	3	1179	Mean Difference (IV, Random, 95% CI)	-0.54 [-0.82, -0.26]
19.2 Pre-2010 or prospective trials registry entry	9	4090	Mean Difference (IV, Random, 95% CI)	-0.38 [-0.55, -0.22]
19.3 No commercial funding	6	1506	Mean Difference (IV, Random, 95% CI)	-0.41 [-0.66, -0.16]
19.4 Low risk of attention bias	6	1834	Mean Difference (IV, Random, 95% CI)	-0.33 [-0.64, -0.02]
19.5 Randomised 250+ participants	5	3813	Mean Difference (IV, Random, 95% CI)	-0.35 [-0.47, -0.23]
19.6 Randomised 100+ participants	7	4104	Mean Difference (IV, Random, 95% CI)	-0.37 [-0.56, -0.18]
20 TC, mmol/L - subgroup by intervention type	10		Mean Difference (IV, Random, 95% CI)	Subtotals only
20.1 Dietary advice	3	2269	Mean Difference (IV, Random, 95% CI)	-0.29 [-0.38, -0.20]
20.2 Supplements (capsules)	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
20.3 Supplemental foods	1	190	Mean Difference (IV, Random, 95% CI)	0.06 [-0.22, 0.34]
20.4 Dietary advice plus supplement	3	257	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.63, 0.55]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.5 Diet (all foods) provided	3	1564	Mean Difference (IV, Random, 95% CI)	-0.58 [-0.91, -0.26]
21 TC, mmol/L - subgroup by replacement	10		Mean Difference (IV, Random, 95% CI)	Subtotals only
21.1 N-6 replacing SFA	8	4200	Mean Difference (IV, Random, 95% CI)	-0.38 [-0.56, -0.21]
21.2 N-6 replacing MUFA	5	2048	Mean Difference (IV, Random, 95% CI)	-0.51 [-0.72, -0.29]
21.3 N-6 replacing nil, low n-6	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
21.4 N-6 replacement unclear	2	231	Mean Difference (IV, Random, 95% CI)	0.16 [-0.18, 0.50]
21.5 N-6 replacing CHO	1	96	Mean Difference (IV, Random, 95% CI)	-0.47 [-0.76, -0.18]
21.6 N-6 replacing protein	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
22 TC, mmol/L - subgroup by baseline CVD risk	10		Mean Difference (IV, Random, 95% CI)	Subtotals only
22.1 Primary prevention - low CVD risk	4	1618	Mean Difference (IV, Random, 95% CI)	-0.41 [-0.77, -0.05]
22.2 Primary prevention - moderate CVD risk	1	96	Mean Difference (IV, Random, 95% CI)	-0.47 [-0.76, -0.18]
22.3 Secondary prevention - existing CVD	5	2566	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.37, -0.06]
23 TC, mmol/L - subgroup by omega-6 dose	10		Mean Difference (IV, Random, 95% CI)	Subtotals only
23.1 N-6 < 4% E	2	1769	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.49, 0.32]
23.2 N-6 4% to 12% E	4	2017	Mean Difference (IV, Random, 95% CI)	-0.42 [-0.51, -0.34]
23.3 N-6 > 12% E	4	494	Mean Difference (IV, Random, 95% CI)	-0.44 [-1.20, 0.31]
24 TC, mmol/L - subgroup by duration	10		Mean Difference (IV, Random, 95% CI)	Subtotals only
24.1 Medium duration 1 to < 2 years in study	3	775	Mean Difference (IV, Random, 95% CI)	-0.41 [-0.87, 0.04]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
24.2 Medium-long duration 2 to < 4 years	3	1931	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.43, 0.10]
24.3 Long duration 4+ years in study	4	1574	Mean Difference (IV, Random, 95% CI)	-0.36 [-0.52, -0.20]
25 TC, mmol/L - subgroup by statin use	10		Mean Difference (IV, Random, 95% CI)	Subtotals only
25.1 ≥ 50% of control group on statins	1	190	Mean Difference (IV, Random, 95% CI)	0.06 [-0.22, 0.34]
25.2 < 50% of control group on statins	9	4090	Mean Difference (IV, Random, 95% CI)	-0.38 [-0.55, -0.22]
25.3 Statin use unclear	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
26 TC, mmol/L - subgroup by baseline omega-6	10		Mean Difference (IV, Random, 95% CI)	Subtotals only
26.1 ≥ 8% E from n-6	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
26.2 5% to < 8% E from n-6	2	2173	Mean Difference (IV, Random, 95% CI)	-0.27 [-0.36, -0.17]
26.3 < 5% E from n-6	3	1564	Mean Difference (IV, Random, 95% CI)	-0.58 [-0.91, -0.26]
26.4 Baseline n-6 not report-ed	5	543	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.48, 0.21]
27 TC, mmol/L - subgroup by sex	10		Mean Difference (IV, Random, 95% CI)	Subtotals only
27.1 Men and women	3	340	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.47, 0.30]
27.2 Sex not reported	1	26	Mean Difference (IV, Random, 95% CI)	-0.49 [-1.34, 0.36]
27.3 Men only	6	3914	Mean Difference (IV, Random, 95% CI)	-0.44 [-0.63, -0.26]
28 Serum triglycerides (TG), mmol/L	5	834	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.23, 0.21]
29 Low-density lipoprotein (LDL), mmol/L	2	244	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.21, 0.14]
30 High-density lipoprotein (HDL), mmol/L	4	1995	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.02]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
31 Body weight, kg	4	358	Mean Difference (IV, Random, 95% CI)	-3.12 [-12.60, 6.36]
32 Body mass index, kg/m^2	1	371	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.56, 0.16]
33 Fat weight, kg	1	30	Mean Difference (IV, Random, 95% CI)	-7.70 [-14.60, -0.80]

Analysis 2.1. Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 1 Myocardial infarction (MI), overall.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	197/1018	225/1015		71.11%	0.87[0.74,1.04]
GLAMT 1993	0/54	1/57		0.2%	0.35[0.01,8.45]
Houtsmuller 1979	0/51	6/51		0.25%	0.08[0,1.33]
MRC 1968	39/199	40/194		13.28%	0.95[0.64,1.41]
NDHS Open 1st 1968	4/726	1/341		0.43%	1.88[0.21,16.75]
Rose 1965	9/28	7/26		2.99%	1.19[0.52,2.74]
Veterans Admin 1969	36/424	44/422		11.73%	0.81[0.54,1.24]
Total (95% CI)	**2500**	**2106**		**100%**	**0.88[0.76,1.02]**
Total events: 285 (Higher omega 6), 324 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=4.43, df=6(P=0.62); I²=0%					
Test for overall effect: Z=1.75(P=0.08)					

Favours higher omega 6   0.5 0.7 1 1.5 2   Favours lower omega 6

Analysis 2.2. Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 2 MI - sensitivity analysis by fixed-effect analysis.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
DART 1989	197/1018	225/1015		69.01%	0.87[0.74,1.04]
GLAMT 1993	0/54	1/57		0.45%	0.35[0.01,8.45]
Houtsmuller 1979	0/51	6/51		1.99%	0.08[0,1.33]
MRC 1968	39/199	40/194		12.41%	0.95[0.64,1.41]
NDHS Open 1st 1968	4/726	1/341		0.42%	1.88[0.21,16.75]
Rose 1965	9/28	7/26		2.22%	1.19[0.52,2.74]
Veterans Admin 1969	36/424	44/422		13.51%	0.81[0.54,1.24]
Total (95% CI)	**2500**	**2106**		**100%**	**0.87[0.75,1]**
Total events: 285 (Higher omega 6), 324 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=4.43, df=6(P=0.62); I²=0%					
Test for overall effect: Z=1.94(P=0.05)					

Favours higher omega 6   0.5 0.7 1 1.5 2   Favours lower omega 6

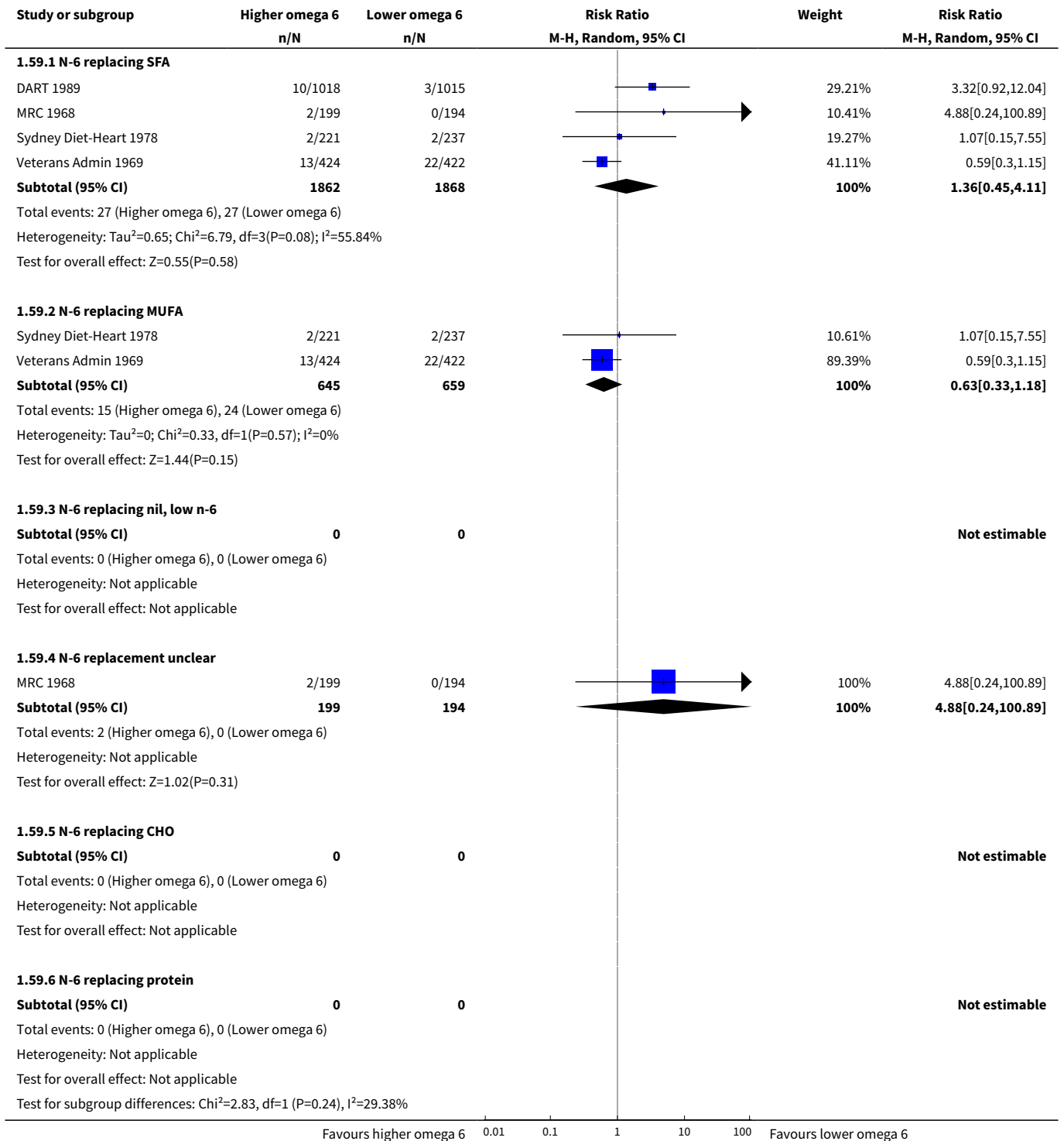## Analysis 2.3.   Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 3 MI - sensitivity analyses.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 Low summary risk of bias					
NDHS Open 1st 1968	4/726	1/341		100%	1.88[0.21,16.75]
Subtotal (95% CI)	**726**	**341**		**100%**	**1.88[0.21,16.75]**
Total events: 4 (Higher omega 6), 1 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.57(P=0.57)					
2.3.2 Pre-2010 or prospective trials registry entry					
DART 1989	197/1018	225/1015		71.11%	0.87[0.74,1.04]
GLAMT 1993	0/54	1/57		0.2%	0.35[0.01,8.45]
Houtsmuller 1979	0/51	6/51		0.25%	0.08[0,1.33]
MRC 1968	39/199	40/194		13.28%	0.95[0.64,1.41]
NDHS Open 1st 1968	4/726	1/341		0.43%	1.88[0.21,16.75]
Rose 1965	9/28	7/26		2.99%	1.19[0.52,2.74]
Veterans Admin 1969	36/424	44/422		11.73%	0.81[0.54,1.24]
Subtotal (95% CI)	**2500**	**2106**		**100%**	**0.88[0.76,1.02]**
Total events: 285 (Higher omega 6), 324 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=4.43, df=6(P=0.62); I²=0%					
Test for overall effect: Z=1.75(P=0.08)					
2.3.3 No commercial funding					
Houtsmuller 1979	0/51	6/51		15.01%	0.08[0,1.33]
MRC 1968	39/199	40/194		62.94%	0.95[0.64,1.41]
NDHS Open 1st 1968	4/726	1/341		22.05%	1.88[0.21,16.75]
Subtotal (95% CI)	**976**	**586**		**100%**	**0.76[0.22,2.65]**
Total events: 43 (Higher omega 6), 47 (Lower omega 6)					
Heterogeneity: Tau²=0.61; Chi²=3.5, df=2(P=0.17); I²=42.8%					
Test for overall effect: Z=0.43(P=0.66)					
2.3.4 Low risk of attention bias					
GLAMT 1993	0/54	1/57		1.33%	0.35[0.01,8.45]
NDHS Open 1st 1968	4/726	1/341		2.81%	1.88[0.21,16.75]
Rose 1965	9/28	7/26		19.45%	1.19[0.52,2.74]
Veterans Admin 1969	36/424	44/422		76.41%	0.81[0.54,1.24]
Subtotal (95% CI)	**1232**	**846**		**100%**	**0.89[0.62,1.28]**
Total events: 49 (Higher omega 6), 53 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=1.43, df=3(P=0.7); I²=0%					
Test for overall effect: Z=0.63(P=0.53)					
2.3.5 Randomised 250+ participants					
DART 1989	197/1018	225/1015		73.65%	0.87[0.74,1.04]
MRC 1968	39/199	40/194		13.75%	0.95[0.64,1.41]
NDHS Open 1st 1968	4/726	1/341		0.45%	1.88[0.21,16.75]
Veterans Admin 1969	36/424	44/422		12.15%	0.81[0.54,1.24]
Subtotal (95% CI)	**2367**	**1972**		**100%**	**0.88[0.76,1.02]**
Total events: 276 (Higher omega 6), 310 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.75, df=3(P=0.86); I²=0%					

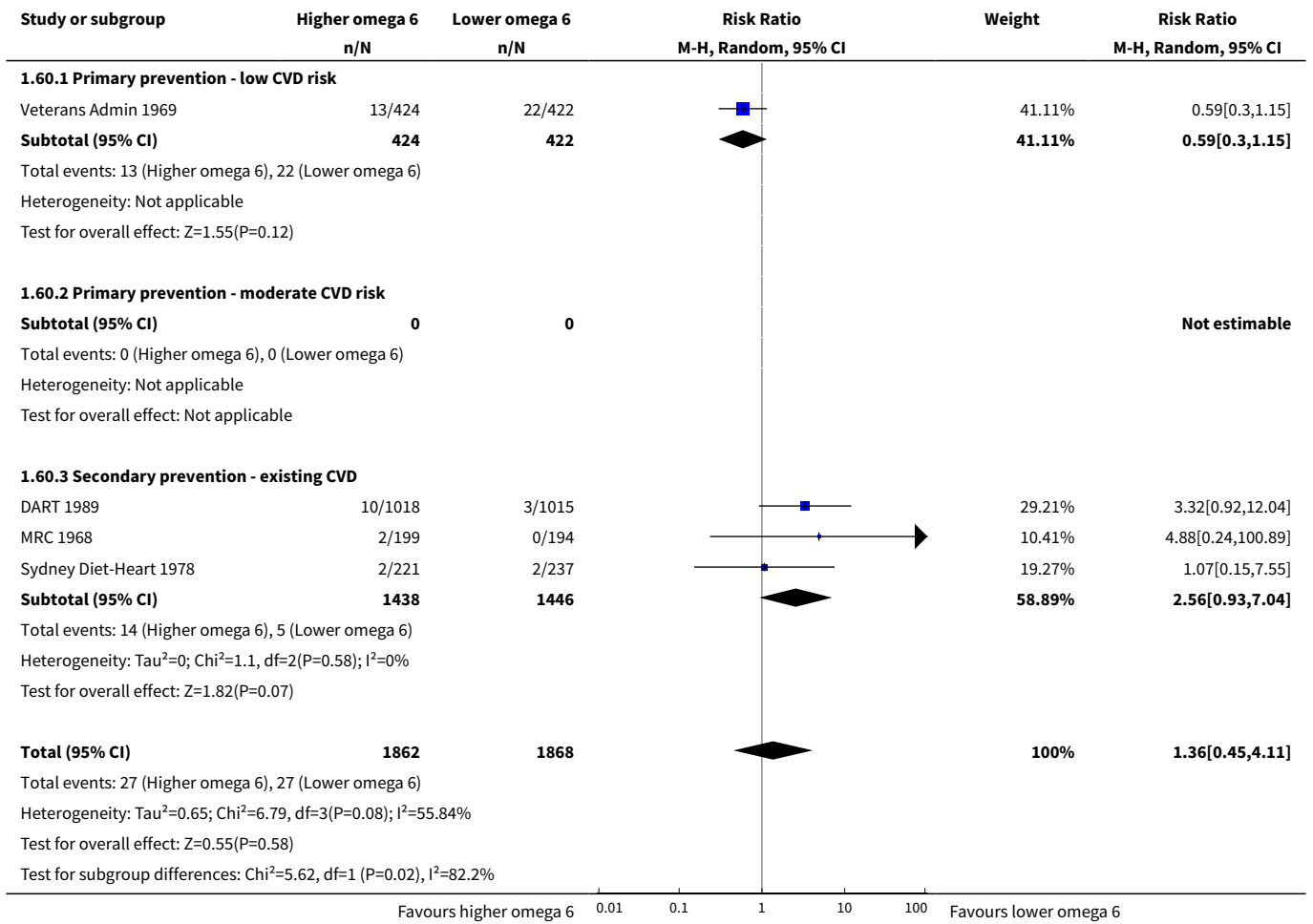Favours higher omega 6   0.05   0.2   1   5   20   Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=1.73(P=0.08)					
2.3.6 Randomised 100+ participants					
DART 1989	197/1018	225/1015		73.3%	0.87[0.74,1.04]
GLAMT 1993	0/54	1/57		0.21%	0.35[0.01,8.45]
Houtsmuller 1979	0/51	6/51		0.26%	0.08[0,1.33]
MRC 1968	39/199	40/194		13.68%	0.95[0.64,1.41]
NDHS Open 1st 1968	4/726	1/341		0.44%	1.88[0.21,16.75]
Veterans Admin 1969	36/424	44/422		12.09%	0.81[0.54,1.24]
Subtotal (95% CI)	**2472**	**2080**		**100%**	**0.87[0.75,1.01]**
Total events: 276 (Higher omega 6), 317 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=3.89, df=5(P=0.57); I²=0%					
Test for overall effect: Z=1.85(P=0.06)					

Favours higher omega 6   0.05   0.2   1   5   20   Favours lower omega 6

Analysis 2.4.   Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 4 MI - subgroup by intervention type.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.4.1 Dietary advice					
DART 1989	197/1018	225/1015		71.11%	0.87[0.74,1.04]
Houtsmuller 1979	0/51	6/51		0.25%	0.08[0,1.33]
Subtotal (95% CI)	**1069**	**1066**		**71.37%**	**0.4[0.04,3.75]**
Total events: 197 (Higher omega 6), 231 (Lower omega 6)					
Heterogeneity: Tau²=1.93; Chi²=2.82, df=1(P=0.09); I²=64.53%					
Test for overall effect: Z=0.81(P=0.42)					
2.4.2 Supplements (capsules)					
GLAMT 1993	0/54	1/57		0.2%	0.35[0.01,8.45]
Subtotal (95% CI)	**54**	**57**		**0.2%**	**0.35[0.01,8.45]**
Total events: 0 (Higher omega 6), 1 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.64(P=0.52)					
2.4.3 Supplemental foods					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
2.4.4 Dietary advice plus supplement					
MRC 1968	39/199	40/194		13.28%	0.95[0.64,1.41]
Rose 1965	9/28	7/26		2.99%	1.19[0.52,2.74]
Subtotal (95% CI)	**227**	**220**		**16.26%**	**0.99[0.69,1.42]**
Total events: 48 (Higher omega 6), 47 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.24, df=1(P=0.63); I²=0%					
Test for overall effect: Z=0.05(P=0.96)					

Favours higher omega 6   0.5   0.7   1   1.5   2   Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.4.5 Diet (all foods) provided					
NDHS Open 1st 1968	4/726	1/341		0.43%	1.88[0.21,16.75]
Veterans Admin 1969	36/424	44/422		11.73%	0.81[0.54,1.24]
Subtotal (95% CI)	**1150**	**763**		**12.16%**	**0.84[0.56,1.27]**
Total events: 40 (Higher omega 6), 45 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.54, df=1(P=0.46); I²=0%					
Test for overall effect: Z=0.84(P=0.4)					
Total (95% CI)	**2500**	**2106**		**100%**	**0.88[0.76,1.02]**
Total events: 285 (Higher omega 6), 324 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=4.43, df=6(P=0.62); I²=0%					
Test for overall effect: Z=1.75(P=0.08)					
Test for subgroup differences: Chi²=1.24, df=1 (P=0.74), I²=0%					

Favours higher omega 6   0.5 0.7 1 1.5 2   Favours lower omega 6

Analysis 2.5. Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 5 MI - subgroup by replacement.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 N-6 replacing SFA					
DART 1989	197/1018	225/1015		73.46%	0.87[0.74,1.04]
Houtsmuller 1979	0/51	6/51		0.26%	0.08[0,1.33]
MRC 1968	39/199	40/194		13.71%	0.95[0.64,1.41]
NDHS Open 1st 1968	4/726	1/341		0.45%	1.88[0.21,16.75]
Veterans Admin 1969	36/424	44/422		12.12%	0.81[0.54,1.24]
Subtotal (95% CI)	**2418**	**2023**		**100%**	**0.87[0.75,1.01]**
Total events: 276 (Higher omega 6), 316 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=3.57, df=4(P=0.47); I²=0%					
Test for overall effect: Z=1.82(P=0.07)					
2.5.2 N-6 replacing MUFA					
NDHS Open 1st 1968	4/726	1/341		2.85%	1.88[0.21,16.75]
Rose 1965	9/28	7/26		19.72%	1.19[0.52,2.74]
Veterans Admin 1969	36/424	44/422		77.44%	0.81[0.54,1.24]
Subtotal (95% CI)	**1178**	**789**		**100%**	**0.9[0.62,1.3]**
Total events: 49 (Higher omega 6), 52 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=1.1, df=2(P=0.58); I²=0%					
Test for overall effect: Z=0.56(P=0.57)					
2.5.3 N-6 replacing nil, low n-6					
GLAMT 1993	0/54	1/57		100%	0.35[0.01,8.45]
Subtotal (95% CI)	**54**	**57**		**100%**	**0.35[0.01,8.45]**
Total events: 0 (Higher omega 6), 1 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.64(P=0.52)					
2.5.4 N-6 replacement unclear					
MRC 1968	39/199	40/194		100%	0.95[0.64,1.41]

Favours higher omega 6   0.5 0.7 1 1.5 2   Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Subtotal (95% CI)	199	194		100%	0.95[0.64,1.41]
Total events: 39 (Higher omega 6), 40 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%					
Test for overall effect: Z=0.25(P=0.8)					
2.5.5 N-6 replacing CHO					
Houtsmuller 1979	0/51	6/51		100%	0.08[0,1.33]
Subtotal (95% CI)	51	51		100%	0.08[0,1.33]
Total events: 0 (Higher omega 6), 6 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.76(P=0.08)					
2.5.6 N-6 replacing protein					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Chi²=3.3, df=1 (P=0.51), I²=0%					

Favours higher omega 6   0.5 0.7 1 1.5 2   Favours lower omega 6

Analysis 2.6. Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 6 MI - subgroup by baseline CVD risk.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.6.1 Primary prevention - low CVD risk					
NDHS Open 1st 1968	4/726	1/341		0.43%	1.88[0.21,16.75]
Veterans Admin 1969	36/424	44/422		11.73%	0.81[0.54,1.24]
Subtotal (95% CI)	1150	763		12.16%	0.84[0.56,1.27]
Total events: 40 (Higher omega 6), 45 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.54, df=1(P=0.46); I²=0%					
Test for overall effect: Z=0.84(P=0.4)					
2.6.2 Primary prevention - moderate CVD risk					
GLAMT 1993	0/54	1/57		0.2%	0.35[0.01,8.45]
Houtsmuller 1979	0/51	6/51		0.25%	0.08[0,1.33]
Subtotal (95% CI)	105	108		0.46%	0.15[0.02,1.26]
Total events: 0 (Higher omega 6), 7 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.51, df=1(P=0.47); I²=0%					
Test for overall effect: Z=1.74(P=0.08)					
2.6.3 Secondary prevention - existing CVD					
DART 1989	197/1018	225/1015		71.11%	0.87[0.74,1.04]
MRC 1968	39/199	40/194		13.28%	0.95[0.64,1.41]
Rose 1965	9/28	7/26		2.99%	1.19[0.52,2.74]
Subtotal (95% CI)	1245	1235		87.38%	0.89[0.77,1.04]
Total events: 245 (Higher omega 6), 272 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.63, df=2(P=0.73); I²=0%					
Test for overall effect: Z=1.43(P=0.15)					

Favours higher omega 6   0.5 0.7 1 1.5 2   Favours lower omega 6

Study or subgroup	Higher omega 6	Lower omega 6	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Total (95% CI)	2500	2106		100%	0.88[0.76,1.02]

Total events: 285 (Higher omega 6), 324 (Lower omega 6)

Heterogeneity: Tau²=0; Chi²=4.43, df=6(P=0.62); I²=0%

Test for overall effect: Z=1.75(P=0.08)

Test for subgroup differences: Chi²=2.73, df=1 (P=0.25), I²=26.82%

Favours higher omega 6   0.5 0.7 1 1.5 2   Favours lower omega 6

Analysis 2.7. Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 7 MI - subgroup by omega-6 dose.

Study or subgroup	Higher omega 6	Lower omega 6	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
2.7.1 N-6 < 4% E					
DART 1989	197/1018	225/1015		71.11%	0.87[0.74,1.04]
GLAMT 1993	0/54	1/57		0.2%	0.35[0.01,8.45]
Subtotal (95% CI)	1072	1072		71.32%	0.87[0.73,1.03]

Total events: 197 (Higher omega 6), 226 (Lower omega 6)

Heterogeneity: Tau²=0; Chi²=0.31, df=1(P=0.58); I²=0%

Test for overall effect: Z=1.6(P=0.11)

2.7.2 N-6 4% to 12% E					
Houtsmuller 1979	0/51	6/51		0.25%	0.08[0,1.33]
NDHS Open 1st 1968	4/726	1/341		0.43%	1.88[0.21,16.75]
Veterans Admin 1969	36/424	44/422		11.73%	0.81[0.54,1.24]
Subtotal (95% CI)	1201	814		12.42%	0.7[0.21,2.29]

Total events: 40 (Higher omega 6), 51 (Lower omega 6)

Heterogeneity: Tau²=0.52; Chi²=3.28, df=2(P=0.19); I²=38.96%

Test for overall effect: Z=0.59(P=0.55)

2.7.3 N-6 > 12% E					
MRC 1968	39/199	40/194		13.28%	0.95[0.64,1.41]
Rose 1965	9/28	7/26		2.99%	1.19[0.52,2.74]
Subtotal (95% CI)	227	220		16.26%	0.99[0.69,1.42]

Total events: 48 (Higher omega 6), 47 (Lower omega 6)

Heterogeneity: Tau²=0; Chi²=0.24, df=1(P=0.63); I²=0%

Test for overall effect: Z=0.05(P=0.96)

Total (95% CI)	2500	2106		100%	0.88[0.76,1.02]

Total events: 285 (Higher omega 6), 324 (Lower omega 6)

Heterogeneity: Tau²=0; Chi²=4.43, df=6(P=0.62); I²=0%

Test for overall effect: Z=1.75(P=0.08)

Test for subgroup differences: Chi²=0.58, df=1 (P=0.75), I²=0%

Favours higher omega 6   0.5 0.7 1 1.5 2   Favours lower omega 6

Analysis 2.8. Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 8 MI - subgroup by duration.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.8.1 Medium duration 1 to < 2 years in study					
GLAMT 1993	0/54	1/57		0.2%	0.35[0.01,8.45]
NDHS Open 1st 1968	4/726	1/341		0.43%	1.88[0.21,16.75]
Subtotal (95% CI)	**780**	**398**		**0.64%**	**1.1[0.18,6.65]**
Total events: 4 (Higher omega 6), 2 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.72, df=1(P=0.39); I²=0%					
Test for overall effect: Z=0.1(P=0.92)					
2.8.2 Medium-long duration 2 to < 4 years in study					
DART 1989	197/1018	225/1015		71.11%	0.87[0.74,1.04]
Rose 1965	9/28	7/26		2.99%	1.19[0.52,2.74]
Subtotal (95% CI)	**1046**	**1041**		**74.1%**	**0.88[0.75,1.04]**
Total events: 206 (Higher omega 6), 232 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.52, df=1(P=0.47); I²=0%					
Test for overall effect: Z=1.45(P=0.15)					
2.8.3 Long duration 4+ years in study					
Houtsmuller 1979	0/51	6/51		0.25%	0.08[0,1.33]
MRC 1968	39/199	40/194		13.28%	0.95[0.64,1.41]
Veterans Admin 1969	36/424	44/422		11.73%	0.81[0.54,1.24]
Subtotal (95% CI)	**674**	**667**		**25.26%**	**0.84[0.55,1.27]**
Total events: 75 (Higher omega 6), 90 (Lower omega 6)					
Heterogeneity: Tau²=0.05; Chi²=3.17, df=2(P=0.2); I²=37%					
Test for overall effect: Z=0.83(P=0.41)					
Total (95% CI)	**2500**	**2106**		**100%**	**0.88[0.76,1.02]**
Total events: 285 (Higher omega 6), 324 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=4.43, df=6(P=0.62); I²=0%					
Test for overall effect: Z=1.75(P=0.08)					
Test for subgroup differences: Chi²=0.11, df=1 (P=0.95), I²=0%					

Favours higher omega 6   0.5   0.7   1   1.5   2   Favours lower omega 6

Analysis 2.9. Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 9 MI - subgroup by statin use.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.9.1 ≥ 50% of control group on statins					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Higher omega 6), 0 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
2.9.2 < 50% of control group on statins					
DART 1989	197/1018	225/1015		71.11%	0.87[0.74,1.04]
Houtsmuller 1979	0/51	6/51		0.25%	0.08[0,1.33]
MRC 1968	39/199	40/194		13.28%	0.95[0.64,1.41]

Favours higher omega 6   0.5   0.7   1   1.5   2   Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
NDHS Open 1st 1968	4/726	1/341		0.43%	1.88[0.21,16.75]
Rose 1965	9/28	7/26		2.99%	1.19[0.52,2.74]
Veterans Admin 1969	36/424	44/422		11.73%	0.81[0.54,1.24]
Subtotal (95% CI)	**2446**	**2049**		**99.8%**	**0.88[0.76,1.02]**

Total events: 285 (Higher omega 6), 323 (Lower omega 6)

Heterogeneity: Tau²=0; Chi²=4.1, df=5(P=0.53); I²=0%

Test for overall effect: Z=1.72(P=0.09)

2.9.3 Statin use unclear

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
GLAMT 1993	0/54	1/57		0.2%	0.35[0.01,8.45]
Subtotal (95% CI)	**54**	**57**		**0.2%**	**0.35[0.01,8.45]**

Total events: 0 (Higher omega 6), 1 (Lower omega 6)

Heterogeneity: Not applicable

Test for overall effect: Z=0.64(P=0.52)

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total (95% CI)	**2500**	**2106**		**100%**	**0.88[0.76,1.02]**

Total events: 285 (Higher omega 6), 324 (Lower omega 6)

Heterogeneity: Tau²=0; Chi²=4.43, df=6(P=0.62); I²=0%

Test for overall effect: Z=1.75(P=0.08)

Test for subgroup differences: Chi²=0.32, df=1 (P=0.57), I²=0%

Favours higher omega 6　　0.5　0.7　1　1.5　2　　Favours lower omega 6

Analysis 2.10. Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 10 MI - subgroup by baseline omega-6.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.10.1 ≥ 8% E from n-6					
Subtotal (95% CI)	**0**	**0**			**Not estimable**

Total events: 0 (Higher omega 6), 0 (Lower omega 6)

Heterogeneity: Not applicable

Test for overall effect: Not applicable

2.10.2 5% to < 8% E from n-6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	197/1018	225/1015		71.11%	0.87[0.74,1.04]
Subtotal (95% CI)	**1018**	**1015**		**71.11%**	**0.87[0.74,1.04]**

Total events: 197 (Higher omega 6), 225 (Lower omega 6)

Heterogeneity: Not applicable

Test for overall effect: Z=1.56(P=0.12)

2.10.3 < 5% E from omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
NDHS Open 1st 1968	4/726	1/341		0.43%	1.88[0.21,16.75]
Veterans Admin 1969	36/424	44/422		11.73%	0.81[0.54,1.24]
Subtotal (95% CI)	**1150**	**763**		**12.16%**	**0.84[0.56,1.27]**

Total events: 40 (Higher omega 6), 45 (Lower omega 6)

Heterogeneity: Tau²=0; Chi²=0.54, df=1(P=0.46); I²=0%

Test for overall effect: Z=0.84(P=0.4)

2.10.4 Baseline n-6 not reported

Favours higher omega 6　　0.5　0.7　1　1.5　2　　Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
GLAMT 1993	0/54	1/57		0.2%	0.35[0.01,8.45]
Houtsmuller 1979	0/51	6/51		0.25%	0.08[0,1.33]
MRC 1968	39/199	40/194		13.28%	0.95[0.64,1.41]
Rose 1965	9/28	7/26		2.99%	1.19[0.52,2.74]
Subtotal (95% CI)	**332**	**328**		**16.72%**	**0.9[0.52,1.57]**

Total events: 48 (Higher omega 6), 54 (Lower omega 6)

Heterogeneity: Tau²=0.08; Chi²=3.88, df=3(P=0.28); I²=22.6%

Test for overall effect: Z=0.36(P=0.72)

Total (95% CI)	**2500**	**2106**		**100%**	**0.88[0.76,1.02]**

Total events: 285 (Higher omega 6), 324 (Lower omega 6)

Heterogeneity: Tau²=0; Chi²=4.43, df=6(P=0.62); I²=0%

Test for overall effect: Z=1.75(P=0.08)

Test for subgroup differences: Chi²=0.05, df=1 (P=0.98), I²=0%

Favours higher omega 6   0.5 0.7 1 1.5 2   Favours lower omega 6

Analysis 2.11. Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 11 MI - subgroup by sex.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.11.1 Men and women					
GLAMT 1993	0/54	1/57		0.2%	0.35[0.01,8.45]
Houtsmuller 1979	0/51	6/51		0.25%	0.08[0,1.33]
Subtotal (95% CI)	**105**	**108**		**0.46%**	**0.15[0.02,1.26]**

Total events: 0 (Higher omega 6), 7 (Lower omega 6)

Heterogeneity: Tau²=0; Chi²=0.51, df=1(P=0.47); I²=0%

Test for overall effect: Z=1.74(P=0.08)

2.11.2 Sex not reported					
Rose 1965	9/28	7/26		2.99%	1.19[0.52,2.74]
Subtotal (95% CI)	**28**	**26**		**2.99%**	**1.19[0.52,2.74]**

Total events: 9 (Higher omega 6), 7 (Lower omega 6)

Heterogeneity: Not applicable

Test for overall effect: Z=0.42(P=0.68)

2.11.3 Men only					
DART 1989	197/1018	225/1015		71.11%	0.87[0.74,1.04]
MRC 1968	39/199	40/194		13.28%	0.95[0.64,1.41]
NDHS Open 1st 1968	4/726	1/341		0.43%	1.88[0.21,16.75]
Veterans Admin 1969	36/424	44/422		11.73%	0.81[0.54,1.24]
Subtotal (95% CI)	**2367**	**1972**		**96.55%**	**0.88[0.76,1.02]**

Total events: 276 (Higher omega 6), 310 (Lower omega 6)

Heterogeneity: Tau²=0; Chi²=0.75, df=3(P=0.86); I²=0%

Test for overall effect: Z=1.73(P=0.08)

Total (95% CI)	**2500**	**2106**		**100%**	**0.88[0.76,1.02]**

Total events: 285 (Higher omega 6), 324 (Lower omega 6)

Heterogeneity: Tau²=0; Chi²=4.43, df=6(P=0.62); I²=0%

Favours higher omega 6   0.5 0.7 1 1.5 2   Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=1.75(P=0.08)					
Test for subgroup differences: Chi²=3.16, df=1 (P=0.21), I²=36.69%					

Favours higher omega 6   0.5 0.7 1 1.5 2   Favours lower omega 6

Analysis 2.12. Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 12 Angina.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Houtsmuller 1979	8/51	24/51		38.28%	0.33[0.17,0.67]
MRC 1968	1/199	4/194		11.36%	0.24[0.03,2.16]
Rose 1965	3/28	2/26		16.32%	1.39[0.25,7.68]
Veterans Admin 1969	11/424	10/422		34.03%	1.09[0.47,2.55]
Total (95% CI)	**702**	**693**		**100%**	**0.61[0.27,1.4]**
Total events: 23 (Higher omega 6), 40 (Lower omega 6)					
Heterogeneity: Tau²=0.34; Chi²=6.18, df=3(P=0.1); I²=51.45%					
Test for overall effect: Z=1.17(P=0.24)					

Favours higher omega 6   0.01 0.1 1 10 100   Favours lower omega 6

Analysis 2.13. Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 13 Sudden cardiac death.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
MRC 1968	8/199	7/194		23.41%	1.11[0.41,3.01]
Rose 1965	3/28	2/26		7.95%	1.39[0.25,7.68]
Veterans Admin 1969	18/424	27/422		68.65%	0.66[0.37,1.19]
Total (95% CI)	**651**	**642**		**100%**	**0.79[0.49,1.29]**
Total events: 29 (Higher omega 6), 36 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=1.23, df=2(P=0.54); I²=0%					
Test for overall effect: Z=0.94(P=0.35)					

Favours higher omega 6   0.01 0.1 1 10 100   Favours lower omega 6

Analysis 2.14. Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 14 Heart failure.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	3/1018	6/1015		84.21%	0.5[0.13,1.99]
MRC 1968	1/199	0/194		15.79%	2.93[0.12,71.37]
Total (95% CI)	**1217**	**1209**		**100%**	**0.66[0.19,2.35]**
Total events: 4 (Higher omega 6), 6 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=1, df=1(P=0.32); I²=0%					

Favours higher omega 6   0.01 0.1 1 10 100   Favours lower omega 6

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=0.64(P=0.52)					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Analysis 2.15. Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 15 Revascularisation - angioplasty or coronary artery bypass grafting.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Vijayakumar 2014	2/100	2/100		100%	1[0.14,6.96]
Total (95% CI)	**100**	**100**		**100%**	**1[0.14,6.96]**
Total events: 2 (Higher omega 6), 2 (Lower omega 6)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Analysis 2.16. Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 16 Peripheral arterial disease events.

Study or subgroup	Higher omega 6 n/N	Lower omega 6 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	0/1018	1/1015		2.62%	0.33[0.01,8.15]
NDHS Open 1st 1968	1/726	0/341		2.62%	1.41[0.06,34.55]
Veterans Admin 1969	26/424	25/422		94.75%	1.04[0.61,1.76]
Total (95% CI)	**2168**	**1778**		**100%**	**1.01[0.6,1.7]**
Total events: 27 (Higher omega 6), 26 (Lower omega 6)					
Heterogeneity: Tau²=0; Chi²=0.51, df=2(P=0.77); I²=0%					
Test for overall effect: Z=0.05(P=0.96)					

Favours higher omega 6   0.01   0.1   1   10   100   Favours lower omega 6

Analysis 2.17. Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 17 Serum total cholesterol (TC), mmol/L.

Study or subgroup	Higher omega 6 N	Mean(SD)	Lower omega 6 N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
DART 1989	855	6.3 (1.1)	860	6.6 (1.1)		15.38%	-0.26[-0.37,-0.15]
Houtsmuller 1979	48	6.4 (0.7)	48	6.9 (0.8)		11%	-0.47[-0.76,-0.18]
Mendis 2001	26	-0.4 (0.5)	28	-0.6 (0.7)		9.91%	0.16[-0.18,0.5]
MRC 1968	88	-1.1 (0)	89	-0.5 (0)			Not estimable
NDHS Faribault 1968	50	-1.1 (0.7)	51	-0.2 (0.6)		11.86%	-0.91[-1.17,-0.65]
NDHS Open 1st 1968	311	-0.7 (0.7)	309	-0.2 (0.6)		15.45%	-0.45[-0.55,-0.35]
Rose 1965	13	-0.5 (1.3)	13	-0 (0.9)		3.22%	-0.49[-1.34,0.36]
Sydney Diet-Heart 1978	221	6.5 (1.2)	237	6.8 (1.1)		13.06%	-0.3[-0.51,-0.09]

Favours higher omega 6   -2   -1   0   1   2   Favours lower omega 6

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Study or subgroup	Higher omega 6		Lower omega 6		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Veterans Admin 1969	423	4.9 (3.7)	420	5.3 (1.9)		8.66%	-0.37[-0.77,0.03]
Vijayakumar 2014	94	3.9 (1.2)	96	3.9 (0.7)		11.45%	0.06[-0.22,0.34]
Total ***	2129		2151			100%	-0.33[-0.5,-0.16]

Heterogeneity: Tau²=0.05; Chi²=42.56, df=8(P<0.0001); I²=81.2%

Test for overall effect: Z=3.84(P=0)

Favours higher omega 6   -2   -1   0   1   2   Favours lower omega 6

Analysis 2.18. Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 18 TC, mmol/L - sensitivity analysis by fixed-effect analysis.

Study or subgroup	Higher omega 6		Lower omega 6		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
DART 1989	855	6.3 (1.1)	860	6.6 (1.1)		33.9%	-0.26[-0.37,-0.15]
Houtsmuller 1979	48	6.4 (0.7)	48	6.9 (0.8)		4.38%	-0.47[-0.76,-0.18]
Mendis 2001	26	-0.4 (0.5)	28	-0.6 (0.7)		3.27%	0.16[-0.18,0.5]
MRC 1968	88	-1.1 (0)	89	-0.5 (0)			Not estimable
NDHS Faribault 1968	50	-1.1 (0.7)	51	-0.2 (0.6)		5.62%	-0.91[-1.17,-0.65]
NDHS Open 1st 1968	311	-0.7 (0.7)	309	-0.2 (0.6)		36.47%	-0.45[-0.55,-0.35]
Rose 1965	13	-0.5 (1.3)	13	-0 (0.9)		0.52%	-0.49[-1.34,0.36]
Sydney Diet-Heart 1978	221	6.5 (1.2)	237	6.8 (1.1)		8.46%	-0.3[-0.51,-0.09]
Veterans Admin 1969	423	4.9 (3.7)	420	5.3 (1.9)		2.4%	-0.37[-0.77,0.03]
Vijayakumar 2014	94	3.9 (1.2)	96	3.9 (0.7)		4.97%	0.06[-0.22,0.34]
Total ***	2129		2151			100%	-0.35[-0.41,-0.29]

Heterogeneity: Tau²=0; Chi²=42.56, df=8(P<0.0001); I²=81.2%

Test for overall effect: Z=11.24(P<0.0001)

Favours higher omega 6   -2   -1   0   1   2   Favours lower omega 6

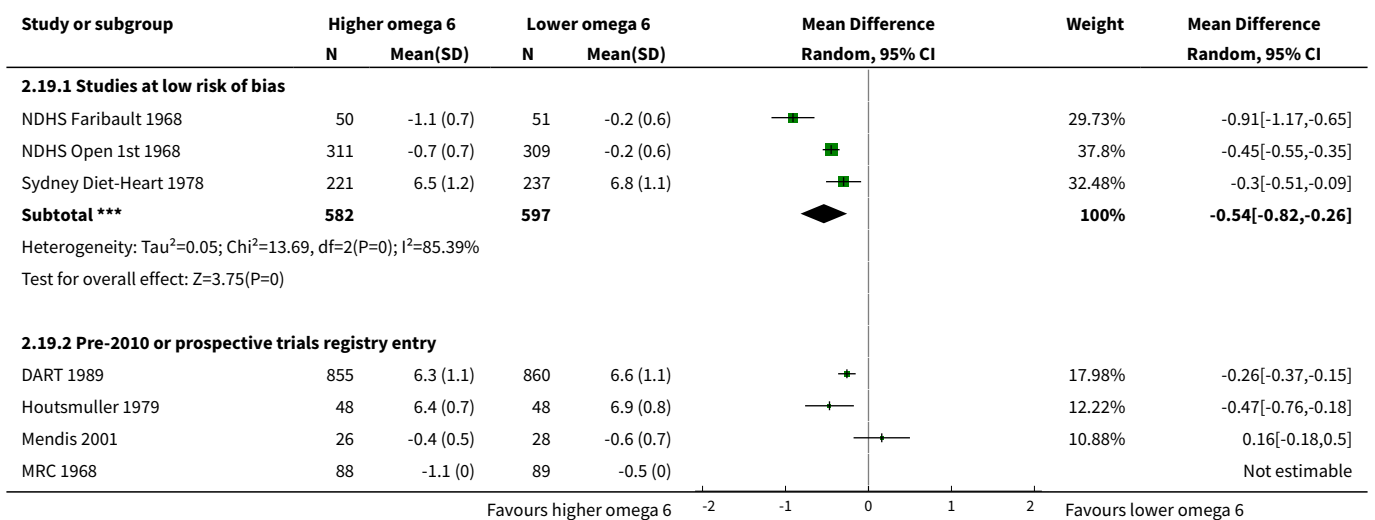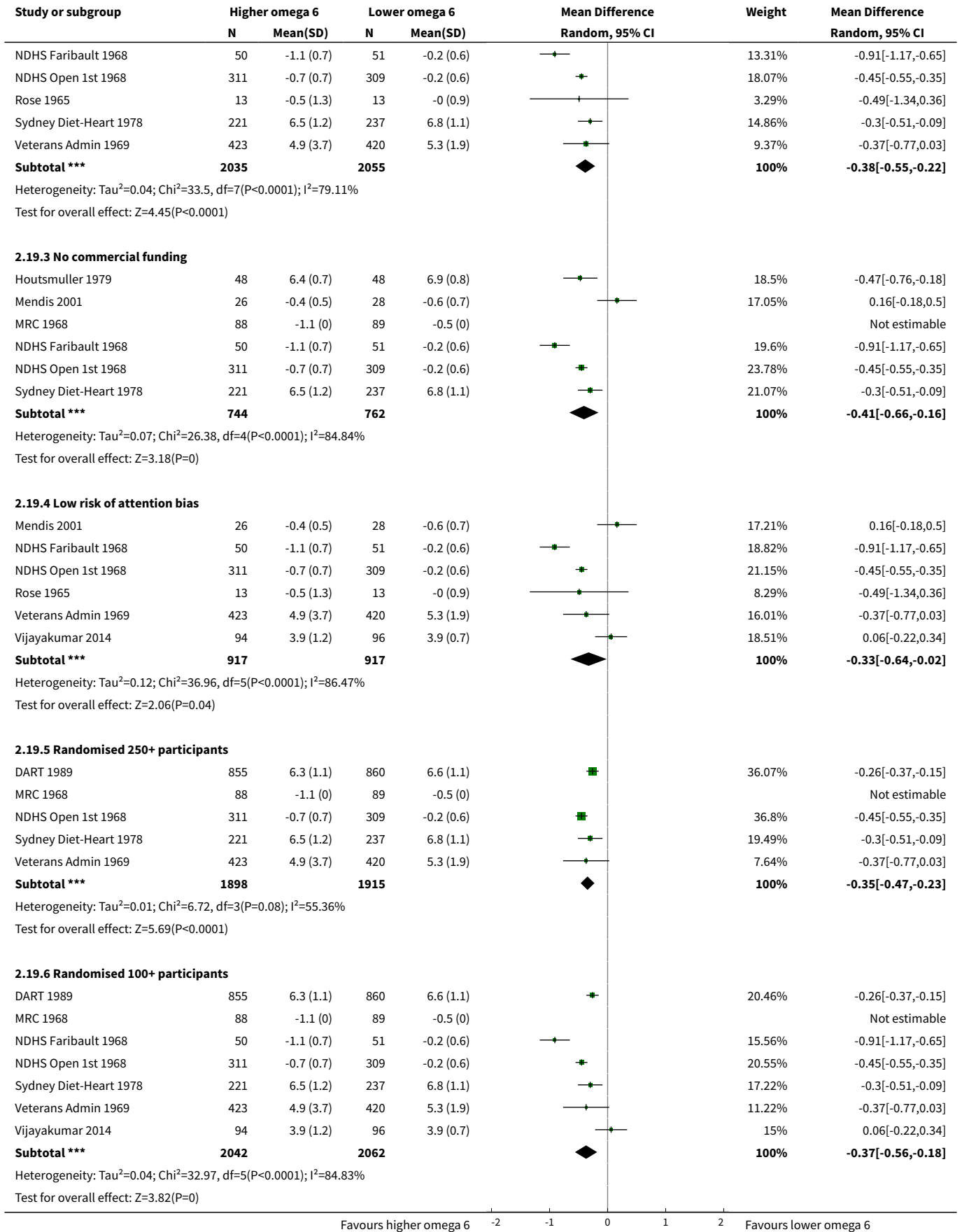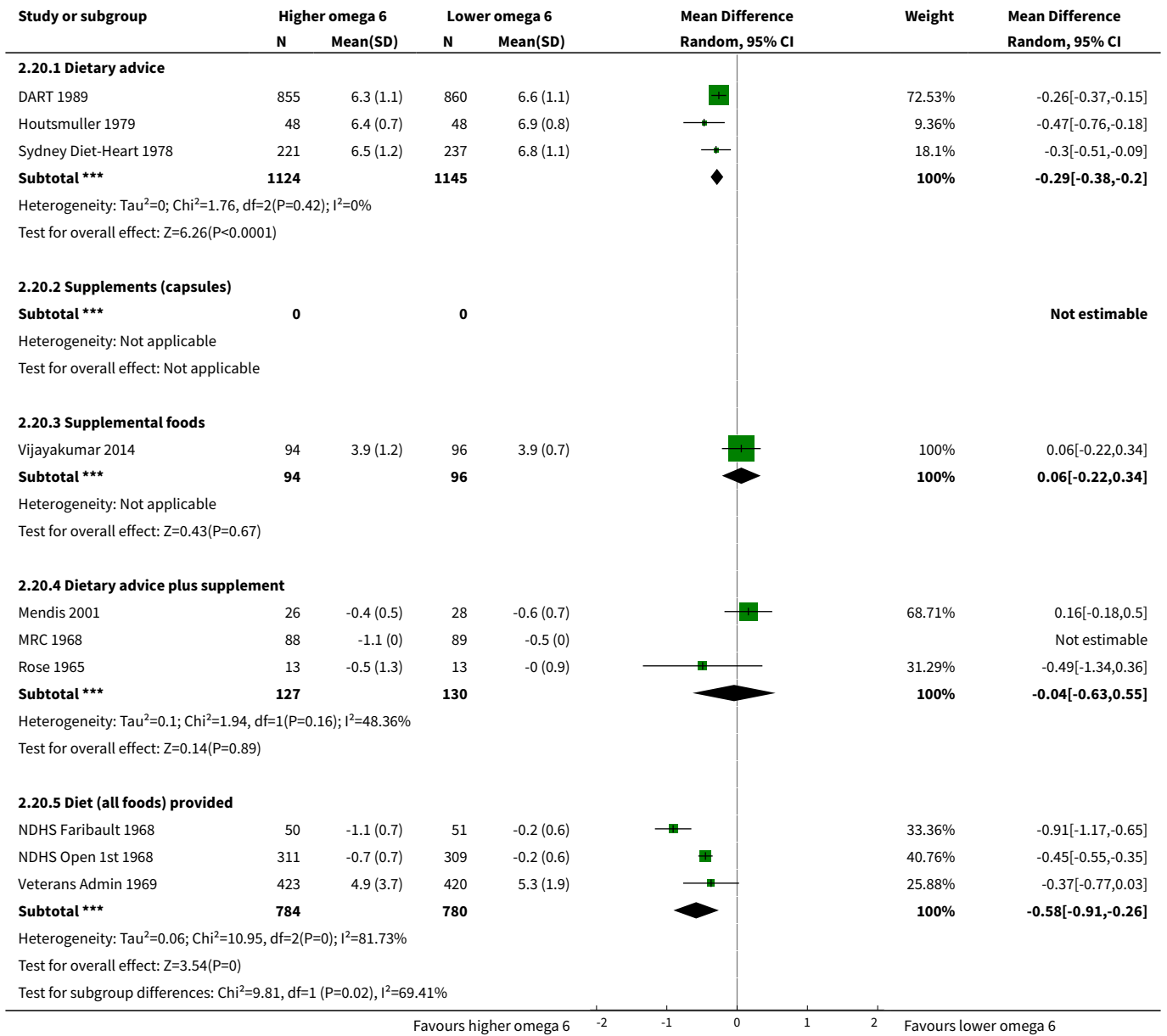### Analysis 2.19. Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 19 TC, mmol/L - sensitivity analyses.

Study or subgroup	Higher omega 6		Lower omega 6		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
2.19.1 Studies at low risk of bias							
NDHS Faribault 1968	50	-1.1 (0.7)	51	-0.2 (0.6)		29.73%	-0.91[-1.17,-0.65]
NDHS Open 1st 1968	311	-0.7 (0.7)	309	-0.2 (0.6)		37.8%	-0.45[-0.55,-0.35]
Sydney Diet-Heart 1978	221	6.5 (1.2)	237	6.8 (1.1)		32.48%	-0.3[-0.51,-0.09]
Subtotal ***	582		597			100%	-0.54[-0.82,-0.26]

Heterogeneity: Tau²=0.05; Chi²=13.69, df=2(P=0); I²=85.39%

Test for overall effect: Z=3.75(P=0)

2.19.2 Pre-2010 or prospective trials registry entry							
DART 1989	855	6.3 (1.1)	860	6.6 (1.1)		17.98%	-0.26[-0.37,-0.15]
Houtsmuller 1979	48	6.4 (0.7)	48	6.9 (0.8)		12.22%	-0.47[-0.76,-0.18]
Mendis 2001	26	-0.4 (0.5)	28	-0.6 (0.7)		10.88%	0.16[-0.18,0.5]
MRC 1968	88	-1.1 (0)	89	-0.5 (0)			Not estimable

Favours higher omega 6   -2   -1   0   1   2   Favours lower omega 6

Study or subgroup	Higher omega 6		Lower omega 6		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
NDHS Faribault 1968	50	-1.1 (0.7)	51	-0.2 (0.6)		13.31%	-0.91[-1.17,-0.65]
NDHS Open 1st 1968	311	-0.7 (0.7)	309	-0.2 (0.6)		18.07%	-0.45[-0.55,-0.35]
Rose 1965	13	-0.5 (1.3)	13	-0 (0.9)		3.29%	-0.49[-1.34,0.36]
Sydney Diet-Heart 1978	221	6.5 (1.2)	237	6.8 (1.1)		14.86%	-0.3[-0.51,-0.09]
Veterans Admin 1969	423	4.9 (3.7)	420	5.3 (1.9)		9.37%	-0.37[-0.77,0.03]
Subtotal ***	**2035**		**2055**			**100%**	**-0.38[-0.55,-0.22]**

Heterogeneity: Tau²=0.04; Chi²=33.5, df=7(P<0.0001); I²=79.11%

Test for overall effect: Z=4.45(P<0.0001)

2.19.3 No commercial funding

Houtsmuller 1979	48	6.4 (0.7)	48	6.9 (0.8)		18.5%	-0.47[-0.76,-0.18]
Mendis 2001	26	-0.4 (0.5)	28	-0.6 (0.7)		17.05%	0.16[-0.18,0.5]
MRC 1968	88	-1.1 (0)	89	-0.5 (0)			Not estimable
NDHS Faribault 1968	50	-1.1 (0.7)	51	-0.2 (0.6)		19.6%	-0.91[-1.17,-0.65]
NDHS Open 1st 1968	311	-0.7 (0.7)	309	-0.2 (0.6)		23.78%	-0.45[-0.55,-0.35]
Sydney Diet-Heart 1978	221	6.5 (1.2)	237	6.8 (1.1)		21.07%	-0.3[-0.51,-0.09]
Subtotal ***	**744**		**762**			**100%**	**-0.41[-0.66,-0.16]**

Heterogeneity: Tau²=0.07; Chi²=26.38, df=4(P<0.0001); I²=84.84%

Test for overall effect: Z=3.18(P=0)

2.19.4 Low risk of attention bias

Mendis 2001	26	-0.4 (0.5)	28	-0.6 (0.7)		17.21%	0.16[-0.18,0.5]
NDHS Faribault 1968	50	-1.1 (0.7)	51	-0.2 (0.6)		18.82%	-0.91[-1.17,-0.65]
NDHS Open 1st 1968	311	-0.7 (0.7)	309	-0.2 (0.6)		21.15%	-0.45[-0.55,-0.35]
Rose 1965	13	-0.5 (1.3)	13	-0 (0.9)		8.29%	-0.49[-1.34,0.36]
Veterans Admin 1969	423	4.9 (3.7)	420	5.3 (1.9)		16.01%	-0.37[-0.77,0.03]
Vijayakumar 2014	94	3.9 (1.2)	96	3.9 (0.7)		18.51%	0.06[-0.22,0.34]
Subtotal ***	**917**		**917**			**100%**	**-0.33[-0.64,-0.02]**

Heterogeneity: Tau²=0.12; Chi²=36.96, df=5(P<0.0001); I²=86.47%

Test for overall effect: Z=2.06(P=0.04)

2.19.5 Randomised 250+ participants

DART 1989	855	6.3 (1.1)	860	6.6 (1.1)		36.07%	-0.26[-0.37,-0.15]
MRC 1968	88	-1.1 (0)	89	-0.5 (0)			Not estimable
NDHS Open 1st 1968	311	-0.7 (0.7)	309	-0.2 (0.6)		36.8%	-0.45[-0.55,-0.35]
Sydney Diet-Heart 1978	221	6.5 (1.2)	237	6.8 (1.1)		19.49%	-0.3[-0.51,-0.09]
Veterans Admin 1969	423	4.9 (3.7)	420	5.3 (1.9)		7.64%	-0.37[-0.77,0.03]
Subtotal ***	**1898**		**1915**			**100%**	**-0.35[-0.47,-0.23]**

Heterogeneity: Tau²=0.01; Chi²=6.72, df=3(P=0.08); I²=55.36%

Test for overall effect: Z=5.69(P<0.0001)

2.19.6 Randomised 100+ participants

DART 1989	855	6.3 (1.1)	860	6.6 (1.1)		20.46%	-0.26[-0.37,-0.15]
MRC 1968	88	-1.1 (0)	89	-0.5 (0)			Not estimable
NDHS Faribault 1968	50	-1.1 (0.7)	51	-0.2 (0.6)		15.56%	-0.91[-1.17,-0.65]
NDHS Open 1st 1968	311	-0.7 (0.7)	309	-0.2 (0.6)		20.55%	-0.45[-0.55,-0.35]
Sydney Diet-Heart 1978	221	6.5 (1.2)	237	6.8 (1.1)		17.22%	-0.3[-0.51,-0.09]
Veterans Admin 1969	423	4.9 (3.7)	420	5.3 (1.9)		11.22%	-0.37[-0.77,0.03]
Vijayakumar 2014	94	3.9 (1.2)	96	3.9 (0.7)		15%	0.06[-0.22,0.34]
Subtotal ***	**2042**		**2062**			**100%**	**-0.37[-0.56,-0.18]**

Heterogeneity: Tau²=0.04; Chi²=32.97, df=5(P<0.0001); I²=84.83%

Test for overall effect: Z=3.82(P=0)

Favours higher omega 6   -2 -1 0 1 2   Favours lower omega 6

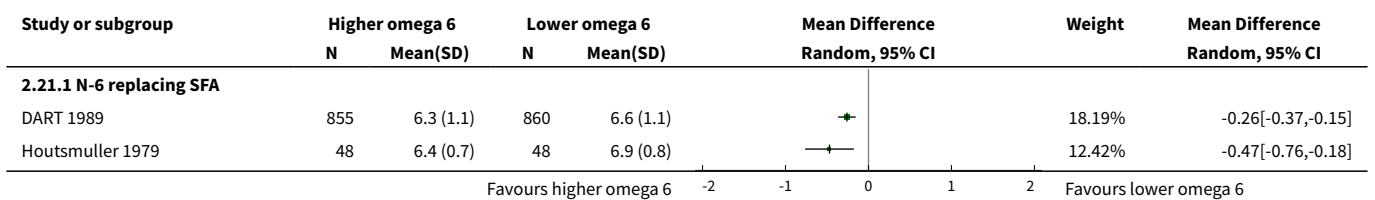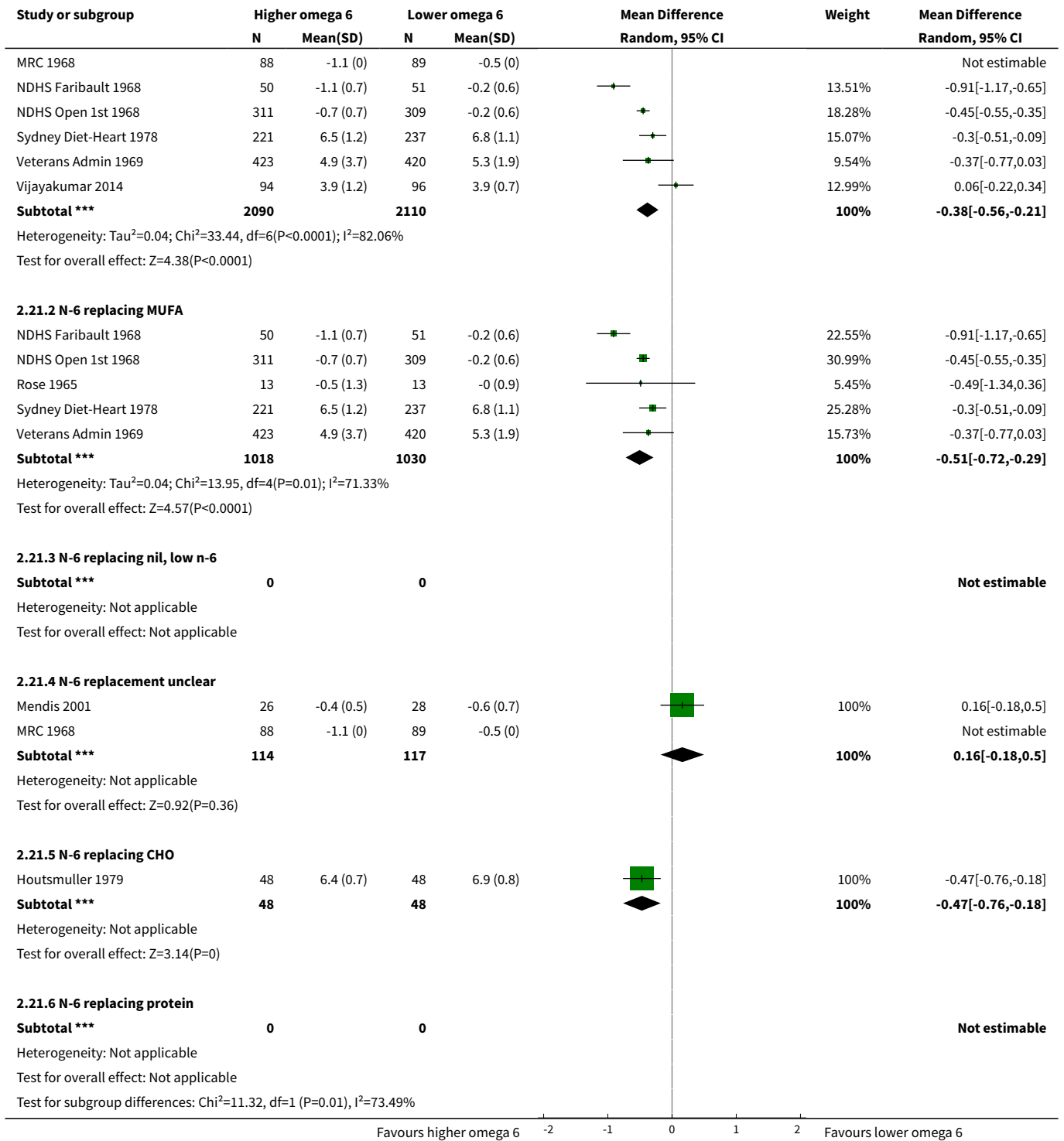## Analysis 2.20. Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 20 TC, mmol/L - subgroup by intervention type.

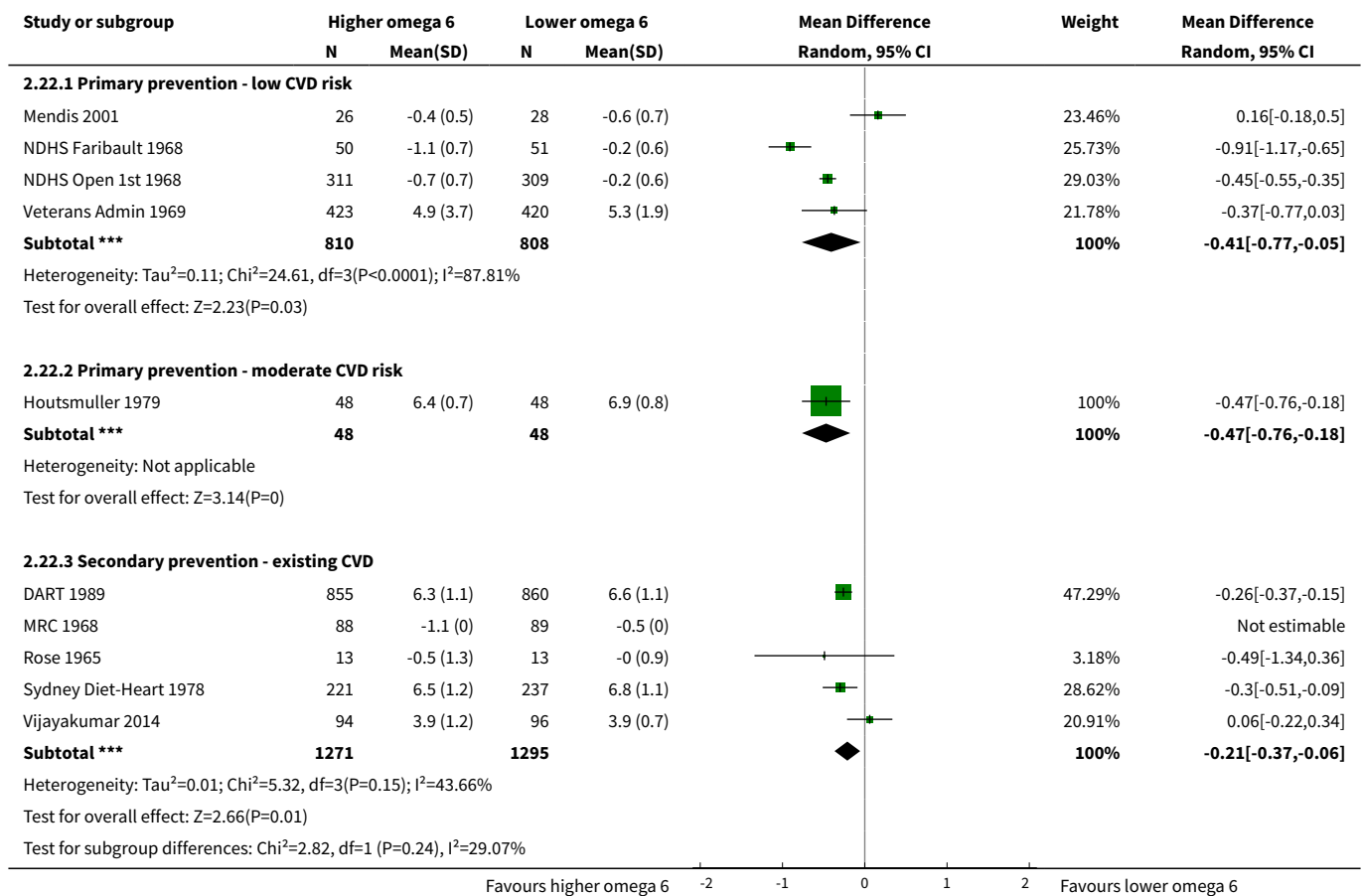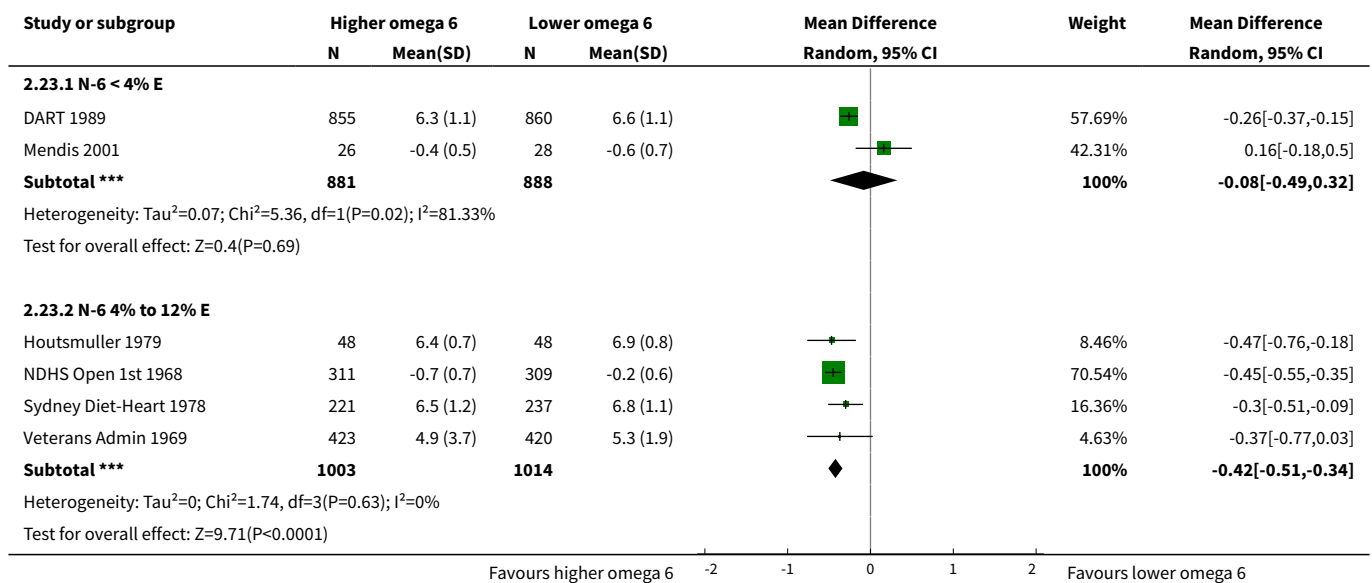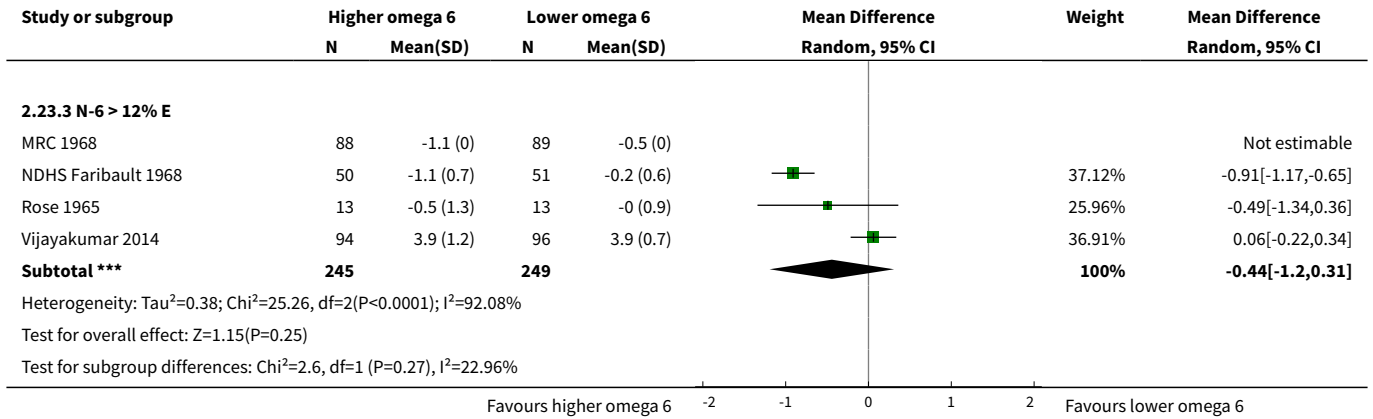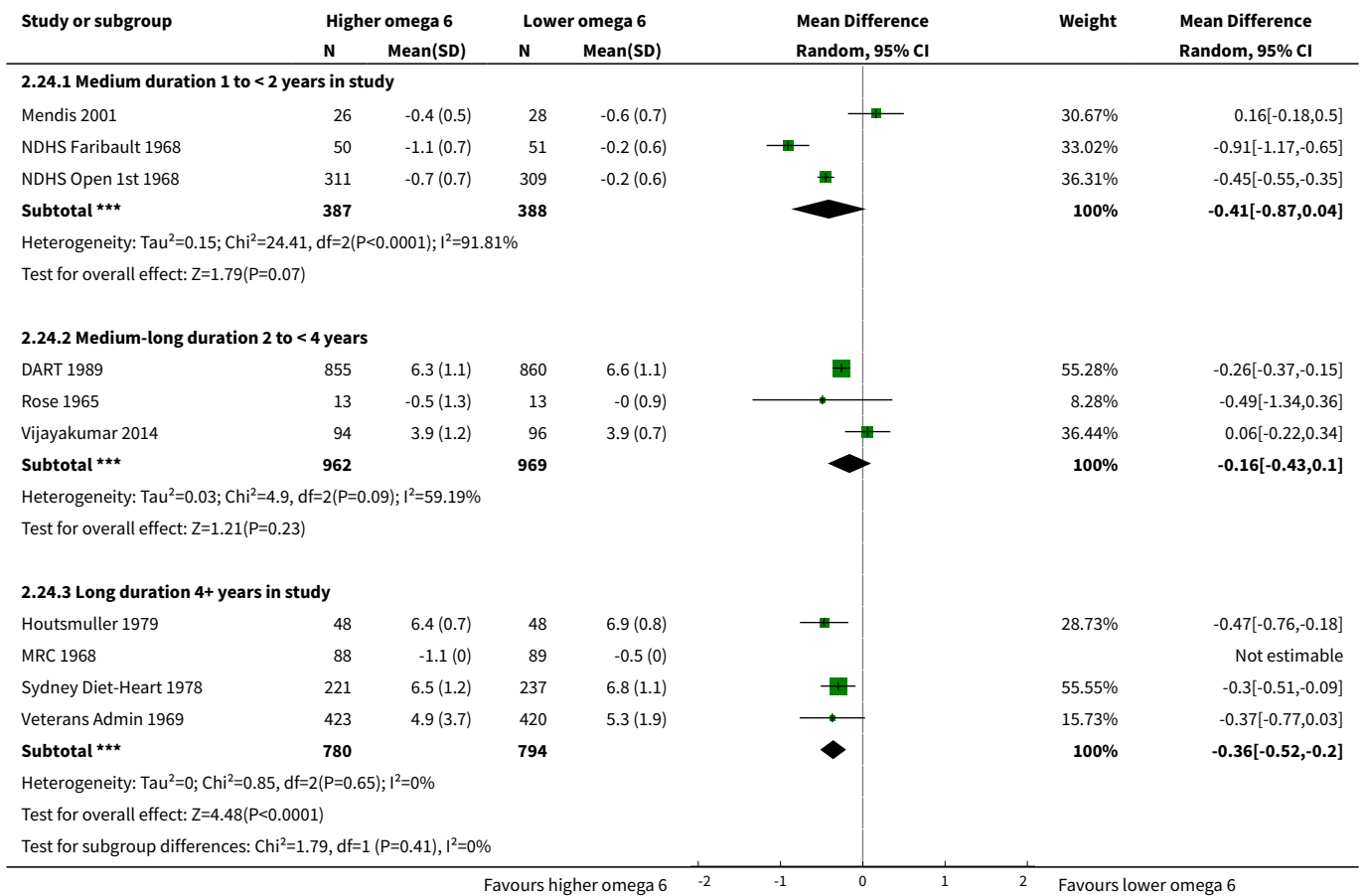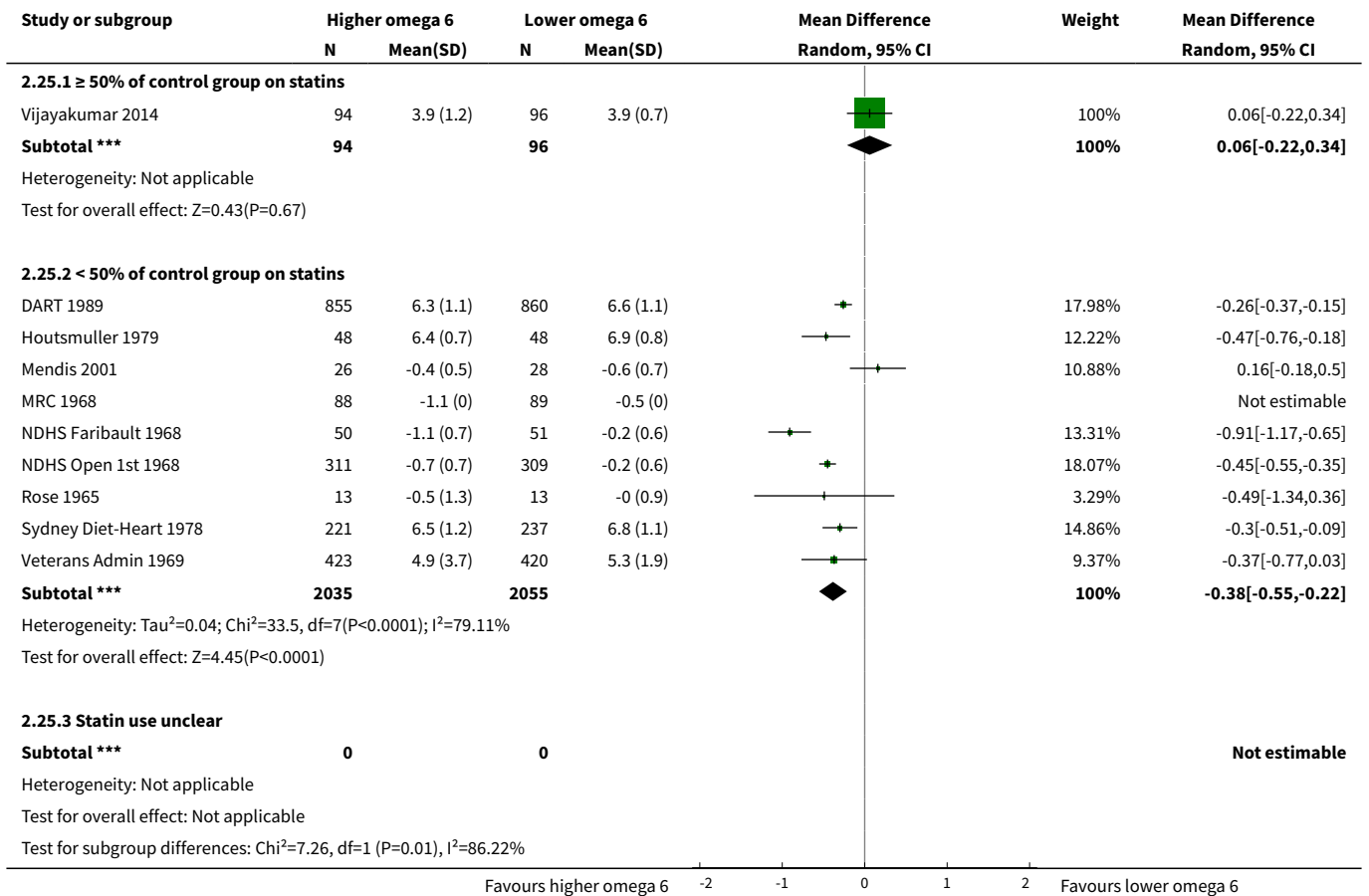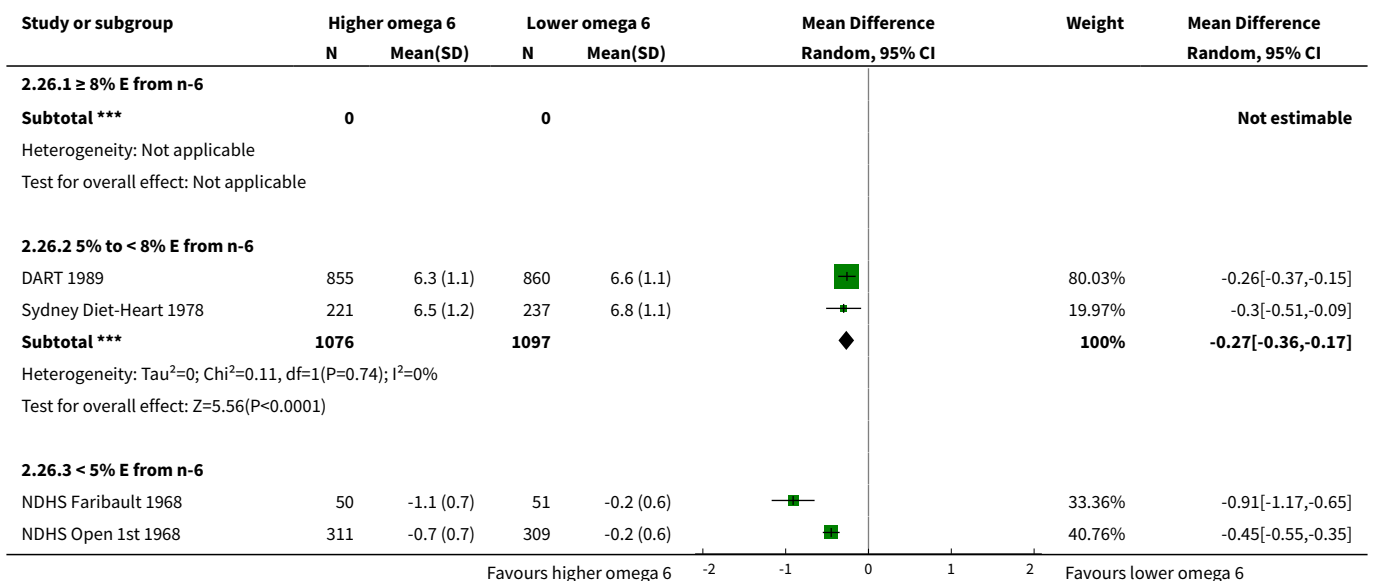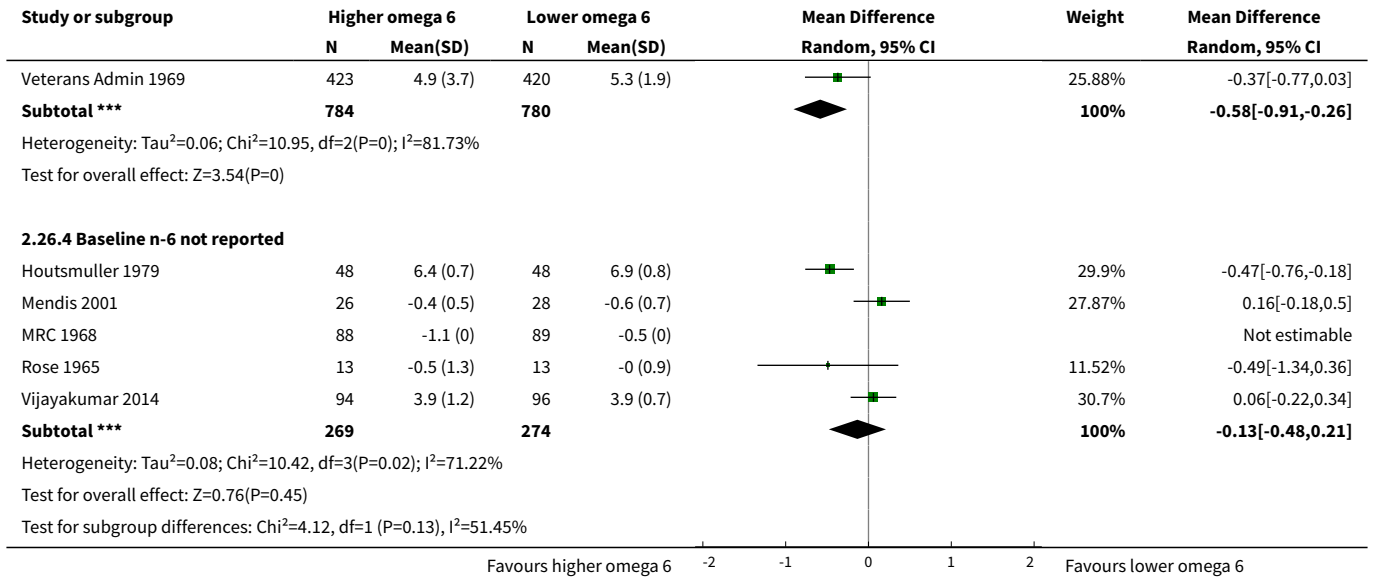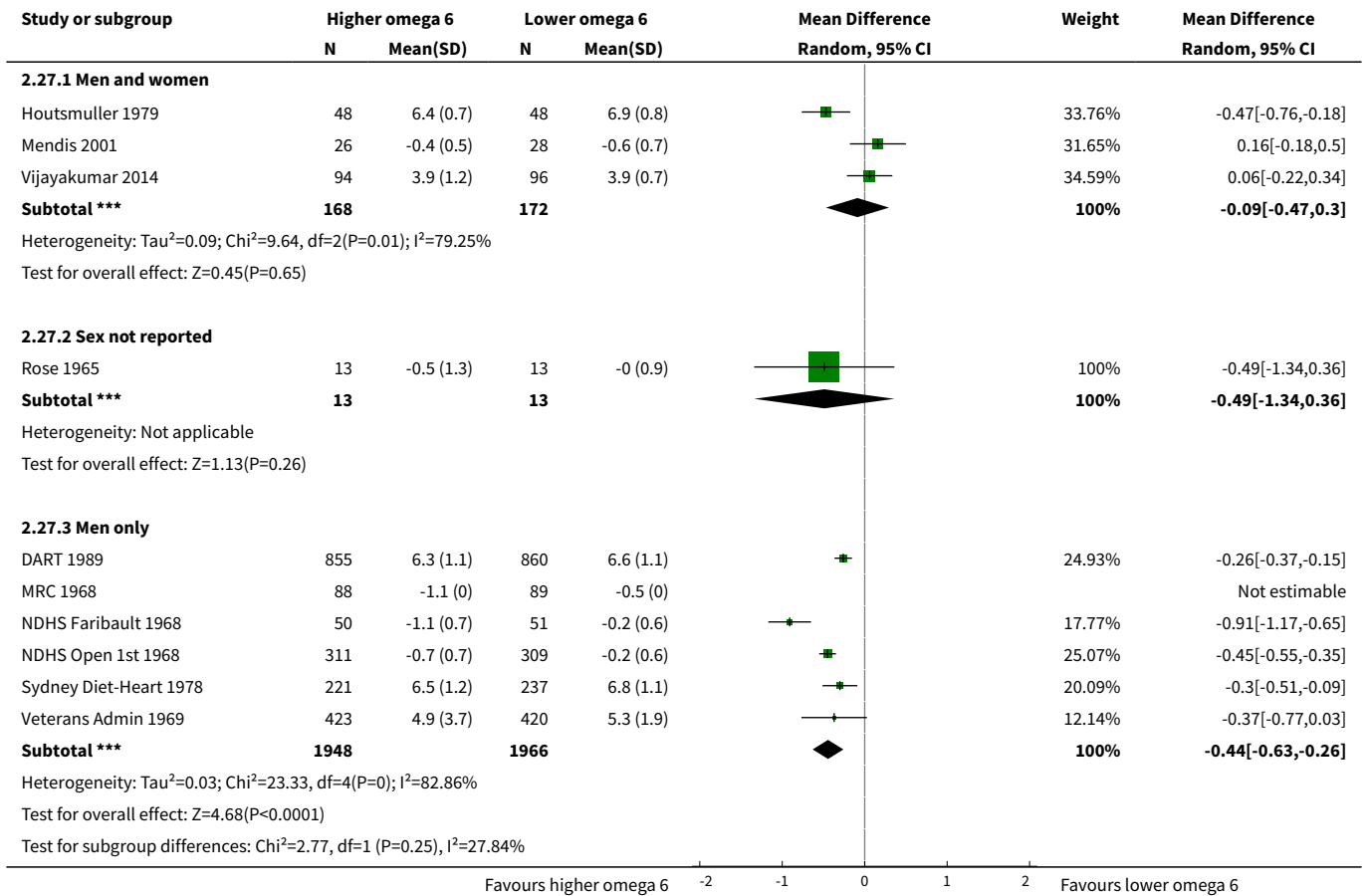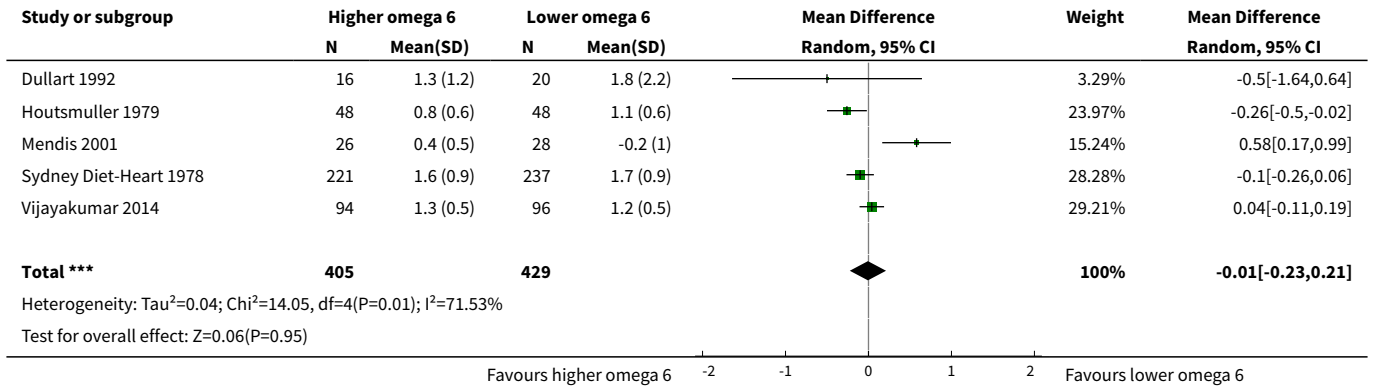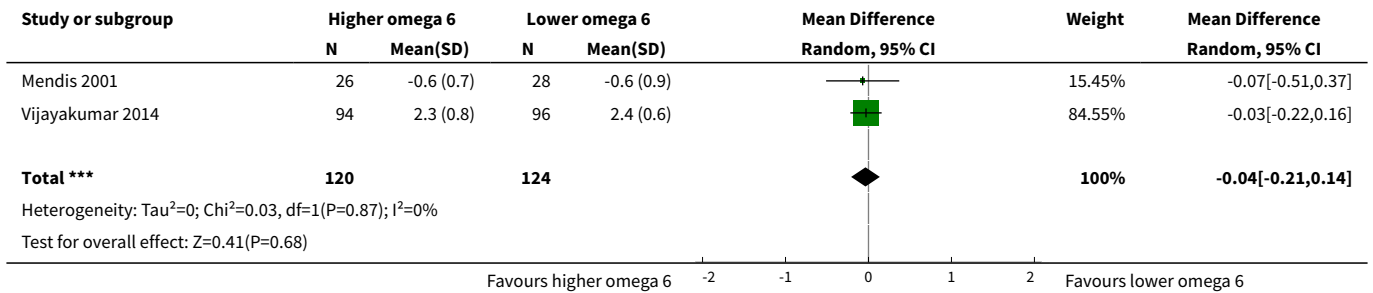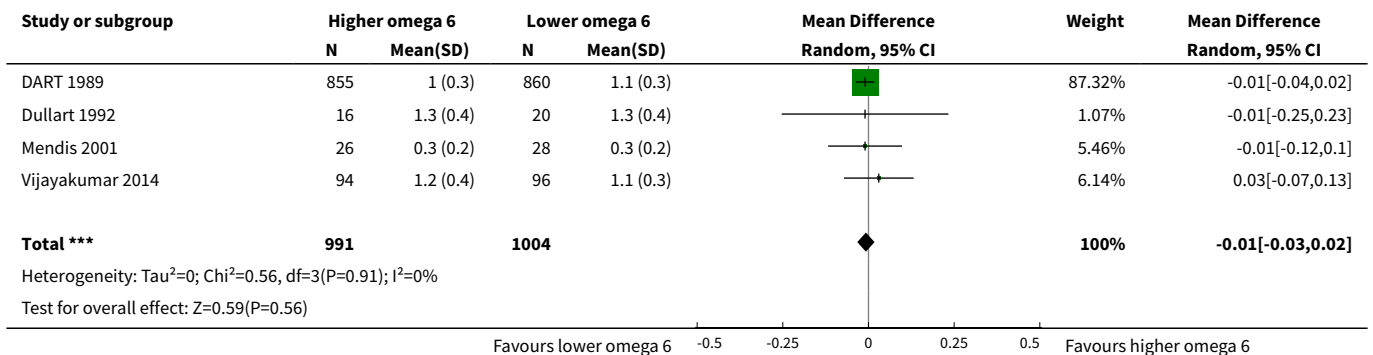| Study or subgroup	Higher omega 6 N	Higher omega 6 Mean(SD)	Lower omega 6 N	Lower omega 6 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.20.1 Dietary advice							
DART 1989	855	6.3 (1.1)	860	6.6 (1.1)		72.53%	-0.26[-0.37,-0.15]
Houtsmuller 1979	48	6.4 (0.7)	48	6.9 (0.8)		9.36%	-0.47[-0.76,-0.18]
Sydney Diet-Heart 1978	221	6.5 (1.2)	237	6.8 (1.1)		18.1%	-0.3[-0.51,-0.09]
Subtotal ***	**1124**		**1145**			**100%**	**-0.29[-0.38,-0.2]**
Heterogeneity: Tau²=0; Chi²=1.76, df=2(P=0.42); I²=0%							
Test for overall effect: Z=6.26(P<0.0001)							
2.20.2 Supplements (capsules)							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.20.3 Supplemental foods							
Vijayakumar 2014	94	3.9 (1.2)	96	3.9 (0.7)		100%	0.06[-0.22,0.34]
Subtotal ***	**94**		**96**			**100%**	**0.06[-0.22,0.34]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.43(P=0.67)							
2.20.4 Dietary advice plus supplement							
Mendis 2001	26	-0.4 (0.5)	28	-0.6 (0.7)		68.71%	0.16[-0.18,0.5]
MRC 1968	88	-1.1 (0)	89	-0.5 (0)			Not estimable
Rose 1965	13	-0.5 (1.3)	13	-0 (0.9)		31.29%	-0.49[-1.34,0.36]
Subtotal ***	**127**		**130**			**100%**	**-0.04[-0.63,0.55]**
Heterogeneity: Tau²=0.1; Chi²=1.94, df=1(P=0.16); I²=48.36%							
Test for overall effect: Z=0.14(P=0.89)							
2.20.5 Diet (all foods) provided							
NDHS Faribault 1968	50	-1.1 (0.7)	51	-0.2 (0.6)		33.36%	-0.91[-1.17,-0.65]
NDHS Open 1st 1968	311	-0.7 (0.7)	309	-0.2 (0.6)		40.76%	-0.45[-0.55,-0.35]
Veterans Admin 1969	423	4.9 (3.7)	420	5.3 (1.9)		25.88%	-0.37[-0.77,0.03]
Subtotal ***	**784**		**780**			**100%**	**-0.58[-0.91,-0.26]**
Heterogeneity: Tau²=0.06; Chi²=10.95, df=2(P=0); I²=81.73%							
Test for overall effect: Z=3.54(P=0)							
Test for subgroup differences: Chi²=9.81, df=1 (P=0.02), I²=69.41%							

Favours higher omega 6   -2 -1 0 1 2   Favours lower omega 6

Analysis 2.21. Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 21 TC, mmol/L - subgroup by replacement.

Study or subgroup	Higher omega 6 N	Higher omega 6 Mean(SD)	Lower omega 6 N	Lower omega 6 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.21.1 N-6 replacing SFA							
DART 1989	855	6.3 (1.1)	860	6.6 (1.1)		18.19%	-0.26[-0.37,-0.15]
Houtsmuller 1979	48	6.4 (0.7)	48	6.9 (0.8)		12.42%	-0.47[-0.76,-0.18]

Favours higher omega 6   -2 -1 0 1 2   Favours lower omega 6

Study or subgroup	Higher omega 6		Lower omega 6		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
MRC 1968	88	-1.1 (0)	89	-0.5 (0)			Not estimable
NDHS Faribault 1968	50	-1.1 (0.7)	51	-0.2 (0.6)		13.51%	-0.91[-1.17,-0.65]
NDHS Open 1st 1968	311	-0.7 (0.7)	309	-0.2 (0.6)		18.28%	-0.45[-0.55,-0.35]
Sydney Diet-Heart 1978	221	6.5 (1.2)	237	6.8 (1.1)		15.07%	-0.3[-0.51,-0.09]
Veterans Admin 1969	423	4.9 (3.7)	420	5.3 (1.9)		9.54%	-0.37[-0.77,0.03]
Vijayakumar 2014	94	3.9 (1.2)	96	3.9 (0.7)		12.99%	0.06[-0.22,0.34]
Subtotal ***	**2090**		**2110**		◆	**100%**	**-0.38[-0.56,-0.21]**

Heterogeneity: Tau²=0.04; Chi²=33.44, df=6(P<0.0001); I²=82.06%

Test for overall effect: Z=4.38(P<0.0001)

2.21.2 N-6 replacing MUFA

NDHS Faribault 1968	50	-1.1 (0.7)	51	-0.2 (0.6)		22.55%	-0.91[-1.17,-0.65]
NDHS Open 1st 1968	311	-0.7 (0.7)	309	-0.2 (0.6)		30.99%	-0.45[-0.55,-0.35]
Rose 1965	13	-0.5 (1.3)	13	-0 (0.9)		5.45%	-0.49[-1.34,0.36]
Sydney Diet-Heart 1978	221	6.5 (1.2)	237	6.8 (1.1)		25.28%	-0.3[-0.51,-0.09]
Veterans Admin 1969	423	4.9 (3.7)	420	5.3 (1.9)		15.73%	-0.37[-0.77,0.03]
Subtotal ***	**1018**		**1030**		◆	**100%**	**-0.51[-0.72,-0.29]**

Heterogeneity: Tau²=0.04; Chi²=13.95, df=4(P=0.01); I²=71.33%

Test for overall effect: Z=4.57(P<0.0001)

2.21.3 N-6 replacing nil, low n-6

Subtotal ***	**0**		**0**				**Not estimable**

Heterogeneity: Not applicable

Test for overall effect: Not applicable

2.21.4 N-6 replacement unclear

Mendis 2001	26	-0.4 (0.5)	28	-0.6 (0.7)		100%	0.16[-0.18,0.5]
MRC 1968	88	-1.1 (0)	89	-0.5 (0)			Not estimable
Subtotal ***	**114**		**117**		◆	**100%**	**0.16[-0.18,0.5]**

Heterogeneity: Not applicable

Test for overall effect: Z=0.92(P=0.36)

2.21.5 N-6 replacing CHO

Houtsmuller 1979	48	6.4 (0.7)	48	6.9 (0.8)		100%	-0.47[-0.76,-0.18]
Subtotal ***	**48**		**48**		◆	**100%**	**-0.47[-0.76,-0.18]**

Heterogeneity: Not applicable

Test for overall effect: Z=3.14(P=0)

2.21.6 N-6 replacing protein

Subtotal ***	**0**		**0**				**Not estimable**

Heterogeneity: Not applicable

Test for overall effect: Not applicable

Test for subgroup differences: Chi²=11.32, df=1 (P=0.01), I²=73.49%

Favours higher omega 6 -2 -1 0 1 2 Favours lower omega 6

Analysis 2.22. Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 22 TC, mmol/L - subgroup by baseline CVD risk.

Study or subgroup	Higher omega 6		Lower omega 6		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
2.22.1 Primary prevention - low CVD risk							
Mendis 2001	26	-0.4 (0.5)	28	-0.6 (0.7)		23.46%	0.16[-0.18,0.5]
NDHS Faribault 1968	50	-1.1 (0.7)	51	-0.2 (0.6)		25.73%	-0.91[-1.17,-0.65]
NDHS Open 1st 1968	311	-0.7 (0.7)	309	-0.2 (0.6)		29.03%	-0.45[-0.55,-0.35]
Veterans Admin 1969	423	4.9 (3.7)	420	5.3 (1.9)		21.78%	-0.37[-0.77,0.03]
Subtotal ***	**810**		**808**			**100%**	**-0.41[-0.77,-0.05]**
Heterogeneity: Tau²=0.11; Chi²=24.61, df=3(P<0.0001); I²=87.81%							
Test for overall effect: Z=2.23(P=0.03)							
2.22.2 Primary prevention - moderate CVD risk							
Houtsmuller 1979	48	6.4 (0.7)	48	6.9 (0.8)		100%	-0.47[-0.76,-0.18]
Subtotal ***	**48**		**48**			**100%**	**-0.47[-0.76,-0.18]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.14(P=0)							
2.22.3 Secondary prevention - existing CVD							
DART 1989	855	6.3 (1.1)	860	6.6 (1.1)		47.29%	-0.26[-0.37,-0.15]
MRC 1968	88	-1.1 (0)	89	-0.5 (0)			Not estimable
Rose 1965	13	-0.5 (1.3)	13	-0 (0.9)		3.18%	-0.49[-1.34,0.36]
Sydney Diet-Heart 1978	221	6.5 (1.2)	237	6.8 (1.1)		28.62%	-0.3[-0.51,-0.09]
Vijayakumar 2014	94	3.9 (1.2)	96	3.9 (0.7)		20.91%	0.06[-0.22,0.34]
Subtotal ***	**1271**		**1295**			**100%**	**-0.21[-0.37,-0.06]**
Heterogeneity: Tau²=0.01; Chi²=5.32, df=3(P=0.15); I²=43.66%							
Test for overall effect: Z=2.66(P=0.01)							
Test for subgroup differences: Chi²=2.82, df=1 (P=0.24), I²=29.07%							

Favours higher omega 6 -2 -1 0 1 2 Favours lower omega 6

Analysis 2.23. Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 23 TC, mmol/L - subgroup by omega-6 dose.

Study or subgroup	Higher omega 6		Lower omega 6		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
2.23.1 N-6 < 4% E							
DART 1989	855	6.3 (1.1)	860	6.6 (1.1)		57.69%	-0.26[-0.37,-0.15]
Mendis 2001	26	-0.4 (0.5)	28	-0.6 (0.7)		42.31%	0.16[-0.18,0.5]
Subtotal ***	**881**		**888**			**100%**	**-0.08[-0.49,0.32]**
Heterogeneity: Tau²=0.07; Chi²=5.36, df=1(P=0.02); I²=81.33%							
Test for overall effect: Z=0.4(P=0.69)							
2.23.2 N-6 4% to 12% E							
Houtsmuller 1979	48	6.4 (0.7)	48	6.9 (0.8)		8.46%	-0.47[-0.76,-0.18]
NDHS Open 1st 1968	311	-0.7 (0.7)	309	-0.2 (0.6)		70.54%	-0.45[-0.55,-0.35]
Sydney Diet-Heart 1978	221	6.5 (1.2)	237	6.8 (1.1)		16.36%	-0.3[-0.51,-0.09]
Veterans Admin 1969	423	4.9 (3.7)	420	5.3 (1.9)		4.63%	-0.37[-0.77,0.03]
Subtotal ***	**1003**		**1014**			**100%**	**-0.42[-0.51,-0.34]**
Heterogeneity: Tau²=0; Chi²=1.74, df=3(P=0.63); I²=0%							
Test for overall effect: Z=9.71(P<0.0001)							

Favours higher omega 6 -2 -1 0 1 2 Favours lower omega 6

Study or subgroup	Higher omega 6		Lower omega 6		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
2.23.3 N-6 > 12% E							
MRC 1968	88	-1.1 (0)	89	-0.5 (0)			Not estimable
NDHS Faribault 1968	50	-1.1 (0.7)	51	-0.2 (0.6)		37.12%	-0.91[-1.17,-0.65]
Rose 1965	13	-0.5 (1.3)	13	-0 (0.9)		25.96%	-0.49[-1.34,0.36]
Vijayakumar 2014	94	3.9 (1.2)	96	3.9 (0.7)		36.91%	0.06[-0.22,0.34]
Subtotal ***	**245**		**249**			**100%**	**-0.44[-1.2,0.31]**
Heterogeneity: Tau²=0.38; Chi²=25.26, df=2(P<0.0001); I²=92.08%							
Test for overall effect: Z=1.15(P=0.25)							
Test for subgroup differences: Chi²=2.6, df=1 (P=0.27), I²=22.96%							

Favours higher omega 6   -2 -1 0 1 2   Favours lower omega 6

Analysis 2.24. Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 24 TC, mmol/L - subgroup by duration.

Study or subgroup	Higher omega 6		Lower omega 6		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
2.24.1 Medium duration 1 to < 2 years in study							
Mendis 2001	26	-0.4 (0.5)	28	-0.6 (0.7)		30.67%	0.16[-0.18,0.5]
NDHS Faribault 1968	50	-1.1 (0.7)	51	-0.2 (0.6)		33.02%	-0.91[-1.17,-0.65]
NDHS Open 1st 1968	311	-0.7 (0.7)	309	-0.2 (0.6)		36.31%	-0.45[-0.55,-0.35]
Subtotal ***	**387**		**388**			**100%**	**-0.41[-0.87,0.04]**
Heterogeneity: Tau²=0.15; Chi²=24.41, df=2(P<0.0001); I²=91.81%							
Test for overall effect: Z=1.79(P=0.07)							
2.24.2 Medium-long duration 2 to < 4 years							
DART 1989	855	6.3 (1.1)	860	6.6 (1.1)		55.28%	-0.26[-0.37,-0.15]
Rose 1965	13	-0.5 (1.3)	13	-0 (0.9)		8.28%	-0.49[-1.34,0.36]
Vijayakumar 2014	94	3.9 (1.2)	96	3.9 (0.7)		36.44%	0.06[-0.22,0.34]
Subtotal ***	**962**		**969**			**100%**	**-0.16[-0.43,0.1]**
Heterogeneity: Tau²=0.03; Chi²=4.9, df=2(P=0.09); I²=59.19%							
Test for overall effect: Z=1.21(P=0.23)							
2.24.3 Long duration 4+ years in study							
Houtsmuller 1979	48	6.4 (0.7)	48	6.9 (0.8)		28.73%	-0.47[-0.76,-0.18]
MRC 1968	88	-1.1 (0)	89	-0.5 (0)			Not estimable
Sydney Diet-Heart 1978	221	6.5 (1.2)	237	6.8 (1.1)		55.55%	-0.3[-0.51,-0.09]
Veterans Admin 1969	423	4.9 (3.7)	420	5.3 (1.9)		15.73%	-0.37[-0.77,0.03]
Subtotal ***	**780**		**794**			**100%**	**-0.36[-0.52,-0.2]**
Heterogeneity: Tau²=0; Chi²=0.85, df=2(P=0.65); I²=0%							
Test for overall effect: Z=4.48(P<0.0001)							
Test for subgroup differences: Chi²=1.79, df=1 (P=0.41), I²=0%							

Favours higher omega 6   -2 -1 0 1 2   Favours lower omega 6

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Analysis 2.25. Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 25 TC, mmol/L - subgroup by statin use.

Study or subgroup	Higher omega 6		Lower omega 6		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
2.25.1 ≥ 50% of control group on statins							
Vijayakumar 2014	94	3.9 (1.2)	96	3.9 (0.7)		100%	0.06[-0.22,0.34]
Subtotal ***	**94**		**96**			**100%**	**0.06[-0.22,0.34]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.43(P=0.67)							
2.25.2 < 50% of control group on statins							
DART 1989	855	6.3 (1.1)	860	6.6 (1.1)		17.98%	-0.26[-0.37,-0.15]
Houtsmuller 1979	48	6.4 (0.7)	48	6.9 (0.8)		12.22%	-0.47[-0.76,-0.18]
Mendis 2001	26	-0.4 (0.5)	28	-0.6 (0.7)		10.88%	0.16[-0.18,0.5]
MRC 1968	88	-1.1 (0)	89	-0.5 (0)			Not estimable
NDHS Faribault 1968	50	-1.1 (0.7)	51	-0.2 (0.6)		13.31%	-0.91[-1.17,-0.65]
NDHS Open 1st 1968	311	-0.7 (0.7)	309	-0.2 (0.6)		18.07%	-0.45[-0.55,-0.35]
Rose 1965	13	-0.5 (1.3)	13	-0 (0.9)		3.29%	-0.49[-1.34,0.36]
Sydney Diet-Heart 1978	221	6.5 (1.2)	237	6.8 (1.1)		14.86%	-0.3[-0.51,-0.09]
Veterans Admin 1969	423	4.9 (3.7)	420	5.3 (1.9)		9.37%	-0.37[-0.77,0.03]
Subtotal ***	**2035**		**2055**			**100%**	**-0.38[-0.55,-0.22]**
Heterogeneity: Tau²=0.04; Chi²=33.5, df=7(P<0.0001); I²=79.11%							
Test for overall effect: Z=4.45(P<0.0001)							
2.25.3 Statin use unclear							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Chi²=7.26, df=1 (P=0.01), I²=86.22%							

Favours higher omega 6   -2 -1 0 1 2   Favours lower omega 6

Analysis 2.26. Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 26 TC, mmol/L - subgroup by baseline omega-6.

Study or subgroup	Higher omega 6		Lower omega 6		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
2.26.1 ≥ 8% E from n-6							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.26.2 5% to < 8% E from n-6							
DART 1989	855	6.3 (1.1)	860	6.6 (1.1)		80.03%	-0.26[-0.37,-0.15]
Sydney Diet-Heart 1978	221	6.5 (1.2)	237	6.8 (1.1)		19.97%	-0.3[-0.51,-0.09]
Subtotal ***	**1076**		**1097**			**100%**	**-0.27[-0.36,-0.17]**
Heterogeneity: Tau²=0; Chi²=0.11, df=1(P=0.74); I²=0%							
Test for overall effect: Z=5.56(P<0.0001)							
2.26.3 < 5% E from n-6							
NDHS Faribault 1968	50	-1.1 (0.7)	51	-0.2 (0.6)		33.36%	-0.91[-1.17,-0.65]
NDHS Open 1st 1968	311	-0.7 (0.7)	309	-0.2 (0.6)		40.76%	-0.45[-0.55,-0.35]

Favours higher omega 6   -2 -1 0 1 2   Favours lower omega 6

Study or subgroup	Higher omega 6		Lower omega 6		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Veterans Admin 1969	423	4.9 (3.7)	420	5.3 (1.9)		25.88%	-0.37[-0.77,0.03]
Subtotal ***	**784**		**780**			**100%**	**-0.58[-0.91,-0.26]**
Heterogeneity: Tau²=0.06; Chi²=10.95, df=2(P=0); I²=81.73%							
Test for overall effect: Z=3.54(P=0)							
2.26.4 Baseline n-6 not reported							
Houtsmuller 1979	48	6.4 (0.7)	48	6.9 (0.8)		29.9%	-0.47[-0.76,-0.18]
Mendis 2001	26	-0.4 (0.5)	28	-0.6 (0.7)		27.87%	0.16[-0.18,0.5]
MRC 1968	88	-1.1 (0)	89	-0.5 (0)			Not estimable
Rose 1965	13	-0.5 (1.3)	13	-0 (0.9)		11.52%	-0.49[-1.34,0.36]
Vijayakumar 2014	94	3.9 (1.2)	96	3.9 (0.7)		30.7%	0.06[-0.22,0.34]
Subtotal ***	**269**		**274**			**100%**	**-0.13[-0.48,0.21]**
Heterogeneity: Tau²=0.08; Chi²=10.42, df=3(P=0.02); I²=71.22%							
Test for overall effect: Z=0.76(P=0.45)							
Test for subgroup differences: Chi²=4.12, df=1 (P=0.13), I²=51.45%							

Favours higher omega 6 -2 -1 0 1 2 Favours lower omega 6

Analysis 2.27.   Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 27 TC, mmol/L - subgroup by sex.

Study or subgroup	Higher omega 6		Lower omega 6		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
2.27.1 Men and women							
Houtsmuller 1979	48	6.4 (0.7)	48	6.9 (0.8)		33.76%	-0.47[-0.76,-0.18]
Mendis 2001	26	-0.4 (0.5)	28	-0.6 (0.7)		31.65%	0.16[-0.18,0.5]
Vijayakumar 2014	94	3.9 (1.2)	96	3.9 (0.7)		34.59%	0.06[-0.22,0.34]
Subtotal ***	**168**		**172**			**100%**	**-0.09[-0.47,0.3]**
Heterogeneity: Tau²=0.09; Chi²=9.64, df=2(P=0.01); I²=79.25%							
Test for overall effect: Z=0.45(P=0.65)							
2.27.2 Sex not reported							
Rose 1965	13	-0.5 (1.3)	13	-0 (0.9)		100%	-0.49[-1.34,0.36]
Subtotal ***	**13**		**13**			**100%**	**-0.49[-1.34,0.36]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.13(P=0.26)							
2.27.3 Men only							
DART 1989	855	6.3 (1.1)	860	6.6 (1.1)		24.93%	-0.26[-0.37,-0.15]
MRC 1968	88	-1.1 (0)	89	-0.5 (0)			Not estimable
NDHS Faribault 1968	50	-1.1 (0.7)	51	-0.2 (0.6)		17.77%	-0.91[-1.17,-0.65]
NDHS Open 1st 1968	311	-0.7 (0.7)	309	-0.2 (0.6)		25.07%	-0.45[-0.55,-0.35]
Sydney Diet-Heart 1978	221	6.5 (1.2)	237	6.8 (1.1)		20.09%	-0.3[-0.51,-0.09]
Veterans Admin 1969	423	4.9 (3.7)	420	5.3 (1.9)		12.14%	-0.37[-0.77,0.03]
Subtotal ***	**1948**		**1966**			**100%**	**-0.44[-0.63,-0.26]**
Heterogeneity: Tau²=0.03; Chi²=23.33, df=4(P=0); I²=82.86%							
Test for overall effect: Z=4.68(P<0.0001)							
Test for subgroup differences: Chi²=2.77, df=1 (P=0.25), I²=27.84%							

Favours higher omega 6 -2 -1 0 1 2 Favours lower omega 6

Analysis 2.28. Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 28 Serum triglycerides (TG), mmol/L.

Study or subgroup	Higher omega 6		Lower omega 6		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Dullart 1992	16	1.3 (1.2)	20	1.8 (2.2)		3.29%	-0.5[-1.64,0.64]
Houtsmuller 1979	48	0.8 (0.6)	48	1.1 (0.6)		23.97%	-0.26[-0.5,-0.02]
Mendis 2001	26	0.4 (0.5)	28	-0.2 (1)		15.24%	0.58[0.17,0.99]
Sydney Diet-Heart 1978	221	1.6 (0.9)	237	1.7 (0.9)		28.28%	-0.1[-0.26,0.06]
Vijayakumar 2014	94	1.3 (0.5)	96	1.2 (0.5)		29.21%	0.04[-0.11,0.19]
Total ***	405		429			100%	-0.01[-0.23,0.21]

Heterogeneity: Tau²=0.04; Chi²=14.05, df=4(P=0.01); I²=71.53%

Test for overall effect: Z=0.06(P=0.95)

Favours higher omega 6 -2 -1 0 1 2 Favours lower omega 6

Analysis 2.29. Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 29 Low-density lipoprotein (LDL), mmol/L.

Study or subgroup	Higher omega 6		Lower omega 6		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Mendis 2001	26	-0.6 (0.7)	28	-0.6 (0.9)		15.45%	-0.07[-0.51,0.37]
Vijayakumar 2014	94	2.3 (0.8)	96	2.4 (0.6)		84.55%	-0.03[-0.22,0.16]
Total ***	120		124			100%	-0.04[-0.21,0.14]

Heterogeneity: Tau²=0; Chi²=0.03, df=1(P=0.87); I²=0%

Test for overall effect: Z=0.41(P=0.68)

Favours higher omega 6 -2 -1 0 1 2 Favours lower omega 6

Analysis 2.30. Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 30 High-density lipoprotein (HDL), mmol/L.

Study or subgroup	Higher omega 6		Lower omega 6		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
DART 1989	855	1 (0.3)	860	1.1 (0.3)		87.32%	-0.01[-0.04,0.02]
Dullart 1992	16	1.3 (0.4)	20	1.3 (0.4)		1.07%	-0.01[-0.25,0.23]
Mendis 2001	26	0.3 (0.2)	28	0.3 (0.2)		5.46%	-0.01[-0.12,0.1]
Vijayakumar 2014	94	1.2 (0.4)	96	1.1 (0.3)		6.14%	0.03[-0.07,0.13]
Total ***	991		1004			100%	-0.01[-0.03,0.02]

Heterogeneity: Tau²=0; Chi²=0.56, df=3(P=0.91); I²=0%

Test for overall effect: Z=0.59(P=0.56)

Favours lower omega 6 -0.5 -0.25 0 0.25 0.5 Favours higher omega 6

Analysis 2.31. Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 31 Body weight, kg.

Study or subgroup	Higher omega 6		Lower omega 6		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Black 1994	58	80 (0)	57	76.5 (0)			Not estimable
Dullart 1992	16	77 (10)	20	76 (11.2)		57.95%	1[-5.94,7.94]
MRC 1968	88	0 (0)	89	-1.4 (0)			Not estimable
Schirmer 2007	13	72.5 (12.9)	17	81.3 (15.9)		42.05%	-8.8[-19.13,1.53]
Total ***	175		183			100%	-3.12[-12.6,6.36]

Heterogeneity: Tau²=27.86; Chi²=2.38, df=1(P=0.12); I²=58.03%

Test for overall effect: Z=0.65(P=0.52)

Favours higher omega 6   -20 -10   0   10   20   Favours lower omega 6

Analysis 2.32. Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 32 Body mass index, kg/m².

Study or subgroup	Higher omega 6		Lower omega 6		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Sydney Diet-Heart 1978	179	24.3 (1.5)	192	24.5 (2)		100%	-0.2[-0.56,0.16]
Total ***	179		192			100%	-0.2[-0.56,0.16]

Heterogeneity: Not applicable

Test for overall effect: Z=1.09(P=0.27)

Favours higher omega 6   -1 -0.5   0   0.5   1   Favours lower omega 6
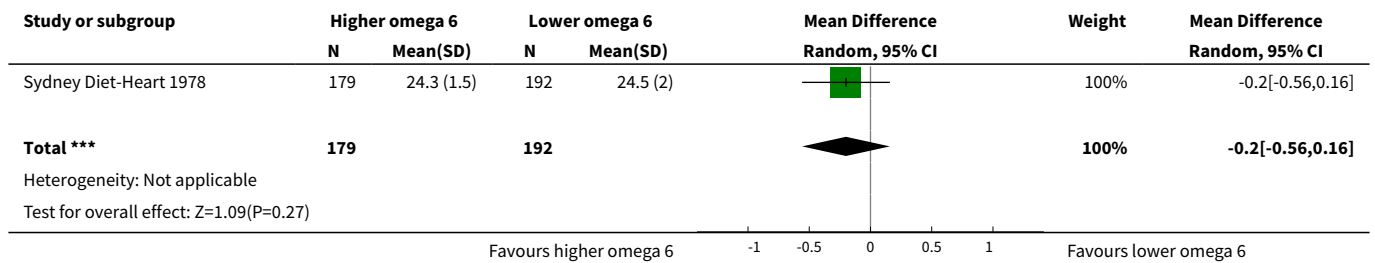
Analysis 2.33. Comparison 2 Secondary outcomes - higher omega-6 vs lower omega-6, Outcome 33 Fat weight, kg.
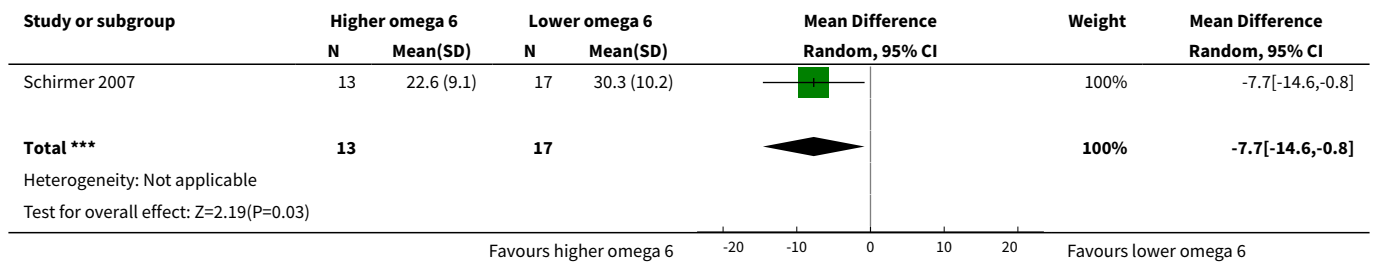
Study or subgroup	Higher omega 6		Lower omega 6		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Schirmer 2007	13	22.6 (9.1)	17	30.3 (10.2)		100%	-7.7[-14.6,-0.8]
Total ***	13		17			100%	-7.7[-14.6,-0.8]

Heterogeneity: Not applicable

Test for overall effect: Z=2.19(P=0.03)

Favours higher omega 6   -20 -10   0   10   20   Favours lower omega 6

Comparison 3.   Tertiary outcomes - higher omega-6 vs lower omega-6

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 BP - systolic and diastolic blood pressure, mmHg	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 sBP - systolic blood pressure, mmHg	2	635	Mean Difference (IV, Random, 95% CI)	-1.10 [-4.05, 1.85]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.2 dBP - diastolic blood pressure	2	635	Mean Difference (IV, Random, 95% CI)	-0.30 [-2.04, 1.44]
2 Dropouts	7	1425	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.52, 1.72]
3 Other serious adverse events	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Pulmonary embolism	2	2087	Risk Ratio (M-H, Random, 95% CI)	2.15 [0.48, 9.57]
3.2 Multiple Sclerosis worsened or had acute attack - GLA supplement	2	268	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.95, 1.30]

Analysis 3.1. Comparison 3 Tertiary outcomes - higher omega-6 vs lower omega-6, Outcome 1 BP - systolic and diastolic blood pressure, mmHg.

Study or subgroup	Higher omega 6		Lower omega 6		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
3.1.1 sBP - systolic blood pressure, mmHg							
MRC 1968	88	2 (0)	89	0 (0)			Not estimable
Sydney Diet-Heart 1978	221	136.8 (16.1)	237	137.9 (16.1)		100%	-1.1 [-4.05, 1.85]
Subtotal ***	309		326			100%	-1.1 [-4.05, 1.85]
Heterogeneity: Not applicable							
Test for overall effect: Z=0.73(P=0.46)							
3.1.2 dBP - diastolic blood pressure							
MRC 1968	88	-1 (0)	89	3 (0)			Not estimable
Sydney Diet-Heart 1978	221	88.4 (9.4)	237	88.7 (9.6)		100%	-0.3 [-2.04, 1.44]
Subtotal ***	309		326			100%	-0.3 [-2.04, 1.44]
Heterogeneity: Not applicable							
Test for overall effect: Z=0.34(P=0.74)							
Test for subgroup differences: Chi²=0.21, df=1 (P=0.65), I²=0%							

Favours higher omega 6 -10 -5 0 5 10 Favours lower omega 6

Analysis 3.2. Comparison 3 Tertiary outcomes - higher omega-6 vs lower omega-6, Outcome 2 Dropouts.

Study or subgroup	Higher omega 6	Lower omega 6	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Bates 1978	0/29	1/29		3.15%	0.33 [0.01, 7.86]
Bates 1978	3/29	6/29		11.74%	0.5 [0.14, 1.81]
Dullart 1992	2/20	4/20		9.21%	0.5 [0.1, 2.43]
GLAMT 1993	10/54	17/57		19.16%	0.62 [0.31, 1.23]
Mendis 2001	4/30	2/30		8.92%	2 [0.4, 10.11]
Rose 1965	3/28	5/26		11.34%	0.56 [0.15, 2.1]
Veterans Admin 1969	117/424	58/422		24.21%	2.01 [1.51, 2.67]

Favours higher omega 6 0.01 0.1 1 10 100 Favours lower omega 6

Study or subgroup	Higher omega 6	Lower omega 6	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Vijayakumar 2014	6/99	4/99		12.27%	1.5[0.44,5.15]
Total (95% CI)	**713**	**712**		**100%**	**0.94[0.52,1.72]**

Total events: 145 (Higher omega 6), 97 (Lower omega 6)

Heterogeneity: Tau²=0.37; Chi²=18.16, df=7(P=0.01); I²=61.45%

Test for overall effect: Z=0.19(P=0.85)

Favours higher omega 6 0.01 0.1 1 10 100 Favours lower omega 6

Analysis 3.3. Comparison 3 Tertiary outcomes - higher omega-6 vs lower omega-6, Outcome 3 Other serious adverse events.

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
3.3.1 Pulmonary embolism					
DART 1989	4/1018	2/1015		77.63%	1.99[0.37,10.86]
Rose 1965	1/28	0/26		22.37%	2.79[0.12,65.66]
Subtotal (95% CI)	**1046**	**1041**		**100%**	**2.15[0.48,9.57]**
Total events: 5 (Higher PUFA), 2 (Lower PUFA)					
Heterogeneity: Tau²=0; Chi²=0.03, df=1(P=0.85); I²=0%					
Test for overall effect: Z=1(P=0.32)					
3.3.2 Multiple Sclerosis worsened or had acute attack - GLA supplement					
Bates 1977	24/76	21/76		9.83%	1.14[0.7,1.87]
Bates 1978	51/58	46/58		90.17%	1.11[0.94,1.3]
Subtotal (95% CI)	**134**	**134**		**100%**	**1.11[0.95,1.3]**
Total events: 75 (Higher PUFA), 67 (Lower PUFA)					
Heterogeneity: Tau²=0; Chi²=0.02, df=1(P=0.89); I²=0%					
Test for overall effect: Z=1.35(P=0.18)					
Test for subgroup differences: Chi²=0.74, df=1 (P=0.39), I²=0%					

Favours higher PUFA 0.2 0.5 1 2 5 Favours lower PUFA

ADDITIONAL TABLES

Table 1. Risk of bias assessment - detailed assessment methods

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 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	The randomisation method was assessed as not truly random and may not produce comparable groups.

Table 1. Risk of bias assessment - detailed assessment methods *(Continued)*

		provide no further information.	
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 random number that links to a specific set of capsules prepared and distributed centrally or by an arms-length pharmacist.	The authors gave insufficient detail as to method.	The allocation was known in advance of participants consenting to take part in the study.
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 we 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 attri-	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).

Table 1.   Risk of bias assessment - detailed assessment methods *(Continued)*

	tion/exclusions between study arms and ≤ 20% of the sample should be lost over a year.		
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 recruitment were unclear.	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.
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.

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Library

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APPENDICES

Appendix 1. Search strategies for the original version of this review

The Cochrane Library

#1MeSH descriptor: (Fatty Acids, Omega-6) this term only
#2"omega 6"
#3(n-6 near/4 acid*)
#4("n 6" near/4 acid*)
#5omega-6
#6"linoleic acid*"
#7(poly* near/4 unsat* near/4 fatty acid*)
#8PUFA
#9MeSH descriptor: (Dietary Fats, Unsaturated) this term only
#10MeSH descriptor: (Corn Oil) this term only
#11((corn or maize or mazola) near/4 oil*)
#12maydol
#13lipomul*
#14MeSH descriptor: (Cottonseed Oil) this term only
#15cottonseed*
#16"cotton seed*"
#17MeSH descriptor: (Soybean Oil) this term only
#18intralipid or nutrilipid
#19((soy bean or soybean) near/4 (oil* or fat* or sauce*))
#20(so?a near/4 oil*)
#21so?aoil*
#22(soy near/4 oil*)
#23soyacal or travamulsion
#24(sunflower near/4 oil*)
#25helianth*
#26MeSH descriptor: (Safflower Oil) this term only
#27(safflower near/4 oil*) .tw.
#28liposyn
#29(grapeseed near/4 oil*)
#30#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
#31MeSH descriptor: (Cardiovascular Diseases) explode all trees
#32cardio*
#33cardia*
#34heart*
#35coronary*
#36angina*
#37ventric*
#38myocard*
#39pericard*
#40isch?em*
#41emboli*
#42arrhythmi*
#43thrombo*
#44atrial next fibrillat*
#45tachycardi*
#46endocardi*
#47(sick next sinus)
#48MeSH descriptor: (Stroke) explode all trees
#49(stroke or stokes)
#50cerebrovasc*
#51cerebral next vascular
#52apoplexy
#53(brain near/2 accident*)

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#54((brain* or cerebral or lacunar) near/2 infarct*)
#55MeSH descriptor: (Hypertension) explode all trees
#56hypertensi*
#57(peripheral next arter* next disease*)
#58((high or increased or elevated) near/2 blood pressure)
#59MeSH descriptor: (Hyperlipidemias) explode all trees
#60hyperlipid*
#61hyperlip?emia*
#62hypercholesterol*
#63hypercholester?emia*
#64hyperlipoprotein?emia*
#65hypertriglycerid?emia*
#66MeSH descriptor: (Arteriosclerosis) explode all trees
#67MeSH descriptor: (Cholesterol) explode all trees
#68cholesterol
#69"coronary risk factor*"
#70MeSH descriptor: (Blood Pressure) this term only
#71"blood pressure"
#72#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 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71
#73#30 and #72

MEDLINE

1. Fatty Acids, Omega-6/
2. omega 6.tw.
3. (n-6 adj4 acid*).tw.
4. (n 6 adj4 acid*).tw.
5. omega-6.tw.
6. linoleic acid*.tw.
7. (poly* adj4 unsat* adj4 fatty acid*).tw.
8. PUFA.tw.
9. Dietary Fats, Unsaturated/
10. corn oil/
11. ((corn or maize or mazola) adj4 oil*).tw.
12. maydol.tw.
13. lipomul*.tw.
14. cottonseed oil/
15. cottonseed*.tw.
16. cotton seed*.tw.
17. soybean oil/
18. intralipid.tw.
19. nutrilipid.tw.
20. ((soy bean or soybean) adj4 (oil* or fat* or sauce*)).tw.
21. (so?a adj4 oil*).tw.
22. so?aoil*.tw.
23. (soy adj4 oil*).tw.
24. soyacal.tw.
25. travamulsion.tw.
26. (sunflower adj4 oil*).tw.
27. helianth*.tw.
28. Safflower Oil/
29. (safflower adj4 oil*).tw.
30. liposyn.tw.
31. (grapeseed adj4 oil*).tw.
32. or/1-31
33. exp Cardiovascular Diseases/
34. cardio*.tw.
35. cardia*.tw.
36. heart*.tw.
37. coronary*.tw.
38. angina*.tw.

39. ventric*.tw.
40. myocard*.tw.
41. pericard*.tw.
42. isch?em*.tw.
43. emboli*.tw.
44. arrhythmi*.tw.
45. thrombo*.tw.
46. atrial fibrillat*.tw.
47. tachycardi*.tw.
48. endocardi*.tw.
49. (sick adj sinus).tw.
50. exp Stroke/
51. (stroke or stokes).tw.
52. cerebrovasc*.tw.
53. cerebral vascular.tw.
54. apoplexy.tw.
55. (brain adj2 accident*).tw.
56. ((brain* or cerebral or lacunar) adj2 infarct*).tw.
57. exp Hypertension/
58. hypertensi*.tw.
59. peripheral arter* disease*.tw.
60. ((high or increased or elevated) adj2 blood pressure).tw.
61. exp Hyperlipidemias/
62. hyperlipid*.tw.
63. hyperlip?emia*.tw.
64. hypercholesterol*.tw.
65. hypercholester?emia*.tw.
66. hyperlipoprotein?emia*.tw.
67. hypertriglycerid?emia*.tw.
68. exp Arteriosclerosis/
69. exp Cholesterol/
70. cholesterol.tw.
71. "coronary risk factor* ".tw.
72. Blood Pressure/
73. blood pressure.tw.
74. or/33-73
75. 32 and 74
76. randomized controlled trial.pt.
77. controlled clinical trial.pt.
78. randomized.ab.
79. placebo.ab.
80. drug therapy.fs.
81. randomly.ab.
82. trial.ab.
83. groups.ab.
84. 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83
85. exp animals/ not humans.sh.
86. 84 not 85
87. 75 and 86

EMBASE

1. omega 6 fatty acid/
2. omega 6.tw.
3. (n-6 adj4 acid*).tw.
4. (n 6 adj4 acid*).tw.
5. omega-6.tw.
6. linoleic acid*.tw.
7. (poly* adj4 unsat* adj4 fatty acid*).tw.
8. PUFA.tw.
9. edible oil/
10. corn oil/

11. ((corn or maize or mazola) adj4 oil*).tw.
12. maydol.tw.
13. lipomul*.tw.
14. cotton seed oil/
15. cottonseed*.tw.
16. cotton seed*.tw.
17. soybean oil/
18. intralipid.tw.
19. nutrilipid.tw.
20. ((soy bean or soybean) adj4 (oil* or fat* or sauce*)).tw.
21. (so?a adj4 oil*).tw.
22. so?aoil*.tw.
23. (soy adj4 oil*).tw.
24. soyacal.tw.
25. travamulsion.tw.
26. sunflower oil/
27. (sunflower adj4 oil*).tw.
28. helianth*.tw.
29. safflower oil/
30. (safflower adj4 oil*).tw.
31. liposyn.tw.
32. (grapeseed adj4 oil*).tw.
33. or/1-32
34. exp cardiovascular disease/
35. cardio*.tw.
36. cardia*.tw.
37. heart*.tw.
38. coronary*.tw.
39. angina*.tw.
40. ventric*.tw.
41. myocard*.tw.
42. pericard*.tw.
43. isch?em*.tw.
44. emboli*.tw.
45. arrhythmi*.tw.
46. thrombo*.tw.
47. atrial fibrillat*.tw.
48. tachycardi*.tw.
49. endocardi*.tw.
50. (sick adj sinus).tw.
51. exp cerebrovascular disease/
52. (stroke or stokes).tw.
53. cerebrovasc*.tw.
54. cerebral vascular.tw.
55. apoplexy.tw.
56. (brain adj2 accident*).tw.
57. ((brain* or cerebral or lacunar) adj2 infarct*).tw.
58. exp hypertension/
59. hypertensi*.tw.
60. peripheral arter* disease*.tw.
61. ((high or increased or elevated) adj2 blood pressure).tw.
62. exp hyperlipidemia/
63. hyperlipid*.tw.
64. hyperlip?emia*.tw.
65. hypercholesterol*.tw.
66. hypercholester?emia*.tw.
67. hyperlipoprotein?emia*.tw.
68. hypertriglycerid?emia*.tw.
69. exp Arteriosclerosis/
70. exp Cholesterol/
71. cholesterol.tw.
72. "coronary risk factor*".tw.

73. Blood Pressure/
74. blood pressure.tw.
75. or/34-74
76. 33 and 75
77. random$.tw.
78. factorial$.tw.
79. crossover$.tw.
80. cross over$.tw.
81. cross-over$.tw.
82. placebo$.tw.
83. (doubl$ adj blind$).tw.
84. (singl$ adj blind$).tw.
85. assign$.tw.
86. allocat$.tw.
87. volunteer$.tw.
88. crossover procedure/
89. double blind procedure/
90. randomized controlled trial/
91. single blind procedure/
92. 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91
93. (animal/ or nonhuman/) not human/
94. 92 not 93
95. 76 and 94
96. limit 95 to embase

Web of Science

19 #18 AND #17
18 TS=(random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*)
17 #16 AND #8
16 #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9
15 TS=(hyperlipid* OR hyperlip?emia* OR hypercholesterol* OR hypercholester?emia* OR hyperlipoprotein?emia* OR hypertriglycerid?emia*)
14 TS=("high blood pressure")
13 TS=(hypertensi* OR "peripheral arter* disease*")
12 TS=(stroke OR stokes OR cerebrovasc* OR cerebral OR apoplexy OR (brain SAME accident*) OR (brain SAME infarct*))
11 TS=("atrial fibrillat*" OR tachycardi* OR endocardi*)
10 TS=(pericard* OR isch?em* OR emboli* OR arrhythmi* OR thrombo*)
9 TS=(cardio* OR cardia* OR heart* OR coronary* OR angina* OR ventric* OR myocard*)
8 #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
7 TS=((grapeseed near/4 oil*))
6 TS=((safflower N4 oil*) or liposyn)
5 TS=((sunflower N4 oil*) or helianth*)
4 TS=(((soy bean or soybean) N4 (oil* or fat* or sauce*)) or (so?a N4 oil*) or intralipid or nutrilipid or so?aoil* or (soy near/4 oil*) or soyacal or travamulsion)
3 TS=(cottonseed* or "cotton seed*")
2 TS=(((corn or maize or mazola) N4 oil*) or maydol or lipomul*)
1 TS=("omega 6" or "omega-6" or (n-6 N4 acid*) or ("n 6" N4 acid*) or "linoleic acid*" or (poly* N4 unsat* N4 fatty acid*) or PUFA)

Clinical trial registers

Omega 6 and Cardio*

Omega 6 and primary prevention OR risk AND Cardio*

Omega 6

Appendix 2. Search strategies for this update of the review

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.

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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

ClinicalTrials.gov and WHO International Clinical Trials Registry Platform

We searched ClinicalTrials.gov (www.ClinicalTrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP, www.who.int/ictrp/en) during September 2016:

(PUFA OR polyunsaturate* OR poly-unsaturate* OR omega-3 OR omega3 OR omega6 OR omega-6 OR fish* OR marine* OR n-3 OR n-6 OR EPA OR DHA OR ALA OR linoleic* OR linolenic*) AND (fat* OR oil* OR supplement* OR capsule*)

Appendix 3. Studies excluded due to duration < 12 months

Excluded studies - excluded due to duration of less than 12 months

Ahrén 2009

(CRSSTD: 2912017)

Ahrén B, Mari A, Fyfe CL, Tsofliou F, Sneddon AA, Wahle KW, et al. Effects of conjugated linoleic acid plus n-3 polyunsaturated fatty acids on insulin secretion and estimated insulin sensitivity in men. European Journal of Clinical Nutrition 2009;63(6):778-86. (CRSREF: 2912018)

Allman-Farinelli 1999

(CRSSTD: 2912019)

Allman-Farinelli MA, Hall D, Kingham K, Pang D, Petocz P, Favaloro EJ. Comparison of the effects of two low fat diets with different alpha-linolenic:linoleic acid ratios on coagulation and fibrinolysis. Atherosclerosis 1999;142(1):159-68. (CRSREF: 2912020)

Anderson 1957

(CRSSTD: 2912021)

Anderson JT, Grande F, Keys A. Essential fatty acids, degree of unsaturation, and effect of corn (maize) oil on the serum-cholesterol level in man. Lancet 1957;272(6959):66-8. (CRSREF: 2912022)

Angela Liou 2009

(CRSSTD: 2912023)

Angela Liou Y, Innis SM. Dietary linoleic acid has no effect on arachidonic acid, but increases n-6 eicosadienoic acid, and lowers dihomo-linolenic and eicosapentaenoic acid in plasma of adult men. Prostaglandins, Leukotrienes, and Essential Fatty Acids 2009;80(4):201-6. (CRSREF: 2912024)

Bachmair 2012

(CRSSTD: 2912025)

Bachmair EM, Bots ML, Mennen LI, Kelder T, Evelo CT, Horgan GW, et al. Effect of supplementation with an 80:20 cis9,trans11 conjugated linoleic acid blend on the human platelet proteome. Molecular Nutrition & Food Research 2012;56(7):1148-59. (CRSREF: 2912026)

Becker 1983

(CRSSTD: 2912027)

Becker N, Illingworth DR, Alaupovic P, Connor WE, Sundberg EE. Effects of saturated, monounsaturated, and omega-6 polyunsaturated fatty acids on plasma lipids, lipoproteins, and apoproteins in humans. American Journal of Clinical Nutrition 1983;37(3):355-60. (CRSREF: 2912028)

Belury 2009

(CRSSTD: 2912029)

Belury M, Collene A, Norris L, Asp M, Hsu J, Li D, et al. Comparison of dietary oils on criteria of metabolic syndrome in postmenopausal women: a randomized crossover clinical intervention study. Journal of Diabetes 2009;1:A34. (CRSREF: 2912030)

Benito 2001

(CRSSTD: 2912035)

Benito P, Nelson GJ, Kelley DS, Bartolini G, Schmidt PC, Simon V. The effect of conjugated linoleic acid on plasma lipoproteins and tissue fatty acid composition in humans. (Erratum appears in Lipids 2001 Aug;36(8):857). Lipids 2001;36(3):229-36. (CRSREF: 2912036)

Bermejo 2012

(CRSSTD: 2912037)

Bermejo LM, Rodriguez-Duran D, Lopez-Plaza B, Zurita-Rosa L, Palma-Milla S, Weber TK, et al. Effects of a functional light cheese naturally enriched with CLA and omega-3 improving blood lipid profile in overweight and obese people treatment. Clinical Nutrition, Supplement 2012;7(1):219. (CRSREF: 2912038)

Bjermo 2012

(CRSSTD: 2912039)

Bjermo H, Iggman D, Kullberg J, Dahlman I, Johansson L, Persson L, et al. Effects of n-6 PUFAs compared with SFAs on liver fat, lipoproteins, and inflammation in abdominal obesity: a randomized controlled trial. American Journal of Clinical Nutrition 2012;95(5):1003-12. (CRSREF: 2912040)

Blair 1993

(CRSSTD: 2912041)

Blair IA, Prakash C, Phillips MA, Dougherty RM, Iacono JM. Dietary modification of omega 6 fatty acid intake and its effect on urinary eicosanoid excretion. American Journal of Clinical Nutrition 1993;57(2):154-60. (CRSREF: 2912042)

Boberg 1986

(CRSSTD: 2912043)

Boberg M, Vessby B, Selinus I. Effects of dietary supplementation with n-6 and n-3 long-chain polyunsaturated fatty acids on serum lipoproteins and platelet function in hypertriglyceridaemic patients. Acta Medica Scandinavica 1986;220(2):153-60. (CRSREF: 2912044)

Bonanome 1992

(CRSSTD: 2912045)

Bonanome A, Pagnan A, Biffanti S, Opportuno A, Sorgato F, Dorella M, et al. Effect of dietary monounsaturated and polyunsaturated fatty acids on the susceptibility of plasma low density lipoproteins to oxidative modification. Arteriosclerosis and Thrombosis 1992;12(4):529-33. (CRSREF: 2912046)

Brady 2004

(CRSSTD: 2912049)

Brady LM, Lovegrove SS, Lesauvage SV, Gower BA, Minihane AM, Williams CM, et al. Increased n-6 polyunsaturated fatty acids do not attenuate the effects of long-chain n-3 polyunsaturated fatty acids on insulin sensitivity or triacylglycerol reduction in Indian Asians. American Journal of Clinical Nutrition 2004;79(6):983-91. (CRSREF: 2912050)

Bronsgeest-Schoute 1979

(CRSSTD: 2912053)

Bronsgeest-Schoute DC, Hermus RJ, Dallinga-Thie GM, Hautvast JG. Dependence of the effects of dietary cholesterol and experimental conditions on serum lipids in man. II. Effects of dietary cholesterol in a linoleic acid-poor diet. American Journal of Clinical Nutrition 1979;32(11):2188-92. (CRSREF: 2912054)

Brox 1981

(CRSSTD: 2912055)

Brox JH, Killie JE, Gunnes S, Nordøy A. The effect of cod liver oil and corn oil on platelets and vessel wall in man. Thrombosis and Haemostasis 1981;46(3):604-11. (CRSREF: 2912056)

Burdge 2004

(CRSSTD: 2912057)

Burdge GC, Lupoli B, Russell JJ, Tricon S, Kew S, Banerjee T, et al. Incorporation of cis-9,trans-11 or trans-10,cis-12 conjugated linoleic acid into plasma and cellular lipids in healthy men. Journal of Lipid Research 2004;45(4):736-41. (CRSREF: 2912058)

Camargo 2013

(CRSSTD: 2912059)

Camargo A, Meneses M, Rangel-Zuniga,O, Pérez-Martínez P, Delgado-Lista J, Marín C, et al. Dietary fat modifies lipid metabolism in the adipose tissue of patients with metabolic syndrome. Annals of Nutrition and Metabolism 2013;62:63. (CRSREF: 2912060)

Carvalho 2012

(CRSSTD: 2912061)

Carvalho RF, Uehara SK, Rosa G. Microencapsulated conjugated linoleic acid associated with hypocaloric diet reduces body fat in sedentary women with metabolic syndrome. Vascular Health and Risk Management 2012;8:661-7. (CRSREF: 2912062)

Cater 1997

(CRSSTD: 2912063)

Cater NB, Heller HJ, Denke MA. Comparison of the effects of medium-chain triacylglycerols, palm oil, and high oleic acid sunflower oil on plasma triacylglycerol fatty acids and lipid and lipoprotein concentrations in humans. American Journal of Clinical Nutrition 1997;65(1):41-5. (CRSREF: 2912064)

Clandinin 1999

(CRSSTD: 2912065)

Clandinin MT, Cook SL, Konrad SD, Goh YK, French MA. The effect of palmitic acid on lipoprotein cholesterol levels and endogenous cholesterol synthesis in hyperlipidemic subjects. Lipids 1999;34 Suppl:S121-4. (CRSREF: 2912066)

Deferne 1992

(CRSSTD: 2912069)

Deferne JL, Leeds AR. The antihypertensive effect of dietary supplementation with a 6-desaturated essential fatty acid concentrate as compared with sunflower seed oil. Journal of Human Hypertension 1992;6(2):113-9. (CRSREF: 2912070)

de Kok 2003

(CRSSTD: 2912071)

de Kok TM, Zwingman I, Moonen EJ, Schilderman PA, Rhijnsburger E, Haenen GR, et al. Analysis of oxidative DNA damage after human dietary supplementation with linoleic acid. Food and Chemical Toxicology 2003;41(3):351-8. (CRSREF: 2912072)

Failor 1988

(CRSSTD: 2912079)

Failor RA, Childs MT, Bierman EL. The effects of omega 3 and omega 6 fatty acid-enriched diets on plasma lipoproteins and apoproteins in familial combined hyperlipidemia. Metabolism: Clinical and Experimental 1988;37(11):1021-8. (CRSREF: 2912080)

Friday 1991

(CRSSTD: 2912085)

Friday KE, Failor RA, Childs MT, Bierman EL. Effects of n-3 and n-6 fatty acid-enriched diets on plasma lipoproteins and apolipoproteins in heterozygous familial hypercholesterolemia. Arteriosclerosis and Thrombosis 1991;11(1):47-54. (CRSREF: 2912086)

Giacco 2007

(CRSSTD: 2912097)

Giacco R, Cuomo V, Vessby B, Uusitupa M, Hermansen K, Meyer BJ, et al. Fish oil, insulin sensitivity, insulin secretion and glucose tolerance in healthy people: is there any effect of fish oil supplementation in relation to the type of background diet and habitual dietary intake of n-6 and n-3 fatty acids? Nutrition, Metabolism, and Cardiovascular Diseases: NMCD 2007;17(8):572-80. (CRSREF: 2912098)

Groen 1965

(CRSSTD: 2912099)

Groen JJ, Balogh M, Yaron E, Freeman J. Influence of the nature of the fat in diets high in carbohydrate (mainly derived from bread) on the serum cholesterol. American Journal of Clinical Nutrition 1965;17(5):296-304. (CRSREF: 2912100)

Grundt 1995

(CRSSTD: 2912101)

Grundt H, Nilsen D, Hetland O, Aarsland T, Baksaas I, Grande T et al. Improvement of serum lipids and blood pressure during intervention with n-3 fatty acids was not associated with changes in insulin levels in subjects with combined hyperlipidaemia. Journal of Internal Medicine 1995;237:249-59. (CRSREF: 2912102)

Grønn 1991

(CRSSTD: 2912103)

Grønn M, Gørbitz C, Christensen E, Levorsen A, Ose L, Hagve TA, et al. Dietary n-6 fatty acids inhibit the incorporation of dietary n-3 fatty acids in thrombocyte and serum phospholipids in humans: a controlled dietetic study. Scandinavian Journal of Clinical and Laboratory Investigation 1991;51(3):255-63. (CRSREF: 2912104)

Haglund 1998

(CRSSTD: 2912105)

Haglund O, Wallin R, Wretling S, Hultberg B, Saldeen T. Effects of fish oil alone and combined with long chain (n-6) fatty acids on some coronary risk factors in male subjects. Journal of Nutritional Biochemistry 1998;9(11):629-35. (CRSREF: 2912106)

Hartwich 2009

(CRSSTD: 2912109)

Hartwich J, Malczewska-Malec M, Kiec-Wilk B, Leszczynska-Golabek I, Dembinska-Kiec A, Pérez-Martinez P, et al. The effect of the N-3/N-6 pufa ratio on the postprandial LDL phenotype and ischemia modified albumin (IMA). The LIPGENE study. In: Atherosclerosis Supplements. Vol. 10. 2009. (CRSREF: 2912110)

Hartwich 2010

(CRSSTD: 2912111)

Hartwich J, Leszczynska-Golabek I, Kiec-Wilk B, Siedlecka D, Pérez-Martinez P, Marin C, et al. Lipoprotein profile, plasma ischemia modified albumin and LDL density change in the course of postprandial lipemia. Insights from the LIPGENE study. Scandinavian Journal of Clinical and Laboratory Investigation 2010;70(3):201-8. (CRSREF: 2912112)

Higdon 2000

(CRSSTD: 2912115)

Higdon JV, Liu J, Du SH, Morrow JD, Ames BN, Wander RC. Supplementation of postmenopausal women with fish oil rich in eicosapentaenoic acid and docosahexaenoic acid is not associated with greater in vivo lipid peroxidation compared with oils rich in oleate and linoleate as assessed by plasma malondialdehyde and F(2)-isoprostanes. American Journal of Clinical Nutrition 2000;72(3):714-22. (CRSREF: 2912116)

Higdon 2001

(CRSSTD: 2912117)

Higdon JV, Du SH, Lee YS, Wu T, Wander RC. Supplementation of postmenopausal women with fish oil does not increase overall oxidation of LDL ex vivo compared to dietary oils rich in oleate and linoleate. Journal of Lipid Research 2001;42(3):407-18. (CRSREF: 2912118)

Ho 1999

(CRSSTD: 2912119)

Ho M, Maple C, Bancroft A, McLaren M, Belch JJ. The beneficial effects of omega-3 and omega-6 essential fatty acid supplementation on red blood cell rheology. Prostaglandins, Leukotrienes, and Essential Fatty Acids 1999;61(1):13-7. (CRSREF: 2912120)

Hodson 2001

(CRSSTD: 2912121)

Hodson L, Skeaff CM, Chisholm WA. The effect of replacing dietary saturated fat with polyunsaturated or monounsaturated fat on plasma lipids in free-living young adults. European Journal of Clinical Nutrition 2001;55(10):908-15. (CRSREF: 2912122)

Hwang 1997

(CRSSTD: 2912125)

Hwang DH, Chanmugam PS, Ryan DH, Boudreau MD, Windhauser MM, Tulley RT, et al. Does vegetable oil attenuate the beneficial effects of fish oil in reducing risk factors for cardiovascular disease? American Journal of Clinical Nutrition 1997;66(1):89-96. (CRSREF: 2912126)

Intorre 2013

(CRSSTD: 2912127)

Intorre F, Venneria E, Finotti E, Foddai MS, Toti E, Catasta G, et al. Fatty acid content of serum lipid fractions and blood lipids in normolipidaemic volunteers fed two types of cheese having different fat compositions: a pilot study. International Journal of Food Sciences and Nutrition 2013;64(2):185-93. (CRSREF: 2912128)

Iwata 2007

(CRSSTD: 2912129)

Iwata T, Kamegai T, Yamauchi-Sato Y, Ogawa A, Kasai M, Aoyama T, et al. Safety of dietary conjugated linoleic acid (CLA) in a 12-weeks trial in healthy overweight Japanese male volunteers. Journal of Oleo Science 2007;56(10):517-25. (CRSREF: 2912130)

Kiecolt-Glaser 2013

(CRSSTD:2912133)

Kiecolt-Glaser JK, Epel ES, Belury MA, Andridge R, Lin J, Glaser R, et al. Omega-3 fatty acids, oxidative stress, and leukocyte telomere length: A randomized controlled trial. Brain, Behavior, and Immunity 2013;28:16-24. (CRSREF: 2912134)

Kim 2009

(CRSSTD: 2912135)

Kim JH, Kim OH, Jung H. Effects of supplementation of conjugated linoleic acid with gammaoryzanol on body fat mass in healthy overweight Korean women. In: FASEB Journal. Vol. 23 (Meeting Abstract Supplement). 2009:563.26. (CRSREF: 2912136)

Kingsbury 1961

(CRSSTD: 2912137)

Kingsbury KJ, Aylott C, Morgan DM, Emmerson R. Effects of ethyl arachidonate, cod-liver oil, and corn oil on the plasma-cholesterol level. A comparison in normal volunteers. Lancet 1961;1(7180):739-41. (CRSREF: 2912138)

Knapp 1989

(CRSSTD: 2912139)

Knapp HR, FitzGerald GA. The antihypertensive effects of fish oil. A controlled study of polyunsaturated fatty acid supplements in essential hypertension. New England Journal of Medicine 1989;320(16):1037-43. (CRSREF: 2912140)

Koyama 2009

(CRSSTD: 2912141)

Koyama N, Suzuki K, Furukawa Y, Arisaka H, Seki T, Kuribayashi K, et al. Effects of safflower seed extract supplementation on oxidation and cardiovascular risk markers in healthy human volunteers. British Journal of Nutrition 2009;101(4):568-75. (CRSREF: 2912142)

Lambert 2007

(CRSSTD: 2912143)

Lambert EV, Goedecke JH, Bluett K, Heggie K, Claassen A, Rae DE, et al. Conjugated linoleic acid versus high-oleic acid sunflower oil: effects on energy metabolism, glucose tolerance, blood lipids, appetite and body composition in regularly exercising individuals. British Journal of Nutrition 2007;97(5):1001-11. (CRSREF: 2912144)

Lee 2012

(CRSSTD: 2912147)

Lee SP, Dart AM, Walker KZ, O'Dea K, Chin-Dusting JP, Skilton MR. Effect of altering dietary n-6:n-3 PUFA ratio on cardiovascular risk measures in patients treated with statins: a pilot study. British Journal of Nutrition 2012;108(7):1280-5. (CRSREF: 2912148)

Legrand 2010

(CRSSTD: 2912149)

Legrand P, Schmitt B, Mourot J, Catheline D, Chesneau G, Mireaux M, et al. The consumption of food products from linseed-fed animals maintains erythrocyte omega-3 fatty acids in obese humans. Lipids 2010;45(1):11-9. (CRSREF: 2912150)

Margolin 1990

(CRSSTD: 2912154)

Margolin G, Huster G, Glueck CJ, Speirs J, Vandegrift J, Illig E. Blood-pressure lowering in the elderly - a double-blind crossover study of omega-3 and omega-6 fatty-acids. American Journal of Clinical Nutrition 1990;51(3):518. (CRSREF: 2912155)

Margolin 1991

(CRSSTD: 2912156)

Margolin G, Huster G, Glueck CJ, Speirs J, Vandegrift J, Illig E, et al. Blood pressure lowering in elderly subjects: a double-blind crossover study of omega-3 and omega-6 fatty acids. American Journal of Clinical Nutrition 1991;53(2):562-72. (CRSREF: 2912157)

McDaniel 2010

(CRSSTD: 2912158)

McDaniel JC, Ahijevych K, Belury M. Effect of n-3 oral supplements on the n-6/n-3 ratio in young adults. Western Journal of Nursing Research 2010;32(1):64-80. (CRSREF: 2912159)

MEMO - Bouwens 2009

(CRSSTD: 2912047)

Bouwens M, van De Rest O, Dellschaft N, Bromhaar MG, De Groot LC, Geleijnse JM, et al. Fish-oil supplementation induces antiinflammatory gene expression profiles in human blood mononuclear cells. American Journal of Clinical Nutrition 2009;90(2):415-24. (CRSREF: 2912048)

Miles 2004

(CRSSTD: 2912162)

Miles EA, Banerjee T, Calder PC. The influence of different combinations of gamma-linolenic, stearidonic and eicosapentaenoic acids on the fatty acid composition of blood lipids and mononuclear cells in human volunteers. Prostaglandins, Leukotrienes, and Essential Fatty Acids 2004;70(6):529-38. (CRSREF: 2912163)

Mills 1989

(CRSSTD: 2912164)

Mills DE, Prkachin KM, Harvey KA, Ward RP. Dietary fatty acid supplementation alters stress reactivity and performance in man. Journal of Human Hypertension 1989;3(2):111-6. (CRSREF: 2912165)

Minihane 2005

(CRSSTD: 2912166)

Minihane AM, Brady LM, Lovegrove SS, Lesauvage SV, Williams CM, Lovegrove JA. Lack of effect of dietary n-6:n-3 PUFA ratio on plasma lipids and markers of insulin responses in Indian Asians living in the UK. European Journal of Nutrition 2005;44(1):26-32. (CRSREF: 2912167)

Misikangas 2001

(CRSSTD: 2912168)

Misikangas M, Freese R, Turpeinen AM, Mutanen M. High linoleic acid, low vegetable, and high oleic acid, high vegetable diets affect platelet activation similarly in healthy women and men. Journal of Nutrition 2001;131(6):1700-5. (CRSREF: 2912169)

Moore 2006

(CRSSTD: 2912006)

Moore CS, Bryant SP, Mishra GD, Krebs JD, Browning LM, Miller GJ, et al. Oily fish reduces plasma triaclyglycerols: a primary prevention study in overweight men and women. Nutrition 2006;22(10):1012-24. (CRSREF: 2912007)

Mortensen 1983

(CRSSTD: 2912170)

Mortensen JZ, Schmidt EB, Nielsen AH, Dyerberg J. The effect of N-6 and N-3 polyunsaturated fatty acids on hemostasis, blood lipids and blood pressure. Thrombosis and Haemostasis 1983;50(2):543-6. (CRSREF: 2912171)

Møller 1992

(CRSSTD: 2912172)

Møller J, Svaneborg N, Lervang HH, Varming K, Madsen P, Dyerberg J, et al. The acute effect of a single very high dose of N-3 fatty acids on coagulation and fibrinolysis. Thrombosis Research 1992;67(5):569-77. (CRSREF: 2912173)

Naber 1992

(CRSSTD: 2912174)

Naber FB, Oudkerk Pool M, Teerlink T, Popp-Snijders C, Gans RO, Bilo HJ. Effect of short-term use of omega-3-type polyunsaturated fatty acids in subjects with hypertriglyceridemia (Dutch). Nederlands Tijdschrift voor Geneeskunde 1992;136(31):1511-4. (CRSREF: 2912175)

Naumann 2006

(CRSSTD: 2912176)

Naumann E, Carpentier YA, Saebo A, Lassel TS, Chardigny JM, Sébédio JM, et al. Cis-9, trans- 11 and trans-10, cis-12 conjugated linoleic acid (CLA) do not affect the plasma lipoprotein profile in moderately overweight subjects with LDL phenotype B. Atherosclerosis 2006;188(1):167-74. (CRSREF: 2912177)

NDHS Open 2nd 1968

(Empty)

Nelson 1997a

(CRSSTD: 2912178)

Nelson GJ, Schmidt PC, Bartolini G, Kelley DS, Phinney SD, Kyle D, et al. The effect of dietary arachidonic acid on plasma lipoprotein distributions, apoproteins, blood lipid levels, and tissue fatty acid composition in humans. Lipids 1997;32(4):427-33. (CRSREF: 2912179)

Nelson 1997b

(CRSSTD: 2912180)

Nelson GJ, Kelley DS, Emken EA, Phinney SD, Kyle D, Ferretti A. A human dietary arachidonic acid supplementation study conducted in a metabolic research unit: rationale and design. Lipids 1997;32(4):415-20. (CRSREF: 2912181)

Nestel 1992

(CRSSTD: 2912182)

Nestel P, Noakes M, Belling GB, McArthur R, Clifton RM, Abbey M. Plasma cholesterol-lowering potential of edible-oil blends suitable for commercial use. American Journal of Clinical Nutrition 1992;55(1):46-50. (CRSREF: 2912183)

Nestel 1995

(CRSSTD: 2912184)

Nestel PJ, Noakes M, Belling GB, McArthur R, Clifton PM. Effect on plasma lipids of interesterifying a mix of edible oils. American Journal of Clinical Nutrition 1995;62(5):950-5. (CRSREF: 2912185)

Noakes 1996

(CRSSTD: 2912186)

Noakes M, Nestel P, Clifton P. Commercial frying fats and plasma lipid-lowering potential. Australian Journal of Nutrition and Dietetics 1996;53(1):25-30. (CRSREF: 2912187)

Oe 2008

(CRSSTD: 2912188)

Oe H, Hozumi T, Murata E, Matsuura H, Negishi K, Matsumura Y, et al. Arachidonic acid and docosahexaenoic acid supplementation increases coronary flow velocity reserve in Japanese elderly individuals. Heart 2008;94(3):316-21. (CRSREF: 2912189)

OPTILIP 2006

(CRSSTD: 2912010)

Griffin MD, Sanders TA, Davies IG, Morgan LM, Millward DJ, Lewis F et al. Effects of altering the ratio of dietary n-6 to n-3 fatty acids on insulin sensitivity, lipoprotein size, and postprandial lipemia in men and postmenopausal women aged 45-70 y: the OPTILIP Study. American Journal of Clinical Nutrition 2006;84(6):1290-8. (CRSREF: 2912011)

* Sanders TAB, Lewis F, Slaughter S, Griffin BA, Griffin M, Davies I, et al. Effect of varying the ratio of n-6 to n-3 fatty acids by increasing the dietary intake of alpha-linolenic acid, eicosapentaenoic and docosahexaenoic acid, or both on fibrinogen and clotting factors VII and XII in persons aged 45-70 y: the OPTILIP study. American Journal of Clinical Nutrition 2006;84(3):513-22. (CRSREF: 2912012)

Paschos 2007

(CRSSTD: 2912190)

Paschos GK, Zampelas A, Panagiotakos DB, Katsiougiannis S, Griffin BA, Votteas V, et al. Effects of flaxseed oil supplementation on plasma adiponectin levels in dyslipidemic men. European Journal of Nutrition 2007;46(6):315-20. (CRSREF: 2912191)

Pałkowska 2012

(CRSSTD: 2912192)

Pałkowska E, Bartnikowska E, Owsiak D. The use of low-caloric diet with modified fatty acids pool in the therapy of the metabolic syndrome. Roczniki Państwowego Zakładu Higieny 2012;63(2):163-9. (CRSREF: 2912193)

Perez-Martinez 2010

(CRSSTD: 2912194)

Perez-Martinez P, Garcia-Quintana J, Yubero-Serrano E, Tasset-Cuevas I, Tunez I, Garcia-Rios A et al. Postprandial oxidative stress is modified by dietary fat: evidence from a human intervention study. Clinical Science 2010;119(6):251-61. (CRSREF: 2912195)

Perkins 1958

(CRSSTD: 2912196)

Perkins R, Wright IS, Gatje BW. Effect of safflower oil emulsion on serum cholesterol levels in young adult males. Its use as a supplement to a normal diet. Journal of the American Medical Association 1958;166(17):2132-5. (CRSREF: 2912197)

Radack 1990

(CRSSTD: 2912198)

Radack K, Deck C, Huster G. The comparative effects of n-3 and n-6 polyunsaturated fatty acids on plasma fibrinogen levels: a controlled clinical trial in hypertriglyceridemic subjects. Journal of the American College of Nutrition 1990;9(4):352-7. (CRSREF: 2912199)

Radack 1991

(CRSSTD: 2912200)

Radack K, Deck C, Huster G. The effects of low doses of n-3 fatty acid supplementation on blood pressure in hypertensive subjects. A randomized controlled trial. Archives of Internal Medicine 1991;151(6):1173-80. (CRSREF: 2912201)

Rajaram 2012

(CRSSTD: 2912202)

Rajaram S, Sabate J, Mohan S. Effect of n-3 polyunsaturated fatty acids on peroxisome proliferator-activated receptor gamma (PPARγ) expression in adults. In: FASEB Journal. Vol. 26. 2012:823.28. (CRSREF: 2912203)

Rallidis 2003

(CRSSTD: 2912204)

Rallidis LS, Paschos G, Liakos GK, Velissaridou AH, Anastasiadis G, Zampelas A. Dietary alpha-linolenic acid decreases C-reactive protein, serum amyloid A and interleukin-6 in dyslipidaemic patients. Atherosclerosis 2003;167(2):237-42. (CRSREF: 2912205)

Rallidis 2004

(CRSSTD: 2912206)

Rallidis LS, Paschos G, Papaioannou M, Liakos GK, Panagiotakos DB, Anastasiadis G, et al. The effect of diet enriched with alpha-linolenic acid on soluble cellular adhesion molecules in dyslipidaemic patients. Atherosclerosis 2004;174(1):127-32. (CRSREF: 2912207)

Ramprasath 2012

(CRSSTD: 2912208)

Ramprasath VR, Jones PJ, Buckley DD, Woollett LA, Heubi JE. Decreased plasma cholesterol concentrations after PUFA-rich diets are not due to reduced cholesterol absorption/synthesis. Lipids 2012;47(11):1063-71. (CRSREF: 2912209)

Reaven 1991

(CRSSTD: 2912210)

Reaven P, Parthasarathy S, Grasse BJ, Miller E, Almazan F, Mattson FH, et al. Feasibility of using an oleate-rich diet to reduce the susceptibility of low-density lipoprotein to oxidative modification in humans. American Journal of Clinical Nutrition 1991;54(4):701-6. (CRSREF: 2912211)

Risérus 2002a

(CRSSTD: 2912212)

Risérus U, Basu S, Jovinge S, Fredrikson G, Arnlöv J, Vessby B. Supplementation with conjugated linoleic acid causes isomer-dependent oxidative stress and elevated C-reactive protein: a potential link to fatty acid-induced insulin resistance. Circulation 2002;106(15):1925-9. (CRSREF: 2912213)

Risérus 2002b

(CRSSTD: 2912214)

Risérus U, Arner P, Brismar K, Vessby B. Treatment with dietary trans10cis12 conjugated linoleic acid causes isomer-specific insulin resistance in obese men with the metabolic syndrome. Diabetes Care 2002;25(9):1516-21. (CRSREF: 2912215)

Risérus 2004

(CRSSTD: 2912216)

Risérus U, Vessby B, Arner P, Zethelius B. Supplementation with trans10cis12-conjugated linoleic acid induces hyperproinsulinaemia in obese men: close association with impaired insulin sensitivity. Diabetologia 2004;47(6):1016-9. (CRSREF: 2912217)

Robertson 2002

(CRSSTD: 2912218)

Robertson MD, Jackson KG, Fielding BA, Morgan LM, Williams CM, Frayn KN. Acute ingestion of a meal rich in n-3 polyunsaturated fatty acids results in rapid gastric emptying in humans. American Journal of Clinical Nutrition 2002;76(1):232-8. (CRSREF: 2912219)

Sanders 1983

(CRSSTD: 2912222)

Sanders TA, Hochland MC. A comparison of the influence on plasma lipids and platelet function of supplements of omega 3 and omega 6 polyunsaturated fatty acids. British Journal of Nutrition 1983;50(3):521-9. (CRSREF: 2912223)

Sanders 1997

(CRSSTD: 2912224)

Sanders TA, Oakley FR, Miller GJ, Mitropoulos KA, Crook D, Oliver MF. Influence of n-6 versus n-3 polyunsaturated fatty acids in diets low in saturated fatty acids on plasma lipoproteins and hemostatic factors. Arteriosclerosis, Thrombosis, and Vascular Biology 1997;17(12):3449-60. (CRSREF: 2912225)

Sarkkinen 1998

(CRSSTD: 2912013)

Sarkkinen ES, Uusitupa MI, Gylling H, Miettinen TA. Fat-modified diets influence serum concentrations of cholesterol precursors and plant sterols in hypercholesterolemic subjects. Metabolism 1998;47(6):744-50. (CRSREF: 2912014)

Singer 1991

(CRSSTD: 2912226)

Singer P, Wirth M, Kretschmer H. Different changes of n-6 fatty acids in lipoproteins from hyperlipemic subjects after diets supplemented with n-3 fatty acids. Prostaglandins, Leukotrienes, and Essential Fatty Acids 1991;42(2):107-11. (CRSREF: 2912227)

Sirtori 1992

(CRSSTD: 2912228)

Sirtori CR, Gatti E, Tremoli E, Galli C, Gianfranceschi G, Franceschini G, et al. Olive oil, corn oil, and n-3 fatty acids differently affect lipids, lipoproteins, platelets, and superoxide formation in type II hypercholesterolemia. American Journal of Clinical Nutrition 1992;56(1):113-22. (CRSREF: 2912229)

Smedman 2001

(CRSSTD: 2912230)

Smedman A, Vessby B. Conjugated linoleic acid supplementation in humans--metabolic effects. Lipids 2001;36(8):773-81. (CRSREF: 2912231)

Sofi 2010

(CRSSTD: 2912232)

Sofi F, Buccioni A, Cesari F, Gori A, Minieri S, Mannini L, et al. Effects of a dairy product (pecorino cheese) naturally rich in cis-9, trans-11 conjugated linoleic acid on lipid, inflammatory and haemorheological variables: a dietary intervention study. Nutrition, Metabolism, and Cardiovascular Diseases 2010;20(2):117-24. (CRSREF: 2912233)

Sofi 2013

(CRSSTD: 2912234)

Sofi F, Giorgi G, Cesari G, Gori AM, Mannini L, Parisi G, et al. The atherosclerotic risk profile is affected differently by fish flesh with a similar EPA and DHA content but different n-6/n-3 ratio. Asia Pacific Journal of Clinical Nutrition 2013;22(1):32-40. (CRSREF: 2912235)

Solà 1997

(CRSSTD: 2912236)

Solà R, La Ville AE, Richard JL, Motta C, Bargalló MT, Girona J, et al. Oleic acid rich diet protects against the oxidative modification of high density lipoprotein. Free Radical Biology & Medicine 1997;22(6):1037-45. (CRSREF: 2912237)

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(CRSSTD: 2912238)

Song HJ, Grant I, Rotondo D, Mohede I, Sattar N, Heys SD, et al. Effect of CLA supplementation on immune function in young healthy volunteers. European Journal of Clinical Nutrition 2005;59(4):508-17. (CRSREF: 2912239)

Steck 2007

(CRSSTD: 2912240)

Steck SE, Chalecki AM, Miller P, Conway J, Austin GL, Hardin JW, et al. Conjugated linoleic acid supplementation for twelve weeks increases lean body mass in obese humans. Journal of Nutrition 2007;137(5):1188-93. (CRSREF: 2912241)

Sundram 1992

(CRSSTD: 2912242)

Sundram K, Hornstra G, von Houwelingen AC, Kester AD. Replacement of dietary fat with palm oil: effect on human serum lipids, lipoproteins and apolipoproteins. British Journal of Nutrition 1992;68(3):677-92. (CRSREF: 2912243)

Svaneborg 1994

(CRSSTD: 2912244)

Svaneborg N, Møller JM, Schmidt EB, Varming K, Lervang HH, Dyerberg J. The acute effects of a single very high dose of n-3 fatty acids on plasma lipids and lipoproteins in healthy subjects. Lipids 1994;29(2):145-7. (CRSREF: 2912245)

Tavakkoli 2010

(CRSSTD: 2912246)

Tavakkoli D, Hosseinpanah F, Tahbaz F, Amiri Z, Tavakkoli D, Hedayati M. Effects of conjugated linoleic acid supplementation on body composition and leptin concentration in post-menopausal women (Arabic). Iranian Journal of Endocrinology and Metabolism 2010;12(1):48-59, 84. (CRSREF: 2912247)

Taylor 2006

(CRSSTD: 2912248)

Taylor JS, Williams SR, Rhys R, James P, Frenneaux MP. Conjugated linoleic acid impairs endothelial function. Arteriosclerosis, Thrombosis, and Vascular Biology 2006;26(2):307-12. (CRSREF: 2912249)

Tholstrup 2008

(CRSSTD: 2912250)

Tholstrup T, Raff M, Straarup EM, Lund P, Basu S, Bruun JM. An oil mixture with trans-10, cis-12 conjugated linoleic acid increases markers of inflammation and in vivo lipid peroxidation compared with cis-9, trans-11 conjugated linoleic acid in postmenopausal women. Journal of Nutrition 2008;138(8):1445-51. (CRSREF: 2912251)

Tierney 2011

(CRSSTD: 2912252)

Tierney AC, McMonagle J, Shaw DI, Gulseth HL, Helal O, Saris WH, et al. Effects of dietary fat modification on insulin sensitivity and on other risk factors of the metabolic syndrome--LIPGENE: a European randomized dietary intervention study. International Journal of Obesity 2011;35(6):800-9. (CRSREF: 2912253)

Truswell 2000

(CRSSTD: 2912254)

Truswell AS. Comparing palmolein with different predominantly monounsaturated oils: effect on plasma lipids. International Journal of Food Sciences and Nutrition 2000;15 Suppl:S73-7. (CRSREF: 2912255)

Tsai 1997

(CRSSTD: 2912256)

Tsai PJ, Lu SC. Fish oil lowers plasma lipid concentrations and increases the susceptibility of low density lipoprotein to oxidative modification in healthy men. Journal of the Formosan Medical Association 1997;96(9):718-26. (CRSREF: 2912257)

Tsofliou 2009

(CRSSTD: 2912258)

Tsofliou F, Fyfe C, Matheson I, Jackson D, Horgan G, Wahle K, et al. Fasted and postprandial plasma lipids in healthy volunteers by a dietary mixture of omega-3 fatty acid modulation and conjugated linoleic acid. Journal of Food Lipids 2009;16:499-513. (CRSREF: 2912259)

Tulk 2009

(CRSSTD: 2912260)

Tulk HM, Robinson LE. Modifying the n-6/n-3 polyunsaturated fatty acid ratio of a high-saturated fat challenge does not acutely attenuate postprandial changes in inflammatory markers in men with metabolic syndrome. Metabolism: Clinical and Experimental 2009;58(12):1709-16. (CRSREF: 2912261)

Valsta 1996

(CRSSTD: 2912262)

Valsta LM, Salminen I, Aro A, Mutanen M. Alpha-linolenic acid in rapeseed oil partly compensates for the effect of fish restriction on plasma long chain n-3 fatty acids. European Journal of Clinical Nutrition 1996;50(4):229-35. (CRSREF: 2912263)

Venter 1988

(CRSSTD: 2912264)

Venter CP, Joubert PH, Booyens J. Effects of essential fatty acids on mild to moderate essential hypertension. Prostaglandins, Leukotrienes, and Essential Fatty Acids 1988;33(1):49-51. (CRSREF: 2912265)

Vericel 1987

(CRSSTD: 2912268)

Vericel E, Lagarde M, Mendy F. Comparative effects of linoleic acid and gamma-linolenic acid intake on plasma lipids and platelet phospholipids in elderly people. Nutrition Research 1987;7:569-80. (CRSREF: 2912269)

Vermunt 2001

(CRSSTD: 2912270)

Vermunt SH, Beaufrère B, Riemersma RA, Sébédio JL, Chardigny JM, Mensink RP, et al. Dietary trans alpha-linolenic acid from deodorised rapeseed oil and plasma lipids and lipoproteins in healthy men: the TransLinE Study. British Journal of Nutrition 2001;85(3):387-92. (CRSREF: 2912271)

Viikari 1986

(CRSSTD: 2912272)

Viikari J, Lehtonen A. Effect of primrose oil on serum lipids and blood pressure in hyperlipidemic subjects. International Journal of Clinical Pharmacology, Therapy, and Toxicology 1986;24(12):668-70. (CRSREF: 2912273)

West 2010

(CRSSTD: 2912274)

West SG, Krick AL, Klein LC, Zhao G, Wojtowicz TF, McGuiness M, et al. Effects of diets high in walnuts and flax oil on hemodynamic responses to stress and vascular endothelial function. Journal of the American College of Nutrition 2010;29(6):595-603. (CRSREF: 2912275)

Wilkinson 2005

(CRSSTD: 2912276)

Wilkinson P, Leach C, Ah-Sing EE, Hussain N, Miller GJ, Millward DJ, et al. Influence of alpha-linolenic acid and fish-oil on markers of cardiovascular risk in subjects with an atherogenic lipoprotein phenotype. Atherosclerosis 2005;181(1):115-24. (CRSREF: 2912277)

Yam 2001

(CRSSTD: 2912278)

Yam D, Bott-Kanner G, Genin I, Shinitzky M, Klainman E. The effect of omega-3 fatty acids on risk factors for cardiovascular diseases (Hebrew). Harefuah 2001;140(12):1156-8, 1230. (CRSREF: 2912279)

Zhao 2004

(CRSSTD: 2912280)

Zhao G, Etherton TD, Martin KR, West SG, Gillies PJ, Kris-Etherton PM. Dietary a-linolenic acid reduces inflammatory and lipid cardiovascular risk factors in hypercholesterolemic men and women. Journal of Nutrition 2004;134(11):2991-7. (CRSREF: 2912281)

Zhao 2007

(CRSSTD: 2912282)

Zhao G, Etherton TD, Martin KR, Gillies PJ, West SG, Kris-Etherton PM. Dietary alpha-linolenic acid inhibits proinflammatory cytokine production by peripheral blood mononuclear cells in hypercholesterolemic subjects. American Journal of Clinical Nutrition 2007;85(2):385-91. (CRSREF: 2912283)

WHAT'S NEW

Date	Event	Description
26 November 2018	New citation required but conclusions have not changed	Clarified methodology on interpretation of effects (no re-interpretation of outcomes was needed) and corrected study flow.
26 November 2018	Amended	Amendments made in methods section and study flow diagram/text.

HISTORY

Protocol first published: Issue 5, 2014
Review first published: Issue 11, 2015

Date	Event	Description
5 December 2017	New search has been performed	For the update from Al-Khudairy 2015, we have introduced some changes, broadening the review to fit with the request of the World Health Organization (WHO) Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health, who requested the update. 1. We included studies in a wider variety of adults, such as those with diabetes or cardiovascular disease at baseline, as the original review was of primary prevention only and excluded diabetes. 2. Effects of dietary changes needed to be assessed over at least one year. 3. We included studies that compared higher omega-6 fat intake with lower omega-6 fat intake (not only usual diet). 4. We added new pre-planned subgroups requested by WHO.
5 December 2017	New citation required and conclusions have changed	The earlier review found no studies examining the effects of either increased or decreased omega-6 fats on our primary clinical outcomes for cardiovascular disease. For this update we included 19 randomised controlled trials in 6461 participants over 1 to 8 years. We have now included studies reporting all-cause mortality, cardiovascular deaths and events, coronary heart disease events, major adverse cardiac and cerebrovascular events, and stroke. We have also updated data on long-term effects of

Date	Event	Description
		omega-6 fats on lipids and adiposity, and we have added data on individual cardiovascular events (all secondary outcomes).

CONTRIBUTIONS OF AUTHORS

KR and LH conceived the review; KR and LA-K led the original version of this review; KR, LA-K and LH were authors of the original version of this review (Al-Khudairy 2015). LH designed the searches, which CB developed, refined, ran and de-duplicated. LH, ASA, SMAA, FS, JSB, KHOD and TJB screened titles and abstracts; LH, ASA, SMAA, KHOD, LA-K, KR and JSB assessed full-text papers for inclusion; LH 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 the 'Risk of bias' assessment; SMAA, JSB, KHOD, TJB, ASA and LH wrote to study authors; LH, KHOD and ASA carried out data checks; SMAA, JSB, TJB, LH and ASA tabulated intake and status data. FS, KHOD, JSB and LH provided methodological support. LH, ASA, SMAA, JSB, TJB, KHOD, DHD, ATO and LEW entered data into RevMan and ran meta-analyses. LH wrote the first draft of the review and of the WHO report and carried out analyses and interpretation. All authors critically read and commented on the final draft and agreed to submit it.

DECLARATIONS OF INTEREST

LH: WHO provided funding to the University of East Anglia to support this review update. Some of this funding was used to fund LH's employment. WHO also funded LH's attendance at WHO NUGAG Subgroup on Diet and Health and CODEX meetings to discuss and present this review and others in this set. No other conflicts known.

LA-K: none known.

ASA: WHO provided funding to the University of East Anglia to support this review update. Some of this funding was used to fund ASA's employment. WHO also funded ASA's attendance at WHO NUGAG Subgroup on Diet and Health meetings to discuss and present this review and others in this set. No other conflicts known.

KR: none known.

JSB: WHO provided funding to the University of East Anglia to support this review update. Some of this funding was used to fund JSB's employment. No other conflicts known.

TJB: WHO provided funding to the University of East Anglia to support this review update. Some of this funding was used to fund TJB's employment. No other conflicts known.

SMAA: WHO provided funding to the University of East Anglia to support this review update. Some of this funding was used to fund SMAA's employment. No other conflicts known.

ATO'B: none known; carried out as part of his MBBS degree at the University of East Anglia.

LEW: none known; carried out as part of her MBBS degree at the University of East Anglia.

DHD: none known; carried out as part of her MBBS degree at the University of East Anglia.

FS: WHO provided funding to the University of East Anglia to support this review update. Some of this funding was used to fund FS's employment. No other conflicts known.

KHOD: WHO provided funding to the University of East Anglia to support this review update. Some of this funding was used to fund KHOD's employment. No other conflicts known.

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Internal sources

- University of East Anglia, UK.
- Warwick Medical School, University of Warwick, UK.

External sources

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For the update, we introduced some changes from Al-Khudairy 2015 to broaden the review to fit with the requirements of WHO NUGAG Subgroup on Diet and Health.

1. We included studies in a wider variety of adults, such as those with diabetes or CVD at baseline, as the original review was of primary prevention only and excluded diabetes.
2. Effects of dietary changes needed to be assessed over at least one year.
3. We included studies that compared higher omega-6 fat intake with lower omega-6 fat intake (not only usual diet).
4. We carried out sensitivity and subgroup analyses for primary review outcomes as planned, and also for key outcomes.
5. Addition of new pre-planned subgroups requested by WHO NUGAG Subgroup on Diet and Health .
6. We performed meta-regression to look for dose-response and duration effects of omega-6 fats within this review and across studies from three reviews (this review, omega-3 (Abdelhamid 2018a) and total PUFA (Abdelhamid 2018b)).

For this review update we intended to assess causality (another aspect of performance bias, where a study intervention included changes other than the change in omega-6 fat intake, when there would be high risk of bias) when assessing risk of bias, but as we limited inclusion to studies where the dietary changes were limited to dietary fats, this was not needed and so omitted. We also intended to assess whether a study was pre-registered on a trials register (registration date was before outcome data collection began; Roberts 2015), but we incorporated the issue of pre-registration into selective outcome reporting and did not use it as a separate form of assessment.

INDEX TERMS

Medical Subject Headings (MeSH)

*Blood Pressure; Cardiovascular Diseases [mortality] [*prevention & control]; Cause of Death; Cerebrovascular Disorders [prevention & control]; Cholesterol [*blood]; Cholesterol, HDL [blood]; Cholesterol, LDL [blood]; Fatty Acids, Omega-6 [*administration & dosage]; Myocardial Infarction [epidemiology] [prevention & control]; Primary Prevention [*methods]; Randomized Controlled Trials as Topic; Secondary Prevention; Triglycerides [*blood]

MeSH check words

Adult; Aged; Female; Humans; Male; Middle Aged