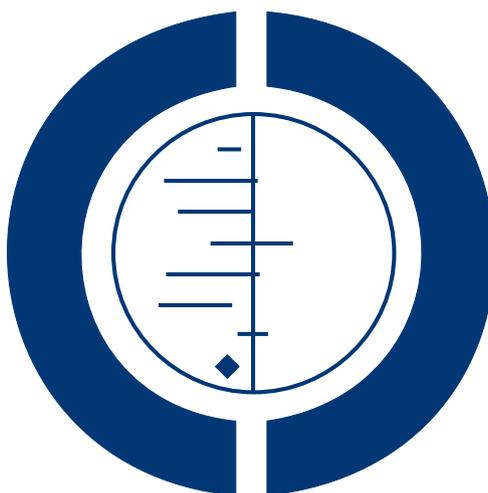


# Omega 6 fatty acids for the primary prevention of cardiovascular disease (Review)

Al-Khudairy L, Hartley L, Clar C, Flowers N, Hooper L, Rees K



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[Intervention Review]

# Omega 6 fatty acids for the primary prevention of cardiovascular disease

Lena Al-Khudairy<sup>1</sup>, Louise Hartley<sup>1</sup>, Christine Clar<sup>2</sup>, Nadine Flowers<sup>1</sup>, Lee Hooper<sup>3</sup>, Karen Rees<sup>1</sup>

<sup>1</sup>Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK. <sup>2</sup>Freelance, Berlin, Germany. <sup>3</sup>Norwich Medical School, University of East Anglia, Norwich, UK

Contact address: Karen Rees, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, CV4 7AL, UK. [Karen.Rees@warwick.ac.uk](mailto:Karen.Rees@warwick.ac.uk). [rees\\_karen@yahoo.co.uk](mailto:rees_karen@yahoo.co.uk).

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## ABSTRACT

### Background

Omega 6 plays a vital role in many physiological functions but there is controversy concerning its effect on cardiovascular disease (CVD) risk. There is conflicting evidence whether increasing or decreasing omega 6 intake results in beneficial effects.

### Objectives

The two primary objectives of this Cochrane review were to determine the effectiveness of:

1. Increasing omega 6 (Linoleic acid (LA), Gamma-linolenic acid (GLA), Dihomo-gamma-linolenic acid (DGLA), Arachidonic acid (AA), or any combination) intake in place of saturated or monounsaturated fats or carbohydrates for the primary prevention of CVD.
2. Decreasing omega 6 (LA, GLA, DGLA, AA, or any combination) intake in place of carbohydrates or protein (or both) for the primary prevention of CVD.

### Search methods

We searched the following electronic databases up to 23 September 2014: the Cochrane Central Register of Controlled Trials (CENTRAL) on the Cochrane Library (Issue 8 of 12, 2014); MEDLINE (Ovid) (1946 to September week 2, 2014); EMBASE Classic and EMBASE (Ovid) (1947 to September 2014); Web of Science Core Collection (Thomson Reuters) (1990 to September 2014); Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment Database, and Health Economics Evaluations Database on the Cochrane Library (Issue 3 of 4, 2014). We searched trial registers and reference lists of reviews for further studies. We applied no language restrictions.

### Selection criteria

Randomised controlled trials (RCTs) of interventions stating an intention to increase or decrease omega 6 fatty acids, lasting at least six months, and including healthy adults or adults at high risk of CVD. The comparison group was given no advice, no supplementation, a placebo, a control diet, or continued with their usual diet. The outcomes of interest were CVD clinical events (all-cause mortality, cardiovascular mortality, non-fatal end points) and CVD risk factors (changes in blood pressure, changes in blood lipids, occurrence of type 2 diabetes). We excluded trials involving exercise or multifactorial interventions to avoid confounding.

## Data collection and analysis

Two review authors independently selected trials for inclusion, extracted the data, and assessed the risk of bias in the included trials.

## Main results

We included four RCTs (five papers) that randomised 660 participants. No ongoing trials were identified. All included trials had at least one domain with an unclear risk of bias. There were no RCTs of omega 6 intake reporting CVD clinical events. Three trials investigated the effect of increased omega 6 intake on lipid levels (total cholesterol, low density lipoprotein (LDL-cholesterol), and high density lipoprotein (HDL-cholesterol)), two trials reported triglycerides, and two trials reported blood pressure (diastolic and systolic blood pressure). Two trials, one with two relevant intervention arms, investigated the effect of decreased omega 6 intake on blood pressure parameters and lipid levels (total cholesterol, LDL-cholesterol, and HDL-cholesterol) and one trial reported triglycerides. Our analyses found no statistically significant effects of either increased or decreased omega 6 intake on CVD risk factors.

Two studies were supported by funding from the UK Food Standards Agency and Medical Research Council. One study was supported by Lipid Nutrition, a commercial company in the Netherlands and the Dutch Ministry of Economic Affairs. The final study was supported by grants from the Finnish Food Research Foundation, Finnish Heart Research Foundation, Aarne and Aili Turnen Foundation, and the Research Council for Health, Academy of Finland.

## Authors' conclusions

We found no studies examining the effects of either increased or decreased omega 6 on our primary outcome CVD clinical endpoints and insufficient evidence to show an effect of increased or decreased omega 6 intake on CVD risk factors such as blood lipids and blood pressure. Very few trials were identified with a relatively small number of participants randomised. There is a need for larger well conducted RCTs assessing cardiovascular events as well as cardiovascular risk factors.

## PLAIN LANGUAGE SUMMARY

### Omega 6 intake to prevent cardiovascular disease

#### Review question

We reviewed randomised controlled trials examining the effect of either increased or decreased omega 6 fatty acids for the primary prevention of CVD in healthy adults or adults at high risk of CVD. Four RCTs met the inclusion criteria for this Cochrane review.

#### Background

Omega 6 is an essential fatty acid because humans cannot make it in their bodies and must obtain it in their diet. Omega 6 can be obtained from a variety of dietary sources, such as vegetable oil and nuts. Omega 6 fatty acids play a vital role in many physiological functions. They are particularly important for maintaining bone health, regulating metabolism, and in stimulating skin and hair growth. Some evidence suggests that a proportionally higher intake of omega 6 fatty acids along with a low intake of saturated fat is associated with significant reductions in coronary heart disease. In contrast, there is concern that high levels of omega 6 fatty acids may worsen cardiovascular risk. There appears to be inconclusive evidence from observational studies and meta-analyses on the benefits of omega 6 intake on CVD outcomes.

#### Study characteristics

The evidence is current to 23 September 2014. In this Cochrane review, four trials met the inclusion criteria and we examined these trials (660 participants) that assessed the effects of either increased or decreased omega 6 intake on lipid levels and blood pressure (major risk factors for cardiovascular disease (CVD)). The diets were followed for 24 weeks. All four trials recruited both male and female participants but varied in the type of participants recruited. Two trials recruited overweight or obese but otherwise healthy adults. One trial recruited older men and post menopausal women, and the remaining trial recruited younger adults with hypercholesterolaemia. Two trials were conducted in the UK, one in the Netherlands, and the remaining trial was conducted in Finland. Trials included a relatively small number of participants and were at some risk of bias.

Two studies were supported by funding from the UK Food Standards Agency and Medical Research Council. One study was supported by Lipid Nutrition, a commercial company in the Netherlands and the Dutch Ministry of Economic Affairs. The final study was supported by grants from the Finnish Food Research Foundation, Finnish Heart Research Foundation, Aarne and Aili Turnen Foundation, and the Research Council for Health, Academy of Finland.

## Key results

No differences in effects of increased or decreased omega 6 intake were seen on blood lipids and blood pressure, but this is based on very few studies. No included trials reported CVD events. There is insufficient evidence to date from randomised controlled trials to recommend increasing or reducing omega 6 for the prevention of CVD.

## Quality of the evidence

There are very few included studies and therefore the results have to be interpreted with caution. Overall we regarded the trials were at unclear risk of bias.

## BACKGROUND

Omega 6 is an essential fatty acid that plays a vital role in many physiological functions but there is controversy concerning its effect on cardiovascular risk. Results from clinical trials and observational studies are inconsistent. There is a need to review the current evidence from randomised controlled trials (RCTs) in this area.

### Description of the condition

Cardiovascular diseases (CVD) are a group of conditions that affect the heart and blood vessels (WHO 2014), and include cerebrovascular disease, coronary heart disease (CHD), and peripheral arterial disease (PAD). One mechanism thought to cause CVD is atherosclerosis, which is where a person's arteries become blocked by plaques or atheromas (NHS 2012). Atherosclerosis can cause CVD when the arteries are completely blocked by a blood clot or when a narrowed artery restricts blood flow limiting the amount of blood and oxygen reaching organs or tissue (BHF 2013). Even though arteries may narrow and become less elastic with age, the process may be accelerated by factors such as smoking, high cholesterol, hypertension, obesity, a sedentary lifestyle, and ethnicity (NHS 2012). Ruptures of unstable plaques may also cause CVD by activating an inflammatory response in the body. This inflammatory response causes the structure of the atherosclerotic plaque to weaken and rupture leading to the formation of blood clots (Spagnoli 2007).

CVDs are the leading causes of death worldwide (WHO 2014), and in 2008 an estimated 30% of all global deaths were due to CVD (WHO 2014). The burden of CVD also varies substantially between regions (Müller-Nordhorn 2008), for example, death from ischaemic heart disease in France is one-quarter of that of the UK (Law 1999). Furthermore, low- and middle-income countries are disproportionately affected (WHO 2014): in 2001, three-quarters of global deaths from CHD took place in low- and middle-income countries (Gaziano 2010). Gaziano 2010 suggested that

this rapid increase in CHD burden is attributable to an increase in life span, socioeconomic changes, and the acquisition of lifestyle-related risk factors.

One key public health priority is targeting modifiable risk factors, including dietary factors, for CVD prevention. Such risk factors are extremely important since their modification has the potential to lower CVD risk, making them a main target for interventions aimed at CVD primary prevention. One major modifiable risk factor is diet and dietary factors, such as a low consumption of fruit and vegetables (Begg 2007), a high intake of saturated fat (Siri-Tarino 2010), and a high consumption of salt (He 2010), which have been found to be associated with CVD risk.

### Description of the intervention

Omega 6 (or n-6) polyunsaturated fatty acids (PUFAs) are characterised by the presence of at least two carbon-carbon double bonds (Harris 2009), as are omega 3 fats. The distinction between omega 6 and omega 3 is based on the position of this double bond from the methyl group end of the fatty acid molecule (Hall 2009; Calder 2013). For omega 6, the double bond pair is sixth from the methyl terminus while for omega 3 the double bond is third (Harris 2009; Calder 2013). Linoleic acid (LA) (18:2n-6), one of the omega 6 fatty acids, is an essential fatty acid because the human body is unable to synthesize it and must be obtained through the diet (Groff 1995). Gamma-linolenic acid (GLA), another omega 6 fatty acid, may become conditionally essential in the event of reduced activity of delta-6-desaturase, which is the enzyme that is necessary for converting LA into GLA (Rincón-Cervera 2009). Other members of the omega 6 group include GLA (18:3n-6), di-homo-gamma-linolenic acid (DGLA) (20:3n-6), and arachidonic acid (AA) (20:4n-6) which can be derived from LA and synthesized in the healthy human body. 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). As with omega 3, omega 6 fatty acids play a vital role in many

physiological functions. They are particularly important for maintaining bone health, regulating metabolism, and in stimulating skin and hair growth. However, evidence on the effect of omega 6 on CVD risk remains controversial. A few studies suggest that a proportionally higher intake of omega 6 fatty acids along with a low intake of saturated fat is associated with significant reductions in CHD (Katan 2009). Indeed, findings from cohort studies have shown omega 6 fatty acids to be inversely associated with cardiovascular death and to be inversely associated with CHD risk (Laaksonen 2005; Oh 2005). Furthermore, studies have shown that omega 6 fatty acids reduce CVD risk factors such as low-density lipoprotein cholesterol (LDL-cholesterol) (Hodson 2001; Jakobsen 2009), and blood pressure (Hall 2009). In contrast, there is concern that high levels of dietary omega 6 will have a pro-inflammatory effect by increasing the production of 2-series prostaglandins and 4-series leukotrienes. Therefore, increased intakes of omega 6 may potentially worsen CVD risk (Russo 2009). However, the American Heart Association recommend consuming around 500 mg/day of omega 3 and 15 mg/day of LA (Harris 2010).

### How the intervention might work

Dietary fat modification can improve CVD risk and risk factors. A meta-analysis of observational studies suggests an inverse relationship between omega 6 intake and CVD risk (Harris 2007). The meta-analysis aimed to evaluate studies assessing the relationship between blood/tissue omega 6 PUFA 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 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. Overall, Farvid 2014 reported a protective effect of LA intake against CHD events and deaths. Replacing saturated fat intake with a 5% energy increase from LA intake was found to be associated with a 9% lower risk of CHD events and a 13% lower risk of CHD deaths (Farvid 2014).

An earlier meta-analysis searched for trials between 1979 to 1999 examining the effect of individual fatty acids on blood lipids. The results included 60 trials randomising 1672 participants and suggested a beneficial effect of PUFAs (including omega 6) on blood lipids (Mensink 2003). This is 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, 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 6 months. The findings suggest that modification

of dietary fat by replacing saturated fats with monounsaturated fatty acids or PUFAs reduces CVD risk (Hooper 2011).

However, there is concern that high levels of omega 6 fatty acids compared with omega 3 fatty acids in the diet increases the production of 2-series prostaglandins and 4-series leukotrienes compared with 3-series prostaglandins and 5-series leukotrienes. As the 2-series prostaglandins and 4-series leukotrienes exert a more potent pro-inflammatory effect, omega 6 fatty acids may theoretically worsen cardiovascular risk (Russo 2009). This relationship is disputed, but has led to the concept that the ratio between omega 6 and omega 3 fatty acids may be crucial, rather than absolute intakes of either omega 6 or omega 3 fatty acids. In addition, there is concern that highly unsaturated fatty acids such as AA may increase the susceptibility of lipoproteins such as LDL and very-low-density lipoproteins (VLDL) to oxidation, making them more atherogenic (Russo 2009).

A number of studies have found no association between omega 6 intakes and risk of CVD. Earlier prospective cohort studies found no association between dietary intakes of omega 6 fatty acids and stroke (He 2003), CHD (McGee 1984; Pietinen 1997) and CHD mortality (Esrey 1996). The Sydney Diet Heart Study, a RCT of 458 men aged between 30 to 59 years with a recent coronary event, reported increased rates of death from all causes, CHD, and CVD when substituting dietary linoleic acid in place of saturated fats (Ramsden 2013). A systematic review of 36 reviewed and peer-reviewed studies reported no effect of LA dietary modification intake on changes in AA levels in plasma, serum or erythrocytes in adults (Whelan 2011). Chowdhury 2014, a recent systematic review of prospective, observational studies and RCTs, reported non-significant associations between omega-6 fatty acids supplementation and coronary disease or outcomes.

### Why it is important to do this review

There appears to be inconclusive evidence from observational studies and meta-analyses on the benefit of omega 6 intake on CVD outcomes. Therefore, an up-to-date systematic review is required to clarify the association between CVD risk and omega 6 intake. This can then provide guidance for national and international agencies, practitioners, and members of the public.

A previous systematic review of RCTs has examined the effect of change in dietary fat intake (including LA) on CVD morbidity in adults with or without CVD (Hooper 2011). Mozaffarian 2010, another systematic review, examined increased total or omega 6 PUFAs in adults with or without CVD events. A recent systematic review summarised the association between fatty acids (including omega 6) and coronary disease. The RCTs of the review included interventions that recorded coronary outcomes as an end point of interest and were conducted predominantly in those with established CVD (Chowdhury 2014). Therefore previous reviews have not explicitly examined increased or decreased omega 6 intake for the primary prevention of CVD (Mozaffarian 2010; Hooper

2011; Chowdhury 2014). With this in mind, we undertook this Cochrane review to assess the current evidence. We included RCTs that stated an intention to increase or decrease omega 6 fats by following dietary advice, omega 6 supplementation, or a provided diet. We examined the effects over longer time periods (at least six months) as these are most relevant for public health interventions.

## OBJECTIVES

The two primary objectives of this Cochrane review were to determine the effectiveness of:

1. Increasing omega 6 (LA, GLA, DGLA, AA, or any combination) intake in place of saturated or monounsaturated fats or carbohydrates for the primary prevention of CVD.
2. Decreasing omega 6 (LA, GLA, DGLA, AA, or any combination) intake in place of carbohydrates or protein (or both) for the primary prevention of CVD.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We included RCTs. We included trials reported as full-text articles, as abstracts only, and unpublished data.

#### Types of participants

Healthy adults (aged  $\geq 18$  years old) from the general worldwide population and adults at moderate to high risk of CVD. As this review focused on the primary prevention of CVD, we excluded people who had experienced a myocardial infarction (MI), stroke, revascularization procedure (coronary artery bypass grafting (CABG), or percutaneous transluminal coronary angioplasty (PTCA)), people with angina, and people with angiographically defined CHD. We also excluded people with type 2 diabetes, as while type 2 diabetes is a risk factor for CVD, interventions targeting this condition are covered by the Cochrane Metabolic and Endocrine Disorders Group.

#### Types of interventions

We included all RCTs of interventions that stated an intention to increase or decrease omega 6 fatty acids. Interventions had to involve dietary advice, supplementation, or provide a diet where

omega 6 fatty acids were either increased or decreased. Studies could include any type of omega 6 or combination of omega 6 fatty acids. We considered trials involving an increase or decrease in omega 6 fatty acids with energy replacement by carbohydrates, omega 3, omega 9, saturated fats, protein, alcohol, or monounsaturated fats, and included studies with additional dietary interventions. We excluded trials with other major concomitant interventions, such as exercise or other multiple lifestyle interventions to avoid confounding.

We also focused on follow-up periods of six months (24 weeks) or longer. Follow-up was considered to be the time elapsed since the start of the intervention and, therefore, we excluded any trials with an intervention period of less than six months as longer term studies examine sustained changes which are more relevant for public health interventions. For the control group, we considered trials where the comparison group was given no advice, no supplementation, a placebo, a control diet, or continued with their usual diet. This included dietary intakes that represent the typical dietary composition for that setting.

### Types of outcome measures

#### Primary outcomes

1. All-cause mortality.
2. Cardiovascular mortality.
3. Non-fatal end points such as MI, CABG, PTCA, angina, angiographically defined CHD, stroke, carotid endarterectomy, and PAD.

#### Secondary outcomes

1. Changes in blood pressure (systolic and diastolic blood pressure) and blood lipids (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides).
2. Occurrence of type 2 diabetes as a major CVD risk factor.
3. Adverse effects (as defined by the authors of the included trials).

### Search methods for identification of studies

#### Electronic searches

We identified trials through systematic searches of the following bibliographic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library) (Issue 8 of 12, 2014).
- MEDLINE (Ovid) (1946 to September week 2, 2014).
- EMBASE Classic + EMBASE (Ovid) (1947 to September 2014).

- Web of Science Core Collection (Thomson Reuters) (1990 to September 2014).
- Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database, and Health Economics Evaluations Database on the Cochrane Library (Issue 3 of 4, 2014).

We adapted the preliminary search strategy for MEDLINE (Ovid) for use in the other databases (Appendix 1). We also applied the Cochrane sensitivity-maximising RCT filter (Lefebvre 2011) to MEDLINE (Ovid) and adaptations of it to the other databases, except CENTRAL.

We searched all databases from their inception to the dates indicated, and imposed no restriction on language of publication.

### Searching other resources

We checked reference lists of all primary studies and review articles for additional references.

We searched the clinical trial registers on the 18 January 2015 (Appendix 1). We also conducted a search of ClinicalTrials.gov ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)), metaRegister of controlled trials (mRCT) ([www.controlled-trials.com/mrct](http://www.controlled-trials.com/mrct)), and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal ([apps.who.int/trialsearch/](http://apps.who.int/trialsearch/)).

We contacted trial authors when necessary for any additional information.

## Data collection and analysis

### Selection of studies

Two review authors (LH, CC or NF) independently screened titles and abstracts for inclusion and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. If there were any disagreements, we asked a third review author to arbitrate (KR). We retrieved the full-text study reports/publication and two authors (LH, CC) independently screened the full-text and identified studies for inclusion, and identified and recorded reasons for exclusion of the ineligible studies. We resolved any disagreements through discussion or, if required, we consulted a third review author (KR). We identified and excluded duplicates and collated multiple reports of the same study so that 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 used a data collection form for trial characteristics and outcome data that had been piloted on at least one trial included in

the review. Two review authors (LA, LH or CC) extracted the following study characteristics from included studies:

1. Methods: trial design, total duration of trial, details of any 'run-in' period, number of trial centres and location, trial setting, withdrawals, and date of trial.
2. Participants: number, mean age, age range, gender, severity of condition, diagnostic criteria, smoking history, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. For intervention and control (during intervention): the percentage of energy from omega 3, omega 6, omega 9, saturated fats, monounsaturated fats, carbohydrates (refined and unrefined if possible), alcohol, protein, and omega 6/omega 3 ratio.
5. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
6. Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (LA, LH or CC) independently extracted outcome data from included trials. We resolved disagreements by consensus or by involving a third review author (KR). One review author (LH) transferred data into RevMan 2014. We double-checked that data were entered correctly by comparing the data presented in the systematic review with the data in the trial reports. A second review author (LA) spot-checked trial characteristics for accuracy against the trial reports.

### Assessment of risk of bias in included studies

Two review authors (LA, LH or CC) independently assessed risk of bias for each included trial using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion or by involving another review author (KR). We assessed the risk of bias according to the following domains:

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias (e.g. industry funding).

We graded each potential source of bias as either 'high', 'low', or 'unclear' and provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. 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 trial author, we noted this in the 'Risk of bias' table.

When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

## Assessment of bias in conducting the systematic review

We conducted this Cochrane review according to its published protocol, [Hartley 2014](#), and reported any 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) or standardised mean difference (SMD) with 95% CIs. We entered data presented as a scale with a consistent direction of effect, with the exception of HDL cholesterol where an increase in this outcome is a positive finding.

We intended to narratively describe skewed data reported as medians and interquartile ranges but this did not apply to any of the included trials.

## Unit of analysis issues

### Studies with multiple intervention groups

Data for the control group have been used for each intervention group comparison. We reduced the weight assigned to the control group by dividing the control group N by the number of intervention groups analysed.

### Cluster-RCTs

We intended to analyse cluster-RCTs using the unit of randomisation (cluster) as the number of observations, and use individual level means and SDs adjusted for clustering together with the number of clusters in the denominator, where needed, in order to weight the trials appropriately. However we did not find any cluster-RCTs that met the inclusion criteria.

### Cross-over studies

For included cross-over studies we only used the first period.

## Dealing with missing data

We contacted trial authors or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only). Where this was not possible, and the missing data were thought to introduce serious bias, we explored the impact of including such studies in the overall assessment of results using a sensitivity analysis. Where papers did not report results as change from baseline we calculated this and for the SD differences followed the methods presented in the *Cochrane Handbook for Systematic Reviews of*

*Interventions* for imputing these (16.1.3.2 Imputing standard deviations for changes from baseline, [Higgins 2011](#)), and assumed a correlation of 0.5 between baseline and follow-up measures as suggested by [Follman 1992](#).

## Assessment of heterogeneity

We used the  $I^2$  statistic to measure heterogeneity among the trials in each analysis. If we identified substantial heterogeneity (heterogeneity of greater than 50%), we reported it and explored possible causes by pre-specified subgroup analysis.

## Assessment of reporting biases

We were unable to pool more than 10 trials and so did not use a funnel plot to explore possible small-study biases for the primary outcomes.

## Data synthesis

We conducted statistical analysis using [RevMan 2014](#). Continuous data were entered as the difference in means and SDs between baseline and follow-up. In the absence of substantial heterogeneity (greater than 50%) and if there was a sufficient number of trials, we combined the results using a fixed-effect model.

## Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses but there were an insufficient number of trials included to do this:

1. Omega 6 alone versus omega 6 plus other dietary components.
2. Baseline risk.
3. Increase or decrease in omega 6.
4. Omega 6/omega 3 ratio.
5. Age.
6. Sex.

We also planned to assess the treatment effects of omega 6 according to energy replacement (e.g. by what omega 6 is replacing or, for a decrease in omega 6, what is replacing omega 6), including:

1. Carbohydrates.
2. Saturated fats.
3. Omega 3 fatty acids.
4. Omega 9 fatty acids.
5. Protein.
6. Alcohol.
7. Monounsaturated fats.

We intended to further explore the effects of the above different energy replacements by using meta-regression on our primary outcomes. However, none of the included trials reported our primary outcomes and there was an insufficient number of included trials reporting our secondary outcomes to conduct these analyses.

We intended to use the formal test for subgroup interactions in [RevMan 2014](#).

### **Sensitivity analysis**

We planned to carry out the following sensitivity analyses but there were an insufficient number of trials included to do this:

1. Only including studies at low risk of bias (assessed using the Cochrane 'Risk of bias' assessment tool).
2. Only including studies where the alteration in omega 6 (and its energy replacement) is the only dietary intervention.

### **Reaching conclusions**

We based our conclusions only on findings from the quantitative or narrative synthesis of included studies for this Cochrane review. We avoided making recommendations for practice and our implications for research suggest priorities for future research and outline what the remaining uncertainties are in the area.

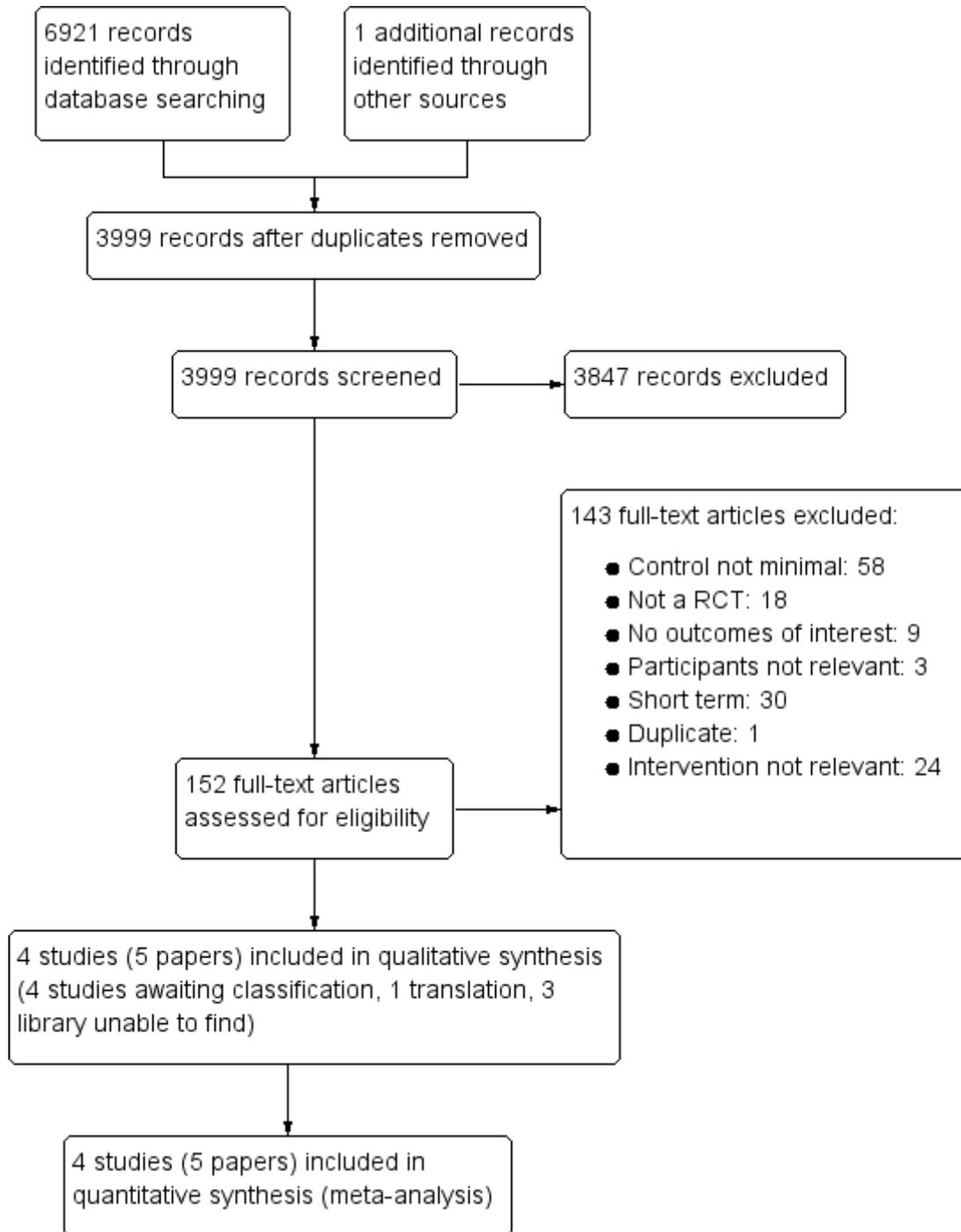
## **RESULTS**

### **Description of studies**

#### **Results of the search**

The searches generated 6921 hits and 3999 after de-duplication. After screening the titles and abstracts, we identified 152 papers for formal inclusion and exclusion. Of these, four RCTs (five papers) met the inclusion criteria, and one of the four RCTs had two relevant intervention arms ([Moore 2006 High LA](#); [Moore 2006 Low LA](#)). We did not identify any ongoing trials. We have presented details of the flow of studies in [Figure 1](#).

**Figure 1. Study flow diagram.**



## Included studies

The details of the methods, participants, intervention, comparison group, and outcome measures for each of the included trials are shown in the 'Characteristics of included studies' table. Four trials, including 664 participants, met the inclusion criteria.

All four trials recruited both male and female participants (Sarkkinen 1998; Moore 2006 High LA; Moore 2006 Low LA; OPTILIP 2006; Sluijs 2010). The trials varied in the participants recruited. Two trials recruited overweight or obese but otherwise healthy adults aged 35 to 65 years (Moore 2006 High LA; Moore 2006 Low LA), and 40 to 70 years (Sluijs 2010). One trial recruited older men and post menopausal women aged 45 to 70 years (OPTILIP 2006). One trial recruited younger adults aged 23 to 58 years with hypercholesterolaemia (Sarkkinen 1998).

Two trials were conducted in the UK (Moore 2006 High LA; Moore 2006 Low LA; OPTILIP 2006), one in the Netherlands (Sluijs 2010), whilst the remaining trial was conducted in Finland (Sarkkinen 1998).

All included trials had the same duration of follow-up (24 weeks) (Sarkkinen 1998; Moore 2006 High LA; Moore 2006 Low LA; OPTILIP 2006; Sluijs 2010).

Three trials reported on the effects of increasing omega 6 intake, and two trials reported on decreasing omega 6 intake.

Three trials increased omega 6 intake and provided high LA oils and spreads throughout the duration of the study (Sarkkinen 1998; Moore 2006 High LA; Sluijs 2010) but the LA content varied across studies.

The high LA intervention arm of the Moore 2006 trial, Moore 2006 High LA, increased the omega 6:omega 3 ratio by providing sunflower fats (LA:  $\alpha$ -linolenic acid (LNA) was 27:1 for sunflower spreads and 63:0.1 for sunflower oil). This trial aimed to maintain a low omega 3 intake hence participants were provided with white fish but the portions were not reported. The control group of Moore 2006 High LA received no intervention.

The third trial increased omega 6 intake by providing detailed written instructions of food consumption, typically consumed in a Finnish diet, tailored to participants own energy levels. In the reduced-fat sunflower oil-enriched intervention diet, the goal was to consume 30% of energy from fat (10% saturated fat, 10% monosaturated fat, 10% polyunsaturated fat), 15% of energy from protein, 55% of energy from carbohydrate, and 15 to 20 g of fibre per day. Additionally, sunflower oil and margarine were provided throughout the study. The content of LA was not provided but the mean consumption throughout the study was reported ( $13.3 \pm 3.5$  g/day). In the high fat, saturated fat-enriched control diet typical of the normal Finnish diet, participants received detailed written instructions on diet at their own energy level. However, the goal was to consume 38% of energy from fat (18% saturated fat, 15%

monosaturated fat, 5% polyunsaturated fat), 15% of energy from protein, 47% of energy from carbohydrate, and 15 to 20 g of fibre per day. Butter and a small amount of low-erucic acid rapeseed oil were provided (Sarkkinen 1998).

Another trial increased omega 6 by using cis-9,trans-11 conjugated linoleic acid (c9,t11 CLA). The c9,t11 CLA oil was manufactured from safflower oil and four capsules of 1 g oil each were taken daily. Placebo capsules contained an equal amount of fat and were composed of a blend of palm oil (80%) and soybean oil (20%), which resembles the average fatty acid composition of the fat consumed by a Western population (Sluijs 2010).

The low LA intervention arm of the Moore 2006 trial, Moore 2006 Low LA, decreased the omega 6:omega 3 ratio by providing rapeseed fats (LA:LNA was 3:1 for rapeseed spread, and 2:1 for rapeseed oil). The trial aimed to maintain a low omega 3 intake hence participants were provided white fish but the portions were not reported. The control group of Moore 2006 Low LA received no intervention.

The second trial, OPTILIP 2006, decreased omega 6 intake by providing oils and spreads for the duration of the study. The spreads contained 4.7 g/100 g of LA and 0.8 g/100 g of ALA. The LA and ALA contents of rapeseed (canola) oil were 19.7 g and 8.9 g/100 g respectively. Participants were also provided with two small cans of tuna/week, the tuna was canned in high linoleic sunflower oil. The diet was designed to keep the intake of saturated and monounsaturated fatty acids constant and to provide ~ 6% of energy from PUFAs. The control had a higher omega 6 content that was similar to the household food consumption as stated by the authors. In the control diet, the LA and ALA contents of the spreads were 39.6 g and 0.5 g/100 g. The LA and ALA contents of high-oleic sunflower oil were 10.6 g and 0.3 g/100 g. Participants in the control group were provided with two small cans of tuna/week, and the tuna was canned in olive oil (OPTILIP 2006).

Four trials are awaiting assessment and we have presented details in the 'Characteristics of studies awaiting classification' section.

One trial with two relevant intervention arms needs to be translated from Norwegian (Natvig 1967 High LA; Natvig 1967 Low LA). The English abstract is presented in the 'Characteristics of studies awaiting classification' table. This is a large trial but it was conducted in the 1960s and there are insufficient details in the abstract to determine the conduct of the trial (methods of randomisation and allocation) and outcome data. The library were unable to provide the full text record for one trial with a relevant intervention arm (Nordoy 1981). We have presented the English abstract in the 'Characteristics of studies awaiting classification' table. This is a very small trial with only 10 participants and there are insufficient details in the abstract to determine the conduct of the trial (study design, follow-up time, and outcomes measured). For the other two studies, no abstract was available and the library

was unable to provide us with full text records (Singer 1991; Ryu 1999). We did not identify any ongoing trials.

alternative designs (not RCTs), and studies were short-term (< six months follow-up) (see Figure 1).

### 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. The most common reasons for exclusion of studies included the control group did not receive a minimal intervention or no intervention, studies included

### 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 the 'Characteristics of included studies' section. Also, we have presented 'Risk of bias' summaries in Figure 2 and Figure 3. We will include a 'Summary of findings' table and GRADE assessment in an update of this Cochrane review.

**Figure 2. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies.**

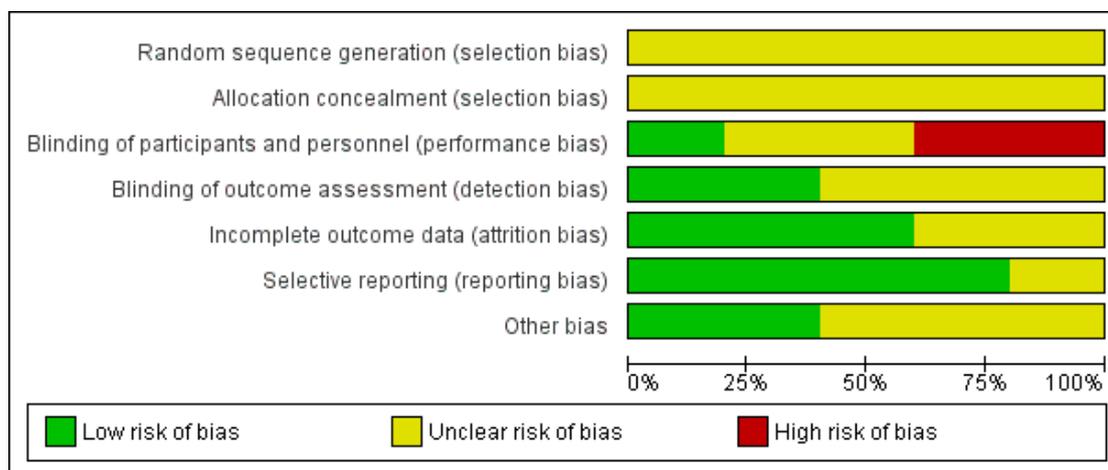


Figure 3. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Moore 2006 High LA	?	?	-	+	+	+	+
Moore 2006 Low LA	?	?	-	+	+	+	+
OPTILIP 2006	?	?	?	?	?	+	?
Sarkkinen 1998	?	?	?	?	?	+	?
Sluijs 2010	?	?	+	?	+	?	?

## Allocation

No details were provided for the method of random sequence generation and allocation concealment in all included trials. We judged this to be at unclear risk of bias for all included trials.

## Blinding

One trial reported that blinding of participants was not carried out and was judged to be at high risk of performance bias (Moore 2006 High LA; Moore 2006 Low LA). One trial reported that the investigators were unaware of treatment allocations for the trial duration and was judged to be at low risk of performance bias (Sluijs 2010). One trial, Moore 2006 High LA; Moore 2006 Low LA, clearly reported that outcome assessment personnel involved in the study were blinded to the randomisation and was judged at low risk of detection bias. One trial did not report details on blinding (OPTILIP 2006) and was judged to be at unclear risk of bias for both domains. One trial, Sarkkinen 1998, reported that spreads were provided on a single-blind basis but no further details were provided and this was judged as unclear risk of bias for both performance and detection.

## Incomplete outcome data

Two trials (Moore 2006 High LA; Moore 2006 Low LA; Sluijs 2010) were judged to be at low risk of bias as the number of drop-outs was clearly presented for each study arm at each stage of the trial. Two trials reported the number of drop-outs for the overall sample but not per study arm and were judged to be at unclear risk of bias (Sarkkinen 1998; OPTILIP 2006). None of the included studies used an intention-to-treat (ITT) analysis.

## Selective reporting

All trials presented outcomes as reported and were judged to be at low risk of bias.

## Other potential sources of bias

One trial, Moore 2006 High LA; Moore 2006 Low LA, was judged to be at low risk of bias as they clearly report power calculations, comparability of baseline characteristics and there was no industry funding. One trial was judged to be at unclear risk as it was not underpowered, baseline characteristics were similar between the two groups, but the study was partially funded by commercial funds (Sluijs 2010). Two trials were judged to be at unclear risk of bias because of insufficient information provided (Sarkkinen 1998; OPTILIP 2006).

## Effects of interventions

### Increased omega 6

#### Primary outcomes

None of the included trials reported data for our primary outcomes (all-cause mortality, cardiovascular mortality, or non-fatal end points such as MI, CABG, PTCA, angina, angiographically defined CHD, stroke, carotid endarterectomy, and PAD) (Sarkkinen 1998; Moore 2006 High LA; OPTILIP 2006; Sluijs 2010).

#### Secondary outcomes

##### Blood pressure

Two trials of increased omega 6 intake reported data on systolic (SBP) and diastolic (DBP) blood pressure. There was no significant heterogeneity ( $I^2$  statistic = 0%) for either SBP or DBP and results are dominated by one larger trial (Sluijs 2010, 346 participants randomised). The pooled analysis of two trials showed no statistically significant effect of increased omega 6 intake on either SBP (MD -0.79, 95% CI -3.0, 1.41; two trials, 387 participants; Analysis 1.1) or DBP (MD -0.02, 95% CI -1.35 to 1.32; two trials, 387 participants; Analysis 1.2).

##### Lipid levels

Three trials reported the effect of increased omega 6 intake on lipid levels (Sarkkinen 1998; Moore 2006 High LA; Sluijs 2010). For total cholesterol, there was significant heterogeneity ( $I^2$  statistic = 51%) and results were dominated by one larger trial (Sluijs 2010). The pooled analysis of three trials showed no statistically significant effect of increased omega 6 intake on total cholesterol (MD 0.02, 95% CI -0.13 to 0.18; three trials, 460 participants; Analysis 1.3).

For LDL-cholesterol, there was moderate heterogeneity ( $I^2$  statistic = 38%) and results were dominated by one larger trial (Sluijs 2010). The pooled analysis of the three trials showed no statistically significant effect of increased omega 6 intake on LDL-cholesterol (MD -0.01, 95% CI -0.14 to 0.12; three trials, 460 participants; Analysis 1.4).

For HDL-cholesterol, there was no heterogeneity ( $I^2$  statistic = 0%) and results were dominated by one larger trial (Sluijs 2010). The pooled analysis of the three trials showed no statistically significant effect of increased omega 6 intake on HDL-cholesterol

(MD 0.01, 95% CI -0.04 to 0.06; three trials, 460 participants; [Analysis 1.5](#)).

For triglycerides, there was no heterogeneity ( $I^2$  statistic = 0%) and results were dominated by one larger trial ([Sluijs 2010](#)). The pooled analysis of the two trials showed no statistically significant effect of increased omega 6 intake on triglycerides levels (MD 0.03, 95% CI -0.07 to 0.12; two trials, 419 participants; [Analysis 1.6](#)).

### Occurrence of type 2 diabetes as a major CVD risk factor

None of the included trials reported data on the occurrence of type 2 diabetes.

### Adverse effects

None of the included studies reported adverse effects.

## Reduced omega 6

### Primary outcomes

Two trials reported the effects of decreasing omega 6 and did not report data for our primary outcomes (all-cause mortality, cardiovascular mortality, or non-fatal end points such as MI, CABG, PTCA, angina, angiographically defined CHD, stroke, carotid endarterectomy, and PAD) ([Moore 2006 Low LA](#); [OPTILIP 2006](#)).

### Secondary outcomes

#### Blood pressure

One trial examined effects of decreasing omega 6 on SBP and DBP ([Moore 2006 Low LA](#)). This single trial reported no statistically significant effect of reduced omega 6 intake on either SBP (MD -0.80, 95% CI -14.34 to 12.74; [Analysis 2.1](#)) or DBP (MD 0.60, 95% CI -6.82 to 8.02; [Analysis 2.2](#)).

#### Lipid levels

Two trials reported the effect of decreased omega 6 intake on lipid levels ([Moore 2006 Low LA](#); [OPTILIP 2006](#)). One of the trials, [OPTILIP 2006](#), included participants on lipid lowering drugs.

For total cholesterol, there was no heterogeneity ( $I^2$  statistic = 0%) and the pooled analysis of the two trials showed no statistically significant effect of decreased omega 6 intake on total cholesterol levels (MD 0.06, 95% -0.31 to 0.43; two trials, 114 participants; [Analysis 2.3](#)).

For LDL-cholesterol, there was no heterogeneity ( $I^2$  statistic = 0%) and the pooled analysis of the two trials showed no statistically significant effect of decreased omega 6 intake on LDL-cholesterol

levels (MD -0.04, 95% CI -0.36 to 0.29; two trials, 114 participants; [Analysis 2.4](#)).

For HDL-cholesterol, there was no heterogeneity ( $I^2$  statistic = 0%) and the pooled analysis of the two trials showed no statistically significant effect of decreased omega 6 intake on HDL-cholesterol levels (MD -0.02, 95% CI -0.16 to 0.12; two trials, 114 participants; [Analysis 2.5](#)).

One trial reported the effect of reducing omega 6 on triglycerides levels ([OPTILIP 2006](#)). The single trial reported no statistically significant effect of reduced omega 6 intake on triglycerides (MD 0.13, 95% CI -0.11 to 0.37; [Analysis 2.6](#)).

### Occurrence of type 2 diabetes as a major CVD risk factor

None of the included trials reported data on the occurrence of type 2 diabetes.

### Adverse effects

None of the included trials reported adverse effects.

## DISCUSSION

### Summary of main results

This Cochrane review included four trials (five papers) that randomised 660 participants. We did not identify any ongoing trials. There were no RCTs on omega 6 intake reporting CVD clinical events. Three trials investigated the effect of increased omega 6 intake on lipid levels (total cholesterol, LDL-cholesterol, and HDL-cholesterol) ([Moore 2006 High LA](#); [Sarkkinen 1998](#); [Sluijs 2010](#)), two trials reported triglycerides ([Sarkkinen 1998](#); [Sluijs 2010](#)), and two trials reported blood pressure (diastolic and systolic blood pressure) ([Moore 2006 High LA](#); [Sluijs 2010](#)). One trial, with two relevant intervention arms, investigated the effect of increased and decreased omega 6 intake on blood pressure parameters ([Moore 2006 High LA](#); [Moore 2006 Low LA](#)). Two trials investigated the effect of decreased omega 6 intake on lipid levels (total cholesterol, LDL-cholesterol, and HDL-cholesterol) ([Moore 2006 Low LA](#); [OPTILIP 2006](#)) and one trial reported triglycerides ([OPTILIP 2006](#)). All included trials were at unclear risk of bias for most risk of bias domains, but all four trials had a low risk of selective reporting bias.

Overall, our analyses found no statistically significant effects of increased omega 6 intake on lipid levels in three trials measuring these, or blood pressure in the two trials reporting this, but results are restricted to very few relatively small trials and are therefore limited. Two trials reported the effects of decreasing omega 6 on blood lipids and found no effects of the intervention. Only one

trial reported the effect of decreasing omega 6 on blood pressure and found no effect of the intervention.

### Overall completeness and applicability of evidence

Very few studies met the inclusion criteria and results are therefore extremely limited. None of the included trials reported our primary outcomes but trials were relatively small and short term. No conclusions can be drawn as to the effects of increasing or decreasing omega 6 on cardiovascular risk factors. Adverse events were not reported in any of the included trials.

Although all included trials provided oils/spreads/capsules to change omega 6 intake, the increased or decreased omega 6: omega 3 ratio varied across studies. One study did not report the LA amount but provided the mean values of LA consumption (Sarkkinen 1998). This trial included foods typically consumed in the Finnish diet but no further details were provided. Food items rich in omega 6, such as poultry, meat, egg, milk, and nuts, were not used to increase omega 6 intakes in any of the included trials hence it is unclear how trial results translate to real life scenarios. All trials included several study arms, some of which were irrelevant to this review, and therefore the number of randomised participants for this review dropped substantially.

### Quality of the evidence

Unclear risk of bias in most 'Risk of bias' domains of the four included trials makes overall interpretation of the data difficult. Sample sizes were small and durations of follow-up did not exceed 24 weeks. None of the included trials used ITT analysis. We will include a 'Summary of findings' table and perform GRADE assessments in an update of this Cochrane review.

### Potential biases in the review process

We performed a comprehensive search across major databases for interventions involving increased or decreased omega 6 intake for this review. In addition, we checked reference lists of all primary studies and review articles for additional references. Two review authors independently performed all screening, inclusion and exclusion determination, and data extraction.

Our strict inclusion criteria limited the number of studies available for inclusion in this review. We only considered trials of follow-up periods of six months (24 weeks) or more. Follow-up was considered to be the time elapsed since the start of the intervention and, therefore, we excluded any trials with an intervention period of less than six months. Whilst trials with longer term follow-up are more relevant for public health interventions, this restriction has substantially reduced the number of eligible studies for inclusion.

### Agreements and disagreements with other studies or reviews

A previous review of controlled trials found that replacement of carbohydrates with PUFAs (which the authors considered may be equal omega 6) was found to significantly reduce total cholesterol levels (estimated regression coefficient for mean change, -0.021mmol/L, 95% CI -0.027 to -0.015), HDL-cholesterol (estimated regression coefficient for mean change, -0.032 mmol/L, 95% CI -0.042 to -0.022), LDL-cholesterol (estimated regression coefficient for mean change, -0.019 mmol/L, 95% CI -0.025 to -0.013) and triacylglycerol (estimated regression coefficient for mean change, -0.026 mmol/L, 95% CI -0.031 to -0.020) (Mensink 2003). Nonetheless, Mensink 2003 included short term interventions and studies were not necessarily randomised. A meta-analysis of cohort studies which explicitly examined the effect of LA intake on CHD outcomes (myocardial infarction, ischemic heart disease, coronary artery bypass graft, sudden cardiac arrest, acute coronary syndrome, and CHD deaths) found a dose-response inverse association between dietary LA intake with CHD risk (Farvid 2014). However, observational studies are open to bias and confounding.

A recent meta-analysis of prospective, observational studies and RCTs examined the association between fatty acids and coronary disease. The meta-analysis of RCTs showed that omega-6 intake did not significantly reduce the risk for coronary disease 0.86 (95% CI 0.69 to 1.07). It should be noted that the RCTs were eligible for this review only if they recorded coronary outcomes as an endpoint of interest (Chowdhury 2014) and were conducted predominantly in those with existing CVD, and so the focus of this review was secondary rather than primary prevention unlike the current review.

There have been previous systematic reviews of RCTs examining the effects of PUFA, including omega 6 intake but not explicitly focusing on this, on cardiovascular risk factors including lipid levels (Mozaffarian 2010; Hooper 2011) and CVD events (Mozaffarian 2010). These reviews used different inclusion criteria to the current review. Participants were included with or without existing CVD so the focus was not on primary prevention (Mozaffarian 2010; Hooper 2011). Additionally, it is difficult to disentangle the effect of omega 6 as this was not explicitly examined in each of the reviews (Mozaffarian 2010; Hooper 2011).

## AUTHORS' CONCLUSIONS

### Implications for practice

We have avoided making implications for practice as there is currently insufficient evidence for the effects of increased or decreased omega 6 intake on CVD events and CVD risk factors.

## Implications for research

Few trials met the inclusion criteria of this Cochrane review. All included trials were small, relatively short term, and at some risk of bias. None reported our primary outcomes. There is a need for large, well-designed, long term RCTs to assess the effect of increased or reduced omega 6 intake on cardiovascular events and risk factors to determine the effectiveness of either intervention for the primary prevention of CVD.

## ACKNOWLEDGEMENTS

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## CHARACTERISTICS OF STUDIES

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

#### Moore 2006 High LA

Methods	RCT with increased dietary omega 6:omega 3 ratio. Study was conducted in the UK	
Participants	<p>157 men and women between the age of 35 to 65 years and a BMI between 25 and 40 kg/m<sup>2</sup> were recruited from the community.</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> <li>• BMI between 25 and 40 kg/m<sup>2</sup>.</li> <li>• Between 35 and 65 years old.</li> <li>• Not taking regular oil supplements.</li> <li>• Not currently prescribed non-steroidal anti-inflammatory drugs, aspirin, steroids, immunosuppressants, or lipid lowering drugs.</li> <li>• No known diagnosis of diabetes, hypertension, hyperlipidaemia, asthma, or chronic inflammatory disease.</li> <li>• Not known or planned pregnancy.</li> </ul>	
Interventions	<p>Intervention:</p> <ul style="list-style-type: none"> <li>• Low n-3 (high LA:LNA): (white fish/sunflower, N = 30, 33% males): white fish and fat spreads and oils. LA:LNA was 27:1 for sunflower spread, and 63:0.1 for sunflower oil.</li> <li>• The fish was obtained from local supermarkets and volunteers selected items from a range, including frozen fish, fishcakes, and tinned fish. The spreads and oils were generously provided by Matthews Foods PLC. (Ossett, West Yorkshire, UK).</li> </ul> <p>Control (N = 34, 34% males):</p> <ul style="list-style-type: none"> <li>• No intervention</li> </ul> <p>Follow-up: 24 weeks</p>	
Outcomes	Blood pressure and lipid levels	
Notes	<p>This was a 5-arm study: High n-3 (high LA:LNA), High n-3 (low LA:LNA), Low n-3 (high LA:LNA), Low n-3 (low LA:LNA), and control. We used just the Low n-3 (high LA:LNA), and control arms only hence total number randomised was 64 participants</p> <p>The control group N was divided in 2 in the meta-analyses to prevent double counting</p> <p>Funding source: This study was supported by funding from the UK Food Standards Agency and Medical Research Council</p>	
<b><i>Risk of bias</i></b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Minimization was used to assign subjects to a control group or one of four parallel intervention groups and to ensure that the treatment arms were balanced for age, BMI, gender, and habitual consumption of oily

**Moore 2006 High LA** (Continued)

		fish based on three categories (0, ≤ 1, or > 1 portion/week)
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Due to the nature of food-based interventions, it was not possible for the principal investigators or subjects to be blinded to the randomisation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory analysts, dietary coders, clinical scientists, and statisticians involved in the study were blinded to the randomisation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of drop-outs was specified and reasons provided.
Selective reporting (reporting bias)	Low risk	All outcomes stated were reported.
Other bias	Low risk	Not underpowered, baseline characteristics are comparable, and the study was not industry funded

**Moore 2006 Low LA**

Methods	RCT with decreased dietary omega 6:omega 3 ratio. Study was conducted in the UK
Participants	157 men and women between the age of 35 to 65 years and a BMI between 25 and 40 kg/m <sup>2</sup> were recruited from the community Inclusion criteria: <ul style="list-style-type: none"> <li>• BMI between 25 and 40 kg/m<sup>2</sup>.</li> <li>• Between 35 and 65 years old.</li> <li>• Not taking regular oil supplements.</li> <li>• Not currently prescribed non-steroidal anti-inflammatory drugs, aspirin, steroids, immunosuppressants, or lipid lowering drugs.</li> <li>• No known diagnosis of diabetes, hypertension, hyperlipidaemia, asthma, or chronic inflammatory disease.</li> <li>• Not known or planned pregnancy.</li> </ul>
Interventions	Intervention: <ul style="list-style-type: none"> <li>• Low n-3 (low LA:LNA): (white fish/rapeseed, N = 29, 38% males): white fish and fat spreads and oils. LA:LNA was 3:1 for rapeseed spread, and 2:1 for rapeseed oil.</li> <li>• The fish was obtained from local supermarkets and volunteers selected items from a range, including frozen fish, fishcakes, and tinned fish. The spreads and oils were generously provided by Matthews Foods Plc. (Ossett, West Yorkshire, UK).</li> </ul> Control (N = 34, 34% males): <ul style="list-style-type: none"> <li>• No intervention.</li> </ul> Follow-up: 24 weeks

**Moore 2006 Low LA** (Continued)

Outcomes	Blood pressure and lipid levels
Notes	<p>This was a 5-arm study: High n-3 (high LA:LNA), High n-3 (low LA:LNA), Low n-3 (high LA:LNA), Low n-3 (low LA:LNA), and control. We used just the Low n-3 (low LA:LNA), and control arms only and control arms only hence total number randomised was 63 participants</p> <p>The control group N was divided in 2 in the meta-analyses to prevent double counting</p> <p>Funding source: This study was supported by funding from the UK Food Standards Agency and Medical Research Council</p>

***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	As above (Moore 2006 High LA).
Allocation concealment (selection bias)	Unclear risk	As above (Moore 2006 High LA).
Blinding of participants and personnel (performance bias) All outcomes	High risk	As above (Moore 2006 High LA).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above (Moore 2006 High LA).
Incomplete outcome data (attrition bias) All outcomes	Low risk	As above (Moore 2006 High LA).
Selective reporting (reporting bias)	Low risk	As above (Moore 2006 High LA).
Other bias	Low risk	As above (Moore 2006 High LA).

**OPTILIP 2006**

Methods	RCT with decreased omega 6 fats. Study was conducted in the UK
Participants	<p>OPTILIP study. 258 men and postmenopausal women aged 45 to 70 years were recruited from general practices participating in the UK Medical Research Council General Practice Research Framework. Staff of King's College London and its associated hospitals were also recruited for this study</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> <li>• Both genders.</li> <li>• Postmenopausal (aged 45 to 70) women. In the younger subjects, postmenopausal status defined as a span of <math>\geq 1</math> year since menstruation and was confirmed by measurement of the serum concentration of follicle-stimulating hormone.</li> <li>• Subjects taking blood pressure or lipid-lowering medication were eligible if their</li> </ul>

	<p>medication regimens were stable.</p> <p>Exclusion criteria:</p> <ul style="list-style-type: none"> <li>• BMI &lt; 20 or &gt; 35 kg/m<sup>2</sup>.</li> <li>• Fasting serum cholesterol &gt; 8 mmol/L or triacylglycerol &gt; 6.0 mmol/L.</li> <li>• Abnormal liver function or hematology.</li> <li>• Clinical history of cholestatic liver disease, pancreatitis, diabetes mellitus, or myocardial infarction.</li> <li>• Current use of anticoagulants (excluding aspirin).</li> </ul>	
Interventions	<p>Intervention (N = 49, 63% males):</p> <ul style="list-style-type: none"> <li>• Moderate linolenate diet where participants were provided with oils and spreads for the duration of the study. The LA and ALA contents of the spreads were 4.7 and 0.8 g/100 g. The LA and ALA contents of rapeseed (canola) oil were 19.7 g and 8.9 g/100 g. Participants were also provided with 2 small cans of tuna/week, the tuna was canned in high linoleic sunflower oil.</li> <li>• The diet was designed to keep the intake of saturated and monounsaturated fatty acids constant and to provide ~ 6% of energy from PUFAs.</li> </ul> <p>Control (N = 44, 68% males):</p> <ul style="list-style-type: none"> <li>• Participants were provided with oils and spreads for the duration of the study. The LA and ALA contents of the spreads were 39.6 g and 0.5 g/100 g. The LA and ALA contents of high-oleic sunflower oil were 10.6 g and 0.3 g/100 g. Participants were also provided with 2 small cans of tuna/week, the tuna was canned in olive oil.</li> <li>• The diet was designed to keep the intake of saturated and monounsaturated fatty acids constant and to provide ~ 6% of energy from PUFAs.</li> </ul> <p>Follow-up: 24 weeks</p>	
Outcomes	Lipid levels	
Notes	<p>The Quantification of the Optimal n6/n3 ratio in the UK Diet (OPTILIP) Study was designed to assess the effects of lowering the dietary n6:n3 on CVD risk factors in older people. The objective was achieved by using a food-based intervention that involved increasing the relative intake of linolenic acid or n3 LC-PUFAs (notably EPA and DHA), or both, in relation to the intake of linoleic acid. This was a 5-arm study: n-3 LC-PUFA + linolenate, n-3 LC-PUFA, moderate linolenate diet, high linolenate, and control. We used just the moderate linolenate (lower omega 6) and control arms (higher omega 6) hence total number randomised was 93 participants</p> <p>Funding source: Supported by the UK Food Standards Agency. Unilever Research, and Mills DA, Norway, provided the spreads and the salmon spread, respectively</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated. "Subjects were randomly assigned to 1 of 5 diets; subjects living together were allocated to the same treat-

		ment”
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details of withdrawals and lost to follow-up were stated but not per study arm. Flow diagram was not provided. ITT analysis was not used
Selective reporting (reporting bias)	Low risk	All outcomes stated were reported.
Other bias	Unclear risk	Insufficient information to judge. However, the study participants received a modest financial reimbursement for their participation in the study. They were provided at regular intervals with some foods (yellow fat spreads (i.e. butter, margarine, and low-fat spreads), oil, and fish) for the dietary intervention period

**Sarkkinen 1998**

Methods	RCT with increased omega 6 fats. Study was conducted in Finland
Participants	160 men and women aged 23 to 58 years old with hypercholesterolemia were recruited through the occupational health care system in the area of Kuopio in Eastern Finland Inclusion criteria: <ul style="list-style-type: none"> <li>• Mild to moderate hypercholesterolaemia.</li> <li>• Serum total cholesterol between 6.5 and 8.0 mmol/L before the study.</li> </ul> Exclusion criteria: <ul style="list-style-type: none"> <li>• Known diseases affecting serum lipid levels.</li> <li>• Irregular eating patterns.</li> <li>• Excess consumption of alcohol (&gt; 45 g ethanol/d).</li> </ul>
Interventions	Intervention (N = 37, 43% males): Reduced-fat sunflower oil-enriched diet: participants received detailed written instructions on diet at their own energy level. The goal was to consume 30% of energy from fat (10% saturated fat, 10% monosaturated fat, 10% polyunsaturated fat), 15% of energy from protein, 55% of energy from carbohydrate, and 15 to 20 g of fibre per day. The diet composed of normal food items, substituting low-fat items for high-fat foods typically consumed in the Finnish diet; fatty acid composition was adjusted by changing quality and quantity of fat spreads. Sunflower oil margarine and sunflower oil were provided Control (N = 36, 47% males): High fat, saturated fat-enriched control diet: participants

	received detailed written instructions on diet at their own energy level. The goal was to consume 38% of energy from fat (18% saturated fat, 15% monosaturated fat, 5% polyunsaturated fat), 15% of energy from protein, 47% of energy from carbohydrate, and 15 to 20 g of fibre per day. The diet composed of normal food items, substituting low-fat items for high-fat foods typically consumed in the Finnish diet; fatty acid composition was adjusted by changing quality and quantity of fat spreads and subjects received detailed written instructions on the diets at their own energy level. Butter and a small amount of low-erucic acid rapeseed oil were provided Follow-up: 24 weeks	
Outcomes	Lipid levels	
Notes	This is a 4-arm study: High fat, saturated fat enriched (control), reduced-fat sunflower oil-enriched, reduced-fat rapeseed oil-enriched, and reduced-fat arm. We used just the control and reduced-fat sunflower oil-enriched arms only hence total number randomised was 73 participants Funding source: Supported by grants from the Finnish Food Research Foundation, Finnish Heart Research Foundation, Aarne and Aili Turunen Foundation, and the Research Council for Health, Academy of Finland	
<b><i>Risk of bias</i></b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Spreads provided on a single-blind basis but no other details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details of withdrawals and lost to follow-up were stated but not per study arm. Flow diagram was not provided. ITT analysis was not used
Selective reporting (reporting bias)	Low risk	All outcomes stated were reported.
Other bias	Unclear risk	Insufficient information to judge. Power calculation was not carried out. Non-industrial funding

Methods	RCT with increased omega 6 supplementation (cis-9,trans-11 conjugated linoleic acid) . Study was conducted in the Netherlands
Participants	401 men and women between the age of 40 to 70 years old and BMI $\geq$ 25 kg/m <sup>2</sup> were recruited through the Julius Center "POKA" database municipal registers of a large and middle-large town in the middle part of the Netherlands Inclusion criteria: <ul style="list-style-type: none"> <li>• Apparently healthy men and women</li> <li>• Aged 40 to 70 years</li> <li>• BMI <math>\geq</math> 25 kg/m<sup>2</sup></li> </ul>
Interventions	Intervention: High omega 6 (4 g CLA/d, N = 201, 48% males): The c9,t11 CLA oil was manufactured from safflower oil. Four capsules of 1 g oil each were taken daily. CLA capsules provided 80% CLA isomers, of which 80% (2.5 g/d) was c9,t11 CLA and 20% (0.6 g/d) was t10,c12 CLA. The percentage of energy provided by c9,t11 CLA and t10,c12 CLA during the intervention was around 1% and around 0.3%, respectively (based on a daily intake of 2000 to 2500 kcal) Control (N = 200, 48.6% males): Placebo capsules contained an equal amount of fat and were composed of a blend of palm oil (80%) and soybean oil (20%), which resembles the average fatty acid composition of the fat consumed by a Western population Follow-up: 24 weeks
Outcomes	Blood pressure and lipid levels
Notes	Funding source: Supported by a grant from the Dutch Ministry of Economic Affairs and by a grant from Lipid Nutrition BV, Wormerveer, Netherlands. Lipid Nutrition is a commercial company focused on developing and producing specialty fats and oils

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Potential participants were recruited through a random selection from the municipal registers of a large and middle-large town in the middle part of the Netherlands. Minimisation was used to assign subjects to a control group or intervention group in a 1:1 ratio. Randomisation was stratified for sex
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded study capsules were supplied in individual, pre-prepared, numbered bottles. The investigators were unaware of treatment allocations for the study duration

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of drop-outs was specified and reasons provided.
Selective reporting (reporting bias)	Unclear risk	All outcomes stated were reported.
Other bias	Unclear risk	Not underpowered, baseline characteristics were similar between the two groups. The study was partially funded by commercial funds

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

Study	Reason for exclusion
Ahrén 2009	Control not minimal and short term trial (12 weeks).
Allman-Farinelli 1999	Control not minimal and short term trial (6 weeks).
Anderson 1957	Short term trial (less than 4 weeks).
Angela Liou 2009	Short term trial (8 weeks).
Bachmair 2012	Control not minimal, irrelevant outcomes and short term trial (3 months)
Becker 1983	Control not minimal and short term trial (4 weeks).
Belury 2009	Control not minimal, participants irrelevant and short term trial (16 weeks)
Bemelmans 2000	Control not minimal (comparison against omega 3 intakes).
Bemelmans 2004	Control not minimal (comparison against omega 3 intakes).
Benito 2001	Control not minimal and short term trial (93 days).
Bermejo 2012	Intervention irrelevant and short term trial (12 weeks).
Bjeremo 2012	Short term trial (10 weeks).
Blair 1993	Irrelevant outcomes and short term trial (100 days).
Boberg 1986	Short term trial (8 weeks).

(Continued)

Bonanome 1992	Control not minimal and short term (3 weeks).
Bouwens 2009	Control not minimal (comparison against omega 3 intakes or low omega 3 intakes but with a similar omega 6 content)
Brady 2004	Short term trial (12 weeks).
Bramkamp 1974	Not a RCT.
Bronsgest-Schoute 1979	Control not minimal and short term trial (6 weeks).
Brox 1981	Control not minimal and short term trial (6 weeks).
Burdge 2004	Intervention, control and outcomes irrelevant and short term trial (8 weeks)
Camargo 2013	Intervention and control irrelevant and short term trial (12 weeks)
Carvalho 2012	Short term trial (90 days).
Cater 1997	Control not minimal and short term trial (3 weeks).
Clandinin 1999	Short term trial (21 days).
Dayton 1962	Irrelevant intervention.
de Kok 2003	Irrelevant outcomes and short term trial (6 weeks).
Deferne 1992	Control not minimal and short term trial (9 weeks).
Dembinska-Kiec 2010	Not a RCT.
Dembinska-Kiec 2011	Not a RCT.
Elisha 2011	Not a RCT.
Failor 1988	Not a RCT and short term trial (3 weeks).
Finnegan 2003a	Irrelevant outcomes and control not minimal.
Finnegan 2003b	Irrelevant intervention.
Friday 1991	Not a RCT and short term trial (3 weeks).
Gaullier 2004	Irrelevant intervention.
Gaullier 2005	Not a RCT and control irrelevant.
Gaullier 2007	Irrelevant intervention.

(Continued)

Ghafoorunissa 1995	Control not minimal and short term trial (8 weeks).
Ghafoorunissa 2002	Not a RCT.
Giacco 2007	Intervention and control irrelevant and short term trial (3 months)
Groen 1965	Short term trial (5 weeks).
Grundt 1995	Intervention and control irrelevant and short term trial (12 weeks)
Grønn 1991	Not a RCT and short term trial (8 weeks).
Haglund 1998	Control not minimal and short term trial (4 weeks).
Harris 2009	Not a RCT.
Hartwich 2009	Control not minimal and short term trial (12 weeks).
Hartwich 2010	Control not minimal and short term trial (8 hours).
Heine 1989	Irrelevant participants.
Higdon 2000	Short term intervention (5 weeks).
Higdon 2001	Short term intervention (5 weeks).
Ho 1999	Irrelevant outcomes, control not minimal and short term trial (12 weeks)
Hodson 2001	Control not minimal and short term trial (2.5 weeks).
Hui 1989	Intervention in rats.
Hwang 1997	Short term trial (12 weeks).
Intorre 2013	Short term trial (4 weeks).
Iwata 2007	Control not minimal and short term trial (12 weeks).
Khan 2003	Irrelevant outcomes.
Kiecolt-Glaser 2013	Irrelevant intervention and outcomes and short term trial (4 months)
Kim 2009	Irrelevant intervention and short term trial (12 weeks).
Kingsbury 1961	Control not minimal and short term trial (6 weeks).
Knapp 1989	Short term trial (3 months).

(Continued)

Koyama 2009	Not a RCT and short term trial (8 weeks).
Lambert 2007	Short term trial (12 weeks).
Lands 1992	Not a RCT.
Lee 2012	Short term trial (4 weeks).
Legrand 2010	Control not minimal and short term trial (90 days).
MARGARIN 2002	Irrelevant intervention.
Margolin 1990	Control not minimal and short term intervention (8 weeks).
Margolin 1991	Control not minimal and short term intervention (8 weeks).
McDaniel 2010	Irrelevant outcomes and short term trial (4 weeks).
Mendis 2001	Irrelevant intervention.
Miles 2004	Control not minimal, irrelevant outcomes and short term trial (12 weeks)
Mills 1989	Short term trial (28 days).
Minihane 2005	Control not minimal and short term trial (6 weeks).
Misikangas 2001	Irrelevant outcomes and short term trial (6 weeks).
Mortensen 1983	Control not minimal and short term trial (4 weeks).
Møller 1992	Control not minimal and short term trial (1 day).
Naber 1992	Short term trial (12 weeks).
Naumann 2006	Sort term trial (13 weeks).
Nelson 1997a	Short term trial (50 days).
Nelson 1997b	Short term trial (65 days).
Nestel 1992	Control not minimal and short term intervention (4 weeks).
Nestel 1995	Control not minimal and short term trial (3 weeks).
Noakes 1996	Control not minimal and short term trial (11 weeks).
Oe 2008	Short term trial (3 months).

(Continued)

Paschos 2007	Control not minimal and short term trial (12 weeks).
Paikowska 2012	Short term trial (12 weeks).
Perez-Martinez 2010	Irrelevant intervention, control and outcomes and short term trial (12 weeks)
Perkins 1958	Short term trial (7 weeks).
Radack 1990	Control not minimal and short term trial (8 weeks).
Radack 1991	Control not minimal and short term trial (12 weeks).
Rajaram 2012	Intervention irrelevant, irrelevant outcomes and short term trial (8 weeks)
Rallidis 2003	Control not minimal and short term trial (3 months).
Rallidis 2004	Control not minimal and short term trial (12 weeks).
Ramprasath 2012	Short term trial (20 days).
Reaven 1991	Short term trial (5 weeks).
Risérus 2002a	Irrelevant intervention and short term trial (12 weeks).
Risérus 2002b	Irrelevant intervention and short term trial (12 weeks).
Risérus 2004	Irrelevant intervention and short term trial (12 weeks).
Robertson 2002	Control not minimal and short term trial (1 day).
Roche 2009	Intervention and control irrelevant.
Sanders 1983	Intervention irrelevant and short term trial (2 weeks).
Sanders 1997	Control not minimal and short term trial (21 days).
Singer 1991	Control not minimal and short term trial (3 months).
Sirtori 1992	Short term trial (6 weeks).
Smedman 2001	Short term trial (12 weeks).
Sofi 2010	Not a RCT and short term trial (10 weeks).
Sofi 2013	Intervention and control irrelevant and short term trial (10 weeks)
Solà 1997	Control not minimal and short term trial (8 weeks).

(Continued)

Song 2005	Control not minimal and short term trial (12 weeks).
Steck 2007	Control not minimal and short term trial (12 weeks).
Sundram 1992	Short term trial (6 weeks).
Svaneborg 1994	Control not minimal and short term trial (1 day).
Tavakkoli 2010	Control not minimal and short term trial (12 weeks).
Taylor 2006	Short term trial (12 weeks).
Tholstrup 2008	Irrelevant intervention and short term trial (16 weeks).
Tierney 2011	Intervention and control irrelevant and short term trial (12 weeks)
Truswell 2000	Short term trial (3 to 5 weeks).
Tsai 1997	Irrelevant control and short term trial (6 weeks).
Tsofliou 2009	Intervention irrelevant and short term trial (12 weeks).
Tulk 2009	No relevant outcomes and short term trial (8 hours).
Valsta 1996	Control not minimal, intervention irrelevant and short term trial (6 weeks)
Venter 1988	Short term trial (12 weeks).
Vergoesen 1980	Not a RCT.
Vericel 1987	Control not minimal and short term trial (2 months).
Vermunt 2001	Short term trial (6 weeks).
Viihari 1986	Not a RCT and short term trial (3 months).
West 2010	Short term trial (18 weeks).
Wilkinson 2005	Control not minimal and short term trial (12 weeks).
Yam 2001	Participants irrelevant and short term trial (12 weeks).
Zhao 2004	Short term (6 weeks).
Zhao 2007	No relevant outcomes and short term trial (6 weeks).

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

### Natvig 1967 High LA

Methods	RCT with increased omega-6 fats
Participants	16,615 men aged 50 to 59 years working in industrial and other firms in different parts of Norway
Interventions	Intervention: <ul style="list-style-type: none"><li>• Sunflower oil: 10 mL/day with approximately 63% LA</li></ul> Control: <ul style="list-style-type: none"><li>• Not given oil</li></ul> Duration of the study: 52 weeks
Outcomes	Morbidity and mortality of coronary and other vascular diseases
Notes	Requires translation from Norwegian to determine details of the conduct of the trial, assessment of risk of bias and outcome data This is a 4-arm trial: Linseed oil, sunflower oil, and two control arms English abstract: In collaboration with industrial physicians in Norway, a controlled 12-month trial was conducted to assess the prophylactic effect of linoleic acid against coronary atherosclerosis, as suggested by P.A. Owren and co-workers on the basis of laboratory experiments. The subjects were 16,615 men aged 50 to 59 years, working in industrial and other firms in different parts of Norway. For each man, a health form was completed after a medical examination or personal interview by the industrial physicians. The men were divided into 2 random groups; 1 group of 6,720 men were given 10 mL of linseed oil daily with 55% of linoleic acid; the other group of 6,692 men were given 10 mL of sunflower oil daily with approximately 63% linoleic acid. Two control groups were not given oil. After 12 months, follow-up health forms for the men were returned from the industrial physicians, and the morbidity and mortality of coronary and other vascular diseases were analysed. There were no statistically significant differences between the linseed oil, sunflower oil, and control groups with regard to total mortality and mortality from coronary disease, the incidence of coronary infarction and atherosclerosis obliterans, apoplexy, and thrombophlebitis. Thus, the trial did not demonstrate any prophylactic effect from a daily dose of linseed oil or sunflower oil. Blood analyses of a 5% random sample of the men in the oil and control groups revealed no significant difference in serum cholesterol levels. As the numbers are small, however, there is no discrepancy between this lack of difference in the groups and a calculated reduction of up to 10 mg% in serum cholesterol. There was no difference in platelet adhesiveness between the oil groups and control groups. The trial revealed a significantly higher rate of coronary infarction, angina pectoris and atherosclerosis obliterans in cigarette smokers than in non-smokers, and in men with persistently elevated blood sedimentation rates compared with men with normal values. The trial clearly demonstrated that it is possible to carry out large-scale prospective epidemiologic studies in Norway in cooperation with the industrial physicians

### Natvig 1967 Low LA

Methods	RCT with decreased omega-6 fats
Participants	As above
Interventions	Intervention: <ul style="list-style-type: none"><li>• Linseed oil: 10 mL/day with 55% of LA</li></ul> Control: <ul style="list-style-type: none"><li>• Not given oil</li></ul>

**Natvig 1967 Low LA** (Continued)

	Duration of the study: 52 weeks
Outcomes	As above
Notes	As above

**Nordoy 1981**

Methods	Cross over design - increased omega 6 fats
Participants	10 healthy male participants
Interventions	<ul style="list-style-type: none"> <li>• 25 mL cod liver oil</li> <li>• 25 mL corn oil</li> <li>• Unclear if there was a control arm</li> </ul>
Outcomes	Not clear if secondary outcomes (lipid levels) were reported
Notes	<p>Library unable to find.</p> <p>Abstract: Ten healthy male subjects on an ordinary diet were given daily dietary supplement of 25 mL cod liver oil (CLO) or corn oil (CO) for periods of 6 weeks in a crossover study. Significant changes were observed in the plasma total fatty acid composition. The main platelet phospholipids fractions were also significantly altered, particularly by CLO with an increase of the eicosapentaenoic acid (EPA): arachidonic acid (AA) ratio. Both supplements reduced collagen induced platelet aggregation and TXB2 production, with CLO as the most potent one. No spontaneous release of an anti-aggregatory substance or 6-keto-PGF1 alpha from vein tissues were found, and the total urinary excretion of prostaglandin metabolites (E and F series) remained unchanged</p>

**Ryu 1999**

Methods	No information.
Participants	No information.
Interventions	No information.
Outcomes	No information.
Notes	Library unable to find.

**Singer 1993**

Methods	No information.
Participants	No information.
Interventions	No information.

**Singer 1993** (Continued)

Outcomes	No information.
Notes	Library unable to find.

## DATA AND ANALYSES

### Comparison 1. Increased omega 6 versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Systolic blood pressure, change from baseline	2	387	Mean Difference (IV, Fixed, 95% CI)	-0.79 [-1.00, 1.41]
2 Diastolic blood pressure, change from baseline	2	387	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-1.35, 1.32]
3 Total cholesterol, change from baseline	3	460	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.13, 0.18]
4 LDL cholesterol, change from baseline	3	460	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.14, 0.12]
5 HDL cholesterol, change from baseline	3	460	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.04, 0.06]
6 Triglycerides, change from baseline	2	419	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.07, 0.12]

### Comparison 2. Reduced omega 6 versus control

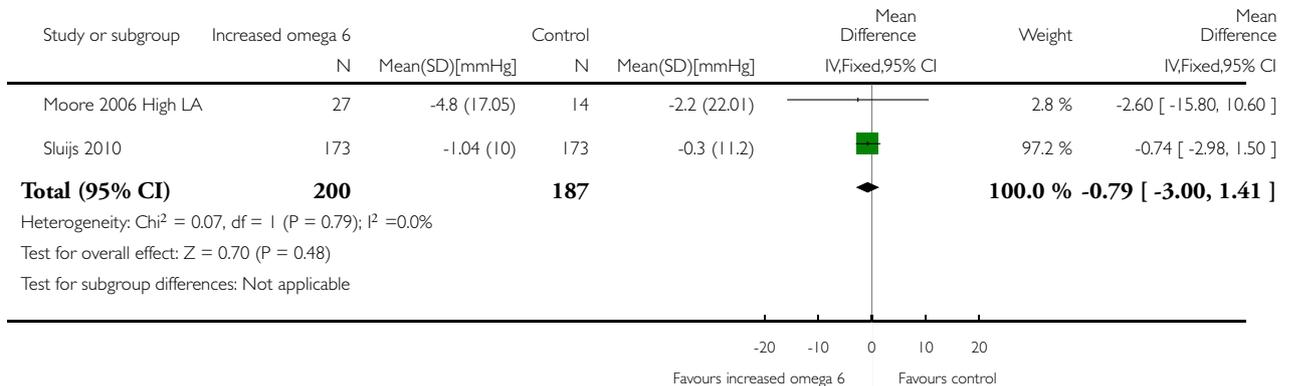
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Systolic blood pressure, change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Diastolic blood pressure, change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Total cholesterol, change from baseline [mmol/L]	2	114	Std. Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.31, 0.43]
4 LDL cholesterol, change from baseline	2	114	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.36, 0.29]
5 HDL cholesterol, change from baseline	2	114	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.16, 0.12]
6 Triglycerides, change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

### Analysis 1.1. Comparison 1 Increased omega 6 versus control, Outcome 1 Systolic blood pressure, change from baseline.

Review: Omega 6 fatty acids for the primary prevention of cardiovascular disease

Comparison: 1 Increased omega 6 versus control

Outcome: 1 Systolic blood pressure, change from baseline

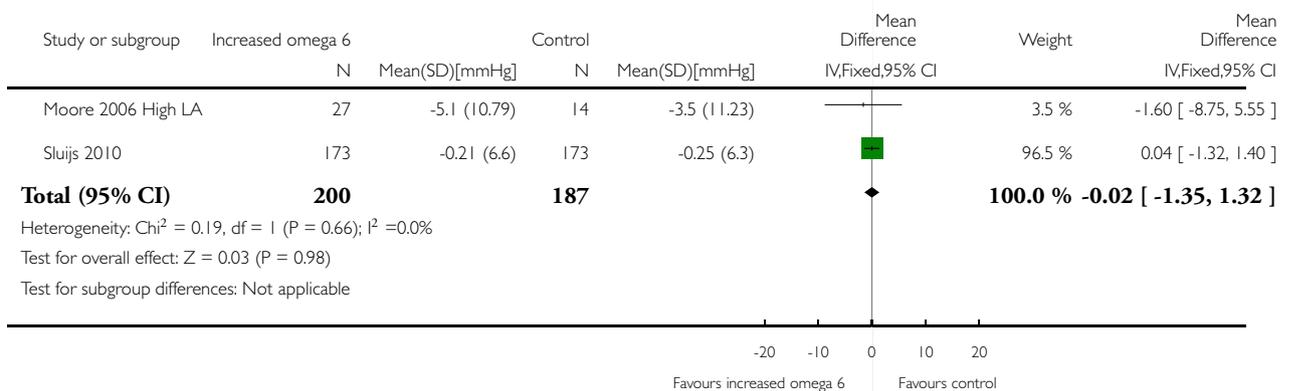


### Analysis 1.2. Comparison 1 Increased omega 6 versus control, Outcome 2 Diastolic blood pressure, change from baseline.

Review: Omega 6 fatty acids for the primary prevention of cardiovascular disease

Comparison: 1 Increased omega 6 versus control

Outcome: 2 Diastolic blood pressure, change from baseline

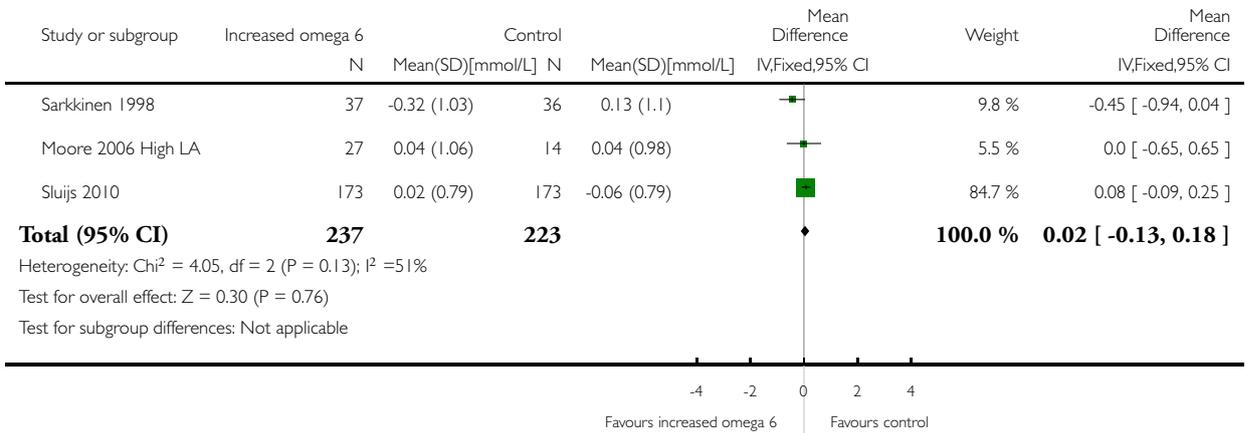


**Analysis 1.3. Comparison 1 Increased omega 6 versus control, Outcome 3 Total cholesterol, change from baseline.**

Review: Omega 6 fatty acids for the primary prevention of cardiovascular disease

Comparison: 1 Increased omega 6 versus control

Outcome: 3 Total cholesterol, change from baseline

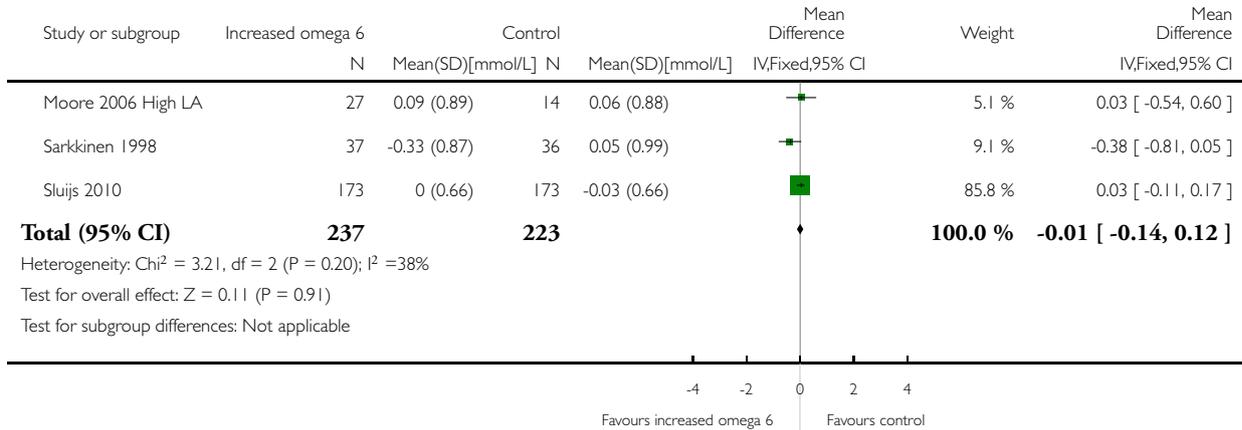


**Analysis 1.4. Comparison 1 Increased omega 6 versus control, Outcome 4 LDL cholesterol, change from baseline.**

Review: Omega 6 fatty acids for the primary prevention of cardiovascular disease

Comparison: 1 Increased omega 6 versus control

Outcome: 4 LDL cholesterol, change from baseline

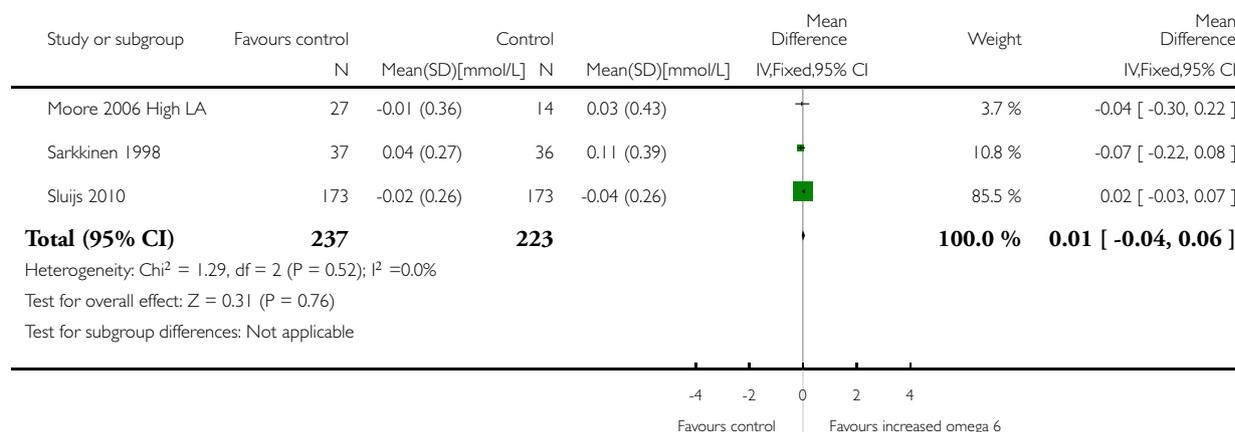


### Analysis 1.5. Comparison 1 Increased omega 6 versus control, Outcome 5 HDL cholesterol, change from baseline.

Review: Omega 6 fatty acids for the primary prevention of cardiovascular disease

Comparison: 1 Increased omega 6 versus control

Outcome: 5 HDL cholesterol, change from baseline

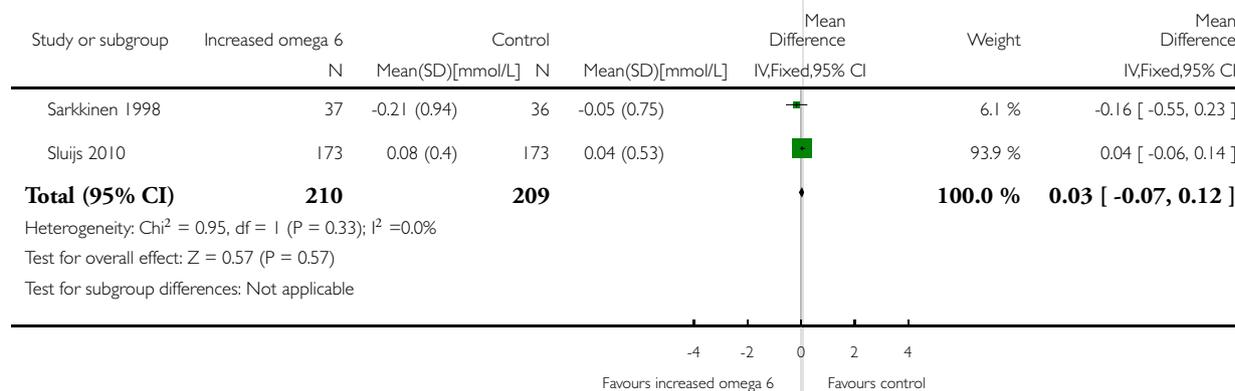


### Analysis 1.6. Comparison 1 Increased omega 6 versus control, Outcome 6 Triglycerides, change from baseline.

Review: Omega 6 fatty acids for the primary prevention of cardiovascular disease

Comparison: 1 Increased omega 6 versus control

Outcome: 6 Triglycerides, change from baseline

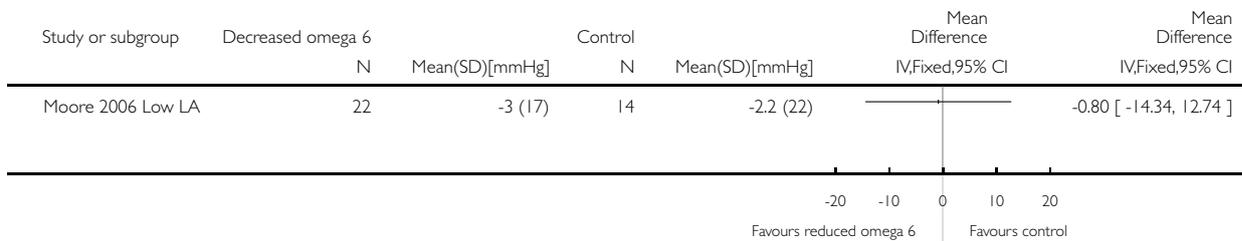


**Analysis 2.1. Comparison 2 Reduced omega 6 versus control, Outcome 1 Systolic blood pressure, change from baseline.**

Review: Omega 6 fatty acids for the primary prevention of cardiovascular disease

Comparison: 2 Reduced omega 6 versus control

Outcome: 1 Systolic blood pressure, change from baseline

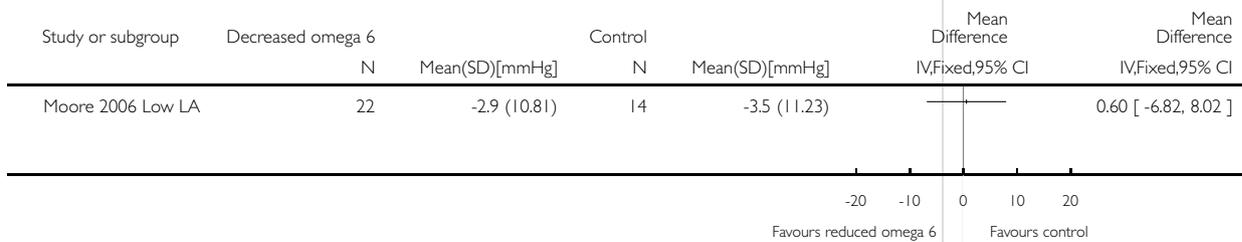


**Analysis 2.2. Comparison 2 Reduced omega 6 versus control, Outcome 2 Diastolic blood pressure, change from baseline.**

Review: Omega 6 fatty acids for the primary prevention of cardiovascular disease

Comparison: 2 Reduced omega 6 versus control

Outcome: 2 Diastolic blood pressure, change from baseline

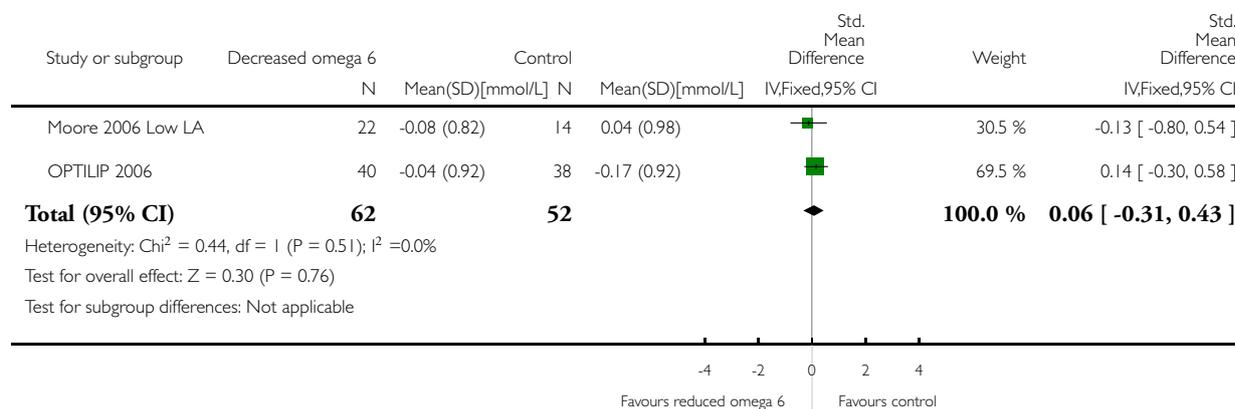


### Analysis 2.3. Comparison 2 Reduced omega 6 versus control, Outcome 3 Total cholesterol, change from baseline [mmol/L].

Review: Omega 6 fatty acids for the primary prevention of cardiovascular disease

Comparison: 2 Reduced omega 6 versus control

Outcome: 3 Total cholesterol, change from baseline [mmol/L]

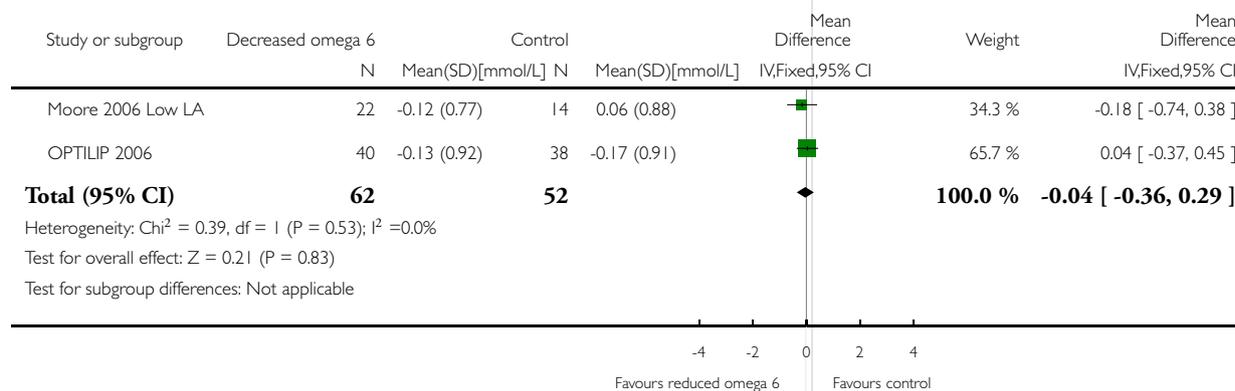


### Analysis 2.4. Comparison 2 Reduced omega 6 versus control, Outcome 4 LDL cholesterol, change from baseline.

Review: Omega 6 fatty acids for the primary prevention of cardiovascular disease

Comparison: 2 Reduced omega 6 versus control

Outcome: 4 LDL cholesterol, change from baseline

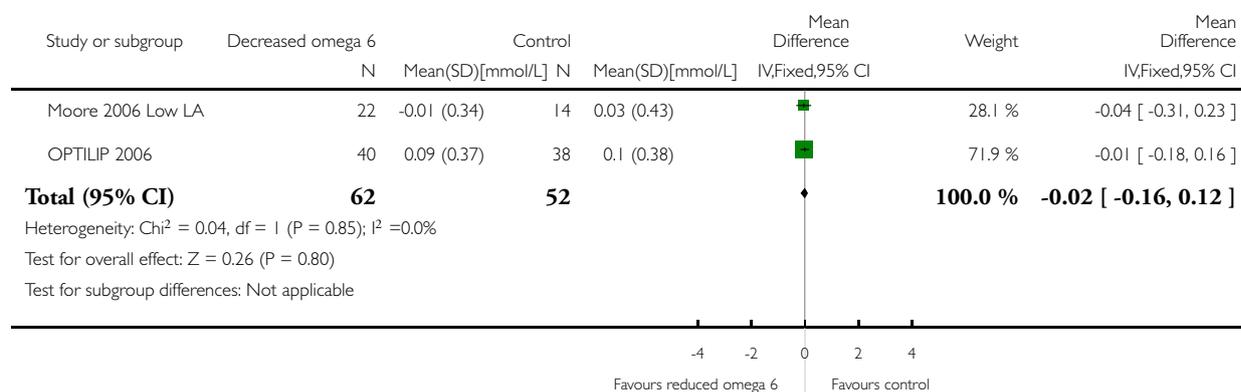


### Analysis 2.5. Comparison 2 Reduced omega 6 versus control, Outcome 5 HDL cholesterol, change from baseline.

Review: Omega 6 fatty acids for the primary prevention of cardiovascular disease

Comparison: 2 Reduced omega 6 versus control

Outcome: 5 HDL cholesterol, change from baseline

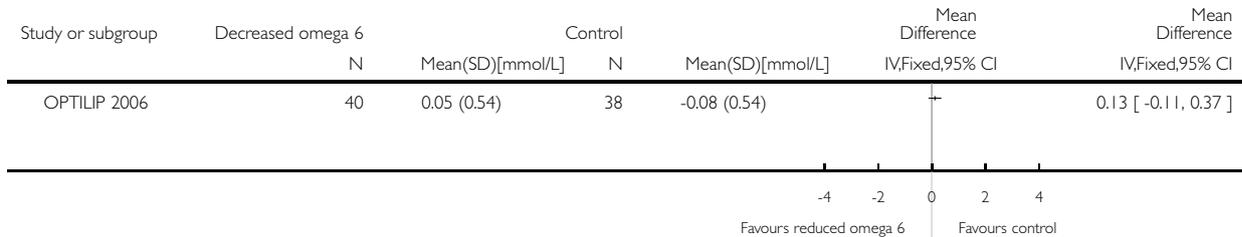


## Analysis 2.6. Comparison 2 Reduced omega 6 versus control, Outcome 6 Triglycerides, change from baseline.

Review: Omega 6 fatty acids for the primary prevention of cardiovascular disease

Comparison: 2 Reduced omega 6 versus control

Outcome: 6 Triglycerides, change from baseline



## APPENDICES

### Appendix I. Search strategies

#### 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\*)  
 #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 fibrillar\*" 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 nutriliplid 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

## **CONTRIBUTIONS OF AUTHORS**

LHo, KR, and LH contributed to the protocol development. LH, CC, and NF screened titles and abstracts and assessed studies for inclusion and exclusion. LA, LH, and CC extracted data and assessed methodological rigour. Analyses were conducted by LA and checked by KR. LH wrote the first draft of the review, which was updated by LA and KR.

## **DECLARATIONS OF INTEREST**

LA: None known

LH: None known

CC: None known

NF: None known

LHo: None known

KR: None known

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## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We did not search AMED, as initially planned in [Hartley 2014](#), because of lack of resources.